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Butenolide synthesis from functionalized cyclopropenones

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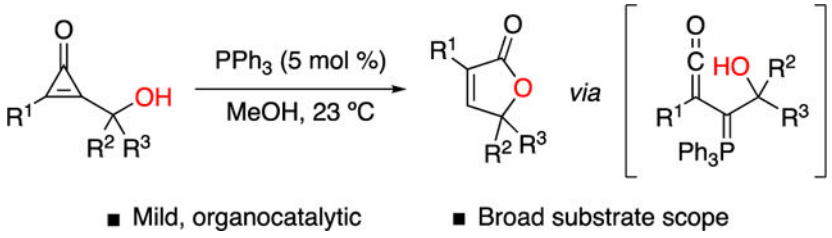
Abstract

A general method to synthesize substituted butenolides from hydroxymethylcyclopropenones is reported. Functionalized cyclopropenones undergo ring-opening reactions with catalytic amounts of phosphine, forming reactive ketene ylides. These intermediates can be trapped by pendant hydroxy groups to afford target butenolide scaffolds. The reaction proceeds efficiently in diverse solvents and with low catalyst loadings. Importantly, the cyclization is tolerant of a broad range of functional groups, yielding a variety of α- and γ-substituted butenolides.

Graphical Abstract



Butenolides are found in a variety of natural product scaffolds and possess desirable bioactive properties.[1] For example, linderalactone (Figure 1A) can protect hepatocytes from oxidative damage.[2] Other butenolides, including (–)-incrustoporin, are potent inhibitors of pathogenic fungi.[3] These and related scaffolds[4] have inspired chemists to develop efficient syntheses of α,β-unsaturated lactones. While several methods now exist,[5–9] most are limited

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Supporting Information

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Experimental details and spectroscopic data for new compounds (PDF)

Crystallographic data on compound **2m** (CIF)

Accession Codes

CCDC 1913684 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.cdcc.cam.ac.uk/data_request/cif, or by emailing data_request@cdcc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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in terms of substitution pattern, functional group tolerance, or starting material accessibility. More general methods to build butenolides are therefore needed.

Cyclopropenones (CpOs) are attractive synthons for butenolide formation. These microcycles map readily onto the target structures and are easily accessible from alkyne precursors.[10] CpOs have only recently been exploited for lactone synthesis, though.[11–13] The groups of Lin and Sun developed methods to convert symmetric CpOs to functionalized butenolides (Figures 1B and 1C). Both transformations proceed via intermolecular 1,2-addition of carbonyl groups into the CpO scaffold, followed by ring opening. The resulting vinyl anion intermediates subsequently cyclize to deliver the desired lactones. While robust, both methods require electron-rich carbonyl fragments. The vinyl anion intermediates are also not compatible with a range of functional groups, limiting the scope of these chemistries. Furthermore, the intermolecular nature of the reactions can present regioselectivity challenges when unsymmetrical CpOs are employed.

We hypothesized that an *intramolecular* reaction could convert CpOs to functionalized butenolides and potentially broaden the scope of accessible products. Toward this end, we drew inspiration from our previous work on bioorthogonal CpOs.[14,15] These motifs undergo conjugate addition reactions with bioorthogonal phosphines, producing ketene-ylide intermediates upon ring fragmentation.[16] The electrophiles can be readily trapped by pendant nucleophiles on the phosphine (Figure 2A) to afford covalent adducts. We surmised that pendant nucleophiles on the CpO – rather than the phosphine – could also trap the ketene (Figure 2B). If the nucleophile was part of a hydroxymethyl tether, the products would comprise lactones. Subsequent ylide protonation and phosphine elimination could ultimately deliver functionalized butenolides. Since the proposed method involves bioorthogonal reagents, it would likely be compatible with a variety of functional groups. The proximity of the hydroxy group on the CpO tether would also promote intramolecular cyclization, outcompeting any exogenous nucleophile in the trapping step.[15]

The regioselectivity of the proposed reaction was further considered. Phosphine addition at C2 (i.e., the carbon bearing the hydroxymethyl tether) would likely provide the desired products. However, phosphine addition at C3 could give undesired β-lactones. Cyclization en route to the β-lactone (4-exo-dig) is disfavored according to Baldwin's rules, but notable examples exist.[17–19] We reasoned that butenolide formation could still predominate in the reaction, even if phosphine attacked C3. Ketene-ylide formation is reversible in the absence of trapping nucleophiles,[14,20] and cyclization en route to the β-lactone would likely be slower than the reverse reaction to reform the CpO. Thus, the reaction could funnel to a butenolide product, regardless of the initial site of phosphine addition.

