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Strain and stereoelectronics in cycloalkyne click chemistry

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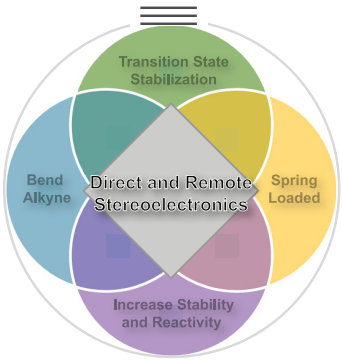
Due to the broad interest to cycloalkynes in metal-free click chemistry, we present a focused review summarizing current approaches to structural and electronic modifications of cycloalkynes. We illustrate how the combination of reactant destabilization and transition state stabilization can lead to the design of more reactive cycloalkynes that are, paradoxically, less strained. We discuss the concept of ring strain in cycloalkynes and show that increased ring strain does not always equate to increased click reactivity. We summarize direct and remote electronic effects that can be used to enhance click reactivity in cycloalkynes and show how inclusion of transition state stabilizing stereoelectronic effects is essential for the rational design of the cycloalkyne click reagents.



Introduction

Once upon a time cycloalkynes were just a curiosity with no apparent applications, confined to the obscure corners of organic chemistry. Nevertheless, their unusual structures pushed the limits of synthetic exploration and many incarnations of these unstable molecules were pursued and, sometimes, created.[1] The transiency of reactive cycloalkynes challenged chemists to push the boundaries of molecular ring strain. Only the advent of click chemistry[2] and the subsequent quest to overcome limitations of metal-catalyzed reactions in bioconjugation[3] brought the practical utility of cycloalkynes into clear focus. The accumulation of stored energy, caused by deforming the alkyne's ideal linear *sp*-hybridized geometry inside the ring, can be harvested and released in a spontaneous reaction with a general alkynophile.

The most widely used reaction with cycloalkynes in click chemistry is a [3+2] cycloaddition with an azide group. Many aspects of this reaction have been reviewed extensively.[4] For a recent informative review of cycloalkynes in the context of cycloadditions with azides, see Dommerholt *et al.*[5] A more general list of reactions, syntheses, and physical properties of cycloalkynes can be found in a comprehensive review by Krebs and Wilke.[1] For an expertly taken snapshot of cycloalkyne reactivity one can also refer to the review by Hopf and Grunenberg.[6] However, a number of more recent discoveries call for a reevaluation of electronic factors that can control cycloalkyne reactivity. The goal of the present review is to fill this gap using a combination of recent literature data and selected DFT calculations.

The role of strain

To effectively use cycloalkynes for click chemistry, one must maintain a balance between stability and reactivity. Historically, the balance between these two variables was sought primarily through manipulation of ring size. The severity of ring strain energy increases as ring size decreases. The strain energy of cycloalkynes as a function of ring size is given in Scheme 1 [the Ring Strain Energy (RSE) values in kcal mol^{-1} are estimated using enthalpy of a hypothetical alkyne insertion reaction suggested by Bach].[7] When the ring is small enough, the boundary between

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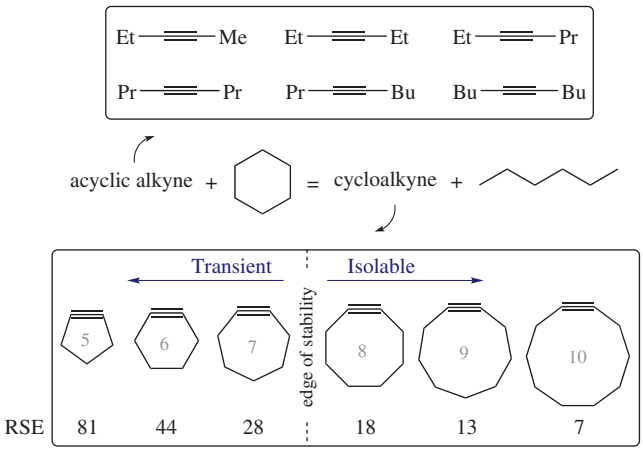


Scheme 1 The adjustment of ring size is the predominant method of maintaining a balance of reactivity and stability. Thermochemical equation to assess ring strain energies (RSEs) of cycloalkynes. Ring strain energies calculated at M06-2X/6-311G+(d,p) level of theory. Energies are in kcal mol^{-1}.

an isolable molecule and a transient species becomes blurred. Because the practical utility of a cycloalkyne depends on whether it can be isolated and used for experiments, changing the ring size is the first method of controlling reactivity. So, is there a perfect size?

The stable larger cycles have lower ring strain and resemble linear alkynes in reactivity, while cycloalkynes with small ring sizes (<8 atoms) easily push the reactivity beyond the edge of stability. These small highly reactive cycloalkynes behave as transient reactive intermediates and must be formed *in situ* with a trapping agent present.[8] Although the inherent high reactivity of small cycloalkynes such as benzyne has been used in the discovery of many new reactions,[9] these transient intermediates currently find no practical use in click chemistry.

Generally, medium-sized cycloalkynes and their derivatives account for nearly all cycloalkynes used in click chemistry today since they offer a reasonable balance between stability and reactivity. The C≡C–C bond angles of cyclooctynes, cyclononynes, and cyclodecynes (~155°,[10] ~165°,[11] ~170°,[11] respectively) indicate moderate to slight deviations from linearity (180°). The strain energies of cyclononyne and cyclodecyne are ~70% and ~40% of strain energy of cyclooctyne (OCT), respectively.

Cyclooctyne is generally considered to provide a good compromise – stable enough to be isolated and stored but reactive towards azides at room temperature. The early reports by Blomquist *et al.*[12] and Wittig *et al.*[13] described the high reactivity of cyclooctyne. Most notably, Blomquist mentioned that it 'explosively' reacted with phenyl azide, a reaction that turned out to be the hallmark of click chemistry. This property made cyclooctyne interesting from both synthetic and theoretical perspectives which subsequently led to an exploratory boom of reactions utilizing its stored energy.[14] The most prevalent classes of reactions used with cyclooctynes have been [3+2], [4+2] and [2+2+2] cycloadditions. Out of the many 1,3-dipoles studied (diazoalkanes,[15] azomethine ylides,[16] nitrile oxides,[2(a)] nitrous oxide,[17] and nitrones[18]) in the Huisgen 1,3-dipolar cycloaddition,[19] that between cyclooctynes and azides has received a remarkable amount of attention because of its ability to connect functional building blocks into hybrid molecular architectures. Furthermore, these processes are experimentally simple and scalable, serving as a powerful tool for click chemistry. The seminal work by Bertozzi demonstrated cyclooctyne's ability to function as a tool for modification of biomolecules and became pivotal stepping stone for bioorthogonal chemistry, reactions that probe biomolecules without interfering with biochemical processes or reacting with the many functionalities present in the physiological environment.[4(a),20]

Also, it is important to note that the alkyne itself can be considered as a high energy functionality.[21] This is why alkyne reactions with azides are exceedingly exothermic, even more than the large amount of strain energy suggests, *i.e.*, the ΔE_{rxn} for the cycloaddition of methyl azide with 2-butyne and cyclooctyne are –67.8 and –79.0 kcal mol^{-1}, respectively.

The reason why the additional strain is helpful is that, despite its high energy content,[21] the alkyne moiety is imbued with intrinsic kinetic stability (*i.e.* triple bond is stronger than a double bond[22]). For example, on the basis of the difference in G3 total energies, the cyclic allene 1,2-cyclooctadiene has an RSE (11.9 kcal mol^{-1}) that is 8.0 kcal mol^{-1} lower than an RSE of the isomeric cyclooctyne, yet 1,2-cyclooctadiene is not readily isolable.[7]

Evaluating strain

Historically, strain in cyclooctynes was evaluated either by thermodynamic methods such as heats of hydrogenation,[23] or by indirect spectroscopic measurements such as ^{13}C NMR chemical shifts of alkyne carbons, $J_{C–C}$ coupling constants,[10] and IR/Raman spectra of alkyne stretching.[1] While these approaches provide useful information, they do not directly measure the strain energy of cycloalkynes. In particular, the relation between reactivity and enthalpy of hydrogenations for alkynes is complicated and its interpretation to describe reactivity or structural properties should be done prudently.[24]

As mentioned earlier, alkynes are high energy functionalities. Their energy content is reflected in high enthalpy of hydrogenation of a linear alkyne such as 4-octyne (ΔH_{hyd} = 35.9 kcal mol^{-1}). Hence the large experimental and calculated ΔH_{hyd} for cyclooctyne (45.5[23] and 50 kcal mol^{-1}, respectively) do not reflect the distortion penalty due to the alkyne bending. A more accurate estimate of this penalty is the $\Delta\Delta H_{hyd}$ value (*i.e.*, the difference in heats of hydrogenation of linear and cyclic alkynes). For cyclooctyne, this difference (10–14 kcal mol^{-1}) is smaller than the RSE calculated *via* the ring closure equation given above. Furthermore, 4-octyne is calculated to have ΔH_{hyd} of ~36 kcal mol^{-1} while cyclononyne has a similar value of ~38 kcal mol^{-1}, yet their reactivities to the reaction with an azide are quite different. Furthermore, as pointed out by Bach,[7] the ΔH_{hyd} of the smaller cycloalkynes increase even faster than their RSEs. The enthalpies of hydrogenation of cycloheptyne, cyclohexyne and cyclopentyne are calculated (G3) to be 56.6, 76.3, and 100.4 kcal mol^{-1}, respectively.

