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Cyclizations of Alkynes: Revisiting Baldwin's Rules for Ring Closure

Kerry Gilmore and Igor V. Alabugin*

Department of Chemistry and Biochemistry, Florida State University, Tallahassee, Florida, 32306-4390

CONTENTS

1. Introduction	6513	3.2.4. Effect of Metal/External Electrophiles on 4-exo/5-endo Regioselectivity	6531
2. Baldwin Rules	6514	3.2.5. Summary of 4/5	6531
2.1. Terminology and Classification of Cyclization Modes	6514	3.3. 5-exo/6-endo Cyclizations	6532
2.1.1. Classification for an Isolated Reactive Center	6514	3.3.1. Radical Cyclizations	6532
2.1.2. Classification for Cyclizations Including Two Orbital Arrays	6514	3.3.2. Anionic Cyclizations	6539
2.2. Summary of the Rules: Favorable and Unfavorable Reactions	6515	3.3.3. Electrophilic Cyclizations	6545
2.2.1. Radical Cyclizations: Beckwith's Guidelines	6515	3.3.4. The Effect of Metal/External Electrophiles on 5-exo/6-endo Regioselectivity	6548
2.3. Rationale for the Baldwin Rules: Originally Proposed Angles of Attack and Favorable Trajectories	6516	3.3.5. Summary of 5/6	6549
2.3.1. General Considerations. Tet and Trig Processes	6516	4. Conclusions: Revised Rules for Alkyne Cyclizations	6549
2.3.2. Attack Trajectories for Alkynes	6516	Author Information	6550
2.4. Differences Between Nucleophilic, Radical, and Electrophilic Trajectories	6517	Biographies	6550
2.4.1. Nucleophile-Promoted Electrophilic Cyclizations	6518	Acknowledgment	6551
2.4.2. Electrophile-Promoted Nucleophilic Cyclizations: Effect of External Electrophile on Trajectory	6518	References	6551
2.5. Secondary Electronic, Structural, and Geometric Effects on Cyclization Trajectories	6519	Note Added after ASAP Publication	6556
2.5.1. Orbital Polarization	6519		
2.5.2. Distortions	6519		
2.6. Thermodynamic Contribution to the Reaction Barriers	6520		
2.7. Rules for Alkynes: Time to Reevaluate?	6521		
3. Specific Patterns of Digonal Cyclizations	6521		
3.1. 3-exo versus 4-endo	6522		
3.1.1. Radical Cyclizations	6522		
3.1.2. Anionic Cyclizations	6522		
3.1.3. Electrophilic Cyclizations	6524		
3.1.4. Summary of 3/4	6524		
3.2. 4-exo versus 5-endo Cyclizations	6525		
3.2.1. Radical Cyclizations	6525		
3.2.2. Anionic Cyclizations	6529		
3.2.3. Electrophilic Cyclizations	6531		

1. INTRODUCTION

According to the CRC dictionary of natural products,¹ 90% of chemically individual molecules discovered in nature contain either a carbocyclic or a heterocyclic subunit.² Not surprisingly, the ability to perform the key bond-forming step which transforms an acyclic precursor into the desired cyclic structure in a regio- and stereo-controlled manner remains critical to the construction of complex molecules. A concise set of guidelines for the rational design of such cyclization steps, known as “the Baldwin rules”, historically has served as one of the most useful tools in the arsenal of synthetic organic chemists. The seminal 1976 paper entitled “Rules for Ring Closure” by Sir Jack E. Baldwin is the most cited article in the 40+ year history of RSC Chemical Communications (Figure 1).³ Not only did this paper define the nomenclature necessary for describing and classifying ring closure steps, but it also utilized empirical knowledge, with basic geometric and orbital overlap considerations, to predict favorable cyclization modes.⁴

Despite the broad utility of the Baldwin rules, the most recent comprehensive review (1993) concentrated only on a subset of examples: the stereoelectronic effects in five- and six-membered ring formation.⁵ The present review will illustrate the important role of the Baldwin rules in the development of organic chemistry, but, at the same time, it will point to the pressing need for the critical reexamination and partial refinement of these rules in relation to the cyclizations of alkynes.

Not only has a larger body of experimental data been accumulated since the time of Baldwin’s original publication,

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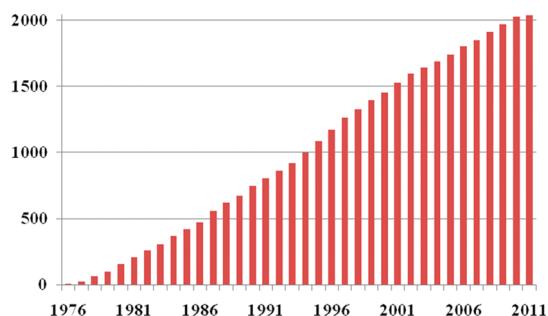


Figure 1. Number of citations for the “Rules for Ring Closure” through May 3, 2011.

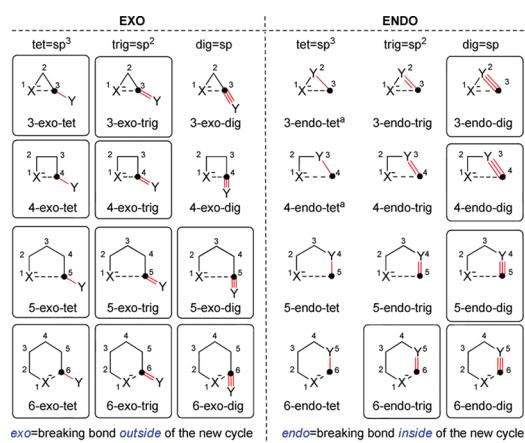


Figure 2. Patterns of ring closure for 3- to 6-membered rings (endo-tet processes do not formally form cyclic products but are included here because, if concerted, they should proceed through the cyclic transition states as well). Reactions predicted to be favorable by Baldwin are boxed.^a denotes no prediction was made.

but the development of more accurate theoretical models and computational methods has led to a better understanding of underlying stereoelectronic principles for the formation and cleavage of chemical bonds, providing both an impetus and an opportunity for a critical reevaluation of structural and electronic effects involved in nucleophilic, radical, and electrophilic ring closure processes. This review will present such reevaluation for alkyne cyclizations. Compared to the cyclizations that proceed at the expense of single or double bond (tet and trig cyclizations), cyclizations of alkynes (digonal cyclizations) remain relatively underrepresented. This, at least partially, may be the result of it being easier to manipulate the reactivity of alkenes via substitution: alkynes simply can not bear the same number of substituents as alkenes. Conversely, cyclizations of alkynes often reflect the fundamental stereoelectronic factors more accurately without the camouflage of steric or electronic effects introduced by multiple substituents.

2. BALDWIN RULES

2.1. Terminology and Classification of Cyclization Modes

2.1.1. Classification for an Isolated Reactive Center. In his seminal publication,⁴ Baldwin developed a unified classification of cyclization processes based on three factors. A cyclization is characterized by three prefixes (e.g., 5-endo-dig, Figure 2), the first of which provides the number of atoms in the forming ring and can adopt any value ≥ 3 . The second prefix, endo- versus exo-,

describes the position of the bond that has to be broken in the cyclization, relative to the forming ring (or the smallest of the rings when several rings are formed simultaneously). Exo indicates that the breaking bond is outside of (exocyclic to) the formed ring, while endo indicates that the breaking bond is inside of (endocyclic to) the new ring. The last prefix, -tet, -trig, and -dig, refers to the hybridization at the ring closure point (dot in Figure 2), -tet (tetrahedral) for sp^3 , -trig (trigonal) for sp^2 , and -dig (digonal) for an sp -hybridized atom.

2.1.2. Classification for Cyclizations Including Two Orbital Arrays.

Subsequently, Baldwin expanded this terminology to include those cases where two orbital arrays need to be aligned in the cycle-closing bond formation, such as the cyclizations of enolates.^{6,7} If the enolate C=C bond is exocyclic to the ring being formed, the cyclization was referred to as an “enolexo” cyclization, while if the enolate is endocyclic to the ring being formed, the process was designated “enolendo”. It is important to note that enolate closure can occur at either the carbon or oxygen, and the stereoelectronic requirements are different for each due to the in-plane lone pair of the oxygen (Figure 3).⁶

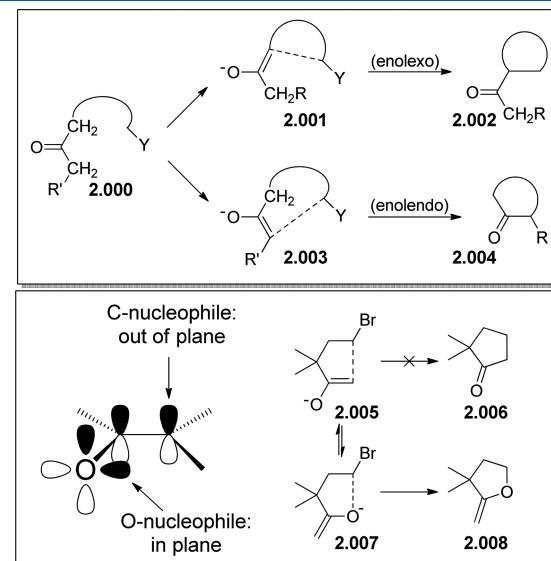
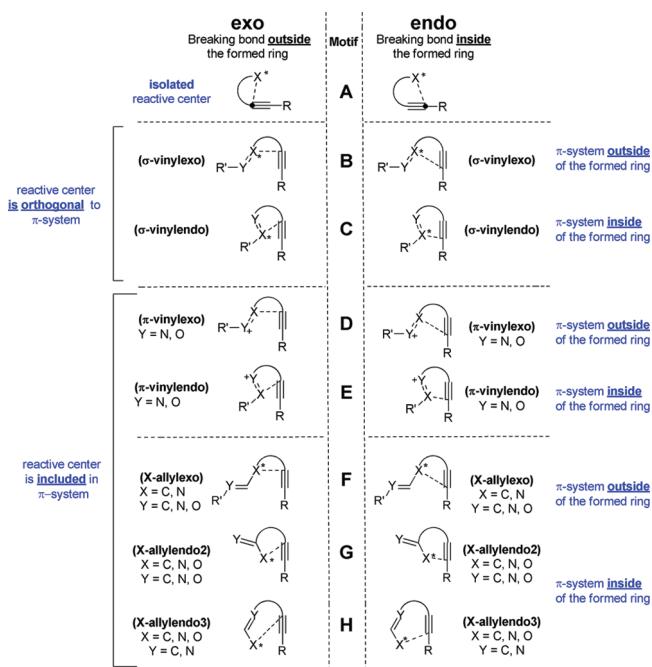


Figure 3. (top) Distinction between (C-enolexo) and (C-enolendo). (bottom) Different stereoelectronic requirements for the C- and O-centered cyclizations of enolates.

As similar stereoelectronic considerations should be applicable to enamines and other allylic and heteroallylic systems, both allylic and heteroallylic cyclizations will fall under this classification (e.g., C/O/N-allyl etc., where the C, O, or N designates the nucleophilic site). One can also extend this classification to electrophilic cyclizations where a cationic center is stabilized by the overlap with an adjacent lone pair, for example, oxycarbenium and iminium ions ($Y = O, N$ (π -vinylexo) and (π -vinylendo), Scheme 1).

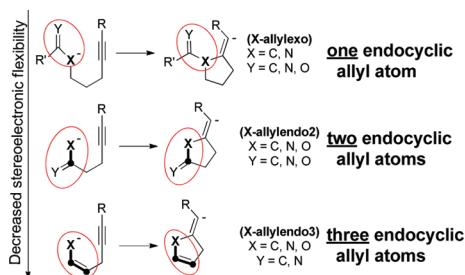
Crich and Fortt have also distinguished between π -exo and π -endo closures in their discussion of 5- and 6-membered ring formation in the digonal cyclizations of vinyl radicals.⁸ Note, however, that here the π -system is not part of the reacting orbital array but constrained to be perpendicular to the attacking radical center. As such, we propose to differentiate these two π -exo/endo systems by describing the orientation of the reactive center, where π -vinylexo/endo (D/E) refers to reactive centers incorporated

Scheme 1. Extended Classification of Possible Ring Closure Patterns Separated into Structural Motifs^a



^a Top: Isolated reactive center ("X*" can either be a cation, anion, or radical). Center: The reactive center is orthogonal to the second π -system. Bottom: The reactive center is included in a larger π -system which can be positioned either outside or inside the formed ring.

Scheme 2. Decreasing Stereoelectronic Flexibility with Increasing Number of Endocyclic sp^2 Centers for the Three (X-Allyl) Systems



into the π -system (i.e., oxycarbenium and iminium ions) and σ -vinyloxo/endo (B/C) refers to reactive centers perpendicular to the π -system (i.e., vinyl anions/radicals). Cyclizations of aryl nucleophiles/radicals fall under the category of σ -vinylenido (C) closures whereas benzylic species fall under π -vinylenido (H) cyclizations. The utility of motifs D and E is limited to radical and electrophilic closures.

Scheme 2 illustrates the differences in stereoelectronic flexibility for the three possible cyclizations of allylic/heteroallylic reagents. The greatest flexibility exists when only one atom of the allylic π -system lies inside the formed ring (X-allylexo, where X indicates the type of atom X at the closure point). The endocyclic π -system can exist in two different ways with either two or three atoms within the forming ring. We propose to differentiate these

Table 1. Baldwin's Rules for Ring Closure^a

		3	4	5	6
-tet	endo-	a	a	x	x
	exo-	✓	✓	✓	✓
-trig	endo-	x	x	x	✓
	exo-	✓	✓	✓	✓
-dig	endo-	✓	✓	✓	✓
	exo-	x	x	✓	✓

^a Green indicates favorable cyclizations, and red indicates unfavorable cyclizations. a indicates that no prediction was made. Columns represent the size of the ring being formed. A revised version of these rules will be provided in final section.

systems as (X-allylenido₂) and (X-allylenido₃), where the number designates the number of atoms from the allylic π -system which are included in the ring.

2.2. Summary of the Rules: Favorable and Unfavorable Reactions

The original "Baldwin rules" are reproduced in Table 1.⁹ All three factors involved in the classification (ring size, exo versus endo attack and hybridization at the site of attack) are critical in determining whether a particular cyclization mode is favorable. Due to a larger atomic radii and bond distances for heavier atoms, one stipulation is that atom X in Scheme 1 must be a first row element. For a similar reason, reactions which involve the cleavage and formation of the much shorter bonds to hydrogen often do not follow the rules as well. For example, radical 1,5-hydrogen transfers, which formally proceed via the unfavorable 6-endo-tet transition state, are quite common.¹⁰

2.2.1. Radical Cyclizations: Beckwith's Guidelines. A well-known set of guidelines for radical reactions was developed by Beckwith¹¹ who combined steric and stereoelectronic factors and complemented general predictions of favorable cyclizations modes with stereochemical analysis. These guidelines do not explicitly separate trigonal and digonal cyclizations and are briefly summarized below.

- (i) *Intramolecular addition under kinetic control in lower alkenyl and alkynyl¹² radicals and related species occurs preferentially in the exo-mode.* In systems, where the chain between the radical and unsaturated system contains five linking carbons or less, the kinetic favorability for exocyclic closure has been observed experimentally.
- (ii) *Substituents on an olefinic bond disfavor homolytic addition at the substituted position.* The preference for exo closure can be overwritten by an appropriate substituent at the internal position of the alkene. Note that this rule has only limited relevance to alkynes where only a single substituent can be present at each of the acetylenic carbons.
- (iii) *Homolytic cleavage is favored when the bond concerned lies close to the plane of an adjacent semioccupied orbital or of an adjacent filled nonbonding or π -orbital.* This stereoelectronic guideline is related to cyclizations because exo-radicals can readily acquire the required orbital overlap, whereas endo-radicals often cannot due to the ring constraints.
- (iv) *1,5-Ring closures of substituted hex-5-enyl and related radicals are stereoselective: 1- or 3-substituted systems afford mainly cis-disubstituted products, whereas 2- or 4-substituted systems give mainly trans-products.* The stereoselectivity observed in 2-, 3-, or 4-substituted

5-hexenyl radicals reflects conformational preferences of the chairlike transition states,¹¹ where the substituents preferentially occupy pseudoequatorial positions.¹³

In both Baldwin's and Beckwith's rules, reactions predicted to be unfavorable are not completely forbidden. Rather, such processes are expected to be relatively slow and incapable of competing with faster reactions (if the latter are available). In principle, a product, defined as unfavorable by the Baldwin rules, may be formed in good yield either when the reaction proceeds under thermodynamic control or when other kinetically favorable pathways are blocked.^{14,15}

A significant point of divergence between the Baldwin and Beckwith rules includes cyclizations of alkynes. Endo-dig cyclizations are favored by the Baldwin rules, whereas the Beckwith rules predict exo-dig cyclizations to be preferred.

2.3. Rationale for the Baldwin Rules: Originally Proposed Angles of Attack and Favorable Trajectories

2.3.1. General Considerations. Tet and Trig Processes.

Baldwin postulated that ring closures were favored to occur "when the length and nature of linking chain enables the terminal atoms to achieve the required trajectories" for bond formation. In contrast, disfavored reactions require severe distortion of bond angles and distances to reach the optimal trajectories and, thus, will not be able to compete with faster alternative pathways, if available.

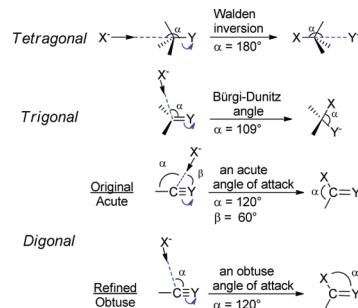
Baldwin suggested three favorable trajectories for closures, one for each of the three common hybridization states of carbon (sp , sp^2 , and sp^3 , dark circle in Scheme 1). In what could be taken as an essentially least motion argument, he stated: "In each case (tetrahedral, trigonal, digonal) the subtended angle α between the three interacting atoms is maintained during the reaction pathway, becoming the angle between these atoms in the product." However, the proposed trajectories also had a stereoelectronic component because the suggested angles maximized the bond-forming, stabilizing two-electron orbital interactions. Indeed, a footnote stated "This angular relationship is to be expected in interactions of p -type orbitals to maximize orbital overlap."

The rules for the cyclizations of enolates included an additional constraint requiring the alignment of the enolate π -orbitals with those of the breaking bond. Particularly, for the intramolecular alkylation of enolates, "the requirements of backside displacement of the leaving group and approach of the electrophilic halide carbon on a trajectory perpendicular to the enolate place at the α -carbon atom" was suggested to be important.^{6,7}

The optimal trajectory for tetrahedral cyclizations was defined based upon the classic backside attack of S_N2 reaction, yielding an attack angle of 180° . Trigonal cyclizations were defined based upon the now well-established Bürgi-Dunitz¹⁶ angle of attack on sp^2 carbon atoms of $\sim 105\text{--}109^\circ$. These trajectories optimize the overlap of incoming nucleophiles with the σ_{C-Y}^* (tet) and $\pi_{C=Y}^*$ (trig) orbitals respectively (Scheme 3). There is no thermodynamic incentive for these trajectories to be closely followed at long incipient distances where these orbital interaction effects are weak.¹⁷ However, the closer the attacking reactive species is to the target, the more potentially stabilizing and favorable the above-mentioned delocalizing bond-forming interactions become.

2.3.2. Attack Trajectories for Alkynes. Out of the two trajectories that would maintain the subtended angle between the three interacting atoms in digonal systems, Baldwin chose the one that corresponds to an acute angle of attack β (60° , Scheme 3 "original") rather than an obtuse angle (120° , Scheme 3

Scheme 3. Original Favored Trajectories for Cyclic Closure in Tetrahedral, Trigonal, and Digonal Systems Suggested by Baldwin.^a



^a Bottom: Comparison of two "least motion" trajectories showing the "conserved subtended angle α " between the three interacting atoms. Note that α is different from the attack angle β for the acute trajectory in alkynes.

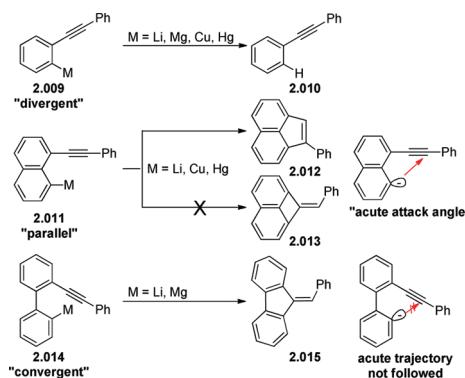


Figure 4. Three examples used to define the original Baldwin rules for alkynes. (a) With a divergent angle of 60° , only the reduced product is obtained. (b) A "neutral" parallel array with the angle of 0° results in 5-endo-dig closure of the carbanion. (c) A convergent angle of 60° exclusively yields the 5-exo-dig product. The expected acute attack angle is shown with a red arrow.

"refined"). This choice was based upon "the X-ray work of Wegner¹⁸ and Baughman",¹⁹ as well as a "general predominance for endoring closures in digonal systems".⁴

The latter statement was primarily derived from the work of Kandil and Dessey²⁰ who compared the reactivities of three carbanions generated in close proximity to acetylenic groups at different geometrical arrays - a *divergent* angle of 60° , *parallel* (angle of 0°) and a *converging* angle of 60° . No cyclic products were obtained when the angle was divergent (2.009). For parallel orbital arrangement 2.011, however, the anionic species cyclized in a 5-endo-dig fashion (2.012). When the geometry of the two functional groups was fixed at a *convergent* angle of 60° (2.014), the aryl anion cyclized exclusively in a 5-exo-dig fashion (Figure 4).

At that time, the absence of the 4-exo product in the "parallel arrangement" case constituted the only available experimental evidence which could be interpreted in favor of an acute attack upon the alkyne moiety. However, this example significantly distorts the intrinsic selectivity due to the additional strain imposed by the polycyclic core on the 4-exo product, whereas the observed lack of 6-endo cyclization products in the less

Table 2. Reaction Energies, Attack Angles, and LUMO Plots Visualizing the Arrangement of Alkyne π^* -Orbital and Nucleophile Lone Pair for the Parent Anionic Additions to Acetylene at the B3LYP/6-31+G(d,p) and M05-2X/6-31+G(d,p) Levels of Theory^a

Nucleophilic addition	ΔE_r , kcal/mol	CC...Nu angle at TS and Product	Nu...C distance at the TS, Å	LUMO of the TS
$\text{HC}\equiv\text{CH} + \text{CH}_3^-$	-48.0 (-51.8)	TS: 120.5 (114.0) P: 123.8 (123.4)	2.763 (2.606)	
$\text{HC}\equiv\text{CH} + \text{NH}_2^-$	-34.6 (-35.8)	TS: 134.6 (122.5) P: 129.3 (128.7)	2.535 (2.435)	
$\text{HC}\equiv\text{CH} + \text{OH}^-$	-23.4 (-25.3)	TS: 132.3 (129.1) P: 129.1 (121.7)	2.309 (2.206)	

^a M05-2X data are given in parentheses.

strained “convergent” pattern is inconsistent with the suggested preference for the acute trajectory (Figure 4).

The proposed digonal trajectory also does not satisfy the stereoelectronic requirements for nucleophilic attack at a π -bond. Basic MO considerations suggest that a better trajectory for attack at the alkyne π^* -orbital is provided by the obtuse approach, analogous to the Bürgi–Dunitz trajectory for trig cyclizations (Figure 6). Indeed, a substantial body of experimental and computational evidence supports this notion, indicating that the Baldwin rules for alkynes need to be redefined (*vide infra*).

In an early computational challenge to the acute attack trajectory, Strozier, Carmella, and Houk calculated transition states for the attack of a hydride anion at acetylene and ethylene.²¹ Not only were the transition state energies found to be very similar for acetylene and ethylene (16.7 and 16.6 kcal/mol) but the angle of attack was also found to be quite similar for the two substrates, with a CC-Nuc angle of 127° and 124°, respectively,²² very different from the 60° acute attack suggested by Baldwin.⁴

Recent higher level calculations²³ have not changed this alternative stereoelectronic preference, providing further support to the notion that the obtuse geometry provides the best trajectory for nucleophilic attack at the triple bond and that TS geometries for nucleophilic addition to alkynes and alkenes are generally similar.

The representative intermolecular attack angles by three nucleophiles (CH_3^- , NH_2^- , OH^-) on the triple bond of ethyne are shown in Table 2.²⁴ Although the angle changes from ~115° to 130° with the transition from an early TS to a late TS, all data agree with the intrinsic stereoelectronic preference for obtuse attack.

The obtuse nucleophilic attack trajectory is also supported by basic stereoelectronic considerations, as this approach avoids the interaction of incoming nucleophiles with the nodal plane of π^* -orbital. If this analysis is applied to the intramolecular nucleophilic attack at the alkyne moiety (aka nucleophilic dig-cyclization), *the obtuse trajectory should be translated into stereoelectronic preference for the exo attack*, in close analogy to that of trig-cyclizations.

It is also important to note that alkynes have two orthogonal π -bonds, thus alleviating the need for the nucleophile to deviate out of plane in order to reach the ideal Bürgi–Dunitz attack at

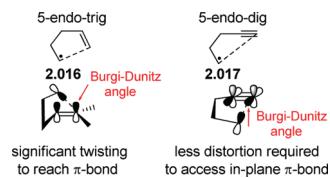


Figure 5. Stereoelectronic differences between alkenes and alkynes arising from the presence of the in-plane π -system in alkynes.

the π^* -orbital. Instead, the incoming reactive center (radical, cation, anion, radical-cation, radical-anion) can attack the *in-plane* π -bond, thus, avoiding the additional distortion penalty inherent to, for example, the 5-endo-trig process (Figure 5).

Alabugin, Gilmore, and Manoharan have recently examined the stereoelectronics of ring closures onto terminal and substituted alkynes for carbon and heteroatom anions and radicals.²⁴ It was observed that as the linker length increases, the obtuse angle of the exo attack decreases from 140° (3-exo) to 116° (5-exo) for carbanions, approaching the angle of intermolecular attack (Table 2).

For the endo attack in small cycles, the cyclic constraints impose an acute angle of nucleophilic attack (76° for 4-endo and 82° for 5-endo closures). As the cycle size increases, the angle of attack changes to a more favorable obtuse approach in 6-endo-dig closure (99°). As expected, 4-endo and 5-endo cyclizations have much earlier transition states than the less exothermic competing exoclosures.

