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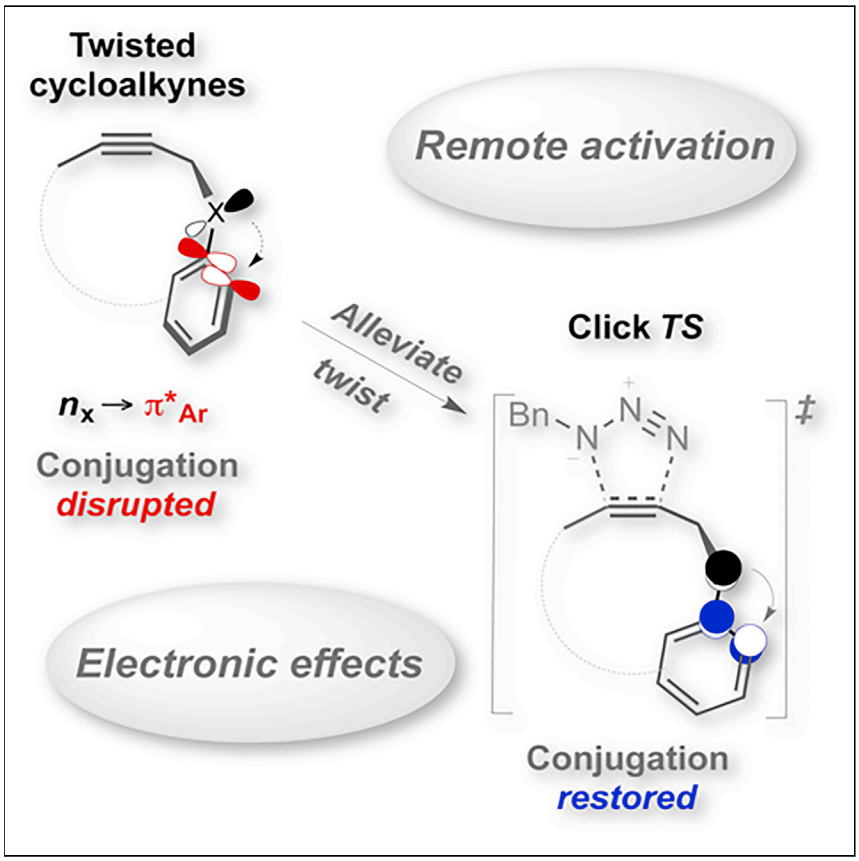
Twisted Cycloalkynes and Remote Activation of "Click" Reactivity



Interaction between donor and acceptor groups incorporated in the backbone of cycloalkynes can be partially disrupted by twisting. The additional electronic energy accumulated as a result of this disruption can be harvested in the alkyne/azide cycloaddition transition state, where an optimal conjugation pattern at a remote location is restored. The design provides electronically activated cyclodecynes that approach "click" reactivity of cyclooctynes. In addition, the twisted cyclodecynes are chiral and thus add axial chirality to the toolbox of properties introduced via "click" chemistry.

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HIGHLIGHTS

Increased "click" reactivity through remote activation

Gram-scale, one-step preparation of enantiopure cycloalkynes

Twisted cyclodecynes approach reactivity of cyclooctynes

Experiments and computational analysis reveal activating role of remote interactions

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Twisted Cycloalkynes and Remote Activation of "Click" Reactivity

Trevor Harris,[1] Gabriel dos Passos Gomes,[1] Suliman Ayad,[1] Ronald J. Clark,[1] Vladislav V. Lobodin,[2] Megan Tuscan,[1] Kenneth Hanson,[1] and Igor V. Alabugin[1,3,*]

SUMMARY

The "twisted and bent" cyclodecyne structural motif, intertwined with dormant electronic effects, opens a conceptually powerful way to control "click" reactivity. The endocyclic heteroatoms of cyclodecynes provide dual electronic activation via hyperconjugative (direct) and conjugative (remote) effects. These effects are weakened by the geometric constraints imposed by the twisted backbone, but structural reorganization in the transition state (TS) removes these constraints and unlocks the power of remote electronic effects for selective TS stabilization. Gram-scale synthesis and purification by recrystallization make this an efficient and practical approach to enantiopure cycloalkynes. Experimental kinetics confirm that these twisted cyclodecynes can be more reactive toward azides than activated cyclononynes and approach the reactivity of cyclooctynes. Furthermore, cycloalkynes with a twisted polyaromatic backbone can potentially add axial chirality to the "click" chemistry toolbox.

INTRODUCTION

"Click" chemistry brings functional group orthogonality, high yields, and broad scope to diverse applications ranging from surface functionalization to drug delivery.[1,2] However, the utility of the prototypical "click" reaction, the Cu-catalyzed alkyne-azide cycloaddition,[3–7] is hampered by the toxicity of copper salts toward living systems and their deleterious effects on redox-sensitive nanoparticles.[8–10] The strain-promoted alkyne-azide cycloaddition was shown to overcome these limitations in bioorthogonal chemistry[11–13] and surface chemistry.[14–16] However, strain-activated cycloalkynes often balance at the edge of instability, which complicates both synthesis and applications of such reactive molecules.[17,18] The search for more reactive "click" combinations continues as illustrated by the inverse electron-demand Diels-Alder reaction between *trans*-cyclooctenes and tetrazines and 1,3-dipolar cycloadditions between diazo groups and acrylates.[19–22]

The seminal report by Baskin et al.[23] of a ~50-fold increase in reactivity of a difluorinated cyclooctyne (**DIFO**) over the parent cyclooctyne indicated that other factors can be harnessed to supplement strain activation. Our computational analysis illustrated that rate enhancement stems from hyperconjugative assistance in the transition state (TS) promoted by the alignment of the sigma acceptor C–X bond with the reacting alkyne π bond (Figure 1A).[24] Because the C–X bond should adopt antiperiplanar geometry to maximize the reactivity of cycloalkynes, the optimal position for the heteroatom X is inside the cycle. Even though hyperconjugative assistance in cyclooctynes provides stabilization to both the reactant

The Bigger Picture

Non-catalyzed alkyne/azide cycloaddition, a widely used "click" reaction in interdisciplinary scientific research, offers a modular, practical, and metal-free approach to building molecular complexity in environments where toxic and redox active species should be avoided. In this paper, we describe a fundamental concept for increasing "click" reactivity through remote interactions with the hope of leading to the development of creative technological innovations. This work also introduces axial chirality as a molecular property that can be achieved by "click" chemistry, which opens the door for the future controlled creation of chiral objects and environments from achiral small molecules, polymers, and surfaces.

