A New Route to Diastereomerically Pure Cyclopropanes Utilizing Stabilized Phosphorus Ylides and γ-Hydroxy Enones Derived from 1,2-Dioxines: Mechanistic Investigations and Scope of Reaction

Thomas D. Avery, Dennis K. Taylor,* and Edward R. T. Tiekink

Department of Chemistry, The University of Adelaide, 5005 Australia

dennis.taylor@adelaide.edu.au

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A new chemical transformation for the construction of diversely functionalized cyclopropanes utilizing 1,2-dioxines and stabilized phosphorus ylides as the key precursors is presented. Through a series of mechanistic studies we have elucidated a clear understanding of the hitherto unknown complex relationship between 1,2-dioxines **1a**−**e**, and their isomeric *cis*/*trans* γ-hydroxy enones (**23** and **21a**−**e**), *cis*/*trans* hemiacetals **24a**−**e**, and β-ketoepoxides (e.g., **26**), and how these precursors can be utilized to construct diversely functionalized cyclopropanes. Furthermore, several new synthetically useful routes to these structural isomers are presented. Key features of the cyclopropanation include the ylide acting as a mild base inducing the ring opening of the 1,2-dioxines to their isomeric *cis* γ-hydroxy enones **23a**−**e**, followed by Michael addition of the ylide to the *cis* γ-hydroxy enones **23a**−**e** and attachment of the electrophilic phosphorus pole of the ylide to the hydroxyl moiety, affording the intermediate 1-2λ^5-oxaphospholanes **4** and setting up the observed *cis* stereochemistry between H1 and H3. Cyclization of the resultant enolate (**30a** or **30b**), expulsion of triphenylphosphine oxide, and proton transfer from the reaction manifold affords the observed cyclopropanes in excellent diastereomeric excess. The utilization of Co(SALEN)$_2$ in a catalytic manner also allows for a dramatic acceleration of reaction rates when entering the reaction manifold from the 1,2-dioxines. While cyclopropanation is favored by the use of ester-stabilized ylides, the use of keto- or aldo-stabilized ylides results in a preference for 1,4-dicarbonyl formation through a competing Kornblum−De La Mare rearrangement of the intermediate hemiacetals. This finding can be attributed to subtle differences in ylide basicity/nucleophilicity. In addition, the use of doubly substituted ester ylides allows for the incorporation of another stereogenic center within the side chain. Finally, our studies have revealed that the isomeric *trans* γ-hydroxy enones and the β-keto epoxides are not involved in the cyclopropanation process; however, they do represent an alternative entry point into this reaction manifold.

Introduction

Cyclopropane-containing natural and nonnatural products receive considerable attention as synthetic targets as the incorporation of the rigidified cyclopropyl motif into bioactive analogues leads to conformationally constrained molecules.[1] Such modifications are "expected" to have significant effects on bioactivities with concomitant medical implications. Cyclopropanes are also generated as transient species in primary and secondary metabolisms including those of man, plants, and microorganisms.[1] Well-known cyclopropyl-containing bioactive molecules include the orally active antifungal/antibacterial ambruticins,[2] the antimitotic curacins A−C,[3] the pyrethroid group of insecticides,[4] cyclopropyl-containing amino acids (peptidomemetics),[5] the constanolactones A−G (potent 5-lipoxygenase inhibitors),[6] and the polycyclopropanated natural products FR-900848 (a potent antifungal agent),[7] U-106305 (a cholesteryl ester transfer protein inhibitor),[8] and the mycolic acids (essential elements of the cell wall architecture of human tuberculosis bacilli).[9] In the main, the most noticeable current strategies for the construction of the cyclopropyl motif include (i) the direct carbene transfer (both stoichiometric and catalytic) from a diazo precursor to an olefin utilizing transition metals (Rh, Cu, Zn, and Pd)[10] and (ii) Michael addition of nucleophiles (usually sulfur ylides) to α,β-

* Tel: +(61 8) 8303 5494, Fax: +(61 8) 8303 4358.

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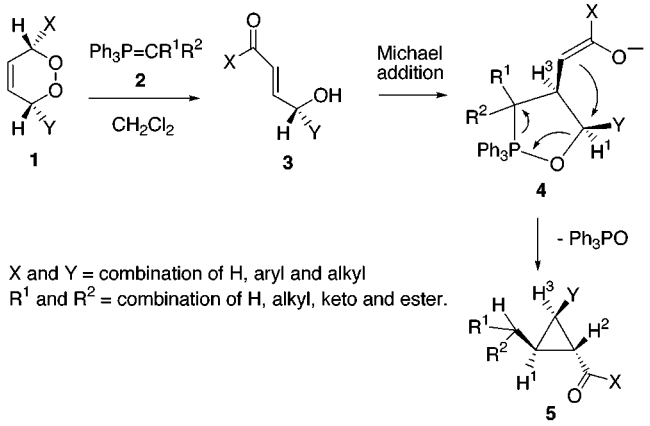
unsaturated ketones and esters, followed by intramolecular cyclization.[11] Despite the great advances in these areas, the efficient synthesis of diastereomerically and enantiomerically pure cyclopropanes still remains a considerable challenge. Of particular importance is the deficiency in methods for the construction of diversely functionalized cyclopropanes that contain greater than disubstitution.

We recently communicated a new approach to diastereomerically pure diversely functionalized cyclopropanes **5** that utilizes 1,2-dioxines (**1**) and stabilized phosphorus ylides (**2**) as the key precursors (Scheme 1).[12] This

Scheme 1



approach avoids the use of potentially explosive diazo precursors and reactions mixtures which must be kept anhydrous. Given the high yields of diversely functionalized cyclopropanes attainable, coupled with the observed high diastereomeric excess and simplicity of reaction, we were stimulated to fully investigate the mechanism of this new transformation. Our initial studies suggested that the isomeric *trans* γ-hydroxy enones **3** may well be the key intermediates along the pathway to cyclopropanation as treatment of isolated **3** with several ylides afforded the observed cyclopropanes. We also postulated that Michael addition of the ylide to **3** in a *syn* manner with respect to the hydroxyl moiety, followed by cyclization, expulsion of triphenylphosphine oxide, and proton transfer from the intermediate 1-2λ^5-oxaphospholane **4** was the rationale behind the observed *cis* stereochemistry between H1 and H3. This contribution therefore reports in full our far-reaching mechanistic findings and highlights further the scope of this cyclopropanation methodology. In addition, this study represents the most important contribution to *cis*/*trans* γ-hydroxy enone equilibria and their reactivity under mild acidic or basic conditions thus far reported.

Results

(1) Global Mechanistic Features. To accumulate widespread mechanistic information while limiting the study to a practical size we decided to investigate the cyclopropanation utilizing five distinctly different 3,6-disubstituted-1,2-dioxines, **1a**−**e**, and seven stabilized phosphorus ylides, **2a**−**g**. The substituents on the 1,2-dioxines (X and Y) were a combination of H, alkyl, and aryl, while the stabilized phosphorus ylides evaluated contained a combination of keto and/or ester functionalities and were either mono- or disubstituted.

(a) Cyclopropane Structure. In general, reaction of equimolar amounts of 1,2-dioxines **1a**−**e** and ylides **2a**−**g** afforded the corresponding *trans* diastereomerically pure cyclopropanes **5**−**9**(**a**−**g**) as the major product, although in some cases the isomeric 1,4-dicarbonyl **15a**−**e** of the corresponding 1,2-dioxine was formed at the expense of the cyclopropane. In a number of cases the *cis* cyclopropanes **10**−**14**(**a**−**g**) were also formed as minor products (Scheme 2). Results of selected experiments are collated in Table 1. Typically the isolated yields were within 10% of those quoted while the cyclopropyl diastereomers were easily separated by column chromatography. The structure and relative stereochemistry of the two cyclopropane series [**5**−**9**(**a**−**g**) and **10**−**14**(**a**−**g**)] were unambiguously elucidated from a combination of ^{1}H, ^{13}C, gCOSY, gHSQC, and gHMBC NMR techniques and X-ray crystallography. The series **5**−**9**(**a**−**g**) all contained a *trans* relationship between the H2 proton and (H1 and H3) as evidenced from the magnitudes of the $^3J_{1-2}$, $^3J_{2-3}$ and $^3J_{1-3}$ coupling constants. For example, reaction of **1a** with ylide **2a** in CH_2Cl_2 afforded **5a** as the sole cyclopropyl product, which displayed $^3J_{1-2}$, and $^3J_{2-3} = 4.8$ Hz while $^3J_{1-3} = 9.2$ Hz. These values ($^3J \approx 4.8$ Hz) are typical for a *trans* relationship about a cyclopropane ring.[13] The stereochemistry was further supported from analysis of the cyclopropyl series **5**−**9**(**a**−**g**) by the ROESY NMR technique; the *trans* stereochemistry exemplified by interactions between H2 with the acetate H4 and H4′ (R^1) protons and the *ortho* phenyl protons and the lack of H1−H2 and H1−H3 interactions. X-ray analysis of **7a**,[12] **6a**,[14] **8a**[15] and the parent acid of **5a**[16] confirmed the structural and stereochemical assignments made above. The relative stereochemistry within the *cis* cyclopropyl series **10**−**14**(**a**−**g**) was easily distinguished not only by the magnitudes of the coupling constants (typically 9.2 Hz for all cyclopropyl protons) but also by the observation of their propensity to undergo an enolene rearrangement (see section on effect of temperature below). To rule out the possibility that the *cis* cyclopropanes **10**−**14**(**a**−**g**) were formed first under the reaction conditions and then isomerized to the thermodynamically more stable *trans* isomers, we treated all *cis* cyclopropanes isolated with excess ylide under identical reaction conditions (with TPPO present) and found no isomerization to the *trans* isomers. Furthermore, addition of excess ylide (entries 5 and 15) to the reaction mixture failed to alter the diastereomeric ratio.

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Scheme 2

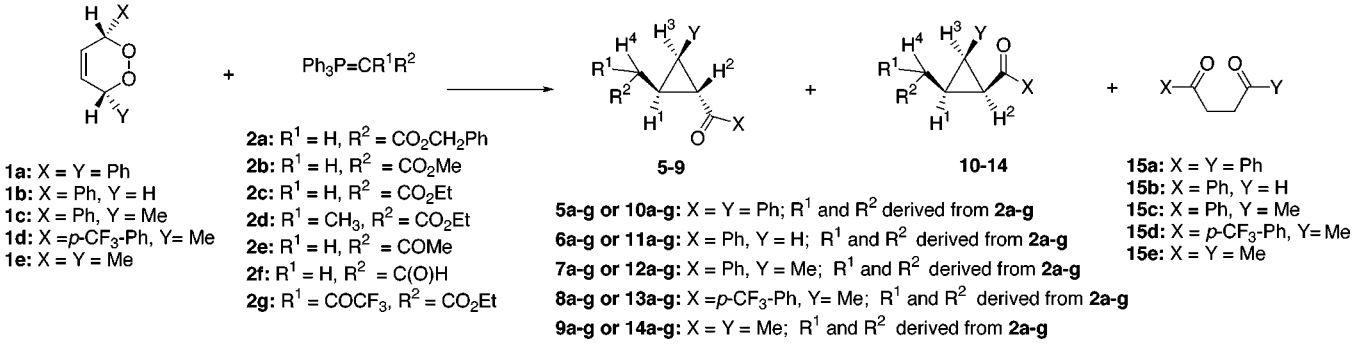

Table 1. Reaction of 1,2-Dioxines 1a−e with Various Stabilized Phosphorus Ylides (2a−g)[a]

entry	1,2-dioxine	ylide	completion time[b]	product(s); yield (%)	entry	1,2-dioxine	ylide	completion time[b]	product(s); yield (%)
1	**1a**	**2a**	3 days	**5a** (96); **15a** (4)	10		**2d**		**6d** (40);[f] **11d**(30); **15b** (30)[g]
2		**2b**		**5b** (96); **15a** (4)	11		**2e**		*g*
3		**2c**		**5c** (97); **15a** (3)	12		**2g**		*e*
4		**2d**[c]		**5d** (41); **15a** (52)	13	**1c**	**2a**	7 days	**7a** (85); **12a** (15)
5		**2d**[c,d]		**5d** (41); **15a** (52)	14		**2b**		**7b** (82); **12b** (18)
6		**2e**		**15a** (100)	15		**2b**[d]		**7b** (82); **12b** (18)
7		**2f**		**15a** (100)	16		**2e**		*h*
8		**2g**		*e*	17	**1d**	**2a**	1 day	**8a** (82); **13a** (18)
9	**1b**	**2a**	1 day	**6a** (100)	18	**1e**	**2a**		*e*

[a] All reactions performed in CH_2Cl_2 with identical reaction volumes and concentrations at ambient temperature; see Experimental Section for a typical procedure. Yields were determined from the ^{1}H NMR spectra (300 or 600 MHz) of the crude reaction mixtures; isolated yields were typically within 10% of those reported above. [b] Determined by ^{1}H NMR monitoring of the reaction mixture at periodic intervals. Value quoted is after all 1,2-dioxine had been consumed. If no value is given, then completion time was not determined. [c] A small amount (7%) of another cyclopropyl isomer was also detected and tentatively assigned as ethyl 1-methyl-2-(2-oxo-2-phenylethyl)-3-phenyl-1-cyclopropanecarboxylate. [d] Excess ylide (3 equiv) utilized. [e] No reaction after 7 days. [f] Characterized as a 3:1 mixture of diastereomers with respect to side chain stereochemistry. [g] The keto-aldehyde **15b** further reacted under the reaction conditions to afford a 10:10:9:1 (total 30%) mixture of *E*- and *Z*-3-(4-benzoyl-1,3-dioxolan-2-yl)-1-phenyl-1-propanone and *E*- and *Z*-ethyl-2-methyl-6-oxo-6-phenyl-2-hexenoate products; see Experimental Section for characterization. [h] Complex mixture of products left uncharacterized.

Inspection of the results collated in Table 1 reveals, at this stage, that it is the substituents about the 1,2-dioxine (X and Y) and not the ylide structure that primarily controls the observed cyclopropyl diastereomeric ratio. For example, while 1,2-dioxines **1a** and **1b** afforded only diastereomerically pure *trans* cyclopropanes with ylide **2a**, 1,2-dioxines **1c** and **1d** afforded minor amounts of the *cis* cyclopropanes along with the *trans* cyclopropanes. Similar trends are noticeable when other ylides were utilized. A further significant finding was that utilization of the doubly substituted phosphorus ylide **2d** led to *trans* cyclopropanes that contained a fourth stereogenic center in the side chain. Moreover, there was a preference for formation of one stereochemistry about the ester moiety over the other at this site. For example, reaction of **1a** with **2d** led to the formation of the *trans* cyclopropane **5d** in moderate yield as a single diastereomer (entry 4). X-ray analysis of the parent acid of this stereoisomer (Figure 1) unambiguously confirmed that not only does the cyclopropyl core contain the *trans* benzoyl grouping but also the sterically bulky side chain groupings are directed away from the substituted cyclopropyl core.

