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## A gold-catalysed enantioselective Cope rearrangement of achiral 1,5-dienes

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### Abstract

Since the discovery of the Cope rearrangement in the 1940s, no asymmetric variant of the rearrangement of achiral 1,5-dienes has emerged, despite the successes that have been achieved with its heteroatom variants (Claisen, aza-Cope, etc.). This article reports the first example of an enantioselective Cope reaction that starts from an achiral diene. The new gold(I) catalyst derived from double Cl<sup>-</sup>-abstraction of ((*S*)-3,5-xylyl-PHANEPHOS(AuCl)<sub>2</sub>), has been developed for the sigmatropic rearrangement of alkenyl-methylenecyclopropanes. The reaction proceeds at low temperature and the synthetically useful vinylcyclopropane products are obtained in high yield and enantioselectivity. Density functional theory calculations predict that: (1) the reaction proceeds via a cyclic carbenium ion intermediate, (2) the relief of strain in the methylenecyclopropane moiety provides the thermodynamic driving force for the rearrangement and (3) metal complexation of the transition-state structure lowers the rearrangement barriers.

The Cope rearrangement is a textbook sigmatropic reaction of 1,5-dienes that occurs at 150–200 °C and has been known for over 70 years<sup>1</sup>. Numerous variants of this rearrangement, including those subject to catalysis, have been reported to lower reaction temperatures, add functionality to the products and provide routes to chiral products in the case of the aza-Cope and Claisen variants<sup>2,3</sup>. Studies demonstrating efficient [1,3]-transfer of chirality in 1,5-dienes are consistent with a concerted reaction that proceeds through an ordered chair-like transition-state structure, a feature that has undoubtedly been key to the development of enantioselective hetero-Cope variants, Overman's Pd-catalysed allylic trichloroacetimidate rearrangement being especially noteworthy (Fig. 1a)<sup>4</sup>. The reaction most resembling an enantioselective Cope reaction was reported by the Davies group. They note that a powerful domino reaction ensues when a chiral Rh(II) vinylcarbene catalyst initiates an allylic C–H insertion. This process is diverted mid-insertion by a competing Cope rearrangement to provide 1,5-dienes with excellent diastereo- and enantio-control (Fig. 1a)<sup>5,6</sup>.

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#### Author contributions

R.J.F., D.W. and M.R.G. conceived and designed the experiments. R.J.F. performed the experiments and analysed the data. R.J.F., D.J.T. and M.R.G. co-wrote the paper. O.G. and D.J.T. performed the DFT calculations. All authors discussed the results and commented on the manuscript.

#### Additional information

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Generally speaking, the Cope rearrangement is constrained by the thermodynamics of alkene substitution in the reactants and products. That is, favourable reactions typically convert less-substituted alkenes into more-substituted alkenes, which leads to large classes (that is, directions) of the Cope rearrangement not being feasible<sup>7</sup>. To the problem of asymmetric induction, these subtle driving forces also lead to reversibility and the consequent loss of kinetic control, a prerequisite for highly asymmetric induction. The consumption of C–C unsaturation<sup>8,9</sup> along with the release of ring strain<sup>10–16</sup>, however, are forces that have been harnessed to drive rearrangement reactions in organic synthesis.

Described herein is an enantioselective methodology for the catalyst-controlled Cope rearrangement of achiral dienes that simultaneously solves issues related to reaction thermodynamics and kinetics. The former provides the means to reverse the normal thermodynamic control elements and allow products with  $\pi$ -bonds less substituted than those of the starting diene to be favoured, and simultaneously create an asymmetric route to synthetically valuable vinylcyclopropanes. Quantum mechanical calculations<sup>17</sup> were used to assess the kinetic feasibility of competing mechanistic pathways and reveal the origins of their thermodynamic favourability.

