

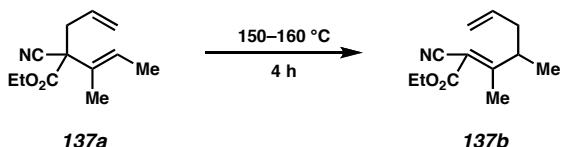
## APPENDIX TWO

### The Cope Rearrangement

#### A2.1 The Cope Rearrangement

In 1940, Arthur Cope discovered a thermal rearrangement of 1,5-diene **137a** to a more conjugated isomeric 1,5-diene (**137b**, Scheme A2.1.1).<sup>1</sup> Cope postulated that his rearrangement was an all-carbon analogue of the Claisen rearrangement,<sup>2</sup> and was intramolecular. He speculated that the reaction proceeded through a six-membered transition state. Cope published these hypotheses 25 years before Woodward and Hoffmann<sup>3</sup> disclosed the first papers on conservation of orbital symmetry, a theory that explained the molecular orbital basis for synchronous Cope rearrangements, calling them [3,3] sigmatropic rearrangements.

*Scheme A2.1.1* The Cope rearrangement

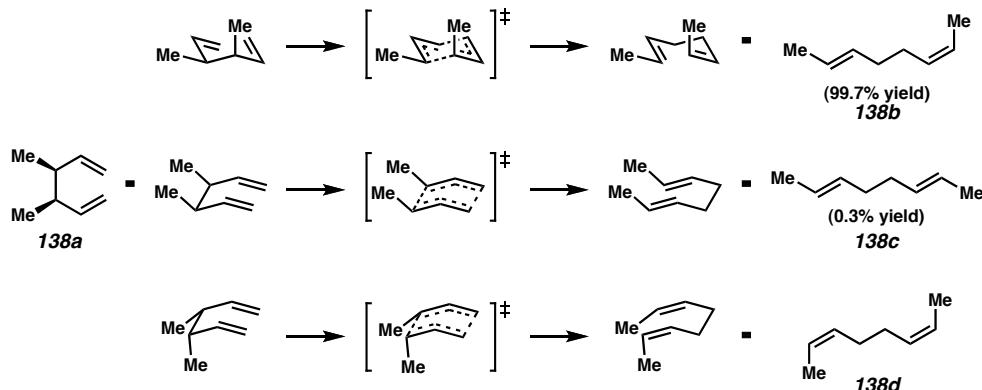


#### A2.2 Transition State Geometry in Concerted Cope Rearrangements<sup>4</sup>

Thermal [3,3] sigmatropic rearrangements occur with suprafacial–suprafacial geometries<sup>3</sup> through a six-membered cyclic transition state in either a chair or boat conformation. In 1962, Doering and Roth<sup>5</sup> determined that in simple cases, the Cope rearrangement proceeded through a chair-like transition state (Scheme A2.2.1). On the basis of product ratios, Doering and Roth estimated that  $\Delta\Delta G^\ddagger$  (boat–chair) for meso

**138a** was 5.7 kcal/mol. Subsequent experiments by Hill excluded the twist (helix) arrangement,<sup>6</sup> which had not been considered by Doering and Roth.

*Scheme A2.2.1* Feasible transition states for the Cope rearrangement

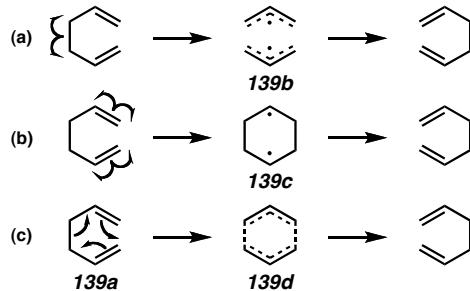


While simple Cope rearrangements employ a chair transition state, the boat transition state is used when molecules are geometrically constrained, as is the case with 1,2-divinyl cyclopropanes in which the vinyl groups are nearly elipsed.<sup>7</sup> Most 1,2-divinylcyclobutanes also proceed through boat transition states,<sup>8,9</sup> but their larger ring size accompanies greater structural flexibility.

