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Alkyne Origami: Folding Oligoalkynes into Polyaromatics

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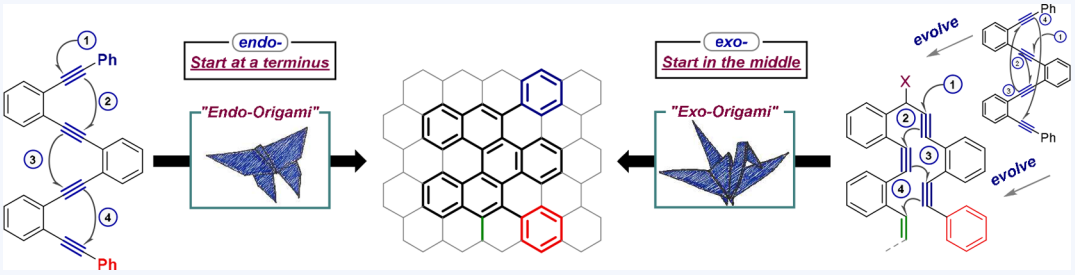

CONSPECTUS: *Do not bend the triple bonds!* This familiar undergraduate mantra must be disobeyed if the alkyne group is used as a building block in molecular construction. This Account will describe our exploits in "alkyne origami", that is, folding oligoalkynes into new shapes via cyclization cascades.

This research stems from a set of guidelines for the cyclizations of alkynes that we suggested in 2011 (Gilmore et al. *Chem. Rev.* **2011**, *111*, 6513; Alabugin et al. *J. Am. Chem. Soc.* **2011**, *133*, 12608). The guidelines blended critical analysis of ∼40 years of experimental research with computations into the comprehensive predictions of the relative favorability of dig-cyclizations of anions and radicals. In this Account, we will show how this new understanding has been instrumental in building polyaromatics. In particular, we illustrate the utility of these stereoelectronic models by developing a toolbox of practical, selective, and efficient synthetic transformations.

The high energy and high carbon content render alkynes the perfect precursors for the preparation of polyaromatic ribbons and other carbon-rich materials with precisely controlled structure and reactivity. Still, the paradox of alkyne reactivity (alkynes store a lot of energy but are protected kinetically by their relatively strong π-bonds) requires precise use of stereoelectronic factors for lowering the activation barriers for alkyne cyclizations. These factors are drastically different in the "all-exo" and the "all-endo" cyclization cascades of oligoynes. This Account will highlight the interplay between the stereoelectronics of bond formation and topology of acyclic precursor "folding" into a polycyclic ribbon.

The topology of folding is simpler for the endo cascades, which are compatible with initiation either at the edge or at the center. In contrast, the exo cascades require precise folding of an oligoalkyne ribbon by starting the cascade exactly at the center of the chain. These differences define the key challenges in the design of these two types of alkyne cyclization cascades.

For the endo processes, the folding is simple, but these processes require a strategy ("LUMO Umpolung") for inverting the usual stereoelectronic requirements of alkyne cyclizations. We also show how alkenes can be used as alkyne equivalents in cyclizations coupled with fragmentations and how one can make endo cyclization products without ever going through an endo cyclization. In contrast, each elementary step of the exo cascades benefits from the inherent exo preference for the radical attack, but these cascades require precise initiation by starting exactly at the central alkyne unit of the oligoyne. This strict selectivity requirement led to the development of traceless directing groups capable of supramolecular assistance to the initiation step and self-terminating departure at the end of the cascade. With attention to electronic effects that can stop radical cascades, oligoalkynes can be selectively converted into precisely shaped and functionalized polyaromatic products. The generality of these concepts is further illustrated by the development of radical "peri annulations" at the zigzag edge of acenes.

INTRODUCTION

The renaissance in the classic field of polyaromatic chemistry has been fueled by the discoveries of remarkable 2D and 3D carbon-rich polyaromatic materials. The transformative potential of these molecular architectures in different areas of materials science calls for new practical strategies for the construction of precisely shaped and functionalized polyaromatic subunits.

The goal of this Account is to illustrate the unique advantages offered for the construction of carbon-rich polycyclic structures from alkyne building blocks. Earlier, we have outlined stereoelectronic advantages of alkynes and their unusual applications as dicarbene analogues and as a "hydrocarbon door" into carbonyl chemistry.[1] In this Account, we will focus on the utility of alkynes as a *high-energy carbon-rich* functionality with stereoelectronic features that can control selectivity of cyclization cascades.

ALKENES AND ALKYNES AS HIGH ENERGY FUNCTIONAL GROUPS

It is not always appreciated how much energy is stored in a π-bond. One can evaluate this energy from the following thought

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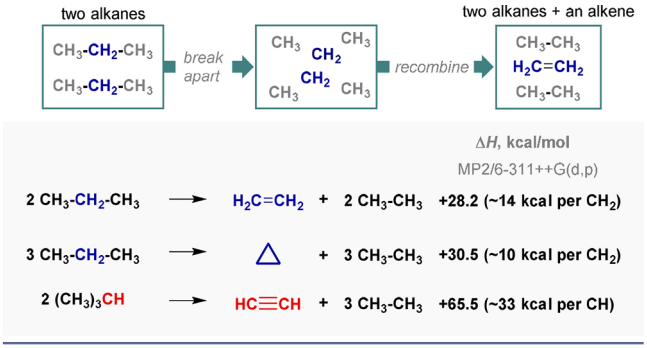
experiment. Let us "reshuffle" two propane molecules by taking out the two central CH_2 groups to form ethylene and combining the remaining four methyl groups to form two ethane molecules (Scheme 1). Because propane and ethane are nearly strain free, the +28 kcal/mol energy of this hypothetical transformation reflects the thermodynamic cost of making a double bond.[2] Remarkably, the total energy content of cyclopropane, a poster-child for high-energy functionalities, is only slightly higher (30 kcal/mol). This comparison shows that, *per carbon*, one can store 40% more energy (~14 kcal/mol) in ethylene than in cyclopropane (~10 kcal/mol). The π-bond clearly qualifies as a high energy functionality.

Scheme 1. Computed Energies for Selected "High-Energy Functionalities"



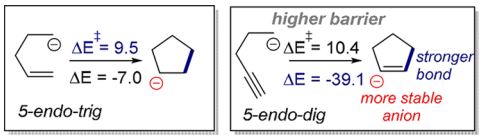
In a similar way, but with 2-methylpropane as a reference point, one can estimate the energy content of ethyne relative to the alkane references. Impressively, the total energy associated with the alkyne formation exceeds 60 kcal/mol, approaching the energy of an excited state! Not surprisingly, many alkyne reactions are highly exergonic and irreversible.

The importance of the energy content is illustrated by comparison of approaches to the aromatic ring formation shown in Scheme 2. In contrast to the ~150 kcal/mol exothermic alkyne trimerization, the "benzene × 3" route remains 7 kcal/mol endothermic even after the initially lost aromaticity is restored. In alkynes, as one set of π-bonds is used to make the new σ-bonds, the other one maintains π-conjugation. In this approach, alkynes serve as "two functional groups in one package"[1] and a perfect carbon-rich "glue" for molecular assembly. Substituting just one benzene with an alkyne dramatically decreases energy penalties relative to the "alkyne-free" π-routes (Scheme 2). However, despite the very favorable thermodynamics, control of alkyne reactivity is far from being trivial. In fact, alkynes have a surprising idiosyncrasy discussed in the next section.

THE PARADOX OF ALKYNE REACTIVITY

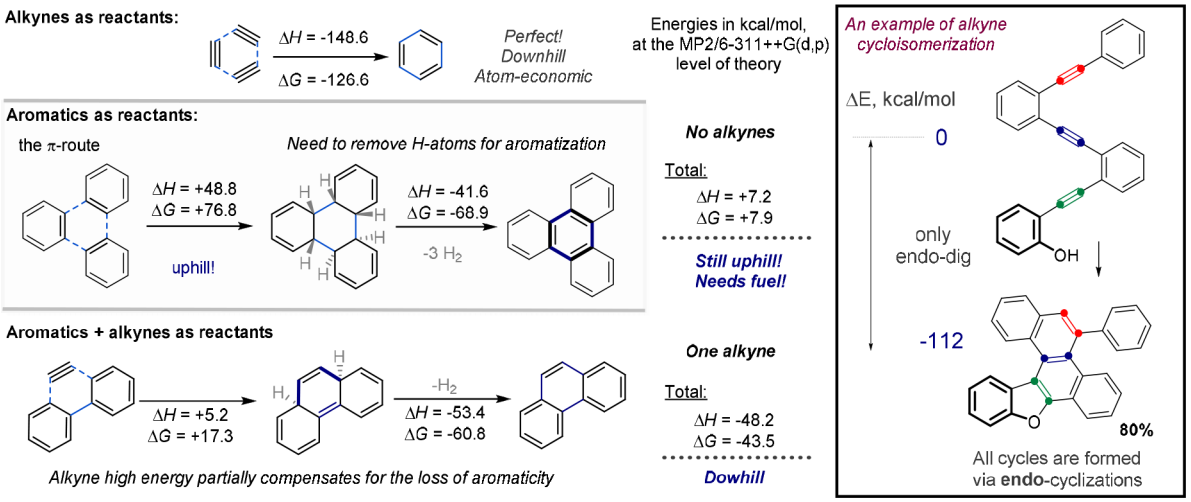
The paradox of alkyne reactivity is illustrated by Scheme 3, where the two analogous reactions of alkenes and alkynes (5-endo-trig and 5-endo-dig cyclizations) have opposite kinetic and thermodynamic favorabilities. The alkene cyclization has a lower barrier even though the alkyne cyclization is 32 kcal/mol more favorable thermodynamically.[3] This example is not an aberration: the disconnect between thermodynamic and kinetic stabilities of alkyne is general; despite the more favorable thermodynamics, alkyne reactions are often slower than the analogous alkene transformations. The origin of this paradox lies in the fact that the shorter alkyne π-bonds are *stronger* than the alkene π-bonds.

