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Copper(II)-Catalyzed Domino Synthesis of Indolo[3,2-*c*]quinolinones via Selective Carbonyl Migration

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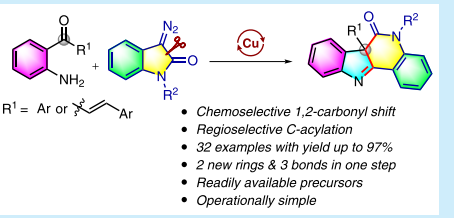
Supporting Information

ABSTRACT: A Cu(II)-catalyzed domino process involving the carbene N−H insertion, intramolecular aldol-type trapping and unprecedented ring-expansion of oxindole core through C3-selective 1,2-carbonyl migration is described for the synthesis of indolo[3,2-*c*]quinolinones. This tetracyclic core, having an all-carbon quaternary center, was efficiently synthesized in high yields from amines and 3-diazo-oxindoles. Mechanistic studies revealed that this reaction proceeds via a stepwise pathway and the involvement of the synergistic catalysis between Lewis acidic copper and hidden Brønsted acidity of in-situ-formed TfOH traces.



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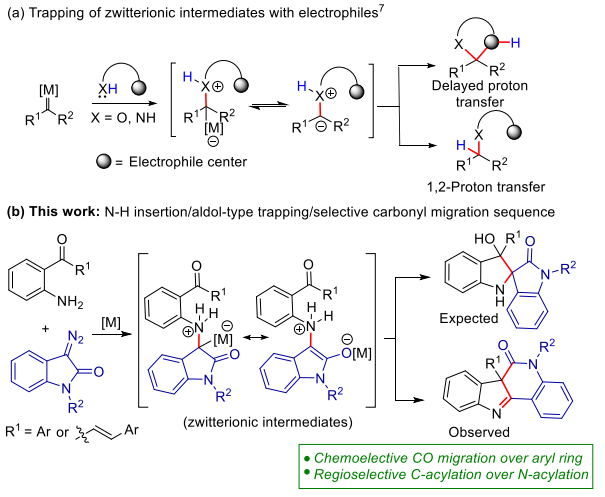
Metal-carbene involving reactions, whether engineered or discovered serendipitously, hold a special place in the construction of several new classes of compounds having unique properties.[1] Among the transformations of these active species,[2−4] the protic onium intermediates generated in situ from metal carbenes and heteroatoms during X−H insertions (X = N, O, S, etc.) could be intercepted with electrophiles such as imines, carbonyls, and Michael acceptors to offer polyfunctionalized materials to the end-users.[5,6] In recent years, remarkable progress has been made on the irreversible trapping of zwitterionic intermediates in an intramolecular fashion to synthesize the key constituent of numerous pharmaceutical drugs, i.e., heterocycles (Scheme 1a).[7] For instance, Hu and co-workers reported the synthesis of 3-hydroxy-2,2,3-trisubstituted indolines using $Rh_2(OAc)_4$ as a catalyst.[8] Moody and co-workers reported the trapping of transient oxonium and ammonium ylides with carbonyl group to synthesize functionalized tetrahydrofurans and pyrrolidines, respectively,[9] and Sun et al. described the synthesis of *N*-heterocycles with diazo compounds and amino alkynes.[10] Nonetheless, the progress in this strategy has been mostly limited to expensive Rh catalysts, the requirement of co-catalysts, and *N*-protected amines as the competitive 1,2-proton transfer might occur with nonprotected amines. Furthermore, the behavior of cyclic diazo compounds is sparsely investigated and mostly the reaction stops at the delayed proton-transfer step with no further transformation.

Scheme 1. Intramolecular Trapping of Zwitterionic Intermediates for the Synthesis of Heterocycles



In continuation of our interest in metallocarbene involving domino reactions and synthesis of structurally complex spiro-templates,[11] we initiated a program to synthesize indoline-fused spirooxindoles from readily accessible precursors. We envisaged that metallocarbene derived from cyclic diazooxindole upon reaction with an amine partner would generate the zwitterionic intermediate which might get trapped by ketone functional group in a concerted or stepwise manner. However, during the course of study, we encountered an unexpected ring expansion of oxindole core through chemoselective and regioselective migration of carbonyl group leading to angularly fused indolo[3,2-*c*]quinolinone framework bearing an all-carbon quaternary center, which is the subject of this communication (Scheme 1b).

