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Rh(III)-Catalyzed Regioselective Annulations of 3-Arylisoxazolones and 3-Aryl-1,4,2-dioxazol-5-ones with Propargyl Alcohols: Access to 4-Arylisoquinolines and 4-Arylisoquinolones

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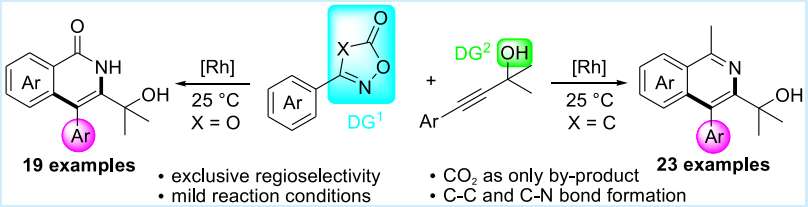
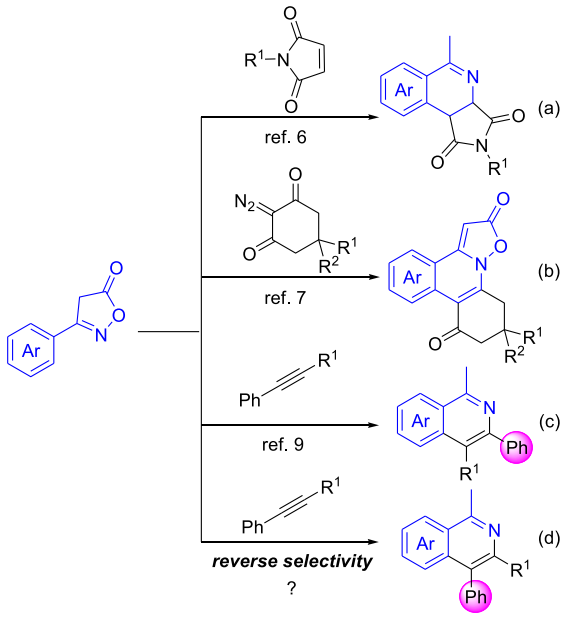


ABSTRACT: The Rh(III)-catalyzed dual directing group assisted C−H activation/annulation of 3-arylisoxazolones with propargyl alcohols has been developed, which expands the application scope of isoxazolones in organic synthesis. This protocol also worked well with 3-aryl-1,4,2-dioxazol-5-ones to produce synthetically and biologically important 4-arylisoquinolones.

Isoxazolones are very interesting as valuable building blocks in organic synthesis because of their diverse modes of reaction.[1] Consequently, significant advances have been made in spirocyclization of activated methylene with polar multiple bonds,[2] transition-metal-catalyzed N−O bond insertions,[3] decarboxylation of the isoxazolone ring,[4] and arylideneisoxazolone-based conjugated additions.[5] However, isoxazolones have rarely been explored as directing groups in the field of C−H functionalization. In 2020, Cui et al. described a Rh(III)-catalyzed ring-opening/C−H bond annulation of 3-arylisoxazolone with maleimides (Scheme 1a).[6] Recently, Shang et al. developed the Rh(III)-catalyzed cascade C−H activation/cyclization of 3-arylisoxazolones with cyclic 2-diazo-1,3-diketones (Scheme 1b).[7] Despite impressive innovations, both reactions are limited to the chemistry of 3-arylisoxazolones with nonalkyne coupling partners for the synthesis of isoquinoline-fused polycyclic compounds. Arguably, annulation reactions with alkynes are one of the most popular methods of this type.[8] However, reports on this type of reactions with alkynes are rather rare. To the best of our knowledge, so far only one example of cascade C−H activation/annulation of 3-arylisoxazolones with alkyne coupling partners was described. The pioneering work by Chiba reported a Rh(III)-catalyzed C−H activation/annulation of aryl ketone *O*-acyloxime with internal alkynes to access quinolines. Further, they extended the methodology to 3-arylisoxazolones by employing isoxazolones as a directing group (Scheme 1c).[9] Despite this elegant achievement, some important challenges are far from being addressed. The scope of internal alkynes as a coupling partner is still limited (mainly symmetrical diphenylacetylene). Further, regioselectivity of the insertion step is an unsolved problem when an unsymmetrical