Scheme 3. Paradox of Alkyne Reactivity: Higher Barriers for More Exergonic Reactions!



The above statement may, at first glance, seem to be at odds with the greater exothermicity of alkyne reactions. This seeming discrepancy is observed because the differences in reaction energies are dominated by energies of the newly formed σ-bonds. For hydrogenation of acetylene and ethylene, for example, each of the two new sp^2 C−H bonds formed in the hydrogenation of ethyne is ~11 kcal/mol stronger than the sp^3 C−H bonds in the analogous ethene hydrogenation.[4] This analysis illustrates that the loss of a π-bond in ethyne costs 12 kcal/mol *more* than the loss of a π-bond in ethene. Alkynes react slower because π-bond *breaking* is more advanced than σ-bond *formation* in the early TSs of exergonic reactions. This peculiar combination of thermodynamic instability with the relative kinetic inertness stresses the

Scheme 2. (left) Atom-Economic Assembly of Aromatic Rings from Alkynes Is Exergonic whereas Use of Aromatic Building Blocks Involves Intermediate High Energy Stages and (right) Representative Alkyne Cascade from This Account



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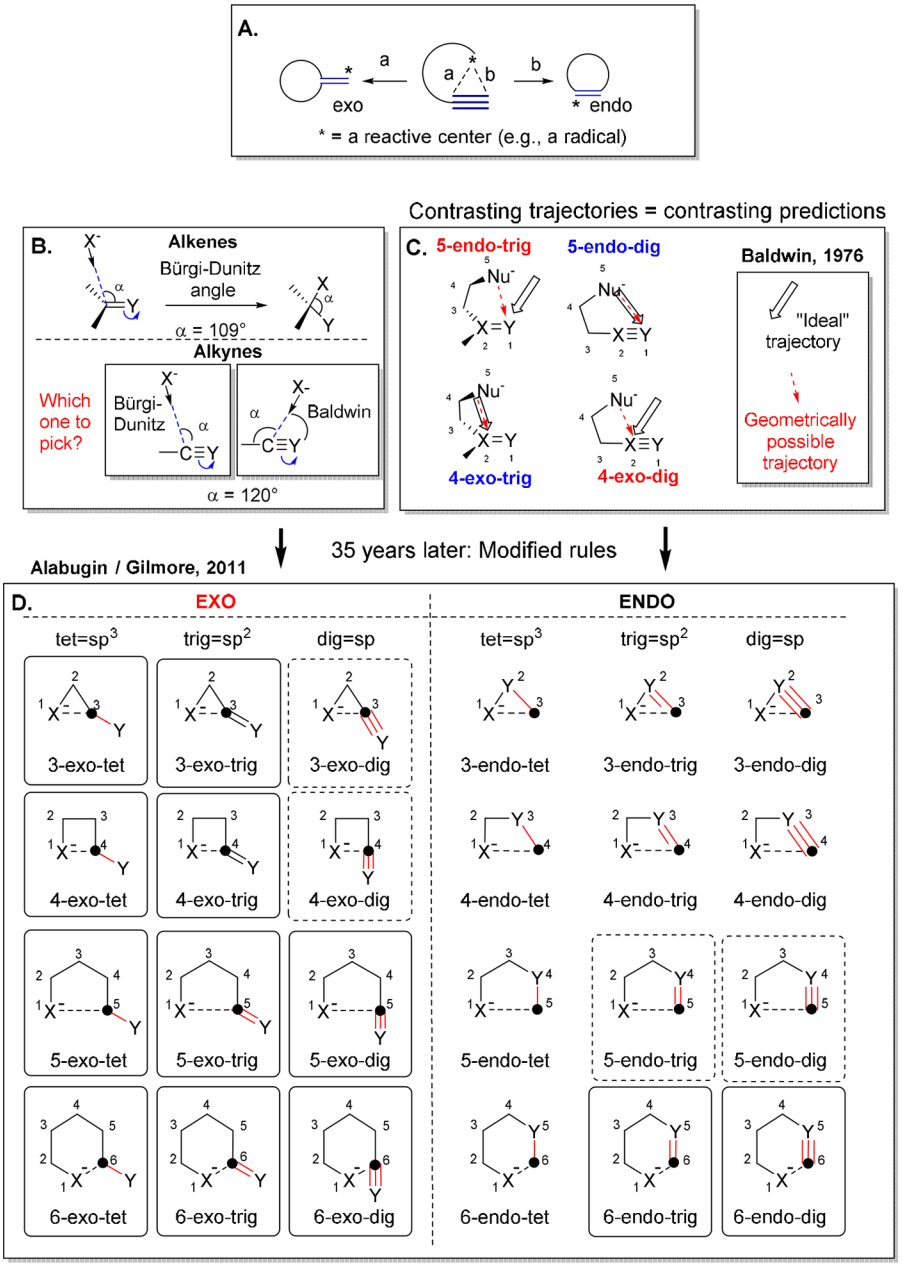
Scheme 4. (A) Exo and Endo Cyclizations of an Alkyne, (B) Possible Trajectories for Nucleophilic Attack at a π-Bond, (C) Contrasting Predictions for Alkene and Alkyne Cyclizations Based on the Acute Trajectory for Alkynes, and (D) Baldwin's Nomenclature and the Updated List of Favorable and Unfavorable Modes of Nucleophilic and Radical Cyclization[a]



[a]Favorable reactions are boxed with solid lines; the borderline reactions, which require additional assistance, are boxed with dashed lines.

importance of fundamental understanding of reactions at the triple bond.

THE FUNDAMENTALS OF ALKYNE REACTIVITY: STEREOELECTRONICS, TRAJECTORIES, AND THE EXO/ENDO DILEMMA

What is known about alkyne reactivity in the context of making a cycle? In cyclizations, intramolecular constraints impose geometric restrictions on the electronically preferred trajectories for the formation of chemical bonds. Any intramolecular attack at any two-atom functionality (such as an alkyne in Scheme 4A) can proceed in two different ways: (a) making a bond at the internal atom, with the breaking bond outside of the forming cycle (i.e., the exo cyclization) and (b) making a bond at the external atom, so the breaking bond is inside of the forming cycle (i.e., the endo cyclization).

The regioselectivity of alkyne cyclizations has been controversial. The classic Baldwin rules for the design of cyclizations were based on the notion that nucleophilic addition to alkenes and alkynes should follow different trajectories.[5] Nucleophilic attack at alkynes was suggested to follow an acute trajectory in sharp contrast to the obtuse "Burgi–Dunitz" trajectory for the nucleophilic attack on double bonds (Scheme 4B).

Combination of different trajectories with intramolecular geometric restraints led to the historical guidelines for the cyclizations of sp^2 (trig) and sp (dig) systems (Scheme 4C).

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For example, 5-endo cyclizations were predicted to be favorable for alkynes but unfavorable for alkenes. For the same stereoelectronic reasons, 4-exo-trig cyclizations were classified as favorable in contrast to 4-exo-dig cyclizations.[6] Although the dramatic differences between alkenes and alkynes in the original Baldwin rules appealed to chemical imagination, it was challenging to explain why alkenes and alkynes, the chemical cousins, behave so differently in cyclizations.

