

Click Organocatalysis: Acceleration of Azide–Alkyne Cycloadditions with Mutually Orthogonal Click Reactions

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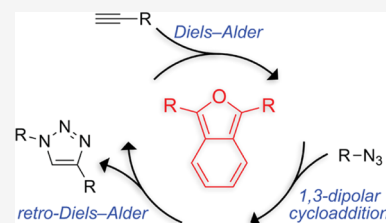


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ABSTRACT: “Click organocatalysis” uses mutually orthogonal click reactions to organocatalyze a click reaction. We report the development of an isobenzofuran organocatalyst that increases the rate and regioselectivity of an azide–alkyne cycloaddition. The organocatalytic cycle consists of (1) a Diels–Alder reaction of an alkyne with a diarylisobenzofuran to form a benzooxanorbornadiene, (2) a 1,3-dipolar cycloaddition with an azide to form a 4,5-dihydro-1,2,3-triazole, and (3) a retro-Diels–Alder reaction that releases the triazole product and regenerates the diarylisobenzofuran organocatalyst. The diarylisobenzofuran organocatalyst was computationally designed to catalyze the reaction of perfluorophenyl azide and methyl propiolate to selectively form a 1,4-triazole product. Experimental validation of the designed organocatalyst was obtained with methyl 4-azido-2,3,5,6-tetrafluorobenzoate and methyl propiolate.



Sharpless proposed the catchy moniker “click chemistry” to describe reactions that occur spontaneously in water, without byproducts, and in good yield.¹ Sharpless and Meldal independently developed the copper-catalyzed reaction of azides with terminal alkynes, which has become the prototype click reaction.^{2,3} Blomquist and Liu described the reaction of cyclooctyne and phenyl azide as being “explosive” in 1952,⁴ and the Bertozzi group developed the copper-free click reaction in 2004 in order to label living cells.⁵ These discoveries and their applications led to the award of the 2022 Nobel Prize to Sharpless, Meldal, and Bertozzi.

The 2021 Nobel Prize in Chemistry was awarded to List and MacMillan for their developments of organocatalysis.^{6,7} We have united these two vibrant fields, click chemistry and organocatalysis, by creating an organocatalytic cycle consisting of mutually orthogonal click reactions. This strategy applied to the catalysis of an azide–alkyne cycloaddition is depicted in Figure 1. The catalytic cycle initiates with a Diels–Alder reaction of a diarylisobenzofuran with an electron-deficient alkyne to form a benzooxanorbornadiene adduct.^{8–11} Subsequent 1,3-dipolar cycloaddition between the benzooxanorbornadiene cycloadduct and an azide forms a 4,5-dihydro-1,2,3-triazole cycloadduct.^{12,13} This cycloadduct then undergoes a retro-Diels–Alder reaction that releases the triazole product and regenerates the isobenzofuran organocatalyst.

The cycloaddition of perfluorophenyl azide (1) and ethyl propiolate shown in Scheme 1 was chosen as a model reaction for the computational design of an organocatalyst. The uncatalyzed reaction requires elevated temperatures and proceeds with a slight regioselectivity in favor of the 1,4-triazole regioisomer. The ideal organocatalyst would increase both the reactivity and the regioselectivity of the uncatalyzed azide–alkyne cycloaddition.

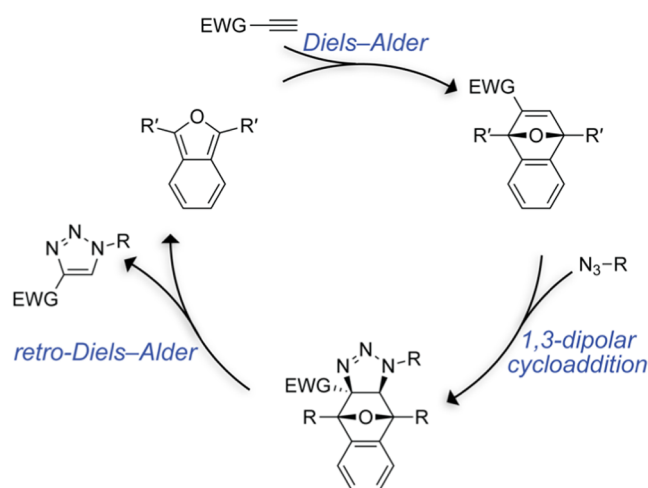


Figure 1. Click organocatalysis: catalytic cycle consisting of mutually orthogonal isobenzofuran–alkyne and benzooxanorbornadiene–azide cycloaddition reactions.

