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Rearrangement Reactions of 1,1-Divinyl-2-phenylcyclopropanes

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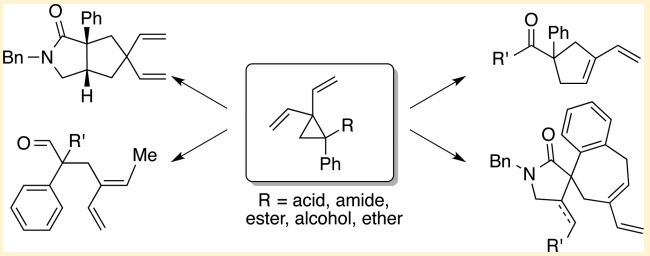
Supporting Information

ABSTRACT: 1,1-Divinyl-2-phenylcyclopropanes are entry points to a rich area of rearrangement chemistry. With *N,N*-diallyl amide substrates, tandem radical cyclizations can be initiated at room temperature. Warming provides products of pure thermal rearrangements with acids, ester, and amides. These isomerizations give vinylcyclopentenes resulting from divinylcyclopropane rearrangements and more deeply rearranged tricyclic spirolactams resulting from aromatic Cope rearrangements followed by ene reactions. Conversion of the carbonyl group to an alcohol or ether opens retro-ene pathways followed by either tautomerization or Claisen rearrangement.



INTRODUCTION

Vinyl-substituted cyclopropanes are readily accessible intermediates that are commonly used in synthesis.[1] Release of the cyclopropane ring strain provides a driving force for a variety of radical[2] and metal-mediated[3] transformations. The archetypical transformation is the rearrangement of vinylcyclopropanes to cyclopentenes at high temperatures (often 300 °C or more),[4] hereafter called the vinylcyclopropane rearrangement (Figure 1a). Suitably substituted vinylcyclopropanes can also undergo other rearrangements including retro-ene reactions.[5]

Among the various substituted vinylcyclopropanes, 1,2-divinyl-cyclopropanes are important precursors for 3,3-sigmatropic reactions like the Cope rearrangement (Figure 1b).[6]

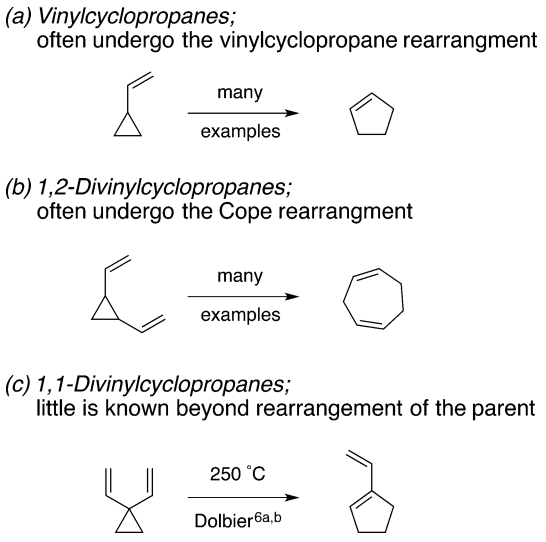


Figure 1. Rearrangement reactions of vinylcyclopropanes and divinylcyclopropanes.

Such rearrangements typically occur at more accessible temperatures (<100 °C) than vinylcyclopropane rearrangements provided that the vinyl groups are disposed 1,2-*cis*. At higher temperatures, *cis* and *trans* isomers often equilibrate, opening a path from the *trans* isomer to the Cope product.

In contrast, relatively little is known about rearrangements of 1,1-divinylcyclopropanes.[7] The parent 1,1-divinylcyclopropane has been studied in detail by Dolbier,[7a,b] and undergoes the vinylcyclopropane rearrangement to give vinylcyclopentene at about 250 °C (Figure 1c).

