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Polycyclic Aromatics

Exo-Dig Radical Cascades of Skipped Enediynes: Building a Naphthalene Moiety within a Polycyclic Framework

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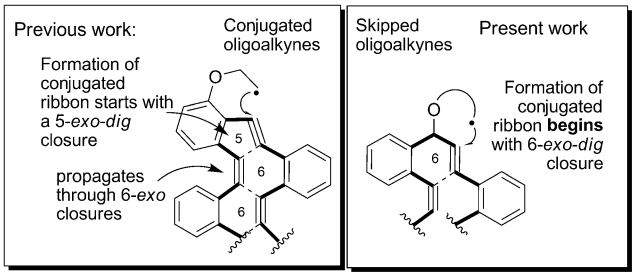
Abstract: Cascade radical transformations of acyclic precursors open efficient, convenient and atom-economical access to functionalized compounds of increased structural complexity. This report describes a selective sequence of 5-*exo-dig* and 6-*exo-dig* cyclizations followed by attack at a pendant aromatic moiety and rearomatization.

The overall transformation is a new approach for building a naphthalene moiety within a polycyclic framework. Furthermore, the high efficiency for the key 6-*exo* step of the cascade paves the way for the preparation of defect-free graphene nanoribbons. Radical cascades are valuable tools for the construction of complex polycyclic frameworks.[1] At their best, these reactions impart striking efficiency to synthetic strategies.[2] The advantage of radical reagents over their ionic counterparts is in the relatively broad functional group tolerance, mild reaction conditions, and the combination of high reactivity with controllable selectivity.[3] Alkynes are attractive precursors for the rapid construction of carbon-rich polycyclic frameworks and materials due to the high carbon content,[4] the possibility of modular assembly via reliable cross-coupling chemistry, and controllable reactivity. We recently utilized these features for the preparation of polyaromatic ribbons from oligoalkynes through selective radical[5] and metal-catalyzed cascade cyclizations,[6] each of which correspond to controlled "polymerization" of alkyne moieties sandwiched between the two rows of aromatic rings (Scheme 1).

The radical version of such approaches to graphene-like nanoribbons relied on a selective initial attack at the central alkyne of the oligoalkyne precursor. Only when the central alkyne is the initial target all alkyne moieties in the precursor are fully converted into expanded polyaromatic framework through a sequence of *exo-dig* cyclizations. For the oligoalkyne with three triple bonds, such selectivity is achievable by the use of selective intermolecular Bu_3Sn radical attack at the central alkyne.[5a] For the systems with four alkyne moieties, the selectivity was achieved through covalent attachment of the initiating group near the central alkyne, so the first attack at the triple bond is intramolecular.[5b] Because both approaches start



Scheme 1. Variations on radical cascade cyclizations of oligoalkynes for conjugated (left) and "skipped" substrates (right).

with conjugated oligoalkynes, the first cyclization that involves two alkynes is the 5-*exo* cyclization. As a consequence, the "polyacetylene ribbon" formed from the oligoalkyne always starts with a pentagon. One of the questions that we wanted to address in this work was whether the presence of this pentagon can be avoided, that is, whether the first reaction between two alkynes could be a 6-*exo-dig* closure. A potential limitation of this approach is that the rate of 6-*exo-dig* cyclization is expected to be approximately 50-fold slower than the 5-*exo-dig* process.[7]

In order to test the alternative design, we changed the oligoalkyne reactant from conjugated to "skipped" by adding one extra carbon. In order to initiate the regioselective formation of the vinyl radical, we took advantage of our earlier finding that C–I bonds can be selectively activated in the presence of several alkyne moieties by the Bu_3SnH/AIBN system. The requisite starting materials **1a**–**k** are readily prepared from the respective 2-bromobenzaldehydes by via the combination of Sonogashira cross-coupling and nucleophilic addition of acetylide anions to the aldehyde[8] (Figure 1).

Sonogashira cross-coupling of 2-bromobenzaldehydes with alkynes proceeded in good yields to produce the library of 2-(phenylethynyl)benzaldehydes in 70–84% yields (Scheme 2). Subsequent treatment with arylethynyl lithium produced the "skipped" acetylenic alcohols. The hydroxyl group in these compounds serves as a convenient point for the attachment of the pendant radical initiator. This was accomplished by treat-

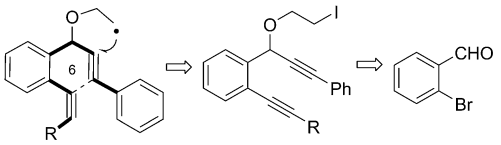


Figure 1. Skipped diynes are readily available.

