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Communication

Could London Dispersion Force Control Regioselective (2 + 2) Cyclodimerizations of Benzynes? YES: Application to the Synthesis of Helical Biphenylenes

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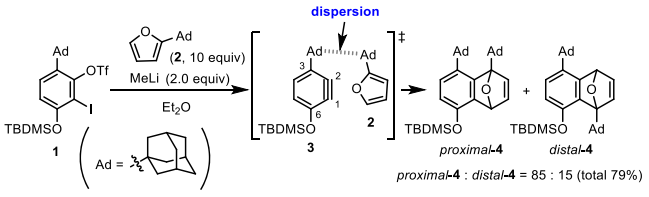
ABSTRACT: In recent years, London dispersion interactions, which are the attractive component of the van der Waals potential, have been found to play an important role in controlling the regio- and/or stereoselectivity of various reactions. Particularly, the dispersion interactions between substrates and catalysts (or ligands) are dominant in various selective catalyzes. In contrast, repulsive steric interactions, rather than the attractive dispersion interactions, between bulky substituents are predominant in most of the noncatalytic reactions. Herein, we demonstrate the first example of London dispersion-controlled noncatalytic (2 + 2) cyclodimerization of substituted benzynes to selectively afford proximal biphenylenes in high yields and regioselectivities, depending on the extent of dispersion interactions in the substituents. This method can be applied for the synthesis of novel helical biphenylenes, which would be fascinating for chemists as these compounds are potential skeletons for ligands, catalysts, and medicines.

London dispersion interactions are the attractive interactions among instantaneous dipoles of molecular fragments.[1] Although they are considered to be weak interactions, they exist in all molecules, and the strength of the interaction increases remarkably with increasing molecular size. London dispersion forces have recently been gaining prominence in organic synthesis and have been vital in controlling substrate−catalyst (or ligand) interactions in several catalytic processes.[2,3] In contrast, reports on the involvement of London dispersion interactions between the substrates in noncatalytic reactions are sparse.[4]

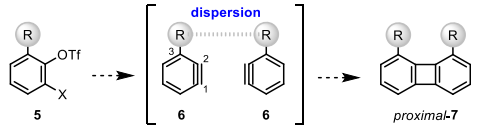
Yamaguchi et al. reported an intriguing regioselective [4 + 2] cycloaddition reaction between 3-adamantylbenzyne **3**, generated from precursor **1**, and 2-adamantylfuran **2** (Scheme 1).[5,6] A good yield of *proximal*-**4**, which contained two sterically hindered adamantyl groups on the same side, was obtained as the major product. The authors in one of the key reviews on London dispersion interactions opined that the formation of *proximal*-**4** might be favored because of the attractive dispersion interaction between the two large alkyl groups,[2b] although the bulky TBDMSO- group on benzyne **3** might enhance the regioselectivity.[7,8]

Scheme 1. Regioselective Cycloaddition between 3 and 2



The (2 + 2) cyclodimerization of benzynes to biphenylenes has been known for a long time.[9−11] However, the reactions are generally low yielding and occur as side reactions. Recently, Müllen et al. reported an elegant synthesis of graphenes using (2 + 2) cyclodimerization of benzynes.[9f] However, only three symmetrically substituted benzynes were employed as substrates in their study, and the biphenylenes were obtained in 10%−17% isolated yields. Substituted biphenylenes are potential skeletons of new ligands, catalysts, and medicines, and therefore, the regiocontrol of the (2 + 2) cyclodimerizations of unsymmetrically substituted benzynes, which

Scheme 2. Proposed Hypothesis for London Dispersion-Controlled (2 + 2) Cyclodimerizations of Benzynes 6



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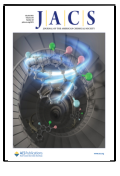

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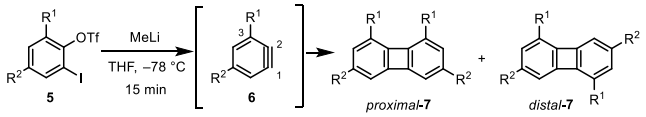
have never been reported so far,[12,13] is urgent and in high demand.