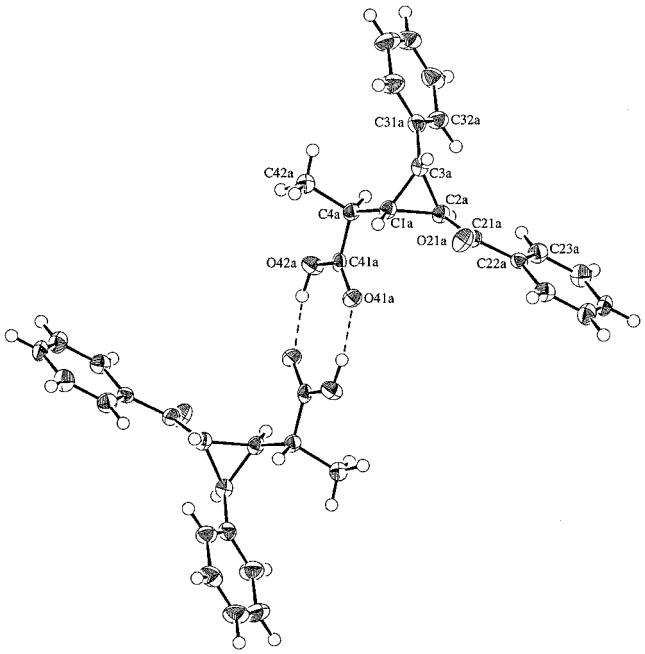

Figure 1. Molecule of the parent acid of diastereomer **5d**.

(b) Yield of Cyclopropane vs 1,4-Dicarbonyl and Overall Reaction Rate. In general, the utilization of monosubstituted ester ylides (**2a−c**) led to excellent yields of the desired cyclopropanes in all cases studied with little or no competitive 1,4-dicarbonyl **15** formation, Table 1. Hence, varying the steric bulk of the ester moiety of these ylides fails to alter the cyclopropane: 1,4-dicarbonyl ratio. The addition of excess ylide to the reaction mixtures failed to alter these ratios (entries 5 and 15) indicating that the 1,4-dicarbonyls are not intermediates along the cyclopropanation pathway. Introduction of added alkyl functionality about the nucleophilic carbon pole of these ester ylides (ylide **2d**, entries 4 and 10) resulted in a decrease in cyclopropane yield with concomitant formation of the 1,4-dicarbonyl, suggesting that there may well be a steric component to the two competing processes. Finally, the monosubstituted

keto ylides (**2e**−**f**) were poor in effecting cyclopropanation and led to significant, if not quantitative 1,4-dicarbonyl formation, entries 6, 7, 11, and 16.

It is now apparent (Table 1) that the genesis of the 1,4-dicarbonyls **15** is primarily a consequence of ylide structure and not 1,2-dioxine structure. Given that the 1,4-dicarbonyls are structural isomers of their respective 1,2-dioxine precursors we suspected at this stage that it may be subtle differences in ylide basicity which controls the cyclopropane:1,4-dicarbonyl ratio. The weak basicity of stabilized phosphoranes has been highlighted.[17] Moreover, base-catalyzed rearrangement (Kornblum−De La Mare decomposition) of cyclic peroxides to their corresponding 1,4-dicarbonyls has been reported previously and is initiated by removal of a proton from the carbon α to the O−O linkage.[18] Indeed, we observed that addition of excess triethylamine to the 1,2-dioxines **1a**−**e** resulted in quantitative isomerization to the 1,4-dicarbonyls **15a**−**e**. To further evaluate the importance of ylide basicity on reaction outcome, we varied the 1,2-dioxine structure while keeping the basicity of the ylide (**2a**) constant, Table 1. Thus, inspection of completion times for entries 1, 9, 13, 17, and 18 clearly indicates that electron-withdrawing substituents enhance the overall rate as a result of increased acidity of the α proton. The importance of how subtle changes in ylide basicity affect cyclopropane yield while keeping the 1,2-dioxine structure constant is discussed later.

(c) Effect of Solvent and Additives. The effect of solvent and additives on the rate of reaction and cyclopropane **5a**:diketone **15a** ratio for the reaction between 1,2-dioxine **1a** and ylide **2a**, Scheme 3, was evaluated; Table 2 summarizes our global findings. With the exception of CH_2Cl_2 the overall rate of reaction was found to increase only slightly with solvent polarity.[19] The small magnitude of the rate increase is inconsistent with a mechanism involving zwitterionic intermediates in the rate determining step and is more in line with a concerted mechanism. For comparison, the "normal" Wittig reaction displays an inverse solvent effect of similar magnitude and is in agreement with a concerted, but not necessarily synchronous, formation of C−C and P−O bonds in the rate determining step.[20] The ratio of **5a**:**15a** varied slightly with a change in solvent polarity (polar solvents favoring cyclopropanation) with the exception of DMF. This anomalous trend in DMF can be rationalized from the known fact that DMF contains trace quantities of amine. As highlighted above, these amines would be "expected" to catalyze the formation of the 1,4-diketone **15a** at the expense of cyclopropane formation. The relative rate and product ratio was unaffected by the addition of tempo (entry 7), suggesting that free radicals are not involved. Furthermore, addition of water (entry 8) had no effect on reaction outcome. This result further suggests that zwitterionic intermediates are not involved as phosphonium alkoxides are extremely hygroscopic and hydrolysis products would be expected.[21] Rapid hydrolysis of the zwitterionic intermediate formed from the interaction of Ph_3P and 2,3-dioxabicyclo[2.2.1]heptane has also been reported.[22] Additionally, the formation of "free" carbenes can be excluded on the basis that addition of excess cyclohexene (entry 9) failed to compete with cyclopropane formation.

Scheme 3

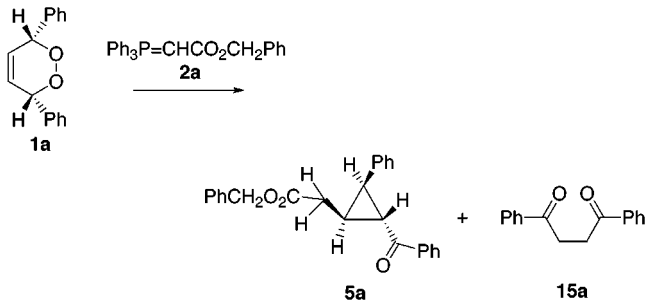

Table 2. Effect of Solvent and Additives on Cyclopropane (5a):Diketone (15a) Ratio[a]

entry	solvent	additive	relative rate[b]	**5a:15a** ratio (%:%)[c]
1	CH_2Cl_2		1.0	97:3
2	CCl_4		1.5	92:8
3	benzene		1.7	82:18
4	hexane			75:25[d]
5	DMF		8.3	16:84
6	CH_3CN		13.3	89:11
7	benzene	tempo (1 equiv)	1.7	78:22
8	benzene	H_2O (10 equiv)	1.5	83:17
9	benzene	cyclohexene (3 equiv)	1.6	85:15
10	benzene	TPP (0.5 equiv)	1.6	73:27

[a] All reactions performed with identical reaction volumes and concentrations at ambient temperature. [b] Determined by ^{1}H NMR monitoring of reaction mixture at periodic intervals (value quoted is after 24 h reaction time); referenced to CH_2Cl_2 as solvent (relative rate = 1.0); actual reaction time approximately 3 days. [c] Ratio determined by ^{1}H NMR after cessation of reaction; all reactions resulted in 100% conversion of the 1,2-dioxine to cyclopropane **5a** or 1,4-diketone **15a**. [d] Ylide and 1,2-dioxine both insoluble at 25 °C; ratio determined after heating at 45 °C.

Although treatment of dioxine **1a** with 1 equiv of Ph_3P led to significant diketone **15a** formation, we discount the possibility that the rearrangement **1a** → **15a** is promoted by "free" Ph_3P liberated during cyclopropanation on the basis of the following experimental evidence: (a) At no time could any free Ph_3P be detected during ^{31}P NMR monitoring of the reaction between **1a** and **2a**. (b) Addition of Ph_3P (0.5 equiv) to the reaction between **1a** and **2a** (entry 10) failed to dramatically change product outcome. (c) The rate of the reaction between Ph_3P and dioxine **1a** leading to **15a** was found to be ca. 5 times slower than that for reaction between **1a** and **2a** in benzene. (d) The lack of free carbene generation (entry 9) is inconsistent with substantial nonreversible release of free Ph_3P. (e) Finally, ^{1}H NMR monitoring of the reaction between **1a** and Ph_3P showed the presence of non-phosphorus containing intermediates that were absent in the reaction of **1a** with **2a**. On the basis of these findings we suggest that formation of **15a** in the reaction of **1a** with **2a** is promoted by the ylide acting as a weak base in a catalytic manner.

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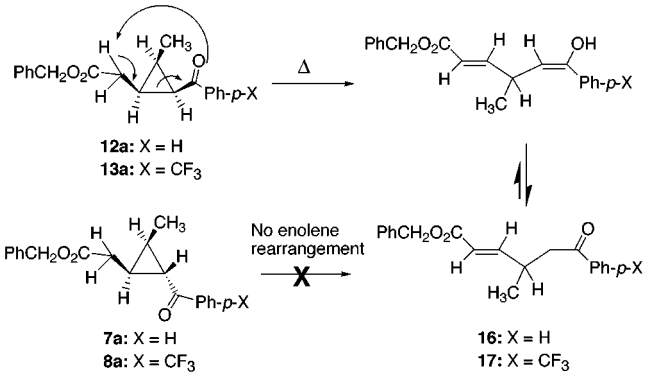
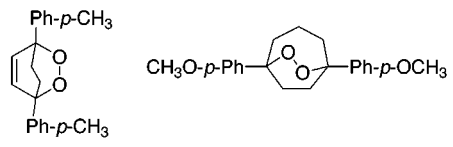
Scheme 4

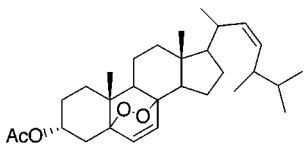


(d) Effect of Temperature. To ascertain whether the cyclopropyl diastereomeric ratio or the formation of the 1,4-dicarbonyls **15a**−**e** was influenced by temperature we carried out several experiments at elevated temperatures, Scheme 4. Performing these reactions at 80 or 110 °C in boiling benzene or toluene, respectively, led to an increased reaction rate without a significant change in product yield or ratio. However, we did observe that, in those cases in which the *cis* cyclopropanes were formed as minor products at ambient temperature, this cyclopropane was no longer present at the elevated temperatures. Instead, they were replaced by an equal amount of the isomeric acyclic *trans* derivative **16** or **17**. Additionally, heating pure **12a** or **13a** (isolated at ambient temperature) to similar temperatures (60 °C) resulted in quantitative isomerization. This isomerization is known as an *enolene rearrangement* or a *homodienyl[1,5] sigmatropic hydrogen shift*[23] and is depicted in Scheme 4.

It has been established that this shift of three electron pairs over seven atoms requires that the two groupings be in a *cis* relationship about the cyclopropyl core.[23] The *trans* cyclopropanes **5**−**9** were thermally stable at these elevated temperatures. Thus, this rearrangement supports our conclusions about the relative stereochemistry of the two cyclopropyl series.

(e) Importance of an Acidic Proton α to the Peroxidic Linkage. Three bicyclic peroxides (**18**−**20**) were also synthesized in order to ascertain the importance of a proton α to the peroxidic linkage. All three failed to react with the stabilized phosphorus ylides **2a**−**g**, even at elevated temperatures, indicating that an acidic proton α to the peroxidic linkage is necessary for cyclopropanation to occur.





(23) Watson, J. M.; Irvine, J. L.; Roberts, R. M. *J. Am. Chem. Soc.* **1973**, *95*, 3348. Roberts, R. M.; Landolt, R. G.; Greene, R. N.; Heyer, E. W. *J. Am. Chem. Soc.* **1967**, *89*, 1404.

(2) Elucidation of Key Intermediates. (a) Isomeric *trans* γ-Hydroxy Enones. A significant mechanistic finding was the observation of the isomeric *trans* γ-hydroxy enones **21c** and **21d** during ^{1}H NMR monitoring of the reactions between the appropriate 1,2-dioxines and ylide **2a**. Both **21c** and **21d** contributed ca. 25% of the reaction mixture after 5 days and 12 h, respectively, while action of the same ylide on 1,2-dioxines **1a** and **1b** resulted only in the formation of a minor (1−2%) amount of the corresponding *trans* γ-hydroxy enones. We were able to isolate a quantity of **21c** and **21d** from the reaction mixture and demonstrate that this lead to significant cyclopropane formation upon addition of ylide.[12] The *trans* configuration about the double bond of these γ-hydroxy enones was typified by a ^3J = 15.4 Hz coupling constant.

Thinking at this stage that the *trans* γ-hydroxy enones **21a**−**d** were the key intermediates along the pathway to cyclopropanation, we decided to evaluate their generation from the precursor 1,2-dioxines and also their effectiveness to generate cyclopropanes upon addition of ylide. After much trial and error we found that the isomerization could be efficiently controlled utilizing a combination of Et_3N and TPP in a molar ratio of 1:0.5 with respect to the 1,2-dioxine. While the typical purified yields were in excess of 77%, it should be noted, however, that the presence of trace amounts of base (Et_3N or ylide) imparted stability to **21a**−**d** (discussed later). In the pure state, all *trans* γ-hydroxy enones underwent rapid dehydration to the corresponding furans **22a**−**d** at ambient temperature. Presumably the mechanism for this dehydration first involves spontaneous stereomutation of the *trans* γ-hydroxy enones **21a**−**d** to the corresponding *cis* γ-hydroxy enones followed by cyclization and loss of water from their cyclic hemiacetals. Indeed, evidence of the spontaneous stereomutation (or equilibrium between *trans* and *cis* forms) was seen (^{1}H NMR) for pure *trans* enone **21d**, which existed in solution along with ca. 5% of the isomeric *cis* enone **23d**. This decomposition could, however, be avoided if **21a**−**d** were stored in solution at 0 °C in the presence of TPP(1%), see below. The utilization of excess Et_3N needed to be avoided as this condition lead to facile competitive isomerization of the *trans* γ-hydroxy enones to the corresponding 1,4-dicarbonyls **15a**−**d**.

We were curious to understand at this stage why this combination of reagents was so effective in causing this isomerization. Hence to gain insight we monitored the isomerization of the 1,2-dioxines in the presence of Et_3N (1 equiv) by ^{1}H NMR and added TPP at periodic intervals. It was observed that Et_3N induces facile rearrangement (<30 min) of the 1,2-dioxines to the corresponding *cis* γ-hydroxy enones, which were in equilibrium with their corresponding cyclic hemiacetals. The characterization and involvement of the *cis* γ-hydroxy enones and their cyclic hemiacetals is discussed in the forthcoming section. Addition of TPP at this stage induces further facile isomerization to the desired *trans* γ-hydroxy enones in essentially a quantitative manner. The mechanism of this latter isomerization presumably involves reversible 1,4-addition to the *cis* γ-hydroxy enones with concomitant formation of the thermodynamically more stable *trans* γ-hydroxy enones. Indeed, TPP has been previously utilized to effect *cis* → *trans* isomerization of enals.[24] The

(24) Sütbeyaz, Y.; Secen, H.; Balci, M. *J. Org. Chem.* **1988**, *53*, 2312.

