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A Radical-Initiated Fragmentary Rearrangement Cascade of Ene-Ynamides to [1,2]-Annulated Indoles via Site-Selective Cyclization

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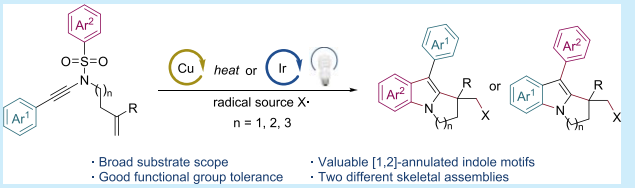
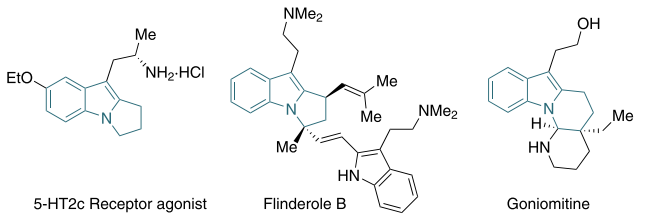
ABSTRACT: Straightforward access to [1,2]-annulated indoles, key substructures in natural products, is highly desirable yet challenging. Herein, a radical triggered fragmentary cyclization cascade reaction of ene-ynamides is presented, providing a rapid access into [1,2]-annulated indoles by an intermolecular radical addition, intramolecular cyclization, desulfonylative aryl migration, and site-selective C(sp^2)-N cyclization sequence. DFT calculations support oxidation of N-centered radical species to cations prior to the C−N bond formation, followed by an unusual aza-Nazarov cyclization.



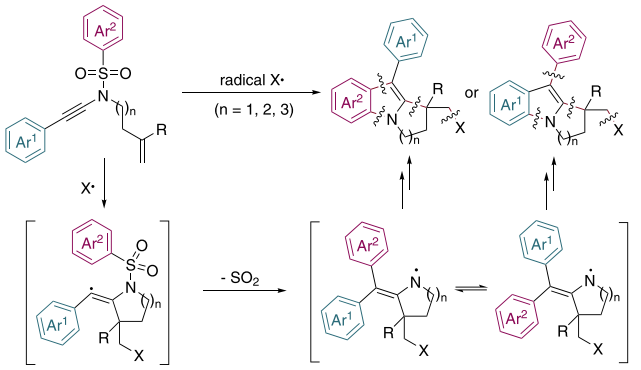
The importance of annulated indole skeletons in biologically active molecules inspires methodology developments toward their effective preparation (Scheme 1a).[1,2] Strategies for the construction of [1,2]-annulated indole structures are commonly based on functionalization of an already intact indole,[3] by methods including transition metal-catalyzed cyclization,[4] radical cyclization reactions,[5] Friedel−Crafts alkylation,[6] and *N*-alkylation.[7] These approaches are limited to those substitution patterns accessible on the starting indole and require relatively linear synthesis. As a result, alternative and versatile approaches into annulated indole motifs that assemble the indole motif are appealing.

Scheme 1. Significance and Strategies to Access [1,2]-Annulated Indoles

a) [1,2]-Annulated indole skeletons as valuable motifs in bioactive compounds.



b) This Work: Synthesis of [1,2]-annulated indoles from ene-ynamides via Smiles rearrangement and site-selective arylation.



Ynamides have received increasing attention over the past decade in reaction discovery, with particular utility in the construction of *N*-heterocyclic systems.[8] Despite the myriad synthetic utilities of ynamides, their radical chemistry is relatively unexplored.[9] Due to our ongoing interest in ynamide based cascade reactions[10] and radical chemistry,[11] we hypothesized that a radical-initiated cascade reaction of ene-ynamides might provide a novel way to construct [1,2]-annulated indoles: Ynamides commonly feature stabilizing aryl sulfonamide groups that could be incorporated into an indole motif through a desulfonylative aryl migration and C(sp^2)−N bond formation pathway initiated by a radical induced cyclization.

