Alkyne Homocoupling

Let the Best Ring Win: Selective Macrocycle Formation through Pd-Catalyzed or Cu-Mediated Alkyne Homocoupling**

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In memory of Virgil Boekelheide

There is considerable interest in highly conjugated organic molecules such as phenylacetylenes and dehydroannulenes for potential applications in next generation electronic and photonic devices.[1] Such extended π-conjugated systems functionalized with electron donor and/or acceptor groups encompass a significant field of current research.[2] In our ongoing studies with dehydrobenzoannulenes (DBAs),[3] we have produced macrocycles with a variety of ring topologies, symmetries, and sizes,[4] as well as unique substitutions of donor, acceptor, and neutral groups.[5] The final ring closure for these systems and many other macrocycles containing diacetylene units typically proceeds by Cu-mediated oxidative homocoupling of terminal alkynes.[3,6,7] There are often problems associated with this type of cyclization, however, such as low yields, formation of oligomeric by-products, and use of pyridine as (co)solvent. Homocoupling of terminal alkynes has recently been reported by using Pd catalysts.[8] Under conditions typically used for Sonogashira cross-coupling reactions[9] (Pd catalyst, CuI, base), addition of a suitable oxidant and exclusion of an organic electrophile produce high yields of homocoupled alkynes. A similar procedure has very recently been applied to macrocycle synthesis; however, the reported yields were low.[10] We have now modified this chemistry for macrocycle formation with excellent results. Furthermore, we have discovered a surprising differentiation between Cu-mediated and Pd-catalyzed cyclizations for ring size and geometry, which leads to selective formation of bisDBAs **1** and **2**, respectively, both of which originate from octayne **3** (Scheme 1).

We[11] and others[12] have encountered difficulties using the standard Cu-mediated cyclization for the formation of diacetylenic macrocycles. Yields can often vary wildly for a given ring size,[5a,11] as well as a simultaneous occurrence of intra- and intermolecular homocoupling reactions.[12] A greatly overlooked consideration when performing this reaction is the geometry in the Cu-containing intermediate

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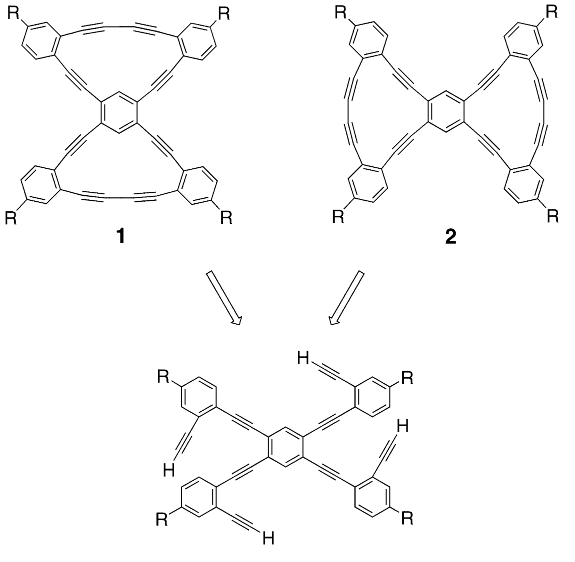
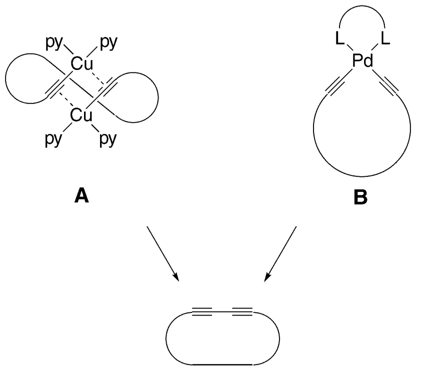


Scheme 1. Retrosynthesis of **1** and **2** from **3**.

