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Intramolecular Hydroalkoxylation and Hydroamination of Alkynes Catalyzed by Cu(I) Complexes Supported by *N*-Heterocyclic Carbene Ligands

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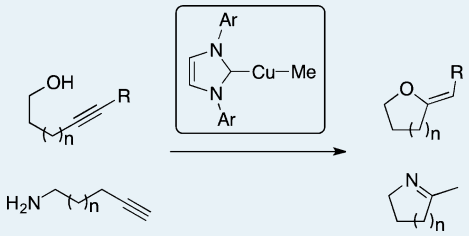
Supporting Information

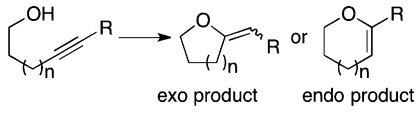
ABSTRACT: Intramolecular addition of O−H and N−H bonds across carbon−carbon triple bonds to form 5- or 6-membered rings with exocyclic methylene groups for ether products and exocyclic methyl groups for imine products is catalyzed by (IPr)Cu(Me) (IPr = 1,3-bis(2,6-diisopropylphenyl)-imidazol-2-ylidene). In a competition study, the cyclization of primary amines was found to be faster than that of alcohols. Kinetic studies for the conversion of 4-pentyn-1-ol reveal that the catalytic reaction is first-order in copper catalyst and zero-order in alkynyl alcohol, and an Eyring analysis yields $\Delta H^{\ddagger}$ = 18.7(4) kcal/mol and $\Delta S^{\ddagger}$ = −26(1) eu. The reaction of 5-phenyl-4-pentyn-1-ol provides (*Z*)-2-benzylidene-tetrahydrofuran in high yield and with quantitative stereoselectivity. Results from combined experimental and DFT studies are consistent with a mechanism that involves alkyne insertion into a Cu−$O_{alkoxide}$ bond followed by protonolysis upon reaction with free alkynyl alcohol.



KEYWORDS: *hydroalkoxylation, alkynes, homogeneous catalysis, copper, N-heterocyclic carbene*

INTRODUCTION

Heterocyclic fragments are present in a wide range of bioactive compounds. As a result, efficient and versatile methods to form such entities from readily available starting materials have been of particular interest. The hydrofunctionalization of unsaturated carbon−carbon bonds is an atom-economical method for the formation of carbon−heteroatom bonds. For example, intramolecular hydroalkoxylation and hydroamination of alkynyl alcohols and alkynyl amines produce cyclic vinyl ethers and imines, and substantial effort has been made toward the development of metal complexes that selectively catalyze these transformations.[1−10] Catalysts for intramolecular hydroamination of alkynes include early transition metal complexes,[6,11−13] lanthanides,[7,14,15] and middle to late transition metals.[16−20] Intramolecular O−H addition to alkynes to form oxygen-heterocycles can be selective for endo or exo products (eq 1). Palladium[21−23]



(1)

and ruthenium[24−26] complexes catalyze endo-selective oxidative cyclization of alkynyl alcohols as well as conversion of hydroxy enynes to furans.[22,27−33] Palladium(II),[22,34] cesium(I),[35] molybdenum(0),[36] rhodium,[37] tungsten(0),[38−41] gold,[42−45] and rhenium(0) complexes can catalyze the formation of cyclic enol ethers by endo-selective cyclization of alkynyl alcohols.[8] Rhodium,[46] iridium,[46,47] platinum,[48,49] gold,[48,50,51] and lanthanum[52] catalysts for dihydroalkoxylations of alkynes have been reported. For the rhodium and iridium catalysts,[46] selectivity for endo versus exo in the initial cyclization varies from 2.4:1 (exo/endo) to 0.4:1 (exo/endo) and is a function of catalyst identity and temperature. Catalysts that selectively form exo products are relatively less common and include silver,[53,54] palladium,[48,55−57] mercury,[58,59] and lanthanum[52,60−62] catalysts. The selectivity of some platinum and gold catalysts is variable, but selective exo cyclization is observed under some conditions.[40,41] Au(III) and Pd(II) catalysts are selective for exo cyclization;[42] however, the substrates are activated with an ester-functionalized alkyne. Although the lanthanide complexes are among the most active catalysts, their poor tolerance of air, water, and some functional groups has led to the pursuit of catalysts derived from earth-abundant late transition metals.

In addition to the low cost, copper catalysts are often tolerant to reactive functional groups and may not require rigorously anaerobic and anhydrous conditions. However, of the reported

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catalysts for exo-selective alkyne hydroxylation and hydroamination, examples of copper complexes are limited. A Cu(II) salt that combines intramolecular alkyne hydroxylation with subsequent reactions of indoles has been reported.[63] $Cu(OTf)_2$ has been reported to catalyze the cyclization of 2-(ethynyl)-benzyl alcohols with high yields; however, the cyclization of aliphatic alkynyl alcohols was not reported.[64] Although a mechanism that involves electrophilic activation of the alkyne by Cu(II) was suggested, studies to probe the reaction pathway were not disclosed.

Several monomeric Cu complexes supported with *N*-heterocyclic carbene (NHC) ligands have been reported.[65−69] Recently, our group reported that Cu(I) complexes of the type (NHC)Cu(X) (X = NHR, SR, or OR) catalyze the intermolecular hydroalkoxylation, hydroamination and hydrothiolation of electron-deficient olefins, including some vinyl arenes.[70−73] Having observed intermolecular X−H addition to activated olefins, we investigated the efficacy of these monomeric NHC−Cu complexes toward cyclization reactions of alkynyl alcohols and amines. Herein, we report that (NHC)-Cu(Me) complexes are catalyst precursors for intramolecular hydroalkoxylation and hydroamination of alkynes that are selective for exo products. In one case, we have demonstrated that performing the reactions under aerobic conditions does not substantially diminish catalytic efficiency. In addition, our mechanistic studies are consistent with Cu-catalyzed hydroalkoxylation that proceeds via coordination of the alkyne and subsequent insertion into a Cu−alkoxide bond. Late transition metal-catalyzed hydroxylation of alkynes is generally proposed to occur by alkyne coordination, which activates the C≡C bond for nucleophilic addition by the heteroatomic group.[42,46−48,56,74,75] Examples of formation of metal-vinylidenes followed by nucleophilic addition of the hydroxy group to the β-carbon have been reported.[76] Thus, we believe that the evidence presented here for a Cu-catalyzed alkyne hydroxylation that proceeds by alkyne insertion into a Cu-alkoxide bond is unique.

EXPERIMENTAL SECTION

General Methods. All procedures were performed in a glovebox under an inert atmosphere of dinitrogen or using standard Schlenk techniques. The glovebox atmosphere was maintained by periodic nitrogen purges and monitored by an oxygen analyzer (O_2(g) < 15 ppm for all reactions). Distillation of solvents was performed under a nitrogen atmosphere after heating at reflux over a desiccant. Benzene was distilled from sodium/benzophenone ketyl. Toluene, hexanes, and hexamethyldisiloxane (TMS_2O) were distilled from sodium. Ethanol was distilled from calcium hydride. All deuterated solvents were stored over 4 Å molecular sieves under an atmosphere of dinitrogen. Syntheses of (IPr)CuCl,[65] (IPr)Cu(Me),[65] (IPr)-Cu(OTf),[70] (IMes)Cu(Me),[77] 2-(aminomethyl)-2-methylpent-4-yn-1-ol,[61] and pent-4-yn-1-ol-d_1[60] have been previously reported. 2,6-Lutidine, 4-pentyn-1-ol, and 5-hexyn-1-ol were distilled and stored over 4 Å molecular sieves. All other reagents were used as received from commercial sources. ^{1}H and ^{13}C NMR measurements were performed on either a Varian Inova 500 MHz or a Varian Mercury Plus 300 MHz spectrometer (operating frequencies for ^{13}C NMR spectrum were 125 and 75 MHz, respectively) and referenced to tetramethylsilane using resonances due to residual protons in the deuterated solvents or the ^{13}C resonances of the deuterated solvents. All spectra that were used to determine percent yields were acquired with a 10 s pulse delay. Low-resolution mass spectra were acquired on a Shimadzu G-17A/QP-5050 GC-MS instrument operating in direct-inlet-MS mode. Mass spectra are reported as M^+ for neutral samples. Observed isotopic envelopes were consistent with the molecular composition reported. Observed rate constants (k_{obs}) were obtained in, at minimum, triplicate from the least-squares slope of plots of concentration of product vs time. Zero-order rate constants (k) were calculated by dividing k_{obs} by the concentration of complex **1**, according to the rate law: Rate = d[product]/dt = k_{obs} = k[**1**]. Turnover frequency (TOF) = k.

Computational Methods. The hybrid B3LYP density functional, in conjunction with the 6-311+G(d) all-electron basis set was used for N, C, O, and H, whereas for Cu, the Stuttgart small-core relativistic effective core potential (ECP) in conjugation with a triple-ζ quality valence basis set was used. The basis set for Cu was augmented with an additional f polarization function with exponent 3.0.[78] All stationary points were of singlet spin multiplicity except for the dissociated fragments used to calculate bond energies; for these, the ground states were found to be doublet multiplicity. All structures were fully optimized using gradient methods without imposing any symmetry constraint. The calculated energy Hessian confirmed the stationary points as minima (no imaginary frequencies) or transition states (only one imaginary frequency). The thermochemistry of the reaction was determined at 1 atm and 298.15 K using unscaled frequencies.