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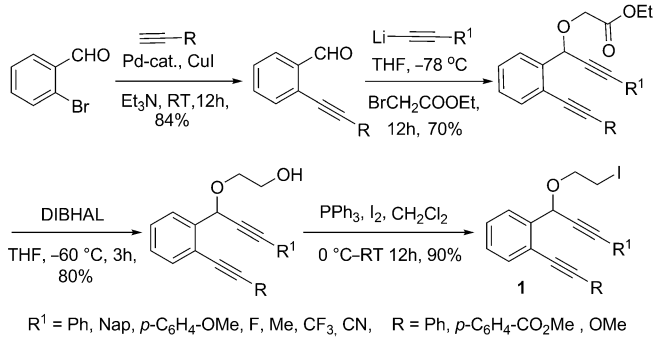


Scheme 2. Synthesis of 1,(2-alkynylphenyl)propargyl iodoethyl ethers. Reaction yields are given for R = R^1 = Ph (see the Supporting Information for additional details).

ment with ethyl bromoacetate to produce the propargyl esters[9] in 60–70% overall yields. Reduction of the esters produces alcohols converted into the requisite iodo precursors **1** for the radical cascade by the Appel reaction.

Table 1 shows screening of reagents and initiators for the key transformation of 1,(2-alkynylphenyl)propargyl iodoethyl ether (**1a**) into dihydro-1*H*-benzo[1,2]fluoreno[3,4-*b*]furan (**2a**).

Table 1. Screening against different reagents, initiators and solvents.

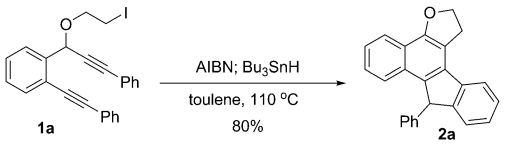
Entry	Reagent/initiator[a]	Conditions	Yield[b] [%]
1	Bu_3SnH/AIBN	benzene, 16 h, 80 °C	65
2	Et_3SiH/AIBN	benzene, 16 h, 80 °C	42
3	Bu_3SnH/AIBN	MeCN, 15 h, 80 °C	45
4	Bu_3SnH/AIBN	toluene, 14 h, 110 °C	80
5	Et_3SiH/AIBN	toluene, 14 h, 110 °C	70
6	Ph_3SnH/AIBN	toluene, 14 h, 110 °C	–[c]
7	Bu_3SnH/ABCN	toluene, 14 h, 110 °C	65
8	Bu_3SnH/DTBPB	toluene, 14 h, 110 °C	–[c]

[a] Reagent: 1.5 equiv; initiator: 0.3 equiv. [b] Product yields are reported after purification from a silica gel column. [c] Mixture of products. ABCN = azobiscyclohexanenitrile; DTBPB = di-*tert*-butyl peroxide.

Although Bu_3SnH/AIBN and Et_3SiH/AIBN in refluxing benzene led to complete consumption of starting iodide **1a**, the first two entries gave only moderate yields (65 and 42%) of the desired **2a**. CH_3CN as solvent decreases the yield of **2a** to 45%, but switch to toluene with the concomitant increase in the reaction temperature had the opposite effect (78 and 70%, respectively, for Bu_3SnH and Et_3SiH, entries 3 and 4). The use Ph_3SnH/AIBN gave a mixture of products in less than 10–15% (entry 6). Entries 7 and 8 describe the effect of different initiators. Whereas Bu_3SnH/ABCN (1.5/0.3 equiv) showed good selectivity with 65% yield, the combination of Bu_3SnH/DTBPB gives a complicated mixture of products. Use of 1 equiv of Bu_3SnH reagent led to incomplete consumption of starting iodide **1a** whereas the over-reduced products were observed with 2 equiv of Bu_3SnH. Overall, Bu_3SnH/AIBN (1.5 equiv/0.3 equiv) in toluene (110 °C, 14 h) was found to be the optimal choice, providing **2a** in 80% yield (entry 4).

In order to evaluate the generality of this approach to fused naphthalenes, we tested the reactions of additional diynes **1b**–**1k** under the optimized conditions (Table 2). The cascade is fully compatible with acceptor (ester, cyano and trifluoromethyl) and donor (methoxy, methyl, methylenedioxy) substitution at either one of the two arylalkynyl termini. In the reaction of a β-naphthyl-substituted bis-alkyne (**1b**), capable of

Table 2. Scope of substrates for radical cascades.



