Modular Synthesis of Functionalized Butenolides by Oxidative Furan Fragmentation

Jiajing Bao,† Hailong Tian,† Peicheng Yang, Jiachen Deng and Jinghan Gui*

CAS Key Laboratory of Synthetic Chemistry of Natural Substances, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

ABSTRACT: The development of new chemical transformations to simplify the synthesis of valuable building blocks is a challenging task in organic chemistry and has been the focus of considerable research effort. From a synthetic perspective, it would be ideal if the natural reactivities of feedstock chemicals could be diverted to the production of high value-added compounds which are otherwise tedious to prepare. Here we report a chemical transformation that enables facile and modular synthesis of synthetically challenging yet biologically important functionalized butenolides from easily accessible furans. Specifically, Diels–Alder reactions between furans and singlet oxygen generate versatile hydroperoxide intermediates, which undergo iron(II)-mediated radical fragmentation in the presence of $Cu(OAc)_2$ or various radical trapping reagents to afford butenolides bearing a wide variety of appended remote functional groups, including olefins, halides, azides and aldehydes. The practical utility of this transformation is demonstrated by easy diversification of the products by means of cross-coupling reactions and, most importantly, by its ability to simplify the syntheses of known building blocks of eight biologically active natural products.

■ INTRODUCTION

Butenolides are a class of five-membered-ring unsaturated lactones that are present in a wide variety of compounds such as food additives, agrochemicals, pharmaceuticals and biologically active natural products. Examples include vitamin C (ascorbic acid, **1**, Figure 1a), which is an essential nutrient found in various foods and is used as a dietary supplement to prevent and treat scurvy; 3-methyl-2*H*-furo[2,3-*c*]pyran-2-one (**2**), which is isolated from plant-derived smoke and promotes germination of the seeds of agricultural weeds;[1] and clavilactone A (**3**)[2] and pyranicin (**4**),[3] natural products that exhibit antifungal, antibacterial, pesticidal, immunosuppressive, and antitumor activities, among others. Compounds **3** and **4** could potentially be accessed convergently via a fragment-coupling strategy involving butenolides with appended remote functional groups as key coupling partners. The various conventional approaches for constructing butenolides have been reviewed[4] and include ring-closing metathesis of unsaturated esters,[3f] intermolecular alkylation of α-sulfenyl γ-lactones,[5] intermolecular Aldol reactions[6] and Pd-catalyzed carbonylation of vinyl iodides.[7] However, these approaches generally suffer from two limitations: they require lengthy and tedious manipulations, and they lack modularity: that is, each structural motif is synthesized by a completely different synthetic strategy. Therefore, the development of a concise and modular approach to functionalized butenolides from simple and readily available starting materials would be highly desirable.

One powerful strategy for rapidly generating molecular complexity is carbon–carbon (C–C) bond fragmentation.[8] This strategy has found numerous applications in natural product synthesis[9] and materials science[10] and has drawn considerable attention from synthetic chemists over the years.[11] Classic examples include the Grob[12] and Eschenmoser–Tanabe[13] fragmentations, dating back to the 1950s, for the expedient synthesis of alkenes and alkynes (Figure 1b). In addition to ionic fragmentation,[14] radical fragmentation is also widely used.[15] Examples pertinent to this study include the seminal work on iron-mediated decomposition reactions of hydroperoxides reported by Kochi,[16] Schreiber,[17] and Newhouse.[18] In these reactions, the O–O bond of the hydroperoxide is cleaved in the presence of an iron(II) salt to give an alkoxy radical, which undergoes β-fragmentation to generate an alkyl radical. Subsequent oxidation of the alkyl radical by a copper(II) salt furnishes the alkene product. Although this strategy is exceptionally powerful for oxidative cleavage of ketones, removal of an isopropenyl group,[11c, 19] and macrolide synthesis,[20] it has rarely been used for selective fragmentation of feedstock chemicals (such as furans) to provide efficient, direct access to high-value-added compounds.

Because furans are inexpensive, readily available, and highly reactive, they are versatile synthons and have frequently been used to access a wide array of valuable building blocks.[21] Typical transformations of furans include Diels–Alder reactions to afford butenolides and 1,4-diketones, Achmatowicz reactions to furnish pyranones and pyridones, and Mukaiyama Aldol reactions to form butenolides (Figure 1c). Despite the frequent application of these classic transformations in natural product synthesis and medicinal chemistry, the use of furans to rapidly generate molecular complexity via C–C bond fragmentation has rarely been reported.[22] Given the easy accessibility of furans, the development of a method for oxidizing the furan ring while concurrently cleaving the adjacent C–C bond to generate functionalized butenolides would be highly appealing (Figure 1c). We speculated that an endoperoxide produced by a Diels–Alder reaction between a furan and singlet oxygen[23] might form a hydroperoxide in MeOH, which could then decompose in the presence of an iron(II) species to give a functionalized butenolide via radical fragmentation. The net outcome of this process would be the conversion of furans to synthetically challenging