(IPr)Cu[C≡C(CH$_2$)$_3$OH] (3). To a solution of (IPr)Cu(Me) (**1**) (0.052 g, 0.11 mmol) in 10 mL of benzene was added 4-pentyn-1-ol (10.5 μL, 0.111 mmol). After stirring overnight, the solution was concentrated in vacuo followed by addition of hexanes to complete the precipitation. The complex was isolated by vacuum filtration, washed with 10 mL of pentane, and dried in vacuo. An off-white solid was isolated (0.045 g, 0.084 mmol, 76% yield). A single crystal suitable for X-ray diffraction was grown by slow diffusion of pentane into a concentrated solution of **3** in toluene. ^{1}H NMR (δ C_6D_6): 7.18 (t, $^3J_{HH}$ = 8 Hz, 2H, aryl para), 7.03 (d, $^3J_{HH}$ = 8 Hz, 4H, aryl meta), 6.20 (s, 2H, NC*H*), 3.88 (t, $^3J_{HH}$ = 6 Hz, 1H, OH), 3.76 (dt, $^3J_{HH}$ = 11 and 6 Hz, 2H, CH_2OH), 2.52 (sept, $^3J_{HH}$ = 7 Hz, 4H, C*H*(CH$_3$)$_2$), 2.17 (t, $^3J_{HH}$ = 8 Hz, 2H, C≡CCH_2), 1.53−1.44 (m, 2H, CH$_2$CH_2CH$_2$), 1.40 (d, $^3J_{HH}$ = 7 Hz, 12H, CH(CH_3)$_2$), 1.05 (d, $^3J_{HH}$ = 7 Hz, 12H, CH(CH_3)$_2$). ^{13}C NMR {^{1}H} (δ C_6D_6): 182.1 (NCN), 145.7 (aryl ipso), 134.9 (CuC≡C), 130.7 (aryl para), 124.3 (aryl meta), 122.4 (NCH), 105.1 (CuC≡*C*), 64.6 (*C*H$_2$OH), 32.5 (CH$_2$*C*H$_2$CH$_2$), 29.0 (CH-(*C*H$_3$)$_2$), 25.3 (*C*H(CH$_3$)$_2$), 23.7 (CH(*C*H$_3$)$_2$), 19.7 (C≡*C*CH$_2$), aryl ortho not observed, likely due to coincidental overlap. The acetylide ligand ^{13}C NMR resonances for (CH$_2$CH$_2$*C*H$_2$) and (C≡*C*CH$_2$) were assigned on the basis of previous data.[79] Anal. calcd. for $C_{32}H_{43}CuN_2O$: C, 71.83; H, 8.10; N, 5.23. Found: C, 72.23; H, 7.91; N, 4.61.

(IPr)Cu[O(CH$_2$)$_3$C≡CPh] (5). To a solution of (IPr)Cu-(Me) (**1**) (0.120 g, 0.257 mmol) in 6 mL of benzene was added 5-phenyl-4-pentyn-1-ol (0.041 g, 0.257 mmol). After stirring for 2 h at 40 °C, the solution was filtered through a plug of Celite. The resulting filtrate was concentrated to ~1 mL. The product was precipitated from the solution with pentane (10 mL). The complex was isolated by vacuum filtration, washed three times with 5 mL of pentane, and dried under vacuum. A white solid was isolated (0.074 g, 0.123 mmol, 48% yield). ^{1}H NMR (δ C_6D_6): 7.50 (d, $^3J_{HH}$ = 7 Hz, 2H, phenyl ortho), 7.22 (t, $^3J_{HH}$ = 8 Hz, 2H, IPr aryl para), 7.06 (d, $^3J_{HH}$ = 8 Hz, 4H, IPr aryl meta), 7.03−6.97 (m, 3H, phenyl meta and para), 6.25

(s, 2H, NC*H*), 3.74 (br s, 2H, CH_2O), 2.55 (sept, $^3J_{HH}$ = 7 Hz, 4H, CH(CH_3)$_2$), 2.44 (t, $^3J_{HH}$ = 7 Hz, 2H, C≡CCH_2), 1.68 (quint, $^3J_{HH}$ = 6 Hz, 2H, $CH_2CH_2CH_2$), 1.37 (d, $^3J_{HH}$ = 7 Hz, 12H, CH(CH_3)$_2$), 1.06 (d, $^3J_{HH}$ = 7 Hz, 12H, CH(CH_3)$_2$). ^{13}C{^{1}H} NMR (δ C_6D_6): 183.7 (NCN), 146.1 (IPr aryl ipso), 135.6 (C≡CPh ipso), 132.3 (C≡CPh ortho), 131.0 (IPr aryl para), 129.7 (C≡CPh para), 128.9 (IPr aryl ortho), 127.5 (C≡CPh meta), 124.7 (IPr aryl meta), 122.8 (NCH), 101.5 (C≡*C*Ph), 94.1 (*C*≡CPh) 67.6 (*C*H_2O), 39.3 ($CH_2CH_2CH_2$), 29.3 (CH(CH_3)$_2$), 25.3 (*C*H(CH_3)$_2$), 24.2 (CH(CH_3)$_2$), 17.1 (C≡*C*CH_2). LRMS: observed *m*/*z* (formula, calc'd *m*/*z*): 610 ($C_{38}H_{47}CuN_2O$, 610).

5-Phthalimido-1-pentyne.[80] A round-bottom flask was charged with 5-chloro-1-pentyne (4.89 g, 47.7 mmol) and 50 mL of dry DMF. Potassium phthalimide (10.6 g, 57.2 mmol) was added to the yellow solution. The yellow suspension was heated at 70 °C for 16 h. The resulting solution was cooled to room temperature, and 150 mL of H_2O was added into the solution. The mixture was extracted under air with Et_2O (4 × 200 mL), and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated on a rotary evaporator. The crude residue was further purified by flash chromatography (DCM) to give 5-phthalimido-1-pentyne as white solid (9.4 g, 93%).

5-Amino-1-pentyne.[80] A round-bottom flask was charged with 5-phthalimido-1-pentyne (5.125 g, 24.04 mmol) and 50 mL EtOH. Hydrazine monohydrate (5.145 g, 102.8 mmol) was added to the white suspension until the solution became homogeneous. The colorless solution was heated at 70 °C for 2 h, during which time a white solid precipitated. The solution was cooled to room temperature, and 75 mL of H_2O was added to the solution, followed by 2N HCl to adjust the pH to ∼3.5. The mixture was filtered to remove the white precipitate, and the filtrate was concentrated under reduced pressure. The residue was cooled to 0 °C and treated with aq NaOH (10 N, 30 mL). The mixture was extracted with DCM (3 × 100 mL), and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated on a rotary evaporator to yield 5-amino-1-pentyne as a yellow-green oil (1.2 g, 60%).

6-Phthalimido-1-hexyne.[81] Synthesis followed the same procedure as 5-phthalimido-1-hexyne, using 6-chloro-1-hexyne to yield 6-phthalimido-1-hexyne as a white solid.

6-amino-1-hexyne.[81] Synthesis followed the same procedure as 5-amino-1-pentyne, using 6-phthalimido-1-hexyne (1.6 g, 7.1 mmol) to yield 6-amino-1-hexyne as a yellow oil (0.54 g, 79%).

Typical NMR Scale Catalytic Reaction for Intramolecular Hydroalkoxylation of Alkynes. To a screw-cap NMR tube was added 0.50 mL of a 0.040 M solution of (IPr)Cu(Me) (9.0 mg, 0.020 mmol) in $C_6D_5NO_2$, followed by 4-pentyn-1-ol (37.0 μL, 0.400 mmol) and TMS_2O as an internal standard (2.0 μL, 9.4 μmol). The tube was capped with a PTFE-lined septum and wrapped with Parafilm, and a ^{1}H NMR spectrum was acquired. The tube was then heated to 120 °C and monitored periodically by ^{1}H NMR spectroscopy until complete conversion of starting materials was observed.

Kinetic Studies for Cyclization of 4-Pentyn-1-ol Catalyzed by (IPr)Cu(Me). A representative example of a kinetic experiment follows (5 mol % [Cu] at 120 °C). A 1.5 mL $C_6D_5NO_2$ solution of (IPr)Cu(Me) (0.028 g, 0.060 mmol), 4-pentyn-1-ol (106 μL, 1.15 mmol), and TMS_2O (10.0 μL, 0.0471 mmol) was prepared. A 450 μL portion of this solution was added via syringe into 3 separate screw-cap NMR tubes. The tubes were sealed with PTFE-lined septa and wrapped with Parafilm, and an initial ^{1}H NMR spectrum was acquired. The tubes were heated in an oil bath at 120 °C for 30 min intervals, followed by cooling in an ice bath to room temperature. After a ^{1}H NMR spectrum was acquired for each sample, the heating cycle was repeated until completion of the reaction.

Eyring Plot. An Eyring study was performed by repeating the cyclization of 4-pentyn-1-ol catalyzed by 5 mol % (IPr)-Cu(Me) at 100, 110, 130, and 140 °C. The rate of each reaction was recorded for three separate reactions at each temperature. The rate constants *k* were fitted to an Eyring plot of $\ln(kT^{-1})$ vs T^{-1} with the three *k* values for all temperatures incorporated.

Reaction of 4-Pentyn-1-ol-d_1. A solution of the deuterated alcohol (0.109 g, 1.28 mmol) and (IPr)Cu(Me) (0.028 g, 0.060 mmol) in 1.5 mL of $C_6D_5NO_2$ was divided into three screw-cap NMR tubes. The tubes were sealed with PTFE-lined septa and wrapped with Parafilm, and initial ^{1}H NMR spectra were acquired. The tubes were heated to 120 °C for 30 min intervals, cooled to room temperature, and analyzed by ^{1}H NMR spectroscopy.

Kinetic Study of the Reaction of Phenylacetylene with (IPr)Cu(Me). A stock solution of (IPr)Cu(Me) (10.9 mg, 0.023 mmol) and TMS_2O (2.0 μL, 9.4 μmol) in 1.50 mL C_6D_6 was prepared. An aliquot (0.50 mL) of this solution was loaded into a screw-cap NMR tube. An initial ^{1}H NMR spectrum was recorded. Following this, 3 equiv (2.6 μL, 0.023 mmol) of phenylacetylene was added via microsyringe through the septum of the NMR tube. The contents were shaken vigorously, and the reaction progress was monitored by ^{1}H NMR spectroscopy. The half-life of the reaction was determined to be ∼10 min.

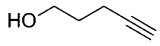
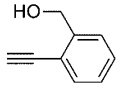
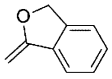
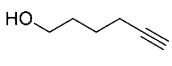
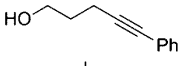
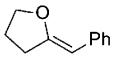
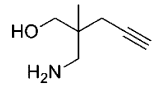
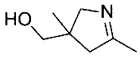
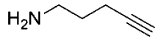
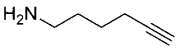
Kinetic Study of the Reaction of Ethanol with (IPr)Cu-(Me). An aliquot (0.50 mL) of the same stock solution prepared for the reaction of phenylacetylene with (IPr)Cu(Me) was loaded into a screw-cap NMR tube. An initial ^{1}H NMR spectrum was recorded, after which 3 equiv (1.4 μL, 0.023 mmol) of ethanol was added via microsyringe through the septum of the NMR tube. The contents were shaken vigorously, and the reaction progress was monitored by ^{1}H NMR spectroscopy. The half-life of the reaction was determined to be ∼45 min. Following complete conversion to (IPr)Cu(OEt), 3 equiv (2.6 μL, 0.023 mmol) of phenylacetylene was added to the NMR tube through the septum, and a ^{1}H NMR spectrum was acquired immediately. Complete conversion of (IPr)Cu(OEt) to (IPr)Cu(CCPh) was achieved with the liberation of EtOH.

