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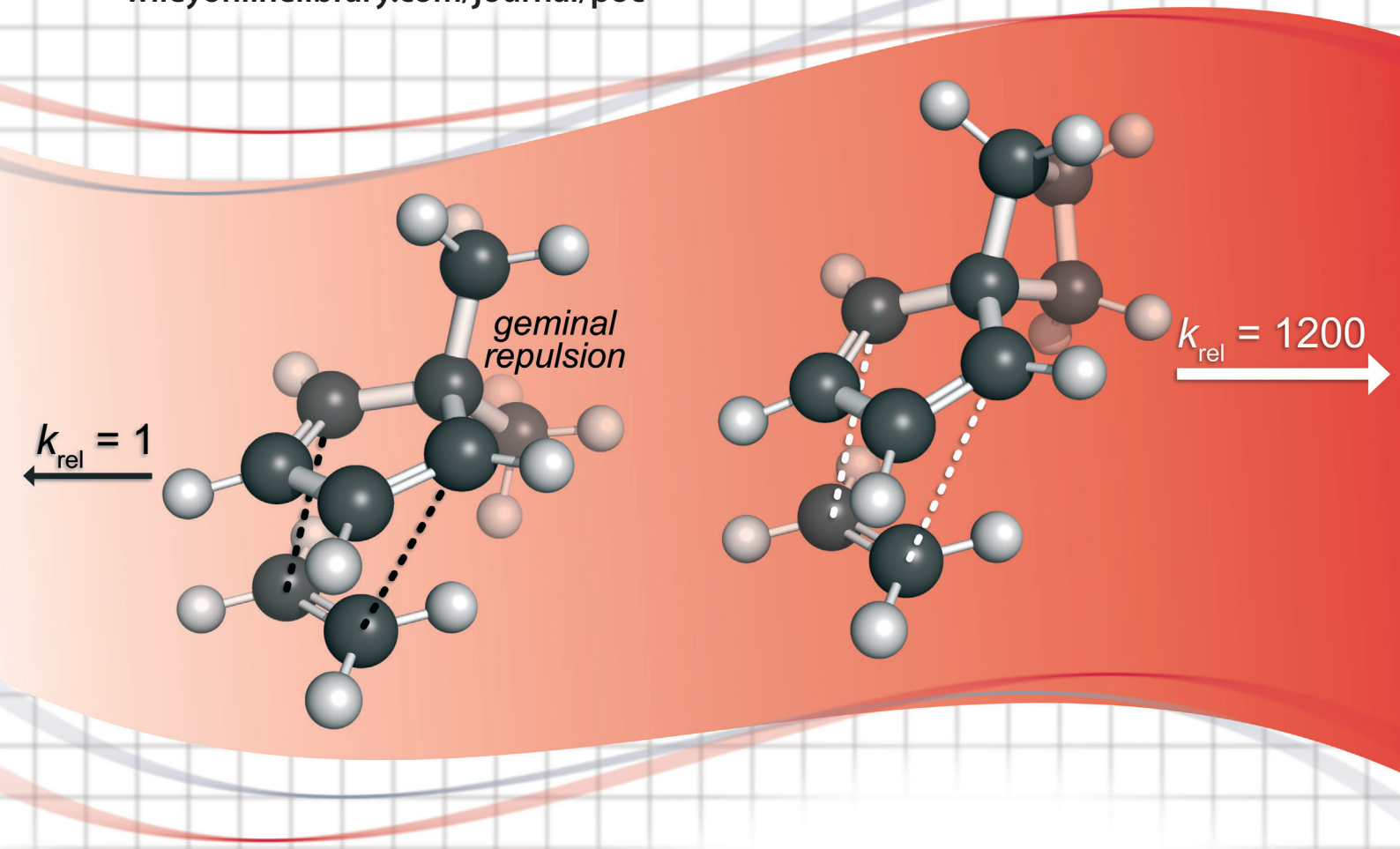

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RESEARCH ARTICLE

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Spirocyclization enhances the Diels–Alder reactivities of geminally substituted cyclopentadienes and 4*H*-pyrazoles