Moreover, the Smiles rearrangement is an intramolecular nucleophilic substitution at the *ipso*-position of an activated aromatic ring system[12] that typically involves aryl sulfides, sulfoxides, sulfones, and amides.[13] Radical versions of the Smiles rearrangement have also been demonstrated.[14] In 2015, the Nevado group[15] reported a copper-catalyzed desulfonylative radical Smiles rearrangement of conjugated tosyl amides. Ye and co-workers reported a novel photoredox-catalyzed radical Smiles rearrangement of α-keto aniline-derived ynamides.[16] Here we represent a rapid assembly of [1,2]-annulated indoles from simple ene-ynamides enabled by radical fragmentary cascade cyclization reaction (Scheme 1b).

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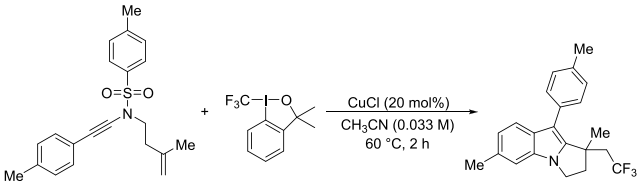
Table 1. Optimization Studies[a]



1a (1.0 equiv) **2** (1.2 equiv) **3a**

entry	deviation from standard conditions	yield of **3a** (%)[b]
1	none	72 (63)
2	CuBr instead of CuCl	67
3	CuI instead of CuCl	67
4	$Cu(OAc)_2$ instead of CuCl	n.d.
5	$Cu(OTf)_2$ instead of CuCl	n.d.
6	room temperature instead of 60 °C	46
7	80 °C instead of 60 °C	59
8	DCM instead of CH_3CN	47
9	THF instead of CH_3CN	n.d.
10	DMA instead of CH_3CN	n.d.
11	Togni reagent II instead of 2	55
12	0.05 M in CH_3CN	62
13	0.02 M in CH_3CN	47
14	no CuCl	n.d.

[a]Standard conditions: **1a** (0.1 mmol), **2** (0.12 mmol, 1.2 equiv), CuCl (20 mol %) in CH_3CN (3 mL) in a Schlenk tube at 60 °C under N_2 atmosphere for 2 h. [b]Yields were determined by ^1H NMR spectroscopy of the crude reaction mixture using mesitylene as an internal standard; an isolated yield is shown in parentheses. Togni reagent II: 1-trifluoromethyl-1,2-benziodoxol-3-(1*H*)-one. n.d. = not detected.

We started our study with ynamide **1a**, using Togni's reagent **2** as the radical source for the putative cascade. After evaluation of various reaction parameters, the annulated indole product **3a** was achieved in 72% ^1H NMR yield using CuCl (20 mol %) in CH_3CN (0.033 M) at 60 °C (Table 1, entry 1). CuBr and CuI were also efficient catalysts in this transformation, albeit giving slightly lower yields (Table 1, entries 2−3). Copper(II) complexes such as $Cu(OAc)_2$ and $Cu(OTf)_2$ failed to deliver the desired product **3a** (Table 1, entries 4−5). An elevated temperature of 60 °C improved the efficiency of the reaction (46% yield at room temperature, Table 1, entry 6) but lower yields were seen at higher temperature (Table 1, entry 7). Other solvents were not suitable for this transformation (Table 1, entries 8−10). Higher or lower concentration of solvent gave diminished yields (Table 1, entries 12−13). A control experiment showed that CuCl was indispensable in this transformation (Table 1, entry 14).

With the optimized reaction conditions in hand, we then set out to evaluate the generality of this approach (Scheme 2). Annulated indoles were obtained in good yields from a series of ynamides with matching *p*-substituted aryl groups on both the ethynyl and sulfonamide regions of the ynamide (**3b**−**3e**, 45%−71%). The structure of **3e** was confirmed by single crystal X-ray diffraction. The practicality and ready implementation of this method is demonstrated by the preparation of **3e** on one gram scale.