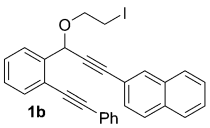
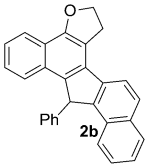
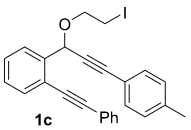
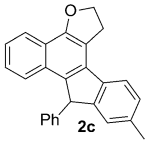
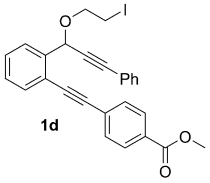
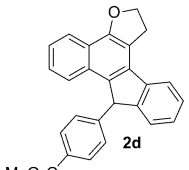
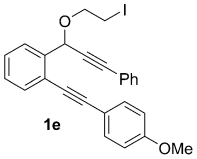
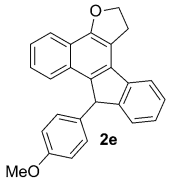
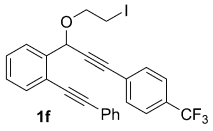
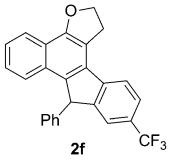
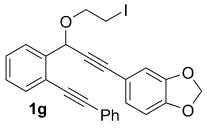
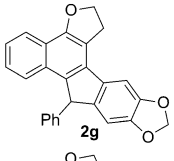
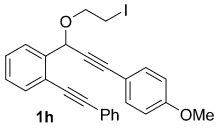
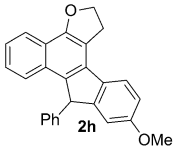
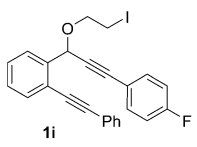
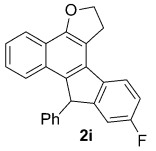
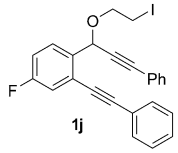
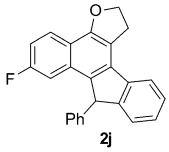
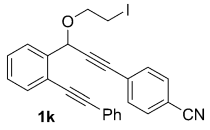
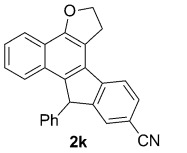
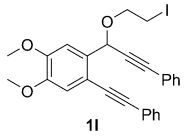
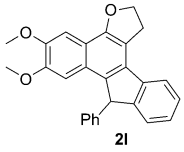
Entry	Substrate	Product	Yield [%]
1			85
2			70
3			58
4			72
5			65
6			70
7			72

Table 2. (Continued)

Entry	Substrate	Product	Yield [%]
8	 **1i**	 **2i**	68
9	 **1j**	 **2j**	60
10	 **1k**	 **2k**	70
11	 **1l**	 **2l**	80

[a] Isolated yields reported after silica column chromatography.

giving a mixture of products in the final step of the cascade (vide infra), formation of a single regioisomer **2b** was observed in 85% yield. These results highlight the broad scope and selectivity of this method.

The structures of the cascade products were confirmed with the combination of HMBC and HSQC NMR spectroscopy techniques and, in the case of compound **2b** and **2h**, with X-ray crystallography[10] (Figure 2). The flat conjugated core of the molecules (dihedral angles between the naphthyl and fused

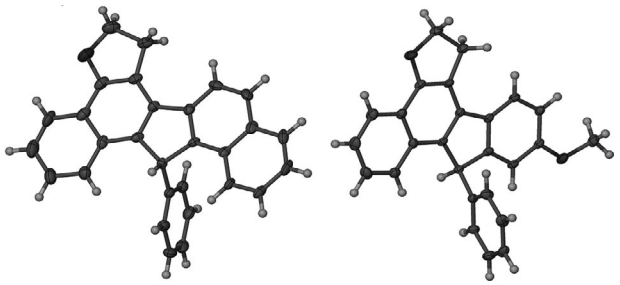
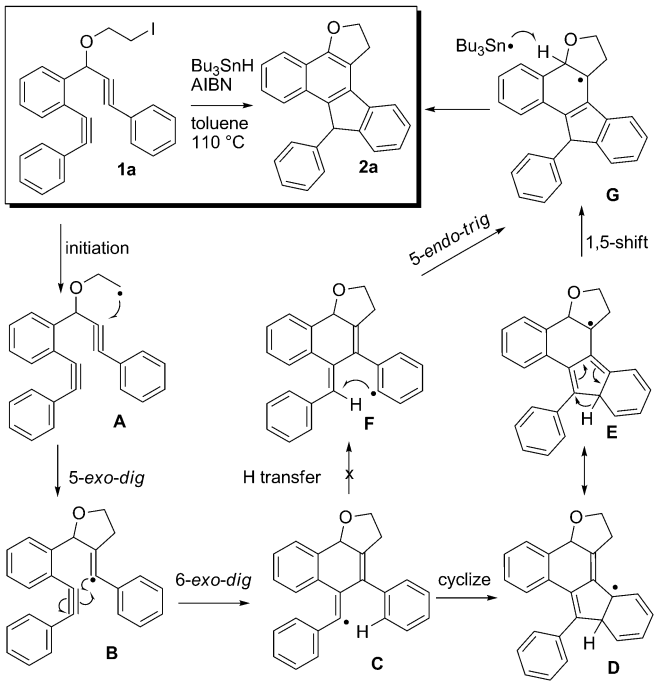


