Strained Molecules

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Strain-Accelerated Formation of Chiral, Optically Active Buta-1,3-dienes**

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Abstract: *The formal [2+2] cycloaddition–retroelectrocyclization (CA–RE) reactions between tetracyanoethylene (TCNE) and strained, electron-rich dibenzo-fused cyclooctynes were studied. The effect of ring strain on the reaction kinetics was quantified, revealing that the rates of cycloaddition using strained, cyclic alkynes are up to 5500 times greater at 298 K than those of reactions using unstrained alkynes. Cyclobutene reaction intermediates, as well as buta-1,3-diene products, were isolated and their structures were studied crystallographically. Isolation of a rare example of a chiral buta-1,3-diene that is optically active and configurationally stable at room temperature is reported. Computational studies on the enantiomerization pathway of the buta-1,3-diene products showed that the eight-membered ring inverts via a boat conformer in a ring-flip mechanism. In agreement with computed values, experimentally measured activation barriers of racemization in these compounds were found to be up to 26 kcal mol^{-1}.*

Ring strain, the increase in the heat of formation of a cyclic molecule relative to that expected for a strain-free reference molecule with the same number of atoms, can be exploited to accelerate or enhance chemical reactivity.[1] Examples of this strategy include the nucleophilic ring opening of epoxides and aziridines,[2] alkene and alkyne metathesis polymerizations,[3] and catalyst-free, 1,3-dipolar cycloaddition reactions of cyclooctynes[4] and cycloheptynes[5] that are facile enough to occur under biological conditions. These precedents inspired us to investigate the effect of ring strain on the formal [2+2] cycloaddition–retroelectrocyclization (CA–RE) reaction between electron-poor alkenes and electron-rich alkynes, which yields donor–acceptor-substituted buta-1,3-dienes.[6] While products of CA–RE reactions using linear alkyne substrates often exhibit remarkable optoelectronic and electrochemical properties,[7] those obtained using cyclic alkyne substrates presented the possibility of accessing new, chiral buta-1,3-dienes that are configurationally stable at room temperature.[8]

Numerous rotationally hindered buta-1,3-dienes have been reported, but these are typically not separable into their constituent enantiomers at ambient conditions due to their relatively low racemization barriers ($\Delta G^{\ddagger}_{298\,K} < 20$ kcal mol^{-1}).[8] The few examples of buta-1,3-dienes with racemization barriers above this threshold are stabilized by sterically bulky substituents or intramolecular metal–π bonding, and include only aliphatic substituents at the 1 and 4 positions of the buta-1,3-diene moiety.[9]

Our strategy for stabilizing the conformation of buta-1,3-dienes, on the other hand, is to constrain their flexibility by using an eight-membered-ring scaffold. With two directives in mind—studying how strain acceleration affects CA–RE reactivity and obtaining functionalized, configurationally stable, chiral buta-1,3-dienes—we explored the reactivity of dibenzo-fused cyclooctynes with tetracyanoethylene (TCNE). We herein report kinetic studies on strain-accelerated CA–RE reactions, as well as computational and experimental investigations on the conformational dynamics of the reaction intermediates and products.

Upon treating various dibenzo-fused cyclooctyne derivatives with TCNE or other electron-deficient alkenes (see the Supporting Information, Section S3 for further details), we found that reactions using TCNE and either methoxy-substituted cyclooctyne **1** or cyclooctadiyne **2** proceeded cleanly to yield well-defined, monomeric products. Cyclooctyne **1** reacted at room temperature to furnish cyclobutene intermediate **3**, which was isolated and subsequently heated to induce RE and formation of diene **4** in quantitative yield with respect to **1** (Scheme 1). Similarly, diyne **2** reacted with 2 equiv TCNE to produce tetraene (±)-**5** as a deep purple solid in 90% yield. Reaction intermediates **6**–**8** were observed by ^{1}H NMR; cyclobutene **6** and cyclobutene-diene **8** were isolated (Scheme 1). Notably, **6** did not undergo RE under a variety of conditions; only [2+2] CA of **6** with a second equivalent of TCNE to yield bis(cyclobutene) **7** was observed, followed by consecutive RE reactions to afford tetraene (±)-**5**.

