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Copper-Catalyzed Vicinal Chloro-thiolation of Alkynes with Sulfonyl Chlorides

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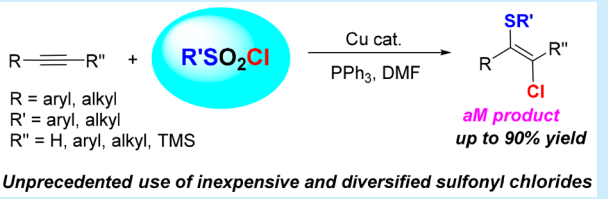
Supporting Information

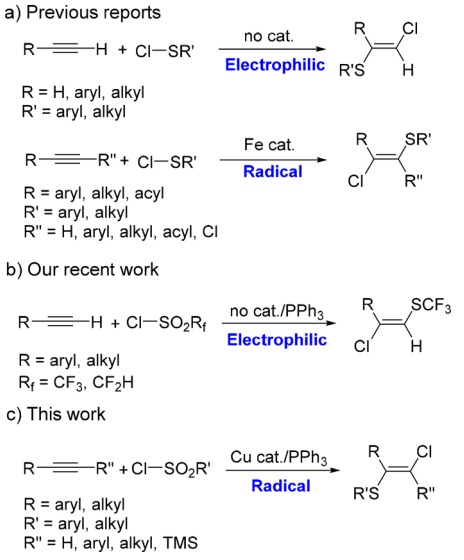
ABSTRACT: A copper-catalyzed vicinal chloro-thiolation of alkynes with inexpensive and diversified sulfonyl chlorides RSO_2Cl (R = aryl, alkyl) has been developed. This practical and scalable reaction could be used for the construction of a number of unexplored bioactive chlorothiolated alkenes. Internal alkynes could also undergo the chloro-thiolation to provide tetrasubstituted alkynes. Preliminary mechanistic investigations revealed a plausible radical process involving a sulfur-centered radical intermediate via copper-mediated homolysis of the S−Cl bond.



Vinyl sulfides are versatile building blocks[1] and convenient intermediates in organic[2] and materials chemistry,[3] and many natural products and biologically active compounds also contain vinyl sulfide moieties.[4] Among them, β-haloalkenyl sulfides are of considerable significance since the halogen moieties can be converted into complex and diverse alkenyl sulfides.

Typically, β-haloalkenyl sulfides are synthesized by the addition of sulfenyl halides to alkynes (Scheme 1).[5] Decades ago, Modena reported the electrophilic chloro-thiolation of terminal alkynes by sulfenyl chloride.[5a] Benati realized the bromo-thiolation by sulfenyl bromine in 1993.[5b] Recently, Nishihara's group has reported the regio- and stereoselective addition of sulfenyl chlorides to alkynes by palladium[5c] and iron[5d] catalysts. Nevertheless, the issues associated with these strategies should be addressed. On the one hand, most of the sulfenyl halides are really unstable compounds and the formation of sulfenyl halides requires toxic and hard-to-handle chlorine (or bromine) or foul-smelling thiols.[6] On the other hand, although the mechanism for the formation of *anti*-Markovnikov products by the addition of sulfur halides to alkynes has been well studied,[7] the limited variety of sulfenyl halides greatly reduces the attractiveness of this reaction. Therefore, the quest for an easy-to-handle and more practical synthetic approach to an *anti*-Markovnikov adduct is still ongoing.

Scheme 1. Chloro-thiolation of Alkynes



Sulfonyl chlorides, as a commercially available cheap material, have been widely used as protecting groups; sulfenylating,[8] sulfonylating,[9] and chloro-sulfonylating agents;[10] or leaving groups in C−C bond formation.[11] It was reported that benzenesulfonyl chloride can generate phenylsulfenyl chloride under reducing conditions.[8a,12] However, no report exists on the use of sulfonyl chlorides as a chloro-thiolation reagent except for one case reported by our group using fluoroalkylsulfonyl chlorides for electrophilic chloro-fluoroalkylthiolation of alkynes.[13] With our continuous interest in exploring the construction of C−S bonds with "RSO_2X" (R = Na, Cl) reagents under reductive conditions,[14] we envisioned that the chloro-thiolation of alkynes can be achieved by general sulfonyl chlorides, which are inexpensive and diversified and could be applied to the construction of various organosulfur compounds.

