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Mechanism and Origin of the Unexpected Chemoselectivity in Fluorocyclization of *o*-Styryl Benzamides with a Hypervalent Fluoroiodane Reagent

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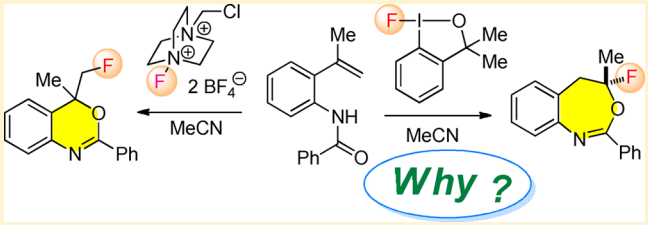
Supporting Information

ABSTRACT: The mechanism and origin of the unexpected chemoselectivity in fluorocyclization of *o*-styryl benzamide with a cyclic hypervalent fluoroiodane reagent were explored with DFT calculations. The calculations suggested an alternative mechanism that is broadly similar to, but also critically different from, the previously proposed mechanism for the formation of an unexpected structurally novel seven-membered 4-fluoro-1,3-benzoxazepine. The amide group of *o*-styryl benzamide was revealed to be crucial for activating the fluoroiodane reagent and facilitating C−F bond formation. In contrast to the popular electrophilic N−F reagent Selectfluor, the F atom in the fluoroiodane reagent is nucleophilic, and the I(III) atom is the most electrophilic site, thus inducing a completely different reactivity pattern. The insights reported here will be valuable for the further development of new reactions based on the hypervalent fluoroiodane reagent.



1. INTRODUCTION

The demand for fluorine-containing compounds is rapidly growing as a result of their widespread application in the pharmaceutical,[1] agrochemical,[2] and materials industries.[3] For example, approximately 30% of all agrochemicals and 20% of all pharmaceuticals on the market contain at least one fluorine atom, including top-selling treatments like the cholesterol-lowering drug Lipitor and the antidepressant Prozac.[1,2] Moreover, ^{18}F-labeled organic compounds are clinically used as contrast agents for positron emission tomography,[3d] which is used routinely for diagnosing, staging, and detecting the recurrence or progression of various diseases. Despite their practical attributes, fluorinated natural products are extremely rare.[4] As a consequence, there has been considerable effort directed toward developing efficient and selective synthetic methodologies for the introduction of fluorine into organic molecules.[5]

Among various methodologies for introducing fluorine into target molecules,[5] electrophilic fluorination is one of the most promising and efficient strategies in the synthesis of organofluoro compounds.[6] The rapid progress of this field is greatly indebted to the appearance of new, safe, and easily accessible electrophilic fluorinating reagents (Figure 1),[7,8] such as Selectfluor (**F2**),[9] NFSI (*N*-fluorobenzenesulfonimide),[10] NFPy (*N*-fluoropyridinium salt),[7f,11] and hypervalent iodine(III) fluoro reagent (**F1**).[12] Among them, the air- and moisture-stable fluoroiodane **F1** has recently received special attention in the development of new fluorination reactions that exihibt novel reactivities and selectivities.[13,14] Most recently, Gulder and co-workers found that fluoroiodane **F1** displayed a completely different chemoselectivity in the fluorocyclization of *o*-styryl benzamides when compared with that of the popular Selectfluor reagent **F2** (Scheme 1).[15] Electrophilic fluorocyclization of *o*-styryl benzamide **1** with Selectfluor **F2** yielded solely six-membered benzoxazine **P2**, whereas application of

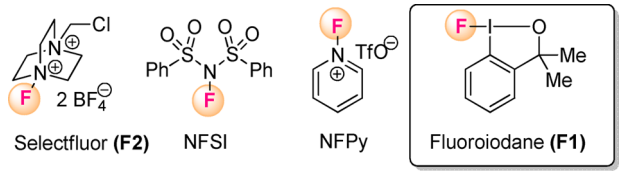
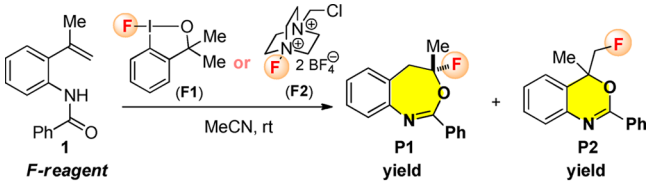


Figure 1. Typical electrophilic fluorine sources.

