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Mono-, Di-, and Trifluoroalkyl Substituent Effects on the Torquoselectivities of Cyclobutene and Oxetene Electrocyclic Ring Openings

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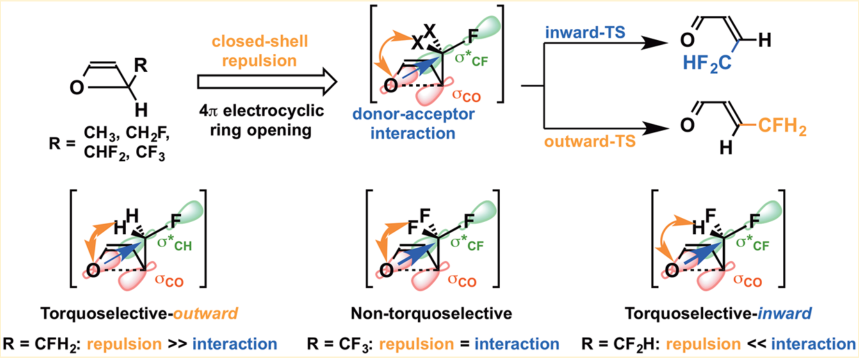
Supporting Information



ABSTRACT: The reactivities and torquoselectivities of electrocyclic ring opening reactions of fluoromethyl-substituted cyclobutenes and oxetenes were studied with M06-2X density functional theory. The torquoselectivities of a series of mono-, di-, and trifluoromethylcyclobutenes and oxetenes result from the interplay of favorable orbital interactions and closed-shell repulsions. When the substituent rotates inward, there can be a favorable interaction between the breaking σ_{CO} bond and the σ_{CF}* orbital ($\sigma_{CO} \rightarrow \sigma_{CF}$*) of the fluoromethyl group in fluoromethyloxetenes. The preference for rotation of a fluoromethyl group is decreased in trifluoromethyloxetenes because closed-shell repulsions between the breaking σ_{CO} bond and trifluoromethyl substituent orbitals compete with the $\sigma_{CO} \rightarrow \sigma_{CF}$* interaction.

INTRODUCTION

One of us (K.N. Houk) joined R.B. Woodward's research group as a first-year graduate student at Harvard in early January of 1965, just when Woodward and Hoffmann published the *JACS* communication, "Stereochemistry of Electrocyclic Reactions".

In that communication, Woodward and Hoffmann defined conrotatory and disrotatory stereoselectivities and gave theoretical insights into the rules that show which stereochemistry is favored, based upon the number of electrons involved. There have been many theoretical elaborations of these rules by correlation diagrams, concepts of aromaticity, and frontier molecular orbitals. This aspect of Woodward–Hoffmann theory remains the most robust aspect, and experimentalists have shown as much as 15 kcal mol^{-1} differences between allowed and forbidden activation barriers.

In the last paragraph of the 1965 communication, Woodward and Hoffmann gave one example of what our group later named "torquoselectivity", the preference for one of the allowed modes of electrocyclic ring opening. Woodward and Hoffmann noted "Ordinarily, simple steric factors will be expected to direct the changes preferentially along one of the two paths, but in some cases, very interesting special stereoelectronic factors may be definitive."[1] They showed the example of a ring opening that occurs upon solvolysis of cyclopropyl tosylates and related species. The leaving groups dictate which disrotatory process occurs.[1]

In 1984, our group explored the selectivity of the conrotatory ring openings of substituted cyclobutenes.[2c] Torquoselectivity is "the preference for inward or outward rotation of substituents in conrotatory or disrotatory electrocyclic reactions", the selectivity as "preferentially along one of two [allowed] paths." In hundreds of papers since then, our groups and others have established the robustness of the torquoselectivity rules. In short, while large groups prefer to rotate outward, as Woodward and Hoffmann anticipated, electronic factors are even more important: π-donors rotate outward, and π-acceptors rotate inward.