REDESIGN OF THE CYCLIZATION RULES: EXO-DIG CYCLIZATIONS ARE FAVORABLE

We turned to the Baldwin rules[5] in studies of reductive C1−C5 photocyclization of enediynes,[6] a key process in the design of a record-breaking family of double-strand DNA photocleavers.[7] Among the possible mechanisms, we considered a 5-endo-dig closure. Surprisingly, computational analysis found that 4-exo-dig cyclizations, "unfavorable" by the rules, are kinetically competitive with 5-endo-dig closures.[8] Subsequent experimental work confirmed these predictions; only with selective TS stabilization could we obtain high yields of the 5-endo products.[9] Subsequent computational studies[1] reevaluated the cyclization guidelines for alkenes and alkynes and found them to be similar (Scheme 4D). Accordingly, the Burgi−Dunitz approach is the favored trajectory for *both* the alkyne and alkene reactions,[1] accounting for the general stereoelectronic preference of exo cyclizations.[10]

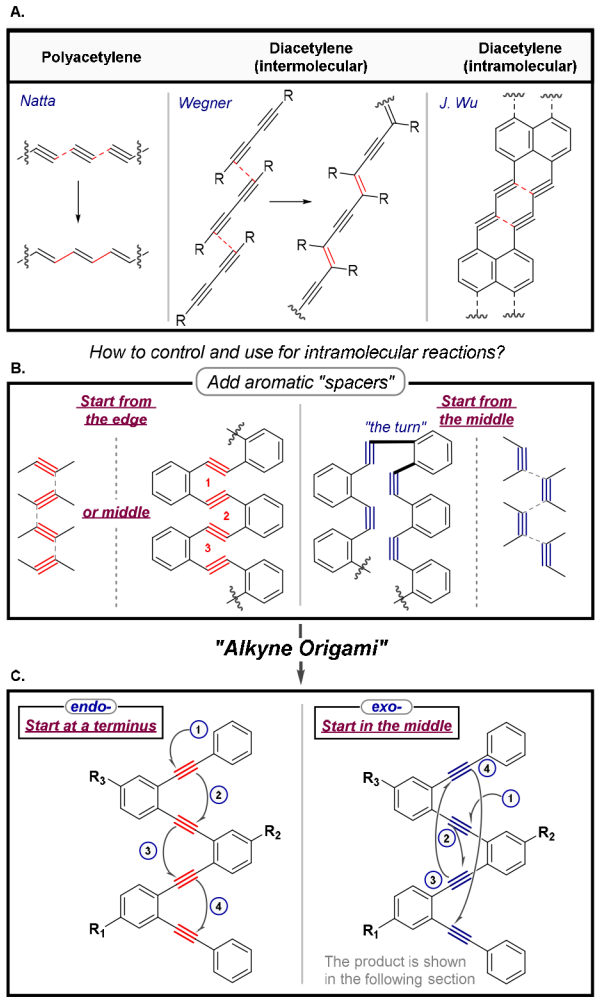
THE ALL-EXO AND ALL-ENDO ROUTES FOR OLIGOALKYNE CASCADES

Armed with a better understanding of stereoelectronics of alkyne cyclizations, we decided to take advantage of this conceptual framework for the design of new reactions. We focused on cascade cyclizations due to their efficiency, quick increase in molecular complexity, and atom-economy.

Use of acetylenes in intermolecular cascade transformations has a long history, from polyacetylene to the topochemical polymerizations of diacetylenes (Scheme 5A).[11] Our goal was to use it in intramolecular settings for making well-defined *molecular* products[12] instead of polymeric networks. We reasoned that aromatic spacers/scaffolds can provide several advantages for organizing the intramolecular cascades (Scheme 5B). Not only can they control the spatial orientation and proximity of the reacting groups, but they can also increase precursor stability, minimize error propagation, and prevent interstrand/cross-link reactions.

Considering the basic folding patterns, it is apparent that an o-poly(phenylene ethynylene) chain can be transformed into a polyaromatic system via two distinctly different topologies, that is, the "all-exo" and "all-endo" routes in Scheme 5C. These two routes have different initiation requirements. To reach full conversion of the alkyne units into an aromatic ribbon, the all-exo cascade must start at the center. As the cascade propagates, the alkyne chain continuously folds, bringing the two termini of the chain together. The folding process is easily "corruptible": attack at any position other than the central alkyne will lead to an incomplete conversion of alkynes into cycles (like a "broken zipper" cascade shown for comparison as the result of an "off-center" initiation step, Scheme 6A). In contrast, the all-endo cascades can either start at the beginning of the oligoalkyne chain and propagate to the opposite end *through* the center or propagate from the middle to the termini, still yielding the perfectly hexagonal cyclic arrays.

Scheme 5. From Alternative Polyacetylene Formation Patterns to the Design of All-Exo and All-Endo Alkyne Cascades Cyclizations



"ALL-EXO CASCADES": EVOLVING DESIGNS FOR SELECTIVE ACTIVATION AND "DEFECT" ELIMINATION

Although the topologically challenging exo cascades in Scheme 5 may look confusing, the key exo-dig step is favorable for radicals. Hence, we decided to explore exo-dig radical cascades of oligoalkynes. Radical cascades have an inherent advantage because the translocation of the radical center due to the formation of new bonds is not associated with the physical transport of a counterion. The challenge that we had to address first was the chemoselectivity of the initial attack at the oligoalkyne chain.

Selectivity

The requirement for activation in the center is crucial for driving the cascade to completion and assuring that each of the alkynes participates in the ring-forming step. Scheme 6 illustrates again how the final polycyclic structure is created by continuous folding of the oligoalkyne backbone, each step initiated by the 6-exo attack of the newly relocated radical center at the next alkyne. The folding starts from the center and continues until the ends meet, creating a fully conjugated ribbon. An off-center initiation misaligns the reacting ends: the radical relocation along the chain of the forming bonds will eventually bring the radical center to the point where no triple bond is waiting. At this stage, a

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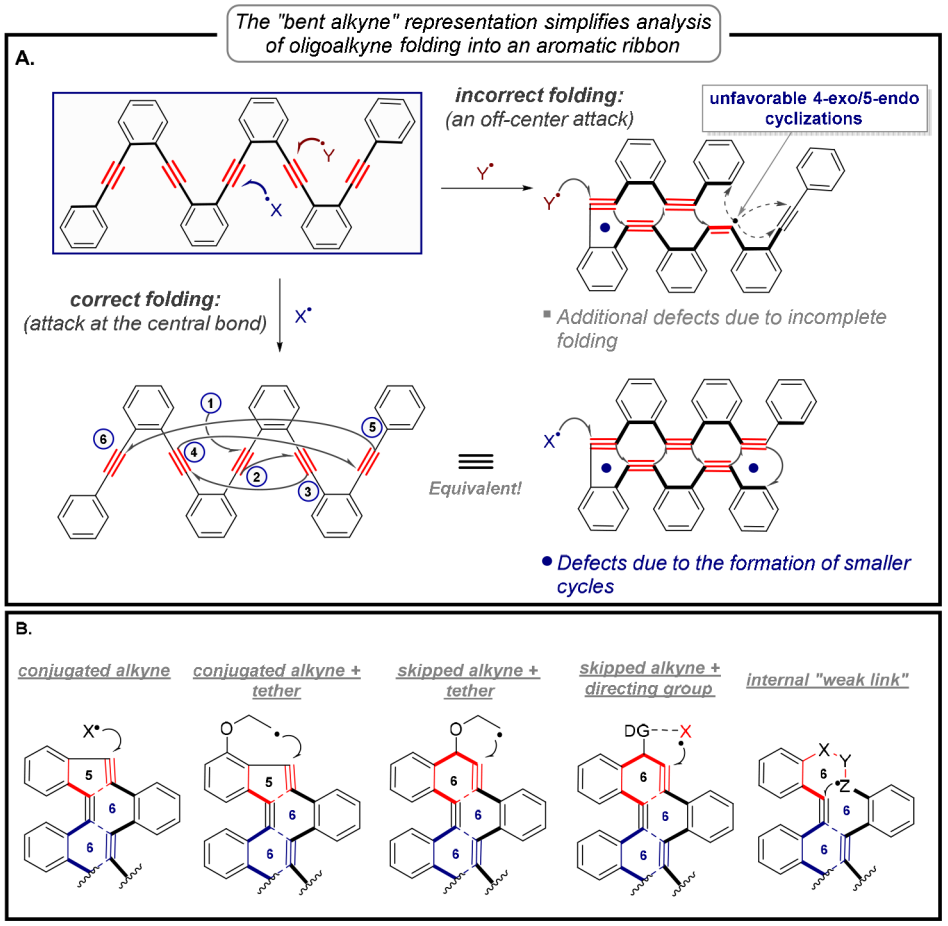
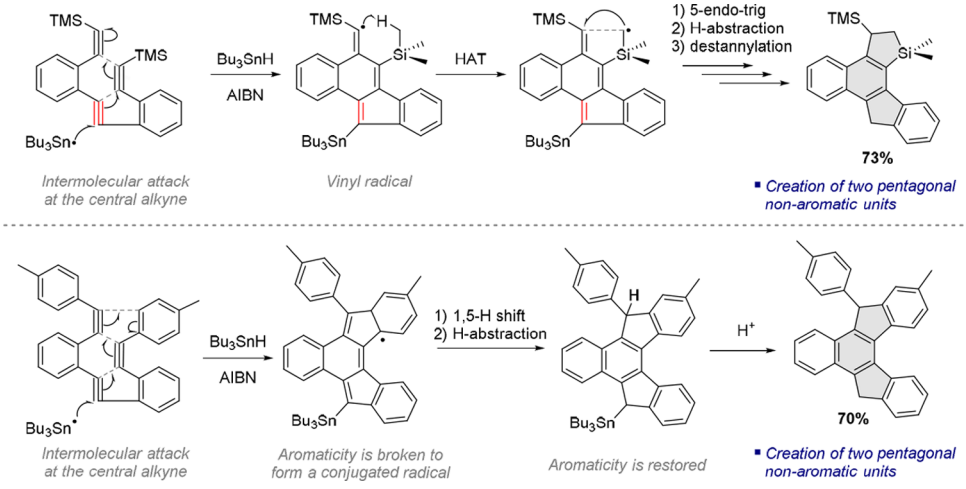
Scheme 6. (A) Problem of Selectivity in Oligoalkyne Cascades and (B) Selected Strategies for Achieving Such Selectivity by Variations in the Structures of Alkyne Reactants: Conjugated versus Skipped Oligoalkynes, with versus without Tethered Initiators, and with External versus Internal Initiator



Scheme 7. Contrasting Cascade Termination in the Presence of TMS and Phenyl Substituents



6-exo-dig cyclization is impossible, and the cascade is terminated prematurely.

