Polycycles

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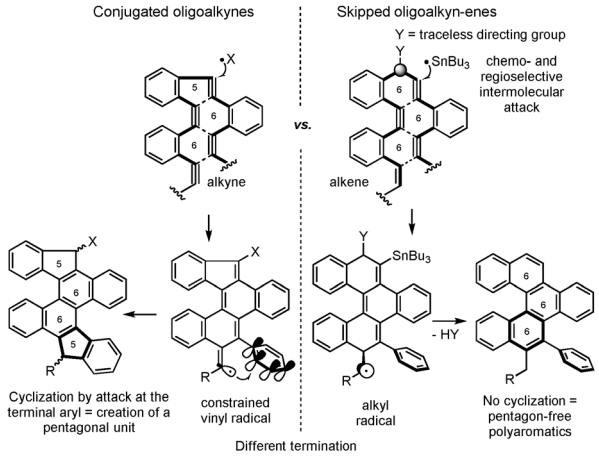
Combining Traceless Directing Groups with Hybridization Control of Radical Reactivity: From Skipped Enynes to Defect-Free Hexagonal Frameworks

*Kamalkishore Pati, Gabriel dos Passos Gomes, and Igor V. Alabugin**

Abstract: *This work discloses the first general solution for converting oligoalkynes into polyaromatic polycyclic systems free of pentagonal defects. The efficiency and selectivity of this cascade originate from the combination of the Bu_3Sn-mediated TDG (traceless directing group) cascade transformations of skipped alkynes where the reactivity of the key radical precursor is tempered by hybridization effects. This approach ensures that the final structure consists of only six-membered rings. Practical implementation of this strategy is readily accomplished by incorporation of a suitably-substituted alkene as a final unit in the domino transformation. This strategy opens a new avenue for the controlled preparation of polyaromatic ribbons. The resulting ester functionality can be used for an additional Friedel–Crafts ring closure which effectively anneals two extra cycles with distinct electronic features to the extended aromatic system formed by the radical cascade.*

The combination of high reactivity with controllable selectivity accounts for the utility of radical cascades[1] for rapid construction of complex polycyclic frameworks.[2] At their best, these processes can combine elegance and efficiency[3] for atom-economical preparation of polycyclic molecules.[4,5] Alkynes are attractive precursors for carbon-rich polycyclic aromatics because of the high carbon content,[6] the possibility of modular assembly by reliable cross-coupling chemistry, and controllable reactivity.[7] We had recently utilized these features for the preparation of polyaromatic ribbons from oligoalkynes. In our earlier work, we found that cyclizations of fully conjugated oligoalkynes lead to the formal reduction of two alkyne carbon atoms: the place of initial attack by tin and the place of final ring closure.

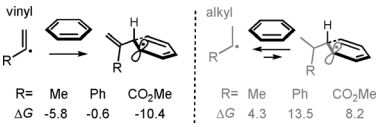
The polycylic systems formed from these precursors have two partially reduced five-membered rings.[8] In more recent work, we avoided both the formation of one of the five-membered rings and the partial reduction at the cascade initiation point by utilizing skipped oligoalkynes equipped with a traceless directing group (Scheme 1).[9] Loss of the directing group proceeds by C–O bond fragmentation driven by aromatization of the top ring in the ribbon.[9]



Scheme 1. Radical cascade termination modes with vinyl or alkyl radicals.

In present work, we disclose an approach towards defect-free polycyclic molecules which do not contain a pentagonal subunit at either end of the polycyclic ribbon. The two structural features in the reactant which deliver perfectly hexagonal polyaromatic molecules are: a) a skipped oligoalkyne equipped with a traceless directing group at the cascade initiation point and b) an alkene at the end of C–C bond-forming sequence. The remaining problem involved disfavoring the final C–C bond formation, that is, the radical attack at the terminal aryl group. Our hypothesis was that this could be accomplished by stabilizing the radical species at this stage by hybridization effects.[10]

Vinyl radicals are so reactive that their addition to aromatic systems is generally exergonic (Scheme 2). However, if an alkene is introduced at the end of the cascade instead of an alkyne, the penultimate radical center would be an alkyl (rather than vinyl) radical. The driving force for interaction of these less-reactive species with π-systems is more than 10 kcal mol^{-1} lower than it is for the similarly substituted vinyl radicals.[11] In particular, reactions of alkyl



Scheme 2. Difference in the reactivity of vinyl and alkyl radicals. Reaction energies are at the UM06-2X(D3)/6-311++G(d,p) level, in kcal mol^{-1}.