We recently used complex yet readily available 1,1-divinylcyclopropanes as key intermediates for tandem radical cyclizations to make meloscine and a variety of analogs.[8] In a typical example (Figure 2), treatment of **1** with tributyltin hydride produced tetracycle **2**, which was further converted to

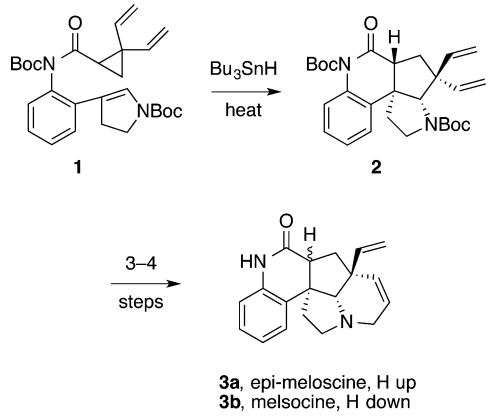


Figure 2. Radical rearrangement of a 1,1-divinylcyclopropane is a key step in a short synthesis of epi-meloscine, meloscine, and analogs.

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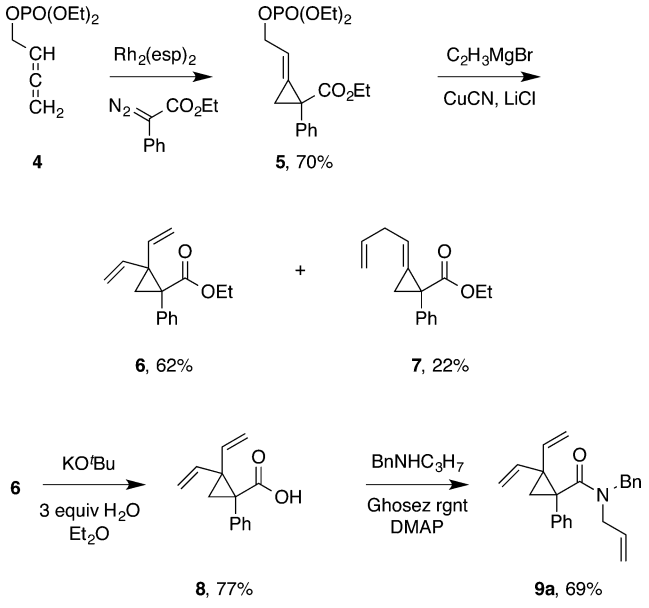
the natural products epi-meloscine **3a** (in 3 steps) and meloscine[9] **3b** (in one more step). While studying the radical-mediated rearrangements of 1,1-divinylcylopropanes with phenyl substituents, we began to encounter facile rearrangements that occurred without radical initiators.

Here we report that suitably substituted 1,1-divinyl-2-phenylcylopropanes undergo a variety of thermal rearrangements in an accessible temperature regime. These include the vinylcyclopropane rearrangement, a tandem aromatic Cope-ene rearrangement, and a retro-ene reaction followed by either tautomerization or Claisen rearrangement. Taken together, the results suggest that substituted 1,1-divinylcylopropanes have a rich and controllable rearrangement chemistry.

RESULTS AND DISCUSSION

We first encountered pure thermal rearrangements of 1,1-divinyl-2-phenylcylopropanes during study of the tandem radical cyclization of benzyl allyl amide **9a**, whose synthesis and onward radical and thermal reactions are shown in Schemes 1 and 2. Amide **9a** is readily made in four steps

Scheme 1. Synthesis of Divinylcyclopropane Precursor 9[a]



[a]esp is C_6H_4-*m*-$(CH_2CH_2CO_2)_2$; Ghosez reagent is $(Me)_2C{=}C(Cl)NMe_2$.

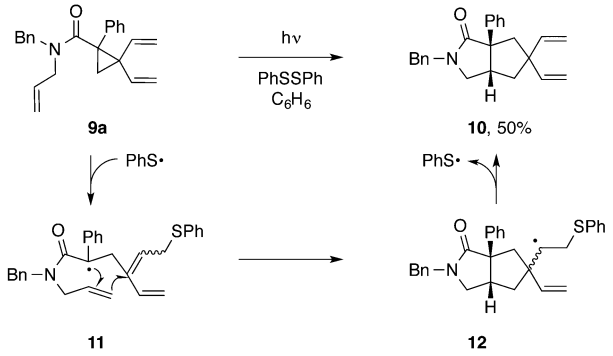
(Scheme 1). Regioselective cyclopropanation of the diethylphosphate ester of buta-2,3-dien-1-ol[10] **4** with ethyl 2-phenyldiazoacetate was catalyzed by $Rh_2(esp)_2$[11] to provide stable methylenecyclopropane **5** in 70% yield.