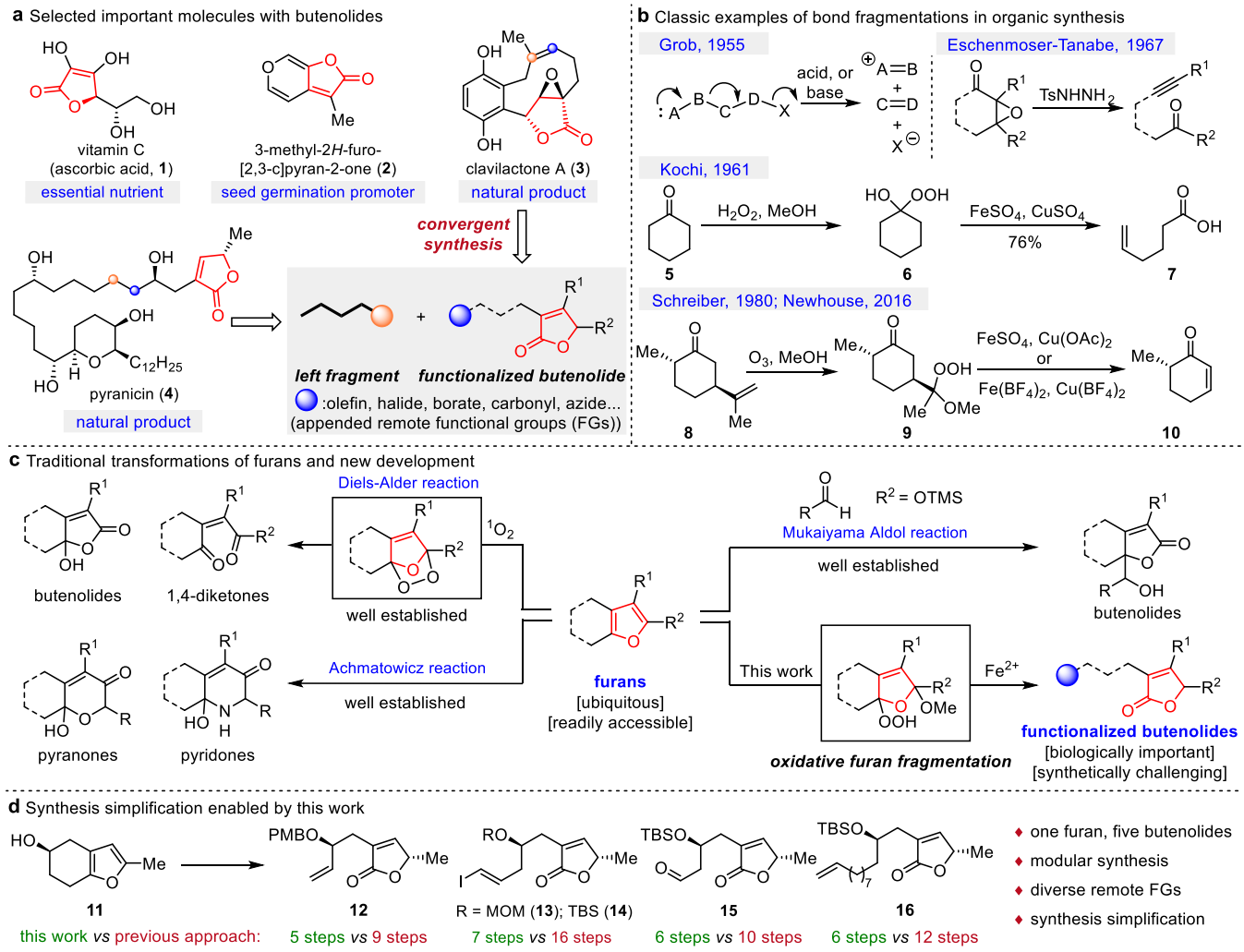


Figure 1. Overview of butenolides, bond-fragmentation strategies, and transformations of furans.

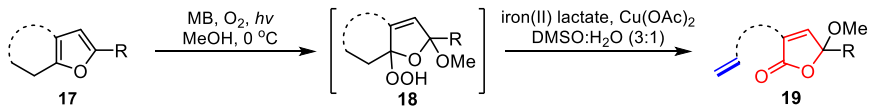
yet biologically important butenolides simply by using singlet oxygen and an inexpensive iron(II) salt. Herein we disclose the development of just such a process: specifically, we report that oxidative fragmentation of furans provides rapid, modular access to functionalized butenolides bearing a broad range of appended remote functional groups, including olefins, halides, azides, and aldehydes. Furthermore, we show that these remote functional groups can undergo various bond-forming reactions (Scheme 1), significantly expanding the chemical space of accessible butenolides. Most importantly, we demonstrate the power of our strategy by using it to simplify and shorten the syntheses of building blocks of eight biologically important natural products (Scheme 2). Examples include butenolides **12**–**16**, which bear diverse remote functional groups and were concisely prepared in a modular fashion from a single starting material (furan **11**, Figure 1d).

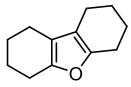
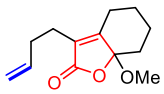
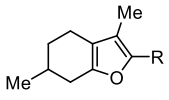
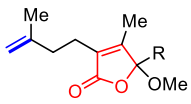
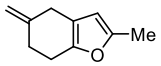
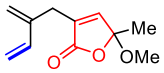
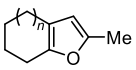
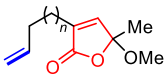
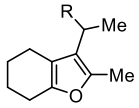
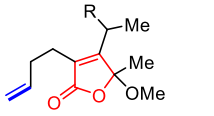
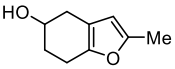
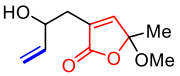
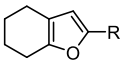
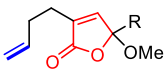
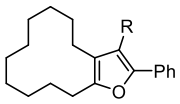
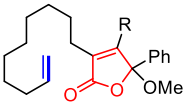
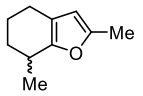
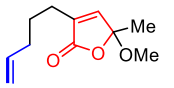
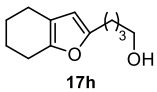
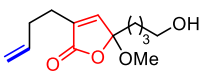
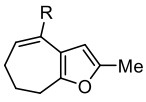
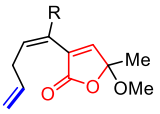
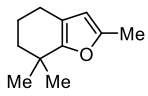
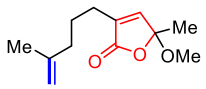
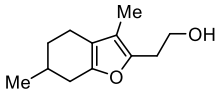
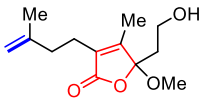
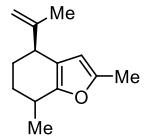
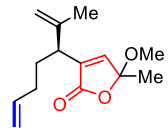
■ RESULTS AND DISCUSSION

