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Copper-Catalyzed Trifluoromethylation of Ynones Coupled with Dearomatizing Spirocyclization of Indoles: Access to CF_3-Containing Spiro[cyclopentane-1,3′-indole]

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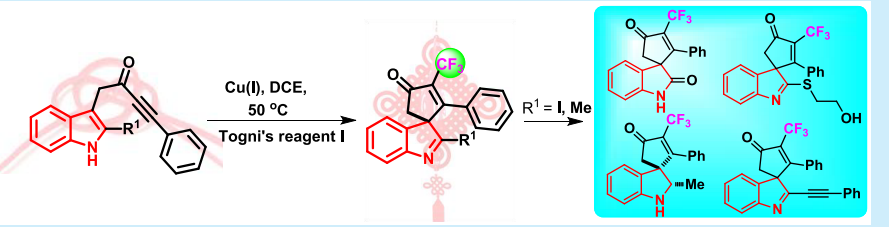

ABSTRACT: A one-pot protocol for the Cu(I)-catalyzed difunctionalization of indolyl ynones has been achieved via trifluoromethylation of alkyne followed by dearomatizing spirocyclization of indoles. This cascade process enables constructing diverse CF_3-containing spiro[cyclopentane-1,3′-indole] scaffolds in moderate to excellent yields which have challenging quaternary spirocyclic carbon and tetrasubstituted alkenes.

The spiroindolenines with a challenging quaternary spirocyclic carbon are present as prominent substructures in bioactive natural products and pharmaceutically relevant compounds that show antitumor, antiinfective, and antiproliferative activities (Figure 1).[1] As such, development of efficient methods for direct construction of the spiroindolenine skeleton is very valuable in synthetic chemistry.[2] Among these methods, the dearomatization of indole derivatives has received the most attention since three-dimensional sophisticated spirocyclic scaffolds can be conveniently obtained from aromatic starting materials,[3] especially indolyl ynones.[4] In general, monofunctionalization of alkyne-tethered indoles can be facilely achieved by intramolecular dearomatizing spirocyclization, catalyzed by Lewis acids such as silver(I), copper(II), and trifluoroacetic acid (TFA).[5] Comparatively, bifunctionalization of indolyl ynones is challenging and meaningful but with only a few studies reported for this transformation. Van der Eycken described a *N*-iodosuccinimide mediated intramolecularipso-iodocyclization of indolyl ynones for the formation of spiroindolenines.[6a] Unsworth and Taylor collaborated to develop a palladium complex as both a π-acid and cross-coupling catalyst that catalyzes a one-pot dearomatizing spirocyclization/cross-coupling cascade reaction for the functionalized spirocycles.[6b] In the present study, we describe Cu(I)-catalyzed difunctionalization of indolyl ynones via trifluoromethylation of alkyne and dearomatizing spirocyclization of indoles.

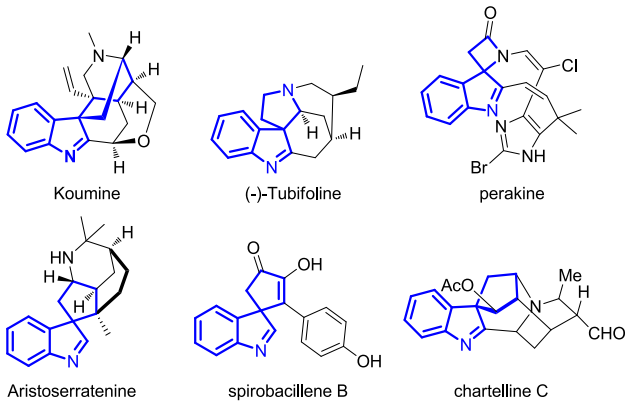

Figure 1. Representative bioactive molecules with spiroindolenine motifs.