At the same time, the incipient C···C distance increases in the exo-series, indicating earlier transition states for the more exothermic cyclizations (3-exo < 4-exo < 5-exo). As will be discussed individually below, comparison of the intrinsic energies²⁵ shows that, in every case, independent of the nature of nucleophile and alkyne substitution, exo cyclizations have lower intrinsic barriers than their endo competitors. Interestingly, the intrinsic exo barriers change relatively little (12–16 kcal/mol), indicating that such variations in the attack trajectory are well tolerated.²⁴

2.4. Differences Between Nucleophilic, Radical, and Electrophilic Trajectories

Another potentially controversial aspect of the Baldwin rules is whether their utility extends beyond nucleophilic closures. Although Baldwin mentioned in his seminal paper that this treatment “also applies to homolytic and cationic processes”,⁴ this statement is valid only in the most general sense as a suggestion that basic stereoelectronic premises based on favorable trajectories would exist for other reactive intermediates. However, one cannot simply “transfer” the guidelines, because the very nature of bond-forming interactions that define the favorable trajectories depends strongly on the attacking species.

For example, the ubiquitous cationic 1,2-shifts involved in the textbook Wagner–Meerwein rearrangements are topologically analogous to the anionic 3-endo-tet process. Although the anionic processes are clearly unfavorable as illustrated by the nonconcerted nature of the [1,2]-Wittig and related anionic rearrangements,²⁶ the ubiquity of cationic processes shows that frontside approach is allowed for electrophilic attack at a σ -bond.

Why do the stereoelectronic requirements differ for nucleophilic and electrophilic attacks? As discussed above, the most important stabilizing two-electron interaction for a nucleophilic attack is the interaction of nucleophile’s HOMO with the

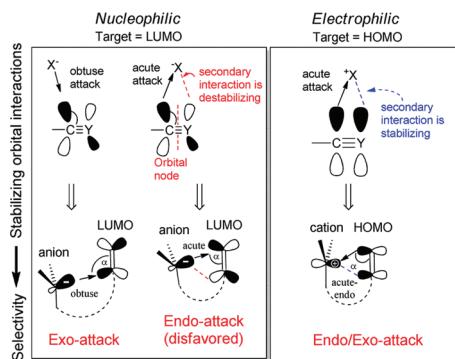


Figure 6. Comparison of orbital interactions and the expected regioselectivities for nucleophilic (left) and electrophilic (right) cyclizations of alkynes. Dominant stabilizing interactions are shown with straight arrows, secondary (stabilizing or destabilizing) interactions are shown with dashed lines.

substrate's LUMO. Such interaction is maximized by an obtuse angle of attack at a π^* -system (alkene or alkyne) or by a backside attack at a σ^* C—Y. Both of the above approaches also minimize the destabilizing HOMO/HOMO interactions (Figure 6). In contrast, attack of an electrophile at a π -bond (alkene or alkyne) is controlled by a favorable 2e-interaction between the electrophile LUMO and the π -bond HOMO. The latter interaction favors an acute trajectory, which brings electrophiles at the center of the π -bond on route to the formation of 3-center, 2-electron nonclassical cations, common species in carbocation chemistry. This trajectory should enable both endo- and exo-ring closures.

In the case of a radical attack at a π -bond, a nearly perpendicular trajectory is observed, as a compromise between the interactions of the SOMO with both the π and π^* alkene/alkyne orbitals.²⁷ Note that the intrinsic differences in the underlying stereoelectronic stabilizations should make endo cyclizations more favorable for cationic species and, to some extent, to electrophilic radicals. As will be discussed in the individual sections below, the differences between the activation barriers of exo- and endocyclic closure are smaller for radicals than for the respective anions, to the point where the more electrophilic oxygen radicals favor 6-endo closure over 5-exo-dig.²⁴

2.4.1. Nucleophile-Promoted Electrophilic Cyclizations.

Unlike nucleophilic and radical closure, electrophilic²⁸ digonal cyclizations are relatively scarce. One reason for this scarcity is that endocyclic closures should lead to the formation of cyclic vinyl cations. These species are sp-hybridized and significantly destabilized by the deviation from linearity imposed by inclusion in a small ring.²⁹ For example, cyclohex-1-enyl and cyclopent-1-enyl cations, with 156° and 141° valence angles at the cationic carbon, are 17 and 27 kcal/mol less stable than the linear (179°) prop-1-enyl cation.³⁰ Cyclobut-1-enyl cation exists as a non-classical bridged ion³¹ and ab initio calculations fail to find a stationary-state structure for the smallest cycloprop-1-enyl cation which opens instead to form prop-2-ynyl cation.^{29b}

Despite this scarcity, the relatively scattered data presented for the individual cyclizations patterns discussed in the following sections will illustrate that, in the absence of strongly directing group, electrophilic cyclizations of alkynes exhibit a notable preference for endocyclic closure, suggesting that the cyclizations of cations have different stereoelectronic preferences in comparison to analogous nucleophilic and radical ring closures (see section 2.4). The delicately poised balance in such closures is

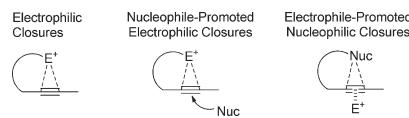


Figure 7. Distinction between electrophilic cyclizations, nucleophile-promoted electrophilic closures (NPEC) and electrophile-promoted (EPNC) nucleophilic closures.

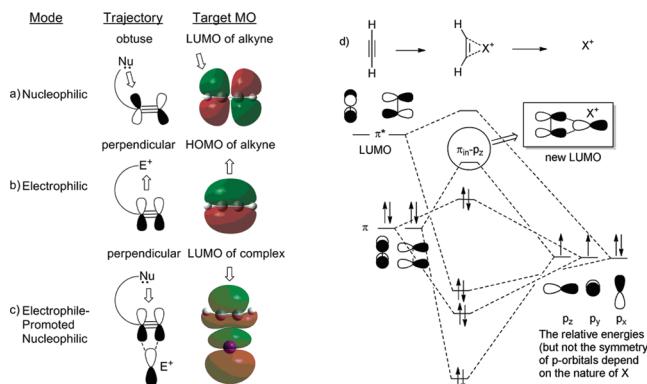


Figure 8. Summary of key stereoelectronic factors involved in bond forming interactions during different modes of ring formation from alkynes. (a, b) The FMOs of C_2H_2 . (c) The LUMO of the I^+ -acetylene complex. Note the analogous symmetry of the top part of the LUMO of the complex and the acetylene HOMO. (d) MO mixing diagram which shows how the alkyne LUMO symmetry changes upon coordination.

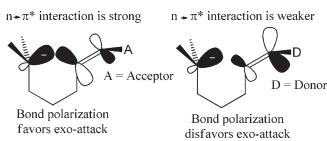
particularly well represented by the 3-exo-/4-endo-dig competition, where both products are formed from a common nonclassical cation intermediate via two alternative directions of nucleophilic attack (see section 3.1.3). The regioselectivity of the nucleophile's attack is dictated by the partial positive charge on the alkynyl carbons, which is determined by the adjacent substituents.

Interception of an incipient vinyl cation by an external nucleophilic attack has been described by Overman and Sharp as a "Nucleophile-Promoted Electrophilic Cyclization" (NPEC).^{32,33} This mechanism provides the only thermodynamically feasible path for endo-dig cationic cyclizations leading to the formation of small cycles.

2.4.2. Electrophile-Promoted Nucleophilic Cyclizations: Effect of External Electrophile on Trajectory. The upturning of NPEC, where an external electrophile coordinates to a π -system, activating it for intramolecular nucleophilic attack, has been described as electrophile-promoted nucleophilic closure (EPNC).²⁴

Although these relatively common cyclizations are sometimes misleadingly referred to as "electrophilic" cyclizations, these two processes are mechanistically different, as illustrated in Figures 7 and 8. Whereas a truly electrophilic closure involves an *intramolecular* attack of an *electrophile* (e.g., carbocation, oxonium, iminium ions) at a π -bond in a *cycle-closing* bond formation, electrophile-induced nucleophilic closures involve *intramolecular nucleophilic* attack at the triple bond. The role of an *external* electrophile (a metal, halogen, selenium, etc) is to coordinate to the π -bond that is subsequently attacked intramolecularly by an internal *nucleophile*. Because it is the nucleophilic attack at a π -bond that closes the cycle, referring to such closures as electrophilic is misleading, even when these reactions do not proceed in the absence of the electrophilic agent.

Scheme 4. Effect of π^* -Orbital Polarization on the Magnitude of Stabilizing Orbital Interaction in a 5-exo-trig Nucleophilic Attack at a π -Bond



Another reason why EPN cyclizations should be considered separately is that reactions which involve the coordination of an external species do not fall under the umbrella of the original Baldwin rules because such coordination modifies the nature of alkyne frontier molecular orbitals (FMOs, Figure 6, Figure 8). For example, even though in *both* the nucleophilic and EPN closures, the nucleophilic attack on an alkyne follows a trajectory which maximizes the overlap between the LUMO of the acetylene and HOMO of the nucleophile, the acetylene LUMO symmetry is *very different* for the two cases.

As the LUMO of free alkynes is a π^* -orbital, purely nucleophilic closures should exhibit exo preference because endo approach brings nucleophile at the π^* -orbital node.

However, when a suitable Lewis acid (LA) complexes with a triple bond, the antibonding combination of alkyne HOMO and empty orbital of the LA creates the new LUMO. Although this orbital is antibonding *between* the LA and alkyne, it has the same symmetry as the original alkyne HOMO (a π -orbital) from the point of an incoming nucleophile. Thus, orbital symmetry offers no additional penalty for an acute attack along the trajectory, analogous to that of an electrophilic species. Because there is no stereoelectronic penalty for the formation of endo products, in contrast to the usual nucleophilic attack at the π^* of a "naked" alkyne (Figure 8), the regioselectivity of nucleophilic closures is often reversed upon addition of an external electrophile such as I_2 .³⁴ The change in the symmetry of the acetylenic LUMO as a result of such coordination enables endocyclic closures in the same way as endo cyclizations of electrophilic species are enabled because of favorable overlap of cationic center with the HOMO of acetylene.

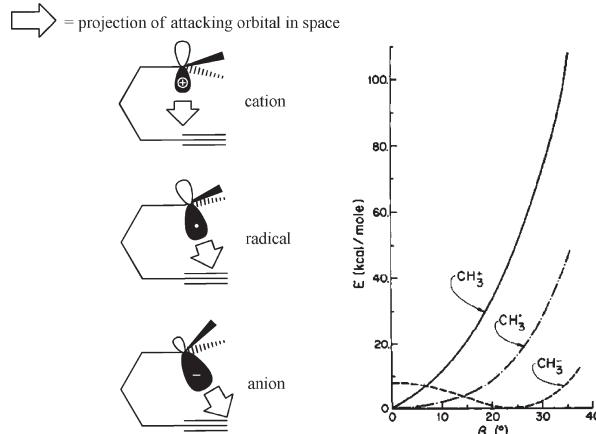
Since a recent review by Godoi, Schumacher, and Zeni provided comprehensive coverage of EPN cyclizations,³⁴ detailed coverage of this topic is out of the scope of this review. For each section, we will only provide a selection of examples to illustrate the reversal of regioselectivity that is observed in a variety of cases when a metal or external electrophile is coordinated to the alkyne.

2.5. Secondary Electronic, Structural, and Geometric Effects on Cyclization Trajectories

2.5.1. Orbital Polarization. Orbital factors in the TS can also be modulated by polarization of the π -bond by an appropriately positioned donor or acceptor substituent. For the substitution pattern illustrated in Scheme 4, the exo cyclization mode would be facilitated by a terminal acceptor and disfavored by a terminal donor group.

2.5.2. Distortions. Setting aside the more complex non-statistical dynamics analysis of reaction trajectories of Carpenter,³⁵ additional factors have to be considered in analyzing the overall energy landscape on the way from an acyclic reactant to a cyclic product. Equally important to the stabilizing two-electron bond-forming interactions are the

Scheme 5. (Left) Differences in the Intrinsic Orientation of the Attacking Orbital at the Reactive Intermediate Center Caused by Progressive Increase in Pyramidalization in Radicals and Anions and (Right) the Total Energies for Deformation of Methyl Reactive Intermediates (β = Deviation from the Molecular Plane)^a



Reproduced with permission from ref 38. Copyright 1976 American Chemical Society.^a LCAO-SCF-MO/4-31G level.

destabilizing effects associated with the deformation of acyclic reagents from their ideal geometries needed in order to reach the TS.³⁶ The energy cost for pyramidalization of alkenes³⁷ and bending in alkynes, as well as strain in the bridge should be considered.

Distortion at the Reactive Intermediate Center (Anion versus Radical versus Cation; Carbon versus Heteroatom). Although the original Baldwin rules concentrated on the orientation and nature of the breaking bond (both exo/endo and tet/trig/dig notations refer to this bond), the requirement of orbital alignment applies to both partners. In particular, the stereoelectronic properties of the attacking orbital and its orientation in space can impose significant effect on the efficiency and regioslectivity of cyclizations. Subsequent work on enolexo and enolendo cyclizations illustrates this point very well.^{6,7} Scheme 5 illustrates how structural deviations along the reaction coordinate also include energy cost for changing the geometry at the reactive center (e.g., pyramidalizing a cation, or planarizing an anion). These data suggest that the anion is the most flexible reactive intermediate, whereas pyramidalization of cations leads to a significant energy penalty.³⁸

The effect of the nature of the attacking atoms on the preferred attack trajectories is not well understood but deserves a more careful study in the future. For example, one would expect that the presence of the two lone pairs at a neutral oxygen atom may increase stereoelectronic flexibility relative to an analogous nitrogen nucleophile with a single lone pair where stereoelectronic adjustments are mostly limited to rehybridization.³⁹

Interestingly, after suggesting the initial preferred angle of attack of 105 ± 5 degrees at a carbonyl moiety by nitrogen nucleophiles, Bürgi et al. performed the same analysis for an oxygen nucleophile attacking a carbonyl ($O \cdots C=O$) and found that the approach angle varied in the broad region of $90\text{--}130^\circ$ with the strongest interactions occurring at an approach of about 110° .¹⁶

Distortion of the Target π -System. In a thorough comparison of pyramidalization of nonbridgehead alkenes and the bending of

alkynes, Borden noted that while the “*trans*-bending of acetylene is considerable easier than anti-pyramidalization of ethylene..*cis*-bending of acetylene has a force constant about 25% greater than that for the syn-pyramidalization of ethylene.”^{37,40} He also identified orbital interactions responsible for making anti-pyramidalization less energetically costly than the syn-pyramidalization in ethylene. Pyramidalization of alkenes also leads to significant orbital changes: the LUMO energy is strongly lowered whereas the HOMO energy is increased, albeit to a lesser extent.^{41,42}

In a thorough computational analysis of “strain-promoted” click reactions with phenyl azide, Houk et al.⁴³ have shown that the distortion of the alkyne moiety in cyclooctyne can provide up to 60% of the barrier decrease (4.6 out of 8 kcal/mol).^{44,45}

Alabugin and Manoharan estimated the energy cost for alkyne bending along the Bergman cyclization pathway, comparing hex-3-ene-1,5-diyne with cyclic enediynes.⁴⁶ While a significant reactant destabilization (~13 kcal/mol) is observed upon constricting the parent enediyne with the 9-membered cycle, the acetylene bond breaking was found to be of only minor importance as indicated by the negligible changes in the C1–C2 NBO π -bond orders (both in-plane and out-of plane) at C1–C6 distances above 3 Å. For Z-hex-3-ene-1,5-diyne, this negligible change in bond order is notable as the C1–C6 distance in the starting geometry is 4.1 Å. The CCC bond angle at this distance (3 Å) is 152°, showing the high flexibility of this functional group. Even at the TS, the π -bonds are only 30% broken.⁴⁷

The effect of acetylene bending on FMO orbital energies and shapes has been analyzed extensively. A significant difference between alkynes and alkenes is that upon *trans*-bending the LUMO of acetylene drops in energy two to three times faster than that of ethylene. While the LUMO drops in a bent transition state, there is an increase in the charge-transfer and electrostatic interactions, which is the cause of the increased reactivity of acetylenes over ethylenes toward nucleophilic attack. However, the authors state, “Bending has very little effect on HOMO energies, so that no “driving force” for bending is present upon interactions with electrophiles.”²¹ Houk et al. used these arguments to correlate the enhanced electrophilicity of benzyne with the LUMO energy lowering in this highly bent alkyne.^{21,48} However, recent HF calculations with a larger 6-311++G(2d,p) basis set suggest that the *cis*-LUMO drop may be smaller than suggested earlier.⁴⁹

The correlation of angle strain and electronic structure of cyclic alkynes is consistent with electron transmission spectroscopy data by Ng et al.⁵⁰ Comparison of vertical electron affinities (EAs), which according to the Koopmans’ theorem correlate with the unfilled orbitals energies, show a strong dependence of the LUMO energy on the degree of bending. For example, the EA of cyclooctyne, where the triple bond is bent by 21.5° increases by ~1 eV in comparison with that in di-*tert*-butylacetylene. In accord with the calculations discussed above, the π and π^* orbital energies, taken as the negatives of the vertical ionization potential (IP) from Photoelectron Spectroscopy (PES) and the vertical EA, respectively, suggest that bending has very little effect on the HOMO.⁵⁰

Deviation from Ideal Trajectories. The favorability of cyclization modes depend strongly on how far reactions can deviate from the previously discussed trajectories without an insurmountable increase in activation energy, and whether one should consider an ensemble of trajectories instead of a single preferred path.⁵¹ Historically, there were conflicting views on this problem. For example, the “orbital steering” theory, related to enzymatic

reactions, proposed that a 10° misalignment of reactant groups relative to an ideal orientation would result in a large decrease in rate,⁵² something that has been disputed in a subsequent literature.^{53,54}

Probing such effects in model systems, Menger and co-workers investigated lactonization reactions in a rigid norbornyl system. By exchanging positions of the hydroxyl and carboxylic acid moieties, the trajectory angles were changed by 10°, yet nearly identical rates of lactonization were obtained, demonstrating that angular displacement of a few degrees is not kinetically significant.⁵¹ Lipscomb et al. also found that potential energy surfaces for carbonyl additions “point strongly to a highly deformable TS.” For example, the addition of methanol to formic acid occurs via a reaction “funnel” that occupies approximately 18% of the hemispherical surface centered at the carbonyl carbon.⁵⁵ Our recent calculations also found little change (12.4–16.2 kcal/mol) in the intrinsic barriers of carbon radical 3-exo-, 4-exo-, and 5-exo-dig closure onto methyl substituted alkynes, even though the angle of attack in the TS ranges from 140° (3-exo) to 116° (5-exo),²⁴ further suggesting that deviation from the ideal intermolecular trajectory is tolerated.

2.6. Thermodynamic Contribution to the Reaction Barriers

It is important to bear in mind that kinetic preferences described by the Baldwin rules are not applicable to transformations that proceed under thermodynamic control. For such situations, relative reaction exothermicities can play a role in determining the cyclization outcome. The entropically disfavored dig and trig cyclizations are usually driven enthalpically by the formation of stronger bonds (e.g., trading a π -bond for a σ -bond). The nature of bonds involved in the ring formation should be considered carefully, in particular for the formation of heterocycles.⁵⁶ If a thermodynamic driving force for the process is small or if the cyclizations is endothermic, kinetic preferences embodied in the Baldwin rules will not be applicable.

However, thermodynamic contributions are important even when reactions proceed under kinetic control because thermodynamic factors can relax stereoelectronic requirements (optimal trajectories) for exothermic cyclizations and modify kinetic preferences embodied in the Baldwin rules in two indirect ways.

First, in accord with the Hammond-Leffler postulate,⁵⁷ exothermic reactions have earlier, reactant-like transition states and consequently require less distortion from the reactant geometry. Decreased distortions alleviate geometric requirements needed to reach the optimal bond-forming trajectories.

Second, favorable thermodynamic contribution directly lowers activation barriers of exothermic cyclizations relative to the intrinsic barrier of an analogous thermoneutral reaction (as illustrated by stereoelectronically unfavorable but highly exothermic reactions with low activation barriers, such as 5-endo-trig cyclizations in the formation of acetonides from 1,2-diols).⁵⁸ As a result, it is inappropriate to compare intrinsic stereoelectronic favorabilities of two reactions with different exothermicities. Such comparisons have to be done for reactions with equal thermodynamic driving force (Figure 9).

The effect of thermodynamics on the activation barrier can be estimated via subtraction of thermodynamic contributions estimated using Marcus theory.^{59–61} In this approach, the energy of activation (ΔE^\ddagger) of a reaction is the sum of the intrinsic barrier and the thermodynamic contribution. The intrinsic barrier (ΔE_o^\ddagger) represents the barrier of a thermoneutral process

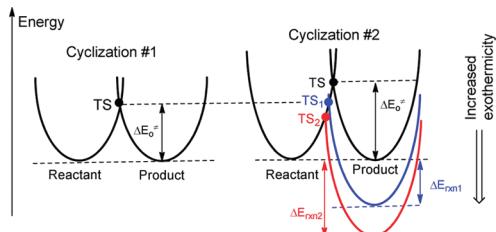


Figure 9. Thermodynamic effects on the activation energy and use of Marcus theory for approximating potential energy curves and separating intrinsic barriers from thermodynamic contributions. In the absence of a thermodynamic bias, the intrinsically unfavorable cyclization #2 has a higher barrier. The parabolic model illustrates how the activation barrier for the unfavorable cyclization becomes identical (blue curve) to the overall barrier for the favorable reaction #1. When the thermodynamic driving force for reaction #2 increases further (red curve), this cyclization becomes more kinetically favorable than the initially favored process #1.

($\Delta E_{rxn} = 0$). The thermodynamic contribution can be either positive or negative depending upon whether the reaction is endothermic or exothermic. The activation energy increases when $\Delta E_{rxn} > 0$ (an endothermic reaction) and decreases when $\Delta E_{rxn} < 0$ (an exothermic reaction). When potential energy surfaces for the reactants and the products are approximated as parabolas, the Marcus barriers can be calculated from eq 1.

$$\Delta E^\ddagger = \Delta E_o^\ddagger + \frac{1}{2}\Delta E_{rxn} + (\Delta E_{rxn})^2/16(\Delta E_o^\ddagger) \quad (1)$$

Alternatively, when the energy of activation (ΔE^\ddagger) and reaction energy (ΔE_{rxn}) are known, one can estimate the intrinsic barrier (ΔE_o^\ddagger) from the eq 2. Equation 2 allows a comparison of intrinsic stereoelectronic properties for cyclizations of different exothermicities.

$$\Delta E_o^\ddagger = \frac{\Delta E^\ddagger - \frac{1}{2}\Delta E_R + \sqrt{\Delta E^{dd2} - \Delta E^\ddagger \Delta E_R}}{2} \quad (2)$$

This analysis affords the understanding as to how even intrinsically unfavorable reactions become competitive once made sufficiently exothermic (Figure 9). This is an important caveat in using the stereoelectronic arguments incorporated in the Baldwin rules for a priori predictions of regioselectivity in a ring closure. To illustrate the potentially misguiding effect of thermodynamics, let us consider the 5-exo/6-endo competition shown in Figure 10. The two reactions have almost identical activation barriers (difference of 0.2 kcal/mol). Does it mean that the two cyclizations are equally favorable stereoelectronically? How does the much greater exothermicity of the aromatic 6-endo-dig product formation ($\Delta E_{rxn} \approx 36$ kcal/mol) affect the activation barrier? Can this effect be large enough to mask the intrinsic trends arising from the orbital alignment requirements? These questions can be readily answered by the energy dissection described above, which can be used to estimate barriers for the situation where 5-exo- and 6-endo-dig cyclizations would have identical exothermicities. For this hypothetical scenario, the 6-endo cyclizations barrier would be much higher (~15 kcal/mol) than that for the 5-exo closure (~5 kcal/mol) and the 6-endo-dig cyclization would not be kinetically competitive (Figure 10). This example illustrates how selective thermodynamic

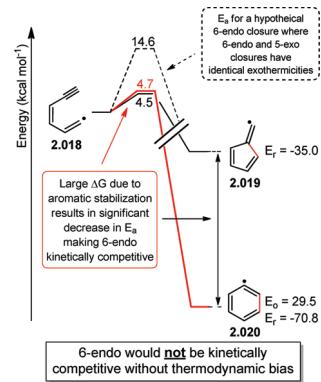


Figure 10. Effect of aromatic stabilization of the 6-endo product on the kinetic competition between 5-exo-/6-endo-dig closures of fully conjugated substrates.

stabilization of the product can mask the intrinsic kinetic preferences based on transition state stereoelectronics.

2.7. Rules for Alkynes: Time to Reevaluate?

In summary, the guidelines regarding the cyclizations of alkynes need to be reassessed and expanded. In particular, the proposed dramatic difference in favorable trajectories for alkynes and alkenes and the subsequent predictions that endo-dig cyclizations are “favorable”, even though the analogous endo-trig cyclizations of alkenes are unfavorable, has to be reevaluated.

The following sections will provide a detailed analysis of the available experimental and theoretical data regarding specific patterns of digonal cyclizations. We will organize this analysis by comparing pairs of reactions that correspond to competing regioselectivities of attack at the same breaking bond (3-exo/4-endo, 4-exo/5-endo, 5-exo/6-endo). Since each of these pairs originates from a common starting material, this choice eliminates many variables of comparison. The caveat, however, is that the observed lack of one of the two possible cyclizations only means that the missing reaction is “relatively” unfavorable in comparison to the observed alternative closure. Different types of reactive intermediates (cations, radicals, anions) for each of the pair will also be examined individually as these intermediates have different stereoelectronic preferences. Following this detailed examination of the literature, the refined rules for digonal cyclizations²⁴ will be discussed.

3. SPECIFIC PATTERNS OF DIGONAL CYCLIZATIONS

This section of the review will constitute a comprehensive review of the literature from 1993-middle of 2010. Pre-1993 work will be incorporated for the scarcely studied topics where only a few examples are available. Closures involving external electrophiles such as metals or halonium ions, for reasons described above (see section 2.4.2), are described only briefly because of their in depth discussion in an excellent recent review.³⁴ The comprehensive coverage will be limited to cyclic systems that include only the first row elements. Heavier elements will be included only in selected cases.

While the activation and intrinsic barriers, as well as the exothermicities, for carbon-, oxygen-, and nitrogen-centered radical cyclizations are similar (vide infra), there is a gap in the literature regarding the closures of the heteroatomic radicals onto carbon–carbon triple bonds.^{62,63} The cyclizations of these species

in trigonal systems, however, has been well documented,¹⁵ particularly for oxygen radicals.⁶⁴

We have organized each section in several “motifs” (Scheme 1), each of which represents a certain combination of attacking species, substitution at the target alkyne and nature of the tether that lead to a characteristic selectivity pattern.

3.1. 3-exo versus 4-endo

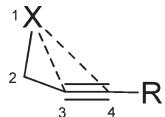


Figure 11

Even though the formation of a σ -bond at the expense of a π -bond is usually favorable, there are very few examples of the synthesis of highly strained three- and four-membered rings through attack at an alkyne. While 4-endo-dig cyclizations are favored by the original Baldwin rules, to the best of our knowledge, there are no examples of simple nucleophilic closures which follow this path and fit into the criteria of this work. However, there are a few examples of the originally “disfavored” 3-exo-dig closure proceeding through both anionic and cationic paths. Interestingly, 4-endo-dig closures are reported only for NPE cyclizations, lending strong support to the notion that the stereoelectronic guidelines are different for nucleophiles and electrophiles (*vide supra*).