To verify the feasibility of our proposed assumption, we started the investigation by selecting the reaction of *p*-tolyacetylene **1a** with benzenesulfonyl chloride **2a** as the model reaction (Table 1). Not surprisingly, the above-mentioned electrophilic type chloro-fluoroalkylthiolation can-

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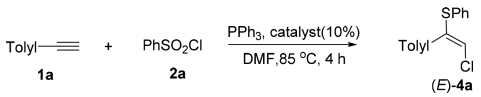
Table 1. Optimization of Reaction Conditions[a]

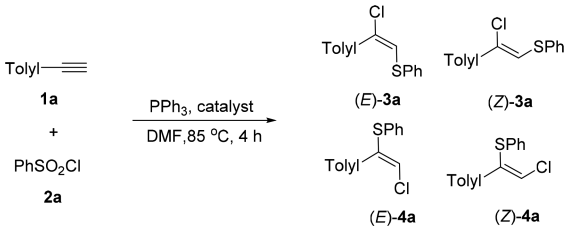


entry	cat. (10%)	solvent	yield (%)[b,c]
1	–	DMF	2
2	$PdCl_2$	DMF	0
3	$Pd(PPh_3)_2Cl_2$	DMF	1
4	$Ni(OAc)_2$	DMF	21
5	$FeCl_2$	DMF	27
6	CuCl	DMF	85
7	CuBr	DMF	53
8	CuI	DMF	25
9	Cu	DMF	19
10	$CuCl_2$	DMF	31
11	$Cu(OAc)_2$	DMF	28
12	CuCl	DMSO	2
13	CuCl	THF	40
14	CuCl	1,4-dioxane	21
15	CuCl	chlorobenzene	26
16	CuCl	DMF	73[d]

[a]Reaction conditions: *p*-tolyacetylene (0.25 mmol), benzenesulfonyl chloride (0.5 mmol), PPh_3 (1 mmol), CuCl (0.025 mmol), DMF (0.5 mL), 85 °C for 4 h. [b]Yield determined by ^1H NMR using 2-phenylacetophenone as an internal standard on crude products. [c]Small amounts of (*E*)-**3a** and (*Z*)-**4a** were present as minor products; see SI. [d]Yield was obtained at 10 mmol scale.

not be extend to the chloro-thiolation by general sulfonyl chlorides. Indeed, when the fluoroalkylsulfonyl chloride was replaced by benzenesulfonyl chloride, only a trace amount of the chloro-thiolated product was observed (Table 1, entry 1). Since transition-metal-catalyzed chloro-sulfonylation and chloro-thiolation of alkynes has been known to provide the corresponding adducts with high regio- and stereoselectivities, a series of transition-metal catalysts were then examined. It was found that although palladium catalysts are known to catalyze the chloro-thiolation of alkynes,[5c] they proved to be ineffective catalysts in this reaction. (Table 1, entries 2−3). Ni and Fe have a certain catalytic effect (Table 1, entries 4−5), but copper salts are much better, facilitating the novel chloro-thiolation to yield (*E*)-**4a** preferentially over three other regio- and stereoisomers (Scheme 2). Metallic copper, Cu(I) and

