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Visible-Light-Induced Cyclization/Aromatization of 2-Vinyloxy Arylalkynes: Synthesis of Thio-Substituted Dibenzofuran Derivatives

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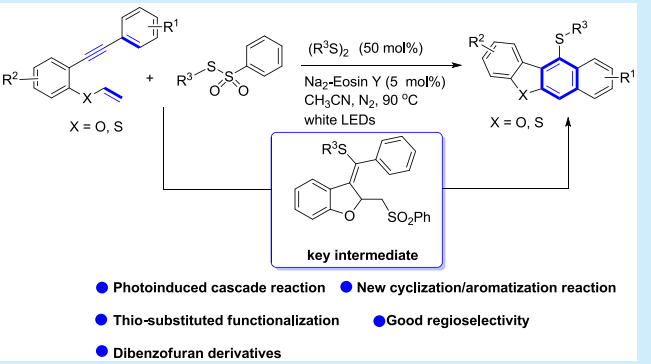
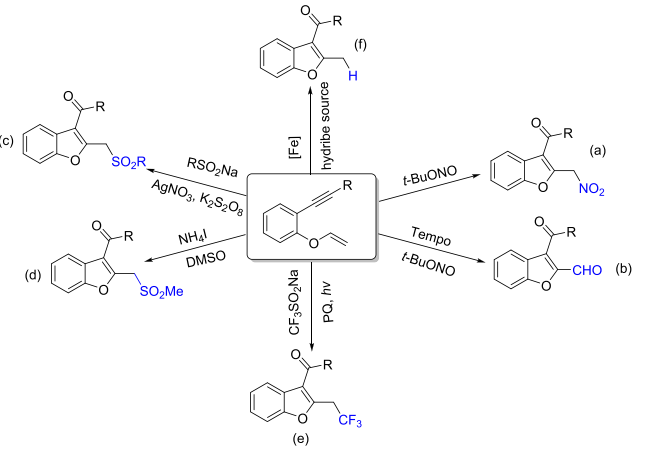
ABSTRACT: A visible-light-induced cascade reaction of 2-vinyloxy arylalkynes with thiosulfonates was developed and provided unexpected thio-substituted dibenzofuran derivatives in moderate yields. Mechanistic studies revealed the thiosulfonylation product of 2-vinyloxy arylalkyne was the key intermediate, and the additive disulfide played the role of hydrogen abstraction in the aromatization process to offer the desired product. This reaction presents a new reaction mode for the construction of polycyclic oxygen heterocycles.



The dibenzofuran core widely exists in natural products[1] and pharmaceutical molecules,[2] and presents diverse biological activities; thus, their synthetic methods attract considerable attention. Traditional methods for the construction of dibenzofurans are via the oxidation/cyclization of 2-arylphenol.[3] The transition-metal-catalyzed intramolecular cyclization of diphenyl ethers bearing a leaving group in the *ortho* position such as nitro[4] and carboxyl[5] has also been applied as a promising strategy. However, relying heavily on transition metals, low functional group tolerance, and harsh conditions in above-reported methods were not negligible.

Recently, the radical cascade reaction of 1,6-enynes has emerged as an attractive approach for the synthesis of heterocycle derivatives.[6] Li's group reported Tempo or nitro radical induced cyclization of 2-vinyloxy arylalkyne which provided two different types of benzofurans (Scheme 1a and 1b).[7] Jiang[8] and Sun's[9] groups achieved the construction of the sulfonylated benzofuran skeleton by using sodium sulfinate and DMSO as the source of sulfonyl in a similar radical pathway, respectively (Scheme 1c and 1d). CF_3SO_2Na was employed as the precursor of the trifluoromethyl radical, generating trifluoromethylated benzofurans (Scheme 1e).[10] Xia's group developed iron-mediated reductive radical cascade cyclization to give 3-acylbenzofurans (Scheme 1f).[11] Despite the remarkable advances that have been made for the assembly of carbonylated benzofuran in the above-mentioned approaches, the development of an efficient method to introduce diverse groups into the benzofuran skeleton is still desirable. Furthermore, the construction of polycyclic benzofurans through the radical cascade reaction of 1,6-enynes has not been reported.