RESULTS AND DISCUSSION

Results from Catalysis. Alkynyl alcohols heated with a catalytic amount of (IPr)Cu(Me) (**1**) cyclize to form exo-selective hydroalkoxylation products (Table 1). For example, in $C_6D_5NO_2$, complex **1** (5 mol %) catalyzes the cyclization of 4-pentyn-1-ol to 2-methylenetetrahydrofuran in quantitative conversion by ^{1}H NMR spectroscopy after 7 h at 120 °C (entry 1). No decrease in reactivity was observed when the reaction mixture was exposed to air prior to heating; however, complex **1** cannot be stored in air. In relatively noncoordinating solvents, the rate of cyclization is dependent on the solvent polarity. For example, the rate of reaction with 4-pentyn-1-ol decreases in the series $C_6D_5NO_2$ > 1,2-dichlorobenzene > toluene-d_8 > C_6D_6 (Table 2).

To determine the steric effects of the NHC ligand, (IMes)-Cu(Me) (**2**) was tested as a catalyst precursor. In $C_6D_5NO_2$, **2** decomposes rapidly; however, after 30 h in C_6D_6, the reaction of 4-pentyn-1-ol catalyzed by **2** proceeds to 60% yield (Table 1,

Table 1. Hydroalkoxylation and Hydroamination of Alkynyl Alcohols and Amines Catalyzed by (IPr)Cu(Me) (1) or (IMes)Cu(Me) (2) (entry 2).[a]

entry	substrate	product[b]	[Cu]	time (h)	yield (%)[c]
1			**1**	7	>95
2[d]			**2**	52	85
3			**1**	22	>95
4			**1**	28	~20
5			**1**	2	>95
6[e]			**1**	2	>95
7[f]			**1**	4	>95
8[f]			**1**	9	>95

[a]0.8 M in $C_6D_5NO_2$ with 5 mol % catalyst at 120 °C unless noted otherwise. [b]By comparison of ^{1}H NMR spectra with published data. [c]By integration of product in ^{1}H NMR spectra versus internal standard. [d]In C_6D_6. [e]In C_6D_6 at 80 °C. [f]110 °C.

Table 2. Dependence of Reaction Rate (120 °C) on Solvent Polarity for the Cyclization of 4-Pentyn-1-ol Using 1 as Catalyst

solvent	ε	TOF[a]
nitrobenzene	34.8	2.9
o-DCB	9.9	0.5
toluene	2.4	0.3
benzene	2.3	0.2

[a]Turnover frequency (h^{-1}).

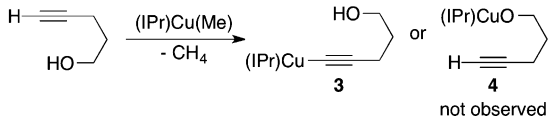
entry 2) compared with 33% yield at this same time with **1** as a catalyst in C_6D_6. These data suggest that **2** is ~2 times more active than **1**, but decomposition of **2** (after 52 h and 85% yield) limits product yield.

Hydroalkoxylation by **1** is also observed for the alkynyl alcohols (2-ethynylphenyl)methanol (entry 3) and 5-hexyn-1-ol (entry 4) to form 1,3-dihydro-1-methylene-isobenzofuran (>95% yield) and tetrahydro-2-methylene-2*H*-pyran (~20% yield). Internal alkynes are also suitable substrates for Cu-catalyzed hydroalkoxylation; the reaction of 5-phenyl-4-pentyn-1-ol catalyzed by **1** in $C_6D_5NO_2$ stereoselectively forms (*Z*)-2-benzylidene-tetrahydrofuran (entry 5). The formation of the cis product in the reaction catalyzed by **1** contrasts the stereoselectivity for reactions catalyzed by Pd[56] or La[60,61] complexes. A reaction of 5-phenyl-4-pentyn-1-ol carried out in the presence of (*E*)-2-benzylidene-tetrahydrofuran does not result in any isomerization of the *E* isomer.

In addition to hydroalkoxylation, **1** was found to catalyze the hydroamination of alkynyl amines (Table 1, entries 6–8). The rate of hydroamination is faster than that of hydroalkoxylation; in a competition between amine and alcohol cyclization catalyzed by **1** (entry 6), the product of hydroamination is formed exclusively, whereas the reverse selectivity was found with a lanthanum catalyst.[61] The reactions of pent-4-yn-1-amine (entry 7) and hex-5-yn-1-amine (entry 8) result in the quantitative formation of their respective cyclic imines after cyclization and tautomerization.

In six separate control experiments, 4-pentyn-1-ol was heated (120 °C, $C_6D_5NO_2$) in the presence of (IPr)Cu(Cl), (IPr)-Cu(OTf), CuCl, $[Cu(NCMe)_4][PF_6]$, $Cu(OTf)_2$, and free IPr to evaluate the catalytic ability of other copper salts and free NHC. For each attempted reaction, there was no evidence of products from cyclization.

Mechanistic Studies. *Initiation Step.* Having demonstrated the feasibility of copper-catalyzed intramolecular hydroalkoxylation and hydroamination of alkynes, we sought to understand the mechanism of this reaction. The first question was the nature of the active catalyst. We have reported that **1** reacts with amines, alcohols, and thiols to release methane and form the corresponding (IPr)Cu(X) (X = OR, NHR, or SR) complexes.[82] The dissolution of (IPr)Cu(Me) and alkynyl alcohol during the preparation of the catalytic reaction results in a brief effervescence, suggesting that formation of the active catalyst involves the release of methane. The reaction of **1** with 1 equiv of 4-pentyn-1-ol in benzene cleanly produces a new complex with a ^{1}H NMR spectrum consistent with the formation of copper acetylide (IPr)Cu[C≡C$(CH_2)_3$OH] (**3**) (eq 2), rather than the copper alkoxide (IPr)Cu[O$(CH_2)_3$C≡CH] (**4**). One diagnostic resonance is a doublet of triplets at 3.76 ppm with coupling constants of 11 and 6 Hz, which has been assigned as the CH_2OH methylene resonances with a $^3J_{HH}$ = 11 Hz



(2)

(triplet splitting) from the adjacent methylene and a $^3J_{HH}$ = 6 Hz (doublet splitting) from the hydroxy proton.

The assignment of **3** as the copper acetylide complex was confirmed after obtaining a solid-state structure from a single crystal X-ray diffraction study (Figure 1). The structure features

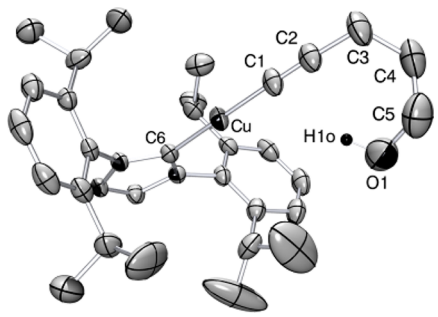


Figure 1. ORTEP of (IPr)Cu[C≡C$(CH_2)_3$OH] (**3**) (30%). Selected bond distances (Å): Cu–C1 1.868(2), Cu–C6 1.892(2), C1–C2 1.203(3). Selected bond angles (°): C1–Cu–C6 177.3(1), C2–C1–Cu 178.0(2).

five consecutive atoms arranged in a nearly linear fashion starting from the carbene carbon of the IPr ligand and going through copper, both carbons of the acetylide, and the carbon α to the acetylide, with bond angles ranging from 177.3(1)° to 178.0(2)°. The Cu1–C1 (acetylide) bond distance of 1.868(2) Å is slightly shorter than the Cu1–C6 (IPr) bond distance of 1.892(2) Å. The C≡C bond length of 1.203(3) Å is typical of a carbon–carbon triple bond, indicating that little if any back-bonding between copper and the acetylide fragment occurs.

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Although the NMR and X-ray data show that the acetylide complex **3** forms from the reaction of **1** and 4-pentyn-1-ol, we sought to determine if the alkoxide complex **4** is formed initially followed by rapid isomerization to **3**. The reaction of **1** with 3 equiv of 4-pentyn-1-ol-d_1 (−OD) leads to the production of both CH_4 and CH_3D (by ^{1}H NMR spectroscopy) in a 5.5:1 molar ratio, implicating the cleavage of both C−H (C≡C−H) and O−D bonds (Figure 2). However, ^{2}H NMR spectroscopy

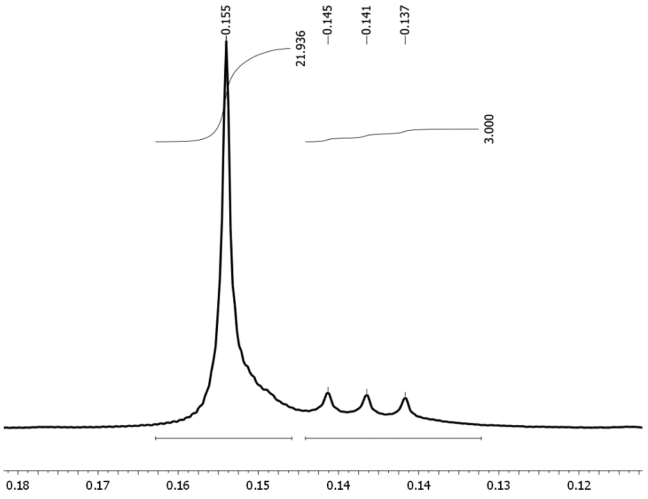
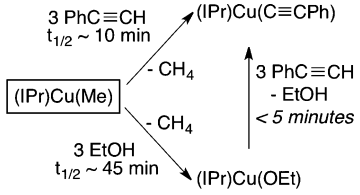


Figure 2. ^{1}H NMR spectrum showing resonances due to CH_4 (singlet at 0.16 ppm) and CH_3D (1:1:1 triplet at 0.14 ppm) formed in the reaction of **1** with 3 equiv of 4-pentyn-1-ol-d_1.

reveals that the deuterated alkynyl alcohol (−OD) undergoes H/D exchange with the terminal alkyne position during the reaction of **1** and 4-pentyn-1-ol-d_1 (−OD) to form **3**. Thus, the CH_3D could result either from O−D cleavage by **1** or from C≡C−D cleavage after isomerization, and these data cannot be used to determine whether the Cu alkoxide complex **4** forms during the reaction of (IPr)Cu(Me) with 4-pentyn-1-ol.