We began our studies by carrying out experiments aimed at optimizing the reaction conditions for oxidative furan fragmentation. Using cyclohexane-fused furan **17a** as a model substrate, we evaluated various iron and copper salts, solvents, and temperatures (Table S1, Supporting Information) in reactions to form butenolide **19a**, which has a terminal olefin group. Photooxidation of **17a** with singlet oxygen in MeOH gave hydroperoxide **18a** in nearly quantitative yield, and optimization experiments revealed that subsequent hydroperoxide fragmentation in the presence of iron(II) lactate (1.2 equiv) and $Cu(OAc)_2$ (1.2 equiv) in 3:1 DMSO/H_2O at room temperature afforded desired product **19a** in 91% isolated yield. With the optimized conditions in hand, we set out to examine the substrate scope of the reaction (Table 1). Cycloalkane-fused furans with various ring sizes (**17b**–**e**, n = 2, 3, 7, and 10, respectively) delivered desired butenolides **19b**–**e** in 69–83% yields. In addition, furans with a C2-alkyl or -hydroxyalkyl substituent (**17f**–**h**) proved to be viable substrates, giving rise to **19f**–**h** in good yields. Menthofuran-derived substrates **17i**–**k**, which have a C2-hydroxyethyl or -aryl group, afforded products bearing a remote isopropenyl group (**19i**–**k**). Substrates with a C3-hydroxyalkyl, -amidylalkyl, -phenyl, or -allyl group (**17l**–**o**) were also compatible with the reaction conditions. However, because of the low solubility of furans **17n** and **17o** in MeOH, petroleum ether was used as a co-solvent. Gratifyingly, substrates with an endo- or exocyclic double bond or a free hydroxyl group on the cycloalkyl ring were also tolerated: **17p**–**r** and **17s** gave dienes **19p**–**r** and allylic alcohol **19s**, respectively.

It should be mentioned that in all the examples mentioned above, hydroperoxide fragmentation generated a primary alkyl radical, which in turn gave rise to a terminal olefin after being oxidized by $Cu(OAc)_2$. Accordingly, in the reactions of substrates **17t**–**v**, radical fragmentation of the corresponding hydroperoxides (**18t**–**v**) could conceivably generate secondary or tertiary alkyl radicals, which could lead to a mixture of

Table 1. Synthesis of butenolides with an appended remote olefin group[a]



furan	butenolide	furan	butenolide	furan	butenolide
 **17a**	 **19a**, 91%	 R = Ph, **17j** R = 4-OMe-C_6H_4, **17k**	 R = Ph, **19j**, 71%[b] R = 4-OMe-Ph, **19k**, 60%[b]	 **17r**	 **19r**, 51%[b]
 n = 2, **17b** n = 3, **17c** n = 7, **17d** n = 10, **17e**	 n = 2, **19b**, 83% n = 3, **19c**, 75% n = 7, **19d**, 76% n = 10, **19e**, 69%	 R = OH, **17l** R = NAcPh, **17m**	 R = OH, **19l**, 67% (d.r. 5:3) R = NAcPh, **19m**, 64%(d.r. 5:2)[b]	 **17s = (±)-11**	 **19s**, 55% (d.r. 1:1)
 R = ^{n}Bu, **17f** R = Bn, **17g**	 R = ^{n}Bu, **19f**, 81% R = Bn, **19g**, 85%	 R = Ph, **17n** R = allyl, **17o**	 R = Ph, **19n**, 73%[c] R = allyl, **19o**, 64%[c]	 **17t**	 **19t**, 69%[d] (T:I = 10:1)[e]
 **17h**	 **19h**, 73%	 R = Ph, **17p** R = ^{n}Bu, **17q**	 R = Ph, **19p**, 87% R = ^{n}Bu, **19q**, 75%	 **17u**	 **19u**, 60%[d] (T:I = 10:1)[e]
 **17i**	 **19i**, 67%			 **17v**	 **19v**, 60%[d] (d.r. 1:1)