Scheme 1. Research Background



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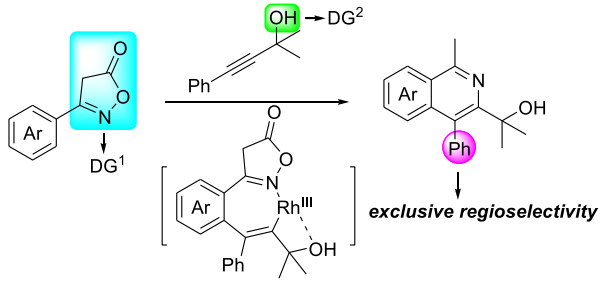
alkyne is involved in the reaction, in which the nucleophile always adds to the phenyl-substituted alkyne carbon atom. Motivated by the aforementioned information and in line with our ongoing interest in C−H functionalization,[10] we decided to explore the possibility of designing a new C−H activation/annulation of 3-arylisoxazolones to reverse the regioselectivity of alkyne insertion (Scheme 1d).

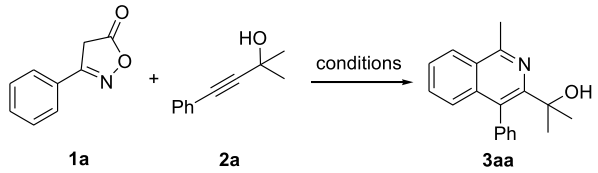
Propargyl alcohols are important classes of functionalized alkynes with an inherent hydroxyl group that can be easily accessible from terminal alkynes and carbonyl compounds.[11] There are a few reports of using tertiary propargyl alcohol such as 2-methyl-4-phenylbut-3-yn-2-ol as a coupling partner with different directing groups (DGs) to obtain benzo-fused heterocyclic compounds in transition-metal-catalyzed C−H functionalization.[12] As seen from these reports, one of the advantages of using this kind of functionalized alkynes as a coupling partner is the binding affinity potential of the hydroxyl group with the transition-metal catalyst which can control the regioselectivity for the insertion of unsymmetrical alkyne.[13] Inspired by these pioneering works, we envisioned an isoxazolone-directed C−H activation reaction with propargyl alcohols that can lead to a simple ring-opening/C−H bond activation followed by regioselective intramolecular annulation, where isoxazolone can function as a traceless DG paving the way to the formation of 3-hydroxyalkyl-4-arylisoquinoline derivatives and the hydroxyl group of propargyl alcohol can provide an interaction with metal catalyst as the second traceless DG to control the regioselectivity of the reaction (Scheme 2).

Scheme 2. Dual DG-Assisted Regioselective Annulation of 3-Arylisoxazolones with Propargyl Alcohols



Initially, we conducted a test reaction between 3-phenyl-5-isoxazolone **1a** and 2-methyl-4-phenylbut-3-yn-2-ol **2a** with 5 mol % catalysts $[RuCl_2(p\text{-cymene})]_2$/ $Cp^*Co(CO)I_2$/ $[Cp^*IrCl_2]_2$ and additive NaOAc (1.0 equiv) at 60 °C for 2 h in dichloroethane (DCE), which did not afford the expected product (Table 1, entries 1−3). Fortunately, attempts with 5 mol % of the $[Cp^*RhCl_2]_2$ catalyst in the place of other catalysts along with the aforementioned reaction conditions led to the desired product **3aa** in 54% yield (entry 4). In the crude NMR of this reaction, no regioisomer of **3aa** was observed, thus confirming the regioselectivity of the reaction. A subsequent nuclear Overhauser effect (NOE) experiment further confirmed the position of the tertiary alcohol at C-3. The structure of **3aa** was further confirmed by single-crystal X-ray diffraction analysis (CCDC 2088321). When other additives such as KOAc, $Zn(OAc)_2$, AgOAc, and CsOAc (entries 5−8) were used as the additive, the reaction worked better, producing **3aa** in 57−65% yield. Among them, CsOAc was the most effective one for the reaction with 65% yield

Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3aa

entry	catalyst[b]	additive	solvent	temp (°C)	time (h)	yield[c] (%)
1	**A**	NaOAc	DCE	60	2	NR
2	**B**	NaOAc	DCE	60	2	NR
3	**C**	NaOAc	DCE	60	2	NR
4	**D**	NaOAc	DCE	60	2	54
5	**D**	KOAc	DCE	60	2	61
6	**D**	$Zn(OAc)_2$	DCE	60	2	58
7	**D**	AgOAc	DCE	60	2	57
8	**D**	CsOAc	DCE	60	2	65
9	**D**	CsOAc	DCE	40	4	70
10	**D**	CsOAc	DCE	25	14	80 (61)[d]
11	**D**	CsOAc	MeCN	40	4	37
12	**D**	CsOAc	TFE	40	4	50
13	**D**	CsOAc	MeOH	40	4	54
14	**D**	CsOAc	THF	40	4	46
15	**D**	CsOAc	DCM	40	4	65

[a]Reactions were conducted with **1a** (0.1 mmol), **2a** (0.15 mmol), catalyst, and additive in solvent (1.5 mL). [b]Catalyst **A** = $[RuCl_2(p\text{-cymene})]_2$. Catalyst **B** = $Cp^*Co(CO)I_2$. Catalyst **C** = $[Cp^*IrCl_2]_2$. Catalyst **D** = $[Cp^*RhCl_2]_2$. [c]Isolated yields. [d]1.0 mmol scale reaction.

(entry 8). Encouraged by these results, we lowered the reaction temperature successively (entries 9 and 10). The results showed that the reaction could proceed smoothly under more mild conditions. At 25 °C, the product yield was 80%, although the reaction required 14 h reach completion (entry 10). Other reaction parameters were also evaluated, but with no further improvement. For instance, other solvents, including MeCN, trifluoroethanol (TFE), MeOH, tetrahydrofuran (THF), and dichloromethane (DCM), all led to low yields (entries 11−15 vs entry 9). Thus, the conditions of entry 10 were selected as the optimal conditions. To showcase the scalability of this method, a 1.0 mmol scale version of the model reaction was then examined. Without further optimization, the product **3aa** was obtained in 61% yield (entry 10).

Under the optimized conditions, the scope of this transformation was investigated (Scheme 3). First, the suitability of 3-aryl-5-isoxazolones **1** was examined by using 2-methyl-4-phenylbut-3-yn-2-ol **2a** as a model substrate. As shown in Scheme 3, various *para*-substituted 3-aryl-5-isoxazolones **1b**−**1f** bearing an electron-donating alkoxyl (OMe) and alkyl (Me) or electron-withdrawing halogen (F, Cl, and Br) substituents could react with **2a** smoothly to furnish cyclization products **3ba**−**3fa** in good yields. Moreover, the trifluoromethyl group, as a useful structural motif in many biologically active molecules,[14] also afforded the corresponding product **3ga**, albeit with low yield. The low yield could be due to the strongly electron-withdrawing effect of the CF_3 group. Besides *para*-substituted 3-aryl-5-isoxazolones, *meta*- and *ortho*-substitutions were also well tolerated in this reaction. For example, the introduction of a phenyl ring with a *m*-methyl or *m*-bromine group allowed the annulation reaction to give the products **3ha** and **3ia** with excellent regioselectivity in 65 and