To examine the overall strategy, model CpO **1a** was synthesized and treated with a panel of phosphines. The reactions were performed in various solvents and monitored using ^{1}H NMR spectroscopy (Tables 1 and S1, Figures S1–S15). 1,3,5-Triaza-7-phosphaadamantane (PTA) was initially selected due to its potent reactivity and unique stability in protic solvents. When combined stoichiometrically with **1a**, PTA afforded rapid conversion to the desired butenolide (entry 1). The reaction slowed significantly when the catalyst loading was reduced to 10 mol % (entry 2). Notably, no intermolecular solvent trapping was observed

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even at the longer reaction times. Sluggish reactivity was not general to all alkyl-substituted phosphines. When **1a** was treated with cyclohexyldiphenylphosphine (CyDPP), rapid formation of **2a** was observed even at low catalyst loadings (entry 3).

Anticipating that alkyl phosphines would be prone to oxidation and thus less general, we further investigated triarylphosphines. We were particularly drawn to tri(*o*-tolyl)phosphine, as this reagent would likely be sufficiently nucleophilic to add into the CpO core, but be reasonably air stable. When CpO **1a** was treated with tri(*o*-tolyl)phosphine, though, no conversion to butenolide **2a** was observed (entry 4). No butenolide was formed even with longer reaction times or elevated temperatures (Table S1, Figures S14–S15). The increased steric bulk surrounding the phosphine likely precluded efficient conjugate addition. Indeed, this phosphine is rarely used in Michael-type reactions and is primarily employed as a metal ligand.[21–23]

We next tested a less sterically encumbered reagent, triphenylphosphine (PPh_3). PPh_3 is commercially available, inexpensive, and bench stable, making it attractive for methods development. When **1a** was treated with stoichiometric amounts of PPh_3 in CD_3OD, rapid conversion to butenolide **2a** was observed (entry 5). Efficient cyclization occurred even at reduced catalyst loadings (entries 10–11) with no evidence of intermolecular solvent trapping. Additionally, in the realm of phosphine organocatalysis, few reactions feature catalyst loadings below 10 mol %, and even fewer use air-stable, commercially available reagents.[24] We were also surprised that low catalyst loadings afforded rapid butenolide formation, considering the diminished nucleophilicity of PPh_3. We hypothesized that the polar protic solvent accelerated the reaction via hydrogen-bond activation of the starting CpO. Similar observations were made when CpOs were tuned for bioorthogonal ligation.[15] When the cyclizations were performed in DMSO-d_6 or C_6D_6, longer reaction times or stoichiometric amounts of PPh_3 were required for full conversion (entries 6–9).

We aimed to test the optimized reaction conditions with a variety of hydroxymethyl CpOs. Such probes can be readily accessed via appropriately functionalized alkynes.[10] We thus prepared a variety of alkyl- and aryl-substituted alkynes via acetylide addition to formaldehyde or Sonogashira cross-coupling reactions, respectively (Scheme S1). Each alkyne also comprised a THP-protected hydroxymethyl tether. The alkyne products were subjected to difluorocarbene, a reagent generated *in situ* via the conditions of Olah[25] (Scheme 1). The resulting difluorocyclopropenes were then hydrolyzed and deprotected to furnish the desired hydroxymethyl CpOs (**1a-u**, Scheme 1). The carbene insertion and hydrolysis sequence was not compatible with alkynes bearing nitrogen heterocycles, and attempts to isolate the corresponding CpOs resulted in decomposition. These results are in stark contrast to heterocyclic alkenes, which undergo robust difluorocarbene insertion.[26,27]