3.1.1. Radical Cyclizations These processes have only been studied computationally. Computational data suggest that the greatest obstacle for the formation of small cycles via these processes is not kinetic but thermodynamic. The radical 3-exo- and 4-endo-dig cyclizations of carbon radicals are endothermic and, thus, are unlikely to be practically viable in their simplest versions as presented in Table 3. These data are consistent with the absence of 3-exo- and 4-endo-dig radical cyclizations in the literature. In agreement with the microscopic reversibility principle, the same stereoelectronic factors which facilitate 3-exo cyclizations render the opening of the strained cyclopropyl rings favorable as well. Indeed, the cyclic products of such exo cyclizations are expected to undergo a fast ring-opening, similar to the ring-opening of cyclopropylmethyl radicals.⁶⁵ However, the significant decrease in endothermicity for the cyclization of the Ph-substituted alkyne suggests that, with a proper effort, it may be possible to shift the equilibrium in favor of the cyclic form and to design efficient 3-exo-dig radical cyclizations, as has been accomplished for the respective trigonal closures (Table 4).¹⁵

3.1.2. Anionic Cyclizations (Table 5). These processes have been unknown experimentally until Johnson and co-workers found that, upon exposure to a source of fluoride ions, silyl enol ethers undergo 3-(C-allylexo)-exo-dig cyclizations (motif F, Scheme 1).⁶⁶ The cyclic closure is rendered irreversible via elimination of a propargylic halide, yielding substituted vinylidene cyclopropanes (VCP) in up to 95%. A similar strategy can be used for transforming acyclic diesters into 3-exo-dig products in 62–90% yields (Scheme 6). This work illustrates that even the thermodynamically unfavorable formation of a small cycle can be kinetically accessible when coupled with a subsequent highly exothermic step.

To the best of our knowledge, there are no examples of nucleophilic 4-endo-digonal closures that do not include the

Table 3. Activation, Reaction, and Intrinsic Energies (kcal/mol) for the Parent 3-exo- and 4-endo-dig Radical Digonal Cyclizations at the B3LYP/6-31+G(d,p) and M05-2X/6-31+G(d,p) Levels of Theory^a

Entry		E _a	ΔE _r	ΔE _o
1		16.3 (17.3)	8.2 (7.2)	11.8 (13.5)
2		36.4 (38.3)	5.4 (4.3)	33.7 (36.1)
3		18.3 (19.7)	12.0 (10.9)	11.5 (13.7)
4		34.2 (36.9)	10.8 (10.5)	28.5 (31.4)
5		15.2 (16.9)	8.8 (7.7)	10.3 (12.8)
6		32.3 (35.4)	13.3 (12.1)	25.2 (29.1)

^aThe M05-2X data are given in parentheses. Ring-closing bonds are shown in red.

Table 4. Activation, Reaction, and Intrinsic Energies (kcal/mol) for the Parent 3-exo- and 4-endo-dig Radical Digonal Cyclizations at the B3LYP/6-31+G(d,p) and M05-2X/6-31+G(d,p) Levels of Theory^a

Entry		E _a	ΔE _r	ΔE _o
1		16.6 (17.7)	8.2 (7.1)	12.3 (13.9)
2		34.4 (36.1)	6.1 (4.7)	31.3 (33.7)
3		12.4 (13.4)	2.4 (1.7)	11.2 (12.5)
4		35.0 (35.7)	5.4 (3.1)	32.2 (34.2)
5		15.4 (16.0)	8.6 (7.7)	10.7 (11.9)
6		37.6 (38.6)	13.8 (11.6)	30.3 (32.6)

^aThe M05-2X data are given in parentheses. Ring-closing bonds are shown in red.

Table 5. Literature Examples of 3-exo/4-endo-dig Anionic Closure with Respect to the Environment of the Anionic Center^a

Motif	3-exo	4-endo
F		✗

^aAn ✗ denotes a gap in the literature. Motif structures are given in Scheme 1. Motifs A–C and G–H are unknown, and D and E do not apply to anionic closures.

addition of metals or external electrophiles. Recent computational analysis²⁴ suggests that this gap reflects the inaccuracy of the original

Scheme 6. 3-exo-dig Cyclizations of Enolates and Propargylic Alcohols

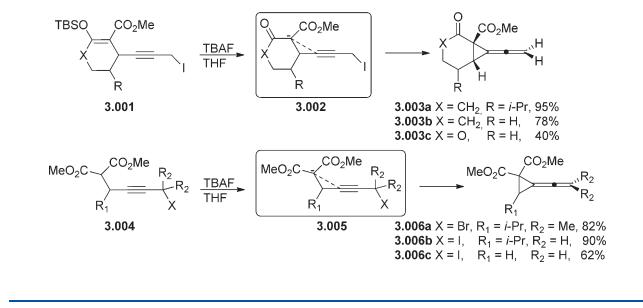


Table 6. Activation, Reaction, and Intrinsic Energies (kcal/mol) for the Parent 3-exo- and 4-endo-dig Anionic Digonal Cyclizations at the B3LYP/6-31+G(d,p) and M05-2X/6-31+G(d,p) Levels of Theory^b

Entry		E _a	ΔE _r	ΔE _o
1		7.8 (9.2)	-5.4 (-7.5)	10.3 (12.7)
2		29.5 (32.3)	-11.8 (-14.0)	35.2 (39.0)
3		13.6 (12.6)	10.4 (6.0)	7.5 (9.3)
4		38.7 (39.1)	6.6 (1.3)	35.3 (38.4)
5		- ^a	- ^a	NA
6		46.5 (46.1)	21.9 (19.0)	34.7 (35.9)

^a The ring-opening reaction is barrierless. ^b The M05-2X data are given in parentheses. Ring-closing bond shown in red.

Baldwin rules rather than difficulties in trapping the cyclobutenyl reactive intermediate before it undergoes ring-opening or another unproductive reaction. On the basis of the >20 kcal/mol difference in activation barriers between 3-exo and 4-endo closures, the absence of nucleophilic 4-endo-dig cyclizations is not surprising, even though the parent 4-endo-dig cyclization is about ~7 kcal/mol more exothermic than its 3-exo-dig counterpart (Table 6, Figure 13).

Anion-stabilizing substituents at the terminal alkyne carbon slightly increase the calculated kinetic preference for the 3-exo-dig closure (Table 7).

Although only computational data are available for this class of cyclizations, they provide sufficient background for illustrating the key trends. The remarkably high activation energy (~30 kcal/mol) for the >10 kcal/mol exothermic 4-endo-dig cyclization of parent but-3-ynyl carbanion⁶⁷ was attributed to homoantiaromaticity^{24,68} and cancellation of the stabilizing $n_{\text{Nu}} \rightarrow \pi^*$ interaction for the acute trajectory which brings the nucleophile at the node of the alkyne in-plane π^* -orbital. The antiaromatic character of the 4-endo TS is illustrated by the positive NICS⁶⁹ value (Table 7) and is consistent with its 4n-electron count (Figure 12).

Table 7. Transition State Geometries, NICS (0) Values, and LUMO Plots for 3-exo/4-endo Carbanionic Cyclizations for the Me-Substituted Alkyne Calculated at the M05-2X/6-31+G** Level^a

Entry	TS Geometry	NICS(0), ppm		LUMO
		E _a	ΔE _r	
1		7.8 (9.0)	-4.5 (-7.4)	9.9 (12.4)
2		7.3 (6.2)	-7.7 (-13.5)	10.8 (12.0)
3		7.5 (6.5)	-3.3 (-7.6)	9.1 (9.9)
4		27.0 (29.4)	-13.0 (-16.1)	33.2 (37.0)
5		32.4 (32.1)	-12.1 (-19.0)	38.2 (41.0)
6		30.1 (30.9)	-4.0 (-8.5)	32.1 (35.0)

^a Bond lengths given in Å. Activation, reaction and intrinsic energies (kcal/mol) for the parent 3-exo- and 4-endo-dig anionic cyclizations at the B3LYP/6-31+G(d,p) and M05-2X/6-31+G(d,p) levels of theory. M05-2X data are given in parentheses. Ring-closing bonds are shown in red.

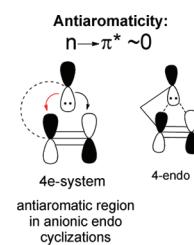


Figure 12. Homoantiaromaticity in an anionic 4-endo-dig transition state.

Even for the formation of strained cycles, all carbanionic cyclizations are exothermic and effectively irreversible due to the conversion of a weaker bond into a stronger bond (π -bond \rightarrow σ -bond) and the concomitant transformation of an alkyl anion into a more stable vinyl anion. This is true even for the formation of strained 3-exo and 4-endo products.

In contrast, the analogous cyclizations of the parent N- and O-centered anions transform a heteroatom-centered anion into a

carbanion. The energy cost due to this unfavorable change is substantial. For the N-anions, this effect renders 3-exo cyclizations ~ 10 kcal/mol endothermic, whereas 4-endo closure is essentially thermoneutral. For these cyclizations, B3LYP underestimates reaction exothermicity in comparison to M05-2X but the activation energies provided by the two methods and the higher level CCSD(T) calculations are similar. For the O-anion, all reactions leading to the formation of 3- and 4-membered rings are strongly endothermic. Such unfavorable cyclizations should be quickly reversible, for example, ring-opening of the 3-exo product has only ~ 3 kcal/mol activation barrier for the N-case, whereas the analogous opening to the more stable O-centered anion is barrierless in silico.

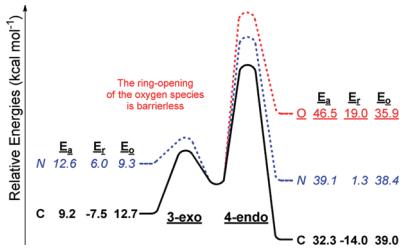


Figure 13. Electronegativity effects on the M05-2X/6-31+G** potential energy surfaces for the 3-exo-/4-endo-dig anionic cyclizations of C- (black solid, bold), N- (blue dashed, *italics*), and O- (red dashed, underlined) centered anions with terminal alkynes.

Table 8. Literature examples of 3-exo/4-endo-dig electrophilic closure with respect to the environment of the cationic center^a

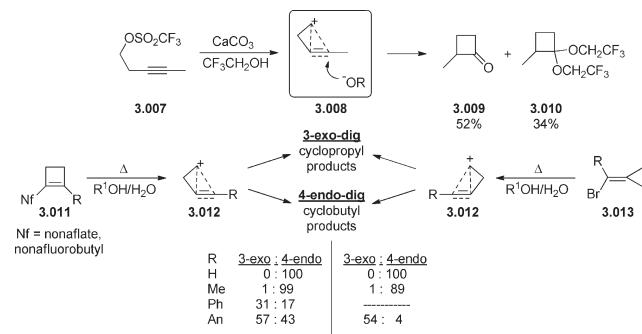
Motif	3-exo	4-endo
A	$R' \equiv C-X$ $X = CR_2$ $R' = Ph, cyclopropyl$	$R' \equiv C-X$ $X = CR_2$ $R' = H, Alkyl$

^a x marks denote gaps in the literature. Motif structures are given in Scheme 1. Motifs B–H are unknown.

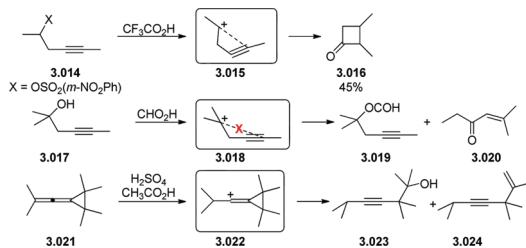
3.1.3. Electrophilic Cyclizations (Table 8). Hanack⁷⁰ and others⁷¹ have investigated the regioselectivity of the parent carbocationic cyclizations and found that, depending on the substitution pattern, products deriving from either a 3-exo- or 4-endo-dig closure can be obtained after trapping of the 3-center, 2-electron nonclassical carbocation by solvent. Through carbon-14 isotope effects, Hanack et al. determined that the bond-breaking and bond-forming events, which occur upon solvolysis of 1-pent-3-ynyl triflate, 3.007 are unsymmetrical and the process has a reactant-like transition state.^{70h} When terminal or alkyl-substituted triple bonds are employed, four-membered rings are mainly observed.^{70g} This observation agrees well with a computational study (MP2/6-311G(d,p) level) by Hopkinson and co-workers^{71c} who found that, for terminal alkynes, the primary vinyl cation (3-exo-dig product) exists only as a transition state between the two cyclobut-1-enyl cations (4-endo-dig product).

The same potential energy surface can be reached via solvolysis of cyclobutene or methylene cyclopropane derivatives. Only when cationic center 3.012 is stabilized by an aromatic or cyclopropyl group does 3-exo formation become favored (Scheme 7).^{70j} Hanack and co-workers also observed exclusive

Scheme 7. Substituent Effect on the 3-exo- versus 4-endo-dig Competing in an Electrophilic Ring Closure



Scheme 8. 4-Endo-dig Cyclizations of Secondary Carbocations and Lack of Cyclization in the Case of Stable Tertiary Carbocations



formation of the 3-exo-dig product for the alkynyl ethyl ether, which is capable of stabilizing the exocyclic vinyl cation through formation of an oxycarbenium intermediate.^{72,73} These reactions are excellent examples of NPE closure, as the regioselectivity of closure is dictated by the position of greatest partial positive charge and, with the possible exception of the alkynyl ethyl ether, the ring closure does not occur until effected by nucleophilic attack.

Secondary carbocations behave similarly, giving 4-endo-dig product 3.016 when the alkyne was substituted with a methyl group (Scheme 8).⁷² Tertiary carbocation 3.018, however, fails to undergo either 3-exo- or 4-endo-dig cyclizations,⁷⁴ presumably because of the higher stability of the acyclic 3° cation with respect to a vinyl cation and the absence of a strong-enough nucleophile to induce the NPEC. This is in full agreement with the work of Poutsma and Ibarbia,⁷⁵ as well as Pasto et al.,⁷⁶ who found that upon generation of cyclopropylidene carbonyl cations from alkenyldenecyclopropane 3.021, only the ring-opened products 3.023 and 3.024 were obtained.

3.1.4. Summary of 3/4. No examples exist of radical 3-exo- or 4-endo-dig closure. Based on the endothermicity and high activation barriers (particularly for 4-endo), these reactions may not be feasible unless a highly stabilizing group is adjacent to the cyclic vinyl radical or the product is trapped via an elimination reaction. Computational studies suggest that simple carbanionic closures are typically exothermic (Tables 6 and 7) because of the conversion of a primary alkyl anion into the more stable vinyl anion. However, only 3-exo closure of enolates has been achieved so far experimentally via coupling of the initial cyclizations product with an exothermic elimination reaction (Scheme 6), a

process that can only occur for exocyclic closure. The regioselectivity of the electrophilic closures of primary and secondary carbonium ions depends upon the substitution of the alkyne, directing nucleophilic attack via the buildup of partial positive charge. Cyclization is not observed for tertiary carbocations in the presence of weak nucleophiles (Scheme 8).

3.2. 4-exo versus 5-endo Cyclizations



Figure 14

Competition in this pair of cyclizations is fundamentally different from other pairs discussed in this work where the thermodynamic driving forces for the two competing cyclizations are similar (*both* products are either strained (3-exo/4-endo) or free of strain (5-exo/6-endo)) and where, in the case of nucleophilic and radical closures, there is usually a clear kinetic preference for the exo path. However, for the 4-exo/5-endo pair, one of the products (exo) is much more strained than the other (endo). As the result, the endo cyclization is much more exothermic, and the competition between 4-exo and 5-endo closure, onto both olefins⁷⁷ and alkynes, becomes delicately balanced due to the thermodynamic contributions selectively facilitating the endo closure (see section 2.6).

This competition also represents an interesting unresolved question regarding stereoelectronic factors in organic reactions. While the product of the stereoelectronically favorable 4-exo-dig closure suffers from considerable strain, the formation of a five-membered ring, via a nucleophilic closure, has to overcome stereoelectronic factors which disfavor anionic endo-dig cyclizations (Figure 6).

3.2.1. Radical Cyclizations (Table 9). Whereas both 3-exo- and 4-endo-dig radical closures were found to be endothermic processes with no examples in the literature (*vide supra*), 4-exo-radical cyclization of the parent radical is essentially thermo-neutral ($\Delta E_r \approx 0$), and 5-endo closure is significantly exothermic (Table 10). Remarkably, the calculated activation barriers suggest that the 4-exo-dig closure should still be capable of competing kinetically with the much more exothermic 5-endo-dig closure. For the parent carbon-centered radical, the 4-exo and 5-endo barriers are very close.⁷⁸

While 4-exo-trig cyclizations are relatively well-documented,⁷⁹ the literature examples of regioselective 4-exo-dig radical closures are scarce.¹⁵ A single example of 4-exo-dig closure of an alkyl radical (motif A, Table 9) has been observed experimentally (3.026, Scheme 9). This transformation has been reported by Malacria et al. as part of radical cascade leading to the formation of bicyclo[3.1.1]heptanes.^{80,81} The overall yield for the product is 85% yield after reaction with MeLi, serving as a lower boundary estimate for the 4-exo-dig step. The surprising efficiency of this unprecedented transformation has been attributed to the fast intramolecular trapping of the exocyclic vinyl radical via 1,6-H transfer from a SiCH₃ moiety.

The only reported literature attempt of a 5-endo-dig cyclization of a simple alkyl radical led to quantitative formation of acyclic reduced product 3.030 (Scheme 10).⁸²

Alabugin and co-workers investigated the apparent discrepancy between the Baldwin rules and the lack of an efficient

Table 9. Literature Examples of 4-exo/5-endo-dig Radical Closure with Respect to the Environment of the Radical Center^b

Motif	4-exo	5-endo
A		
B		
C		
H		

^a Outside scope of Baldwin Rules. ^b x marks denote gaps in the literature. Motif structures are given in Scheme 1, and motifs D–G are unknown.

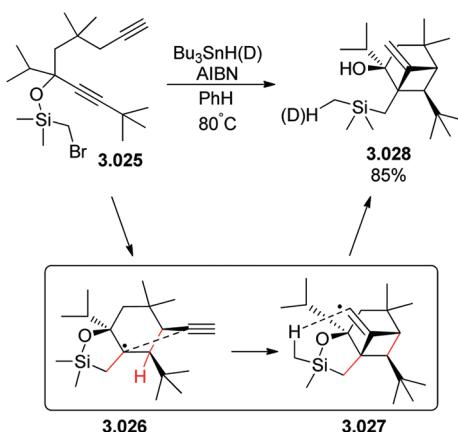
Table 10. Activation, Reaction, and Intrinsic Energies (kcal/mol) for the Parent (A), (σ -vinylexo, B), (σ -vinylendo, C), and (C-alllylendo3, H) 4-exo- and 5-endo-dig Radical Digonal Cyclizations^c

Motif	Entry	E_a	ΔE_r	ΔE_o
A	1	18.0 ^a (19.1)	0.4 ^a (0.3)	17.8 ^a (19.0)
	2	18.0 ^a (18.4)	-16.4 ^a (-18.9)	25.5 ^a (27.1)
B	3	14.1 ^b	-12.0 ^b	19.6 ^b
	4	14.9 ^b	-32.1 ^b	28.7 ^b
C	5	14.2 ^b	-11.7 ^b	19.6 ^b
	6	13.1 ^b	-11.7 ^b	27.4 ^b
H	7	40.2 ^b	26.4 ^b	25.3 ^b
	8	40.2 ^b	3.6 ^b	38.4 ^b
A	9	20.9 ^a (23.3)	2.1 ^a (1.6)	19.8 ^a (22.5)
	10	21.4 (23.2)	-11.0 (-13.5)	26.6 ^a (29.5)
A	11	17.9 ^a (21.5)	-0.1 ^a (-0.9)	18.0 ^a (22.0)
	12	20.7 (23.8)	-10.2 (-13.3)	25.5 ^a (30.1)

^a B3LYP/6-31+G(d,p) and M05-2X/6-31+G(d,p) levels, ref 24.

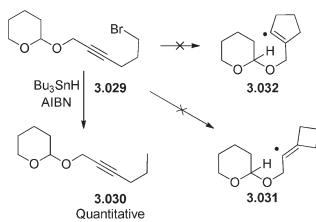
^b B3LYP/6-31G** level, ref 83. ^c Ring-closing bonds are shown in red.

Scheme 9. 4-exo-dig Cyclization of an sp^3 -Carbon with a Fully Saturated Linker As Part of a Cascade^a



^a Bonds formed in the initial 5-exo-dig/1,6-H transfer/6-endo-trig cascade steps occurring before the 4-exo-dig closure are shown in red.

Scheme 10. Exclusive Formation of an Acyclic Product in the Reaciton of Primary Bromide 3.029 with $Bu_3SnH/AIBN^a$



^a No evidence of the 4-exo- or 5-endo-dig product was found.

radical 5-endo-dig cyclizations in an initial computational and subsequent experimental study.⁷⁸ Analysis of the general factors controlling the efficiency of this process, using coupled cluster and DFT methods, revealed that the barriers for the parent 5-endo-dig and 4-exo-dig cyclizations are essentially identical, despite the much higher exothermicity for the 5-endo-dig closure.⁸³ According to these data, both cyclizations are expected to be sufficiently slow ($E_a = 19.1, 18.4$ kcal/mol for 4-exo and 5-endo, respectively, at M05-2X/6-31+G(d,p) level), potentially allowing atom transfer to become kinetically competitive.

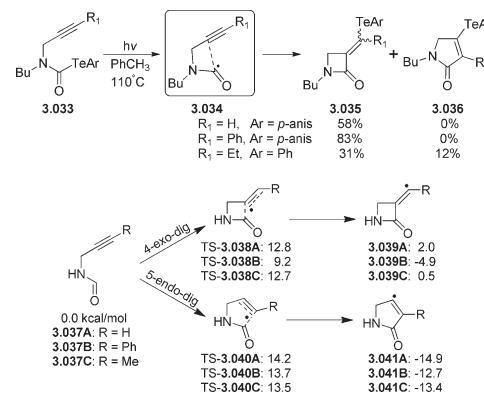
According to the DFT computations, the analogous cyclizations of vinyl radicals are significantly faster ($E_a = \sim 13-15$ kcal/mol, Table 10). Notably, the position of the double bond in the reactant is predicted to have a noticeable effect on the cyclization energy and selectivity. An interesting prediction (not confirmed yet experimentally) is that when the vinyl moiety is inside the new 5-membered ring (the σ -vinylendo closure), 5-endo-dig cyclization should be kinetically favored over the 4-exo closure. In contrast, when the vinyl group is outside of the new ring (the σ -vinylexo closure), 4-exo-dig cyclization has a 0.8 kcal/mol lower barrier, despite being less exothermic than the 5-endo-dig process (Table 10). Cyclizations of stabilized allyl radical are unfavorable because of the significant penalty caused by the 90° rotation of the radical orbital out-of-conjugation before it can reach the in-plane π -bond of the target alkyne.

Table 11. Activation, Reaction, and Intrinsic Energies (kcal/mol) for the Parent 4-exo- and 5-endo-dig Radical Digonal Cyclizations at the B3LYP/6-31+G(d,p) and M05-2X/6-31+G(d,p) Levels of Theory^a

Entry		E_a	ΔE_r	ΔE_o
1		17.8 (19.1)	0.4 (0.1)	17.6 (19.0)
2		18.0 (18.0)	-14.1 (-17.3)	24.5 (26.0)
3		15.0 (15.7)	-5.6 (-5.9)	17.7 (18.5)
4		18.9 (17.9)	-13.7 (-18.6)	25.2 (26.4)
5		17.4 (18.2)	0.8 (0.7)	17.0 (17.9)
6		19.6 (18.6)	-6.6 (-11.0)	22.8 (23.8)

^a The M05-2X data are given in parentheses. Ring-closing bonds are shown in red.

Scheme 11. (Top) Regioselective 4-exo-dig Cyclization of N-Acyl Radicals onto Terminal and Phenyl-Substituted Alkynes and (Bottom) Relative Energies of the Radical Intermediates Calculated at B3LYP/6-311G(d,p) and UB3PW91/cc-pVTZ (in Parentheses) Levels

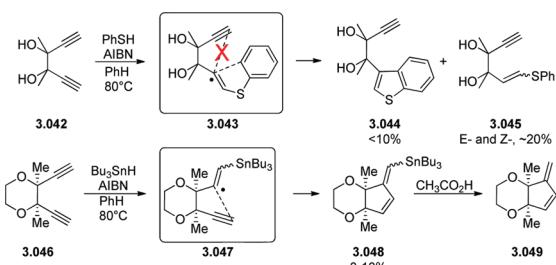


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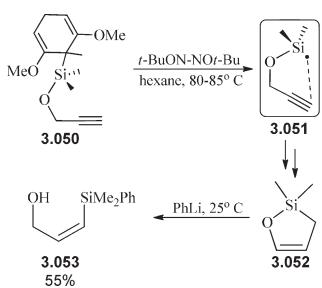
Further information regarding substituent effects on the 4-exo-/5-endo-dig cyclizations has been provided by recent DFT calculations.²⁴ Regardless of the substituent, the 5-endo product is >6 kcal/mol more stable than the 4-exo product, where the reactions are essentially thermoneutral for R = Me, TMS. The phenyl group sufficiently stabilizes the exocyclic vinyl radical, making 4-exo closure exothermic and giving it a clear kinetic preference. Removing thermodynamic contribution using Marcus theory reveals the inherent preference for exocyclic closure (Table 11).

A remarkable deviation from Baldwin's original predictions for the relative favorabilities of the competition between 4-exo-/5-endo-dig cyclizations, though in line with the computed activation barriers (Table 10), has been reported by Fujiwara et al.⁸⁴ Carbamoyl radicals (motif B), generated via photolysis of carbamotelluroates, proceed with high 4-exo selectivity for

Scheme 12. Lack of Efficient 5-endo-dig Closures in PhSH and Bu₃SnH-Radical Reactions of 1,5-Hexadiynes



Scheme 13. 5-endo-dig Radical Cyclization of Si-Centered Radical



terminal and phenyl-substituted alkynes in up to 83% yield. Only when R₁ was an ethyl group did 5-endo-dig closure become competitive (4-exo/5-endo ratio = 2.5:1). In accordance with the experimental findings, DFT calculations found that the 4-exo pathway is strongly preferred kinetically over the 5-endo process for R = Ph but by a much smaller margin (0.8 kcal/mol) when R = Me (Scheme 11). This important work suggests that efforts into these unusual radical cyclizations (4-exo-dig) should be continued.