Despite the discouraging literature precedents,[13] no additional means for selectivity control were needed in the Bu_3Sn-mediated radical cyclizations of o-phenylene ethynylenes with three nearly identical triple bonds.[14] Notwithstanding the statistical disadvantage, the attack at the central alkyne was favored over the attack at the two external alkynes. Extension of the radical cascade by reaction with the terminal Ar or TMS substituents is outlined in Scheme 7.

However, the same conditions produced unattractive mixtures of products from longer oligoynes, suggesting that the problem of chemoselectivity is crucial for the practical expansion of these cascades.

To address the selectivity problem, we have utilized a "weak link" (a chemically orthogonal group, COG) tethered to the

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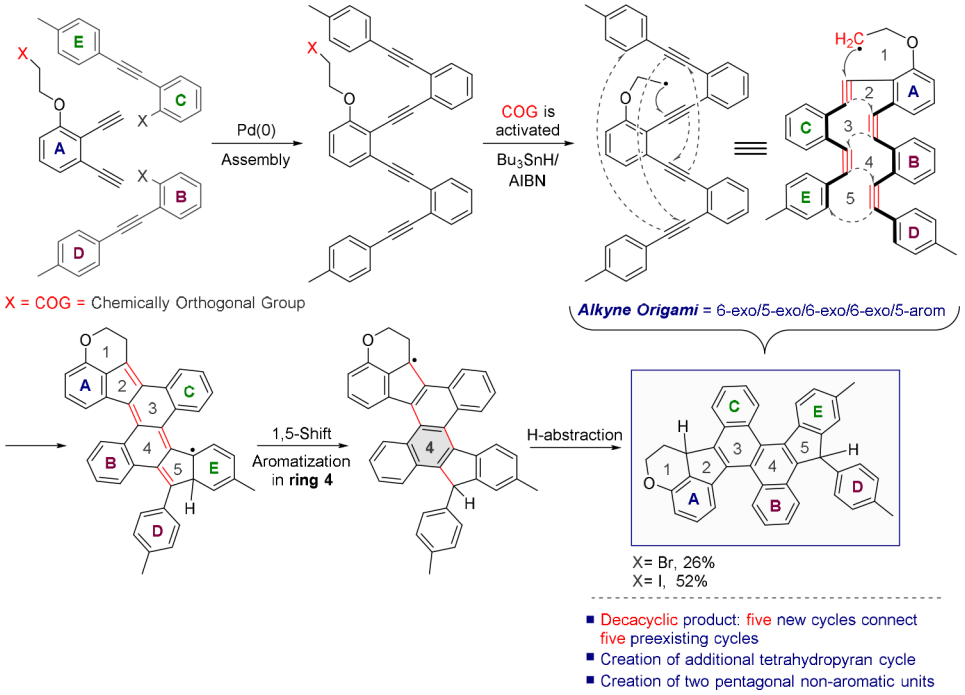
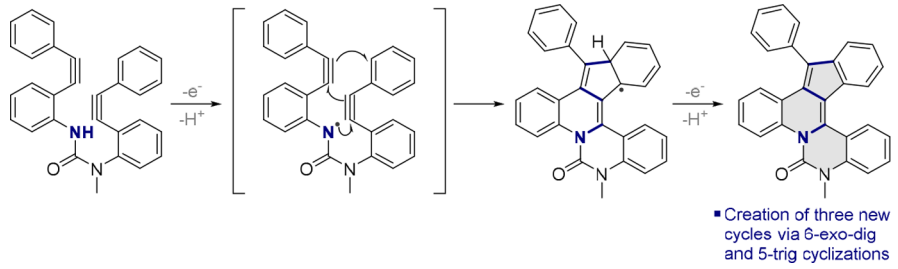
Scheme 8. This "Proof-of-Principle" Initiation Clearly Confirmed That, If the Problem of Selectivity Is Properly Addressed, The Extended Cascades Are Possible, but It Also Called for an Improved Substrate Design to Avoid the Three Structural Defects (Partially Reduced Cycles) in the Ribbon



Scheme 9. Synthesis of Polycyclic *N*-Heteroaromatics through an Electrochemical Cascade



central aromatic ring, so the radical formed from the COG can only reach the central alkyne unit.[15] In a proof-of-principle experiment with a C–I COG, the all-exo-dig cascade proceeded as designed, providing a decacyclic product after five consecutive cyclizations in 52% yield (93% per step, Scheme 8).

The presence of the additional ring from the initiator is not always a disadvantage, and further synthetic opportunities to use it creatively undoubtedly exist. For example, Xu and co-workers[16] demonstrated the nascent power of electrochemical activation for inducing selective transformations of diynes to *N*-heteroaromatics (Scheme 9). Under the electrochemical conditions, the cascade is terminated in a different manner than in the Sn-mediated cyclizations: the final five-membered ring remains conjugated (presumably via an oxidation/deprotonation sequence). Initiation by a N-centered radical positioned inside of the forming ribbon led to formal N-doping of the product.

THE ADVANTAGE OF SKIPPED OLIGOALKYNES

An observant reader has probably noticed that the fully folded ribbons formed from a conjugated oligoalkyne must include two pentagonal "defects". The first defect is formed from a 5-exo-dig cyclization at the beginning of the ribbon-forming cascade. A logical way to avoid formation of this five-membered ring is to start with a "skipped" oligoalkyne where the first triple bond is separated from the aromatic backbone by an extra atom. In this design, the first reaction between the two alkynes would follow a 6-exo path.

Reemploying the "Weak Link"

Because the 6-exo-dig cyclization is expected to be slower than its 5-exo-dig counterpart, we decided to minimize the unknowns and started by equipping skipped oligoalkynes with the same pendant C–I COG. The resulting process is outlined in Scheme 10. Formation of a single regioisomer from the β-naphthyl substrate distinguishes between the two possible pathways for the formation of the final ring. In the first scenario, the vinyl radical attacks the π system of the terminal phenyl group. Alternatively, the same radical could abstract a hydrogen from an aromatic C–H bond and the "translocated" aryl radical attacks back the alkene moiety via a 5-endo-trig cyclization. Only the first mechanism agrees with the observed isomer that originates from the favorable radical attack at the naphthalene. This mechanistic insight was helpful later for creating an approach to "defect-free" ribbons (vide infra).

These experiments also indicated that the first six-membered ring formed from skipped alkynes can aromatize under the