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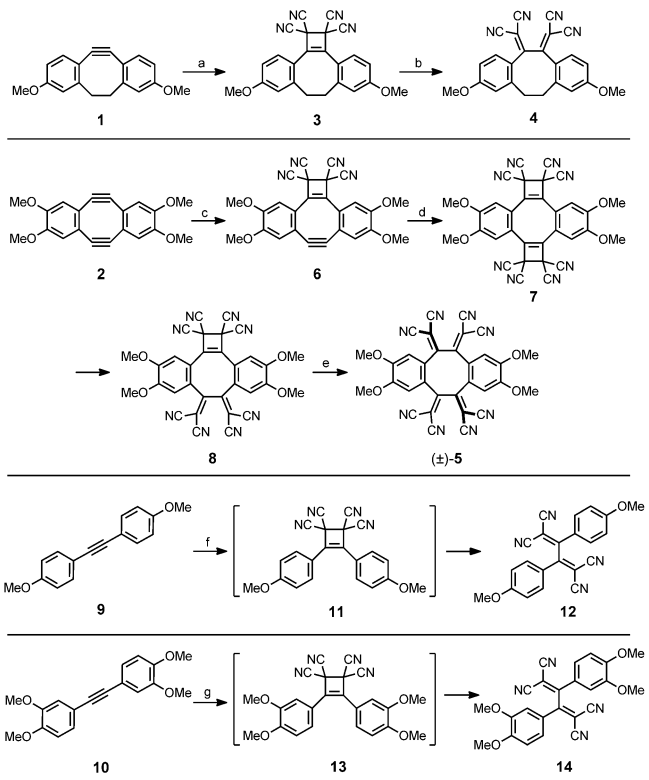


Scheme 1. [2+2] Cycloaddition—retroelectrocyclization reactions explored in this work. a) TCNE (1.00 equiv), 25 °C, 24 h; b) 80 °C, 12 h, yield (**4**): 99% over 2 steps; c) [**2**] = 10^{-3} M, TCNE (1.00 equiv), 25 °C, 12 h; d) TCNE (1.00 equiv), 40 °C, 16 h; e) 80 °C, 12 h, yield ((±)-**5**): 90% over four steps (one pot); f) TCNE (1.00 equiv), 80 °C, 24 h, yield (**12**): 99%; g) TCNE (1.00 equiv), 80 °C, 24 h, yield (**14**): 89%. All reactions were performed in $(CDCl_2)_2$.

Single crystals of reaction products **4** and (±)-**5**, and of intermediates **3**, **6**, and **8** were studied by X-ray diffraction; their molecular structures are shown in Figure 1.[10] Interestingly, the eight-membered rings in these compounds exhibited a uniform and unprecedented preference for the twist (**4** and **5**) or twistoid (**3** and **8**) conformations, which have previously been proposed only as high-energy intermediates in the pseudorotation of eight-membered rings.[11] The buta-1,3-diene moieties in **4**, **5**, and **8** are strongly skewed by ca. 106°, which is presumably due to mutual repulsion of the terminal cyano groups; this torsional strain sets the preferred conformation of the eight-membered ring. In contrast, only chair, twist-boat, or rarely, boat conformations have been observed in crystal structures of all other known compounds containing eight-membered rings with two opposing torsion angles fixed at zero degrees (see the Supporting Information, Section S4 for further details about the single-crystal structures and conformational space of known eight-membered rings).[12] Computational studies confirm that the twist conformations of **4** and **5** are favored (see Figure 2 and the Supporting Information, Section S9 for additional computational details). Finally, the structures of **3**, **6**, and **8** represent rare crystallographic characterizations of cyclobutene intermediates for a CA–RE reaction, which have been observed primarily as unstable, transient species.[13]

