group of the GcpE protein in *E. coli*. This enzyme efficiently converts cyclodiphosphate **7** into HMBPP (**8**) in the presence of flavodoxin, flavodoxin reductase, and NADPH. Whether the latter system is the effective regeneration system in *E. coli* still has to be determined. The oxygen sensitivity of the GcpE Fe/S cluster is one of the major reasons for the failure of crude cell-free systems to convert intermediates of this pathway into IPP (**9**), DMAPP (**10**), or further metabolites, and for the late discovery of the MEP pathway.

Experimental Section

Supporting information for this article (expression, purification, and characterization of the GcpE protein) is available on the WWW under http://www.angewandte.org.

Reconstitution of the FeS centers in the apoenzyme: The apo-GcpE solution (250 μL, 197 μM), a 20 mM Na_2S solution in argon-saturated buffer (50 mM Tris–HCl, pH 8), a 20 mM $FeCl_3$ and a 100 mM DTT solution in water were deoxygenated separately in Eppendorf tubes for 1 h under a stream of moist argon. All tubes were transferred to a glovebox (Jacomex BS531 NMT) equipped with an oxymeter (ARELCO ARC) and filled with argon containing less than 2 ppm O_2, where they were left to stand overnight at 15 °C before beginning the reconstitution procedure. DTT (to a final concentration of 5 mM) as well as $FeCl_3$ and Na_2S (in a fivefold molar excess with respect to the apoenzyme) were added successively to the enzyme solution. After 5 h, the reaction mixture was desalted on a PD 10 column (Pharmacia) equilibrated with 50 mM Tris–HCl buffer (pH 8). For recording the UV/Vis absorption spectrum, a fraction of the reconstituted protein was directly transferred into a cuvette, which was closed with a septum before being removed from the glove box.

GcpE assay with flavodoxin and flavodoxin reductase: Flavodoxin and flavodoxin reductase from *E. coli* were obtained as previously described.[8] A mixture (70 μL final volume) containing [^{14}C2]**7** (39 μM, 0.04 μCi), DTT (5 mM), NADPH (1 mM), flavodoxin (1 μM), flavodoxin reductase (0.5 μM) in Tris–HCl (50 mM, pH 8) was degassed for 45 min at room temperature under a stream of moist argon before adding the previously reconstructed GcpE with a gas-tight syringe to a final concentration of 2 μM. The incubation was performed in anaerobic conditions at 37 °C for 4 h.

GcpE assay with 5-deazaflavin: A mixture (70 μL final volume) containing [^{14}C2]**7** (39 μM, 0.04 μCi), DTT (5 mM) in Tris–HCl (50 mM, pH 8) was degassed for 45 min at room temperature under a stream of wet argon before adding successively, through a gas-tight syringe, the GcpE solution (final concentration: 2 μM) and a degassed 5-deazaflavin solution (final concentration: 50 μM) in the above-mentioned buffer. After generation of the reducing semiquinone radical from 5-deazaflavin and Tris–HCl by irradiation with a white fluorescent tube (30 °C, 1 h), the assay was incubated at 37 °C for 15 min or up to 3 h.

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Expanded Cubane: Synthesis of a Cage Compound with a C_{56} Core by Acetylenic Scaffolding and Gas-Phase Transformations into Fullerenes[**]

Peter Manini, Walter Amrein, Volker Gramlich, and François Diederich[*]

We have been interested since the early 1990s in the geometrically defined expansion of molecules by the introduction of buta-1,3-diynediyl fragments between all C−C single bonds, thereby enhancing both the carbon atom content and the optoelectronic properties of the resulting chromophores.[1] Application of this general concept to linear systems led from poly(acetylenes) to poly(triacetylenes)[2] and from dendralenes to expanded dendralenes.[3] Novel macrocyclic systems prepared following this strategy were dehydro[*n*]annulenes[4] and expanded radialenes.[1,5] We now report the first

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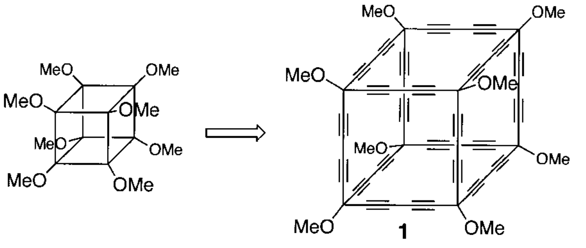
application of this concept[6] to form three-dimensional structures.

