

Net Intermolecular Silyloxypyrrone-Based (5+2) Cycloadditions Utilizing Amides as Enabling and Cleavable Tethers

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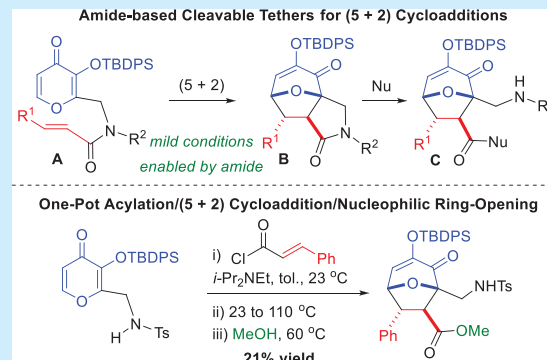


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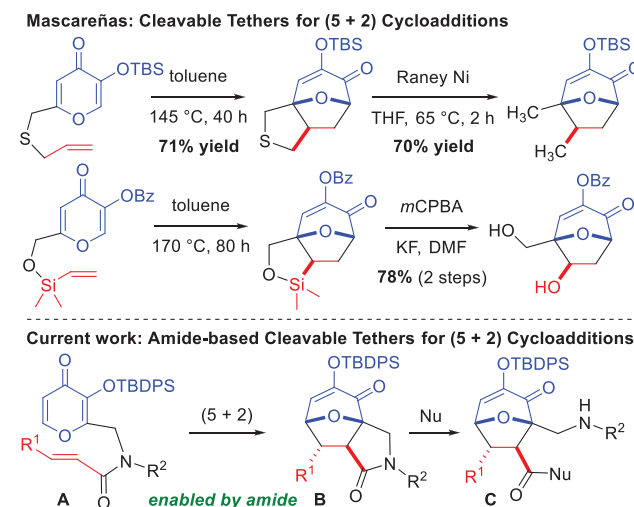
ABSTRACT: Silyloxypyrrone-based (5+2) cycloadditions were facilitated by amides that allowed for increased reactivity and a pathway for cleaving the tether to afford net intermolecular cycloadducts. Various amides underwent facile cycloaddition, and several experiments revealed steric and electronic factors that accelerate the reaction. *tert*-Butyl amides reacted faster than less hindered variants in multiple cases. In the case of dearomative oxidopyrylium-indole (5+2) cycloadditions, an amine-based tether was ineffective, whereas amides enabled this powerful transformation. Theoretical calculations evidenced a concerted asynchronous reaction in which the amide facilitates a conformational driving force enabling cycloaddition. Finally, a one-pot acylation/(5+2) cycloaddition/nucleophilic lactam opening and other examples of tosyl lactam opening of a modified cycloadduct were demonstrated.



Intermolecular cycloadditions¹ afford straightforward access to complex, three-dimensional products with excellent atom economy.² However, entropic factors often contribute to substantial regio- and stereoselectivity deficiencies. Though intramolecular variants lack the same entropic problems and often give high selectivity, these reactions are necessarily limited by the need for a specific tether. One elegant strategy for overcoming these limitations is to utilize a temporary tether that can be cleaved upon successful cycloaddition.³ This has previously been accomplished with oxidopyrylium-based (5+2) cycloadditions⁴ utilizing sulfur and silicon tethers⁵ (Scheme 1, Mascareñas) and applied in attempts to synthesize the arteminolide natural products.⁶ Although these silyloxypyrrone variants required vigorous heating for long reaction times,⁵ the tether was subsequently cleaved to afford cycloadducts that could not have been accessed by the direct intermolecular approach. Herein, we report amide-based tethers (Scheme 1, this work) that enable milder construction of novel cycloadducts with potential for ring opening of the resulting lactams.⁷

An initial investigation of PMB amide-tethered (5+2) cycloadditions utilized heating in toluene at 110 °C (Scheme 2) to ensure complete conversion, although reactivity was observed at lower temperatures. Styrenyl-substituted amides **1a–c** delivered cycloadducts **2a–c**, respectively, in good yields, and amides **1d** and **1e** were slightly less efficient. Ester-substituted amide **1f** afforded cycloadduct **2f** in excellent yield, and the reaction proceeded with complete conversion in only 30 min. Other variants afforded good to excellent yields of cycloadducts **2g–i**. Using cinnamyl-derived amides **1j–r**,

Scheme 1. (5+2) Cycloadditions That Utilize Cleavable Tethers en Route to Net Intermolecular Products

