JOC The Journal of Organic Chemistry

JOCSynopsis

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"Two Functional Groups in One Package": Using Both Alkyne π-Bonds in Cascade Transformations

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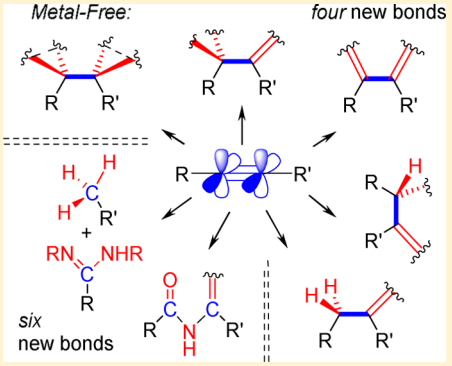
ABSTRACT: Spatial orthogonality of the two independently addressable π-systems in alkynes can be used for the design and control of metal-free cascade transformations. Examples include ionic chemistry of neutral hydrocarbons, preparation of radicals without radical initiators, generation of excited states without light, "1,2-dicarbene reactivity" of alkynes in "boomerang" radical processes, selective conversion of alkynes into carbonyl compounds, and full disassembly of the alkyne moiety.



The alkyne, one of the simplest organic functional groups, has many interesting features associated with the presence of two types of bonds (π and σ) and the spatial orthogonality of the two π-systems. Furthermore, alkynes are in the same oxidation state as the $-CH_2C(O)-$ moiety and, thus, can be introduced in organocatalytic carbonyl pathways without the need for external redox agents.

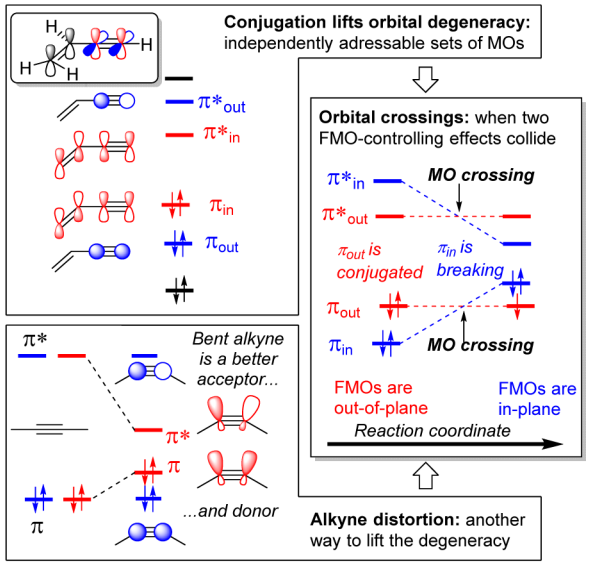
This combination of electronic features, together with the relatively high energy of alkynes, accounts for their rich chemistry and for the unique role of this functional group as a platform for the design of new reactions and for the discovery of new modes of chemical reactivity. In this Synopsis, we will illustrate how the key structural, energetic and stereoelectronic features of alkynes are used for the discovery and control of new organic cascades. Because of space restrictions, we will not discuss transition-metal catalysis and include only a selection of radical, nucleophilic, and pericyclic organic transformations which involve C−C, C−H, C−N, and C−O bond formations.

■ ORTHOGONAL π-ORBITALS: TWO FUNCTIONAL GROUPS IN ONE PACKAGE

The unusual stereoelectronic features of alkynes stem from the presence of two mutually orthogonal sets of π-orbitals. Although the parent alkyne π-cloud has the cylindrical $D_{\infty h}$ symmetry, the symmetry can be lowered by substitution (Scheme 1). The ability to separate the two orbital sets and to engage them in parallel but independent transformations plays an important role in alkyne chemistry.

The two useful ways for "desymmetrizing" alkyne MOs involve (a) incorporation of conjugative substituents and (b) structural distortions associated with chemical reactivity. Despite conceptual differences between the two approaches, i.e., conjugation being stabilizing and bending being destabilizing, both of these effects decrease the HOMO−LUMO gap,

Scheme 1. Possibilities for Control of Frontier MO (FMO) Energies in Alkynes



rendering such modified alkyne systems better donors and better acceptors than the parent acetylene.

Because of the increase in HOMO energy,[1] bent alkynes are stronger donors in hyperconjugatiive interactions.[2] This effect renders alkynes with propargylic σ-acceptors more flexible and can be used in selective transition state stabilization in alkyne/azide cycloadditions (Scheme 2).[3] When this effect is complemented by synergistic C−H...F interactions, the

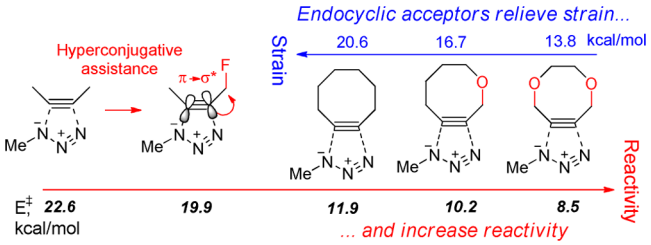
Received: May 21, 2013
Published: July 5, 2013

   dx.doi.org/10.1021/jo401091w | J. Org. Chem. 2013, 78, 7777−7784

combined TS stabilization removes ~80% of the difference in the 1,3-dipolar cycloaddition barriers between acyclic alkynes and cyclooctyne with methyl azide (~1 million fold acceleration). Incorporation of endocyclic σ-acceptors increases cycloalkyne reactivity with simultaneous relief of the strain.[3] Computations suggest that such alkynes should be more reactive than cyclooctyne and less strained.