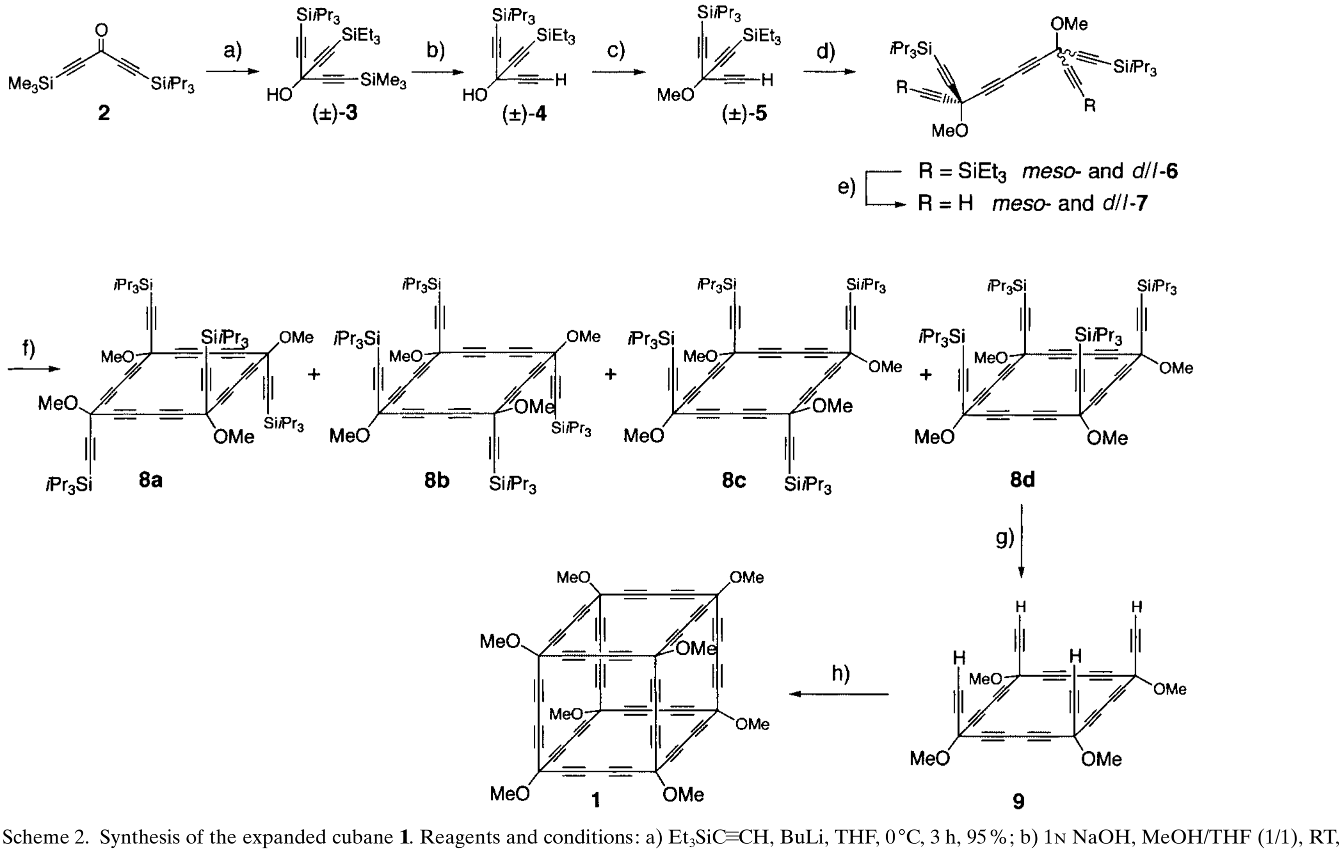
In 1964, Eaton and Cole, Jr., achieved the first synthesis of cubane.[7] This "platonic hydrocarbon" possesses remarkable kinetic stability despite its highly strained structure.[7,8] The expanded platonic molecule **1** with a C_{56} core is obtained by formal insertion of buta-1,3-diynediyl moeties into all twelve C–C single bonds of octamethoxycubane (Scheme 1). Here, we describe the first synthesis of **1** as well as investigations of its gas-phase ion chemistry which leads to the formation of fullerenes[9,10] and subsequent fullerene coalescence reactions.[11]



Scheme 1. From cubane to expanded cubane by formal insertion of twelve buta-1,3-diynediyl moieties.

