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Visible-Light-Promoted Vinylation of Tetrahydrofuran with Alkynes through Direct C−H Bond Functionalization

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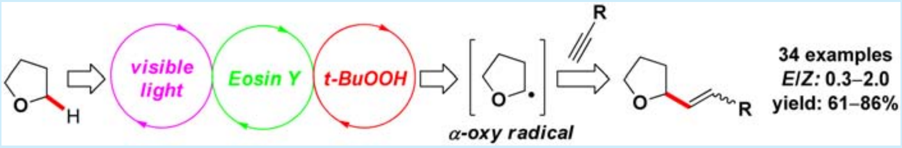
Supporting Information



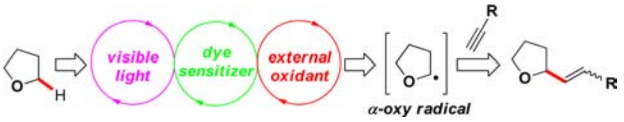
ABSTRACT: Mild and direct C−H bond functionalizations and vinylations of tetrahydrofuran with alkynes have been accomplished through visible light photocatalysis, yielding a range of vinyl tetrahydrofurans under the synergistic actions of organic dye-type photocatalyst eosin Y, *tert*-butyl hydroperoxide (*t*-BuOOH), and a 45 W household lightbulb. A significant kinetic isotope effect (KIE) was recorded, which helps shed light on the mechanistic course.

Direct functionalization of the inert sp^3 C−H bond has become an increasingly significant subject in modern synthetic organic chemistry.[1] Progress in this field, when coupled with reaction economics, operational simplicity, and environmental friendliness, demands further achievements in uncovering new protocols that can function under truly mild conditions. In recent years, the practices in visible light photocatalysis[2] have actively responded to this critical challenge due to abundant solar energy, convenient reaction devices, and novel mechanistic paradigms.[3] Not surprisingly, as most organic compounds cannot directly absorb visible light, the design and implementation of such processes must therefore require the participation of an appropriate photocatalyst. Within this context, organic dye-type photocatalysts, for example, commercially readily available eosin Y, seem to represent likely superior alternatives to their transition-metal-derived counterparts, such as ruthenium− and iridium−pyridyl complexes, in terms of the criteria mentioned above. These dye photosensitizers therefore attracted our particular attention.[4]

In this paper, we report the preparation of a range of vinyl tetrahydrofurans that serve as recurring structural motifs found in various biological, pharmaceutical, and natural products.[5] Although these structures have been accessed with known literature disclosures, notably UV light[6−11] or metal-mediated[12−16] unifications of alkenes or alkynes with tetrahydrofuran under medium-to-high reaction temperatures or microwave stimulations, a merge of radical chemistry with organic dye substance sensitized visible light photocatalysis as uncovered herein clearly emerged as the arguably simplest alternative.

Our design concept, as shown in Scheme 1, envisioned that a hydrogen abstraction event might be initiated on tetrahydrofuran via synergistic interactions of visible light stimulation, organic dye sensitization, and external oxidation, thereby yielding a relatively long-lived α-oxy radical species.[17] Subsequent radical addition to an alkyne partner would accomplish formal C−H to C−C bond conversion and furnish vinyl-functionalized tetrahydrofurans. Within this design scenario the choice of an external oxidant is pivotal since it ideally could function not only as a hydrogen acceptor but also as a radical precursor. Alkyl hydroperoxide substances seem to be viable candidates fitting with this purpose, a representative structure being *t*-BuOOH. The challenge in experimental realization of this proposal clearly lies in identifying reaction conditions that are conducive for simultaneously supporting operations of all of the above-mentioned events.

Scheme 1. Visible-Light-Promoted C−H Functionalization Strategy to Vinyl Tetrahydrofurans



With 1-chloro-4-ethynylbenzene (**1**) as the model substrate and a 45 W household bulb as the visible light source, we initially discovered that the desired vinyl tetrahydrofuran **2** was produced in 36% yield with an E/Z ratio of 1:1 (entry 1, Table 1) in a mixed solvent of MeCN and tetrahydrofuran (1:1 volume ratio with concentration $c = 0.05$ M) at room temperature with organic dye eosin Y (0.05 equiv) and *t*-BuOOH (4.00 equiv, 5.5 M in decane) under an argon balloon atmosphere for 36 h. When a basic Cs_2CO_3 (entry 2), Lewis acidic $Mg(ClO_4)_2$ (entry 3), or a relatively neutral salt $HCOONH_4$ (entry 4) was employed as the additive, the reaction was found to be completely inhibited. The yield of **2** was improved to 52% when the protic acid HCOOH was added into the reaction (entry 5). As a comparison, CH_3COOH was shown to be much less effective (24% yield,