Addition of vinyl magnesium bromide (C_2H_3MgBr) to a solution of CuCN (0.2 equiv), LiCl (0.2 equiv), and **5** followed by workup and chromatography provided a 62% yield of 1,1-divinylcyclo-propane ester **6** resulting from S_N2' displacement of the phosphate. Also isolated in 22% yield was regioisomer **7** resulting from S_N2 displacement. Despite the minor S_N2 product, this two-step route to the divinylcyclopropane **6** is more direct and more efficient than the five-step route used for the divinylcyclopropanes in the meloscine work.[8]

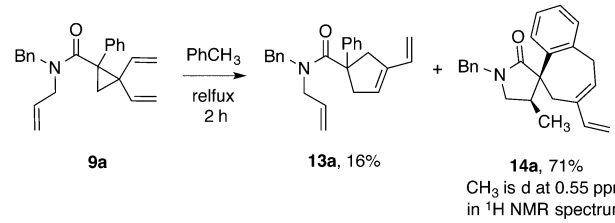
Base-promoted hydrolysis of hindered ester **6** in ether with excess potassium *tert*-butoxide and a limited amount of water (3 equiv) provided acid **8** after standard workup. This classic

Scheme 2. Results of Rearrangement Reactions of 9a under Radical (a) and Pure Thermal (b) Conditions

(a) Room temperature, radical conditions



(b) Thermal conditions, no additives



Gassman hydrolysis method[12] succeeds at room temperature. This is important because standard saponification of the hindered ester of **7** did not occur at room temperature. Heating gave multiple products, some of which we later understood to arise from thermal rearrangements (see below).

Acid **8** became a pivotal intermediate in synthesis of substrates for the rearrangement studies, so the crude product was purified by flash chromatography to provide a high quality sample in 77% yield. Reaction of **8** with the 1-chloro-*N*,*N*-2-trimethyl-1-propenylamine (Ghosez reagent),[13] 4-(*N*,*N*-dimethylamino)-pyridine (DMAP), and allylbenzylamine provided amide **9a** in 69% yield.

In a typical tandem radical reaction experiment (Scheme 2a),[8,14] a benzene solution of **9a** and diphenyl disulfide was irradiated with a UV lamp at room temperature. Evaporation and flash chromatography provided the target azabicyclooctane **10** in 50% yield. This product presumably results from the sequence of elementary steps summarized in Scheme 2a. Addition of PhS· to one of the vinyl groups of **9a** induces cyclopropane opening to give dienyl sulfide **11**. This undergoes two successive 5-*exo* radical cyclizations to give bicyclic *β*-thiophenyl radical **12**, which in turn fragments to provide **10** and give back PhS·.

In reactions of **9a** with various radical-generating species (PhSSPh, Bu_3SnH) conducted above room temperature,[15] we consistently observed two new products by TLC analysis alongside **10**. This was reminiscent of the above attempts at thermal saponification, which also gave unexpected products. So we hypothesized that background thermal chemistry was occurring.

In a control experiment shown in Scheme 2b, divinylcyclopropane **9a** was simply heated alone in refluxing toluene. After 2 h, both precursor **9a** and tandem radical product **10** were absent by TLC analysis; the spots for the two new thermally formed products were the only ones present. Evaporation and

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flash chromatography provided these two products in pure form.

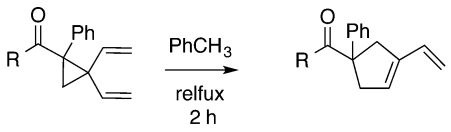
The minor product, isolated in 16% yield, was the vinylcyclopentene **13a**. This is the product of a vinylcyclopropane rearrangement in which one of the vinyl groups of the divinylcyclopropane participates and the other is a substituent.[7a] The rearrangement is regioselective with migration to the more-substituted cyclopropane carbon atom (the one bearing the amide and phenyl groups).