Scheme 1. Fluorocyclization of *o*-Styryl Benzamide



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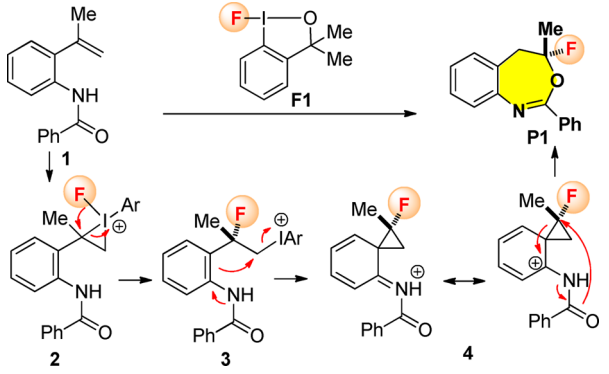
fluoroiodane **F1** induced a complete chemoselectivity switch and led to unprecedented seven-membered 4-fluoro-1,3-benzoxazepine **P1** under the same reaction conditions (Scheme 1). This chemoselectivity provides access to structurally novel 4-fluoro-1,3-benzoxazepines that are pharmacologically very interesting heterocycles.[16]

Although fluoroiodane **F1** has emerged as an efficient and versatile fluorinating reagent for organic synthesis,[13,14] it has remained poorly understood with regard to its fluorination mechanism. There is particularly little insight into the origin of the observed intriguing chemoselectivity in the fluorocyclization of *o*-styryl benzamides with this reagent.[15] A better understanding of the fluorination mechanism and origin of the unexpected chemoselectivity would, however, greatly facilitate the design of new reactions. As part of our continued interest in understanding the reactivities and mechanisms of fluorinating and fluoroalkylating reagents in organic synthesis,[17] we herein report the results from our density functional theory (DFT) calculations on the detailed mechanism of the fluorocyclization of *o*-styryl benzamide with fluoroiodane reagent **F1**. The calculations revealed an alternative mechanism wherein the amide group of *o*-styryl benzamide is crucial for activating the fluoroiodane reagent and facilitating C−F bond formation. Moreover, in contrast to the popular electrophilic N−F reagent Selectfluor, the F atom in the fluoroiodane reagent is nucleophilic, and the I(III) atom is the most electrophilic site, thus resulting in a completely different reactivity pattern. The greater understanding of the intriguing reactivities and selectivities of **F1** demonstrated herein should facilitate the future development of new transformations that employ this fluoroiodane reagent.

Scheme 2. Previously Proposed Mechanism for the Fluorocyclization of *o*-Styryl Benzamide[15]



2. COMPUTATIONAL METHODS

The newly developed MN12-L[18] and B97-D[19] functionals have been demonstrated to be accurate for barrier heights and noncovalent interactions. Accordingly, this work employs the Gibbs free energies obtained at the (SMD)MN12-L/[6-311++G(d,p)+SDD(I)]//(SMD)B97-D/[6-31+G(d)+SDD(I)] level of theory. Similar results were obtained at the (SMD)B97-D/[6-311++G(d, p)+SDD(I)]//(SMD)B97-D/[6-31+G(d)+SDD(I)) level of theory (see Supporting Information Figure S1). Geometry optimizations, vibrational frequencies, and thermal energy corrections were performed with the B97-D functional in conjunction with a mixed basis set of the SDD[20] pseudopotential for iodine and 6-31+G(d)[21] for all other atoms. The SMD