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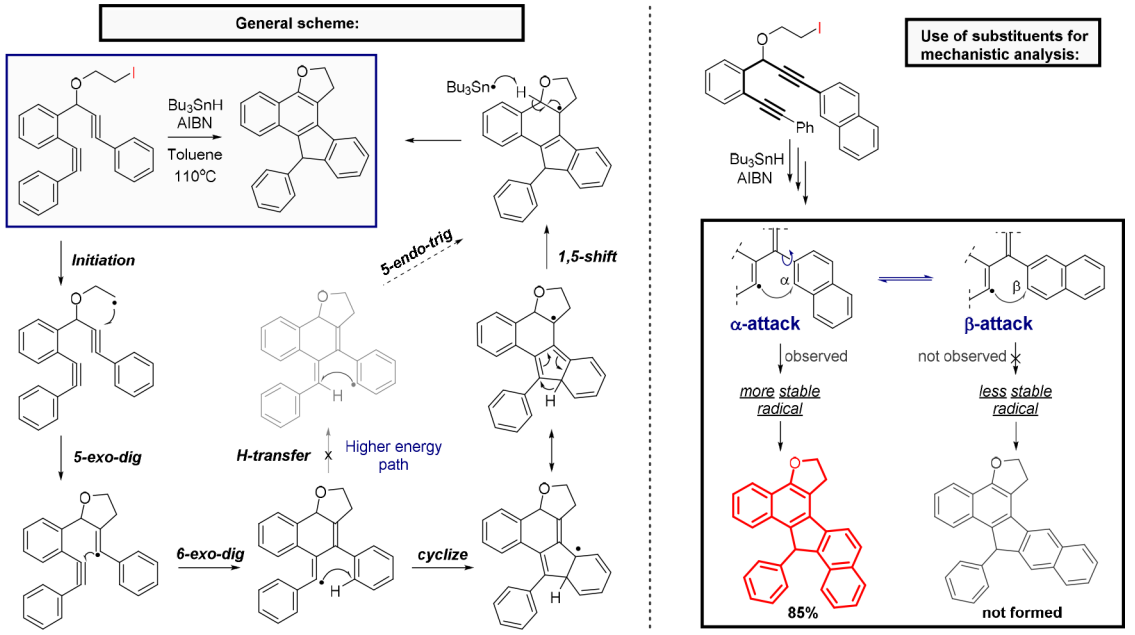
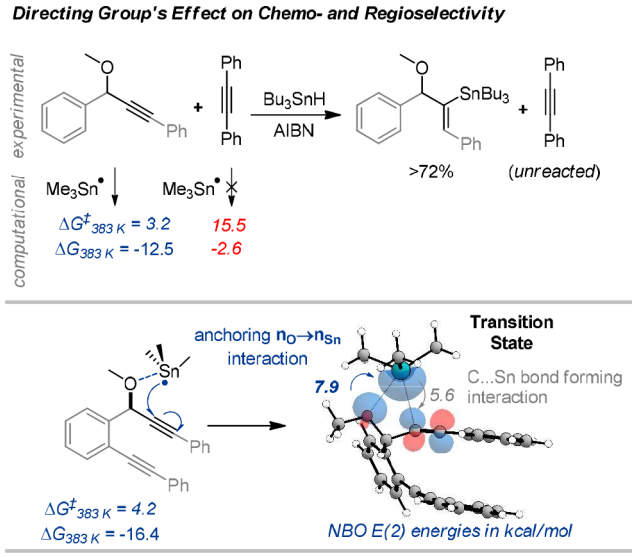
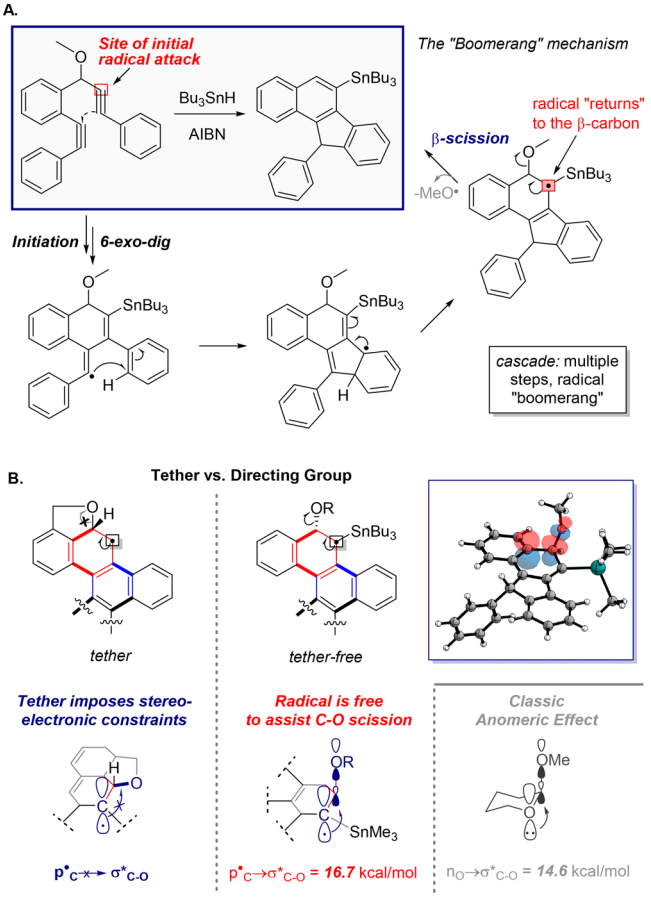
Scheme 10. Mechanistic Scenarios for the Cyclizations of Skipped Diynes



Scheme 11. Radical Addition to Propargylic Ethers Is Assisted by Supramolecular Interactions



Scheme 12. (A) Radical Journey Leads to a Boomerang Translocation and Scission of the Directing Group and (B) Radical Orbital Alignment with σ^*_{C-O} Weakens the C−O Bond



reaction conditions. Furthermore, the five-membered ring introduced by the tether can also be aromatized, hence offering potential access to fused furans. However, for the purely benzenoic fusion, one must redesign this cascade to allow tether-free intermolecular activation described in the next section.

LOSING THE TETHER: USE OF REMOVABLE DIRECTING GROUPS IN BOOMERANG CASCADES

The Directing Effect

A supramolecular strategy for chemoselective reactions of oligoalkynes does not need to rely on a COG for initiation. Instead, it achieves selective *intermolecular* attack by using a propargylic alkoxy group as a chaperon for directing the Bu_3Sn radical at the correct alkyne target.

Although the directing effect of propargylic ethers at the Sn radical attack has been documented, its origin remained controversial.[17] Our experiments confirmed that the Sn radical attack at the propargylic position is preferred over the addition to tolane, and our computations found that the respective free energy barrier is ~10 kcal/mol lower.[18] The low TS energy stems

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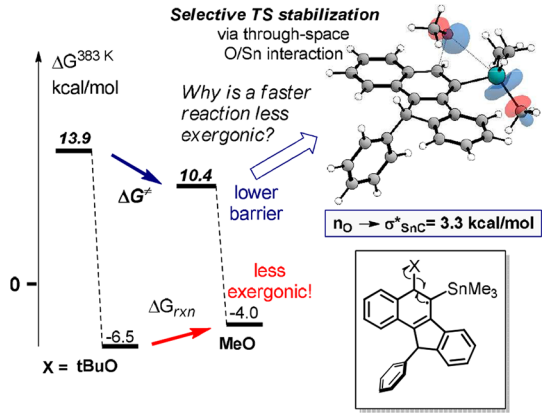
Scheme 13. Uncoupling Kinetics from Thermodynamics: Steric Decompression Is Assisted by through-Space Sn/O Interaction



from synergy of through-space interactions between the substrate and the radical shown in Scheme 11. Natural bond orbital (NBO) analysis highlighted the role of three-electron interactions between the lone pair of oxygen and the Sn radical orbital in the observed TS stabilization. In this scenario, oxygen guides the radical attack by anchoring the radical next to the target. Synergy between the Sn−O and Sn−C interactions decreases the entropic penalty for the formation of supramolecular contacts.

Without a Trace: Elimination of the Directing Group via Homolytic C−O Scission

The mechanistic path for the cascade illustrates that the directing group is expelled in the last step of the cascade, with concomitant aromatization of the newly formed polycyclic ribbon.[19] This expulsion is efficient because the sequence of bond forming and bond breaking steps in the cascade is precisely coordinated (Scheme 12). The journey of the radical center through the molecule returns it, like a boomerang, to the position of the initial intermolecular radical attack. This is exactly where the radical needs to be to assist in the β-scission that severs the C−O bond toward the directing group.

The final aromatization is assisted by a combination of steric decompression and stereoelectronic effects that facilitate direct elimination of an alkoxy radical. The lack of intramolecular constraints by the tether offers a stereoelectronic advantage since the Bu_3Sn moiety forces the free OR bond to adopt a geometry where the C−O bond is aligned with the radical. This alignment weakens the C−O bond and facilitates removal of the directing group. An unusual through-space attractive $n_O \rightarrow \sigma^*_{Sn-C}$ interaction provides significant stabilization to the fragmentation TS, explaining why the least "sterically loaded" reactant undergoes the fastest fragmentation (Scheme 13).[20]

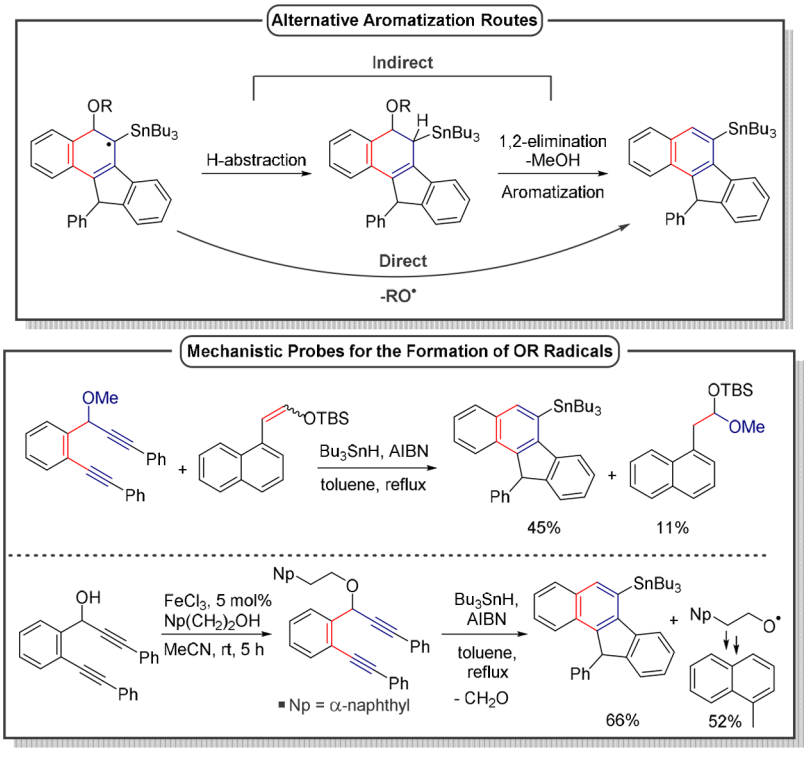
Direct experimental evidence for the homolytic C−O bond scission was provided by intermolecular trapping and by cascade fragmentations (Scheme 14). Such reactions provide a clear mechanistic fingerprint for the OR radicals.

