

----- SUPPORTING INFORMATION -----

The Hunt for Reactive Alkynes in Bio-Orthogonal Click Reactions: Insights from Mechanochemical and Conceptual DFT Calculations

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Table of contents

1. Improvement of the extended COGEF model	3
Figure S1. The $r(\varphi)$ profiles indicate a quadratic relation between r and the deviation from linearity of the alkyne.....	3
Figure S2. The improved equation for bending forces (dashed lines) does not lead to significant deviations from the simple linear relation (solid lines) in equation 5.	4
2. Validation of equation (5)	5
Figure S3. The gradient on the propargylic C-atom (C_3) was first projected in the plane defined by C_1 , C_2 and C_3 (see g'). g_{\perp}' is the component of this vector perpendicular to the C_2 - C_3 bond.....	5
Figure S4. F_{ext} calculated with equation (5) and equation (S3) as well as the gradient on C_3 as a function of the bending angle φ	6
Table S1. Overview of the angles between g and the $C_1C_2C_3$ plane and between g' and the C_2 - C_3 bond (in °) as well as the norm of g , g' , g_{\perp}' and F_{ext} calculated by equation (5) and (S3) (all in nN).....	7
3. Monobenzocycloalkynes	8
Figure S5. Bond angles around the triple bond in monobenzocyclooctynes.	8

Figure S6. Correlation between r and the bond angle around the triple bond at the substituent side in monobenzocyclooctynes.	9
4. Fukui function and local softness	10
Figure S7. (a) $f^-(r)$ increases when the triple bond is stressed by a bending force, indicating that smaller cyclic alkynes become more nucleophilic; (b) $s^-(r)$ increases when the triple bond is bent. Both descriptors were calculated according to the Hirshfeld population analysis.	10
Figure S8. (a) $f^+(r)$ increases when the triple bond is stressed by a bending force, indicating that smaller cyclic alkynes become more nucleophilic; (b) $s^+(r)$ increases when the triple bond is bent. Both descriptors were calculated according to the NPA population analysis.	11
Figure S9. (a) $f^-(r)$ increases when the triple bond is stressed by a bending force, indicating that smaller cyclic alkynes become more nucleophilic; (b) $s^-(r)$ increases when the triple bond is bent. Both descriptors were calculated according to the NPA population analysis.	12

1. Improvement of the extended COGEF model

In equation (2) and (3) of the main text, $|\vec{r}|$ is assumed to be constant upon bending, which is not the case in our bending experiments. The derivation of the formula for calculating the external force is not heavily impacted if $|\vec{r}|$ changes with φ , *i.e.* $|\vec{r}|(\varphi)$. Solving equation (3) for $|\vec{F}_{\text{ext}}|$ then yields

$$|\vec{F}_{\text{ext}}| = \frac{2a\varphi}{|\vec{r}|(\varphi)} \quad (\text{S1})$$

In Figure S1, $|\vec{r}|$ is plotted against φ for all systems in Figure 4. Based on the shape of these curves, a harmonic model for $|\vec{r}|(\varphi)$ was chosen:

$$|\vec{r}|(\varphi) = \alpha\varphi^2 + \beta\varphi + r_0 \quad (\text{S2})$$

where r_0 is the value of $|\vec{r}|$ that was used in Figure 4, *i.e.* the bond length in the equilibrium geometry ($\varphi = 0^\circ$). Equation (S1) then becomes

$$|\vec{F}_{\text{ext}}| = \frac{2a\varphi}{\alpha\varphi^2 + \beta\varphi + r_0} \quad (\text{S3})$$