The panel of hydroxymethyl-tethered CpOs was subjected to butenolide formation conditions (Scheme 1). As anticipated, the cyclization was tolerant of a broad range of functional groups. α-Alkyl-substituted CpOs (**2a-d**), including branched (**2b**), and cyclic (**2c**) substrates, were efficiently converted. The reaction also proceeded in the presence of competing nucleophiles (**2d**), albeit with lower yields. α-Aryl substituted CpOs also generated butenolides in the presence of PPh_3. Both electron-donating (**2e-2l**) and electron-

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withdrawing (**2p**-**2u**) groups were examined, along with thiophene heterocycles (**2l**). Notably, robust product formation was observed even in the presence of electrophilic esters (**2t**) and cyano groups (**2q**). The reaction was also tolerant of different substitution patterns on the aryl ring (**2f**-**2j, 2s**).

The CpO-phosphine reaction further enabled access to more highly substituted butenolides. As noted above, the cyclization is tolerant of numerous α-substituents (Scheme 1). These groups are positioned away from the ketene, and thus minimally interfere with trapping. Additional substituents on the hydroxymethyl tether provided access to α,γ-disubstituted butenolides (**2m**-**2o**). Compound **2n**, in particular, comprises the α,γ-substitution pattern present in incrustoporin (Figure 1A) and related natural products (Figure 1A). While the CpO reaction cannot provide β-substituted butenolides, such scaffolds are readily accessible post-cyclization. Cycloadditions[28,29] and Heck couplings[30] can be used in this regard, along with several other methods.[31,32] Notably, functionalized butenolides can also serve as gateways to butyrolactones[33–36] and other interesting scaffolds.[37,38]

Our collective results demonstrated that butenolides are favored in the hydroxymethyl CpO-phosphine reaction. All but one of the cyclizations proceeded with no competing β-lactone formation. Such side products were observed only when CpO **1m** was subjected to low catalyst loadings in meth-anol (Figures 3A, S16). The *gem*-dimethyl groups on **1m** likely promoted phosphine addition to the more accessible C3 position and accelerated β-lactone cyclization to provide **3a-b**.[39] An appreciable amount of product **2m** was still formed under these challenging conditions, supporting the original hypothesis that butenolide formation can predominate, despite the potential for competing pathways.

We carried out additional experiments to examine the propensity for hydroxymethyl CpOs to form butenolides. The observed product distributions likely reflect the faster rate of five- versus four-membered ring cyclization following ketene formation (Figure 2B). An alternative explanation is that phosphine attack is favored at C2. To investigate these possibilities, we devised a competitive trapping experiment with diol **1d**. This compound comprises two hydroxy group tethers, and is capable of cyclizing to five- or six-membered rings, depending on the ketene formed. We anticipated that **1d** would provide a mixture of γ- and δ-lactones upon phosphine treatment, as the steric environments around C2 and C3 are similar and unlikely to bias phosphine addition. Additionally, five- or six-membered ring formation (post-ketene generation) should be similarly facile. When diol **1d** was treated with PPh_3, a mixture of γ-lactones was observed, in addition to butenolide **2d** (Figure S15). No δ-lactone (**5**) formed, though, to our surprise (Figures 3B, S17). The ketene en route to **4** was capable of forming and cyclizing, as demonstrated with a CpO probe outfitted with a single hydroxyethyl tether (Figure S18). These data suggest that phosphine addition to C2 could be preferred when CpOs are functionalized with hydroxymethyl appendages. The exact mechanism is the subject of ongoing work, but the tether could promote internal hydrogen-bond activation, preorganizing the CpO for C2 attack.

In conclusion, we developed a method to prepare substituted butenolides using mild and bioorthogonal reagents: hydroxymethyl-tethered cyclopropenones and aryl phosphines. This method features mild reaction conditions and low catalyst loadings, and can produce a

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variety of targets. The reaction exhibits wide functional group tolerance, typical of biocompatible reagents. The reported transformation is complementary to existing methods that furnish α,γ-substituted butenolides,[40–49] but is potentially more generalizable. Importantly, the requisite hydroxymethyl CpOs can be derived from propargyl alcohols, widely used and available materials in organic synthesis. We further anticipate that CpOs and other bioorthogonal reagents will continue to inspire the development of useful methodologies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