Scheme 2 shows that the Diels–Alder reaction of 1,3-diphenylisobenzofuran and methyl propiolate (2) results in the formation of a bis-adduct through a benzooxanorbornadiene intermediate (3). This byproduct must be avoided for isobenzofurans to be effective organocatalysts.

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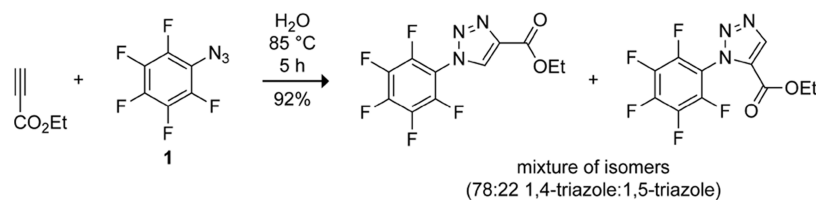
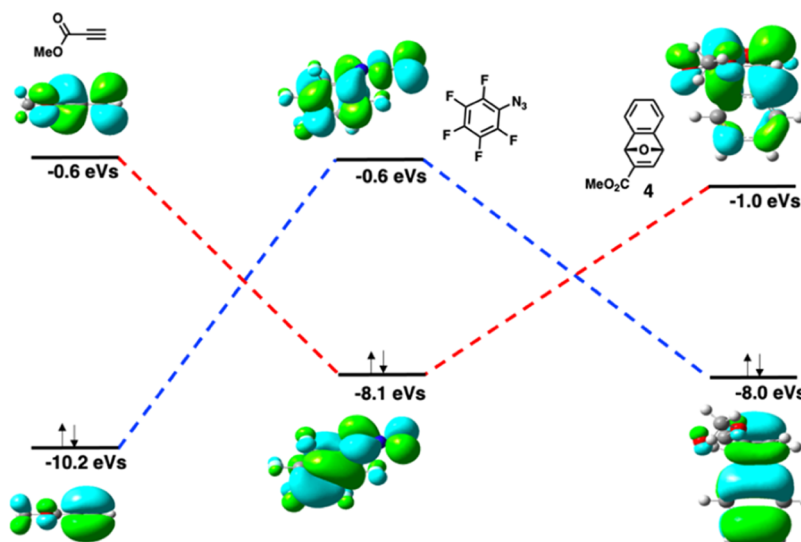
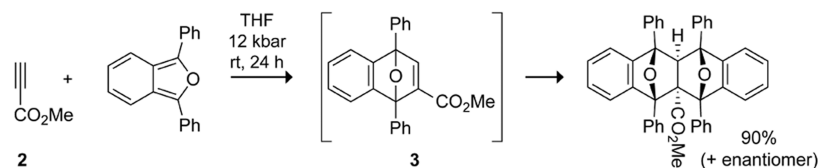
Scheme 1. Uncatalyzed 1,3-Dipolar Cycloaddition of Perfluorophenyl Azide with Ethyl Propiolate¹⁴Scheme 2. Diels–Alder Cycloaddition of 1,3-Diphenylisobenzofuran and Methyl Propiolate¹⁰

Figure 2. Frontier MOs of **2** (left), **1** (center), and **4** (right). Normal (red) and inverse (blue) electron-demand frontier molecular orbital interactions were observed between azide **1** and dipolarophiles **2** and **4**.

RESULTS AND DISCUSSION

Strained dipolarophiles are often more reactive than their linear counterparts. While such reactions are considered to be strain-promoted or distortion-accelerated, alteration of frontier molecular orbital (FMO) energies also accelerates the reactions of strained dienophiles or dipolarophiles.^{15–18} An FMO analysis of azide **1** and dipolarophiles **2** and **4** was carried out using density functional theory (DFT) at the M06-2X/6-311++G(d,p)-SMD(H₂O)//M06-2X/6-31G(d) level of theory.¹⁹ The FMOs of these compounds are shown with their energies in Figure 2.