A different way to utilize bond breaking is embodied in the MO crossing concept, an approach for control of reactivity based on intramolecular electron transfer between two orthogonal orbital systems in reductive cycloaromatizations. In such reactions, an unfavorable effect, i.e., antiaromaticity[4] or destabilization by electron donors,[5] is removed when relative energies of the in-plane and out-of-plane MOs interchange ("MOs cross", Scheme 1, right) at the cyclization transition state.

Scheme 2. (Left) TS Stabilization via Hyperconjugative Assistance in Cycloadditions of Acyclic Alkynes. (Right) Combining Strain with Hyperconjugation: Increasing Stability and Reactivity

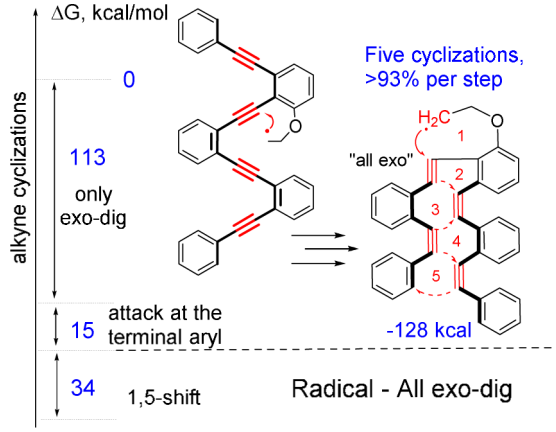


DOWN THE "SLIPPERY SLOPE": THERMODYNAMICS OF ALKYNE TRANSFORMATIONS

Sacrificing Strong π-Bonds for Even Stronger σ-Bonds. Although π-bonds of alkynes are shorter and *stronger* than the π-bonds of alkenes, reactions of alkynes are more exothermic. Nicolaides and Borden[6] rationalized this paradox by pointing out that the strength of each of the two new sp^2 C−H bonds formed in hydrogenation of acetylene is ~11 kcal/mol greater than the strength of the sp^3 C−H bonds formed in hydrogenation of ethylene. Because stronger π-bonds offer kinetic protection, even highly exothermic reactions of an alkyne may have a higher barrier than the analogous alkene reaction.[7] This trend is sometimes masked in bimolecular reactions, i.e., in some 1,3-dipolar cycloadditions where distortion of the second partner (the 1,3-dipole) provides the dominant contribution to the activation barrier.[1]

On the other hand, the high energy content of the alkyne functionality allows one to design multistep chemical cascades without worrying about their reversibility. An example of energy flow in highly exothermic alkyne cascades is provided by the potential energy surface for the "all exo" cyclizations of oligoalkynes, topologically equivalent to the formation of a "polyacetylene ribbon" via controlled radical polymerization between two rows of aromatic rings (Scheme 3).[8,9] The four alkyne cyclizations are ~113 kcal/mol exergonic due to the transformations of π-bonds into σ-bonds and the increase in π-conjugation.

Scheme 3. Controlled Alkyne "Polymerization" for the Preparation of Carbon Nanoribbons

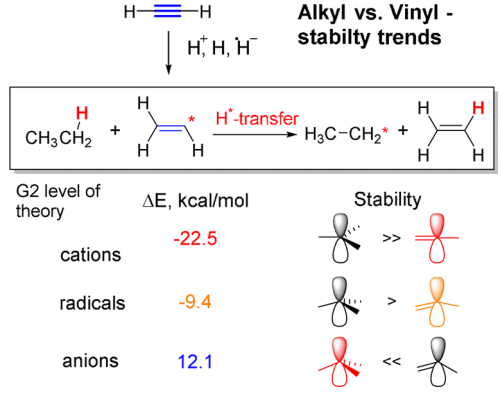


CHOOSING THE RIGHT DESTINATION. VINYL CATIONS, RADICALS, AND ANIONS: RELATIVE STABILITY OF REACTIVE INTERMEDIATES DERIVED FROM ALKYNES

Alkynes, like alkenes, can be transformed into radical, anionic, and cationic reactive intermediates, but at a different energy cost (Scheme 4). Vinyl cations are strongly (>20 kcal/mol) disfavored relative to alkyl cations.[10] The difference in stability decreases (~10 kcal/mol) for the radical species; vinyl radicals are reactive[11,12] but can be generated readily.

The relative stability of vinyl anions assists in nucleophilic cyclizations of alkynes[13] and is partially responsible for the unusual features of "aborted" [2,3]-sigmatropic shifts where the cyclic structure, analogous to the pericyclic TS, is stabilized to the extent where it becomes the global minimum. Such aborted sigmatropic shifts masquerade as nucleophilic 5-endo cyclizations[14,15] and take full advantage of the unusual electronic properties of alkynes, i.e., the parent 5-*endo-dig* cyclization is 32 kcal/mol more exothermic than the analogous alkene cyclization.

