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DFT and Experimental Exploration of Intramolecular [2 + 2 + 2] Cycloaddition of Oxanorbornadienedicarboxylates and Analogues

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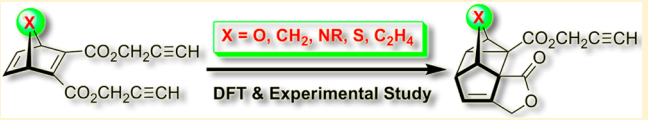
Supporting Information

ABSTRACT: The facile intramolecular [2 + 2 + 2] homo-Diels–Alder cycloadditions of oxanorbornadienedicarboxylates and analogues have been investigated by theoretical calculations using B3LYP and M06-2X density functional methods and experimental confirmation. The oxanorbornadienedicarboxylates formed from furans and but-2-ynedioates undergo the resulting intramolecular [2 + 2 + 2] cycloaddition in a concerted but asynchronous fashion, requiring energy barriers of about 30 kcal/mol to construct five- and three-membered rings simultaneously. Bridgehead substitutents have little influence on the regioselectivity, whereas 5-substitutents involving steric hindrance or electron-acceptor groups are predicted to attenuate the cycloaddition at the substituted side. Furthermore, the linker length, unsaturated bonds, and bridge-ring size are very sensitive to the cyclization rate. Additionally, aza- and norbornadienedicarboxylates demonstrate less reactivity, while thionorbornadienedicarboxylates show more reactivity with the challenge of their synthesis. The intermolecular version was also evaluated in comparison with the intramolecular version. Finally, our experimental tests verified the calculational prediction of the regioselectivity and reactivity.

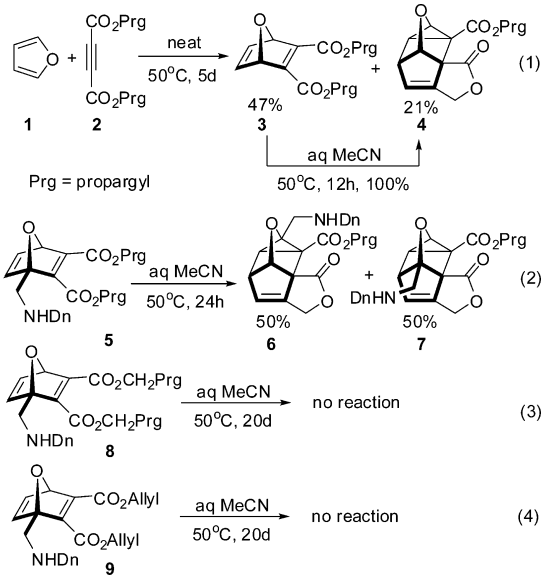


INTRODUCTION

Oxanorbornadienedicarboxylates (ONDs) have attracted considerable attention in the realm of biochemistry because of their powerful ability of fluorogenic probes for the labeling of proteins. The unique feature of ONDs is the electrophilicity of a maleate moiety embedded in a homoconjugated bicycle, which turns out to be realized with the Diels–Alder (D–A) cycloaddition of another molecule of furan,[1] the nucleophilic addition of organic azides[2] and aliphatic thiols,[3] and quenching a pendant dansyl fluorophore via photoinduced electron transfer.[4] In addition, the reactivity and stability of OND reagents have also been reported with the degradation pathways including the saponifications and intra-/intermolecular conjugative addition, followed by retro-D–A cleavage.[5]

In addition to the above D–A cycloaddition, hydrolysis, Michael addition, and retro-D–A reaction pathways, a facile and efficient intramolecular [2 + 2 + 2] homo-Diels–Alder cycloaddition of propargylic OND esters in polar media was encountered by Finn and co-workers during exploration of their reactivity and stability (Scheme 1).[5] OND ester **3** was generated in situ from furan (**1**) and dipropargyl but-2-ynedioate (**2**), along with γ-lactone product **4**, which can be converted quantitatively from OND ester **3** (Scheme 1, eq 1). In the case of unsymmetric OND ester **5** that possesses a substituent at one of the bridgehead carbon atoms, the cycloaddition was accomplished in an excellent yield without any regioselectivity (Scheme 1, eq 2). Nonetheless, OND ester **8** with the additional linker length cannot deliver the expected δ-lactone product, even with a prolonged reaction time (Scheme 1, eq 3). Likewise, the cyclization of OND ester **9** involving the allyl moiety cannot take place with a prolonged reaction time (Scheme 1, eq 4).

Scheme 1. Reported Intramolecular [2 + 2 + 2] Cycloadditions of Oxanorbornadienedicarboxylates



The metal-free intramolecular [2 + 2 + 2] cycloadditions of triynes have been widely studied by Ley et al.,[6] Roglans et al.,[7] and Danheiser et al.[8] and investigated theoretically by our[9] and

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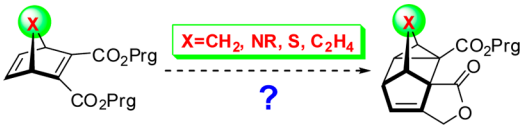
Houk's groups.[10] To the best of our knowledge, this facile and novel intramolecular [2 + 2 + 2] cycloaddition of dienynes is a new potential methodology to construct complex hemibasketanes, first discovered by Finn's group in 2011, without an in-depth mechanistic investigation. The origins of the regioselectivity and reactivity are still unclear and await further studies. Alternatively, we wonder whether oxanorbornadienedicarboxylates could be expanded to their analogues, such as aza-, thio-, norbornadienedicarboxylates and bicyclo[2.2.1]hepa-2,5-dienedicarboxylates to undergo the intramolecular [2 + 2 + 2] cycloaddition (Scheme 2). Herein, we focus on the

Scheme 2. Proposed Aza-, Thio-, and Norbornadienedicarboxylates and Bicyclo[2.2.1]hepa-2,5-dienedicarboxylates for Intramolecular [2 + 2 + 2] Cycloaddition



unraveling mechanism of the cycloaddition, in particular concerned about the regioselectivity and reactivity. Moreover, on the basis of the DFT calculations, we hope to design norbornadienedicarboxylates and analogues to realize the cycloaddition experimentally. These findings will not only provide a good understanding on this novel [2 + 2 + 2] cycloaddition at the molecular level but also guide further rational design of new active norbornadienedicarboxylates for the cycloaddition, while inert norbornadienedicarboxylates are more useful for use as stable fluorogenic probes.