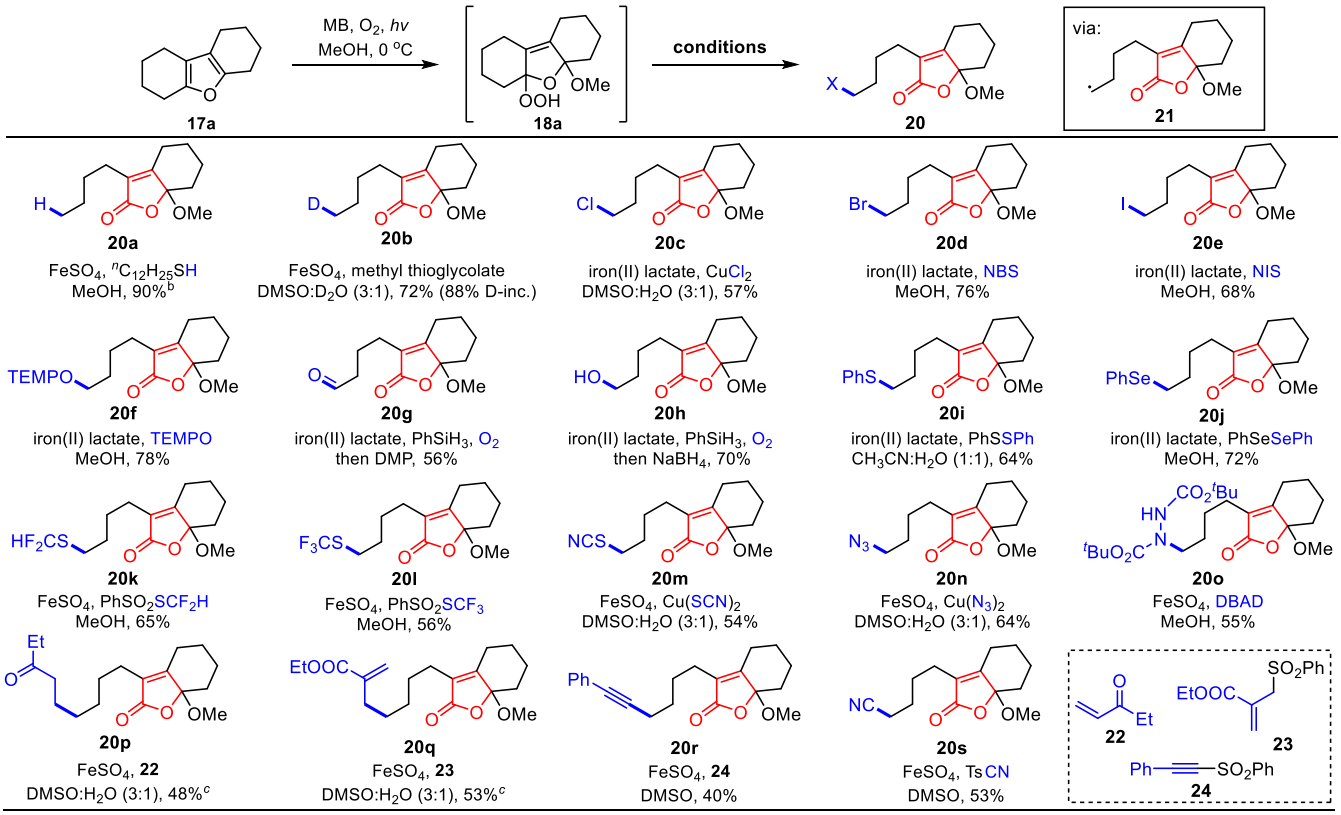
[a]Reaction conditions: **17** (0.1–1 mmol), MB (1 mol%), MeOH, O_2, *hv*, 0 °C, 30 min, then iron(II) lactate (1.2 equiv), $Cu(OAc)_2$ (1.2 equiv), DMSO/H_2O (3/1), rt, 0.5 h; Isolated yields are shown. [b]iron(II) lactate (1.5 equiv), $Cu(OAc)_2$ (1.5 equiv); [c]MeOH/petroleum ether (4/1) was used instead of MeOH; [d]Iron(II) lactate (1.2 equiv), TEMPO (1.5 equiv), MeOH, rt, 0.5 h, then DCB/^{i}Pr$_2$NH (10:1), 200 °C (MW), 5 h; [e]Ratios of terminal olefin to internal olefin. Abbreviations: MB = methylene blue, DMSO = dimethylsulfoxide, TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy, DCB = 1,2-dichlorobenzene.

terminal- and internal-olefin products after oxidation. Indeed, when these substrates were subjected to the standard conditions, a 2:1 to 4:1 mixture favoring the terminal-olefin products was obtained. Therefore, to increase the regioselectivity of these reactions, we used TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) instead of $Cu(OAc)_2$ to trap the alkyl radicals, which afforded butenolides with a remote TEMPO group. Subsequent removal of the TEMPO group[24] by means of microwave heating gave desired products **19t**–**v** in good yields with high regioselectivities. Notably, the use of this two-step procedure for dihydrocarvone-derived furan **17v** yielded terminal olefin **19v** as the sole product.

Compared with the species generated by ionic fragmentation, alkyl radical intermediates generated by radical fragmentation are more versatile, and they can be intercepted by a variety of functional groups, thereby providing rapid, divergent access to underexplored chemical space by means of radical functionalization. Having synthesized butenolides with an appended remote olefin group, we next turned our attention to trapping alkyl radical intermediate **21** (Table 2) with various radical coupling partners. This turned out to be nontrivial and necessitated considerable effort to optimize the reaction conditions. In general, either of two iron salts (iron(II) lactate or $FeSO_4$) and one of three solvent systems (MeOH, DMSO/H_2O or CH_3CN/H_2O) provided the best results. Specifically, after photo-oxidation of **17a**, addition of $FeSO_4$ and *n*-dodecyl mercaptan (a hydrogen atom donor) led to the isolation of reduced butenolide **20a** in 90% yield. Remarkably, this reaction was complete within 25s, as indicated by a color change (a photographic description is given on page S14 of Supporting Information). Gratifyingly, the use of 3:1 DMSO/D_2O[25] resulted in selective deuteration at the terminal position, giving **20b** in 72% yield with 88% deuterium incorporation. Given the documented importance of deuterium labeling in drug discovery,[26] this reaction can be expected to be useful in the search for drug candidates with deuterated butenolide motifs.