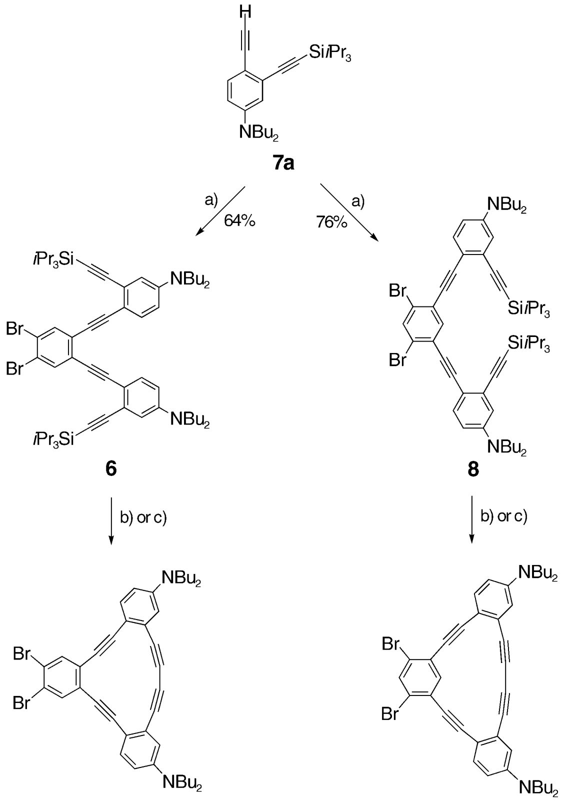
prior to "reductive elimination". Although still subject to interpretation and debate, the most reasonable and most accepted mechanistic picture involves a dimeric Cu^I acetylide (**A**, Scheme 2) arranged in a pseudo-*trans* configuration.[13]



Scheme 2. Proposed metal–acetylide intermediates in Cu-mediated (**A**) and Pd-catalyzed (**B**) diacetylene-forming reactions.

Formation of this pseudo-*trans* geometry in the intermediate species is likely to be difficult for certain systems that would need to adopt a highly strained configuration for homocoupling to occur, and thus could lead to low product yields and large amounts of oligomeric/polymeric by-products, as we found in the synthesis of dehydrobenzo[14]annulene **4** (see below). We have discovered that through use of an oxidative Pd-catalyzed route, control of the geometry of the metal bis(σ-acetylide) intermediate is possible by the selection of an appropriate ligand. For systems in which *cis* over *trans* configuration in the intermediate is favored, such as DBA **4**, Pd catalysts with *cis*-bidentate ligands (**B**, Scheme 2) give us much higher yields for macrocycle formation. Conversely, if a *trans* configuration of the terminal alkynes in the annulene precursor is favorable, such as for DBA **5**, Cu-mediated routes provide superior results.

This selectivity is demonstrated in the syntheses of DBAs **4** and **5** (Scheme 3), which are key pieces in later bisannulene assemblies. Precursor **6** was constructed by Sonogashira cross-coupling of diyne **7a**[5a,14] to 1,2-dibromo-4,5-diiodobenzene,[15] thus providing an *ortho* substitution of the alkynes on the central ring. Protiodesilylation of the triisopropylsilyl groups by Bu_4NF and MeOH followed by slow injection of this precursor into a pyridine solution of $Cu(OAc)_2$ furnished DBA **4** in a low yield (24%) along with large amounts of oligomeric/polymeric by-products. Other Cu species and variations of this procedure failed to notably affect yields. We surmised that these poor yields were most likely due to difficulties in the formation of intermediate **A**. Based on simple molecular modeling calculations,[16] the geometry and sterics of our system should instead favor a *cis* orientation of the terminal alkynes to a metal center, which is the preferred geometry in the reductive-elimination step of a Sonogashira reaction.[9,17] This geometry was enforced about the metal center by use of *cis*-bidentate ligated $[PdCl_2(dppe)]$ (dppe = 1,2-bis(diphenylphosphanyl)ethane), which resulted in a dramatic increase in the yield of cyclization (76%). Our best results were obtained with a slow injection of desilylated