A more accurate way to evaluate strain is the use of homodesmotic equations,[25] which can provide a direct comparison of strain energies for a series of related cycloalkynes (Scheme 1).[26] Creating a meaningful thermochemical equation requires isolating out the ring strain energy component while keeping the other energy-changing factors as close to constant as possible.[25,27] Thermochemical equations that conserve such factors as bond types, hybridizations *etc*. are more accurate in the interpretation of strain energy of cycloalkynes. Careful interpretation of these results reveals additional factors for variations in strain energies for a series of related cycloalkynes such as the absence or presence of stereoelectronic effects.[28]

The reactivity of cycloalkynes is most affected by alkyne angle strain, *i.e.*, how much the alkyne deviates from linearity (∠C≡C–C < 180°). Using a linear, acyclic model system such as 2-butyne, we can directly extract the dependence of strain energy on alkyne bending (Figure 1) without the contribution of other structural effects. By overlaying the ring strain energy for a series of related carbocyclic alkynes with the cost for alkyne bending, one can dissect the contribution of angle strain towards

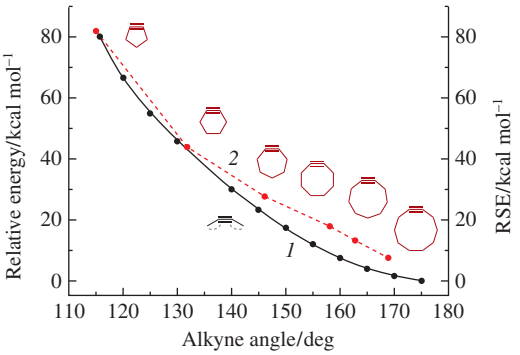


Figure 1 (*1*) Penalty for alkyne bending in 2-butyne *vs*. (*2*) ring strain energy for cyclodecyne, cyclononyne, cyclooctyne, cycloheptyne, cyclohexyne, and cyclopentyne using equation from Scheme 1. RSEs and relaxed energy scan calculated at M06-2X/6-311G+(d,p) level of theory.

the total ring strain energy of the cycloalkynes. As expected, there is a penalty for alkyne bending, ranging from 0 to ~80 kcal mol^{-1} (black line). The ring strain energies for all cycloalkynes (red dashed line) match closely to the cost for alkyne bending, reaffirming that bending the alkyne is a large component to ring strain.

Is strain always in control?

Although strain is, without doubt, a key factor in cycloalkyne chemistry, the small differences in strain alone cannot serve as a reliable indicator of reactivity. In order to illustrate it, let us consider the family of three monobenzocyclooctynes (MOBOs) to see if there is a connection between their RSEs and click reactivity (Figure 2).[29] As the position of the benzene is moved, the strain energies do not remain the same. The calculated strain energies for 3,4-MOBO, 4,5-MOBO, and 5,6-MOBO are 15.0, 17.0, and 15.5 kcal mol^{-1}, respectively. The structural distortions in the cyclooctyne ring are also different. For example, the deformation of the alkyne moiety for 3,4-MOBO, 4,5-MOBO, and 5,6-MOBO is reflected in ∠C≡C–C bond angles of 155°/157°, 153°/157°, and 153°/153°, respectively. Moving the position of the fused benzene ring further away from the alkyne results in a larger deviation of the alkyne angle from 180°. However, the greatest alkyne angle compression observed for 5,6-MOBO does not lead to the greatest strain energy due to the presence of a secondary structural distortion associated with eclipsing conformations (*i.e.*, the torsional strain) in the constrained methylene groups of 3,4-MOBO and 4,5-MOBO.

The lack of correlation between alkyne angle compression and RSE of monobenzocyclooctynes contrasts the reliable RSEs correlation with cycloalkynes ring size (Figure 1). The lower torsional strain in the saturated part of the 5,6-MOBO backbone does not deactivate this alkyne relative to the 4,5-MOBO (where the saturated part is more strained) because strain in the saturated part is not relieved (or aggravated) by the click reaction to the same extent as strain due to alkyne bending is alleviated. Another surprising result is that, although 4,5-MOBO has a greater alkyne angle compression than 3,4-MOBO, 4,5-MOBO has a higher activation barrier in the click reaction with methyl azide. The lower activation barrier found for 3,4-MOBO over 4,5-MOBO indicates the presence of additional effects that contribute to the reactivity.

The above example illustrates that greater RSE does not necessarily lead to greater click reactivity. An especially relevant case is the incorporation of endocyclic heteroatoms in the cyclooctyne backbone that alleviate ring strain but do not sacrifice reactivity in comparison to their carbocyclic counterparts.[28(b)] This small case study of additional substituents in the cycloalkyne backbone challenges the notion that modifying alkyne angle compression is the only design tool for increasing the alkyne click reactivity. Instead, it opens the opportunity to discover new structural and electronic features that can be harnessed to create more reactive and more selective cycloalkynes for click chemistry.

Strategies for destabilizing cycloalkyne reactants

As we discussed so far, cycloalkynes mostly owe their increased reactivity to the rise in reactant energy. Initially, alkyne destabilization in click chemistry was accomplished by bending the alkyne through incorporation in the cyclooctyl backbone. However, this structural effect was insufficient for making cyclooctyne a perfect cellular probe – it reacts too slowly to be useful for the many interesting biochemical timescales, requiring relatively long incubation times and higher concentration loading. In addition, this cellular probe is less selective towards its intended bioconjugation partner than the Bertozzi-Staudinger ligation[30] (although the latter suffered from an even slower reaction kinetics and oxidation of the phosphorous substituent).

This limitation spurred many efforts focused on imparting even more ring strain with the goal of further increasing cyclooctyne's reactivity. The most popular early strategy was based on incorporating additional sp^2 centers in the ring in order to

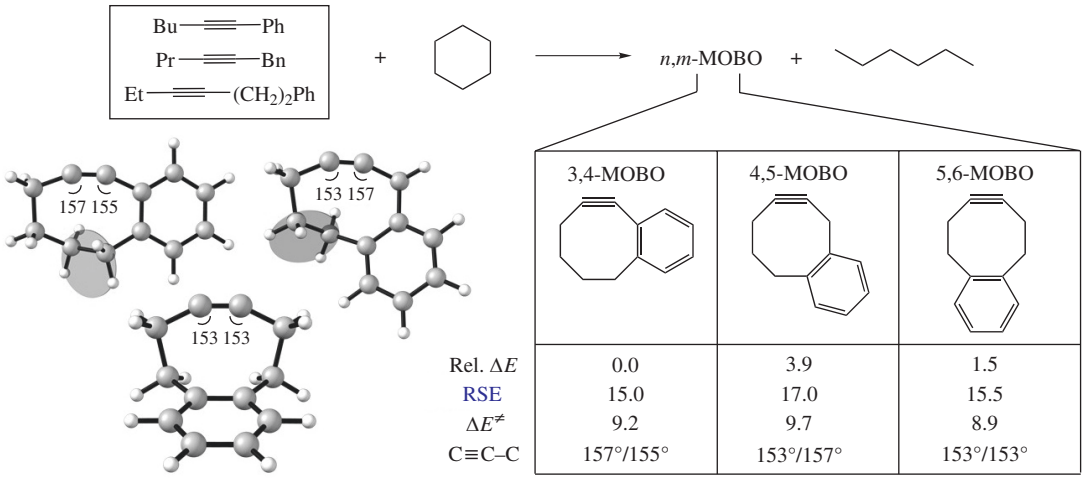


Figure 2 The ring strain energies of three monobenzocyclooctynes from an isodesmic equation do not correlate with their calculated activation energies for the cycloaddition with methyl azide at M06-2X(D3)/6-311G+(d,p). The lowest activation barriers were used and correspond to the 1,5-regioisomeric TS for 3,4-MOBO and 1,4-regioisomeric TS for 4,5-MOBO. For activation and reaction energies for all MOBOs, see Table S1. Molecular models shown with the alkyne bond angles for each system. Torsion strain indicated with plane bisecting the eclipsing C–H interactions in 3,4-MOBO and 4,5-MOBO. Energies are in kcal mol^{-1}.

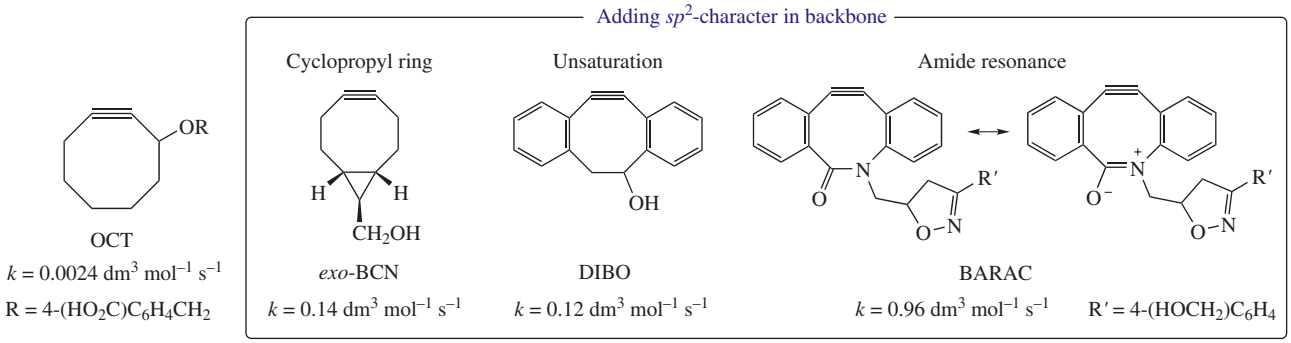


Figure 3 Structural modifications based on reactant destabilization increases click reactivity. Rate constants reported in the cycloaddition with benzyl azide.

compress and rigidify the backbone and render the cycloalkyne even more 'spring-loaded'.

The most conventional method of adding 'sp^2 hybridized units' is to anneal unsaturated cycles to the cycloalkyne backbone. For example, DIBO,[31] which has two benzene rings fused to backbone, shows 50-fold increase in reactivity compared to the seminal Bertozzi's cyclooctyne in the cycloaddition with benzyl azide (Figure 3). The observed increase in reactivity is even more impressive if one takes into account the steric clash between the *ortho* C–H's of the aryl rings and the azide during the click reaction.