Scheme 5

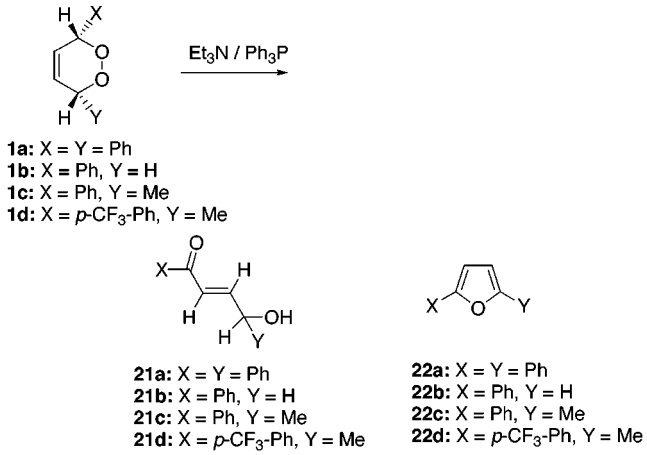


Table 3. Reaction of *trans* γ-Hydroxy Enones 21a−d with Ylides 2a−g[a]

entry	enone	ylide	product(s); yield (%)	completion time
1	**21a**	**2a**	**5a** (44); **15a** (56)	2 weeks
2		**2d**	**5d** (5); **15a** (95)	7 days
3		**2e**	**15a** (100)	4 days
4	**21b**	**2a**	**6a** (100)	2 weeks[b]
5		**2b**	**6b** (100)	2 weeks[b]
6	**21c**	**2a**	**7a** (77); **12a** (18); **15c** (5)	4 weeks[b]
7		**2e**	**15c** (100)	2 weeks
8	**21d**	**2a**	**8a** (78); **13a** (15); **15d** (7)	8 days

[a] All reactions in CH_2Cl_2 at ambient temperature; yields were determined from the ^{1}H NMR spectra (300 or 600 MHz) of the crude reaction mixtures; isolated yields were typically within 10% of those reported above. [b] 50% conversion only.

use of TPPO failed to effect this latter isomerization. Prolonged exposure of the 1,2-dioxines to Et_3N in the absence of TPP was also found to induce formation of the *trans* γ-hydroxy enones, however, competitive formation of the isomeric 1,4-dicarbonyls also resulted, making this method of formation unattractive. With the *trans* γ-hydroxy enones **21a**−**d** now in hand we investigated their reactions with a variety of ylides, the results of which are collated in Table 3. It can now be seen that a major discrepancy existed. Whereas previously 1,2-dioxine **1a** and ylide **2a** afforded cyclopropane **5a** in essentially quantitative yield (entry 1, Table 1) we now find that the corresponding isomeric *trans* γ-hydroxy enone **21a** affords the same cyclopropane in only 44% with the remaining material being the 1,4-dicarbonyl **15a**. In fact the results in Table 3 indicate, with the exception of enone **21b**, that in all cases, while the *trans* enones will afford the desired cyclopropanes there is a strong competition for 1,4-dicarbonyl formation from these precursors that is not observed from the 1,2-dioxines. We also observed, although only qualitatively, that all these reactions were substantially slower than those involving the 1,2-dioxines directly. For example, whereas previously reaction of 1,2-dioxines **1a**−**d** with ylide **2a** had completion times of 3, 1, 7, and 1 day(s), respectively (Table 1), under the same reaction conditions the corresponding *trans* γ-hydroxy enones **21a**−**d** now had completion times in the order of weeks. This suggested to us at this stage that cyclopropanation occurs from a more reactive intermediate that is being formed prior to the *trans* γ-hydroxy enones, while 1,4-dicarbonyl formation may occur after a significant amount of the *trans* γ-hydroxy enones have been formed.

One final point worth highlighting is the observed regiochemical isomerization. Both Et_3N and the ylides effect isomerization of the 1,2-dioxines **1a**−**d** to their corresponding *trans* γ-hydroxy enones **21a**−**d** by removing the most acidic proton α to the O−O linkage. Thus, steric factors play little part in these isomerizations. Base-catalyzed isomerizations of cyclic peroxides to acyclic γ-hydroxy enones (essentially a Kornblum−De La Mare decomposition) are extremely rare as 1,4-dicarbonyls usually result; however, a few examples of the formation of cyclic γ-hydroxy enones may be found in the literature.[25]

(b) Isomeric *cis* γ-Hydroxy Enones and Their Cyclic Hemiacetals. During the base (Et_3N)-catalyzed isomerization of the 1,2-dioxine **1a** to the isomeric *trans* γ-hydroxy enone **21a** we observed (^{1}H NMR) the formation of an intermediate that later disappeared with concomitant formation of **21a**. Consideration of the *cis* relationship about the carbon−carbon double bond in the precursor 1,2-dioxine led us to speculate at this stage that this intermediate was in fact the isomeric *cis* γ-hydroxy enone or its isomeric *cis* and/or *trans* hemiacetal. We were fortunate to be able to isolate a sample of this material by flash chromatography. Analysis by ^{1}H NMR spectroscopy confirmed our suspicions: a thermodynamic mixture of the *cis* γ-hydroxy enone **23a** and their corresponding *cis* and *trans* cyclic hemiacetals **24a** are formed. Addition of ylide **2a** to this mixture lead to essentially quantitative cyclopropane **5a** formation in a facile manner with only a trace of 1,4-dicarbonyl **15a** being detectable, Table 5. Thus, it was highly likely that this mixture represented the true intermediate(s) along the cyclopropanation pathway.

Unfortunately, under these sensitive base conditions, competitive isomerization to the thermodynamically more stable *trans* γ-hydroxy enone or aromatization to the furan resulted in our being able to isolate only minor quantities (ca. 30%, based on starting 1,2-dioxine) of pure sample. Therefore, realizing that the formation of these intermediates utilizing base isomerization would not be of a practical nature we searched for alternative methods of preparation from the precursor 1,2-dioxines that would avoid the use of base. Although the *cis* γ-hydroxy enone **23a** has been speculated as an intermediate during photoreactions on the parent 1,2-dioxine **1a** in the presence of tetracyanoethene, this method was unattractive as it failed to lead to isolation of **23a** in the pure state.[26] An alternative method of preparation which appeared very attractive hinged on the work of Foote and O'Shea.[27] They showed that *cis* 3,6-dimethyl-3,6-dihydro-1,2-dioxine (**1e**) undergoes a facile free-radical Co(SALEN)$_2$-catalyzed isomerization to form a thermodynamic mixture of the corresponding *cis* and *trans* hemiacetals (**24e**) and a small amount of the *cis* γ-hydroxy enone **23e**. Although they stated that no such intermediates were observable during similar rearrangement of the 1,2-dioxine **1a** during ^{1}H NMR monitoring of the reaction mixture, we felt compelled to attempt the reaction. In our hands, we were able to achieve quantita-

(25) Adam, W.; Balci, M.; Rivera, J. *Synthesis* **1979**, 807. Matsumoto, M.; Kondo, K. *J. Am. Chem. Soc.* **1976**, *99*, 2393. Herz, W.; Ligon, R. C.; Turner, J. A.; Blount, J. F. *J. Org. Chem.* **1977**, *42*, 1885. Adam, W.; Balci, M. *J. Am. Chem. Soc.* **1980**, *102*, 1961. Zagorski, M. G.; Salomon, R. G. *J. Am. Chem. Soc.* **1980**, *102*, 2501.

(26) Takahashi, Y.; Wakamatsu, K.; Morishima, S.-I.; Miyashi, T. *J. Chem. Soc., Perkin Trans. 2* **1993**, 243.

(27) O'Shea, K. E.; Foote, C. S. *J. Org. Chem.* **1989**, *54*, 3475.

Table 4. Ratio of *cis* γ-Hydroxy Enones 23a−e to *cis*/*trans* Hemiacetals 24a−e in $CDCl_3$[a]

entry	1,2-dioxine	method of prep[b]	yield (%)	enone:*cis*:*trans* hemiacetal ratio (%)
1	**1a**	A	95	**23a** (67): ***cis*−24a** (14): ***trans*−24a** (19)
2	**1b**	B	82	**23b** (100): ***cis*−24b** (0): ***trans*−24b** (0)
3	**1c**	B	72	**23c** (79): ***cis*−24c** (10): ***trans*−24c** (11)
4	**1d**	B	76	**23d** (29): ***cis*−24d** (33): ***trans*−24d** (38)
5	**1e**	A	90	**23e** (18): ***cis*−24e** (37): ***trans*−24e** (45)

[a] All ratios were determined in $CDCl_3$ (600 MHz ^1H NMR) at ambient temperature with identical reaction volumes and concentrations. Typical procedure; the enone/hemiacetal (15 mg) was dissolved in $CDCl_3$ (0.70 mL). [b] Methods (A and B) refer to procedures utilizing $Co(SALEN)_2$ and Et_3N, respectively. Refer to Experimental Section for general procedures.

Table 5. Reaction of *cis* γ-Hydroxy Enones 23a−e/ Hemiacetals 24a−e with Various Ylides[a]

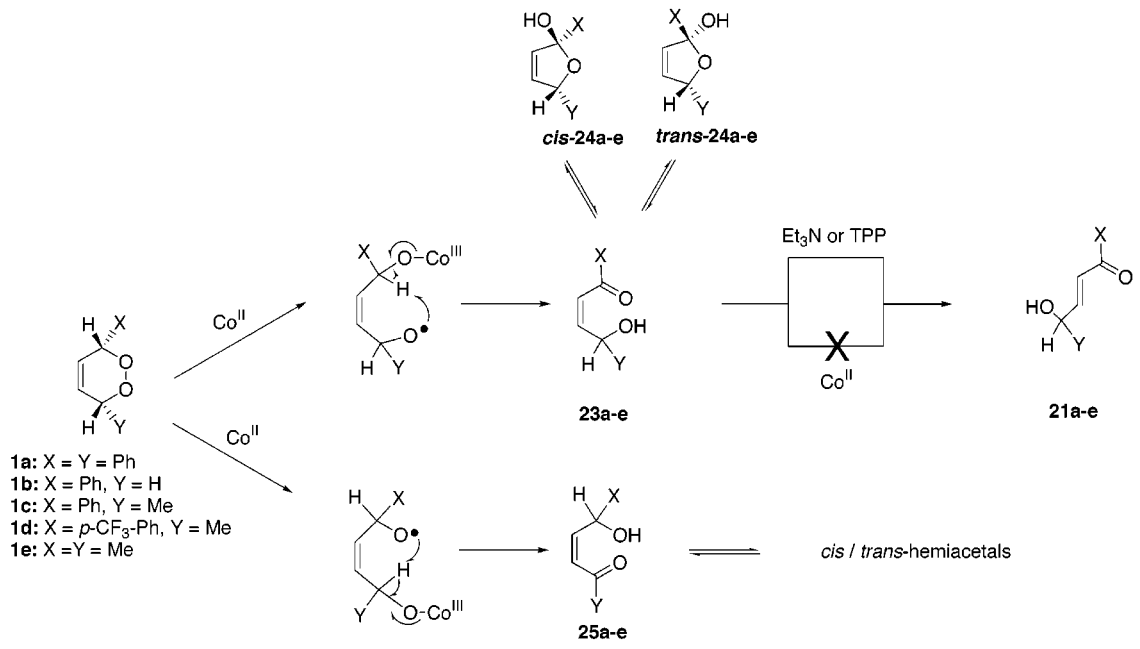
entry	enone	ylide	product(s); yield (%)
1	**23a**	**2a**	**5a** (98); **15a** (2)
2		**2d**	**5d** (41); **15a** (52)[b]
3		**2e**	**15a** (100)
4	**23b**	**2a**	**6a** (100)
5		**2b**	**6b** (100)
6	**23c**	**2a**	**7a** (84); **12a** (16)
7		**2b**	**7b** (82); **12b** (18)
8	**23d**	**2a**	**8a** (82); **13a** (18)
9	**23e**	**2a**	**9a** (84); **14a** (16)

[a] All reactions performed in $CDCl_3$ at ambient temperature unless otherwise specified. Typical procedure; the enone/hemiacetal (15 mg) was dissolved in $CDCl_3$ (0.70 mL) followed by the introduction of ylide (1 equiv). Yields were determined from the ^1H NMR spectra (300 or 600 MHz) of the crude reaction mixtures; isolated yields were typically within 10% of those reported above. [b] See footnote c, Table 1.

tive isomerization of 1,2-dioxines **1a** and **1e** to their corresponding thermodynamic mixtures of *cis* γ-hydroxy enones (**23a** and **23e** respectively) and their cyclic hemiacetals (**24a** and **24e** respectively), Table 4. We are uncertain of the reason for the discrepancy between our findings and their result; however, we have ruled out moisture as the reason as both $Co(SALEN)_2$ and $Co(SALEN)_2{\cdot}6H_2O$ induce the rearrangement equally well. Treatment of *cis* γ-hydroxy enone **23a** generated from this method with ylide **2a** (1 equiv) again afforded the *trans*-cyclopropane **5a** quantitatively within several hours at ambient temperature. Monitoring the reaction of the *cis* γ-hydroxy enone **23a** with ylide **2a** by ^{31}P NMR at subambient temperatures (reaction ceases at −40 °C) failed to lead to the observation of any intermediates, indicating that the collapse of the intermediate 1-2λ^5-oxaphospholane **4** must be extremely facile.

Given these observations it now appeared logical that the isomerization of the 1,2-dioxines **1a**−**e** into the isomeric *cis* γ-hydroxy enones **23a**−**e** was paramount to the success of cyclopropanation. Coupling this with the observed slow reaction rates of the ylides with the 1,2-dioxines (see Table 1) led us to speculate that we should be able to accelerate the reaction dramatically by adding a trace of $Co(SALEN)_2$ from the outset of the reaction. Indeed, treatment of the 1,2-dioxine **1a** with ylide **2a** in the presence of $Co(SALEN)_2$ (2 mol %) under reaction conditions identical to those employed in Table 1 led to complete cyclopropanation in 3 h as opposed to 3 days without $Co(SALEN)_2$ present. Moreover, 1,2-dioxine **1e** was unreactive toward ylide **2a** over a period of a week (entry 18, Table 1). However, prior formation of the isomeric *cis* γ-hydroxy enone **23e** by the $Co(SALEN)_2$ method allowed for essentially quantitative cyclopropanation upon addition of ylide **2a**, entry 9, Table 5. It is noteworthy however, that the free-radical $Co(SALEN)_2$-catalyzed rearrangement of 1,2-dioxines to the isomeric *cis* γ-hydroxy enones is superior to the Et_3N-catalyzed method in terms of yield. This is due to the $Co(SALEN)_2$ failing to further isomerize the *cis* γ-hydroxy enones to the thermodynamically more stable *trans* γ-hydroxy enones as a result of the lack of nucleophiles in solution, Scheme 6. While this approach works well for symmetrical 1,2-dioxines we found one major drawback in

Scheme 6

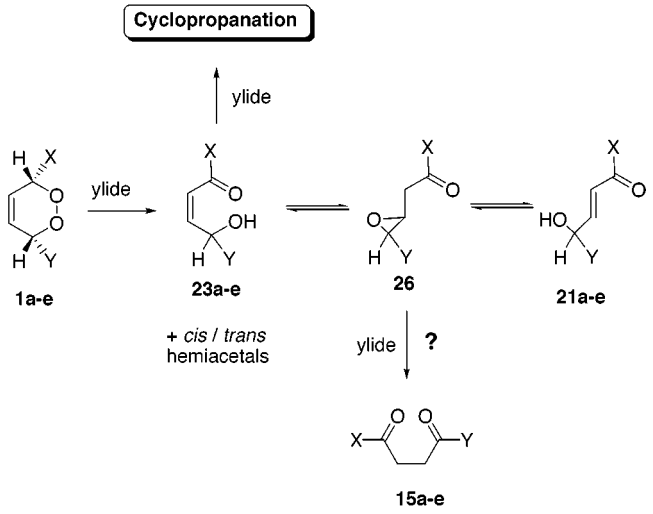


that when unsymmetrical 1,2-dioxines such as **1b**−**d** are subjected to $Co(SALEN)_2$-catalyzed rearrangement, not only was the expected thermodynamic mixture of *cis* γ-hydroxy enone and their cyclic *cis*/*trans*-hemiacetals formed but also the corresponding isomeric regioisomers **25b**−**d**, Scheme 6. This regiochemical competition can be attributed to differences in C−H bond strengths and steric factors α to the O−O linkage.[28] Given the difficulty in separation of the regioisomers we were forced to utilize the aforementioned more selective, however, lower yielding, Et_3N-catalyzed rearrangement to prepare pure *cis* γ-hydroxy enones **21b**−**d**, Table 4. The *cis*-configuration about the double bond of these γ-hydroxy enones (**23a**−**e**) was typified by a $^3J = 12$ Hz coupling constant, while the characterization of the *cis* and *trans*-hemiacetals and a rationale of how substituents affect the enone (**23**): hemiacetal (**24**) ratio will be reported in respect to another study.[28]

With the thermodynamic mixtures of *cis* γ-hydroxy enones **23a**−**e** and cyclic *cis*/*trans* hemiacetals **24a**−**e** now in hand, we evaluated their reactivity toward a variety of ylides. The results of selected experiments being collated in Table 5. All reactions were complete within several hours at ambient temperature, while the diastereomeric cyclopropane ratios were identical to those found when starting with the 1,2-dioxines. Comparison of the results collated in Tables 1−3 also indicates that the cyclopropane yields are all superior when starting from the thermodynamic mixtures of *cis* γ-hydroxy enones **21a**−**e** and cyclic *cis*/*trans* hemiacetals **24a**−**e**. Furthermore, cyclopropanation results from direct reaction of the ylides with the *cis* γ-hydroxy enones and not the cyclic *cis*/*trans*-hemiacetals, as *cis* γ-hydroxy enones **23b** exists solely in its uncyclized form.