The major product was a more deeply rearranged tricyclic spirolactam **14a**, isolated in 71% yield as a single stereoisomer. The structure of **14a** was assigned by a series of 1D and 2D NMR experiments (see Supporting Information). The upfield chemical shift of the protons of the methyl substituent on the lactam ring (d, 0.55 ppm) shows that this group is *cis* to the adjacent phenyl ring. Spirolactam **14** forms by an aromatic Cope rearrangement followed by an ene reaction, as discussed in more detail below.

The conversion of **9a** to **13a** and **14a** occurs at slower but still significant rates at temperatures as low as 40 °C (about 40% conversion after 36 h). Storage for a few days at ambient temperatures does not give much rearrangement, but a freezer is recommended for long-term storage of **9a** and related divinylcyclopropanes.

We next studied both of these rearrangement pathways with the aid of readily available acid **8** as a common precursor for a dozen assorted substrates. (Here we focus on the rearrangement chemistry; see the Supporting Information for full details on substrate preparation and characterization.) To study the vinylcyclopropane rearrangement, we used precursors shown in Table 1 either without a pendant enophile (acid **8** itself and the

Table 1. Vinylcyclopropane Rearrangement Products and Yields



precursor product

entry	precursor	R	product	yield[a]
1	**8**	OH	**15**	86%
2	**16a**	OEt	**17a**	87%
3	**16b**		**17b**	73%
4	**9b**		**13b**	90%
5	**9c**		**13c**	91%
6	**9d**		**13d**	80%

[a]After automated flash chromatography.

saturated ester **16a** and amide **9b**) or precursors with an enophile that is held in an unfavorable geometry for an ene reaction (allyl ester **16b** and cyclic allyl amides **9c** and **9d**).

As shown by the results in Table 1, these substrates all provided solely the products of regioselective vinylcyclopropane rearrangements in good yields. For example, heating of parent acid **8** in refluxing toluene for 2 h, followed by cooling, evaporation, and flash chromatography, provided ring expanded vinylcyclopentenyl acid **15** in 86% yield (Table 1, entry 1). Likewise, the derived esters **16a**,**b** and amides **9b**–**d** provided the corresponding ring-expanded products **17a**,**b** and **13b**–**d** in spot-to-spot reactions and with uniformly good isolated yields (73–91%, entries 2–6).

Returning to the major spirolactam product **14a** of Scheme 1b, we suggest that this forms by the back-to-back sigmatropic reactions shown in Figure 3. First, the phenyl ring and the

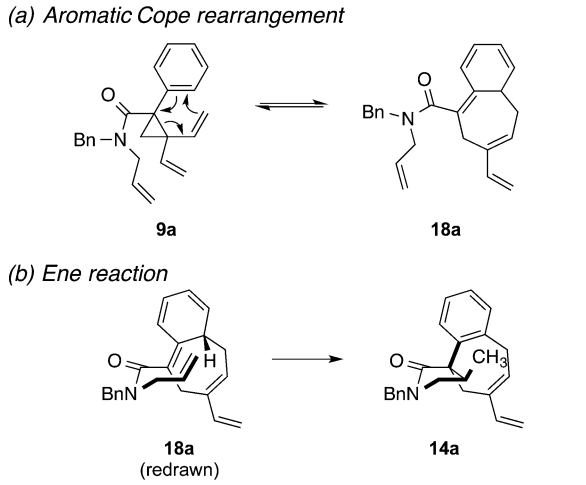


Figure 3. Spirolactam **14a** forms by a rare and probably reversible aromatic Cope rearrangement followed by an irreversible ene reaction.

adjacent *cis*-vinyl group combine in a 3,3-sigmatropic reaction that is a rare example of an aromatic Cope rearrangement[16] to give **18a** (Figure 3a). This rearrangement may be endothermic, but the release of strain energy of the cyclopropane at least partially compensates for the loss of aromaticity of the phenyl ring.

The intermediate **18a** was not observed. The exomethylene cyclohexadiene in **18a** is a highly reactive enophile, and the ensuing intramolecular ene reaction provides the aromatized spirolactam **14a** (Figure 3b). The geometry of the ene reaction necessitates that the new CH_3 group in the product is *cis* to the aromatic ring.