Scheme 2. Addition of Benzenesulfenyl Chloride to Phenylacetylene

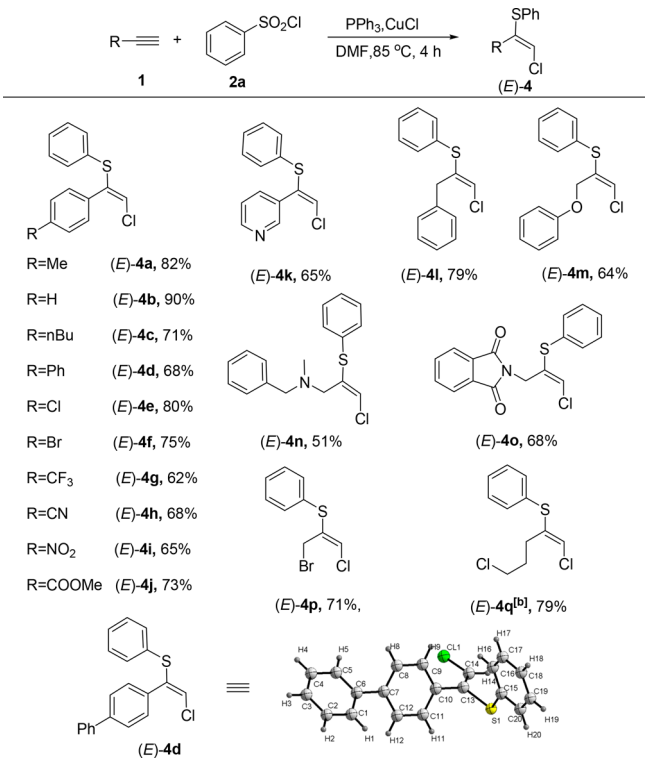


Cu(II) salts were all effective to catalyze the chloro-thiolation. Among them, CuCl was shown to be the optimal catalyst, and the desired product (*E*)-**4a** was obtained in 85% yield in the presence of CuCl (10 mol %) (Table 1, entries 6). The choice of the solvent was found to be crucial. DMF proved to be the best solvent, whereas DMSO, THF, 1,4-dioxane, and chlorobenzene were inferior (Table 1, entries 12−15).[15]

Notably, when the reaction was performed in MeOH or AcOH, (*E*)-**3a** will be the major product in about 20% yields.[15] The reaction temperature and time were also optimized; the best option was to react at 85 °C for 4 h. A lower temperature resulted in poor yield of the product, and a higher temperature will decrease the stereoselectivity; the proportion of (*Z*)-**4a** will greatly increase in the product.[15] The reaction could be conducted on a 10 mmol scale, and 1.9 g (*E*)-**4a** (73%) was isolated (Table 1, entry 16). To the best of our knowledge, this is the first example of using readily available and diversified sulfonyl chlorides for chloro-thiolation without an additional chlorine source.

With the optimized conditions in hand, a series of terminal alkynes were performed in the reaction to investigate the scope and generality of the chloro-thiolation (Scheme 3). Terminal

Scheme 3. Chloro-thiolation of Terminal Alkynes[a]



[a]Reaction conditions: alkyne (0.25 mmol), $PhSO_2Cl$ (0.5 mmol), PPh_3 (1 mmol), CuCl (0.025 mmol), in DMF (0.5 mL) at 85 °C for 4 h; isolated yields. [b]Obtained as a mixture of stereoisomers in an 88:12 ratio.

arylethynes that contain electron-donating (methyl, *n*-butyl, and phenyl) and -withdrawing (halogen, trifluoromethy, cyano, nitro, and ester) groups reacted with **2a** to give the corresponding products (*E*)-**4a**−**4j** in moderate to excellent yields. The precise configuration was unambiguously confirmed by single-crystal X-ray analysis of (*E*)-**4d**. Pyridine acetylene was also applied in the reaction successfully to afford (*E*)-**4k** with satisfactory results. Similarly, reaction of propargylbenzene, propargylphenylether, paragyline, and *N*-prop-2-ynylphthalimide occurred to give products (*E*)-**4l**−**4o** in 51−79% yields. It was worth mentioning that products (*E*)-**4p**, (*E*)-**4q** were generated from the reaction of aliphatic terminal alkynes.