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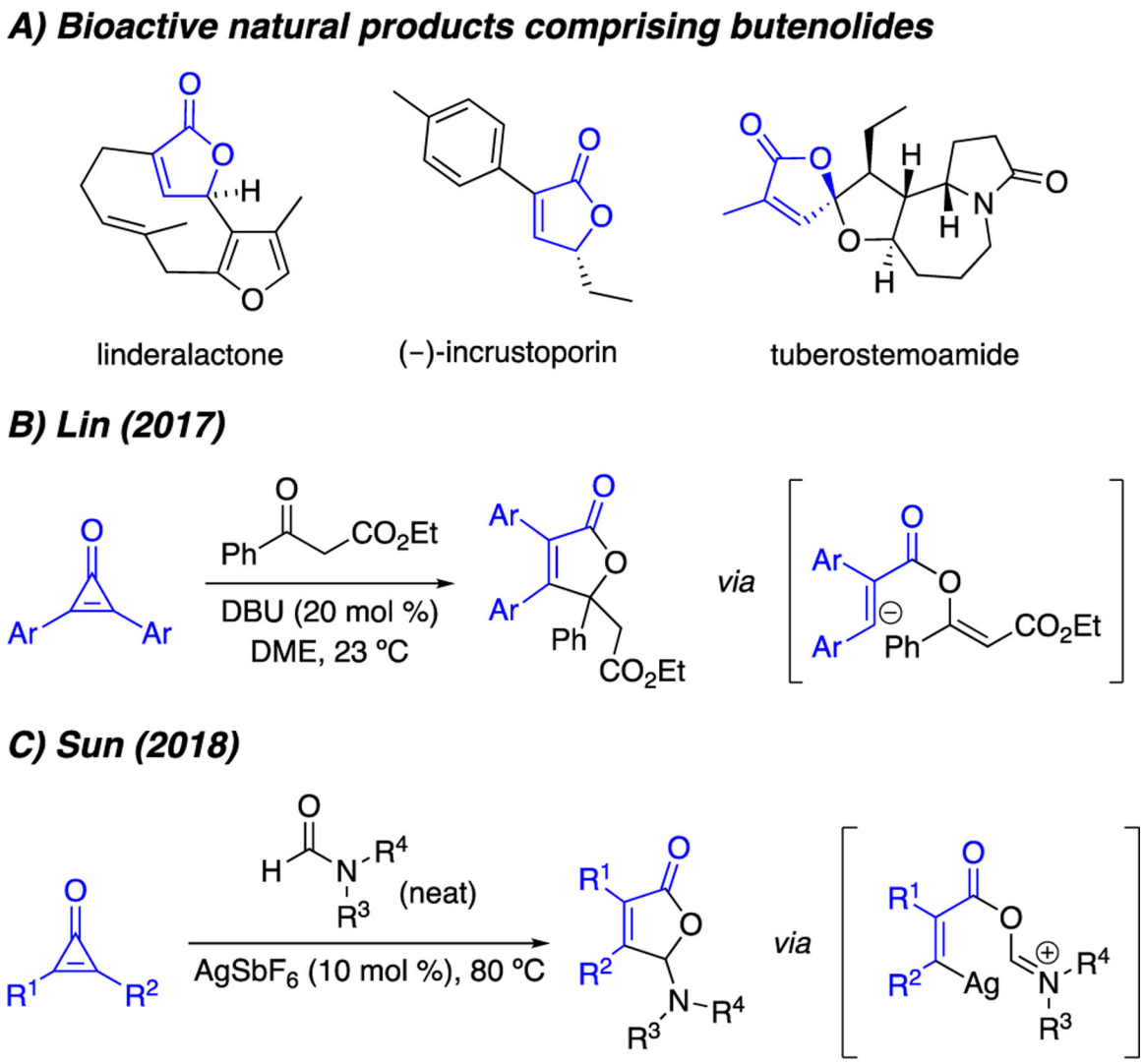

Figure 1.

(A) Butenolides (blue) are common motifs in bioactive natural products. Recent work by (B) Lin and (C) Sun featured intermolecular reactions between CpOs and carbonyls to generate functionalized butenolides.