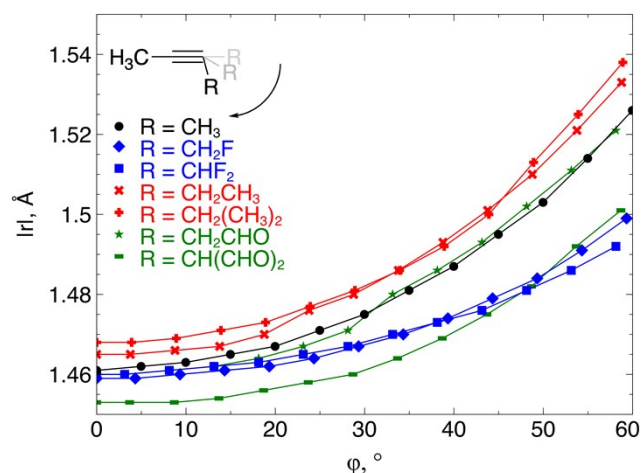


Figure S1. The $|\vec{r}|(\varphi)$ profiles indicate a quadratic relation between $|\vec{r}|$ and the deviation from linearity of the alkyne.

In Figure S2, the bending force is plotted against φ , according to equation (5) in the main text and the improved equation (S3). For the sake of clarity in this picture only the $R = \text{CH}_3$, CH_2F , CH_2CH_3 and CH_2CHO curves are shown.

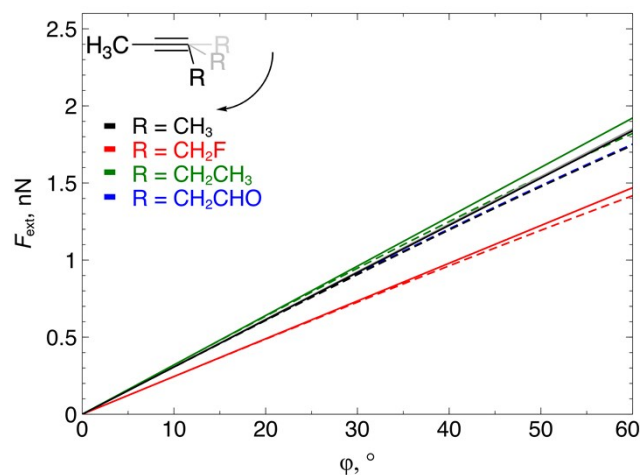


Figure S2. The improved equation for bending forces (dashed lines) does not lead to significant deviations from the simple linear relation (solid lines) in equation 5.

From Figure S2, it is clear that the improved model (dashed lines) does not deviate significantly from the linear relation between $|\vec{F}_{\text{ext}}|$ and φ in equation 5 (solid lines). In particular for the smaller distortions, the solid and dashed lines coincide because $|\vec{r}|$ is almost constant for small values of φ (see Figure S1).

2. Validation of equation (5)

In the main text of this article, a simple relation between $|\vec{F}_{\text{ext}}|$ and φ was found, and this equation was used to calculate the force needed to bend an acetylene from a linear conformation to a certain angle φ . In this part, we validate this simple equation [equation (5) in the main text] as well as the improved model in equation (S3) by calculating the gradient on the propargylic C-atom in 2-butyne and comparing it to $|\vec{F}_{\text{ext}}|$. Importantly, $|\vec{F}_{\text{ext}}|$ is the force perpendicular to the C-C bond adjacent to the triple bond. Therefore, the gradient on the propargylic C-atom was first projected into the plane defined by C₁, C₂ and C₃ (see g' in Figure S3). The norm of the perpendicular component – perpendicular to the C₂-C₃ bond – of this vector (g'_{\perp} in Figure S3) was validated with $|\vec{F}_{\text{ext}}|$ obtained by equation (5) and (S3). Figure S4 shows $|\vec{F}_{\text{ext}}|$ and $|g'_{\perp}|$ as a function of φ for 2-butyne.