Although the kinetic product from the reaction of **1** with 4-pentyn-1-ol could not be unambiguously determined, the relative rates of reaction of **1** with phenylacetylene and ethanol are informative. The isolation of both (IPr)Cu(C≡CPh) and (IPr)Cu(OEt) have been reported.[82] In C_6D_6, the conversions of complex **1** and 3 equiv of phenylacetylene to (IPr)Cu(C≡CPh) occurs with a $t_{1/2}$ of ∼10 min at room temperature (Scheme 1). The reaction of **1** and 3 equiv of ethanol to form

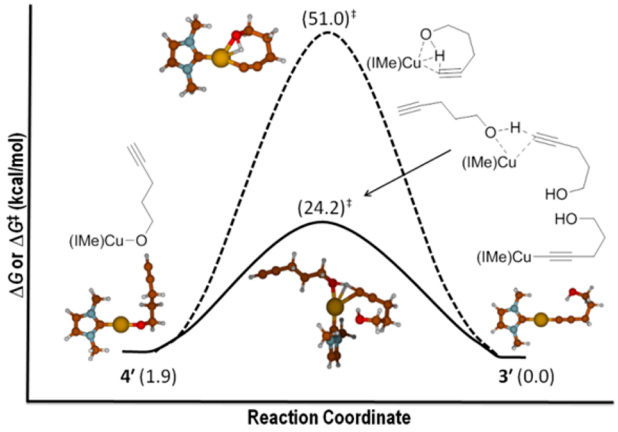
Scheme 1. Reaction of (IPr)Cu(Me) (1) with Phenylacetylene and Ethanol



(IPr)Cu(OEt) occurs with $t_{1/2}$ ∼45 min at room temperature. Perhaps coincidentally, the ratio of the approximate half-lives (4.5:1) is similar to the 5.5:1 molar ratio of CH_3D and CH_4 from the reaction of **1** with 4-pentyn-1-ol-d_1 (see above). The addition of 3 equiv of phenylacetylene to the mixture containing (IPr)Cu(OEt) and excess ethanol results in the immediate (<5 min) conversion to (IPr)Cu(C≡CPh), which is consistent with the proposal that (IPr)Cu[C≡C$(CH_2)_3$OH] (**3**) is thermally favored over the alkoxide complex (IPr)Cu[O$(CH_2)_3$C≡CH] (**4**).

Computational Studies of Initiation Step. DFT studies were performed to evaluate the acetylide complex **3** and the alkoxide complex **4**. To facilitate computations, the diisopropylphenyl groups in IPr were modeled as methyl groups (abbreviated as IMe below). Computed model complexes are denoted with a prime. The calculated $\Delta\Delta G$ for formation of **3′** versus **4′** is 1.9 kcal/mol favoring Cu acetylide **3′** (Scheme 2),

Scheme 2. Calculated Intramolecular (top, dashed line) and Intermolecular (bottom, solid line) Pathways for Isomerization between 3′ and 4′[a]



[a]Computed free energies are given in kcal/mol.

which is consistent with experimental observations (see above). Pathways for the isomerization between **4** and **3** were explored.

Two mechanisms for interconversion between **3′** and **4′** were calculated (Scheme 2). The energetics of an intramolecular pathway, which involves unimolecular isomerization via a cyclic transition state, and an intermolecular pathway, in which **3′** or **4′** reacts with free alkynyl alcohol, were calculated. For the intramolecular pathway, which is calculated to be the higher energy pathway with $\Delta G^{\ddagger}$ = 51.0 kcal/mol from **3′**, the proton from one terminus is transferred to the other while both termini are bound to Cu. The second pathway, in which free alkynyl alcohol transfers the proton from the hydroxy terminus to the acetylide carbon of **3′** to form copper alkoxide **4′** or from the alkyne terminus to the alkoxide oxygen of **4′** to form **3′**, has a calculated $\Delta G^{\ddagger}$ of 24.2 kcal/mol from **3′**, which renders it reasonable, given the experimentally determined $\Delta G^{\ddagger}$ of 28.8(1) kcal/mol (at 120 °C) for the catalytic reaction (see below). Marks et al. have proposed similar cross metathesis of La−O$(CH_2)_3$C≡CH and free 4-pentyn-1-ol to yield La−C≡C$(CH_2)_3$OH and the reverse reaction, to explain isotopic scrambling in La-catalyzed cyclization of deuterated 4-pentyn-1-ol.[61]

Kinetics. Kinetic data for the cyclization of 4-pentyn-1-ol were obtained by ^{1}H NMR spectroscopy in $C_6D_5NO_2$ at 120 °C. Figure 3 shows a representative plot of the concentration of 2-methylenetetrahydrofuran versus time using 5 mol % of complex **1** as the catalyst precursor. This plot shows a zero-order dependence of the rate of cyclization on the concentration of the alkynyl alcohol substrate. The addition of 2.6 equiv (based on [**1**]) of *tert*-butylisonitrile to the reaction

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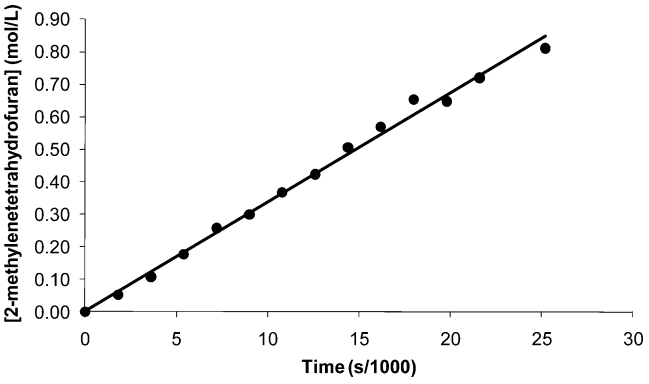

Figure 3. Representative plot (R^2 = 0.99) of [2-methylenetetrahydrofuran] vs time for cyclization of 4-pentyn-1-ol catalyzed by 5 mol % (0.04 M) of **1** at 120 °C (k_{obs} = 3.3(1) × 10^{-5} M s^{-1}, average of three runs).

with 5 mol % **1** and 4-pentyn-1-ol increases the rate of reaction by ∼30%. The concentration of **1** was varied using 5, 7.5, and 10 mol %, and plots of the concentration of 2-methylenetetrahydrofuran versus time were all linear. From these data, a plot of k_{obs} versus concentration of complex **1** was generated. A linear relationship is observed, indicating a first-order dependence on complex **1** (Figure 4). Extrapolation of this plot to the

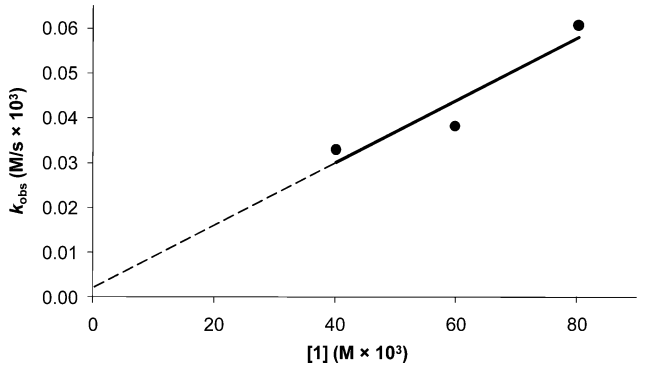

Figure 4. Plot of k_{obs} vs [**1**] for the cyclization of 4-pentyn-1-ol (120 °C) showing first-order dependence on **1** (R^2 = 0.89).

y-axis reveals that the intercept is near the origin. Thus, the experimentally determined rate law is rate = $k[\mathbf{1}]^1[\text{4-pentyn-1-ol}]^0 = k[\mathbf{1}]$, with k = 8.3(1) × 10^{-4} s^{-1} (after dividing k_{obs} by [**1**]) and $\Delta G^{‡}$ = 28.8(1) kcal/mol at 120 °C.

To determine the activation parameters, the rate of cyclization of 4-pentyn-1-ol was determined at 100, 110, 120, 130, and 140 °C. All plots of [2-methylenetetrahydrofuran] vs time have a good linear fit (Figure 5), and the 40 °C temperature range allows a reasonably reliable determination of the activation parameters. The Eyring plot leads to the activation parameters $\Delta H^{‡}$ = 18.7(4) kcal/mol and $\Delta S^{‡}$ = −26(1) eu (Figure 6).

Deuterium Labeling. A catalytic reaction was performed in triplicate with the deuterated isotopomer (−OD) 4-pentyn-1-ol-d_1. Upon completion of the reaction, a ^{2}H NMR spectrum was acquired, and a 1:1.6 ratio of the *E*- and *Z*-isomers of 2-methylenetetrahydrofuran-d_1 was found (Figure 7 and Scheme 3). Comparing the rate of reaction of 4-pentyn-1-ol with 4-pentyn-1-ol-d_1 revealed a small kinetic isotope effect (KIE) of k_H/k_D = 1.52(5); however, interpretation of the observed KIE as well as the formation of *E*- and *Z*-isotopomers is complicated by H/D

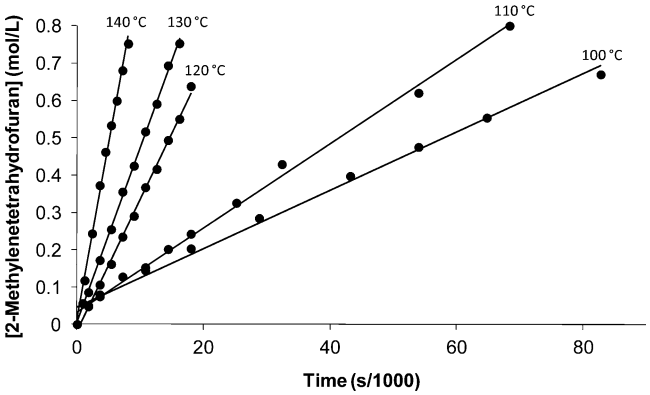

Figure 5. Plot of [2-methylenetetrahydrofuran] vs time for the cyclization of 4-pentyn-1-ol catalyzed by 5 mol % of **1** at 100, 110, 120, 130, and 140 °C.

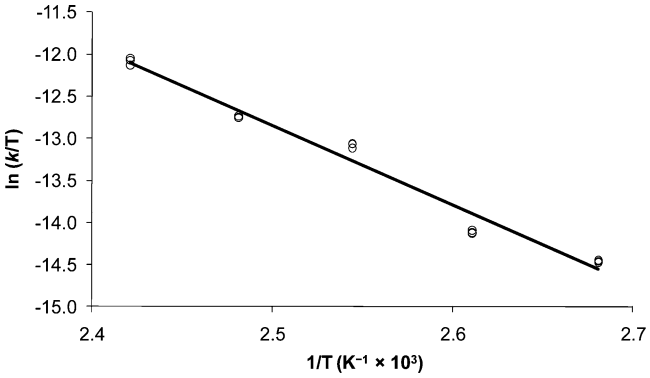

Figure 6. Eyring plot for cyclization of 4-pentyn-1-ol by **1** incorporating three experiments at each temperature. $\Delta H^{‡}$ = 18.7(4) kcal/mol and $\Delta S^{‡}$ = −26(1) eu (R^2 = 0.97).