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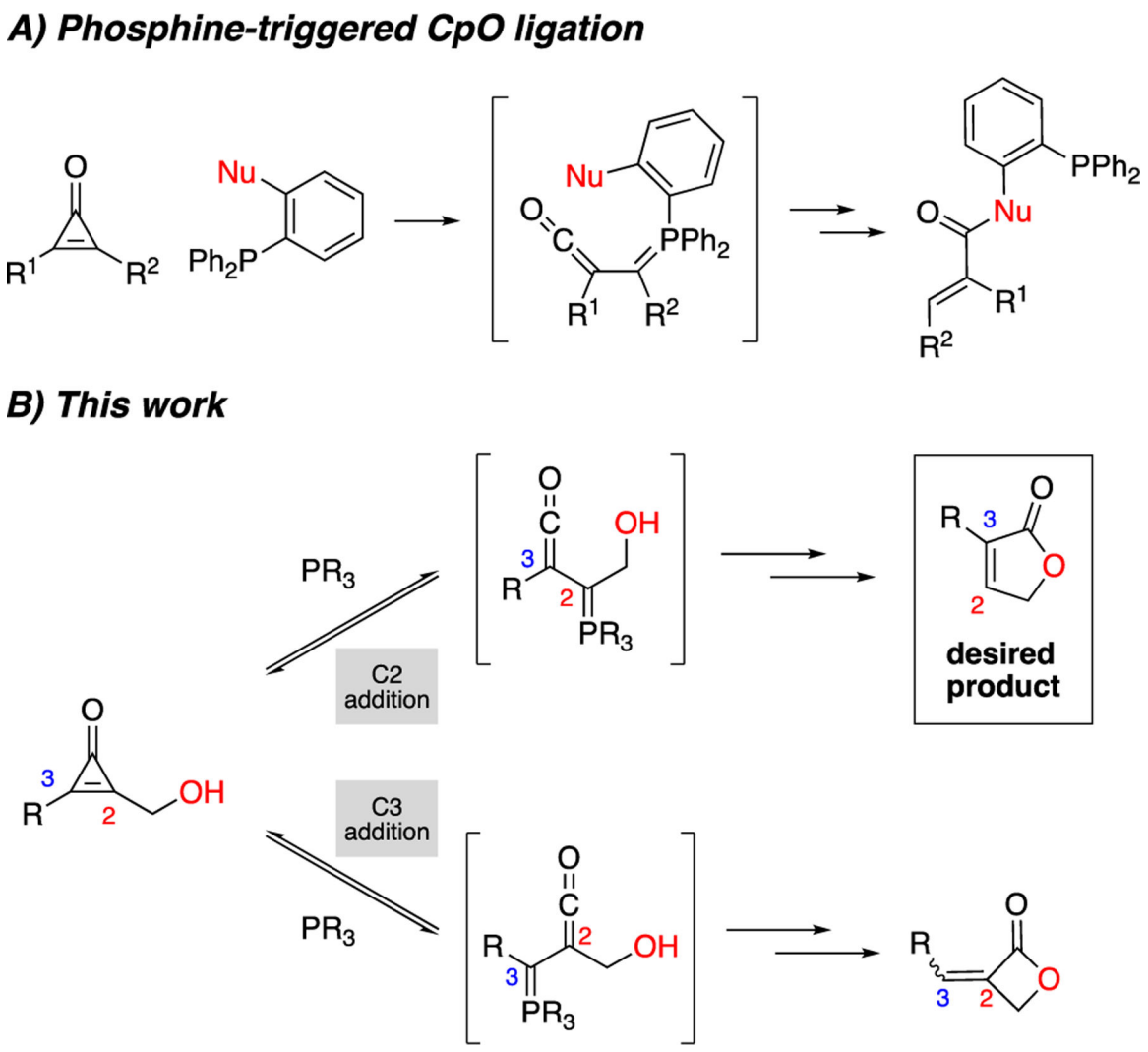

Figure 2.

CpOs react with phosphines to reveal ketene ylides. These intermediates can be trapped with (A) pendant nucleophiles on bioorthogonal phosphines or (B) hydroxy group nucleophiles on CpO scaffolds. In the latter case, phosphine addition at C2 affords butenolides (top). Phosphine addition at C3 could provide undesired β-lactones (bottom).