Trifluoromethylation has been established as a critical strategy in agrochemicals and medicinal chemistry to modulate chemical and metabolic stability and increase their lipophilicity, bioavailability, and protein-binding affinity.[7] Thus, a great deal of attention has been paid to develop selective,

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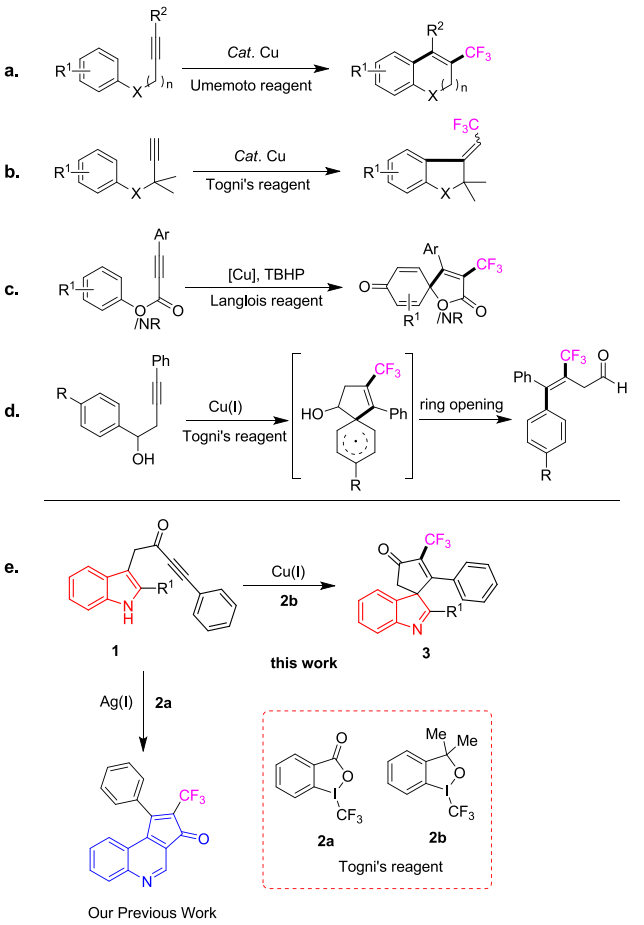
efficient, and versatile trifluoromethylation methods.[8] In particular, transition-metal-catalyzed or mediated trifluoromethylations of alkynes based on a difunctionalization strategy have undergone rapid development.[9−12] The direct carbotrifluoromethylation of alkynes was utilized to synthesize complicated trifluoromethylated conjugated rings or spirocyclic compounds. For example, the Fu and Liu groups independently demonstrated Cu-catalyzed aryltrifluoromethylation of alkynes for the synthesis of CF_3-containing heterocycles (Scheme 1a, b).[12g,h] Comparatively, synthesis of

Scheme 1. Metal-Catalyzed Carbotrifluoromethylation of Alkynes

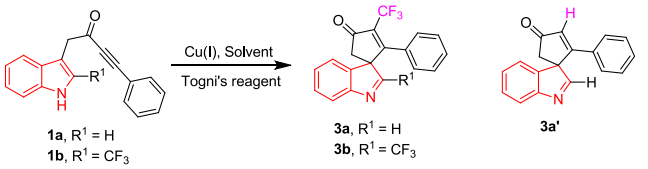


spirocyclic compounds containing C(vinyl)−CF_3 is much challenging. The spiroskelecton has a strong preference for an intramolecular migration or ring-open reaction due to the large ring strain and/or the driving force of rearomatization (Scheme 1d).[12b,c] Accordingly, there is only one study demonstrating the formation of the spiroskelecton compounds through Cu(I)-catalyzed trifluoromethylation and dearomatization cyclization tandem process of alkynes (Scheme 1c).[12l]

Recently, we found that Ag(I)-catalyzed cascade reaction of the substituted indolyl ynones (**1**) with the Togni reagent (**2a**) resulted in the formation of cyclopentaquinolinone instead of the corresponding spiroindolenines possibly because the spirocyclic compounds are unstable in the presence of Lewis acid (i.e., Ag(I)) and underwent further ring expansion and rearomatization (Scheme 1e).[13] Theoretically, inhibiting the rearrangement and rearomatization would be a good strategy to obtain spiroindolenines (**3**), which have challenging quaternary spirocyclic carbon and tetrasubstituted alkenes. Herein, we report the synthesis of CF_3-containing spiro[cyclopentane-1,3′-indole] using the Cu(I)-catalyzed difunctionalization of indolyl ynones in the presence of Togni's reagent.