Scheme 1. Reported Radical Cascade Reaction of 2-Vinyloxy Arylalkyne



Meanwhile, substantial efforts have been devoted to explore the facile synthesis of thio-substituted heterocycles because of their potential pharmacological activity.[12] Undoubtedly, cascade reaction is a highly valuable approach for the assembly of thio-substituted heterocycles in terms of atom economy and

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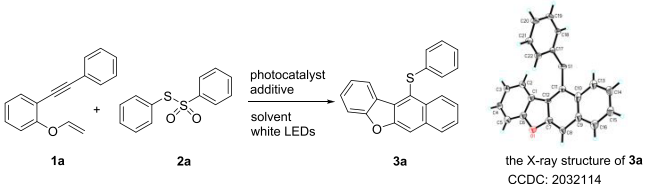
operability. The sulfonium ion attacked the C≡C triple bonds, followed by the electrophilic cascade cyclization of 2-alkynylphenol derivatives to give 3-sulfenylbenzofuran.[13] The domino reaction of enoic acid with disulfide[14] or thiol[15] offered thio-substituted lactones as product. Pan and co-workers developed electrocatalytic radical [3 + 2] cycloaddition of vinyl azides, thiophenols, and pyridines to provide sulfide imidazo[1,2-*a*]pyridines.[16] Sahoo and co-workers reported a thio radical induced cyclization of yne-ynamides to synthesize 4-thioaryl-pyrroles.[17] To our knowledge, the reports of preparing thio-substituted polycyclic heterocycles via radical cascade reaction were rare. In this context and in continuation of our interest in photocatalysis,[18] we describe a visible-light-induced cyclization/aromatization of 2-vinyloxy arylalkynes with thiosulfonates to give thio-substituted dibenzofuran derivatives. This method presents a new reaction mode for the construction of polycyclic oxygen heterocycles.

Initially, the reaction of **1a** (1-(phenylethynyl)-2-(vinyloxy)-benzene) and **2a** (*S*-phenyl benzenesulfonothioate) under the catalysis of 5 mol % Na_2-Eosin Y in CH_3CN irradiated by 30 W white LEDs at 80 °C under a nitrogen atmosphere was studied. Delightly, unexpected product **3a** was obtained in 55% yield which was confirmed by X-ray crystal structure analysis. Then, the reaction conditions were further screened, and the results are shown in Table 1. Without the addition of a photocatalyst, only a trace amount of **3a** was observed (Table 1, entry 2), indicating that the photocatalyst was necessary. Other photocatalysts were screened, and Na_2-Eosin Y was proven to be the best catalyst (Table 1, entries 3−9). Solvents such as DCE, DMF, toluene, EtOAc, and 1,4-dioxane were unsuitable, resulting in the significant decrease in product yield (see Supporting Information). The higher temperature 90 °C was favorable for this transformation, giving **3a** in 60% yield (Table 1, entry 10). However, **3a** was only obtained in 56% yield when the reaction was carried out at 100 °C (Table 1, entry 11). 1,2-Diphenyldisulfane was used as an additive, and the yield of **3a** was improved to 70% (Table 1, entries 12 and 13). When the reaction was conducted under an air atmosphere, only a trace amount of **3a** was detected, and almost all of **1a** was decomposed (Table 1, entry 14). When this reaction was carried out in the dark, no **3a** was observed and most of **1a** was recovered (Table 1, entry 15). Therefore, the optimal conditions for the synthesis of **3a** were as follows: 5 mol % Na_2-Eosin Y and 50 mol % 1,2-diphenyldisulfane in CH_3CN under the irradiation of 30 W white LEDs at 90 °C under a nitrogen atmosphere with stirring for 12 h.

With the optimized conditions in hand, the substrate scope of 2-vinyloxyphenylacetylene **1** and sulfonothioate **2** was investigated, and the results are summarized in Scheme 2.