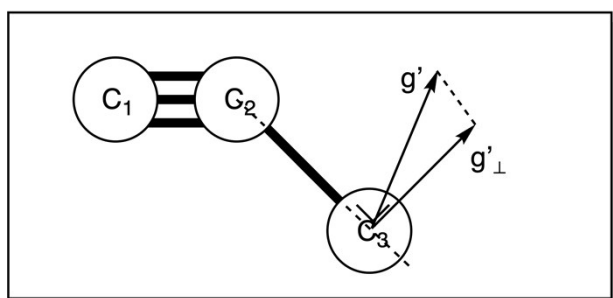
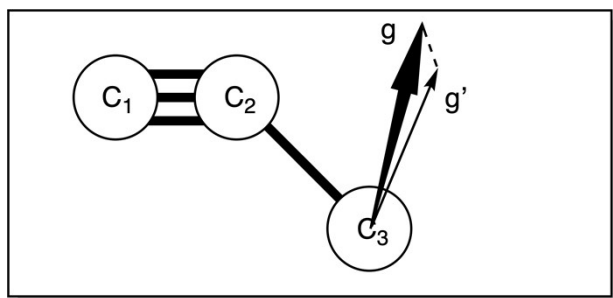


Figure S3. The gradient on the propargylic C-atom (C_3) was first projected in the plane defined by C_1 , C_2 and C_3 (see g'). g'_{\perp} is the component of this vector perpendicular to the C_2 - C_3 bond.

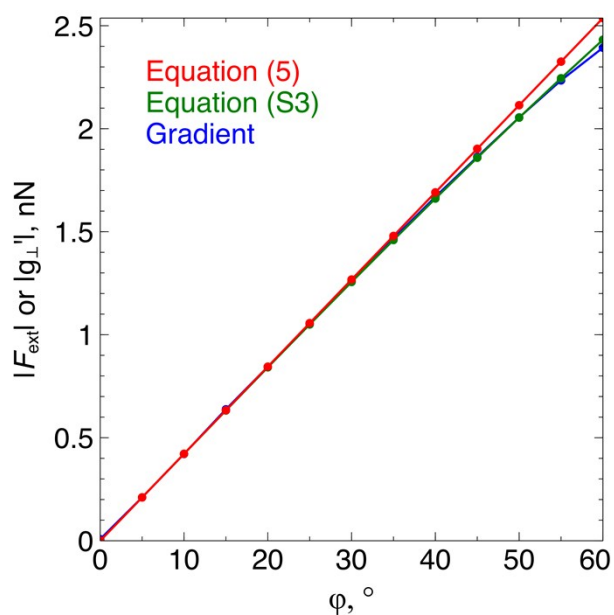


Figure S4. $|\vec{F}_{\text{ext}}|$ calculated with equation (5) and equation (S3) as well as the gradient on C_3 as a function of the bending angle φ .

From Figure S4, the linear correlation between $|\vec{F}_{\text{ext}}|$ and φ is found for equation (5) and the curve for the improved model in equation (S3) lies slightly lower. The gradient (blue line) is very close to the values of $|\vec{F}_{\text{ext}}|$ obtained by equation (S3), validating the proposed model for calculating bending forces.

It is important to notice that the projections in Figure S3 do not drastically influence the norm of the gradient, due to the very small angle between g and the $C_1C_2C_3$ plane as well as the nearly 90° angle between g' and the C_2-C_3 bond. Therefore, $|g|$ and $|g_{\square}'|$ are practically identical. In Table S1, these angles as well as the norm of g , g' , g_{\square}' and \vec{F}_{ext} are summarized.

Table S1. Overview of the angles between g and the $C_1C_2C_3$ plane and between g' and the C_2-C_3 bond (in $^\circ$) as well as the norm of g , g' , g_{\square}' and \vec{F}_{ext} calculated by equation (5) and (S3) (all in nN).

φ	$ g $	Angle g and $C_1C_2C_3$ plane	$ g' $	Angle g' and C_2-C_3 bond	$ g_{\square}' $	$ \vec{F}_{\text{ext}} $ by eq. (5)	$ \vec{F}_{\text{ext}} $ by eq. (S3)
0	0.008	16.86	0.008	100.15	0.008	0.000	0.000
5	0.210	0.06	0.210	89.97	0.210	0.210	0.210
10	0.421	0.03	0.421	89.96	0.421	0.422	0.422
15	0.638	0.19	0.638	90.11	0.638	0.633	0.632
20	0.844	0.00	0.844	90.00	0.844	0.845	0.842
25	1.053	0.00	1.053	90.00	1.053	1.056	1.050
30	1.260	0.00	1.260	90.01	1.260	1.268	1.256
35	1.466	0.02	1.466	89.99	1.466	1.479	1.460