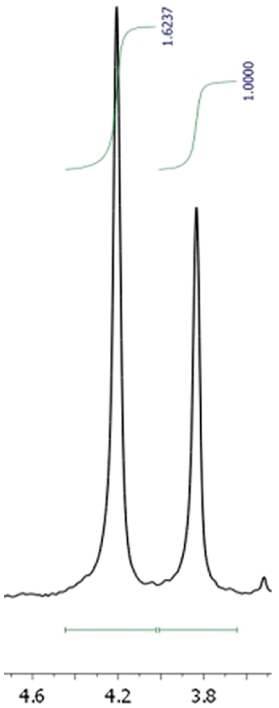

Figure 7. Final ^{2}H NMR spectrum for conversion of 4-pentyn-1-ol-d_1 to 2-methylenetetrahydrofuran showing a 1:1.6 *E*/*Z* ratio of deuterium incorporation into the exocyclic olefin position.

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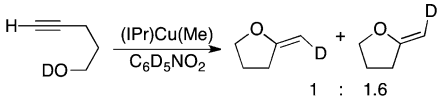
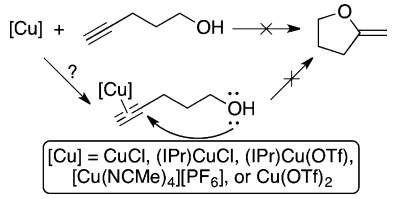
Scheme 3. Deuterium is Incorporated into Both the *E*- and *Z*-Positions in a 1:1.6 Ratio



scrambling in the alkynyl alcohol (see above). Similar to the results with complex **1**, the Marks group has reported that cyclization of 4-pentyn-1-ol-d_1 using a La catalyst gives a mixture of *E*- and *Z*-deuterated isomers (in addition to protio and dideutero isomers) with an *E*/*Z* ratio of ~2:1.[61]

Possible Mechanisms and Computational Studies. There are several plausible mechanisms that could account for the observed copper-catalyzed ring closing reaction. One such mechanism involves the in situ formation of an electrophilic Cu complex that coordinates the alkyne and activates it toward nucleophilic addition by the hydroxyl group, as has been proposed with other late metal catalysts (Scheme 4).[17,42,46−48,56,64,74,75]

Scheme 4. The Conversion of 4-pentyn-1-ol to 2-Methylenetetrahydrofuran Is Not Catalyzed by Simple Copper(I) Salts

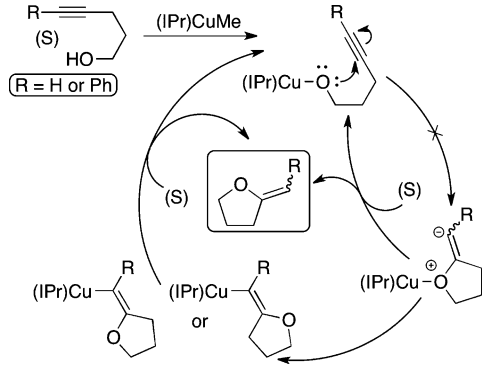


However, the inability of the copper salts CuCl, (IPr)CuCl, (IPr)Cu(OTf), $[Cu(NCMe)_4][PF_6]$, and $Cu(OTf)_2$ to catalyze the cyclization of 4-pentyn-1-ol to 2-methylenetetrahydrofuran provides evidence against this mechanism. Furthermore, such a pathway should be suppressed by addition of a ligand that can compete with the alkyne for Cu coordination; however, the addition of *tert*-butylisonitrile provides a slight acceleration of the reaction (see below for a discussion of this observation). These data are inconsistent with a mechanism that involves electrophilic activation of the alkyne upon coordination to Cu. Intramolecular hydroalkoxylation by middle transition metals (e.g., Cr, Mo, W, Ru, and Rh) has been proposed to occur via initial formation of metal vinylidene complexes, followed by intramolecular nucleophilic addition; however, these reactions are generally endo-selective (see eq 1).[71]

Another mechanism that could be considered for the catalytic ring closing reaction is an intramolecular nucleophilic addition pathway similar to the proposed mechanism for intermolecular addition to activated olefins previously reported by our group.[70−73] In this mechanism, the copper alkoxide species undergoes intramolecular O−C bond formation to *uncoordinated* alkyne to form a zwitterionic species, which is then protonated by the free substrate or rearranges to form a Cu−C isomer (Scheme 5). However, nucleophilic attack on an unactivated alkyne appears unlikely, and computational efforts toward resolving the initial zwitterionic product of this reaction were unsuccessful. Thus, investigation of this pathway was not pursued further.

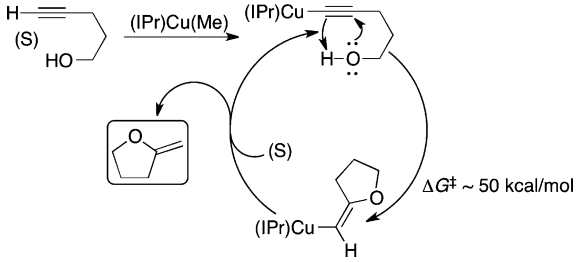
Upon isolation of the Cu acetylide complex **3**, we considered the possibility that cyclization occurs by O−H addition across the acetylide bond (Scheme 6). Gold acetylide complexes have

Scheme 5. Catalytic Cycle for Intramolecular Nucleophilic Addition from a Copper Alkoxide Species[a]



[a]A model of the zwitterionic species did not correspond to a stable stationary point on the computational potential energy surface.

Scheme 6. Catalytic Cycle for Addition of O−H Bond across Cu-Bound Acetylide Moiety[a]



[a]Calculations reveal a $\Delta G^{\ddagger}$ that is too high for this reaction to be considered viable.

been implicated as intermediates in catalytic cycloaddition reactions.[83−85] However, the calculated barrier for the reaction in Scheme 6 (NHC = IMe) is ~50 kcal/mol. In addition, since formation of a Cu acetylide complex is not possible using 5-phenyl-4-pentyn-1-ol, the successful conversion of this substrate to cyclized product reveals that a Cu acetylide complex is not required for catalysis.

Successful conversion of 5-phenyl-4-pentyn-1-ol also suggests a fourth possible mechanism (Scheme 7). In this pathway, acetylide complex **3** isomerizes to the unobserved Cu alkoxide **4**, followed by subsequent insertion of the alkyne into the Cu−O bond. Protonolysis by an additional molecule of substrate releases product and reforms **4**.

Having deduced from DFT calculations that the observed copper acetylide **3** has an energetically viable pathway to isomerize to **4** (see above), the remainder of the catalytic cycle was modeled (Scheme 8). The calculations suggest that insertion of the alkyne moiety into the Cu−O bond of **4′** is a stepwise process. Coordination of the alkyne is calculated to occur with a small activation barrier of ~11 kcal/mol, with the η^2-alkyne complex unfavorable relative to **4′** by 6.4 kcal/mol (Scheme 8). From the coordinated alkyne complex, the calculated $\Delta G^{\ddagger}$ for alkyne insertion is 18.5 kcal/mol, giving an overall $\Delta G^{\ddagger}$ = 24.9 kcal/mol for alkyne insertion starting from the alkoxide complex **4′**. Relative to the acetylide complex **3′**, the overall $\Delta G^{\ddagger}$ for alkyne insertion is calculated to be 26.8 kcal/mol. The insertion product is calculated to be exergonic relative to **4′** by 9.2 kcal/mol (Scheme 8). The alkyne insertion gives a product in which the olefinic hydrogen is oriented trans

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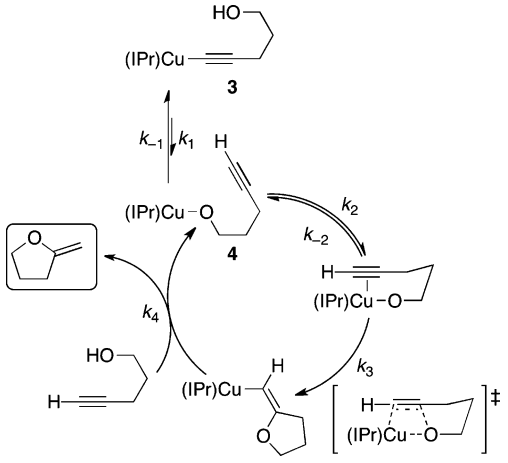
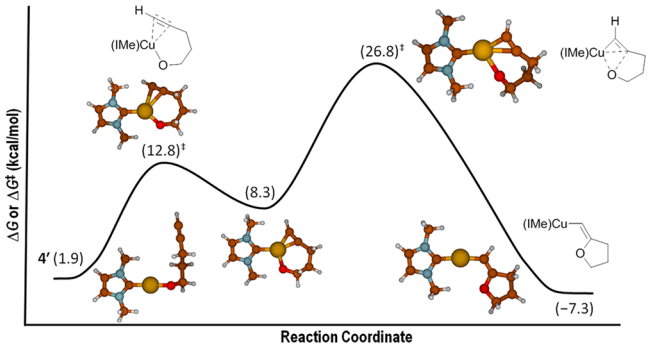
Scheme 7. Catalytic Cycle That Involves Insertion of Alkyne into Cu−O Bond of an Alkoxide Complex[a]



[a]Calculations predict that interconversion between **3** and **4** is facilitated by alkynyl alcohol substrate in both directions.

Scheme 8. Computed Free Energies (kcal/mol) for Alkyne Coordination and Insertion[a]



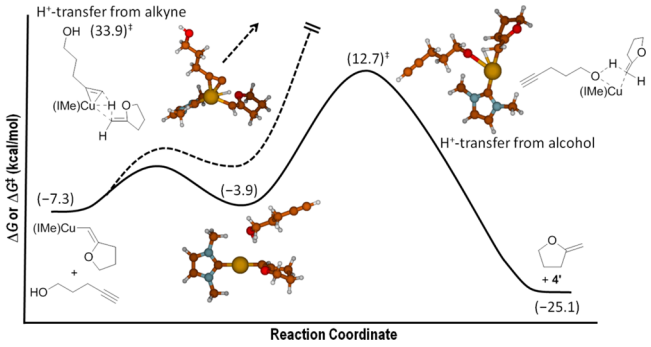
[a]Calculated energies (G) are relative to the Cu-acetylide complex **3′**.

to the oxygen. The isomer in which the olefinic hydrogen and oxygen are in a cis orientation is calculated to be less favorable by 0.7 kcal/mol.