### A2.3 Mechanistic Variety: Stepwise Biradical Vs. Concerted Pericyclic Processes<sup>4</sup>

The Cope rearrangement mechanism is controversial. Disputes focus on whether the Cope rearrangement occurs through a stepwise biradical process (either dissociative or associative), or a concerted pericyclic process (synchronous<sup>10</sup> or asynchronous). In the first scenario, the  $\sigma$  bond breaks before a new  $\sigma$  bond is made, to generate a pair of allyl radicals (Scheme A2.3.1a). In a second biradical sequence,  $\sigma$  bond formation precedes  $\sigma$  bond cleavage, resulting in an intermediate 1,5-cyclohexanediyl biradical (**139c**, Scheme A2.3.1b). In the pericyclic process, the transition state is symmetrical (**139d**, Scheme A2.3.1c).

*Scheme A2.3.1* Stepwise biradical and concerted pericyclic mechanistic proposals<sup>11</sup>



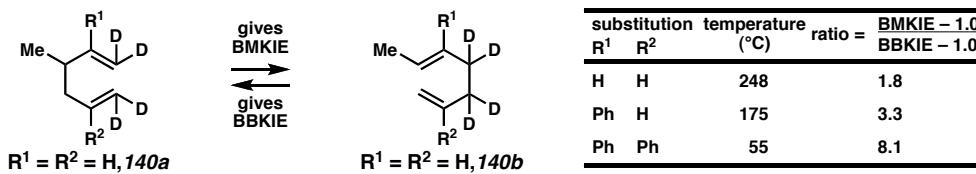
Parent system **139a** does not proceed through a dissociative biradical mechanism (**139b**). In 1,5-hexadiene (**139a**), the heat of formation is less than would be expected for two allyl radicals. Additionally, Humski excluded the dissociative mechanism by determining that this reaction involved only a [3,3]- and not [1,3]-shift.<sup>12</sup> Nevertheless, a few geometrically constrained systems involved bis-allyl radicals.<sup>13</sup>

Doering pointed out that an associative radical mechanism was not ruled out by kinetics of the Cope rearrangement of 1,1-dideutero-1,5-hexadiene (Scheme A2.3.2).<sup>14</sup> Further, a 1,5-cyclohexanediyil biradical was consistent with dramatic substituent effects on the Cope reaction rate.<sup>4</sup> In fact, several key experiments were advanced in order to differentiate between the associative radical and concerted mechanisms, but without providing clear support for a single mechanism.

To differentiate between associative radical and concerted mechanisms, Gajewski defined two secondary isotope effects: the bond making and bond breaking kinetic isotope effects (BMKIE and BBKIE, respectively, Scheme A2.3.2).<sup>15</sup> He used the ratio of the two to indicate the relative extents of bond formation and breaking in transition state structures. This ratio varied with substitution – radical stabilizing groups at C(2) and C(5) correlated with a greater degree of bond formation (more associative character), while radical stabilizing groups at C(3) and C(4) facilitated earlier bond fission (more

dissociative character). This type of analysis was represented with a More O’Ferrall–Jencks plot,<sup>16</sup> and described with the concept of a “perpendicular” effect by Thornton.<sup>17</sup> Taken alone, these advances did not provide clear evidence favoring a single mechanism.