We hypothesized that the relatively strong London dispersion interaction of the sterically hindered substituents R on benzynes **6** at the 3-position should enable direct regioselective (2 + 2) cyclodimerization reactions for accessing *proximal*-**7** in good yields (Scheme 2).

First, we generated a wide variety of 3-substituted benzynes **6** from 2-iodophenyl triflates **5** in the absence of arynophiles using MeLi in THF at −78 °C (Table 1). Unsubstituted

Table 1. (2 + 2) Cyclodimerization Regioselectivities of 3-Substituted Benzynes 6[a]



entry	R^1	R^2	5, 6	ratio[b] *proximal*:*distal*	7	yield (%)[c]
1	H	H	**5a**, **6a**	–	**7a**	20[d]
2	OMe	H	**5b**, **6b**	–	**7b**	0[e]
3	Me	Me	**5c**, **6c**	1.1:1	**7c**	36
4	$SiMe_3$	Me	**5d**, **6d**	1.1:1	**7d**	85[d]
5	Si(*t*-Bu)Me_2	Me	**5e**, **6e**	7.0:1	**7e**	80[d]
6	Si(*i*-Pr)$_3$	Me	**5f**, **6f**	9.5:1	**7f**	56[d]
7	*i*-Pr	*i*-Pr	**5g**, **6g**	7.7:1	**7g**	51[d]
8	*t*-Bu	Me	**5h**, **6h**	16:1	**7h**	52
9	Ad[f]	Me	**5i**, **6i**	>20:1[g]	**7i**	54

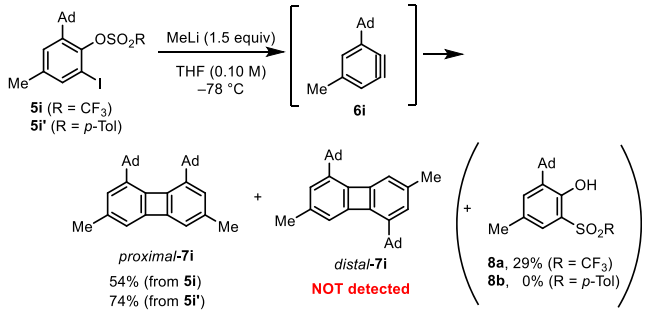
[a]Conditions: 1.0 equiv of **5**, 1.5 equiv of MeLi in THF (0.10 M) at −78 °C for 15 min. [b]Ratio between *proximal*-**7** and *distal*-**7** was determined by ^{1}H NMR analysis of crude products. [c]Combined isolated yield of **7**. [d]Combined ^{1}H NMR yield of **7**. [e]Complex mixture was obtained. [f]Ad = adamantyl. [g]*distal*-**7i** could not be detected.

benzyne **6a** underwent (2 + 2) cyclodimerization to provide biphenylene **7a** in 20% yield (entry 1); however, 3-methoxybenzyne **6b**, which is known to give coupling products in good yield with varieous arynophiles, did not afford biphenylenes **7b** (entry 2).[12] The reaction of 3-methylbenzyne **6c** gave *proximal*-**7c** and *distal*-**7c** in a 1.1:1 ratio in a combined 36% yield (entry 3). In contrast, a similar reaction with 3-(trimethylsilyl)benzyne **6d** produced the corresponding biphenylene **7d** in 85% yield, albeit with poor regioselectivity (1.1:1) (entry 4). Eventually, we were delighted to see the expected proximal selectivity (7.0:1) and good yield (80%) when a *tert*-butyldimethylsilyl (TBDMS) group was adopted as the directing group (entry 5). The reaction with the triisopropylsilyl (TIPS) directing group exhibited in higher regioselectivity (9.5:1) (entry 6).

Next, we surveyed the alkyl directing groups (entries 7−9). The ratio of the proximal and distal biphenylenes **7g** was 7.7:1 using 3-isopropylbenzyne **6g**, and the combined yield of these two products was 51% (entry 7). Notably, the proximal selectivities improved according to the bulkiness of the R^1 alkyl substituent (entries 3, 7, and 8). Finally, the (2 + 2) cyclodimerization of 3-adamantylbenzyne **6i** provided *proximal*-**7i** exclusively in 54% yield (entry 9). These results (Table 1) indicate that the London dispersion interaction between the C3-directing groups successfully controls not only the orientation of the reactions but also the product yields.