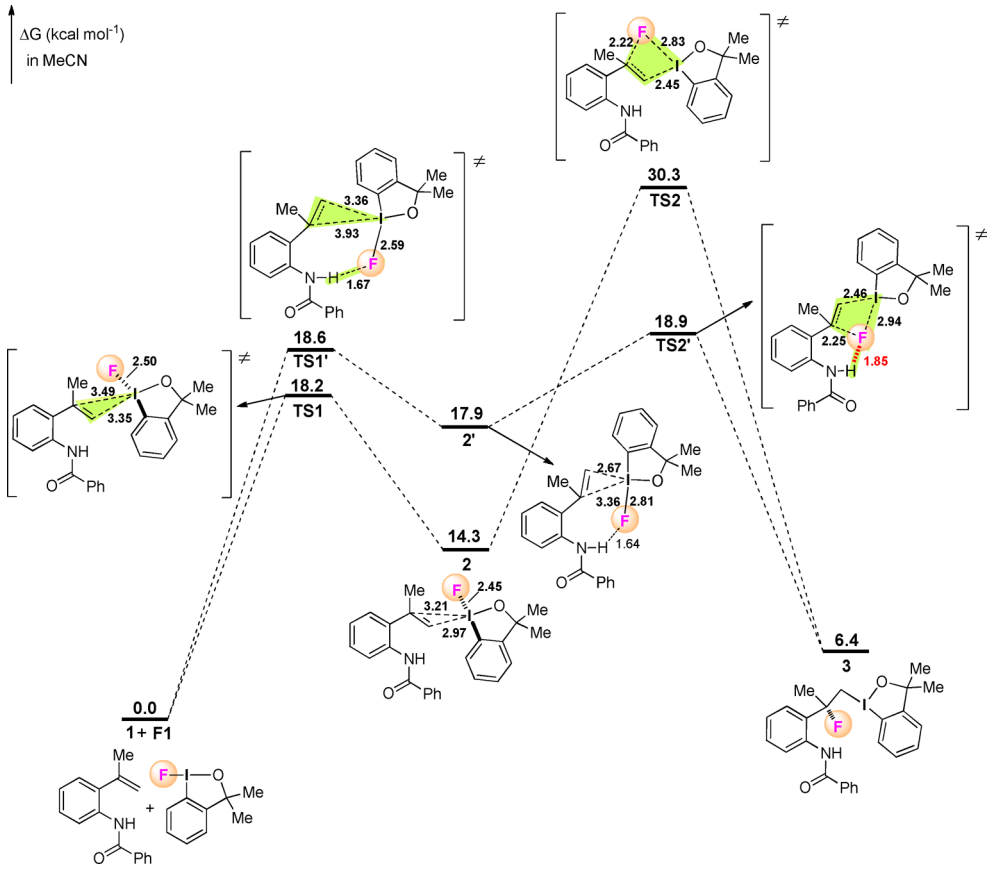


Figure 2. Calculated potential energy surface for the fluorination step in the fluorocyclization of *o*-styryl benzamide with fluoroiodane **F1** at the (SMD)MN12-L/[6-311++G(d, p)+SDD(I)]//(SMD)B97-D/[6-31+G(d)+SDD(I)] level of theory.

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solvation model[22] was used to account for the effects of acetonitrile solution. All optimized structures were confirmed by frequency calculations to be either minima or transition states at the same level of theory. To obtain more accurate electronic energies, single-point energy calculations were performed at the (SMD)MN12-L/[6-311++G(d,p)+SDD(I)] and (SMD)B97-D/[6-311++G(d, p)+SDD(I)] levels with the (SMD)B97-D/6-31+G(d) optimized structures. Structures were generated using CYLview.[23] Reported free energies are in kcal mol^{-1} in the solution phase. All calculations were carried out with Gaussian 09 packages.[24]

3. RESULTS AND DISCUSSION

Previously, Gulder et al. proposed a fluorination/1,2-aryl migration/cyclization cascade mechanism (Scheme 2) for the formation of seven-membered benzoxazepine **P1**.[15] In this, the first step is the nucleophilic attack of fluoroiodane **F1** by the olefinic double bond, leading to iodo(III)ranium ion **2**. Then, the three-membered heterocycle is selectively opened at the benzylic position proceeding via an intramolecular 1,2-fluoro shift to form intermediate **3**. Subsequent displacement of the iodobenzene by nucleophilic attack of the aryl ring gives cyclopropyl compound **4**, which was hypothesized to be in equilibrium with the phenonium ion. Finally, ring opening of the spirocyclopropyl ring proceeds through a 6-endo cyclization with simultaneous ring expansion, affording **P1**.