The synthesis of expanded cubane **1** was planned to proceed through the formation of corners, edges, and faces as key building blocks and intermediates (Scheme 2). Addition of lithium triethylsilylacetylide to bispropargylic ketone **2**[12] afforded the racemic corner module (±)-**3** with three differentially protected alkyne moieties[1] in 95% yield.[13] The $SiMe_3$ protecting group was selectively removed by stirring (±)-**3** for 1 h in MeOH/THF (1/1) containing a few drops of 1N NaOH and yielded (±)-**4** in 86% yield. Traces of bisdeprotected compound were readily separated by column chromatography (SiO_2; hexane/CH_2Cl_2 (2/1)). Subsequent methylation using BuLi at −78 °C followed by addition of MeI provided (±)-**5** in 98% yield. Oxidative Hay coupling[14] of (±)-**5** was carried out in CH_2Cl_2 to afford edge **6** as an unseparable mixture of stereoisomers (*meso* and *d*/*l* forms) in 97% yield. Subsequent cleavage of the $SiEt_3$ protecting groups with K_2CO_3 in MeOH/THF (1/1) gave *meso*- and *d*/*l*-**7** (93% yield), which was subjected to oxidative coupling under high dilution conditions. The macrocyclic product **8** was obtained in a remarkable 72% yield as a powder consisting of four diastereoisomers. Separation of the mixture by column chromatography (SiO_2; hexane/CH_2Cl_2 (3/1→1/3)) provided, in the order of elution, **8a** (8%), **8b** (18%), **8c** (36%), and the desired diastereoisomer **8d** (10%). The four compounds are stable in the solid state at room temperature, but decompose in CH_2Cl_2 solution within a few days.

The structural assignments for the four macrocycles were unambiguously made based on ^{13}C NMR spectroscopic analysis ($CDCl_3$), X-ray analysis, and chemical reactivity studies. The C_{2h}-symmetrical structure of **8b** was proven by X-ray analysis and ^{13}C NMR spectroscopy (10 out of 10 resonances



Scheme 2. Synthesis of the expanded cubane **1**. Reagents and conditions: a) $Et_3SiC{\equiv}CH$, BuLi, THF, 0 °C, 3 h, 95%; b) 1N NaOH, MeOH/THF (1/1), RT, 1 h, 86%; c) BuLi, THF, −78 °C, 10 min, then MeI, −78 °C→RT, 16 h, 98%; d) CuCl, TMEDA, air, CH_2Cl_2, RT, 5 h, 97%; e) K_2CO_3, MeOH/THF (1/1), RT, 2.5 h, 93%; f) CuCl, TMEDA, air, CH_2Cl_2, RT, 18 h, 8% (**8a**), 18% (**8b**), 36% (**8c**), 10% (**8d**); g) Bu_4NF, wet THF, −15 °C, 2.5 h, 87%; h) CuCl, TMEDA, air, CH_2Cl_2, RT, 3 h, 16%. TMEDA = *N*,*N*,*N*′,*N*′-tetramethyl-1,2-ethanediamine.

observed). Diastereoisomer **8c** possesses the lowest symmetry (C_s), which is reflected by a much larger number of resonances in the ^{13}C NMR spectrum (15 out of 26 observed). Both D_{2d}-symmetrical **8a** and C_{4v}-symmetrical **8d** show the expected eight resonances in their ^{13}C NMR spectra; differentiation between the two diastereoisomers is based on the fact that only **8d** continued to react to give expanded cubane **1**.