Scheme 4. Relative Stability of Five Reactive Intermediates Derived from Alkynes and Alkenes

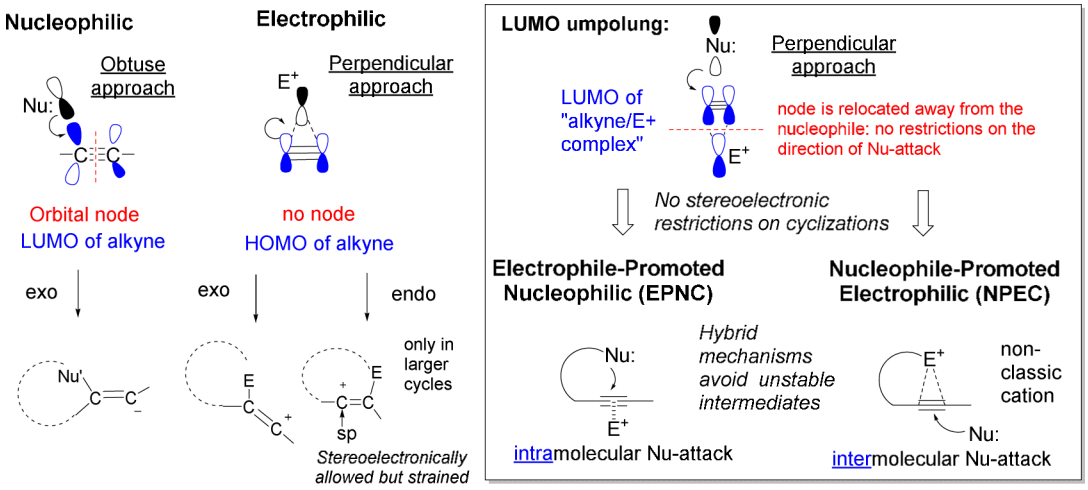


CHOOSING THE RIGHT PATH: STEREOELECTRONICS OF ALKYNE REACTIONS

Stereoelectronics of alkynes have been surprisingly controversial. In the classic 1976 paper,[16] Baldwin supported dramatically different guidelines for the cyclizations of sp^2 (trig) and sp (dig)

dx.doi.org/10.1021/jo401091w | J. Org. Chem. 2013, 78, 7777−7784

Scheme 5. Different Stereoelectronic Preferences of Reactive Intermediates for Attack at a Triple Bond Have Important Implications for the Selectivity of Alkyne Cyclizations



systems based on the notion that nucleophilic addition to alkynes follows an unusual acute trajectory.

More recent experimental and computational analysis converged on the notion that basic stereoelectronic guidelines for alkenes and alkynes are similar. The acute trajectory is stereoelectronically unfavorable, as it brings the nucleophile at the node of the target π^*-orbital. In 2011, we suggested new rules for nucleophilic and radical cyclizations of alkynes which reverse Baldwin's original predictions (Scheme 5).[17]

Stereoelectronic preferences embodied in the new rules offer many options for the design of anionic and radical exo-dig cyclizations (i.e., the "all-exo"-cascades in Scheme 3). The design of endocyclizations of alkynes is much more difficult because the best stereoelectronic option, a cationic ring closure, provides an endocyclic vinyl cation. Because vinyl cations prefer linear geometry at the cationic center, inclusion of such a center in a small cycle is unfavorable.

Two routes can overcome this penalty. In NPEC, nucleophile-promoted electrophilic cyclizations, i.e., the cyclizations of homopropargylic cations,[18] the progress is "frozen" until the nonclassic cation is attacked by a nucleophile.[19] Alternatively, stereoelectronic requirements of nucleophilic cyclizations can be inversed by coordination of the alkyne to an external Lewis acid ("LUMO umpolung"[16]) in electrophile-promoted nucleophilic cyclizations, or EPNCs.[20]

TAKING ADVANTAGE OF ORBITAL ORTHOGONALITY IN REACTION DESIGN

A. Indirect Involvement of the Second π-System. Dehydropericyclic Reactions: Building Potential Energy Cages for Transition States. Unique electronic features of alkynes are well illustrated by their "hexadehydropericyclic"[21] reactions, processes created by the introduction of an extra π-bond at *each* of the six carbon atoms in a pericyclic transition state (Scheme 6).

Dehydropericyclic reactions lend themselves to the preparation of highly reactive species, i.e., hexadehydro Diels–Alder reaction yields *o*-benzynes.[22] The next section illustrates how even the ultimate example of chemical instability – transition states, can still be trapped in a potential energy cage engineered by an alkyne chemist. Furthermore, the presence of two orthogonal sets of π-orbitals in alkynes can be used for converting transition states into trappable diradicals, zwitterions and excited states.