(c) Isomeric 3,4-Epoxy-1-ones and Their Involvement. At this point we were puzzled by the fact that while the 1,2-dioxines **1a**−**e** and the thermodynamic mixture of *cis* γ-hydroxy enones **23a**−**e** and *cis*/*trans*-hemiacetals **24a**−**e** in the presence of ylide afforded cyclopropanes in excellent yields (Tables 1 and 5), the corresponding *trans* γ-hydroxy enones **21a**−**d** led only to cyclopropanation in moderate yield, with the remaining material formed being the 1,4-dicarbonyls **15a**−**d**, Table 3. Hence, we now needed to answer the question: where were the 1,4-dicarbonyls arising from? Scheme 7 contains one possible scenario and summarizes the mechanistic picture at this stage. Thus, the ylide acts as a weak base, removing an acidic hydrogen from the 1,2-dioxine, resulting in the formation of the *cis* γ-hydroxy enones along with their hemiacetals. Interception of the *cis* γ-hydroxy enone by the ylide affords in a facile manner the observed cyclopropanes. In some cases the *cis* γ-hydroxy enones isomerize to the *trans* γ-hydroxy enones which still may form cyclopropanes but also lead to a greater percentage of 1,4-dicarbonyl. To examine the possibility that the *cis*/*trans* γ-hydroxy enone equilibrium may involve the intermediacy of the epoxy ketone **26** and that it may be the attack of the ylide on this intermediate

Scheme 7



that leads to the 1,4-dicarbonyl formation, we prepared epoxy ketone **26**.

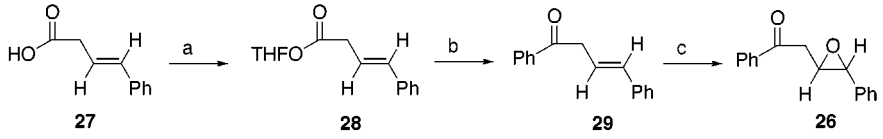
The synthetic strategy adopted for the synthesis of *trans* epoxy ketone **26** utilized the new method for expeditious ketone synthesis from acids via acyl hemiacetals reported by Rappoport.[29] Thus, protection of acid **27** as the 2-tetrahydrofuranyl ester followed by the addition of phenylmagnesium bromide and acidic workup afforded the desired β,γ-unsaturated ketone **29**, Scheme 8. Simple epoxidation afforded the necessary *trans* epoxy ketone **26**.With **26** now in hand we evaluated its reactivity toward various ylides and additives, Table 6. With no additives present, the epoxy ketone **26** underwent slow rearrangement (4 days) at 50 °C to the parent furan **22a**, entry 1. This rearrangement was dramatically accelerated by the addition of acid (entry 8) and is consistent with the mechanism proposed by Padwa,[30] which involves the intermediacy of the thermodynamic mixture of the isomeric *cis* γ-hydroxy enone **23a** and *cis*/*trans* hemiacetals **24a**. However, the observation that furan formation is slow at 50 °C is inconsistent with the fact that the epoxy ketone is an intermediate between the *cis*/*trans* γ-hydroxy enone equilibrium as both enones undergo rapid furan formation (ca. 2 h) at ambient temperature. Treatment of **26** with ylides (**2a**, **2d**, and **2e**, entries 2−4, respectively) and monitoring of the reaction by ^1H NMR clearly showed the formation of the isomeric *trans* γ-hydroxy enone **21a** in all cases. This material was slowly consumed to afford the desired cyclopropane and/or 1,4-diketone **15a**. Comparison of these observations (yield and product(s)) with those collated in Table 3 (entries 1−3) clearly indicates that the ylide is once again behaving as a mild base, first inducing rearrangement to the isomeric *trans* γ-hydroxy enone **21a** followed by formation of the cyclopropane or diketone. In addition, the overall reaction rate of **26** with these ylides is slower than when starting from the *trans* γ-hydroxy enone (Table 3, entries 1−3) and therefore rules out any involvement of these isomeric epoxy ketones in 1,4-dicarbonyl formation during ylide "attack" on the 1,2-dioxines or the *cis*/*trans* γ-hydroxy enones. Moreover, while TPPO and TPP had no effect on the slow decom-

(28) A mechanistic study on the $Co(SALEN)_2$ isomerization of unsymmetrical 1,2-dioxines is currently underway and will be reported in due course along with the characterization of all hemiacetals prepared in this work. Furthermore, this upcoming manuscript will include the use of modified $Co(SALEN)_2$ complexes and the use of optically pure cobalt salen based complexes (e.g., Jacobson's catalyst) to induce enantioselectivity into the 1,2-dioxine/*cis* γ-hydroxy enone isomerization and as such enantioselectivity into the cyclopropanation reported here.

(29) Mattson, M. N.; Rapoport, H. *J. Org. Chem.* **1996**, *61*, 6071.

(30) Padwa, A.; Crumrine, D.; Hartman, R.; Layton, R. *J. Am. Chem. Soc.* **1967**, *89*, 4435.

Scheme 8



[a] Key: a) THF, cat. PTSA; b) PhMgBr; c) *m*-CPBA.

Table 6. Reaction of Epoxide 26 with Various Ylides and Additives[a]

entry	ylide or additive	time (days)	product(s); yield (%)	entry	ylide or additive	time (days)	product(s); yield (%)
1		4	**22a** (100)	5	TPPO	4	**22a** (100)
2	**2**	14	**5a** (36); **15a** (64)	6	Ph_3P	4	**22a** (100)
3	**2d**	14	**15a** (100)	7	Et_3N	3	**15a** (100)
4	**2e**	5	**15a** (100)	8	PTSA	*b*	**22a** (100)

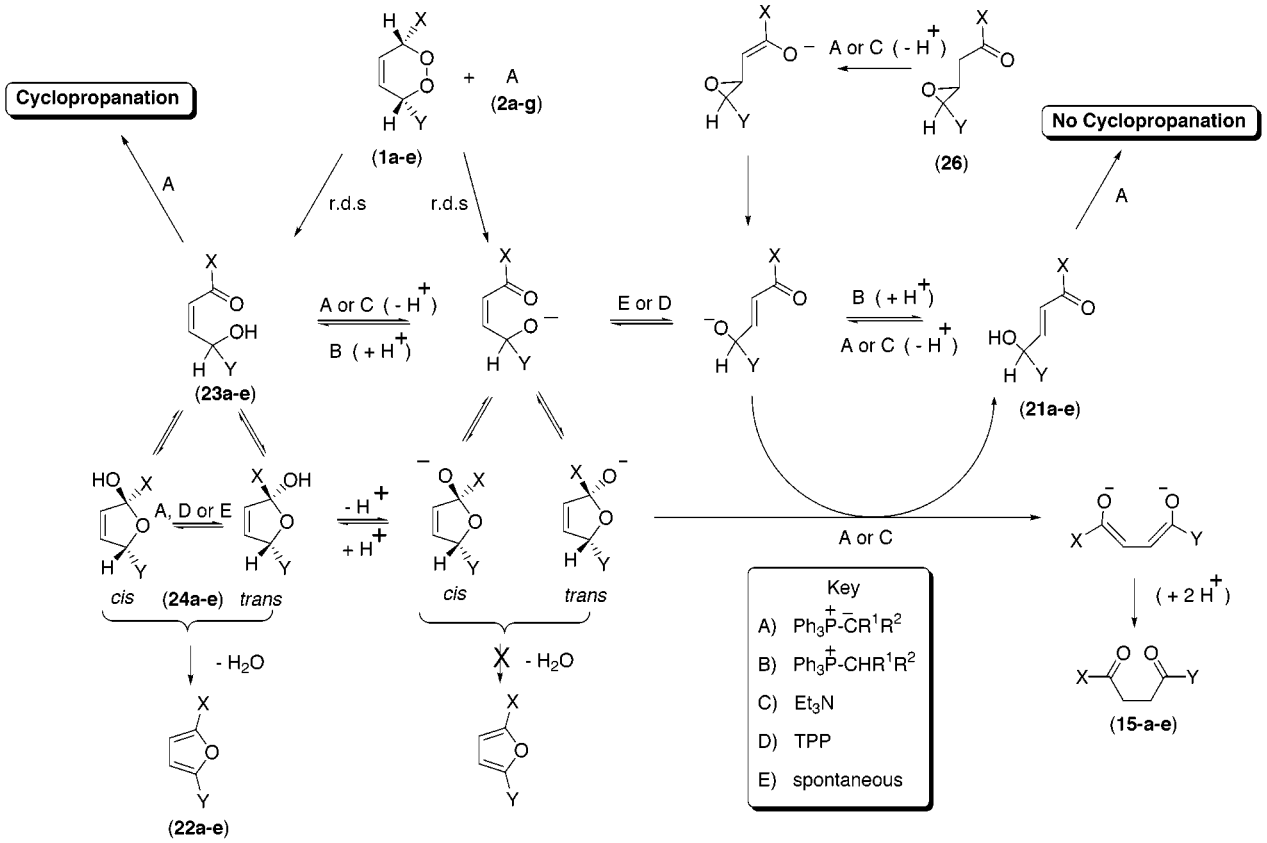
[a] All reactions performed in $CDCl_3$ at a temperature of 50 °C. Typical procedure; epoxide **26** dissolved in $CDCl_3$ (0.70 mL) followed by the introduction of additive (1 equiv). Yields were determined from the ^1H NMR spectra (300 MHz) of the crude reaction mixtures; isolated yields were typically within 10% of those reported above. [b] Reaction time < 1 min at ambient temperature.

position of **29** to furan **22a**, entries 5 and 6, the addition of Et_3N once again led exclusively to diketone **15a** formation through the intermediacy of the *trans* γ-hydroxy enone. We therefore conclude, that the epoxy ketone **26** is not the intermediate that leads to 1,4-dicarbonyl formation but rather is simply an alternative precursor for entry into this complicated reaction manifold via the base (ylide)-induced isomerization to the isomeric *trans* γ-hydroxy enone **21a**.

Discussion

Examination of the results collated within Tables 1−6 provides a clear mechanistic picture of the hitherto unknown complex relationship between 1,2-dioxines **1a**−**e** and their isomeric *cis*/*trans* γ-hydroxy enones **23** and **21a**−**e**, *cis*/*trans* hemiacetals **24a**−**e**, and β-ketoepoxides (e.g., **26**) and how these precursors can be utilized to construct diversely functionalized cyclopropanes when allowed to interact with stabilized phosphorus ylides, Scheme 9. Thus, the ylide first acts as a weak base removing in a regiochemical fashion the most acidic proton α to the O−O linkage within the 1,2-dioxines, resulting in the formation of the isomeric *cis* γ-hydroxy enones **23a**−**e** and regeneration of the ylide. This isomerization was found to be the rate-determining step, as the isolated *cis* γ-hydroxy enones reacted with the ylides to afford the observed cyclopropanes in a facile manner, as shown by comparison of the results listed in Tables 1 and 5. Furthermore, the fact that reaction of these *cis* γ-hydroxy enones **23a**−**e** with ylide afforded cyclopropane diastereomeric ratios and cyclopropane/1,4-dicarbonyl ratios **15a**−**e** identical to those obtained when entering

Scheme 9



the reaction manifold directly from the 1,2-dioxines strongly suggests that the *cis* γ-hydroxy enones are the key intermediates leading to cyclopropanation. There appears to be no precedence in the literature of the use of stabilized phosphorus ylides to promote base-induced isomerizations of this type.

These sensitive *cis* γ-hydroxy enones could be prepared independently by a variety of methods and were shown to exist in equilibrium with their isomeric *cis*/*trans* hemiacetals **24a**−**e** with the exception of *cis* γ-hydroxy enone **23b**, which existed solely as the enone, Table 4. Although the factors that influence the position of this equilibrium and the *cis*/*trans* hemiacetal ratio are yet to be understood, there are several examples reported in the literature.[30,31] Under neutral or acidic conditions these *cis* γ-hydroxy enones **23a**−**e** were found to be extremely sensitive, undergoing facile dehydration with concomitant formation of the appropriate furans **22a**−**e**. However, under buffered conditions, (i.e., with ylide present), the *cis* γ-hydroxy enones **23a**−**e** were found to be extremely stable. This is clearly a result of an acid (enone/hemiacetal)/base (ylide) equilibrium buffering effect resulting in the formation of minor amounts of the corresponding conjugate acids and bases as depicted in Scheme 9. Consequently, in terms of the overall transformation of 1,2-dioxines to cyclopropanes utilizing stabilized phosphorus ylides, furans are not expected to be seen as products as a result of the presence of the weak ylide base.