40	1.670	0.04	1.670	90.05	1.670	1.691	1.661
45	1.863	0.00	1.863	90.01	1.863	1.903	1.859
50	2.055	0.01	2.055	90.00	2.055	2.114	2.054
55	2.235	0.01	2.235	90.00	2.235	2.326	2.245
60	2.393	0.00	2.393	90.00	2.393	2.537	2.432

3. Monobenzocycloalkynes

In addition to the structural trends in the cyclic alkynes, we investigated a series of monobenzocycloalkynes in order to test the effect of electron withdrawing/donating effects (see Figure S5). The mesomeric electron-donating ($X = \text{OH}, \text{NHCHO}, \text{NH}_2$) and electron-withdrawing substituents ($X = \text{CN}, \text{CFO}, \text{NO}_2$) were placed in the *para* position and the correlation in Figure S6 suggests that there is also a remarkable influence of the electron-donating/withdrawing character of the substituent. It is noteworthy that the data on the monobenzocyclooctynes are in a much narrower range of angles than the substitutions on the propargylic C-atom in the saturated cyclooctynes. Nevertheless, there is again an increasing trend, meaning that the electron-rich bonds are more difficult to bend compared to electron-poor bonds, resulting in smaller angles if Y is an electron-withdrawing substituent in Figure S5.

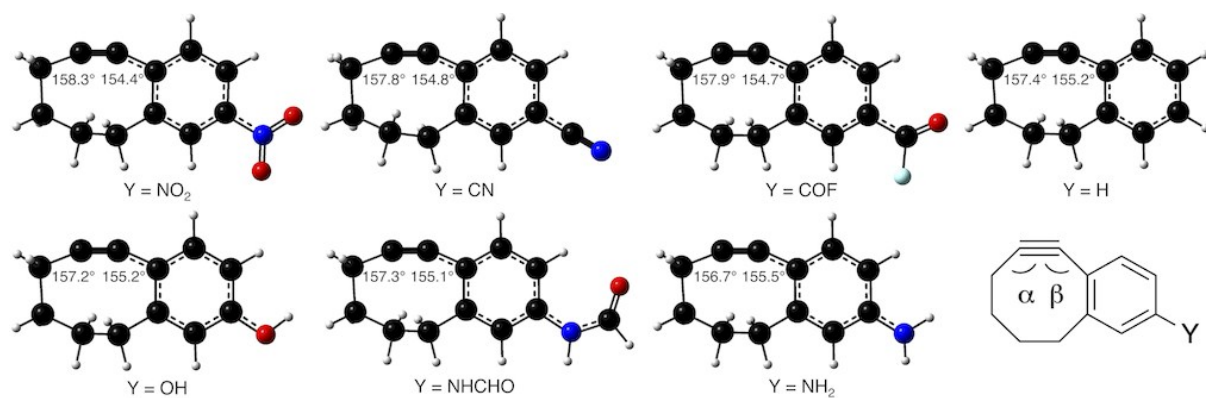


Figure S5. Bond angles around the triple bond in monobenzocyclooctynes.

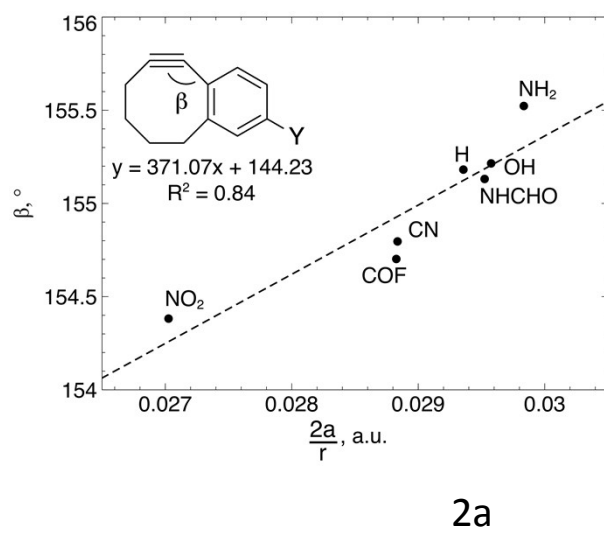


Figure S6. Correlation between β and the bond angle around the triple bond at the substituent side in monobenzocyclooctynes.