The calculation predicted that the nucleophilic attack of fluoroiodane **F1** by the olefinic double bond in *o*-styryl benzamide **1**, affording intermediate **2**, is a facile process with an activation free energy of 18.2 kcal mol^{-1} (**TS1**, Figure 2). However, the activation barrier for the subsequent intramolecular 1,2-fluoro shift is very high, involving a transition state (**TS2**) that lies 30.3 kcal mol^{-1} above the ground state. Such a high barrier is not consistent with the rapid formation of the seven-membered benzoxazepine at room temperature.[15] We thus turned to alternative pathways for the formation of intermediate **3**.

Literature precedents have demonstrated that fluorination reactions of aryliodofluride reagents with various substrates can be facilitated in the presence of Brönsted/Lewis acids, which were hypothesized to be involved in the activation of aryliodofluride reagents through polarization of the I–F bond.[25,26] We reasoned that the amide functionality of *o*-styryl benzamide **1**

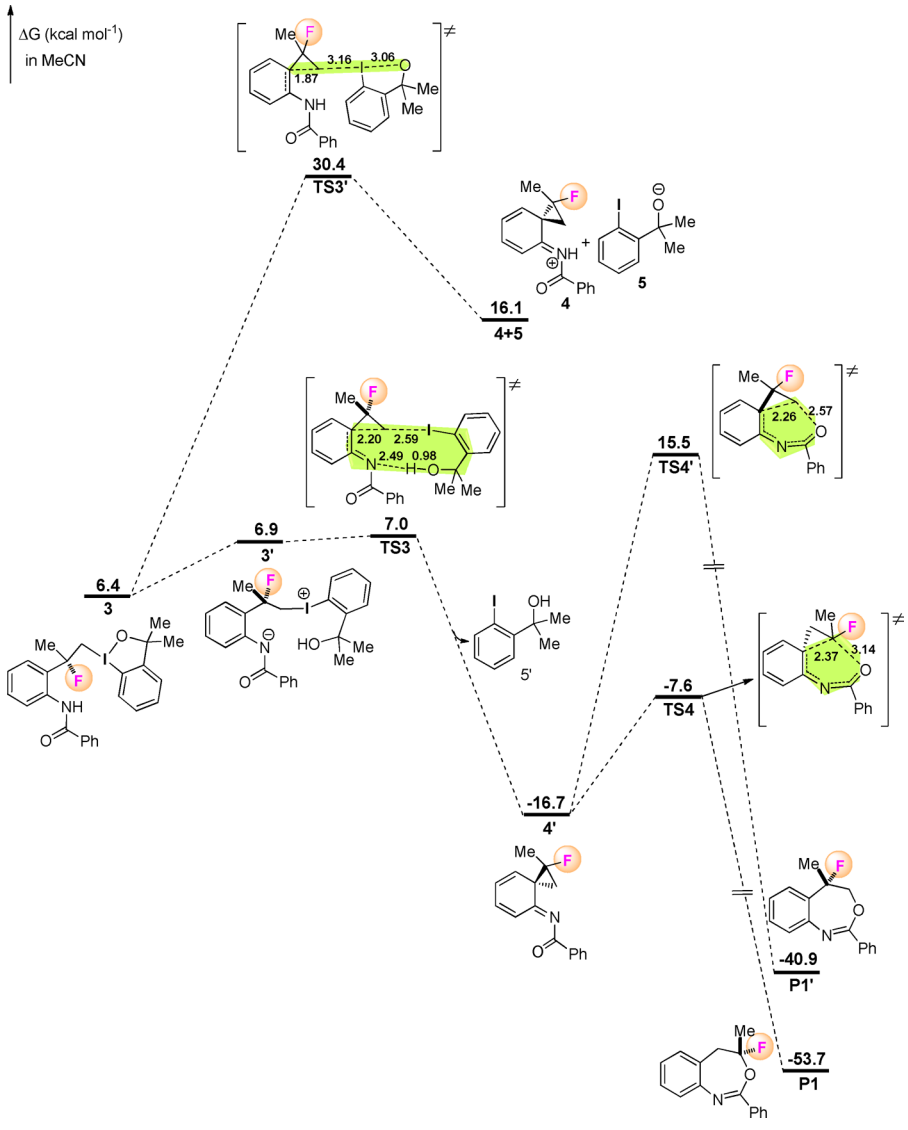

Figure 3. Calculated potential energy surface for 1,2-aryl migration and cyclization steps in the fluorocyclization of *o*-styryl benzamide with fluoroiodane **F1** at the (SMD)MN12-L/[6-311++G(d, p)+SDD(I)]//(SMD)B97-D/[6-31+G(d)+SDD(I)] level of theory.