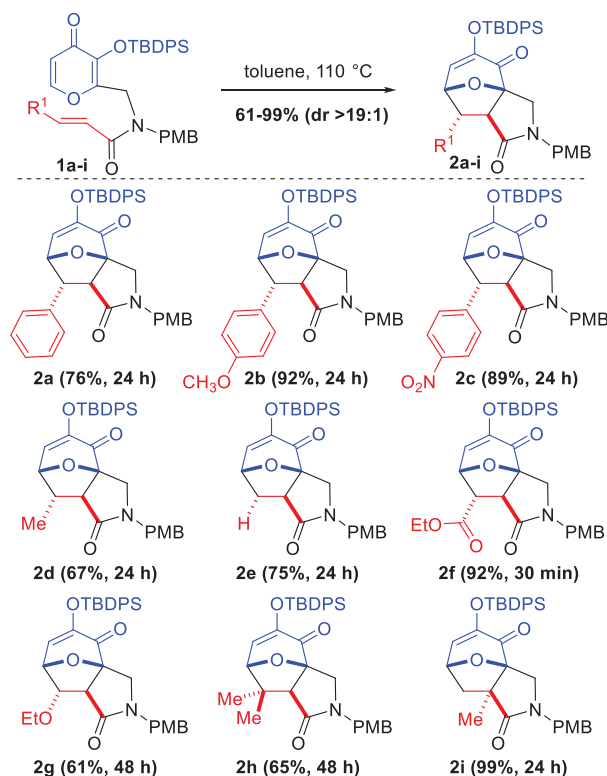


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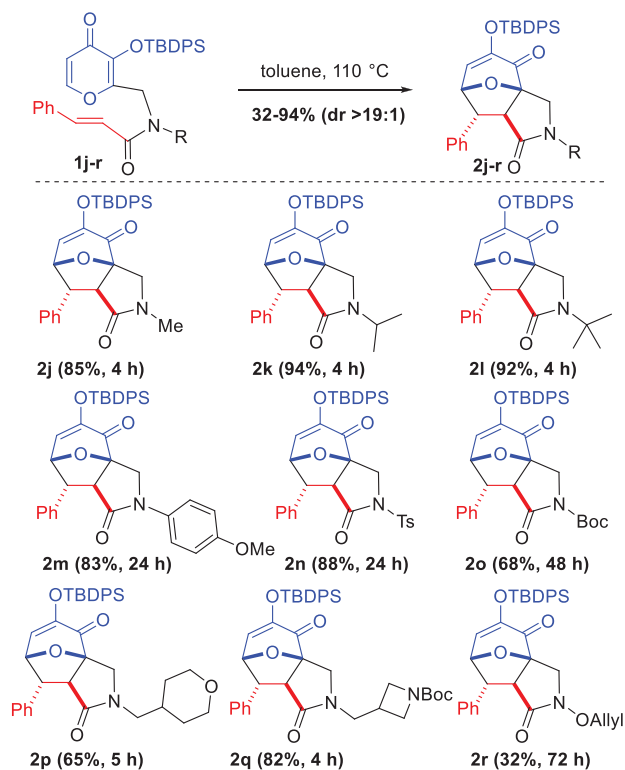
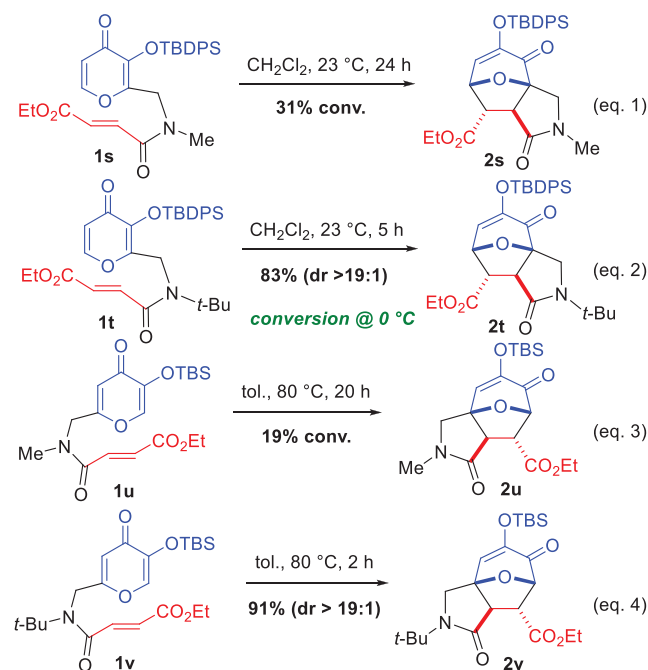
Scheme 2. (5+2) Cycloadditions with PMB Amides