The observation, isolation, and characterization of these cyclobutene intermediates, combined with the clean and quantitative nature of the [2+2] CA–RE reactions, all signified amenability to kinetic studies. The reactions of TCNE with four alkynes of interest, dibenzo-fused cyclooctynes **1** and **2**, and their respective acyclic analogues, diarylethynes **9** and **10** (Scheme 1), were monitored by ^{1}H NMR spectroscopy at various temperatures; the kinetic data were subjected to Eyring analysis (Table 1). Comparison of activation parameters and rates of reactions using cyclic versus linear substrates enabled quantification of strain acceleration. A qualitative reactivity difference between the two classes of substrates was immediately apparent: **9** and **10** converted directly to their respective buta-1,3-diene products, **12** and **14**, without accumulation of cyclobutene intermediates. This observation indicates that the rate-determining step in the [2+2] CA–RE using **9** and **10** is the initial cycloaddition, which is consistent with previous experimental and computational results.[6d]

Table 1: CA–RE reaction activation parameters at 298 K in $(CDCl_2)_2$ determined by monitoring the respective reaction using ^{1}H NMR spectroscopy and subsequent Eyring analysis.

Reaction[a]	$\Delta G^{\ddagger}$ [kcal mol^{-1}]	$\Delta H^{\ddagger}$ [kcal mol^{-1}]	$\Delta S^{\ddagger}$ [cal mol^{-1} K^{-1}]
1 + TCNE → **3**	20.1 ± 0.2	9.17 ± 0.17	−36.7 ± 0.5
3 → **4**	26.9 ± 0.3	27.2 ± 0.2	−0.7 ± 0.7
2 + TCNE → **6**	19.1 ± 0.6	5.0 ± 0.4	−47.4 ± 1.3
6 + TCNE → **7** → **8**	21.6 ± 0.6	14.0 ± 0.5	−25.4 ± 1.4
8 → (±)-**5**	27.6 ± 0.6	27.3 ± 0.4	−0.9 ± 1.2
9 + TCNE → **12**	24.9 ± 0.5	11.3 ± 0.4	−45.7 ± 1.1
10 + TCNE → **14**	24.2 ± 0.4	10.4 ± 0.3	−46.3 ± 0.8

[a] All CA reactions with TCNE were found to be second order, and all RE reactions were found to be first order.

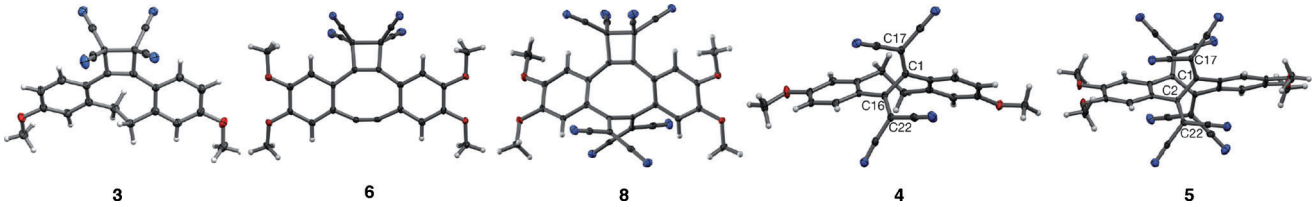


Figure 1. X-ray single-crystal structures of intermediates **3**, **6**, and **8**, and diene products **4** and **5**. Only one enantiomer each of **3**, **4**, **5**, and **8** are shown; both enantiomers were found in the crystals. Thermal ellipsoids are shown at the 50% probability level. Selected torsion angles: C17-C1-C16-C22 −105.5(1)° (**4**); C17-C1-C2-C22 −105.9(1)° (**5**).