Expansion to Longer Ribbons

The traceless directing group method worked as planned with the larger oligoalkyne systems. The success of the expanded cascades is consistent with the higher rate of the 6-exo-dig cyclization of the intermediate vinyl radicals relative to their attack at the aromatic ring (Scheme 15A).

Introduction of the fourth alkyne moiety adds a new level of structural complexity in the cascade products and leads to the fusion of two [5]helicenes: one made entirely of benzene rings and the other containing a pentagon. The preferred geometries of the two fused chirality units are strongly coupled: the two stable conformations correspond to the same chirality of the two helicenes (either P, P or M, M). The mismatched isomers are >5 kcal/mol higher in energy. In contrast, the effect of chirality

Scheme 14. Solving Mechanistic Dichotomy and Confirming OR-Radical Formation



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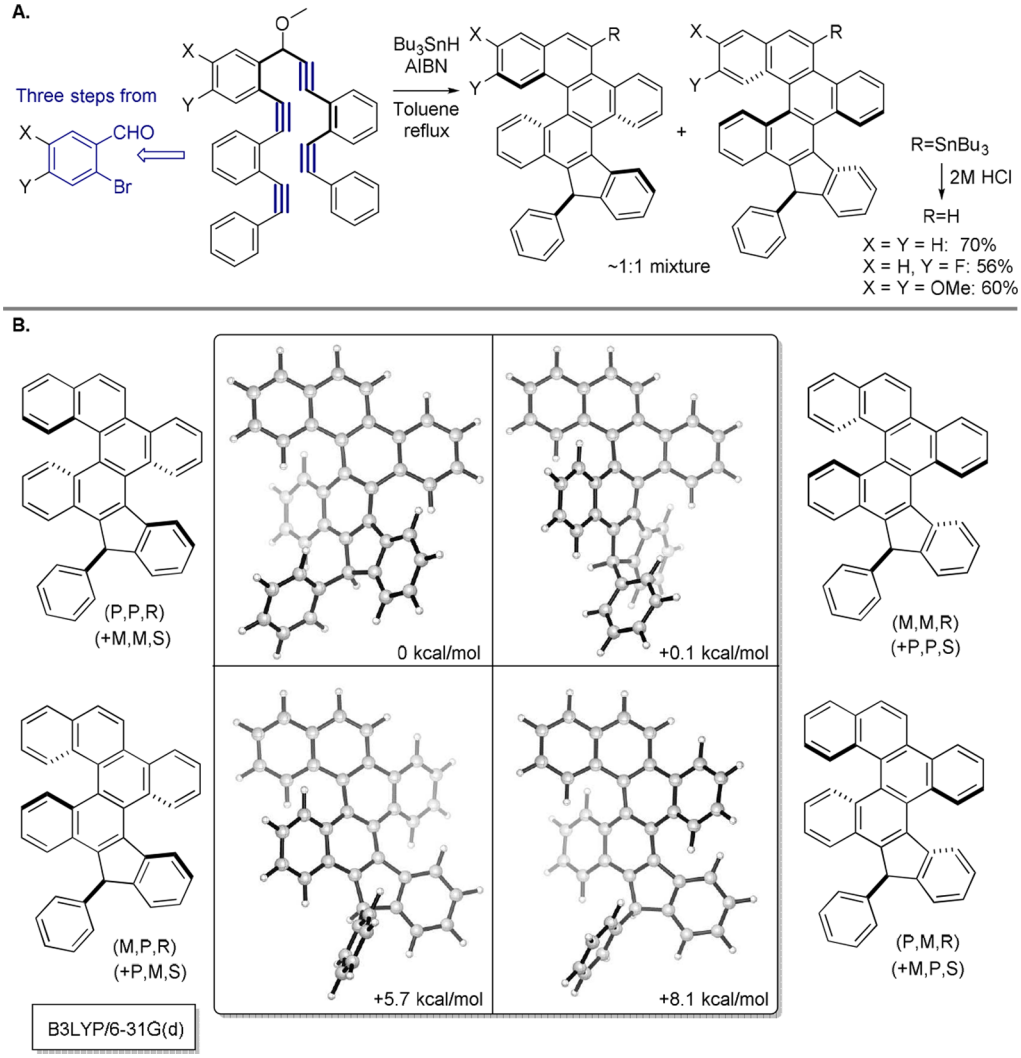
Scheme 15. (A) 4-Alkyne Cascade for the Synthesis of Two Fused [5]Helicenes and (B) Preferred Geometries of the Two Fused Chirality Units



at the asymmetric sp^3-carbon in the two stable stereoisomers is minor (~0.1 kcal/mol; Scheme 15B). Incorporation of a tin moiety allowed for further functionalization via cross-coupling reactions.

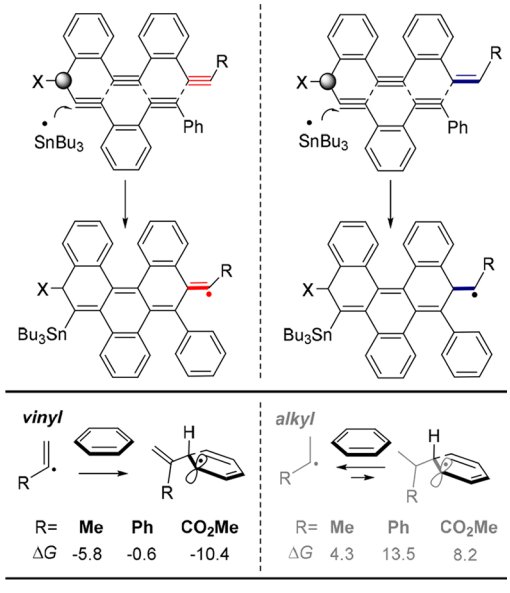
Removing the Terminal Pentagon

At the final stage, we concentrated on terminating the cascade without forming five-membered defects. The two choices included making a hexagon or not making any cycle at all. The latter idea was realized by using hybridization control over radical reactivity,[21] that is, by incorporating an alkene at the end of the cyclization path. A 6-exo-trig attack at the alkene forms an alkyl radical that is insufficiently reactive to attack the terminal aromatic ring (Scheme 16).[22]

This approach ensures that the final structure consists of only six-membered rings and opens a new avenue for the controlled preparation of polyaromatic ribbons (Scheme 17). The resulting ester functionality can be used for an additional Friedel–Crafts ring closure that effectively anneals a phenol cycle to the extended aromatic system formed by the radical cascade.

"Peri cyclizations" of vinyl radicals formed from propargylic ethers provide a viable strategy for benzannulation at the L-region of acenes. The initially formed cyclic products can be trapped via either a reductive or an oxidative path with the concomitant loss of the alkoxy directing group (Scheme 18).[23]

Scheme 16. Hybridization of the Final Radical (from Vinyl to Alkyl) Is Crucial for the Pentagon-Free Terminated Cascade To Occur



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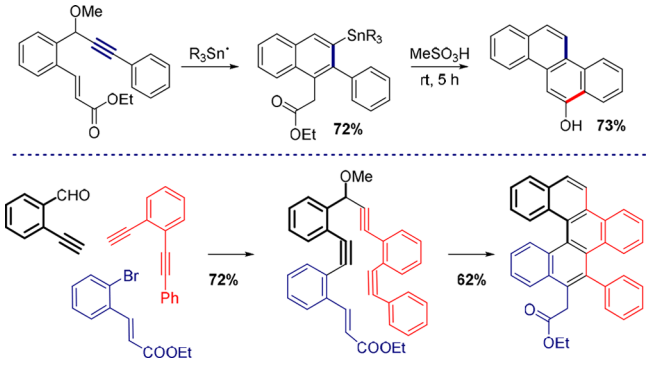
Scheme 17. Five-Step Cascade That Forms Six-Membered Rings Only[a]



[a]The pendant ester group can serve as a chemical handle in future transformations.

In summary, the first part of this Account described the evolution of radical all-exo cascades: from conjugated to skipped, from intramolecular (tethered COG) initiation to a supramolecular traceless directing group, and from the all-alkyne cascades to mixed cascades with alkene termination. In the next section, we get back to the all-endo cascades. *Do they have a chance?*

ROUTES TO ENDO-DIG PRODUCTS AND CYCLIZATION CASCADES

Consecutive endo cyclizations are appealing because they fold oligoalkynes into polyaromatics naturally. Furthermore, it is easier to make the terminal alkyne moiety different from the other alkynes for selective initiation at one of the termini. However, radical and anionic endo cyclizations are stereoelectronically handicapped and, despite the help of aromaticity, the 6-endo-dig cyclizations are often slower than their 5-exo-dig counterparts.[24] Consequently, the radical endo cascades of oligoalkynes are nonselective.[25−27]

Ring Expansions

We developed an indirect pathway to *circumvent* the slow endo cyclization step and form the endo products through a mechanistic "detour". For example, a combination of exo-trig cyclization with homoallylic ring expansion (HRE)[18] illustrates how a sequence of three exo cyclizations can give an endo product. Such expansion cascades (which we call "exo catalysis")[18,28] use alkenes as alkyne equivalents and bridge the enyne and enediyne product spaces via a fragmentation.[29] The enyne system is an interesting mechanistic playground,[30] but with the right choice of substituents, the 5-exo product can continue down the homoallylic path to the formal 6-endo product that undergoes aromatization via C−C scission (Scheme 19A). The full HRE/fragmentation sequence provides useful building blocks for making interesting polyaromatics (e.g., fused helicenes,[31] Scheme 19B). Multiple enyne units can be appended to the same central core, so three cascades can be run in parallel to accomplish a 15-step one-pot transformation in 75% yield (Scheme 19C).[18]

The final fragmentation step stops the C−C bond propagating sequence by "casting off" the radical species. Because this is a self-terminating cascade, it cannot be used in cascades that bridge multiple alkynes and will not be discussed in further detail.

