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Polyaromatic Ribbon/Benzofuran Fusion via Consecutive Endo Cyclizations of Ene-diynes

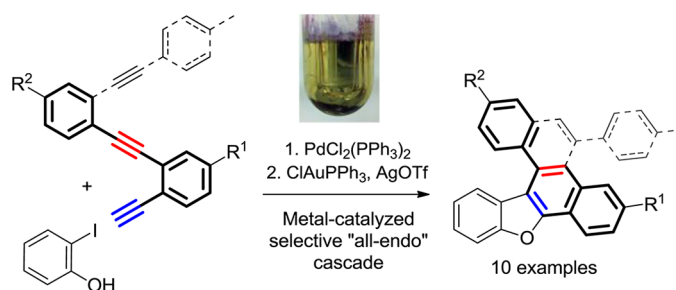
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ABSTRACT



The Sonogashira/5-endo-dig/6-endo-dig cascade fuses a polycyclic aromatic backbone to the electron-rich furan subunit. The transformation proceeds in modest yields as a one-pot reaction. Efficiency of the full cascade is increased by removal of base prior to the addition of gold catalyst. Under these conditions, conversion to the full cascade products is achieved in nearly quantitative yields without purification of the intermediate products. Extension of the cascade toward triynes opens access to benzofuran-fused chrysene derivatives.

Alkynes are valuable precursors for the preparation of carbon-rich materials¹ due to their high carbon content, modular assembly via reliable cross-coupling chemistry, and propensity for participating in coordinated and efficient cascade transformations leading to the construction of polycyclic frameworks.² Heteroatom incorporation into polycyclic aromatic frameworks fine-tunes their electronic properties, leading to major advances in the field of organic materials. Annealing of donor heterocycles can expand

the utility of carbon-rich compounds in materials^{3,4} and molecular devices.⁵

As a continuation of our work on alkyne cyclizations,⁶ we recently reported a cascade transformation of four alkynes into extended polyaromatic structures through a

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sequence of four *exo-dig* radical cyclizations.⁷ The exclusive exoselectivity in that reaction design relied on the revised rules for alkyne cyclizations⁸ where, contrary to the original Baldwin rules,⁹ the preferred approach of a radical or a nucleophile follows the Burgi–Dunitz trajectory (Figure 1).¹⁰

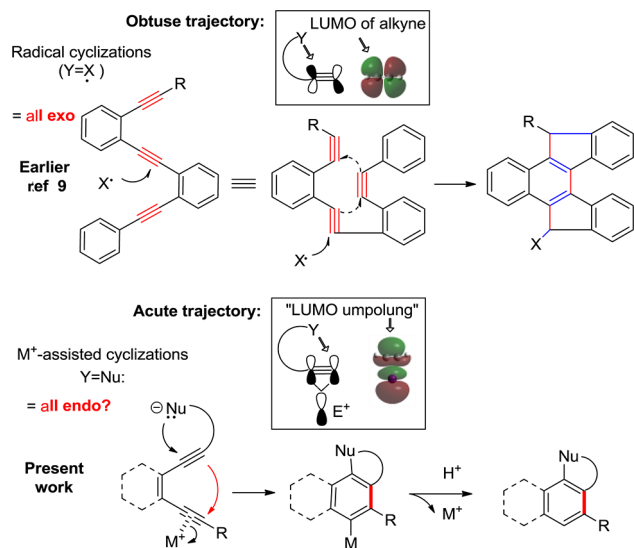


Figure 1. Preferred trajectories for alkyne cyclizations and the possible switch from the “all-*exo*” radical cascade to the “all-*endo*” metal-assisted cascade.

Guided by stereoelectronic reasons (“the LUMO-umpolung”) for the switch to *endo* selectivity in alkyne cyclizations when an alkyne coordinates to an external Lewis acid (“electrophile-assisted cyclizations”)⁸ and intrigued by the expanding list of Au-mediated organic approaches toward polycyclic compounds,¹¹ we investigated the feasibility of a sequence which would involve *only endo-dig cyclizations* by merging three metal-catalyzed steps: (1) Sonogashira cross-coupling, (2) 5-*endo-dig* cyclization of *o*-alkynylphenols, and (3) Au-catalyzed alkyne cyclizations. We also tested whether this cascade can be expanded further via the participation of additional alkynes. These tandem transformations would allow benzofuran fusion to naphthalene, chrysene, and related polyaromatic cores. Tandem Sonogashira cross-coupling/5-*endo-dig* cyclization with a nucleophilic group at the ortho-position (e.g., –OH) has ample literature precedents.¹²

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Scheme 1. Synthesis of Enediynes