Note that indole-fused polyheterocycles represent privileged subunits distributed in natural occurring alkaloids and pharmaceutically active substances (as shown in Figure 1).[12] Noteworthy examples are reserpine and isocryptolepine, an effective hypotensive and antimalarial agent, respectively.[13] Despite its pharmaceutical potential, the synthetic approaches to this class of framework are restricted to multistep synthesized precursors having preinstalled indoles, harsh reaction conditions, and linearly fused rings.[14] Moreover, to

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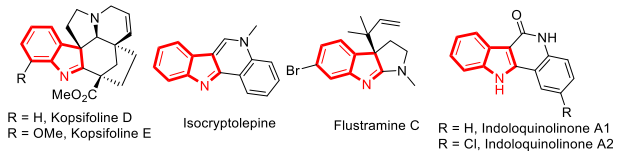
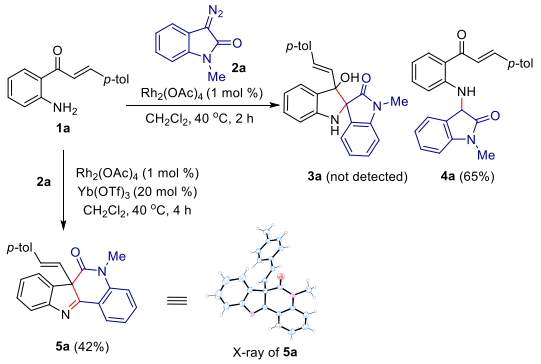


Figure 1. Representative structures of indole-containing alkaloids.

the best of our knowledge, the direct synthesis of indoloquinolinones having an all-carbon quaternary center is not accomplished so far.

To begin, we chose 2′-aminochalcones (**1a**) and *N*-methyl-3-diazo-oxindole (**2a**) as model substrates and the initial reaction was performed in the presence of 1 mol % $Rh_2(OAc)_4$ as a catalyst in CH_2Cl_2 at 40 °C (Scheme 2). A complete

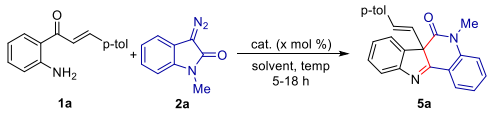
Scheme 2. Results of Initial Attempts for the Synthesis of Indole-Fused Spiro-oxindole 3a and an Unexpected Formation of Indolo[3,2-*c*]quinolinone 5a



conversion of **1a** was observed within 2 h but instead of desired spiro-oxindole **3a** formation, a traditional N−H insertion product **4a** via 1,2-proton transfer was isolated in 65% yield. It has been presumed that lowering the LUMO level of the carbonyl group of **1a** could help the intramolecular cyclization.[15] Thus, 20 mol % of $Yb(OTf)_3$ was included as a co-catalyst, expecting that the carbonyl functionality would undergo activation by chelation. A sole product was isolated in 42%. The one-dimensional (1D) and two-dimensional (2D) nuclear magnetic resonance (NMR) spectroscopy and high-resoultion mass spectroscopy (HRMS) data analyses suggested the unexpected rearrangement and the structure was tentatively assigned as indolo[3,2-*c*]quinolinone **5a**. The structure was confirmed by X-ray crystallography during the course of the study. The unusual ring expansion of the oxindole moiety via selective 1,2-carbonyl migration and structurally appealing tetracyclic indolo[3,2-*c*]quinolinone skeleton piqued our curiosity to develop a methodology and the optimization of the reaction conditions was commenced.

In order to improve the efficiency, Brønsted acid was utilized as a co-catalyst. The racemic BINOL phosphoric acid gave the desired product in 35% yield (Table 1, entry 1). While continuing the screening of Lewis acids, $Cu(OTf)_2$ was found to be effective to afford **5a** (58%, Table 1, entry 2). As part of the control experiments, a reaction was performed in the absence of $Rh_2(OAc)_4$ to realize its role. To our delight, it resulted in the increment of yield to 65% after 5 h (Table 1, entry 3). The effects of solvent and temperature were investigated. A substantial increase in the yield of **5a** was observed while using chloroform (86%, Table 1, entry 5).