For alkyne **2**, the FMO energies of the lowest occupied molecular orbital (LUMO) and relevant high-lying occupied molecular orbital (HOMO–1) are –0.6 and –10.2 eV, respectively. For oxanorbornadienes **3** and **4**, the FMO energies are –0.6 eV for the LUMO and –8.1 eV for the HOMO. Transforming the unstrained alkyne **2** into the strained benzooxanorbornadiene lowers the LUMO energy by 0.4 eV and raises the HOMO energy by 2.2 eVs.

Azides are ambiphilic dipoles, possessing both nucleophilic and electrophilic characters.^{20–23} For ambiphilic cycloaddends, both the normal (NED) and inverse (IED) electron-demand FMO interactions play important roles in determining

reactivity. The computed energies of the HOMO and LUMO of azide **1** are –8.1 and –0.6 eV, respectively. The NED and IED energy gaps between **1** and **4** are 8.7 and 9.6 eV, respectively. With **3** as the dipolarophile, the NED and IED FMO energy gaps are significantly smaller at 7.1 and 7.4 eV, respectively. The increased reactivity of the benzooxanorbornadiene scaffold is a result of the 1.6 and 2.2 eV decrease in the NED and IED FMO energy gaps, respectively. This mechanism of activation differs from that of other covalent organocatalysts.²⁴ For example, in iminium catalysis,^{6,25} the conversion of a ketone or aldehyde to an iminium ion lowers both the LUMO and HOMO energies of the substrate.²⁶ The lowering of the HOMO results in fewer stabilizing IED FMO interactions that counteract but do not override the stabilizing effects of a lower LUMO. Here, the conversion of alkyne **2** into a benzooxanorbornadiene raises the HOMO and lowers the LUMO, resulting in NED and IED FMO interactions that are both more stabilizing.

The 1,3-dipolar cycloadditions of **1** with **2**, **3**, and **4** were analyzed with the Distortion/Interaction–Activation Strain model.²⁷ This analysis deconstructs the electronic activation energies into distortion and interaction energies along the intrinsic reaction coordinate (IRC). The distortion energy is

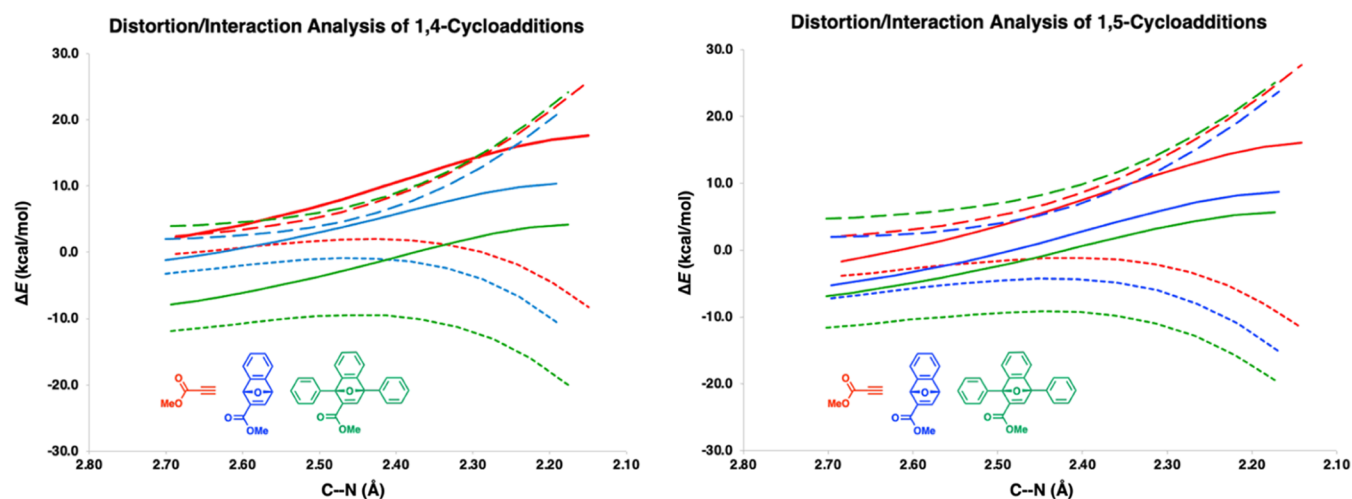


Figure 3. Distortion/interaction analysis for the $[3 + 2]$ dipolar cycloadditions of **1** with dipolarophiles **2** (red), **3**, (green) and **4** (blue). Activation energies, solid lines; distortion energies, long dashes; interaction energies, short dashes. Forming bond lengths are reported in Angstroms starting from reactant complexes. Energies (ΔE) reported at the M06-2X/6-311++G(d,p)-SMD(H_2O)/M06-2X/6-31G(d) level of theory.