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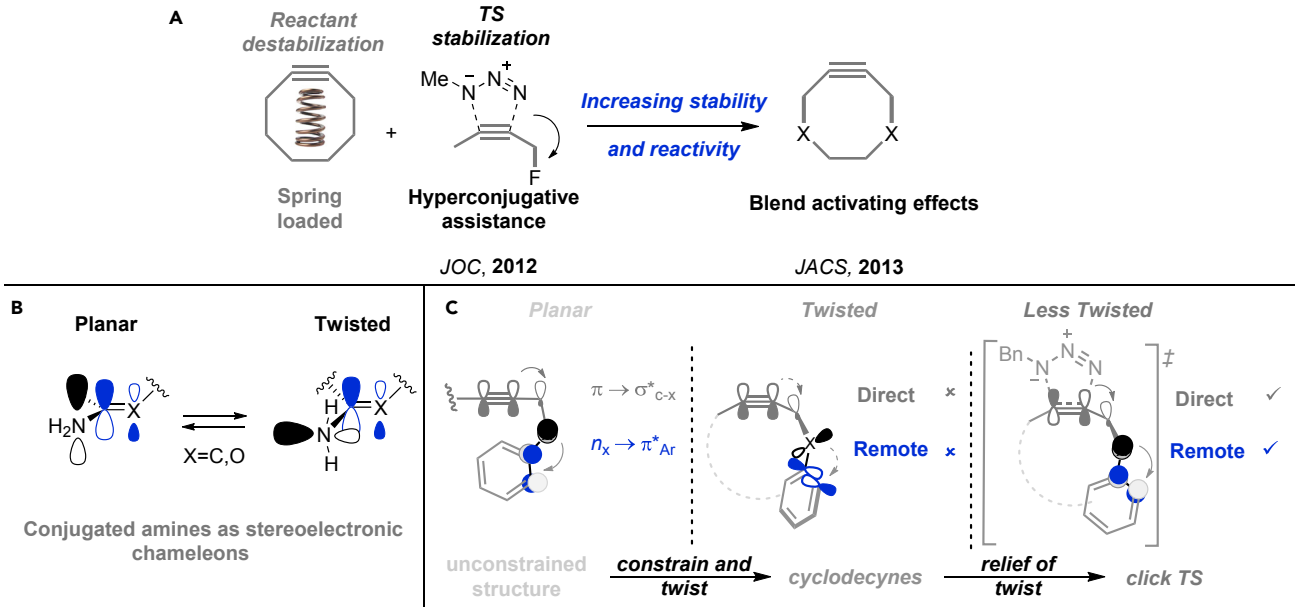

Figure 1. Modifying Reactivity with Stereoelectronic Effects

For a Figure360 author presentation of Figure 1, see http://dx.doi.org/10.1016/j.chempr.2017.07.011#mmc2.

(A) The combination of alkyne distortion and sigma acceptors in cyclooctynes leads to reactivity enhancement in click cycloadditions.[24,25]

(B) Disruption of nitrogen resonance by conformational changes affects the electronic properties of nitrogen.

(C) Structural changes in the backbone of cyclodecynes turn on direct and remote electronic effects.

Figure360: an author presentation of Figure 1.

(counterproductive for reactivity) and the cycloaddition TS, the overall reaction acceleration is observed because the TS stabilization is greater.[25] Although the synthesis of endocyclic heteroatoms in cycloalkynes has been challenging, the available results are promising.[26–29] For example, Ni et al.[27] have shown that a cyclononyne with an endocyclic oxygen and nitrogen is comparable in reactivity to DIFO.

The previous success of using C–X bonds in cycloalkynes relies heavily on their utility as σ acceptors. However, because of their dual nature to also serve as n_X donors, we thought to access this untapped potential through conjugative assistance. For creative inspiration, we looked to twisted amides and twisted enamines where their reactivity is coupled to bond rotation (Figure 1B).[30–35] These "stereoelectronic chameleons"[36] can switch their electronic nature simply by rotation relative to the rest of the molecule. In this work, we offer a new approach to selective TS stabilization in "click" cycloadditions through a combination of stereoelectronic effects[37] where the endocyclic heteroatom acts as both an acceptor, through direct activation, and a donor, through remote activation (Figure 1C). The heteroatom, which is remote from the alkyne, is misaligned with the adjacent π_{aryl} system in the cycloalkyne, rotates, and forms stronger conjugative interactions in the reaction TS, thereby unlocking the power of remote activation of "click" reactivity.

Generally, the structural design of cycloalkynes in "click" chemistry includes alkyne bending,[13] sometimes amplified by other external factors such as ion sensing.[38] The present design introduces twisting along the cycloalkyne backbone that starts from the alkyne and passes through the endocyclic C–X bonds to a biaryl core. We show that electronic energy stored in the twisted structure can be harvested

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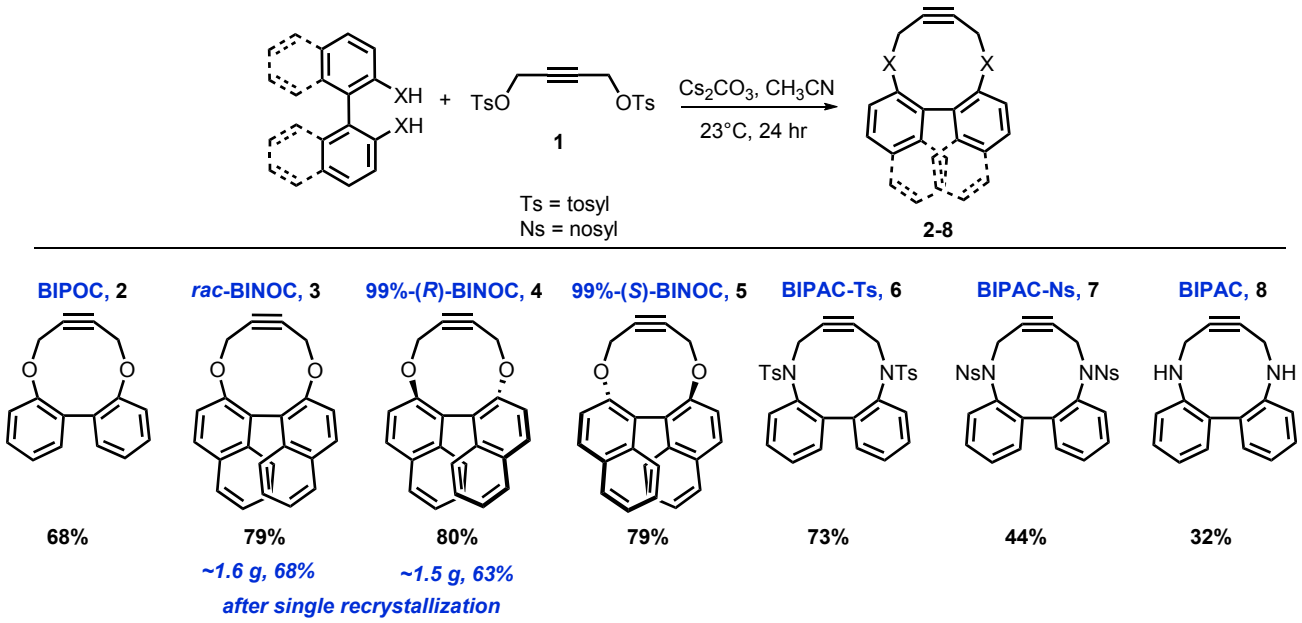

Figure 2. Synthesis of Cyclodecynes

For **2**–**7**, ^{1}H nuclear magnetic resonance yield determined with an internal standard. For **6**–**8**, dimethylformamide, 35°C, 72 hr. For **8**, isolated yield; one-pot cyclization-deprotection; see Supplemental Information.

in the "click" cycloaddition TS. In addition, the biaryl moiety introduces axial chirality because restricted bond rotation creates atropisomers.[39]

RESULTS AND DISCUSSION

Introduction of a twisted chiral backbone into a cycloalkyne requires larger cycles (i.e., cyclodecynes), which are intrinsically less strained than smaller cycloalkynes. The loss of strain associated with the larger cycles makes the use of stereoelectronic effects critical for the activation of cyclodecynes toward "click" cycloadditions. We envisioned that the chiral architecture and the endocyclic heteroatoms could be incorporated into the cycle from commercially available 2,2′-biaryl nucleophiles (Figure 2, top). A few examples of cycloalkynes incorporating a biaryl backbone have been reported,[40,41] with one example reported after this paper was submitted for peer review.[42]

Assembly of the cyclodecyne frame involves simple nucleophilic substitutions. The direct nucleophilic substitution approach to make smaller cycloalkynes is difficult because of the entropic and enthalpic penalty for the formation of strained rings. Instead, previous success of cyclononyne synthesis relied heavily on the Nicholas reaction to assemble the ring, an approach that activates the electrophilic partner but requires two additional steps to protect and deprotect the alkyne.[27,28] Here, direct access to the cycloalkyne is feasible through the favorable combination of the mild base and low ring strain of cyclodecyne products. Furthermore, the use of a mild base prevents undesired alkyne-allene isomerization.

