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Selective Oxidative Cleavage of 3-Methylindoles with Primary Amines Affording Quinazolinones

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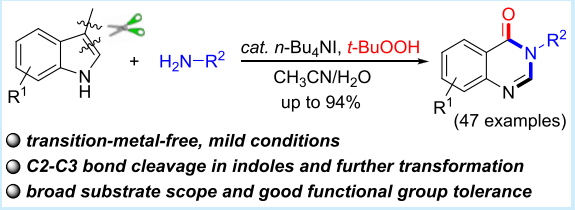
ABSTRACT: A selective functionalization of C−C═C bonds toward N−C═O bonds is realized by an *n*-Bu_4NI-catalyzed reaction of 3-methylindoles with primary amines using TBHP as the unique oxidant. The systematic process involves oxygenation, nitrogenation, ring-opening, and recyclization, affording a broad range of quinazolinones in good to excellent yields.

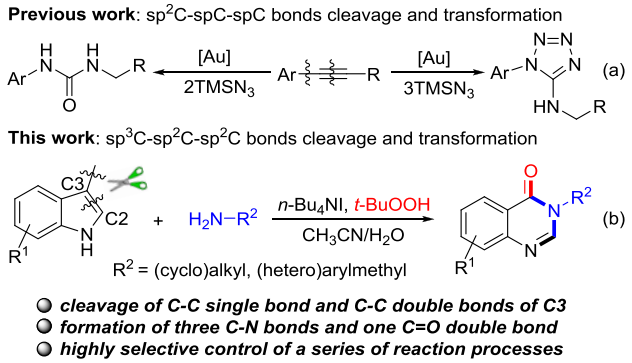


The C−C bond is the most fundamental unit in organic molecules. Comparable to C−H bond activation, the selective functionalization of C−C bonds allows the formation of new C−heteroatom bonds directly from inert feedstocks and is a very important topic in organic synthesis.[1] Due to thermodynamic and kinetic stability, the selective functionalization (cleavage along with their transformation) of unstrained C−C bonds is a very challenging task in modern organic chemistry. To meet such a challenge, transition-metal complexes and harsh reaction conditions are commonly required.[1−4]

Over the past two decades, the functionalization of C−C single bonds,[2] double bonds,[3] and triple bonds[4] has been extensively explored,[1] inter alia, by Milstein,[1a,2a] Dong,[2k−m] Bower,[1g,2i,j] and Jiao.[1c,3g−i,4d,f] In contrast, the selective functionalization of multiple C−C bonds is very limited.[5] For example, Shi and Jiao[5a] have reported a selective functionalization of C−C≡C bonds (sp^2C−spC−spC) of aryl alkynes by Au-catalyzed nitrogenation of alkynes (Scheme 1a), and the carbon atoms are all incorporated in the desired products. Another C−C≡C bond (spC−spC−spC) cleavage has been reported by Yamamoto[5b] for hydroamination of diynes with substituted aminophenols via Ru or Pd catalysis; however, the middle carbon atom is transferred to the byproduct.

Herein, we report a highly selective oxidative cleavage of multiple C−C bonds of 3-methylindoles and incorporation of primary amines to yield quinazolinones (Scheme 1b). By the treatment of 3-methylindoles and primary amines with *tert*-butyl hydroperoxide (TBHP) using *n*-Bu_4NI (TBAI) as the catalyst under transition-metal-free conditions, oxidative C2−C3 bond cleavage of indoles occurs along with oxygenation, nitrogenation, ring-opening and recyclization, and various quinazolinones,[6] an important scaffold in numerous pharmaceuticals and naturally occurring alkaloids,[7] are produced in good to excellent yields.