An alternative way of incorporating sp^2 hybrid orbitals inside the cyclooctyne backbone is based on cyclopropane ring fusion. The banana orbitals that form the cyclopropyl C–C bonds take more *p*-character (~sp^5) in comparison to the C–C bonds of non-strained saturated hydrocarbons. Due to the conservation of the total *s*- and *p*-character, the exocyclic cyclopropyl C–C bonds that expand in the cyclooctyl ring become ~sp^2-hybridized.[32] The value of this approach is demonstrated by BCN which is ~60-fold more reactive than cyclooctyne.[33]

Partial double bond character in the ring can also be added through electron delocalization. By combining an internal amide functional group with annealed benzene rings in the BARAC[34] molecule, Bertozzi and coworkers were able to achieve remarkably fast reaction with benzyl azide (400-fold more reactive than cyclooctyne). These strategies of increasing ring strain through reactant destabilization have inspired many variations of cyclooctynes[29(*b*),(*c*),35] exhibiting reaction kinetics faster than seminal cyclooctyne.[3]

A tradeoff in the method of reactant destabilization by annealing hydrophobic carbocycles is the decrease of solubility in aqueous environments. Low yields observed in the non-catalyzed click reaction for *in vivo* applications in mice has been attributed to the increased hydrophobicity of cyclooctynes which led to cyclooctynes being sequestered from the bloodstream prematurely due to non-specific binding with proteins.[36] This also leads to an increase in non-specific background labeling during *in vitro* bioconjugation experiments. In response to these results, cyclooctynes were modified to incorporate more hydrophilic groups to increase bioavailability and decrease non-specific background labeling.[37] However, there is another trade-off, because reactivity of hydrophobic cyclooctynes is enhanced in aqueous environments due to a hydrophobic effect.[38] Therefore, reaction kinetics and hydrophilicity are inversely proportional for these systems (Figure 4).[39]

While benzannulated cyclooctynes are more reactive, they also reveal a fundamental drawback in the principle of destabilizing reactants. By bending the alkyne to the geometry required for the click TS, the starting material is not only moved up in energy, but it also moves closer in geometry to the activated complex of possible side reactions, such as the reaction with nucleophiles. In other words, strain activates cycloalkynes non-selectively, and

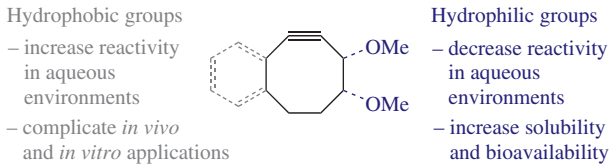


Figure 4 Trade-offs of hydrophobic and hydrophilic groups in bioapplications of cycloalkynes.

both the desired and undesired reactions are facilitated. Hence, cyclooctynes, activated by reactant destabilization, are inherently unstable. Bertozzi has expressed this dilemma in molecular design by stating that such molecules '...brush against the line between stability and reactivity without crossing it.'[34] For highly activated molecules, this design leads to practical limitations associated with their short lifetime and the need to store such 'spring-loaded' reagents at a low temperature, away from light and oxygen.

In principle, additional kinetic stabilization can be provided by shielding the reacting alkyne center to decrease the cyclooctyne's non-specific background labeling. This approach was demonstrated by Bertozzi and co-workers by using a sterically protected tetramethylthiacycloheptyne for tagging azide-functionalized glycoproteins.[40] Although this steric protection strategy can 'tame' a cycloalkyne, it still does not solve the problem of insufficient selectivity due to the presence of side-reactions.

An alternative route to relatively stable cycloalkynes is the design of molecules that are activated 'on demand',[41] ideally as they react with the target. If selective transition state stabilization is possible, such reagents can be both highly kinetically activated, and paradoxically, thermodynamically stabilized. Although achieving the two seemingly disparate goals is a difficult challenge, we will show below that this challenge has been addressed by transition state stabilization of the click reaction *via* stereoelectronic assistance.

While most research concentrated on destabilizing the cycloalkyne, an earlier report of increased reactivity of a difluorinated cyclooctyne, DIFO,[42] illuminated a different path. This discovery suggested that additional factors such as electronic effects could be harnessed to influence reactivity without the penalty for reactant destabilization.

The combination of factors responsible for the increased reactivity of DIFO is complex. For example, DIFO incorporates sp^2 hybrid orbitals in the ring through fluorine substitution due to Bent's rule, which states that atoms direct hybrid orbitals with more *p*-character toward more electronegative substituents.[43] This effect makes the two endocyclic C–C bonds at the fluorinated carbon shorter and would be expected to make this molecule more strained than cyclooctyne. However, as we will show in the following section, the presence of the stabilizing interactions between the donor (distorted alkyne π-system) and acceptor (the σ^*_{C-F} orbital) functionalities in DIFO can counteract the

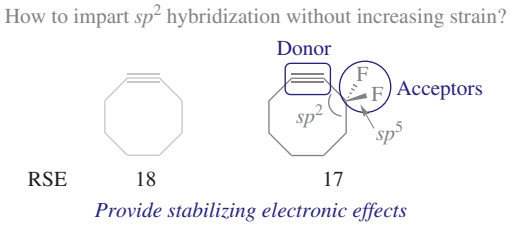


Figure 5 Favorable electronic interactions offset destabilizing hybridization changes to DIFO's backbone. Ring strain energies are in kcal mol^{-1}.

structural effect of rehybridization. As the result, DIFO has a lower ring strain energy than cyclooctyne[28(*b*)] despite being more reactive (Figure 5). Clearly, a new paradigm was needed to explain this puzzling disagreement between the lower strain and the higher reactivity.

Origin of electronic effects in alkyne cycloadditions

The stabilizing donor–acceptor interaction between the alkyne and vicinal substituents can directly influence the electronics of the alkyne–azide click cycloaddition by providing assistance to both the alkyne bending and to the C–N bond formation. Together, these donor–acceptor stereoelectronic effects can lead to reaction acceleration by providing selective TS stabilization. In addition to vicinal substituents, remote substituents on the alkyne backbone can influence click reactivity through hyperconjugative, conjugative, and through-space effects.

Assistance to bending. Because the donor ability of alkynes increases upon their bending,[28(*b*)] the magnitude of hyperconjugative interaction with an appropriately positioned σ-acceptor increases as the alkyne moiety bends [Figure 6(*a*)].

This stabilizing effect can partially offset the distortion penalty as illustrated by the lower energy penalty for bending 1-fluoro-

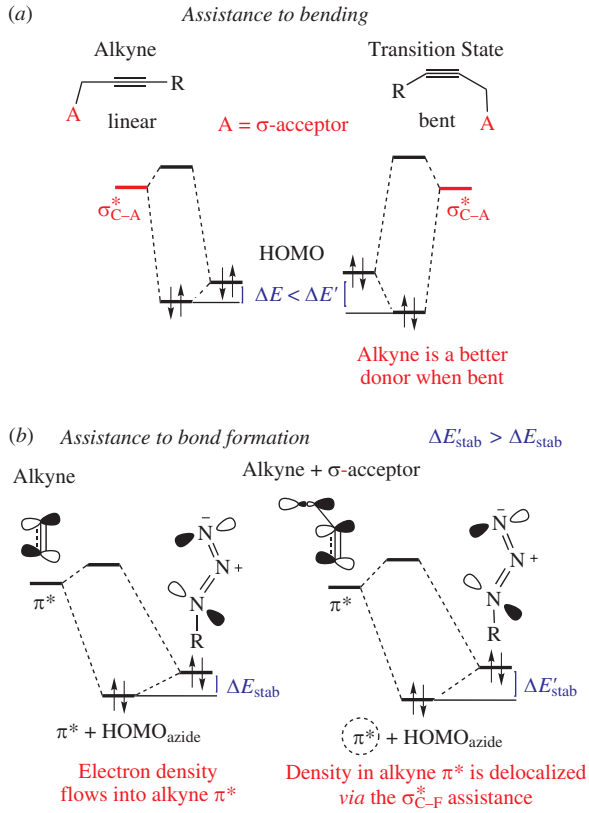


Figure 6 Two components to the stereoelectronic assistance to alkyne–azide cycloadditions: 'assistance to bending' is a consequence of increased donor ability of distorted π-bonds, 'assistance to bond formation' delocalizes electron density enhancing the C–N bond forming $HOMO_{azide}/LUMO_{alkyne}$ interaction.

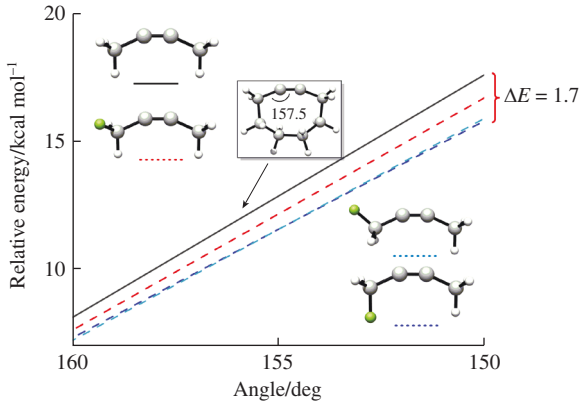


Figure 7 Relaxed energy scans for the symmetric bending of 2-butyne and 1-fluoro-2-butyne at the B3LYP/6-31G(d,p) level of theory. Cyclooctyne geometry is shown as a reference point for the relevant range of geometries. Data taken from ref. 28(*a*).

2-butyne in comparison with 2-butyne (Figure 7). The stereoelectronic[44] origin of this effect is evident from its dependence on the relative orientation of the distorted π-bond and the σ-acceptor.[45] The antiperiplanar σ^*_{C-F} acceptor decreases the cost of distortion to the ~150° C–C≡C angle (typical for the cycloaddition TS) by 1.7 kcal mol^{-1} whereas the stabilizing effect is smaller (0.9 kcal mol^{-1}) for the *gauche* arrangement.

Assistance to bond formation. Interestingly, the accelerating effect of a C–F bond on the energy of the full TS (*i.e.*, with the azide moiety included) is greater than its assistance to bending of the alkyne reagent. In particular, the activation barriers are lowered relative to the 2-butyne cycloaddition with methyl azide, when the σ^*_{C-F} orbital is antiperiplanar to the forming C–N bonds, by 2.1 and 3.0 kcal mol^{-1} (for the 1,5 and 1,4-isomers, respectively). These findings illustrate that the C–F bond presence also increases stabilizing bond-forming interactions between the distorted alkyne and azide moieties in the TS. These interactions (referred to as 'assistance to bond formation') originate from the polar nature of the cycloaddition transition state. The dominating Frontier MO (FMO) interaction in this process is between the $HOMO_{azide}$ and $LUMO_{alkyne}$. Due to this interaction, electron density can delocalize from the π^*_{alkyne} to the propargylic σ^*_{C-F} [Figure 6(*b*)].

Stereoelectronic effects in cycloalkyne cycloadditions

Direct effects. The stereoelectronic effects outlined in the previous section are manifested in DIFO, where the hyperconjugative interactions between the alkyne and the carbon–fluorine bonds stabilize both the reactant cycloalkyne and the click TS by decreasing the cost for alkyne bending and assisting bond formation. However, DIFO cannot harness the full potential of hyperconjugative assistance because the exocyclic fluorine atoms are *gauche* and cannot properly align with the reacting π-system. To fully take advantage of hyperconjugative assistance, the donor and acceptor functional groups should be endocyclic, so they can adopt an antiperiplanar arrangement (Figure 8). While the alternative factors used to explain the increased reactivity of DIFO (*e.g.*, LUMO lowering, electrostatics, and

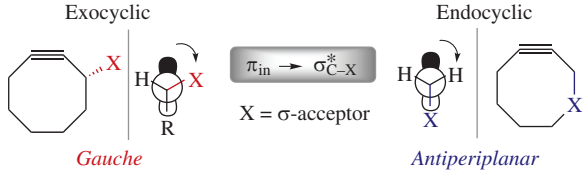


Figure 8 Endocyclic σ-acceptors maximize hyperconjugation in a cycloalkyne.