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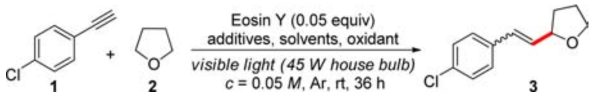
Table 1. Identification of the Optimal Reaction Conditions



entry	catalyst (0.05 equiv)	additives[c] (2.00 equiv)	solvents (v/v = 1:1)	oxidant[d] (4.00 equiv)	yield[e] (%)
1	eosin Y		MeCN/THF	*t*-BuOOH	36
2	eosin Y	Cs_2CO_3	MeCN/THF	*t*-BuOOH	trace
3	eosin Y	$MgClO_4$	MeCN/THF	*t*-BuOOH	11
4	eosin Y	NH_4COOH	MeCN/THF	*t*-BuOOH	trace
5	eosin Y	HCOOH	MeCN/THF	*t*-BuOOH	52
6	eosin Y	CH_3COOH	MeCN/THF	*t*-BuOOH	24
7	eosin Y	4 Å MS	MeCN/THF	*t*-BuOOH	45
8	**eosin Y**	**4 Å MS + HCOOH**	**MeCN/THF**	***t*-BuOOH**	**86**
9	eosin Y	4 Å MS + HCOOH	DMF/THF	*t*-BuOOH	7
10	eosin Y	4 Å MS + HCOOH	NMP/THF	*t*-BuOOH	10
11	eosin Y	4 Å MS + HCOOH	toluene/THF	*t*-BuOOH	32
12	eosin Y	4 Å MS + HCOOH	CH_2Cl_2/THF	*t*-BuOOH	43
13	eosin Y	4 Å MS + HCOOH	Et_2O/THF	*t*-BuOOH	46
14	eosin Y	4 Å MS + HCOOH	DCE/THF	*t*-BuOOH	49
15	eosin Y	4 Å MS + HCOOH	MeOH/THF	*t*-BuOOH	73
16	eosin Y	4 Å MS + HCOOH	THF	*t*-BuOOH	9
17	eosin Y	4 Å MS + HCOOH	MeCN/THF	$(t\text{-BuO})_2$	34
18	eosin Y	4 Å MS + HCOOH	MeCN/THF	H_2O_2	12
19	eosin Y	4 Å MS + HCOOH	MeCN/THF	Bz_2O_2	trace
20[a]	eosin Y	4 Å MS + HCOOH	MeCN/THF	*t*-BuOOH	trace
21	$Ru(bpy)_3Cl_2$	4 Å MS + HCOOH	MeCN/THF	*t*-BuOOH	0
22	$Ir(ppy)_3$	4 Å MS + HCOOH	MeCN/THF	*t*-BuOOH	21
23		4 Å MS + HCOOH	MeCN/THF	*t*-BuOOH	0
24[b]	eosin Y	4 Å MS + HCOOH	MeCN/THF	*t*-BuOOH	0
25	eosin Y	4 Å MS + HCOOH	MeCN/THF		0

[a] *t*-BuOOH 70% in water. [b] No light. [c] 4 Å MS loading is 2 wt %. [d] *t*-BuOOH 5.5 M in decane. [e] ^{1}H NMR yield of *E*/*Z* isomers.

entry 6). Interestingly, the addition of 4 Å molecular sieves was found to be advantageous to the reaction (45% yield, entry 7). When a combination of HCOOH and 4 Å molecular sieves was employed, a respectable 86% yield of **2** was recorded (entry 8). Furthermore, the solvent effect was shown to be fairly significant during this transformation. When dimethylformamide (DMF), *N*-methylpyrrolidone (NMP), toluene, CH_2Cl_2, Et_2O, or 1,2-dichloroethane (DCE) was used in place of MeCN in the mixed solvent under otherwise comparable conditions, the product was furnished in lower yields under otherwise identical reaction conditions (7−49% in entries 9−14). The yield of **2** was 73% when MeOH was mixed with THF as the solvent (entry 15) and was merely 9% when THF was used alone (entry 16). The choice of an oxidant was also confirmed to be critical, as the use of $(t\text{-BuO})_2$, H_2O_2, Bz_2O_2, or even aqueous *t*-BuOOH (in 70% water) led to significant reductions or complete inhibitions in reactivities (entries 17−20). Furthermore, attempts using $Ru(bpy)_3Cl_2$ or $Ir(ppy)_3$ as an alternative photocatalyst were again found to be detrimental, leading to either no product or merely 21% yield, respectively (entries 21 and 22). Finally, control experiments conducted under the absence of either a photocatalyst, visible light, or oxidant (entries 23−25) unambiguously pointed to complete inhibition of the reactivity. Collectively, these screening results established the optimal reaction conditions to be the following: 0.05 equiv of eosin Y, 2 wt % of activated powdered 4 Å molecular sieves, 4.00 equiv of *t*-BuOOH, and 2.00 equiv of HCOOH in a 1:1 mixed solvent of MeCN and THF under a balloon-argon atmosphere at room temperature. Although we began the explorations with a somewhat defined mechanistic plan, it should be acknowledged herein that it was only through extensive synergies between conceptual design and experimental serendipity that we eventually arrived at the identified protocol.