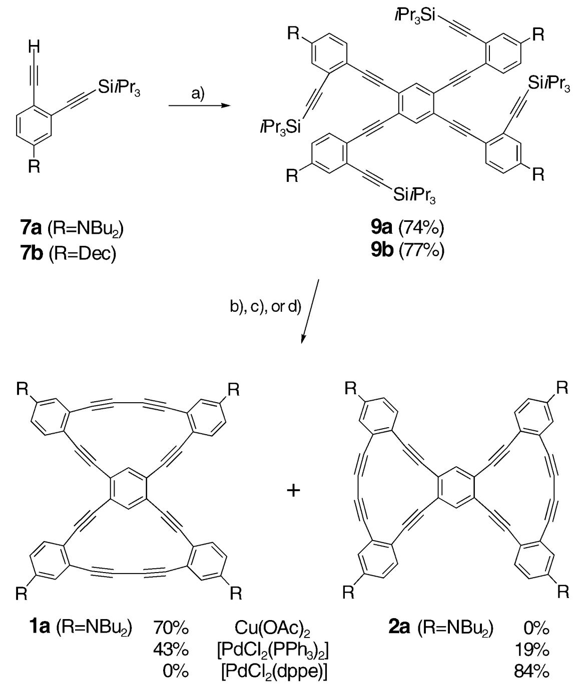


4		5
24%	$Cu(OAc)_2$	80%
35%	CuCl	76%
67%	$[PdCl_2(PPh_3)_{2+}]$	24%
76%	$[PdCl_2(dppe)]$	12%

Scheme 3. Reagents and conditions: a) 1,2-dibromo-4,5-diiodobenzene or 1,5-dibromo-2,4-diiodobenzene, $[Pd(PPh_3)_4]$, CuI, iPr_2NH, THF, 45 °C; b) Bu_4NF, MeOH, THF; then "Cu", pyridine, 60 °C; c) Bu_4NF, MeOH, THF; then "Pd", CuI, I_2, iPr_2NH, THF, 50 °C.

polyyne **6** into the Pd/Cu solution to minimize cyclooligomerization and by facilitating reoxidation of the Pd catalyst with I_2 and leaving the flask open to air. It is also noteworthy that heating to 50 °C was required for product formation, while no reaction occurred below this temperature. Slightly lower yields for the cyclization of **4** were also obtained with other Pd catalysts, while the best yields were seen with [$PdCl_2$(dppe)]. In contrast to precursor **6**, the meta-fused phenylacetylene **8**, constructed by a similar manner from 1,5-dibromo-2,4-diiodobenzene,[18] gave very good yields of the [15]annulene **5** by using the Cu/pyridine cyclization (80 %), while Pd routes resulted in lower yields (12–24 %) owing to the increased distance and the poor alignment of the terminal alkynes as required in **B**. Interestingly, intermolecular dimer formation was competitive in the latter Pd-catalyzed reactions, which suggests that this might be a viable alternative intermolecular homocoupling procedure for macrocycle formation where similar Cu-mediated reactions had previously failed or worked poorly.[12]

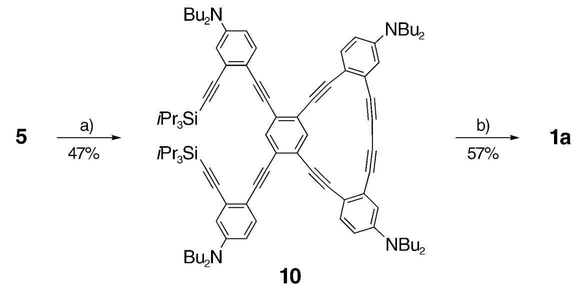
To further study the selectivity differences between Pd and Cu cyclizations, polyyne **9a** was constructed by a four-fold cross-coupling of diyne **7a** to 1,2,4,5-tetraiodobenzene[19] (Scheme 4). In this unique system, there is a possibility of formation of either bis[15]annulene **1a** by cyclization across the *meta*-fused diynes or bis[14]annulene **2a** by *ortho* fused cyclization. We first tested the cyclization of **9a** by using the classical Glaser method and isolated only one annulenic product in 70 % yield. Since we observed that *meta* fusion of the diynes tends to favor the *trans* orientation and thus Cu-mediated cyclizations, we hypothesized that this product was bis[15]DBA **1a**. Next, we cyclized **9a** by a Pd-mediated route by using [$PdCl_2(PPh_3)_2$] and observed formation of the same material in 43 % yield along with 19 % of another annulene, most likely bis[14]DBA **2a**. As expected, cyclization with [$PdCl_2$(dppe)] gave exclusively this second product in a respectable 84 % yield, with no observation of the annulene formed by the Cu/pyridine route, hence providing complete selectivity between the two DBA products. This method was also successfully extended to the decyl-substituted bisDBAs **1b** and **2b**, which were selectively synthesized in moderate yields.