The X-ray crystal structure of **8b** (Figure 1) revealed that the symmetry in the crystal (C_i) is reduced from the ideal C_{2h} symmetry, as a result of crystal packing effects.[15] The cyclic framework is planar with a mean out-of-plane deviation of 0.041 Å and a maximum deviation of 0.09 Å (C(5)).[16] The distances between neighboring C(sp^3) atoms are 6.64 Å (C(5)–C(10)) and 6.69 Å (C(5)–C(10a)). Strain in the 20-membered ring is mainly expressed by weak bends in the four butadiynediyl moieties. The C≡C–C(sp^3) angles are as low as 172.4°, and the maximal reduction of the C≡C-C(sp) angles from the ideal 180° is approximately 5°. In contrast, the angles at the corner C(sp^3) atoms ((C(9)-C(10)-C(1a): 106.8°; C(4)-C(5)-C(6): 107.3°) are close to the ideal tetrahedral angle of 109.5°.

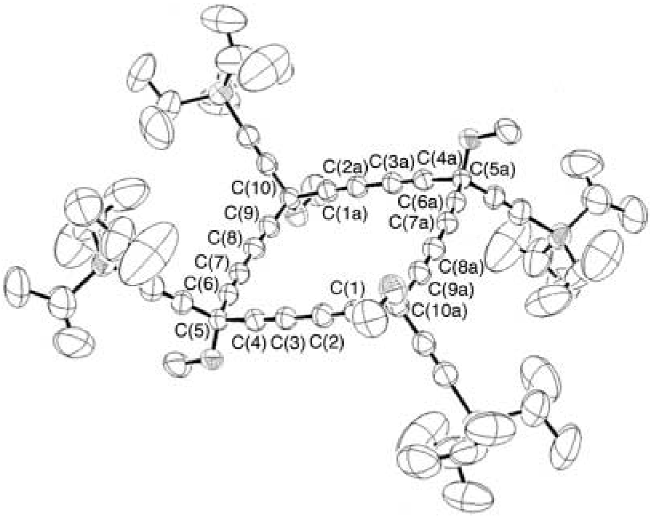


Figure 1. ORTEP plot of **8b** with arbitrary numbering. H atoms are omitted for clarity. Atomic displacement parameters at 293 K are drawn at the 50 % probability level. Selected bond lengths [Å] and bond angles [°]: C(1)-C(2) 1.190(5), C(2)-C(3) 1.373(6), C(3)-C(4) 1.188(5), C(4)-C(5) 1.476(5), C(5)-C(6) 1.485(5), C(6)-C(7) 1.193(5), C(7)-C(8) 1.378(6), C(8)-C(9) 1.186(5), C(9)-C(10) 1.481(5), C(10)-C(1a) 1.481(5); C(10a)-C(1)-C(2) 175.5(4), C(1)-C(2)-C(3) 178.3(4), C(2)-C(3)-C(4) 179.0(4), C(3)-C(4)-C(5) 175.9(4), C(4)-C(5)-C(6) 107.3(3), C(5)-C(6)-C(7) 172.7(3), C(6)-C(7)-C(8) 175.2(4), C(7)-C(8)-C(9) 174.7(4), C(8)-C(9)-C(10) 172.4(4), C(9)-C(10)-C(1a) 106.8(3).

For the completion of the synthesis of **1**, **8d** was deprotected with Bu$_4$NF in wet THF at −15 °C to give powdery **9** in 87 % yield after column chromatography (SiO$_2$; hexane/EtOAc (2/1)). Deprotection at room temperature failed because of complete decomposition. Although **9** is explosive, and detonates upon scratching, it was fully characterized, with the ^{13}C NMR spectrum (CDCl$_3$) depicting the expected six resonances at 77.42, 75.97, 74.50, 69.03, 61.09, and 53.61 ppm. Oxidative cyclization of **9** under Hay conditions in CH$_2$Cl$_2$ afforded **1** in low yield (up to 16 %). Purification and characterization were severely hampered by the instability of the target compound, which, similar to **9**, explodes upon scraping.[16d,17] Nevertheless, the substantial amounts of side products could mostly be removed by tedious column chromatography (SiO$_2$; hexane/CH$_2$Cl$_2$ (1/2)) to leave a brownish powder of sufficient purity for complete spectral characterization.