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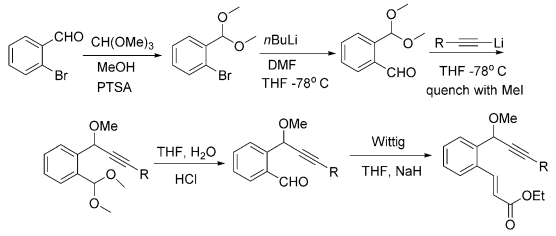
radicals with simple aromatics are endergonic and, thus, should be reversible (Scheme 2). If necessary, one can further deactivate the alkyl radical by attaching a radical stabilizing group at the terminal alkene carbon atom of the precursor (i.e., methyl versus ester). Intriguingly, the deactivating effect of the ester functionality operates only for the alkyl radical (see the Supporting Information for additional analysis).

Encouraged by these findings, we have prepared the substrates **1a–l** in several efficient steps starting from 2-bromobenzaldehyde (Scheme 3). The preparatory stage of



Scheme 3. General synthetic approach to the substrates for radical cyclizations. DMF = *N*,*N*-dimethylformamide, PTSA = *p*-toluenesulfonic acid, THF = tetrahydrofuran.

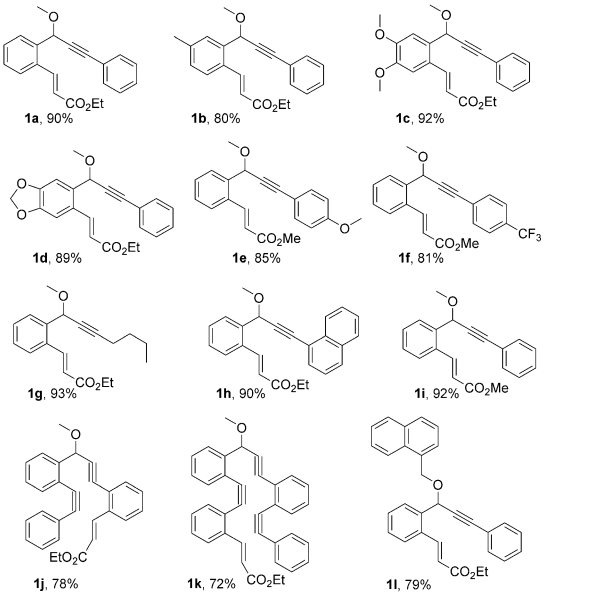
the synthesis provided monoprotected phthalaldehyde by acetal formation and subsequent *ortho* formylation. Reaction of the aldehyde with alkynyllithium compounds yielded propargylic intermediates (*o*-methoxyprop-2-ynyl acetal arenes) after in situ addition of methyl iodide. Acid hydrolysis deprotected the second aldehyde from which a library of skipped 1,6-enyne substrates [3-(2-(1-methoxy-3-phenylprop-2-yn-1-yl)phenyl) acrylates (**1**)] was generated by a Wittig reaction. The scope of prepared substrates is shown in Table 1.

The screening of radical reagents and initiators for the model transformation of **1a** into **2a** revealed that, similar to our earlier experience,[9,12] the combination of Bu_3SnH and AIBN in refluxing toluene was efficient whereas silicon reagents did not provide a successful cascade (Table 2, entries 1 and 2). The reaction conditions were further optimized by changing molar ratios of Bu_3SnH/ AIBN and varying flow rate using a syringe pump. We found that maintaining steady concentration of AIBN is preferred over the addition of initiator in a single portion in the beginning of reaction. The addition of a Bu_3SnH/AIBN mixture in 2 mL of toluene, at a flow rate of 1 mL h^{-1}, to the 0.04 M solution of substrate in toluene (110 °C) provided **2a** in excellent (91%) yield. Structures of the products were determined by a combination of spectroscopic methods and, in the case of **2c**, by X-ray crystallography (Figure 1).