To further study the aromatic Cope-ene path, we prepared the four amides **9e**–**h** shown in Scheme 3. Like **9a**, each of these substrates has an accessible ene component of an ene reaction (alkene or alkyne) present on the amide N-substituent. As usual, these precursors were made in good yields from the pivotal acid **8**. Heating of *N*,*N*-diallylamide **9e** at reflux in toluene for 2 h, followed by evaporation and chromatography, provided spirolactam **14e** in 65% again as a single isomer. Isolated alongside this was the vinyl cyclopentene **13e** in 16% yield. Likewise, the phenyl-substituted diallyl amide **9f** provided **14f** as a single stereoisomer in 45% yield. In this and the following examples, we stopped targeting isolation of the minor vinylcyclopentene products, but these were present in small amounts prior to the chromatography.

Thermal reactions of the two *N*-propargyl amides **9g** and **9h** gave similar ratios of spirolactams-to-vinylcyclopentenes, roughly 6/1 according to ^{1}H NMR integration of the crude products. The major spirolactams **14g** and **14h** were isolated in 73% and 53% yield, respectively. In the case of propargyl silane **9h**, the alkenyl silane product **14h** was a single Z-isomer, again resulting from the geometry of the intramolecular ene reaction.

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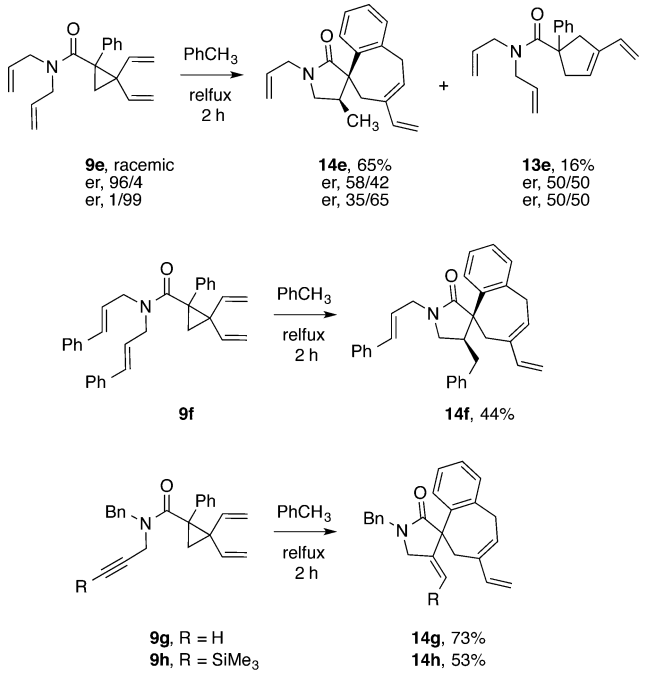
Scheme 3. Additional Examples of Formation of Sequential Cope-Ene Spirolactam Products



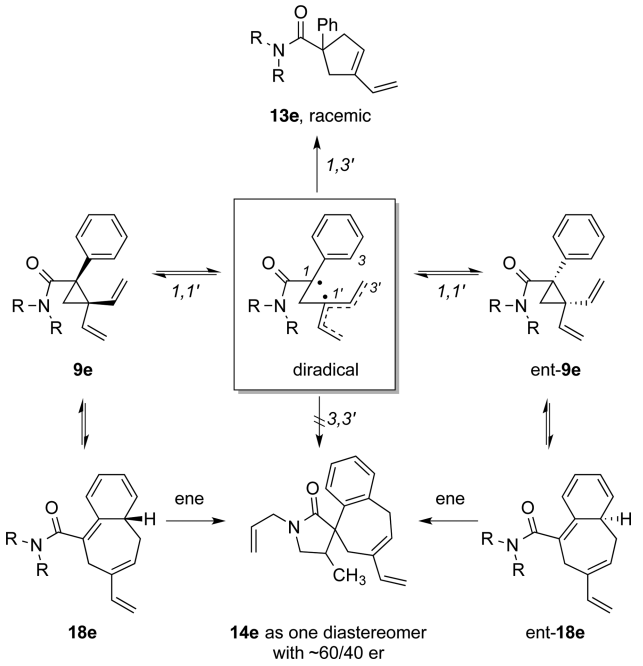


Figure 4. Possible mechanistic scenario for competing vinylcyclopropane and Cope-ene rearrangement paths with a focus on stereochemistry. Reaction conditions, toluene reflux, 2 h; *R* = allyl.