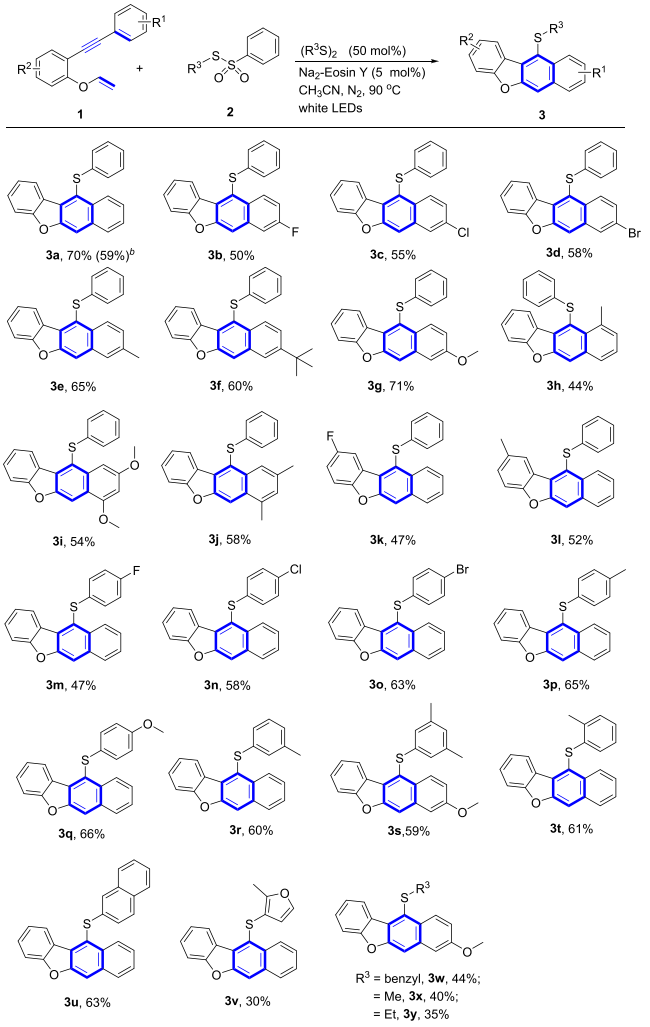
Table 1. Condition Optimization[a]



Entry	Photocatalyst	Additive	Temp (°C)	Yield (%)
1	Na_2-Eosin Y	no	80	55
2	no	no	80	trace
3	Eosin Y	no	80	31
4	Mes-AcrPh$^+BF_4$	no	80	trace
5	Rhodamine B	no	80	50
6	Bengal Rose	no	80	43
7	$Ru(bpy)_3Cl_2$	no	80	trace
8	$Ir(ppy)_3$	no	80	20
9	$Ir(bpy)(ppy)_2PF_6$	no	80	25
10	Na_2-Eosin Y	no	90	60
11	Na_2-Eosin Y	no	100	56
12[b]	Na_2-Eosin Y	$(PhS)_2$	90	65
13[c]	Na_2-Eosin Y	$(PhS)_2$	90	70
14[c,d]	Na_2-Eosin Y	$(PhS)_2$	90	trace
15[c,e]	Na_2-Eosin Y	$(PhS)_2$	90	0

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), and photocatalyst (5 mol %) in solvent (2.0 mL) under the irradiation of 30 W white LEDs at 80 °C under a nitrogen atmosphere were stirred for 12 h; data in parentheses are the yields of isolated products. [b]$(PhS)_2$ (20 mol %) was used. [c]$(PhS)_2$ (50 mol %) was used. [d]The reaction was performed under an air atmosphere. [e]The reaction was carried out in the dark.

Scheme 2. Scope of 2-Vinyloxyphenylacetylene and Sulfonothioate[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), Na_2-Eosin Y (5 mol %) and disulfide (50 mol %) in CH_3CN (2.0 mL) under the irradiation of 30 W white LEDs at 90 °C at nitrogen atmosphere was stirred for 12 h. [b]**1a** was used in mmol scale.