Scheme 1. Selective Functionalization of Multiple C−C Bonds



We commenced the investigation with the treatment of 3-methylindole (**1a**, 0.2 mmol) and benzylamine (**2a**, 2.0 equiv) in the presence of *n*-Bu_4NI (20 mol %) and TBHP (70% in H_2O, 6.0 equiv) in CH_3CN at 100 °C for 12 h, the formation of 3-benzylquinazolin-4(3*H*)-one (**3a**) was observed in 74% GC yield (Table 1, entry 1). This finding encouraged us to further optimize the reaction conditions. Tetrabutylammonium iodide was essential for the reaction (Table 1, entries 2−15). Other iodide sources, such as NaI, KI, CuI, NIS, and I_2, were inferior to *n*-Bu_4NI (Table 1, entries 2−6). In the absence of the iodide catalyst, the reaction did not take place (Table 1, entry 7). Increasing the use of TBAI to 30 mol % did not improved the yield of the product (Table 1, entry 8). TBHP

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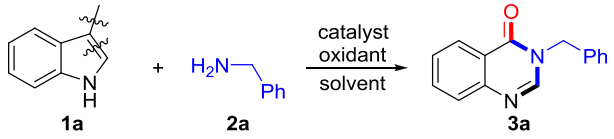
Table 1. Optimization of the Reaction Conditions[a]



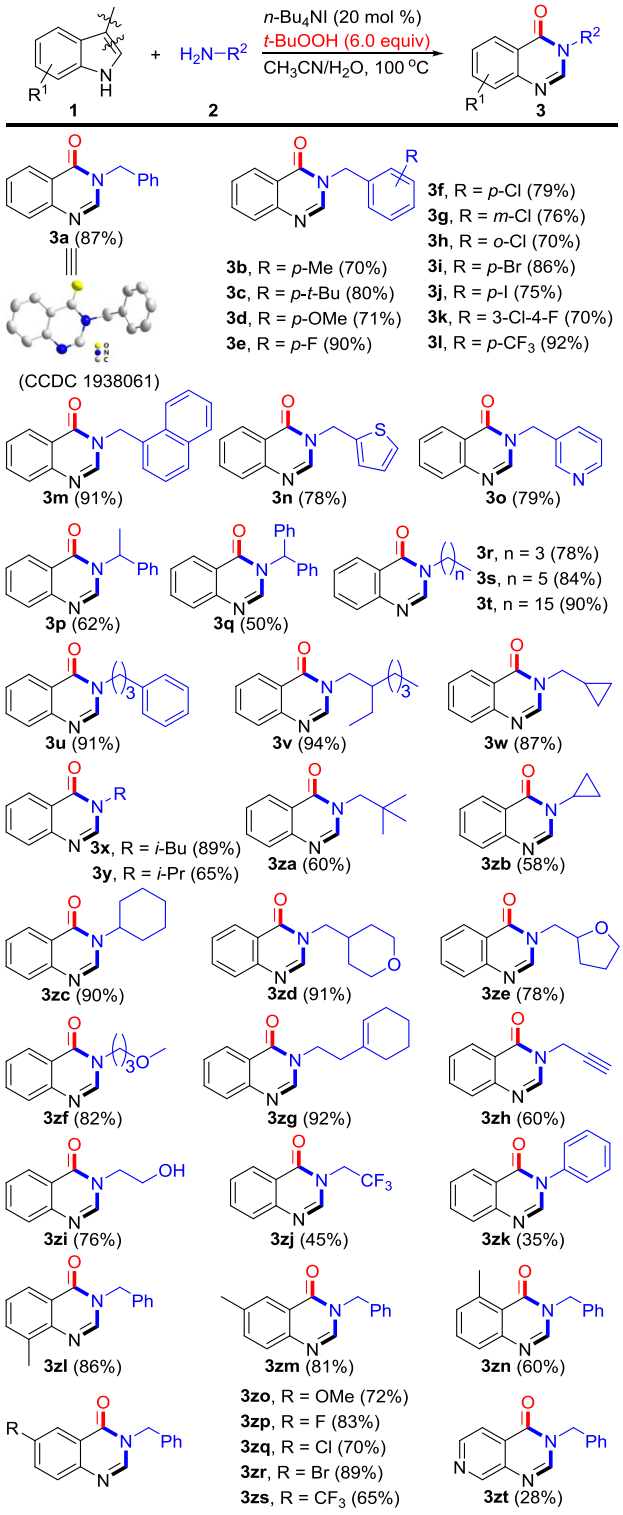
entry	catalyst	oxidant	solvent	yield[b] (%)
1	*n*-Bu_4NI	TBHP	CH_3CN	74
2	NaI	TBHP	CH_3CN	31
3	KI	TBHP	CH_3CN	52
4	CuI	TBHP	CH_3CN	trace
5	NIS	TBHP	CH_3CN	30
6	I_2	TBHP	CH_3CN	31
7		TBHP	CH_3CN	0
8[c]	*n*-Bu_4NI	TBHP	CH_3CN	71
9	*n*-Bu_4NI	TBPB	CH_3CN	0
10	*n*-Bu_4NI	DTBP	CH_3CN	0
11	*n*-Bu_4NI	$K_2S_2O_8$	CH_3CN	0
12	*n*-Bu_4NI	H_2O_2	CH_3CN	0
13	*n*-Bu_4NI	O_2	CH_3CN	0
14[d]	*n*-Bu_4NI	TBHP	CH_3CN	58
15[e]	*n*-Bu_4NI	TBHP	CH_3CN	73
16	*n*-Bu_4NI	TBHP	DMSO	11
17	*n*-Bu_4NI	TBHP	DMF	12
18	*n*-Bu_4NI	TBHP	toluene	10
19	*n*-Bu_4NI	TBHP	H_2O	21
20[f]	*n*-Bu_4NI	TBHP	CH_3CN/H_2O	92
21[f,g]	*n*-Bu_4NI	TBHP	CH_3CN/H_2O	82
22[f,h]	*n*-Bu_4NI	TBHP	CH_3CN/H_2O	80
23[f,i]	*n*-Bu_4NI	TBHP	CH_3CN/H_2O	84