Alkynes as Synthetic Analogues of Diradicals. In the hexadehydropericyclic version of the Cope rearrangement (the Bergman cyclization[23]), aromatic stabilization "interrupts"[24] the [3,3]-sigmatropic shift and converts the cyclic TS into an intermediate which resides in a deep energy minimum. Because *two* bonds are broken and only *one* bond is formed in this process, it leads to a net loss of a chemical bond.[25] This reaction illustrates the key role of the "bystander" out-of-plane orbitals which, albeit not participating directly in making the ring-closing σ-bond and the two radical centers, stabilize the cyclic structure by aromaticity.

Not only is the thermal transformation of bis-alkynes into diradicals responsible for the remarkable biological activity of natural enediyne antibiotics, but it also lends itself to the design of new reactions. For example, *p*-benzyne can be trapped through cyclization with pendant π-systems (alkenes[26] or aromatic rings[27]) or via relocation of radical centers via 1,2-shifts.[28] Remarkable "memory of chirality" in reactions of enediynes with chiral substituents results from radical translocation followed by an intramolecular coupling of the two radical centers without significant loss of chiral integrity.[29] Conformationally gated H-abstraction, potentially involved in autoprotection in the enediyne producing microorganisms, led to the discovery of new σ-bond transpositions in enediynes equipped with carbohydrate mimics.[30] The radical fragmentation/rearrangement leading to O→C transposition was used to develop an efficient metal-free synthesis of benzoic amides and esters from the corresponding phenols.[31]

Alkynes as Synthetic Analogues of Zwitterions or Ionic Chemistry of Neutral Hydrocarbons. Commonly, the "lost bond" is converted into two radical centers but cycloaromatizations can also proceed via a different scenario where both electrons remain at the same atom (analogous to the heterolytic bond cleavage).[33−35] Even neutral enediynes can display ionic chemistry due to the very small HOMO–LUMO gap in the *p*-benzyne diradical.[36]

Alkynes as an Entry Point for the Preparation of Excited States by Thermal Reactions. The zwitterionic reactivity for the σ,π-didehydrotoluene product of the Myers–Saito cyclization,[37] where the two radicals reside in orthogonal orbitals follows a surprisingly complex mechanistic scenario[38] with a post-

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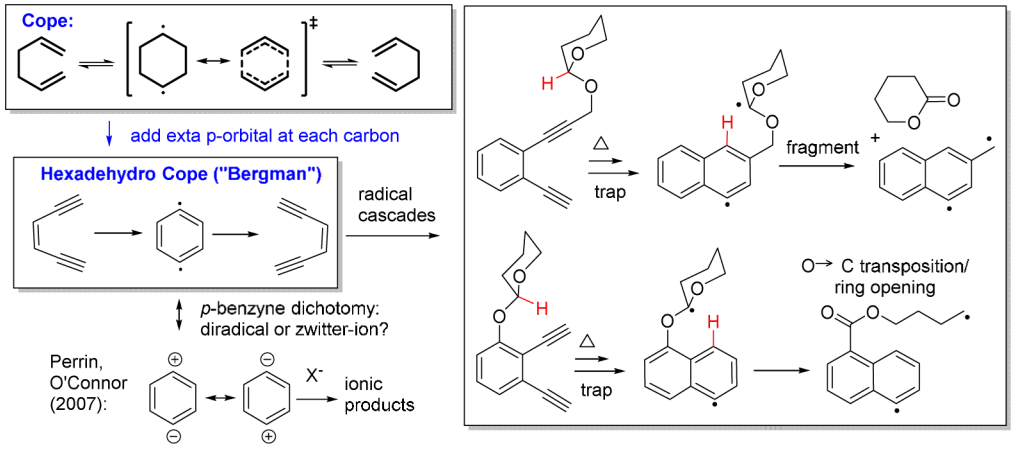
Scheme 6. (Left) Bergman Cyclization as "Interrupted" Cope Rearrangement[32] Where Aromatic Stabilization Converts the Cyclic Cope TS into a Trappable Diradical/Zwitterion. (Right) Examples of σ-Bond Transpositions in *p*-Benzynes

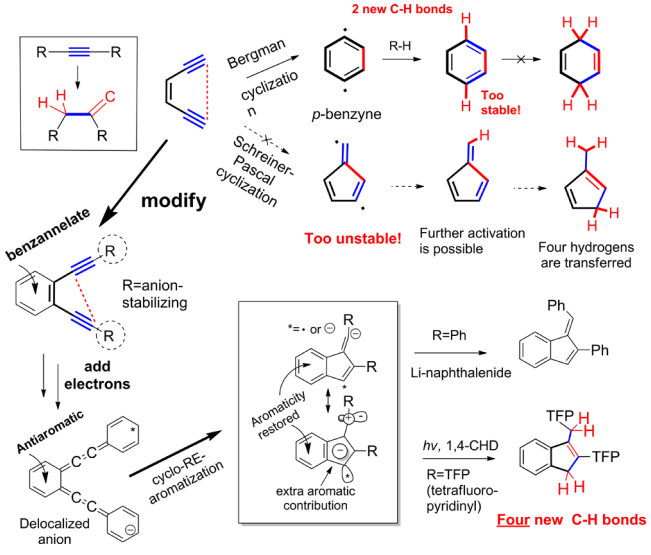


transition state bifurcation leading to the excited state zwitterion.[39] A thermal reaction that starts from a strain-free all-carbon reactant and forms an excited-state product is a remarkable illustration of alkyne energy content.