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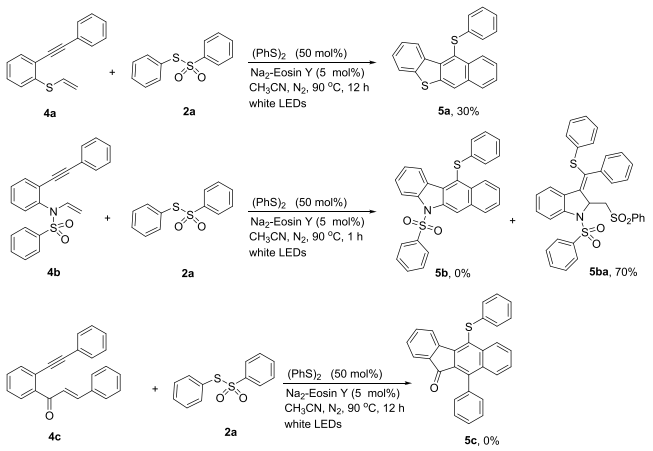
Aryl alkyne bearing an electron-withdrawing group such as 4-F, 4-Cl, and 4-Br in the R^1 position resulted in the slight decrease in the product yield, affording the desired products **3b**−**3d** in 50−58% yield. The introduction of electron-donating substituents such as 4-Me, 4-*t*-Bu, and 4-MeO gave **3e**−**3g** in 60−71% yield. The 2-Me group was also employed, however, affording **3h** in 44% yield, indicating that steric hindrance had a significant impact on this reaction. 3,5-Dimethoxyl and 3,5-dimethyl were tolerant, providing **3i** and **3j** in 54% and 58% yields, respectively. The vinyloxybenzene ring was assembled with 4-F or 4-Me, giving **3k** and **3l** in 47% and 52% yields, respectively. In the moiety of sulfonothioate, the benzene ring bearing an electron-withdrawing group (4-F, 4-Cl and 4-Br) and electron-donating group (4-Me and 4-MeO) reacted smoothly, providing the corresponding product **3m**−**3q** in 47−66% yield. The 3-Me, 3,5-dimethyl, and 2-Me group exerted negligible effect on this transformation, affording **3r**−**3t** in 59−61% yield. *S*-(Naphthalen-2-yl) benzenesulfonothioate was suitable, generating **3u** in 63% yield. 2-Methylfuran-3-yl was applied and provided **3v** in 30% yield. It is noteworthy that alkyl thio-substituted sulfonothioates were tolerant, providing **3w**−**3y** in 35−44% yield. Finally, the reaction of **1a** and **2a** was performed in 1 mmol scale, and **3a** was obtained 59% yield.