*Scheme A2.3.2* Gajewski defined the BMKIE and BBKIE



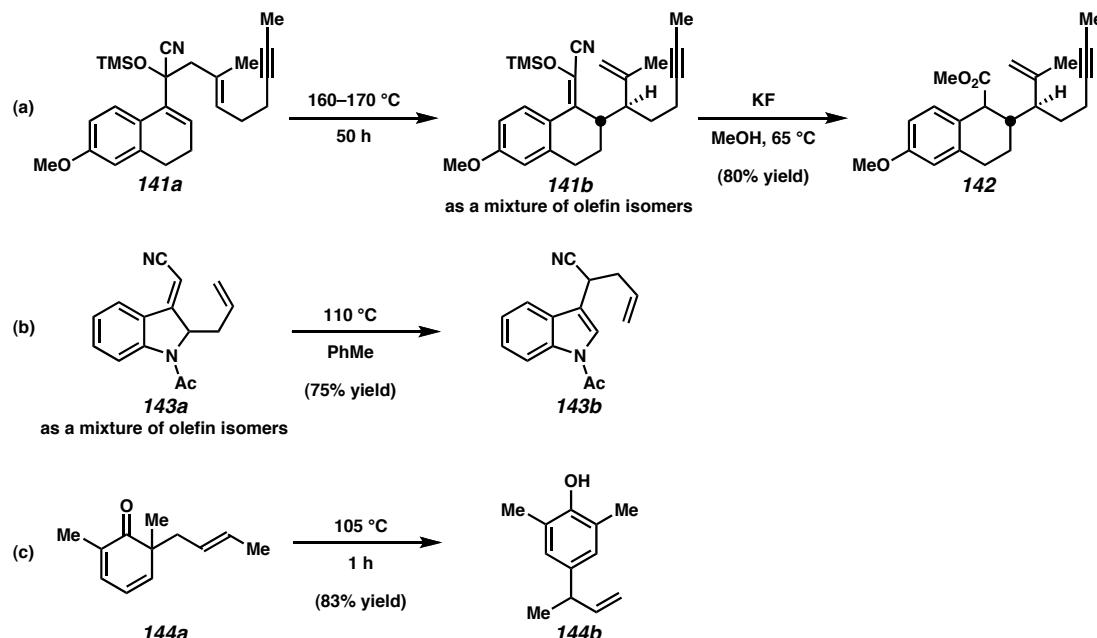
This controversy has driven advances in computational<sup>18</sup> methods. Ab initio quantum mechanical calculations consistently suggest that 1,5-hexadiene reacts in a predominantly concerted mechanism.<sup>19</sup> In more complex systems, the Cope rearrangement may be regarded as a hybrid of three processes: a single concerted transformation, a dissociative (bis-allyl), or an associative (1,4-cyclohexanediyl) stepwise diradical process. The Cope mechanism can be shifted toward either of the diradical intermediates when the system incorporates radical-stabilizing substituents,<sup>19a</sup> or is geometrically constrained.<sup>13</sup>

#### A2.4 Favoring Product Formation in the Cope Rearrangement

The Cope rearrangement is reversible, but any practical process must furnish the product “irreversibly.” The product may be favored because it contains more substituted double bonds, or because the newly formed double bonds are stabilized through conjugation (Scheme A2.4.1a).<sup>20</sup> The Cope product may incorporate a new olefin into an aromatic ring (Scheme A2.4.1b).<sup>21</sup> Alternatively, the Cope product alkene may be able to tautomerize into an aromatic ring (Scheme A2.4.1a).<sup>22</sup> Similarly, the Cope product double bonds may be able to tautomerize to a carbonyl (vida infra). In alicycle-forming

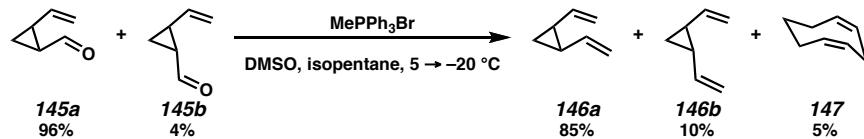
Cope rearrangements, ring strain may be used to pre-pay any energetic costs associated with formation of larger rings (vida infra).

#### *Scheme A2.4.1 Strategies to facilitate irreversible product formation*



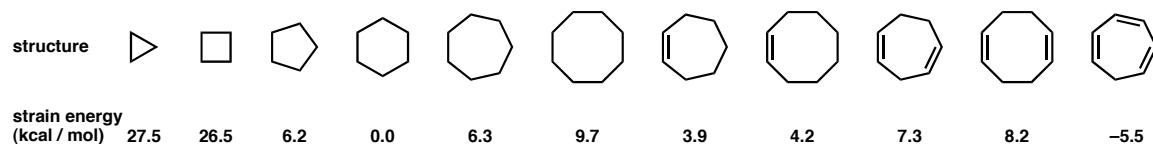
In 1958 and 1960, Vogel reported the first rearrangements of divinylcyclobutanes<sup>23</sup> and divinylcyclopropanes.<sup>24</sup> Vogel could not isolate divinylcyclopropane **146a** because it rearranged to cycloheptadiene **147** too rapidly. It was not until 1973 that Brown<sup>25</sup> was able to observe parent divinylcyclopropane **146a** (Scheme A2.4.2). Brown found that the half-life of this divinylcyclopropane (in  $\text{CFCl}_3$ ) is 90 seconds at 35 °C, or 25.75 min at 11.3 °C, and the free energy of activation is 20.6 kcal/mol.