With the optimized reaction conditions in hand, we examined the substrate scope by testing reactivity of the additional 3-[2-(1-methoxy-3-phenylprop-2-yn-1-yl)phenyl] acrylates (**1b–i;** Table 3). The radical cyclization is fully compatible with both the acceptor and donor substituents, as well as aliphatic chains at the alkyne termini.

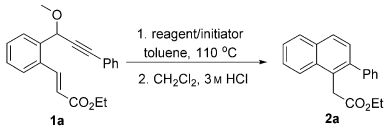
The absence of final closure at the terminal aryl group has a mechanistic consequence. In the all-alkyne cascade the final attack at the Ph ring creates a π-radical center, thus assisting

Table 1: Scope with respect to the substrates (**1a–l**) and yields for the final step of their preparation.



Yield is that of isolated product.

Table 2: Screening conditions.



Entry	Reagent/Initiator	Conditions	Yield [%][b]
1	No reagent/initiator	Toluene, 16 h, 110 °C	SM
2	Et_3SiH/AIBN	Toluene, 16 h, 80 °C	mix
3	Bu_3SnH/AIBN	Toluene, 10 h, 110 °C	91
4	PPh_3SnH/AIBN	Toluene, 14 h, 110 °C	52
5	Bu_3SnH/ABCN	Toluene, 14 h, 110 °C	63
6	Bu_3SnH/DTBPB	Toluene, 14 h, 110 °C	58

[a] Reagent: 1.3 equiv. Initiator: 0.4 equiv. [b] Product yields are reported after purification from a silica gel column. SM = starting material, mix = mixture of products. ABCN = 1,1′-azobis(cyclohexanecarbonitrile), AIBN = 2,2′-azobis(2-methylpropionitrile), DTBPB = 2,2-bis(*tert*-butylperoxy)butane.

in the removal of the directing OMe group by radical β-scission (Scheme 4). In contrast, the radical density in the alkyne–ene cascade never "arrives back" at the correct position to assist the aromatization step. Remarkably, aromatization still occurs readily under the reaction conditions, possibly as a simple 1,4-elimination of methanol.

The presence of Bu_3Sn and ester groups in the products opens convenient opportunities for further synthetic transformations. Not only can the tin functionality directly react with electrophiles, but the polarity of these naphthalene building blocks can be reversed by conversion of stannanes into iodides (Scheme 5), so a variety of electrophilic naphthyl building blocks is now readily available. Furthermore, the ester group can be converted into an acylating Friedel–Crafts