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Abstract

The Diels–Alder reactivity of 5-membered dienes is tunable through spirocyclization at the saturated center. As the size of the spirocycle decreases, the Diels–Alder reactivity increases with the cyclobutane spirocycle, spiro[3.4]octa-5,7-diene, being the most reactive. Density functional theory calculations suggest that spiro[3.4]octa-5,7-diene dimerizes 220,000-fold faster than 5,5-dimethylcyclopentadiene and undergoes a Diels–Alder reaction with ethylene 1200-fold faster than 5,5-dimethylcyclopentadiene. These findings show that spirocyclization is an effective way to enhance the Diels–Alder reactivity of geminally substituted 5-membered dienes.

KEYWORDS

click chemistry, cycloaddition, density functional theory, Diels–Alder reaction, spirocycle

1 | INTRODUCTION

5-Membered cyclic dienes are highly reactive toward dienophiles because they require minimal geometric distortion to achieve the envelope-like geometry of the Diels–Alder transition state.[1] The most reactive 5-membered dienes are those with electron-withdrawing groups at the saturated center.[2–5] Negative hyperconjugation of the electron-withdrawing group invokes antiaromatic 4π electron delocalization.[6,7] This antiaromatic electron delocalization destabilizes the 5-membered diene and promotes reactivity.[3,8] These highly reactive, antiaromatic 5-membered dienes are useful in click chemistry applications.[9]

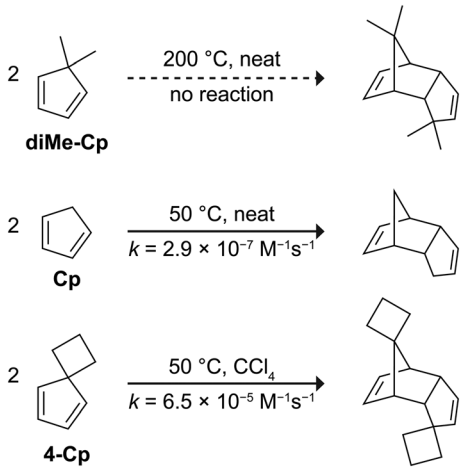
We have shown that geminal dimethyl substituted 5-membered dienes react poorly as Diels–Alder dienes because of the increased geminal repulsion about the geminal dimethyl center in the transition state geometry.[10] The increased transition state geminal repulsion explains why geminally substituted 5-membered dienes, such as 5,5-dimethylcyclopentadiene (diMe-Cp), do not readily dimerize. As shown in Scheme 1, diMe-Cp does not dimerize even at temperatures as high as 200°C.[11,12] This recalcitrance is in contrast to cyclopentadiene (Cp), which readily dimerizes with a half-life of ∼28 h at 25°C.[13,14] The cyclobutane–cyclopentadiene spirocycle, spiro[3.4]octa-5,7-diene (4-Cp), also readily dimerizes.[15–17] At 50°C, the rate constant suggests that the dimerization of 4-Cp occurs ∼220-fold faster than the dimerization of Cp.[15,18] The increased rate of dimerization observed in 4-Cp interests us because it suggests that spirocyclization enhances the Diels–Alder reactivity of 5-membered dienes.

2 | COMPUTATIONAL METHODS

We have computationally explored the Diels–Alder reactions of spirocyclic 5-membered diene systems using density functional theory. The M06-2X functional, which has been shown to reproduce the energetics of cycloadditions accurately, was used to calculate both the geometries and energies.[19] Geometry optimizations were carried out in Gaussian 16 rev. C[20] with the 6-31G(d) basis set. Energetic data were obtained from single-point energy calculations with the 6-311++G(d,p) basis set. All calculations were performed in the gas phase, assuming a standard state of 1 M at 298 K and 1 atm. Cartesian coordinates and energies are listed in the Supporting Information.