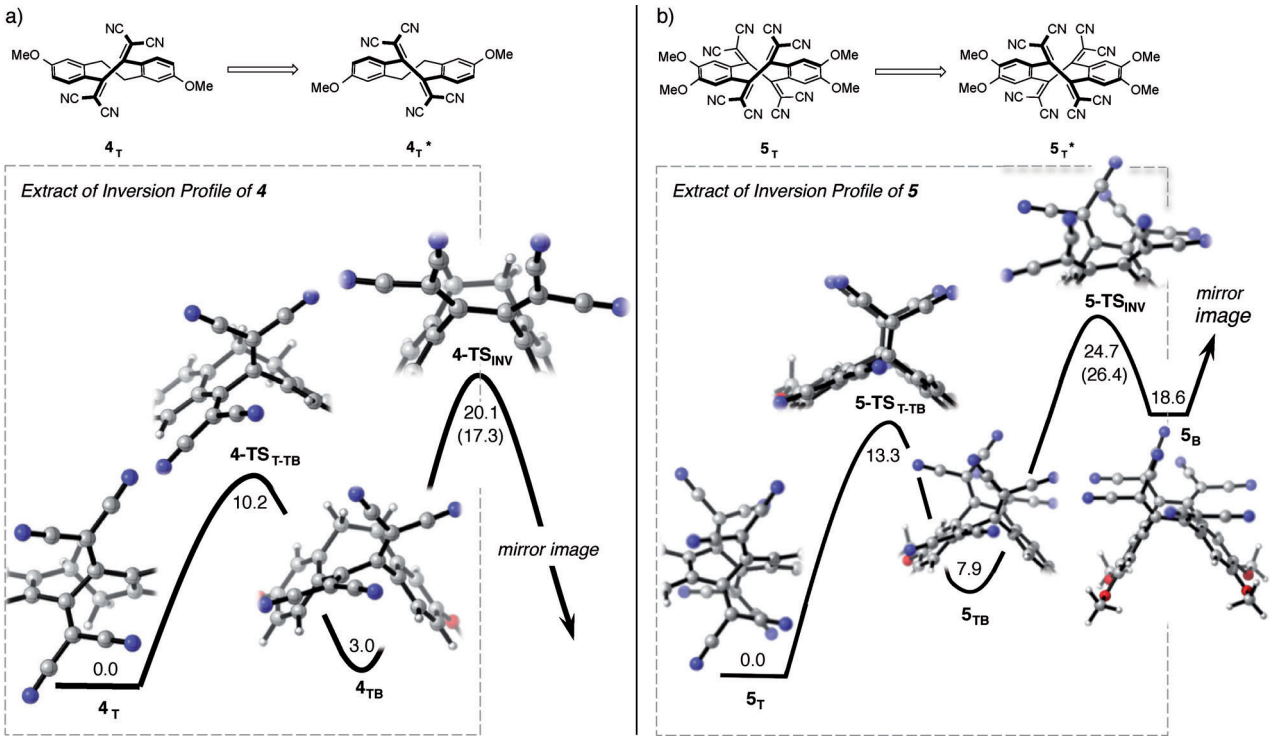
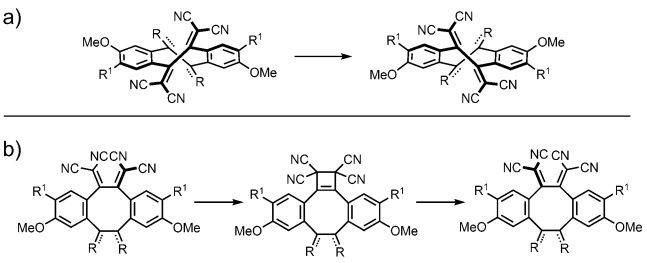


Figure 2. Proposed mechanisms for the enantiomerization of compounds a) **4** and b) **5**. Free enthalpy profiles (ΔG_{298K} in kcal mol^{-1}) calculated at the COSMO-RS ($(CHCl_2)_2$) M062X/6-31+G(d)//B3LYP/6-31G(d) level of theory.[15] Experimental values are given in parentheses.