In the conversion of **5i**, a significant amount (29%) of the thia-Fries rearrangement side-product **8a** was observed,[14] which *cannot be formed via benzyne* ***6i*** (Scheme 3). The **8a**

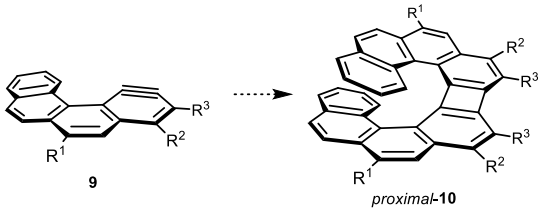
Scheme 3. Inhibition of Thia-Fries Rearrangement



formation indicated that the yield of *proximal*-**7i** could be improved further by improving the benzyne generation from precursor **5**. After several trials, a new 3-adamantylbenzyne precursor **5i′**, bearing the *p*-toluenesulfonyloxy moiety, was found as the leaving group and improved the yield of *proximal*-**7i** to 74%, while maintaining complete proximal selectivity, with the absence of the thia-Fries rearrangement product **8b** (Scheme 3). These varied results are likely due to the higher bond strength of the O−S single bond of the *p*-toluenesulfonyloxy group than that of the trifluoromethanesulfonyloxy group.

With these exciting results in hand, we hypothesized that more attractive helical biphenylenes,[15] such as *proximal*-**10**, could be synthesized through the proximal-selective (2 + 2) cyclodimerization of the fused tetracyclic benzyne **9**. We expected that the $\pi-\pi$ interaction between two molecules of **9**, which is the key contributor of the dispersion force, would work well as in the case of **6i** (Scheme 4).[16]

Scheme 4. Proximal-Selective (2 + 2) Cyclodimerization of Benzo[*c*]phenanthryne 9 and Synthesis of Helical Biphenylenes, *proximal*-10



Before experimental verification of this hypothesis (Scheme 4), we conducted several theoretical studies (Figures 1 and 2). The optimized structure of the desired product *proximal*-**10a** (R^1−R^3 = H) and undesired *distal-syn*-**10a** and *distal-anti*-**10a** were calculated at the B3LYP-D3(BJ)/PCM/def2-TZVP level, where the Conductor-like Polarizable Continuum Model (PCM) was adopted for including the solvent effects of tetrahydrofuran (THF). The free energy difference among them was evaluated at the DLPNO-CCSD(T)/def2-TZVP level. Notably, the energy of the most sterically demanding *proximal*-**10a** was the lowest and was 6.0 kcal/mol lower than that of *distal-anti*-**10a** [Figure 1(a)]. While this large stabilization of *proximal*-**10a** was unexpected, it would be desirable for achieving regioselective (2 + 2) cyclodimerizations of fused benzynes **9**. To rationalize the stability of

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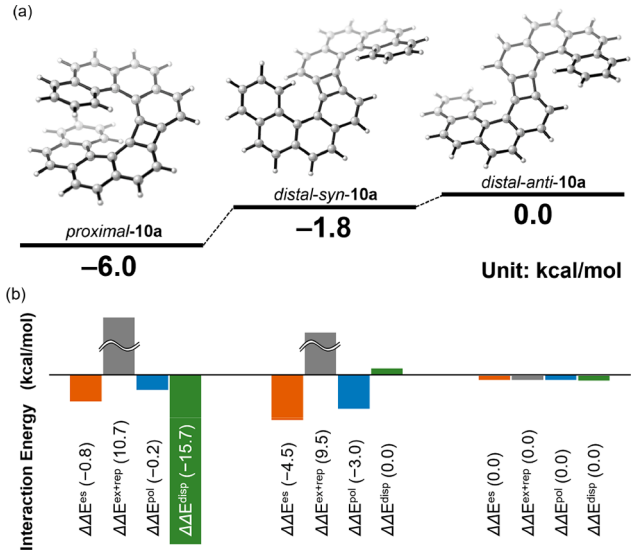


