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Selective Syntheses of $\Delta^{\alpha,\beta}$ and $\Delta^{\beta,\gamma}$ Butenolides from Allylic Cyclopropenecarboxylates via Tandem Ring Expansion/[3,3]-Sigmatropic Rearrangements

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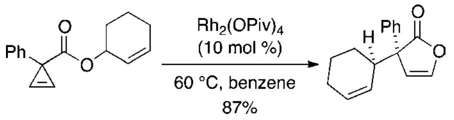
ABSTRACT



Allylic cyclopropenecarboxylates undergo ring expansion reactions to give 2-allyloxyfuran intermediates, which subsequently rearrange to $\Delta^{\beta,\gamma}$ butenolides via a Claisen rearrangement or to the corresponding $\Delta^{\alpha,\beta}$ butenolides via further Cope rearrangement. Also described are methods for chirality transfer in the rearrangement of nonracemic allylic esters.

Compounds with $\Delta^{\alpha,\beta}$ and $\Delta^{\beta,\gamma}$ butenolide substructures have received much interest for their utility in synthesis[1] and their prevalence in biologically active molecules and natural products.[2] A number of methods for preparing $\Delta^{\alpha,\beta}$ butenolides involve the reactivity of furan derivatives, including asymmetric variants based on the Michael,[3] Mukaiyama–Michael,[4] vinylogous Mannich,[5] Morita–Baylis–Hillman,[6] and aldol reactions[7] that utilize siloxyfurans to provide enantiomerically enriched $\Delta^{\alpha,\beta}$ butenolides. There are also a number of enantiospecific syntheses of $\Delta^{\alpha,\beta}$ butenolides in which epoxides[8] or allenoates[9] are used as precursors.

Relative to methods for preparing $\Delta^{\alpha,\beta}$ butenolides,[1d,10] the methods for accessing $\Delta^{\beta,\gamma}$ isomers are few, especially for butenolides that bear a quaternary α-stereocenter.

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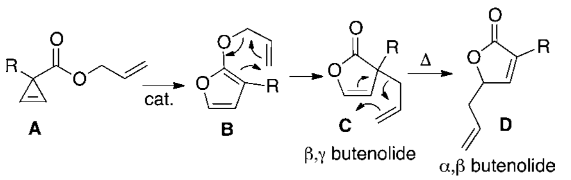
Cycloisomerization and iodolactonization reactions have been used in the construction of $\Delta^{\beta,\gamma}$ butenolides that bear α-quaternary stereocenters.[11] Vedejs[12] and Smith[13] have catalyzed carboxyl migration reactions of 5-arylfuran derived enol carbonates to give $\Delta^{\alpha,\beta}$ and $\Delta^{\beta,\gamma}$ butenolides.[12] Burger has demonstrated that allylic alkoxides can engage 2-fluoro-3-trifluoromethylfurans in tandem S_NAr/Claisen reactivity to produce $\Delta^{\beta,\gamma}$ butenolides.[14] Recently, Ma described iodide catalyzed, regioselective alkylation of 2-methoxyfuran-3-carboxylic esters to give $\Delta^{\alpha,\beta}$ and $\Delta^{\beta,\gamma}$ butenolides.[15]

Very recently, Arseniyadis and Cossy have elegantly reported enantioselective Tsuji–Trost type reactions[16] of allyl furan-2-yl carbonates.[17] Quaternary centers were established in 69–90% ee to give $\Delta^{\beta,\gamma}$ butenolides via Claisen rearrangement and the corresponding $\Delta^{\alpha,\beta}$ butenolides via further Cope rearrangement.[17]

Scheme 1. Tandem Ring Expansion/Claisen Rearrangements



Cyclopropene carboxylic esters are attractive precursors for the preparation of butenolides,[18] as they can be readily prepared by catalytic cyclopropenation of alkynes. The conversion of cyclopropene carboxylic esters to 2- alkoxyfurans is a well-known transformation that can be catalyzed by a variety of metals,[19] and elegant studies have extended the scope of such reactions to the synthesis of fused heterocycles.[18] Of the catalysts that promote ring expansion of cyclopropenes, Rh-based catalysts are among the most useful, and one-pot syntheses of furans from alkynes and diazo compounds have been achieved.[19–21] Furthermore, Rh(I) and Rh(II) catalysts lead to distinct regioselectivities in the ring expansion. Liebeskind[19a] and Padwa[22] have proposed a mechanism that describes the differing regioselectivities induced by Rh(I) and Rh(II) catalysts.