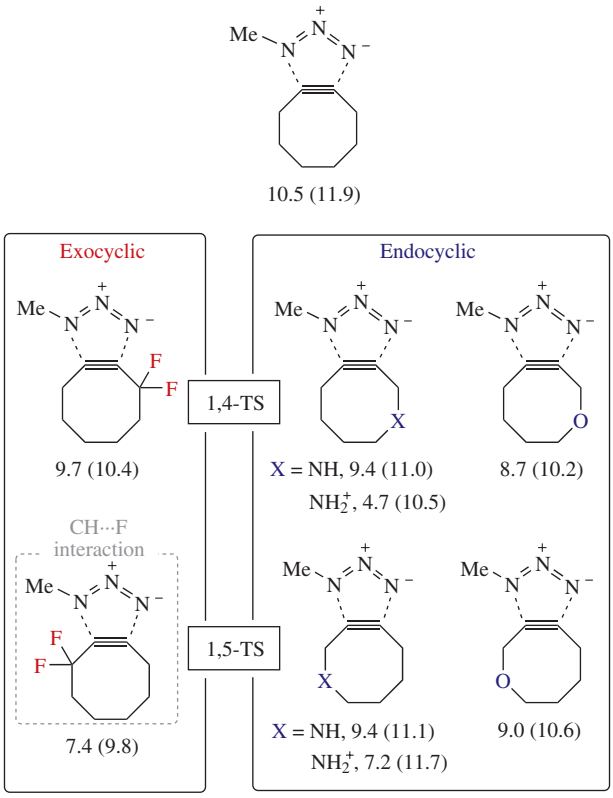


Figure 9 Comparative analysis for the click reaction of methyl azide with cyclooctynes containing exocyclic or endocyclic σ-acceptors. Activation energies in kcal mol^{-1} obtained at the B3LYP/6-31G(d) level of theory. CPCM (water) solvation corrections are given in parentheses. Data taken from ref. 28(*b*).

inductive effects)[7,29(*a*),46,47] are important, the stereoelectronic model underlies the mechanism of this specific TS stabilizing effect and lends itself for intuitive structural design.

The advantage of endocyclic heteroatoms is clearly shown in the comparison of click cycloadditions between an azide and cyclooctynes containing either exocyclic fluorines or endocyclic nitrogen or oxygen atoms (Figure 9). The gas phase calculations show that in the 1,4-TS, a single properly aligned nitrogen or oxygen is as efficient or better than two imprecisely aligned fluorines. The magnitude of acceleration correlates with the acceptor ability of the endocyclic group (NH < O < NH_2^+). Although this trend remains the same in the 1,5-TS for the endocyclic groups, a lower activation barrier is found in the 1,5-TS of DIFO due to the presence of additional C–H···F intermolecular interactions. While calculations using an implicit water model show the diminishing effect of solvation, the accelerating effect of incorporating endocyclic heteroatoms is still significant.

In the design of new systems that use propargylic endocyclic heteroatoms, one has to keep in mind that not all heteroatoms are ideal σ-acceptors. Propargylic sulfur atoms have been used in several cyclooctynes and cyclononynes,[48] but the consequence of using a sulfur heteroatom is the longer C–S bond which decreases ring strain. For example, in the click reaction with benzyl azide, a cyclononyne with an endocyclic sulfur atom is three orders of magnitude slower than the equivalent cyclononyne with a nitrogen heteroatom.[48(*b*)] On the other hand, the longer C–S bonds allow one to use cycloheptynes, thus recovering some of the lost strain and reactivity.[40]

Although the synthesis of cycloalkynes with propargylic endocyclic heteroatoms has been challenging, the available reports are promising. Bräse and co-workers were able to synthesize a cyclooctyne containing sulfur and oxygen heteroatoms using a double Nicholas reaction.[48(*a*)] Tomooka and co-workers were also able to demonstrate the utility of the Nicholas reaction for making cyclooctynes, cyclononynes, and cyclodecynes with various endocyclic heteroatom combinations.[48(*b*)] The reactivity of larger cycloalkynes with properly aligned endocyclic σ-acceptors outcompete the smaller rivals with improperly positioned σ-acceptors (Figure 10). For example, Tomooka's cyclononyne with two endocyclic N–Ts groups is more reactive than cyclooctyne with an exocyclic O atom. Replacing one N–Ts group for a better acceptor (O) results in four-fold increased reactivity of a cyclononyne that approaches the reactivity of DIFO. Interestingly, a cyclooctyne with a good acceptor (N–Ts) and a weaker acceptor (S) is more reactive than the cyclononyne with two N–Ts groups. This comparison illustrates that electronic activation does not completely replace reactant destabilization but shows the amplifying effect of combining reactant destabilization with TS stabilization. Finally, recent work of Balova *et al.*[49] describe inclusion of additional functionalities in the heteroatom-substituted cycloalkyne backbone.

With these promising results, avenues to the synthesis of cyclooctynes and cyclononynes with two propargylic endocyclic O atoms remain open and should be explored in the future. In total, combining TS stabilization through hyperconjugative assistance with reactant destabilization offers a powerful way to increase click reactivity without additional strain in cycloalkynes.

Remote effects. The aforementioned successful examples of using C–X bonds in cycloalkynes relied on their capacity as σ-acceptors. However, many heteroatoms are also potential donors due to the presence of high energy non-bonding orbitals (the n_X lone pairs). Thus, connecting such heteroatoms to a suitable acceptor functionality can be used to maximize the potential of stereoelectronic assistance of heteroatoms (Figure 11). By connecting an acceptor group directly to the heteroatom, the *p*-type lone pair can communicate with the adjoining π-system. Since this interaction is not directly involved in the bonds that

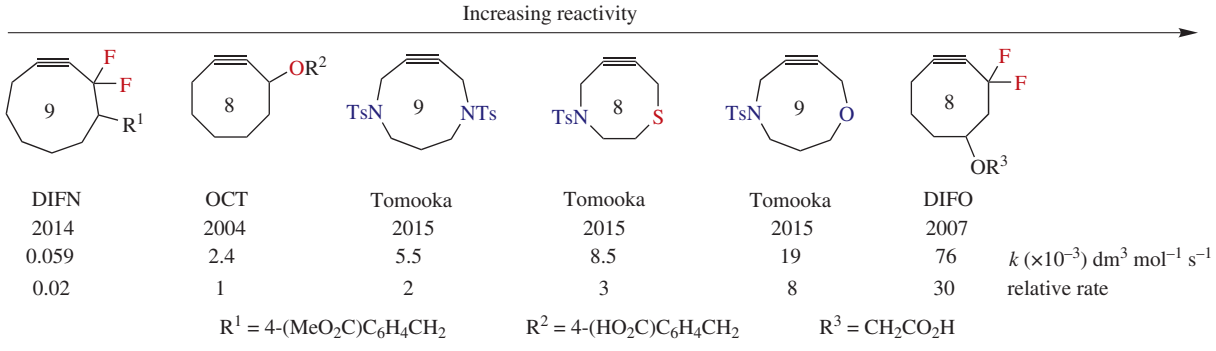


Figure 10 Reactivity comparison of cycloalkynes with exocyclic or endocyclic heteroatoms. Rate constants are reported for the reaction with benzyl azide in CD_3CN.

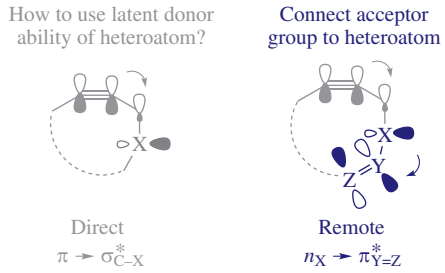


Figure 11 Combination of direct and remote interactions in cycloalkynes can be used to maximize the donor and acceptor properies of heteroatoms.

are breaking and forming during the click reaction, this would be classified as a remote interaction.

This design approach opens the potential to modulate the remote interaction through conformational and structural changes in the cycloalkyne backbone. To implement the activation of remote interactions through conformational changes, twisted amides and enamines can be turned to for inspiration.[50] These molecules can switch their electronic nature simply by rotating around the N–CX bond and 'turn off'/'turn on' electronic communication between the lone pair of nitrogen and the π_{C-X} system. Electronic communication in amides and enamines is either switched off or weakened when the nitrogen nonbonding electrons and the adjacent π-system are twisted out of alignment [Figure 12(*a*)]. Through a conformational rotation, this electronic communication is turned back on or strengthened in the planar geometry. In doing so, the conjugated amine system behaves like a 'stereoelectronic chameleon'[51] and changes its 'colors' through a conformational change.

The activation of remote interactions in the cycloalkyne backbone was implemented in twisted cyclodecynes with a biaryl backbone.[28(c)] In addition to the traditional alkyne bending, such biaryl-based cyclodecynes also incorporate a twisted backbone.[52] An interesting property of such cycloalkynes is that they are chiral and can be separated into the individual enantiomers.[53]

In the twisted cyclodecyne framework, additional electronic energy can be stored in the reactant if the interaction between donor and acceptor groups is disrupted. Ideally, both direct (hyperconjugative) and remote (conjugative) interactions should be weakened in the reactant but restored in the TS. Indeed, the structural changes that accompany the click reaction of twisted cyclodecynes turn on both the direct and the remote interactions,

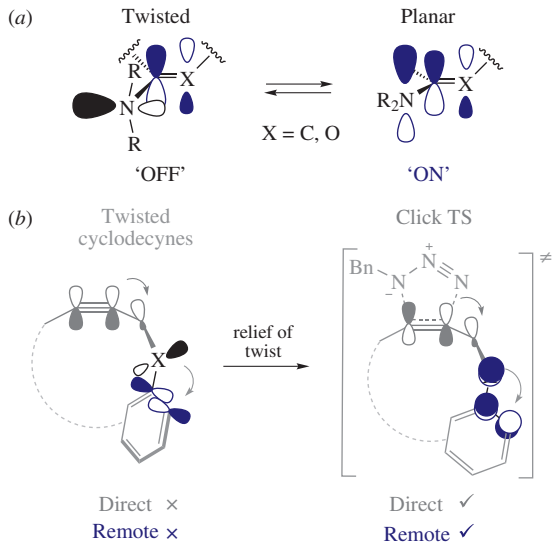


Figure 12 (*a*) Disruption of resonance by conformational rotation affects electronic properties of nitrogen. (*b*) Structural changes in the backbone of twisted cyclodecynes turn on direct and remote electronic effects in the click TS.