B. Direct Involvement of the Second π-System: Design of Extended Cascades. *Avoiding Overstabilized Pathways.* The Bergman cyclization does not provide a perfect solution for double stranded (ds) DNA cleavage because natural enediynes cannot differentiate between cancer and healthy cells (hence the many efforts to design enediynes triggered "on demand"[40]) and because of the low efficiency of ds cleavage (~25% for calicheamicin). Our first foray in alkyne chemistry focused on improving efficiency and selectivity of ds-DNA cleavage by designing a photochemical process that could transfer a greater number of hydrogens from DNA. A possible way to achieve the latter goal involves incorporation of the initial product into additional bond-forming events (Scheme 7).

However, the high stability of the aromatic core, the very factor that rendered the Bergman cyclization possible, becomes a disadvantage for the subsequent transformations. The situation

Scheme 7. (Top) Comparison of Bergman and C_1-C_5 Cyclizations as Tools for Inducing DNA Damage. (Bottom) Design of C_1-C_5 Cyclizations Activated by Electron Injection



changes when the product of the enediyne cyclization is conjugated but not aromatic, i.e., when the regioselectivity of ring closure is shifted to the C_1-C_5 mode. The C_1-C_5 cyclization of enediynes is generally unfavorable[41] but can be enabled by electron transfer to the enediyne moiety. Although electron injection to enediynes requires potent donors (i.e., Li-naphthalenide),[42] this process can be greatly facilitated using photoinduced electron transfer (PET) when, even such moderately strong donors as 1,4-CHD (or DNA) efficiently transfer electrons to excited enediynes with acceptor tetrafluoropyridinyl (TFP) groups.[43] TFP-substituted enediynes display the efficiency of ds DNA-cleavage that rivals[44] or surpasses calicheamicin.[45]

Alkynes as Synthetic Analogues of Dicarbenes: Formal C–H Insertion and Cyclopropanation via "Boomerang" Radical Translocation. The recent explosion of metal-catalyzed cationic alkyne isomerizations[46] illustrates the possibility of 1,2-dicarbene-like reactivity without the formation of true dicarbenes. Instead, both alkyne π-bonds can be involved directly in the chemical bond formation via sequential translocation of cationic centers assisted by stabilization provided by the metal center.

The relative stability of reactive intermediates suggests that the energy gradient for the sp→sp^2→sp^3 cascades is favorable not only for the cationic, but for the radical processes as well. Whereas strongly stabilizing catalysts/substituents are needed to compensate for the initial vinyl cation formation, vinyl radicals present an attractive compromise between reactivity and stability.

For unlocking the carbene-like reactivity patterns, vinyl radicals should undergo a reaction that initially translocates the radical center and then brings its attack back at the *same* atom where the radical was positioned initially (Scheme 8). Below, we will show the two ways of launching such "radical boomerangs": via C–H translocation and via alkene cycloadditions.

Radical Translocation via H-Atom Transfer. The first process is based on radical translocation pioneered by Curran[47] with the difference that the initial vinyl radical is formed from an alkyne instead of a vinyl halide. "Carbene-like reactivity" from radical cascades in Scheme 9 includes sequential formation of C–H and C–C bonds at the alkyne carbons via stepwise radical translocation.[48]

Radical Translocation in Cycloadditions. The second process, boomerang cycloadditions, involved a "walk" of an