Figure 1. (a) Total molecular energy difference among *proximal*-**10a**, *distal-syn*-**10a**, and *distal-anti*-**10a** (DLPNO-CCSD(T)/def2-TZVP//B3LYP-D3(BJ)/PCM/def2-TZVP). (b) Energy decomposition analysis (EDA) (MP2/cc-pVDZ//B3LYP-D3(BJ)/PCM/def2-TZVP). E_{es}: Electrostatic interaction energy. E_{ex+rep}: Exchange-repulsion energy. E_{pol}: Polarization energy. E_{disp}: Dispersion interaction energy.

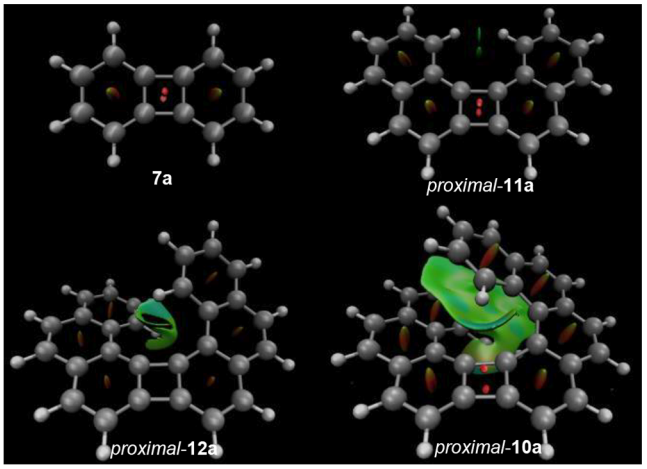


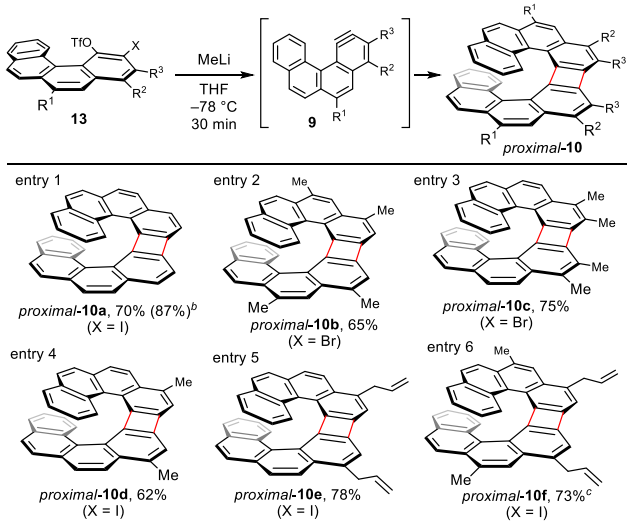
Figure 2. Noncovalent interaction (NCI) plots (s = 0.6 au/−3.0 < ρ < +3.0 au). Repulsion is color-coded red, and attractive interaction is color-coded green. Geometry optimization: B3LYP-D3(BJ)/PCM/def2-TZVP, solvent: THF.

proximal-**10a**, the energy decomposition analyses (EDA) of *proximal*-**10a**, *distal-syn*-**10a**, and *distal-anti*-**10a** were performed at the MP2/cc-pVDZ//B3LYP-D3(BJ)/PCM/def2-TZVP level [Figure 1(b)].[17,18] The EDA results indicated that the large dispersion component of *proximal*-**10a**, which is the main part of the $\pi-\pi$ interaction, should be the most important contributor to the stabilization of *proximal*-**10a** despite its highest steric interaction.