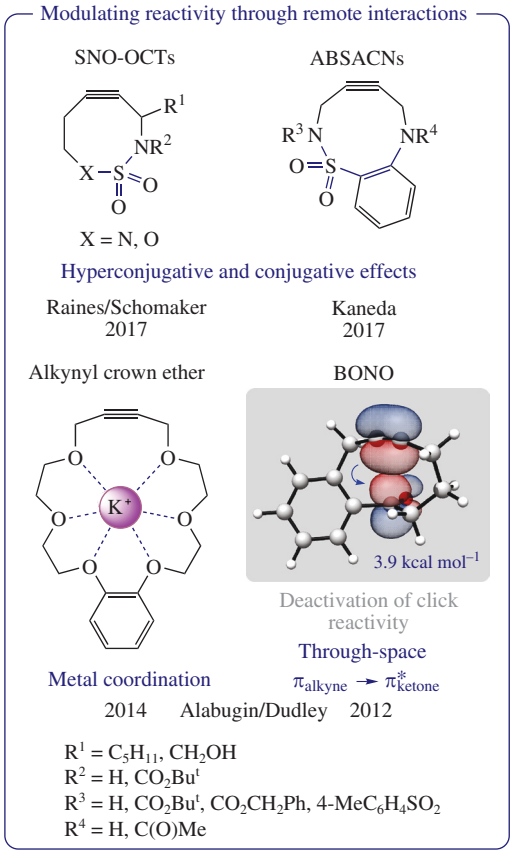


Figure 13 Remote interactions can be used to increase or decrease click reactivity of cycloalkynes. BONO calculated at M06-2X/6-311G+(d,p) with NBO 2nd order perturbation energy to illustrate through-space reactant stabilization.

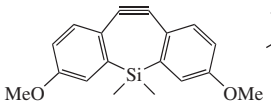
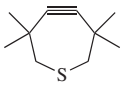
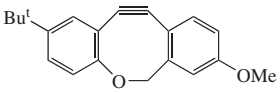
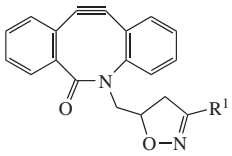
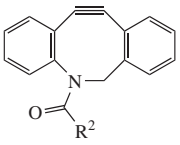
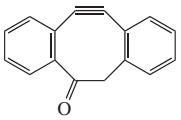
releasing their stored electronic energy in the TS [Figure 12(*b*)]. This strategy leads to cyclodecynes that are more reactive than their smaller rivals, cyclononynes and approach the reactivity of an electronically activated cyclooctyne (Table 1).[28(c)] Structural reorganization in the TS offers a unique way of unlocking the power of remote electronic effects for selective TS stabilization.

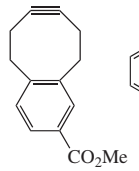
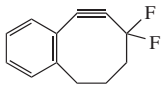
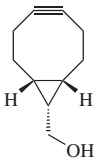
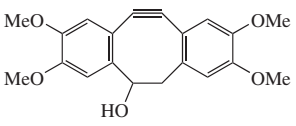
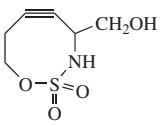
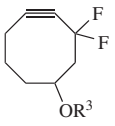
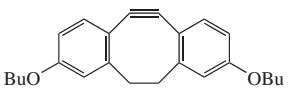
Modifying click reactivity through remote interactions in the cycloalkyne backbone was also utilized by the collaborative work from the groups of Raines and Schomaker (Figure 13).[54] These authors developed an elegant approach to cyclooctynes with sulfamate and sulfamide backbones *via* a mild ring expansion of silylated methyleneaziridines. These cyclooctynes (SNO-OCTs) exhibited extremely fast click kinetics in addition to superior stability to strong acids and bases. They also remained inert to glutathione, a strong indication of their true biorthogonality. Because of the combination of activated direct and remote electronic effects, these systems were more reactive than DIFO and the dibenzannulated cyclooctyne DIBO (Table 1).

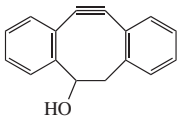
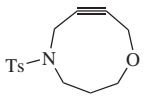
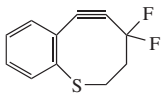
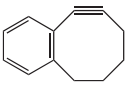
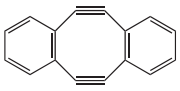
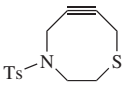
Kaneda and co-workers used the Nicholas reaction to make cyclononynes with 2-aminobenzenesulfonamide backbones (ABSACNs). Activity of these compounds is based on a similar structural strategy of combining direct and remote interactions between functional groups in the cycloalkyne backbone.[55]

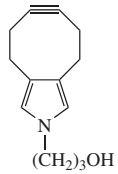
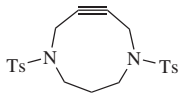
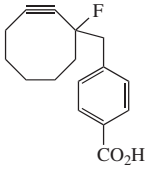
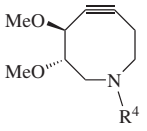
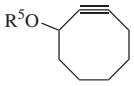
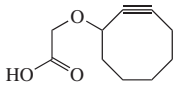
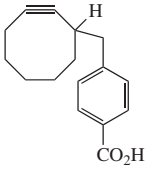
Heteroatoms in cycloalkynes can also be combined with metal coordination to influence click reactivity, for example, Alabugin, Dudley *et al.*[56] explored the binding of positively charged metal ions to the heteroatoms in alkynyl crown ethers. The macrocyclic crown ether can amplify TS stabilization by preorganizing the propargylic acceptors for optimal orbital alignment through metal coordination. Not all remote interactions lead to increased click reactivity, for example, benzocyclononynes (BONOs) were synthesized[57] through an elegant ring expansion–fragmentation

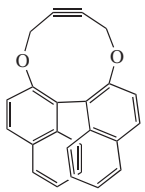
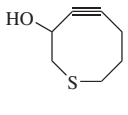
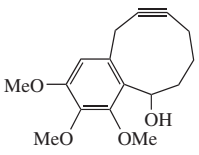
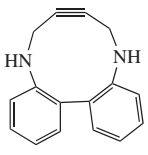
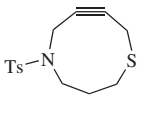
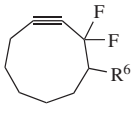
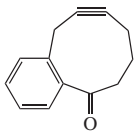
Table 1 Representative examples of cycloalkynes with various structural and electronic modifications and their corresponding rate constants in the click reaction with azides. All rate constants ($\times10^{-3}$ dm^3 mol^{-1} s^{-1}) reported at room temperature (23–25 °C) in the reaction with benzyl azide except for Sondheimer cycloalkyne which is reported using phenyl azide.[59]

					
Klan	**TMTH**	**ODIBO**	**BARAC**	**DIBAC**	**DIBONE**
2016	2012	2012	2010	2010	2011
22500	4000	1660	960	310	259
MeOH	CD_3CN	MeOH	CD_3CN	CD_3OD	MeOH

						
COMBO	**DIFBO**	**BCN**	**TMDIBO**	**SNO-OCT**	**DIFO**	**DIBC**
2012	2010	2010	2011	2017	2007	2009
235	220	140	98	87	76	76
CD_3CN	CD_3CN	CD_3CN–D_2O	$CDCl_3$	CD_3CN	CD_3CN	MeOH

					
DIBO	**Tomooka**	**thiaDIFBO**	**MOBO**	**Sondheimer**	**Tomooka**
2011	2015	2012	2010	2011	2015
57	19	14	9.5	8.8	8.5
MeOH	CD_3CN	CD_3CN	CD_3CN	MeOH	CD_3CN

						
PYRROC	**Tomooka**	**MOFO**	**DIMAC**	**OCT**	**ALO**	**Bertozzi**
2015	2015	2006	2008	2004	2006	2006
6.0	5.5	4.3	3.0	2.4	1.3	1.2
CD_3CN	CD_3CN	CD_3CN	CD_3CN	CD_3CN	CD_3CN	CD_3CN

						
BINOC	**thiaOCT**	**Dudley**	**BIPAC**	**Tomooka**	**DIFN**	**Dudley**
2017	2012	2012	2017	2015	2014	2012
0.54	0.32	0.2	0.17	0.081	0.059	0.0009
CD_3CN	CD_3CN	CD_3CN	CD_3CN	CD_3CN	CD_3CN	CD_3CN

R^1 = 4-(HOCH$_2$)C$_6$H$_4$, R^2 = C(O)C$_3$H$_6$CO$_2$Me, R^3 = OCH$_2$CO$_2$H, R^4 = C(O)C$_2$H$_4$CO$_2$H, R^5 = 4-(HO$_2$C)C$_6$H$_4$CH$_2$, R^6 = 4-(MeO$_2$C)C$_6$H$_4$CH$_2$.

reaction of vinylogous acyl triflates. One such example contained a stabilizing through-space interaction between the alkyne and a distal keto group ($\pi\rightarrow\pi^*_{C=O}/\pi\rightarrow\sigma^*_{C-O}$) which created unproductive reactant stabilization and decreased the click reactivity over the reduced alcohol form.[58]

Table 1 contains an expanded list of cycloalkynes, which contain the aforementioned structural and electronic features, along with rate constants for the click reaction with azides.

Reevaluating dibenzocyclooctynes: more than strain?