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst (20 mol %), and TBHP (6.0 equiv) in solvent (1.5 mL) at 100 °C under N_2 for 12 h. [b]GC yield using *n*-tridecane as an internal standard. [c]*n*-Bu_4NI (30 mol %). [d]TBHP (4.0 equiv). [e]TBHP (8.0 equiv). [f]CH_3CN/H_2O (1.5 mL, v/v = 2:1). [g]80 °C. [h]120 °C. [i]Under air.

showed a unique effect in this reaction, and other oxidants such as *tert*-butyl peroxybenzoate (TBPB), di-*tert*-butyl peroxide (DTBP), $K_2S_2O_8$, H_2O_2 (30% in water), and O_2[8] were ineffective (Table 1, entries 9−13). When the amount of TBHP was decreased to 4.0 equiv, the yield of **3a** was reduced to 58% (Table 1, entry 14); while an increased amount of TBHP exhibited little influence on the yield of **3a** (Table 1, entry 15). The investigation of the solvent showed that CH_3CN was the best choice for the reaction, other solvents such as DMSO, DMF, toluene, and H_2O gave low yields of **3a** (10−21%; Table 1, entries 16−19). The yield of the desired product was significantly improved using a mixture of CH_3CN and H_2O as solvent (92% yield, Table 1, entry 20). Either increase or decrease in temperatures had negative effect on the yields (Table 1, entries 21 and 22). The reaction also took place under real conditions, producing **3a** in 84% yield (Table 1, entry 23).

Amines are easily oxidized to an array of products under oxidative conditions, which often results in limited generality in their oxidative transformation reactions.[9] Thus, we first examined the compatibility of amines. As shown in Scheme 2, this tandem reaction displayed a broad substrate scope with good functional group tolerance, selectively producing various quinazolinones in good to excellent yields. Arylmethanamines with either electron-donating or electron-withdrawing groups on any position (*ortho*-, *meta*-, and *para*-positions) of the

Scheme 2. Substrate Scope[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), *n*-Bu_4NI (20 mol %), TBHP (6.0 equiv), CH_3CN/H_2O (1.5 mL, v/v = 2:1), N_2, 100 °C, 12 h. Isolated yields are provided.

phenyl ring were good substrates for the reaction, yielding the corresponding products (**3a−l**) in 70−92% yields. A variety of functional groups, such as alkyl, halogens (fluoro, chloro, bromo, and iodo), methoxy, and trifluoromethyl, were well tolerated. The structure of **3a** was further confirmed by single-