COMPUTATIONAL METHODS

All optimized geometries were calculated at the DFT B3LYP level[11] with the 6-311+G(d,p) basis set for all atoms with the Gaussian 09 suite of programs.[12] Frequency calculations at the B3LYP level at 298 K were performed to confirm each stationary point to be either a minimum or a transition structure. Single-point energies based on the structures obtained at the B3LYP level using the same basis set were obtained by the M06-2X calculations in order to take the dispersion energies into consideration.[13] Solvation energies were evaluated at the M06-2X level by a self-consistent reaction field (SCRF) using the CPCM model, where UFF radii were used. The combined method has been used recently in calculations of cycloadditions by Houk[10,14] and justified in Table S1 (Supporting Information). The reported energies are Gibbs free energies in water or acetonitrile solution (ΔG_{H2O} or ΔG_{MeCN}), Gibbs free energies (ΔG), and zero-point energy-corrected enthalpies (ΔH). Frontier molecular orbital (FMO) analyses for the cycloaddition were also employed at the HF/6-31G(d) level with the former optimized structures.[15] Figures 2 and 4 were prepared using CYLView.[16]

RESULTS AND DISCUSSION

DFT Investigation. *1. Mechanism of the Tandem D–A and Intramolecular [2 + 2 + 2] Cycloadditions.* We provide the whole potential energy profile of the tandem cycloaddition process in Figure 1 and various conformers of species with small differences in energy in Figures S1–S4 (Supporting Information). The general mechanism shows that the first step of the cascade reaction corresponding to the D–A cycloaddition proceeds via the transition state **TS1** with an activation free energy of 27.1 kcal/mol in a concerted but significantly asynchronous fashion, and both the diene and dienophile

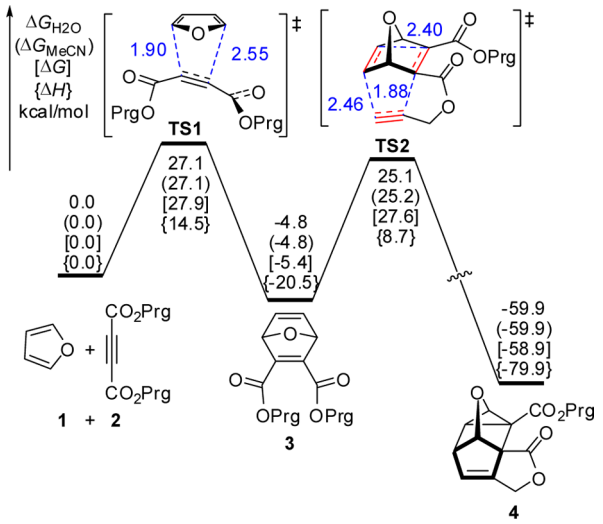


Figure 1. Potential energy profile of the tandem cycloaddition reaction of **1** with **2** (the blue numbers are forming bond distances).

appear to be symmetrical.[17,18] The formation of the D–A adduct **3** is exergonic by 4.8 kcal/mol. The subsequent step is intramolecular [2 + 2 + 2] cycloaddition with an activation free energy of 29.9 kcal/mol in water (30.0 kcal/mol in MeCN). The three forming C–C bond distances in **TS2** are 2.40, 2.46, and 1.88 Å, respectively, indicating that the cycloaddition occurs in a concerted but asynchronous fashion as well to construct the novel structure of hemibasketane. The thermodynamic stable product **4** lies 59.9 kcal/mol below the substrates. Reviewing the whole energy profiles, we found that the energies in water and MeCN are very close. Solvation has small impact on the D–A cycloaddition, with a remarkable effect on the [2 + 2 + 2] cycloaddition.

2. Substituent Effect on the Regioselectivity. In the previous experiments, OND ester **5** shows no regioselectivity in the intramolecular [2 + 2 + 2] cycloaddition, which enhances the difficulty in the separation of products, even somewhat limits the application of this novel strategy. Therefore, we are interested in unraveling which substituents would affect the regioselectivity (Figure 2). First, the simple model of 1-methyl-substituted OND ester **5′** was examined. It is expected that the transition structure **TS3-H** resembles **TS3-Me** and both required activation free energies are very close. The slight difference is qualitatively consistent with the experimentally observed poor regioselectivity.

Furthermore, the model of 5-methyl-substituted OND ester was subjected to further investigation into the regioselectivity. It is interesting to discover that the 5-methyl-substituted OND ester was predicted to demonstrate good regioselectivity at the unsubstituted side since the **TS4-H** is favored by 4.3 kcal/mol in free energy relative to **TS4-Me**. The origin of this vantage can be understood on the basis of the difference in steric interactions between the 5- and 6-positions. We had envisioned that the substituents on the terminal alkyne would increase the steric interaction to increase the energy barrier. Nonetheless, similar trends in the regioselectivity were observed in analogous OND esters substituted by methyl on the terminal propargylic carbon atom, in which the **TS5-H** is only 3.7 kcal/mol lower in free energy than **TS5-Me**. This erosion of the regioselectivity is likely attributed to the gauche conformation of the two methyl groups (45° of the dihedral angle). Thus, the substituents on

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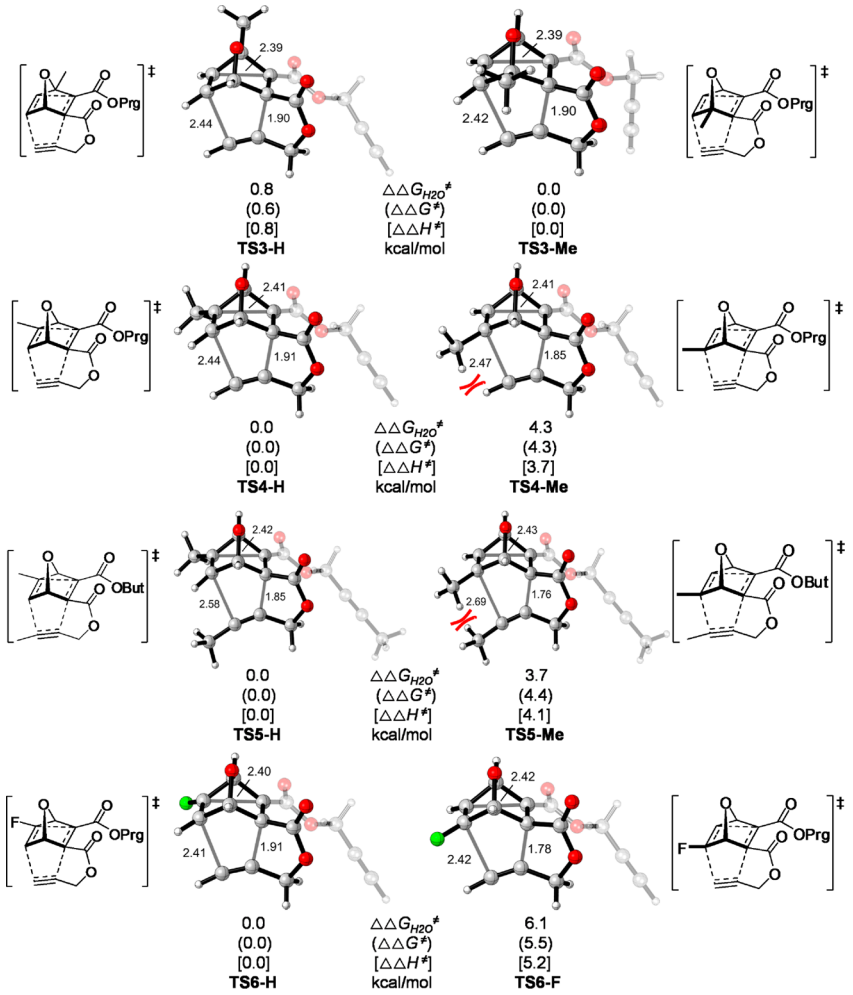

Figure 2. Regioselectivity in the intramolecular [2 + 2 + 2] cycloaddition with substituents at different sites.

the terminal alkyne cannot improve the regioselectivity any more.