Table 1. Optimization of the Reaction Conditions[a,b]



entry	catalyst (mol %)	solvent	*t* (°C)	yield of **5a** (%)
1	$Rh_2(OAc)_4$ (1)/BPA (20)	CH_2Cl_2	40	35
2	$Rh_2(OAc)_4$(1)/$Cu(OTf)_2$(20)	CH_2Cl_2	40	58
3	$Cu(OTf)_2$ (20)	CH_2Cl_2	40	65
4	$Cu(OTf)_2$ (20)	1,2-DCE	40	79
5	$Cu(OTf)_2$ (20)	$CHCl_3$	40	86
6	$Cu(OTf)_2$ (20)	$CHCl_3$	60	91
7	$Cu(OTf)_2$ (20)	$CHCl_3$	rt	45
8	$(CuOTf)_2$·tol (20)	$CHCl_3$	60	75
9	$Fe(OTf)_3$ (20)	$CHCl_3$	60	33
10	$Y(OTf)_3$ (20)	$CHCl_3$	60	20
11	$Cu(OAc)_2$ (20)	$CHCl_3$	60	–
12	$CuCl_2$ (20)	$CHCl_3$	60	–
13	**$Cu(OTf)_2$ (10)**	**$CHCl_3$**	**60**	**93 (91)**[c]
14	$Cu(OTf)_2$ (5)	$CHCl_3$	60	76

[a]Reaction conditions: **1a** (0.1 mmol) in 0.5 mL solvent. **2a** (0.15 mmol) in 0.5 mL solvent was added over 1 h by a syringe pump. [b]Yields were determined by ^1H NMR analysis of crude reaction using a 1,3,5-trimethoxybenzene as an internal standard. [c]Value in parentheses represents the yield after column chromatography. BPA = (±)-Binol-phosphoric acid. DCE = dichloroethane.

Raising the temperature to 60 °C led to an increase in yield to 91% (Table 1, entry 6). Switching to Cu(I)OTf·toluene complex as the catalyst led to a decrease in yield (75%, Table 1, entry 8). Interestingly, $Fe(OTf)_3$ could also promote the cyclization, albeit in lower yield (Table 1, entry 9). Other copper catalysts such as $Cu(OAc)_2$ and $CuCl_2$ failed to catalyze the reaction, which indicates that strong Lewis acidity of the catalyst is necessary for the current transformation (Table 1, entries 11 and 12). Screening of the catalyst loading manifested that 10 mol % of $Cu(OTf)_2$ was efficient to catalyze the domino reaction to get the maximum yield of 93% (Table 1, entry 13). Significantly, $Cu(OTf)_2$ serves a triple role of metal carbene formation, carbonyl group activation for aldol-type cyclization, as well as triggering the rearrangement.

Having found the optimized conditions, the generality of this domino reaction was investigated and the results are summarized in Scheme 3. Initially, a variety of 2′-amino-chalcones **1** was subjected to access the diverse range of substituted indolo[3,2-*c*]quinolinones **5**. The electron-donating and electron-withdrawing substituents present at the *para* position of aryl group participated with almost similar efficiency to deliver the corresponding products (**5c**−**5k**) in 83%−95% yields. Halo-substituents present at the *meta*-position were also well-tolerated under the reaction conditions (**5l**−**5n**). Notably, the sterically more demanding groups such as 2-OMe and 2,6-dichloro attached 2′-aminochalcones were smoothly converted to the products (**5p** and **5q**) in 86% and 85% yields, respectively. Chalcone having naphthyl and thienyl units were also amenable substrates to furnish the desired products in good yields (**5r** and **5s**). When 5′-Br substituted aminochalcone **1t** was used as a substrate, the corresponding indoloquinolinone **5t** was obtained in comparable yield. Various C5-substituted 3-diazooxindoles had an insignificant impact on the reaction; thus, the corresponding products (**5v**−**5y**) were isolated in 84%−94% yield. However, 5-NO_2 bearing