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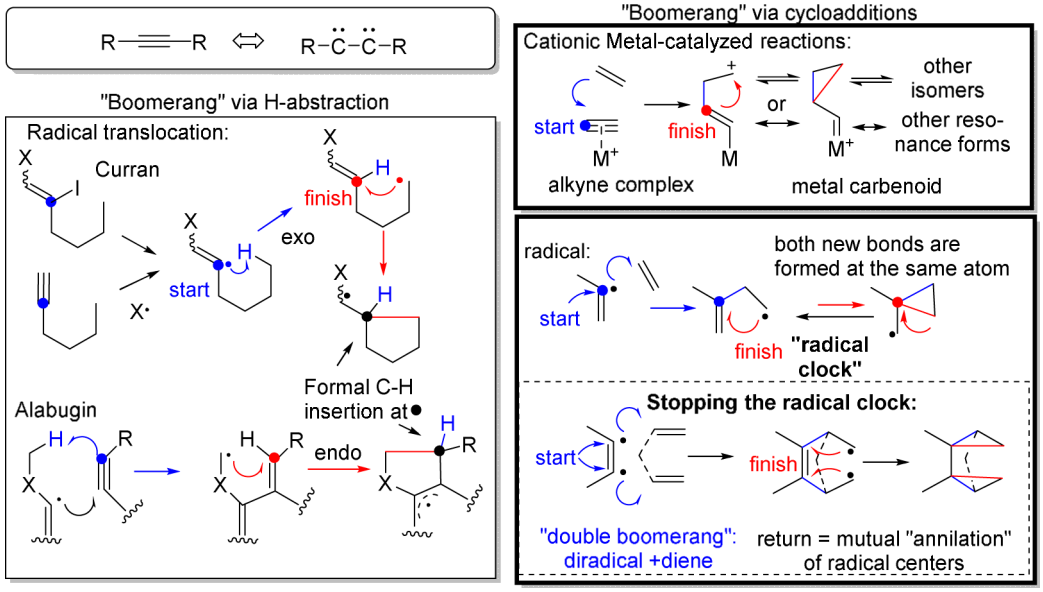
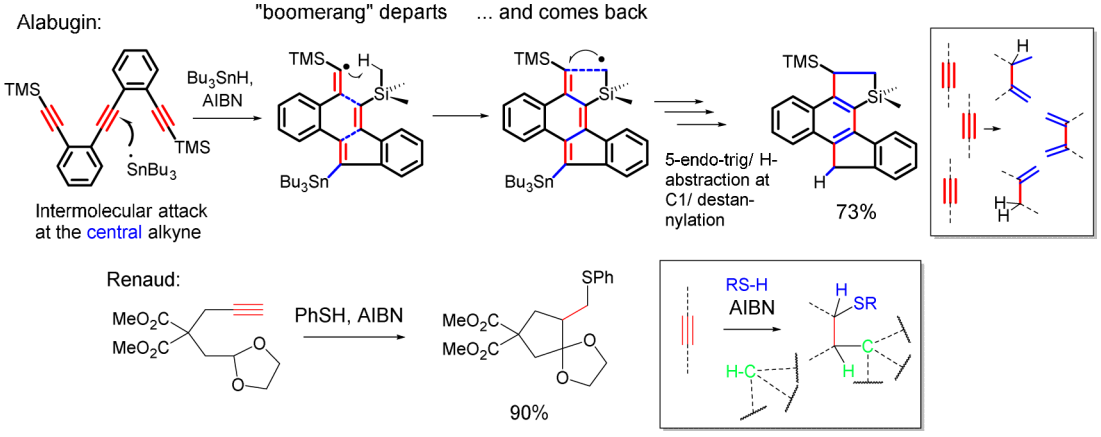
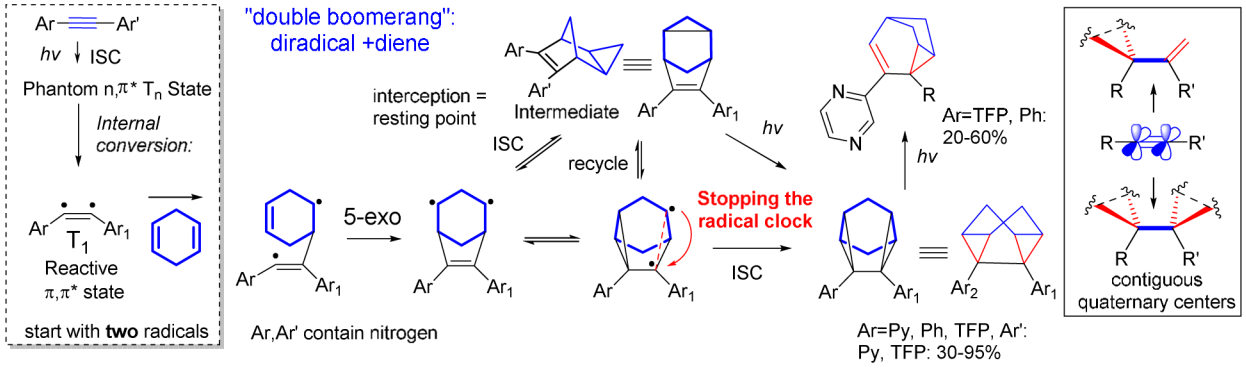
Scheme 8. Unmasking Dicarbene Functionality Hidden in Alkynes. (Left) Radical Translocations Lead to C−H Insertion. (Right) "Boomerang" Cycloadditions Lead to Cyclopropanation



Scheme 9. Selected Examples of Insertion of Alkyne Carbons into C−H Bonds



Scheme 10. Proposed Mechanism for the "Parachute" Triplet Photoreaction of Acetylenes with 1,4-CHD. Reaction Starts with a Diradical, but the Second Round of Activation Gives the Formal "Dicarbene" Product