## Results

In the course of examining the reactivity of polyenes with a 1,5-substitution pattern we discovered that compounds with a terminal methylenecyclopropane preferentially rearrange to the Cope product rather than cascade through ionic pathways to polycyclic products<sup>18–20</sup>. For example, when triene **1a** was reacted with 10 mol% Ph<sub>3</sub>PAuNTf<sub>2</sub> (ref. 21; Tf = trifluoromethanesulfonyl) the vinylcyclopropane product **2a** was obtained (Fig. 1b). Of significance in this reaction is the decrease in alkene substitution on going from the alkylidene cyclopropane to the vinylcyclopropane. Beginning with Overman's report of a PdCl<sub>2</sub>(NPh)<sub>2</sub>-catalysed Cope rearrangement of 1,5-dienes, a number of studies showed that electrophilic metal catalysts can mediate this reaction through a transient cyclo-carbenium ion (**A**), which fragments to the Cope product under significantly milder conditions (room temperature (r.t.)) than those required under thermal conditions (150–200 °C, Fig. 1b)<sup>22–25</sup>. Although the Cope reaction necessitates a product whose alkenes are more substituted than the starting diene, it and its variants (aza-Cope, oxy-Cope) have nevertheless found widespread use in organic synthesis<sup>26,27</sup>.

On observing the facile nature of the Au(I)-catalysed rearrangement (r.t., two hours, Fig. 1b), other known catalysts for the Cope rearrangement were tested. Unfortunately, none were found to react at r.t. and elevated temperatures usually led to a large number of unidentified products; for example, PdCl<sub>2</sub>(MeCN)<sub>2</sub> in MeCN, PdCl<sub>2</sub>(NPh)<sub>2</sub> in MeCN or tetrahydrofuran (THF) and PtCl<sub>2</sub> in toluene<sup>22–24,28,29</sup>. The dearth of approaches to the asymmetric Cope rearrangement led us to search next for an enantioselective variant of the Au(I) catalyst<sup>30–38</sup>. To this end, the solvent, temperature and silver salt were optimized using the chiral bis(gold) catalyst (*R*)-xylyl-BINAP(AuCl)<sub>2</sub> (BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl; see Supplementary Information), and this was followed by a screen of representative commercially available chiral ligands. Table 1 shows the results of this screening with compound **1b**.

The enantioselectivity was, in most cases, dishearteningly low, with (*R*)-xylyl-BINAP performing better than most of the other diphosphine ligands (34% enantiomeric excess (e.e., –20 °C (Table 2, entry 2)). Monodentate ligands (Table 2, entry 11)<sup>32</sup> and chiral anions (Table 2, entry 12) did not fare better. Ligands that previously exhibited high asymmetric induction in Au(I) catalysis (Table 2, entries 3, 4 and 11) were unselective or unreactive. The catalyst derived from (*S*)-3,5-xylyl-PHANEPHOS(AuCl)<sub>2</sub> (**4**)

(PHANEPHOS = 4,12-bis(diphenylphosphino)-[2.2]-paracyclophane), however, was uniquely enantioselective (Table 2, entry 10), representing its first effective use in Au(I) asymmetric catalysis<sup>20,37</sup>. In the X-ray crystal structure of **4** shown in Fig. 1c, the long Au–Au distance (5.620 Å) indicates that no Au...Au interactions are feasible in this inactivated form.

A second round of catalyst optimization was performed with **4**, which led to the optimal conditions of 5 mol% of **4** and 20 mol% of AgSbF<sub>6</sub> in a 1:9 mixture of dichloromethane (DCM) to 1,2-dichloroethane (1,2-DCE) at –35 °C (see Supplementary Information for details). This protocol was applied to various substrates, as reported in Table 2.

Methylenecyclopropanes of this type were prepared in moderate yield via the Wittig reaction of the aldehyde precursor with cyclopropyltriphenylphosphonium bromide<sup>39</sup>.

Alkyl- and aryl-substituted 1,5-dienes were good reactants with triene **1a** and gave the highest enantioselectivity, 93%. Good activity and selectivity were achieved with unfunctionalized alkyl and aromatic substrates (Table 2, entries 1–4) and a number of functional groups were tolerated, including tetrahydropyranyl (THP)- and acetyl-protected alcohols (Table 2, entries 7 and 8), free alcohols (Table 2, entry 9) and phenols (Table 2, entry 6). Although these more functionalized substrates required longer reaction times, the products were obtained in good yields and enantioselectivities. The diminished yield of **1i** resulted from deleterious side reactions, although suitably protected variants made for good reactions. A protected amine substrate, naphthalimide **1j**, also underwent the Cope rearrangement to give **2j**, but additionally gave 23% of **3j**, the product of an unusual cyclopropene rearrangement. This cyclobutene product was not detected in any other reactions, but was documented previously under PtCl<sub>2</sub>/CO conditions<sup>14</sup> by Fürstner on simple alkylidenecyclopropanes, and by Toste in pinacol-like ring expansion of cyclopropanols to cyclobutanones<sup>40</sup>. Compound **1k**, whose Cope product probably lies uphill in energy because of the additional penalty of loss of alkene conjugation to one phenyl ring, was unreactive (*vide infra*).