Cyclobutenes undergo thermal conrotatory 4π electrocyclic ring opening reactions to afford 1,3-butadienes.[1] Substituents

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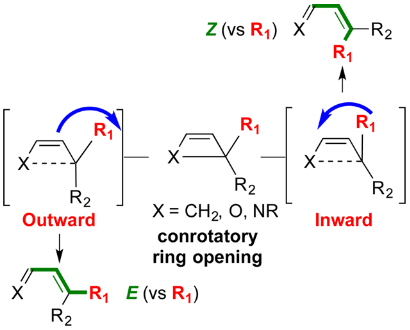
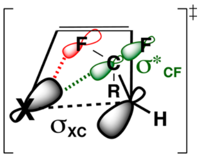
may rotate "inward' or "outward" during the course of reaction; a preference for one of these diastereomeric transition states is called torquoselectivity.[2] This selectivity has been shown to arise from interactions between the substituent orbitals and those of the breaking bond. Donors rotate outward to avoid repulsive filled−filled interactions with the HOMO of cyclobutene upon inward rotation. Acceptors have low-lying vacant orbitals and the best acceptors (CHO, − SiR_3, − GeR_3) preferentially rotate inward. The reactivities and torquoselectivities of four-membered heterocycles such as 2-azetines,[3] oxetenes, and thietes[4] have received renewed attention. These cyclobutenes and heterocyclic derivatives can be designed to undergo ring opening reactions to afford functionalized dienes and heterodienes stereoselectively. The trifluoromethyl group is of great importance in synthetic organic chemistry[5] and medicinal[6] chemistry because of its unique steric and electronic properties.[7] While major strides have been made in late-stage functionalization of heteroaromatic substrates with the CF_3 group, stereoselective functionalization of tri- and tetrasubstituted alkenes is quite limited.[8] Recent work by Mikami et al. fills this void in the literature by utilizing a torquoselective electrocyclic ring opening reaction of oxetenes[9] (Scheme 1) inspired by earlier reports by Houk et al. on the electrocyclic ring opening of 3-trifluoromethylcyclobutene.[10]

Scheme 1. 4*π*-Electrocyclic Ring Opening of Carbocyclic and Heterocyclic Four-Membered Rings



Thermal 4*π*-electrocyclic ring openings proceed via conrotation of the termini to form the corresponding dienes, in accordance with the Woodward−Hoffmann rules.[11] 3-Trifluoromethylcyclobutenes undergo slightly torquoselective electrocyclic ring opening reactions with inward rotation of the trifluoromethyl group.[10] Mikami and co-workers report high torquoselectivities for the electrocyclic ring opening of 3-trifluoroalkyloxetenes (>75% inward rotation product). These studies suggest that a through-space orbital interaction between the breaking σ_{CO} orbital with the σ_{CF}* orbital of the trifluoromethyl group is responsible for the preference of inward rotation in oxetenes. Scheme 2 illustrates this orbital interaction in transition structures where the fluoroalkyl group rotates inward. The favorable ($\sigma_{CO} \rightarrow \sigma_{CF}$*) interaction is shown in green, and unfavorable closed-shell repulsions between the fluorine lone pair orbitals and the breaking σ_{CO} orbital (^{n}F−σ_{CO}) are shown in red. The interplay of these effects will be discussed in the second part of this report for oxetenes **11−18**.

Scheme 2. Orbital Interactions upon Inward Rotation of the Fluoroalkyl Substituent



Scheme 2 shows the relative stability of trifluoromethyl-substituted oxetenes at ambient conditions. In contrast, other oxetenes undergo rapid electrocyclic ring opening to afford *α*,*β*-unsaturated carbonyl compounds without isolation of the oxetene intermediates (Scheme 3).[5a]

We have applied density functional theory to understand the origin of reactivities and torquoselectivities of mono-, di-, and trifluoromethyloxetenes. Scheme 4 shows the scope of cyclobutenes and oxetenes studied here. The electrocyclic ring opening reactions of oxetenes and cyclobutenes without alkenyl substituents (**1−10**), 2-phenyloxetenes bearing mono-, di-, and trifluoromethyl groups at the 2-position (**11−18**), and 2-phenyloxetenes disubstituted at the 2-positions were studied to determine the origin of the reactivities and torquoselectivities.

■ COMPUTATIONAL METHODS

All computations were carried out with Gaussian09, Rev.D01.[12] Reactants, transition states, and products were optimized with the density functional M06-2X using the 6-31+G(d,p) basis set and the IEF-PCM[13] model for toluene to correct for solvent effects. Vibrational analysis confirmed all stationary points to be minima (no imaginary frequencies) or transition structures (one imaginary frequency). Thermal corrections were computed from unscaled frequencies for the standard state of 1 atm and 298.15 K.