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may serve as a hydrogen-bond donor to activate fluoroiodane **F1** (through a I–F···H–N hydrogen-bonding interaction[27]) to facilitate the intramolecular 1,2-fluoro shift process. Indeed, the activation energy barrier for the amide group assisted formation of the C–F bond via **TS2′** is significantly reduced: **TS2′** is 11.4 kcal mol^{-1} more stable than **TS2**. This result has an important implication for the development of new reactions: The presence of a hydrogen-bond donor such as the amide group in substrates is crucial for this type of fluorocyclization reaction. Intermediate **3** was found to lie 6.4 kcal mol^{-1} above the reactants.

In the previously proposed mechanism (Scheme 2), the formation of intermediate **3** is followed by the displacement of iodobenzene by nucleophilic attack of the aryl ring to afford cyclopropyl intermediate **4** (Scheme 2).[15] However, direct displacement of the iodobenzene by nucleophilic attack of the aryl ring proceeding via **TS3′** was calculated to have a very high activation free energy barrier of 24.0 kcal mol^{-1} relative to **3** (Figure 3). Alternatively, upon proton transfer from the N–H moiety of *o*-styryl benzamide **1** to the O atom of fluoroiodane **F1**, the activation barrier for the displacement (leading to **4′**) could be substantially reduced (**TS3** is 23.4 kcal mol^{-1} more stable than **TS3′**, as shown in Figure 3).

The final step is the ring opening of the spirocyclopropyl ring in intermediate **4′** (instead of **4**) with simultaneous ring expansion to furnish the seven-ring product **P1**. For the ring expansion process, the nucleophilic attack of the amide oxygen could occur either at the F-bearing carbon atom (more electrophilic) or at the unsubstituted carbon atom (less electrophilic) of the cyclopropane unit.[15] It can be seen from Figure 3 that attacking the F-bearing carbon atom is preferred over attacking the unsubstituted carbon by ca. 23 kcal mol^{-1}, thereby rationalizing the experimental observation that only **P1** was obtained in this reaction.[15]

Reviewing the calculated energy profile of the overall reaction pathway for the formation of seven-membered benzoxazepine **P1**, we found that the amide group assisted C–F bond formation is the rate-limiting step, with an overall activation free energy of 18.9 kcal mol^{-1} in acetonitrile. The formation of **P1** is highly exergonic (−53.7 kcal mol^{-1}). On the other hand, the activation free energy for the formation of six-membered oxazine **P2** via **TS5** was calculated to be as high as 38.2 kcal mol^{-1} (Figure 4), which is at least 19 kcal mol^{-1} higher in energy than that required for the formation of seven-membered benzoxazepine **P1**. This could be the reason why **P2** was not observed.[15] Interestingly, the activation free energy for the formation of six-membered oxazine **P2** is drastically lowered to 19.1 kcal mol^{-1} (**TS6**, Figure 4) when the fluorine source is changed from fluoroiodane **F1** to Selectfluor **F2**. Therefore, although the formation of six-membered oxazine **P2** is kinetically unfavorable ($\Delta G^{\ddagger}$: 38.2 kcal mol^{-1}) with fluoroiodane **F1**, it is a kinetically favorable process when using Selectfluor **F2** as the electrophilic fluorine source. This could explain the experimentally observed chemoselectivity switch.