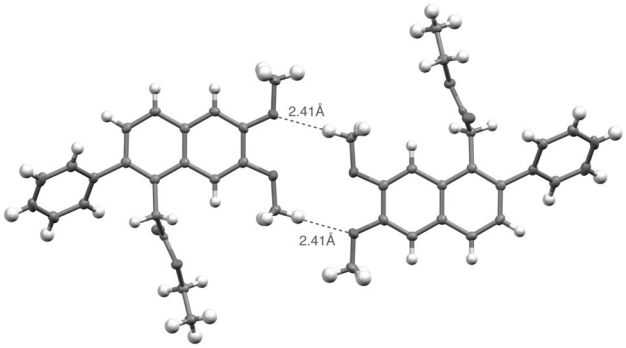
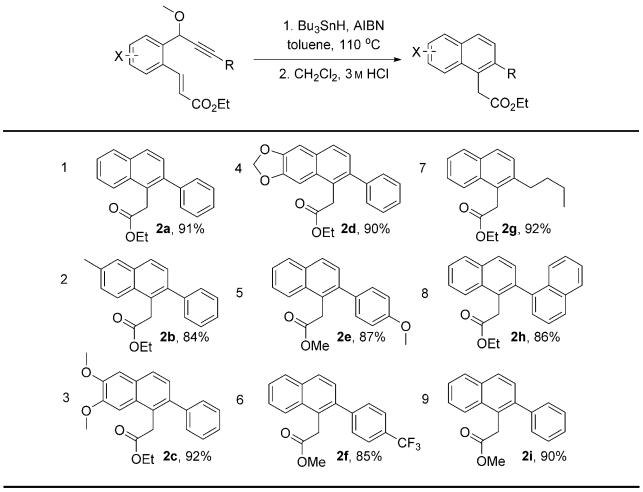
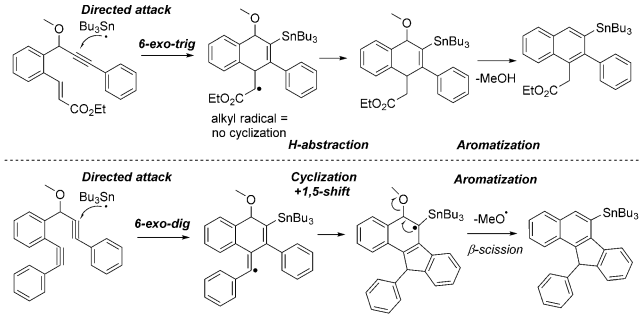


Figure 1. The ORTEP representation for **2c**.[13] Thermal ellipsoids are shown at the 50% probability. Note the supramolecular C–H···O dimer formation through C–H bonds "acidified" by interaction with the antiperiplanar $\sigma^*_{O\text{-}C}$ orbitals.

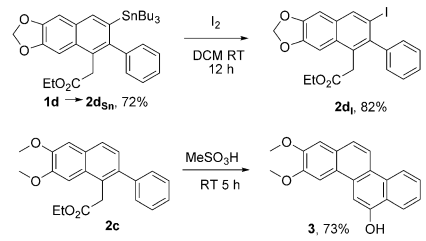
Table 3: Scope of substrates for radical cascade.





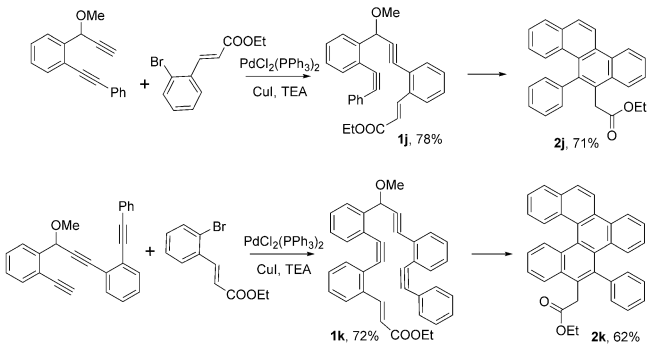
Scheme 4. Comparison of cascade transformations of bis-alkynes and enynes.

electrophile upon activation with $MeSO_3H$. In particular, conversion of the ester **2c** into 2,3-dimethoxychrysen-6-ol (**3**) proceeded in 73% yield.[14] Such polycycles find applications for the preparation of natural products and pharmaceuticals.[15]



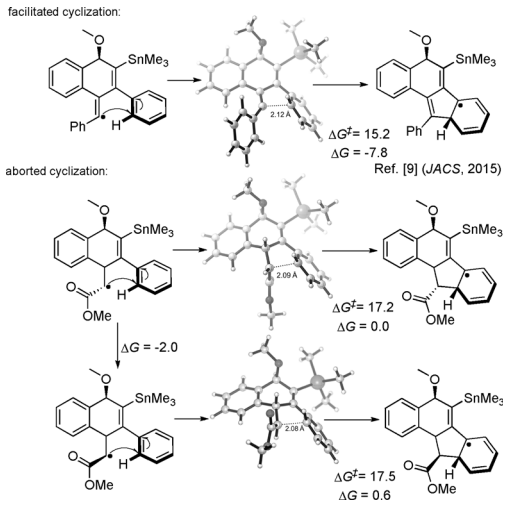
Scheme 5. Further transformations of radical cascade products. Top: iodo-destannylation. Bottom: Friedel–Crafts cyclization to substituted chrysenes. DCM = dichloromethane.