First, we investigated the reaction of substrate **1a** with Togni's reagent (**2a**)[14] using CuI as catalyst at 37 °C under argon atmosphere in DCM. ^{19}F NMR results showed that complicated products exist including the C2-trifluoromethylated indolyl ynone **1b** (20%) together with (bis)-trifluoromethylated spiroindolenine **3b** with challenging quaternary spirocyclic carbon and tetrasubstituted alkene (17%, Table 1, entry 1). The structures of **1b** and **3b** were

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	Togni's reagent	solvent	yield[b] (%) **3b**
1[c]	CuI	**2a**	DCM	17
2[c]	CuBr	**2a**	DCM	20
3[c]	CuCl	**2a**	DCM	21
4[c]	$Cu(OAc)_2$	**2a**	DCM	trace
5[c]	CuOTf	**2a**	DCM	trace
6[d,f]	CuCl	**2a**	DCE	35
7[d,f]	CuCl	**2b**	DCE	80 (78)[e]
8[d,f]	CuBr	**2b**	DCE	44
9[d,f]	CuI	**2b**	DCE	40
10[d,f]	CuCN	**2b**	DCE	38
11[d,f]	CuOTf	**2b**	DCE	39
12[d,f]	$Cu(OAc)_2$	**2b**	DCE	29
13[d,f]	CuCl	**2b**	DMSO	trace
14[d,f]	CuCl	**2b**	CH_3CN	77
15[d,f]	CuCl	**2b**	dioxane	trace
16[d,f]	CuCl	**2b**	EA	44
17[d,f]	CuCl	**2b**	EtOH	13
18[d,f]		**2b**	DCE	trace

[a]Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), catalyst (0.02 mmol), solvent (2 mL), 37 °C, 48 h, under Ar. [b]The yield of the compound **3b** which was determined by ^{19}F NMR analysis with (trifluoromethyl)benzene as an internal standard. [c]**1a** was used as a substrate. [d]**1b** was used as a substrate. [e]The value in parentheses indicates the isolated yield. [f]Reaction temperature, 50 °C.

determined by X-ray crystallographic analysis (see the Supporting Information). The formation of the spiroindolenine **3b** stimulated us to further investigate various copper catalysts including CuBr, CuCl, $Cu(OAc)_2$, and CuOTf. Unfortunately, the yield of **3b** was not improved, and **3a′** was separated as the main byproduct that does not bear a trifluoromethyl group. Considering that the Togni's reagent (**2a**) will give *o*-iodobenzoic acid as the byproduct, the substrates **1a** are easily converted into hydrogenated analogues, the spiroindolines (**3a′**), under acid conditions,[5] Togni's reagent (**2b**) was used as the source of CF_3. Using **1a** as the substrate, unidentified byproducts were generated in this reaction. Gratifyingly, using the C2-substituted compound **1b** as the substrate, the spiroindolenine **3b** was obtained in 80% yield (entry 7). Other copper catalysts including CuBr, CuI,