Cesium carbonate was found to be an excellent base for the cyclization (Table S1). Bistosylate of but-2-yne-1,4-diol **1** is a readily available electrophile (we prepared 22 g of **1** in a one-step 98% yield operation) with excellent reactivity toward heteroatomic nucleophiles.[43] Its reaction with 2,2′-biphenol gave the target

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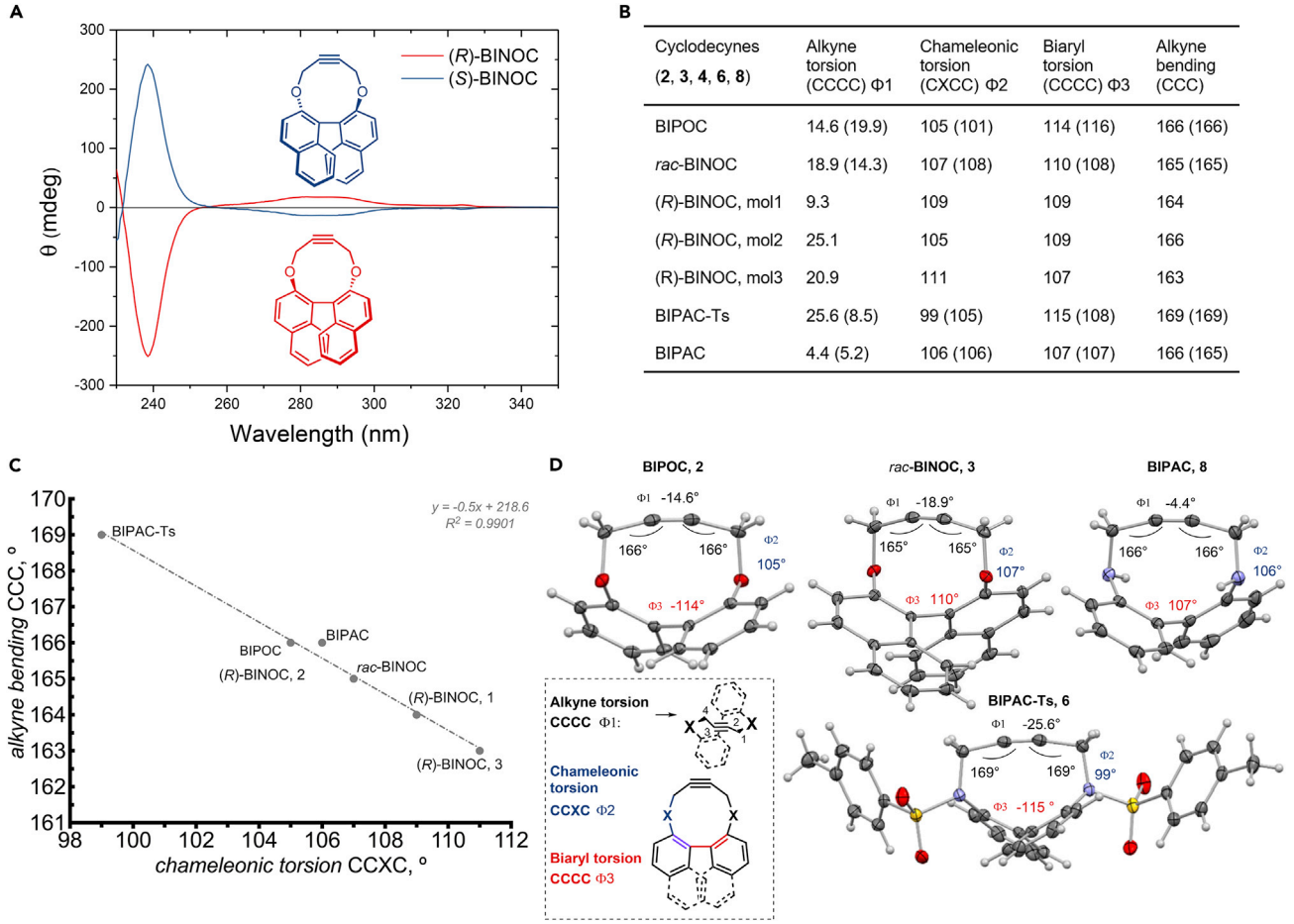

Cyclodecynes (**2**, **3**, **4**, **6**, **8**)	Alkyne torsion (CCCC) Φ1	Chameleonic torsion (CXCC) Φ2	Biaryl torsion (CCCC) Φ3	Alkyne bending (CCC)
BIPOC	14.6 (19.9)	105 (101)	114 (116)	166 (166)
rac-BINOC	18.9 (14.3)	107 (108)	110 (108)	165 (165)
(*R*)-BINOC, mol1	9.3	109	109	164
(*R*)-BINOC, mol2	25.1	105	109	166
(R)-BINOC, mol3	20.9	111	107	163
BIPAC-Ts	25.6 (8.5)	99 (105)	115 (108)	169 (169)
BIPAC	4.4 (5.2)	106 (106)	107 (107)	166 (165)

Figure 3. Structural Properties of Chiral Cyclodecynes

(A) Overlap of circular dichroism spectra for (*R*)-BINOC and (*S*)-BINOC.

(B) Summary of X-ray and solvent-corrected density functional theory (DFT) geometries. DFT values, (SMD = $CHCl_3$)/M06-2X(D3)/6-311++G(d,p) level of theory, are in parentheses. Angles are in degrees and shown as the absolute values. (SMD = $CHCl_3$)/M06-2X(D3)/6-31+G(d,p) level for BIPAC-Ts.

(C) Correlation of chameleonic torsion and alkyne bending with the use of X-ray data.

(D) ORTEP of BIPOC, *rac*-BINOC, BIPAC, and BIPAC-Ts. Ellipsoids are at the 50% probability level. All non-hydrogen atoms were refined anisotropically, whereas all hydrogen atoms were placed in their geometrically calculated positions and fixed. (Bottom) Various twisting modes in chiral cyclodecynes: alkyne torsion, chameleonic torsion, and biaryl torsion. BIPAC has a similar framework ($C_{(sp2)}$-NH-CH_2-$C_{(sp)}$) to cyclononyne ABSACN,[28] however the cyclononyne is more bent (159°).

2,2′-biphenyldioxacyclodecyne (**BIPOC**) **2** in a 68% yield (Figure 2, bottom). The optimized cyclization conditions can be extended to the more sterically demanding racemic 2,2′-binaphthol (**BINOL**) to obtain *rac*-2,2′-binaphthyldioxacyclodecyne (*rac*-**BINOC**) **3** in 79% yield. The individual (*R*) and (*S*) enantiomers of **BINOL** (~99% purity) gave enantiopure (*R*)-**BINOC 4** and (*S*)-**BINOC 5** in 80% and 79% yields, respectively, without loss of chiral integrity (Figure S19). Circular dichroism spectra of (*R*)- and (*S*)-BINOC displayed Cotton effects that resemble the atropisomeric binaphthyl backbones of (*R*)- and (*S*)-**BINOL** (Figure 3A). To compare the effect of endocyclic heteroatoms on reactivity, we also prepared the nitrogen analogs **BIPAC-Ts 6** and **BIPAC-Ns 7** from the corresponding bistosylate and bisnosylate of 2,2′-biphenyldiamine. Under these conditions, the direct use of 2,2′-biphenyldiamine gave recovered starting diamine and tosylate, presumably as a result of lower nucleophilicity of unsubstituted anilines. However, a one-pot cyclization-deprotection sequence with the more reactive nosylate

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produced the free bisamine **8** (2,2′-biphenyldiaminocyclodecyne, **BIPAC**) in 32% yield.