The above report is consistent with earlier observations that most vinyl radicals generated by addition of radical species to the terminal carbon of 1,5-hexadiynes do not undergo 5-endo-dig closure or do it very inefficiently (Scheme 12).⁷⁸ The bulk of the reaction mixtures corresponds to polymeric materials which were proposed to originate from the 4-exo products, unstable under the reaction conditions. For PhS-substituted radicals, attack at the phenyl ring is preferred to 5-endo-dig cyclization.

The first efficient 5-endo-dig cyclization under kinetic control was reported by Studer and co-workers for a Si-centered radical (Scheme 13).⁸⁵ The increased efficiency of this 5-endo cyclization is in excellent agreement with the calculated low cyclization barrier of ~6 kcal/mol.⁸³ In addition to the stereoelectronic consequences caused by the presence of long C–Si bonds, this process is assisted by the captodative SOMO–LUMO and HOMO–SOMO interactions and the β-Si-effect.⁸⁶

The first efficient 5-endo-dig radical closure of a carbon-centered radical, reported by Alabugin et al.,⁷⁸ was discovered when radical cyclizations of 1,5-diyne were triggered with tosyl radicals (Scheme 14). The 5-endo-dig product was formed in 51–72% yield upon photolytical generation of Ts radicals from TsBr at the room temperature. Yields were noticeably lower (2–23%) upon thermal activation (refluxing C₆H₆, AIBN).

Interestingly, the cyclizations were also stereoselective, since the sulfonyl moiety is capable of selectively lowering the activation barrier for 5-endo-dig closure through a favorable hydrogen-bonding interaction with the relatively acidic acetylenic C–H bond (Table 12). A favorable stereoelectronic alignment of the vicinal diols (the gauche effect⁸⁷) preorganized the two π-systems for cyclization without the introduction of concomitant strain.

Scheme 14. First Efficient 5-endo-dig Cyclization of a Carbon-Centered Radical

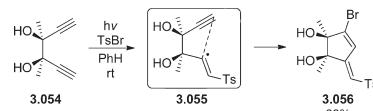


Table 12. Activation and Reaction Energies (kcal/mol) for 4-exo-dig and 5-endo-dig Cyclizations Calculated at the UBLYP/6-311+G**//UBLYP/6-31G** Level

		X		
		H	Br	Ts
	4-exo	Ea	13.8	13.9
		ΔE _r	-6.0	-6.4
	5-endo	Ea	14.1	13.7
		ΔE _r	-24.8	-24.4
	4-exo	Ea	13.8	14.1
		ΔE _r	-6.0	-2.4
	5-endo	Ea	14.1	14.2
		ΔE _r	-24.8	-21.4

Both the increased efficiency of the 5-endo-dig cyclization and the observed stereoselectivity were fully supported by calculated activation barriers for the cyclizations. The sulfonyl group introduction next to the radical center leads to a >2 kcal/mol decrease in the 5-endo-dig activation barrier, which is sufficient for switching the selectivity toward the five-membered ring formation (Table 12).

An earlier report of the 5-endo-dig closure of O- and S-centered radicals, formed from 2-methoxyphenyl and 2-methylthiophenyl substituted phosphorus ylides, proceeded only under drastic conditions (flash vacuum pyrolysis (FVP) at 850 °C, Scheme 15).⁸⁸

The activation barriers for these closures were calculated by Alabugin and Manoharan (Table 13).⁸³ As evidenced by the experimental conditions, the cyclizations are only expected to proceed under high temperatures. The trends in calculated reaction energies are controlled by the interplay of gain of aromatic stabilization and loss of conjugative radical stabilization as the starting materials are transformed into the products. The differences in reaction exothermicities are partially translated into the activation barriers. Interestingly, the cyclizations of CN and NMe₂ substituted radicals (Entries 4, 5) have almost identical reaction energies but the barrier is more than 10 kcal/mol lower in the case of the donor substituent. The data strongly suggest that both the activation energy ($ΔE^‡$) and the intrinsic reaction barrier ($ΔE_o$) decrease dramatically when electron density increases at the radical center.⁸⁹

Scheme 15. 5-endo-dig Radical Cyclizations Involved in FVP of Substituted Phosphorus Ylides

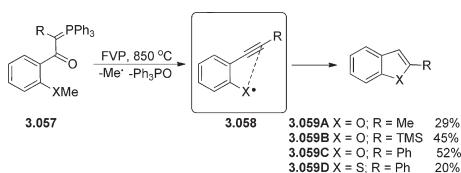


Table 13. Calculated Activation Barriers, Reaction Energies, and Intrinsic Barriers (kcal/mol) for the 5-endo-dig Cyclization of *o*-X-Substituted ($X = \text{N}, \text{O}$, and CR_2) Ethynyl Benzenes Along with the Incipient $\text{C}\cdots\text{X}$ Distances (\AA) at the B3LYP/6-31G** Level

Entry	r(TS)	ΔE^{\ddagger}	ΔE_r	ΔE_o	
1	$\text{X}=\text{NH}$	2.060	29.9	-13.0	36.1
2	$\text{X}=\text{O}$	1.922	31.7	-0.5	32.0
3	$\text{X}=\text{CH}_2$	2.316	31.1	-5.5	33.8
4	$\text{X}=\text{CHCN}$	2.216	31.9	6.0	28.2
5	$\text{X}=\text{CHNMe}_2$	2.325	21.3	5.0	18.7

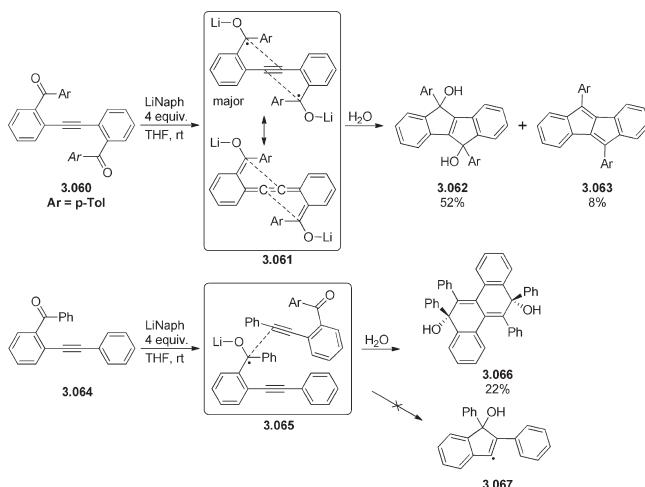
Despite the above-mentioned penalty associated with the loss of benzylic conjugation (Table 10), Yamaguchi et al. provide an example of motif H, corresponding to 5-endo-dig closure.⁹⁰ Upon treatment with four equivalents of lithium naphthalenide (LiNaph), substituted bis(arylcarbonyl)-diphenylacetylenes are transformed into two tetracyclic compounds, 3.062, 3.063, in ~60% combined yield. According to B3LYP/6-31+G(d) computations with solvation and the counterion Li^+ included, the two radical-anions are mostly localized on the carbonyl groups. The authors propose a highly unusual synchronous double-radical 5-endo-dig cyclization. In agreement with this scenario and the computational results in Table 13, single 5-endo-dig closure does not occur. Instead, reduction of the mono(arylcarbonyl)diphenylacetylene gives dimeric product 3.066 derived from intermolecular attack of the carbonyl radical anion at the triple bond (Scheme 16).

Several other possible examples of 5-endo-dig cyclizations can be found in the literature. Anthony and co-workers⁹¹ considered the involvement of a 5-endo-dig cyclization as a part of an unprecedented 6-endo-dig/5-endo-dig cascade leading to a relatively efficient (73% yield, Scheme 17) transformation of a constrained enediyne system into phenanthrene derivatives. Subsequent computational analysis, however, suggested that this transformation is likely to proceed via an alternative mechanism which includes intermolecular attack of Sn-radical at the triple bond, 5-exo-dig closure, attack at the aromatic ring and protodesannylation (3.071, 3.072, Scheme 17).⁸³

The final examples are not formally covered by the Baldwin rules as it involves long C–S bonds in the formed cycle. However, 5-endo-dig radical cyclizations are so scarce that we will briefly discuss these results below.

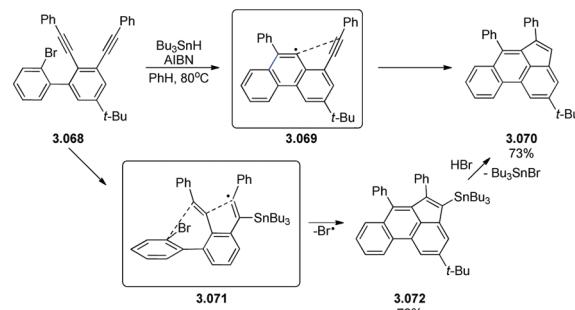
Matzger and co-workers⁹² reported that a radical cascade initiated by Bergman cycloaromatization can be terminated via a 5-(σ -vinylendo)-endo-dig closure (motif C), albeit in low yields (<2.3%, Scheme 18). Although formation of acyclic reduced

Scheme 16. Proposed Synchronous Double-Radical 5-endo-dig Cyclization of Substituted Bis(arylcarbonyl)diphenylacetylenes upon Reduction with LiNaph^a



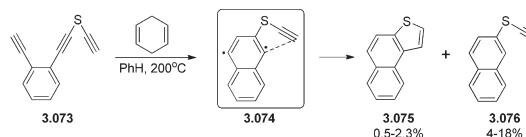
^a A dimerization product resulting from initial intermolecular attack is observed for the mono(arylcarbonyl)diphenylacetylene.

Scheme 17. Proposed 6-endo-dig/5-endo-dig Radical Cyclization Cascade in Brominated Biphenyl Diacetylenes (Top) and an Alternative 5-exo-dig Mechanism (Bottom)



products is still the dominant process, this important result showed that 5-endo-dig cyclizations are capable of competing (though not very efficiently) with H-abstraction even in the presence of a good H-atom donor (1,4-cyclohexadiene).

Scheme 18. 5-(σ -Vinylendo)-endo-dig Cyclization of the Diradical Intermediate Formed upon Bergman Cyclization



The experimental observations agree very well with the computed activation barrier for this reaction by Alabugin and Manoharan.⁸³ The barrier is decreased (by 4.9 kcal/mol) to the extent where the cyclization should be able to compete with H-atom abstraction from C–H donors. Most of the decrease comes from

Table 14. Activation, Reaction and Intrinsic Energies (kcal/mol) for the Parent 4-exo- and 5-endo-dig Radical Digonal Cyclizations at the B3LYP/6-31+G(d,p) and M05-2X/6-31+G(d,p) Levels of Theory^a

Entry		E_a	ΔE_r	ΔE_o
1		7.3 (9.0)	-14.4 (-16.8)	13.6 (16.3)
2		8.5 (10.4)	-34.0 (-39.1)	22.2 (26.3)
3		12.7 (14.4)	1.3 (-0.8)	12.1 (14.8)
4		12.0 (13.6)	-15.0 (-19.8)	18.7 (22.4)
5		18.2 (19.4)	16.0 (14.4)	8.2 (11.1)
6		16.7 (17.8)	1.7 (-3.3)	15.8 (19.4)

^a The M05-2X data are given in parentheses and the ring-closing bond is shown in red.

Table 15. Transition state geometries, NICS (0) values and LUMO plots for 4-exo/5-endo carbanionic cyclizations for the Me-substituted alkyne calculated at the M05-2X/6-31+G** Level. Bond lengths given in Å. Activation, reaction and intrinsic energies (kcal/mol) for the parent 4-exo- and 5-endo-dig anionic cyclizations at the B3LYP/6-31+G(d,p) and M05-2X/6-31+G(d,p) levels of theory^a

Entry	TS Geometry	NICS(0), ppm		LUMO
		E_a	ΔE_r	
1		7.7 (8.9)	-11.9 (-15.2)	12.9 (15.6)
2		3.8 (3.8)	-22.0 (-28.4)	12.4 (14.6)
3		4.4 (4.4)	-14.7 (-18.8)	10.5 (11.9)
4		8.1 (9.4)	-33.6 (-39.8)	21.7 (25.4)
5		7.3 (6.7)	-37.0 (-47.3)	21.9 (24.7)
6		6.3 (6.2)	-27.7 (-35.4)	17.4 (20.0)

^a M05-2X data are given in parentheses. Ring-closing bonds are shown in red.

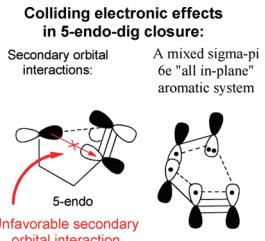


Figure 15. Conflict between unfavorable secondary orbital interactions (crossed red arrow) and in-plane aromaticity in anionic 5-endo-dig cyclizations.

the thermodynamic component as aromaticity of the benzothiophene moiety provides an additional 12–16 kcal/mol stabilization to the product. Thus, this example provides the first demonstration of aromatic stabilization being a driving force for 5-endo-dig radical cyclizations. Longer C–S bonds also help in alleviating the geometric requirements in achieving the required attack angle.

Table 16. Literature Examples of 4-exo/5-endo-dig Anionic Closure with Respect to the Environment of the Anionic Center^a

Motif	4-exo	5-endo
A		
C		
F		
H		

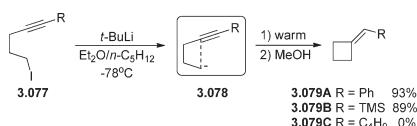
^a \times marks denote gaps in the literature. Motif structures are given in Scheme 1. Motifs B and G are unknown, and D and E do not apply to anionic closures.

3.2.2. Anionic Cyclizations (Table 16). Recent computational analysis²⁴ revealed that, unlike the smaller (3-exo/4-endo) and larger (5-exo/6-endo) analogs, the activation barriers of 4-exo- and 5-endo-dig anionic closure of the parent systems are quite similar (Table 14). This seemingly irregular trend has been suggested to stem not purely from stereoelectronic factors, but rather originate from their interplay with thermodynamic contributions to the activation barrier.²⁴ When thermodynamic driving forces for the two cyclizations are similar (*both* products are either strained (3-exo/4-endo) or not (5-exo/6-endo)), there is a clear kinetic preference for the exo path. Only for the special case where the exo-product is much more strained than the endo product (the 4-exo/5-endo pair) and the endo cyclization is much more exothermic, the exo/endo kinetic competition becomes relatively close.⁹³

Another factor aiding in the low 5-endo-dig activation barrier is revealed in the negative NICS value⁹⁴ observed for the 5-endo TS, unexpectedly suggesting σ -aromaticity and an increase in σ -delocalization in the TS, clearly reflected in the LUMO structure given in Table 15.²⁴ This observation was attributed to a σ -bridge mediated coupling of the nucleophile lone pair and alkyne π^* -orbital (Figure 15).⁹⁵ This symmetry-allowed stabilizing interaction provides an appealing explanation as to why the intrinsic barrier is lower for 5-endo-dig closure than it is for the 6-endo-dig cyclization, where σ -aromaticity is disrupted by an additional methylene group.

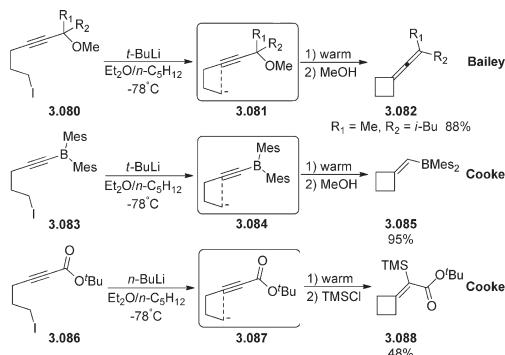
The above-mentioned computational data agree well with the findings of Bailey and Ovaska who reported that “The formation of four-membered rings by 4-exo-dig cyclization of a 6-phenyl-5-pentyn-1-yllithium is an unexpectedly rapid and clean process” and observed 93% yields of benzylideneacyclobutane 3.079A with no trace of the 5-endo-dig product.⁹⁶ While TMS substituted alkynes also undergo regioselective 4-exo-dig closure, Bailey and co-workers were unable to facilitate closure with alkyl-substituted alkynes. It is noted that 4-exo-dig closure of these systems are “significantly slower” than that of the analogous 5-exo-dig cyclizations (Scheme 19).^{96b}

Scheme 19. 4-exo-dig Cyclizations of the Parent System Are Very Efficient for Phenyl- and Silyl-Substituted Alkynes



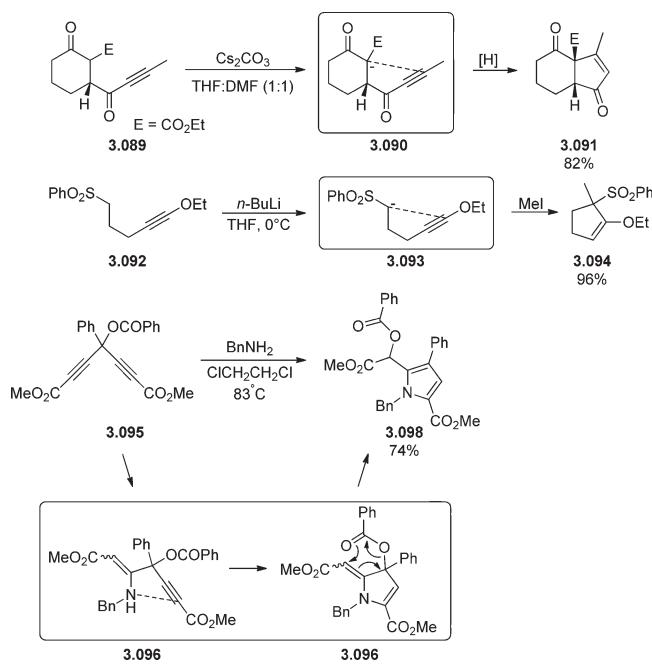
Other substituents on the alkyne are tolerated in 4-exo-dig anionic closures if they can either trap or sufficiently stabilize the vinyl anion. Alkyl-substituted alkynes can be utilized in 4-exo-dig closures terminated via β -elimination if they are functionalized with an appropriate leaving group, similar to the strategy utilized for the anionic 3-exo-dig closure in Scheme 6. For example, Bailey and Aspris have shown that a propargylic methoxy group is eliminated by the exocyclic vinyl lithium to trap the 4-exo-dig product in 72–88% yield (Scheme 20).⁹⁷ Cooke has demonstrated that dimesitylboryl substitution can stabilize the cyclic anion through resonance with the empty orbital of boron.⁹⁸ *tert*-Butyl esters 3.086 gave a complex mixture of products containing only 11% of the desired product. However, if TMSCl was used as the electrophile, the 4-exo-dig product 3.088 can be trapped in 48% yield (Scheme 20).⁹⁹

Scheme 20. Nucleophilic 4-exo-dig Products Can Be Obtained upon Trapping or Sufficiently Stabilizing the Vinyl Anion



As with the radical cyclizations discussed above, the regioslectivity can be reversed by changing the polarity of the alkyne. When the carbonyl group is relocated to the interior propargylic position, the enolate carbanion of compound 3.089 (motif F) cyclizes efficiently and selectively in a 5-endo-dig fashion in 82% yield (Scheme 21).¹⁰⁰ Donor groups can also modify the regioslectivity (see Section 2.5.1), as shown by the efficient endocyclic closure of ethyoxyalkyne 3.092 (motif A).¹⁰¹ The effects of alkyne polarity can be overturned if the alternate pathway can produce an aromatic product. After the initial Michael addition of a primary amine to skipped diyne 3.095 the nitrogen closes the ring in an anti-Michael fashion onto an adjacent alkynoate. This intermediate is trapped by a [3,3]-sigmatropic rearrangement to give the substituted pyrrole 3.098 in up to 74% yield (Scheme 21).¹⁰²

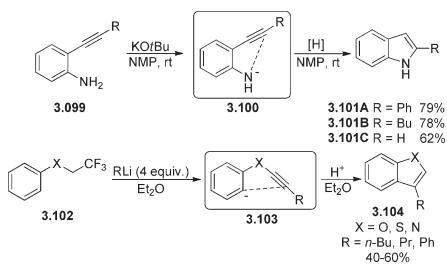
Scheme 21. Regioselectivity of Anionic Closure Can Be Tuned Towards 5-endo-dig through Polarization of the Triple Bond or Stabilization of the Product by Aromatization



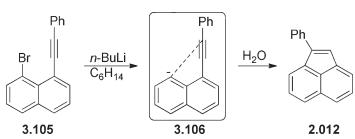
Pyrroles can be obtained directly from the anionic 5-endo-dig cyclization of *o*-ethynylanilines upon reaction with a suitable base. The choice of base and particularly the counterion was found to be critical for the reaction success (NaH, 60 °C, <5%: KH, 25 °C, 72%).¹⁰³ An alternate pathway to form aromatic heterocyclic rings would be the cyclization of a carbanion onto a heteroatom-substituted alkyne. Johnson and Subramanian reported that aryl anion 3.103 regioselectively attacks the *ortho*-ethynyl ether (generated *in situ* by elimination/substitution of the corresponding 2,2,2-trifluoroethyl ether) and, upon work up, gives the substituted benzofuran 3.104 in 40% yield. The authors were able to form thianaphthalenes and indoles using this method in up to 60% (Scheme 22).¹⁰⁴

5-endo-dig cyclization can also occur if the 4-exo pathway is sufficiently destabilized through strain. As discussed by Baldwin,⁴

Scheme 22. Aromatic Products Obtained Directly via a 5-endo-dig Closure of Heteroatom- or Carbon-Centered Anions



Scheme 23. Selective 5-endo Pathway in a Strained Polycyclic System



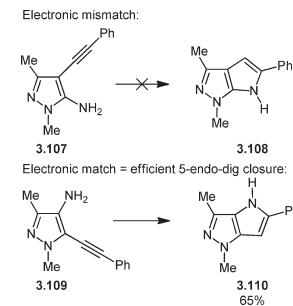
when compound 3.105 is exposed to *n*-BuLi, the resulting carbanion closes regioselectively in a 5-endo-dig fashion. The deformation necessary for annealing the highly strained four-membered ring at the *peri*-positions¹⁰⁵ shifts the balance in favor of the 5-endo pathway (Scheme 23).²⁰

An interesting example of electronic control of 5-endo-dig cyclization of *o*-ethynyl substituted heteroaromatic amines was reported by Vasilevsky et al.¹⁰⁶ The authors could not force the 5-endo-dig closure in 4-phenylethynyl-5-amino pyrazole 3.107 where electronic properties of the substituents were mismatched (the fifth position in pyrazoles where the nucleophile is attached is the most electron poor whereas the fourth position is electron rich). In contrast, the cyclization proceeded smoothly in 3.109 where the two substituents are switched (Scheme 24).

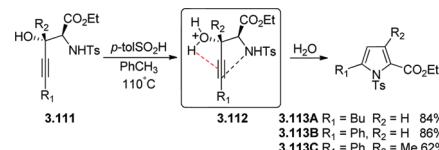
Knight et al. obtained 5-endo pyrrole products in 76–86% yields in the reaction of γ -alkynyl-ss-hydroxy- α -amino esters 3.111 with 0.5 equiv of *p*-toluenesulfonic acid (Scheme 25).¹⁰⁷ It has been suggested that intramolecular coordination of alkyne with the protonated propargylic alcohol 3.112 assists the cyclizations, in analogy to similar 5-endo-dig cyclizations promoted by electrophiles such as I₂.¹⁰⁸

3.2.3. Electrophilic Cyclizations. As discussed above, the 4-exo/5-endo competition is much closer than it is for the 3-exo/4-endo and 5-exo/6-endo pairs of cyclizations, owing largely to the strain destabilization of only one (the four-membered) of the two products. However, the situation changes in cationic closures where the 5-endo product would be highly strained as well because of the inclusion of an sp-hybridized cationic center in the ring. The instability of vinyl cations is the likely reason why electrophilic 4-exo/5-endo closures are not described in the literature and several reactions which could potentially follow these paths were found to give different products. For example, Hanack reported that no cyclic products were observed in the solvolysis of primary triflates 3.114,¹⁰⁹ whereas Rychnovsky and co-workers have found that the formation of oxycarbenium intermediates did not lead to either 4-exo- or 5-endo-dig cyclizations (Scheme 26).¹¹⁰

Scheme 24. (Top) No Cyclization Observed when the Amine Was Attached to the Most Electron-Poor Position in the Ring, whereas Efficient Cyclization Occurs when the Amine Is in the Most Electron-Rich Position (Bottom)



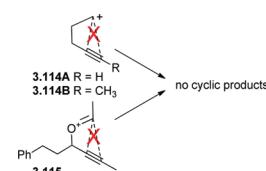
Scheme 25. Acid-Catalyzed Transformation of γ -Alkynyl-ss-hydroxy- α -amino Esters to the Corresponding Pyrroles^a



^a The possible proton-coordination is shown in red.

A more detailed study is needed to shed the light on this topic, but this lack of cyclic products is presumably due to the higher thermodynamic stability of the acyclic cations relative to that of the cyclic vinyl cations.

Scheme 26. Neither 4-exo nor 5-endo Products Are Observed upon Generation of Either Primary Carbocations 3.114A/B or Oxycarbenium Ion 3.115



3.2.4. Effect of Metal/External Electrophiles on 4-exo/5-endo Regioselectivity. As has been shown by Toste¹¹¹ and Iwasawa¹¹² using Au(I) and W(CO)₅(L) catalysts, respectively (Scheme 27), enolates exhibit complete 5-(C-allyl)-endo-dig regioselectivity without the need for built-in bond polarization, such as the carbonyl group in Scheme 21. A variety of oxygen nucleophiles undergo 5-endo-dig closure as well when exposed to I₂,¹¹³ Cu(I),¹¹⁴ and Zn(II)¹¹⁵ salts. A number of regioselectively 5-endo-dig cyclizations has been reported for nitrogen nucleophiles in the presence of soft Lewis acids.¹¹⁶

3.2.5. Summary of 4/5. DFT calculations illustrated in Figure 16 suggest that the radical 4-exo-/5-endo-dig competition is delicately poised. For the parent C-, N-, and O-centered radicals, the difference between 4-exo- and 5-endo-dig activation energies lies with the expected computational margin of error. Although there is currently not enough experimental data to fully

Scheme 27. Selection of 5-endo-dig Cyclizations of Carbon, Oxygen, and Nitrogen Nucleophiles with a Variety of External Electrophiles

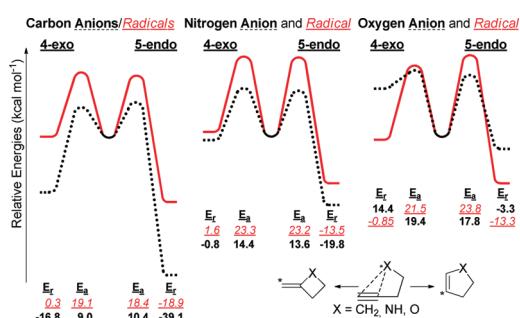
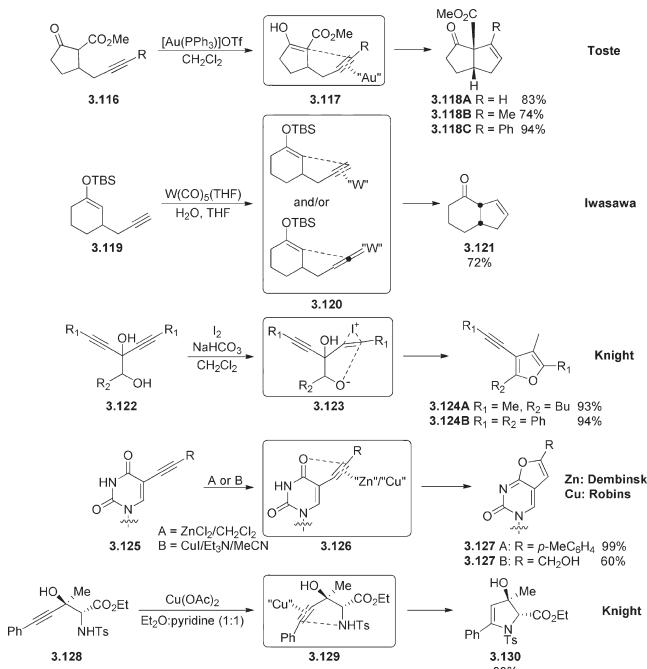


Figure 16. Electronegativity effects on the M05-2X/6-31+G** potential energy surfaces for the 4-exo-/5-endo-dig anionic and radical cyclizations of C-, N-, and O-centered anions (black dashed, bold) and radicals (red solid, italics, underlined) with terminal alkynes. (*) denotes radical/anion.

test these predictions, the available data suggest that the nature of the radical does play a role in the cyclizations selectivity. Simple radicals seem to prefer slightly the 4-exo-dig closure but this preference can be overcome by structural and electronic factors.