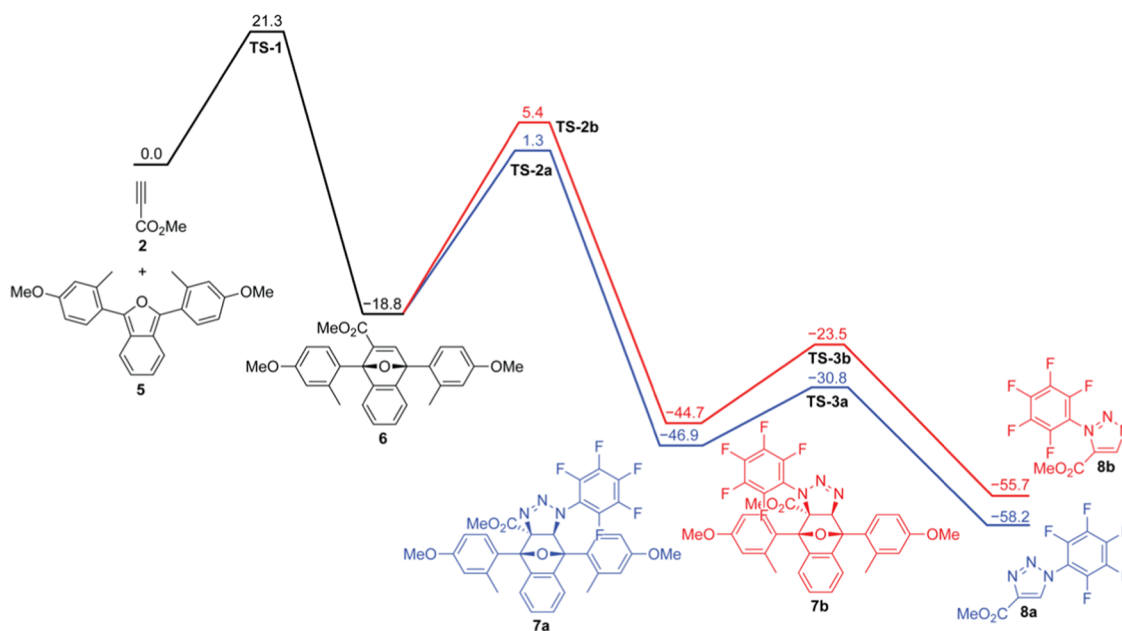


Figure 4. Gibbs free energies (kcal/mol) calculated for the reaction of azide **1** and alkyne **2** catalyzed by isobenzofuran **5** to form 1,4-triazole (**8a**; blue) and 1,5-triazole (**8b**; red).

the energy required to geometrically deform the ground state geometries of the reacting species into transition state geometries. The interaction energy is the energy exchange that arises from the interaction of the reactants during the course of bond formation. The results of the distortion/interaction analysis for the 1,3-dipolar cycloadditions of azide **1** with dipolarophiles **2**–**4** are shown in Figure 3. The distortion energy of the unstrained alkyne, **2**, is similar to that of the strained oxanorbornadienes, **3** and **4**. The increased reactivity of the strained dipolarophiles arises from the interaction energies, which are more stabilizing relative to that of unstrained alkyne **2**.

This additional increase in the reactivity of **3** can be attributed to stabilizing noncovalent aryl–aryl (π -stacking) interactions between a phenyl group of benzooxanorbornadiene **3** and the perfluorophenyl group of **1** in the transition state.²⁸ Electron-donating groups on the phenyl should

strengthen the π -stacking interaction with the electron-deficient aryl group of azide **1** and further enhance both the rate and the regioselectivity of the reaction.

