

Substituent Effects and Nearly Degenerate Transition States: Rational Design of Substrates for the Tandem Wolff–Cope Reaction

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The Cope reaction is a degenerate transformation whose synthetic utility lies in its versatility as a *stereospecific relay of functionality*.¹ Expanding the reaction's functional scope while preserving its specificity allows for more direct formation of desired products. Recently, Stoltz et al. have discovered² a novel tandem Wolff–Cope reaction involving the rearrangement of vinylcyclopropyl ketene intermediates (e.g., **2** and **7**) to [*n* – 7] bicyclic structures (e.g., **3** and **9**) that serve as a motif for a number of natural product syntheses (Scheme 1). The reaction produces products cleanly and in high yield with a variety of substrates, but interestingly is thwarted by substitution at certain positions (**4** and **5**, see Table 2). First-principles quantum mechanics (B3LYP flavor of unrestricted density functional theory, 6-31G** basis functions)³ indicate this substituent limitation to be a direct consequence of a competing low-barrier pathway that leads to an unstable and undesired *trans*-olefin product via a boatlike transition state. *The lowered barrier of the competing pathway is a direct result of the appended ketene functionality*. Understanding how methyl substituents influence our *specific* Wolff–Cope transition state leads us to the design of new 4,5-substituted substrates predicted to rearrange successfully. Understanding how ketene and related functionalities influence the *general* Cope transition state leads us to insights into transition-state mutability which may be exploited in other reaction designs.

Divinylcyclopropane analogues of **4** have been observed⁴ to rearrange into fused cycloheptadienes (e.g., **6**) in high yield. The relative instability of the *trans*-olefin product **5** drives its corresponding activation energy upward to a safely inaccessible level.⁵ We now consider the reaction of ketene vinylcyclopropane substrate **7**. Products **8** and **9** are conjugated to the newly formed carbonyl, and are equally stabilized relative to **5** and **6**, but transition state **11** is more stabilized relative to **10** than **13** is relative to **12** (Figure 1). The energies of transition states **11** and **13** (Figure 2) are thus similar, and the reaction outcome becomes highly sensitive to substituent effects that can change the relative ordering of the two energies.

Geometries **10** and **12** are nearly intermediate between the starting structures and products, and are termed synchronous; in contrast, geometries **11** and **13** display a higher degree of asynchronicity, so that the new carbon–carbon bond is more fully formed when the cyclopropane bond begins to break.⁶ The additional radicaloid character of transition state **11** is stabilized by conjugation through the forming carbonyl.⁷ A comparison with allene substrates (not shown) indicates that the relative stabilization is due in equal parts to an allylic radical effect and to the increased electronegativity of the oxygen center.

To explain why the ketene group stabilizes **11** and **13** to nearly equal energies, we first note that Cope transition states can be viewed as a resonance hybrid of aromatic and diradical forms.⁸ Comparing the relative energies of generalized valence bond (GVB) pairs (Table 1) in model transition states **14**–**16**, we see that a diradical form contributes significantly to **16**-chair but not **16**-boat,

Scheme 1. Tandem Wolff–Cope Rearrangement

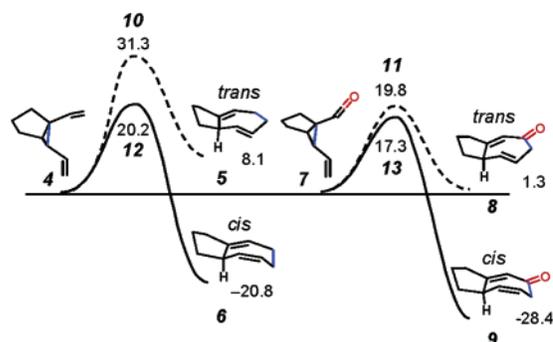
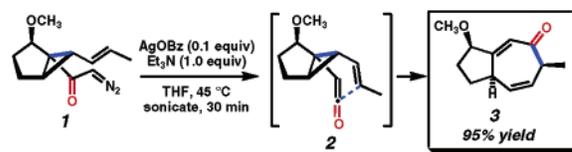


Figure 1. (a) Cope reaction pathways available to a divinylcyclopropane substrate lead to either the desired *cis*-olefin product or a less stable undesired *trans*-olefin product. (b) Analogous pathways for a ketene-substituted substrate show a smaller activation energy difference (ΔG in kcal/mol, $T = 298$ K). All structures are drawn from actual coordinates.

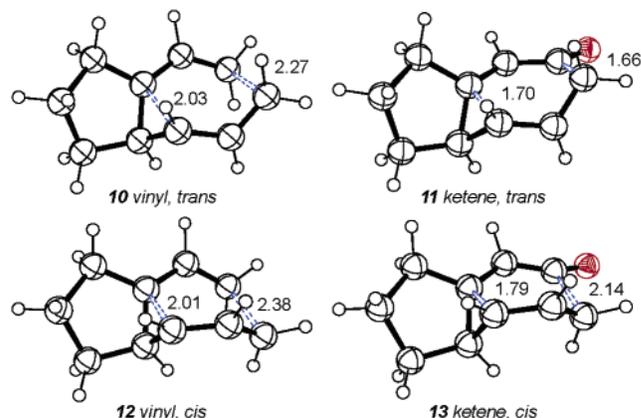


Figure 2. Transition states leading to the *trans* (**10**, **11**) and *cis* (**12**, **13**) products from vinyl-substituted (**10**, **12**) and ketene-substituted (**11**, **13**) substrates. Transition state **11** differs from the others in its radicaloid character and extreme degree of asynchronous bond formation (distances in angstroms).