After formation of the alkyne insertion product, two pathways were deemed plausible for product release from the Cu catalyst (shown in dashed and solid lines in Scheme 9), both of which occur by protonolysis by a molecule of alkynyl alcohol substrate. In one pathway (shown in dashed line), the proton is transferred from the terminal alkyne. In the second pathway (shown in solid line), the proton is provided by the alcohol functional group of the alkynyl alcohol. The former (dashed) is calculated to have a free energy barrier that is more than 20 kcal/mol higher than the pathway in which the proton originates at the hydroxy group (solid line). Coordination of the alkynyl alcohol to the alkyne insertion product is endergonic by 3.4 kcal/mol, and the proton transfer is calculated to occur with a barrier of 20.0 kcal/mol from the starting Cu-vinyl complex and free alkynyl alcohol. Thus, product release likely occurs through proton transfer from the alcohol group of 4-pentyn-1-ol.

The alkyne insertion TS is calculated to be the highest energy stationary point, which is consistent with kinetic experiments that show a zero-order dependence on free alkyne (see above for discussion of kinetic data). Given a steady-state approximation, the rate law for the insertion mechanism (Scheme 7) is shown

Scheme 9. Computed Pathways for Product Release from the Ring-Closed Cu-Bound Vinyl Complex[a]



[a]Calculated energies (G) are relative to the Cu-acetylide complex **3′**.

in eq 3 (rate constants are shown in Scheme 7), with [S] representing the concentration of substrate 4-pentyn-1-ol. Our calculations show that the term $k_1k_2k_3$ in the denominator, which contains only rate constants that lead to product formation, is small. Thus, the rate equation suggests a cyclization reaction that is zero-order in substrate, as is observed in experimental studies.

$$\text{rate} = -\frac{d[S]}{dt} = (k_1k_2k_3k_4[S][Cu]_{tot})/(k_1k_3k_4[S] + k_1k_{-2}k_4[S] + k_{-1}k_3k_4[S] + k_{-1}k_{-2}k_4[S] + k_1k_2k_4[S]k_1k_2k_3) \quad (3)$$

The proposed pathway for the catalytic cycle (Scheme 7) is similar to that proposed for lanthanide-catalyzed hydroalkoxylation reactions. For example, $La[N(SiMe_3)_2]_3$ has been reported as a precatalyst for the intramolecular hydroalkoxylation of alkynes, and the proposed mechanism involves alkyne insertion into a La−O bond, which is followed by protonolysis upon reaction with free alkynyl alcohol.[60,61] Catalysis by complex **1** reveals features that are similar to the La catalyst. For example, the experimental $\Delta H^{‡}$'s for the reaction of 4-pentyn-1-ol are statistically comparable (18.7(4) kcal/mol for **1** vs 20.2(1.0) kcal/mol for the La catalyst), and $\Delta S^{‡}$'s for both catalysts are relatively large and negative (−26(1) eu for **1** and −11.8(3) eu for the La catalyst).[61] Marks et al. found an inverse correlation between lanthanide size (ionic radii ranging from 1.160 to 0.977 Å for La, Nd, Sm, Y, Lu) and the rate of cyclization of 4-pentyn-1-ol. By comparison, the ionic radius of Cu(I) is much smaller at 0.77 Å.[86] If the Cu-catalyzed pathway is similar to that of the lanthanide catalysts, it is not surprising that the activity would be reduced relative to the larger lanthanide metals. For both catalysts, the catalytic reaction with deuterated (−OD) 4-pentyn-1-ol-d_1 results in deuterium incorporation into both of the alkene positions of the product (see above). For the reaction with **1**, we have demonstrated that H/D exchange between the hydroxy and acetylide positions occurs under catalytic conditions, and the H/D scrambling is potentially responsible for the appearance of deuterium into both positions of the alkene. Reactions catalyzed by both copper and lanthanum complexes are first-order in metal complex and zero-order in alkynyl alcohol.

The similarities of these experimental data combined with our computational results suggest that both **1** and the lanthanide catalysts operate by a similar mechanism. There are,

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however, some differences between catalysis with **1** and the lanthanide catalysts that warrant consideration. These include the effect on the rate of the reaction by added Lewis base (e.g., ^{t}BuNC; see above), and differences between Marks' La system and the copper catalyst studied herein for both the stereoselectivity of the cyclization of a substrate with an internal alkyne and the relative rates of cyclization for amines and alcohols.

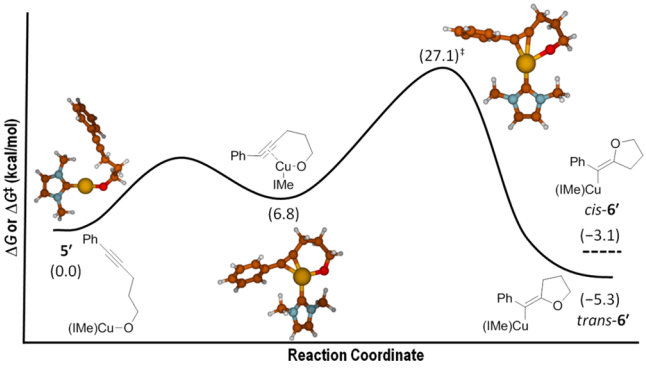
The addition of 2.6 equiv of ^{t}BuNC with respect to **1** to a catalytic reaction with 4-pentyn-1-ol results in a ∼30% enhancement of the rate of reaction. We anticipated that cyclization via an electrophilic pathway that involves alkyne coordination as the initial step would be suppressed by the presence of excess isonitrile because the isonitrile should compete with the alkyne for coordination to copper. However, from the CN^{t}Bu adduct, (IMe)Cu(CN^{t}Bu)[O(CH$_2$)$_3$C≡CH] (Scheme 10), the

Scheme 10. The Barrier to Alkyne Insertion into the Cu−O Bond with ^{t}BuNC Coordinated Is Calculated To Be 25.3 kcal/mol, Compared with 24.9 kcal/mol without Added Isonitrile

calculated $\Delta G^{‡}$ for alkyne insertion is 25.3 kcal/mol, which is nearly identical to the calculated $\Delta G^{‡}$ for alkyne insertion of 24.9 kcal/mol from **4′** (Scheme 8). Given the uncertainty in the calculated $\Delta G^{‡}$ values, the calculations are not inconsistent with a minor acceleration in the rate of cyclization upon addition of ^{t}BuNC.

Stereochemistry of Catalytic Reaction. The conversion of 5-phenyl-4-pentyn-1-ol with **1** in $C_6D_5NO_2$ results in stereoselective formation of (*Z*)-2-benzylidene-tetrahydrofuran. The formation of the cis product contrasts the stereoselectivity for reactions using Pd[56] or La[60,61] catalysts. We performed calculations relevant to the conversion of 5-phenyl-4-pentyn-1-ol to 2-benzylidene-tetrahydrofuran. The calculated reaction coordinate shown in Scheme 11 has an energetic profile that is

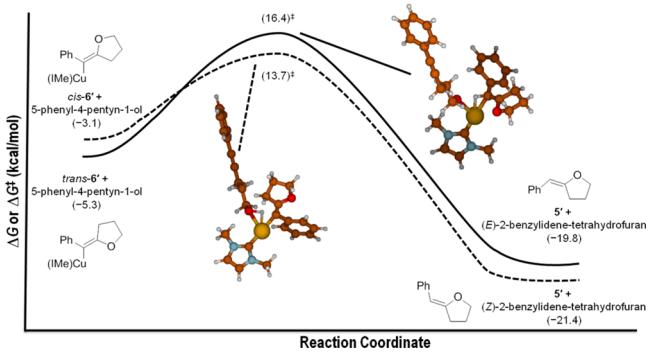
Scheme 11. Computed Energetics (kcal/mol) for the Cu-Catalyzed Cyclization of 5-Phenyl-4-pentyn-1-ol and *trans*-6′, with *cis*-6′ Displayed for Comparison



similar to the calculations for the parent alkynyl alcohol. Starting from the metal alkoxide (**5′**) with uncoordinated alkyne, the free energy barrier to alkyne insertion to a copper-bound tetrahydrofuran **6′** is calculated to be 27.1 kcal/mol (Scheme 11) for the internal alkyne versus 24.9 kcal/mol for 4-pentyn-1-ol (Scheme 8). The trans cyclization product *trans*-**6′** (to retain consistent labeling with product, the trans/cis labels of **6′** refer to the orientation of the phenyl and oxygen atom) is formed from the alkyne insertion and is exergonic from **5′** by −5.3 kcal/mol. Concerted alkyne insertion is expected to be a stereospecific reaction that forms *trans*-**6**. The complex *cis*-**6′** is calculated to be −3.1 kcal/mol with respect to **5′** and, thus, +2.2 kcal/mol with respect to *trans*-**6′**. Formation of the initial cyclization product such that the phenyl and oxygen are cis to each other will be discussed below.

Release of product proceeds by a similar mechanism to release of product in the parent reaction, with proton transfer from the alcohol of 5-phenyl-4-pentyn-1-ol (Scheme 12). The

Scheme 12. Computed Pathway for Release of (*Z*)-2-Benzylidene-tetrahydrofuran from *cis*-6′ and (*E*)-2-Benzylidene-tetrahydrofuran from *trans*-6′ by Protonolysis



relative barriers for product release from the cyclized metal complexes are 21.7 kcal/mol from the trans complex *trans*-**6′** to form **5′** and (*E*)-2-benzylidene-tetrahydrofuran and 16.8 kcal/mol from the cis complex *cis*-**6′** to form **5′** and (*Z*)-2-benzylidene-tetrahydrofuran. The experimentally observed (*Z*)-2-benzylidene-tetrahydrofuran is calculated to be more stable than the *E* isomer by 1.6 kcal/mol. Thus, the calculations predict more facile formation of (*Z*)-2-benzylidene-tetrahydrofuran, which is the observed product of catalysis, if a kinetically competent mechanism for isomerization is accessible after alkyne insertion.

If (*E*)-2-benzylidene-tetrahydrofuran is the kinetic product of Cu-catalyzed cyclization, isomerization to the observed *Z* isomer may occur under the reaction conditions. However, no isomerization was observed in a catalytic reaction that was doped with independently prepared (*E*)-2-benzylidene-tetrahydrofuran. Thus, the Cu catalyst does not catalyze isomerization of (*E*)-2-benzylidene-tetrahydrofuran to (*Z*)-2-benzylidene-tetrahydrofuran, suggesting that the product stereochemistry is set during the catalytic reaction before release of product. Attempts to calculate TSs that led directly to *cis*-**6′** from copper alkoxide **5′** were either very high in energy or led to previously found TSs for product release (see Scheme 11), so isomerization of *trans*-**6** to *cis*-**6** prior to protonolysis was studied.