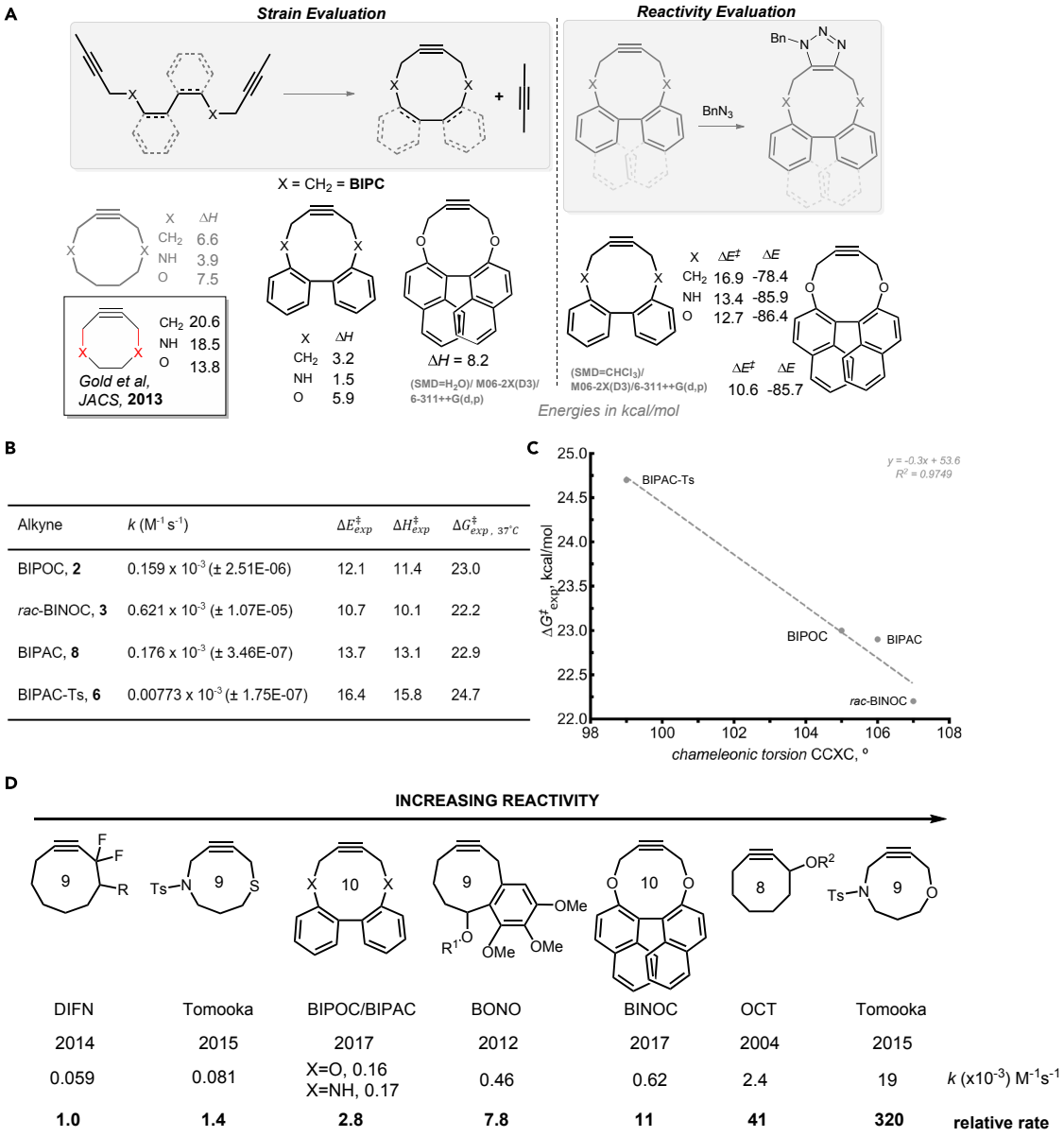
Twisting and bending of the cyclodecynes were elucidated with X-ray analysis and computations (Figures 3B and 3D). The magnitude of alkyne bending (163°–169°) is comparable (or slightly lower) with that in known cyclononynes.[27] The alkyne torsions Φ1 range from 4° to 25°, indicating *trans*-bent geometry, an overlooked structural distortion in cycloalkynes, most likely caused by the twisted backbone (Figure S11). The "chameleonic" torsion Φ2 shows the alignment of the $C_{(sp3)}$–X bonds with the aryl ring and reflects delocalization (or lack thereof) of heteroatom lone pairs into the aryl ring. In the near-perpendicular geometries (99°–111°) observed, the heteroatoms p-type lone pair is misaligned with the aromatic π system. The biaryl torsions Φ3 range from 107° to 115°, much closer to the perpendicular geometry than 2,2′-biphenol (torsion angle of 48°).[44,45]

Remarkably, crystal data of (*R*)-**BINOC** revealed three distinct molecules (mol1, mol2, and mol3) in the asymmetric unit cell (Figure S7). The variable geometries observed for the three molecules of (*R*)-**BINOC** indicate that the backbone of cyclodecynes is sufficiently flexible to respond to changes in its chemical environment. Analysis of the structural parameters for the cyclodecynes reveals a strong correlation between "chameleonic" torsion Φ2 and alkyne bending (Figure 3C); forcing the $C_{(sp3)}$–X bonds to be orthogonal to the aryl ring partially alleviates alkyne bending. Both effects are destabilizing and the tug-of-war between them can be used to store potential energy that can be released en route from reactants to products.

We have used computations to quantify the effect of strain on the reactivity of four cyclodecynes twisted in relation to the carbocyclic analog biphenylcyclodecyne (**BIPC**). First, the cycloadditions of **BIPOC** and **BIPAC** are ~8 kcal/mol more exergonic than that of **BIPC**, indicating greater energy "stored" in the heterocyclic cyclodecynes. Furthermore, in sharp contrast to the analogous cyclooctynes,[25] the presence of endocyclic oxygen atoms does not alleviate strain in relation to **BIPC** (Figure 4A, left). We attribute this finding to the twisted geometry adopted by the starting materials where the C–X bond must make a choice whether to align with the aryl group or with the alkyne. Another stark difference to cyclooctynes is that ring fusion decreases the cyclodecyne strain energy (by ~2–3 kcal/mol). This behavior can be attributed to the removal of torsion strain and transannular interactions.