We envisioned that readily prepared allylic cyclopropenecarboxylates (**A**) could engage in ring expansion reactions to give 2-allyloxyfuran intermediates (**B**) and that the resulting allyloxyfurans would subsequently rearrange to $\Delta^{\beta,\gamma}$ butenolides (**C**) via Claisen rearrangement or to the corresponding $\Delta^{\alpha,\beta}$ butenolides (**D**) via further Cope rearrangement (Scheme 1). Herein, we describe catalytic methods for realizing these processes and for selective formation of either $\Delta^{\beta,\gamma}$ or $\Delta^{\alpha,\beta}$ butenolides (**C** vs **D**). The procedure is not restricted to the reactivity of simple allyl esters, but it also functions for prenyl esters, progargyl esters, and esters derived from cyclic and acyclic secondary allylic alcohols. For more substituted analogs of **A**, we describe methods for controlling regioselectivity and chirality transfer from nonracemic allylic esters. Our work complements the very recent work of Arseniyadis and Cossy, where asymmetric catalysis is used to transfer unfunctionalized allyl groups.[17a]

In general, allylic cycloprop-2-enecarboxylates could be prepared in good yields by alkylation of the corresponding acids with allylbromide/DBU or by Steglich esterification. The rearrangement to $\Delta^{\beta,\gamma}$ butenolides was first studied with allylic esters of cycloprop-2-enecarboxylates without vinylic substitution. A number of catalysts were surveyed, and $Rh_2(OPiv)_4$ was found to be highly effective. Allyl 3-phenylcycloprop-2-enecarboxylate (**1a**) gave butenolide **2a** in 90% yield. Also rearrangements of

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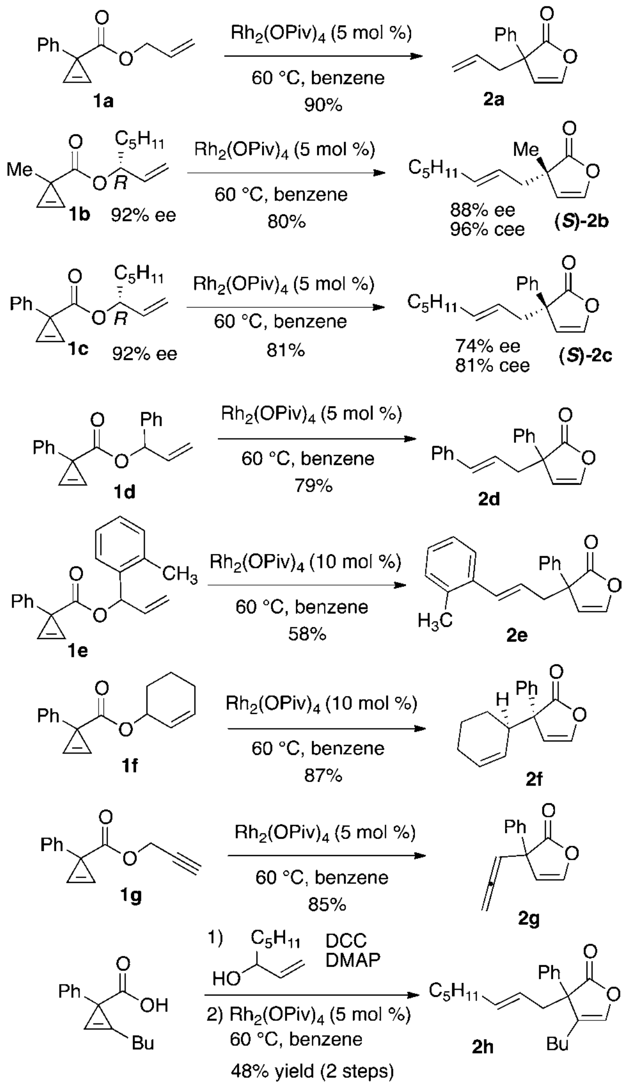
3-phenylcycloprop-2-enecarboxylates (**1b**–**e**) derived from secondary allylic alcohols were studied. Successful rearrangements were realized with substrates with *n*-pentyl (**1b**,**c**), phenyl (**1d**), or *o*-tolyl (**1e**) substituents at the allylic position to give **2b**–**e** in 58–81% yields.