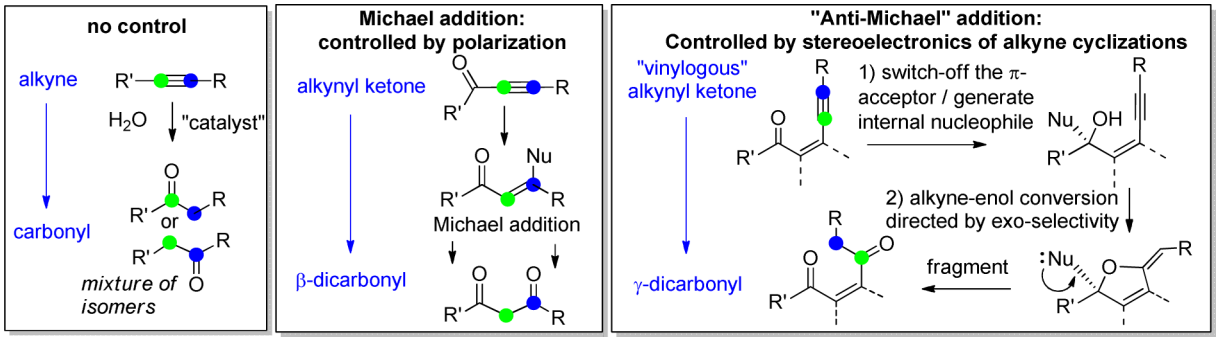


initially formed radical center through an alkene before the "return" at the same carbon (Scheme 8). The serious problem with this approach, however, is that the penultimate cyclopropyl radical may undergo a fast "radical clock" ring-opening. This diversion has to be eliminated, i.e., by running two of such clocks in the "opposite directions" (i.e., in a reaction of a diradical with a diene), so the two radicals "self-annihilate".

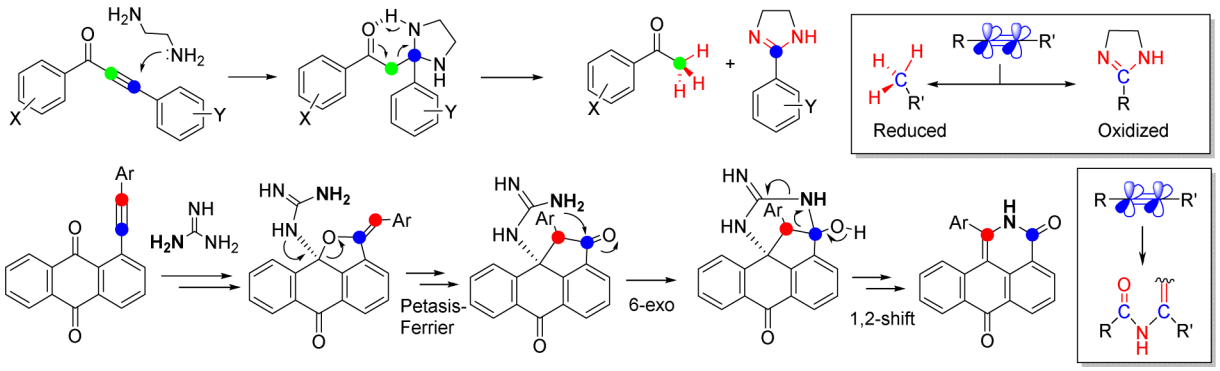
The early reported yields for the bis-cyclopropane formation in photoreactions of acetylenes with alkenes were low.[49] We had found that efficiency increases when nitrogen in heteroaryl substituents acts as an internal sensitizer accelerating ISC

dx.doi.org/10.1021/jo401091w | J. Org. Chem. 2013, 78, 7777−7784

Scheme 11. Synthetic Equivalency of Alkynes and Carbonyl Compounds and Selected Approaches to Regioselective Alkyne/Carbonyl Transformations



Scheme 12. Two Approaches to Alkyne "Disassembly" via Carbonyl Cascades



(intersystem crossing) through a "phantom state" effect.[50,51] Efficient entry into the triplet manifold precludes the formation of [2 + 2] products and allows the cascade to proceed along the "boomerang" path. The overall process corresponds to a metal-free formal addition of a 1,2-dicarbene to a diene (Scheme 10).

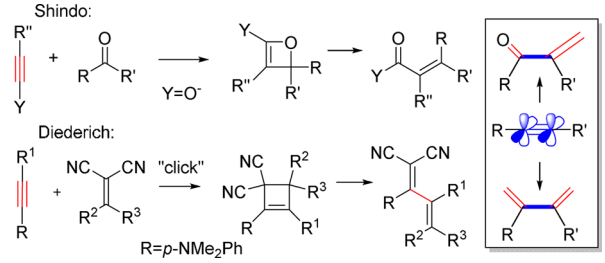
Alkynes as an Entry Point into Carbonyl Chemistry. Because alkynes have the same oxidation level as carbonyl compounds, new alkyne cascade transformations can be engineered by unmasking the hidden "carbonyl nature" of alkynes. In this Synopsis, we discuss nucleophilic cascades that, for O- and N-nucleophiles, immediately transform alkynes into enol and enamine derivatives. Because the regiochemistry of the initial C–X attack chooses between the two latent carbonyl functionalities, controlling this step is crucial for the success of cascade transformations.[52] One can leverage the stereoelectronic control associated with cyclization preferences into regiochemical control for the alkyne–carbonyl conversion to overcome the polarization effects. For example, "anchoring" of multifunctional nucleophiles via 1,2-addition at the carbonyl of ketoacetylenes sets[53] up an intramolecular "anti-Michael" attack which can be used for selective preparation of γ-dicarbonyls (Scheme 11).