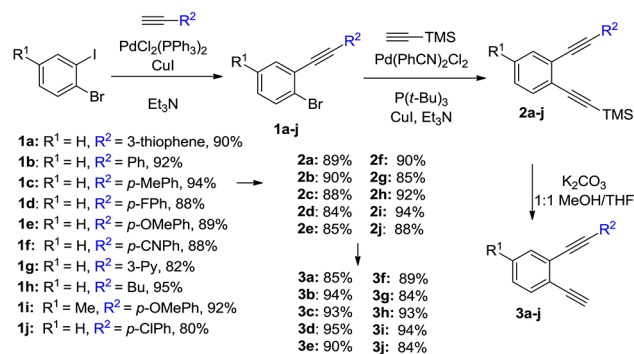


Table 1. Optimization of the Catalyst System

entry ^a	catalyst (%)	product: yield ^b (%)
1	PdCl ₂ (PPh ₃) ₂ 5% no Au	4a: 57%/5a: 0%
effect of Au:		
2	AuCl 5%	4a: 12%/5a: 0%
3	AuCl 10%	4a: 20%/5a: 0%
4	ClAuPPh ₃ 10%	4a: 19%/5a: 0%
5	AuCl ₃ 10%	4a: 10%/5a: 0%
effect of Ag:		
6	AgOTf 10%	4a: 19%/5a: 0%
7	AuCl 10%	4a: 13%/5a: 1%
8	AgOTf 10%	4a: 32%/5a: 16%
9	ClAuPPh ₃ 10%	4a: 22%/5a: 12%
10	ClAuPPh ₃ 10%	4a: 57%/5a: 21%
effect of base:		
11 ^c	ClAuPPh ₃ 10%	4a: 64%/5a: 11%
12 ^d	AgOTf 10%	4a: 0%/5a: 0%
effect of metals:		
13	ClAuPPh ₃ 10%	4a: 18%/5a: 0%
14 ^e	AgOTf 10%	4a: 15%/5a: 0%
15 ^e	ClAuPPh ₃ 10%	4a: 5%/5a: 0%

^a 0.1 M substrate in *o*-xylene and 2 equiv of triethylamine were used unless stated otherwise. All reactions were run for 8 h. ^b Yields were determined by ¹H NMR except, for example, **9**, where the product was isolated. ^c 1 equiv of Et₃N. ^d K₂CO₃ was used as a base. ^e Reaction was run without PdCl₂(PPh₃)₂.

Our challenge was in extending the cyclization process past the initial 5-*endo-dig* cyclization toward annealing additional

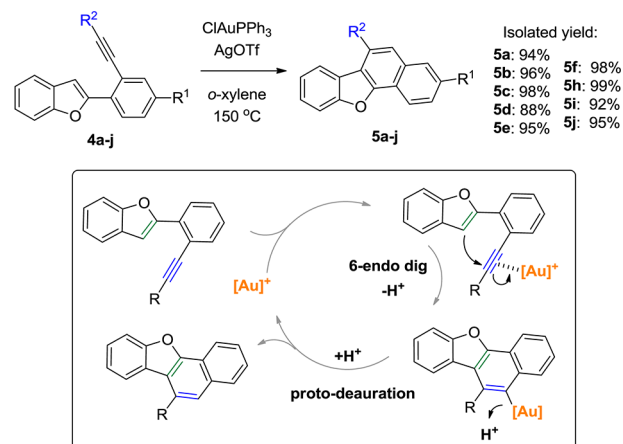
Table 2. Tandem Sonogashira/Cascade of Substituted Eneidyne

entry	enediynes	product: yield ^a
1	3a	4a: 57% 5a: 21%
2	3b	4b: 65% 5b: 24%
3	3c	4c: 62% 5c: 29%
4	3d	4d: 47% 5d: 18%
5	3e	4e: 56% 5e: 32%
6	3f	4f: 63% 5f: 27%
7	3g	4g: 54% 5g: 0%
8	3h	4h: 68% 5h: 23%
9	3i	4i: 50% 5i: 21%
10	3j	4j: 45% 5j: 24%

^a Isolated yield (%).

aromatic rings and extending the conjugated framework. In our strategy, we were guided by the work of Ohno and co-workers, which demonstrated the efficiency of Au-catalyzed

Scheme 2. Au-Assisted 6-endo-dig Cyclization



hydroamination/hydroarylation cascades for the preparation of fused indoles and carbazoles.¹³ Wu et al. have demonstrated the utility of similar cascades mediated by iodine.¹⁴ Hashmi used Au(I) catalysis for the synthesis of naphthalene derivatives from enediynes.¹⁵

The library of enediynes was prepared using the differentiated reactivity of the two halogen atoms of 2-bromoiodobenzene in Sonogashira reactions. The aryl iodide was coupled at room temperature under standard Sonogashira conditions using $\text{PdCl}_2(\text{PPh}_3)_2$ and CuI in triethylamine, whereas subsequent coupling with the less reactive aryl bromide necessitated $\text{Pd}(\text{PhCN})_2\text{Cl}_2/\text{P}(t\text{-Bu})_3$ as catalyst with the bulky electron-rich ligand (Scheme 1).¹⁶

Conditions for the cyclization cascades were optimized using 3-((2-ethynylphenyl)ethynyl)thiophene as a model substrate (Table 1). In the presence of Au species, the use of standard Sonogashira solvents (i.e., neat amines) gave low yields of the monocyclized 5-endo product. Use of only 2 equiv of base along with *o*-xylene as a high-boiling solvent increased the benzofuran yield to 57%. In the absence of Pd the yields were dramatically decreased (entries 14 and 15).¹⁷ Formation of homocoupled products due to the Hay reaction was minimized by utilizing Cu-free conditions. Although addition of Au(I) and Au(III) species decreased the efficiency of benzofuran formation, the addition of Ag salts restored the reactivity.