The recent remarkable experimental efforts in the chemistry of dibenzocyclooctynes, especially from the groups of Boons, Popik, Bertozzi, and Rutjes, produced a large body of intriguing results illustrating the role of remote substituents on cycloalkyne reactivity. As we have discussed earlier, the original hypothesis for the increased reactivity of these cycloalkynes in comparison to the parent cyclooctyne OCT, was based on the possible introduction

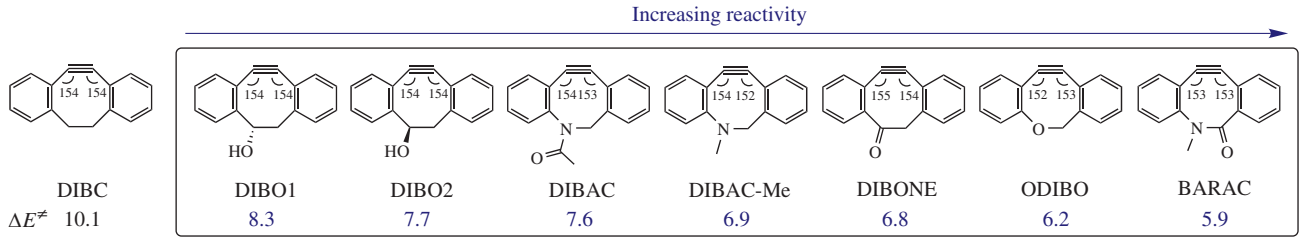


Figure 14 Reactivity enhancement of dibenzocyclooctynes through remote substitutions in the backbone. Calculated activation energies for the click reaction with methylazide using M06-2X(D3)/6-311G+(d,p). Energies of activation are in kcal mol^{-1}. The lowest activation energies are reported which correspond to the 1,4-TS for all dibenzocyclooctynes. For activation and reaction energies for both regioisomers of the dibenzocyclooctynes see Table S2.

of additional strain due to the presence of 'sp^2 atoms' in the cycle. However, the widely different reactivities of dibenzocyclooctynes that differ primarily by the remote substituents on the Ar–X–CR_2–Ar bridge (ODIBO,[60] BARAC,[34,61] DIBAC,[62] DIBONE,[63] DIBO,[60,64] and DIBC,[65] see Table 1) suggest that this hypothesis needs to be reevaluated. To find out if the higher reactivity of the dibenzo systems is due to the additional strain, *i.e.*, greater reactant destabilization, we first needed to understand the contribution of the remote substituents to click reactivity. To accomplish this, we compared a carbocyclic dibenzocyclooctyne (DIBC) with no heteroatom functionalities to the analogous systems with heteroatoms embedded or attached to the backbone bridge (Figure 14). All the systems with different heteroatom functional group combinations are more reactive than DIBC by 1.8–4.2 kcal mol^{-1}. Despite the difference in reactivity, the alkyne angle compression for these molecules varies very little (152–154°), suggesting alkyne bending has little to do with the observed variations in reactivity of these systems.

To identify the underlying cause of the different reactivities of the dibenzocyclooctynes, we turned to the distortion–interaction analysis.[66] This method, developed by Houk and Bickelhaupt, breaks down the activation barrier for a bimolecular reaction into two components – the distortion energy (E_d), *i.e.*, the penalty for distorting the reactants in their TS geometries, and the interaction energy (E_i), *i.e.*, the stabilization due to interactions between the two reacting partners. The interaction energy is negative if favorable electronic, electrostatic, and other interactions outweigh the repulsive interactions. The total distortion energy for the click cycloadditions is comprised of the azide and alkyne distortions ($E_{d,total} = E_{d,azide} + E_{d,alkyne}$).

The distortion–interaction analysis results are illustrated in Figure 15. First, the distortion energy has the largest effect on the overall barrier compared to the interaction energy [Figures 15(*a*),(*b*)]. The absolute values and variations for alkyne distortions are relatively small (2.5–3.8 kcal mol^{-1}) as compared to the azide distortions (15–18 kcal mol^{-1}) [Figures 15(*c*),(*d*)]. This difference is expected for the high-energy pre-distorted alkynes. These results also reveal the cause for the lower activation energies of the dibenzo systems with heteroatoms on the backbone over DIBC, lower azide and alkyne distortions. The lower azide distortions

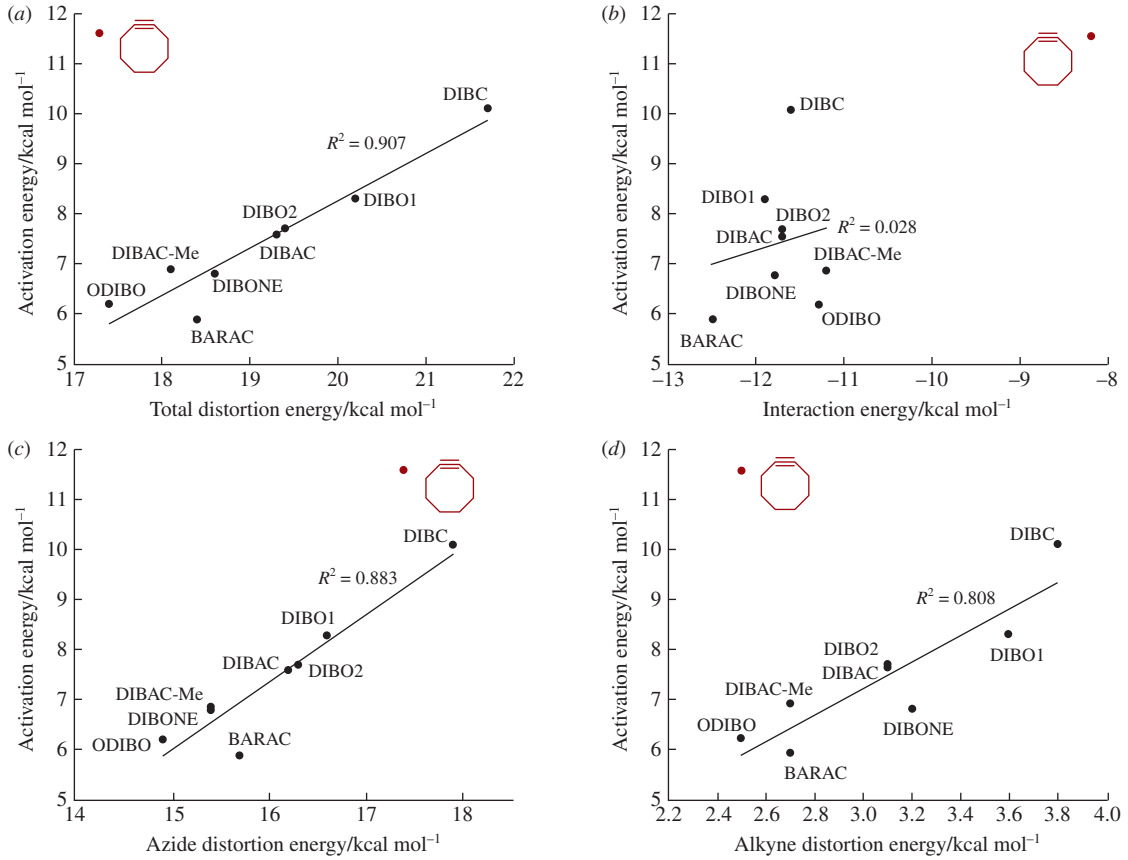


Figure 15 (*a*) Total distortion energy *vs.* activation energy for dibenzocyclooctynes in the click reaction with methyl azide. (*b*) Interaction energy *vs.* activation energy. (*c*) Azide distortion energy *vs.* activation energy. (*d*) Alkyne distortion energy *vs.* activation energy. Cyclooctyne's distortion and interaction energies (red) in the reaction with methyl azide are added to illustrate contrasting differences in distortion and interaction. Calculated energies for the click reaction with methylazide using M06-2X(D3)/6-311G+(d,p) level of theory.

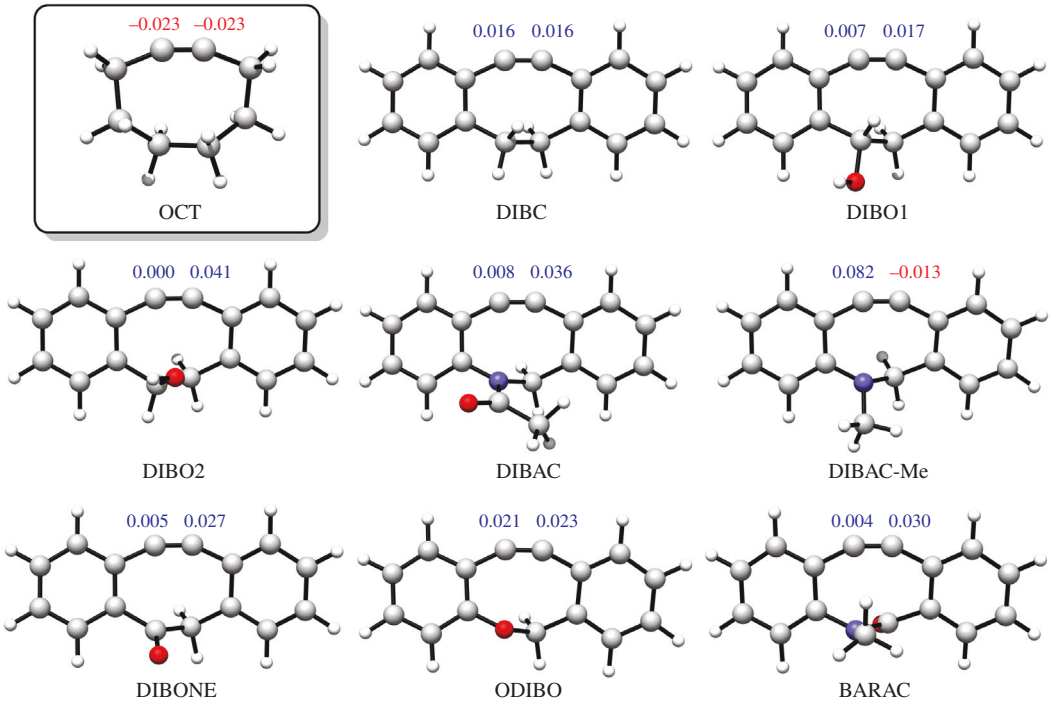


Figure 16 NBO charges on alkyne carbons of cyclooctyne (OCT) and dibenzocyclooctynes.

manifest in an earlier and more asynchronous TS, which can be seen in the longer and divergent C···N distances between the azides and alkynes (see Table S3, Online Supplementary Materials).

A surprising observation is that all the dibenzocyclooctynes have higher total distortion penalties than parent cyclooctyne [see Figure 15(*a*)]. This finding goes against an expectation that dibenzocyclooctynes should have additional strain introduced through the aryl ring fusions and require a lower distortion penalty to reach the click TS. Additionally, the higher distortion penalties of the dibenzocyclooctynes over cyclooctyne [see Figure 15(*d*)] are in a seeming contradiction with the fact that the dibenzo systems are more bent than cyclooctyne (alkyne angle of 158°).

Since focus in explaining reactivity is on the energetic consequences of strain (rather than geometries), the greater additional bending penalty in the dibenzo systems as clearly shown by their greater distortion energies, should lead to their lower reactivity. However, this is clearly not the case.

If dibenzocyclooctynes suffer the greater distortion penalties for reaching the TS, why do they react faster than cyclooctyne itself? According to the distortion/interaction analysis, the higher distortion energies for the dibenzocyclooctynes are off-set by large interaction energies [see Figure 15(*b*)]. These energies are much larger than the analogous cyclooctyne interaction energy (–12.5 to –11.2 *vs.* –8 kcal mol^{-1}). Therefore, the higher reactivity for dibenzocyclooctynes is not due to the additional strain of the sp^2 units, as it was previously thought. Instead, it stems from the greater interaction energy.[67] Although this finding resolves the paradox stated at the beginning of this paragraph, it also brings yet another question – why is the interaction energy greater for the dibenzo systems?