Alternatively, the hydrogen bond between H and F atoms identified as a key interaction may be responsible for the reversal in the regioselectivity. To our surprise, the regioselectivity still remains on unsubstituted side, even more significantly because **TS6-H** was found to be 6.1 kcal/mol lower in free energy than **TS6-F**. It has been shown that the distance between the terminal H and F atoms in **TS6-F** is as long as 2.53 Å with weak interactions. The NBO charges on the dienyne moiety of **TS6-H** and **TS6-F** were then calculated for further analysis (Figure 3). It was found that **TS6-F** has more notable charge repulsion between forming bonds than **TS6-H**, which accounts well for the higher energy level of **TS6-F**. Therefore, the electronic effect at the 5-position has a significant effect on the regioselectivity of the cycloaddition when the steric hindrance is neglectable.

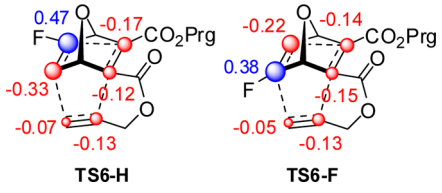

Figure 3. NBO charges on the dienyne moiety of **TS6-H** and **TS6-F**.

From the above analysis, we can propose that the 5-substituents with steric hindrance or electron-acceptor groups can increase the energy barrier for the cycloaddition, resulting in the good regioselectivity at the other side, while the substituents at the 1-position and terminal alkyne have no influence on the regioselectivity.

3. Linker Length and Unsaturated Bonds for the Reactivity. The linker length and the unsaturated bonds play an important role on the cyclization rate in Finn's reaction, which inspires us to explore the reactivity of the analogous OND esters **3**, **8′**, and **9′**. The energy profiles drawn in Figure 4 for the comparison imply that OND esters **3** is most facile to undergo the intramolecular [2 + 2 + 2] cycloaddition, while the cycloaddition of homopropargyl OND ester **8′** via **TS7** suffer from an activation free energy of 42.5 kcal/mol that appears too high to allow cyclization to furnish the expected *δ*-lactone product **10** under the conditions used. The origin of the low reactivity of OND ester **8′** can be interpreted in term of the ring strain force in the precursor of the six-membered lactone ring in **TS7**, as the angles around the ring are far from the normal ones. For OND ester **9′** involving the allylic moiety, **TS8** is found to be 2.3 kcal/mol higher in free energy than **TS2**, and the **TS8** structure resembles **TS2**. This slight high energetic barrier due to the lower reactivity of alkene relative to alkyne, may have the potential to allow cyclization to proceed under more harsh conditions.

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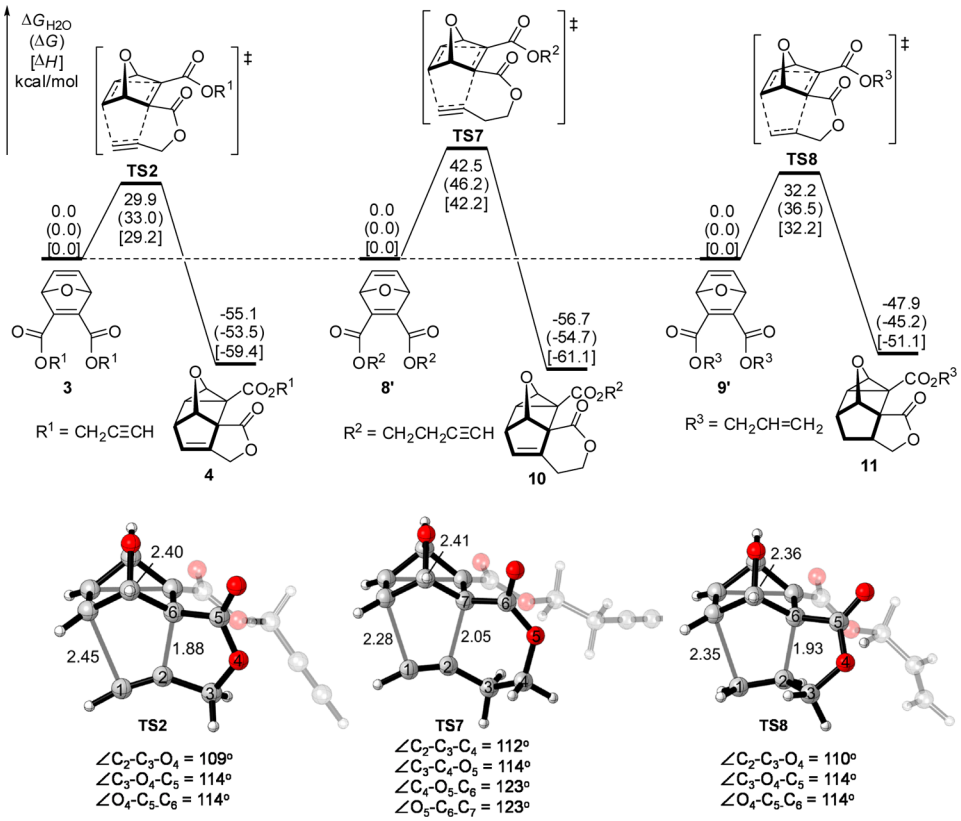
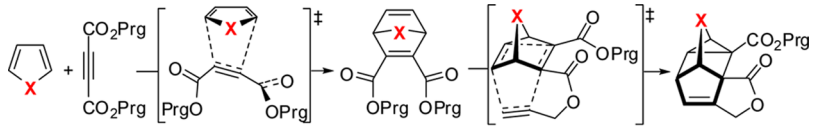


Figure 4. Reactivity of ONDs **3**, **8′**, and **9′** in the intramolecular [2 + 2 + 2] cycloaddition.