Guided by these results, we have expanded this cascade to the preparation of larger polyaromatics from starting materials which are readily available by modular assembly through reliable cross-coupling chemistry. To our delight, we found that cascades originating from the bis- and tris(alkyne)s retain their selectivity and efficiency (Scheme 6). The high yields of the expected products illustrate the overall robustness of our traceless directing group approach. These approaches open new avenues for the preparation of polyaromatics of varying sizes and shapes.



Scheme 6. Extended polyaromatics from the traceless directing group mediated alkyne–alkene cascades. TEA = trimethylamine.

To gain a deeper insight into the observed differences between the radical cascades of oligoalkynes and enynes, we have analyzed the energetics of the final cyclization step computationally. The differences are instructive. Not only is the attack of alkyl radical at the terminal aromatic ring much slower (≈ 2 kcal mol^{-1} higher activation barrier) in comparison to the analogous reaction of vinyl radical, but the former reaction is about 8 kcal mol^{-1} less exergonic. In fact, DFT calculations[16] suggest the thermodynamic driving force for the putative cyclization of the alkyl radical is close to zero and, thus, the cyclization should be reversible. The main reason for the large decrease in reaction exergonicity is the greater reactivity of vinyl radicals in comparison with alkyl radicals.[17] Furthermore, the stabilizing group of alkyl radical (i.e., the ester in Scheme 7, bottom) has no conjugating partner in the product whereas the Ph group (Scheme 7, top) trades conjugation with the radical in the reactant to conjugation with the vinyl moiety in the product.



Scheme 7. Stabilization of alkyl radicals interrupt further cyclizations. Calculations performed at the UM06-2X/LanL2DZ level of theory, simulating the reaction temperatures ($T = 383$ K). Energies in kcal mol^{-1}.

In summary, the formation of the pentagonal unit in the last cyclization step of the skipped oligoyne cascade can be prevented by utilizing the fundamental differences in the reactivity of vinyl and alkyl radicals. Switching to an alkene terminating unit yields the final cascade product composed exclusively from the six-membered rings. This reaction sequence serves as a new approach to the efficient transformation of acyclic polyunsaturated substrates into polycyclic ribbons of tunable dimensions. The regioselectivity of the initial attack is directed by a propargylic OR group which is eliminated at the end of cascade, thus serving as a traceless directing functionality. Incorporation of a tin moiety allows additional functionalization of the initial site of radical attack through subsequent chemoselective reactions with electrophiles. The ester group at the alkene terminus serves a dual role: a) as a stabilizing group that prevents the undesired radical attack at the terminal aryl group, and b) as a valuable synthetic handle for the formation of additional cycles.

Acknowledgments

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Keywords: alkynes · cyclizations · polycycles · radicals · tin

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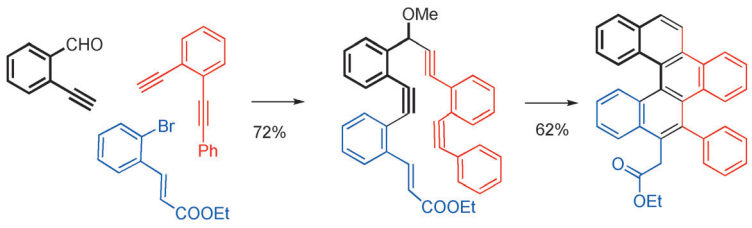
Combining Traceless Directing Groups with Hybridization Control of Radical Reactivity: From Skipped Enynes to Defect-Free Hexagonal Frameworks



Without a trace: Oligoalkynes can be converted into polyaromatic polycyclic systems consisting of only six-membered rings. The efficiency and selectivity of this cascade originate from the combination of the Bu_3Sn-mediated traceless directing group cascade transformation of skipped alkynes. This strategy opens a new avenue for the controlled preparation of polyaromatic ribbons.