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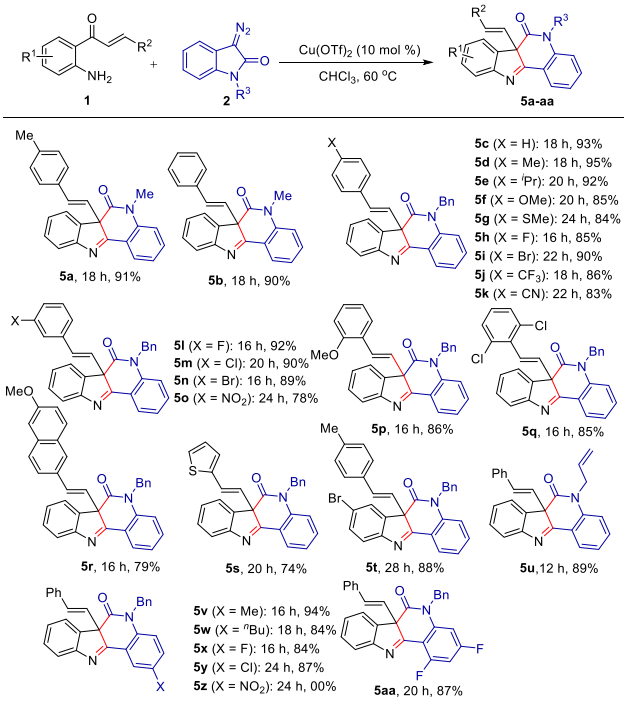
Scheme 3. Substrate Scope with 2-Aminochalcones and 3-Diazo-oxindoles[a]



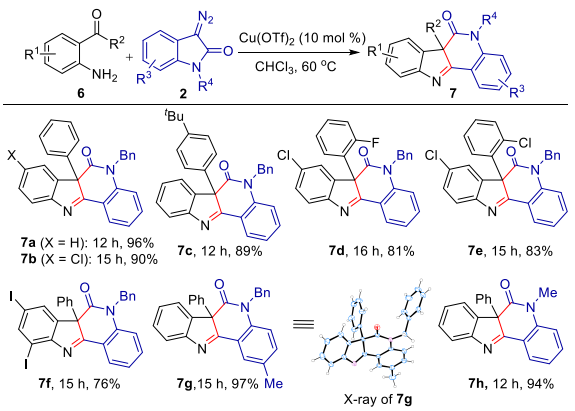
[a]For reactions conditions, see Table 1, entry 13.

3-diazo-oxindole did not yield the desired product **5z**, apparently because of the poor stability of the corresponding metallocarbene intermediate. The substrate scope investigation asserted that the chemoselective migration of the carbonyl group over the aryl ring of oxindole was not affected by the electronic and steric nature of the precursors.

Buoyed by the success of (*E*)-styrenyl-armed indolo[3,2-*c*]quinolinone synthesis, the next attention was turned toward the utilization of readily available 2-aminobenzophenone derivatives **6** in this domino cyclization (Scheme 4). It represents a significant challenge, given the formation of comparatively more congested all-carbon quaternary center.

It was established that the employment of 2-amino-benzophenone **6a** under optimized reaction conditions

Scheme 4. Domino Reaction with 2-Aminobenzophenone Derivatives[a]

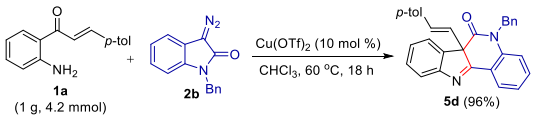


[a]For reactions conditions, see Table 1, entry 13.

furnished the desired tetracyclic compound **7a** nearly in quantitative yield. Aminobenzophenones bearing electron-rich and halogen substituents at *para* and *ortho* positions gave the corresponding indoloquinolinones (**7b**–**7f**) in high yields (76%–90%).

To demonstrate the practicability of the present protocol, a larger-scale reaction was performed with **1a** and **2b** (Scheme 5). Pleasingly, our reaction has shown excellent efficiency, compared to the pilot reaction, in terms of yield.