Table 1. Energies of the Intramolecular [2 + 2 + 2] Cycloaddition of Aza-, Thio-, and Norbornadienedicarboxylates[a]



X		12 + 2	TS9	13	TS10	14
O	ΔG_{H2O}	0	27.1	-4.8	25.1 (29.9)	-59.9
	ΔG	0	27.9	-5.4	27.6 (33.0)	-58.9
	ΔH	0	14.5	-20.5	8.7 (29.2)	-79.9
CH_2	ΔG_{H2O}	0	23.3	-25.5	7.0 (32.5)	-77.4
	ΔG	0	23.5	-26.9	7.2 (34.1)	-77.5
	ΔH	0	10.1	-42.3	-12.3 (30.0)	-98.6
NH	ΔG_{H2O}	0	28.0	5.4	35.5 (30.1)	-51.9
	ΔG	0	29.9	2.9	36.6 (33.7)	-53.6
	ΔH	0	16.3	-12.4	17.4 (29.8)	-74.5
S	ΔG_{H2O}	0	36.4	-3.7	25.6 (29.3)	-56.3
	ΔG	0	37.6	-4.6	27.7 (32.3)	-54.6
	ΔH	0	24.4	-19.9	8.7 (28.6)	-77.5

[a]All energies shown in kcal/mol. The energies in relation to **13** are shown in the parentheses.

4. Hetero- and Norbornadienedicarboxylates for the Reactivity. The formation and intramolecular [2 + 2 + 2] cycloaddition reactions of aza-, thio-, and norbornadienedicarboxylates were explored extensively (Table 1). When cyclopentadiene **12-C** is reacted with **2**, norbornadienedicarboxylate **13-C** is formed facilely with the lowest activation free energy of 23.3 kcal/mol. The transformation is significantly exergonic by 25.5 kcal/mol to make **13-C** thermodynamically stable. The intramolecular [2 + 2 + 2] cycloaddition reaction of **13-C** requires an activation free energy of 32.5 kcal/mol, which is 2.6 kcal/mol higher than that of **13-O**. The energetic barrier of **TS9-N** in conversion of pyrrole to azanorbornadienedicarboxylate **13-N** is 28.0 kcal/mol, slightly higher than that of **TS9-O**. In contrary to other cases, this process is endergonic and reversible. The following intramolecular [2 + 2 + 2] cycloaddition requires an activation free energy of 30.1 kcal/mol, 0.2 kcal/mol higher than that of **13-O**. When thiophene **12-S** is employed, the transformation suffers from an energetic barrier that appears too high to allow cycloaddition to proceed under general thermal conditions. The resulting process has a tendency to behave similar to the process for oxanorbornadienedicarboxylate. Compared with the four cases, it was found that X atoms play a crucial role in the formation of hetero- and norbornadienedicarboxylates, while serving as a micro-regulator to the intramolecular [2 + 2 + 2] cycloaddition reaction.

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5. Bridge-Ring Size Effect on the Reactivity. Cyclohexadiene **15** is also applicable to the cycloaddition, giving the bicyclo[2.2.2]octa-2,5-diene-2,3-dicarboxylate **16**, a homonorbornadienedicarboxylate. The calculational results shown in Figure 5 demonstrate that the generation of **16** is facile and

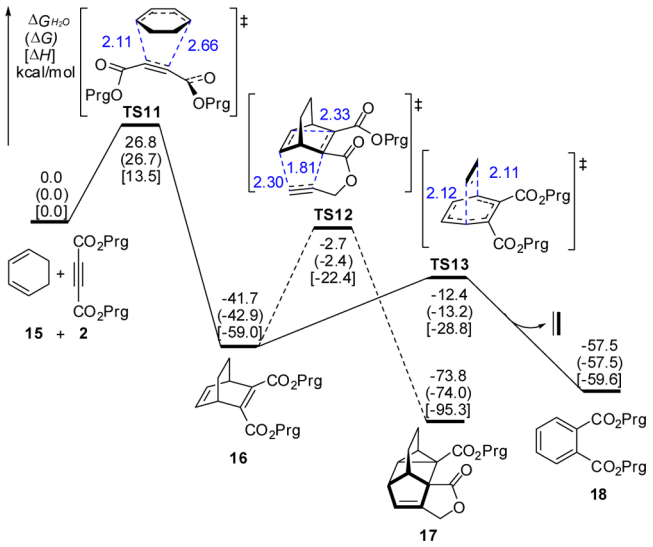
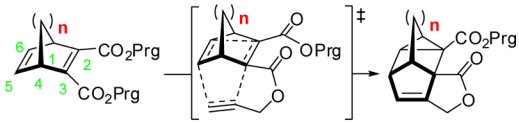


Figure 5. Potential energy profiles of the tandem cycloaddition reaction of **15** with **2** (the blue numbers are forming/breaking bond distances).

thermodynamically stable, whereas the following intramolecular [2 + 2 + 2] cycloaddition requires a high activation free energy of 39.0 kcal/mol, making it kinetically unfeasible. In addition, an alternative conversion of **16** is found to undergo [4 + 2] cycloreversion with the release of one molecule of ethene to deliver benzenedicarboxylate **18**. The cycloreversion with a free energy barrier of 29.3 kcal/mol is very competitive to the [2 + 2 + 2] cycloaddition and predicted to occur under common thermal conditions. Furthermore, this process is exergonic by 15.8 kcal/mol but exothermic by 0.6 kcal/mol, indicating that the increase of entropy with the release of ethene is the driving force of the cycloreversion.

Given the importance of the bridge-ring size, we commenced investigation of the cycloaddition of series of bicyclo[2.2.*n*]alka-2,5-diene-2,3-dicarboxylates (Table 2). When bicyclo[2.2.0]-hexa-2,5-diene-2,3-dicarboxylate **19-0** was examined, the [2 + 2 + 2] cycloaddition via **TS14-0** required an activation-free energy as high as 40.0 kcal/mol. It is kinetically unfeasible, although the substrate **19-0** possesses ring strain and the conversion is substantially exergonic. The cycloaddition of bicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate **19-1** requires an activation free energy of 34.1 kcal/mol, which is the lowest one in cycloadditions of bicyclo[2.2.*n*]alka-2,5-diene-2,3-dicarboxylates. It is also the most predominantly exergonic. Increasing the bicycle ring to bicyclo[2.2.2]octa-2,5-diene-2,3-dicarboxylate **19-2** results in an enhanced activation free energy of 40.5 kcal/mol and a ascending reaction free energy. When an even larger bicycle [2.2.∞] compound was evaluated, cyclohexa-1,4-diene-1,2-dicarboxylate **19-∞** as a simple model underwent the cycloaddition with the highest activation free energy of 53.5 kcal/mol. The adduct **20-∞** was also the least thermodynamically stable compared with other cases. Reviewing the whole energy table, we found that only the bicycle [2.2.1]hepta-2,5-diene-2,3-dicarboxylate was predicted to