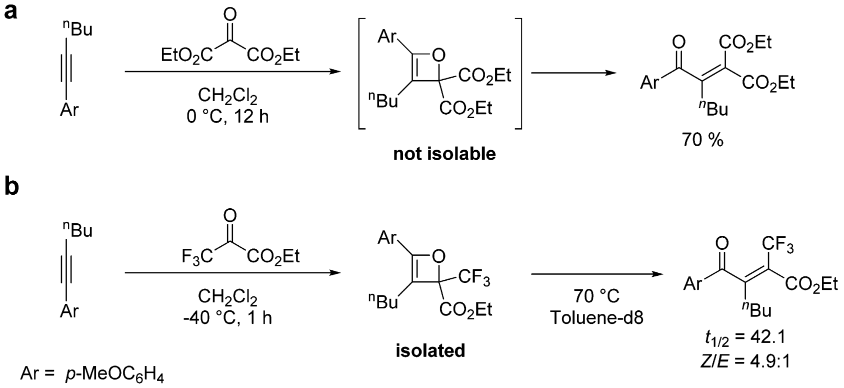
■ RESULTS AND DISCUSSION

The lowest energy transition structures for both modes of conrotation for parent cyclobutenes (**1−5**) and oxetene derivatives (**6−10**) are given in Figure 1. For all transition structures, possible steric clashes are indicated by dotted black lines for contacts with radii less than the sum of their van der Waals radii.[14] The disfavored transition structures are given in the Supporting Information with their activation free energies.

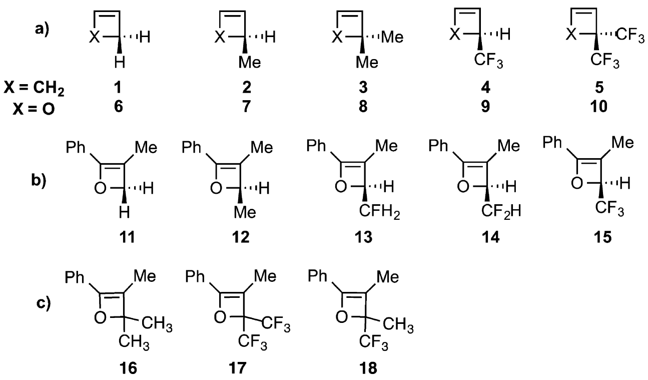
The breaking C−C bond lengths range from 2.13 to 2.18 Å in the carbocyclic transition structures (**TS1−TS5**). The activation free energy ($\Delta G^{\ddagger}$) of cyclobutene is 35.2 kcal mol^{-1}. The 3-methylcyclobutene is torquoselective for the "out" transition structure and has an activation free energy ($\Delta G^{\ddagger}$ = 32.6 kcal mol^{-1}) lower than that of cyclobutene. The 3-trifluoromethylcyclobutene also prefers to rotate outward but is predicted to undergo electrocyclic ring opening much more slowly ($\Delta G^{\ddagger}$ = 36.6 kcal mol^{-1}). The preference for the "out" transition state is due to the decreased steric congestion in that mode of conrotatory ring opening. The disubstituted cyclobutenes (**3** and **5**) have relatively bulky substituents (CF_3 and CH_3), and their transition states feature relatively long C−C and C−O breaking bond lengths (2.18 Å) to minimize closed-shell repulsion between the substituents and the breaking σ_{CC} orbital. The unavoidable steric clashes in **TS3** and **TS5** result in relatively high activation free energies (37.4 and 38.2 kcal mol^{-1}, respectively).

