

Copper-Catalyzed Formal [4 + 2] Annulation between Alkyne and Fullerene Bromide

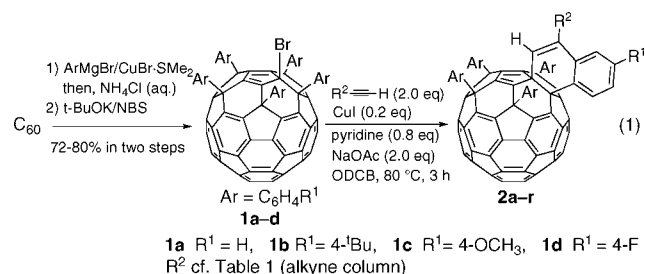
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Abstract: A copper-catalyzed reaction of arylacetylene or enyne with $C_{60}Ar_5Br$ effects a formal [4 + 2] annulation reaction to form a dihydronaphthalene ring fused to the fullerene core. The reaction involves a formal C–H bond activation and takes place by a copper-mediated radical mechanism. This reaction takes place in 60–75% overall yield from [60]fullerene and creates axial chirality in the product because of restricted rotation of the top aryl groups.

The diversity and complexity of the reactivity of fullerenes, as well as their unprecedented large spherical structure, have led to the discovery of new reactions and novel chemical structures.¹ We report herein the serendipitous discovery of an unusual and effective copper-catalyzed C–C bond-forming reaction and a novel array of aromatic rings constructed on the fullerene sphere (eq 1). The reaction efficiently couples an arylacetylene or enyne to a fullerene bromide (**1**) in a formal [4 + 2] fashion to form a dihydronaphthalene ring fused to a fullerene sphere (**2**). This reaction represents one of the rare catalytic reactions of fullerenes² and involves a formal C–H bond-activation process. The uniqueness of the product structure is highlighted by the binaphthyl-type compound **2k** obtained in 86% yield (Table 1, entry 11). Axial chirality is generated for the bond colored in green in Figure 1a because rotation of the bond is restricted by the remote phenyl groups, including the CH– π interaction indicated by a purple broken line (see Figure 1).



The optimized reaction on a gram scale illustrates the simplicity and efficiency of the new synthetic reaction. A mixture of $C_{60}Ph_5Br$ (1.00 g, 0.84 mmol), CuI (32 mg, 0.17 mmol), NaOAc (138 mg, 1.68 mmol), 4-ethynylanisole (220 μ L, 1.68 mmol), and pyridine (54 μ L, 0.67 mmol) in 1,2-dichlorobenzene (ODCB, 100 mL) was stirred vigorously to make a finely dispersed red suspension at room temperature, which was then heated at 80 °C for 3 h. The resulting

Table 1. Copper-Catalyzed Annulative Coupling of $C_{60}Ar_5Br$ and Alkynes^a

entry	1 ($C_{60}(C_6H_4R^1)_5Br$)	alkyne ($R^2C\equiv CH$)	2	% yield ^b
1	1a	4-MeOC ₆ H ₄ C≡CH	2a	94 (91)
2	1a	C ₆ H ₅ C≡CH	2b	87
3	1a	4-CF ₃ C ₆ H ₄ C≡CH	2c	91
4	1a	4-BrC ₆ H ₄ C≡CH	2d	92
5	1a	4-NCC ₆ H ₄ C≡CH	2e	90
6	1a	4-CHOC ₆ H ₄ C≡CH	2f	89
7	1a	3,5-(MeO) ₂ C ₆ H ₃ C≡CH	2g	84
8	1a	2,4,5-Me ₃ C ₆ H ₂ C≡CH	2h	90
9	1a		2i	87
10	1a		2j	88
11	1a		2k	86
12	1a		2l	78 (78)
13 ^c	1a	n-C ₆ H ₁₃ -C≡CH	2m	13
14	1a		2n	90
15	1b	C ₆ H ₅ C≡CH	2o	86
16	1c	C ₆ H ₅ C≡CH	2p	85
17	1c	4-MeC ₆ H ₄ C≡CH	2q	88
18	1c	3-MeC ₆ H ₄ C≡CH	2r	85
19	1d	4-MeOC ₆ H ₄ C≡CH	2s	82

^a The reaction was carried out at 80 °C for 3 h using ~50 mg of the fullerene bromide (eq 1). Details are shown in the Supporting Information. ^b Isolated yields (yields in parentheses are on a 1 g scale). The side product in all cases was largely $C_{60}Ar_5H$. ^c For 6 h using 4 equiv of alkyne.

clear red solution was poured into MeOH (600 mL) to obtain the desired product as a precipitate. Filtration and purification by silica gel column chromatography (eluent: 3/1 CS₂/toluene) afforded **2a** (948 mg, 0.77 mmol, 91%).