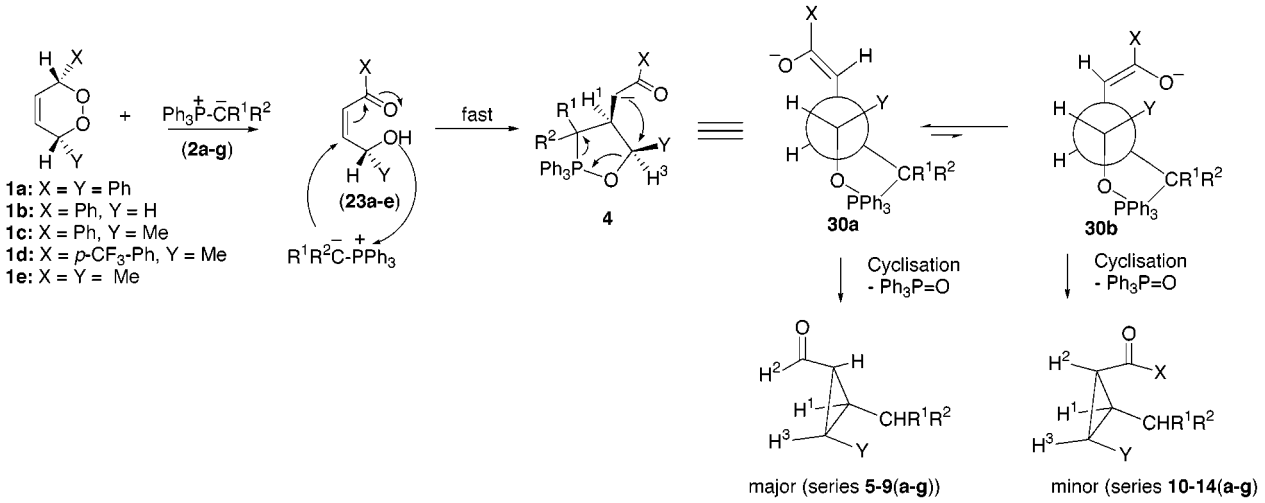
The isomeric *trans* γ-hydroxy enones **21a**−**e** were also observed to be formed during several of these cyclopropanation reactions. However, independent synthesis utilizing a combination of Et_3N and TPP and subsequent treatment with ylide clearly indicated that these isomers are not the key intermediates during cyclopropanation even though they may be utilized as an entry point into the reaction manifold and proceed through to the observed cyclopropanes via the *trans*/*cis* γ-hydroxy enone equilibrium, Scheme 9. In addition, there is a strong preference for 1,4-dicarbonyl formation at the expense of cyclopropanation, which is not observed from the 1,2-dioxine **1a**−**e** or *cis* γ-hydroxy enone **23a**−**e** precursors, as shown by the results collated in Tables 1, 3, and 5. Although the isomerization of the *cis* γ-hydroxy enones **23a**−**e** to the *trans* γ-hydroxy enones **21a**−**e** was observed to be extremely slow with ylide present, this isomerization was found to be greatly accelerated by the addition of external nucleophiles, e.g., TPP, Scheme 5, and as such these reactions must be carried out utilizing ylides that are free of traces of TPP. The β-keto epoxide **26** was shown not to be involved in the *cis*/*trans* γ-hydroxy enone equilibrium as elevated temperatures were required to induce ring opening under acidic or basic conditions, Table 6. In fact, these isomeric precursors were found to play no role in the overall reaction manifold except to represent an alternative mode of entry for cyclopropanation.

Overall, the genesis of the 1,4-dicarbonyls **15a**−**e** is a consequence of the presence of strong bases within the reaction manifold. For example, addition of excess triethylamine to the purified *cis* γ-hydroxy enones/hemiacetals resulted in quantitative formation of the 1,4-dicarbonyls **15a**−**e**. This rearrangement of *cis* γ-hydroxy enones/hemiacetals to 1,4-dicarbonyls (a Kornblum−De La Mare rearrangement) originates from base removal of a proton from the intermediate conjugate bases of the hemiacetals as outlined in Scheme 9.[18] The results collated in Tables 1, 3, and 5 demonstrate that, while the keto-, aldo-, and ester-stabilized ylides all have sufficient basicity to effect the isomerization of the 1,2-dioxines **1a**−**e** to their isomeric *cis* γ-hydroxy enones **23a**−**e**, only the ester-stabilized ylides lead to cyclopropanation while the keto and aldo ylides only effect further isomerization to the 1,4-dicarbonyls **15a**−**e**. This dramatic difference in reaction outcome is attributed to subtle differences in ylide basicity/nucleophilicity.[17] Thus, while the ester ylides are stronger bases than their keto counterparts, they are superior nucleophiles in Michael addition and as such rapidly react with the *cis* γ-hydroxy enones **23a**−**e** to ultimately form cyclopropanes. Conversely, the keto ylides, which are weaker nucleophiles for Michael addition, are unable to effect this transformation under the reaction conditions and simply are left with no other choice than to utilize their basicity strength to attack the hemiacetals and ultimately lead to 1,4-dicarbonyl formation, Scheme 9. We have also observed that at low temperature (−78 °C) during the cobalt-catalyzed (Jacobson's catalyst) rearrangement of 1,2-dioxine **1a** the equilibrium between the initially formed *cis* γ-hydroxy enone **23a** and the *cis*/*trans* hemiacetals **24a** is slow to establish.[28] Thus, Michael addition of the ylide to the *cis* γ-hydroxy enones in this preequilibrium state would favor cyclopropanation as base (ylide)-induced isomerization of the hemiacetals cannot occur until they are present in solution. This situation is only applicable to those cases where ester ylides were utilized, as the keto/aldo ylides are unable to compete in Michael addition as a result of their lower nucleophilicity.

A further consequence of this rationale is that we would expect that in those cases where the *cis* γ-hydroxy enone/hemiacetal equilibria lies totally in favor of the *cis* γ-hydroxy enone, that base-induced formation of 1,4-dicarbonyl would be nonexistent. Indeed, *cis* γ-hydroxy enone **23b** was found to exist solely in its acyclic form, and as a result, treatment of either pure *cis* or *trans* γ-hydroxy enone (**23b** or **21b**) with ylide (e.g., entries 4 of Tables 3 and 5) resulted in only cyclopropane formation. The reaction of the *trans* γ-hydroxy enones with ylide is of course substantially slower as a result of the fact that spontaneous stereomutation of the *trans* γ-hydroxy enones to the *cis* γ-hydroxy enones is thermodynamically unfavorable. Furthermore, this difference in thermodynamic stability also accounts for the fact that under basic conditions the *trans* γ-hydroxy enones are clearly more stable than the *cis* γ-hydroxy enones and suggests that the formation of the 1,4-dicarbonyls results from attack by base on the *cis*/*trans* hemiacetals. Comparison of the results within Tables 3 and 5 also reveals that the *cis* γ-hydroxy enone/hemiacetal equilibrium ratio is not an important factor in terms of cyclopropanation outcome when entering the reaction manifold from these precursors. However, this equilibrium ratio is vital when entering the reaction manifold from the isomeric *trans* γ-hydroxy enones **21a**−**e**. For example, reaction of the *cis* γ-hydroxy enone **23a**, which exists in an enone/hemiacetal equilibrium ratio of 67:33 (entry 1, Table 4), with ylide (e.g., **2a**) affords cyclopropane essentially quantitatively, entry 1, Table 5. However, reaction of the *trans* γ-hydroxy enone **21a** with the same ylide under

(31) Nishio, T.; Omote, Y. *Chem. Lett.* **1976**, 103. Friedrich, L. E.; Cormier, R. A. *J. Org. Chem.* **1971**, *36*, 3011 and references therein.

Scheme 10



identical reaction conditions only results in a moderate yield of cyclopropane (44%) along with a moderate yield of 1,4-dicarbonyl (56%), entry 1, Table 3. The fact that the only difference in reaction conditions is whether the precursor enone has the *cis* or *trans* configuration suggests that the increase in 1,4-dicarbonyl **15a** formation, when starting from the *trans* γ-hydroxy enone **21a**, is in fact a consequence of the *trans* configuration of the enone. This dramatic difference in reaction outcome can be attributed to the existence of an intramolecular hydrogen bond within the *cis* γ-hydroxy enones and the lack of any such interaction within the *trans* γ-hydroxy enone series. Given that a hydrogen atom of the hydroxy group involved in an intramolecular hydrogen bond is held to the molecule much more strongly than in the absence of such a bond,[32] removal of the hydroxyl proton from the *cis* γ-hydroxy enones by the ylide appears to not occur under these reaction conditions. However, establishment of an acid/base equilibrium between the ylide and the *trans* γ-hydroxy enones **21a**−**e** is much more likely because not only is the hydroxyl proton held less tightly as a result of the absence of hydrogen bonding but also the acidity of this proton is higher than in the corresponding *cis* γ-hydroxy enone series. Consequently, this presence of a small percentage of the conjugate base of the *trans* γ-hydroxy enones **21a**−**e** is sufficient to cause the base-catalyzed Kornblum−De La Mare rearrangement of any hemiacetals present in solution. In summary, while the *trans* γ-hydroxy enones are thermodynamically more stable than the *cis* γ-hydroxy enones, they not only are sterically less accessible to Michael addition by the ylide but also are kinetically more labile to the establishment of an ylide/enone, acid/base equilibria as a result of the absence of intramolecular hydrogen bonding; this tends to favor 1,4-dicarbonyl **21a**−**e** formation at the expense of cyclopropanation.

The cyclopropanations described herein proceed with useful levels of diastereoselectivity. In particular, reactions involving the 1,2-dioxines **1a**−**e** and monosubstituted ester-stabilized phosphorus ylides **2a**−**c** led exclusively in most cases to cyclopropanes in which the carbonyl moiety is *trans* to the remaining substituents as depicted in Scheme 10, series **5**−**9**(**a**−**g**). The most plausible rationale behind the stereochemical course of these cyclopropanations is as follows. Michael addition of the ylide to the *cis* γ-hydroxy enones **23a**−**e** and attachment of the electrophilic phosphorus pole of the ylide to the hydroxyl moiety occurs in a *syn* manner with respect to the hydroxyl moiety, affording the intermediate 1-2λ^5-oxaphospholanes **4** and setting up the observed *cis* stereochemistry between H1 and H3. Cyclization of the resultant enolate **30a** or **30b**, expulsion of TPPO and proton transfer from the reaction manifold affords the observed cyclopropanes. The preference for the formation of the thermodynamically favored *trans* cyclopropanes is attributed to the steric bulk of the enolate being directed away from the cyclic 1-2λ^5-oxaphospholane moiety as depicted in **30a**. Similar stereochemical outcomes during cyclopropane formation from enolates have been cited.[33] This preference for cyclization through enolate **30a** was found to be independent of the steric bulk of substituent Y as *cis* γ-hydroxy enones **23a** and **23b** containing substituents Y = Ph and H, respectively, afforded only the *trans* cyclopropane, while in all cases in which the substituent Y was alkyl some "all *cis*" cyclopropane was always formed, Tables 1 and 5, Scheme 10. The rationale behind this observation is yet to be fully explored. Finally, utilization of doubly substituted stabilized ester ylides leads to the preferential formation of one stereochemical outcome within the side chain. Presumably this is a result of proton "pickup" being directed by the newly formed stereogenic centers of the cyclopropane core.

Conclusion

In conclusion, we have presented here a new chemical transformation for the construction of diversely functionalized cyclopropanes utilizing 1,2-dioxines and stabilized phosphorus ylides as the key precursors. Through a series of mechanistic studies we have also elucidated a clear understanding of the hitherto unknown complex relationship between 1,2-dioxines **1a**−**e** and their isomeric *cis*/*trans* γ-hydroxy enones **23** and **21a**−**e**, *cis*/*trans* hemiacetals **24a**−**e**, and β-ketoepoxides, (e.g., **26**) and how these precursors can be utilized to construct diversely functionalized cyclopropanes when allowed to

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interact with stabilized phosphorus ylides, Scheme 9. Key features include the ylide acting as a mild base inducing the ring opening of the 1,2-dioxines to their isomeric *cis* γ-hydroxy enones **23a**−**e**, followed by Michael addition of the ylide to the *cis* γ-hydroxy enones **23a**−**e**, and attachment of the electrophilic phosphorus pole of the ylide to the hydroxyl moiety affording the intermediate 1-2λ^5-oxaphospholanes **4** and setting up the observed *cis* stereochemistry between H1 and H3. Cyclization of the resultant enolate **30a** or **30b**, expulsion of TPPO, and proton transfer from the reaction manifold affords the observed cyclopropanes in excellent diastereomeric excess. While cyclopropanation is favored by the use of ester-stabilized ylides, the use of keto- or aldo-stabilized ylides results in a preference for 1,4-dicarbonyl formation through a competing Kornblum−De La Mare rearrangement of the intermediate hemiacetals. This finding can be attributed to subtle differences in ylide basicity/nucleophilicity. In addition, the use of doubly substituted ester ylides allows for the incorporation of another stereogenic center in the side chain. Finally, our studies have revealed that the isomeric *trans* γ-hydroxy enones and the β-keto epoxides are not involved in the cyclopropanation process but do, however, represent an alternative entry point into this reaction manifold.

Experimental Section

General Methods. Solvents were dried by appropriate methods wherever needed. All organic extracts were dried over anhydrous magnesium sulfate. All γ-hydroxy enones and hemiacetals were purified by column chromatography utilizing silica gel (40−63 μm) or florisil as adsorbent purchased from Merck. Thin-layer chromatography (TLC) used aluminum sheets silica gel 60 F_{254} (40 mm × 80 mm) from Merck. All yields reported refer to isolated material judged to be homogeneous by TLC and NMR spectroscopy. The following materials were purchased from Aldrich and used without further purification: triphenylalkyidenephosphoranes (**2a**−**g**), Co(SALEN)$_2$, *trans*,*trans*-1,4-diphenyl-1,3-butadiene, Rose Bengal, bis(triethylammonium)salt, 2,3-dihydrofuran. The following materials were identified by comparison with the physical and chemical properties reported for the known compounds or authentic samples were prepared were necessary: 1,4-diphenyl-1,4-butanedione (**15a**),[30] 4-oxo-4-phenylbutanal (**15b**),[34] 1-phenyl-1,4-pentanedione (**15c**),[35] 2,5-hexanedione (**15e**) from Aldrich, peroxide (**18**),[36] peroxide (**19**),[37] ergosterol acetate peroxide (**20**),[38] 2,5-diphenylfuran (**22a**),[34] 2-phenylfuran (**22b**),[31] 2-methyl-5-phenylfuran (**22c**),[31] 2,5-dimethylfuran (**22e**) from Aldrich, mixture of (*Z*)-5-hydroxy-3-hexen-2-one (**23e**) and *cis*/*trans* hemiacetals (**24e**).[27]

General Procedure for the Preparation of 1,2-Dioxines (1a−e). All 1,2-dioxines were prepared by the Rose Bengal, bis(triethylammonium)salt sensitized [4π + 2π] cycloaddition of singlet oxygen and the corresponding substituted 1,3-butadiene. The requisite 1,3-butadienes were acquired as follows: 1-[(1*E*)-1,3-butadienyl]benzene was prepared in 98% yield from the action of methylene(triphenyl)phosphorane on *trans*-cinnamaldehyde; 1-[(1*E*,3*E*)-1,3-pentadienyl]benzene was prepared in 99% yield from the action of triphenyl(phenylmethylene)phosphorane on *trans*-crotonaldehyde.; 1-[(1*E*,3*E*)-1,3-pentadienyl]-4-(trifluoromethyl)benzene and the (1*Z*:3*E*) isomer were prepared in 96% yield (1*E*:1*Z* ratio ca. 1:1) from the action of triphenyl{[4-(trifluoromethyl)phenyl]methylene}-phosphorane on *trans*-crotonaldehyde; (2*E*,4*E*)-2,4-hexadiene and the (2E,4Z) isomer were prepared in 95% yield (4*E*:4*Z* ratio ca. 1:2) from the action of ethylene(triphenyl)phosphorane on *trans*-crotonaldehyde. The appropriate 1,3-butadiene (3 g) and rose bengal, bis(triethylammonium)salt (100 mg) were dissolved in dry dichloromethane (100 mL) and the reaction vessel was semi-immersed in an ice bath so that the reaction mixture maintained a temperature ca. 5−10 °C. A stream of oxygen was then passed through the solution, while irradiating with a tungsten halogen lamp (500 W) at a distance of 10 cm from the reaction vessel for ca. 6 h. The volatiles were then removed in vacuo and the residue subjected to column chromatography. All 1,2-dioxines prepared in this work were manipulated with Teflon coated spatulas to prevent premature decomposition. All 1,2-dioxines except **1d** are thermally stable to at least 120 °C and can be stored on the bench without decomposition. **3,6-Diphenyl-3,6-dihydro-1,2-dioxine (1a):** 97% yield, R_f 0.50 (9:1 hexane/ethyl acetate); mp 89.5−90.5 °C (hexane) (lit.[39] mp 83.5−84 °C). **3-Phenyl-3,6-dihydro-1,2-dioxine (1b):**[39] 30% yield, R_f 0.60 (9:1 hexane/ethyl acetate. **3-Methyl-6-phenyl-3,6-dihydro-1,2-dioxine (1c):**[39] 77% yield, R_f 0.50 (9:1 hexane/ethyl acetate). **3-Methyl-6-[4-(trifluoromethyl)phenyl]-3,6-dihydro-1,2-dioxine (1d):** 30% yield, R_f 0.50 (9:1 hexane/ethyl acetate); IR (neat) 2981, 1620, 1417, 1327, 846 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.32 (d, J = 6.6 Hz, 3H), 4.81−4.85 (m, 1H), 5.48 (s, 1H), 6.07−6.13 (m, 2H), 7.52−7.53 (m, 1H), 7.62−7.64 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 18.0, 74.5, 79.0, 124.1 (q, J = 270 Hz), 125.1, 125.4 (q, J = 4.0 Hz), 128.5, 130.6 (q, J = 32 Hz), 142.3; MS *m*/*z* (%) 244 (M$^+$, 5), 233 (100), 220 (53), 198 (30), 167 (90). The titled 1,2-dioxine (1d) was found to slowly polymerize at ambient temperature. **3,6-Dimethyl-3,6-dihydro-1,2-dioxine (1e):**[39] 50% yield, R_f 0.60 (9:1 hexane/ethyl acetate.