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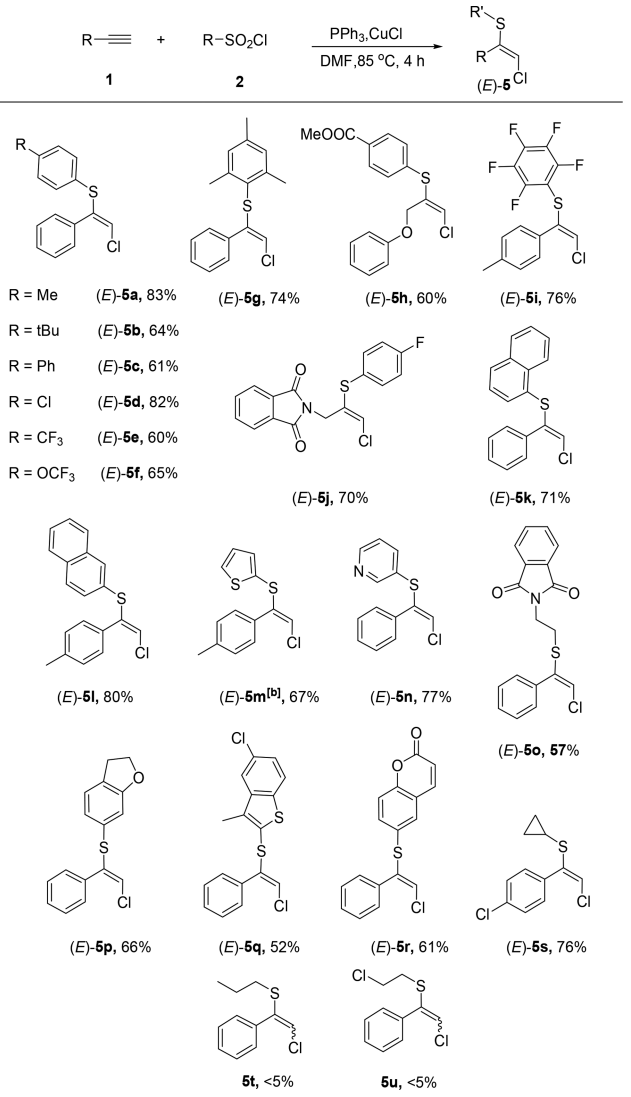
Next, the scope of sulfonyl chloride was tested (Scheme 4). Benzenesulfonyl chloride also exhibited a certain tolerance for

Scheme 4. Chloro-thiolation of Sulfonyl Chlorides[a]

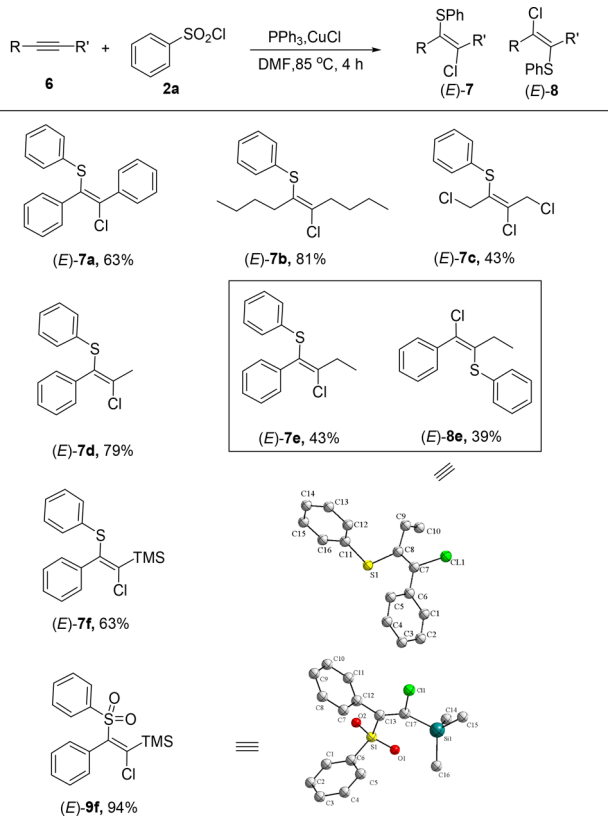


[a]Reaction conditions: alkyne (0.25 mmol), RSO_2Cl (0.5 mmol), PPh_3 (1 mmol), CuCl (0.025 mmol), in DMF (0.5 mL) at 85 °C for 4 h; isolated yields. [b]Obtained as a mixture of stereoisomers in an 85:15 ratio.