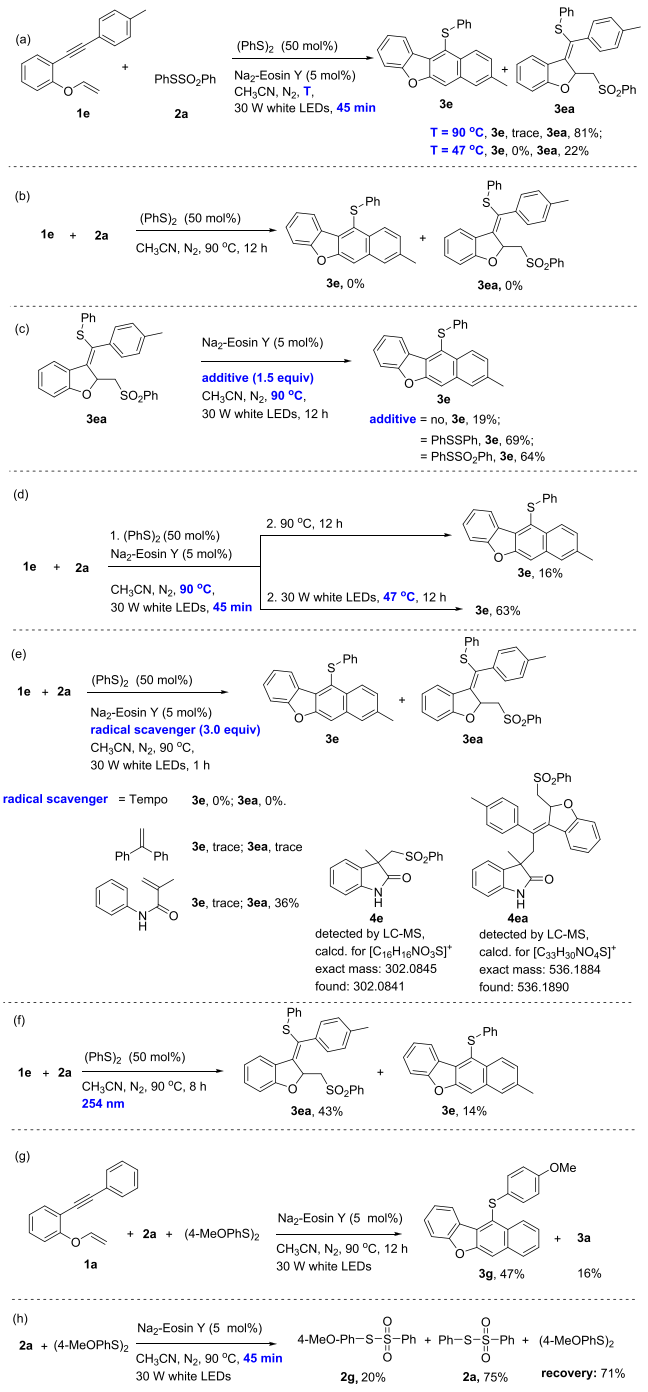
The vinylthio and vinylamino benzene were considered next (Scheme 3). Unfortunately, **4a** only gave **5a** in 30% yield, and most of **4a** was decomposed. **4b** was applied, but no **5b** was observed, giving difunctional product **5ba** in 70% yield. When the reaction time was prolonged to 12 h, **5ba** decomposed. *α*,*β*-Unsaturated ketone **4c** was also applied, but no **5c** was observed and most of **4c** was recovered.

Scheme 3. Other Types of Substrates



To probe the possible mechanism, several controlled experiments were conducted. First, the reaction of **1e** and **2a** was carried out under the standard conditions for 45 min. Yet, only a trace amount of **3e** was observed, and intermediate **3ea** was isolated in 81% yield; however, **3ea** was seriously inhibited when the reaction was conducted at lower temperature or without light irradiation, indicating that light irradiation and high temperature were necessary for the formation of **3ea** (Scheme 4a and 4b). Then, **3ea** was proven as the key intermediate, and the transformation of **3ea** to **3e** was promoted by the sulfur radical through the contrast experiments of additives (Scheme 4c). On the other hand, the one-pot two-step operation indicated that light irradiation was more impactful than high temperature in the transformation of **3ea** to **3e** (Scheme 4d). The reaction of **1e** and **2a** was seriously inhibited by radical scavengers. Furthermore, the radical adducts **4e** and **4ea** were detected by LC-MS (Scheme 4e). When the reaction of **1e** and **2a** was conducted under irradiation of 254 nm light, **3ea** and **3e** were obtained in 43% and 14% yield, respectively, meaning a radical pathway induced by energy transfer was preferred (Scheme 4f). 1,2-Bis(4-methoxyphenyl)disulfane was used as the additive instead of 1,2-diphenyldisulfane in the reaction of **1a** and **2a**, which generated **3a** and **3g** in 16% and 47% yield (Scheme 4g). Then, the 1:1 mixture of **2a** and 1,2-bis(4-methoxyphenyl)disulfane was conducted under standard conditions for 45 min, only