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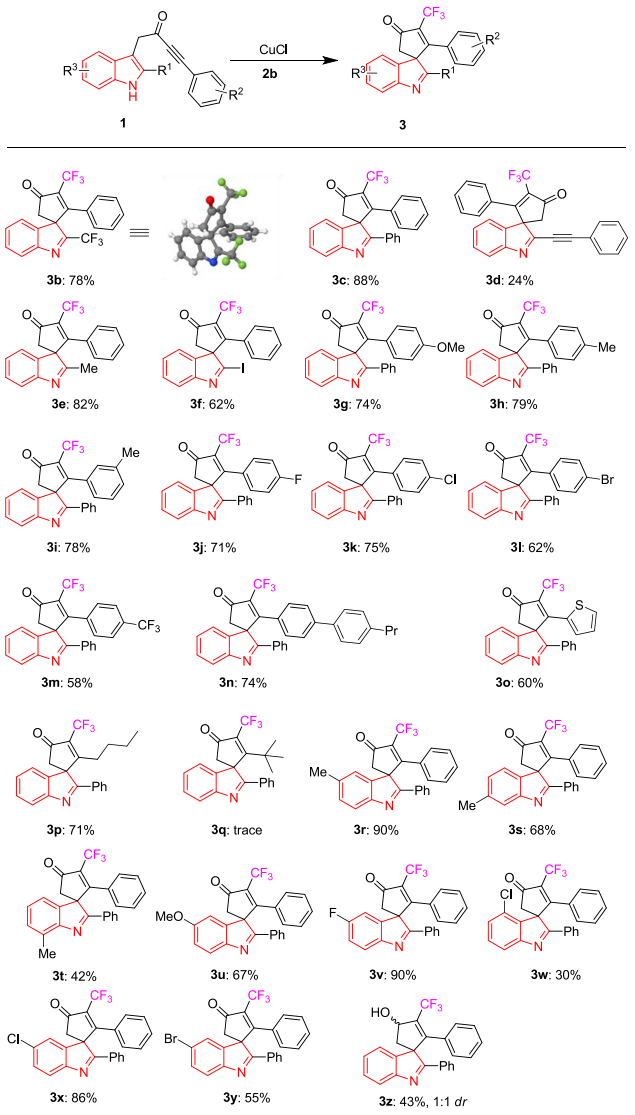
CuCN, CuOTf, and $Cu(OAc)_2$ were also tested (entries 8−12), but the results were not improved. Evaluation of various solvents (entries 13−17) revealed that the reaction was highly dependent on the solvents: the use of acetonitrile gave a good yield (entry 14), whereas in DMSO or 1,4-dioxane, none of the desired product was detected. A control experiment revealed that the copper catalyst was essential for the reaction (entry 18).

With the optimized reaction conditions established (Table 1, entry 7), we next investigated the substrate scope for the trifluoromethylation/dearomatizing spirocyclization reaction using various indolyl ynones. The results are summarized in Scheme 2. The use of 2-Ph indolyl ynone **1c** under the optimized reaction conditions led to the corresponding **3c** in high yields (88%). Similarly, the desired products **3d**−**3f** were obtained in moderate yields from the indolyl ynones with substituents (R^1) of 2-phenylacetylene, methyl, and iodo groups. Then the effect of the substituents on the phenyl ynones (R^2) was explored. It seems that the electronic effect of the substituents has an influence on the reaction. The indolyl ynones with electron-donating groups (**1g**−**i**) afforded the desired products with high yields, while electron-withdrawing groups (**1j**−**m**) resulted in the corresponding spiroskelecton products (**3j**−**m**) with slightly lower efficiency. It is noteworthy that a substrate with a thiophene-yl group attached to the triple bond (**1o**) successfully provided the desired product in 60% yield. The substrate with an alkyl group (**1p**) afforded 71% of the desired product (**3p**), while this is not the case for bulky *tert*-butyl-substituted ynone **1q** (to form **3q**). Furthermore, we studied the effect of the substituents on the indole ring (R^3). The substrates with either an electron-withdrawing or electron-donating group at the C4- to C7-positions of the indole ring were all tolerated. In particular, the substrate with a 5-MeO group (**1u**) and substrates (**1r**−**1t**) with a Me group at the 5-, 6-, or 7-position of the indole ring were efficiently transformed into the corresponding spiroindolenines **3u** and **3r**−**3t**, respectively, in moderate to high yields. As for the electron-withdrawing substituents (e.g., Br, Cl and F), the desired products (**3v**−**3y**) were obtained in moderate yields. The steric hindrance at the C4-position (**1w**) was unfavorable for the dearomatizing spirocyclization. Finally, alcohol derivative **1z** was also a suitable substrate which led to spiroindolenine **3z** in 43% yield with 1:1 dr under the standard conditions.