Halogenation reactions proceeded smoothly to give chloride **20c**, bromide **20d** and iodide **20e** in moderate to good yields. As expected, addition of TEMPO to the reaction mixture delivered **20f** in 79% yield. Interestingly, alkyl radical **21** could be intercepted by O_2 to generate a mixture of aldehyde **20g** and alcohol **20h** in the presence of $PhSiH_3$. The aldehyde or the alcohol could be obtained selectively by subjecting the fragmentation reaction mixture to Dess–Martin oxidation conditions or to $NaBH_4$ reduction conditions, respectively. In addition to C–O bond formation, C–S and C–Se bond formation could be accomplished by employing Ph_2S_2 and Ph_2Se_2 as radical acceptors to obtain **20i** and **20j**, respectively. We were pleased to find that we could introduce difluoromethylthio and trifluoromethylthio groups by trapping **21** with $PhSO_2SCF_2H$[27] and $PhSO_2SCF_3$;[28] this transformation can be expected to find numerous applications in medicinal chemistry owing to the change of molecular lipophilicity induced by introduction of these groups. Furthermore, butenolides with a thiocyano group or an azide group (**20m** and **20n**) were generated by reaction with freshly prepared $Cu(SCN)_2$ and $Cu(N_3)_2$.[29] Alternatively, **20o** could be

Table 2. Synthesis of butenolides with various appended remote functional groups[a]



[a]Reaction conditions: **17a** (0.1 or 0.3 mmol), MB (1 mol%), MeOH, O_2, *hv*, 0 °C, 30 min, then iron(II) salt (1.2–2.5 equiv), radical trapping reagent (1.2–3 equiv), solvent, rt, 0.5 h; Isolated yields are shown. [b]The reaction was completed in 25s as indicated by a color change. [c]$Cu(OAc)_2$ (1.5 equiv) and LiOAc (3 equiv) were added. Abbreviations: NBS = *N*-bromosuccinimide, NIS = *N*-iodosuccinimide, DMP = Dess-Martin periodinane, DBAD = di-*tert*-butyl azodicarboxylate, Ts = *p*-toluenesulfonyl.

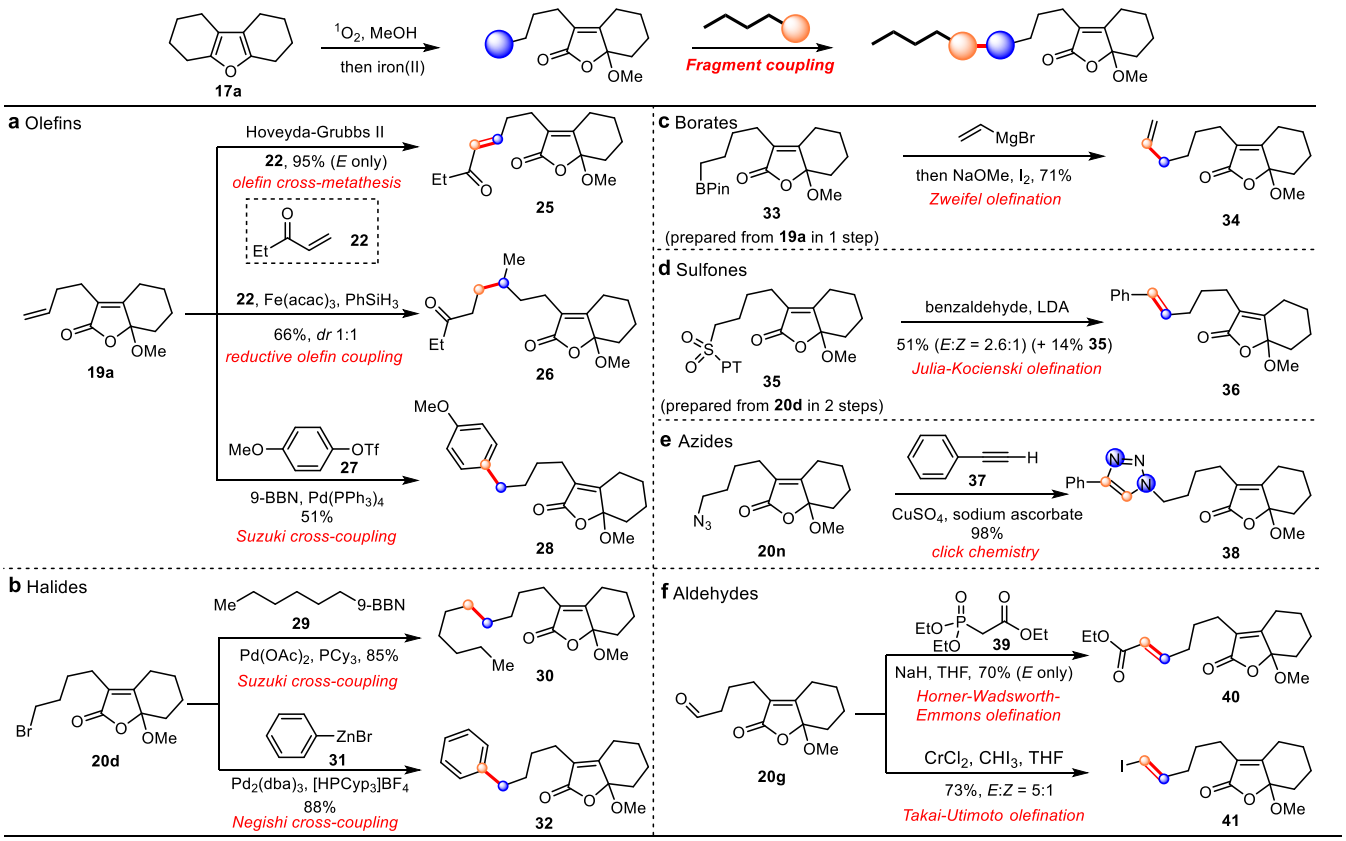
obtained via C–N bond formation when di-*tert*-butyl azodicarboxylate was used as the acceptor.