a difference consistent with divergent radical-chair vs. aromatic-boat pathways in the ketene Cope reaction. In the full system, we find that **13** is predominantly aromatic ($\Delta E_{\text{singlet-triplet}}^{\text{vertical}} = 51.0$ kcal/mol) while **11** has some radical character ($\Delta E_{\text{singlet-triplet}}^{\text{vertical}} = 31.6$ kcal/mol) and is thus more susceptible to the influence of the radical-stabilizing carbonyl.⁹

The addition of methyl substituents (Table 2) leaves the geometries of the *cis* (boat) and *trans* (chair) transition states largely

Table 1. Single Point Energies (kcal/mol) of Alternate GVB Pairings in Model Transition-State Structures^a

#	Reactant	TS			
14		boat	9.1	14.0	9.1
		chair	0.0	16.5	0.0
15		boat	18.7	40.8	41.4
		chair	0.0	33.6	42.6
16		boat	0.0	20.6	23.9
		chair	1.9	2.0	13.6

^a The diradical pair (shaded) makes a significant resonance contribution (lower energy) to the ketene chair structure but not the ketene boat structure, a difference present to a lesser extent in model allene **15** as well.

Table 2. Effect of Single Methyl Substituents on the Relative Activation Energies of Cis/Trans Pathways^a

#	subst pos.	ΔG_{cis}^\ddagger	$\Delta G_{trans}^\ddagger$	$\Delta G_{cis-trans}^\ddagger$
13	7 none	15.8	18.3	-2.5
	17a 1	15.0	17.4	-2.4
	17b 2	14.6	19.2	-4.6
	17c 3	16.6	20.0	-3.4
	17d 4	22.4	19.7	2.7
17e 5	18.3	17.3	1.0	

^a Shading indicates reactions predicted to fail ($\Delta G_{cis-trans} > 0$). Of twelve substrates (similar to **17a–e**) tried experimentally, seven were predicted to rearrange and did so, and five were predicted to fail and did so.¹⁰

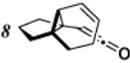
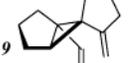
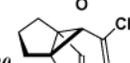
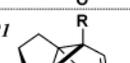
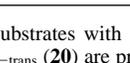
unperturbed. Positions 4 and 5 are separated by only 2.13 Å in **13**, so substitution at either position causes a large (6.6 and 2.5 kcal/mol, respectively) destabilization. The substituents in **11** are spaced farther apart; the largest substituent effect (1.7 kcal/mol) arises from a near-eclipsing interaction between position 3 and the carbonyl oxygen. The end result is consistent with experimental observation: substitution at positions 4 or 5 causes destabilization of the desired cis transition state relative to the undesired trans transition state and causes the reaction to fail.¹⁰

To design substrates that will successfully undergo the Wolff–Cope rearrangement, we may either stabilize **13** or destabilize **11**. Cyclic substrates **18** and **19** (Table 3) enforce the cis transition state while making it impossible for the substrate to attain a trans transition-state configuration. Such a strategy has been employed successfully to achieve rearrangement of a bis-quaternary substrate (e.g., **18**).²

Although substrate **17e** with substitution at position 5 alone does not rearrange, we expect that substrate **20** with substitution at both positions 5 and 2 will rearrange, due to destabilization of **11** from a 1,3-diaxial interaction. Preliminary experimental efforts suggest that this strategy may promote an alternate cis pathway that leaves the cyclopropane ring intact. Finally, substitution at position 4 (**17d**) is still problematic and, as shown with substrates **21–23**, cannot be reversed by Me, ^tBu, or Si(CH₃)₃ (TMS) substitution at position 1.

In conclusion, in the tandem Wolff–Cope reaction the ketene group preferentially stabilizes radical over aromatic pathways, causing two normally energy-separated transition states to become nearly degenerate. We can use small changes in transition-state stabilities ($\Delta G^\ddagger \approx 2$ kcal/mol) to select between two highly disparate products (trans vs cis cycloheptenes, $\Delta G \approx 29$ kcal/mol) in a controlled fashion. For pericyclic reactions in general, this reaction highlights the need to consider high-lying transition states that may

Table 3. Designed Substrates and Their Calculated Activation Energies^a

#	Geometry (cis vs. trans) (R =)	ΔG_{cis}^\ddagger	$\Delta G_{trans}^\ddagger$	$\Delta G_{cis-trans}^\ddagger$
18	 -	16.0	-	-
19	 -	13.1	-	-
20	 -	15.5	19.5	-4.0
21	 TMS	20.7	17.9	2.8
22	 CH ₃	21.9	20.4	1.6
23	 ^t Bu	23.6	22.9	0.7

^a Substrates with an enforced cis transition state (**18**, **19**) or negative $\Delta G_{cis-trans}$ (**20**) are predicted to rearrange successfully; the others (**21–23**) have positive $\Delta G_{cis-trans}$ and are predicted to fail.

become accessible with newly added functionality. The study also suggests new opportunities for reaction control via the deliberate construction of polymorphic transition states.

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Supporting Information Available: Energies, ball-and-stick figures, Cartesian coordinates, and vibrational frequencies for **4–23** (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- We have found that **13** is geometrically similar to a boatlike diradical transition structure ($\Delta G^\ddagger = 44.3$ kcal/mol, $\Delta E_{\text{triplet-singlet}} = 17.3$ kcal/mol); the separate transition structure suggests that geometric constraints may prevent **13** from effectively resonating with a diradical form.
- Products were observed consistent with further reaction of a *trans*-cycloheptene intermediate: at low temperatures only homologated acid was recovered, and at higher temperatures a complex mixture of undesired products was recovered. No starting material was recovered.

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