Isolation and thermolysis of the putative Cu-vinyl complex *trans*-**6** might allow observation of isomerization between the trans and cis isomers; however, several attempts to heat **5** in the absence of 5-phenyl-4-pentyn-1-ol in hopes of isolating **6** resulted in protonolysis by a residual proton source that we

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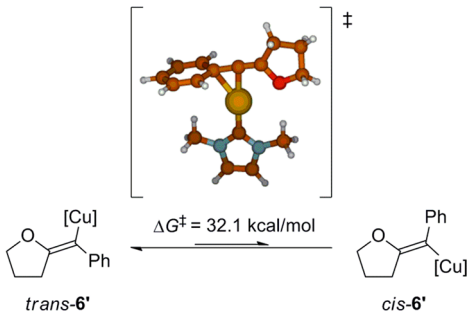
were unable to exclude from the reaction mixture. However, heating **5** without the free alkynyl alcohol 5-phenyl-4-pentyn-1-ol results in the formation of not just (*Z*)-2-benzylidene-tetrahydrofuran, as observed in the catalytic reaction, but also the *E* isomer. Thus, although the alkyne insertion from **5** is expected to form *trans*-**6** in a stereospecific manner, the conversion of **5** and 5-phenyl-4-pentyn-1-ol to form (*Z*)-2-benzylidene-tetrahydrofuran is obviously not stereospecific. The observation of (*E*)-2-benzylidene-tetrahydrofuran from thermolysis of **5** in the absence of free 5-phenyl-4-pentyn-1-ol suggests that the stereoselectivity of the catalytic reaction is likely dependent on the proton source that reacts with complex **6** to generate the final cyclized product, (*Z*)-2-benzylidene-tetrahydrofuran or (*E*)-2-benzylidene-tetrahydrofuran.

Since we were unable to experimentally isolate **6**, we studied the potential for isomerization computationally. We first considered isomerization of the *trans*-**6** to the *cis*-**6** via simple rotation about the C=C bond (Scheme 13). The presence of the O donor group might provide access to isomerization about the C=C bond of the Cu-vinyl complex. Isomerization of a *Z*-isomer to an *E*-isomer via formal rotation about a C=C bond has been observed by Langer et al. with an ester group as the substituent with a $\Delta G^{\ddagger}$ of 24 kcal/mol.[87] Similarly, Gundersen's group observed *Z*-to-*E* isomerization with a bulkier purine group with a $\Delta G^{\ddagger}$ of 28 kcal/mol.[88] These data suggest that a *Z*-to-*E* isomerization with the Cu-based catalyst may be feasible under the reaction conditions and must be considered as a mechanistic pathway. However, in the present case, calculations indicate that isomerization of the trans insertion product to the cis must overcome a barrier of 32.1 kcal/mol. Given the relatively low activation barriers for the protonolysis step to release free product, isomerization by simple rotation is not likely a viable pathway to form (*Z*)-2-benzylidene-tetrahydrofuran from complex **5**.

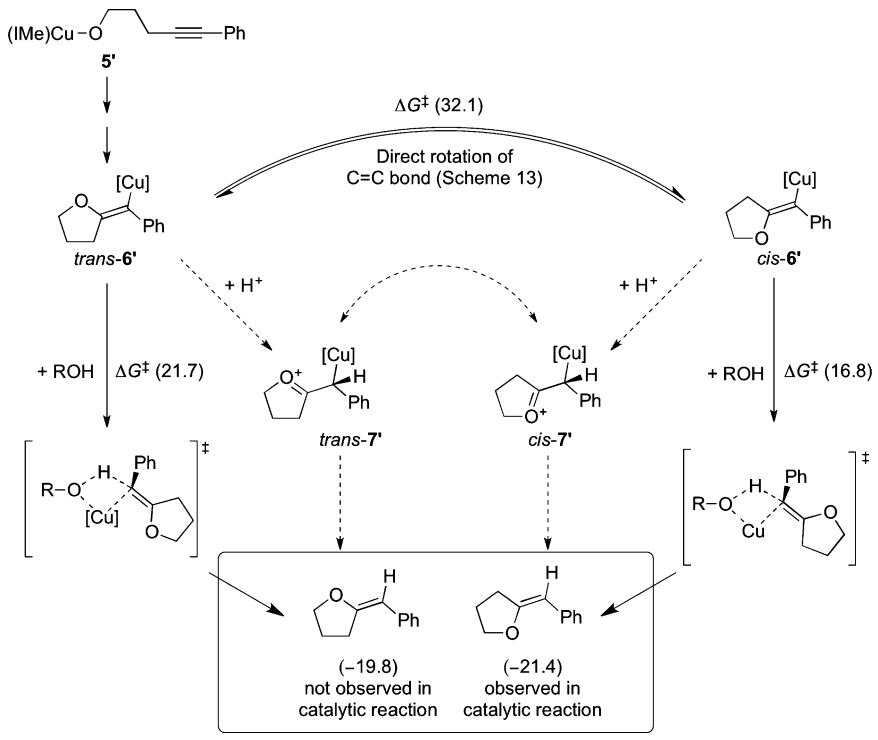
Reaction pathways that provide a tentative explanation for the stereoselectivity observed in the cyclization of 5-phenyl-4-pentyn-1-ol are shown in Scheme 14. Although calculations suggest that the activation barrier for isomerization of *trans*-**6′** and *cis*-**6′** is prohibitively high, isomerization should be facile from the product of protonation of **6** (i.e., *trans*-**7′** and *cis*-**7′** in Scheme 14). In this scenario, the formation of product would fall under Curtin−Hammett conditions and would be a function of the equilibrium of *cis*-**7** and *trans*-**7** and the rates at which they form product. In the catalytic cycle, the proton source (Scheme 14) is the alkynyl alcohol. The lifetime of species **7′** might be expected to vary with the identity of the conjugate base of the proton source, which is consistent with the different stereoselectivities described above. Unfortunately, we could not computationally isolate *trans*-**7′** or *cis*-**7′** and, thus, could not calculate the activation barrier for interconversion.

Scheme 13. Computed Activation Barrier for Isomerization of *trans*-6′ to *cis*-6′ by Direct Torsion of the C=C Bond[a]



[a][Cu] = (IMe)Cu.

Scheme 14. Proposed Pathways for Formation of (*E*)- and (*Z*)-2-Benzylidene-tetrahydrofuran from 5′[a]



[a]Calculated free energies (kcal/mol) are given in parentheses. [Cu] = (IMe)Cu.

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Despite this, with current data, we believe that the isomerization from a short-lived Cu vinyl complex, such as 7′, provides the best explanation for the observed stereoselectivity.

C−O versus C−N Bond Formation. A competition study revealed that the cyclization of primary amines using Cu catalyst **1** is more rapid than the cyclization of alcohols (entry 6, Table 1). In contrast, the opposite rates are observed for La catalysts.[61] The different relative rates for the two catalysts are not understood at this point; however, the observation for the La catalyst is perhaps surprising. Marks et al. have reported experimentally determined activation parameters for cyclization of alkynyl alcohols and amines.[61] For cyclization of 4-pentyn-1-amine by a Sm catalyst, the $\Delta H^{\ddagger}$ is 10.7(8) kcal/mol and the $\Delta S^{\ddagger}$ is −27.4(6) eu (E_a = 11.3(2.0) kcal/mol). In contrast, the cyclization of 4-pentyn-1-ol by a La catalyst occurs with $\Delta H^{\ddagger}$ = 20.2(1.0) kcal/mol and $\Delta S^{\ddagger}$ = −11.8 eu (E_a = 20.9(3) kcal/mol). Thus, the cyclization of the alkynyl alcohol exhibits a greater activation energy than the alkynyl amine. Although a direct comparison between Sm and La catalysts is tenuous, catalytic cyclization of 4-pentyn-1-ol is slower with Sm than La, likely providing an even larger advantage for the amine cyclization. The more facile Cu-catalyzed cyclization of amines is consistent with the activation parameters. It should also be noted that preliminary kinetic analysis of catalytic cyclization of alkynyl amines using **1** reveals a more complicated profile than for the cyclization of alkynyl alcohols, which suggests the likelihood of mechanism change.

SUMMARY AND CONCLUSIONS

Monomeric NHC−Cu(I) complexes catalyze the intramolecular hydroalkoxylation and hydroamination of alkynyl alcohols and alkynyl amines in good yield and selectivity. The major complementary feature of reactivity between NHC-Cu(I) and La catalysts is the formation of (*Z*)-2-benzylidene-tetrahydrofuran from the cyclization of 5-phenyl-4-pentyn-1-ol by **1**, whereas the La catalysts are selective for the formation of (*E*)-2-benzylidene-tetrahydrofuran. The different stereoselectivity for the Cu-based catalyst is explained by access to isomerization during the product-forming protonolysis step. Combined experimental and computational studies suggest that cyclization likely occurs through a pathway that is akin to that proposed for La catalysts with turnover-limiting insertion of alkyne into a copper−alkoxide bond. We believe that this catalytic pathway is unique among late transition metal catalysts.