The ^{1}H and ^{13}C NMR spectra of **1** in CDCl$_3$ demonstrate its O_h symmetry. The proton resonances of the MeO groups appear as a singlet at $\delta = 3.44$ ppm, whereas the ^{13}C NMR spectrum depicts the expected four resonances at $\delta = 54.38$ (MeO), 61.98 (C(sp^3)), 70.82 (C(sp)), and 79.39 ppm (C(sp); Figure 2). The C(sp)-H stretching band at 3302 cm^{-1}, typical of **9**, is completely absent in the IR spectrum (CHCl$_3$).

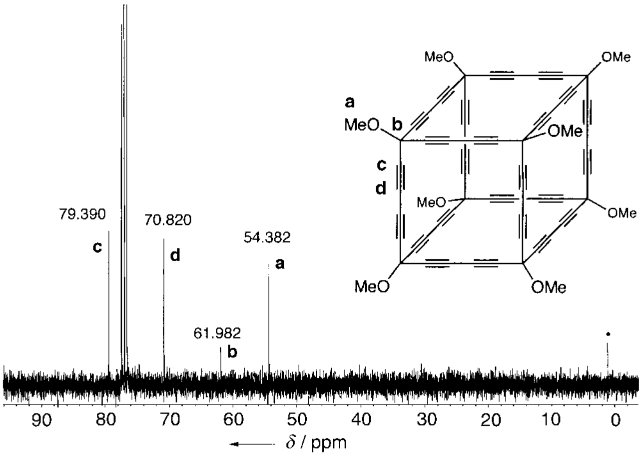


Figure 2. ^{13}C NMR (75 MHz, CDCl$_3$) spectrum of expanded cubane **1** at 298 K; ●: impurity.

In matrix-assisted laser-desorption-ionization time-of-flight (MALDI-TOF) experiments in the negative ion mode, expanded cubane **1** readily undergoes a loss of a methoxy group. The peak for the [M^-–OMe] ion at m/z: 889 is actually the only major one in the entire spectrum (Figure 3). None of the numerous spectra recorded from crude or purified product gave any evidence for oxidative trimerization or higher cyclo-oligomerizations of **9** to give larger carbon cages.

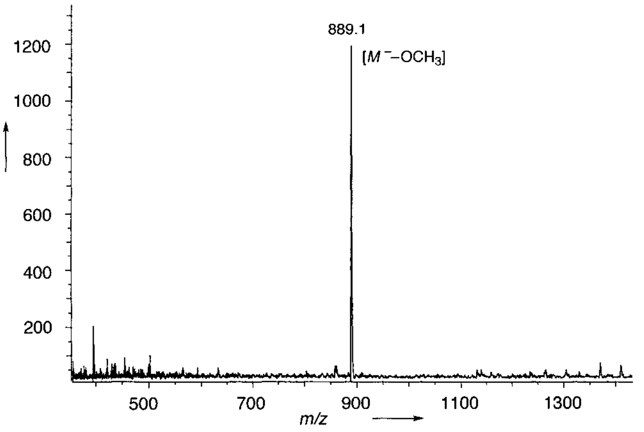


Figure 3. MALDI-TOF mass spectra of **1** in the negative ion mode; N$_2$ laser (337 nm, 7 ns duration), matrix: 2-[(2*E*)-3-(4-*tert*-butylphenyl)-2-methylprop-2-enylidene] malononitrile (DCTB).

Very promising results were obtained by high-resolution Fourier-transform ion-cyclotron-resonance (HR-FT-ICR) MALDI mass spectrometry. The stepwise loss of up to six MeO fragments is observed in the negative ion mode (Figure 4 a). The C_{56}^- ion, which results from the loss of all eight MeO groups, is weakly visible at lower mass (*m*/*z*: 672). However, it is rather improbable that this ion has the structure of the expanded cubane. Rather, we prefer to assign this weak peak to a fullerene ion resulting from rapid isomerization of the initially formed anionic C_{56} cluster. This hypothesis is supported by the subsequent facile C_2 fragmentations, which are highly characteristic of fullerenes.[18] Thus, C_2 fragmentations of C_{56}^- generate intense peaks which we assign to the fullerene ions C_{54}^- (*m*/*z*: 648), C_{52}^- (*m*/*z*: 624), and C_{50}^- (*m*/*z*: 600).