Scheme 4. Controlled Experiments



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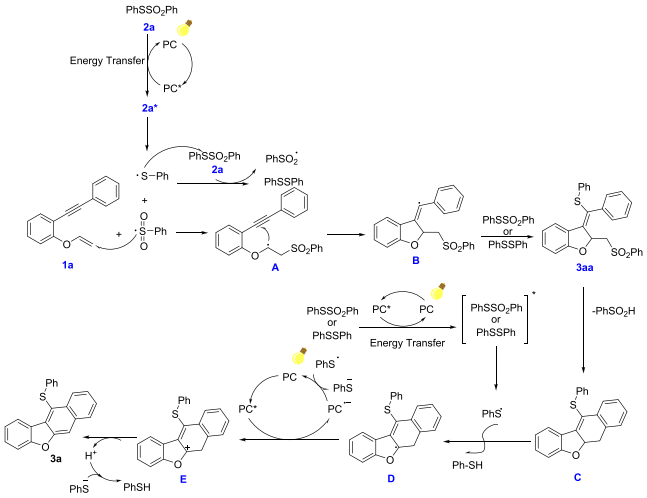
giving **2g** in 20% yield with recovered **2a** and 1,2-bis(4-methoxyphenyl)disulfane in 75% and 71% yield. The crossing experiment indicated the thio group in the final compound mainly came from disulfide.

On the basis of the above controlled experiments and the reported literature, a possible mechanism was proposed as described in Scheme 5. First, the photocatalyst Na_2-Eosin Y

Scheme 5. Proposed Pathway for the Synthesis of Thio-Substituted Dibenzofuran



reached an excited state under the irradiation of white LEDs which underwent energy transfer to **2a** and offered an excited **2a***.[19] The excited **2a*** underwent homolytic cleavage of the SO_2–S bond, offering a sulfur radical and sulfonyl radical. Addition of the sulfonyl radical to **1a** gave radical intermediate **A**; simultaneously, the sulfur radical attacked **2a** with the generation of 1,2-diphenyldisulfane and the sulfonyl radical. The radical cyclization of **A** furnished intermediate **B** which attacked 1,2-diphenyldisulfane or **2a** and gave **3aa**. The intramolecular cyclization of **3aa** provided intermediate **C** which abstracted a hydrogen atom by the sulfur radical with the generation of radical **D**.[20] **D** was oxidized into cation **E** by the excited photocatalyst along with the formation of the photocatalyst radical anion. The photocatalyst radical anion transformed an electron to the sulfur radical, giving the sulfur anion and finishing the photocatalyst recycle. Finally, **E** underwent deprotonation to provide product **3a**.

To understand the photophysical properties of the thio-substituted dibenzofurans, the steady-state absorption and photoluminescence (PL) measurements for the **3g**, **3i**, **3q**, **3s**, **3u**, **3w**, and **3y** in DCE were studied (Figure 1). The fluorescence spectra of the above-mentioned compounds show emission maxima in the 382–442 nm range.

In summary, we have developed a visible-light-induced cascade reaction of thiosulfonates with 2-vinyloxy arylalkynes which offered thio-substituted dibenzofuran derivatives in moderate yields. The mechanistic study supported the thiosulfonylation product of 2-vinyloxy arylalkyne as the key intermediate, and the following cyclization/aromatization gave the final product. And the additive disulfide was found to play a role in hydrogen abstraction in the aromatization process. This cascade reaction features metal-free conditions, a novel product, and good regioselectivity and also presents a new reaction mode for the construction of polycyclic oxygen

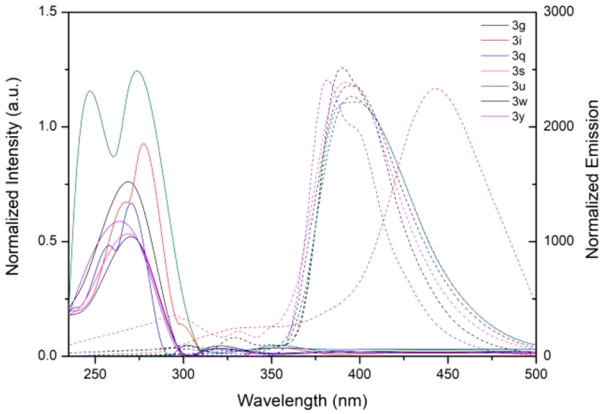


Figure 1. UV–vis absorption (solid line) and normalized fluorescence spectra (dashed line) of thio-substituted dibenzofuran in DCE (1×10^{-5} M).

heterocycles. Steady-state absorption and photoluminescence measurements for the obtained thio-substituted dibenzofurans were also examined.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03876.

Experimental procedure, characterization data, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 2032114 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.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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Notes

The authors declare no competing financial interest.

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