Next, we evaluated the use of this radical fragmentation–functionalization cascade for C–C bond formation, which was much more difficult than carbon–heteroatom bond formation. For example, a Giese-type reaction with ethyl vinyl ketone **22** as the radical acceptor gave only a low yield (ca. 20%) of desired product **20p**, along with major byproducts arising from oligomerization of the vinyl ketone. Extensive optimization studies revealed that using $Cu(OAc)_2$ and LiOAc as additives and employing a reverse addition procedure (adding hydroperoxide to the reaction mixture) improved the yield of **20p** to 48%. Butenolide **20q**, which has a remote acrylate ester group, was obtained in 53% yield by reaction with **23** under the same conditions. Finally, radical alkynylation and cyanation proceeded in moderate yields when sulfone **24** and tosyl cyanide (commercially available), respectively, were used to trap the radical intermediate.

This oxidative furan fragmentation reaction provides facile, modular access to functionalized butenolides with various appended remote functional groups, including olefins, halides, aldehydes and azides. To demonstrate its broad utility for organic synthesis, we were interested in connecting these butenolides with other partners via fragment-coupling reactions (Scheme 1), aiming to: 1) further expand the chemical space of accessible butenolides; and 2) facilitate its application in natural product synthesis. Olefins are among the most versatile functional groups in organic chemistry, and we explored some of the numerous methods available for their diverse transformations. For example, an olefin cross-metathesis reaction[30] between butenolide **19a** and **22** in the presence of Hoveyda–Grubbs II catalyst furnished desired product (*E*)-**25** in 95% yield (Scheme 1a). Alternatively, **19a** could react with **22** under Baran's reductive olefin-coupling conditions[31] to give rise to **26** in 66% yield. A B-alkyl Suzuki–Miyaura cross-coupling reaction,[32] a classic tool for total synthesis, between **19a** and **27** afforded hydroarylated product **28** in 51% yield. We also carried out some transformations of bromo-substituted butenolide **22d**. Although bromides are well-known to undergo S_N2 substitution, pioneering work by Fu and co-workers demonstrated that they are also ideal electrophiles for a range of transition-metal-catalyzed cross-coupling reactions to form C–C bonds.[33] We found that palladium-catalyzed Suzuki[34] and Negishi[35] cross-coupling reactions of **22d** under Fu's conditions led to excellent yields of desired cross-coupling products **30** and **32**, respectively (Scheme 1b).

Organoboron compounds, which can be easily accessed by means of olefin hydroboration, are versatile substrates for a wide array of transformations, including Suzuki coupling reactions, Zweifel olefination reactions,[36] lithiation-borylation chemistry[37] and conjunctive cross-coupling reactions.[38] For instance, borate **33**, which was synthesized via iridium-catalyzed hydroboration[39] of **19a**, smoothly underwent Zweifel olefination to give two-carbon-extended olefin **34** in 71% yield (Scheme 1c). Sulfones are also valuable functionalities that can be used for Ramberg–Bäcklund reactions, Julia olefination reactions, and radical cross-coupling reactions.[40] We found that a Julia–Kocienski olefination reaction between 1-phenyl-1*H*-

Scheme 1. Fragment-coupling reactions of functionalized butenolides[a]



[a]Yields of isolated products were shown. Abbreviations: acac = acetylacetonyl, 9-BBN = 9-borabicyclo[3.3.1]nonane, Cy = cyclohexyl, dba = dibenzylideneacetone, Cyp = cyclopentyl, PT = 1-phenyl-1*H*-tetrazol-5-yl, LDA = lithium diisopropylamide.