The answer to the above question is still unknown and it is likely that a variety of small effects contribute to this trend. In order to get a deeper insight in the origin of the higher interaction energies for dibenzocyclooctynes over cyclooctyne, we compared charges of the alkynyl carbons in these systems (Figure 16). Computations suggest that the alkyne carbons in the parent dibenzo systems are more electron deficient than in cyclooctyne (+0.02 e *vs.* –0.02 e). This trend is preserved for the substituted dibenzocyclooctynes. It has been shown before that cycloalkynes serve as acceptors in the reaction with methyl azide,[28] and, hence, the greater electron deficiency of the alkynyl carbons in the dibenzocyclooctynes may explain why the cycloaddition with the azide is faster for these dibenzannulated systems. These findings also point out to a possible drawback of these systems – their greater electron deficiency may inadvertently cause faster nucleophilic addition side-reactions. It is also interesting that remote substituents can cause alkyne polarization. For example, the two alkyne carbons in DIBAC-Me have charges of 0.08 and –0.01 electron.

Interestingly, the backbone twisting leads to disruption of several common stereoelectronic effect usually observed for endocyclic heteroatoms. For example, the OCH_2 group is known to have a chameleonic character – it serves as a *p*-donor to the ring connected to the oxygen end and a $\sigma^*_{C–O}$ acceptor to the ring connected to the carbon end.[68] However, inspection of the geometries for the ether moiety of ODIBO indicates that it cannot reach its usual stereoelectronically preferred conformation in this constrained cycle. Similar strain and steric inhibition of stereoelectronic effects is observed in some of the other functionalities (the amide groups, the ketone group *etc.*). However, these distortions are generally not relieved at the TS stage and, hence, most of this additional electronic energy is not harvested at this key reaction stage.

Conclusion

The concerted synthetic and theoretical efforts led to the design of new cycloalkynes that combine activation by strain and by electronic effects. The diverse selection of electronic effects involves assistance to alkyne bending, assistance to the C–N bond formation in the cycloaddition TS, as well as remote contributions associated with the relief of twisting and activation of remote orbital interactions. The existence of previously unrecognized direct and remote stereoelectronic effects in cycloalkyne reactions can complement the established paradigm of alkyne destabilization in the design of even more reactive cycloalkynes.

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Online Supplementary Materials

Supplementary data associated with this article (computational details and cartesian coordinates) can be found in the online version at doi: 10.1016/j.mencom.2019.05.001.

References

1 A. Krebs and J. Wilke, *Top. Curr. Chem*., 1983, **109**, 189.
2 (*a*) H. C. Kolb, M. G. Finn and K. B. Sharpless, *Angew. Chem. Int. Ed*., 2001, **40**, 2004; (*b*) V. V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless, *Angew. Chem. Int. Ed*., 2002, **41**, 2596.
3 N. J. Agard, J. A. Prescher and C. R. Bertozzi, *J. Am. Chem. Soc*., 2004, **126**, 15046.
4 (*a*) E. M. Sletten and C. R. Bertozzi, *Angew. Chem. Int. Ed*., 2009, **48**, 6974; (*b*) R. K. V. Lim and Q. Lin, *Chem. Commun*., 2010, **46**, 1589; (*c*) M. F. Debets, S. S. van Berkel, J. Dommerholt, A. J. Dirks, F. P. J. T. Rutjes and F. L. van Delft, *Acc. Chem. Res*., 2011, **44**, 805; (*d*) E. M. Sletten and C. R. Bertozzi, *Acc. Chem. Res*., 2011, **44**, 666; (*e*) M. D. Best, M. M. Rowland and H. E. Bostic, *Acc. Chem. Res*., 2011, **44**, 686; (*f*) J. M. Baskin and C. R. Bertozzi, *Aldrichimica Acta*, 2010, **43**, 15.
5 J. Dommerholt, F. P. J. T. Rutjes and F. L. van Delft, *Top. Curr. Chem*., 2016, **374**, 16.
6 H. Hopf and J. Grunenberg, in *Strained Hydrocarbons: Beyond the van't Hoff and Le Bel Hypothesis*, ed. H. Dodziuk, Wiley-VCH, Weinheim, 2009, pp. 375–398.
7 R. D. Bach, *J. Am. Chem. Soc*., 2009, **131**, 5233.
8 (*a*) J. M. Medina, T. C. McMahon, G. Jiménez-Osés, K. N. Houk and N. K. Garg, *J. Am. Chem. Soc*., 2014, **136**, 14706; (*b*) D. P. Maurer, R. Fan and D. M. Thamattoor, *Angew. Chem. Int. Ed*., 2017, **56**, 4499; (*c*) R. Fan, Y. Wen and D. M. Thamattoor, *Org. Biomol. Chem*., 2017, **15**, 8270; (*d*) G. Wittig and J. Heyn, *Liebigs Ann. Chem*., 1969, **726**, 57; (*e*) L. K. Montgomery and L. E. Applegate, *J. Am. Chem. Soc*., 1967, **89**, 5305; (*f*) G. Wittig, A. Krebs and R. Pohlke, *Angew. Chem*., 1960, **72**, 324; (*g*) F. Scardiglia and J. D. Roberts, *Tetrahedron*, 1957, **1**, 343.
9 (*a*) H. H. Wenk, M. Winkler and W. Sander, *Angew. Chem. Int. Ed*., 2003, **42**, 502; (*b*) C. Wu and F. Shi, *Asian J. Org. Chem*., 2013, **2**, 116; (*c*) P. M. Tadross and B. M. Stoltz, *Chem. Rev*., 2012, **112**, 3550; (*d*) S. P. Ross and T. R. Hoye, *Nat. Chem*., 2017, **9**, 523; (*e*) M. Mesgar, J. Nguyen-Le and O. Daugulis, *J. Am. Chem. Soc*., 2018, **140**, 13703; (*f*) S. Umezu, G. dos Passos Gomes, T. Yoshinaga, M. Sakae, K. Matsumoto, T. Iwata, I. Alabugin and M. Shindo, *Angew. Chem. Int. Ed*., 2017, **56**, 1298; (*g*) S.-E. Suh, S. Chen, K. N. Houk and D. M. Chenoweth, *Chem. Sci*., 2018, **9**, 7688; (*h*) N. N. T. Le, J. Just, J. M. Pankauski, P. R. Rablen and D. M. Thamattoor, *Molecules*, 2019, **24**, 593.
10 (*a*) M. Trætteberg, W. Lüttke, R. Machinek, A. Krebs and H. J. Hohlt, *J. Mol. Struct*., 1985, **128**, 217; (*b*) E. Goldstein, B. Ma, J.-H. Lii and N. L. Allinger, *J. Phys. Org. Chem*., 1996, **9**, 191.
11 V. Typke, J. Haase and A. Krebs, *J. Mol. Struct*., 1979, **56**, 77.
12 A. T. Blomquist and L. H. Liu, *J. Am. Chem. Soc*., 1953, **75**, 2153.
13 G. Wittig and A. Krebs, *Chem. Ber*., 1961, **94**, 3260.
14 T. Harris and I. V. Alabugin, *e-EROS*, 2017, doi:10.1002/047084289X.rn02079.
15 (*a*) P. König, J. Zountsas, K. Bleckmann and H. Meier, *Chem. Ber*., 1983, **116**, 3580; (*b*) E. V. Shulishov, Yu. V. Tomilov and O. M. Nefedov, *Mendeleev Commun*., 2013, **23**, 187.
16 (*a*) K. Elender, H. Nöth, P. Riebel, A. Weber and J. Sauer, *Tetrahedron*, 2000, **56**, 5443; (*b*) K. Elender, P. Riebel, A. Weber and J. Sauer, *Tetrahedron*, 2000, **56**, 4261; (*c*) P. Riebel, A. Weber, T. Troll and J. Sauer, *Tetrahedron Lett*., 1996, **37**, 1583.
17 K. Banert and O. Plefka, *Angew. Chem. Int. Ed*., 2011, **50**, 6171.
18 M. Strmiskova, D. A. Bilodeau, M. Chigrinova and J. P. Pezacki, *Can. J. Chem*., 2019, **97**, 1, and references cited therein.
19 R. Huisgen, *Proc. Chem. Soc*., 1961, 357.
20 D. M. Patterson, L. A. Nazarova and J. A. Prescher, *ACS Chem. Biol*., 2014, **9**, 592.
21 (*a*) I. V. Alabugin and B. Gold, *J. Org. Chem*., 2013, **78**, 7777; (*b*) I. V. Alabugin and E. Gonzalez-Rodriguez, *Acc. Chem. Res*., 2018, **51**, 1206; (*c*) V. V. Voronin, M. S. Ledovskaya, A. S. Bogachenkov, K. S. Rodygin and V. P. Ananikov, *Molecules*, 2018, **23**, 2442.
22 (*a*) A. Nicolaides and W. T. Borden, *J. Am. Chem Soc*., 1991, **113**, 6750; (*b*) K. M. Ervin, S. Gronert, S. E. Barlow, M. K. Gilles, A. G. Harrison, V. M. Bierbaum, C. H. DePuy, W. C. Lineberger and G. B. Ellison, *J. Am. Chem. Soc*., 1990, **112**, 5750.
23 R. B. Turner, A. D. Jarrett, P. Goebel and B. J. Mallon, *J. Am. Chem. Soc*., 1973, **95**, 790.
24 (*a*) D. W. Rogers, N. Matsunaga, A. A. Zavitsas, F. J. McLafferty and J. F. Liebman, *Org. Lett*., 2003, **5**, 2373; (*b*) P. D. Jarowski, M. D. Wodrich, C. S. Wannere, P. v. R. Schleyer and K. N. Houk, *J. Am. Chem. Soc*., 2004, **126**, 15036.
25 S. E. Wheeler, K. N. Houk, P. v. R. Schleyer and W. D. Allen, *J. Am. Chem. Soc*., 2009, **131**, 2547.
26 N. A. Danilkina, A. G. Lyapunova, A. F. Khlebinkov, G. L. Starova, S. Bräse and I. A. Balova, *J. Org. Chem*., 2015, **80**, 5546.
27 G. dos Passos Gomes and I. Alabugin, in *Applied Theoretical Organic Chemistry*, ed. D. J. Tantillo, World Scientific, 2018, pp. 451–502.
28 (*a*) B. Gold, N. E. Shevchenko, N. Bonus, G. B. Dudley and I. V. Alabugin, *J. Org. Chem*., 2012, **77**, 75; (*b*) B. Gold, G. B. Dudley and I. V. Alabugin, *J. Am. Chem. Soc*., 2013, **135**, 1558; (*c*) T. Harris, G. dos Passos Gomes, S. Ayad, R. J. Clark, V. V. Lobodin, M. Tuscan, K. Hanson and I. V. Alabugin, *Chem*., 2017, **3**, 629.
29 (*a*) K. Chenoweth, D. Chenoweth and W. A. Goddard III, *Org. Biomol. Chem*., 2009, **7**, 5255; (*b*) E. M. Sletten, H. Nakamura, J. C. Jewett and C. R. Bertozzi, *J. Am. Chem. Soc*., 2010, **132**, 11799; (*c*) B. R. Varga, M. Kállay, K. Hegyi, S. Béni and P. Kele, *Chem. Eur. J*., 2012, **18**, 822.
30 E. Saxon and C. R. Bertozzi, *Science*, 2000, **287**, 2007.
31 X. Ning, R. P. Temming, J. Dommerholt, J. Guo, D. B. Ania, M. F. Debets, M. A. Wolfert, G.-J. Boons and F. L. van Delft, *Angew. Chem. Int. Ed*., 2010, **49**, 3065.
32 I. V. Alabugin, S. Bresch and G. dos Passos Gomes, *J. Phys. Org. Chem*., 2015, **28**, 147.
33 J. Dommerholt, S. Schmidt, R. Temming, L. J. A. Hendriks, F. P. J. T. Rutjes, J. C. M. van Hest, D. J. L. Lefeber, P. Friedl and F. L. van Delft, *Angew. Chem. Int. Ed*., 2010, **49**, 9422.
34 J. C. Jewett, E. M. Sletten and C. R. Bertozzi, *J. Am. Chem. Soc*., 2010, **132**, 3688.
35 (*a*) M. F. Debets, S. S. van Berkel, S. Schoffelen, F. P. J. T. Rutjes, J. C. M. van Hest and F. L. van Delft, *Chem. Commun*., 2010, **46**, 97; (*b*) C. Gröst and T. Berg, *Org. Biomol. Chem*., 2015, **13**, 3866.
36 P. V. Chang, J. A. Prescher, E. M. Sletten, J. M. Baskin, I. A. Miller, N. J. Agard, A. Lo and C. R. Bertozzi, *Proc. Natl. Acad. Sci. USA*, 2010, **107**, 1821.
37 E. M. Sletten and C. R. Bertozzi, *Org. Lett*., 2008, **10**, 3097.
38 D. C. Rideout and R. Breslow, *J. Am. Chem. Soc*., 1980, **102**, 7816.
39 M. F. Debets, J. C. M. van Hest and F. P. J. T. Rutjes, *Org. Biomol. Chem*., 2013, **11**, 6439.
40 G. d. Almeida, E. M. Sletten, H. Nakamura, K. K. Palaniappan and C. R. Bertozzi, *Angew. Chem. Int. Ed*., 2012, **51**, 2443.
41 W. Luo, P. Gobbo, C. D. McNitt, D. A. Sutton, V. V. Popik and M. S. Workentin, *Chem. Eur. J*., 2017, **23**, 1052.
42 J. M. Baskin, J. A. Prescher, S. T. Laughlin, N. J. Agard, P. V. Chang, I. A. Miller, A. Lo, J. A. Codelli and C. R. Bertozzi, *Proc. Natl. Acad. Sci. USA*, 2007, **104**, 16793.
43 (*a*) H. A. Bent, *J. Chem. Phys*., 1960, **33**, 1258; (*b*) H. A. Bent, *Chem. Rev*., 1961, **61**, 275; (*c*) I. V. Alabugin, S. Bresch and M. Manoharan, *J. Phys. Chem. A*, 2014, **118**, 3663.
44 I. V. Alabugin, *Stereoelectronic Effects: A Bridge Between Structure and Reactivity*, Wiley, 2016.
45 I. V. Alabugin, G. dos Passos Gomes and M. A. Abdo, *WIREs Comput. Mol. Sci*., 2018, **9**, e1389.
46 D. H. Ess, G. O. Jones and K. N. Houk, *Org. Lett*., 2008, **10**, 1633.
47 J. Garcia-Hartjes, J. Dommerholt, T. Wennekes, F. L. van Delft and H. Zuilholf, *Eur. J. Org. Chem*., 2013, 3712.
48 (*a*) T. Hagendorn and S. Bräse, *RSC Adv*., 2014, **4**, 15493; (*b*) R. Ni, N. Mitsuda, T. Kashiwagi, K. Igawa and K. Tomooka, *Angew. Chem. Int. Ed*., 2015, **54**, 1190.
49 (*a*) A. G. Lyapunova, N. A. Danilkina, A. F. Khlebnikov, B. Köberle, S. Bräse and I. A. Balova, *Eur. J. Org. Chem*., 2016, 4842; (*b*) A. G. Lyapunova, N. A. Danilkina, A. M. Rumyantsev, A. F. Khlebnikov, M. V. Chislov, G. L. Starova, E. V. Sambuk, A. I. Govdi, S. Bräse and I. A. Balova, *J. Org. Chem.*, 2018, **83**, 2788.
50 (*a*) M.-X. Wang, *Chem. Commun*., 2015, **51**, 6039; (*b*) M. Liniger, D. G. VanderVelde, M. K. Takase, M. Shahgholi and B. M. Stoltz, *J. Am. Chem. Soc*., 2016, **138**, 969; (*c*) M. Szostak and J. Aubé, *Org. Biomol. Chem*., 2011, **9**, 27; (*d*) C. Liu and M. Szostak, *Chem. Eur. J*., 2017, **23**, 7157; (*e*) W. von E. Doering, L. Birladeanu, D. W. Andrews and M. Pagnotta, *J. Am. Chem. Soc*., 1985, **107**, 428; (*f*) A. J. Kirby, I. V. Komarov and N. Feeder, *J. Am. Chem. Soc*., 1998, **120**, 7101.