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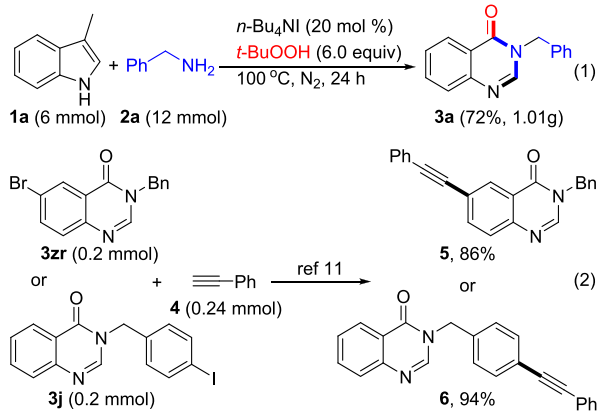
crystal X-ray structure analysis.[10] In addition, the more sterically encumbered naphthyl group was well suited for this transformation, giving the desired product (**3m**) in a 91% yield. Expectedly, heteroarylmethanamines participated in the metal-free reaction, yielding products **3n** and **3o** in 78% and 79% yields, respectively. Common aliphatic amines, such as *n*-butylamine (**3r**), *n*-hexylamine (**3s**), long chain *n*-hexadecylamine (**3t**), branched amines (**3v** and **3x**−**za**), cyclic amines (**3zb** and **3zc**), and heteroatom-containing amines (**3zd**−**zf** and **3zi**) were also good substrates, and the corresponding quinazolinones were produced in 58−94% yields. Interestingly, aliphatic amine containing an internal alkenyl group, which is a reactive radical acceptor, was also well tolerated, producing the desired product in excellent yield (**3zg**, 92%). Whereas, terminal alkynyl group resulted in lower yield (60%) of the desired product (**3zh**). The presence of substituents on the *α*-carbon atom of the arylmethanamines resulted in lower yield, and the products **3p** and **3q** were obtained in 62% and 50% yields, respectively. Amines containing *β*-*tert*-carbon atom also showed low reactivity (**3za**, 60% yield; **3zj**, 45% yield). Due to the low nucleophilicity of aniline (*vide infra*), its reaction with **1a** produced the corresponding product (**3zk**) in a 35% yield. The procedure was applicable to various indoles substituted with methyl, methoxy, halogen groups and trifluoromethyl at the C4, C5, C6, and C7 positions and the desired products (**3zl**−**zs**) were obtained in 60−89% yields. The reactivity of 6-azaindole was also investigated, and 3-benzylpyrido[3,4-*d*]pyrimidin-4(3*H*)-one (**3zt**) was isolated in a 28% yield.

A scale-up reaction was performed to investigate the potential practicality of this method (Scheme 3, eq 1), and