For the isobenzofuran–alkyne and benzooxanorbornadiene–azide click reactions to be mutually orthogonal, the formation of isobenzofuran bisadducts must be prevented. Isobenzofurans bearing *o*-tolyl groups are significantly less reactive toward benzooxanorbornadiene than isobenzofurans bearing unsubstituted phenyl groups.²⁹ The steric clash of the *o*-tolyl groups in both isobenzofuran and the benzooxanorbornadiene cycloadduct significantly inhibits bis-adduct formation.

The ideal organocatalyst for an azide–alkyne cycloaddition would be a 1,3-diphenylisobenzofuran bearing an electron-donating group at the *para* position to optimize the noncovalent π -stacking interactions and a methyl group at the *ortho* position to prevent bis-adduct formation. Figure 4 shows the organocatalytic cycle computed for 1,3-diphenylisobenzofuran.

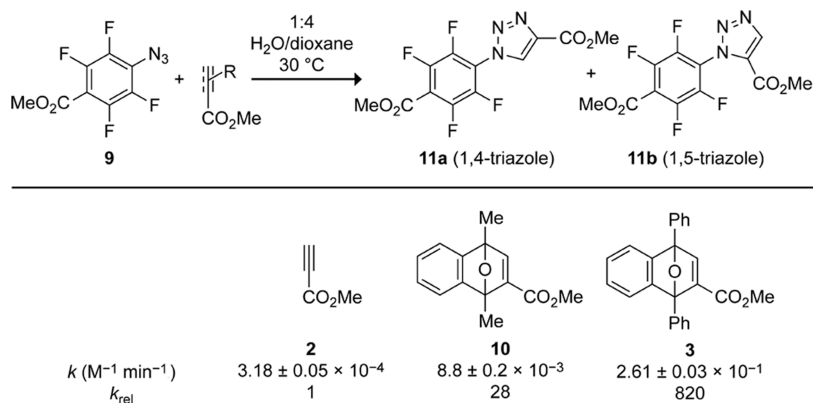


Figure 5. Rate constants for the reactions of azide **9** with dipolarophiles **2**, **10**, and **3**. Triazoles **11a** (which is also accessible with copper catalysis) and **11b** are from the cycloaddition of azide **9** and alkyne **2**.

benzofuran (**5**), which is substituted with *p*-methoxy and *o*-methyl groups on the phenyl rings, and **2**. The initial cycloaddition with **2** to form the oxanorbornadiene cycloadduct (**6**) is predicted to be the rate-determining step, with an activation energy of 21.3 kcal/mol. The reaction of 1,3-diphenylisobenzofuran-oxanorbornadiene cycloadduct **6** with azide **1** can lead to cycloadducts **7a** and **7b**. This cycloaddition determines the regioselectivity of the reaction. The calculations suggest that the reaction will be regioselective for the pathway that leads to the formation of 1,4-triazole (**8a**) with a 4.1 kcal/mol kinetic preference over the formation of 1,5-triazole (**8b**). Moreover, this computed reaction profile suggests that the initial cycloaddition of 1,3-diphenylisobenzofuran **5** with **2** will be the rate-determining step of the organocatalytic cycle.

Isobenzofuran **5** was synthesized by adapting a literature route.^{30,31} The reaction of this isobenzofuran with alkyne **2** in 1:4 H₂O/dioxane at 30 °C proceeded with a rate constant of $(2.57 \pm 0.04) \times 10^{-3}$ M⁻¹ min⁻¹, and the reaction of the product, oxanorbornadiene adduct **6**, with methyl 4-azido-2,3,5,6-tetrafluorobenzoate (**9**) proceeded with a rate constant of $(4.4 \pm 0.1) \times 10^{-1}$ M⁻¹ min⁻¹. (Azide **9** was used because azide **1** was not sufficiently soluble in 1:4 H₂O/dioxane.) The uncatalyzed cycloaddition between alkyne **2** and azide **9** under the same conditions had a rate constant of $(1.06 \pm 0.02) \times 10^{-3}$ M⁻¹ min⁻¹, indicating that the organocatalyst increased the rate of the rate-determining step. Diarylisobenzofurans without *ortho* substitution gave higher rates but at the cost of rapid deactivation by the formation of a bis-adduct (Table S1). No bis-adduct was observed in the reaction with isobenzofuran **5**, indicating that its *o*-methyl groups prevented the formation of an undesired byproduct. The cycloaddition of azide **9** with the propiolate adduct of 1,3-dimethylisobenzofuran (**10**) was faster than the background reaction but slower than the reaction with 1,3-diarylisobenzofuran adducts (Table S1 and Figure 5), consistent with a role for both strain and aryl–aryl interactions in increasing the reaction rate.