4. Fukui function and local softness

From Figure S7, the nucleophilic behavior of an angle-constrained alkyne is clearly similar to the electrophilic behavior. For angular distortions of 25° and larger, $f^-(\mathbf{r})$ is barely affected by the bending and $s^-(\mathbf{r})$ only increases significantly for bends of 15° and larger, similar to the global softness in Figure 8 in the main text. It is important to remark that $f^-(\mathbf{r})$ does not increase as much as $f^+(\mathbf{r})$. Nevertheless, the nucleophilic and electrophilic character of the triple bond is increased upon bending, however, a ring-system with 8 atoms or less is required in order to significantly enhance the reactivity of the alkyne.

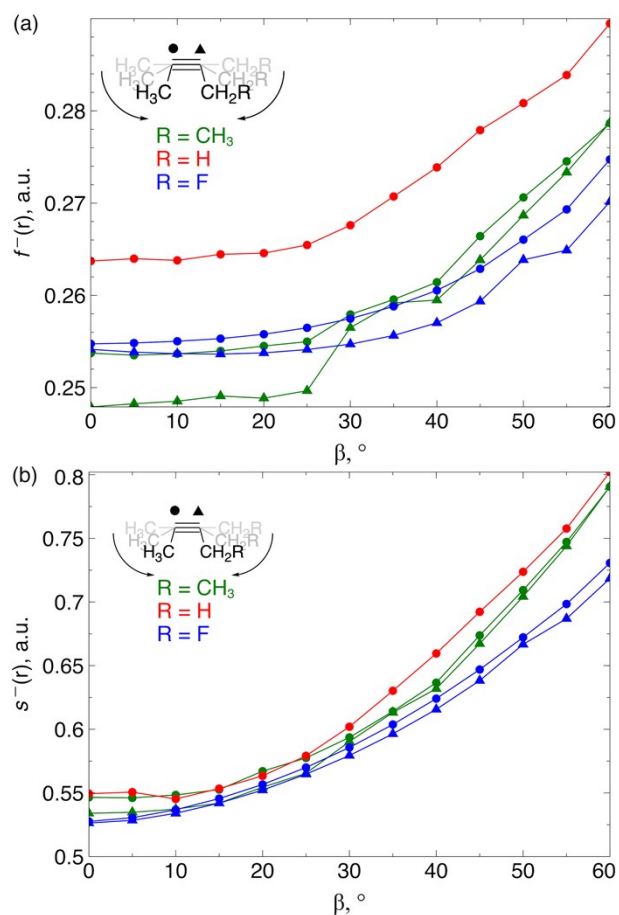


Figure S7. (a) $f^-(r)$ increases when the triple bond is stressed by a bending force, indicating that smaller cyclic alkynes become more nucleophilic; (b) $s^-(r)$ increases when the triple bond is bent. Both descriptors were calculated according to the Hirshfeld population analysis.