Initial studies with ynamides containing different aryl groups on the sulfonamide and alkyne showed that isomeric products could be realized from these reactions. Either aryl group can be incorporated into the indole motif. For example, a substrate bearing electronically similar aryl substituents at the alkyne and the sulfonamide group affords a ∼1:1 mixture of inseparable regioisomers (**3f**, **3f′**). The regioisomeric ratio improved to 2.8:1.0 (**3g**:**3g′**) where cyclization onto the *p*-tolyl group from the sulfonamide was favored over cyclization onto the alkynes *m*-methoxyphenyl group. Replacing the *m*-methoxyphenyl substituent on the ynamide with a fluorobenzene substituent led to greater selectivity (**3h**:**3h′** = 4.0:1.0). A single product **3i** was obtained from the *m*-fluoro-substituted ynamide in 64% yield, demonstrating that sole indole products might be obtained by exploiting electronic differences between the two aryl groups.

The scope of the reaction was then explored with consideration of the electronic properties between two aryl groups. First, a series of ynamides containing *p*-alkyl and *p*-alkoxy substituents on the sulfonamide and electron-withdrawing substituents on the aryl ethynyl portion were examined. Exclusive formation of the indole products resulting from cyclization onto the sulfonamide-derived aryl unit was observed. Halide (**3j**−**3n**), ester (**3o**), including those derived from (−)-menthol and (+)-fenchol (**3r**; **3s**), and nitrile (**3p**; **3q**) groups on the other aryl ring were well tolerated.

Selective cascade reactions that deliver a different skeletal assembly can also be realized by inverting the electronic properties of the two aryl groups: Substrates with more electron-deficient aryl groups on the sulfonamide and electron-donating substituents on the aryl ethynyl moiety see the latter aryl group incorporated into the indole (**3t**−**3ad**, 43%−70%). Alkyl-, alkoxy-, and thioether substituents are all tolerated. The use of *p*-substituted aryl groups lead to 6-substituted indoles, while a 3,5-dimethylbenzene derivative provides access to the 5,7-substituted indole **3aa**. Aryl sulfonamides bearing *o*-, *m*-, and *p*-halo, 3,5-difluoro, *p*-trifluoromethyl, and *p*-nitro groups were all effective in the reaction. The reaction also proceeded using an ynamide with a monosubstituted alkene to generate a tertiary stereocenter (**3y**). In addition, a pyridine-containing substrate also functioned well in the reaction, with cyclization observed onto the *p*-methoxyphenyl unit derived from the alkyne substituent (**3ad**).

Isomeric sets of starting materials (**4a**/**4a′** and **4b**/**4b′**, Scheme 3a) showed very similar reaction efficiencies under standard reaction conditions and converged to the same regioisomers (**5a** and **5b**, respectively), with more electron-rich *p*-methoxyphenyl group embedded in the indole regardless of its original position. Hence starting materials can be designed and prepared on the basis of synthetic accessibility.

More diverse [1,2]-annulated indole skeletons can also be prepared by this approach. Pyrido[1,2-*a*]indole and azepino-[1,2-*a*]indole (**7a**−**7c**) are accessed by increasing the alkyl chain length between the alkene and the nitrogen (Scheme 3b). Unbranched and "butyl branched alkene groups are also tolerated. In all cases site-selective C(sp^2)−N bond formation occurs onto the more electron-rich aryl group.

Next, we examined the reaction efficiency of this cascade process under photoredox-catalyzed conditions with different radical precursors. Analogous [1,2]-annulated indole systems could be formed under iridium photoredox-catalysis allowing the introduction of the α,α-difluoroamidyl and α,α-difluoroacarbonyl functional groups (**8a**−**8e**, Scheme 3c). The site-selective arylation was also retained under these photoredox conditions (**8d** and **8e**). Keto-ynamide **9** underwent fast