Scheme 4. Reagents and conditions: a) 1,2,4,5-tetraiodobenzene, $Pd(PPh_3)_4$, CuI, *i*Pr_2NH, THF, 40 °C; b) Bu_4NF, MeOH, THF; then $Cu(OAc)_2$, pyridine, 60 °C; c) Bu_4NF, MeOH, THF; then [$PdCl_2(PPh_3)_2$], CuI, I_2, *i*Pr_2NH, THF, 50 °C; d) Bu_4NF, MeOH, THF; then [$PdCl_2$(dppe)], CuI, I_2, *i*Pr_2NH, THF, 50 °C. Dec = decyl.

As structural isomers, bisannulenes **1** and **2** have very similar spectral data making specific identification difficult, although one key difference was observed in their proton NMR spectra. The singlet for the two protons on central benzene of the annulene from the Cu-mediated route displayed a large downfield shift upon cyclization (**1a**: $\delta = 8.42$ ppm, **1b**: $\delta = 8.49$ ppm) while a lesser shift (**2a**: $\delta = 8.24$ ppm, **2b**: $\delta = 8.38$ ppm) was seen for the same singlet from the DBA acquired by Pd-catalyzed cyclization. Molecular modeling calculations[16] showed that the intraannular protons of the bis[15]DBA were closer to the alkyne groups than the analogous protons on the bis[14]DBA. Therefore, an increased anisotropic deshielding effect from the triple bonds would make the central protons of **1** more downfield shifted than those of **2**. Similar differences between NMR spectral data were also observed for **4** and **5** and have been reported with other [14]- and [15]annulenes.[12f,20]

To further prove that our structural assignments of **1** and **2** were correct, we have definitively synthesized **1a** for spectral comparison by cyclizing one ring at a time (Scheme 5). This route allowed no possibility for formation of 14-membered rings. Dibromo-mono[15]annulene **5** was the ideal starting point for the synthesis, to which two equivalents of diyne **7a** were attached providing precursor **10**. Deprotection and Cu-mediated cyclization of the second ring gave bis[15]annulene **1a** whose spectral data were an exact match with those of the material made by Cu-mediated cyclization of polyyne **9**.



Scheme 5. Reagents and conditions: a) **7a**, [$Pd(PPh_3)_4$], CuI, *i*Pr_2NH, THF, 80 °C; b) Bu_4NF, MeOH, THF; then $Cu(OAc)_2$, pyridine, 60 °C.

Cyclization of phenylacetylene macrocycles by oxidative Pd-catalyzed coupling is proving to be a reliable alternative or complementary reaction to Cu-mediated cyclization. The Pd route displays benefits over the Cu/pyridine procedure such as catalytic use of the metal species (while the Cu-mediated route typically requires over 20 equivalents), solvents such as THF and Et_3N are used, which are easily removed and more benign than pyridine, and yields are higher for many macrocycles. However, the versatility of the Pd catalyst is probably the most important advantage. A variety of different ligands can be attached to the Pd center to facilitate the shape and geometry of the alkyne species such as *trans* versus *cis* configuration or even chiral ligands for further enhancement of the selectivity. We are currently employing this methodology for the construction of donor/acceptor functionalized systems as well annulenes of other ring shapes and sizes. We continue to obtain excellent selectivity and will report this work in due course.

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Keywords: alkynes · C–C coupling · dehydroannulenes · homocoupling · macrocycles

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