We commenced quantitative studies using cyclooctyne **1** because it possesses only one reactive alkyne moiety. Both the second-order CA (**1** + TCNE → **3**) and first-order RE (**3** → **4**) steps of the overall transformation could be monitored separately (Table 1). For the second, rate-determining RE step, $\Delta G^{\ddagger} = 26.9$ kcal mol^{-1}, wherein the primary contribution was enthalpic ($\Delta H^{\ddagger} = 27.2$ kcal mol^{-1}, Table 1). Strain accelerates the CA step: $|\Delta\Delta G^{\ddagger}| = 4.8$ kcal mol^{-1} for CA of cyclooctyne **1** with TCNE relative to the analogous reaction using linear alkyne **9**.[14] This difference corresponds to a roughly 3300-fold rate enhancement at 298 K. For the overall CA–RE transformation at 383 K, a temperature at which reactions using cyclooctyne **1** and linear alkyne **9** could be monitored under identical conditions, strain contributes to a 16-fold rate enhancement: $k_{\mathbf{1}\rightarrow\mathbf{4}} = 3.13 \times 10^{-4}\,\mathrm{M^{-1}\,s^{-1}}$ und $k_{\mathbf{9}\rightarrow\mathbf{12}} = 4.94 \times 10^{-5}\,\mathrm{M^{-1}\,s^{-1}}$.

Strain acceleration was even more pronounced in reactions using cyclooctadiyne **2**. Quantitative studies on this system (results shown in Table 1), which possesses two reactive C≡C bonds, required careful selection of reaction conditions such that clean conversion to each intermediate and the final product could be individually monitored. Monoaddition of TCNE with **2** yielded **6** quantitatively, followed by a second CA step to form bis-adduct **7**, which spontaneously converted to cyclobutene-butadiene intermediate **8**. The final RE step (**8** → (±)-**5**) was shown to be the rate-determining step of the overall transformation ($\Delta G^{\ddagger} = 27.6$ kcal mol^{-1}). Strain substantially lowers the activation free enthalpy of CA of cyclooctadiyne **2** compared to linear alkyne **10**: $|\Delta\Delta G^{\ddagger}| = 5.1$ kcal mol^{-1} for the first CA step, and 2.6 kcal mol^{-1} for the second CA step, corresponding to rate enhancements of 5500- and 80-fold, respectively, at 298 K.

Having experimentally quantified the rate acceleration in [2+2] CA–RE reactions using cyclic substrates **1** and **2**, we turned our attention to investigating the potential enantiomerization pathways of the exocyclic butadiene products **4** and **5** using density functional theory computations[15] (see the Supporting Information, Section S9 for details).[16] Two enantiomerization pathways were considered: 1) a direct ring flip (Scheme 2a) and 2) a pericyclic sequence involving ring-closure of one butadiene enantiomer to give a planar cyclobutene intermediate, followed by ring-opening to give the other enantiomer (Scheme 2b). The former was found to be the lowest-energy enantiomerization pathway for all compounds investigated, and is illustrated for butadiene **4** in Figure 2a. Twist conformation $\mathbf{4_T}$ isomerizes to a twist-boat conformation ($\mathbf{4_{TB}}$) via transition state **4-TS$_{T\text{-}TB}$**. Inversion



Scheme 2. Potential pathways for enantiomerization of butadienes, studied computationally: a) direct ring flip; b) pericyclic ring closure followed by ring opening.

then occurs via a boat transition state (**4-TS$_{INV}$**), with an overall activation barrier of 20.1 kcal mol^{-1} to yield the enantiomeric intermediate **4$_{TB}$***.[17]