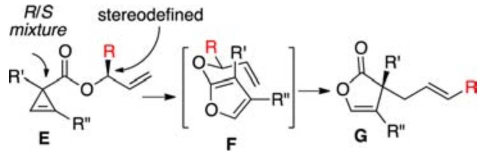
As shown in Scheme 2, cyclohex-2-en-1-yl ester **1f** rearranges to compound **2f** in 87% yield and with >95:5 diastereoselectivity. Propargyl ether **1g** also undergoes tandem ring expansion/Claisen rearrangement to give α-allenyl-α-phenyl-$\Delta\beta,\gamma$ butenolide (**2g**) in 85% yield. Also successful was the rearrangement of a cyclopropene that is substituted at both the vinylic and allylic positions. Butenolide **2h** was obtained in 48% yield by a two-step procedure, in which the intermediate ester was purified only by filtration through a plug of silica gel. The relatively low yield of **2h** was a result of the difficulty of this particular Steglich esterification, and not the Rh-catalyzed rearrangement.

Scheme 2. Tandem Ring-Expansion/Claisen Rearrangements



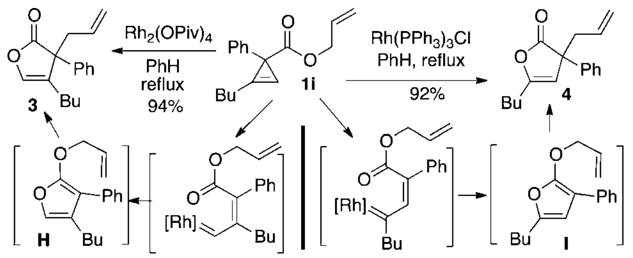
A model set forth in Scheme 3 predicts that the tandem ring expansion/Claisen rearrangements would be stereospecifically controlled by a chair transition state (**F**) with the allylic substituent in an equatorial position. This model predicts that the absolute configuration of the butenolides **G** is set by the absolute configuration of the ester side chain of cyclopropene **E**, which can be readily derived from enantiomerically enriched allylic alcohols. Chirality transfer was measured for the rearrangements of cyclopropenes **1b** and **1c**. For **1b**, a high conversion of enantiomeric excess (96% cee) was indeed observed, and the absolute configuration was confirmed by conversion to (*S*)-3-allyl-3-methylfuran-2(3*H*)-one.[17] Chirality transfer was also observed for the reaction of **1c** to **2c** (at 60 °C), albeit with a reduced conversion of enantiomeric excess (81% cee).[22] The ready availability of nonracemic allylic alcohols makes the method presented in Scheme 2 an attractive method for the synthesis of enantiomerically enriched butenolides.

Scheme 3. Model for Chirality Transfer



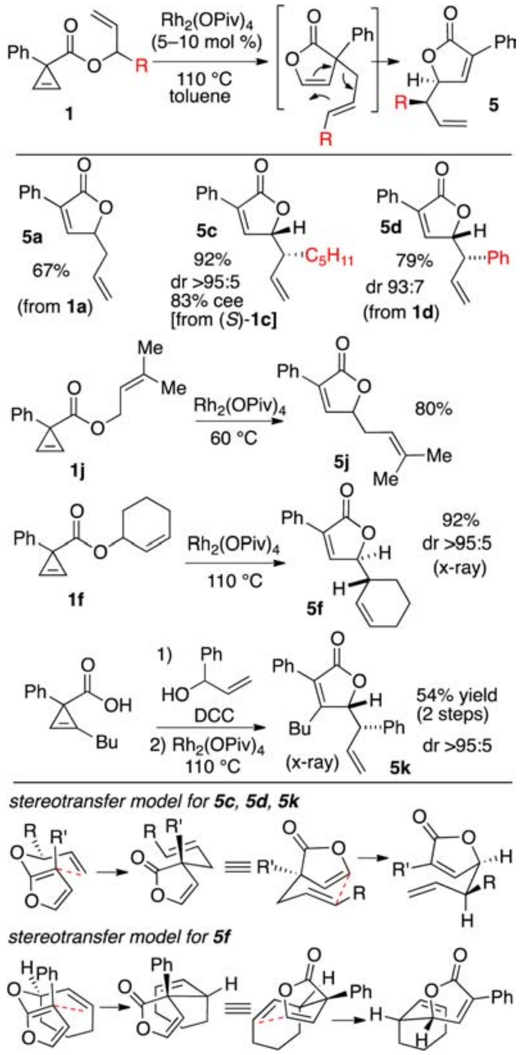
Rh(I) and Rh(II) catalysts lead to distinct regioselectivities in the ring expansion of cyclopropenecarboxylates.[17a,20] We hypothesized that allylic cycloprop-2-enecarboxylates with C-2 substitution would undergo rearrangement to allyloxyfurans and subsequently to $\Delta^{\beta,\gamma}$ butenolides with catalyst-dependent regioselectivity (Scheme 4). Indeed, we found that treatment of **1i** with Wilkinson's catalyst in refluxing benzene gave **4** in 92% yield via putative intermediate **I**. Conversely, treatment of **1i** with $Rh_2(OPiv)_4$ leads to the complementary regioisomer **3** in 94% yield via putative **H**. Consistent with this mechanism,[19a,22] nonracemic **1i** (82% ee) gives racemic **4** in a reaction catalyzed by Wilkinson's catalyst.