the substituents. Reactions of a variety of benzenesulfonyl chlorides with electron-donating and -withdrawing groups occurred in good yields under standard condition ((*E*)-**5a**−**5j**). Naphthalene-1-sulfonyl chloride and naphthalene-2- sulfonyl chloride afforded the products (*E*)-**5k** and (*E*)-**5l** in 71% and 80% yields, respectively. Heterocyclic sulfonyl chlorides (thiophene-2-sulfonyl chloride, pyridine-3-sulfonyl chloride, and 2-phthalimidoethanesulfonyl chloride) smoothly reacted with alkynes and gave the desired product in 57%−77% yields. Notably, complex sulfonyl chlorides were also applied in this reaction, and potentially bioactive compounds (*E*)-**5p**−**5r** were obtained in reasonable yields.[16] In addition to aromatic sulfonyl chloride, cyclopropanesulfonyl chloride could also afford the desired products (*E*)-**5s** in good yield. However, other aliphatic sulfonyl chlorides such as 1-butanesulfonyl chloride or 2-chloroethanesulfonyl chloride only gave a small amount (<5%) of chloro-thiolated product (**5t**, **5u**). The remaining alkyne does not participate in the reaction; 1-chloropropane/1,2-dichloroethane and Ph_3PS were obtained as the major product.[17]

To further broaden the chloro-thiolate scope, internal alkenes were also examined (Scheme 5). Symmetrical internal

Scheme 5. Chloro-thiolation of Internal Alkynes[a]



[a]Reaction conditions: alkyne (0.25 mmol), $PhSO_2Cl$ (0.5 mmol), PPh_3 (1 mmol), CuCl (0.025 mmol), in DMF (0.5 mL) at 85 °C for 4 h; isolated yields.

alkynes produced the corresponding product in moderate to high yields ((*E*)-**7a**−**c**). Unsymmetric internal alkynes methyl-(phenyl)et-hyne and trimethyl(phenylethynyl)silane were also converted to the chloro-thiolated products (*E*)-**7d** and (*E*)-**7f** in 79% and 63% yields. Notably, in the case of ethylphenyl-acetylene, the reaction gave a mixture of almost 1:1 (*E*)-**7e** and (*E*)-**8e**. The stereochemistry of (*E*)-**7f** was determined by single-crystal X-ray analysis of (*E*)-**9f**, which were prepared by oxidation of (*E*)-**7f**.

To investigate the reaction mechanism, several control experiments were designed and conducted (Scheme 6). (*E*)-(2- Chloro-1-(phenylsulfonyl)vinyl) benzene **10** was not observed when the reaction was carried out in the absence of triphenylphosphane (Scheme 6a), which indicated that **4a** was not the reduction product of **10**. Addition of sulfenyl chloride **11a** to phenylacetylene yielded 25% (*E*)-**4a** in 4 h. In sharp contrast, when the reaction was performed under the catalysis of copper(I) chloride, the yield increased to 94% under the same conditions (Scheme 6b). It can be concluded that sulfenyl chloride could directly add to alkynes and copper(I) chloride has a significant catalytic effect in this reaction. The reaction was inhibited in the presence of

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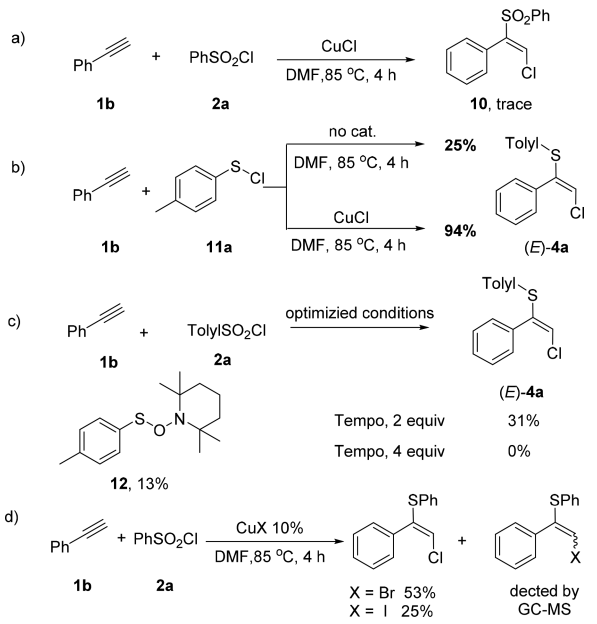
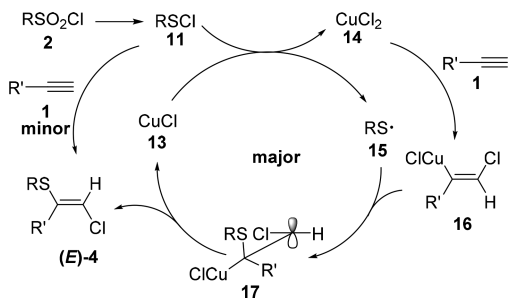
Scheme 6. Control Experiment