Table 2. Energies of the Intramolecular [2 + 2 + 2] Cycloaddition of Bicyclo[2.2.*n*]alka-2,5-diene-2,3-dicarboxylates and Key Optimized Geometries[a]



n		19	TS14	20
0	ΔG	0	40.0	-40.7
	ΔH	0	35.9	-46.4
1	ΔG	0	34.1	-50.6
	ΔH	0	30.0	-56.3
2	ΔG	0	40.5	-31.1
	ΔH	0	36.6	-36.3
∞	ΔG	0	53.5	-15.8
	ΔH	0	48.4	-22.4
R(Å) = C_2-C_6, A(°) = C_2-C_1-C_6, D(°) = C_2-C_4-C_1-C_6				
0	R	2.59	2.46	1.55
	A	116.1	109.2	62.2
	D	116.7	109.6	62.3
1	R	2.47	2.36	1.53
	A	106.6	101.5	60.9
	D	114.0	107.9	64.5
2	R	2.46	2.33	1.54
	A	108.3	101.0	61.3
	D	116.7	114.5	69.3
∞	R	2.52	2.33	1.54
	A	113.7	101.2	61.2
	D	179.3	119.3	70.5

[a]All energies shown in kcal/mol.

undergo the intramolecular [2 + 2 + 2] cycloaddition. Both increasing and decreasing the bridge-ring size of bicycle [2.2.*n*] compounds would enhance energetic barriers and make the cycloaddition kinetically unfeasible.

From the viewpoint of the structures, it was found that the ring strain in the formation of cyclopropane has a salient impact on energetic barriers of the [2 + 2 + 2] cycloaddition. Thus, we concentrated on the optimized geometries of the formation of cyclopropane for further discussion. Compounds **19-1** and **19-2** have smaller C_2−C_6 distances, which are favorable to bond formation in relation to other two cases. In addition, with respect to the angle of C_2−C_1−C_6, **19-1** has the smallest distance, demonstrating the highest activation to the three-membered ring-closure. More importantly, the dihedral angle of C_2−C_4−C_1−C_6 is essentially related to the nature of the frontier molecular orbitals (FMOs) (Figure 6). Given the smallest dihedral angle of 114°, **19−1** exhibits the largest curved overlap of FMOs, in complete accord with the lowest activation free energy. Compounds **19-0** and **19-2** possess a little larger dihedral angle of 117°, both in good agreement with the higher activation free energies. Increasing the dihedral angle to 179° in **19-∞** results in the enhanced energetic barrier. Therefore, the dihedral angle of C_2−C_4−C_1−C_6 is the key geometry for the feasibility of the cycloaddition and decreasing it would facilitate the transformation.

6. Intermolecular [2 + 2 + 2] Cycloaddition. Finally, the intermolecular [2 + 2 + 2] cycloaddition reaction was investigated to compare with the intramolecular one (Table 3). When ethyne (**21a**) reacted with OND **22**, the intermolecular [2 + 2 + 2] cycloaddition required an activation enthalpy of 28.8 kcal/mol, which is even 0.4 kcal/mol lower than that of the intramolecular one. However, the decrease of the entropy has a significant effect in the intermolecular cycloaddition, leading to a higher activation free energy of 40.6

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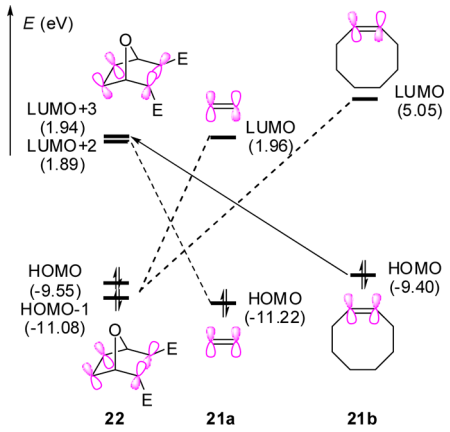
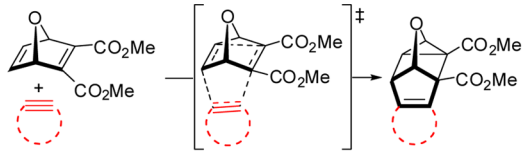


Figure 6. Frontier molecular orbitals and their energies of OND **22** with different alkynes **21** at HF/6-31G(d).

Table 3. Energies of the Intermolecular [2 + 2 + 2] Cycloaddition of Different Alkynes 21a–b with ONDs 22[a]



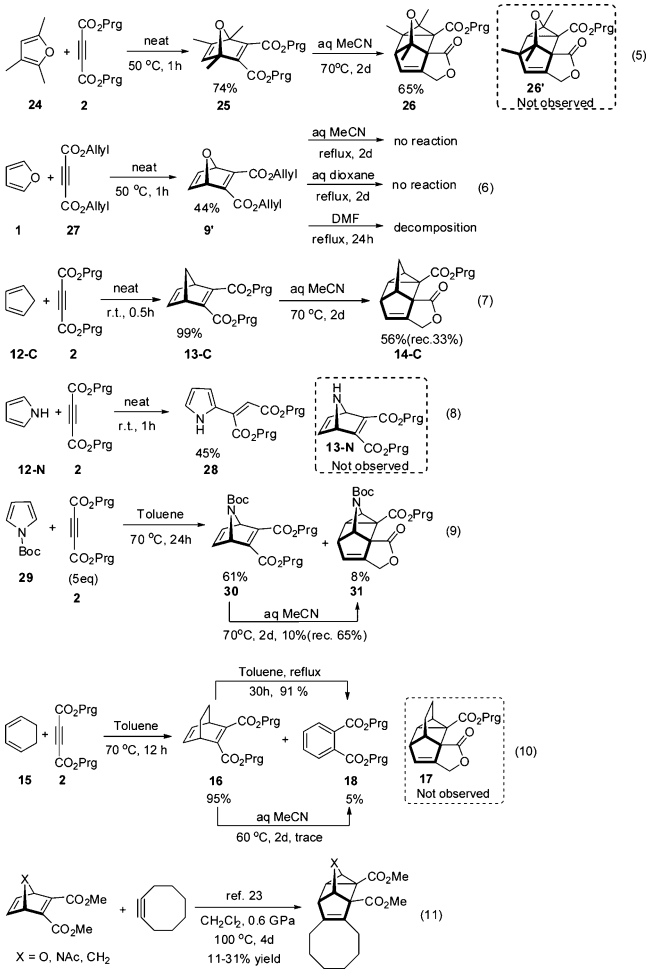
Alkyne **21** +		**22**	**TS15**	**23**
Ethyne	ΔG	0	40.6	-58.0
	ΔH	0	28.8	-72.1
	$-T\Delta S$	0	11.8	14.1
Cyclo-octyne	ΔG	0	28.4	-62.6
	ΔH	0	14.2	-79.0
	$-T\Delta S$	0	14.2	16.4

[a]All energies shown in kcal/mol.

kcal/mol. It appears to be remarkably high (7.6 kcal/mol higher than that of the intramolecular one) and becomes kinetically unfeasible. When cyclooctyne (**21b**) is used as an active alkyne, the activation enthalpy of **TS15b** drops to 14.2 kcal/mol. Finally, the activation free energy is only 28.4 kcal/mol, which is kinetically feasible, although the decrease of the entropy contributes an energetic portion of 14.2 kcal/mol. Therefore, the calculational results suggest that only the active alkynes could be prone to undergo the intermolecular [2 + 2 + 2] cycloaddition with the low activation enthalpy and the inescapable decrease of entropy.