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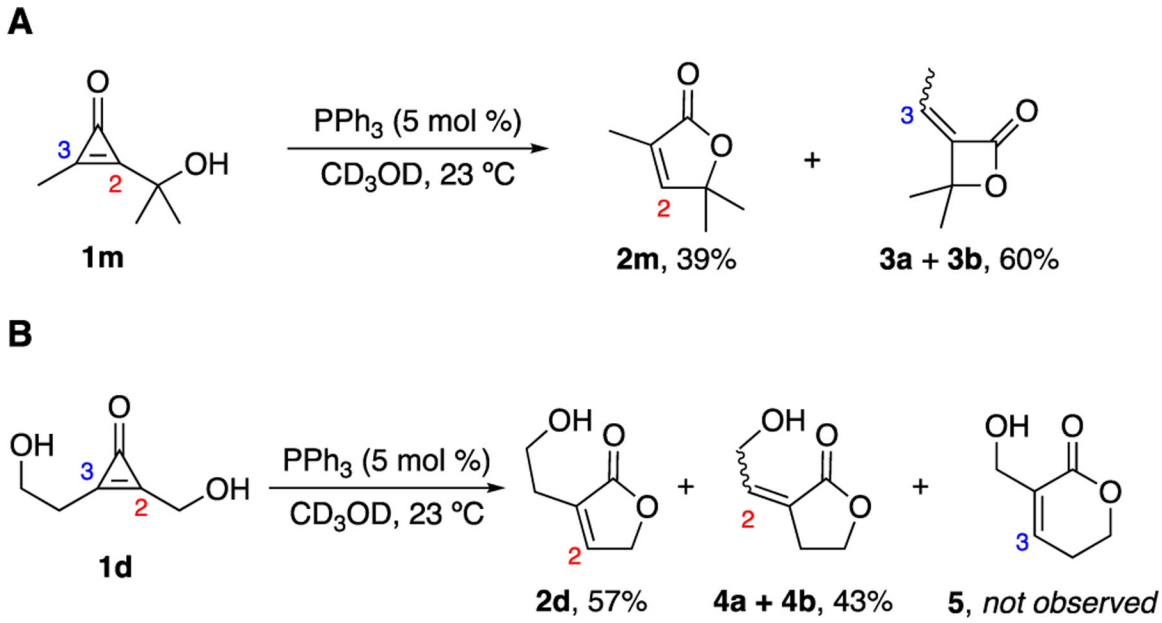
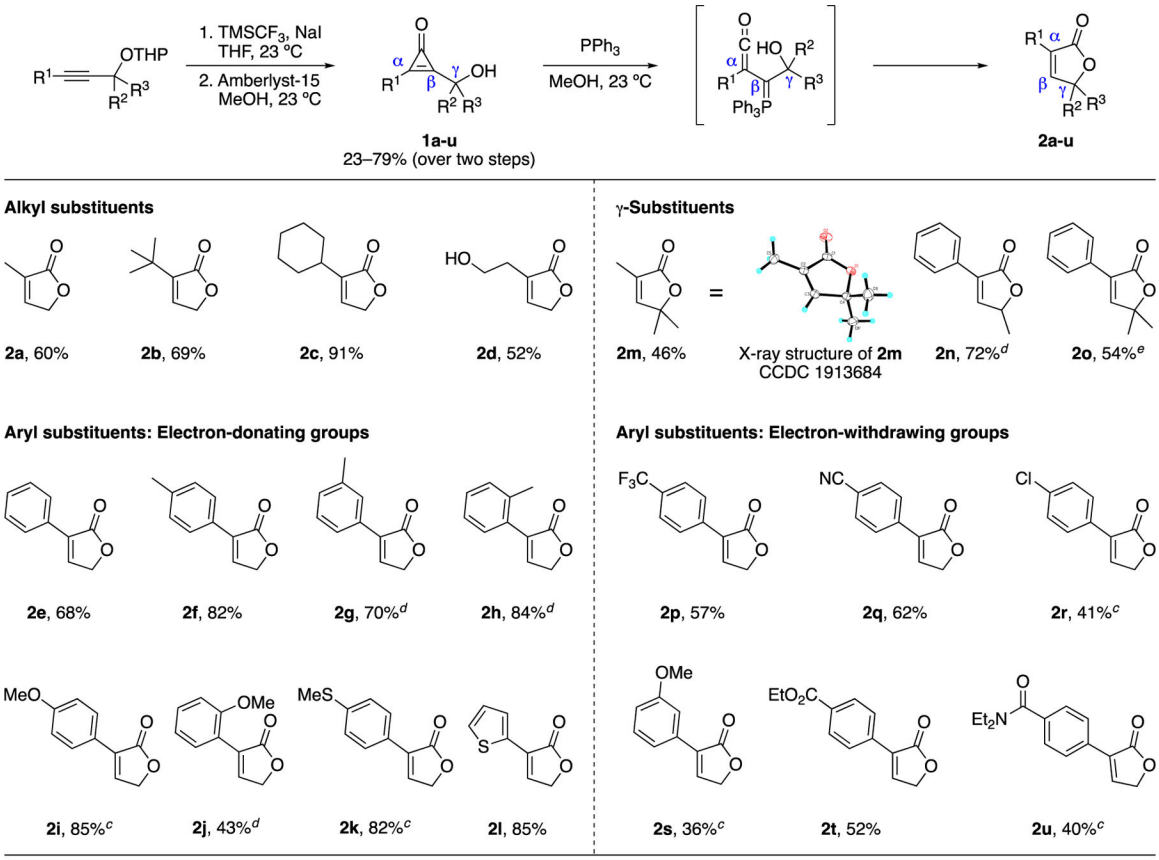