Primary carbanions regioselectively close in a 4-exo-dig fashion. The cyclizations proceeded especially efficiently when the alkyne is substituted with a terminal group bearing a σ , p , or π acceptor (σ^*_{C-L} , n_B , or $\pi^*_{C=O}$, Scheme 20). If the polarity is reversed, that is, a carbonyl group replaced the interior propargylic methylene, enolates have been shown to close in a 5-endo-dig fashion (Scheme 21). Benzylic or aryl anions, like the radical examples, also preferentially underwent 5-endo-dig closure in the few available literature examples (Scheme 23). Aromaticity facilitates a number of heterocyclic 5-endo closures (Scheme 22).

EAN closures provide a way to overcome the intrinsic exo preference and obtain 5-endo products in good yields. A variety of soft Lewis acids can be used to fine-tune these processes, accounting for their increased practical utility.

Neither 4-exo- nor 5-endo-dig cationic closures are known. Several attempts to accomplish such cyclizations led to the formation of only acyclic products. This is probably associated with the greater thermodynamic stability of isomeric acyclic cations and very low barriers for the ring-opening.

3.3. 5-exo/6-endo Cyclizations

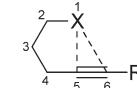


Figure 17

This section represents the most fully studied and understood class of cyclizations involving alkynes. Both 5-exo- and 6-endo-dig closures are favorable and their competition is often controlled by subtle structural modifications. As will be seen below, radical closures have been thoroughly investigated both computationally and experimentally and many examples clearly reveal the underlying stereoelectronic effects governing regioselectivity.

3.3.1. Radical Cyclizations (Table 17). Recent computational data for the 5-exo- and 6-endo-dig cyclizations of parent C-, N-, and O-radical species are assembled in Tables 18 and 19.

Stalinski and Curran have thoroughly examined the cyclizations of the parent system (motif A) for a series of mono- or dihalo-4-phenylhex-1-ynes. With a rate constant of $2.19 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ for closure onto a terminal alkyne, complete 5-exo regioselectivity was observed with high yields (up to 99%).¹¹⁷ The relatively fast 5-exo-dig closure matches the fairly low E_a for this process well (Scheme 28). In agreement with the calculated activation barriers for substituted alkynes (Table 19), substitution of the alkyne does not alter the regioselectivity. For example, Zhou and co-workers obtained good yields of cyclic products from phenyl, butyl and TMS- substituted alkynes. Radicals were generated via chemoselective reduction of a primary bromide with SmI_2 . Presence of an acceptor substituent at the alkyne slightly decreases the yield of cyclic products, e.g. 41% for the N,N-diethylamide derivative. Due to a competing reduction pathway, no cyclic products were observed when $R = \text{CO}_2\text{Me}$ (3.136, Scheme 28).¹¹⁸ Tributyltin radicals can also be used to generate radical species for selective 5-exo-dig closure onto alkyl-substituted alkynes (Scheme 28).¹¹⁹

Martinez-Grau and Curran found that 5-exo closure is sensitive to substitution at the interior propargylic position for silyl ether 3.140. However, even when the detrimental effect of substituents stops exocyclic closure, no 6-endo-dig products were observed (Scheme 29).¹²⁰

5-exo-dig radical cyclizations have been used for the preparation of interesting polycyclic systems. Both spiro (3.145)¹²¹ and fused (3.148)¹²² compounds have been synthesized in high yields following regioselective 5-exo closure onto terminal alkynes (Scheme 30). It is possible to include 5-exo-dig closures into further cascades as illustrated by the efficient trapping of the resulting vinyl radical in a subsequent 5-exo-trig closure (Scheme 30).¹²³ However, Marco-Contelles et al. reported that the 6-endo-dig closure becomes possible when a strained fused [3.3.0] bicyclic system is

Table 17. Literature Examples of 5-exo/6-endo-dig Radical Closure with Respect to the Environment of the Radical Center^a

Motif	5-exo	6-endo
A		
C		
D		✗
E	✗	
F		✗
G		✗
H		✗

^a ✗ marks denote gaps in the literature. Motif structures are given in Scheme 1. Motif B is unknown.

present in the reactant, possibly due to the lower strain in the 6-endo product (Scheme 30, 3.155).¹²⁴

Further accumulation of strain, for example, via annealing of a trans-fused 5-membered cycle,¹²⁵ completely reverses the 5-exo/6-endo selectivity in favor of the larger cycle. Hoffmann and co-workers have shown that the *trans*-fused ring does not have to be preinstalled but can be synthesized as part of a cascade. The secondary carbon radical initially underwent a 5-exo cyclization at the adjacent alkene or alkyne, giving either an alkyl or a vinyl radical, respectively. Interestingly, the reactivity of these two radicals was drastically different. The alkyl radical was converted into a tricyclic product via an efficient 6-endo-dig closure.^{126,127} By substituting the relay olefin for a 1-cyclopentenyl group, the yield can be increased to 78%. In contrast, the analogous vinyl radical underwent neither 5-exo- nor 6-endo-dig closure (Scheme 31).¹²⁶ Although this difference in reactivity suggests that dig-cyclizations of vinyl radicals are more sensitive to strain effects than analogous cyclizations of alkyl radicals, numerous examples of vinyl and aryl radicals undergoing 5-exo-/6-endo-dig closure are known in less strained systems (*vide infra*).

Table 18. Activation, Reaction, and Intrinsic Energies (kcal/mol) for the Parent 5-exo- and 6-endo-dig Radical Cyclizations at the B3LYP/6-31+G(d,p) and M05-2X/6-31+G(d,p) Levels of Theory^c

Motif	Entry		E _a	ΔE _r	ΔE _o
A	1		7.3 ^a (7.5)	-20.6 ^a (-22.9)	15.9 ^a (17.0)
	2		9.9 ^a (10.2)	-27.1 ^a (-29.8)	21.3 ^a (22.7)
C	3		4.4 ^b	-38.2 ^b	18.3 ^b
	4		8.9 ^b	-40.9 ^b	25.2 ^b
C	5		4.5 ^b	-35.0 ^b	17.1 ^b
	6		4.7 ^b	-70.9 ^b	29.5 ^b
A	7		10.1 ^a (11.8)	-17.8 ^a (-20.3)	17.9 ^a (20.7)
	8		11.2 ^a (13.1)	-21.1 ^a (-24.2)	20.4 ^a (23.6)
A	9		7.2 ^a (10.2)	-18.5 ^a (-21.7)	15.0 ^a (19.5)
	10		7.2 ^a (9.7)	-21.0 ^a (-24.8)	16.0 ^a (20.2)

^a B3LYP/6-31+G(d,p) and M05-2X/6-31+G(d,p) levels of theory. The M05-2X data are given in parentheses.²⁴ ^b B3LYP/6-31G** level.¹³⁵

^c The M05-2X data are given in parentheses. Corresponding motifs are given and the ring-closing bond is shown in red.

The sensitivity of radical cyclizations to the nature of substituents of the triple bond increases when the radical center is a part of a conjugated system. While Zhou et al. found that primary carbon radicals close regioselectively (5-exo) whether the alkynyl substituent was aromatic or aliphatic (Scheme 28),¹¹⁸ Choi and Hart observed that carbon-radicals α to the nitrogen of a lactam undergo relatively inefficient but regioselective 6-(π -vinyleno)-endo-dig closure (motif E) onto sterically hindered alkynes ($R = Me$, 27% in addition to 61% of the reduced product). Only in the presence of bulkier groups such as TMS, *t*-Bu C(CH₃)₂OMe, at the alkyne terminus is the 5-exo-dig selectivity restored. Medium-sized groups (*i*-Pr and *n*-Pr) gave mixtures with the 5-exo/6-endo ratio correlating with the steric bulk of the substituents (~2:1 and ~5:4, respectively, Scheme 32).¹²⁸ Carbamoylmethyl radicals, (both C-allylendo¹²⁹ and C-allylexo,¹³⁰ Scheme 32) also undergo selective 5-exo-dig cyclizations with terminal and TMS-substituted alkynes, respectively.

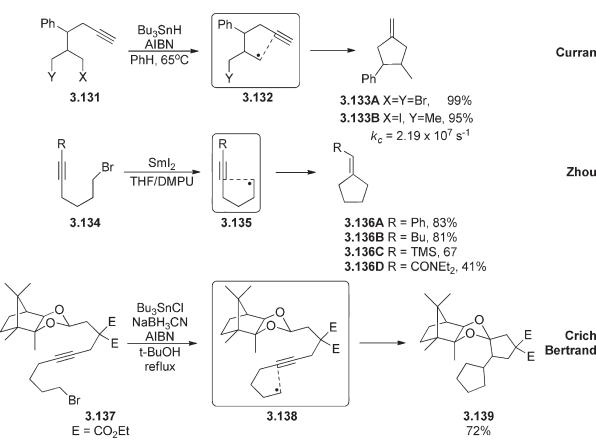
Benzyl radicals (motif H) close efficiently despite being conjugated with the aromatic system, as shown by the regioselective 5-exo closure of an α -pyridyl radical onto the alkyl-substituted alkyne. The resulting vinyl radical was trapped via hydrogen abstraction from

Table 19. Activation, Reaction, and Intrinsic Energies (kcal/mol) for the Parent 5-exo- and 6-endo-dig Radical Cyclizations at the B3LYP/6-31+G(d,p) and M05-2X/6-31+G(d,p) Levels of Theory^a

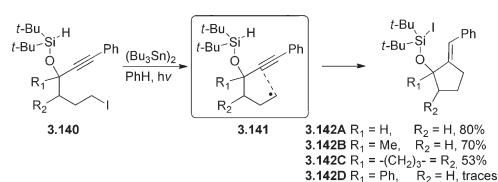
Entry		E _a	ΔE _r	ΔE _o
1		7.1 (7.4)	-20.4 (23.1)	14.7 (17.0)
2		10.4 (9.9)	-23.8 (-27.7)	20.5 (21.6)
3		4.5 (4.7)	-26.5 (-28.8)	14.7 (16.1)
4		11.9 (10.9)	-22.5 (-27.9)	21.7 (22.7)
5		6.7 (6.7)	-19.7 (-22.0)	15.0 (15.8)
6		12.0 (10.7)	-16.3 (-21.3)	19.3 (19.9)

^a The M05-2X data are given in parentheses.²⁴ All cyclizations correspond to Motif A and the ring-closing bond is shown in red.

Scheme 28. Regioselective 5-exo-dig Cyclization of Primary Carbon Radicals onto a Variety of Substituted Alkynes



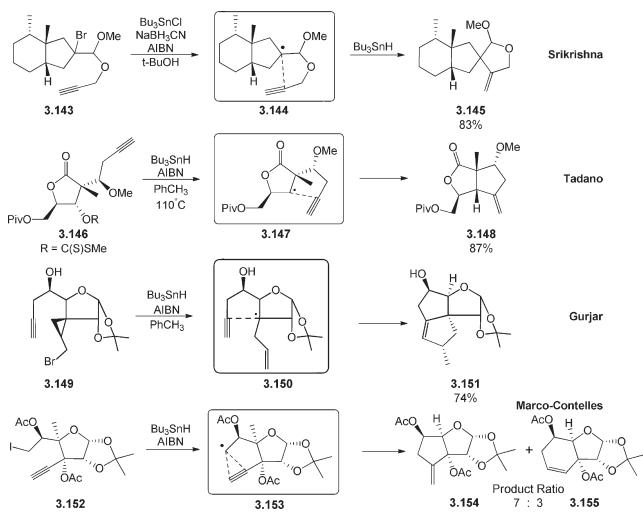
Scheme 29. Effect of Substitution at the Interior Propargylic Position on the Yield of 5-exo-dig Product



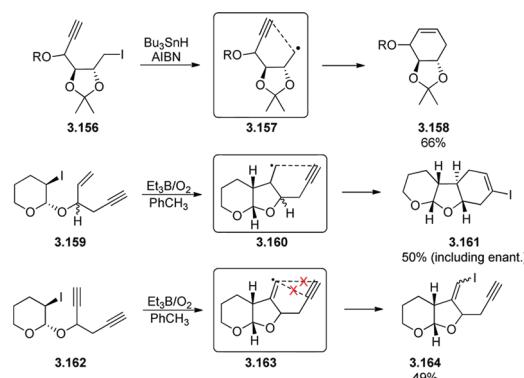
the silyl group. Subsequent 5-exo-trig closure completed the cascade and yielded the final tricyclic product (Scheme 33).¹³¹

While polarization controls the regioselectivity of anionic cyclizations effectively (Scheme 21 and Scheme 53), Weavers et al. observed

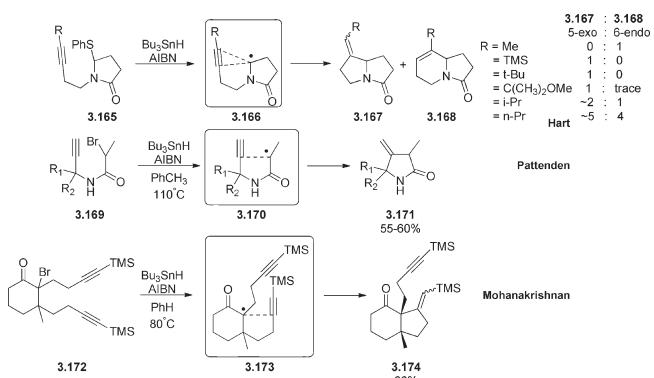
Scheme 30. Formation of Bi- and Polycyclic Products by Regioselective Radical 5-exo-dig Cyclizations and Erosion of Regioselectivity Because Increased Strain in a [3.3.0] System



Scheme 31. Strain-Controlled Radical 6-endo-dig Cyclizations in Cyclic trans-Fused Systems



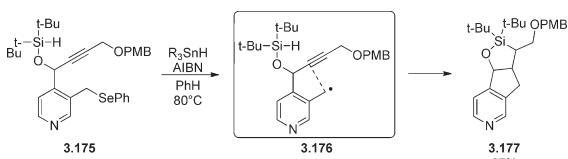
Scheme 32. Cyclizations of Conjugated 2° and 3° Carbon Radicals Corresponding to Motifs E–G



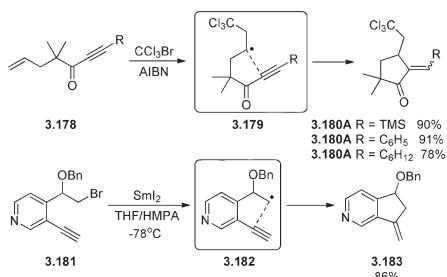
5-exo-dig closure for silyl, aryl alkyl substituted alkynes instead of radical conjugate addition (RCA)¹³² which would provide the 6-endo

products.¹³³ In a similar way, conjugation with a β -pyridine moiety does not affect the exocyclic regioselectivity either (Scheme 34).¹³⁴ Because of the stereoelectronic features of the alkyne moiety, the incipient radical in these two examples remains orthogonal to the internal π -systems in the transition state and, thus, the 6-endo-dig closure does not receive any conjugative assistance.

Scheme 33. Regioselective 5-exo-dig Cyclizations of Benzylic Radical



Scheme 34. Regioselective 5-exo-dig Cyclizations of Internal Alkynes with Acyclic Carbon Radicals



As with the smaller rings (4-exo/5-endo cyclizations, Table 10),⁸³ the closures of sp^2 -hybridized radicals (motifs B, C) have lower activation barriers due the higher exothermicity of the conjugated products formation (Table 20) relative to the parent systems (Table 18). However, while the exo/endo barriers are close for 4-exo/5-endo pair, a clear stereoelectronic 5-exo preference is observed for σ -vinylexo and σ -vinylendo closures, despite these processes being less exothermic than their 6-endo counterparts.¹³⁵ The slight differences observed for motifs B and C are due to the greater stability of endocyclic alkenes and trans-dienes relative to exocyclic alkenes and cis-dienes¹³⁶ (Table 20).

The 5-exo barriers are relatively insensitive to structural changes (Table 20, entries 1, 3, 5), while the 6-endo barriers vary significantly. As the result, the kinetic preference for the formation of 5-exo products significantly decreases in motif B compared to motif C. It is interesting that the intrinsic barriers for both the 5-(σ -vinylendo)-exo and 6-(σ -vinylendo)-endo cyclizations (motif C) are ~ 2 kcal/mol higher than for the respective " σ -vinylexo" cyclizations. Although these differences are consistent with the orientation of radical orbitals in the two reagents (the radical orbital for the σ -vinylexo radical is tilted outward, which should facilitate attack at the alkyne's terminal carbon, see red arrows in Table 20), it is not clear whether this is a determining factor. Because of the unfavorable orientation of the radical orbital in the reactant, locking the reacting vinyl group in a benzene ring (motif C) leads to a further increase in the 6-endo barrier.

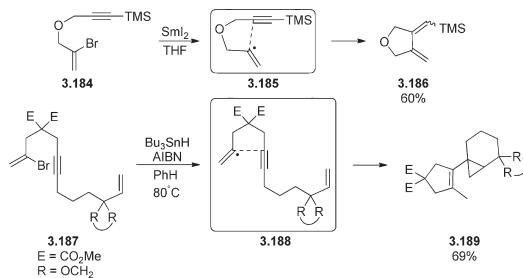
Starting from the vinyl bromide (motif B), Montevicchi and co-workers found that, as with the other cyclizations

Table 20. Activation Barriers, Reaction Energies, and Intrinsic Barriers (kcal/mol) for 5-exo-dig and 6-endo-dig Cyclizations of sp^2 -Radicals with a Saturated Bridge between the Vinyl and a Terminal Alkyne Moieties (B3LYP/6-31G Level)^a**

Motif	SOMO	Entry	E_a	ΔE_r	ΔE_o
B		1	4.5	-32.3	16.8
		2	7.2	-41.6	23.4
C		3	4.4	-38.2	18.3
		4	8.9	-40.9	25.2
C		5	4.1	-38.0	18.1
		6	11.5	-40.8	28.2

^a Arrows overlaid with the SOMOs of parent vinyl radicals (motif B, C) show projection of the radical orbital in space.¹³⁵ Ring-closing bonds are shown in red.

Scheme 35. Regioselective 5-(σ -Vinylexo)-exo-dig Cyclizations of Carbon-Centered Radicals

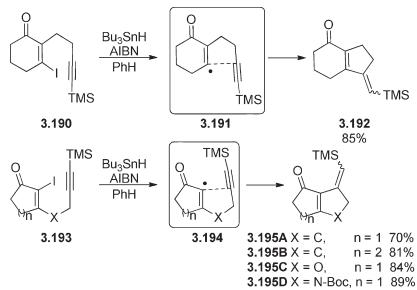


discussed in this section, TMS-substitution facilitates regioselective 5-exo attack (54% yield, Scheme 35).¹³⁷ Journet and Malacria published an efficient cascade initiated by a similar regioselective closure onto an alkyl-substituted triple bond (Scheme 35).¹³⁸

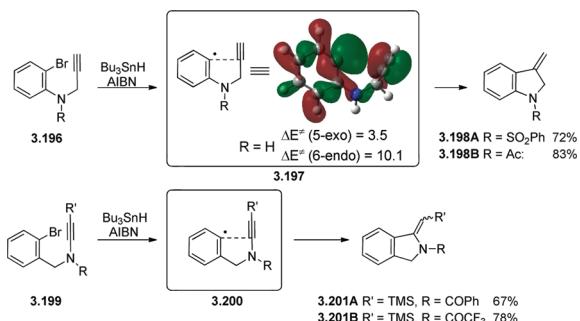
Sha and co-workers have found that both α - and β -vinyl radicals (motif C) in an enone system undergo clean 5-(σ -vinylendo)-exo-dig cyclizations onto TMS-substituted alkynes. Both [4.3.0] and [3.3.0]-bicyclic ring systems, as well as heterocycles, are formed in 70–89% yields (Scheme 36).¹³⁹ It is noteworthy that in the second example, even when $n = 1$, the cyclization is regioselective for exocyclic closure onto the TMS substituted alkyne, forming the 5–5 bicyclic system (Scheme 36).¹⁴⁰

Five-membered heterocycles can also be efficiently and regioselectively synthesized using aryl radicals (motif C, Scheme 37).¹⁴¹ The experimental data are in good agreement with the DFT analysis

Scheme 36. Regioselective Cyclizations of Enone Radicals onto TMS-Capped Alkynes



Scheme 37. 5-exo-dig Cyclizations of Aryl Radicals with an Aminomethylene Bridge between the Acetylene and Aryl Moieties^a



^a SOMO of reacting radical and comparison of calculated 5-exo and 6-endo activation barriers (B3LYP/6-31G(d,p), energies in kcal/mol).

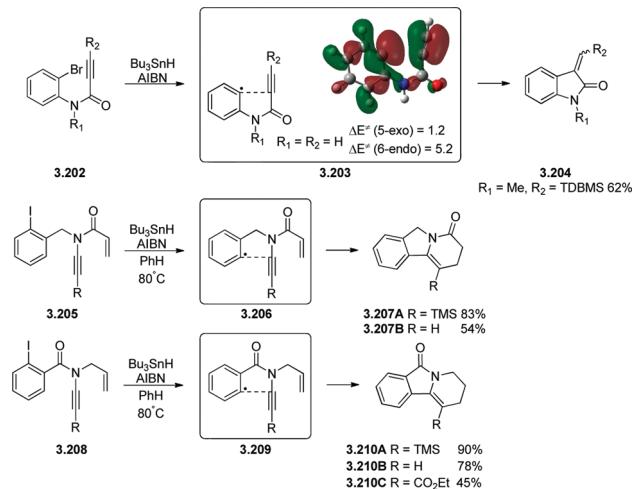
performed by Alabugin and Manoharan, who found that incorporation of the nitrogen atom lowers the barrier with respect to the all-carbon analog and confirms that 5-exo path is kinetically favored.¹³⁵ The apparent selectivity and efficiency are independent of whether the nitrogen atom is attached to the benzene ring or to the triple bond.

Connection through the nitrogen of the amide (ynamide) provides two more possibilities for structural variation, with the carbonyl inside or outside the formed ring. Experimentally, higher yields for 5-(σ -vinylendo)-exo closure onto ynamides were obtained when the carbonyl was inside the formed cycle, particularly for terminal alkynes. Introduction of an electron-withdrawing carboxyl group at the alkyne terminus lowered the yield;¹⁴² however, all cyclizations were regioselective for the exocyclic closure.

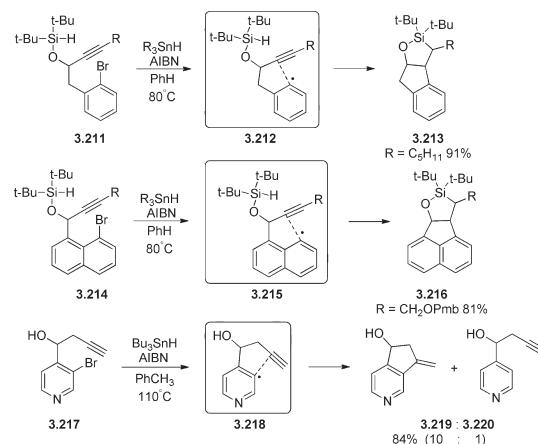
Brunton and Jones connected a TBDMS-capped triple bond to the carbonyl of the amide and attained, upon reductive dehalogenation, the 5-exo-dig product in 62% yield (3.204, Scheme 38). No cyclization was observed with terminal alkynes due to competing hydrostannylation.¹⁴³ Alabugin and Manoharan showed that introduction of an amide moiety significantly lowers the cyclization barriers and renders them more exothermic.¹³⁵

Phenyl and naphthyl radicals close efficiently and regioselectively onto alkyl-substituted propargylic silyl ethers (Scheme 39), similar to the sp³-radicals discussed earlier (Scheme 33). The resulting vinyl radical is efficiently trapped via hydrogen

Scheme 38. Regioselective Closure of Aryl Radicals onto Ynones and Ynamides



Scheme 39. 5-exo-dig Cyclizations of Aryl Radicals with Saturated Linkers



abstraction from the silane and subsequent 5-endo-trig closure. Introduction of the third sp²-carbon in the bridge in naphthyl radical 3.215 did not change the observed 5-exo selectivity.¹³¹ However, in the absence of this trap, pyridyl radical 3.218 has been shown to yield a 10:1 mixture of 5-exo and reduced products in an overall 84% yield. No 6-endo product was obtained.¹⁴⁴

The 5-exo/6-endo competition is more complicated when the bridge is fully unsaturated and, thus, the cyclization can produce completely conjugated molecules. In the case of 6-endo closure, aromaticity of the products renders it much more exothermic than 5-exo-dig. The strong thermodynamic contribution selectively decreases the 6-endo-dig activation barrier for the cyclization of the parent conjugated 1,3-hexadiene-5-yn-1-yl radical (Figure 10, Table 18), which is considered as the possible key step in the formation of polycyclic aromatic hydrocarbons (PAH)¹⁴⁵ during combustion of hydrocarbons.¹⁴⁶ Most recently, Olivella and Solé¹⁴⁷ carefully studied the kinetic competition between 5-exo and 6-endo cyclizations in this system using both DFT and high level multiconfigurational (CASSCF and

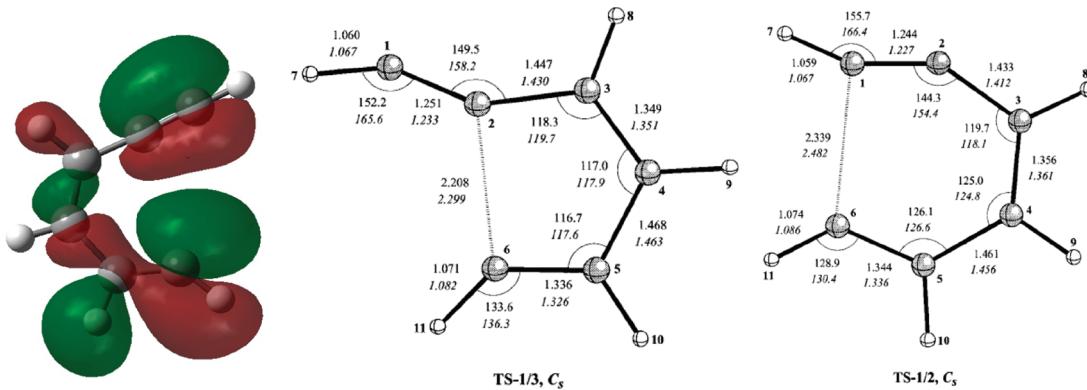


Figure 18. Reactant SOMO (left) and transition state geometries for 5-exo-dig (center) and 6-endo-dig (right) cyclizations of the 1,3-hexadien-5-yn-1-yl radical. (CASSCF/6-31G(d)). Reproduced with permission from refs 135 and 147. Copyright 2005 and 2000 American Chemical Society.