From the FMOs in Figure 6, we can see that the HOMO, HOMO-1, LUMO+2, and LUMO+3 of OND **22** are mostly localized on the two C–C double bonds, respectively. The computed results show that the energy gaps between HOMOs of **22** and LUMO of **21a** (11.5 and 13.0 eV) are close to those between LUMOs of **22** and HOMO of **21a** (13.1 and 13.2 eV). However, both of them appear too high to allow interaction to proceed. Compound **21b** as an active alkyne has enhanced the FMO energy level relative to **21a**, leading to the low energy gaps between LUMOs of **22** and HOMO of **21b** (11.3 eV). The degressive energy gaps allow the interaction of FMOs to occur and make the cycloaddition feasible.

Experimental Verification for the DFT Prediction. To verify our prediction that the 5-substituted OND can undergo intramolecular [2 + 2 + 2] cycloaddition to afford the sole product regioselectively and to gain more information about the reactivity of aza-, thio-, and norbornadienedicarboxylates, we embarked on the experimental studies of these reactions. When 2,3,5-trimethylfuran (**24**) was employed in the reaction with **2** at 50 °C for 1 h, 1,4,5-trimethyl OND **25** was successfully obtained in 74% yield. Treatment of **25** in aqueous acetonitrile at 70 °C for 2 d gave the intramolecular [2 + 2 + 2] adduct **26** in 65% yield as the sole product, as determined by ^{1}H NMR analysis (eq 5). When the reaction was run at higher



or lower temperature, even with prolonged time, the yield decreased but the regioselectivity was completely consistent with our calculation results in Figure 4. To confirm the lower reactivity of the allyl group, we reconducted the reaction of diallyl OND **9′** under different thermal conditions; however, no [2 + 2 + 2] cycloaddition was observed (eq 6). In addition, norbornadienedicarboxylate **13-C** was also synthesized by the cycloaddition of cyclopentadiene and **2** at room temperature in 99% yield.[19] It successfully afforded the [2 + 2 + 2] adduct **14-C** in 56% yield under the standard conditions, with recovery of 33% of substrate (eq 7). Prolonging the reaction time did not improve the yield because of the increasing amount of decomposition. When pyrrole was reacted with **2**, the Michael adduct **28** was formed instead of azabornadienedicarboxylate **13-N** (eq 8).[20] It was found that Boc-protecting pyrrole could take part in the D–A reaction with **2** to give the azabornadienedicarboxylate **30** in 61% yield,[21] along with the final intramolecular [2 + 2 + 2] adduct **31** in 8% yield. We realized the intramolecular [2 + 2 + 2] cycloaddition of azobornadienedicarboxylate **30** although it showed low conversion into adduct **31** only in 10% yield under the

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standard conditions (eq 9). On the other hand, the inert aza- and norbornadienedicarboxylates can be considered as stable fluorogenic probes. The synthesis of thionorbornadienedicarboxylates still remained a challenge after our endeavor.

1,3-Cyclohexadiene was also applicable to the D−A reaction, giving the bicyclodienedicarboxylate **16** in 95% yield, along with 5% yield of phthalate **18**, which arose from a [4 + 2] cycloreversion with the release of one molecule of ethene.[22] Treatment of bicyclodienedicarboxylate **16** under the standard cycloaddition conditions did not result in the [2 + 2 + 2] adduct **17** and phthalate **18**, whereas a solution of **16** in toluene was refluxed for 30 h to afford phthalate **18** in 91% (eq 10). These experimental findings gave concrete evidence to support the computational predictions.

For the intermolecular [2 + 2 + 2] cycloaddition, there has been one and only one report that aza-, oxa-, and norbornadienedicarboxylates react with cyclooctyne in CH_2Cl_2 at 100 °C for 4 d to give intermolecular [2 + 2 + 2] adducts in 11−31% yields (eq 11).[23] Our calculations in Table 3 are once again consistent with the experimental results.

■ CONCLUSIONS

In summary, we have explored the facile intramolecular [2 + 2 + 2] homo-D−A cycloaddition of oxanorbornadienedicarboxylates and their analogues with the aid of the DFT calculations and experimental confirmation. The oxanorbornadienedicarboxylates were generated from furans and but-2-ynedioates and undergo the resulting intramolecular [2 + 2 + 2] cycloaddition in a concerted but asynchronous fashion with slightly higher energy barriers to construct the complex hemibasketanes. Bridgehead substituents have little influence on the regioselectivity, whereas 5-substituents involving steric hindrance or electron-acceptor groups are predicted to attenuate the cycloaddition at the substituted side. Furthermore, the alkene moiety is much less reactive relative to alkyne, and a linker length longer than five atoms shows significantly disfavored energy barrier due to the ring stain in the transition state. Additionally, aza- and norbornadienedicarboxylates demonstrate less reactivity, while thionorbornadienedicarboxylates show more reactivity, but with the challenge of their synthesis. The bridge-ring size plays a crucial role that only the bicyclo[2.2.1]hepa-2,5-dienedicarboxylates can undergo the cycloaddition feasibly. The corresponding intermolecular reaction was also evaluated to compare with the intramolecular one, in which the active alkynes are indispensable. Eventually, our experimental results comfirm the calculational prediction of the regioselectivity at the 5-unsubstituted side, slightly less reactivity of aza- and norbornadienedicarboxylates, and competitive cycloreversion reaction of bicyclo[2.2.2] octa-2,5-dienedicarboxylates.

■ EXPERIMENTAL SECTION

General Information. Melting points were obtained on a melting point apparatus and are uncorrected. All NMR spectra were recorded on a 400 MHz spectrometer with TMS as an internal standard in $CDCl_3$ solution, and the chemical shifts (δ) are reported in ppm. IR spectra were determined directly. MS spectra were obtained on an ESI mass spectrometer. HRMS spectra were performed by the ESI ionization technique on an LC/MSD TOF mass spectrometer. TLC separations were performed on silica gel GF_{254} plates, and the plates were visualized with UV light.