To learn about chirality transfer in these rearrangements, we selected diallyl amide **9e** because two reactions (aromatic Cope and vinylcyclopentene rearrangements) can be probed in one experiment. Racemic **9e** was resolved into its component enantiomers by chiral HPLC (see Supporting Information), and then these enantiomers were heated individually under the usual conditions. The results of these experiments are also shown in Scheme 3.

Starting from highly enriched precursors **9e** (er 96/4 and 1/99), the Cope-ene products **14e** showed low levels of enantioenrichment (58/42 and 35/65) while the vinylcyclopentene products **13e** were racemic (50/50). Further, chiral HPLC analysis of starting material at partial conversion showed that racemization of **9e** competed efficiently with its onward reactions. In a typical experiment, the conversion of **9e** at 60 min was 76% and the er of remaining **9e** was 54/46 (initial er 96/4).

Figure 4 shows a plausible interpretation of these results. The starting divinylcyclopropane **9e** or ent-**9e** opens to a diradical[17] (boxed intermediate) that is either achiral or more likely chiral but racemic due to rapid σ-bond rotations. Both components of the diradical are well stabilized by conjugation, accounting for the relatively low temperature of bond cleavage. Reclosure of the diradical in a 1,1′-fashion racemizes the precursor while closure in a 1,3′-fashion provides the fully racemic vinylcyclopropane rearrangement product **13e**.[6a]

The aromatic Cope rearrangement could be concerted and stereospecific with **9e** giving **18e** and ent-**9e** giving ent-**18e**. (A boat transition state with both π-groups endo to the cyclopropane ring is expected.[6a]) However, this rearrangement is probably reversible and either it or the ensuing ene reaction competes ineffectively with the racemization of the precursor **9e** in refluxing toluene.

It is also possible that the aromatic Cope rearrangement is not concerted, but instead, product **18e** arises by 3,3′-closure of the diradical. However, recall that the vinylcyclopropane product **13e** is racemic but that the Cope-ene product **14e** is not. This suggests that the diradical may not be a common intermediate in their formation. Instead, the partial (but not complete) racemization of the precursor may better account for the low (but not zero) level of chirality transfer from **9e** to **14e**.

The types of products that we observe provide an interesting contrast to recent observations by Stephenson and coworkers.[16b] They generated vinyl phenylcyclopropanes like **19** in situ by radical cyclizations and observed that these underwent rearrangements to **21**, presumably by an aromatic Cope rearrangement to **20** followed by rearomatization by 1,3-hydrogen shift. The reaction conditions were mild: DMF, 40 °C for several hours. Stephenson observed no vinylcyclopropane rearrangement products at all, and our substrates never gave products of aromatic Cope rearrangements followed by hydrogen shift. This is surprising because rearomatization by 1,3-shift is a common reaction of exomethylene cyclohexadienes.[16a,18] The concerted shift is thermally forbidden, but deprotontation/reprotonation or other stepwise mechanisms are possible.

In our substrates, the vinylcyclopropane rearrangement competes with the Cope-ene rearrangement of **9a** and **9e−h** as indicated by the consistent observation minor cyclopentene products **13a** and **13e−h** (Schemes 2 and 3). With the substrates in Table 1, where onward ene reactions are either impossible or disfavored by geometry, we isolate only the vinylcyclopropane rearrangement products. For example, the reaction of **16a** did not produce any rearomatized aromatic Cope product **23** (Figure 5b), only vinylcyclopentene **17a**.