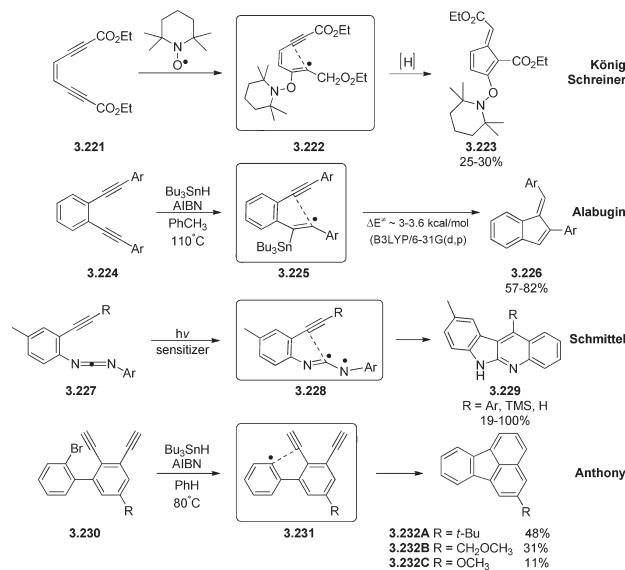
RCCSD(T)) calculations and found that the 5-exo activation barrier is only 1.4 kcal/mol lower than the 6-endo barrier (at the ZPVE-corrected RCCSD(T)6-311+G(3df,2p)//CASSCF/6-31G(d) level): a noticeable leveling in comparison to the difference between the respective digonal cyclizations of motifs B and C.¹⁴⁸ Even still, the authors suggested that the lowest energy pathway for the formation of phenyl radical involves the rearrangement of the 5-exo product via bicyclo[3.1.0]hex-3,5-dien-2-yl radical intermediate instead of direct 6-endo cyclization.

The difference between the reaction energies of 5-exo and 6-endo cyclizations is close to the difference in the stabilities of benzene and fulvene. Interestingly, the incipient C · · · C bonds in the fully conjugated radicals are 0.3–0.6 Å shorter than in radicals with a saturated bridge. This trend, along with the high exothermicities, accounts for very early transition states for motif C digonal cyclizations (Figure 18).¹³⁵

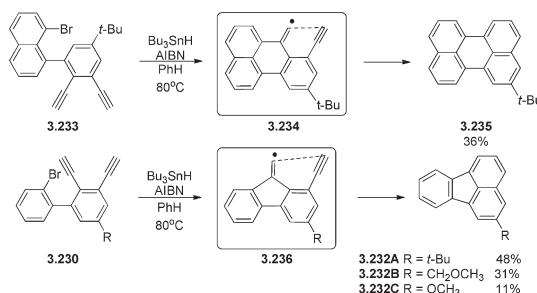
The majority of the literature examples agree with the calculated intrinsic 5-exo preference for the addition of vinyl radicals to triple bonds in conjugated systems. For example, König, Schreiner and co-workers¹⁴⁹ reported an example of the 5-exo-dig cyclization of an enediyne promoted by TEMPO (2,2,5,5-tetramethyl-4-piperidin-1-oxyl) radical (Scheme 40). Alabugin and co-workers found that Bu₃Sn-initiated cyclizations of diaryl substituted enediynes proceed through the same pathway but with considerably improved yields,¹⁵⁰ thus providing a convenient synthetic approach to substituted fulvenes and indenes (Scheme 40).¹⁵¹ Schmittel et al. found that triplet diradicals formed photochemically from enyne-carbodiimides (Scheme 40) and enyne-ketenimines undergo exclusively 5-exo-dig cyclization.¹⁵² Similar to the examples discussed previously (Scheme 39), aryl radicals (made by abstraction of a bromine atom) also close regioselectively in a 5-exo-dig fashion in conjugated systems.¹⁵³

However, this “intrinsic preference” is not absolute and aromaticity-driven 6-endo cyclizations in conjugated systems can compete with the 5-exo pathway.¹⁵⁴ For example, Anthony and co-workers^{153,155} reported that initial 5-exo-dig closure is followed by a surprisingly efficient 6-endo cyclizations in several constrained enediyne systems (Scheme 41). Matzger et al.¹⁵⁶ also described thermal cycloaromatization of tri- and tetracyclic systems where, following the 5-exo-dig closure discussed above (Scheme 40), formation of the final product may potentially include, among other possibilities, a selective 6-endo-dig closure (Scheme 41).

Scheme 40. Regioselective 5-exo-dig Cyclizations in Conjugated Systems

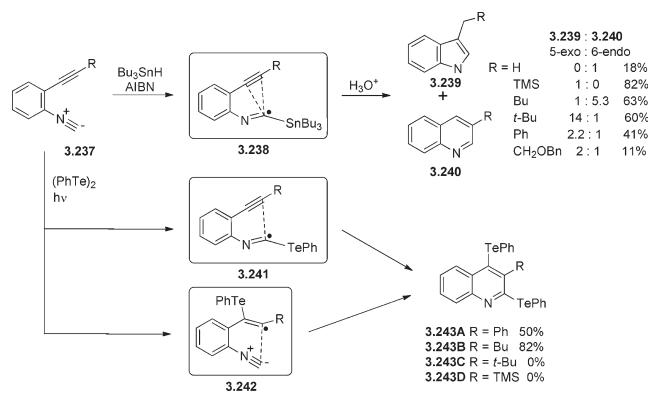


Scheme 41. Selective 6-endo-dig Cyclizations



Moreover, in many cases, the ratio of 5-exo- and 6-endo-dig products is sensitive to the substitution pattern, for example, in the cyclizations of α-Bu₃Sn-imidoyl radicals 3.238¹⁵⁷ reported by Rainier and Kennedy (Scheme 42). As with the previous

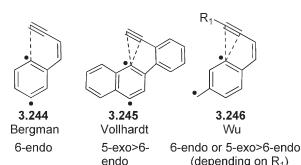
Scheme 42. Regioselectivity of Ring Closure Involving Aryl Isocyanides Is Dependent upon the Conditions



examples, the TMS-capped alkyne reacts selectively in a 5-exo-dig fashion. The simple alkyl substituted ($R = Bu$) and terminal alkyne, however, showed a preference for 6-endo-dig closure. The regioselectivity is altered when thermal initiation/stannyl radicals are replaced by photolytic cleavage of diphenyl ditelluride. Under these conditions, Ogawa and coworkers found that only the 6-endo-dig product was obtained for both alkyl and aromatic substituted reagents in 28–82% yields, while the bulkier TMS and *t*-Bu groups resulted in no reaction.¹⁵⁹ This is in contrast to the findings of Rainier and Kennedy and may be the result addition of the Te radical to the alkyne,¹⁶⁰ followed by regioselective closure at the carbon of the isocyanide.

Another intriguing example is provided by the topologically related diradicals produced in the course of Bergman and Myers–Saito cyclizations (Scheme 43). Although Bergman and co-workers reported only the formation of naphthalene product (>10%) in the “double cycloaromatization” of (*Z,Z*)-deca-3,7-diene-1,5,9-triyne,¹⁶¹ Vollhardt and Matzger found both the 5-exo (19%) and the 6-endo products (2.5%) in a similar system.¹⁶² Moreover, Wu and co-workers reported that, depending on the substitution, didehydrotoluene diradicals formed by the Myers–Saito cyclization yield either exclusively the 6-endo product (18%) or a mixture of 5-exo and 6-endo products in a ~4:1 ratio and a 63% combined yield.¹⁶³

Scheme 43. Examples of Competing 5-exo-dig/6-endo-dig Cyclizations of Conjugated Radicals



In a detailed theoretical study aimed at providing a unified description of digonal radical cyclizations, Alabugin and Manoharan addressed the question whether the basic stereochemical requirements for these reactions (exemplified by the Baldwin rules) are absolute or can be attenuated or even reversed by thermodynamic contributions to the reaction barriers.¹⁶⁵ They concluded that although the 5-exo pathway usually has a lower barrier, the formation of a new aromatic ring (in conjugated systems)

not only increases the thermodynamic favorability of endocyclic closure but also lowers its activation barrier to the extent where the 5-exo/6-endo selectivity can be fine-tuned by a number of factors, such as the higher sensitivity of the 5-exo pathway to strain. As the result, one reaches a crossover in selectivity: the 6-endo cyclization is kinetically favored in smaller (and strained) bicycles, whereas the 5-exo cyclization has lower barriers when the reactive centers are fused with a larger ring.

In particular, strain becomes an especially important factor in cascade radical cyclizations, where rigid polycyclic frameworks are created as the result of sequential cyclizations. Strain effects were estimated by annealing a cyclopentene ring at all possible positions (3.249, 3.251, 3.252). Remarkably, independent of the exact pattern in Figure 19, such a structural change leads to an inversion of selectivity in comparison to the acyclic systems and renders the 6-endo cyclization the kinetically preferred pathway.

Because 5-membered rings are more strained than 6-membered rings, annealing the bridge alkene to a cyclopropene introduces ~34 kcal/mol of strain in the 5-exo product but only 19 kcal/mol for 6-endo product. Differences between the acyclic and cyclobutene systems are still significant: 19 (5-exo) versus 7 kcal/mol (6-endo). As a result, the product strain should create a 5-exo → 6-endo crossover in selectivity and render the 6-endo pathway kinetically favored in the more strained systems. This observation is of practical value in the design of selective radical processes and in understanding available experimental results.¹⁶⁴ For example, it readily rationalizes the switch in selectivity from 5-exo to 6-endo in strained systems illustrated in Scheme 31 and Figure 19.

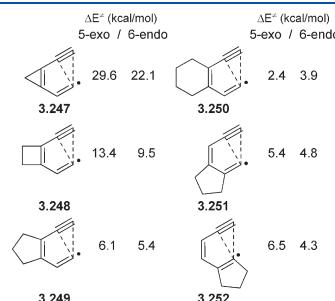


Figure 19. Activation barriers for 5-exo-dig and 6-endo-dig cyclizations of conjugated vinyl radicals fused with rings of varying size (B3LYP/6-31G** level).

Other structural modifications besides strain can perturb the relatively close competition between the two cyclizations of motif C.¹⁶⁵ For example, as with the parent system (Table 19), one can further differentiate the two cyclizations via introduction of aryl substituents at the terminal carbons. This modification imposes a number of effects on the cyclization (Table 21). For example, 5-exo cyclizations of the isomeric radicals in entries 1 and 3 are accompanied with gain or loss of benzylic conjugation, respectively, and thus have very different thermodynamic components. In contrast, even when the reactant radical is stabilized by benzylic conjugation, the conjugation is invariably lost in the 6-endo process. Additionally, the double substitution at the termini further disfavors the 6-endo process for α,ω -disubstituted substrates (Table 21) because of the significant steric destabilization caused by the repulsion of two Ph-substituents in the naphthalene product. The products of 5-exo cyclization do not suffer from this steric repulsion between the terminal

Table 21. SOMOs for the Reacting Radicals, Activation Barriers, Reaction Energies, and Intrinsic Barriers (in kcal/mol) for 5-exo-dig and 6-endo-dig Cyclizations of Phenyl-Substituted Vinyl Radicals^a

SOMO	Entry	E _a	ΔE _r	ΔE ₀
	1	0.6	-43.7	13.8
	2	4.6	-56.4	24.8
	3	5.0	-27.9	15.9
	4	6.3	-51.1	25.4
	5	3.6	-32.9	15.8
	6	9.9	-40.2	26.1

^a All values in kcal/mol and ring-closing bonds are shown in red (B3LYP/6-31G** level).

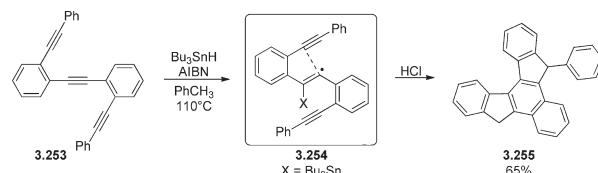
substituents and are still stabilized by benzylic conjugation. Here, both steric and thermodynamics combine to further decrease the 5-exo barrier, accounting for the 5-fold increase in the kinetic preference for this pathway (>6 kcal/mol) relative to the competing 6-endo-dig closure in comparison with the preference for the entries 3 and 5 (~1.3 kcal/mol).

Note that for the last two cases (Table 21), intrinsic barriers do not change and calculated barriers are only affected by different reaction thermodynamics. The intrinsic barriers for 5-exo cyclizations (entries 3 and 5) are identical and differences in the overall activation barriers are solely due to the thermodynamic component (loss of benzylic conjugation in the first case). In contrast, the 6-endo intrinsic barrier increases for the latter case which suggests that steric interaction between the terminal substituents is already present at the TS stage.

Interestingly, the intrinsic barriers for entries 2 and 4 are also similar, suggesting that the deactivating effect of benzylic conjugation is compensated by the difference in hybridization and geometry. Aryl-substituted radicals have very little s-character and almost linear geometry at the radical center, whereas simple vinyl radicals have significant amount of s-character and are noticeably bent. Besides the usual consequences for chemical reactivity and orbital energies, hybridization also controls molecular geometry and determines the direction in which the radical orbitals are projected in space (the valence angles), as well as the relative size of the two lobes of a nonbonding orbital.¹⁶⁶ Such differences in the projection trajectory should have stereoelectronic consequences for the attack at the acetylene π-system (see section 2.5.2).

On the basis of the above results, Alabugin et al. developed a radical cyclization cascade transforming polyynes into conjugated structures similar to those present at the tip of carbon nanotubes. When triyne molecules are capped with either phenyl, *p*-tolyl, or trimethylsilyl groups, the radical cascade proceeded smoothly in ~70% yields (Scheme 44).¹⁶⁷ The success of the cascade relies upon the regioselective intermolecular attack of the

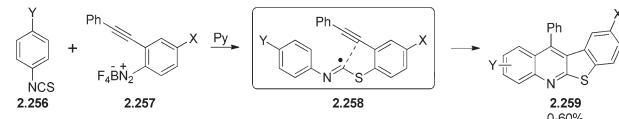
Scheme 44. 5-exo-dig/6-exo-dig Radical Cascade Initiated by Regioselective Tributyltin Radical Addition to the Center Triple Bond



Bu₃Sn radical at the central triple bond. A vinyl radical, produced in the intermolecular step, is trapped selectively 5-exo-dig cyclization. This step is critical for the initiation of the cascade and is completely regioselective: no cyclic products derived from the 6-endo closure of the initial radical has been observed. The resulting vinyl radical is trapped by the third alkyne in a 6-exo-dig cyclization. In the case of phenyl, *p*-tolyl, and *p*-anisyl, the fourth step of the cascade is proposed to be cyclization upon the aromatic ring followed by a 1,5 H-translocation and aromatization to give the final polycyclic structure. When the triyne is capped with TMS, the fourth step consists of hydrogen abstraction from a silyl methyl and subsequent 5-endo-trig cyclization and aromatization to yield the final product.

Another interesting radical cascade cyclization results from the reaction of an aryl isothiocyanate with an *o*-phenylethylnyl aryl radical (created from the corresponding diazonium tetrafluoroborate).¹⁶⁸ Higher yields were attained when the arene ring of the radical species is with a cyano group substituted *para*- to the radical (Scheme 45). The resulting carbon-centered radical cyclizes in a 5-exo-dig fashion, which outcompetes the α-fragmentation of the aryl sulfanyl radical. Unlike the previous examples, the 5-exo closure, rather than the 6-endo, provides an aromatic product and, accordingly, no 6-endo products were detected.

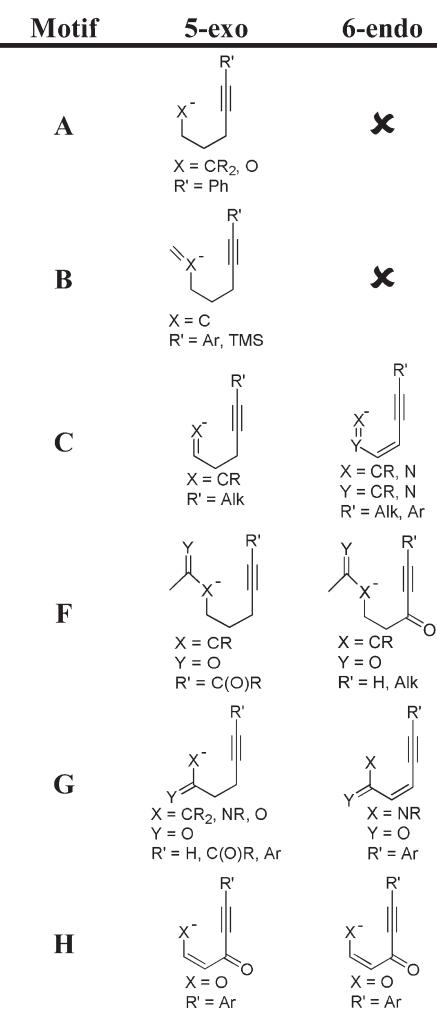
Scheme 45. Formation of Isomeric Quinoline Structures Resulting from a Radical Cascade Initiated by Addition of an Aryl Radical to the Carbon–Sulfur Double Bond



3.3.2. Anionic Cyclizations (Table 22). As with the smaller analogs, 5-exo-/6-endo-dig closures of the parent anionic systems exhibit lower intrinsic and activation barriers for exocyclic closure. Unique to this system, however, are the similar exothermicities for both exo- and endocyclic closure. While the conversion of a weaker bond into a stronger bond (π -bond → σ -bond) and the concomitant transformation of an alkyl anion into a more stable vinyl anion makes carbanionic closure effectively irreversible, closure of oxygen anions, however, are either thermo-neutral or weakly endothermic (Figure 20 and Table 23).²⁴

The 5-exo trajectory of carbanionic closure approaches that of the intermolecular angle of attack, and because of the longer linking chain within this system, the endocyclic transition state now attains an obtuse trajectory (Table 24).

Table 22. Literature Examples of 5-exo/6-endo-dig Anionic Closure with Respect to the Environment of the Anionic Center^a



^a ✗ marks denote gaps in the literature. Motif structures are given in Scheme 1, and D–E do not apply to anionic closures.

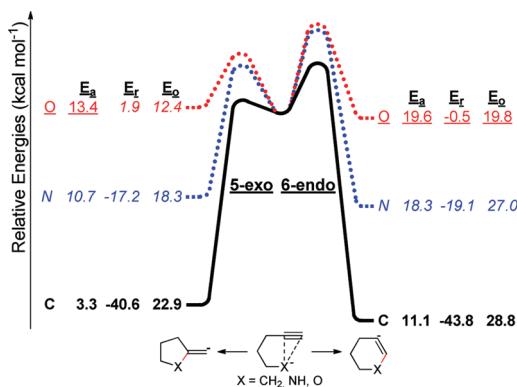


Figure 20. Electronegativity effects on the M05-2X/6-31+G** potential energy surfaces for the 5-exo-/6-endo-dig anionic cyclizations of C- (black solid, bold), N- (blue dashed, *italicized*), and O- (red dashed, underlined) centered anions with terminal alkynes.

According to DFT calculations, carbanionic 5-exo-dig closure is barrierless in the case of the Ph-substituted alkyne but not

Table 23. Activation, Reaction, and Intrinsic Energies (kcal/mol) for the Parent 5-exo- and 6-endo-dig Radical Digonal Cyclizations at the B3LYP/6-31+G(d,p) and M05-2X/6-31+G(d,p) Levels of Theory^a

Entry		E _a	ΔE _r	ΔE _o
1		1.3 (3.3)	-35.9 (-40.6)	13.1 (22.9)
2		10.7 (11.1)	-39.0 (-43.8)	17.9 (28.8)
3		8.8 (10.7)	-13.4 (-17.2)	14.8 (18.3)
4		18.4 (18.3)	-13.9 (-19.1)	24.9 (27.0)
5		11.8 (13.4)	5.8 (1.9)	8.7 (12.4)
6		19.0 (19.6)	4.3 (-0.5)	16.8 (19.8)

^a The M05-2X data are given in parentheses and the ring-closing bond is shown in red.

so for the analogous H, Me, and TMS-substituted alkynes. The most important effect of the anion-stabilizing terminal phenyl group is that its presence renders this 5-exo-dig closure >12 kcal/mol more exothermic than the other 5-exo-dig closures in (Table 23, Table 24). Marcus theory readily demonstrates that the effect of this additional product stabilization should be sufficient to make the reaction barrier disappear. Indeed, once the reaction energy and the intrinsic barrier¹⁶⁹ for this reaction are substituted to the Marcus eq 1, the reaction barrier vanishes.²⁴

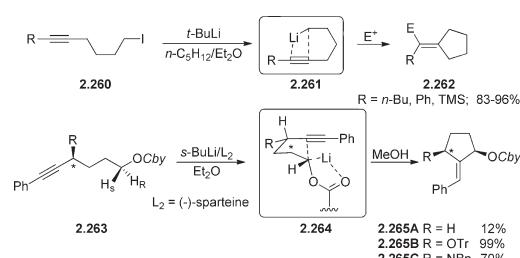
The cyclizations of alkyl lithium reagents, generated from alkyl iodides¹⁷⁰ and connected to an alkyne via a fully saturated linker, proceeds exclusively via the 5-exo-dig pathway (motif A). Bailey and co-workers have analyzed this anionic competition comprehensively and found no evidence for the formation of 6-endo-dig products. For alkyl substituted alkynes, the cyclization is relatively sluggish at the room temperature, in a full agreement with the measured activation parameters (a half-life of ~7 min at ~29 °C, $\Delta H^\ddagger = 23 \pm 0.9$ kcal/mol, $\Delta S^\ddagger = +4 \pm 3.3$ eu). The relatively high activation barriers are likely to reflect the effects of aggregation, solvation as well as nature of the counterions. The phenyl-substituted analogue cyclizes much faster (a half-life ~6 min at -51 °C, suggesting $\sim 10^6$ times acceleration at the low temperatures).¹⁷¹ TMS-substituted alkyne also shows complete 5-exo regioselectivity and ~95% yield (Scheme 46).^{96,172} Stereoselective syn-addition is observed, suggesting that the Li atom is transferred intramolecularly to the developing carbanionic center. Physical basis for these results has been suggested to lie in the stereochemical requirements of the ring closure transition state. This intramolecular coordination could not occur in the 6-endo-dig transition state and may be one of the factors that aid in the complete regioselectivity observed.²⁴ With a bulky group at the propargylic carbon, the well-defined TS allows for stereoselective synthesis of chiral cyclopentanoid building blocks in 70–99% yields (Scheme 46).¹⁷³

Table 24. Transition State Geometries, NICS (0) Values, and LUMO Plots for 5-exo/6-endo Carbanionic Cyclizations for the Me-Substituted Alkyne Calculated at the M05-2X/6-31+G** Level^c

Entry	TS Geometry	NICS(0), ppm	LUMO
		E _a	ΔE _r
			ΔE _o
1		1.3 (2.3)	-32.5 (-39.1)
2		- ^b	-45.6 (-54.3)
3		1.1 (1.5)	-33.6 (-41.0)
		E _a	ΔE _r
			ΔE _o
4		8.5 (7.8)	-37.8 (-45.1)
5		9.2 (11.0)	-41.7 (-52.1)
6		8.0 (4.4)	-30.1 (-39.3)
		E _a	ΔE _r
			ΔE _o

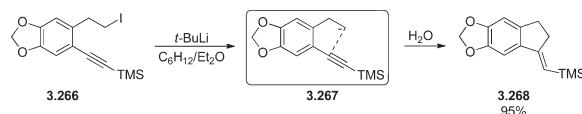
^a Energies are given relative to the near-attack conformations (NAC). The anti-anti conformation is ~4–5 kcal/mol stable than the NACs. ^b This cyclization is barrierless. ^c Bond lengths given in Å. Activation, reaction, and intrinsic energies (kcal/mol) for the parent 5-exo- and 6-endo-dig anionic cyclizations at the B3LYP/6-31+G(d,p) and M05-2X/6-31+G(d,p) levels of theory. M05-2X data are given in parentheses and the ring-closing bonds are shown in red.