Scheme 12 illustrates new cascades based on these approaches. Alkynes with acceptor substituents undergo regioselective reactions that reveal masked β-dicarbonyls. Subsequent retro-Mannich-like fragmentation leads to complete disassembly of the alkyne moiety via disproportionation.[54]

Alternatively, an "anchored" nucleophile initiates an "anti-Michael" cascade that inserts a nitrogen atom between the two alkyne carbons.[51a] This transformation leads to the formation of *six* new bonds at the two alkyne carbons with complete disassembly of the alkyne moiety. Note that the cascade is mediated by classic carbonyl chemistry, i.e., the fragmentation–recyclization analogues of the Petasis–Ferrier rearrangement and the [1,2]-shift converting the cyclic heminal into a lactam, similar to the final step of the Baeyer–Villiger oxidation.

Pericyclic Entries into Carbonyl Chemistry of Alkynes. Reactions of donor alkynes and carbonyls transfers the carbonyl moiety to one of the alkyne carbons and can be used for olefination of ketones (Scheme 13).[55] An analogous reaction with dicyanoalkenes has been suggested as a new click reaction.[56]

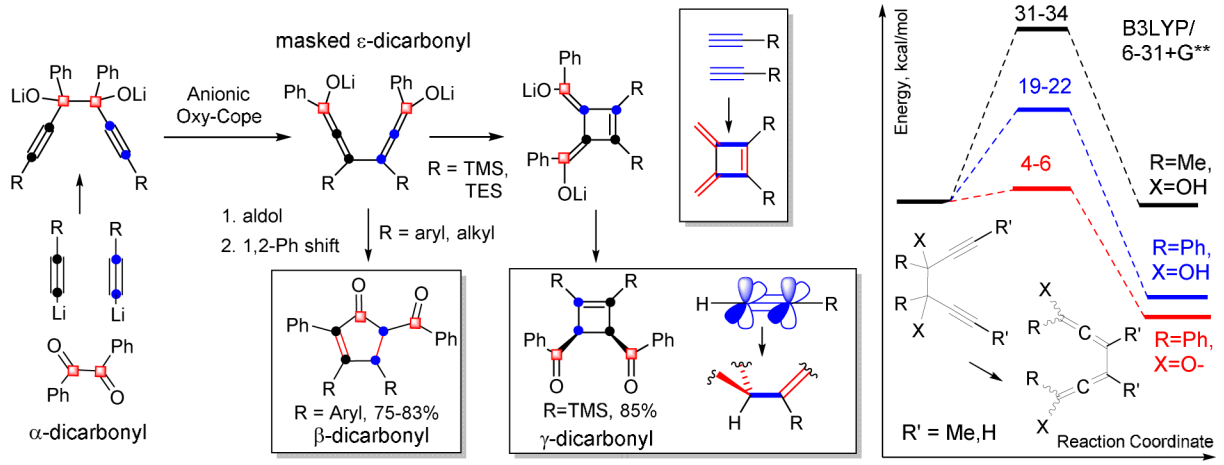
Scheme 13. From Forbidden Reactivity to Carbonyl Olefination and Click Chemistry



Oxy-Cope rearrangements of bis-alkynes produced by reaction of acetylides with benzil proceed below room temperature and open another connection with the carbonyl chemistry (Scheme 14).[57] The oxyanionic radical-stabilizing groups significantly decrease the rearrangement barrier and can be considered as a latent dicarbonyl functionality revealed by the oxy-Cope process in its bis-enolized state. The cascades can continue via either a pericyclic path (electrocyclic ring closure) or classic carbonyl chemistry (intramolecular aldol condensation).

dx.doi.org/10.1021/jo401091w | J. Org. Chem. 2013, 78, 7777–7784

Scheme 14. Conversion of α-Dicarbonyls into β-, γ-, and ε-Dicarbonyls and via Alkyne Chemistry



CONCLUSIONS

The presence of two orthogonal π-systems in alkynes can be used for the design of unusual chemical reactions. The indirect effect of the orthogonal π-system allows for the preparation of radicals without radical initiators, generation of excited states without light, conversion of neutral hydrocarbons into zwitterions, and the existence of "interrupted" and "aborted" pericyclic processes.

When the second π -system is directly involved in a cascade, two or three new bonds can be formed at each of the alkyne carbons. Examples involve the sequential "boomerang" radical processes and selective conversion of alkynes into carbonyl compounds. Such processes can be controlled stereoelectronically and combined with pericyclic reactions.

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Notes

The authors declare no competing financial interest.

Biography

Igor V. Alabugin is a Professor at the Florida State University where he utilizes experimental and computational methods to study chemical reactivity with the focus on alkyne chemistry. Brian Gold was inspired by his undergraduate experiences in Professor Harold Kroto's laboratory to continue to his doctoral studies in Organic Chemistry at FSU. Among his accomplishments is the design of stable, yet reactive, alkyne reagents for catalyst-free click reactions.

ACKNOWLEDGMENTS

Financial support by the NSF (Grant Nos. CHE-1152491 and CHE-1213578) is gratefully acknowledged. We thank Professors Greg Dudley (FSU) and Sergei F. Vasilevsky (Institute of Chemical Kinetics and Combustion, Russian Academy of Sciences) for productive exchanges of ideas.

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NOTE ADDED AFTER ASAP PUBLICATION

This paper was published ASAP on July 17, 2013. Scheme 7 was updated. The revised paper was reposted on August 2, 2013.