3 | RESULTS AND DISCUSSION

The calculated transition state structures along with the activation and reaction energies for the dimerization of diMe-Cp, cyclopentadiene, and 4-Cp are shown in Figure 1. These structures are *endo* and bis-pericyclic.[21,22] For the dimerization reactions of diMe-Cp, Cp, and 4-Cp, the Gibbs activation energies are 33.9, 28.8, and 26.6 kcal/mol, respectively. The dimerization of Cp and 4-Cp are 5500- and 220,000-fold faster than the dimerization of diMe-Cp, respectively. The predicted reactivity trend from the calculated Gibbs activation energies is consistent with the experimental reactivity trend shown in Scheme 1. The reactions are exergonic, with Gibbs reactions energies of −3.6, −6.3, and −10.9 kcal/mol for the dimerization reactions of diMe-Cp, Cp, and 4-Cp, respectively.



SCHEME 1 Experimental rate constants for the dimerization reactions of diMe-Cp,[12] Cp,[18] and 4-Cp[17]

To see how spirocyclization influences the Diels–Alder reactivity of 5-membered dienes, we computationally surveyed the Diels–Alder reactions of diMe-Cp, spiro[4.7]-dodec-1,3-diene (8-Cp), spiro[4.6]-undec-1,3-diene (7-Cp), spiro[4.5]deca-1,3-diene (6-CP), spiro[4.4]nona-1,-3-diene (5-Cp), 4-Cp, spiro[2.4]hepta-4,6-diene (3-Cp), and Cp with ethylene. The calculated Gibbs activation energies range from 35.1 to 29.1 kcal/mol (Figure 2). The most reactive spirocycle, 4-Cp, is predicted to be 24,000-fold more reactive than 8-Cp, 1200-fold more reactive than diMe-Cp, and fourfold more reactive than Cp. Between 8-Cp and 4-Cp, the reactivity gradually increases as the size of the spirocycle decreases. The smallest spirocycle, 3-Cp, has a similar predicted reactivity to that of 5-Cp with activation energies of 32.0 and 32.1 kcal/mol, respectively. The reactions are all exergonic, with reaction energies ranging from −9.2 kcal/mol for 3-Cp to −15.4 kcal/mol for 4-Cp.

We analyzed the reactions of the spirocyclic cyclopentadienes with the distortion/interaction model to reveal the factors that contribute to the reactivity trend.[23] The distortion/interaction analysis deconstructs the electronic activation energies into distortion and interaction energies. The distortion energy is the energy required for the reactants to adopt the geometry of the transition state structure. The interaction energy is the energy that arises from the association of the reacting species during bond

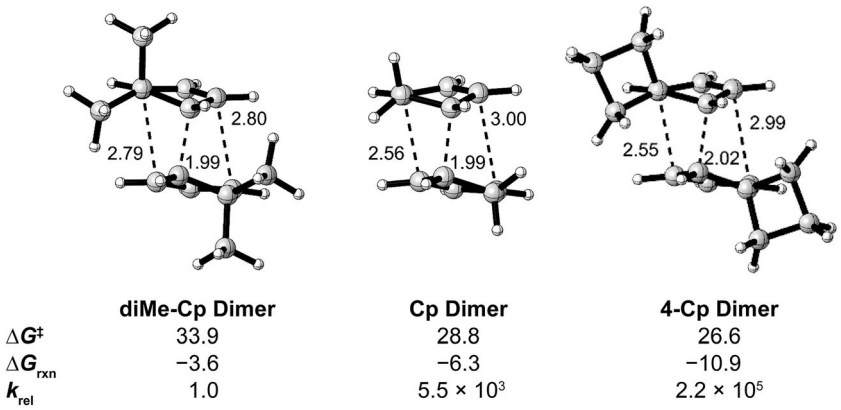


FIGURE 1 Transition state structures for the dimerization reactions of diMe-Cp, Cp, and 4-Cp. Gibbs energies of activation ($\Delta G^{\ddagger}$) and reaction (ΔG°) are in kcal/mol. The forming bond lengths are in Å. Rate constants relative to the dimerization of diMe-Cp (k_{rel}) were calculated with the Arrhenius equation.

formation. It includes orbital, electrostatic, repulsive, and dispersive interactions between the two reacting components. The distortion/interaction analysis was performed on structures with forming bond lengths of 2.26 Å to ensure that the reactions are compared at the same position along the reaction coordinate.[24] Forming bond lengths of 2.26 Å were chosen for the distortion/interaction analysis because 2.26 Å is near that of the transition state geometries for the spirocyclic dienes.