Initially, the reactivity of cyclodecynes was evaluated from competition between **BIPOC** and an analogous electronically activated acyclic alkyne toward benzyl azide (Scheme S1). In agreement with the superior reactivity of **BIPOC**, less than 1% of the product was derived from the linear alkyne as per ^{1}H nuclear magnetic resonance analysis of the reaction mixture. Given that thiols are common competing traps for cyclooctynes, we tested the selectivity of the cycloaddition with an azide in the presence of an equimolar amount of thiophenol. The reaction gave 92% of the triazole product (Scheme S2).[46]

Experimental second-order rate constants and activation parameters provided quantitative evaluation of the "click" reactivity of twisted cyclodecynes **BIPOC**, **BINOC**, **BIPAC-Ts**, and **BIPAC** in reaction with benzyl azide (Figures 4B and S20–S39 and Schemes S3–S10 for Arrhenius and Eyring plots). These experimental trends were corroborated with computational analysis (Figure 4A, right). Although endocyclic acceptors have a different effect on ring strain, they increase reactivity similar to cyclooctynes[25] and cyclononynes,[27,28] suggesting a common TS



Alkyne	k ($M^{-1}s^{-1}$)	$\Delta E^{\ddagger}_{exp}$	$\Delta H^{\ddagger}_{exp}$	$\Delta G^{\ddagger}_{exp,\ 37^{\circ}C}$
BIPOC, **2**	0.159 x 10^{-3} (± 2.51E-06)	12.1	11.4	23.0
rac-BINOC, **3**	0.621 x 10^{-3} (± 1.07E-05)	10.7	10.1	22.2
BIPAC, **8**	0.176 x 10^{-3} (± 3.46E-07)	13.7	13.1	22.9
BIPAC-Ts, **6**	0.00773 x 10^{-3} (± 1.75E-07)	16.4	15.8	24.7

Figure 4. Strain and Reactivity of Cyclodecynes

(A) Computational evaluation of strain and reactivity with isodesmic equations and activation energies, respectively.

(B) Experimental second-order rate constants determined through ^{1}H nuclear magnetic resonance kinetics with benzyl azide at 25°C in $CDCl_3$ and activation parameters (in kcal/mol). Kinetic experiments were performed in triplicate and the average rate is reported. The second-order rate constant for BIPOC with benzyl azide at 25°C in CD_3CN is $0.18 \times 10^{-3}\ M^{-1}\ s^{-1}$.

(C) Correlation between X-ray chameleonic torsion and experimental $\Delta G^{\ddagger}$ for BIPOC, BINOC, BIPAC-Ts, and BIPAC.

(D) Literature precedents of non-catalyzed cycloadditions of alkynes with benzyl azide. Note: all kinetics display second-order rate constants in $M^{-1}\ s^{-1}$ at 25°C in CD_3CN.[13,27] BIPOC and BINOC rate constants reported are in $CDCl_3$. The changes in reactivity for BIPOC in different solvents are small.

stabilizing effect, i.e., hyperconjugation. The enthalpy of activation for **BIPOC** is low (11.4 kcal/mol) but, as expected for a bimolecular process, the unfavorable entropic contribution raises the free energy of activation (23.0 kcal/mol at 37°C). **BINOC** with an enthalpy of activation of 10.7 kcal/mol is ~10-fold more reactive than **BIPOC**. The experimental kinetics suggest strong correlation between the free energy of activation and "chameleonic" torsion Φ2 (Figure 4C). The more the molecules are

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A

Alkyne	$\Delta E^{\ddagger}_{calc}$	ΔE_{rxn}	E_{int}	E^{azide}_{dist}	E^{alkyne}_{dist}	E^{total}_{dist}
BIPC	16.9	-78.4	-11.8	22.5	6.2	28.7
BIPAC	13.4	-85.9	-9.3	18.7	4.0	22.7
BIPOC	12.7	-86.4	-12.1	20.8	4.0	24.8
BINOC	10.6	-85.7	-13.3	20.4	3.5	23.9

B

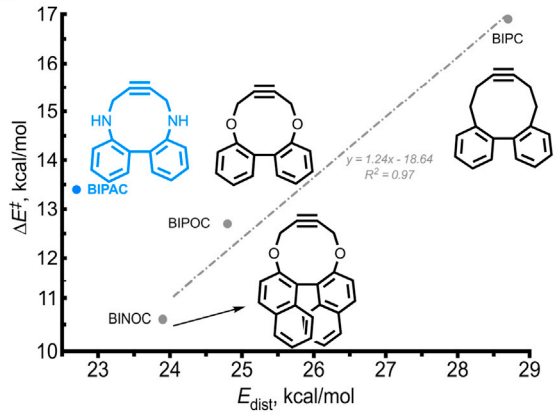

Figure 5. Distortion-Interaction Analysis

(A) Activation, reaction, interaction, and distortion energies.

(B) Correlation of total distortion energy and activation energy.

twisted from the perpendicular geometry, the lower is the activation barrier (see Figures S12–S16 for additional correlation graphs). Similar but slightly weaker correlation was found with alkyne bending (Figure S17).

It is instructive to compare the reactivity of **BIPOC** and **BINOC** with known cycloalkynes in Figure 4D. Gratifyingly, twisted cyclodecynes outcompete many of their smaller rivals, cyclononynes. For example, **BINOC** is more reactive than difluorinated cyclononyne (**DIFN**),[47] including an activated cyclononyne with endocyclic nitrogen and sulfur atoms and **BONO**.[48] Furthermore, **BINOC** reacts only four times slower than **OCT**, a monosubstituted cyclooctyne. Surprisingly, when a strong acceptor $C_{(sp3)}$–O is exchanged for a weaker $C_{(sp3)}$–N acceptor (**BIPOC** → **BIPAC**), neither the experimental rate nor the free energy of activation change; **BIPAC** is very similar in reactivity to **BIPOC**.

Furthermore, **BIPAC-Ts** reacts with benzyl azide ~100-fold slower than **BIPAC**. This observation further contradicts the expectation that a stronger acceptor should increase reactivity. The lower reactivity of **BIPAC-Ts** agrees well with an activation enthalpy of 15.8 kcal/mol and the decreased alkyne angle strain (169°) in the X-ray geometry. Distortion-interaction energy analysis[49] (Figure 5B) revealed that, relative to the all-carbon analog **BIPC**, the endocyclic acceptors lower total distortion energies. This trend is consistent with hyperconjugative assistance of propargylic C–X acceptors to alkyne bending and alkyne-azide bond formation identified by us earlier.[25] However, **BIPAC** does not follow the usually observed correlation between the activation barrier and the total distortion penalty. Although **BIPAC**'s alkyne geometry distorts the most from the ground state geometry in the TS

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(166°–159°), paradoxically this TS also has the lowest total distortion energy among the four entries in Figure 5A.

The paradoxical features of **BIPAC** stem from unique constraints that twisted cyclodecynes impose on the propargylic heteroatoms connected to the biaryl core. Each C–X moiety is sandwiched between the triple bond and the aryl group. In the absence of structural constraints, the C–X bridge is expected to play distinctly different electronic roles toward functionalities at its opposing ends: serve as a σ^*_{C-X} acceptor (hyperconjugation) in relation to the alkyne but act as the n_X donor in relation to the aryl group (conjugation). Because of the geometric constraint in the twisted cycloalkyne framework, both interactions are weakened. As the cyclodecynes structurally reorganize in the TS, these conjugative interactions are strengthened and stabilize the TS.

We quantified the conjugative $n_X \rightarrow \pi^*_{CCaryl}$ interactions with natural bond orbital (NBO) analysis by deleting the orbital specific interactions and recalculating the wavefunction energy. Although the usual conjugation ($n_X \rightarrow \pi^*_{CCaryl}$) is weakened in the cycloalkynes by geometric constraints, this interaction increases in the TS. For oxygen, which has two lone pairs, conjugation cannot be completely switched off in the cycloalkyne, and the change from ground state to TS is moderate as reflected in a 4 kcal/mol increase in the NBO energies of the respective interactions (ΔE_{del}). However, unlike oxygen, nitrogen has only one lone pair and the change in NBO ($n_X \rightarrow \pi^*_{CCaryl}$) conjugation energy is much larger (ΔE_{del} ~10 kcal/mol) (Figure 6A). The geometric assistance to resonance is further facilitated by rehybridization[50] of the nitrogen lone pair (sp^5 to sp^7). This increase in conjugative stabilization through the activation of remote stereoelectronic interactions explains the low total distortion energy in the TS for **BIPAC** and similar reactivity to **BIPOC**.