Furan, cyclopentadiene, pyrrole, and 1,3-cyclohexadiene were commercially available, whereas *N*-Boc-pyrrole (**29**) was synthesized according to the previous reports.[24] Acetylenedicarboxylates **2** and **27** were prepared by acid-catalyzed esterification of acetylenedicarboxylic acid with azeotropic removal of water as described by Finn.[5] 2,3,5-Trimethylfuran (**24**) was prepared from 3-methylhexane-2,5-dione by the general procedure of the Paal−Knorr synthesis method.[25]

General Procedure for Synthesis of ONDs 25 and 9′. A solution of a furan (2 mmol) and acetylenedicarboxylate **2** (380 mg, 2 mmol) was stirred at 50 °C for 1 h. The residue was chromatographed on a column of silica gel with ethyl acetate and petroleum ether (1:10, v/v) as an eluent.

*Diprop-2-ynyl 1,4,5-trimethyl-7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (**25**):* isolated yield 74% (444 mg); pale yellow oil; R_f 0.38 (20% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.42 (d, J = 1.6 Hz, 1H), 4.79 (d, J = 2.0 Hz, 4H), 2.50 (t, J = 2.0 Hz, 2H), 1.90 (d, J = 1.6 Hz, 3H), 1.77 (s, 3H), 1.73 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.4, 163.3, 157.7, 155.6, 154.9, 138.6, 93.6, 91.4, 77.4, 75.6, 52.7, 52.7, 15.7, 13.9, 13.0. IR (KBr) ν_{max} 3278, 2937, 2129, 1773, 1719, 1356, 1271, 1232, 1205, 1114, 988 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{20}NO_5$ [M + NH_4^+] 318.1341, found 318.1338.

*Diallyl 7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (**9′**):* isolated yield 44% (230 mg); pale yellow oil; R_f 0.30 (20% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (s, 2H), 5.93 (ddt, J = 17.2, 10.4, 6.0 Hz, 2H), 5.70 (s, 2H), 5.36 (dd, J = 17.2, 1.2 Hz, 2H), 5.27 (dd, J = 10.4, 1.2 Hz, 2H), 4.71 (ddd, J = 6.0, 1.2, 1.2 Hz, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 162.7, 153.0, 143.4, 131.5, 119.1, 85.3, 66.1; IR (KBr) ν_{max} 3084, 3025, 2952, 1711, 1640, 1270, 1206, 1111, 989, 932, 709 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{15}O_5$ [M + H^+] 263.0919, found 263.0910; calcd for $C_{14}H_{14}NaO_5$ [M + Na^+] 285.0739, found 285.0731.

*Diprop-2-ynyl Bicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (**13-C**).* According to a literature procedure,[19] acetylenedicarboxylate **2** (380 mg, 2 mmol) was added dropwise to freshly distilled cyclopentadiene (132 mg, 2 mmol), cooling the mixture with a water bath when the temperature exceeded 45 °C. The mixture was stirred for an additional 1 h. The resulting (505 mg, 99% yield) of colorless oil is pure diprop-2-ynyl bicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (**13-C**) by ^{1}H NMR: R_f 0.27 (20% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (s, 2H), 4.83 (d, J = 2.4 Hz, 2H), 4.79 (d, J = 2.4 Hz, 4H), 3.98 (s, 2H), 2.57 (t, J = 2.4 Hz, 1H), 2.50 (t, J = 2.4 Hz, 2H), 2.31 (d, J = 6.8 Hz, 1H), 2.12 (d, J = 6.8 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.1, 152.7, 142.5, 77.4, 75.4, 73.3, 53.7, 52.6; IR (KBr) ν_{max} 3291, 2946, 2129, 1719, 1624, 1375, 1250, 714 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{13}O_4$ [M + H^+] 257.0814, found 257.0811.

*Diprop-2-ynyl 2-(pyrrol-2-yl)butenedioate (**28**).* As the literature procedure,[20] a solution of pyrrole (134 mg, 2 mmol) and acetylenedicarboxylate **2** (380 mg, 2 mmol) was stirred at room temperature for 1 h. The brown solution was chromatographed on a column of silica gel with ethyl acetate and petroleum ether (1:10, v/v) as an eluent to afford diprop-2-ynyl 2-(pyrrol-2-yl)butenedioate (**28**) as yellow crystals: 231 mg, yield 45%; mp 86−87 °C; R_f 0.50 (20% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.42 (s, 1H), 7.08 (d, J = 0.6 Hz, 1H), 6.82 (m, 1H), 6.32 (dt, J = 4.0, 2.4 Hz, 1H), 5.99 (s, 1H), 4.89 (d, J = 2.4 Hz, 2H), 4.80 (d, J = 2.4 Hz, 2H), 2.56 (t, J = 2.4 Hz, 1H), 2.52 (t, J = 2.4 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 167.8, 166.8, 139.1, 125.8, 124.7, 119.1, 111.1, 108.9, 77.4, 76.9, 75.9, 75.4, 53.4, 52.8; IR (KBr) ν_{max} 3291, 2923, 2129, 1735, 1686, 1578, 1401, 1368, 1284, 1216, 1182, 753 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{12}NO_4$ [M + H^+] 258.0766, found 258.0759.

*7-tert-Butyl 2,3-Di(prop-2-ynyl) 7-Azabicyclo[2.2.1]hepta-2,5-diene-2,3,7-tricarboxylate (**30**).* Based on the literature procedure,[21] a solution of *N*-Boc-pyrrole **29** (167 mg, 1 mmol) and acetylenedicarboxylates **2** (951 mg, 5 mmol) in 10 mL of toluene was stirred at 70 °C for 24 h. The volatiles were removed under vacuum, and the residue was then purified by silica gel flash chromatography with ethyl acetate and petroleum ether (1:10, v/v, then 1:5, v/v) as an eluent to afford 7-*tert*-butyl 2,3-di(prop-2-ynyl) 7-azabicyclo[2.2.1]hepta-2,5-diene-2,3,7-tricarboxylate (**30**) as a colorless oil: 218 mg, yield 61%; R_f 0.35 (20% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (s, 2H), 5.50 (s, 2H), 4.81 (d, J = 2.0 Hz, 4H), 2.51 (t, J = 2.4 Hz, 1H), 1.41 (s, 9H); ^{13}C NMR (100.6

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MHz, $CDCl_3$) δ 154.0, 81.8, 77.0, 75.7, 69.1, 53.0, 28.2; IR (KBr) ν_{max} 3286, 2979, 2130, 1778, 1716, 1631, 1257, 1162, 677 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{19}NNaO_6$ [M + Na^+] 380.1110, found 380.1109.