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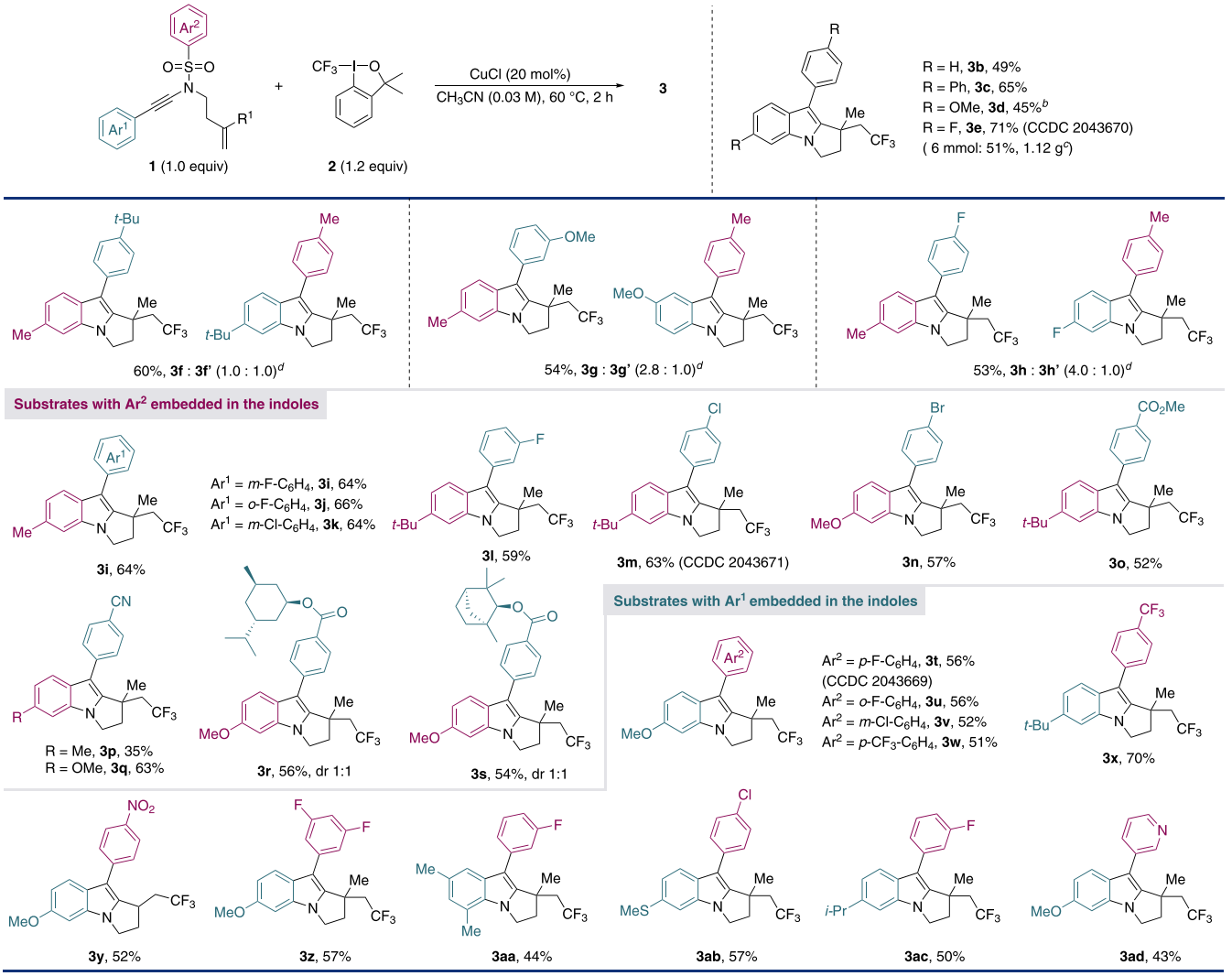
Scheme 2. Substrate Scope[a]