The noncovalent interaction (NCI) plots[19] of the optimized biphenylene **7a** and multifused biphenylenes, *proximal*-**11a**, *proximal*-**12a**, and *proximal*-**10a**, were obtained by DFT calculation (B3LYP-D3(BJ)/PCM/def2-TZVP, Figure 2). Biphenylene **7a** and *proximal*-**11a**, which are the (2 + 2) cyclodimerization products of benzyne **6a** and 1,2-naphthalyne **S1**, respectively, have completely flat structures and show almost no intramolecular interactions in their structure. The structure of *proximal*-**12a**, which might be formed from the tricyclic 1,2-phenanthlyne **S2**, is helical with minor overlapping of the aromatic rings and has a narrow NCI area (green part in Figure 2). On the other hand, the large attractive noncovalent interaction area, probably derived from $\pi-\pi$ attractive interaction, is observed in the expected helical (2 + 2) cyclodimerization product *proximal*-**10a** of the tetracyclicbenzyne **9a**. The stabilization of *proximal*-**10a** by intramolecular interactions renders its energy the lowest among **10a** isomers [Figure 1(a)]. We have evaluated the energy difference between B3LYP-D3(BJ) and B3LYP for evaluating the dispersion correction of the proximal products (see Figure S7 in the Supporting Information). With an increase in the number of the benzene rings, the energy difference increases, as the contact of the hydrophobic moieties increases. This means that dispersion interaction can control the stability of the proximal products at least at the equilibrium geometries. Although the (2 + 2) cyclodimerization of **9** may not be thermodynamically controlled, we expected that the dispersion interaction would also stabilize the transition state structures in the rate-determining step. Encouraged by the theoretical studies presented in Figures 1 and 2, we turned our attention to the experimental evaluation of the regioselective (2 + 2) cyclodimerizations of the tetracyclic benzynes **9**.

As expected, the helical molecules, *proximal*-**10a−f** were selectively obtained by the (2 + 2) cyclodimerization of fused tetracyclic benzynes, benzo[*c*]phenanthrynes **9**, generated from precursors **13**, in 62−78% isolated yields (Table 2). The

Table 2. Scope of (2 + 2) Cyclodimerizations of Benzo[*c*]phenanthrynes 9[a]



[a]Conditions: 1.0 equiv of **13**, 1.5 equiv of MeLi in THF (0.10 M) at −78 °C for 30 min. [b]Determined by ^{1}H NMR. [c]2.8 equiv of MeLi was used.

unsubstituted model compound, *proximal*-**10a**, was isolated in 70% yield with perfect regioselectivity (87% ^{1}H NMR yield, entry 1). Variations in the aromatic ring substituents, such as methyl and allyl groups, did not influence the high regioselectivity and high yield; regioisomers such as *distal*-**10b−10f** were not observed in the ^{1}H NMR analysis of the crude mixtures after the reactions in all cases.

It should be emphasized that the reaction of the bicyclic and tricyclic benzynes or naphthalyne **S1** and benzophenanthryne

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S2 did not produce any *proximal*-**11a**/**12a** or *distal*- **11a**/**12a** biphenylene derivatives under the same conditions. These results suggest that the dispersion interactions from the tetracyclic structure of benzynes **9** are important in the formation of the biphenylene derivative *proximal*-**10** in good yields. Additionally, the (2 + 2) cyclodimerization of fused benzyne **9d** generated from **13d** did not occur in toluene and gave a complex mixture, despite only the [4 + 2] cycloaddition of **9d** with 2,3-dimethylfuran in toluene (Supporting Information, Scheme S1).[7] This variation in reactivity is likely caused by the weakening of the intermolecular $\pi-\pi$ interactions among the fused benzyne molecules **9b** in toluene.

The structures of *proximal*-**10a, 10b**, **10d**, and **10e** were determined by single-crystal X-ray analysis. The two intramolecular head-to-tail aromatic π rings were clearly overlapped in the X-ray structure of *proximal*-**10a** (Figure 3). The shortest

