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Atroposelective Synthesis of *N*-Arylindoles via Enantioselective N−H Bond Insertion

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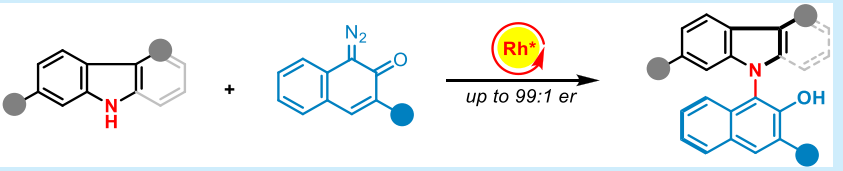


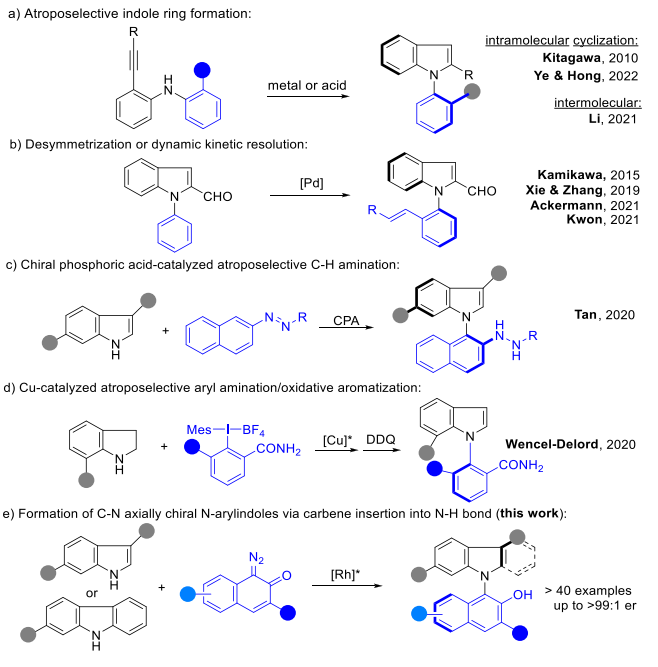
ABSTRACT: We present here a rhodium-catalyzed asymmetric N−H insertion reaction, which is a concerted process revealed by DFT calculations, for the synthesis of novel axially chiral *N*-arylindoles by the reaction between indoles and diazonaphthoquinones. The reaction occurs at the N1 rather than C2/C3 positions of indoles, providing the chiral *N*-arylindoles in good yields and excellent enantiomeric ratios. Furthermore, this protocol is also amenable to the synthesis of chiral *N*-arylcarbazoles with excellent enantiocontrol.

C−N axially chiral *N*-arylindoles are key structural motifs in chiral ligands and natural products.[1] Compared with the well-established methods for the synthesis of chiral 6/6 membered biaryls,[2] the enantioselective construction of C−N axially chiral compounds,[3] especially *N*-arylindoles, remains challenging.[4]

For the synthesis of axially chiral *N*-arylindoles, three types of strategies have been commonly used. In 2010, Kitagawa pioneered the first atroposelective synthesis via a Pd-catalyzed cyclization of *o*-alkynylanilines (Scheme 1a).[5] Recently, Li described a Rh-catalyzed [3 + 2] annulation of anilines with internal alkynes via C−H bond activation.[6] Ye reported an elegant Brønsted acid-catalyzed cyclization of ynamides.[7] Besides these reactions,[8] the catalytic desymmetrization and C−H olefination have also been utilized by Kamikawa,[9] Xie,[10] Ackermann[11] and Kwon,[12] respectively (Scheme 1b). In addition, direct amination reactions, which are the most efficient ones, have also been reported. For example, Tan developed the first phosphoric acid catalyzed C−H amination to give atropisomeric *N*-arylindoles (Scheme 1c).[13] Wencel-Delord reported a copper-catalyzed atroposelective amination of indolines with hypervalent iodine reagents followed by oxidative aromatization to produce the *N*-arylindoles (Scheme 1d).[14]