The oxetene transition structures have C−O breaking bond lengths that range from 1.96 to 2.06 Å, somewhat shorter than those of the carbocyclic transition structures. The C−O breaking bond lengths are shorter in the reactant state, which are reflected in the transition structures. The oxetenes have

Scheme 3. Synthesis of Oxetenes via a [2 + 2] Cycloaddition and Subsequent Ring Opening Reaction[9a]



Scheme 4. Mono- and Disubstituted Cyclobutene and Oxetene Derivatives



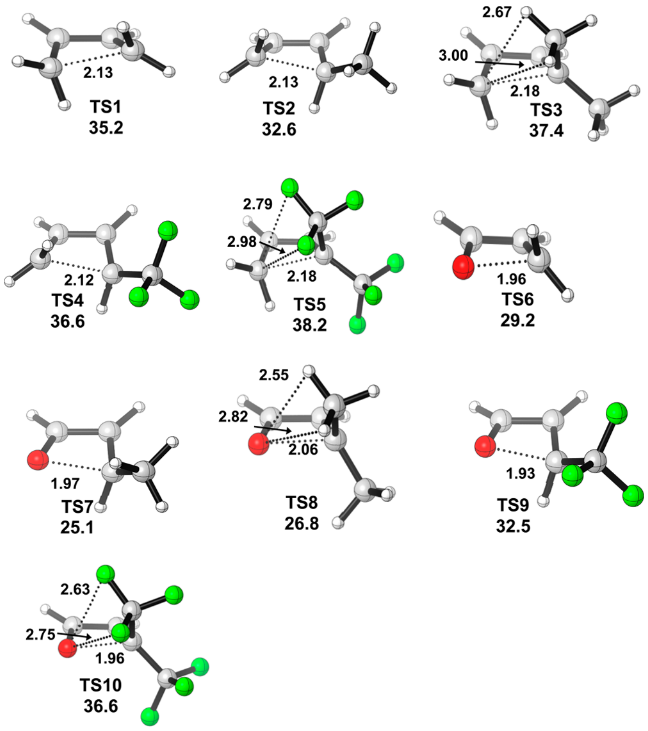


Figure 1. Optimized transition structures of model cyclobutenes and oxetenes. Distances and energies are reported in angstroms and kcal mol^{-1}, respectively.

activation free energies that are 4−10 kcal mol^{-1} lower than those of the cyclobutene derivatives. The difference is large for the parent and alkyl-substituted cases but lowest for the trifluoromethyl-substituted oxetenes. The electrocyclic ring openings of both 2-methyloxetene (**7**) and 2-trifluoromethyloxetene (**9**) prefer outward rotation of the substituent and have activation free energies of 25.1 and 32.5 kcal mol^{-1}, respectively. 3,3-Disubstituted oxetenes (**8** and **10**) have relatively high activation barriers due to unavoidable closed-shell substituent−σ_{CO} interactions in these transition states.

In this section, we report transition structures for 2-phenyl-substituted oxetenes and evaluate how different fluoroalkyl groups affect the reactivities and torquoselectivities of oxetenes **11**−**15**. The transition structures for both modes of conrotatory ring opening and corresponding activation free energies are shown in Figure 2.

Reactivity. The 2-phenyloxetenes have activation free energies ~1 kcal mol^{-1} higher than that of the parent oxetene. The breaking C−O bond length in these transition structures ranges from 1.95 to 2.02 Å; they are relatively unchanged from those of the **TS6**−**TS10** without the phenyl. The 2-monosubstituted oxetenes bearing substituents with increasing σ-acceptor characteristics have higher activation barriers along the series **12**, **13**, **14**, and **15** (26.8−34.0 kcal mol^{-1}). The 7.2 kcal mol^{-1} increase in activation free energy makes the ring opening of **15** approximately 500-fold slower than that for **12**, which is in line with the elevated temperatures required for the ring opening of **15** (70 °C; Scheme 2).

Torquoselectivity. Torquoselectivity is the difference in activation free energies between the two modes of conrotation ($\Delta\Delta G^{\ddagger}$). The electrocyclic ring opening of 2-methyloxetene **12** is predicted to be the most facile of the reactions shown in Figure 3. The $\Delta G^{\ddagger}$ of **TS12-out** is 26.8 kcal mol^{-1} and is predicted to be the most torquoselective for outward rotation of CH_3 ($\Delta\Delta G^{\ddagger}$ = 5.8 kcal mol^{-1}). The $\Delta G^{\ddagger}$ for the ring opening of monofluoromethyloxetene **13** is 2.2 kcal mol^{-1} higher and less torquoselective but still favors the outward rotation of CH_2F by 2.6 kcal mol^{-1}. The decreased torquoselectivity stems from the stabilization of the "in" transition structure via a through-space interaction ($\sigma_{CO} \rightarrow \sigma_{CF}^*$) between the σ_{CO} orbital and the σ_{CF}^* orbital ($\sigma_{CO} \rightarrow \sigma_{CF}^*$). The C−F bond in **TS13-in** is oriented to maximize $\sigma_{CO} \rightarrow \sigma_{CF}^*$.