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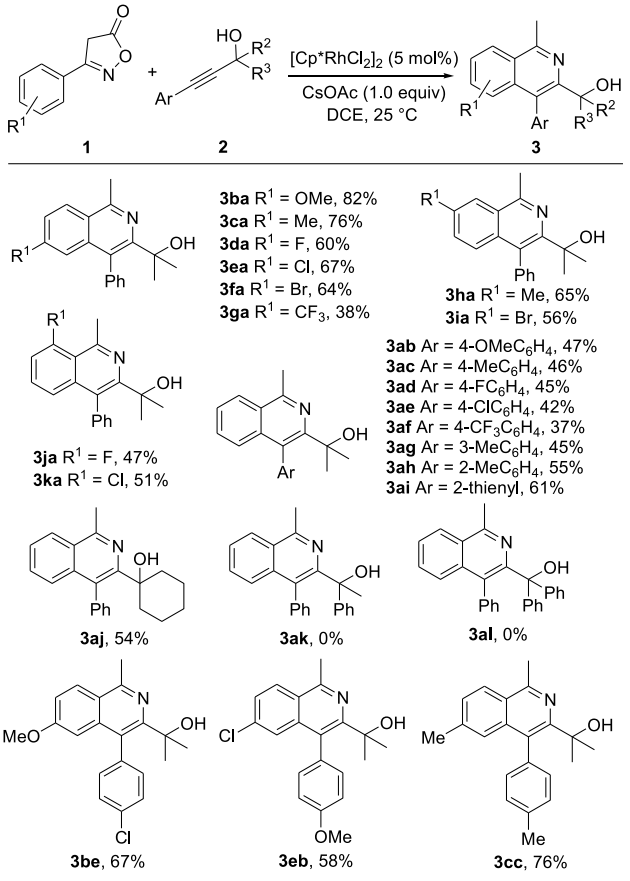
Scheme 3. Substrate Scope for the Synthesis of 4-Arylisoquinolines[a]

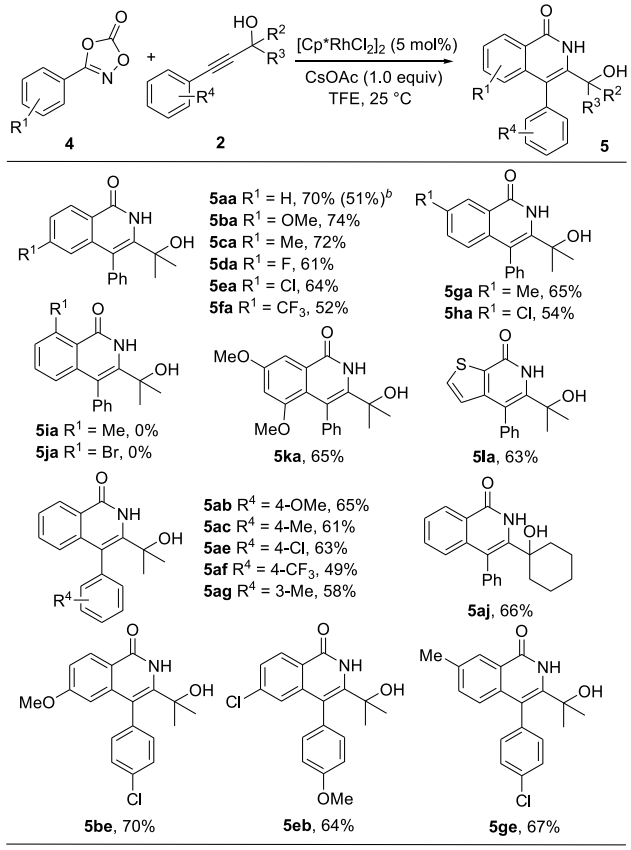


[a]Reactions were run on 0.1 mmol scale under the optimal conditions. Yields for isolated products.

56% yields, respectively. For **1** bearing an *ortho*-substituent such as **1j** and **1k**, the reaction also took place regioselectively on the less hindered *ortho* site to give **3ja** and **3ka**. We next set out to evaluate the tolerance of various propargyl alcohols **2** to our optimized reaction conditions. The results showed that while propargyl alcohols bearing electron-donating (**2b**, **2c**, **2g**, and **2h**) and electron-withdrawing (**2d**−**2f**) substituents on the phenyl ring were all suitable substrates to form the 4-arylisoquinoline products, the use of substituted propargyl alcohols leads to lower yields of the products (37−55%) when compared to the unsubstituted propargyl alcohol **2a**. When a 2-thienyl propargyl alcohol (**2i**) was subjected to the optimal reaction conditions, the reaction still work well to deliver the product **3ai** in 61% yield. The coupling reaction could also be extended to include propargyl alcohol **2j** bearing a cyclohexyl group as the R^2 and R^3 moieties, in which the reaction proceeded smoothly under standard reaction conditions to form compound **3aj** in 54% yield. To see if the reaction is suitable for other R^2 and R^3 units, the standard conditions were applied to 2,4-diphenylbut-3-yn-2-ol **2k** and 1,1,3-triphenylprop-2-yn-1-ol **2l**. However, neither of them gave the desired product, probably due to the steric hindrance effect. Finally, various substituted 3-aryl-5-isoxazolones **1** and propargyl alcohols **2** were subjected to the above optimal reaction conditions. To our delight, when there were substituents on both phenyl rings, the reaction could also produce the target products **3be**, **3eb**, and **3cc** in good yields. Unfortunately, 4-substituted 5-isoxazolones such as 4-methyl-3-phenylisoxazolone are not suitable reaction substrates currently because their reactions with **2a** did not give synthetically significant yields of products under the present conditions.