Still, the reversible aromatic Cope rearrangement must be occurring at least to some extent with **16a** and related substrates because they are so structurally similar to amides **9a** and **9e−g** (only the amide or ester group differs). As they reflect this similarity, all the precursors react under the same conditions independent of which products are finally formed. Evidently then, rearomatization of the transient aromatic Cope

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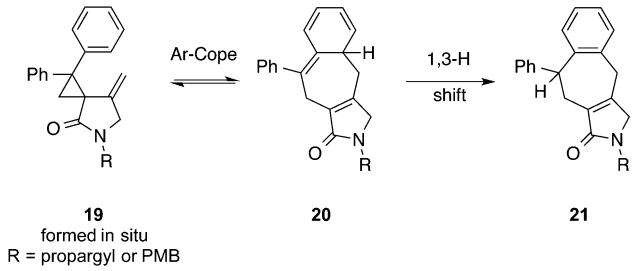
(a) Stephenson's substrates; 1,3-H shift is favored



*(b) With ester **16a**, the vinylcyclopropane rearrangment product **17a** forms even when acid or base is added*

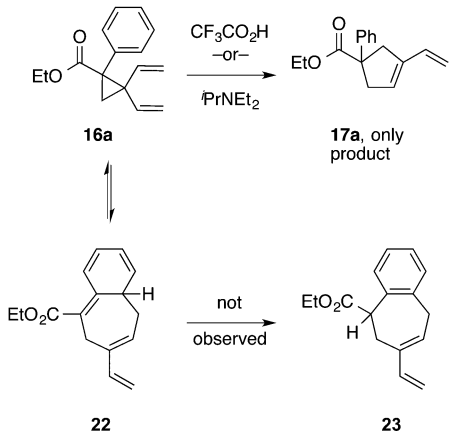


Figure 5. Contrasts with the results of Stephenson.

rearrangement products like **22** cannot compete with either the onward ene reaction (when available) or the vinylcyclopropane rearrangement.

In an effort to induce rearomatization by hydrogen-shift, we heated ester **16a** in toluene with either acid (CF_3CO_2H, 2 equiv) or base (iPr_2NEt, 2 equiv); however, no new rearomatization product **23** was observed (Figure 5b). Instead, the usual vinylcyclopentene **17a** was the only apparent product, and it was formed at about the same rate as in the experiment with no additive (Table 1, entry 2).

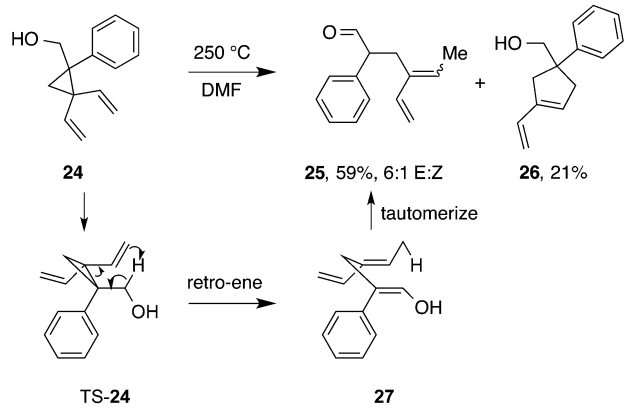
Finally, to learn about the role of the carbonyl group in these acid, ester, and amide substrates, we prepared alcohol **24** by reduction of ester **6** with lithium aluminum hydride (91% yield, see Supporting Information), then converted this to allyl ether **28** with NaH and allyl bromide (67% yield). The rearrangement chemistry of these two substrates is summarized in Scheme 4.

To start, both **24** and **28** were stable in refluxing toluene for several hours. So, the carbonyl group is an important activator in the acid, ester, and amide substrates even though it is not a direct participant in either the vinylcyclopropane or aromatic Cope rearrangements.

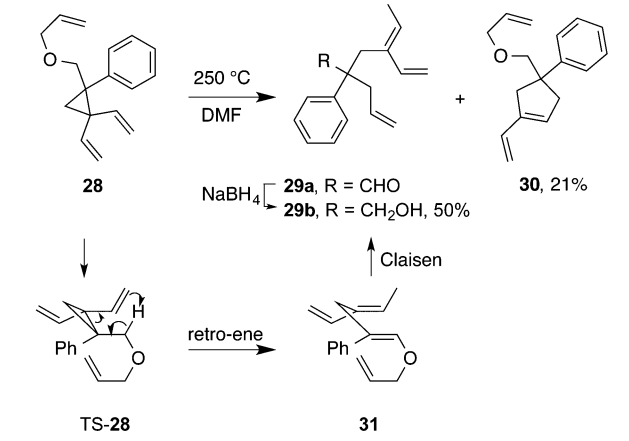
The reduced substrates **24** and **28** both underwent clean rearrangements at 250 °C in DMF in a microwave apparatus to give new types of products. Rearrangement of alcohol **24** (Scheme 4a) provided dienyl aldehyde **25** in 59% yield as a 6/1 mixture of E/Z isomers alongside 21% of the vinylcyclopropane rearrangement product **26**. Aldehyde **25** probably arises from the retro-ene reaction[5] of **24** via TS-**24** to form enol **27**, which then tautomerizes.