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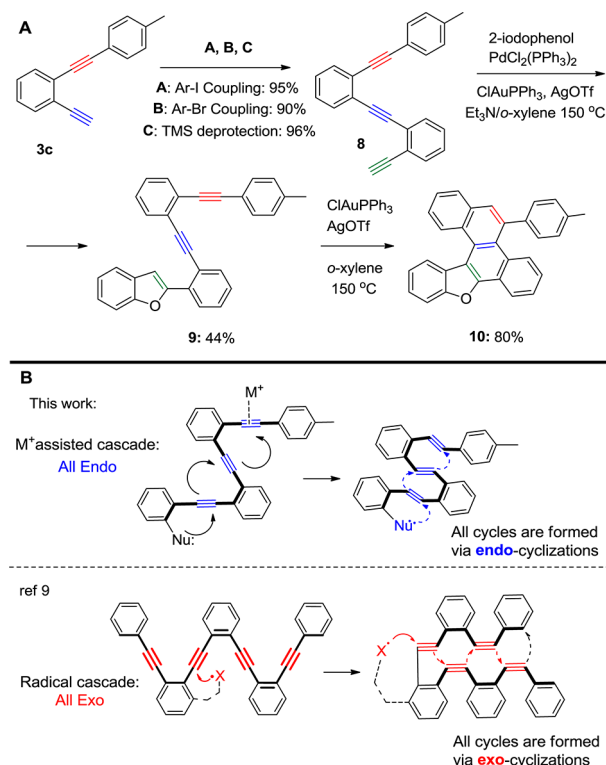


Figure 2. Triyne synthesis and cascade reaction with 2-iodophenol (A) and comparison of “all-exo” and “all-endo” strategies toward the preparation of graphene ribbons (B).

The 10% ClAuPPh₃/AgOTf system provided the first evidence that the full cascade is viable, albeit in a low yield. Better yields of the cascade products **5** were obtained when enediyne, 2-iodophenol, Et₃N, and PdCl₂(PPh₃)₂ were allowed to react in *o*-xylene for 1 h at room temperature before the addition of ClAuPPh₃/AgOTf and heating in a sealed tube.

The overall cascade merges the two metal-catalyzed transformations. First, 2-iodophenol cross-couples with a terminal alkyne via the classic Sonogashira path, followed by 5-*endo-dig* attack of oxygen at the activated alkyne (Table 2). In domino reactions of this nature, a variety of soft Lewis acidic metals can activate alkynes for an intramolecular nucleophilic attack.¹⁸

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In the second part of the transformation, gold(I) activates the alkyne toward the 6-*endo-dig* cyclization where the electron-rich furan moiety serves as a nucleophile (Scheme 2). Because the catalytic Au(I) species are regenerated by proto-deauration of the cyclized intermediates, the presence of base in the Sonogashira conditions may be responsible for the relative inefficiency of the full cascade by preventing protodemetalation.¹⁹ Alternatively, basic amines may inhibit the addition step by directly coordinating at gold.²⁰

Considering the two possible roles of the basic media, we heated the monocyclized substituted benzofurans in *o*-xylene with 10 mol % of ClAuPPh₃/AgOTf in the absence of base. Indeed, all intermediate products were converted into the full cascade product in excellent yields.

In order to extend the Au-catalyzed transformation further, triyne **8** was prepared from enediyne **3c**. Reaction of this triyne with 2-iodophenol under the Sonogashira conditions provided only traces of the full cascade product. However, after removal of the base, the 5-*endo* product underwent clean metal-assisted cascade ring closure induced by ClAuPPh₃/AgOTf in *o*-xylene. The intermediate products corresponding to monocyclization of the 5-*endo* product **9** were not observed (Figure 2).

In conclusion, cross-coupling of 2-iodophenol with a terminal enediyne or triyne sets up an “all-endo” cascade of alkyne cyclizations. The full cascade is more efficient in a two-step procedure that removes base but does not require further purification or isolation. The final alkyne cyclizations are promoted by ClAuPPh₃/AgOTf system in *o*-xylene at 150 °C. Future work will optimize reaction conditions for the cyclizations of extended *o*-alkyne oligomers in these domino reactions.

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Supporting Information Available. Full synthetic procedures, ¹H and ¹³C NMR spectra, and HRMS of all new compounds; gHMBC and gHMQC data for compound **5a** and **10**; UV-absorbance data for **5a–j** and **10**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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The authors declare no competing financial interest.