Isobenzofuran **5** proved to be competent for promoting the overall cycloaddition of azide **9** and alkyne **2** (Figure 6). With a 20 mol % catalyst loading, we observed a 2.4-fold increase in the initial reaction rate, and the reaction proceeded to complete conversion of the azide without evident deactivation of the catalyst (Figure S1). The rate enhancement increased to 5.3-fold with a 100 mol % catalyst loading, again with no evidence of catalyst deactivation.

Finally, isobenzofuran **5** increased the regioselectivity of the cycloaddition. The uncatalyzed reaction between azide **9** and

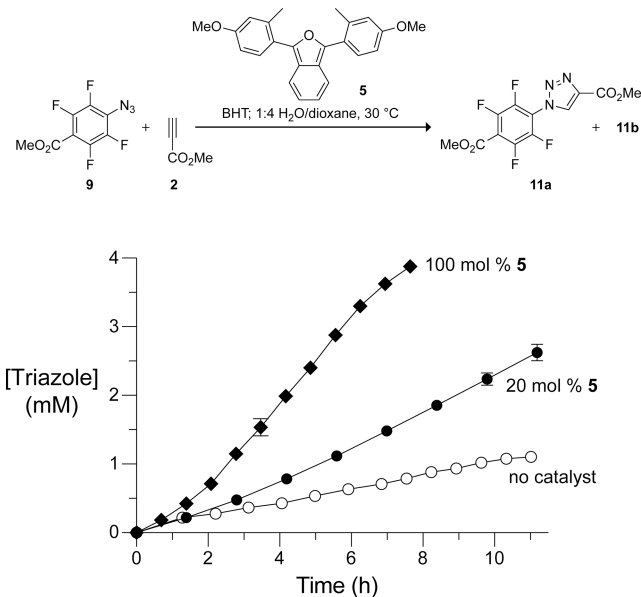


Figure 6. Graph showing the rate of the catalyzed and uncatalyzed cycloaddition of azide **9** (0.040 M) and alkyne **2** (0.22 M) to form triazole regioisomers **11a** and **11b** in 1:4 H₂O/dioxane at 30 °C containing BHT (0.040 M) as an oxygen scavenger. Values are the mean \pm SD for three independent reactions.

alkyne **2** yielded an 83:17 ratio of the 1,4-triazole:1,5-triazole regioisomers (Figure S2). That ratio is similar to the 78:22 ratio for the analogous reaction shown in Scheme 1.¹⁴ In contrast and in accord with calculated energies (Figure 4), organocatalyst **5** produced the 1,4-triazole from **9** and **2** with nearly complete regioselectivity, 96:4 (Figure S3).

In conclusion, we have computationally designed and experimentally validated an organocatalyst for an azide–alkyne cycloaddition. Although the observed rate enhancement for this debut organocatalytic azide–alkyne cycloaddition is modest, isobenzofuran is a competent organocatalyst that is capable of turnover and favors the 1,4-triazole product almost exclusively. Our findings provide a new modality that combines organocatalysis with click chemistry.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.joc.3c02182>.

Computational methods; cartesian coordinates and energies of all optimized structures; experimental procedures; rate constants for the cycloaddition of alkyne **2** with isobenzofurans and corresponding oxanorbornadiene adducts with azide **9** (Table S1); full reaction progress curves for the reaction of alkyne **2** and azide **9** catalyzed by isobenzofuran **5**; representative high-performance liquid chromatography (HPLC) traces for the uncatalyzed reaction of alkyne **2** and azide **9**; representative HPLC traces for the reaction of alkyne **2** and azide **9** catalyzed by isobenzofuran **5** (Figures S1–S3), and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