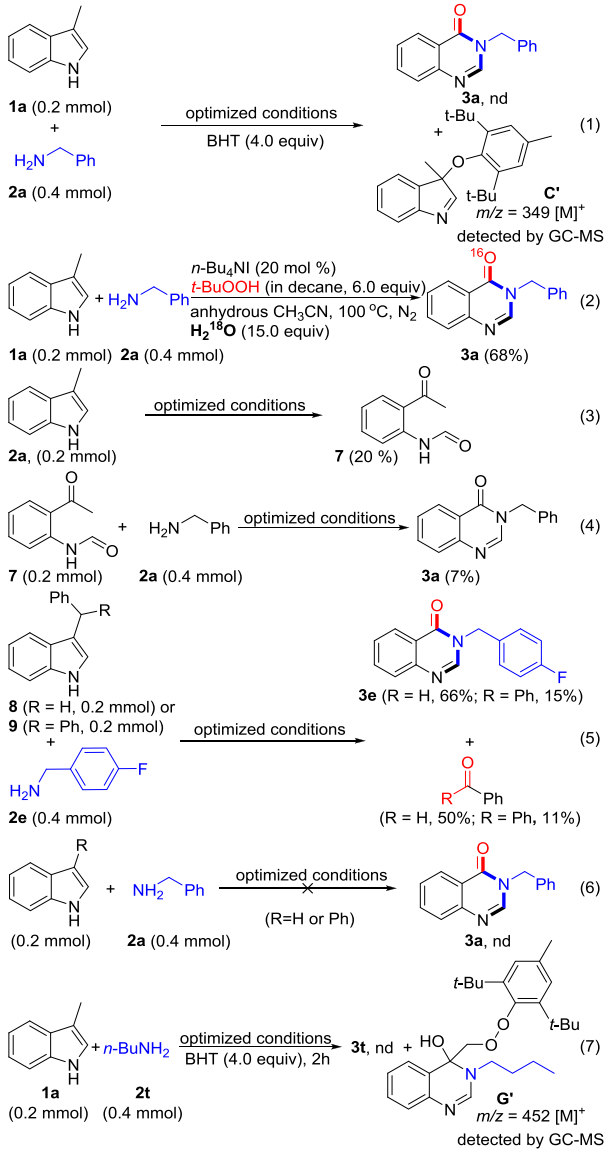
Scheme 3. Synthetic Utility



1.01 g of **3a** (72% yield) was successfully obtained by the treatment of 6 mmol of **1a** with 12 mmol of **2a** under similar conditions. The halogenated aryl compounds are important organic feedstocks for the synthesis of complex molecules by cross-coupling reactions.[11] For example, the reaction of **3zr** and **3j** with phenylacetylene (**4**) could yield more functionalized compounds **5** and **6** in 86% and 94% yields, respectively, by the Pd-catalyzed cross-coupling (Scheme 3, eq 2; for details, see the Supporting Information). These results verified that this reaction was practical for the construction of complex organic molecules.

To understand the reaction mechanism, several control experiments were conducted (for details, see the SI). Initially, the reaction could be completely suppressed by the radical inhibitor BHT (Scheme 4, eq 1) with observation of radical

Scheme 4. Control Experiments



adduct **C′**. Radical adduct **C′** could also be obtained by the direct reaction of **1a** with BHT. These results suggested that a free radical process was involved in the reaction. It was initiated by hydrogen abstraction of N−H bonds of indoles with *tert*-butoxyl or *tert*-butylperoxy radicals (vide infra).[12] The addition of 15 equiv of $H_2{}^{18}O$ to the reaction produced **3a** in 68% yield without observation of ^{18}O-labeled product (Scheme 4, eq 2), which suggested that the carbonyl oxygen atom of the product came from TBHP.[13] The oxidation of indole could produce *N*-(2-acetylphenyl)formamide (**7**) via cleavage of its C2−C3 double bond,[14] However, only a 20% amount of **7** was observed by the treatment of **1a** under the oxidative system (Scheme 4, eq 3); indeed, the reaction of **7** with **2a** only gave the desired product (**3a**) in a 7% yield (Scheme 4, eq 4). These results indicated that **7** did not serve as the reaction intermediate, i.e., nitrogenation of C2 atom was prior to the oxidative cleavage of the C2−C3 bond (for details, see the SI).

The reaction of 3-benzylindole (**8**) and 3-diphenylmethylindole (**9**) with 4-fluorobenzylamine (**2e**) could also produce the desired product (**3e**, 66% and 15% yield, respectively) with the concomitant generation of benzaldehyde (50% yield) and