Antonchick and Waldmann[15] pioneered the use of diazonaphthoquinones in constructing axial biaryls via chelation-assisted C−H activation. Other groups also applied diazonaphthoquinones in preparing chiral biaryls.[16] Recently, we reported the first atroposelective synthesis of chiral biaryls via a C−H bond insertion reaction,[17] which proceeds through the initial formation of central chirality followed by the point-to-axis chirality transfer. Wang described an elegant atroposelective synthesis of chiral *N*-arylindolocarbazoles via

Scheme 1. Access to Axially Chiral *N*-Arylindoles



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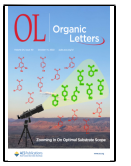
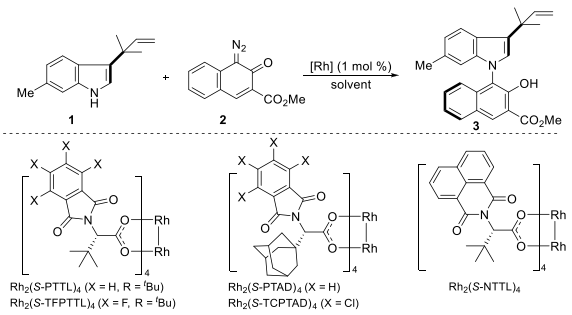


N−H insertion (NHI) reaction, but they only used one typical type of substrate.[18] Here we report our effort to synthesize axially chiral *N*-arylindoles by direct carbene insertion using indoles and carbazoles as the N−H nucleophiles (Scheme 1e).

We commenced our studies by using indole **1** and diazo **2** to optimize this reaction (Table 1). We first tried to use

Table 1. Optimization of the Reaction Conditions[a]



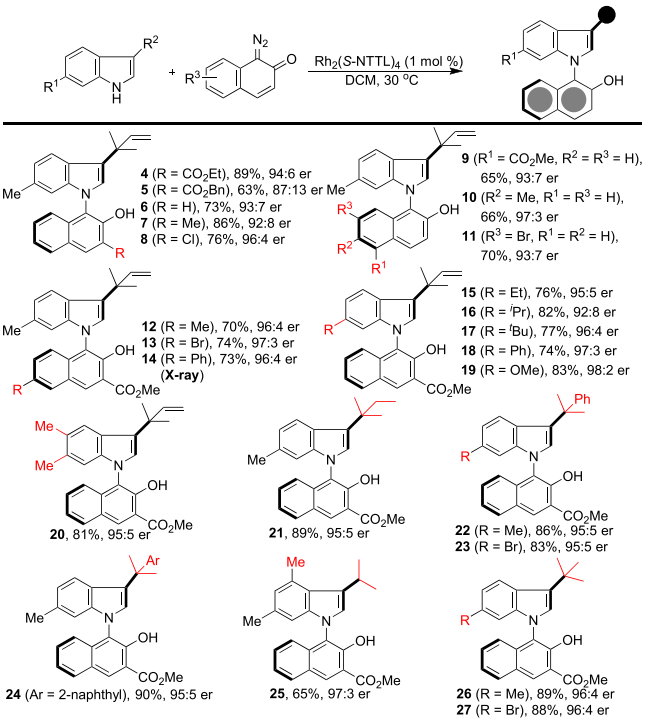
entry	Rh_2L_4	solvent	T (°C)	yield (%)[b]	er (%)[c]
1	Rh_2(*S*-PTTL)$_4$	CH_2Cl_2	30	71	89:11
2	Rh_2(*S*-TFPTTL)$_4$	CH_2Cl_2	30	66	90:10
3	Rh_2(*S*-PTAD)$_4$	CH_2Cl_2	30	58	88:12
4	Rh_2(*S*-TCPTAD)$_4$	CH_2Cl_2	30	55	93:7
5	Rh_2(*S*-NTTL)$_4$	CH_2Cl_2	30	70	96:4
6	Rh_2(*S*-NTTL)$_4$	DCE	30	67	95:5
7	Rh_2(*S*-NTTL)$_4$	toluene	30	66	96:4
8	Rh_2(*S*-NTTL)$_4$	hexane	30	<5	–
9	Rh_2(*S*-NTTL)$_4$	CH_2Cl_2	10	42	97:3
10	Rh_2(*S*-NTTL)$_4$	CH_2Cl_2	40	70	96:4
11[d]	Rh_2(*S*-NTTL)$_4$	CH_2Cl_2	30	87	96:4