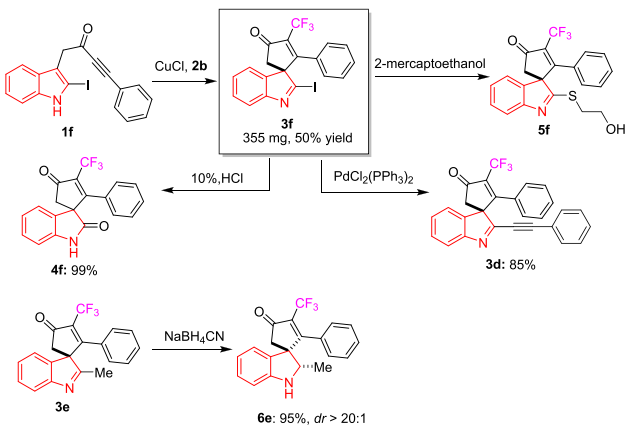
We also investigated the synthetic versatility of the resulting spiro[cyclopentane-1,3′-indole] (Scheme 3).[5c] A large-scale reaction was performed with the substrate **1f** (600 mg, 1.56 mmol), and the corresponding product **3f** was obtained in a slightly lower yield (50% vs 62%). Then compound **3f** was hydrolyzed using aqueous HCl in THF to afford CF_3-containing spirocyclicoxindole **4f** in almost quantitative yield. Nucleophilic substitution of **3f** with 2-mercaptoethanol led to the formation of compound **5f** in 90% yield, while the Songashira reaction of **3f** with ethynylbenzene led to **3d** in 85% yield with the total yield of 53% in two steps from **1f**, higher than one step from **1d** (24%). Reduction of **3e** by $NaBH_3CN$ afforded the spiro[cyclopentane-1,3′-indoline] **6e** with good stereoselectivity (dr >20:1) in excellent yield (95%).

Scheme 2. Substrate Scope of CuCl-Catalyzed Cascade Reaction[a]



[a]Reaction conditions: **1** (0.2 mmol), **2b** (0.4 mmol), CuCl (0.02 mmol), DCE (2 mL), 50 °C, 36−48 h, under Ar atmosphere.

Scheme 3. Transformations of Spiro[cyclopentane-1,3′-indole][a]



[a]Reaction conditions: (a) 10% HCl (aq), THF, rt, 4 h; (b) 2-mercaptoethanol, Et_3N, MeCN, rt, 22 h, under Ar; (c) ethynylbenzene, Et_3N, $PdCl_2(PPh_3)_2$, CuI, THF, rt, 12 h, under Ar; (e) $NaBH_3CN$, TFA, EtOH, 1 h.

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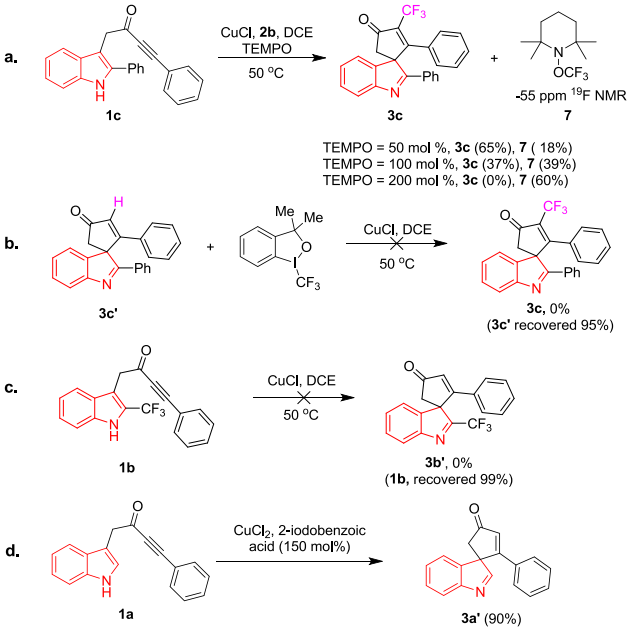
To obtain more insight into the reaction mechanism, we performed several control experiments (Scheme 4). First,