[a]Standard conditions: **1** (0.2 mmol), **2** (1.2 equiv, 0.24 mmol), CuCl (20 mol %), and CH_3CN (6 mL) in a Schlenk tube at 60 °C under N_2 atmosphere for 2 h. Isolated yields are reported. Unless otherwise stated, the regioisomeric ratio is >20:1. [b]Reaction was performed at room temperature. [c]See Supporting Information for details. [d]Ratio was determined by ^{19}F NMR spectroscopy of the crude reaction mixture. [t]Bu = *tert*-butyl, [i]Pr = *iso*-propyl.

decomposition under the copper-catalyzed conditions but afforded the desired 3-acyl pyrrolo[1,2-*a*]indole **10a** using the photoredox conditions alongside a small amount of **10b** resulting from *otho*-vinylation of the sulfonamide after the initial cyclization step.

DFT calculations verified that an aza-Nazarov type cyclization is responsible for the excellent site-selectivity observed in the C(sp^2)-N bond forming step (see Supporting Information for details). On the basis of the results and literature precedent,[15,16] a proposed mechanism is depicted in Scheme 4. First, the radical precursor undergoes single electron transfer with copper(I) complex (or the photoexcited *Ir^{III} catalyst) to generate a copper(II) species (or Ir^{IV} species) and radical ·X (·CF_2R) which then undergoes intermolecular addition to the alkene part in the ynamide **1** furnishing alkyl radical intermediate **I**.[17] Intramolecular cyclization to generate vinyl radical intermediate **II** precedes *ipso*-cyclization onto the sulfonamide and desulfonylation to generate the N-centered radical intermediate **III**. Oxidation of **III** by copper(II) complex (or Ir^{IV} species) would generate the extended cation **IV** and regenerate the copper(I) catalyst (or Ir^{III} catalyst). The electrocyclization occurs selectively through the 4π system incorporating the more electron-rich aryl group to give **V**,[18] affording the indole **3** on deprotonation.

In summary, a straightforward access to pyrrolo[1,2-*a*]indole, pyrido[1,2-*a*]indole, and azepino[1,2-*a*]indole motifs has been achieved using a nontrivial radical-initiated fragmentary rearrangement cascade of ene-ynamides. This strategy provides a novel approach for the skeletal assembly of these important heterocyclic structures from readily assemble ynamides. The new transformation provides ready access into molecules displaying biological activities allowing for potential application in medicinal chemistry. The reaction represents a unique example of a site-selective C(sp^2)−N arylation, with DFT calculations supporting aza-Nazarov type cyclization following a radical Smiles rearrangement process.