[a]Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), catalyst (1 mol %) in 2 mL solvent and was stirred for 4 h. [b]Isolated yields. [c]Determined by chiral HPLC analysis. [d]0.26 mmol of **2** was used.

palladium catalysts,[19] finding that those attempts gave **3** in good yields but zero enantiomeric ratio (er). Encouraged by our recent achievements on the asymmetric N−H/C−H insertion reactions,[17,20] we then tested the chiral dirhodium tetracarboxylates in dichloromethane at 30 °C (Table 1). Both Rh_2(*S*-PTTL)$_4$[21] and Rh_2(*S*-TFPTTL)$_4$[22] afforded **3** in moderate yields and enantioselectivities (entries 1 and 2). Changing the *tert*-butyl to adamantyl in the skeleton of the catalyst, the resulting Rh_2(*S*-TCPTAD)$_4$[23] showed lower catalytic activity, albeit with slightly higher er (entries 3 and 4). To our delight, catalyst Rh_2(*S*-NTTL)$_4$[24] gave a promising result because **3** was obtained in 70% yield and a 96:4 er (entry 5). The use of other solvents and reaction temperatures gave inferior results (entries 6−10). However, changing the ratio of **1** to **2** from 1.5 to 1.3 increased the yield to 87% without erosion of the er (entry 11). Therefore, we chose entry 11 as the optimal conditions for studying the reaction scope.

First, various 1-diazonaphthoquinones were examined (Scheme 2). Substrate **4** with an ethyl group gave similar yield and slightly decreased er (89% yield and 94:6 er) compared to substrate **2** with a methyl group, while substrate **5** with a Bn group gave dramatically lower yield and er. To identify whether the 3′-ester in the substrate was crucial or not, we then tested substrates by replacing the ester group with a hydrogen, a methyl, and a chloro group. We found that biaryls **6** (in 73% yield and 93:7 er), **7** (in 86% yield and 92:8 er), and **8** (in 76% yield with 96:4 er) were obtained, indicating that the

Scheme 2. Atroposelective Synthesis of *N*-Arylindoles[a,b]



[a]Reaction conditions: indole (0.2 mmol), diazo (0.26 mmol), Rh_2(*S*-NTTL)$_4$ (1 mol %) in 2 mL CH_2Cl_2, 30 °C, 4 h. [b]Isolated yields.

3′-methyl ester was not essential for both reactivity and enantioselectivity. For the 5′-ester group, 65% yield and 93:7 er of **9** was achieved. The substituents in the C6 or C7 position of 1-diazonaphthoquinones were explored, showing that 6′-methyl product **10** was formed in 66% yield and 97:3 er, while 7′-bromo biaryl **11** was formed in 70% yield with 93:7 er. The 3′-methyl ester-6′-methyl compound **12** was obtained in 70% yield and 96:4 er, and the 3′-ester-6′-bromo **13** was generated in 74% yield and 97:3 er. With respect to 6′-phenyl product **14**, 73% yield and 96:4 er were observed. The absolute configuration of **14** was determined by single crystal X-ray diffraction.[24]

We then evaluated the scope of indoles. The reaction of **2** with 6-alkyl indoles gave 6-ethyl (**15**, 95:5 er), 6-isopropyl (**16**, 92:8 er), and 6-*tert*-butyl (**17**, 96:4 er). Introduction of a phenyl group delivered **18** in 74% yield and 97:3 er. For 6-methoxy indole, **19** was generated in good yield with 98:2 er. For 5,6-dimethylindole, **20** was formed in 81% yield and 95:5 er. Indoles containing 3-*tert*-pentyl, 3-cumene, 3-isopropyl, and 3-*tert*-butyl were all tolerated, providing **21**−**27** in both good yields and er. Installation of a bromo group at C6 reacted well, affording **23** and **27** in good yield and high er. It should be noted that the bulky substituent at indole C3 and a substituent at C6 is essential to this reaction. Without a substituent at C6, the product is racemic. Also, indoles containing substituents at both C2 and C3 positions are inert to this reaction. Moreover, the use of C3-methyl, ethylindoles gave a very low yield of the desired products since the strong competitive C−H insertion reaction occurred at the C2-position.