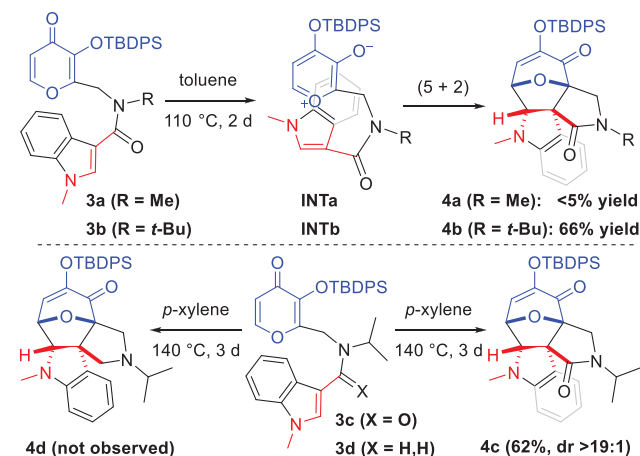
variation of the substituent on nitrogen delivered cycloadducts 2j–r, respectively, in generally good yields (Scheme 3).

To further probe this amide-based (5+2) cycloaddition, a series of experiments were designed (Schemes 4 and 5). First,

Scheme 3. (5+2) Cycloadditions with Various Cinnamides

Scheme 4. Comparison of Methyl and *tert*-Butyl Amides 1s–v

Scheme 5. Dearomative Oxidopyrylium-indole (5+2) Cycloadditions Enabled by Amides 3a–c

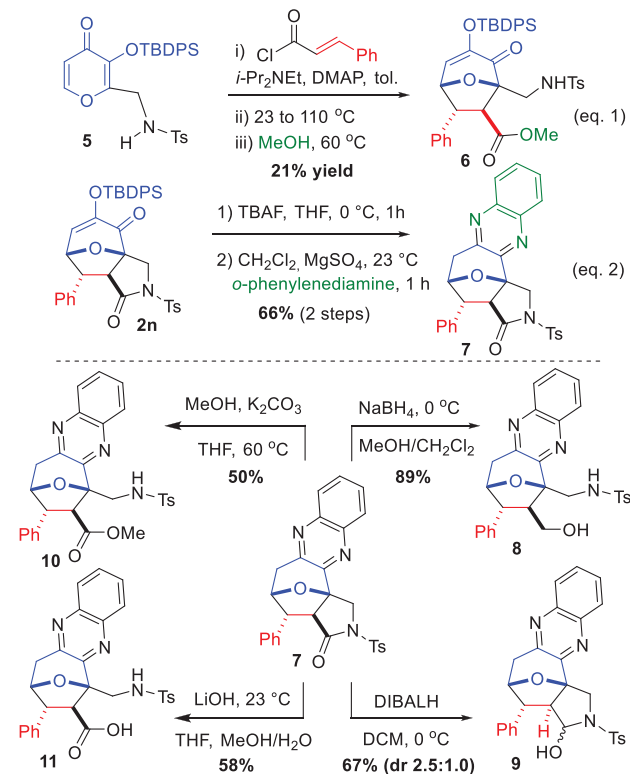


methyl amide 1s was stirred at room temperature in CH_2Cl_2 for 24 h to give 31% conversion to cycloadduct 2s (Scheme 4, eq 1). Even more striking was the fact that *tert*-butyl amide 1t gave complete conversion in < 5 h because the yield of 2t includes acylation of the amine⁸ (Scheme 4, eq 2). In fact, conversion to adduct 2t was observed at 0 °C.⁹ Comparison to the intramolecular Diels–Alder cycloaddition is quite informative. Whereas *tert*-butyl acrylamides tethered to furans afforded cycloadducts spontaneously upon acylation at room temperature,¹⁰ examples of less hindered amides in similar systems required refluxing to achieve cycloaddition.¹¹ Amides derived from kojic acid are far less reactive than those derived from maltol in general, but a similar trend was observed with significant acceleration of *tert*-butyl amide 1v as compared to methyl amide 1u (Scheme 4, eqs 3 and 4). Compared to similar systems with carbon tethers,¹² amides 1s–v are significantly more reactive. Next, dearomative oxidopyrylium-

indole (5+2) cycloadditions¹³ were investigated (Scheme 5). Whereas *N*-Me amide **3a** gave only trace conversion at 110 °C, *tert*-butyl amide **3b** afforded 66% yield. When heated to 150 °C, *N*-Me amide **3a** gave an only 10% yield with significant decomposition,⁸ further illustrating the positive effect of steric bulk on the amide. Isopropyl amide **3c** delivered the desired cycloadduct **4c** in 62% yield with increased heating, but amine **3d** gave no cycloadduct **4d** under identical conditions.¹⁴ Previous work by Li¹³ on carbon-tethered systems utilized the preactivation conditions developed by Wender.¹⁵