The loss of all methoxy groups and subsequent rearrangement to fullerene ions seems even more favorable in the positive ion mode (Figure 4 b). Neither the fragment ions $[M^+ - n\,OCH_3]$ ($n = 1$–7) nor the C_{56}^+ ion can be detected. The spectrum is instead dominated by the fullerene ions C_{54}^+, C_{52}^+, and C_{50}^+, which result from C_2 fragmentations. Furthermore, these ions undergo remarkable ion–molecule coalescence reactions[11] with formation of higher fullerene ions from C_{100}^+ (*m*/*z*: 1201) to C_{106}^+ (*m*/*z*: 1273), which, upon C_2 fragmentation, generate the fullerene ions C_{94}^+, C_{96}^+, and C_{98}^+.

We are now continuing the gas-phase ion studies with **1** in greater detail, by using collaboration methods to possibly isolate some of the fullerenes after mass selection and neutralization. Also, we are working on further improving the synthesis of **1** and target differently substituted derivatives. The results of the gas-phase investigations actually suggest that the loss of a tris-propargylic MeO group leading to a highly unstable nonplanar carbocation might be at the origin of the highly exothermic decomposition of **1**. Therefore, we plan adding other substituents such as alkyl or aryl groups to the eight corner $C(sp^3)$ atoms to generate more stable expanded cubanes that are amenable to X-ray crystallography.

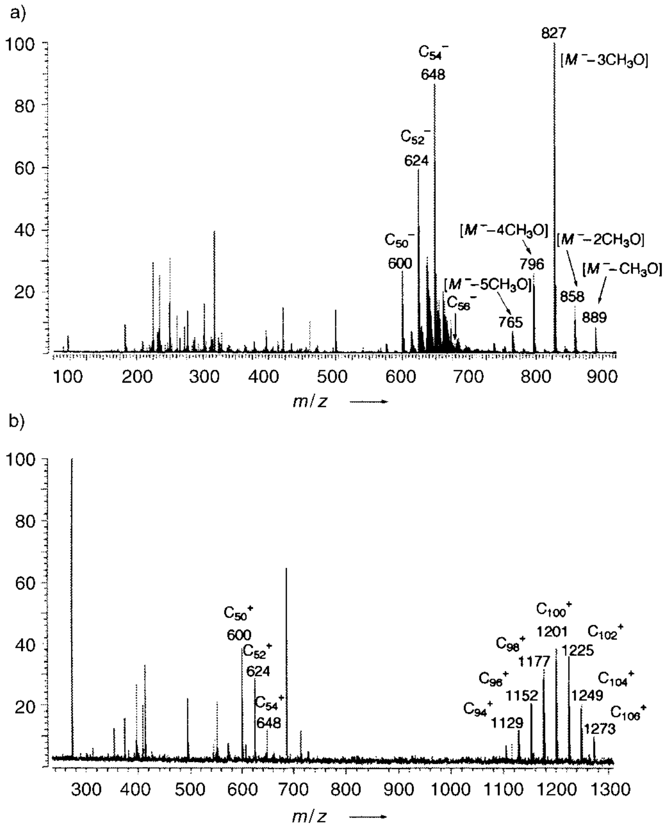


Figure 4. HR-FT-ICR-MALDI mass spectra of **1** a) in the negative (matrix: DCTB) and b) in the positive ion mode (matrix 2,5-dihydroxybenzoic acid). A N_2 laser (337 nm) was employed. All observed *m*/*z* values were accurate to within 2 ppm of the postulated elemental compositions.

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[15] X-ray crystal data for **8b** at 293 K ($C_{68}H_{96}O_4Si_4$, $M_r = 1089.81$): monoclinic, space group $P2_1/n$ (no. 14), $\rho_{calcd} = 0.981\ g\,cm^{-3}$, $Z = 2$, $a = 10.789(10)$, $b = 14.865(13)$, $c = 23.07(2)$ Å, $\beta = 94.23(8)°$, $V = 3690(6)$ Å^3. Picker–Stoe diffractometer, $Cu_{K\alpha}$ radiation, $\lambda = 1.5418$ Å. A single crystal with linear dimensions of about $0.1 \times 0.04 \times 0.03$ mm, grown by vapor-phase diffusion of hexane into a CH_2Cl_2 solution at RT, was used. The structure was solved by direct methods and refined by full-matrix least-squares analysis (SHELXTL). All heavy atoms were refined anisotropically and H-atoms fixed isotropically with atomic positions based on stereochemical considerations. Final $R(F) = 0.061$, $wR(F^2) = 0.157$ for 343 parameters and 3074 reflections with $I > 2\sigma(I)$ and $3.54 < \theta < 50.0°$ (corresponding R values based on all 3795 reflections are 0.075 and