*Scheme A2.4.2* Brown observed the parent divinylcyclopropane



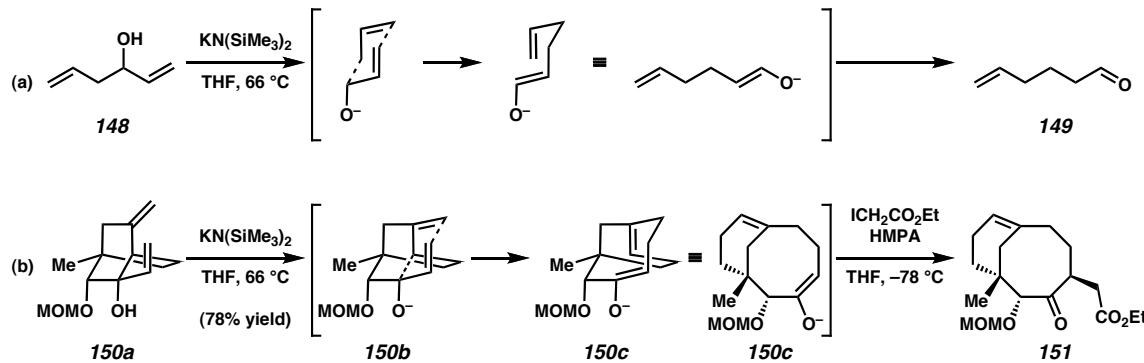
In Cope rearrangements where the breaking sigma bond is part of a strained ring, the reactant–product equilibrium usually favors the product because energy is released when this strained ring is broken (e.g., Scheme A2.4.2; Figure A2.4.1). For example, a 1,4-cycloheptadiene involves around 20.2 kcal/mol less strain energy than a cyclopropane that would be the backbone of a Cope precursor. Similarly, a 1,5-cyclooctadiene involves around 18.3 kcal/mol less strain energy than a cyclobutane that could be part of a Cope precursor.

Figure A2.4.1 Strain energy of relevant structural motifs<sup>26</sup>



Shortly after Vogel's seminal publications, Jones and Benson<sup>27</sup> found that product formation could be favored through hydroxy substitution at C(3) or C(4). Such substitution furnished an enol upon Cope rearrangement, and this enol could tautomerize to a carbonyl. Benson and Walsh<sup>28</sup> showed that in this oxy-Cope rearrangement, the hydroxy group lowered the bond dissociation energy by 24 kcal/mol. This reaction became more practical when Evans<sup>29</sup> reported rate enhancements of  $10^{10}$ – $10^{17}$  by using an alkoxide in lieu of a hydroxy to enable an anionic oxy-Cope reaction. Evans and Goddard<sup>30</sup> determined that the alkoxide facilitated the Cope rearrangement by weakening the carbon–carbon  $\sigma$ -bond.

*Scheme A2.4.3* Examples of the anionic oxy-Cope rearrangement that are (a) general, or (b) from Paquette<sup>31</sup>

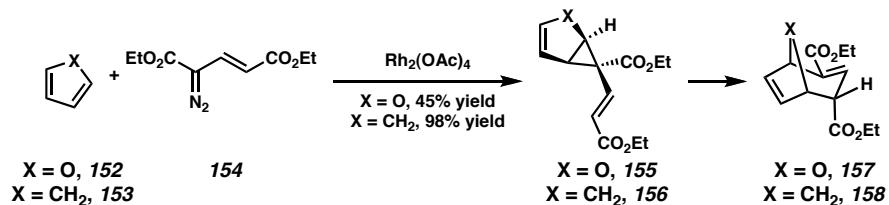


## A2.5 Tandem Cope Rearrangements in Synthesis

The Cope rearrangement has been co-opted in many tandem reactions, two of which feature prominently in efforts toward the total synthesis of ineleganolide: the tandem cyclopropanation/Cope, developed largely by Davies<sup>32-36</sup> and Wolff/Cope rearrangements, investigated by Stoltz.