Figure 2. The ORTEP for **2b** and **2h**. Probability level 50%.

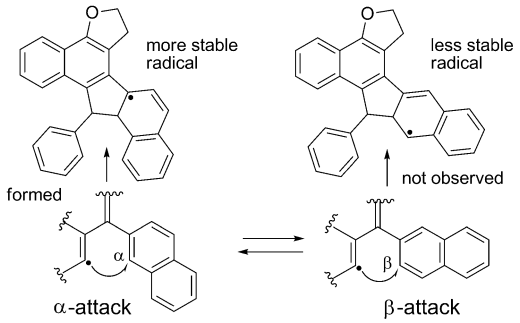
aryl systems in **2b** and **2h** are $<6^{\circ}$) facilitates conjugation between the alkoxysubstituted naphthalene and the annealed aromatic rings. Significant changes observed in the UV spectra as a function of substitution (see the Supporting Information) suggest that electronic communication between the fused rings is efficient.

The two possible mechanisms for this cascade transformation are shown in Scheme 3. Both paths start with the same chemoselective formation of an alkyl radical **A** from the intermolecular attack of the Bu_3Sn radical at the C–I bond of the reactant **1a**. The chemoselectivity is noteworthy since Bu_3Sn radical is well known to attack similarly substituted alkynes.[11] The intermediate **A** undergoes 5-*exo-dig* cyclization to form the first cycle and the first vinyl radical intermediate **B**. The latter undergoes 6-*exo-dig* cyclization at the remaining triple bond with the formation of a second vinyl radical **C**. The two possible mechanisms diverge at this point.



Scheme 3. The two mechanistic alternatives for the proposed cascade.

In the first scenario, the vinyl radical attacks the π system of the neighboring phenyl group. In the second scenario, the same radical abstracts a hydrogen from an aromatic C–H bond. Although the C_{sp2}–H bonds are relatively strong, such path would avoid transient loss of aromaticity. The "translocated" aryl radical **F** produced via such H abstraction can "come back" at the alkene moiety via a 5-*endo-trig* cyclization.[12] Alternatively, the first path produces delocalized radical **D** capable of rearomatization via a fast 1,5-hydrogen shift. Such shifts were shown in our previous work to have low activation barriers.[13] At this point, the two mechanisms converge to give the penultimate intermediate **G**, which provides the final dihydro-1*H*-benzo[1,2]fluoreno[3,4-*b*]furan product (**2a**) after the final H-abstraction step.[14] The difference between the two mechanisms is important in those nonsymmetrically substituted alkynes when the final ring formation can provide a mixture of products. Formation of a single regioisomer in the cyclization of naphthyl-substituted substrate **1b** provides a key insight that allows us to differentiate between the two pathways. The



Scheme 4. Regioselectivity of radical attack agrees with the radical addition to the terminal aromatic system in the final cyclization step.

observed isomer corresponds to the more favorable direction of radical attack at the naphthalene moiety (confirmed by the X-ray diffraction study; Scheme 4). We had shown earlier that a radical attack at the α position is more favorable than a β attack and provided a theoretical rationale to this selectivity.[15] Absence of product formation through β attack clearly shows that the product is formed via a path that involves the intermediate **D** (Scheme 3).

In summary, we have developed a new approach to substituted benzo[1,2]fluoreno[3,4-*b*]furan derivatives from skipped enediynes through intramolecular radical cascade cyclization which involves formation of three new cycles via sequence of 5-*exo-dig*, 6-*exo-dig* ring closures and attack at the aromatic ring. Subsequent aromatization furnishes the fused naphthalene products in high yields. This radical cascade opens a new avenue for the preparation of polycyclic frameworks. Future work includes expansion of this radical cascade toward longer and wider polycyclics.

Acknowledgements

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Keywords: 6-*exo-dig* · cyclization · naphthalene · polycyclic aromatics · radical cascade

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