Scheme 46. sp³-Anionic 5-exo-dig Closures with Completely Saturated Linkers



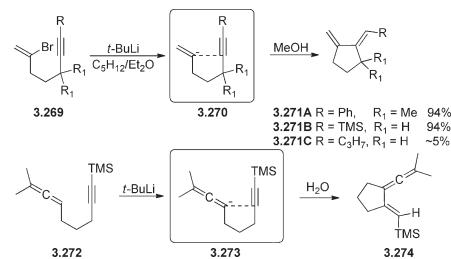
The regioselectivity of alkyl lithium reagents for TMS-substituted alkynes is unaffected by two sp³ carbon in the bridge, affording the 5-exo-dig closure in excellent yields (94–100%, Scheme 47).^{172b}

Scheme 47. sp³-Nucleophiles with Two sp² Centers in the Chain Linking the Nucleophile with the Alkyne



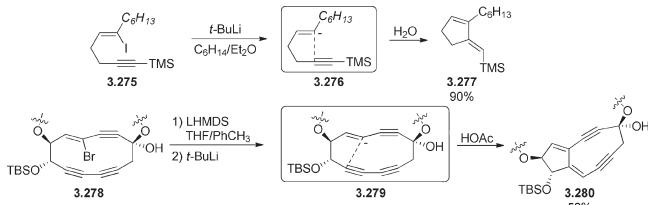
Although the analogous cyclizations of σ -vinylexo anions (motif B) are still fully 5-exo-dig selective, the reactions are much slower (sp²-hybridized carbanions are less reactive) and simple alkyl substituted alkynes mostly give the products resulting from intermolecular capture of the intermediate acyclic vinyl anion (Scheme 48). This limitation notwithstanding, the cyclizations of aryl or silylated alkynes proceed smoothly (83–94%).^{172b,174}

Scheme 48. Nucleophilic 5-(σ -Vinylexo)-exo-dig Ring Closure of Vinyl Lithiums



Negishi and co-workers have shown that simple σ -vinylendo anions (motif C) also undergo selective 5-exo-dig cyclizations^{172b} (Scheme 49). Later, Myers and co-workers have utilized such regioselective closure of reactive species formed via Br–Li exchange at an endocyclic vinyl bromide adjacent to an ethynyl moiety in the development of synthetic approaches toward Kedarcidin and related natural products. These examples of 5-(σ -vinylendo)-exo-dig cyclizations gave the desired product in up to 52% (Scheme 49).¹⁷⁵ At the reported experimental conditions (−78 °C in THF), this reaction is believed to proceed through a carbanionic pathway.^{172b,176}

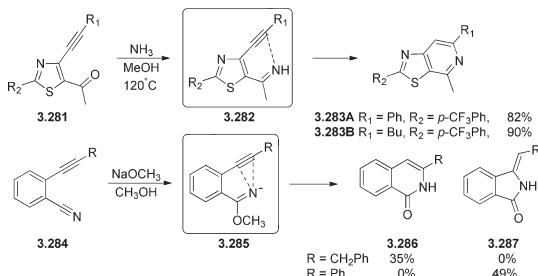
Scheme 49. Regioselective 5-(σ -Vinylendo)-exo-dig Cyclizations



Using a thiazole bridge, Arcadi et al. have proposed that an imine intermediate is what undergoes a 6-(σ -vinylendo)-endo-dig cyclization onto aromatic- and aliphatic-substituted alkynes in 74–95% yields (Scheme 50).¹⁷⁷ Wu and co-workers found that when an iminyl anion is attached to a benzene ring, the regioselectivity can be tuned based on the nature of the alkynyl

substituent.¹⁷⁸ Upon addition of methoxide to the nitrile, the nitrogen anion regioselectively attacked in a 6-*endo* fashion when the alkyne was terminated with an alkyl group. Conversely, when R was an aromatic group, the ring closure was exclusively 5-exo (Scheme 50).

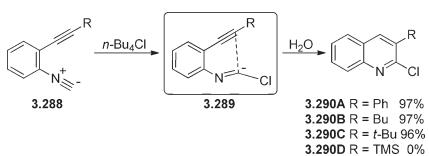
Scheme 50. Regioselective N-Centered 6-(σ -Vinylendo)-endo-dig Closure with a Thiazole Linker Regardless of the Nature of the Alkynyl Substituent^a



^a Benzene-linkers allow for tunable cyclizations based on substitution.

Zhu et al. have found that when the nitrile moiety is replaced by an isonitrile (formed in situ by the dehydration of *o*-ethynyl formamides), exclusive formation of the 6-*endo*-dig product 3.290 is observed when exposed to *n*-Bu₄Cl.¹⁷⁹ Interestingly, while excellent yields were obtained for both alkyl and aromatic substituents, the TMS derivative resulted in no cyclic product while the sterically similar *t*-Bu group closed efficiently (Scheme 51). The radical version of the same TMS derivative resulted in an 82% yield of the 5-exo product (Scheme 42).

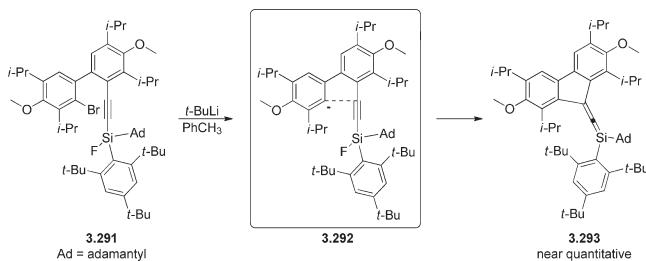
Scheme 51. Carbanions Derived from Isonitriles Close Efficiently and Regioselectively in a 6-(σ -Vinylendo)-endo-dig Fashion



Aryl carbanions conjugated to the alkyne moiety can form the nonaromatic product (5-(σ -vinylendo)-exo-dig) if the acetylenic group has a leaving group, which West and co-workers utilized for the first preparation of a 1-silaallene moiety in near quantitative yield.¹⁸⁰ One has to note, however, that steric effects imposed by the bulky silyl groups are likely to play substantial role in this example as well (Scheme 52).

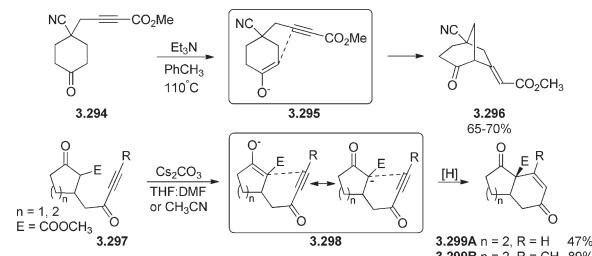
An interesting comparison, which illustrates the potentially useful effect of alkyne polarization on the regioselectivity of ring closure, is provided in Scheme 53. Trost and co-workers have shown that enolates (C-allylexo) regioselectively undergo 1,4-Michael addition onto ester-substituted alkynes (Scheme 53).¹⁸¹ When the polarization of the alkyne is reversed, Lavallée and co-workers have shown that enolate closure follows the 6-(C-allylexo)-endo-dig pathway. The 6-*endo* Michael addition products are formed for terminal and internal alkyl-substituted alkynes in 47–89% yields.¹⁰⁰ One has to note, of course, that the different nature of nucleophiles, with regards to stability, in these two

Scheme 52. 5-exo-dig Product, Trapped through Elimination of a Fluoride Ion, Is Formed Regioselectively, although the 6-*endo*-dig Product would be Aromatic



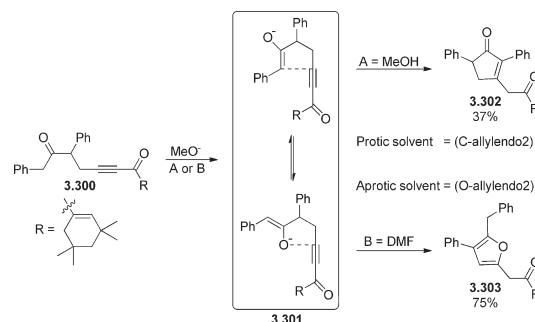
examples should have an effect on the observed reactivity as well. Enolendo substrates ((C-allylendo2), motif G), with the carbonyl in the exterior propargylic position, react similarly to the respective enolexo nucleophiles.¹⁸²

Scheme 53. Anionic 5-exo-dig Closures Controlled by Polarization of the Triple Bonds



While the above allylexo examples are chemoselective for closure through the carbon atom of the enol, Arcadia and co-workers have observed an interestingly solvent dependence for the chemoselectivity of allylendo closures. While closure via the carbon nucleophile (C-allylendo2) is observed in a protic solvent, when an aprotic solvent is used, furans are obtained exclusively by 5-(O-allylendo2)-exo-dig closure (Scheme 54). The same chem- and regioselectivity is observed for oxygen attack onto terminal and aryl-substituted alkynes (vide infra, Scheme 57).¹⁸²

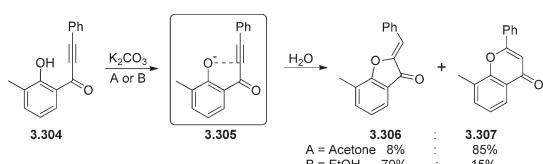
Scheme 54. Chemoselectivity of 5-(Allylendo)-exo-dig Closure Controlled by the Nature of the Solvent



Solvent can also modify the observed regioselectivity. For example, in nucleophilic cyclizations of motif H for oxygen nucleophiles

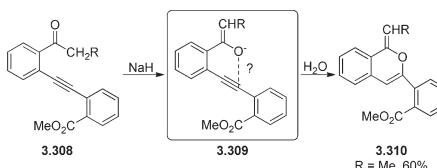
(O-allylendo3), Miranda and co-workers¹⁸³ found that the “anti-Michael” 5-(O-allylendo3)-exo-dig product is formed in 79% yield when using a protic solvent (EtOH). However, in acetone, the major product derives from the formal 6-(O-allylendo3)-endo-dig closure. These observations suggest that the 5-exo cyclization is kinetically favorable and gives the product as long as the cyclized carbanion is quickly and irreversibly trapped by protonation. In an aprotic solvent, the initially formed 5-exo-dig vinyl anion has enough time to rearrange to the more stable 6-endo-dig product, as has been suggested in similar systems (Scheme 55).^{184,56} Tietze and co-workers have used this strategy for six-membered ring formation in their syntheses of several anthrapyrans natural products.¹⁸⁵

Scheme 55. Solvent-Dependent Cyclizations of Oxygen Anions with Three sp^2 -Atoms in the Linking Chain



A formal 6-(O-allylendo2)-endo-dig cyclization has been reported by Padwa et al. (Scheme 56).¹⁸⁶ However, the authors do not exclude the initial formation of a 5-exo product which could rearrange in the six-membered benzopyran ring under workup conditions, similar to an analogous rearrangement reported by them for similar benzylic alcohols (vide infra, Scheme 57).

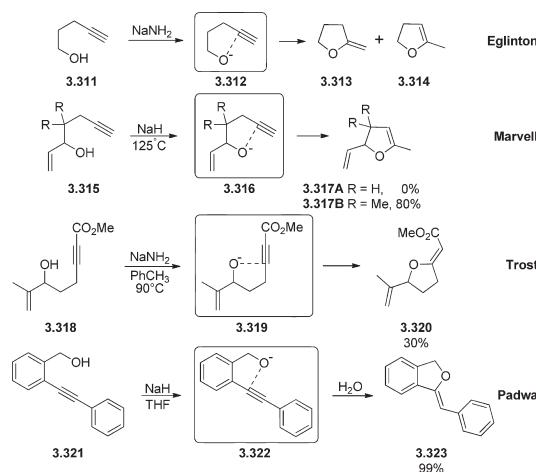
Scheme 56. Formal O-6-(enolendo)-endo Cyclization Closure onto Aryl-Substituted Alkynes



Cyclizations of other oxygen nucleophiles corresponding to motif A are also common. As expected based on the above calculations (Table 23), base-catalyzed cyclizations of aliphatic alcohols exclusively follow the 5-exo path, the vinyl anion serving as the base for another acyclic alcohol. When a secondary allylic alcohol,¹⁸⁷ is used as opposed to a primary alcohol,¹⁸⁸ gem-dimethyl groups are required to facilitate the regioselective transformation. Trost and Runge found that reactions of secondary allylic alcohols with electron deficient alkynes were inefficient (<30%) but led to the tetrahydrofuran through the formal 1,4-Michael addition (aka 5-exo-dig closure) to the polarized alkyne bond.¹⁸⁹ The incorporation of additional sp^2 atoms in the bridge does not change 5-exo-dig selectivity for oxygen nucleophiles (Scheme 57).¹⁸⁶

Vasilevsky, Alabugin, and co-workers sought a deeper understanding of the factors controlling exo/endo selectivity in cyclizations of alkynes through analysis of the possible cyclization pathways in the system shown in Scheme 58.¹⁹⁰ This system combines an activated alkyne moiety with a polyfunctional hemiaminal

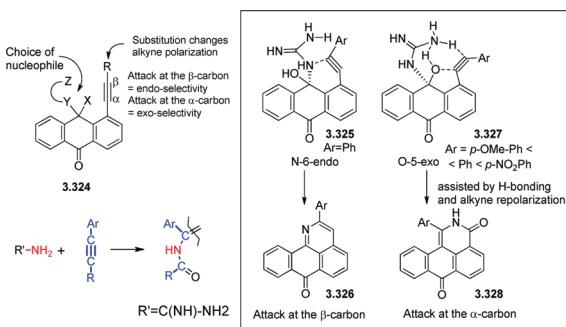
Scheme 57. Base-Catalyzed 5-exo-dig Cyclizations of Primary and Secondary Alcohols onto Terminal Triple Bonds^a



^a Benzylic alcohols also close regioselectively onto phenyl-substituted acetylenes.

group derived from addition of guanidine to the carbonyl moiety of peri-substituted acetylenic anthraquinones 3.324. The presence of several nucleophilic and electrophilic centers in this group accounts for the multichannel mode of its interaction with the adjacent alkyne and several reaction cascades potentially originating from alternative cyclization modes. Interestingly, the nature of substituent R has the ability to control partitioning between these cascades through modulation of the polarization of the triple bond. Presence of an acceptor substituent at the β -carbon decreases electron density at the α -carbon, thus facilitating favors the 5-exo attack of the oxygen atom in the hemiacetal intermediate (Scheme 4). Subsequent transformations in this cascade lead to a remarkable transformation that is formally equivalent to the full cleavage of the triple bond and insertion of a nitrogen atom between the two acetylenic carbons.

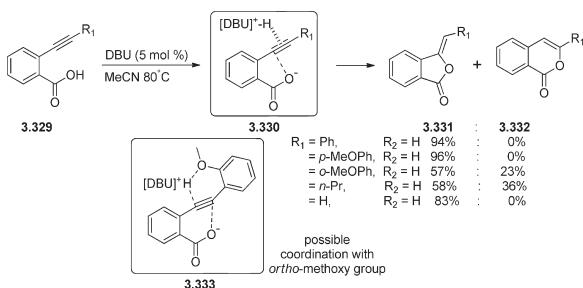
Scheme 58. Diverging Mechanistic Pathways and Factors Responsible for the Multichannel Character of Reactions in Adducts of Peri-Substituted Acetylenyl-9,10-anthraquinones and Guanidine



Activation of the alkyne moiety has been suggested to be important for weaker O-nucleophiles such as benzoates. Kanazawa and Terada¹⁹² proposed that the conjugate acid of the base facilitates formation of the exocyclic vinyl anion and quickly traps the cyclic product through protonation.^{191–193} The

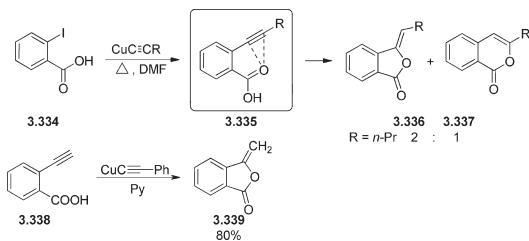
majority of the aromatic-substituted alkynes exclusively gave the five-membered ring with high yields (80–99%). However, appreciable amounts of 6-endo-dig products were observed for *o*-MeO-C₆H₄ (Scheme 59), which is possibly the result of a 6-membered coordination with the acid activating position “6” (3.333). Interestingly, while *n*-pr showed only a slight preference for 5-exo cyclization ($S/6 = 58:36$), 2-propenyl substitution gave only 5-exo-dig closure. The authors also note that the introduction of an electron-withdrawing group *para* to the alkyne (Ac) “markedly retards the (5-exo) cyclization” and leads to the formation of 8% of the 6-endo-dig product (Scheme 64). The regioselectivity for closures of this system is reversed, however, under acidic conditions (see section 3.3.3).

Scheme 59. Weaker Oxygen Nucleophiles (Benzoates), under Catalytic Amine-Base Conditions, Observe a Loss in 5-exo Regioselectivity with Certain Alkyne-Substituents



Castro and co-workers showed that the condensation of *o*-halobenzoic acids with substituted copper acetylides in DMF or pyridine leads, in most cases, to 5-membered lactones. Only in the case of *n*-propylacetylide has some of the 6-endo product been observed (phthalide:isocoumarin ratio 2:1).¹⁹⁴ The analogous cyclization of *o*-ethynylbenzoic acid also afforded the γ -lactone product of 5-exo-dig closure (Scheme 60).¹⁹⁵ The involvement of Cu- π -complexes and the role of EPN processes in these reactions is unexplored.

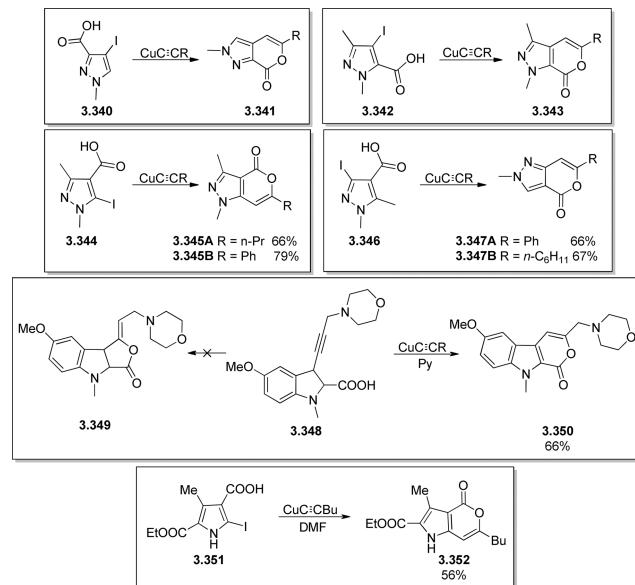
Scheme 60. Cyclizations of Benzoic Acids, Following Cuprate Addition, Prefers the 5-exo-dig Pathway



Interestingly, the 5-exo-dig preference observed for the benzoic acid derivatives can be completely overruled when a more strained five-membered heterocyclic core is used. A variety of N-containing heterocycles, shown in Scheme 61, exhibit complete 6-endo-dig selectivity.^{195,196} These observations are consistent with the earlier discussed role of strain on the competition between closely matched radical cyclization (section 3.3.1 on 5-exo/6-endo-dig radical).

The involvement of Cu- π -complexes and the role of EPN processes in these reactions is unexplored.

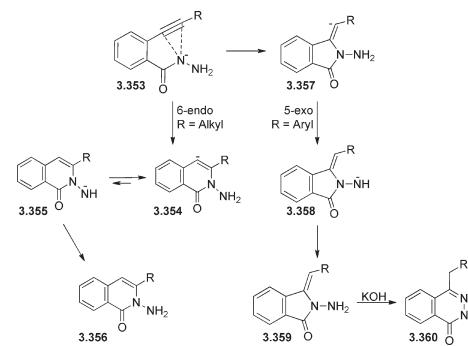
Scheme 61. Cuprate Coupling and Subsequent Regioselective 6-endo-dig Cyclizations of Carboxylic Acids Where the Two Functional Groups Are Fused to a 5-Membered Ring



The questions of 5-exo/6-endo selectivity in digonal cyclizations of N-nucleophiles (motif G) have been studied by Vasilevsky, Alabugin and co-workers.⁵⁶ Alkyl substituents at the alkyne terminus favor the 6-endo-dig closure, whereas aryl groups greatly facilitate the alternative 5-exo-dig path.

The competing cyclization pathways were fully analyzed computationally. Both the decreased 5-exo-dig activation energies and increased stability of the 5-exo products for R = Ph confirm that the Ph group steers the cyclization selectively down the 5-exo path by providing benzylic stabilization to the anionic center in the product. In contrast, the competition between the 5-exo- and 6-endo-dig closures is close for alkyl substituted acetylenes. For R = Me, the values of the cyclization barriers are within 1 kcal/mol from each other and thus, both cyclizations can proceed with comparable rates. Although the 5-exo

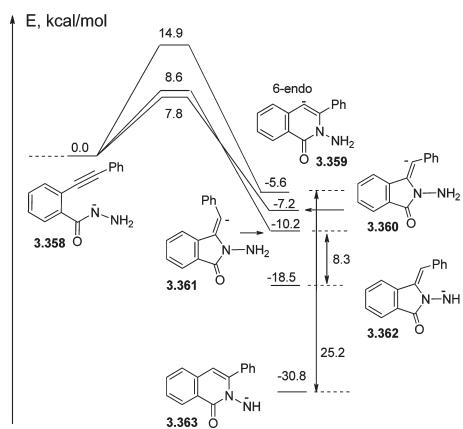
Scheme 62. Fine-Tuning of the Regioselectivity of N-Amide Nucleophilic Closures via Electronics of the Alkyne Moiety



cyclization has a 0.6 kcal/mol lower barrier than the 6-endo closure in the gas phase, introduction of solvation reverses this preference. Moreover, the 5-exo-dig cyclization is predicted to be endothermic and readily reversible in solution, whereas the 6-endo-dig closure is \sim 10 kcal/mol exothermic. The higher computed activation barriers for both 6-endo and 5-exo cyclizations of alkyl substituted alkynes are consistent with experimental observations (Scheme 62).⁵⁶

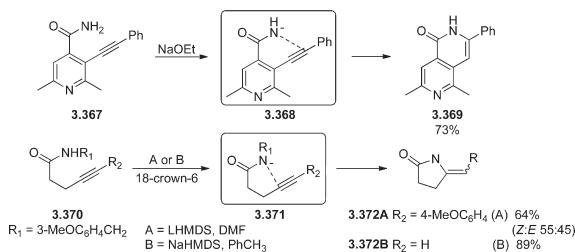
These anionic cyclizations lack a significant thermodynamic driving force because the gain in stability due transformation of a weak π -bond into a stronger σ -bond is offset by the transformation of a stable nitrogen anion into an inherently less stable carbanionic center. Formation of the final products is negotiated through several proton shifts, ultimately leading to the most stable tautomeric anion as a thermodynamic sink (Scheme 63).⁵⁶

Scheme 63. Full Potential Energy Surface for the Competing 6-endo and 5-exo Cyclizations of Hydrazide Anions at B3LYP/6-31+G(d,p) Level of Theory



In contrast, aryl amides cyclize under basic conditions into the 6-membered products even with a phenyl-substituted alkyne (73%, Scheme 64).¹⁹⁷ However, when the linking chain is saturated, the cyclizations of β -alkynyl amides proceed exclusively through the 5-(N-allylendo)-exo-dig pathway (Scheme 64).¹⁹⁸

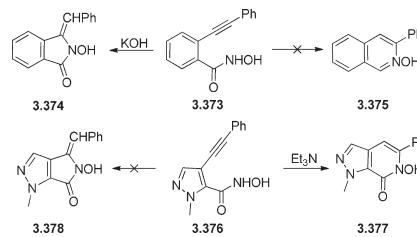
Scheme 64. Regioselectivity of Anionic Cyclizations of β -Alkynyl Amides Is Influenced by the Nature of the Linking Carbons



The regioselectivity of anionic closure of *o*-ethynyl-benzene-hydroxamic acids has been found to depend on the nature of the aromatic linker. Interestingly, change to a pyrazolyl core again leads to the switch from 5-exo to 6-endo selectivity, even in the

case where only 5-exo product has been observed for a benzene-derived substrate (Scheme 65). This observation is likely to have its origin in the same strain effects as those discussed previously for radical closures (Figure 19). O-attack via a 6-exo or 7-endo closure was not observed.¹⁹⁹

Scheme 65. Switch in the 5-exo/6-endo Selectivity As the Function of Annealed Ring Size



3.3.3. Electrophilic Cyclizations (Table 25). Unlike the 3-exo/4-endo and 4-exo/5-endo pairs, electrophilic 5-exo/6-endo cyclizations are relatively well studied. The electrophilic closure of carbocations (motif A) and oxonium ions (π -vinylexo/endo, motifs D, E) are particularly well represented. The latter process is referred to as the “Prins-type” closure. Cyclizations onto diazonium salts (σ -vinylendo, motifs B, C), called the Richter cyclization, have also been investigated.

Table 25. Literature Examples of 5-exo/6-endo-dig Electrophilic Closure with Respect to the Environment of the Electrophilic Center^a

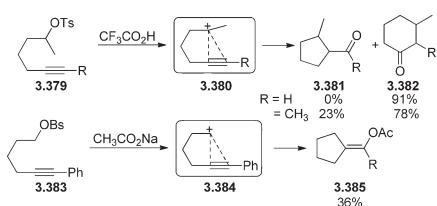
Motif	5-exo	6-endo
A		
C		
D		
E		

^a \times marks denote gaps in the literature. Motif structures are given in Scheme 1. Motifs B and F–H are unknown.

The regioselectivity of the parent carbocationic system is dictated, as with the 3/4 analogs, by the substituent on

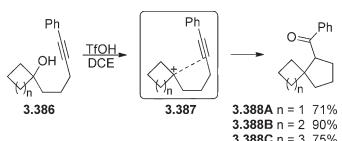
the alkyne (NPEC). Upon solvolysis in acid, primary triflates¹⁰⁹ and secondary tosylates²⁰⁰ exhibit complete endocyclic regioselectivity in cyclizations with terminal alkynes. Likewise, when a strongly stabilizing group such as a phenyl caps the triple bond, complete exo regioselectivity is observed.²⁰¹ Unlike homopropargylic cations, where methyl substitution resulted in almost exclusive formation of the 4-endo-dig product (Scheme 7, Scheme 8), both primary and secondary carbocations yield a mixture of the 5-exo- and 6-endo-dig products, favoring the exocyclic pathway (Scheme 66).^{109,200}

Scheme 66. Regioselectivity of 1° and 2° Carbocationic Closure Is Dictated by the Alkynyl Substituent



Tertiary carbocations behave similarly, yielding the regioselective formation of spirocyclic²⁰² or bicyclic²⁰³ ketones resulting from the 5-exo-dig closure onto phenyl-substituted alkynes. The cyclization is equally successful under acidic solvolysis of 3° alcohols or protonation of an olefin (Scheme 67).