Because NBO interaction energy quantifies only a single component from the complex combination of electronic, electrostatic, and structural effects, we have also evaluated the total energy cost of these distortions directly by using dihedral scans shown in Figure 6B. The chameleonic torsions for **BIPOC** and **BIPAC** (78° and 72°, respectively) indicate the presence of energy stored by the geometric constraints of a strained cycle. Computational analysis confirmed that the out-of-plane C–X bonds rotate in the TS to become less twisted and increase conjugation with the aryl rings. Such change brings only 0.2 kcal/mol (~0.1 × 2) for **BIPOC** where, because of the presence of two lone pairs at oxygens, the resonance cannot be completely switched off by rotation. However, stabilization is much larger (~2 kcal/mol) for **BIPAC**, a better "chameleon." Increased reactivity of **BIPAC** reveals that the modulation of aniline resonance by structural constraints finds a new role in alkyne cycloadditions.

An independent experimental confirmation for the suggested changes in conjugation between the starting 2,2′-biaryl nucleophiles, cyclodecynes, and the triazole products can be provided by UV-visible (UV-vis) spectroscopy (Figure 6C). In the twisted cyclodecynes, where the lone pairs are misaligned because of geometric restraint, a hypsochromic shift is observed in relation to the acyclic structures where the lone pairs can have unobstructed communication with the aryl rings. The azide/alkyne "click" reaction partially relieves the twisting of the backbone and restores the lone pair/biphenyl communication, leading to a bathochromic shift in the triazole product in relation to the alkyne. These findings are fully supported by the trends in the computed spectra that reproduce the magnitude of the spectral

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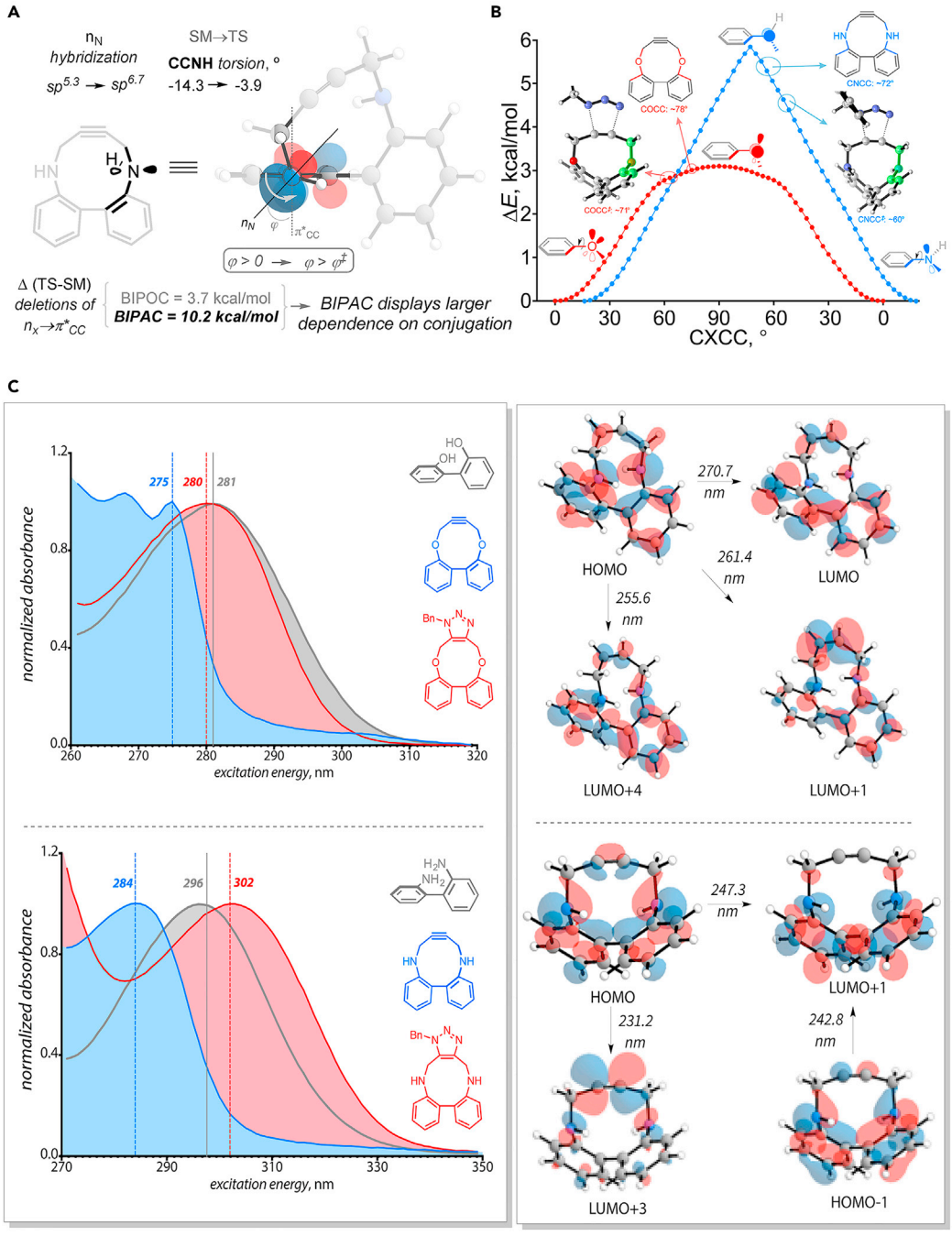

Figure 6. Stereoelectronic Chameleons in Twisted Cyclodecynes

(A) Hybridization, evaluation of conjugation via NBO deletions of $n_N \rightarrow \pi^*_{CCaryl}$ interactions for BIPOC and BIPAC, and geometric changes account for BIPAC's reactivity.

(B) CXCC dihedral scans for anisole (X = O, red) and *N*-methylaniline (X = N, blue). The CXCC dihedrals for BIPOC and BIPAC are shown in their respective parent systems' potential energy surface (PES) scans to illustrate their "stored" energy. $CXCC^{\ddagger}$ indicates dihedrals for their respective click reactions transition states.

(C) (Left) Experimental UV-vis spectra of 2,2′-biaryl nucleophiles, BIPOC, BIPAC, and corresponding triazole products (normalized absorptions). For the calculated TD-DFT UV-vis spectra of 2,2′-biaryl nucleophiles, BIPOC, BIPAC, and corresponding products that show the identical trend, see the Supplemental Information. (Right) Selected MOs involved in the TD-DFT transitions of BIPOC and BIPAC.

shifts and illustrate that the heteroatom lone pairs are involved in the multiconfigurational excitations (Figure S1).

In summary, twisted cyclodecynes are stable crystalline compounds available via a mild and scalable one-step synthetic procedure, which can be isolated by filtration and purified by recrystallization. Although the present work did not take advantage of the chirality of twisted cyclodecynes, we hope the large pool of available chiral biaryls will open synthetic access to many new chiral cycloalkynes in the future, facilitating applications of "click" chemistry for the creation of asymmetric assemblies or the transfer of chirality.[51] This work illustrates how structural reorganization in the TS can unlock the power of remote electronic effects for selective TS stabilization. In the present design, the embedded heteroatoms provide TS stabilization during the "click" reaction with azides via a combination of hyperconjugative acceptor and conjugative donor effects. In particular, the aza-cyclodecyne **BIPAC** draws increased reactivity from a remote stereoelectronic effect on the basis of modulation of aniline resonance. We hope that this concept will lead to new creative designs that can take full advantage of selective TS stabilization for the development of fast and reliable non-catalyzed "click" reactions.