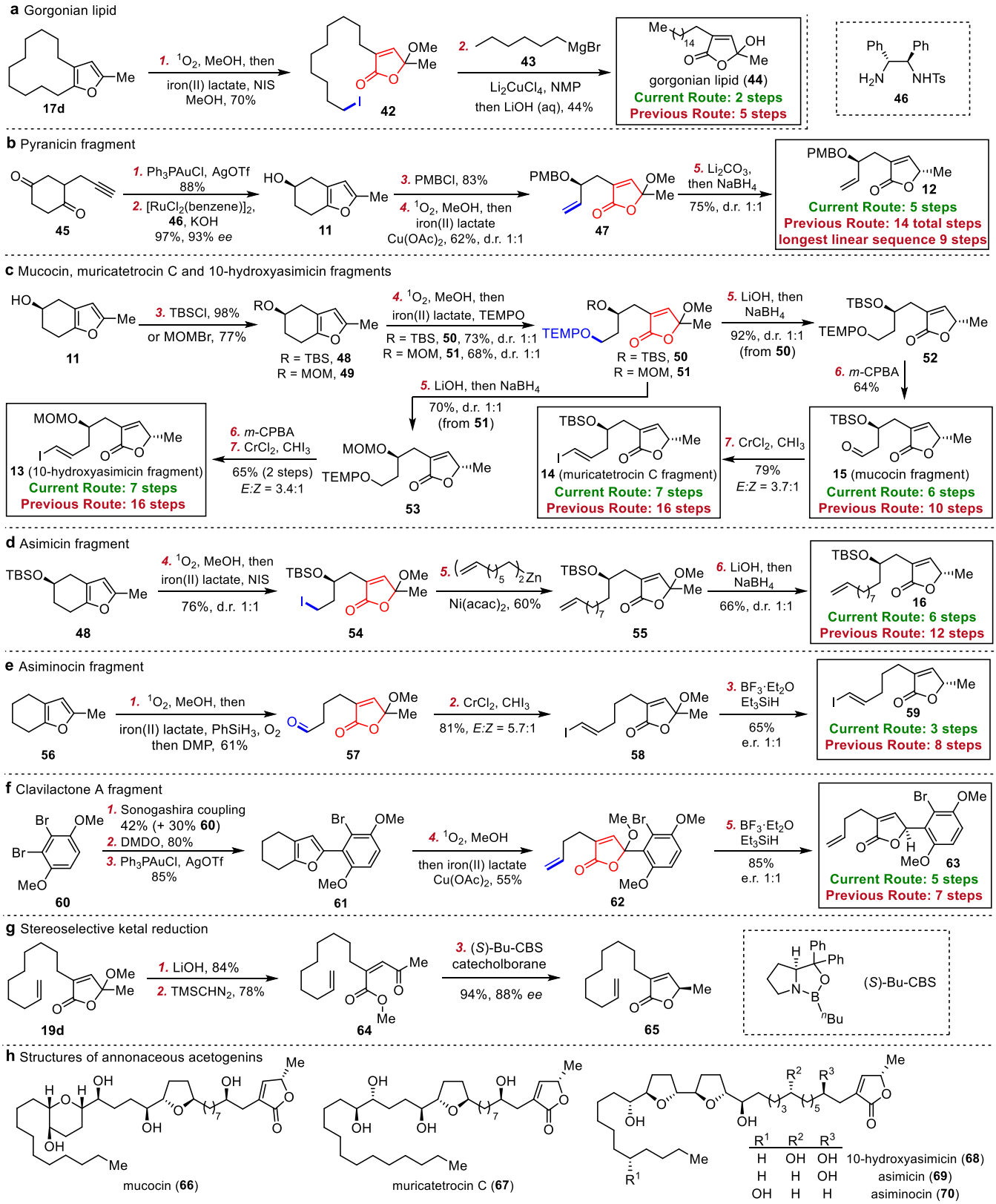
tetrazol-5-yl sulfone **35** (prepared from **20d** in two steps) and benzaldehyde delivered olefin **36** in 51% yield (Scheme 1d). Azides are widely used not only for generating amines but also for aza-Wittig reactions and click chemistry.[41] Treatment of azide **20n** with phenylacetylene in the presence of catalytic $CuSO_4$ gave rise to 1,2,3-triazole **38** in excellent yield (Scheme 1e).[42] Lastly, because aldehydes are known to be useful for generating C–C bonds via nucleophilic addition reactions, olefination reactions, and so on, we subjected aldehyde **20g** to Horner–Wadsworth–Emmons olefination conditions and Takai–Utimoto olefination conditions and obtained good yields of desired unsaturated ester **40** and vinyl iodide **41**, respectively (Scheme 1f).

To further illustrate the power of this new transformation, we present eight examples in which its use simplified the synthesis of a natural product (**44**) or known building blocks for natural products (**12**–**16**, **59**, **63**) (Scheme 2; detailed comparisons with prior work are provided in Figure S1 of Supporting Information). The first synthetic target was gorgonian lipid **44**, which belongs to a class of anti-inflammatory fatty acid γ-hydroxybutenolides.[43] The reported five-step procedure for its synthesis involves alkylation of a lithiated silyloxyfuran as the key step. In contrast, our synthesis commenced with an oxidative fragmentation reaction of known furan **17d** (Scheme 2a). Addition of *N*-iodosuccinimide to the reaction mixture afforded butenolide **42**, which has a terminal iodide. Copper-catalyzed alkyl–alkyl cross-coupling[44] followed by *in situ* hydrolysis furnished **44** in 44% yield, thus completing its synthesis in only two steps from **17d**.

Next, we turned our attention to the annonaceous acetogenins, a large family of polyketide natural products found in Annonaceae species, with more than 400 family members having been isolated so far.[45] Structurally, these compounds are characterized by an unbranched 32- or 34-carbon chain bearing some oxygenated functional groups (e.g., hydroxyl, ketone, epoxide, tetrahydrofuran, tetrahydropyran) and a terminal γ-butenolide. Annonaceous acetogenins exhibit a wide array of biological activities, including antiparasitic, pesticidal, antifeedant, antimicrobial, immunosuppressive and antitumor activities, and have therefore attracted substantial attention from the chemistry community.[46] Although considerable progress has been made in the synthesis of the butenolide fragments, the reported routes generally suffer from being long and inefficient, and they lack modularity. For example, structurally similar butenolides **12**–**16** (Scheme 2b–d), which are known synthetic intermediates of acetogenins pyranicin (**4**),[3f] 10-hydroxyasimicin (**68**),[47] muricatetrocin C (**67**),[6a] mucocin (**66**)[48] and asimicin (**69**),[7a] respectively, were previously prepared in 10–16 steps from four distinct starting materials via four completely different sequences (see Supporting Information for details). In sharp contrast, the protocol we have described herein enabled concise, divergent and modular syntheses of all five of these intermediates from a single starting material (furan **11**) and more importantly, via a single strategy: oxidative furan fragmentation (as shown in Tables 1 and 2) followed by fragment coupling (as shown in Scheme 1).