The results from the distortion/interaction analysis are shown in Figure 3. The dienophile distortion energies are similar, ranging from 6.8 to 5.7 kcal/mol. The diene distortion energies gradually decrease as the size of the spirocycle decreases from 19.8 kcal/mol for 8-Cp to 14.2 kcal/mol for 3-Cp. Despite having the smallest ring size and lowest diene distortion energy, 3-Cp does not have the lowest activation energy. That dichotomy is due to the weak interaction energy of −1.7 kcal/mol compared with −6.0 to −5.5 kcal/mol for the other spirocyclic dienes.

The Diels–Alder reactivity of cyclic dienes is controlled by the extent to which the diene double bonds

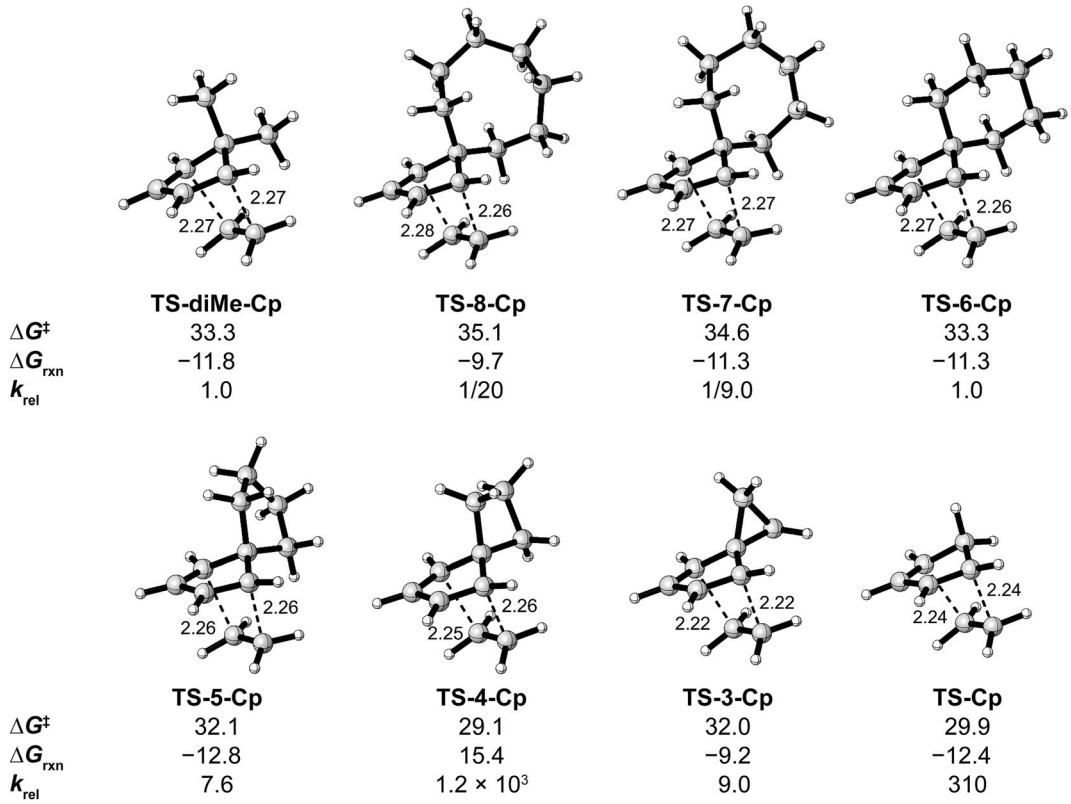


FIGURE 2 Transition state structures for the Diels–Alder reactions of diMe-Cp, 8-Cp, 7-Cp, 6-Cp, 5-Cp, 4-Cp, 3-Cp, and Cp with ethylene. Gibbs energies of activation ($\Delta G^{\ddagger}$) and reaction (ΔG°) are in kcal/mol. The forming bond lengths are in Å. Rate constants relative to the dimerization of diMe-Cp (k_{rel}) were calculated with the Arrhenius equation.