EXPERIMENTAL PROCEDURES

Circular dichroism spectra were obtained with an AVIV 410 CD spectrometer with a 2 mm × 4 cm quartz cuvette in methylene chloride. The UV-vis spectra were recorded at room temperature with an Agilent Cary 60 UV-vis spectrophotometer with a 1 cm × 4 cm quartz cuvette in methylene chloride. All measurements were performed with neat solvent as the blank. Full details on the computational analysis and their references are present in the Supplemental Information. All calculations were performed with Gaussian '09 D.01. We used the (SMD = solvent)/M06-2X(D3)/6-311++G(d,p) level of theory; SMD = H_2O was used for the preliminary calculations and ring strain evaluations; SMD = $CHCl_3$ was used for everything else. NBO6 was used to evaluate second-order perturbation interactions at the (SMD = $CHCl_3$)/M06-2X(D3)/6-311++G(d,p) level of theory. Because of basis set size restrictions, deletions were performed at the (SMD = $CHCl_3$)/HF/6-311G(d,p) level of theory with NBO6 interfaced with Gaussian '09.

Full experimental procedures can be found in the Supplemental Information.

ACCESSION NUMBERS

The data for X-ray crystallographic structures **2**–**4**, **6**, **8**, **10**, and **12** have been deposited in the Cambridge Crystallographic Database Center under accession numbers CCDC: 1561087, 1561089, 1561093, 1561091, 1561092, 1561088, and 1561090, respectively.

SUPPLEMENTAL INFORMATION

Supplemental Information includes computational details, Supplemental Experimental Procedures, 67 figures, 10 schemes, 1 table, and 7 data files and can be found with this article online at http://dx.doi.org/10.1016/j.chempr.2017.07.011.

AUTHOR CONTRIBUTIONS

T.H. contributed to project conception and development, syntheses, crystal growth, kinetics, UV-vis, writing of the manuscript and Supplemental Information, and supervision of M.T.; G.d.P.G. performed all calculations, contributed to theoretical

discussions, helped create figures, and assisted in writing the manuscript and Supplemental Information; S.A. performed circular dichroism, UV-vis, chiral supercritical fluid chromatography, and optical rotation experiments; R.J.C. performed the X-ray crystallography; V.V.L. assisted with mass spectrometry characterization using Fourier transform ion cyclotron resonance; M.T. assisted in syntheses and kinetics; K.H. contributed to interpretation of the photophysical results and supervised S.A; I.V.A. guided project development and writing of the manuscript and supervised T.H. and G.d.P.G.; and all authors commented on the manuscript during its preparation.

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REFERENCES AND NOTES

1. Kolb, H.C., Finn, M.G., and Sharpless, K.B. (2001). Click chemistry: diverse chemical function from a few good reactions. Angew. Chem. Int. Ed. *40*, 2004–2021.
2. Thirumurugan, P., Matosiuk, D., and Jozwiak, K. (2013). Click chemistry for drug development and diverse chemical-biology applications. Chem. Rev. *113*, 4905–4979.
3. Rostovtsev, V.V., Green, L.G., Fokin, V.V., and Sharpless, K.B. (2002). A stepwise Huisgen cycloaddition process: copper(I)-catalyzed regioselective "ligation" of azides and terminal alkynes. Angew. Chem. Int. Ed. *41*, 2596–2599.
4. Hein, J.E., and Fokin, V.V. (2010). Copper-catalyzed azide-alkyne cycloaddition (CuAAC) and beyond: new reactivity of copper (I) acetylides. Chem. Soc. Rev. *39*, 1302–1315.
5. Wang, Q., Chan, T.R., Hilgraf, R., Fokin, V.V., Sharpless, K.B., and Finn, M.G. (2003). Bioconjugation by copper(I)-catalyzed azide-alkyne [3+2] cycloaddition. J. Am. Chem. Soc. *125*, 3192–3193.
6. Hong, V., Steinmetz, N.F., Manchester, M., and Finn, M.G. (2010). Labeling live cells by copper-catalyzed alkyne-azide click chemistry. Bioconjug. Chem. *21*, 1912–1916.
7. Meldal, M., and Tornøe, C.W. (2008). Cu-catalyzed azide-alkyne cycloaddition. Chem. Rev. *108*, 2952–3015.
8. Binder, W.H., Sachsenhofer, R., Straif, C.J., and Zirbs, R. (2007). Surface-modified nanoparticles via thermal and Cu(I)-mediated "click" chemistry: generation of luminescent CdSe nanoparticles with polar ligands guiding supramolecular recognition. J. Mater. Chem. *17*, 2125–2132.
9. Bernardin, A., Cazet, A., Guyon, L., Delannoy, P., Vinet, F., Bonnaffe, D., and Texier, I. (2010). Copper-free click chemistry for highly luminescent quantum dot conjugates: application to in vivo metabolic imaging. Bioconjug. Chem. *21*, 583–588.
10. Han, H.-S., Devaraj, N.K., Lee, J., Hilderbrand, S.A., Weissleder, R., and Bawendi, M.G. (2010). Development of a bioorthogonal and highly efficient conjugation method for quantum dots using tetrazine-norbornene cycloaddition. J. Am. Chem. Soc. *132*, 7838–7839.
11. Sletten, E.M., and Bertozzi, C.R. (2009). Bioorthogonal chemistry: fishing for selectivity in a sea of functionality. Angew. Chem. Int. Ed. *48*, 6974–6998.
12. Patterson, D.M., Nazarova, L.A., and Prescher, J.A. (2014). Finding the right (bioorthogonal) chemistry. ACS Chem. Biol. *9*, 592–605.
13. Agard, N.J., Prescher, J.A., and Bertozzi, C.R. (2004). A strain-promoted [3+2] azide-alkyne cycloaddition for covalent modification of biomolecules in living systems. J. Am. Chem. Soc. *126*, 15046–15047.
14. Escorihuela, J., Marcelis, A.T.M., and Zuilhof, H. (2015). Metal-free click chemistry reactions on surfaces. Adv. Mater. Interfaces *2*, 1–42.
15. Manova, R., van Beek, T.A., and Zuilhof, H. (2011). Surface functionalization by strain-promoted alkyne-azide click reactions. Angew. Chem. Int. Ed. *50*, 5428–5430.
16. Arnold, R.M., Patton, D.L., Popik, V.V., and Locklin, J. (2014). A dynamic duo: pairing click chemistry and postpolymerization modification to design complex surfaces. Acc. Chem. Res. *47*, 2999–3008.
17. Jewett, J.C., Sletten, E.M., and Bertozzi, C.R. (2010). Rapid Cu-free click chemistry with readily synthesized biarylazacyclooctynones. J. Am. Chem. Soc. *132*, 3688–3690.
18. Sletten, E.M., Nakamura, H., Jewett, J.C., and Bertozzi, C.R. (2010). Difluorobenzocyclooctyne: synthesis, reactivity, and stabilization by β-cyclodextrin. J. Am. Chem. Soc. *132*, 11799–11805.
19. Blackman, M.L., Royzen, M., and Fox, J.M. (2008). Tetrazine ligation: fast bioconjugation based on inverse-electron-demand Diels-Alder reactivity. J. Am. Chem. Soc. *130*, 13518–13519.
20. Taylor, M.T., Blackman, M.L., Dmitrenko, O., and Fox, J.M. (2011). Design and synthesis of highly reactive dienophiles for the tetrazine-trans-cyclooctene ligation. J. Am. Chem. Soc. *133*, 9646–9649.
21. Andersen, K.A., Aronoff, M.R., McGrath, N.A., and Raines, R.T. (2015). Diazo groups endure metabolism and enable chemoselectivity in cellulo. J. Am. Chem. Soc. *137*, 2412–2415.

22. Gold, B., Arnoff, M.R., and Raines, R.T. (2016). Decreasing distortion energies without strain: diazo-selective 1,3-dipolar cycloadditions. J. Org. Chem. *81*, 5998–6006.