Reaction of 1,2-Dioxines 1a−e with Various Phosphoranes (2a−g). Typical Procedure. A mixture of 3,6-diphenyl-3,6-dihydro-1,2-dioxine (**1a**) (353 mg, 1.56 mmol) was allowed to react with benzyl 2-(triphenyl-λ^5-phosphanylidene) acetate (**2a**) (657 mg, 1.60 mmol) in anhydrous dichloromethane (10 mL) under a nitrogen gas atmosphere at ambient temperature for 3 days. Removal of the volatiles in vacuo afforded the crude cyclopropane **5a** along with diketone **15a**. All examples collated in Table 1 were carried out under these standard conditions. Refer to Table 1 for reaction times and yields. Subsequent silica gel chromatography on the crude reaction mixtures afforded the pure cyclopropanes. Analytical samples of the cyclopropanes were recrystallized from heptane.

***trans*-(±)-Benzyl 2-(2-benzoyl-3-phenylcyclopropyl)-acetate (5a):** R_f 0.50 (4:1 hexane/ethyl acetate); mp 89.5−90.5 °C (heptane); IR 1727, 1663, 1598, 1164 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.20 (dd, J = 16.1, 8.3 Hz, 1H), 2.35 (dddd, J = 9.3, 8.3, 6.4, 4.9 Hz, 1H), 2.44 (dd, J = 16.1, 6.4 Hz, 1H), 3.10 (dd, J = 4.9, 4.9 Hz, 1H), 3.13 (dd, J = 9.3, 4.9 Hz, 1H), 5.04 and 5.07 (AB_q, J = 12.6 Hz, 2H), 7.21−7.32 (m, 10H), 7.48−7.51 (m, 2H), 7.58−7.62 (m, 1H), 8.04−8.07 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 27.1, 29.3, 33.1, 33.5, 66.4, 127.1, 128.2, 128.2, 128.3, 128.6, 128.7, 129.0, 133.1, 135.7, 135.9, 137.8, (one aromatic carbon masked), 172.0, 198.7; MS *m*/*z* (%) 370 (M$^+$, 0.1), 279 (100), 221 (15), 105 (83), 91 (52). Anal. Calcd for $C_{25}H_{22}O_3$ (370.4): C, 81.06; H, 5.99. Found: C, 80.62; H, 5.98.

***trans*-(±)-Methyl 2-(2-benzoyl-3-phenylcyclopropyl)-acetate (5b):** R_f 0.40 (3:1 hexane/ethyl acetate); mp 86−87 °C (heptane); IR 1738, 1657, 1597, 1170 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.16 (dd, J = 16.3, 8.2 Hz, 1H), 2.31 (dddd, J = 9.2, 8.2, 6.5, 4.8 Hz, 1H), 2.37 (dd, J = 16.3, 6.5 Hz, 1H), 3.11 (dd, J = 4.8, 4.8 Hz, 1H), 3.15 (dd, J = 9.2, 4.8 Hz, 1H), 3.61 (s, 3H), 7.24−7.28 (m, 3H), 7.31−7.35 (m, 2H), 7.50−7.54 (m, 2H), 7.58−7.62 (m, 1H), 8.07−8.10 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 27.3, 29.4, 32.9, 33.4, 51.7, 127.0, 128.1, 128.4, 128.6, 128.8, 133.0, 135.8, 137.7, 172.4, 198.4; MS *m*/*z* (%) 294 (M$^+$, 1), 262 (40), 221 (10), 105 (100), 77 (38). Anal. Calcd for $C_{19}H_{18}O_3$ (294.3): C, 77.53; H, 6.12. Found: C, 77.47; H, 6.21.

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***trans*-(±)-Ethyl 2-(2-benzoyl-3-phenylcyclopropyl)acetate (5c):** R_f 0.55 (4:1 hexane/ethyl acetate); mp 54−56 °C (heptane); IR 1731, 1657, 1597, 1165 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.15 (t, J = 7.1 Hz, 3H), 2.14 (dd, J = 16.0, 8.1 Hz, 1H), 2.31 (dddd, J = 9.3, 8.1, 6.4, 5.1 Hz, 1H), 2.38 (dd, J = 16.0, 6.4 Hz, 1H), 3.10 (dd, J = 5.1, 5.1 Hz, 1H), 3.15 (dd, J = 9.3, 5.1 Hz, 1H), 4.03−4.10 (m, AB portion of ABX_3, 2H), 7.24−7.27 (m, 3H), 7.31−7.34 (m, 2H), 7.50−7.53 (m, 2H), 7.58−7.61 (m, 1H), 8.07−8.09 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 22.4, 34.0, 35.8, 39.0, 39.2, 62.7, 120.4, 121.4, 121.7, 121.8, 122.1, 125.6, 128.2, 129.8, 159.5, 182.5; MS m/z (%) 308 (M^+, 63), 262 (100), 221 (98), 220 (90), 129 (22), 105 (68). Anal. Calcd for $C_{20}H_{20}O_3$ (308.4): C, 77.90; H, 6.54. Found: C, 77.80; H, 6.36.

***trans*-(±)-Ethyl 2-(2-benzoyl-3-phenylcyclopropyl)propanoate (5d):** R_f 0.55 (4:1 hexane/ethyl acetate); mp 61−62 °C (heptane); IR (neat) 1730, 1668, 1599, 1581, 1450, 1219 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.05 (d, J = 6.6 Hz, 3H), 1.10 (t, J = 7.0 Hz, 3H), 2.01 (dq, J = 10.5, 6.6 Hz, 1H), 2.07 (ddd, J = 10.5, 9.0, 5.0 Hz, 1H), 3.16 (dd, J = 9.0, 5.0 Hz, 1H), 3.33 (dd, J = 5.0, 5.0 Hz, 1H),), 4.04−4.08 (m, AB portion of ABX_3, 2H), 7.22−7.36 (m, 5H), 7.48−7.51 (m, 2H), 7.56−7.59 (m, 1H), 8.06−8.08 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.0, 15.9, 28.7, 33.3, 35.7, 38.2, 60.5, 126.8, 128.1, 128.4, 128.5, 128.5, 132.9, 135.36, 137.7, 175.1, 198.3; MS m/z (%) 322 (M^+, 8), 276 (10), 222 (99), 143 (49), 105 (100). Anal. Calcd for $C_{21}H_{22}O_3$ (322.4): C, 78.23; H, 6.88. Found: C, 77.98; H, 6.81.

Parent Acid of 5d. To a mixture of **5d** (0.50 g, 1.55 mmol) in methanolic water (10 mL, 1:9) was added potassium hydroxide (0.26 g, 3 equiv). Stirring was continued for 3 h after which time the mixture was acidified to pH = 1 with concentrated hydrochloric acid. Extraction with dichloromethane (4 × 20 mL) and desiccation followed by removal of the volatiles in vacuo afforded the parent acid of **5d** (0.42 g, 92%): mp 190−192 °C (heptane); IR 3300−2800, 1724, 1686, 1597, 1144 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.07 (d, J = 6.7 Hz, 3H), 2.03 (dq, J = 10.7, 6.7 Hz, 1H), 2.08 (ddd, J = 10.7, 9.1, 5.0 Hz, 1H), 3.14 (dd, J = 9.1, 5.0 Hz, 1H), 3.35 (dd, J = 5.0, 5.0 Hz, 1H), 7.26−7.32 (m, 3H), 7.34−7.36 (m, 2H), 7.46−7.49 (m, 2H), 7.55−7.58 (m, 1H), 8.06−8.06 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 15.8, 28.5, 33.4, 35.1, 37.5, 127.0, 128.2, 128.5, 128.5, 128.6, 133.0, 135.2, 137.7, 180.3, 198.2; MS m/z (%) 294 (M^+, 10), 276 (29), 221 (63), 128 (13), 105 (100).

X-ray Structure of the Parent Acid of 5d. Crystals of the parent acid of **5d** suitable for X-ray crystallography were grown by slow (2 days) crystallization from a combination of dichloromethane/benzene in excess heptane. Crystallographic data were collected at 173 K on a Nonius Kappa CCD. Data processing and refinement was with teXsan;[40] the structure was solved by direct methods.[41] The compound frequently crystallized as twins; however, a colorless single needle (0.02 × 0.04 × 0.14 mm^3) provided a data set suitable for analysis. Crystals of $C_{19}H_{18}O_3$ (294.5) are triclinic, space group $P\bar{1}$, a = 5.5902(1) Å, b = 10.1536(3) Å, c = 27.4509(8) Å, α = 88.834-(2)°, β = 87.481(2)°, γ = 88.823(2)°, V = 1556.00(6) $Å^3$, Z = 4 and D = 1.256 g/cm^3. Two independent molecules comprise the asymmetric unit (molecule *a* is represented in Figure 1, drawn at 50% displacement ellipsoids[42]). Non-H atoms were refined anisotropically and H atoms were included in the model in their calculated positions: R = 0.080 [3908 data with $I \geq 3.0\sigma(I)$], R_w = 0.107, GOF = 2.76; a correction was applied for extinction.[43] Other experimental parameters along with fractional atomic coordinates and thermal parameters are given as a CIF in Supporting Information. There are no major differences between the independent molecules comprising the asymmetric unit; differences that do exist relate to the relative disposition of the carboxylic acid and benzoyl functions. In the crystal lattice, centrosymmetrically related molecules associate to form carboxylic acid-bound dimers as shown for molecule *a* in Figure 1; the O(42a)···O(41a)^{i} and O(42b)···O(41b)^{ii} distances are 2.697(5) and 2.644(5) Å, respectively (symmetry operation i: $-x$, $1-y$, $1-z$, ii: $-1-x$, $-y$, $-z$).

***trans*-(±)-Benzyl 2-(2-benzoylcyclopropyl)acetate (6a):** R_f 0.40 (4:1 hexane/ethyl acetate); mp 44−45 °C (heptane); IR 1723, 1663, 1175 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.00 (ddd, J = 8.5, 6.8, 4.8 Hz, 1H), 1.55 (ddd, J = 8.9, 4.8, 4.8 Hz, 1H), 1.90 (ddddd, J = 8.9, 7.8, 6.8, 6.1, 4.8 Hz, 1H), 2.38 (dd, J = 16.0, 7.8 Hz, 1H), 2.59 (ddd, J = 8.5, 4.8, 4.8 Hz, 1H), 2.62 (dd, J = 16.0, 6.1 Hz, 1H), 5.11 and 5.13 (AB_q, J = 12.6 Hz, 2H), 7.28−7.31 (m, 5H), 7.44−7.46 (m, 2H), 7.54−7.57 (m, 1H), 7.96−7.99 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 17.7, 21.4, 24.3, 38.1, 66.5, 128.1, 128.1, 128.2, 128.5, 128.5, 132.8, 135.7, 137.8, 171.6, 199.1; MS m/z (%) 294 (M^+, 15), 276 (10), 235 (33), 105 (70), 91 (100). Anal. Calcd for $C_{19}H_{18}O_3$ (294.4): C, 77.53; H, 6.16. Found: C, 77.73; H, 6.14.

***trans*-(±)-Methyl 2-(2-benzoylcyclopropyl)acetate (6b):** R_f 0.25 (10:1 benzene/ethyl acetate); IR (neat) 1738, 1668, 1598, 1578, 1450, 1223, 753, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 0.99 (ddd, J = 8.4, 5.4, 4.8 Hz, 1H), 1.56 (ddd, J = 8.4, 5.4, 4.8 Hz, 1H), 1.88 (ddddd, J = 8.4, 7.8, 6.6, 5.4, 4.8 Hz, 1H), 2.36 (dd, J = 15.6, 7.8 Hz, 1H), 2.55 (dd, J = 15.6, 6.6 Hz, 1H), 2.60 (ddd, J = 8.4, 4.8, 4.8 Hz, 1H), 3.68 (s, 3H), 7.46−7.49 (m, 2H), 7.55−7.58 (m, 1H), 8.00−8.02 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 17.6, 21.4, 24.4, 37.9, 51.8, 128.1, 128.5, 132.8, 137.9, 172.2, 199.1; MS m/z (%) 218 (M^+, 3), 159 (21), 145 (86), 144 (95), 105 (100); HRMS of **6b** ($C_{13}H_{14}O_3$) calcd, 218.0943; found, 218.0932.