51 S. Z. Vatsadze, Y. D. Loginova, G. dos Passos Gomes and I. V. Alabugin, *Chem Eur. J*., 2017, **23**, 3225.

52 (*a*) A. Del Grosso, L.-D. Galanopoulos, C. K. C. Chiu, G. J. Clarkson, P. B. O'Connor and M. Wills, *Org. Biomol. Chem*., 2017, **15**, 4517; (*b*) A. Mistry, R. C. Knighton, S. Forshaw, Z. Dualeh, J. S. Parker and M. Wills, *Org. Biomol. Chem*., 2018, **16**, 8965.

53 T. Taniguchi, T. Suzuki, H. Satoh, Y. Shichibu, K. Konishi and K. Monde, *J. Am. Chem. Soc*., 2018, **140**, 15577.

54 E. G. Burke, B. Gold, T. T. Hoang, R. T. Raines and J. M. Schomaker, *J. Am. Chem. Soc*., 2017, **139**, 8029.

55 K. Kaneda, R. Naruse and S. Yamamoto, *Org. Lett*., 2017, **19**, 1096.

56 B. Gold, P. Batsomboon, G. B. Dudley and I. V. Alabugin, *J. Org. Chem*., 2014, **79**, 6221.

57 (*a*) J. Tummatorn, P. Batsomboon, R. J. Clark, I. V. Alabugin and G. B. Dudley, *J. Org. Chem*., 2012, **77**, 2093; (*b*) J. Tummatorn and G. B. Dudley, *Org. Lett*., 2011, **13**, 1572.

58 N. P. Tsvetkov, A. Bayir, S. Schneider and M. Brewer, *Org. Lett*., 2012, **14**, 264.

59 (*a*) M. Martínek, L. Filipová, J. Galeta, L. Ludvíková and P. Klán, *Org. Lett*., 2016, **18**, 4892; (*b*) H. Stöckmann, A. A. Neves, S. Stairs, H. I. Zecchini, K. M. Brindle and F. J. Leeper, *Chem. Sci*., 2011, **2**, 932; (*c*) S. Yoshida, A. Shiraishi, K. Kanno, T. Matsushita, K. Johmoto, H. Uekusa and T. Hosoya, *Sci. Rep*., 2011, **1**, 82; (*d*) N. J. Agard, J. M. Baskin, J. A. Prescher, A. Lo and C. R. Bertozzi, *ACS Chem. Biol*., 2006, **1**, 644; (*e*) E. M. Sletten, G. de Almeida and C. R. Bertozzi, *Org. Lett*., 2014, **16**, 1634.

60 (*a*) C. D. McNitt and V. V. Popik, *Org. Biomol. Chem*., 2012, **10**, 8200; (*b*) S. Nainar, M. Kubota, C. D. McNitt, C. Tran, V. V. Popik and R. C. Spitale, *J. Am. Chem. Soc*., 2017, **139**, 8090.

61 C. G. Gordon, J. L. Mackey, J. C. Jewett, E. M. Sletten, K. N. Houk and C. R. Bertozzi, *J. Am. Chem. Soc*., 2012, **134**, 9199.

62 M. F. Debets, J. S. Prins, D. Merkx, S. S. van Berkel, F. L. van Delft, J. C. M. van Hest and F. P. J. T. Rutjes, *Org. Biomol. Chem*., 2014, **12**, 5031.

63 N. E. Mbua, J. Guo, M. A. Wolfert, R. Steet and G.-J. Boons, *ChemBioChem*., 2011, **12**, 1912.

64 X. Ning, J. Guo, M. A. Wolfert and G.-J. Boons, *Angew. Chem. Int. Ed*., 2008, **47**, 2253.

65 A. A. Poloukhtine, N. E. Mbua, M. A. Wolfert, G.-J. Boons and V. V. Popik, *J. Am. Chem. Soc*., 2009, **131**, 15769.

66 (*a*) F. M. Bickelhaupt and K. N. Houk, *Angew. Chem. Int. Ed*., 2017, **56**, 10070; (*b*) F. Liu, Y. Liang and K. N. Houk, *Acc. Chem. Res*., 2017, **50**, 2297; (*c*) G. dos Passos Gomes and I. V. Alabugin, *J. Am. Chem. Soc*., 2017, **139**, 3406.

67 T. A. Hamlin, B. J. Levandowski, A. K. Narsaria, K. N. Houk and F. M. Bickelhaupt, *Chem. Eur. J*., 2019, doi:10.1002/chem.201900295.

68 P. W. Peterson, N. Shevchenko and I. V. Alabugin, *Org. Lett*., 2013, **15**, 2238.

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