The reversal of torquoselectivity occurs when monofluoromethyl is changed to difluoromethyl; the **TS14-in** of the difluoromethyl case is increased by 3.2 kcal mol^{-1} compared to **TS13-out**. However, the **TS14-in** is now lower in energy than **TS14-out** by 1.4 kcal mol^{-1}. Thus, the ring opening of **14** is torquoselective for inward rotation; the energy of the σ_{CF}^*

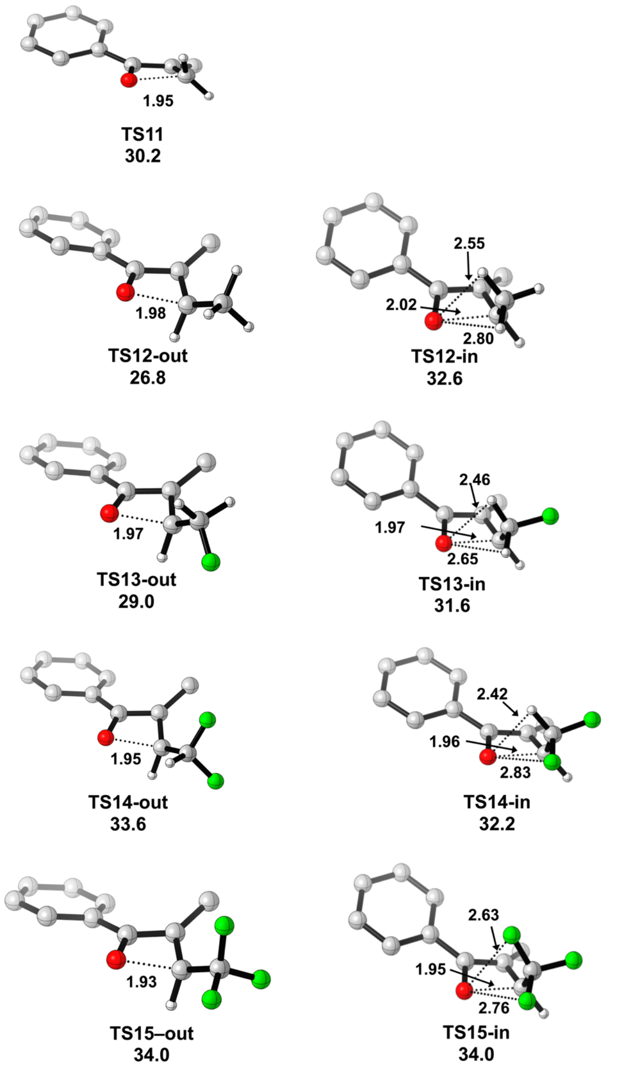


Figure 2. Two transition structures for conrotatory electrocyclic ring openings of **11**−**15**. Distances and energies are reported in angstroms and kcal mol^{-1}, respectively.

orbital is lower than that of **13** because of the additional geminal fluorine, and the $\sigma_{CO} \rightarrow \sigma_{CF}{}^*$ becomes more favorable. The activation free energies of the trifluoromethyl case, **TS15-out** and **TS15-in**, are both 34.0 kcal mol^{-1}. This reaction is not torquoselective because **TS15-in** has a competition of the $\sigma_{CO} \rightarrow \sigma_{CF}{}^*$ effect and unavoidable closed-shell repulsions between fluorine lone pair orbitals (^{n}F) and (σ_{CO}) upon inward rotation. These interaction lengths are 2.63 and 2.76 Å, which are less than the sum of the oxygen and fluorine van der Waals radii (2.99 Å).[14] The geometry of **TS15-out** does not allow for $\sigma_{CO} \rightarrow \sigma_{CF}{}^*$ stabilization. An NBO analysis shows that the $\sigma_{CO} \rightarrow \sigma_{CF}{}^*$ is present when the fluoroalkyl substituents rotate inward.[9b]