***trans*-(±)-Ethyl 2-(2-benzoylcyclopropyl)propanoate (6d):** isolated as a 3:1 mixture with respect to side chain stereochemistry; R_f 0.60 (20:1 ether/benzene). Anal. Calcd for $C_{15}H_{18}O_3$ (246.3): C, 73.15; H, 7.37. Found: C, 73.18; H, 7.39. Major isomer: ^1H NMR ($CDCl_3$, 600 MHz) δ 1.14 (ddd, J = 8.5, 6.4, 4.0 Hz, 1H), 1.25 (d, J = 7.0 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.51 (ddd, J = 10.5, 6.4, 4.5 Hz, 1H), 1.84, (dddd, J = 10.5, 8.8, 4.5, 4.0 Hz, 1H), 2.17 (dq, J = 8.8, 7.0 Hz, 1H), 2.55 (ddd, J = 8.5, 4.5, 4.5 Hz, 1H), 4.12−4.20 (m, AB portion of ABX_3, 2H), 7.45−7.50 (m, 2H), 7.54−7.58 (m, 1H), 8.00−8.02 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.1, 16.1, 17.0, 23.3, 28.8, 42.7, 60.4, 128.0, 128.5, 132.8, 137.8, 174.7, 199.2. Minor isomer: ^1H NMR ($CDCl_3$, 600 MHz) δ 0.94 (ddd, J = 8.5, 6.5, 4.2 Hz, 1H), 1.15 (t, J = 7.2 Hz, 3H), 1.30 (d, J = 7.0 Hz, 3H), 1.56 (ddd, J = 8.7, 6.5, 4.7 Hz, 1H), 1.73, (dddd, J = 9.3, 8.7, 4.7, 4.0 Hz, 1H), 2.06 (dq, J = 9.3, 7.0 Hz, 1H), 2.73 (ddd, J = 8.5, 4.7, 4.7 Hz, 1H), 4.09 (q, J = 7.2 Hz, 2H), 7.44−7.50 (m, 2H), 7.54−7.58 (m, 1H), 7.99−8.01 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.0, 16.2, 16.4, 23.9, 29.3, 43.4, 60.5, 128.0, 128.4, 132.8, 137.9, 174.8, 199.0.

***cis*-(±)-Ethyl 2-(2-benzoylcyclopropyl)propanoate (11d):** R_f 0.55 (20:1 ether/benzene); enriched sample containing some isomer **6d**; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.00 (d, J = 7.0 Hz, 3H), 1.28 (t, J = 7.0 Hz, 3H), 1.23 (ddd, J = 7.5, 5.6, 4.5 Hz, 1H), 1.56 (ddd, J = 7.5, 5.6, 4.5 Hz, 1H), 1.74, (dddd, J = 10.6, 8.8, 7.5, 4.5 Hz, 1H), 2.48 (dq, J = 10.6, 7.0 Hz, 1H), 2.83 (ddd, J = 8.8, 7.5, 5.8 Hz, 1H), 4.14−4.20 (m, AB portion of ABX_3, 2H), 7.47−7.50 (m, 2H), 7.56−7.58 (m, 1H), 8.00−8.02 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 14.1, 14.5, 17.4, 21.9, 29.2, 37.2, 60.3, 128.0, 128.6, 132.8, 138.6, 175.8, 198.4. Anal. Calcd for $C_{15}H_{18}O_3$ (contains some isomeric **6d**, 246.3): C, 73.15; H, 7.37. Found: C, 73.29; H, 7.36.

During the isolation of these aforementioned cyclopropanes (**6d** and **11d**) it was found that the 1,4-dicarbonyl **15b** had undergone not only self-condensation with ylide **2d** to afford the "expected" Wittig product alkenes but also dimerization to afford a mixture of (*E*) and (*Z*)-1,3-dioxolanes. See footnote g, Table 1.

Ethyl (*E*)-2-methyl-6-oxo-6-phenyl-2-hexenoate: R_f 0.37 (4:1 hexane/ethyl acetate); IR 1708, 1687, 1649, 1597, 1581, 1261 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.29 (t, J = 6.9 Hz, 3H), 1.89 (d, J = 1.5 Hz, 3H), 2.62 (dt, J = 7.0, 6.6 Hz, 2H), 3.13 (t, J = 7.0 Hz, 2H), 4.18 (q, J = 6.9 Hz, 2H), 6.78 (tq, J = 6.6, 1.5 Hz, 1H), 7.45−7.50 (m, 2H), 7.54−7.59 (m, 1H), 7.94−7.98 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 12.3, 14.2,

(40) *teXsan: Structure Analysis Software*; Molecular Structure Corp.: The Woodlands, TX.

(41) Altomare, A.; Cascarano, M.; Giacovazzo, C.; Guagliardi, A. *J. Appl. Cryst.* **1993**, *26*, 343.

(42) Johnson, C. K. *ORTEP*, report ORNL-5138; Oak Ridge National Laboratory: Oak Ridge, TN, 1976.

(43) Zachariasen, W. H. *Acta Crystallogr.* **1967**, *23*, 558.

23.0, 37.1, 60.4, 127.9, 128.5, 128.8, 133.1, 136.6, 140.1, 167.9, 198.5; MS *m*/*z* (%) 246 (M^+, 10), 200 (32), 172 (25), 105 (100); HRMS of titled compound, $C_{15}H_{18}O_3$ calcd, 246.1256; found, 246.1262. The corresponding (*Z*)-isomer was left uncharacterized as a result of insufficient material being isolated, while the characterization of the **(*E*)** and **(*Z*)-3-[4-(2-oxo-2-phenylethyl)-1,3-dioxolan-2-yl]-1-phenyl-1-propanones** has been reported elsewhere.[44]

***trans*-(±)-Benzyl 2-(2-benzoyl-3-methylcyclopropyl)acetate (7a):** R_f 0.37 (4:1 hexane/ethyl acetate); mp 54.5−56 °C (heptane); IR 1726, 1659, 1171 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.21 (d, J = 6.6 Hz, 3H), 1.87 (ddq, J = 10.8, 6.6, 4.4 Hz, 1H), 2.08 (dddd, J = 10.8, 7.8, 6.8, 4.4 Hz, 1H), 2.26 (dd, J = 4.4, 4.4 Hz, 1H), 2.52 (dd, J = 16.1, 7.8 Hz, 1H), 2.61 (dd, J = 16.1, 6.8 Hz, 1H), 5.12 (s, 2H), 7.29−7.30 (m, 5H), 7.43−7.46 (m, 2H), 7.53−7.56 (m, 1H), 7.93−7.95 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 10.1, 22.2, 24.1, 30.3, 30.5, 64.2, 125.7, 125.9, 126.0, 126.2, 126.3, 130.4, 133.5, 135.8, 169.8, 196.9; MS *m*/*z* (%) 308 (M^+, 5), 217 (37), 105 (84), 91 (100). Anal. Calcd for $C_{20}H_{20}O_3$ (308.4): C, 77.90; H, 6.54. Found: C, 78.04; H, 6.52.

***cis*-(±)-Benzyl 2-(2-benzoyl-3-methylcyclopropyl)acetate (12a):** R_f 0.42 (4:1 hexane/ethyl acetate); IR (neat) 1737, 1664, 1597, 1578, 1448, 1213, 1168 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.21 (d, J = 6.0 Hz, 3H), 1.83 (ddq, J = 8.8, 8.8, 6.0 Hz, 1H), 1.93 (dddd, J = 8.8, 8.8, 7.8, 6.8 Hz, 1H), 2.80 (dd, J = 8.8, 8.8 Hz, 1H), 2.91 (dd, J = 17.6, 6.8 Hz, 1H), 2.99 (dd, J = 17.6, 7.8 Hz, 1H), 5.08 and 5.10 (AB_q, J = 12.6 Hz, 2H),7.28−7.33 (m, 5H), 7.42−7.46 (m, 2H), 7.53−7.56 (m, 1H), 7.90−7.94 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 7.3, 22.0, 23.1, 24.3, 27.8, 66.1, 127.7, 128.0, 128.4, 128.5, 128.7, 132.3, 136.1, 139.8, 173.1, 199.5. The titled compound (**12a**) was found to be unstable at ambient temperature undergoing an enolene rearrangement over several days to afford **16**. See below for characterization of **16**.

***trans*-(±)-Methyl 2-(2-benzoyl-3-methylcyclopropyl)acetate (7b):** R_f 0.37 (4:1 hexane/ethyl acetate); IR (neat) 2954, 1740, 1662, 1598, 1581, 1450, 1044 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.23 (d, J = 6.0 Hz, 3H), 1.87 (ddq, J = 9.0, 6.0, 4.2 Hz, 1H), 2.04 (dddd, J = 9.0, 7.8, 7.2, 4.2 Hz, 1H), 2.26 (dd, J = 4.2, 4.2 Hz, 1H), 2.48 (dd, J = 15.6, 7.8 Hz, 1H), 2.55 (dd, J = 15.6, 7.2 Hz, 1H), 3.68 (s, 3H), 7.45−7.48 (m, 2H), 7.54−7.57 (m, 1H), 7.96−7.98 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 12.4, 24.4, 26.5, 32.5, 32.6, 51.8, 128.0, 128.5, 132.6, 138.0, 172.6, 199.1; MS *m*/*z* (%) 232 (M^+, 5), 217 (7), 200 (18), 159 (83), 115 (13), 105 (100). Anal. Calcd for $C_{14}H_{16}O_3$ (232.3): C, 72.39; H, 6.94. Found: C, 72.18; H, 6.94.

***cis*-(±)-Methyl 2-(2-benzoyl-3-methylcyclopropyl)acetate (12b):** R_f 0.42 (4:1 hexane/ethyl acetate); IR (neat) 2953, 1739, 1664, 1597, 1580, 1448, 1213, 724 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.22 (d, J = 6.6 Hz, 3H), 1.83 (ddq, J = 8.4, 8.4, 6.6 Hz, 1H), 1.91 (dddd, J = 8.4, 8.4, 7.2, 6.6 Hz, 1H), 2.80 (dd, J = 8.4, 8.4 Hz, 1H), 2.86 (dd, J = 18.0, 6.6 Hz, 1H), 2.9 (dd, J = 18.0, 7.2 Hz, 1H), 3.64 (s, 3H), 7.43−7.48 (m, 2H), 7.51−7.54 (m, 1H), 7.92−7.95 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 7.2, 21.8, 23.0, 24.3, 27.5, 51.5, 127.7, 128.3, 133.1, 139.8, 173.7, 199.5. The titled compound (**12b**) was found to be unstable at ambient temperature undergoing an enolene rearrangement over several days to afford known methyl (*E*)-4-methyl-6-oxo-6-phenyl-2-hexenoate, R_f 0.30 (4:1 hexane/ethyl acetate), which displayed physical and chemical properties identical with those reported.[45]

***trans*-(±)-Benzyl 2-{2-methyl-3-[4-(trifluoromethyl)benzoyl]cyclopropyl}acetate (8a):** R_f 0.50 (4:1 hexane/ethyl acetate); mp 91−92 °C (heptane); IR 1726, 1666, 1327, 1173 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.23 (d, J = 6.6 Hz, 3H), 1.92 (ddq, J = 9.3, 6.6, 4.2 Hz, 1H), 2.08 (dddd, J = 9.3, 8.4, 6.6, 4.2 Hz, 1H), 2.24 (dd, J = 4.2, 4.2 Hz, 1H), 2.49 (dd, J = 16.2, 8.4 Hz, 1H), 2.66 (dd, J = 16.2, 6.6 Hz, 1H), 5.13 and 5.11 (AB_q, J = 13.2 Hz, 2H), 7.26−7.29 (m, 5H), 7.67−7.69 (m, 2H), 8.00−8.02 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 12.5, 25.1, 27.8, 32.8, 32.9, 66.6, 123.7 (q, J = 271 Hz), 125.5 (q, J = 3.5 Hz), 128.2, 128.3, 128.3, 128.5, 133.9 (q, J = 33 Hz), 135.6, 140.6, 171.9, 198.3; MS *m*/*z* (%) 376 (M^+, 1), 358 (2), 285 (18), 173 (33), 145 (13), 91 (100). Anal. Calcd for $C_{21}H_{19}F_3O_3$ (376.4): C, 67.02; H, 5.09. Found: C, 66.97; H, 5.11.

***cis*-(±)-Benzyl 2-{2-methyl-3-[4-(trifluoromethyl)benzoyl]cyclopropyl}acetate (13a):** R_f 0.55 (4:1 hexane/ethyl acetate). The titled compound (**13a**) was found to be unstable at ambient temperature undergoing an enolene rearrangement over several days to afford **17**. See below for characterization of **17**.

***trans*-(±)-Benzyl 2-(2-acetyl-3-methylcyclopropyl)acetate (9a):** R_f 0.30 (4:1 hexane/ethyl acetate); IR (neat) 1734, 1694, 1498, 1259, 1169 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.10 (d, J = 6.0 Hz, 3H), 1.51 (dd, J = 4.2, 4.2 Hz, 1H), 1.65 (ddq, J = 9.6, 6.0, 4.2 Hz, 1H), 1.82 (dddd, J = 9.6, 8.8, 8.4, 4.2 Hz, 1H), 2.16 (s, 3H), 2.41 (dd, J = 16.8, 8.4 Hz, 1H), 2.49 (dd, J = 16.8, 8.8 Hz, 1H), 5.14 (s, 2H), 7.31−7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 12.2, 23.2, 25.6, 30.3, 32.6, 36.4, 66.4, 128.1, 128.2, 128.5, 135.8, 171.9, 207.0; MS *m*/*z* (%) 246 (M^+, 2), 186 (5), 155 (9), 91 (100). Anal. Calcd for $C_{15}H_{18}O_3$ (246.3): C, 73.15; H, 7.37. Found: C, 73.34; H, 7.20.

***cis*-(±)-Benzyl 2-(2-acetyl-3-methylcyclopropyl)acetate (14a):** R_f 0.46 (4:1 hexane/ethyl acetate); IR (neat) 1736, 1691, 1558, 1390, 1166, 740, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 1.14 (d, J = 6.4 Hz, 3H), 1.63 (ddq, J = 8.5, 8.5, 6.4 Hz, 1H), 1.74 (dddd, J = 8.5, 8.5, 8.2, 6.4 Hz, 1H), 2.11 (dd, J = 8.5, 8.5 Hz, 1H), 2.22 (s, 3H), 2.77 (dd, J = 17.6, 8.2 Hz, 1H), 2.84 (dd, J = 17.6, 6.4 Hz, 1H), 5.09 and 5.12 (AB_q, J = 9.9 Hz, 2H), 7.30−7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 6.9, 21.5, 23.0, 27.3, 27.3, 33.3, 66.2, 128.1, 128.1, 128.9, 136.1, 173.1, 207.6; MS *m*/*z* (%) 246 (M^+, 2), 221 (8), 155 (32), 105 (48), 91 (100), 83 (30); HRMS of **14a**, $C_{15}H_{18}O_3$ calcd, 246.1256; found, 246.1259.

Formation of 16 and 17 by Enolene Rearrangement. Heating pure **12a** or **13a** in benzene-d_6 at 60 °C for 5 h resulted in quantitative isomerization to **16** and **17**, respectively.

Benzyl (*E*)-4-methyl-6-oxo-6-phenyl-2-hexenoate (16): R_f 0.60 (4:1 hexane/ethyl acetate); IR 1712, 1687, 1654, 1599, 1581, 1450, cm^{-1}; ^1H NMR (C_6D_6, 600 MHz) δ 0.87 (d, J = 6.6 Hz, 3H), 2.46 (dd, J = 17.1, 7.8 Hz, 1H), 2.57 (dd, J = 17.1, 5.9 Hz, 1H), 2.90 (dddq, J = 7.8, 7.0, 6.6, 5.9 Hz, 1H), 5.06 and 5.07 (AB_q, J_{AB} = 12.6 Hz, 2H), 5.84 (d, J = 15.7 Hz, 1H), 7.00 (dd, J = 15.7, 7.0 Hz, 1H), 7.05−7.27 (m, 8H), 7.68−7.72 (m, 2H); ^{13}C NMR (C_6D_6, 150 MHz) δ 18.9, 31.9, 44.0, 66.2, 120.1, 128.2, 128.3, 128.6, 128.6, 128.7, 133.0, 136.6, 137.2, 153.5, 166.4, 197.3; MS *m*/*z* (%) 308 (M^+, 0.1), 290 (3), 262 (18), 174 (12), 105 (100), 91 (76), 82 (63). Anal. Calcd for $C_{20}H_{20}O_3$ (308.4): C, 77.90; H, 6.54. Found: C, 77.92; H, 6.48.