Figure 3.

Mechanistic studies involving butenolide formation. (A) Upon phosphine treatment, CpO **1m** formed β-lactone products **3a-b**. The additional steric bulk at C2 likely disfavored phosphine addition. (B) δ-Lactone **5** was not observed when diol-CpO **1d** was treated with PPh_3. This reaction produced a mixture of γ-lactones (**4a-b**), in addition to the desired butenolide **2d**. For (A)-(B), percent conversion values (from NMR analyses) are reported.



[a]Reaction conditions: CpO (1 equiv), PPh_3 (5 mol %), methanol (0.25 M). [b]Isolated yields. [c]10 mol % PPh_3. [d]20 mol % PPh_3. [e]C_6H_6 (0.25 M) was used.

Scheme 1.

Diverse butenolides were synthesized from substituted CpOs[a,b]

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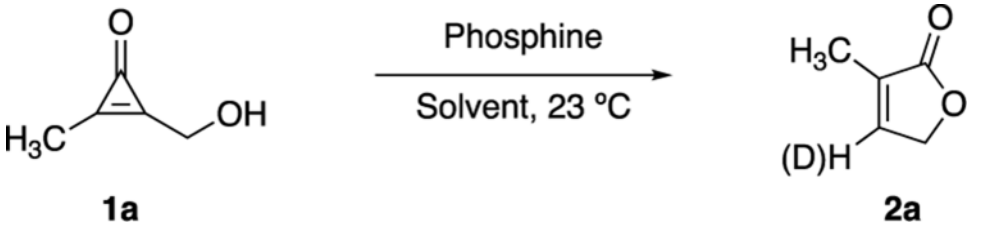
Table 1.

Optimization of butenolide cyclization



1a **2a**

entry	phosphine (mol %)	solvent	time	conversion *(%)*[b]
1	PTA (100)	CD_3OD	10 min	>95
2	PTA (10)	CD_3OD	2 h	67
3	CyDPP (5)	CD_3OD	2.5 h	90
4	P(*o*-tolyl)$_3$ (5)	CD_3OD	2.5 h	0
5	PPh_3 (100)	CD_3OD	10 min	>95
6	PPh_3 (100)	DMSO-d_6	22 h	>95
7	PPh_3 (5)	DMSO-d_6	24 h	16
8	PPh_3 (100)	C_6D_6	1 h	>95
9	PPh_3 (5)	C_6D_6	24 h	94
10	PPh_3(10)	CD_3OD	1.5 h	>95
11	**PPh_3 (5)**	**CD_3OD**	**2.5 h**	**>95**

[a] Reaction conditions: CpO (15 μmol), TMS-acetylene (3 μmol), solvent (600 μL)

[b] NMR conversion, calculated from integral ratios between starting CpO and butenolide product