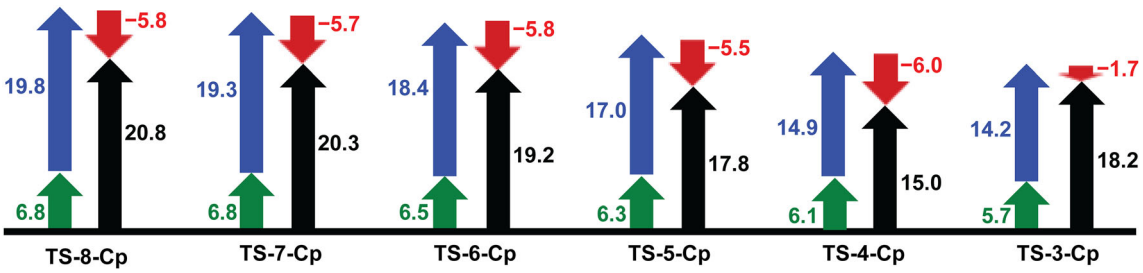


FIGURE 3 Distortion/interaction analysis performed on consistent structures with forming bond lengths of 2.26 Å for the spirocyclic diene series, 8-Cp to 3-Cp (green, distortion energy of dienophile; blue, distortion energy of diene; red, interaction energy; black, electronic activation energy; all in kcal/mol)

distort out of the plane of the diene to achieve the transition state geometry.[1] As the cyclopentadiene puckers to form the envelope-like geometry of the transition state, the diene double bonds distort and lose planarity. This distortion unfavorably reduces the π-bond overlap and can be measured by θ_p shown in Scheme 2. The parameter θ_p measures how puckered the cyclopentadiene saturated center is from the plane of the diene defined by the C_1 to C_4 carbon atoms. The values of θ_p measured from the consistent transition state structures with forming bond lengths of 2.26 Å are shown in Scheme 2. The puckering of the cyclopentadiene ring gradually decreases from 19.6° in 8-Cp to 15.9° in 3-Cp. Increased puckering results in higher diene distortion energies and decreased Diels–Alder reactivities.[1,3]

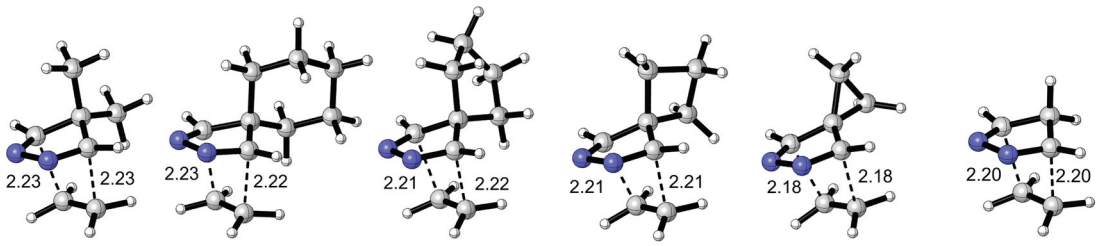
We also measured how the interior angle of the cycloalkane ring where it is connected to the spirocenter changes between the ground and consistent transition state geometry. This angle is defined as θ_s in Scheme 2. Distortions to θ_s between the ground and consistent transition state geometries increase the ring strain of the cycloalkane. The angle decreases 5.1° in 8-Cp, 3.5° in 7-Cp, 3.3° in 6-Cp, and 1.2° in 5-Cp. In 4-Cp and 3-Cp, the angle increases by 0.6° and 1.4°, respectively. The larger spirocyclic dienes experience more distortion about θ_s and θ_p than the smaller spirocyclic dienes between the ground and consistent transition state geometries. The trend in the diene distortion energies can be explained by the increased distortion of θ_p and θ_s required to achieve the transition state geometries of the larger spirocyclic dienes.