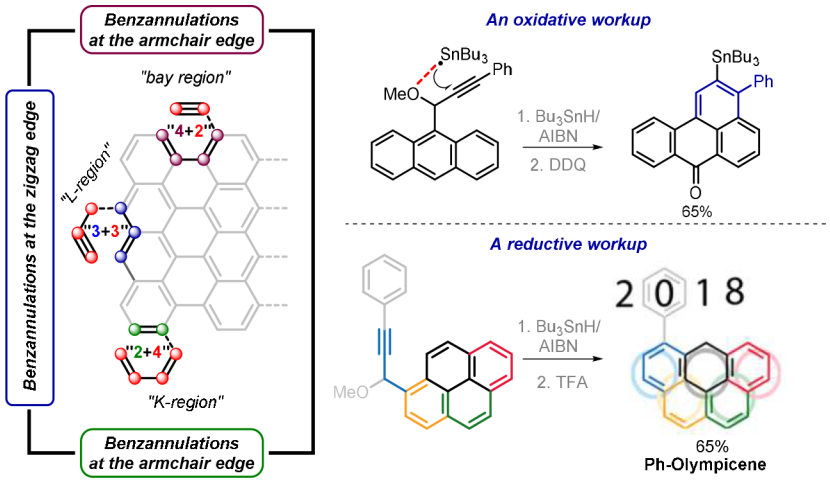
LUMO Umpolung

A general solution to enabling the propagating "all-endo" cascades comes from rewriting the basic stereoelectronic preferences for the attack at an alkyne group. The same fundamental knowledge that served as a foundation for the new rules tells one how to break them!

Conceptually, the selectivity can be reversed by changing the symmetry of interacting orbitals, for example, removing the node at the π-target along the attack trajectory. Unfortunately, the most obvious stereoelectronic option for favoring an endo-dig cyclization (i.e., a cationic ring closure that targets the "alkyne HOMO"), comes with the high thermodynamic cost of generating an endocyclic vinyl cation. Such cations are unstable because their formation forces an sp-hybridized cation into a cycle. This thermodynamic penalty can be avoided by bypassing the vinyl cation and inverting the stereoelectronic requirements via coordination of an external Lewis acid to the alkyne. We call such inversion "LUMO umpolung" because the *LUMO* of the alkyne/Lewis acid complex has the same stereoelectronic profile for an intramolecular *nucleophilic* attack as the *HOMO* of the free alkyne has for the *electrophilic* attack (Scheme 20).

LUMO umpolung provides stereoelectronic assistance to C−C bond formation in cycloaromatization reactions, for example, the Bergman cyclization (BC).[32] Coordination of $[Me_3P{-}Au]^+$ to an enediyne triple bond dramatically decreases the barrier and renders the cyclization exergonic. The catalytic power of Au(I) in BC is further enhanced by crossover from a diradical to a zwitterionic mechanism. The catalyst's dual ability

Scheme 18. (left) Patterns for Benzannulation and (right) Examples of Peri Cyclizations



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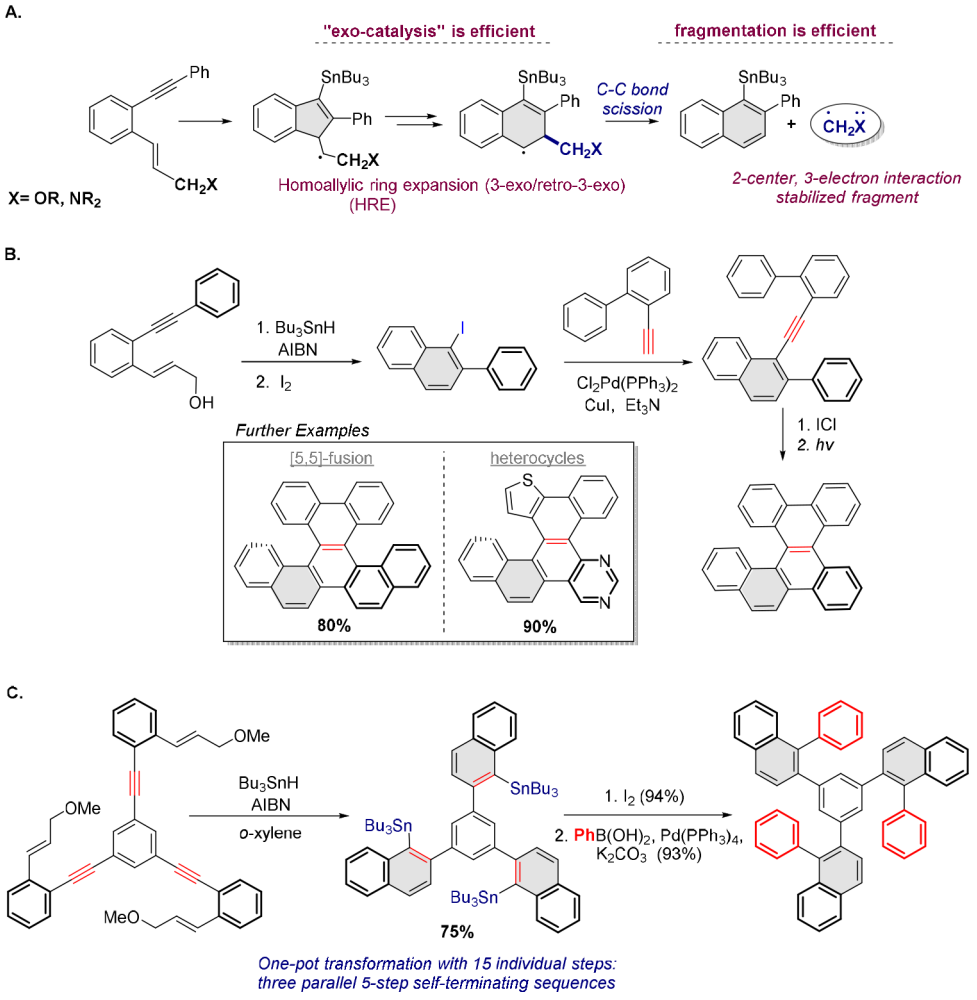
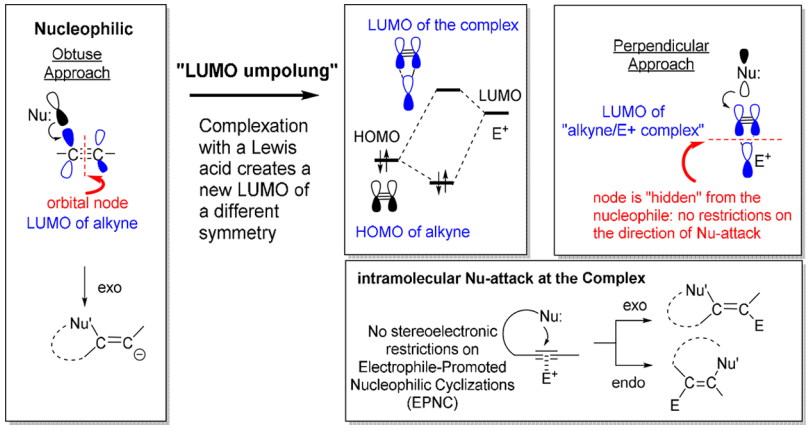
Scheme 19. (A) Substituents Can Extend the HRE Path to the Formal 6-endo-dig Products and (B, C) Examples of Conversion of Enyne Precursors into Polyaromatics via the α-Sn Naphthalene Building Blocks



Scheme 20. Exo Preference for the Nucleophilic Attack at a π-Bond Is Removed by Changing Symmetry of the Target LUMO[a]



[a]The orbital node in the new LUMO is moved away from the nucleophile's attack trajectory, rendering endo-dig cyclizations common in electrophile-promoted nucleophilic cyclizations (EPNC).

to stabilize both the negative and positive charges helps the *p*-benzyne diradical to morph into a masked zwitterion.

We quantified the evolution of substrate/catalyst interactions using distortion-interaction analysis (DIA).[33] Although this theoretical approach has been generally applied to bimolecular reactions, it can serve for understanding many catalytic processes.