We note that a copper(I) or copper(II) catalyst is essential; however, the choice of organic and/or inorganic base is not too critical (e.g., pyridine/NaOAc or pyridine/Ag₂CO₃; see Table S1 in the Supporting Information). The fullerene bromides **1a–d** were synthesized quantitatively by the reaction of *N*-bromosuccinimide with $C_{60}Ar_5H$,³ which in turn was prepared in a single step in 92–99% yield by the reaction of C_{60} and PhMgBr/CuBr·SMe₂.⁴ The overall yield of compounds **1a–d** from C_{60} was therefore 72–80%.

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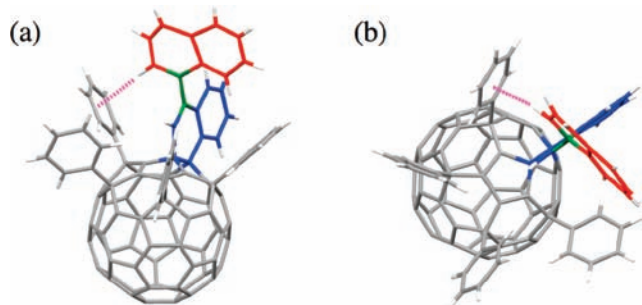
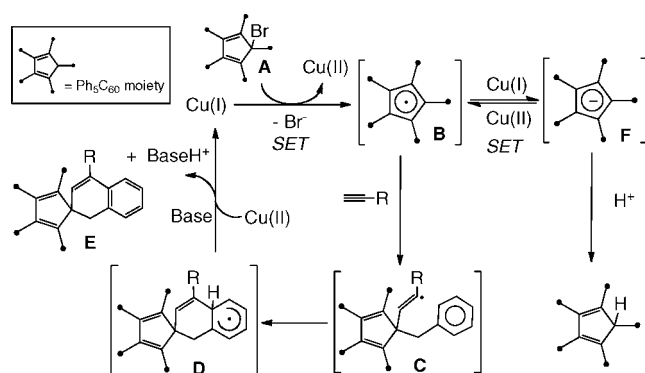


Figure 1. Capped-sticks drawings of the X-ray crystal structure of **2k**: (a) side view; (b) top view. The top naphthyl ring is shown in red, the bottom fullerene-fused naphthyl ring in blue, the C–C bond responsible for axial chirality in green, and a CH– π interaction in purple.

Scheme 1. Mechanistic Rationale for the [4 + 2] Annulation



The scope and limitations of the reaction are illustrated in Table 1. The reaction is applicable to a variety of terminal alkynes, including arylacetylene, enyne, and 1-octyne, although the last of these was low-yielding, and for various penta(aryl)[60]fullerenes $C_{60}Ar_5Br$ (yields mostly ranging between 80 and 94%). A remarkable feature of the reaction is its tolerance for a wide variety of functional groups. Ether, CF_3 , bromide, cyano, pyridinyl, thiophenyl, and even aldehyde groups survived the reaction (entries 1–11).

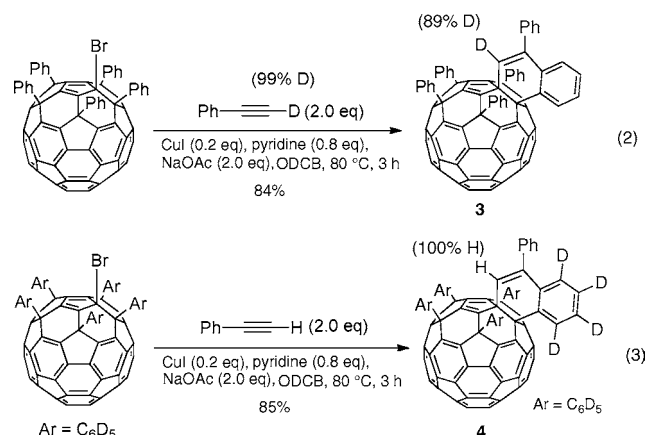
The reaction rate was found to be qualitatively insensitive to the electronic properties of the arylacetylene substrates. For instance, the electron-deficient 4- $CF_3C_6H_4C\equiv CH$ (entry 3) and the highly electron-rich ethynylferrocene (entry 12) reacted equally smoothly. The latter provides a simple and effective synthesis of a donor–acceptor dyad system⁵ on a gram scale. The contrast between the poor-yielding 1-octyne (13%; entry 13) and the high-yielding 1-ethynylcyclohexene (90%; entry 14) is mechanistically noteworthy (see below). Internal alkynes such as 1,2-diphenylacetylene and 1-phenyl-1-propyne did not take part in the reaction at all (data not shown). Notably, the reaction was found to be insensitive to the electronic properties of the aryl groups attached to the fullerene core substituent (4-MeO-, 4-^tBu-, and 4-F-phenyl groups in entries 15–19).