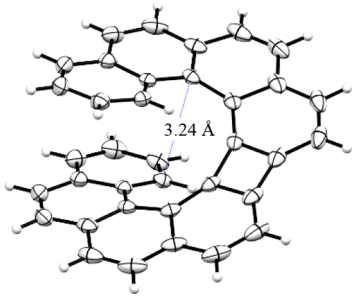
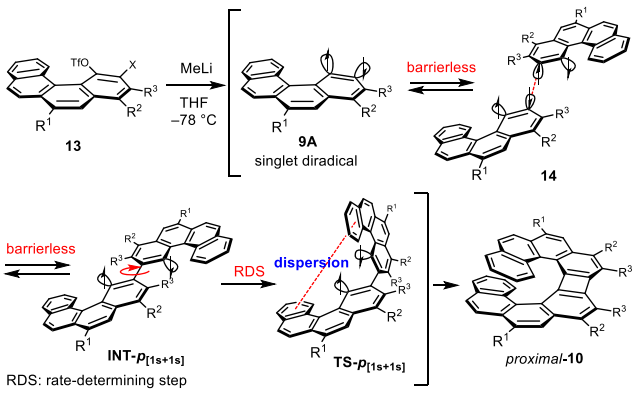


Figure 3. ORTEP structure of *proximal*-**10a**.

C−C length (3.24 Å) between these two π rings is shorter by 2-fold than that of the van der Waals' radius of a carbon atom (1.7 Å), which is in line with the results obtained from the NCI plots of *proximal*-**10a** with a large attractive interaction between them (Figure 2). The structures of *proximal*-**7e**, **7f**, **7h**, and **7i**, and *distal*-**7f** (Table 1) were also determined by X-ray analyses.

The mechanism of (2 + 2) cyclodimerizations of benzynes has not been theoretically studied in the past (see the Supporting Information).[20,21] A plausible reaction mechanism for the cyclodimerizations discussed above is shown in Scheme 5. The reaction mechanism likely comprises a stepwise transformation involving singlet diradical intermediate **9A**. Preliminary theoretical calculations indicated that the (2 + 2) cycloaddition reactions might commence from the one-to-one

Scheme 5. Plausible Reaction Mechanism of (2 + 2) Cyclodimerizations of Benzo[*c*]phenanthrynes 9



orbital interaction between the two **9A** molecules (as shown in **14**). The energy of the carbene intermediate **INT**-$p_{[2s+1s]}$, formed through a two-to-one interaction, is much higher (52.6 kcal/mol) than that of the diradical **INT**-$p_{[1s+1s]}$ formed through a one-to-one interaction (Figure S1). The reaction path for the formation of **INT**-$p_{[1s+1s]}$ seems to be barrierless, and the stabilization energy is quite low (≈0.1 kcal/mol, Figure S2). Therefore, the first step likely involves an equilibrium between the two diradicals **9A** and **INT**-$p_{[1s+1s]}$. Next, the aryl ring of **INT**-$p_{[1s+1s]}$ would rotate around the newly formed σ-bond, followed by complete rotation.[20d] The barrier for rotation around the $\pi-\pi$-bond of **INT**-$p_{[1s+1s]}$ was 4.6 kcal/mol, and the second step is likely the rate-determining step (RDS) (Figures S3 and S4).

We believe that the attractive London dispersion interactions between the extended π-systems of **9** would facilitate the rotation, and the energy of the transition state **TS**-$p_{[1s+1s]}$ might become lower than those of the other (2 + 2) cycloadditions of less fused benzynes, such as naphthalyne **S1** and phenanthlyne **S2**. Eventually, we could obtain *proximal*-**10** from tetracyclic benzynes **9** in good yields with excellent proximal selectivities (Table 2).

In conclusion, we developed London dispersion-controlled (2 + 2) cyclodimerizations of substituted benzynes. Notably, the proximal selectivities and yields of the products were linearly related to the strength of the London dispersion interactions between the substituents on the benzynes at the 3-position. The adamantyl group on the benzyne completely controlled the reaction and produced the proximal adduct exclusively in a good yield. The developed reactions were applied to the synthesis of helical molecules using fused tetracyclic benzynes. The obtained novel helical biphenylenes will serve as new chiral molecule platforms and will promote a wide array of applications. The applications and mechanistic studies using sophisticated theoretical calculations are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c05434.

General procedures, synthesis of benzyne precursors, analytical data, additional preliminary theoretical studies, and X-ray crystallography data (PDF)

NMR spectra (PDF)

Accession Codes

CCDC 2019842, 2019846, 2019852−2019854, 2019859, 2019862, 2019865, and 2035060 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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