The aromaticity of Diels–Alder dienes assessed by nuclear independent chemical shift (NICS) calculations has been shown to correlate with their Diels–Alder reactivities.[25,26] A NICS(0) calculation measures the magnetic shielding at the center of a cyclic system.[27] From 8-Cp to 4-Cp, the NICS(0) values are similar, ranging from −1.1 to −1.0. With a NICS(0) value of −2.5, 3-Cp exhibits increased aromatic electron delocalization relative to the other spirocyclic dienes. The overlap of the cyclopropane quasi-π Walsh orbitals with the diene π system in 3-Cp increases the aromatic electron delocalization.[28,29] This increased aromatic electron delocalization, and the weaker interaction energies decrease the Diels–Alder reactivity and explain why 3-Cp does not fit the reactivity trend observed in the spirocyclic diene series.

We also studied the effect of spirocyclization on the 4*H*-pyrazole (i.e., 2,3-diazacyclopentadiene) scaffold. Figure 4 shows the activation energies and transition state structures for the Diels–Alder reactions of spirocyclic (6N to 3N), 4,4-dimethyl (diMeN), and the

	8-Cp	7-Cp	6-Cp	5-Cp	4-Cp	3-Cp
θ_p	19.6°	19.6°	19.4°	18.9°	18.2°	15.9°
$\theta_{s\text{-GS}}$	114.5°	113.1°	109.4°	100.7°	86.4°	58.1°
$\theta_{s\text{-TS}}$	109.4°	109.6°	106.1°	99.5°	87.0°	59.5°
$\Delta\theta_s$	−5.1°	−3.5°	−3.3°	−1.2°	0.6°	1.4°

SCHEME 2 Structural parameters, θ_s and θ_p, in the spirocyclic diene series from 8-Cp to 3-Cp taken from the consistent transition state structure with forming bond lengths of 2.26 Å



	TS-diMeN	TS-6N	TS-5N	TS-4N	TS-3N	TS-N
$\Delta G^{\ddagger}$	31.4	31.3	30.6	28.3	31.6	29.2
k_{rel}	1.0	1.2	3.9	190	0.71	41

FIGURE 4 Transition state structures for the Diels–Alder reactions of the spirocyclic, 4,4-dimethyl, and unsubstituted 4*H*-pyrazoles with ethylene. Gibbs energies of activation ($\Delta G^{\ddagger}$) are in kcal/mol. The forming bond lengths are in Å. Rate constants relative to the dimerization of diMeN (k_{rel}) were calculated with the Arrhenius equation.

unsubstituted (N) 4*H*-pyrazoles with ethylene. We found that the reactivity trend of the spirocyclic 4*H*-pyrazoles parallels that of the cyclopentadiene spirocycles. The cyclobutane 4*H*-pyrazole-2,3-diazaspiro[3.4]octa-1,3-diene (4N) is the most reactive toward ethylene. 4,4-Dimethyl-4*H*-pyrazoles are unreactive as Diels–Alder dienes unless activated with an acid catalyst.[30] The predicted rate constants suggest that 4N is 190-fold more reactive than diMeN as a Diels–Alder diene toward ethylene. These findings suggest that spirocyclization with a cyclobutane ring is an effective way to promote the Diels–Alder reactivity of the 4*H*-pyrazole scaffold.

4 | CONCLUSIONS

We have shown computationally that the spirocyclization of geminally substituted 5-membered cyclic dienes enhances their Diels–Alder reactivity. This effect is evident in the rapid dimerization of 4-Cp relative to diMeCp, which fails to dimerize even at elevated temperatures. Smaller spirocycles result in less diene distortion energy and increased Diels–Alder reactivity. 3-Cp, the smallest spirocycle, is an exception to the reactivity trend because its low diene distortion energy is offset by weak interaction energies. Thus, we predict the most reactive spirocycle to be the cyclobutane spirocycle. Spirocyclization is an effective way to increase the Diels–Alder reactivity by circumventing the disrupting effects of geminal repulsion in acyclic geminally substituted 5-membered dienes. The acceleration of Diels–Alder reactions through spirocyclization will be of use in the development of highly reactive Diels–Alder dienes for click chemistry applications.[9]

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CONFLICT OF INTEREST

The authors declare no competing financial interests.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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