DIA reveals two stages in the Au-catalyzed Bergman cyclization. First, Au/enediyne coordination relocates the node for LUMO umpolung and assures the correct symmetry for the bond-forming interaction. The potentially counterproductive exergonicity of the Au/substrate complex formation (~34 kcal/mol) is compensated by an even greater transition state stabilization derived mostly from

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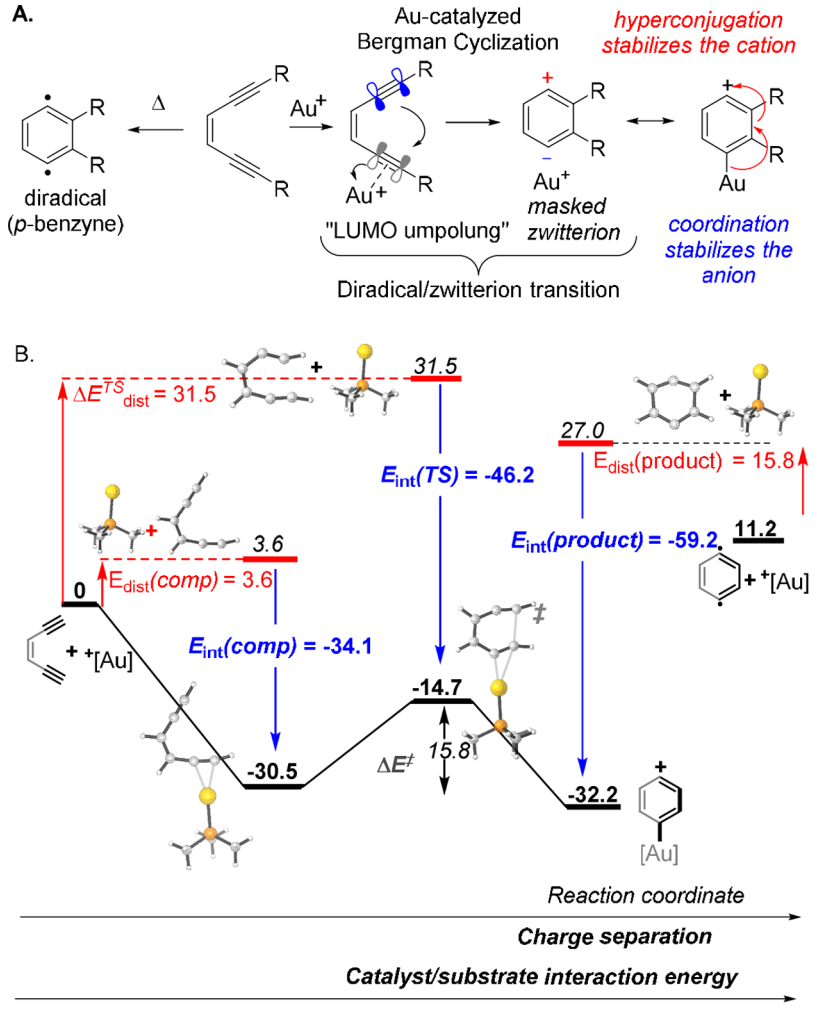
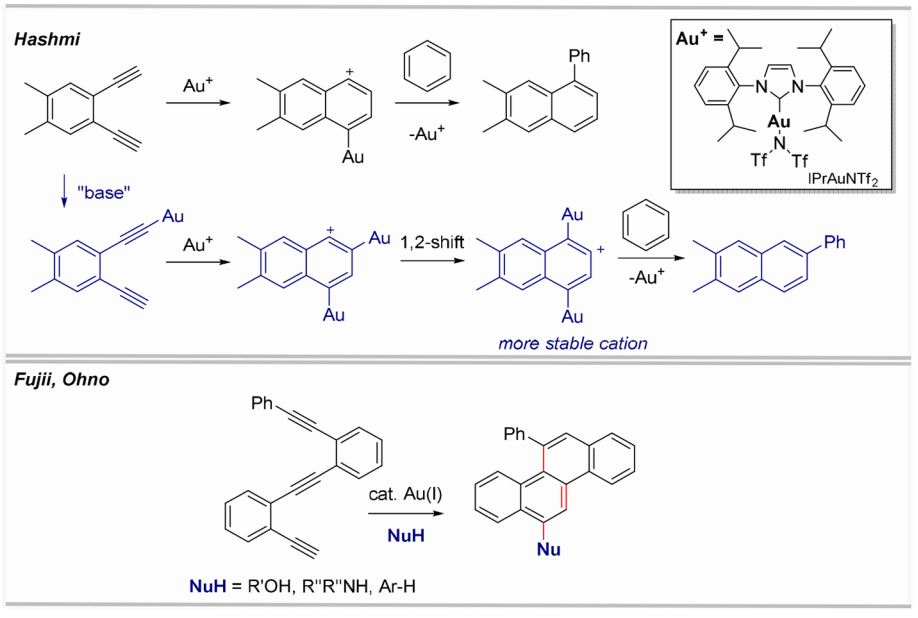
Scheme 21. (A) Solving Symmetry Mismatch with "LUMO Umpolung" and Moving Bergman Cyclization to a Zwitterionic Manifold with Au Catalysis and (B) Distortion-Interaction Analysis of the Au-Catalyzed Bergman Cyclization



Scheme 22. Au-Catalyzed Cycloaromatization of Enediynes Intercepted by Nucleophilic Addition



the dramatic increase in the interaction energy between the Au catalyst and the substrate (−34 to −46 kcal/mol!). This increase provides most of the ∼13 kcal/mol difference between the activation barriers of the thermal and Au-catalyzed BC (Scheme 21).[34]

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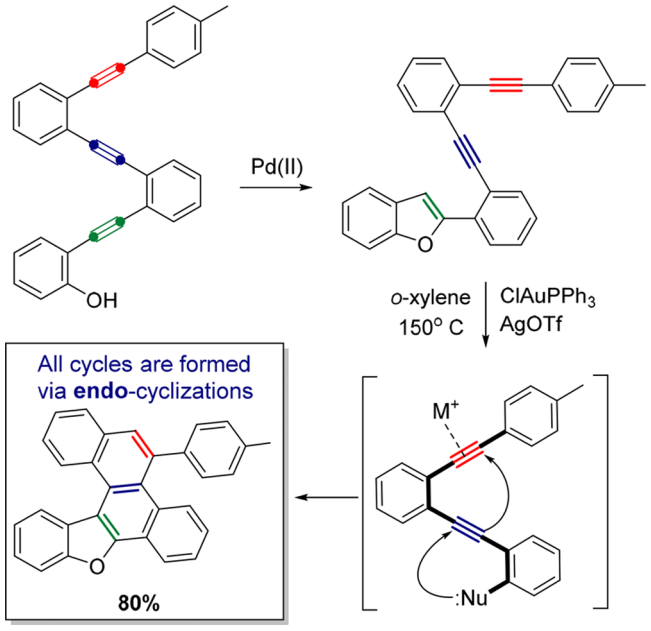
Not only does this analysis rationalize the possibility of over a *hundred-billion-fold* acceleration of the Bergman cyclization by Au catalysis, but it also highlights the features that are promising for cascade transformations. First, it introduces charge separation that can facilitate additional reaction steps. Furthermore, the continuous reinforcement of the substrate/catalyst interaction converts the BC into an "aborted" sigmatropic shift[3] where the cyclic species becomes a deep energy minimum. Trapping such a cyclic intermediate with a pendant nucleophile opens a new approach towards polycyclic molecules.

The power of LUMO umpolung has been documented in the recent explosion of Au-catalyzed Bergman cyclizations (BCs).[35] These fast reactions switch from diradical to zwitterionic mechanism where the charge separation finds utility in the design of C−C bond forming cascades. For example, Hashmi and co-workers illustrated that the Bergman cycloaromatization can be accompanied by intermolecular Friedel−Crafts arylations,[36] whereas Fujii, Ohno, and co-workers developed Au-catalyzed cascades propagated by reaction with another alkyne (Scheme 22).[37]

The mechanistic picture of the above cycloaromatizations of terminal alkynes is complicated by the involvement of Au acetylides. However, the Au-catalyzed cascades of internal alkynes bypass the Au acetylide route but still provide an efficient path to polyaromatics via an "all-endo" cyclization sequence (Scheme 23). We have set up such cascades via Pd-catalyzed cross-coupling of 2-iodophenol with a terminal enediyne or triyne.[38]

Scheme 23. Combination of Zwitterionic Bergman Cyclization and Intramolecular "Cation Capture" for the Preparation of Polyaromatic Structures



CONCLUSIONS AND OUTLOOK

The power of stereoelectronic guidelines guided the discovery of the new alkyne transformations discussed in this Account. Although the many ingredients, both conceptual and practical, for the controlled assembly of unusual polyaromatics are still unknown, we hope that the synergistic efforts of the international community of organic chemists will facilitate the arrival of the golden age of polyaromatic chemistry. Synthetic progress in this field is important because, in addition to the aesthetic beauty of symmetric molecular forms, there are many unanswered questions of how structure is related to properties and reactivity. It is necessary to provide the key understanding of how delocalization evolves from a single molecule of benzene to the infinite 2D structure of graphene, depending on molecular shape and dimensions. The only way to answer these questions is to make well-defined graphene substructures. It is not practical to cut them from graphene. Instead, these substructures have to be made via a "bottom-up" approach where alkynes can serve as tunable high-energy carbon-rich building blocks.

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The authors declare no competing financial interest.

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Edgar Gonzalez-Rodriguez received his undergraduate education at LaSalle University in Mexico City. He joined the laboratory of Professor Alabugin as a graduate student in 2016.

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