ASSOCIATED CONTENT

Supporting Information

^{1}H NMR spectrum of complex **5** is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079−3159.
(2) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675−703.
(3) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368−3398.
(4) Brunet, J.-J.; Neibecker, D. Catalytic Hydroamination of Unsaturated Carbon-Carbon Bonds. In *Catalytic Heterofunctionalization*;, Togni, A., Grützmacher, H., Eds.; Wiley-VCH Verlag GmbH: Weinheim, FRG., 2001.
(5) Tani, K.; Kataoka, Y. O−H Activation and Addition to Unsaturated Systems. In *Catalytic Heterofunctionalization*; Togni, A., Grützmacher, H., Eds.; Wiley-VCH Verlag GmbH: Weinheim, FRG, 2001; pp 171−216.
(6) Pohlki, F.; Doye, S. *Chem. Soc. Rev.* **2003**, *32*, 104−114.
(7) Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673−686.
(8) McDonald, F. E. *Chem.—Eur. J.* **1999**, *5*, 3103−3106.
(9) Togni, A.; Grützmacher, H., *Catalytic Heterofunctionalization: From Hydroamination to Hydrozirconation*; Wiley-VCH: Weinheim, 2001.
(10) Roundhill, D. M. *Chem. Rev.* **1992**, *92*, 1−27.
(11) Ackermann, L.; Bergman, R. G.; Loy, R. N. *J. Am. Chem. Soc.* **2003**, *125*, 11956−11963.
(12) Doye, S. *Synlett* **2004**, *10*, 1653−1672.
(13) Li, C.; Thomson, R. K.; Gillon, B.; Patrick, B. O.; Schafer, L. L. *Chem. Commun.* **2003**, 2462−2463.
(14) Li, Y. W.; Fu, P. F.; Marks, T. J. *Organometallics* **1994**, *13*, 439−440.
(15) Li, Y. W.; Marks, T. J. *J. Am. Chem. Soc.* **1996**, *118*, 9295−9306.
(16) Müller, T. E.; Grosche, M.; Herdtweck, E.; Pleier, A.-K.; Walter, E.; Yan, Y.-K. *Organometallics* **2000**, *19*, 170−183.
(17) Müller, T. E.; Pleier, A. K. *J. Chem. Soc., Dalton Trans.* **1999**, 583−587.
(18) Kondo, T.; Okada, T.; Suzuki, T.; Mitsudo, T.-a. *J. Organomet. Chem.* **2001**, *622*, 149−154.
(19) Tokunaga, M.; Eckert, M.; Wakatsuki, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 3222−3225.
(20) Field, L. D.; Messerle, B. A.; Vuong, K. Q.; Turner, P. *Organometallics* **2005**, *24*, 4241−4250.
(21) Compain, P.; Goré, J.; Vatèle, J.-M. *Tetrahedron* **1996**, *52*, 10405−10416.
(22) Cacchi, S. *J. Organomet. Chem.* **1999**, *576*, 42−64.
(23) Wakabayashi, Y.; Fukuda, Y.; Shiragami, H.; Utimoto, K.; Nozaki, H. *Tetrahedron* **1985**, *41*, 3655−3661.
(24) Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **1999**, *121*, 11680−11683.
(25) Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **2002**, *124*, 2528−2533.
(26) Kücükbay, H.; Cetinkaya, B.; Guesmi, S.; Dixneuf, P. H. *Organometallics* **1996**, *15*, 2434−2439.
(27) Gabriele, B.; Salerno, G.; De Pascali, F.; Scianò, G. T.; Costa, M.; Chiusoli, G. P. *Tetrahedron Lett.* **1997**, *38*, 6877−6880.
(28) Gabriele, B.; Salerno, G.; Lauria, E. *J. Org. Chem.* **1999**, *64*, 7687−7692.
(29) Schabbert, S.; Schaumann, E. *Eur. J. Org. Chem.* **1998**, 1873−1878.
(30) Seiller, B.; Bruneau, C.; Dixneuf, P. H. *J. Chem. Soc., Chem. Commun.* **1994**, 493−494.
(31) Seiller, B.; Bruneau, C.; Dixneuf, P. H. *Tetrahedron* **1995**, *51*, 13089−13102.
(32) Qing, F.-L.; Gao, W.-Z.; Ying, J. *J. Org. Chem.* **2000**, *65*, 2003−2006.
(33) Qing, F.-L.; Gao, W.-Z. *Tetrahedron Lett.* **2000**, *41*, 7727−7730.
(34) Utimoto, K. *Pure Appl. Chem.* **1983**, *55*, 1845−1852.
(35) Tzalis, D.; Koradin, C.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 6193−6195.

(36) McDonald, F. E.; Connolly, C. B.; Gleason, M. M.; Towne, T. B.; Treiber, K. D. *J. Org. Chem.* **1993**, *58*, 6952−6953.
(37) Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **2003**, *125*, 7482−7483.
(38) McDonald, F. E.; Reddy, K. S.; Díaz, Y. *J. Am. Chem. Soc.* **2000**, *122*, 4304−4309.
(39) McDonald, F. E.; Reddy, K. S. *J. Organomet. Chem.* **2001**, *617*−*618*, 444−452.
(40) Sheng, Y. H.; Musaev, D. G.; Reddy, K. S.; McDonald, F. E.; Morokuma, K. *J. Am. Chem. Soc.* **2002**, *124*, 4149−4157.
(41) Wipf, P.; Graham, T. H. *J. Org. Chem.* **2003**, *68*, 8798−8807.
(42) Hashmi, A. S. K.; Schäfer, S.; Wölfle, M.; Diez Gil, C.; Fischer, P.; Laguna, A.; Blanco, M. C.; Gimeno, M. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 6184−6187.
(43) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896−7936.
(44) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180−3211.
(45) Rudolph, M.; Hashmi, A. S. K. *Chem. Commun.* **2011**, *47*, 6536−6544.
(46) Ho, J. H. H.; Hodgson, R.; Wagler, J.; Messerle, B. A. *Dalton Trans.* **2010**, *39*, 4062−4069.
(47) Genin, E.; Antoniotti, S.; Michelet, V.; Genêt, J.-P. *Angew. Chem., Int. Ed.* **2005**, *44*, 4949−4953.
(48) Liu, B.; De Brabander, J. K. *Org. Lett.* **2006**, *8*, 4907−4910.
(49) Diéguez-Vázquez, A.; Tzschucke, C. C.; Lam, W. Y.; Ley, S. V. *Angew. Chem., Int. Ed.* **2008**, *47*, 209−212.
(50) Diéguez-Vázquez, A.; Tzschucke, C. C.; Crecente-Campo, J.; McGrath, S.; Ley, S. V. *Eur. J. Org. Chem.* **2009**, 1698−1706.
(51) Hashmi, A. S. K.; Bührle, M.; Wölfle, M.; Rudolph, M.; Wieteck, M.; Rominger, F.; Frey, W. *Chem.—Eur. J.* **2010**, *16*, 9846−9854.
(52) Seo, S.; Marks, T. J. *Chem.—Eur. J.* **2010**, *16*, 5148−5162.
(53) Pale, P.; Chuche, J. *Eur. J. Org. Chem.* **2000**, 1019−1025.
(54) Pale, P.; Chuche, J. *Tetrahedron Lett.* **1987**, *28*, 6447−6448.
(55) Villemin, D.; Goussu, D. *Heterocycles* **1989**, *29*, 1255−1261.
(56) Luo, F. T.; Schreuder, I.; Wang, R. T. *J. Org. Chem.* **1992**, *57*, 2213−2215.
(57) Gabriele, B.; Salerno, G.; Fazio, A.; Pittelli, R. *Tetrahedron* **2003**, *59*, 6251−6259.
(58) Riediker, M.; Schwartz, J. *J. Am. Chem. Soc.* **1982**, *104*, 5842−5844.
(59) Suzuki, M.; Yanagisawa, A.; Noyori, R. *Tetrahedron Lett.* **1983**, *24*, 1187−1188.
(60) Yu, X. H.; Seo, S.; Marks, T. J. *J. Am. Chem. Soc.* **2007**, *129*, 7244−7245.
(61) Seo, S. Y.; Yu, X. H.; Marks, T. J. *J. Am. Chem. Soc.* **2009**, *131*, 263−276.
(62) Motta, A.; Fragalà, I. L.; Marks, T. J. *Organometallics* **2010**, *29*, 2004−2012.
(63) Patil, N. T.; Raut, V. S.; Kavthe, R. D.; Reddy, V. V. N.; Raju, P. V. K. *Tetrahedron Lett.* **2009**, *50*, 6576−6579.
(64) Praveen, C.; Iyyappan, C.; Perumal, P. T. *Tetrahedron Lett.* **2010**, *51*, 4767−4771.
(65) Mankad, N. P.; Gray, T. G.; Laitar, D. S.; Sadighi, J. P. *Organometallics* **2004**, *23*, 1191−1193.
(66) Laitar, D. S.; Tsui, E. Y.; Sadighi, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 11036−11037.
(67) Boogaerts, I. I. F.; Fortman, G. C.; Furst, M. R. L.; Cazin, C. S. J.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2010**, *49*, 8674−8677.
(68) Díez-González, S.; Escudero-Adán, E. C.; Benet-Buchholz, J.; Stevens, E. D.; Slawin, A. M. Z.; Nolan, S. P. *Dalton Trans.* **2010**, *39*, 7595−7606.
(69) Fortman, G. C.; Slawin, A. M. Z.; Nolan, S. P. *Organometallics* **2010**, *29*, 3966−3972.
(70) Munro-Leighton, C.; Blue, E. D.; Gunnoe, T. B. *J. Am. Chem. Soc.* **2006**, *128*, 1446−1447.
(71) Delp, S. A.; Munro-Leighton, C.; Goj, L. A.; Ramirez, M. A.; Gunnoe, T. B.; Petersen, J. L.; Boyle, P. D. *Inorg. Chem.* **2007**, *46*, 2365−2367.
(72) Munro-Leighton, C.; Delp, S. A.; Blue, E. D.; Gunnoe, T. B. *Organometallics* **2007**, *26*, 1483−1493.
(73) Munro-Leighton, C.; Delp, S. A.; Alsop, N. M.; Blue, E. D.; Gunnoe, T. B. *Chem. Commun.* **2008**, 111−113.
(74) Messerle, B. A.; Vuong, K. Q. *Organometallics* **2007**, *26*, 3031−3040.
(75) Antoniotti, S.; Genin, E.; Michelet, V.; Genêt, J.-P. *J. Am. Chem. Soc.* **2005**, *127*, 9976−9977.
(76) Fjermestad, T.; Ho, J. H. H.; Macgregor, S. A.; Messerle, B. A.; Tuna, D. *Organometallics* **2011**, *30*, 618−626 and references therein.
(77) Goj, L. A.; Blue, E. D.; Delp, S. A.; Gunnoe, T. B.; Cundari, T. R.; Petersen, J. L. *Organometallics* **2006**, *25*, 4097−4104.
(78) Bauschlicher, C. W.; Roos, B. O. *J. Chem. Phys.* **1989**, *91*, 4785−4792.
(79) Shoulders, B.; Welch, S. C. *J. Chem. Educ.* **1987**, *64*, 915−918.
(80) Yu, T. B.; Bai, J. Z.; Guan, Z. B. *Angew. Chem., Int. Ed.* **2009**, *48*, 1097−1101.
(81) Rozkiewicz, D. I.; Janczewski, D.; Verboom, W.; Ravoo, B. J.; Reinhoudt, D. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 5292−5296.
(82) Goj, L. A.; Blue, E. D.; Munro-Leighton, C.; Gunnoe, T. B.; Petersen, J. L. *Inorg. Chem.* **2005**, *44*, 8647−8649.
(83) Hashmi, A. S. K.; Braun, I.; Rudolph, M.; Rominger, F. *Organometallics* **2012**, *31*, 644−661.
(84) Hashmi, A. S. K.; Wieteck, M.; Braun, I.; Nösel, P.; Jongbloed, L.; Rudolph, M.; Rominger, F. *Adv. Synth. Catal.* **2012**, *354*, 555−562.
(85) Hashmi, A. S. K.; Braun, I.; Nösel, P.; Schädlich, J.; Wieteck, M.; Rudolph, M.; Rominger, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 4456−4460.
(86) Shannon, R. *Acta Crystallogr., Sect. A* **1976**, *32*, 751−767.
(87) Langer, P.; Freifeld, I. *Chem.—Eur. J.* **2001**, *7*, 565−572.
(88) Berg, T. C.; Gundersen, L. L.; Eriksen, A. B.; Malterud, K. E. *Eur. J. Org. Chem.* **2005**, 4988−4994.