Our syntheses started with the preparation of chiral furan **11** via cyclization of known alkynyl ketone **45**, followed by Noyori reduction (93% *ee*) (Scheme 2b). After protection of the

Scheme 2. Synthetic simplifications enabled by oxidative furan fragmentation[a]



[a]Yields of isolated products were shown. Abbreviations: NMP = *N*-methyl-2-pyrrolidinone, PMB = *para*-methoxybenzyl, TBS = *tert*-butyldimethylsilyl, MOM = methoxymethyl, *m*-CPBA = *meta*-chloroperbenzoic acid, DMDO = dimethyl dioxirane, CBS = Corey-Bakshi-Shibata reagent.

hydroxyl group with a PMB group, reaction under our standard conditions delivered desired olefinic butenolide **47** in 62% yield. Basic hydrolysis and subsequent reduction produced **12** in 75% yield. Alternatively, protection of the hydroxyl group of **11** with

a TBS group, followed by oxidative furan fragmentation (iron(II)lactate, TEMPO) and basic reduction, delivered a diastereomeric mixture of butenolide **52** (Scheme 2c). Subsequent removal of TEMPO by *m*-CPBA afforded desired aldehyde **15**, which was subjected to Takai olefination to give vinyl iodide **14** in 79% yield. If the hydroxyl group of **11** was protected with a MOM group instead of a TBS group, vinyl iodide **13** could be easily obtained via the same sequence. Moreover, butenolide **16**, which has a long terminal-olefin side chain, could be accessed from furan **48** in three steps via oxidative fragmentation (iron(II) lactate, *N*-iodosuccinimide), nickel-catalyzed alkyl–alkyl cross-coupling (under Knochel's conditions)[49] and subsequent reduction (Scheme 2d). In a similar manner, vinyl iodide **59**, a known synthetic intermediate of asiminocin **70**[5a], could be prepared via oxidative fragmentation, Takai olefination and reduction in three steps from known furan **56** (Scheme 2e). Notably, the previously reported approach to **59** required eight steps.

Finally, we prepared compound **63,** an intermediate in the synthesis of clavilactone A (**3**), which belongs to a family of natural products with antifungal and antibacterial activities, as well as potent inhibitory activities against Ret/ptc1 and epidermal growth factor receptor tyrosine kinases (Scheme 2f).[2d] The previous approach to **63** required seven steps, with a relay ring-closing metathesis reaction as the key step. Our synthetic sequence commenced with the preparation of C2-aryl furan **61** by means of Sonogashira coupling, epoxidation and Au-catalyzed cyclization. Furan **61** was subjected to the standard fragmentation condition and then ketal reduction, which furnished **63** in five steps from commercially available **60**.

It should be pointed out that one unsolved problem with the above-described syntheses is the nonstereoselective reduction of the ketal moiety, which led to a diastereomeric mixture of the butenolide product. To provide a proof-of-principle solution to this problem, we used ketal **19d** as a model substrate and converted it to γ-ketoester **64** in two steps. Gratifyingly, subsequent Corey-Bakshi-Shibata reduction[50] of **64** gave rise to butenolide **65** in good yield with good enantioselectivity (Scheme 2g).

■ CONCLUSIONS

In summary, we have developed a practical and efficient strategy to access underexplored functionalized butenolides from readily accessible furans via photo-oxidation with singlet oxygen and subsequent iron(II)-mediated radical fragmentation. The key aspects of this strategy are as follows: 1) it features mild reaction conditions, inexpensive reagents and operational simplicity; 2) it allows for precise and divergent installation of remote functional groups (such as olefins, halides, aldehydes, alcohols and azides) at a position distal to the butenolide moiety; 3) it has a broad substrate scope and generates diverse products; and 4) it has great potential to simplify retrosynthetic analysis. We have illustrated that readily available furans, which have traditionally been employed as surrogates for a number of four-carbon building blocks, can undergo selective fragmentation to deliver valuable building blocks that are otherwise difficult or tedious to prepare. Moreover, we have shown that a variety of butenolides with diverse structural features can be expediently synthesized by means of a modular strategy involving oxidative furan fragmentation and subsequent cross-coupling reactions.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, NMR spectra for all new compounds (PDF)

AUTHOR INFORMATION

Corresponding Author

* guijh@sioc.ac.cn

Author Contributions

†These authors (J. B. and H. T.) contributed equally to this work.

Notes

The authors declare no competing financial interest.

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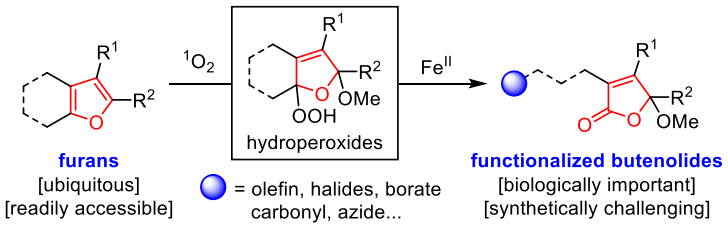
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