After realizing the construction of 4-arylisoquinolines through the simple cascade C−H activation/annulation, we conceived that the variation of the DG on the phenyl ring of compound **1** (from isoxazolone to dioxazolone) may result in the formation of 4-arylisoquinolone (Scheme 4). We initially

Scheme 4. Substrate Scope for the Synthesis of 4-Arylisoquinolones[a]



[a]Reactions were run on 0.1 mmol scale under the optimized conditions. Yields for isolated products. [b]1.0 mmol scale reaction.

attempted to react 3-phenyl-1,4,2-dioxazol-5-one **4a** with **2a** using the developed protocol. Fortunately, our methodology is equally efficient for the synthesis of 4-arylisoquinolone systems and the desired product **5aa** could be prepared in good yield by a slight modification of the experimental procedure. While performing this study, it was found that the yield was actually higher when the reaction was carried out in TFE solvent compared with other solvents, so all of the reactions with dioxazolones **4a**−**4l** were run in TFE. As shown in Scheme 4, when 3-phenyl-1,4,2-dioxazol-5-ones bearing various substituents were used as the substrate, the corresponding 4-arylisoquinolones were also obtained in good yield. We examined both electron-donating and electron-withdrawing groups on both aromatic rings in a manner similar to the investigation of 4-arylisoquinolines (Scheme 3). Various substrates with different substituents at the aromatic rings of 1,4,2-dioxazol-5-ones and propargyl alcohols were easily converted to the corresponding cyclization products in

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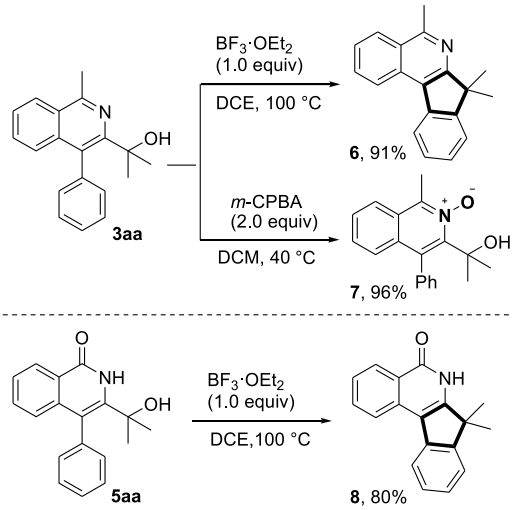
moderate to good yields. It is worth noting that multi-substituted 3-phenyl 1,4,2-dioxazol-5-one **4k** and heterocyclic 3-(thiophen-2-yl)-1,4,2-dioxazol-5-one **4l** were all uneventfully accommodated. However, no desired products **5ia** and **5ja** were observed when using the substrate possessing an *ortho* substituent at the phenyl ring (**4i** and **4j**), probably attributed to the *ortho*-position effect of the substituent.

To highlight the synthetic utility of this methodology, several chemical transformations were carried out (Scheme 5).