- (1) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. Click Chemistry: Diverse Chemical Function from a Few Good Reactions. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004–2021.
- (2) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. A Stepwise Huisgen Cycloaddition Process: Copper(I)-Catalyzed Regioselective “Ligation” of Azides and Terminal Alkynes. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599.
- (3) Tornøe, C. W.; Christensen, C.; Meldal, M. Peptidotriazoles on Solid Phase: [1,2,3]-Triazoles by Regiospecific Copper(I)-Catalyzed 1,3-Dipolar Cycloadditions of Terminal Alkynes to Azides. *J. Org. Chem.* **2002**, *67*, 3057–3064.
- (4) Blomquist, A. T.; Liu, L. H. Many-Membered Carbon Rings. VII. Cyclooctyne. *J. Am. Chem. Soc.* **1953**, *75*, 2153–2154.
- (5) Agard, N. J.; Prescher, J. A.; Bertozzi, C. R. A Strain-Promoted [3 + 2] Azide–Alkyne Cycloaddition for Covalent Modification of Biomolecules in Living Systems. *J. Am. Chem. Soc.* **2004**, *126*, 15046–15047.
- (6) List, B.; Lerner, R. A.; Barbas, C. F. Proline-Catalyzed Direct Asymmetric Aldol Reactions. *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.
- (7) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. New Strategies for Organic Catalysis: The First Highly Enantioselective Organocatalytic Diels–Alder Reaction. *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244.
- (8) Berson, J. A. Reactions of 1,3-Diphenylisobenzofuran with Acetylenic Dienophiles. *J. Am. Chem. Soc.* **1953**, *75*, 1240–1241.
- (9) Matheson, R. A. F.; McCulloch, A. W.; McInnes, A. G.; Smith, D. G. Photochemistry of 1,4-Diphenyl-1,4-Epoxy-1,4-Dihydronaphthalene 2-Carboxylate and 2,3-Dicarboxylate Esters. *Can. J. Chem.* **1977**, *55*, 1422–1432.
- (10) Pichon, N.; Harrison-Marchand, A.; Mailliet, P.; Maddaluno, J. Diastereoselective Syntheses of New Analogues of the Farnesyltransferase Inhibitor RPR 130401. *J. Org. Chem.* **2004**, *69*, 7220–7227.
- (11) Narayanan, P.; Sethusankar, K.; Nandhakumar, M.; Mohanakrishnan, A. K. Ethyl 1,3,10,12-Tetra-Phenyl-19,20-Dioxahexa-Cyclo-[10.6.1.1.0.0.0]icosa-4(9),5,7,13(18),14,16-Hexa-Ene-2-Carboxyl-Ate. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2010**, *66*, No. o3155.
- (12) Fišera, L.; Pavlovič, D. 1,3-Dipolar Cycloadditions to 2,3-Dimethoxycarbonyl-7-oxabicyclo[2,2,1]-2,5-Heptadiene, 1,4-Epoxy-1,4-Dihydronaphthalene, and Exo-Endo-1,6-Dimethoxycarbonyl-11,12-Dioxatetracyclo-[4,4,0,12,5,17,10]-3,8-Dodecadiene. *Collect. Czech. Chem. Commun.* **1984**, *49*, 1990–2000.
- (13) van Berkel, S. S.; Dirks, A. (T.) J.; Debets, M. F.; van Delft, F. L.; Cornelissen, J. J. L. M.; Nolte, R. J. M.; Rutjes, F. P. J. T. Metal-Free Triazole Formation as a Tool for Bioconjugation. *ChemBioChem* **2007**, *8*, 1504–1508.
- (14) Kloss, F.; Köhn, U.; Jahn, B. O.; Hager, M. D.; Görls, H.; Schubert, U. S. Metal-Free 1,5-Regioselective Azide–Alkyne [3 + 2]-Cycloaddition. *Chem. - Asian J.* **2011**, *6*, 2816–2824.
- (15) Wannere, C. S.; Paul, A.; Herges, R.; Houk, K. N.; Schaefer, H. F., 3rd; von Ragué Schleyer, P. The Existence of Secondary Orbital Interactions. *J. Comput. Chem.* **2007**, *28*, 344–361.
- (16) Levandowski, B. J.; Hamlin, T. A.; Bickelhaupt, F. M.; Houk, K. N. Role of Orbital Interactions and Activation Strain (Distortion Energies) on Reactivities in the Normal and Inverse Electron-Demand Cycloadditions of Strained and Unstrained Cycloalkenes. *J. Org. Chem.* **2017**, *82*, 8668–8675.
- (17) Levandowski, B. J.; Svatoněk, D.; Sohr, B.; Mikula, H.; Houk, K. N. Secondary Orbital Interactions Enhance the Reactivity of Alkynes in Diels–Alder Cycloadditions. *J. Am. Chem. Soc.* **2019**, *141*, 2224–2227.
- (18) Hamlin, T. A.; Levandowski, B. J.; Narsaria, A. K.; Houk, K. N.; Bickelhaupt, F. M. Structural Distortion of Cycloalkynes Influences Cycloaddition Rates Both by Strain and Interaction Energies. *Chem. - Eur. J.* **2019**, *25*, 6342–6348.
- (19) Zhao, Y.; Truhlar, D. G. The M06 Suite of Density Functionals for Main Group Thermochemistry, Thermochemical Kinetics, Noncovalent Interactions, Excited States, and Transition Elements: Two New Functionals and Systematic Testing of Four M06-Class Functionals and 12 Other Functionals. *Theor. Chem. Acc.* **2008**, *120*, 215–241.
- (20) Sustmann, R. A Simple Model for Substituent Effects in Cycloaddition Reactions. I. 1,3-Dipolar Cycloadditions. *Tetrahedron Lett.* **1971**, *12*, 2717–2720.