Scheme 5. Large-Scale Reaction



With regard to the possible mechanism, there are three major questions:

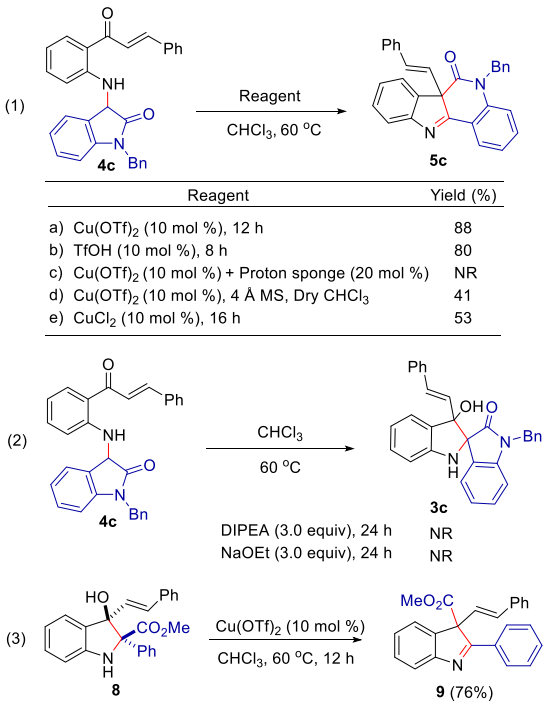
(1) Does the reaction proceed via the concerted trapping of ammonium ylides or in a stepwise manner?

(2) What is the real catalyst of the reaction, since $Cu(OTf)_2$ could also act as a "hidden Brønsted acid catalyst" through the in situ generation of trace amounts of TfOH?[16]

(3) Why does the carbonyl group selectively migrate over the aryl ring of the oxindole?

To address the first question, we exposed the N–H insertion product **4c** to the standard conditions. The corresponding cyclized product **5c** was obtained in 88% yield after 12 h (Scheme 6, 1a). This result confirms the involvement of a stepwise pathway with a sharp contrast to similar concerted trapping reactions.[8−10] To explore the second question, **4c** was treated with 10 mol % TfOH to probe the hidden Brønsted acid catalysis (see Schemes 6 and 1b). A clean transformation

Scheme 6. Control Experiments



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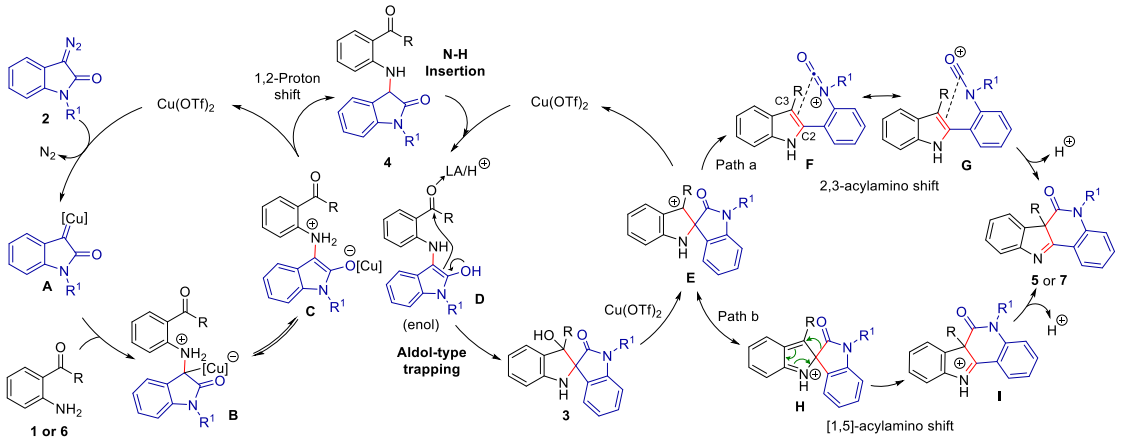
Scheme 7. Proposed Catalytic Cycle



occurred to produce **5c** in 80% yield after 8 h, which suggests that the in-situ-formed TfOH could also catalyze the aldol-type trapping and subsequent carbonyl migration steps.[17]