On the basis of the observed reactivity profile and functional group tolerance combined with the reported observation that $C_{60}Ph_5Cl$ reductively forms a chloride anion and $Ph_5C_{60}^{\bullet}$,⁶ we consider a copper-mediated radical pathway starting with a single-electron transfer⁷ from Cu(I) to $C_{60}Ph_5Br$ (**A**) to generate a cyclopentadienyl radical **B** (Scheme 1). The contrasting reactivities of 1-octyne, 1-ethynylcyclohexene, and phenylacetylene suggest a vinyl radical intermediate **C**, which adds to a nearby aryl group to form **D**. The prominent effect of the R group (aryl or vinyl vs alkyl) suggests the need to stabilize the vinyl radical **C**. Oxidation of **D**

by Cu(II) in the presence of a base produces the annulation product **E** and a protonated base, regenerating Cu(I).

We obtained a set of experimental information that sheds light on the mechanism of the reaction. First, the reaction of copper(I) phenylacetylide and $C_{60}Ph_5Br$ produced no annulation product, which rules out the involvement of the copper(I) acetylide species in the reaction. More conclusively, when we treated $C_{60}Ph_5Br$ with a mixture of $CuC\equiv CPh$ (0.2 equiv) and 4-ethynylanisole (2 equiv), the reaction exclusively produced the 4-ethynylanisole annulation product (58% yield) instead of the phenylacetylene annulation product, indicating that a neutral acetylene serves as the substrate. Second, the reaction with 1 equiv of CuI gave $C_{60}Ph_5H$ in 50% yield and the annulation product in 40% yield. We can consider that the reduction of **B** to the anion **F** with excess Cu(I) effectively competed with the desired path leading to **C**.

We used deuterium labeling to probe the origin of the vinylic hydrogen atom located on the newly formed cyclohexene ring. First, the reaction of 1-deutero-2-phenylacetylene gave 89% deuterium incorporation at the vinylic hydrogen (eq 2). We consider that the partial deuterium loss occurred prematurely before the annulation reaction. Second, the reaction of $C_{60}(C_6D_5)_5Br$ with phenylacetylene resulted in no incorporation of deuterium at the vinylic position (eq 3). These results are consistent with the pathway shown in Scheme 1.⁸



Finally, we point out that the reaction creates axial chirality⁹ in **2k** (Figure 1). This chirality is unique in that the remote phenyl groups prevent the rotation around the C–C bond shown in green, which should otherwise occur via the anti transition state usually found for binaphthyl rotation.¹⁰ Thus, the ¹H and ¹³C NMR spectra indicating the C_1 symmetry of **2k** show no sign of line broadening up to 150 °C. Similarly, the C–C bond rotation in the 2,4,5-trimethylphenyl compound **2h** did not take place this time because of the neighboring *o*-methyl group (see the Supporting Information).

In contrast, the room-temperature NMR spectra of compounds **2n** and **2r** showed C_s symmetry, indicating fast rotation of the top 1-cyclohexenyl or 3-methylphenyl group; this rotation slowed when the temperature was lowered. The rotational barriers (ΔG^\ddagger) for **2n** and **2r** were 11.1 and 13.4 kcal/mol, respectively (see the Supporting Information for details).

In summary, we have discovered a new copper-mediated radical reaction that couples a variety of terminal alkynes with a penta(aryl)[60]fullerene molecule. The reaction may be related mechanistically to the well-known radical polymerization or cyclization reactions catalyzed by copper.¹¹ The reaction allows us to construct a complex and rigid structure in three steps from [60]fullerene in good overall yield. The intriguing [4 + 2] annulation includes direct functionalization of an aromatic ring via

formal C–H bond activation. Extension of the present discovery to the design of homochiral compounds and to the development of similar annulation reactions for ordinary organic molecules will be interesting future possibilities.

Acknowledgment. This work was generously supported by MEXT, Japan (KAKENHI to E.N., 22000008, the Global COE). We thank Dr. K. Harano for helpful discussions on the variable-temperature NMR studies.

Supporting Information Available: Synthetic procedures and spectral data for all new compounds and crystallographic data for **2a**, **2d**, and **2k** (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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JA1056399