Scheme 4. Regioselective Expansion/Claisen Rearrangement



Because compounds **2** are 1,5-dienes, it was anticipated that they could undergo a Cope rearrangement subsequent to the Claisen rearrangement at elevated temperature and that the sequence of ring expansion/Claisen/Cope rearrangement could take place in one flask. As displayed in

Scheme 5. Expansion/Claisen/Cope Rearrangements

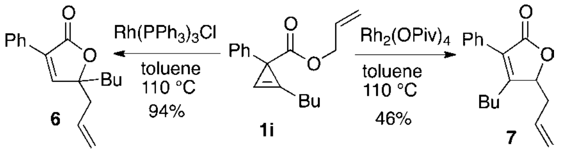


Scheme 5, a number of allylic cycloprop-2-enecarboxylate derivatives undergo rearrangement to $\Delta^{\alpha,\beta}$ butenolides utilizing $Rh_2(OPiv)_4$ at 110 °C in toluene. Allyl 1-phenylcycloprop-2-enecarboxylate (**1a**), which rearranged to **2a** at 60 °C, rearranges to **5a** at 110 °C. Prenyl ester **1j** undergoes spontaneous Claisen/Cope rearrangement to give $\Delta^{\alpha,\beta}$ butenolide **5j**; the $\Delta^{\beta,\gamma}$ butenolide was not observed. We rationalize that the Thorpe–Ingold effect of the gem-dimethyl accelerates the rate of Cope rearrangement for the putative $\Delta^{\beta,\gamma}$ butenolide intermediate. For cycloprop-2-enecarboxylates derived from secondary allyl alcohols, sequential ring expansion/Claisen/Cope rearrangements can produce diastereomers. For such substrates (**5c**, **5d**, **5f**, **5k**), the diastereoselectivity was high (≥93:7). The stereoselectivity of the tandem rearrangement is rationalized via successive chair transition states, as shown at the bottom of Scheme 5. With enantiomerically enriched **1c**, compound **5c** was obtained with 83% ee. To see if the Cope rearrangement is Rh-catalyzed, the rate of the transformation of **2d** to **5d** was measured by ^{1}H NMR (0.04 M in toluene-d_6, 100 °C). Without the catalyst, the rate was measured to be 6.0×10^{-4} s^{-1}. For an identical experiment with 10 mol % $Rh_2(OPiv)_4$, the rate was measured as 5.9×10^{-4} s^{-1}. These data suggest that the Cope rearrangement step is not catalyzed by $Rh_2(OPiv)_4$.

As was observed in the synthesis of $\Delta^{\beta,\gamma}$ butenolides, catalyst-dependent regioselectivity could be realized for $\Delta^{\alpha,\beta}$ butenolide synthesis via the rearrangement of cyclopropene **1i**, which is substituted at the vinylic position of the cyclopropene. Thus, **1i** rearranged to **6** in 94% yield utilizing Wilkinson's catalyst at 110 °C, whereas **7** was formed in 46% yield when $Rh_2(OPiv)_4$ was employed as the catalyst (Scheme 6).

In summary, we describe that allylic cyclopropenecarboxylates engage in Rh-catalyzed ring expansion reactions to give 2-allyloxyfuran intermediates and that the resulting allyloxyfurans would subsequently rearrange to $\Delta^{\beta,\gamma}$ butenolides via a Claisen rearrangement or to the corresponding $\Delta^{\alpha,\beta}$ butenolides via further Cope rearrangement. For allyloxycycloprop-2-enecarboxylates with C-2 substitution, the regioselectivity can be controlled through catalyst choice. Enantiomerically enriched butenolides can be prepared with good levels of stereospecificity with cyclopropenecarboxylates derived from enantiomerically enriched allylic alcohols. Propargyl cycloprop-2-enecarboxylates also participate in a tandem rearrangement to give Δβ,γ butenolides with allenic substitution.

Scheme 6. Catalyst Control over Regioselectivity



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Supporting Information Available. Full experimental details, two cif files, and ^{1}H and ^{13}C NMR spectra are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.