## Discussion

To probe the energetics of the Cope rearrangement, several model compounds were studied using density functional theory (DFT)<sup>17,41,42</sup>. Reported structures were optimized using DFT (M06-2X/6-31G(d) in the gas phase for uncatalysed systems and in 1,2-DCE (CPCM<sup>43</sup> model) using M06/6-31G(d)-(LANL2DZ for Au) for organometallic systems) as implemented in

First, rearrangement in the absence of catalyst was examined. Although predicted barriers are high for these reactions, ~30 kcal mol<sup>-1</sup>, the rearrangements are significantly exothermic due to the release of ring strain on rearrangement (Table 3)<sup>44,45</sup>. As expected, methyl substitution at the C5 position (R<sup>1</sup>) only slightly changes this thermodynamic preference, but greater effects are predicted for alkyl substitution at the C6 (R<sup>2</sup>) position (Table 3, entries 3 and 2, respectively). In sum, the relief of ring strain in the Cope reaction overcomes the otherwise unfavourable conversion into a less substituted product and provides a novel route to versatile vinylcyclopropanes.

Consistent with this outcome is the failure of rearrangement reactions on methylenecyclopentene or acyclic dimethylated terminal alkene substrates, which lack the requisite ring strain. Methylenecyclobutene analogues, like methylenecyclopropanes, are reactive to gold catalysts, but give several products.

The Au-catalysed rearrangement was predicted to proceed via a cyclic intermediate (Fig. 2, akin to that proposed for Pd(II)-promoted Cope rearrangements (**A**, Fig. 1b))<sup>22–25</sup>. Even

though the complexation of Au(I) to the methylenecyclopropane (Fig. 2b) is slightly less favourable than complexation to the trisubstituted olefin (Fig. 2a), the kinetically preferred pathway is that shown in Fig. 2b; that is, the pathway in which a tertiary carbocation substructure, rather than a secondary cyclopropylcarbanyl cation substructure, is formed. Overall, the rearrangement is predicted to proceed with a barrier of  $\sim 15$  kcal mol<sup>-1</sup>, which is  $\sim 20$  kcal mol<sup>-1</sup> lower than that for the uncatalysed rearrangement (Table 3, R<sup>1</sup> = R<sup>2</sup> = Me). In addition, calculations on substrate **1a**, which failed to cyclize (equation (1), Fig. 1b), predict that, although cation–olefin bicyclization is actually kinetically favoured by  $\sim 7$  kcal mol<sup>-1</sup> over the formation of **2a**, this process is less exergonic and reversible, allowing the product of Cope rearrangement to form preferentially (see Supplementary Information for further details). Additional calculations indicated that gold cations could, indeed, induce the rearrangement of methylenecyclopropanes into cyclobutenes (for example, **3j**), but the barrier for such a process is predicted to be higher (by more than 10 kcal mol<sup>-1</sup>) than that for the Cope rearrangement (see Supplementary Information for details). The competitiveness of this process for **1j** is intriguing and will be investigated independently.

In conclusion, a new chiral Au(I) catalyst was developed for the enantioselective Cope rearrangement of alkenyl-methylenecyclopropanes. This is the first example of a Cope reaction in which the enantioselectivity is not provided by either a pre-existing stereocentre or through a multistep sequence. The reaction is applicable to alkyl, aromatic and oxygen- and nitrogen-containing substrates, with high yields and good-to-excellent enantioselectivities. Quantum chemical calculations show that the reaction is thermodynamically driven by the relief of ring strain from the cyclopropylidene moiety, and that the Au(I) catalyst greatly lowers the barrier for rearrangement. The type of strain relief described herein has potential as a general tool for the development of alternatives to otherwise unfavourable sigmatropic reactions<sup>11,12</sup>.

## Methods

Characterization details for all new compounds and representative synthetic procedures, as well as complete X-ray diffraction data, along with coordinates and energies for all computed structures, and the complete reference 17 and additional details on results from computations, are available in the Supplementary Information.