Analogous studies on tetraene **5**, which possesses two chiral axes, suggest that enantiomerization proceeds in a two-step fashion. The increased rigidity of tetraene **5** relative to butadiene **4** is manifested in higher-energy intermediates and activation energies associated with racemization (Figure 2b). Similar to butadiene **4**, twist conformation **5$_T$** converts to twist-boat conformation **5$_{TB}$**, which does not directly racemize, but must first overcome a 24.7 kcal mol^{-1} activation barrier to reach the achiral, C_s-symmetric boat intermediate **5$_B$**. Thus, enantiomers of **5** were predicted to be configurationally stable at room temperature. Given these insights, we sought to probe the conformational dynamics of these compounds experimentally.

At room temperature in $(CDCl_2)_2$, the ^{1}H NMR spectrum of butadiene **4** showed two signals corresponding to the geminal methylene protons on the eight-membered ring, indicating that enantiomer interconversion was slow on the NMR timescale. Coalescence of these signals was observed at elevated temperatures (Figure 3a). Conversely, in cyclobutene intermediate **3**, the geminal methylene protons on the eight-membered ring gave rise to only one signal in the ^{1}H NMR spectrum in CD_2Cl_2 at room temperature; decoalescence to two signals occurred upon cooling (Figure 3b). By performing iterative lineshape analysis on ^{1}H NMR spectra of these compounds acquired at varied temperatures, we derived rate constants for enantiomer interconversion at each temperature. Free enthalpies of activation for enantiomer interconversion were determined using Eyring analysis.

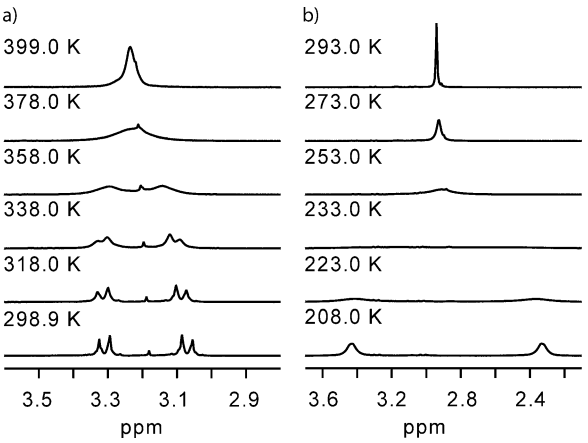


Figure 3. Variable-temperature ^{1}H NMR spectra (500 MHz) of a) butadiene **4** in $(CDCl_2)_2$, and b) cyclobutene **3** in CD_2Cl_2.

A value of 10.4 kcal mol^{-1} was obtained for cyclobutene **3**, while that for butadiene **4** was 17.3 kcal mol^{-1} (Table 2). The latter is in agreement with the computed value, but insufficient for enantiomer separation at room temperature. We hypothesized that the ethylene bridge of the eight-membered ring was the source of conformational fluxionality in butadiene **4**, and therefore turned our attention to tetraene **5**, where we predicted that the additional exocyclic butadiene moiety might render the eight-membered ring more rigid.

Table 2: Activation parameters at 298 K for the racemization of cyclobutene **3** and dienes **4** and **5**.

Compound	$\Delta G^{\ddagger}$ [kcal mol^{-1}]	$\Delta H^{\ddagger}$ [kcal mol^{-1}]	$\Delta S^{\ddagger}$ [cal mol^{-1} K^{-1}]
3[a]	10.40 ± 0.07	9.80 ± 0.05	−2.01 ± 0.17
4[a]	17.3 ± 1.8	15.2 ± 1.4	−7.0 ± 4.0
5[b]	26.4 ± 2.0	37.6 ± 1.6	37.4 ± 5.0

[a] Determined using iterative lineshape fitting of variable-temperature ^{1}H NMR spectra recorded in CD_2Cl_2 (**3**) or $(CDCl_2)_2$ (**4**) and subsequent Eyring analysis. [b] Determined using Eyring analysis on variable-temperature ECD measurements in $(CHCl_2)_2$.