When carbazoles were used, low yields were observed in the presence of Rh_2(*S*-NTTL)$_4$ (see the SI for details). By slightly modifying the reaction conditions by using Rh_2(*S*-PTTL)$_4$ as the catalyst, the atroposelective NHI of carbazoles can be

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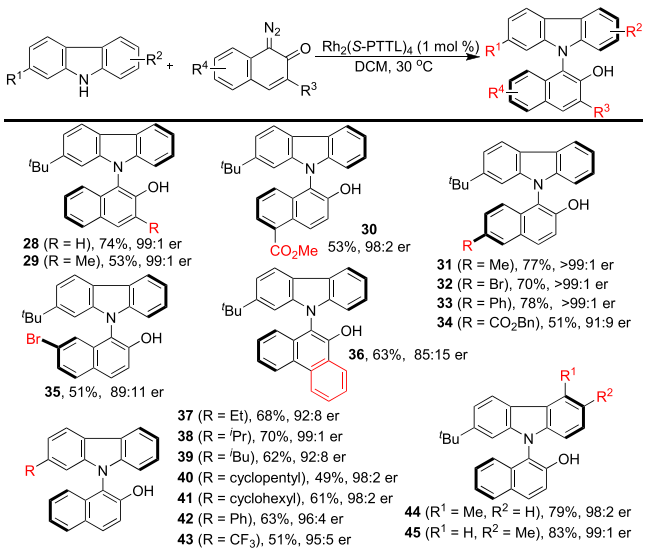
realized (Scheme 3). The reaction of 2-*tert*-butyl carbazole with diazonaphthoquinone gave **28** in 74% yield with 99:1 er.

Scheme 3. Atroposelective Synthesis of *N*-Arylcarbazoles[a,b]



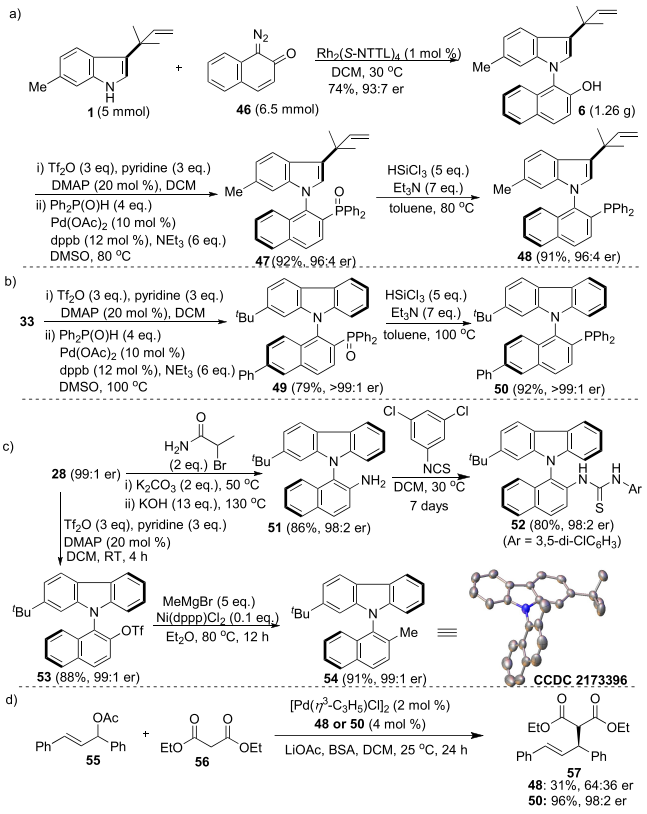
[a]Reaction conditions: carbazole (0.2 mmol), diazo (0.4 mmol), Rh_2(*S*-PTTL)$_4$ (1 mol %) in 4 mL CH_2Cl_2, 30 °C, 1 h. [b]Isolated yields.