### General procedure for the preparation of substrates by the Wittig reaction

To a flame-dried Schlenk flask loaded with a suspension of dry NaH (0.075 g, 3.15 mmol, 1.3 equiv.) in THF (13 ml) under N<sub>2</sub> atmosphere was added cyclopropyltriphenylphosphonium bromide (1.21 g, 3.15 mmol, 1.3 equiv.) at r.t. The reaction flask was then equipped with a condenser and heated to 62 °C for 18 hours. To the resulting orange suspension was then added the aldehyde precursor (of **1**, 0.469 g, 2.42 mmol, 1 equiv.) and tris(2-(2-methoxyethoxy)ethyl)amine (0.077 ml, 0.242 mmol, 0.1 equiv.) in THF (4 ml). The reaction was stirred for two hours at 62 °C before cooling to r.t. and quenching with saturated aqueous NaHCO<sub>3</sub>. The reaction was diluted with deionized H<sub>2</sub>O and Et<sub>2</sub>O before separating the layers. The aqueous layer was extracted with Et<sub>2</sub>O (twice) and the combined organic layers were then washed with brine (twice). The organic layer was dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. Purification by silica gel chromatography (hexanes) provided the product compound (**1**) as a colourless oil (0.283 g, 53%). A small amount of CH<sub>2</sub>Cl<sub>2</sub> was used to load the material onto the column.

### General procedure for the Au(I)-catalysed Cope rearrangement

To a vial loaded with silver hexafluoroantimonate (3.2 mg, 0.0092 mmol, 0.2 equiv.) was added a 1:9 CH<sub>2</sub>Cl<sub>2</sub>:1,2-DCE solution (1 ml). Au(I) catalyst **4** (2.6 mg, 0.0023 mmol, 0.05

equiv.) was then added and the reaction stirred at r.t. for 15 minutes. The reaction was then placed into a NesLab Cryobath CB-80 maintained at  $-35\text{ }^{\circ}\text{C}$  and stirred for 10 minutes before the addition of **1a** (10 mg, 0.046 mmol, 1 equiv.). The reaction was then stirred for 18 hours at  $-35\text{ }^{\circ}\text{C}$  before concentrating the reaction *in vacuo*, after which the product was isolated by a silica gel pipette column (hexanes) to give **2a** as a colourless oil (9.4 mg, 94%).

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

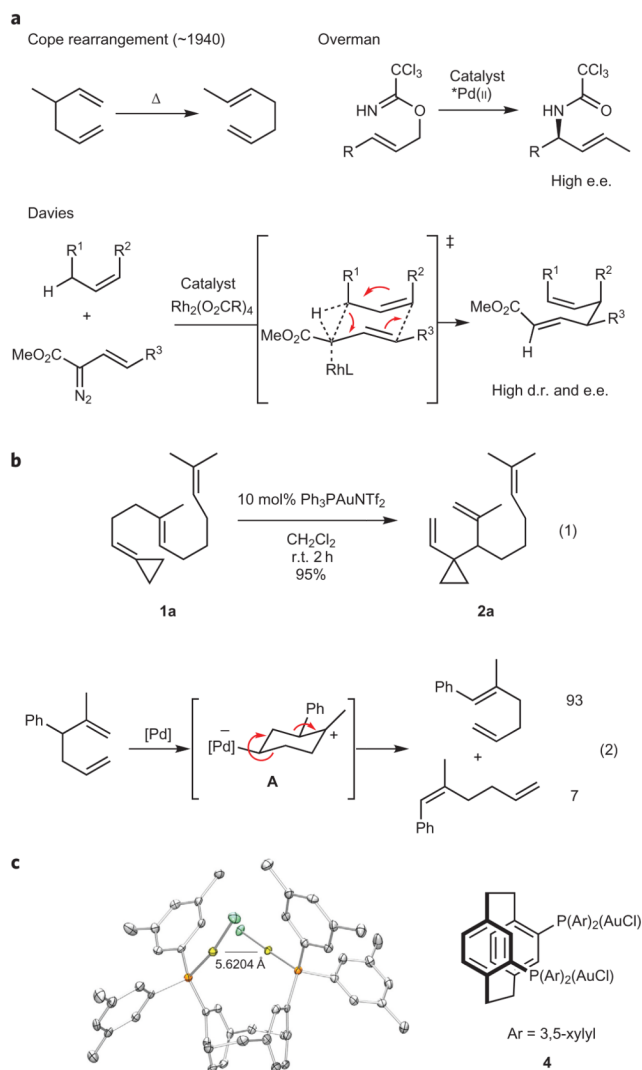
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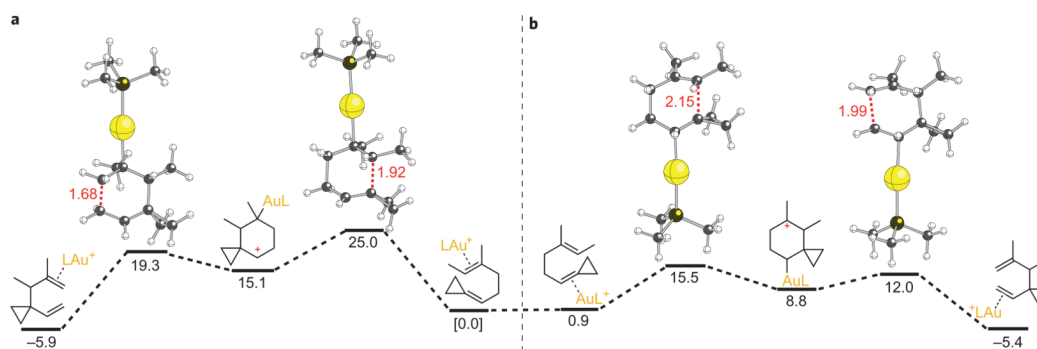
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### Figure 1. Transition-metal catalysed Cope rearrangements