For the goal of net intermolecular cycloaddition, amine **5** was subjected to a one-pot acylation/(5+2) cycloaddition/nucleophilic lactam opening, albeit in modest yield to afford cycloadduct **6** (Scheme 6, eq 1). Desilylation plagued this

Scheme 6. Ring Opening of Tosyl Lactams



reaction, and a significant excess of the nucleophile (i.e., MeOH) was required; therefore, the silyl enol ether was converted into quinoxaline¹⁶ **7** (eq 2) to directly investigate the propensity for ring opening of the tosyl lactam. To that end, NaBH₄ afforded alcohol **8** in excellent yield, and half-reduction with DIBAL-H was also effective. Treatment with MeOH/K₂CO₃ gave ester **10** in 50% yield, and carboxylic acid **11** was obtained in 58% yield with LiOH. It should be noted that the corresponding PMB lactam did not undergo ring opening, thus providing evidence for the electron-withdrawing tosyl facilitating this reaction.

A detailed computational study was undertaken to investigate these amide-tethered cycloadditions in comparison to previous carbon-tethered variants.^{9,17} Initial conformational searches were carried out using CREST,¹⁸ and subsequent DFT calculations were carried out with Gaussian16.¹⁹ The M06-2X functional with D3(0) dispersion correction²⁰ was used to locate stationary points, because this functional is known to perform well for main group thermochemistry and

kinetic studies.²¹ We employed a 6-31G(d) basis set and the SMD continuum solvation model for geometry optimizations.²² The larger 6-311G(d,p) basis set was used to compute single-point energies. Reported Gibbs free energies include thermal corrections from frequency calculations at the M06-2X-D3(0)/6-31G(d) level.⁸ Slight modifications were made to structures (i.e., TBS and methyl ester) to simplify the calculations. The overall barrier via rate-determining concerted asynchronous (5+2) cycloaddition for amide ester **1t'** was predicted to be only 19.7 kcal/mol (Figure 1a), which

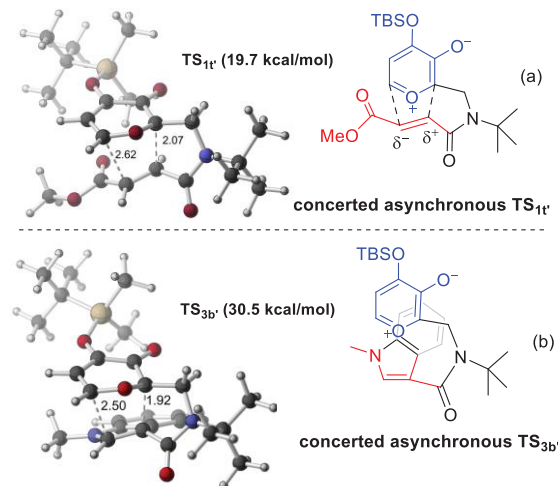


Figure 1. (a) TS for concerted asynchronous (5+2) cycloaddition of amide **1t'**. (b) TS for concerted asynchronous (5+2) cycloaddition of amide **3b'**.

correlates to experimental results in which conversion was observed at 0 °C (cf. Scheme 4, eq 2). In contrast, the dearomative oxidopyrylium-indole (5+2) cycloaddition of amide **3b'** was predicted to have a barrier of 30.5 kcal/mol (Figure 1b), which is also in line with experimental results that required heating for an extended time but was faster than that of less hindered variants (cf. Scheme 5). In fact, as the steric hindrance increases from Me to *i*-Pr to *t*-Bu, the energy barrier decreases (34.0, 31.9, and 30.5 kcal/mol, respectively). We compared key geometric parameters for both reactants and TS2.⁸ For example, while methyl substitution allows C–N–C bond angles of 124° in the reactant and 118° in TS2, angles of 114–115° are enforced for both structures with a *tert*-butyl substituent. We attribute this constraint to steric repulsion exerted by bulky *tert*-butyl groups. The fact that the angle is the smallest and nearly identical in both the reactant and TS2 indicates that the *tert*-butyl group enforces a productive conformation with the pyrone. In addition, the steric hindrance has an impact on the π -conjugation of the amide group. Regardless of the substituent, the C–N bond length decreases and the C–N–C–O dihedral angle approaches 180° as the reaction proceeds, which is consistent with an increased level of amide conjugation during cycloaddition. The *tert*-butyl has the strongest effect on conjugation as the reaction proceeds, because it is the least conjugated in the reactant based on these structural criteria.⁸