0.169, respectively). CCDC-192482 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

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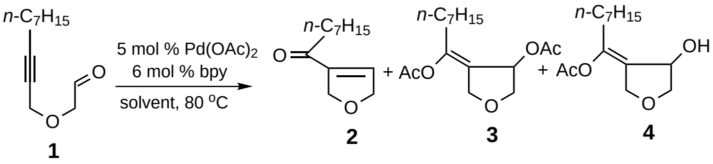
Pd^{II}-Catalyzed Cyclization of Alkynes Containing Aldehyde, Ketone, or Nitrile Groups Initiated by the Acetoxypalladation of Alkynes[**]

Ligang Zhao and Xiyan Lu[*]

The insertion of carbon–carbon multiple bonds into carbon–transition-metal bonds as a facile method of carbon–carbon bond formation is a very important fundamental reaction in transition-metal organometallic chemistry.[1] However, in contrast to the numerous reports regarding the insertion of carbon–carbon multiple bonds into carbon–transition-metal bonds, direct insertion of carbon–heteroatom multiple bonds, such as carbonyl and nitrile groups, without using stoichiometric organometallic reagents, has received scant attention.[1] The disadvantages of such insertion processes are that the carbon–heteroatom π bond is stronger than the carbon–carbon π bond,[2] and that electrophilic metals tend to form σ complexes with the heteroatom of carbon–heteroatom multiple bonds, instead of π complexes,[3] which makes the insertion unfavorable. Such obstacles make this area of research particularly challenging. Recently, some examples of the insertion of carbonyl groups into late-transition-metal–carbon bonds, for example with Rh[4] and Ni,[5] have been reported, although most of these require the use of stoichiometric organometallic reagents or additives. In palladium chemistry, a limited number of examples catalyzed by Pd^0 have been reported by Vicente,[6] Yamamoto,[7a–d] Yang,[8a–c] and Larock.[8d,e] To the best of our knowledge, there are no examples of the direct insertion of a carbonyl or nitrile group into a carbon–palladium bond by reactions catalyzed by a palladium(II) species through the acetoxypalladation of alkynes.

The fact that a Pd^{II} species is formed after quenching an oxygen–palladium bond through protonolysis, even in Pd^0-catalyzed reactions, suggests that a redox system must be involved in the reported Pd^0-catalyzed carbonyl insertion reactions. It occurs to us that a Pd^{II}-catalyzed reaction may be advantageous for such insertion reactions. Recently, we reported a Pd^{II}-catalyzed cyclization reaction of enyne esters initiated by the acetoxypalladation of alkynes which utilized bipyridine as a ligand.[9] This novel catalytic system encouraged us to develop new reactions using carbon–heteroatom multiple bonds as insertion species, instead of carbon–carbon double bonds. Herein, we wish to exhibit another mechanism involving the cyclization of alkynes with carbonyl or nitrile groups through the acetoxypalladation of alkynes, followed by the insertion of carbon–heteroatom multiple bonds into the carbon–palladium bond and subsequent protonolysis.

Our investigation of the reaction conditions began by using dec-2-ynyloxyacetaldehyde (**1**, 0.5 mmol), $Pd(OAc)_2$ (5 mol %) as the catalyst, and 2,2′-bipyridine (bpy, 6 mol %) as the ligand in acetic acid (5 mL) at 80 °C (Scheme 1). The reaction afforded products **2**–**4** (**2**:**3**:**4** 20:40:40) in 78 % total yield. Control experiments confirmed that **4** can partially transform into either **3** (by acetylation) or **2** (by transformation) in this system. Reactions with ketones gave the corresponding tertiary alcohols as a single product in good yield using acetic acid/dioxane as the solvent, while the reactions of aldehydes proceeded smoothly to afford the sole product **3** in moderate yield (50 %) using acetic acid/1,4-



Scheme 1. Pd^{II}-catalyzed cyclization of an aldehyde-containing alkyne.

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