Insights into the different reactivity pattern between fluoroiodane **F1** and Selectfluor **F2** can be gained from the calculated atomic charges. As shown in Scheme 3, the F atom carries −0.567*e* in **F1**, whereas it carries 0.243*e* in **F2**, indicating that electrophilic fluorine transfer from **F1** should be much less favorable than from **F2**. Moreover, the I(III) atom in fluoroiodane **F1** carries 0.900*e* and thus should be the most electrophilic site. Accordingly, nucleophilic attack of fluoroiodane **F1** would occur at the most electrophilic I(III) atom instead of the nucleophilic F atom. Consequently, fluoroiodane **F1** would display a different reactivity pattern compared with that of traditional electrophilic N–F fluorinating agents.

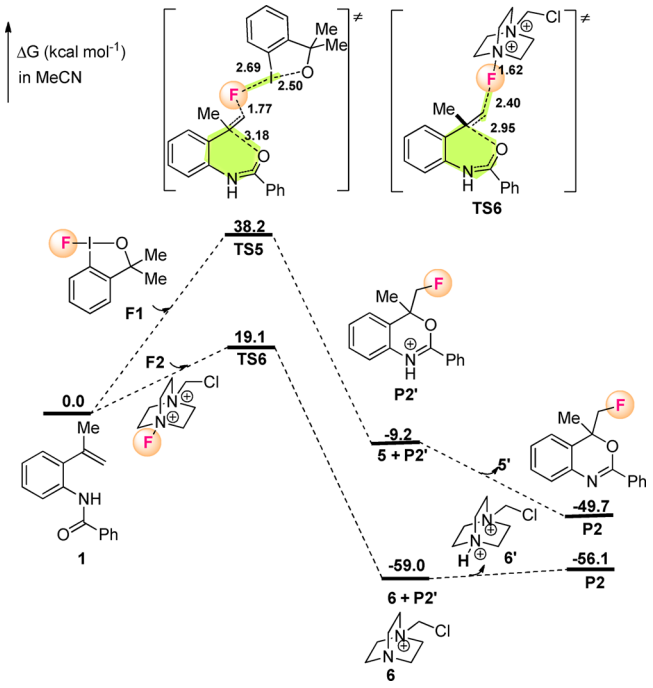
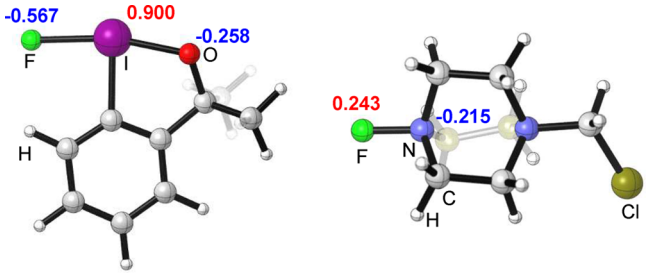


Figure 4. Calculated potential energy surfaces for the formation of six-membered oxazine **P2** from the fluorocyclization of *o*-styryl benzamide with fluoroiodane **F1** and Selectfluor **F2** at the (SMD)MN12-L/[6-311++G(d, p)+SDD(I)]//(SMD)B97-D/[6-31+G(d)+SDD(I)] level of theory.

Scheme 3. Calculated Mulliken Charges for Fluoroiodane F1 and Selectfluor F2 using (SMD)MN12-L/[6-311++G(d, p)+SDD(I)]//(SMD)B97-D/[6-31+G(d)+SDD(I)]



4. CONCLUSIONS

The mechanism and origin of the unexpected fluorocyclization chemoselectivity of *o*-styryl benzamide with a cyclic hypervalent fluoroiodane reagent were revealed through DFT calculations. The calculations uncovered a novel mechanism for the formation of unprecedented seven-membered 4-fluoro-1,3-benzoxazepines that are pharmacologically very interesting heterocycles. The new mechanism well rationalizes the observed intriguing chemoselectivity. In contrast to common electrophilic N–F reagents, the F atom in the hypervalent fluoroiodane reagent is nucleophilic, and the I(III) atom is, in fact, the most electrophilic site, therefore inducing a completely different reactivity pattern. The mechanistic insights disclosed in this study should facilitate the future development of new fluorination reactions based on the hypervalent fluoroiodane reagent.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01642.

Calculated potential energy surface for the fluorocyclization of *o*-styryl benzamide with fluoroiodane **F1** and optimized geometries of all computed species (PDF)

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Notes

The authors declare no competing financial interest.

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