Introduction of a methyl group at C3 delivered **29** in 99:1 er. The similar result was observed for 5′-ester **30** (53%, 98:2 er). Substituents such as methyl, bromo, and phenyl can also be installed in the 6′-position with excellent enantiocontrol (**31**: 77%, >99:1 er; **32**: 70%, >99:1 er; **33**: 78%, >99:1 er). Comparatively, 6′-ester gave **34** in 51% yield and 91:9 er. A bromo group at the 7′ position provided **35** in 89:11 er. Likewise, biaryl **36** was obtained in 85:15 er. For the scope of carbazoles, the introduction of a sterically hindered group at C2 was essential. Substituents such as ethyl, isopropyl, isobutyl, cyclopentyl, cyclohexyl, phenyl, and trifluoromethyl were all tolerated, furnishing **37**−**43** in acceptable yields with good er. The installation of another methyl group at C5/C6 was possible, providing the desired products in good yield and excellent er (**44**: 79%, 98:2 er; **45**: 83%, 99:1 er).

To demonstrate the synthetic utility, a gram-scale reaction was performed. The reaction of 5 mmol of **1** produced **6** in 74% yield with 93:7 er (Scheme 4a). A two-step derivative reaction delivered **47** in 92% yield and 96:4 er, which can be reduced to **48** as a phosphine ligand in 91% yield and 96:4 er. Using a similar route, **50** can be obtained over 99:1 er (Scheme 4b). Treatment of **28** with 2-bromopropanamide followed by hydrolysis afforded **51** in 86% yield with 98:2 er, which reacted with isothiocyanate to give **52** in 80% yield and 98:2 er (Scheme 4c).[25] Next, triflation of **28** provided **53** in 88% yield and 99:1 er, which reacted with MeMgBr to deliver **54** in 91% yield with 99:1 er. The absolute configuration of **54** was determined by single crystal X-ray diffraction. We further demonstrated that the chiral phosphine ligands are useful by applying them in Pd-catalyzed asymmetric allylic alkylation: the reaction using **48** delivered **57** in 31% yield and 64:36 er, while using **50** gave the product in 96% yield with 98:2 er (Scheme 4d).

Finally, DFT calculations were performed to study the key transition states of the NHI reaction (Figure 1). Rh carbenoid

Scheme 4. Gram-Scale and Derivative Reactions



2-Rh is generated from the reaction of **2** with Rh catalyst. Then **2-Rh** undergoes the NHI reaction with **1**, via a five-membered-ring transition state **TS1** (here we used a simplified catalyst $Rh_2(HCOO)_4$), requiring a Gibbs free energy of activation of 6.0 kcal/mol (Figure 1a). Intrinsic reaction coordinate (IRC) calculations demonstrated the NHI is concerted but highly asynchronous, where the C−N bond forms earlier than the O−H bond (see the SI for the free energy surface with selected structures from IRC). This is contrast to the stepwise process of many carbene insertions into X−H bonds (X = O, N).[26] In order to elucidate the enantioselectivity of this reaction, we calculated the key transition states and intermediates of the NHI reaction using Rh_2(*S*-NTTL)$_4$ (Figure 1b). The Rh carbenoid **INT1** is generated from the nitrogen release of **2** via **TS-N$_2$**, requiring an activation free energy of 18.6 kcal/mol. Our calculations show that Rh_2(*S*-NTTL)$_4$ provides a chiral crown cavity in **INT1** (Figure 1b, bottom): all the *N*-naphthaloyl groups are aligned on the same face to form a cavity, providing a chiral face for the subsequent reaction (see the SI for other conformers). This so-called *α*,*α*,*α*,*α*-conformation of Rh_2(*S*-NTTL)$_4$ has been supported by an X-ray experiment.[27] Then **TS-S** and **TS-R** were found as the most favored transition states to generate (*S*)- and (*R*)-products, respectively. **TS-S** (leading to **3**) is favored over **TS-R** by 2.2 kcal/mol, suggesting a 98:2 er of this reaction, consistent with the experimental results. The enantioselectivity originates from the different steric repulsions in the chiral crown structure: in **TS-S**, the substituents at the C3 position of **1** and the ester group of Rh carbenoid locate at the gap between the *N*-naphthaloyl groups, while in **TS-R**, both the substituents point to the bulky *N*-naphthaloyl groups, experiencing a larger steric repulsion.