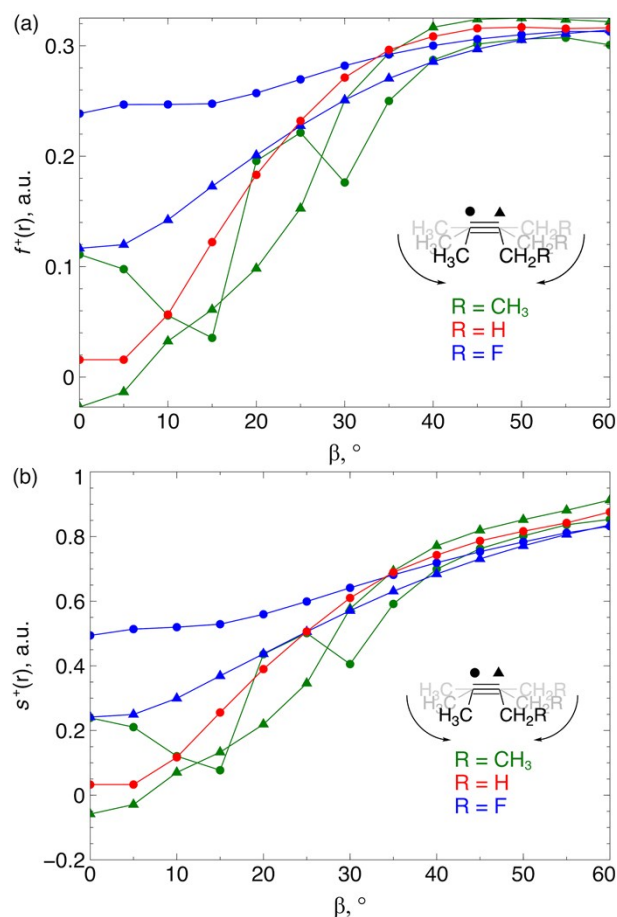


Figure S8. (a) $f^+(\mathbf{r})$ increases when the triple bond is stressed by a bending force, indicating that smaller cyclic alkynes become more nucleophilic; (b) $s^+(\mathbf{r})$ increases when the triple bond is bent. Both descriptors were calculated according to the NPA population analysis.

The electrophilic Fukui function and local softness show very similar profiles with the Hirshfeld population analysis in Figure 9 of the main text and with the NPA method in Figure S8 in the Supporting Information. In Figure S9a, $f^-(\mathbf{r})$ is again not as much influenced as $f^+(\mathbf{r})$ in Figure S8a, which was also the case with the Hirshfeld population method. On the other hand, $s^-(\mathbf{r})$ does show a clear increasing trend for distortions of 15° and larger.

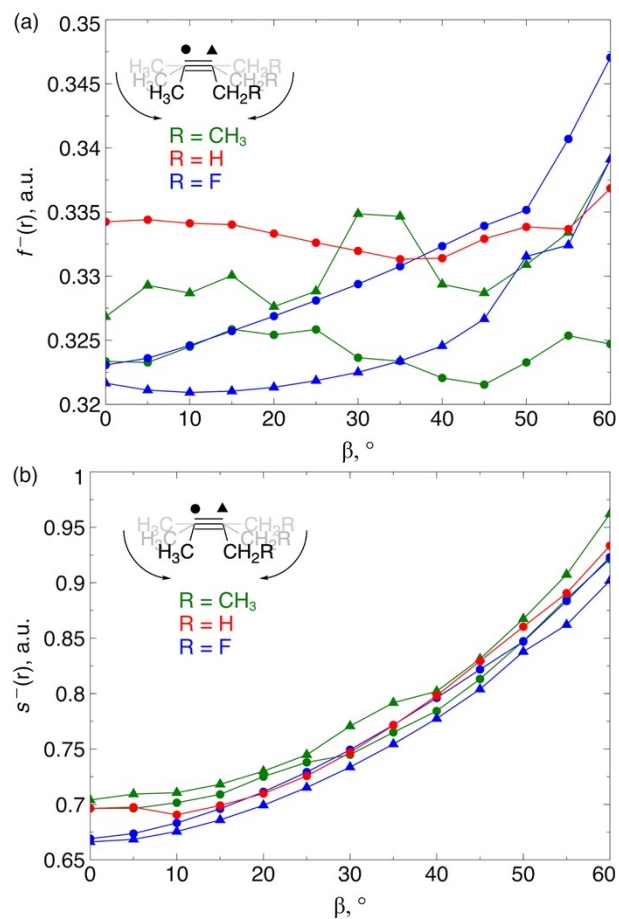


Figure S9. (a) $f^-(r)$ increases when the triple bond is stressed by a bending force, indicating that smaller cyclic alkynes become more nucleophilic; (b) $s^-(r)$ increases when the triple bond is bent. Both descriptors were calculated according to the NPA population analysis.