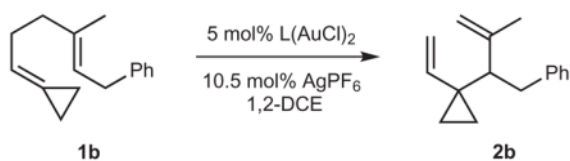
**a**, The Cope rearrangement has been known for over 70 years, and although there are enantioselective variants (**a**, Overman) and intermolecular processes that resemble the Cope rearrangement (**a**, Davies), no asymmetric variants had been developed. **b**, The Au-catalysed Cope rearrangement of **1a** to vinylcyclopropane **2a** is conjectured to operate by electrophilic activation of the substrate, resembling the Pd-catalysed Cope rearrangement discovered by Overman. **c**, ORTEP representation of **4** with 50% probability ellipsoids; hydrogen atoms and two solvent molecules (benzene) are omitted for clarity. Au–Au distance is 5.6204 Å. d.r. =diastereomeric ratio; L =ligand.





**Figure 2. Computational investigation of the rearrangement pathway**

**a,b**, Two pathways for the  $\text{Au}^+\text{-PMe}_3$ -promoted Cope rearrangement of the  $\text{R}^1 = \text{R}^2 = \text{Me}$  system were investigated. In the first pathway (**a**) the Au catalyst activates the dimethyl substituted alkene. In the second pathway (**b**) the Au catalyst activates the cyclopropyl-substituted alkene. The calculations clearly show the latter pathway to be more favourable as judged by its lower barrier heights. The relative free energies ( $\text{kcal mol}^{-1}$ , at 298 K) for stationary points were calculated using M06 with the 6-31G(d) basis set for P, C and H, and LANL2DZ for Au, in 1,2-DCE (CPCM).<sup>17,41,42</sup> Selected distances are given in Å. L = ligand.

**Table 1**Ligand optimization for the Au(I)-catalysed Cope rearrangement of **1b**.\*

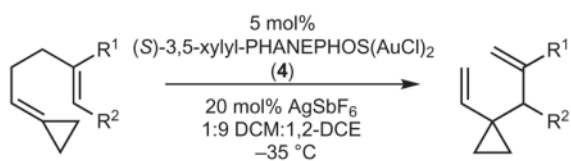
Entry <sup>*</sup>	Ligand (L)	T (°C)	e.e. (%) <sup>†</sup>
1	( <i>R</i> )-xylyl-BINAP	0	28
2	( <i>R</i> )-xylyl-BINAP	-20	34
3	( <i>R</i> )-xylyl-MeO-BIPHEP	-20	19
4	( <i>R</i> )-DTBM-SEGPPOS	-20	25
5	( <i>R</i> )-SEGPPOS	-20	16
6	( <i>R</i> )-DIFLUORPHOS	-20	9
7	( <i>R</i> )-xylyl-SDP	-20	5
8	( <i>R,R</i> )-Me-DuPHOS	0	2
9	( <i>R</i> )-SYNPHOS	0	15
10	( <i>S</i> )-3,5-xylyl-PHANEPHOS ( <b>4</b> )	-20	79
11	( <i>S</i> )-SIPHOS-PE	0	7
12	Ag-( <i>R</i> )-(5)	r.t.	–

\* Reaction conditions: catalyst (5 mol%), AgPF<sub>6</sub> (10.5 mol%), 1,2-DCE, 18 hours.