Amide-tethered silyloxypyryone-based (5+2) cycloadditions demonstrated both enabling reactivity and the propensity to be cleaved to form net intermolecular products that are otherwise inaccessible. A variety of amides were constructed and smoothly underwent cycloaddition. The amide functionality

in general enables efficient cycloaddition with increased steric bulk (i.e., *tert*-butyl) accelerating the process. In the case of a dearomative oxidopyrylium-indole (5+2) cycloaddition, the amide quite drastically enables the reaction, whereas the corresponding amine is ineffective. Theoretical calculations indicate that although the rate-determining cycloaddition is concerted, it is asynchronous. Finally, ring opening of tosyl lactams was used to demonstrate the feasibility of a net intermolecular process.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its [Supporting Information](#).

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.3c02635>.

Experimental section ([PDF](#))

Spectra ([PDF](#))

Theoretical background ([PDF](#))

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Notes

The authors declare no competing financial interest.

■ REFERENCES

- (1) (a) Nishiwaki, N. *Methods and Applications of Cycloaddition Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2014. (b) Kobayashi, S.; Jørgensen, K. A. *Cycloaddition Reactions in Organic Chemistry*; Wiley-VCH: Weinheim, Germany, 2002. (c) Caruthers, W. *Cycloaddition Reactions in Organic Chemistry*, Vol. 8; Tetrahedron Organic Chemistry; Pergamon: Oxford, U.K., 1990.
- (2) Trost, B. M. The Atom Economy – The Search for Synthetic Efficiency. *Science* **1991**, *254*, 1471–1477.
- (3) (a) Gauthier, D. R.; Zandi, K. S.; Shea, K. J. Disposable Tethers in Synthetic Organic Chemistry. *Tetrahedron* **1998**, *54*, 2289–2338. (b) Bols, M.; Skrydstrup, T. Silicon-Tethered Reactions. *Chem. Rev.* **1995**, *95*, 1253–1277.
- (4) (a) Bejcek, L. P.; Murelli, R. P. Oxidopyrylium (5+2) cycloaddition chemistry: Historical Perspective and recent advances (2008–2018). *Tetrahedron* **2018**, *74*, 2501–2521. (b) Singh, V.; Murali Krishna, U.; Vikrant, V.; Trivedi, G. K. Cycloaddition of oxidopyrylium species in organic synthesis. *Tetrahedron* **2008**, *64*, 3405–3428. (c) Mascareñas, J. L. The (5+2) Cycloaddition Chemistry of β -Alkoxy- γ -pyrones. *Advances in Cycloaddition* **1999**, *6*, 1–54.
- (5) Rumbo, A.; Castedo, L.; Mourino, A.; Mascareñas, J. L. Temporary Tethering Strategies for [5+2] Pyrone-Alkene Cycloadditions. *J. Org. Chem.* **1993**, *58*, 5585–5586.
- (6) Sohn, J.-H. Silicon-Tethered Intramolecular [5+2] Oxidopyrylium-Based Cycloaddition and Reductive Cleavage of Ether Bridge: Synthetic Studies Toward Arteminolides. *Bull. Korean Chem. Soc.* **2014**, *35*, 23–24.
- (7) (a) Gao, P.; Rahman, M. M.; Zamalloa, A.; Feliciano, J.; Szostak, M. Classes of Amides that Undergo Selective N–C Amide Bond Activation: The Emergence of Ground-State Destabilization. *J. Org. Chem.* **2022**, DOI: [10.1021/acs.joc.2c01094](https://doi.org/10.1021/acs.joc.2c01094). (b) Caruano, J.; Muccioli, G. G.; Robiette, R. Biological active γ -lactam: synthesis and natural sources. *Org. Biomol. Chem.* **2016**, *14*, 10134–10156.
- (8) See the [Supporting Information](#).
- (9) Youman, A. J.; Rokey, S. N.; Grabowski, J. P.; Guo, W.; Sun, Q.; Angles, S. N.; Goodell, J. R.; Tantillo, D. J.; Mitchell, T. A. Experimental and Theoretical Investigation of the Synchronicity of Ambident Silyloxypyrrone-Based (5+2) Cycloadditions. *J. Org. Chem.* **2023**, *88*, 5972–5981.
- (10) Fulgheri, T.; Cornwall, P.; Turner, A. R.; Sweeney, J. B.; Gill, D. M. Parallel Kinetic Resolution of Intramolecular Furan Diels-Alder Cycloadducts via Asymmetric Hydroboration. *Eur. J. Org. Chem.* **2019**, *2019*, 7223–7227.
- (11) Lin, Y.-T.; Lin, R.-Y.; Isobe, M. Novel Synthesis of the ABC Rings of Solanoelepin A. *Org. Lett.* **2014**, *16*, 5948–5951.
- (12) Bulandr, J. J.; Grabowski, J. P.; Law, C. M.; Shaw, J. L.; Goodell, J. R.; Mitchell, T. A. Investigation of Transfer Group, Tether Proximity, and Alkene Substitution for Intramolecular Silyloxypyrrone-Based (5+2) Cycloadditions. *J. Org. Chem.* **2019**, *84*, 10306–10320.
- (13) Mei, G.; Yuan, H.; Gu, Y.; Chen, W.; Chung, L. W.; Li, C.-C. Dearomative Indole [5+2] Cycloaddition Reactions: Stereoselective Synthesis of Highly Functionalized Cyclohepta[b]indoles. *Angew. Chem., Int. Ed.* **2014**, *53*, 11051–11055.
- (14) The corresponding *tert*-butyl amine could not be accessed via reductive amination.
- (15) (a) Wender, P. A.; Mascareñas, J. L. Studies on Tumor Promoters. 11. A New [5+2] Cycloaddition Method and Its Application to the Synthesis of BC Ring Precursors of Phoboids. *J. Org. Chem.* **1991**, *56*, 6267–6269. (b) Wender, P. A.; Mascareñas, J.