To determine the role of Cu, we designed a few more control experiments. A non-nucleophilic base, 1,8-bis-(dimethylamino)naphthalene (proton sponge) was included in the reaction conditions to prevent the background reaction caused by the traces of TfOH (see Schemes 6 and 1c). Although the formation of **5c** was completely suppressed, the proton trap could also inhibit the $Cu(OTf)_2$ via a coordination, as reported by Doyle et al.[18] The reaction with molecular sieves in an anhydrous atmosphere to dodge the hydrolysis of $Cu(OTf)_2$ gave a 41% yield of **5c**, which implies that there is also a Lewis acid interaction operating between Cu and the carbonyl functionality present in **4** (see Schemes 6 and 1d). To further support the statement, $CuCl_2$ also yielded **5c** in 53% (Scheme 6, 1e). This set of experiments does suggest that the traces of TfOH aids to get high yields and the involvement of strong synergistic catalysis between the Lewis acidic Cu and hidden Brønsted acidity of TfOH during the aldol trapping and 1,2-carbonyl migration steps.

We surmise that spiro-oxindole intermediate **3** was not isolable because of the fast 1,2-carbonyl migration. In order to access **3c**, **4c** was treated with bases such as DIPEA and NaOEt in an attempt to force the intramolecular aldol reaction, given that the H atom present at C3 of oxindole is quite acidic (see Schemes 6 and 2). However, **3c** was not detected, which suggests that the activation of the carbonyl group is necessary for the cyclization. Later, 3-hydroxy-2,2,3-trisubstituted indoline **8** was exposed to standard conditions to compare the migratory aptitude between the phenyl and ester moieties (see Schemes 6 and 3). The chemoselective migration of the ester moiety over the phenyl ring occurred to give 3*H*-indole **9** in 76% yield via the rearrangement triggered by formation of carbocation. This result was in good agreement with those results obtained by Bach, Driver, and other researchers, wherein the selective migration of carbonyl group was noted over electron-rich aryl or alkyl substituents.[19]

Based on the results of our control experiments and literature precedent,[19,20] a plausible reaction mechanism is depicted in Scheme 7. At first, Cu-catalyzed decomposition of **2** generates Cu-carbenoid intermediate **A**, which subsequently reacts with nucleophilic amine (**1** or **6**) to form the Cu-associated ammonium zwitterionic intermediate **B** or its corresponding tautomer **C**. Next, a rapid 1,2-proton shift occurs rather than a direct attack to the carbonyl group to provide the N−H insertion product **4**, which can experience an enolization to form the intermediate **D**. Then, an intramolecular aldol-type trapping of enol with an activated carbonyl group leads to the tertiary alcohol bearing spiro-oxindole intermediate **3**. The −OH was cleaved under the activation of $Cu(OTf)_2$ to give the spirocyclic cationic intermediate **E**, which could lead to product in two pathways (path a and path b). In path a, the lone pair at N atom of oxindole can assist the 2,3-acylamino shift via stabilization by isocyanate intermediate **F** and its acylium ion tautomer **G** to give the product. This additional stabilization may serve as a driving force for the selective carbonyl rearrangement. Alternatively, regarding the intermediate **H**, the resonance form of **E** could undergo a concerted [1,5]-sigmatropic acylamino shift to form the final product **5** or **7** (path b), as examined computationally by Driver and Tantillo.[21] However, further studies on the mechanism and asymmetric variant are currently underway in our laboratory and will be reported in due course.

In summary, we have developed a novel and efficient method to access all-carbon quaternary center bearing tetracyclic indolo[3,2-*c*]quinolinones using an inexpensive Cu catalyst, which involves a sequence of reactions comprising of N−H insertion, intramolecular aldol-type cyclization, and unusual ring expansion of oxindole core. The current protocol highlights a wide substrate scope and the desired products were isolated in good yields with a chemoselective and regioselective carbonyl migration. The mechanistic studies conferred that the developed reaction follows a stepwise pathway and involvement of synergistic effect between Cu and in-situ-formed traces of TfOH.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03557.

Experimental procedures, characterization data for all products, NMR spectra, and single-crystal XRD data (PDF)

Accession Codes

CCDC 1838846 and 1871970 contain the supplementary crystallographic data for this paper. These data can be obtained

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Notes

The authors declare no competing financial interest.

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