*Diprop-2-ynyl Bicyclo[2.2.2]octa-2,5-diene-2,3-dicarboxylate (**16**).* Based on a literature procedure,[22] a solution of 1,3-cyclohexadiene (240 mg, 3 mmol) and acetylenedicarboxylates **2** (380 mg, 2 mmol) in 20 mL of toluene was stirred at 70 °C for 12 h. The volatiles were removed under vacuum, and the residue was then purified by silica gel flash chromatography with ethyl acetate and petroleum ether (1:10, v/v) as an eluent to afford diprop-2-ynyl bicyclo[2.2.2]octa-2,5-diene-2,3-dicarboxylate (**16**) as a colorless oil: 513 mg, yield 95%; R_f 0.56 (20% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.39 (t, J = 3.6 Hz 2H), 4.78 (d, J = 2.0 Hz, 4H), 4.08 (s, 2H), 2.50 (s, 2H), 1.50 (d, J = 7.8 Hz, 2H), 1.42 (d, J = 7.7 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 165.1, 142.3, 133.7, 75.4, 52.7, 39.1, 24.6; IR (KBr) ν_{max} 3288, 2946, 2875, 2130, 1717, 1642, 1377, 1257, 706 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{15}O_4$ [M + H^+] 271.0970, found 271.0966; calcd for $C_{16}H_{14}NaO_4$ [M + Na^+] 293.0790, found 293.0783.

General Procedure for the Intramolecular [2 + 2 + 2] Cycloaddition.[5] Oxa-, aza-, or norbornadienedicarboxylate precursor (0.5 mmol) was dissolved in MeCN (10 mL). Water (10 mL) was added, and the reaction mixture was heated at 70 °C for 2 d. The reaction mixture was concentrated and the residue was purified by silica gel flash chromatography with ethyl acetate and petroleum ether (1:10, v/v, then 1:4, v/v) as eluent.

*Prop-2-ynyl 8,10,11-trimethyl-3,9-dioxa-2-oxopentacyclo-[6.4.0.0^{1,5}.0^{7,11}.0^{10,12}]dodec-5-ene-12-carboxylate (**26**):* isolated yield 65% (97 mg); colorless crystals; mp 177−178 °C; R_f 0.23 (25% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.06 (s, 1H), 5.11 (dd, J = 14.0, 2.0 Hz, 1H), 5.01 (d, J = 14.0 Hz, 1H), 4.81 (dd, J = 15.6, 2.0 Hz, 1H), 4.58 (dd, J = 15.6, 2.0 Hz, 1H), 2.85 (d, J = 3.2 Hz, 1H), 2.47 (t, J = 2.0 Hz, 3H), 1.87 (s, 3H), 1.32 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.8, 167.1, 145.8, 122.2, 104.7, 79.3, 77.0, 75.5, 68.0, 65.4, 65.0, 52.5, 51.6, 51.3, 10.4, 9.6, 7.6; IR (KBr) ν_{max} 3262, 2938, 2132, 1758, 1707, 1445, 1389, 1358, 1321, 1203 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{20}NO_5$ [M + NH_4^+] 318.1341, found 318.1334.

*Prop-2-ynyl 3-oxa-2-oxopentacyclo[6.4.0.0^{1,5}.0^{7,11}.0^{10,12}]dodec-5-ene-12-carboxylate (**14-C**):* isolated yield 56% (72 mg); colorless crystals; mp 119−200 °C; R_f 0.42 (25% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98 (s, 1H), 5.14 (dd, J = 13.6, 2.0 Hz, 1H), 4.98 (d, J = 13.6 Hz, 1H), 4.76 (dd, J = 15.6, 1.6 Hz, 1H), 4.61 (dd, J = 15.6, 1.6 Hz, 1H), 3.14 (s, 1H), 2.81 (d, J = 5.2 Hz, 1H), 2.65 (s, 1H), 2.47 (s, 1H), 2.36 (d, J = 5.2 Hz, 1H), 2.20 (d, J = 12.0 Hz, 1H), 1.66 (d, J = 12.0 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.5, 170.8, 147.2, 124.7, 77.3, 75.3, 68.4, 68.2, 61.4, 56.3, 52.5, 43.3, 38.8, 36.5, 31.8; IR (KBr) ν_{max} 3275, 2939, 2128, 1767, 1725, 1437, 1384, 1353, 1242, 1221, 1168, 1103, 982 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{16}NO_4$ [M + NH_4^+] 274.1079, found 274.1071.

*9-tert-Butyl-12-prop-2-ynyl 9-aza-3-oxa-2-oxopentacyclo-[6.4.0.0^{1,5}.0^{7,11}.0^{10,12}]dodec-5-ene-9,12-dicarboxylate (**31**):* isolated yield 10% (18 mg); yellow oil; R_f 0.25 (33% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.02 (m, 1H), 5.09 (dd, J = 14.0, 2.4 Hz, 1H), 5.02 (dd, J = 14.0, 1.2 Hz, 1H), 4.92 (s, 1H), 4.77 (dd, J = 15.6, 2.4 Hz, 1H), 4.64 (dd, J = 15.6, 2.4 Hz, 1H), 4.34 (s, 1H), 3.18 (d, J = 2.0 Hz, 1H), 2.56 (d, J = 4.4 Hz, 1H), 2.48 (t, J = 2.4 Hz, 1H), 1.48 (s, 9H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 172.7, 168.3, 145.4, 122.3, 82.1, 77.0, 75.7, 67.8, 60.1, 50.9, 44.4, 28.2; IR (KBr) ν_{max} 3274, 2978, 2129, 1772, 1713, 1371, 1302, 1257, 1162, 1049, 987 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{23}N_2O_6$ [M + NH_4^+] 375.1556, found 375.1550.

*Diprop-2-ynyl Phthalate (**18**).* A solution of **16** (135 mg, 0.5 mmol) in 10 mL of toluene was refluxed for 30 h. The reaction mixture was concentrated, and the residue was purified by silica gel flash chromatography with ethyl acetate and petroleum ether (1:6, v/v) as an eluent to afford diprop-2-ynyl phthalate (**18**) (110 mg) as a colorless oil: yield 91%; R_f 0.50 (20% EtOAc/petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, J = 5.6, 3.1 Hz, 2H), 7.56 (dd, J = 5.6, 3.1 Hz, 2H), 4.92 (s, 4H), 2.55 (d, J = 1.0 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 166.4, 131.4, 131.1, 129.1, 76.7, 75.4, 53.1; IR (KBr) ν_{max} 3279, 2923, 2854, 2128, 1724, 1598, 1268, 743 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{11}O_4$ [M + H^+] 243.0657, found 243.0652; calcd for $C_{14}H_{10}NaO_4$ [M + Na^+] 265.0477, found 265.0471.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR and HRMS spectra for all new compounds, justification of computational methods, calculation of conformations in the [2 + 2 + 2] cycloaddition, computational details of energies, and coordinates of all stationary points. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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