23. Baskin, J.M., Prescher, J.A., Laughlin, S.T., Agard, N.J., Chang, P.V., Miller, I.A., Lo, A., Codelli, J.A., and Bertozzi, C.R. (2007). Copper-free click chemistry for dynamic in vivo imaging. Proc. Natl. Acad. Sci. USA *104*, 16793–16797.

24. Gold, B., Shevchenko, N.E., Bonus, N., Dudley, G.B., and Alabugin, I.V. (2012). Selective transition state stabilization via hyperconjugative and conjugative assistance: stereoelectronic concept for copper-free click chemistry. J. Org. Chem. *77*, 75–89.

25. Gold, B., Dudley, G.B., and Alabugin, I.V. (2013). Moderating strain without sacrificing reactivity: design of fast and tunable noncatalyzed alkyne-azide cycloadditions via stereoelectronically controlled transition state stabilization. J. Am. Chem. Soc. *135*, 1558–1569.

26. Hagendorn, T., and Bräse, S. (2014). A new route to dithia- and thiaoxacyclooctynes via Nicholas reaction. RSC Adv. *4*, 15493–15495.

27. Ni, R., Mitsuda, N., Kashiwagi, T., Igawa, K., and Tomooka, K. (2015). Heteroatom-embedded medium-sized cycloalkynes: concise synthesis, structural analysis, and reactions. Angew. Chem. Int. Ed. *54*, 1190–1194.

28. Kaneda, K., Naruse, R., and Yamamoto, S. (2017). 2-Aminobenzenesulfonamide-containing cyclononyne as adjustable click reagent for strain-promoted azide-alkyne cycloaddition. Org. Lett. *19*, 1096–1099.

29. Burke, E.G., Gold, B., Hoang, T.T., Raines, R.T., and Schomaker, J.M. (2017). Fine-tuning strain and electronic activation of strain-promoted 1,3-dipolar cycloadditions with endocyclic sulfamates in SNO-OCTs. J. Am. Chem. Soc. *139*, 8029–8037.

30. Wang, M.-X. (2015). Exploring tertiary enamides as versatile synthons in organic synthesis. Chem. Commun. *51*, 6039–6049.

31. Liniger, M., VanderVelde, D.G., Takase, M.K., Shahgholi, M., and Stoltz, B.M. (2016). Total synthesis and characterization of 7-hypoquinuclidonium tetrafluoroborate and 7-hypoquinuclidone BF3 complex. J. Am. Chem. Soc. *138*, 969–974.

32. Szostak, M., and Aube, J. (2011). Medium-bridged lactams: a new class of non-planar amides. Org. Biomol. Chem. *9*, 27–35.

33. Liu, C., and Szostak, M. (2017). Twisted amides: from obscurity to broadly useful transition-metal-catalyzed reactions by n-c amide bond activation. Chem. Eur. J. *23*, 7157–7173.

34. Doering, W.v.E., Birladeanu, L., Andrews, D.W., and Pagnotta, M. (1985). Conjugative interaction in the orthogonal enamine, 1-azabicyclo[3.2.2]non-2-ene. J. Am. Chem. Soc. *107*, 428–432.

35. Kirby, A.J., Komarov, I.V., and Feeder, N. (1998). Spontaneous millisecond formation of a twisted amide from the amino acid, and the crystal structure of a tetrahedral intermediate. J. Am. Chem. Soc. *120*, 7101–7102.

36. Vatsadze, S.Z., Loginova, Y.D., Dos Passos Gomes, G., and Alabugin, I.V. (2017). Stereoelectronic chameleons: the donor-acceptor dichotomy of functional groups. Chem. Eur. J. *23*, 3225–3245.

37. Alabugin, I.V. (2016). Stereoelectronic Effects: A Bridge between Structure and Reactivity (Wiley), p. 97.

38. Gold, B., Batsomboon, P., Dudley, G.B., and Alabugin, I.V. (2014). Alkynyl crown ethers as a scaffold for hyperconjugative assistance in noncatalyzed azide-alkyne click reactions: ion sensing through enhanced transition-state stabilization. J. Org. Chem. *79*, 6221–6232.

39. For an example of cyclooctynes with centers of chirality, see: Dommerholt, J., Schmidt, S., Temming, R., Hendriks, L.J.A., Rutjes, F.P.J.T., van Hest, J.C.M., Lefeber, D.J., Friedl, P., and van Delft, F.L. (2010). Readily accessible bicyclononynes for bioorthogonal labeling and three-dimensional imaging of living cells Angew. Chem. Int. Ed. *49*, 9422–9425.

40. Pomeranz, U.K., Hansen, H.-J., and Schmid, H. (1973). Die durch Silberionen katalysierte Umlagerung von Propargyl-phenylather. Helv. Chim. Acta *56*, 2981–3004.

41. Lustenberger, P., Martinborough, E., Denti, T.M., and Diederich, F. (1998). Geometrical optimisation of 1,1′-binaphthalene receptors for enantioselective molecular recognition of excitatory amino acid derivatives. J. Chem. Soc. Perkin Trans. *2*, 747–762.

42. Del Grosso, A., Galanopoulos, L.-D., Chiu, C.K.C., Clarkson, G.J., O'Connor, P.B., and Wills, M. (2017). Strained alkynes derived from 2,2′-dihydroxy-1,1′-biaryls; synthesis and copper-free cycloaddition with azides. Org. Biomol. Chem. *15*, 4517–4521.

43. Kotha, S., and Waghule, G.T. (2012). Diversity oriented approach to crownophanes by enyne metathesis and Diels-Alder reaction as key steps. J. Org. Chem. *77*, 6314–6318.

44. Byrne, J.J., Chavant, P.Y., Averbuch-Pouchot, M.-T., and Vallee, Y. (1998). 2,2′-Biphenol. Acta Crystallogr *C54*, 1154–1156.

45. In the solid state, rac-BINOC is less twisted than 2,2′-binaphthol (89°), where twisting is not affected by bending. For BINOL X-ray data, see Lee, T., and Peng, J.F. (2010). Photoluminescence and crystal structures of chiro-optical 1,1′-bi-2-naphthol crystals and their inclusion compounds with dimethyl sulfoxide. Cryst. Growth Des. *10*, 3547–3554.

46. Jewett, J.C., and Bertozzi, C.R. (2010). Cu-free click cycloaddition reactions in chemical biology. Chem. Soc. Rev. *39*, 1272–1279.

47. Sletten, E.M., de Almeida, G., and Bertozzi, C.R. (2014). A homologation approach to the synthesis of difluorinated cycloalkynes. Org. Lett. *16*, 1634–1637.

48. Tummatorn, J., Batsomboon, P., Clark, R.J., Alabugin, I.V., and Dudley, G.B. (2012). Strain-promoted azide-alkyne cycloadditions of benzocyclononynes. J. Org. Chem. *77*, 2093–2097.

49. Ess, D.H., and Houk, K.N. (2008). Theory of 1,3-dipolar cycloadditions: distortions/interaction and frontier molecular orbital models. J. Am. Chem. Soc. *130*, 10187–10198.

50. Alabugin, I.V., Bresch, S., and Gomes, G.P. (2015). Orbital hybridization: a key electronic factor in control of structure and reactivity. J. Phys. Org. Chem. *28*, 147–162.

51. Stetsovych, O., Svec, M., Vacek, J., Chocholousova, J.V., Jancarik, A., Rybacek, J., Kosmider, K., Stara, I.G., Jelinek, P., and Stary, I. (2017). From helical to planar chirality by on-surface chemistry. Nat. Chem. *9*, 213–218.