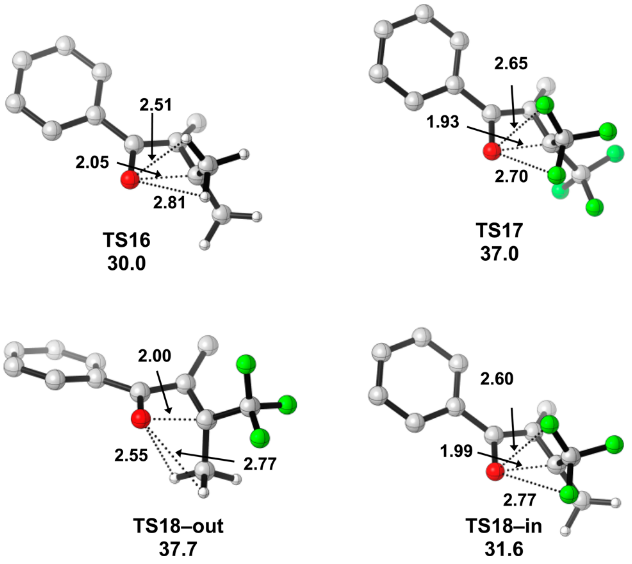


Figure 3. Transition structures for the electrocyclic ring opening reactions of disubstituted oxetenes **16**−**18**. Distances and energies are reported in angstroms and kcal mol^{-1}, respectively. Computed using M06-2X/6-31+G(d,p)/PCM^{tol}.

We also explored a number of reactions of 2,2-disubstituted substrates. These substituents are mono-, di-, and trifluoromethyl groups like **12**−**15** (CH_2F, CHF_2, and CF_3, respectively). The subsequent discussion will focus on the ring opening of 2,2-dimethyloxetene (**16**), 2,2-bistrifluoromethyloxetene (**17**), and 2-methyl-2-trifluoromethyloxetene (**18**). The transition structures and activation free energies for these reactions are given in Figure 3. The transition structures, coordinates, and energies of the other 2,2-disubstituted oxetenes can be found in the Supporting Information.

The 2,2-disubstituted oxetenes have activation free energies generally higher than those of the 2-monosubstituted oxetenes. The $\Delta G^‡$ values of **TS16** and **TS17** are 30.0 and 37.0 kcal mol^{-1}, respectively. The $\Delta G^‡$ values for 2-methyloxetene (**12**) and 2-trifluoromethyloxtene (**15**) are 26.8 and 34.0 kcal mol^{-1}, respectively. These barriers are higher by ~3 kcal mol^{-1} because unavoidable closed-shell repulsions (^{n}F−σ_{CO}) make the transition states more unfavorable. The electrocyclic ring opening of **18** can involve either outward rotation of CH_3 and inward rotation of CF_3 (**TS18-out**) or inward rotation of CH_3 and outward rotation of CF_3 (**TS18-out**). The $\Delta G^‡$ for the favored transition state (**TS18-in**) is 31.6 kcal mol^{-1}. This ring opening is very torquoselective ($\Delta\Delta G^‡$ = 6.1 kcal mol^{-1}) because of simultaneously favorable outward rotation of CH_3 and inward rotation of CF_3. Inward rotation of CF_3 facilitates $\sigma_{CO} \rightarrow \sigma_{CF}{}^*$ while avoiding closed-shell repulsions between methyl hydrogens with σ_{CO}.

■ CONCLUSION

The reactivities of oxetene electrocyclic ring openings are controlled by the electronic character of the substituent of 2-substituted oxetenes. Oxetene ring opening is accelerated when the substituent at the 2-position is a σ-donor. σ-Acceptors cause the ring opening to occur less readily due to stronger ^{n}F−σ_{CO} interaction upon inward rotation of the fluoromethyl substituent, in particular. The torquoselectivities are thus controlled by a competition of $\sigma_{CO} \rightarrow \sigma_{CF}{}^*$ effect and unfavorable closed-shell repulsions. Our calculations suggest that 2-difluoromethyloxetenes prefer inward rotation because the favorable $\sigma_{CO} \rightarrow \sigma_{CF}{}^*$ orbital effect outweighs closed-shell repulsions in the transition state.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01361.

Structures and energies of all considerable reactants and transition structures (PDF)

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Notes

The authors declare no competing financial interest.

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