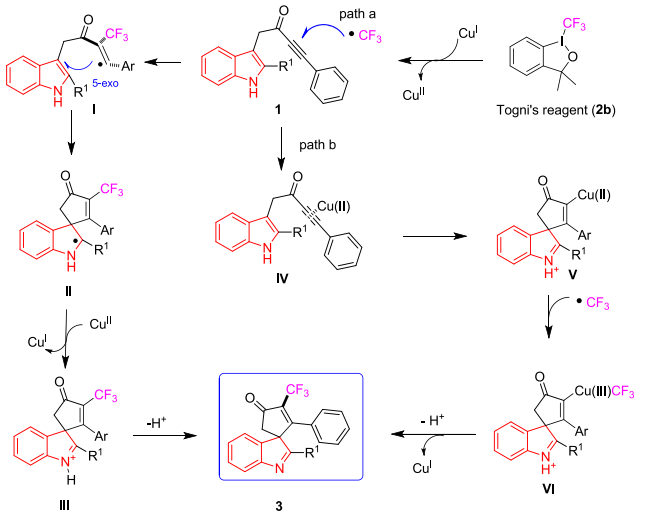
Scheme 4. Control Experiments



radical-trapping experiments were conducted by employing 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO). In the presence of 200 mol % of TEMPO, ^{19}F NMR spectroscopy showed that the reaction was inhibited and the radical-trapping product TEMPO-CF_3 was obtained in 60% yield. In addition, the reaction of spirocycle **3c′** and Togni's reagent (**2b**) could not afford the corresponding product **3c** under standard conditions with almost complete recovery of **3c′**, implying that the spirocycle **3c′** was not the active intermediate. Furthermore, indole **1b** proved to be inactive for this transformation in the absence of Togni's reagent (**2b**) (Scheme 4c), but Cu(II) with 2-iodobenzoic acid converted compound **1a** into spiroindolines **3a′** in 90% yield (Scheme 4d). These results suggest that unlike Ag(I)[5a,b] and Cu(II), CuCl as a weak Lewis acid is not able to induce intramolecular dearomatizing spirocyclization under the standard conditions.

On the basis of the above control experiments and previously reported results,[12] two plausible mechanisms for this cascade reaction are proposed (Scheme 5). For the first mechanism, the Togni's reagent (**2b**) is first activated by Cu(I) by means of a single-electron transfer to generate highly reactive CF_3 radical and Cu(II). Then CF_3 radical regioselectively attacks aryl ynones **1** at the α-position to form a C(sp^2)−CF_3 bond together with the generation of benzylcarbon-centered radical **I**. Subsequently, the carbon-centered radical **I** undergoes 5-*exo* dearomatizing cyclization onto the electron-rich C-3 position of the indole to give the spirocyclic intermediate **II**, rather than a 6-*endo* cyclization leading to the carbazol-3-one.[15] The radical **II** is then oxidized by Cu(II) to iminium ion **III**. Finally, the deprotonation of the iminium ion **III** is transformed into the desired product **3**. On the other hand, the Cu-mediated electrophilic spirocyclization may be also feasible. Coordination of Cu(II) with a triple bond of ynones promotes spirocyclization of compound **1** to give the intermediate complex **V**, which further reacts with CF_3 radical to afford the intermediate **VI**. Reductive elimination of **VI**

Scheme 5. Proposed Reaction Mechanism



leads to the product **3** and the regeneration of the catalyst Cu(I). The exact mechanism for this domino process still remains unclear at present and deserves further detailed studies.

In summary, we have developed an operationally simple, highly efficient copper-catalyzed cascade reaction which involves trifluoromethylation of alkynes and dearomatizing spirocyclization of indoles. The use of Cu(I)/Togni reagent **2b** instead of Ag(I)/Togni reagent **2a** prevents the Lewis acid induced rearomatization of the spiroindolenines.[13] This methodology enables regiospecific construction of trifluoromethylated spiro[cyclopentane-1,3′-indole] scaffolds containing quaternary spirocyclic carbon and tetrasubstituted alkenes under mild conditions in good to excellent yields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01097.

Detailed experimental procedures characterization data, X-ray structure of **1b**, **3b** and the copies of ^{1}H, ^{19}F and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 1955808 and 1955810 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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