<sup>†</sup> e.e. determined by chiral gas chromatography (GC). BIPHEP, 2,2'-bis(diphenylphosphino)-1,1'-biphenyl; DTBM, 3,5-di-*t*-butyl-4-methoxyphenyl; SEGPPOS, 5,5'-bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole; DTBM-SEGPPOS, 5,5'-bis[di(3,5-di-*t*-butyl-4-methoxyphenyl)phosphino]-4,4'-bi-1,3-benzodioxole; DIFLUORPHOS, 5,5'-bis(diphenylphosphino)-2,2,2',2'-tetrafluoro-4,4'-bi-1,3-benzodioxole; SDP, 7,7'-bis(diphenylphosphino)-2,2',3,3'-tetrahydro-1,1'-spirobiindane; (*R,R*)-Me-DuPHOS, 1,2-bis((2*R*,5*R*)-2,5-dimethylphospholano)benzene; SYNPHOS, 6,6'-bis(diphenylphosphino)-2,2',3,3'-tetrahydro-5,5'-bi-1,4-benzodioxin; SIPHOS-PE, 10,11,12,13-tetrahydroindeno[7,1-*de*:1',7'-*fg*][1,3,2]dioxaphosphocin-5-bis[(*R*)-1-phenylethyl]amine.

**Table 2**Reaction scope under optimized conditions with (*S*)-3,5-xylyl-PHANEPHOS(AuCl)<sub>2</sub>\*.

Entry	Substrate	Product	Yield (%) <sup>†</sup>	e.e. (%) <sup>‡</sup>
1			94	93
	<b>1a</b>	<b>2a</b>		
2			89	87
	<b>1b</b>	<b>2b</b>		
3			87	84
	<b>1c</b>	<b>2c</b>		
4			90	82
	<b>1d</b>	<b>2d</b>		
5			98	–
	<b>1e</b>	<b>2e</b>		
6			71	70
	<b>1f</b>	<b>2f</b>		



Entry	Substrate	Product	Yield (%) <sup>†</sup>	e.e. (%) <sup>‡</sup>
7			60	73 <sup>§</sup>
8			70	82 <sup>  </sup>
9			35	76 <sup>¶</sup>
10			45	58 <sup>#</sup>
			23	–
11			–	–

\* Reaction conditions: catalyst (5 mol%), AgSbF<sub>6</sub> (20 mol%), 1:9 DCM:1,2-DCE, –35 °C, 18 hours.

<sup>†</sup> Isolated yield.

<sup>‡</sup> e.e. determined by chiral GC.

<sup>§</sup> 72 hours at –35 °C, 1:1 diastereomeric ratio.

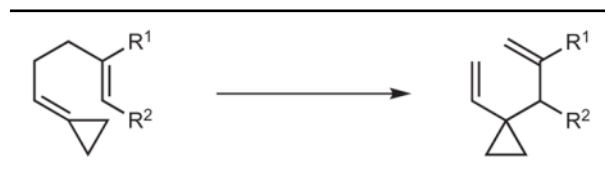
<sup>||</sup> 72 hours at –35 °C.

<sup>¶</sup> e.e. determined by conversion to the acetate **2h**.

<sup>#</sup> e.e. determined by chiral supercritical fluid chromatography.

**Table 3**

Gas-phase free energies for thermal [3,3]-sigmatropic rearrangements of substituted alkenyl-methylenecyclopropanes.\*



	$\Delta G^\ddagger$ ( $\Delta H^\ddagger$ )	$\Delta G$ ( $\Delta H$ )
R <sup>1</sup> = R <sup>2</sup> = Me	35.1 (30.1)	-3.6 (-6.2)
R <sup>1</sup> = H, R <sup>2</sup> = Me	36.1 (32.4)	-4.4 (-6.0)
R <sup>1</sup> = Me, R <sup>2</sup> = H	32.0 (29.5)	-7.0 (-7.5)
R <sup>1</sup> , R <sup>2</sup> = H	33.4 (30.1)	-7.3 (-8.4)

\* Using the DFT M06-2X/6-31G(d) method.