Separation of enantiomers of tetraene (±)-**5** by chiral HPLC was extremely challenging due to the very low solubility of the compound in solvents that enabled optical resolution, causing partial crystallization on the column (Supporting Information, Section S7). However, enantiomerically enriched samples of **5** were isolated ((+)-**5**: 14% *ee* and (−)-**5**: 21% *ee*) and their electronic circular dichroism (ECD) spectra were recorded. Figure 4 shows the ECD spectra for the enantiomerically pure compounds, which were calculated from the experimental spectra of the enantiomerically enriched samples. The absolute configurations of the enantiomers, *P*,*P*-(+)-**5** and *M*,*M*-(−)-**5**, were assigned by comparison of simulated ECD spectra (CAM-B3LYP/6-31G(d)) with the experimental spectra (Supporting Information, Section S10). Because tetraene **5** is a D_2-symmetric molecule and lacks diastereotopic protons, dynamic NMR techniques could not be used to monitor the enantiomer interconversion. However, first-order rate constants for the racemization process of the enantiomerically enriched samples were obtained by monitoring the ECD signal decay over time at various temperatures in $(CHCl_2)_2$. Subsequent Eyring analysis showed that $\Delta G^{\ddagger} = 26.4 \pm 2$ kcal mol^{-1} for racemization of tetraene **5**, which is in good agreement with the computationally predicted value (Table 2).[18] Compared to previously

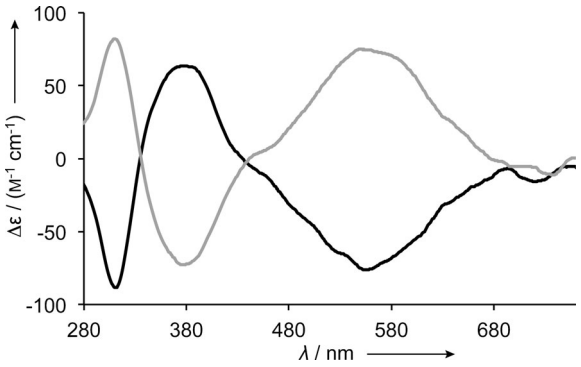


Figure 4. ECD spectra of enantiomerically pure *P*,*P*-(+)-**5** (gray) and *M*,*M*-(−)-**5** (black line) in $(CHCl_2)_2$ at 298 K, calculated from the experimental spectra measured for enantiomerically enriched samples (see the Supporting Information, Section S7).

reported examples of rotationally hindered butadienes, this value is among the highest observed.[8,9]

In summary, we have demonstrated and quantified strain-accelerated reactivity in the context of a formal [2+2] cycloaddition–retroelectrocyclization (CA–RE) sequence between electron-deficient alkenes and electron-rich alkynes; in addition, we isolated a rare example of a chiral buta-1,3-diene that is optically active and configurationally stable at room temperature. Isolation of reaction intermediates enabled kinetic studies on these systems, revealing that the rates of cycloaddition using strained alkynes are up to 5500 times greater at 298 K than those of unstrained systems. Computational studies elucidated the enantiomerization mechanism of the resulting buta-1,3-diene products, indicating that enantiomerization of these eight-membered rings occurs via a direct ring-flip mechanism involving initial isomerization to a boat conformer. In agreement with computed values, experimentally measured activation barriers to racemization were found to be up to 26 kcal mol^{-1} in the case of tetraene **5**. Having isolated members of this new class of configurationally stable, chiral buta-1,3-dienes, and studied the mechanism for their formation and enantiomerization, we envision future applications in chiral sensors,[19] chiral molecular magnets,[20] and chiral memory units,[21] and as novel atropisomeric diene ligands for asymmetric catalysis.[22]

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