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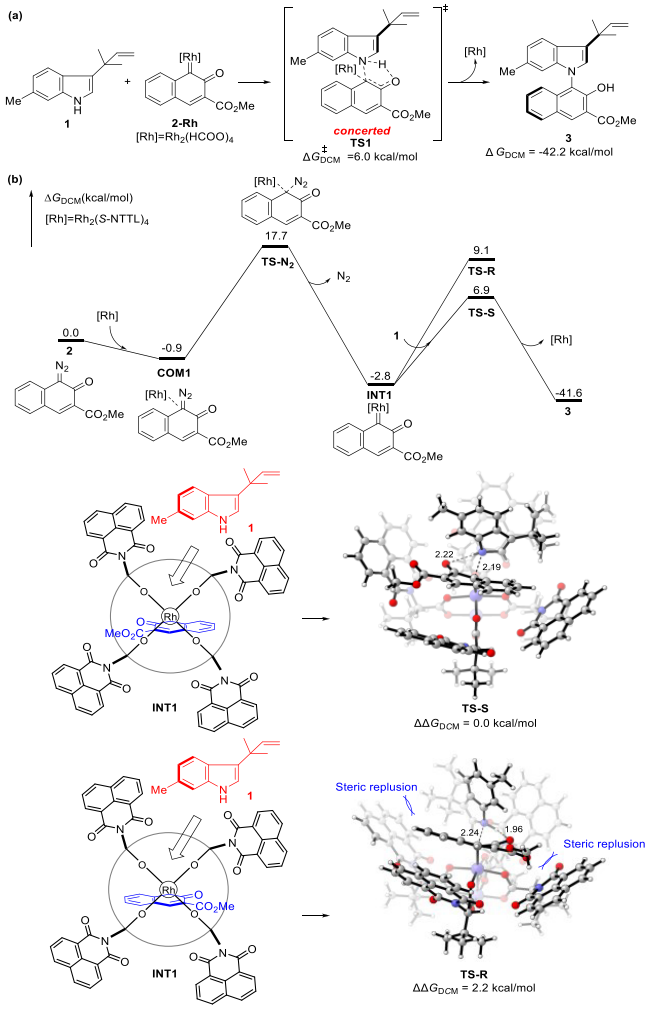

Figure 1. DFT calculations on the NHI of Rh carbenoid at SMD(DCM)-M06-L/TZVP//B3LYP/def2-SVP level. (a) The transition state of NHI of Rh carbenoid using $Rh_2(HCOO)_4$ as the catalyst. (b) The enantioselective transition states of NHI of Rh carbenoid using $Rh_2(S\text{-NTTL})_4$ as the catalyst. Black numbers show the bond lengths in angstroms. Color scheme: O, red; N, blue; Rh, purple; C, gray; H, white.

In summary, we have developed a novel approach for the atroposelective synthesis of axially chiral *N*-arylindoles and *N*-arylcarbazoles via rhodium-catalyzed NHI reaction, affording the C−N axially chiral N-hetero biaryls in good yields with excellent enantiomeric ratios. This protocol features the use of 1 mol % of rhodium catalyst to complete the transformation without the requirement of additives and other reagents, providing a simple but efficient one-step reaction for the direct construction of C−N axial axis. The target *N*-aryl heterobiaryls can easily be used to synthesize novel chiral ligands and catalysts. DFT calculations have been applied to study the mechanism, showing that the N−H insertion is concerted. A steric model to explain the enantioselectivity of this NHI reaction was also provided. Further demonstration of these chiral skeletons in asymmetric catalysis is 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/acs.orglett.2c03003.

DFT study, experimental procedures along with characterizing data and copies of NMR spectra (PDF)

Accession Codes

CCDC 2173395−2173396 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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Author Contributions

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Notes

The authors declare no competing financial interest.

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