Scheme 67. Tertiary Carbocations Close Efficiently and Regioselectively onto Phenyl-Substituted Alkynes

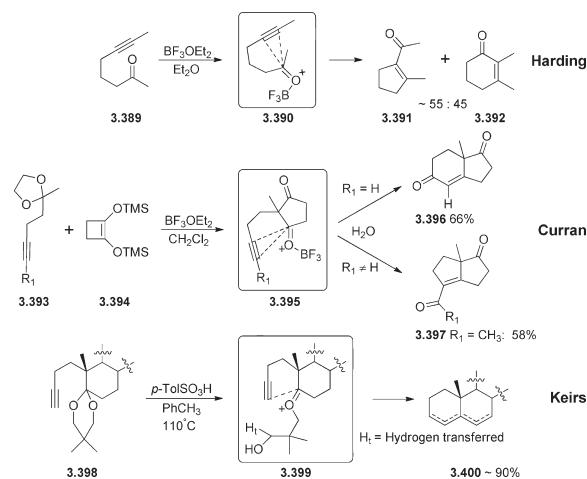


Harding and King described the formation of 5-exo and 6-endo products (π -vinylexo, motif D) in \sim 55:45 ratio upon the exposure of hept-6-yn-2-one to $\text{BF}_3\text{Et}_2\text{O}$ or HCl .²⁰⁴ However, when bicyclic products are formed, the regioselectivity can be efficiently controlled through substitution of the triple bond. The exclusive formation of the 6-(π -vinylexo)-endo-dig product upon reaction with terminal alkynes suggests that the stability of the intermediate vinyl cation plays the decisive role in regioselectivity of this ring closure.²⁰⁵ These results are in accord with earlier findings by Keirs et al., who observed 6-(π -vinylexo)-endo-dig closure for terminal alkynes. In the latter case, the cyclic vinyl cation was trapped through intramolecular hydride transfer (Scheme 68).²⁰⁶ Exocyclic closure has been observed for internal alkynes.²⁰⁵

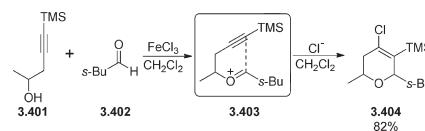
The Prins-type cyclization, resulting from homoallylic alcohols and aldehydes has been shown to favor the 6-endo products.²⁰⁷ Homopropargylic alcohols also undergo this transformation via a 6-(π -vinylene)-endo-dig product when exposed to a Lewis acid, for example FeCl_3 (Scheme 69).²⁰⁸

DFT analysis (B3LYP/6-31G(d) level) revealed that the electronic effect of the TMS group is crucial for the formation

Scheme 68. 5-(π -Vinylexo)-exo and 6-(π -Vinylexo)-endo-dig Electrophilic Cyclizations of Oxocarbenium Ions



Scheme 69. Selective 6-endo-dig Closure in the Prins-Type Cyclization of Homopropargylic Alkynes



of a dihydropyranyl cation.²⁰⁹ While the TMS-containing cyclic cation is a shallow minimum whose formation is 5.4 kcal/mol endothermic, the parent dihydropyranyl cation is not even an energy minimum but exists only as a TS for the Cope rearrangement TS ($\Delta E^\ddagger \approx 7$ kcal/mol, Figure 21). The alternative 5-exo-dig direction has not been considered and it is not clear whether the 5-exo product may be formed transiently and rearrange to the dihydropyran.

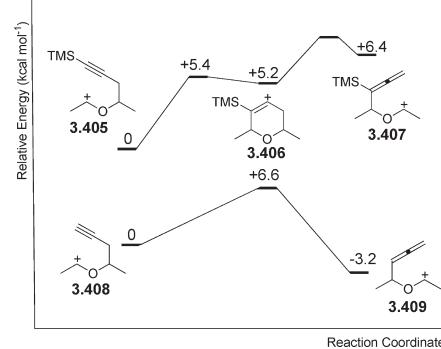
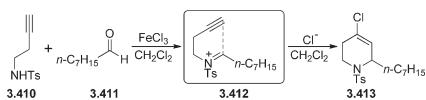


Figure 21. Relative stability of the cationic intermediates of the Prins-type cyclization at the B3LYP/6-31G(d) level.

In a seeming conflict with this computational data, terminal alkynes also react regioselectively in a 6-endo-dig fashion in Prins²⁰⁷ and aza-Prins reactions²¹⁰ promoted by Fe(III) halides (Scheme 70). It should be noted however, as discussed by Martín, Padrón, and co-workers, FeX_3 not only activates the carbonyl moiety as a Lewis acid but also participates in “forming

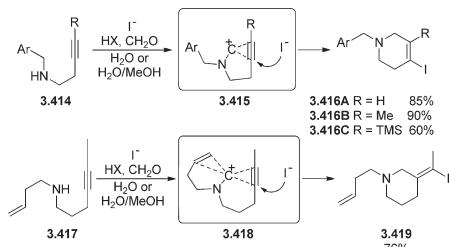
alkyne-iron complexes that may be an initial step in further chemical events.²¹¹

Scheme 70. Prins-Type Closure of Terminal Alkynes



The presence of the external nucleophile also plays a critical role in the cyclizations of these stabilized acyclic cations. Overman and Sharp examined the NPE cyclizations of a series ofaza-Prins cyclizations, observing a lack of cyclic products in the absence of external nucleophile and chemoselective 6-exo closure onto an alkyne in the presence of a pendant alkene capable of undergoing 5-exo-/6-endo-trig closure. While exocyclic closure is observed in the 6/7 pair for terminal and internal alkynes, electrophilic cyclization proceeded exclusively in a 6-endo-dig pathway upon exposure to either bromide or iodide (Scheme 71).^{32,33}

Scheme 71. Nucleophile-Promoted Electrophilic Closures of Iminium Ions with Alkynes in the Presence of Strong Nucleophiles^a

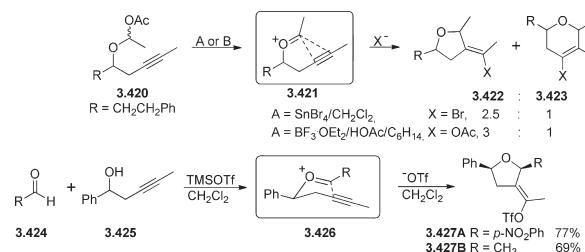


^a HX = camphorsulfonic acid.

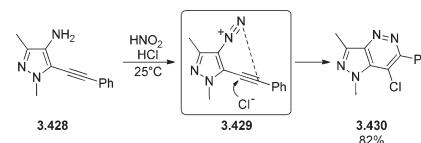
Aside from facilitating the cyclization, the external nucleophile, as well as the Lewis acid, can modify or even control the regioselectivity of the cyclization. While the above FeCl_3 -induced closures were all endo selective, a mixture of products favoring 5-(π -vinyleno)-exo-dig closure is observed for SnBr_4 or $\text{BF}_3 \cdot \text{OEt}_2$.¹¹⁰ Cho and co-workers have shown that, through two subtle modifications (a 2° benzylic homopropargylic alcohol as opposed to a 2° aliphatic and using TMSOTf as a Lewis acid) the regioselectivity can be completely tuned toward 5-(π -vinyleno)-exo-dig closure (Scheme 72).²¹² A highly selective and efficient 5-exo-dig ring closure of a Ph-substituted alkyne, which may proceed through a similar oxocarbenium intermediate, is also known.²¹³

NPEC can also occur between “two” triple bonds ($\text{C}\equiv\text{C}$ and $\text{N}\equiv\text{N}$), as exemplified by the Richter reaction,²¹⁴ where cyclization between a vicinal alkyne and diazonium salt is observed only in the presence of a suitable nucleophile (motif C, Scheme 73). Initial studies observed the formation of hydroxy-cinnoline derivatives, where simultaneous attack of a water molecule on the interior carbon of the alkyne and C–N bond formation was proposed.²¹⁵ Vasilevsky and Tretyakov found that nucleophilic attack by a less nucleophilic halogen anion can outcompete that of water at room temperature, giving halogenated 6,6 (cinnolines) and 5,6 (pyrazolopyridazines)²¹⁶

Scheme 72. Effects of Lewis Acid/Nucleophile upon the Regioselectivity of Prins-Type Cyclizations of Homopropargylic Alcohols



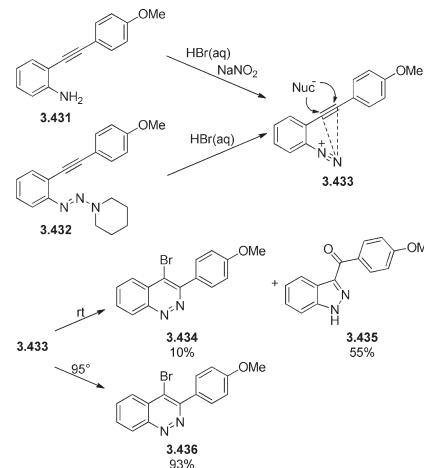
Scheme 73. In situ Formation of Diazonium Salt, Trapped by 6-endo-dig Closure upon Intermolecular Attack of a Chlorine Anion



in up to 53 and 93% yields for the chloro- and bromo-derivatives, respectively.²¹⁷

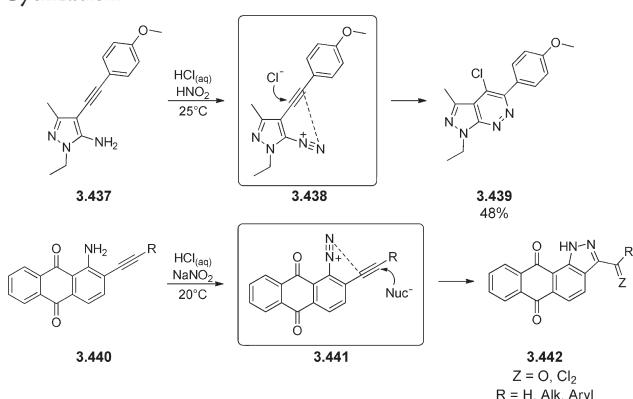
The effect of temperature is also critical to the products obtained. When alkyne 3.433 is treated with $\text{HBr}_{(\text{aq})}$ at 95 °C, exclusive formation of 6-endo-dig product 3.436 is observed;²¹⁸ however, at room temperature the major product was that of 5-exo-dig cyclization (3.435, Scheme 74).²¹⁹

Scheme 74. Effects of Temperature on Product Distribution of the Richter Cyclization with (*p*-MeOC₆H₄)-Substituted Alkynes

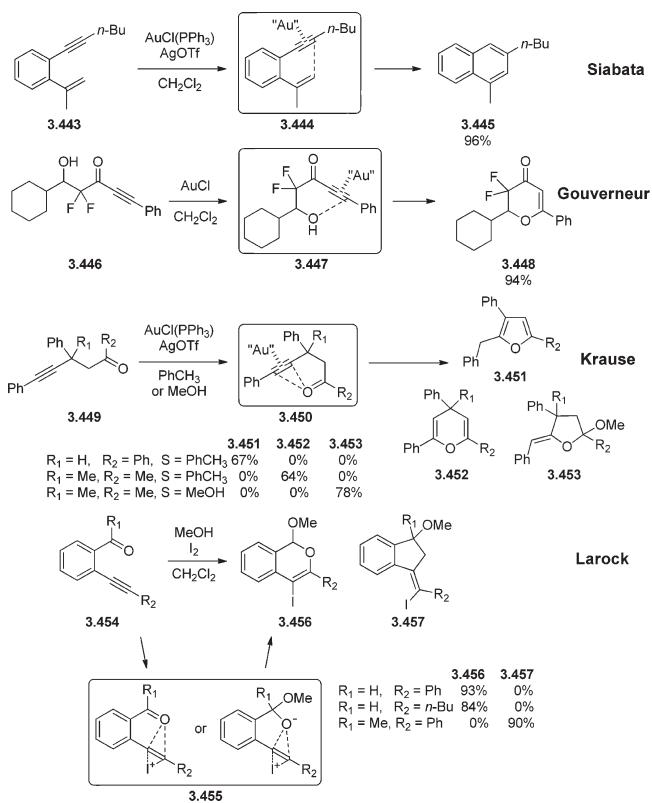


The nature of the cyclic core also has a significant influence on the regioselectivity of cyclization. The effects of temperature can be superseded by those of strain, as shown by Vasilevsky et al., where no formation of the 5,5-bicyclic product was observed (Scheme 75).²¹⁶ When 2-acetylenic anthraquinone-1-diazonium salts are exposed to similar conditions at room temperature,

Scheme 75. Effects of Aromatic Core on Regioselectivity of Cyclization



Scheme 76. Electrophile-Induced Nucleophilic Cyclizations of Carbon and Oxygen Species



exclusive formation of the NPE-5-exo-dig product is observed for terminal as well as alkyl- and aryl-substituted alkynes.²²⁰

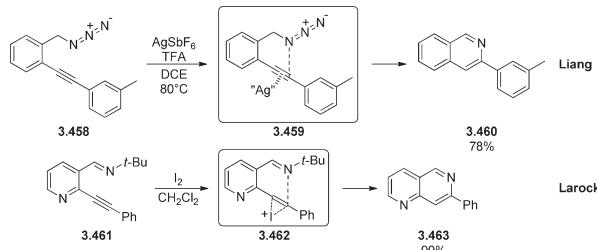
3.3.4. The Effect of Metal/External Electrophiles on 5-exo/6-endo Regioselectivity. Representative examples provided in this section²²¹ illustrate that, in contrast to the uncatalyzed cyclizations of carbon nucleophiles which usually proceed with a 5-exo-dig regioselectivity, formation of the 6-endo product is common in cyclizations promoted by coordination of an external Lewis acid, particularly when an aromatic product is formed (Scheme 76).²²² In a similar manner, sp^3 -hybridized oxygen

nucleophiles (Scheme 57) close regioselectively onto terminal or alkyl-substituted triple bonds in a 6-endo-dig fashion in the presence of an external electrophile^{223,224} (Scheme 76).

Interestingly, the regioselectivity of oxygen nucleophiles derived from addition to, or tautomerization of, a ketone (using a Au cat.) depends on the substitution at the bridge carbon as well as the nature of solvent (Scheme 76).²²⁵ When a nonmetal external electrophile is used such as I₂ or PhSeBr, hemiacetates derived from benzaldehyde undergo addition and subsequently close regioselectively onto phenyl or alkyl-substituted alkynes in a 6-endo-dig fashion. When the aldehyde was exchanged for a methyl ketone, however, only the 5-exo-dig product was obtained.²²⁶

sp^2 -Hybridized nitrogen nucleophiles undergo efficient and regioselective 6-(σ -vinylendo)-endo (imines,²²⁷ hydrazides,²²⁸ oximes²²⁹) and 6-(σ -vinylexo)-endo (azides²³⁰) -dig closure in the presence of external electrophiles such as I₂, Pd, or Ag²³¹ (Scheme 77).

Scheme 77. Regioselective 6-(σ -Vinylendo)- and 6-(σ -vinylexo)-endo-dig Closures of Nitrogen Nucleophiles in the Presence of External Electrophiles



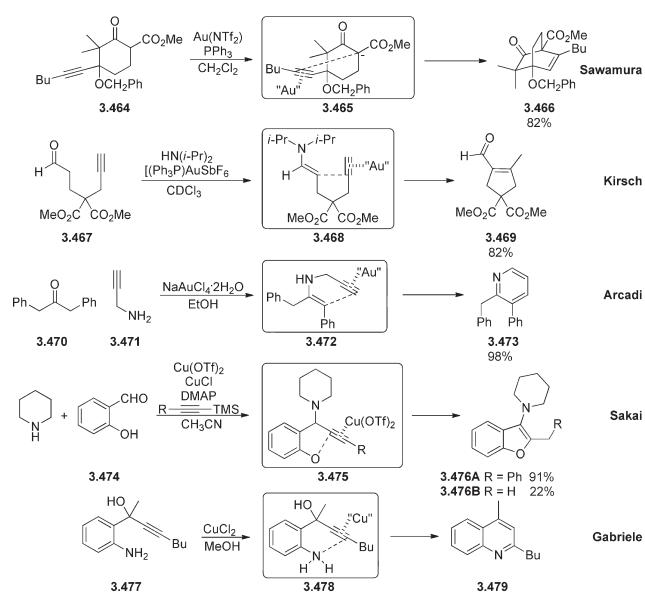
Formation of [2.2.2]-bicyclic structures from stabilized enolates via a selective 6-endo fashion has been reported to occur in up to 89% yield in the presence of Au(I) salts (Scheme 78).²³² Endo-²³³ and exocyclic enamines were reported to close differently in the presence of a gold catalyst²³⁴ (Scheme 78). The formation of aromatic products directs the Cu(II) cyclizations of 3.475 and 3.476, resulting from regioselective O-centered²³⁵ 5-exo- and N-centered²³⁶ 6-endo-dig closures, respectively (Scheme 78).

Contrary to several examples discussed above (Scheme 61), the ring-closure of carboxylic acid derivatives, whether attached to a 5- or 6-membered ring, regioselectively close in a 6-endo-dig fashion when exposed to Cu(I) and (II) salts,²³⁷ Ir(III) hydrides,²³⁸ or I₂ (Scheme 79).²³⁹ When benzamides are exposed to a variety of external nonmetal electrophiles, only modest to good selectivity for 5-exo-dig closure is observed.²⁴⁰

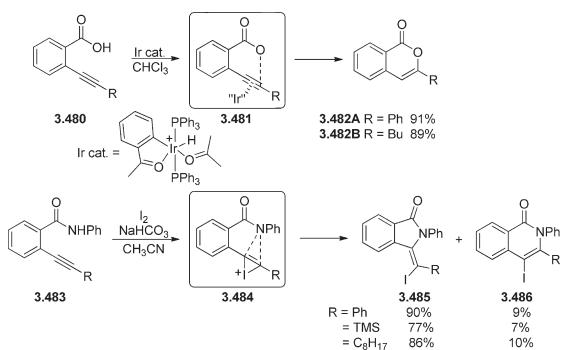
3.3.5. Summary of 5/6. The parent carbon-centered radicals and anions close regioselectively in a 5-exo fashion, matching the calculated activation barriers (Figure 22). However, the exo/endo barriers for carbon radicals are less than 3 kcal/mol apart and if the linking chain is a trans-fused 5-membered ring, increased strain in the smaller ring selectively directs the radical closures (motif A) along the 6-endo-dig path (Scheme 31). The effects of fused rings on the regioselectivity of (σ -vinylendo, motif C) radicals has been examined computationally (Figure 19). Regardless of the alkynyl substitution or the possibility of the formation of an aromatic product, the majority of σ -vinyl radicals close in an exocyclic fashion.

Similarly, anions also are generally regioselective for the 5-exo-dig mode of closure, including primary and vinyl (σ -vinylexo/endo) carbanions (Scheme 46-Scheme 49), primary, secondary, and benzylic

Scheme 78. Regioselective Closures of Enols, Enamines, and Aniline Derivatives in the Presence of Metal Species



Scheme 79. EIN Closure of Benzoic Acid and Benzamide Derivatives



oxygen nucleophiles (Scheme 57) as well as hydrazides (Scheme 63). The regioselectivity of the respective enolate closures can be tuned based on the polarity of the alkyne; when a carbonyl group is in the exterior propargylic position, enolates close in a 5-exo fashion. When the polarity is reversed, so is the regioselectivity (Scheme 53). Finally, while benzamides have been shown to close regioselectively (6-endo, Scheme 64), the cyclizations of aromatic hydroxamic acids are more sensitive to the size of the aromatic core (6-membered rings result in 5-exo cyclization, 5-membered rings yield the 6-endo products, Scheme 65).

The regioselectivity of NPE 5-exo/6-endo closures, as with the 3/4 series, depends upon the nature of the Lewis acid and alkynyl substitution. Exclusive formation of 5-membered rings is observed for Prins-type closures using TMSOTf (Scheme 72), while only 6-endo-dig products are obtained using FeCl₃ (Scheme 69, Scheme 70). Mixtures are formed when either SnBr₄ or BF₃·OEt₂ (Scheme 72) is used, as well as for non-Prins-type oxycarbenium closures in the absence of a

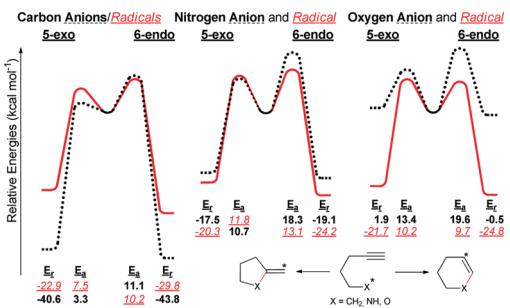


Figure 22. Electronegativity effects on the M05–2X/6-31+G potential energy surfaces for the 5-exo-/6-endo-dig anionic and radical cyclizations of C-, N-, and O-centered anions (black dashed, bold) and radicals (red solid, italics, underlined) with terminal alkynes.**

strongly stabilizing group (Scheme 68). Carbocations close regioselectively in a 5-exo fashion onto phenyl substituted alkynes (Scheme 67). The same regioselectivity is not always observed, however, for nitrogen electrophiles (Richter cyclizations, Scheme 74, Scheme 75).

4. CONCLUSIONS: REVISED RULES FOR ALKyne CYCLIZATIONS

Literature reports of cyclization modes predicted to be unfavorable together with the lack of several cyclizations modes predicted to be favorable by the original rules, (for example, anionic/radical 4-endo-dig closures) call for a revised set of rules for alkyne cyclizations. We propose several modifications. First, we suggest to modify the classification system and expand the types of cyclizations to favored (green in Table 26), borderline (yellow), and disfavored (red). This “middle ground” was added to describe a select number of examples, where a varying degree of assistance is required to attain the desired product (e.g., adjacent leaving groups, strongly delocalizing and stabilizing substituents, thermodynamical stabilization of the product by aromaticity etc.).

In addition, “favorability” has two components: intrinsic stereoelectronics that originate from the differences in the orbital overlap patterns, and full activation barriers which combine the intrinsic barriers with thermodynamic components. From the fundamental and didactical perspectives, the first definition is valuable but the second is more useful in practice. Based on the first criterion with regards to anionic and radical closure (Table 26), one can clearly classify all exo-dig cyclizations as favorable. However, because of the inherent strain of 3- and 4-membered rings, these closures are less kinetically favorable²⁴¹ than closures with normal thermodynamic driving forces and require careful experimental design, justifying their classification as “borderline”. The formation of 3- and 4-membered rings via endocyclic closure is unfavorable. Under certain conditions and structural modifications, 5- and 6-endo-dig closure of anions can be obtained regioselectively and as such have been labeled “borderline”. Because of the differences in the stabilizing interactions of the LUMO and SOMO with alkynes, radical 6-endo cyclizations are more favorable than their anionic counterparts.²⁴²

With respect to electrophilic closures, the following rules can be suggested on the basis of a still rather limited data set (Table 27). As with the cyclizations of anionic/radical intermediates, 3-endo-dig closure is a disfavored reaction. Products resulting from nucleophilic attack (NPE) onto 3-center, 2-electron nonclassic cation (3-exo/

Table 26. Revised Baldwin Rules for Digonal Cyclizations of Anions and Radicals^a

Anionic	3	4	5	6	
Dig	endo-	x	x	✓	✓
	exo-	✓	✓	✓✓	✓✓

Radical	3	4	5	6	
Dig	endo-	x	x	✓	✓✓
	exo-	✓	✓	✓✓	✓✓

^a Red squares correspond to disfavored, yellow squares to borderline/problematic, and green to favored modes of ring-closure.

Table 27. Revised Baldwin Rules for Digonal Cyclizations of Cationic Intermediates^a

Cationic	3	4	5	6
Dig	endo-	x	✓	✓
	exo-	✓	✓	✓✓

^a Red squares correspond to disfavored, yellow squares to borderline/problematic, and green to favored modes of ring-closure.

4-endo pair), under the right conditions can proceed efficiently and even be obtained regioselectively, and these closures are deemed “borderline”. While there are no examples of electrophilic 4-exo- and 5-endo-dig closures in the literature, we predict these cyclizations to be difficult but potentially achievable given the appropriate substitution/conditions. Finally, both 5-exo and 6-endo products can be obtained regioselectively, depending upon substitution and the nucleophile, and are classified as favorable.

In summary, the combination of computational, theoretical and experimental data presented herein has clearly shown that both anionic and radical endo-dig cyclizations are intrinsically less favorable than the competing exo-dig closures. The origin of this preference lies in the greater magnitude of stabilizing bond-forming interactions for the obtuse angle of nucleophilic (and to a lesser extent, radical) attack. This stereoelectronic preference is similar to the well-established Bürgi–Dunitz trajectory for the cyclizations of alkenes. Intrinsic stereoelectronic preferences for exo-dig closure can be overshadowed by additional factors, such as polarization of the π -system and thermodynamic effects (e.g., strain in one of the products and aromaticity in the other), which can tip the balance in favor of the endo products. The cationic dig-cyclizations have limited importance and are essentially unknown for the 3-exo/4-endo and 4-exo/5-endo pairs, unless they proceed via a nucleophile-assisted path. A more important and increasingly popular approach to the formation of endo adducts involves electrophile-promoted nucleophilic cyclizations, where the symmetry of the alkyne LUMO is reversed by coordination with a suitable soft Lewis acid and endo-dig closure of nucleophilic species becomes possible. These cyclizations are not included in the present sets of rules.

Modern organic synthesis deals with molecular targets of ever increasing complexity and new synthetic methods continue to emerge. The progress of organic chemistry leads to birth, aging, and death of a number of concepts dealing with chemical structure and reactivity. However, after the redesign and expansion described in this manuscript, the basic stereoelectronic concepts embodied by the Baldwin rules will continue to serve the broad chemical community.

AUTHOR INFORMATION

Corresponding Author

*E-mail: alabugin@chem.fsu.edu.

BIOGRAPHIES



Kerry Gilmore was born in 1984 in Brewster, Massachusetts. He received B.S.s in Biology and Chemistry from Roger Williams University in 2006 working under the direction of Prof. Dan von Reisen. After that, he began his doctoral studies at Florida State University under the direction of Prof. Igor Alabugin. He is also a 2011 Fulbright scholar, working in Bologna, Italy under the direction of Dr. Chrys Chatgilialoglu. His Ph.D. studies include discovery of new cyclizations of alkynes, incorporation of these processes into cascade transformations, as well as the dissection and reevaluation of the structural and electronic effects involved in nucleophilic, radical, and electrophilic ring closure processes.



Igor V. Alabugin was born in Novokuznetsk, Russia, in 1969. He received his undergraduate degree in 1991 and his Ph.D. degree in 1995 from the Moscow State University under the supervision of Professors N. S. Zefirov, N. V. Zyk, and V. K. Brel. After a postdoctoral study at the University of Wisconsin-Madison with Professor H. E. Zimmerman, he joined the Department of Chemistry and Biochemistry of the Florida State University in 2000, where he is currently a Full Professor.

His research interests are at the intersection of photochemistry and organic synthesis with biochemistry and materials science including the design, discovery and development of: photochemical double-stranded DNA cleavage agents with built-in selectivity to cancer cells, pH-gated DNA binding and modification, new

radical cyclizations, cascade transformations of alkynes for the construction of graphene nanoribbons, electronic and conformational control of the Bergman cyclization, conformationally gated cyclization/fragmentation pathways which provide a potential biochemical autoprotection mechanism from DNA-damaging cycloaromatization, metal-free conversion of phenols into esters and amides of aromatic carboxylic acids, as well as studies of stereo-electronic and rehybridization effects in organic and supramolecular chemistry.

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- (241) The current exception to this is Malacria's example of a carbon-centered radical closing onto a terminal alkyne in a 4-exo-dig fashion, which was trapped via a 1,5-H atom transfer from the methyl of a silyloxy group (see Scheme 9, ref 75 and 76).
- (242) Note that the 6-endo-dig closure is particularly favored by more electrophilic O-centered radicals. See Figure 22.

NOTE ADDED AFTER ASAP PUBLICATION

An error in Table 15 was discovered in the version published on 8/23/2011. This was corrected in the version published on 9/16/2011.