A series of structurally variable aromatic terminal alkynes **4** were next subjected to the above-defined optimal reaction conditions, and the results are compiled in Scheme 2. The reactivity appears to be quite general, yielding smoothly in each case the corresponding vinyl tetrahydrofuran product **5** in moderate to good isolated yields (63−86%) and with *E*/*Z* isomeric ratios ranging from 0.3 to 2.0. Neither electron-withdrawing or -donating properties nor the substitution patterns (*ortho*, *meta*, *para*) on the aryl rings (i.e., **5a−p**) seemed to have posed a significant influence on the reaction efficiency and *E*/*Z* ratios. An aryl ring with more conjugation (**5v**) or a heteroatom (**5w**) is a comparably competent substrate. This visible light photocatalytic C−H functionalization method clearly tolerates a broad spectrum of alkyne partners.

The protocol was further extended to propiolate-type internal alkynes structured as **6**. The results are summarized in Scheme 3. Again a range of substrates were readily implementable, and the observed reactivities are virtually irrespective of aryl ring substitutions, as their corresponding products **7** were all consistently furnished in 61−86% isolated yields and 0.5−1.3 double-bond *E*/*Z* selectivities.

The synthetic application of this new visible light-enabled photocatalytic C−H functionalization technology was further manifested through staightforward structural editings on some pharmaceutically meaningful substances. For example, diosge-

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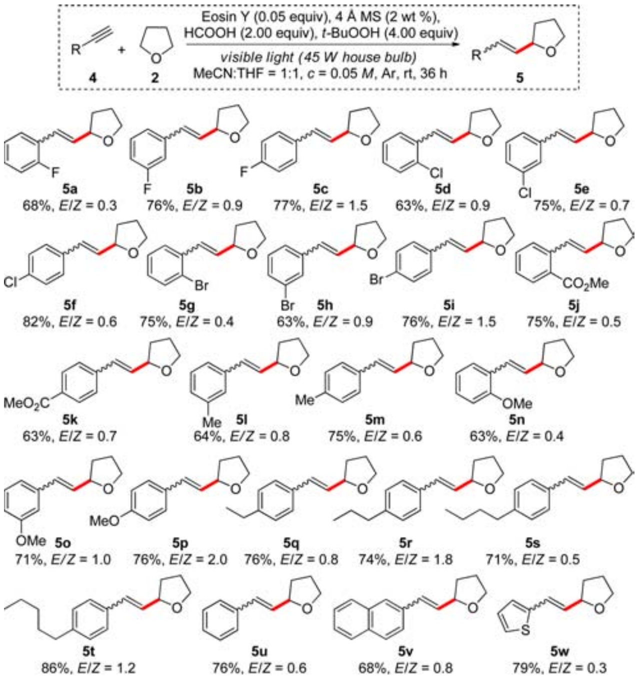
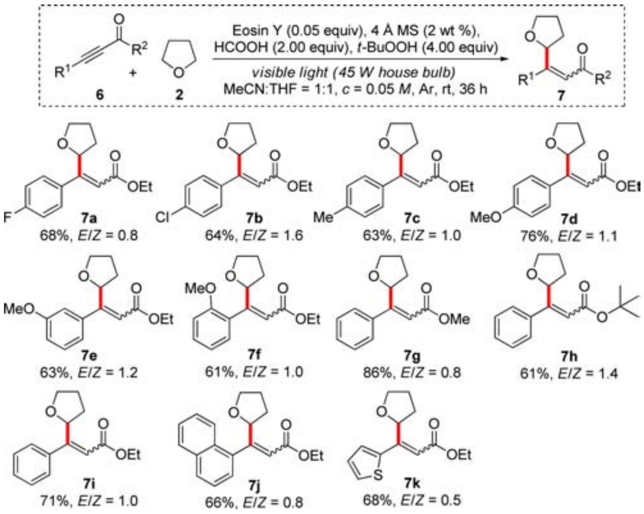
Scheme 2. Reactivity Screenings on Terminal Alkynes