Scheme 4. Thermal Rearrangements of Reduced Alcohol 24 (a) and Allyl Ether 28 (b)

*(a) Rearrangement of alcohol **24***



*(b) Rearrangement of allyl ether **28***



Allyl ether **28** was then prepared because it has the requisite functionality to undergo all three types of thermal rearrangements observed so far. These are (1) the aromatic Cope-ene rearrangement (the allyl group of the ether is the potential ene component of **28**); (2) the vinylcyclopropane rearrangement; and (3) the retro-ene reaction.

In the event, heating of allyl ether **28** at 250 °C provided a mixture of a major aldehyde product **29a** and a minor vinylcyclopropane rearrangement product **30**. These products could not be separated by direct flash chromatography, so the mixture was exposed to sodium borohydride. This reduced the aldehyde **29a** to the more polar alcohol **29b**, which was then isolated in 50% yield by flash chromatography. The less polar vinylcyclopropane rearrangement product **30** survived the $NaBH_4$ reduction, and was isolated in 21% yield.

Aldehyde **29a** presumably arises from an initial retro-ene reaction through TS-**28** that gives allyl vinyl either **31**. Subsequent 3,3-sigmatropic rearrangement of this intermediate (a Claisen rearrangement) provides the major product **29a**. The aromatic Cope-ene product from this substrate would be a spiro ether, but there is no evidence for its formation.

■ CONCLUSIONS

These results suggest that 1,1-divinyl-2-phenylcyclopropanes are a class of substrates that have an especially rich array of rearrangement reactions. Figure 6 summarizes the different

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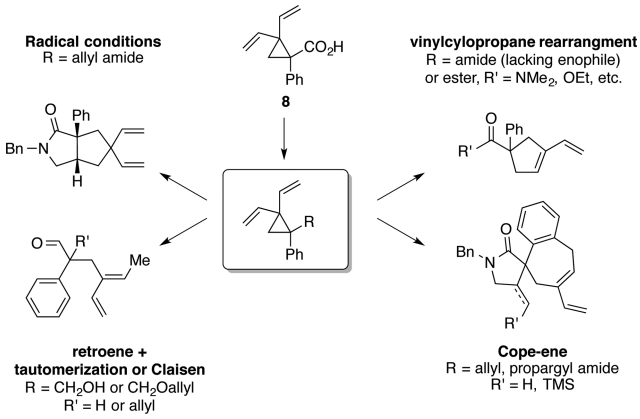

Figure 6. Common acid precursor **8** provides a diverse set of rearrangement products in 1−3 steps.

pathways observed herein. Starting from derivatives of a single divinylcyclopropane acid **8**, we have isolated the products of tandem radical reactions, vinylcyclopropane rearrangements, aromatic Cope-ene rearrangements, and retroene rearrangements followed by either tautomerization or Claisen rearrangement.

Each of the structure types can be formed as the major (though not always exclusive) product. The default thermal reaction seems to be the vinylcyclopropane rearrangement, which gives vinylcyclopentene products in high yields when the other paths are disfavored or impossible. However, the other paths are easily dialed in by choice of R group and reaction conditions.

The radical reaction path regenerates a 1,1-divinyl substituent in the product. In contrast, all three types of thermal reactions produce 1,3-dienes that directly result from the divinylcyclopropane. However, the structural setting of these dienes is very different depending on the reaction. The versatility of the reactions and the diversity of the products suggest that substituted 1,1-divinylcyclopropanes could be useful intermediates in synthesis, perhaps even on par someday with their much more well studied monovinyl- and 1,2-divinylcyclopropane relatives.

■ ASSOCIATED CONTENT

Supporting Information

Complete experimental details and copies of NMR spectra of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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