- (21) Sustmann, R.; Trill, H. Substituent Effects in 1,3-Dipolar Cycloadditions of Phenyl Azide. *Angew. Chem., Int. Ed.* **1972**, *11*, 838–840.
- (22) Geittner, J.; Huisgen, R.; Sustmann, R. Kinetics of 1,3-Dipolar Cycloaddition Reactions of Diazomethane; A Correlation with HOMO–LUMO Energies. *Tetrahedron Lett.* **1977**, *18*, 881–884.
- (23) Chen, P.-P.; Ma, P.; He, X.; Svatunek, D.; Liu, F.; Houk, K. N. Computational Exploration of Ambiphilic Reactivity of Azides and Sustmann's Paradigmatic Parabola. *J. Org. Chem.* **2021**, *86*, 5792–5804.
- (24) Hamlin, T. A.; Bickelhaupt, F. M.; Fernández, I. The Pauli Repulsion-Lowering Concept in Catalysis. *Acc. Chem. Res.* **2021**, *54*, 1972–1981.
- (25) Erkkilä, A.; Majander, I.; Pihko, P. M. Iminium Catalysis. *Chem. Rev.* **2007**, *107*, 5416–5470.
- (26) Vermeeren, P.; Hamlin, T. A.; Fernández, I.; Bickelhaupt, F. M. Origin of Rate Enhancement and Asynchronicity in Iminium Catalyzed Diels–Alder Reactions. *Chem. Sci.* **2020**, *11*, 8105–8112.
- (27) Bickelhaupt, F. M.; Houk, K. N. Analyzing Reaction Rates with the Distortion/Interaction-Activation Strain Model. *Angew. Chem., Int. Ed.* **2017**, *56*, 10070–10086.
- (28) Wheeler, S. E.; McNeil, A. J.; Müller, P.; Swager, T. M.; Houk, K. N. Probing Substituent Effects in Aryl–Aryl Interactions Using Stereoselective Diels–Alder Cycloadditions. *J. Am. Chem. Soc.* **2010**, *132*, 3304–3311.
- (29) Eda, S.; Eguchi, F.; Haneda, H.; Hamura, T. A New Synthetic Route to Substituted Tetracenes and Penacenes via Stereoselective [4 + 2] Cycloadditions of 1,4-Dihydro-1,4-Epoxy-naphthalene and Isobenzofuran. *Chem. Commun.* **2015**, *51*, 5963–5966.
- (30) Einhorn, J.; Benderradji, F.; Nechab, M.; Einhorn, C. A Single-Step Synthesis of Symmetrical 1,3-Diaryl-isobenzofurans. *Synlett* **2006**, *2006*, 2035–2038.
- (31) Fukase, K.; Doi, T. *Middle Molecular Strategy: Flow Synthesis to Functional Molecules*; Springer Nature, 2021.