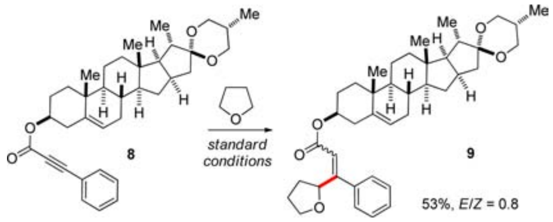


Scheme 3. Reactivity Screenings on Propiolate Derivates



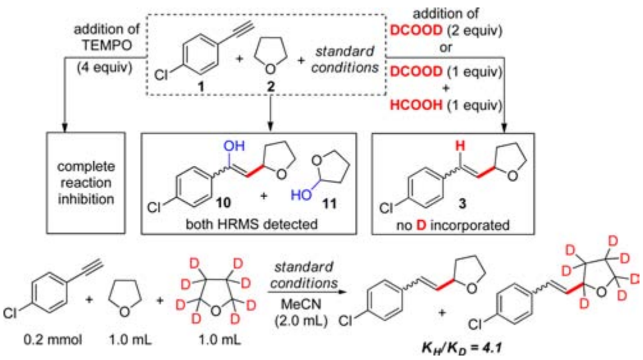
nin, a steroid sapogenin that is often employed in the preparations of pregnenolone, cortisone, progesterone, and other related steroid products, serves as an illustrative system.[18] As shown in Scheme 4, under the standard conditions, diosgenin derivate **8** was smoothly converted to **9** in 53% isolated yield and 0.8 *E*/*Z* isomeric ratio. This representative structral elaboration helps demonstrate the methodology's value in providing rapid access into a focused library of a range of structural analogs bearing newly installed functional groups.

Scheme 4. Synthetic Elaboration on a Diosgenin Derivative



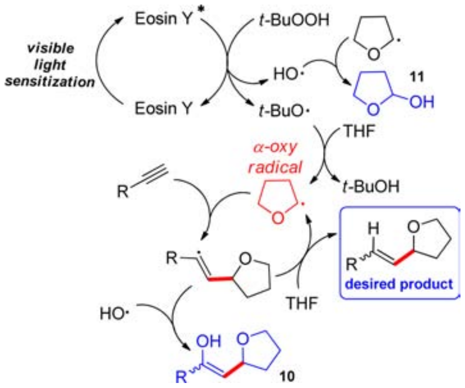
Mechnistic experiments were next conducted to shed light on the potential reaction pathways. As summarized in Scheme 5, again using vinylation of tetrahydrofuran with alkyne **1** as the model reaction, the addition of a widely known radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) led to complete inhibition of the intended reactivity, implying strongly involvement of radical intermediates. Structures **10** and **11**, both readily conceivable from a shared α-oxy radical on THF, were in fact both detected by high-resolution mass spectrum (HRMS) analysis of the reactio mixture. Furthermore, addition of either 2 equiv of deuterated formic acid (DCOOD) or a 1:1 mixtrue of DCOOD and HCOOH to the reaction did not lead to any deuterium-containing products, thus practically ruling out the possibility that formic acid might act as the hydrogen source. Finally, a significant kinetic isotope effect (K_H/K_D = 4.1) was recorded in the process, providing direct evidence that C−H bond cleavage event might have constituted a rate-determining step.

Scheme 5. Experimental Probes on Reaction Mechanism



The observed reactivities coupled with the above investigations collectively point to a plausible mechanistic network shown in Scheme 6. The sequence would be initiated through catalytic visible light sensitization of eosin Y which, upon returning to its ground state, transfers energy to *t*-BuOOH and in turn induces scission of its weak O−O bond to give rise to simultaneously two radical species: hydroxyl radical HO$^\bullet$ and *tert*-butoxy radical *t*-BuO$^\bullet$. Abstraction of hydrogen from tetrahydrofuran would thus generate the key α-oxy radical,

Scheme 6. Proposed Mechanistic Network



which may then engage on three competing pathways, i.e., addition to 1-chloro-4-ethynylbenzene to produce the desired vinylated tetrahydrofuran product, or recombine with hydroxyl radical at different stages to furnish structures **10** and **11**, respectively. The beneficial roles of $HCOOH$ and 4 Å molecular sieves in the context are likely attributable to their scavenging of **11** and water that could have been formed when the hydroxyl radical abstracts hydrogen from tetrahydrofuran.

In summary, motivated by an initial design concept of exploring direct vinylation of tetrahydrofuran through combining the power of C—H functionalization and visible light photocatalysis, we have established a straightforward and versatile protocol that employed abundantly available alkynes as vinyl-function donors and operated under exceptionally mild reaction conditions. Of central importance to this discovery is likely the identification of mutual and synergistic parameters that allows for reliable generation of the tetrahydrofuran α-oxy radical intermediate. With this robust reactive species in hand, many further synthetic utilities could well be conceived on a wider platform of visible light photocatalysis, and new developments will thus be continuously pursued and reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectral data for all new compounds. This material is available freeof charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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