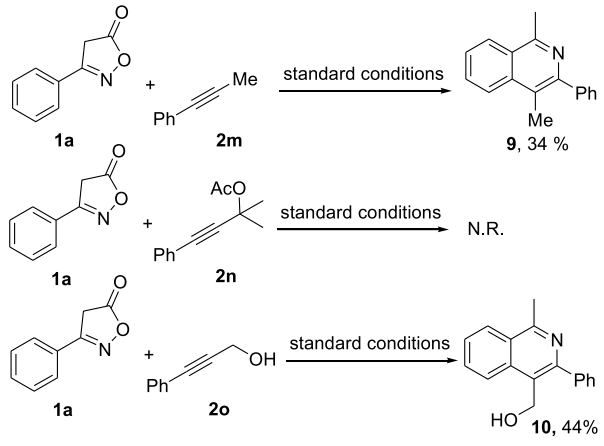
Scheme 5. Further Transformations



Treatment of 3-hydroxyalkyl-4-phenylisoquinoline **3aa** with $BF_3{\cdot}OEt_2$ in DCE at 100 °C afford fused polycyclic compound **6** in 91% yield. In addition, *N*-oxide **7** can be readily obtained by *m*-chloroperoxybenzoic acid (*m*-CPBA) oxidation of the parent isoquinoline **3aa** in DCM. The cyclization reaction of **5aa** was also achieved by $BF_3{\cdot}OEt_2$ in DCE to give compound **8** in 80% yield.

To gain more insights into the effect of the hydroxyl group for these transformations, several control experiments were conducted (Scheme 6). A control experiment between **1a** and 1-(prop-1-ynyl)benzene **2m** led to the formation of 3-phenyl-substituted product **9** with contrary regioselectivity compared with progargyl alcohols. When 2-methyl-4-phenylbut-3-yn-2-yl acetate **2n** was subjected to the standard conditions, no reaction was observed. These results showed that the hydroxyl

Scheme 6. Control Experiments



group in the propargyl alcohol is essential for the selective formation of 4-aryl-substituted products **3** and **4**. On the other hand, primary alcohol **2o** also resulted in contrary regioselectivity compared with tertiary alcohols, affording 3-phenyl-substituted product **10**. This result showed that the steric hindrance between *gem*-dimethyl and the C5-H of the substrates **1** and **4** might also be another reason for the regioselectivity in the present reaction.[13b,15]

On the basis of the experimental data obtained from control experiments and previous reports on Rh-catalyzed C−H activation reactions,[13,16] a possible reaction mechanism was proposed (Scheme S1). Initially, the reaction of $[Cp^*RhCl_2]_2$ complex with CsOAc forms an active catalyst $Cp^*Rh(OAc)_2$ **A**. Next, coordination of the nitrogen atom of the substrate **1** to **A** then undergoes a C−H activation to afford the five-membered rhodacycle **B**. The regioselective coordinative insertion of propargyl alcohol **2** into the C−Rh bond of complex **B** affords a seven-membered rhodacycle **D**, which would undergo the reductive elimination to generate intermediate **E** and rhodium(I) species. The intermediate **E** can be oxidized by the O−N bond to form rhodium(III) species **F** which is protonated to furnish the 4-arylisoquinoline **3** and regenerates the active catalyst for the next catalytic cycle. On the other hand, it should be noted that Glorius et al. have proposed an alternative mechanism for these kinds of systems where N−O bond cleavage occurs before reductive elimination to give a Rh(V) nitrene intermediate.[17]

In summary, we have developed an efficient Rh(III)-catalyzed C−H activation/annulation reaction between tertiary propargyl alcohols and 3-arylisoxazolones or 3-aryl-1,4,2-dioxazol-5-ones, which involves the significant challenges associated with controlling regioselectivity for the insertion of unsymmetrical alkyne. The hydroxyl group at the propargyl alcohol moiety behaved as the second traceless DG to control the regioselectivity of the reaction, leading to the selective formation of 3-hydroxyalkyl-4-arylisoquinoline or 4-arylisoquinolone derivatives rather than the 3-arylisoquinoline or 3-arylisoquinolone ones. To the best of our knowledge, this represents the first example of regioselective coupling between alkynes and 3-arylisoxazolones or 3-aryl-1,4,2-dioxazol-5-ones.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02049.

Experimental procedures, characterization data, copies of NMR spectra of compounds, and X-ray crystal structure of **3aa** (PDF)

Accession Codes

CCDC 2088321 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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