L. Preparation and Cycloadditions of a 4-Methoxy-3-Oxidopyrylium Ylid: A Reagent for the Synthesis of Highly Substituted Seven-membered Rings and Tetrahydrofurans. *Tetrahedron Lett.* **1992**, 33, 2115–2118.

(16) Foley, D. J.; Craven, P. G. E.; Collins, P. M.; Doveston, R. G.; Aimon, A.; Talon, R.; Churcher, I.; von Delft, F.; Marsden, S. P.; Nelson, A. Synthesis and Demonstration of the Biological Relevance of sp^3 -rich Scaffolds Distantly Related to Natural Product Frameworks. *Chem. - Eur. J.* **2017**, 23, 15227–15232.

(17) Corrie, S. I.; Pearce, A. C.; Grabowski, J. P.; Randolph, K. A.; Guo, W.; Tantillo, D. J.; Mitchell, A. T. Boron-tethered oxidopyrylium-based (5+2) cycloadditions. *Tetrahedron Lett.* **2022**, 107, 154094.

(18) Grimme, S. Exploration of Chemical Compound, Conformer, and Reaction Space with Meta-Dynamics Simulations Based on Tight-Binding Quantum Chemical Calculations. *J. Chem. Theory Comput.* **2019**, 15, 2847–2862.

(19) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. *Gaussian 16*, rev. A.03; Gaussian, Inc.: Wallingford, CT, 2016.

(20) Grimme, S. Density functional theory with London dispersion corrections. *WIREs Comput. Mol. Sci.* **2011**, 1, 211–228.

(21) (a) 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. (b) Zhao, Y.; Truhlar, D. G. Construction of a generalized gradient approximation by restoring the density-gradient expansion and enforcing a tight Lieb–Oxford bound. *J. Chem. Phys.* **2008**, 128, 184109–184118. (c) Vermeeren, P.; Dalla Tiezza, M.; Wolf, M. E.; Lahm, M. E.; Allen, W. D.; Schaefer, H. F., III; Hamlin, T. A.; Bickelhaupt, F. M. Pericyclic reaction benchmarks: hierarchical computations targeting CCSDT(Q)/CBS and analysis of DFT performance. *Phys. Chem. Chem. Phys.* **2022**, 24, 18028–18042.

(22) (a) Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. Self-consistent molecular orbital methods. XX. A basis set for correlated wave functions. *J. Chem. Phys.* **1980**, 72, 650–654. (b) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielectric Constant and Atomic Surface Tensions. *J. Phys. Chem. B* **2009**, 113, 6378–6396.