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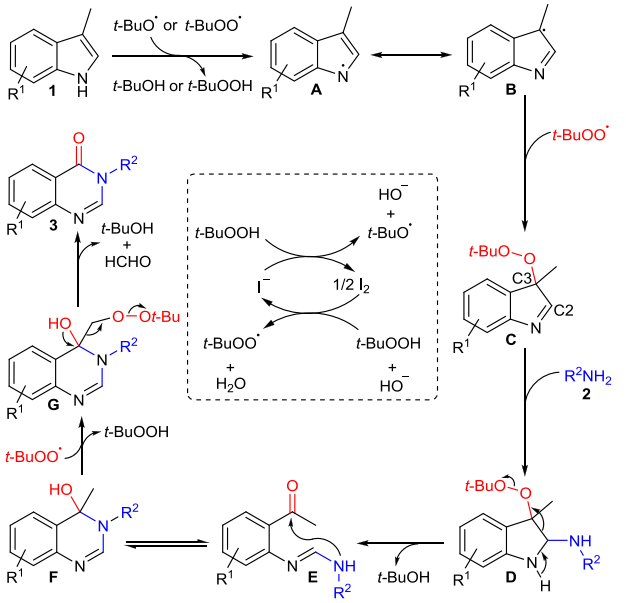
diphenyl ketone (11% yield), respectively, (Scheme 4, eq 5). The replacement of **1a** with indole or 3-phenylindole without sp^3C-H bonds did not produce the desired product at all (Scheme 4, eq 6).[14b] These results demonstrated that the oxygenation of sp^3C-H bonds was involved and was indispensable for the reaction. Indeed, another O-radical adduct **G′**, analogous to **G** (vide infra), was observed upon the addition of BHT to the reaction system (Scheme 4, eq 7) (for details, see the SI), which also suggested that **G** was the reaction intermediate.

Based on the above results and literature reports,[12,15−17] a plausible mechanistic pathway is illustrated in Scheme 5. First,

Scheme 5. Possible Mechanistic Pathway



tert-butoxyl and *tert*-butylperoxy radicals are easily formed by the exposure of TBHP to *n*-Bu_4NI,[12b,15] which initiates hydrogen abstraction of **1** to afford indolyl radical **A** and its resonance species **B**. According to the persistent radical effect, the adduction of longer-lived *tert*-butylperoxy radical to radical **B** affords intermediate **C**.[12] Subsequently, the nucleophilic addition of amine to **C** forms **D**.[12a,b] An intramolecular C−C bond cleavage of **D** with elimination of *tert*-butyl alcohol then produces intermediate **E**,[12c,16] which can isomerize to intermediate **F** by intramolecular nucleophilic addition. Finally, hydrogen abstraction of **F** occurs to form peroxide intermediate **G**, followed by rearrangement of **G**, which leads to C−C bond cleavage,[17a] producing the desired product (**3**).[17]

According to the proposed reaction pathway, electron-donating groups on the indoles favor the formation of the radical intermediates **A** and **B**; however, they also favor the undesired oxidation of indoles. Similarly, electron-donating groups on amines favor the nucleophilic attack of amines to intermediate **C**, however, it results in the undesired oxidation of amines. Indeed, both lower and higher yields (compared with 87% of **3a** without the substituents) of the products were observed for the substrates with electron-donating groups, as well as with the electron-withdrawing groups.

In summary, we have developed a novel and highly selective functionalization of multiple C−C bonds in which C3 atoms of 3-methylindoles are highly selectively transformed into N−C═O bonds with amines via C−C═C bond cleavage. This reaction takes place under metal-free conditions using *n*-Bu_4NI as the catalyst and TBHP as the unique oxidant, and the indoles and easily oxidizable amines are highly selectively incorporated in quinazolinone scaffolds in good to excellent yields with broad substrate scope and good functional group tolerance. This mild procedure allows the cleavage of the sp^3C-sp^2C single bond and sp^2C-sp^2C double bonds, along with the formation of three C−N bonds and one C═O double bond. Mechanistic investigation revealed that the systematic process is initiated by the oxygenation of C3 atoms of indoles with *tert*-butylperoxy radicals, and probably involves the nitrogenation of the C2 atoms, ring-opening by the cleavage of the C2−C3 bonds, recyclization by nitrogenation of C2 atoms, and oxidative cleavage of C3−sp^3C single bonds, which are readily controllable under oxidative conditions. This reaction not only represents a new type of functionalization of multiple C−C bonds but also provides a mild, efficient, and straightforward method to develop valuable quinazolinones. Further studies on the synthetic applications and detailed mechanism of the reaction are ongoing in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00271.

Experimental procedures, full spectroscopic data, and copies of ^1H, ^{13}C and ^{19}F spectroscopies (PDF)

Accession Codes

CCDC 1938061 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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