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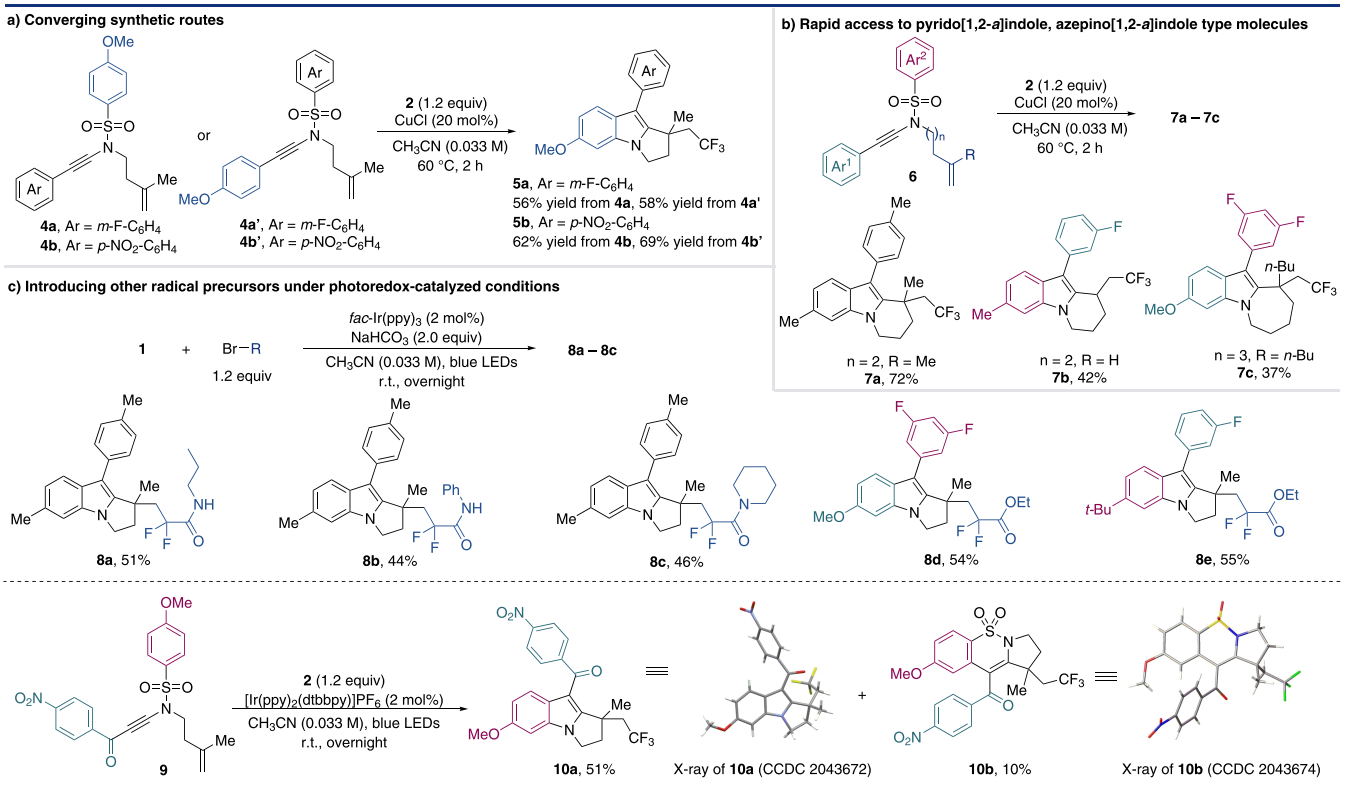
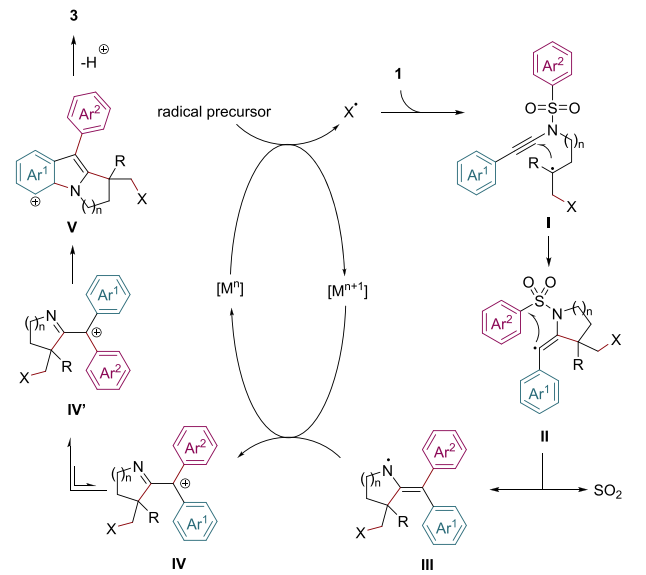
Scheme 3. a) Regioconvergent Methods; b) Access to Pyrido[1,2-*a*]indole and Azepino[1,2-*a*]indole Motifs; c) Reactions under Photoredox-Catalyzed Conditions



Scheme 4. Proposed Mechanism



[a]Substrate **1** with Ar^1 = electron-rich aryl group, Ar^2 = electron-deficient aryl group was taken as example for clarity. n = 1, 2, 3.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02519.

Experimental procedures, mechanistic investigations, characterization data, energy level diagrams, computational details, Cartesian coordinates, crystal data, and copies of NMR spectra for all products (PDF)

Accession Codes

CCDC 2043669−2043672 and 2043674 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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