TEMPO (4 equiv), and a 13% yield of **12** was obtained (Scheme 6c), suggesting the chloro-thiolation may proceed by a radical process. Furthermore, when CuBr/CuI was used as the catalyst, the corresponding bromo-thiolated/iodo-thiolated product was also detected by GC-MS (Scheme 6d), indicating that the copper catalyst may participate in the reaction in more ways, except for the radical initiation.

Based on these observations, a plausible mechanism to rationalize this reaction is illustrated in Scheme 7. First,

Scheme 7. Proposed Reaction Mechanism



reduction of sulfonyl chloride initiated by triphenylphosphine leads to sulfenyl chloride **11**, which then undergoes the copper- mediated homolysis of the S−Cl bond to yield the corresponding sulfenyl radical **15**. Next, an alkyne and *in situ* generated $CuCl_2$ formed a $\pi-\delta$ coordination bond and finally produced intermediate **16**;[18] this step may control the excellent regioselectivity of the reaction. The high *anti*-Markovnikov selectivity of the reaction can be rationalized by comparing the energy of *anti*-Markovnikov and Markovnikov intermediates, which were calculated on the basis of DFT (density functional theory) studies with two methods (PRBE, BLYP) (Figure 1). Then, sulfur-centered radical **15** added to **16** to form the alkyl radical **17**. Finally, radical **17** was converted to the *trans* addition product (*E*)-**4**, which is more stable, and regenerates CuCl. Besides the major path, there might be a minor path in which the direct electrophilic addition of **11** and an alkyne affords (*E*)-**4**.

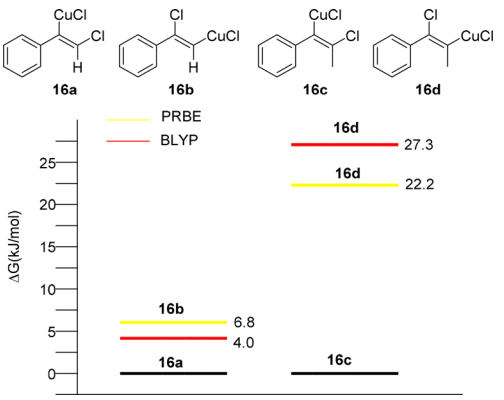


Figure 1. Calculated values of some possible intermediates' energy based on DFT.

With respect to the regioselectivity in the chloro-thiolation of internal alkynes, the generated intermediate **16** of the unsymmetric internal alkynes has also been considered (Figure 1). As the *anti*-Markovnikov intermediates have a lower energy (Figure 1, **16d**), (*E*)-**7d** and (*E*)-**7f** were obtained with high regioselectivity. On the other hand, the formation of (*E*)-**8e** can be explained as the result of the Markovnikov intermediate.

In summary, we have developed a new method achieving chloro-thiolation of alkynes with sulfonyl chloride by employing a copper catalyst. Several mechanistic studies revealed a possible free radical reaction pathway. Compared to previously reported methods, the present method is more practical and suitable for large-scale chloro-thiolation reactions, since sulfonyl chlorides have a much wider variety and are cheaper and easy-to-handle. Considering the good regio- and stereoselectivity as well as high functional group tolerance, this method is expected to find application in the synthesis of bioactive complex alkenyl sulfides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02929.

Experimental procedures, characterization data, and ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR for products (PDF)

Accession Codes

CCDC 1832473−1832474 and 1865063 contain 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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