Benzyl (*E*)-4-methyl-6-oxo-6-[4-(trifluoromethyl)phenyl]-2-hexenoate (17): R_f 0.45 (4:1 hexane/ethyl acetate); IR ($CHCl_3$) 1714, 1697, 1655, 1583, 1512, 1456, 1410, 1173, 1066 cm^{-1}; ^1H NMR (600 MHz) δ 1.17 (d, J = 6.8 Hz, 3H), 2.98−3.18 (m, 3H), 5.17 (s, 2H), 5.91 (d, J = 15.7 Hz, 1H), 7.02 (dd, J = 15.7, 6.8 Hz, 1H), 7.30−7.39 (m, 5H), 7.70−7.78 (m, 2H) 8.01−8.07 (m, 2H); ^{13}C NMR (150 MHz) δ 19.1, 31.8, 42.9, 66.2, 120.1, 123.7 (q, J = 274 Hz), 125.8 (q, J = 3.9 Hz), 128.3, 128.3, 128.4, 128.6, 134.5 (q, J = 33 Hz), 136.0, 152.8, 171.7, 197.0; MS *m*/*z* (%) 376 (M^+, 0.1), 270 (8), 242 (11), 173 (62), 145 (28), 91 (100), 82 (83); HRMS of **17**, $C_{21}H_{19}F_3O_3$ calcd, 376.1286; found, 376.1274.

General Procedure for Preparation of *trans* γ-Hydroxy Enones 21a−d from 1a−d. To a mixture of the 1,2-dioxine (1.2 mmol) in dichloromethane (2 mL) at ambient temperature was added a mixture of triethylamine (1.2 mmol) and TPP (0.6 mmol) dissolved in dichloromethane (0.5 mL). Stirring was continued until cessation of reaction (TLC, ca. 2 h) after which time the volatiles were removed and the residue subjected to column chromatography to afford the desired *trans* γ-hydroxy enone.

(*E*)-4-Hydroxy-1,4-diphenyl-2-buten-1-one (21a): yield 82%; R_f 0.50 (2:1 hexane/ethyl acetate); IR ($CDCl_3$) 3419, 1670, 1624, 1599, 1579, 1448 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ

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(45) Enders, D.; Frank, U.; Fey, P.; Jandeleit, B.; Lohray, B. B. *J. Organomet. Chem*. **1996**, *519*, 147. Methyl (*E*)-4-methyl-6-oxo-6-phenyl-2-hexenoate was incorrectly named in this publication.

2.16 (d, J = 3.9 Hz, exch. D_2O, 1H), 5.50 (ddd, J = 4.4, 3.9, 1.7 Hz, 1H), 7.14 (dd, J = 15.4, 4.4 Hz, 1H), 7.28 (dd, J = 15.4, 1.7 Hz, 1H), 7.32−7.35 (m, 1H), 7.37−7.44 (m, 4H), 7.46−7.50 (m, 2H), 7.55−7.58 (m, 1H), 7.96−7.98 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 74.0, 123.6, 126.7, 128.5, 128.6, 128.6, 128.9, 133.0, 137.6, 140.9, 148.4, 190.5. In the absence of trace quantities of base, the titled compound was thermally labile, undergoing facile quantitative decomposition to furan **22a** in solution at ambient temperature; however, it was found to be stable at 0 °C. Monitoring by ^{1}H NMR (600 MHz) showed no evidence of the intermediacy of the isomeric *cis* γ-hydroxy enone **23a** or hemiacetals **24a**.

(*E*)-4-Hydroxy-1-phenyl-2-buten-1-one (21b): yield 85%; R_f 0.40 (11:9 hexane/ethyl acetate); IR ($CDCl_3$) 3427, 1672, 1628, 1599, 1579, 1448 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.65 (t, J = 5.4 Hz, exch. D_2O, 1H), 4.49 (ddd, J = 5.4, 3.6, 1.8 Hz, 2H), 7.14 (dt, J = 15.0, 3.6 Hz, 1H), 7.23 (dt, J = 15.0, 1.8 Hz, 1H), 7.46−7.51 (m, 2H), 7.56−7.60 (m, 1H), 7.96−8.00 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 62.3, 124.0, 128.6, 128.6, 132.9, 137.7, 146.9, 190.5. In the absence of trace quantities of base, the titled compound was thermally labile, undergoing facile quantitative decomposition to furan **22b** in solution at ambient temperature; however, it was found to be relatively stable at 0 °C. Monitoring by ^{1}H NMR (600 MHz) showed no evidence of the intermediacy of the isomeric *cis* γ-hydroxy enone **23b**.

(*E*)-4-Hydroxy-1-phenyl-2-penten-1-one (21c): yield 95%; R_f 0.50 (3:2 hexane/ethyl acetate); IR ($CDCl_3$) 3434, 1668, 1628, 1599, 1579, 1448 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.39 (d, J = 7.2 Hz, 3H), 2.60 (bs, exch. D_2O, 1H), 4.59 (ddq, J = 7.2, 5.3, 1.2 Hz, 1H), 7.05 (dd, J = 15.4, 5.3 Hz, 1H), 7.14 (dd, J = 15.4, 1.2 Hz, 1H), 7.42−7.50 (m, 2H), 7.53−7.58 (m, 1H), 7.92−7.96 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.9, 67.5, 123.3, 128.5, 128.6, 132.9, 137.7, 151.2, 190.8. In the absence of trace quantities of base, the titled compound was thermally labile, undergoing slow quantitative decomposition to furan **22c** in solution at ambient temperature; however, if was found to be relatively stable at 0 °C. Monitoring by ^{1}H NMR (600 MHz) showed no evidence of the intermediacy of the isomeric *cis* γ-hydroxy enone **23c** or hemiacetals **24c**.

(*E*)-4-Hydroxy-1-[4-(trifluoromethyl)phenyl]-2-penten-1-one (21d): yield 77%; R_f 0.50 (2:1 hexane/ethyl acetate); IR (neat) 3429, 1673, 1627, 1580, 1512, 1326, 1013, 837 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.41 (d, J = 6.6 Hz, 3H), 1.96 (bs, exch. D_2O, 1H), 4.64 (dq, J = 6.6, 2.7 Hz, 1H), 7.18−7.23 (m, 2H), 7.72−7.75 (m, 2H), 8.02−8.05 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.9, 67.5, 121.8, 123.6(q, J = 271 Hz), 125.6 (q, J = 4.0 Hz), 128.9, 129.7 (q, J = 32 Hz), 136.0, 152.4, 189.8. In the absence of trace quantities of base, the titled compound was thermally labile, undergoing slow quantitative decomposition to furan **22d** in solution at ambient temperature; however, it was found to be relatively stable at 0 °C. Monitoring by ^{1}H NMR (600 MHz) showed that the titled compound existed along with ca. 5% of the isomeric *cis* γ-hydroxy enone **23d** and hemiacetals **24d**.

1-[4-(Trifluoromethyl)phenyl]-1,4-pentanedione (15d): R_f 0.50 (2:1 hexane/ethyl acetate); mp 79−80 °C; IR 1708, 1682, 1577, 1134, 845 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.25 (s, 3H), 2.91 (t, J = 5.7 Hz, 2H), 3.27 (d, J = 5.7 Hz, 2H), 7.71−7.74 (m, 2H), 8.06−8.09 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 29.9, 32.6, 36.9, 123.6 (q, J = 272 Hz), 125.7 (q, J = 3.8 Hz), 128.4, 134.5 (q, J = 33 Hz), 139.4, 197.8, 207.0; MS m/z (%) 226 (M^+, 13), 229 (34), 201 (10), 173 (100), 145 (57), 43 (71). Anal. Calcd for $C_{12}H_{11}F_3O_2$ (244.2): C, 59.02; H, 4.54. Found: C, 59.14; H, 4.32.

2-Methyl-5-[4-(trifluoromethyl)phenyl]furan (22d): R_f 0.60 (hexane); mp 56−57 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.39 (d, J = 2.0 Hz, 3H), 6.10 (dq, J = 6.6, 2.0 Hz, 1H), 6.66 (d, J = 6.6 Hz, 1H), 7.58−7.61 (m, 2H), 7.69−7.72 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 13.6, 108.0, 108.1, 124.3 (q, J = 270 Hz), 125.7 (q, J = 3.8 Hz), 128.4 (q, J = 33 Hz), 134.3, 150.9, 153.3; MS m/z (%) 226 (M^+, 57), 207 (11), 177 (19), 145 (21), 129 (32), 53 (2), 43 (100). Anal. Calcd for $C_{12}H_9F_3O$ (226.2): C, 63.72; H, 4.01. Found: C, 64.04; H, 4.16.

General Procedure for Preparation of *cis* γ-Hydroxy Enones 23a−d and *cis*/*trans*-Hemiacetals 24a−d. The thermodynamic mixture of the *cis* γ-hydroxy enones **23a**−**e** and the *cis*/*trans* hemiacetals **24a**−**d** were prepared from the corresponding 1,2-dioxines by one of the following two general methods. Refer to Table 4 for method type, isolated yield and relative ratios. The full characterization of the *cis* and *trans*-hemiacetals **24a**−**d** will be reported elseware.[28] These mixtures were found to be extremely sensitive in the pure state, undergoing facile dehydration in a matter of hours to their corresponding parent furans **22**.

Method A. To a mixture of the 1,2-dioxine (50 mg) in dichloromethane (2 mL) was added $Co(SALEN)_2$ (5 mg), and the mixture was left to react for 5 h. The volatiles were then removed in vacuo and the residue triturated with hexane (3 × 5 mL). The combined hexane extracts were then evaporated to afford a mixture of the *cis* γ-hydroxy enones and *cis*/*trans*-hemiacetals, which were judged to be greater than 98% purity by ^{1}H NMR.

Method B. To a mixture of the 1,2-dioxine (50 mg) in dichloromethane (2 mL) under nitrogen was added two drops of a triethylamine solution (0.069 M solution in dichloromethane). The mixture was allowed to stand for 2.5 h, and then the volatiles were removed in vacuo. The residue was immediately subjected to silica gel chromatography (8 cm × 1.5 cm column) eluting with hexane/ethyl acetate (3:2). The volatiles were then removed in vacuo to afford a mixture of the *cis* γ-hydroxy enones and *cis*/*trans*-hemiacetals, which were judged to be greater than 98% purity by ^{1}H NMR.

(*Z*)-4-Hydroxy-1,4-diphenyl-2-buten-1-one (23a): R_f 0.60 (2:1 hexane/ethyl acetate); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.68 (d, J = 3.9 Hz, exch. D_2O, 1H), 5.92 (ddd, J = 7.5, 3.9, 0.9 Hz, 1H), 6.55 (dd, J = 11.7, 7.5 Hz, 1H), 6.96 (dd, J = 11.7, 0.9 Hz, 1H), 7.25−7.7.59 (m, 8H), 7.97−8.00 (m, 2H).

(*Z*)-4-Hydroxy-1-phenyl-2-buten-1-one (23b): R_f 0.50 (3:2 hexane/ethyl acetate); IR ($CDCl_3$) 3446, 1662, 1608, 1521, 1448 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 3.15 (bs, exch. D_2O, 1H), 4.60 (dd, J = 5.1, 1.5 Hz, 1H), 6.63 (dt, J = 12.0, 5.1 Hz, 1H), 7.02 (dt, J = 12.0, 1.5 Hz, 1H), 7.25−7.7.59 (m, 8H), 7.97−8.00 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 61.1, 123.7, 128.5, 128.7, 133.2, 137.7, 147.8, 191.9.

(*Z*)-4-Hydroxy-1-phenyl-2-penten-1-one (23c): R_f 0.50 (3:2 hexane/ethyl acetate); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.40 (d, J = 6.6 Hz, 3H), 3.50 (d, J = 3.6 Hz, exch. D_2O, 1H), 4.88 (dddq, J = 6.6, 6.6, 3.6, 1.2 Hz, 1H), 6.43 (dd, J = 12.0, 6.6 Hz, 1H), 6.92 (dd, J = 12.0, 1.2 Hz, 1H), 7.45−7.60 (m, 3H), 7.94−7.98 (m, 2H).

(*Z*)-4-Hydroxy-1-[4-(trifluoromethyl)phenyl]-2-penten-1-one (23d): R_f 0.50 (3:2 hexane/ethyl acetate); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.40 (d, J = 6.5 Hz, 3H), 3.30 (bs, Hz, exch. D_2O, 1H), 4.93 (ddq, J = 6.5, 6.5, 1.5 Hz, 1H), 6.48 (dd, J = 11.7, 6.5, Hz, 1H), 6.89 (dd, J = 11.7, 1.5 Hz, 1H), 7.60−7.75 (m, 2H), 8.07−8.09 (m, 2H).

(*E*)-1-Phenyl-2-(3-phenyl-2-oxiranyl)-1-ethanone (26). The precursor (*E*)-1,4-diphenyl-3-buten-1-one (**29**) was prepared by the action of phenylmagnesium bromide on the THF protected ester **28** of styryl acetic acid (**27**) according to the general procedure outlined by Rapoport et al.[29] Thus, to a mixture of **27** (5.0 g, 30.8 mmol) in dichloromethane (120 mL) at −20 °C was added 2,3-dihydrofuran (2.26 g, 32.3 mmol) followed by methane sulfonic acid (6 mg, 0.062 mmol) dissolved in a solution of dichloromethane (0.4 mL). The mixture was allowed to warm to 0 °C over 4 h and then recooled to −20 °C. To this mixture was then added dropwise phenylmagnesium bromide (25 mL, 30.8 mmol, 1.23 M in ether) over 5 min. Stirring was continued for an additional 30 min, and then the solution was allowed to warm to ambient temperature over 18 h. The mixture was then cooled to 0 °C and added dropwise to a solution of H_3PO_4 (40 mL, 1.0 M) at 0 °C. The mixture was then allowed to warm to ambient temperature, diluted with water (30 mL) and dichloromethane (150 mL). The organic layer was removed, and the aqueous phase was washed with dichloromethane (3 × 30 mL). The organics were combined, dried and evaporated in vacuo to afford crude **29**, which was further purified by flash chromatography (R_f 0.5, 9:1

hexane/ethyl acetate) followed by recrystalization from hexane. Yield (3.28 g, 47%); mp 83−84 °C; lit.[30] mp 93 °C. Conversion of **29** into the titled compound (**26**) was achieved by *m*-CPBA oxidation as outline by Padwa:[30] mp 102−103 °C (1:4 ether/hexane); lit.[30] mp 112−113 °C; IR ($CHCl_3$) 3500, 1670, 1597, 1549, 1448 cm^{-1}; ^1H NMR ($CHCl_3$, 600 MHz) δ 3.31 (1H, dd, J = 16.8, 5.0 Hz), 3.45 (1H, dd, J = 16.8, 5.8), 3.51 (1H, ddd, J = 5.8, 5.0, 2.0 Hz), 3.75 (1H, d, J = 2.0 Hz), 7.26−7.38 (3H, m), 7.48−7.51 (2H, m), 7.59−7.61 (1H, m), 7.97−7.99 (2H, m); ^{13}C NMR ($CHCl_3$, 75 MHz) δ 41.9, 58.2, 58.4, 125.7, 128.1, 128.2, 128.4, 128.7, 133.4, 136.6, 136.8, 196.9.

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