Davies reported the first cyclopropanation/Cope in 1985 with the reaction of furan (**152**) with vinyl diazoester **154** in the presence of rhodium(II) acetate to furnish 45% isolated yield of a bridged [2.3.1] bicycle (**157**, Scheme A2.5.1).<sup>33</sup> Within two years, he had unraveled its mechanism: he reacted cyclopentadiene (**153**) with vinyl diazoesters (e.g., **154**), and isolated divinylcyclopropane **156** that underwent a Cope rearrangement on heating to form bridged **158**.<sup>34</sup>

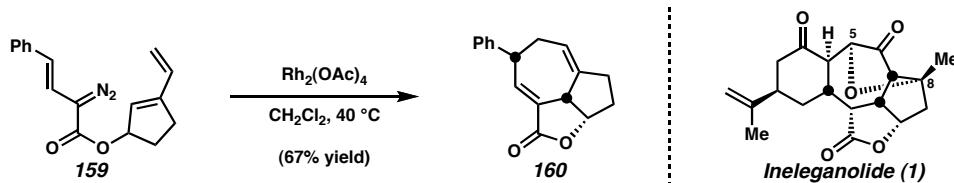
*Scheme A2.5.1* Davies initial tandem cyclopropanation/Cope systems



Davies advanced this method to diastereoselective intramolecular reactions.<sup>35</sup>

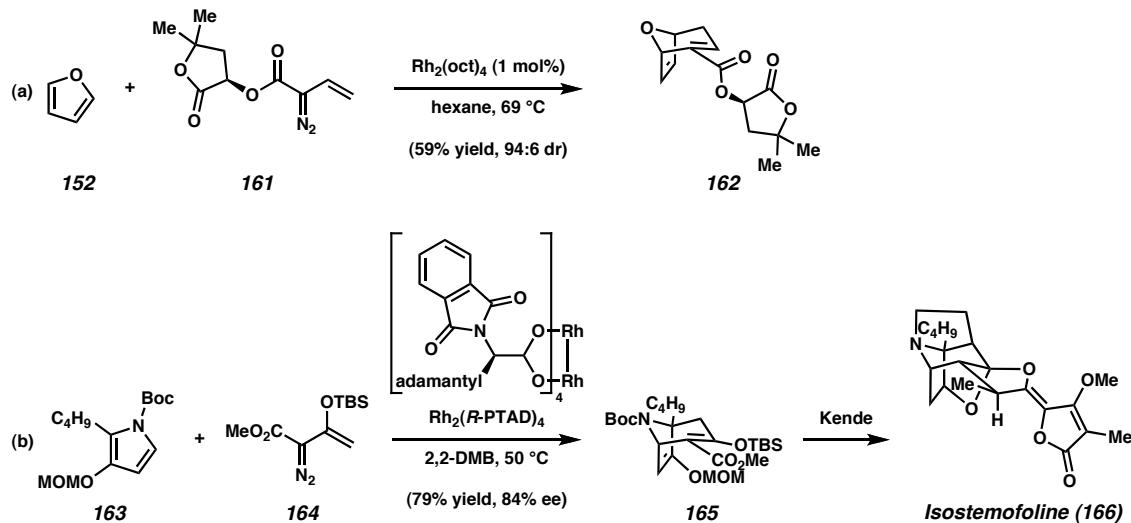
Among the systems tested was a scaffold that was similar to the framework of ineleganolide (e.g., **159** → **160**, **1**).

*Scheme A2.5.2* Davies intramolecular cyclopropanation/Cope systems



Davies developed technologies to enable asymmetric cyclopropanation/Cope sequences. Chiral auxiliaries, such as (*R*)-pantolactone, direct diastereoselective formation of oxabicycles, such as bridged **162**,<sup>36</sup> which is used as an intermediate in Phillips synthesis of norhalichondrin B, a macrolactone containing 55 carbon atoms.<sup>37</sup> Additionally, enantioselective rhodium catalysts enabled these inter<sup>38</sup> and intramolecular<sup>39</sup> cyclopropanation/Cope sequences. With this technology, Davies undertook an asymmetric formal synthesis of isostemofoline (**166**),<sup>40</sup> using the key cyclopropanation/Cope reaction employed by Kende in its racemic synthesis.<sup>41</sup>

Scheme A2.5.3 Davies innovations facilitated enantio- and diastereoselective reactions



These developments have been extended through their application in total syntheses,<sup>42</sup> a few via [3.2.1]bicyclic cyclopropanation/Cope products.<sup>43, 36b</sup>

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