Improving the Configurational Stability of Chiral-at-Iron Catalysts Containing Two $N$-(2-Pyridyl)-Substituted $N$-Heterocyclic Carbene Ligands

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ABSTRACT: Recently, we introduced the first example of chiral-at-iron catalysts in which two achiral $N$-(2-pyridyl)-substituted $N$-heterocyclic carbene (NHC) ligands in addition to two labile acetonitriles are coordinated around a central iron, to generate a stereogenic metal center [Hong, Y. et al. Chiral-at-Iron Catalyst: Expanding the Chemical Space for Asymmetric Earth-Abundant Metal Catalysis. *J. Am. Chem. Soc.* 2019, 141, 4569−4572]. A more facile synthesis of such chiral-at-iron catalysts was developed, which omits the use of expensive silver salts and an elaborate electrochemical setup. Configurational robustness was improved by replacing the imidazol-2-ylidene carbene moieties with benzimidazol-2-ylidenes. The $\pi$-acceptor properties of the altered NHCs were investigated by Ganter’s $^{77}$Se NMR method. The obtained benzimidazol-2-ylidene chiral-at-iron complex is an excellent catalyst for an asymmetric hetero-Diels–Alder reaction under open-flask conditions.

**INTRODUCTION**

With a rising interest in sustainable chemical synthesis, the spotlight is on using earth-abundant rather than noble metals for the development of new transition-metal catalysts. The earth-abundant metal iron is gaining particular attention due to its high abundance in the Earth’s crust together with a low-toxicity profile. Profound advancements have been achieved over the past two decades regarding asymmetric iron catalysis based on a comprehensive selection of chiral iron complexes. Nevertheless, many challenges remain with respect to improving catalytic performance, identifying new iron catalyst scaffolds, discovering new catalytic processes, and establishing economic syntheses of such chiral iron catalysts.

The development of chiral transition-metal catalysts, including chiral iron catalysts, is predomnately based on coordinating carefully tailored chiral ligands to a central metal. However, in a systematic research program, our group demonstrated the merit of chiral-at-metal catalysts in which the overall chirality is exclusively the consequence of a stereogenic metal center with all coordinating ligands being achiral. Our initial work was based on the noble metals iridium(III), rhodium(III), and ruthenium(II) due to their intrinsically high configurational stability, which is at the heart of the chiral-at-metal design. Nonetheless, recently, we introduced the first examples of chiral iron catalysts consisting exclusively of achiral ligands and revealed their application to asymmetric Cannizzaro reaction, a Nazarov cyclization, and hetero-Diels–Alder reactions. In this catalyst scaffold, iron(II) is coordinated by two chelating $N$-(2-pyridyl)-substituted $N$-heterocyclic carbene ligands (PyNHC) in a $C_2$-symmetric manner, thereby providing a helical topology with a stereogenic iron center in the $\Delta$ (left-handed helicity) or $\Lambda$ (right-handed helicity) configuration. Two acetonitriles complement the overall octahedral coordination sphere. In this design, the two PyNHC ligands are supposed to be configurationally inert to retain the stereochemical information, while the acetonitrile ligands are supposed to be labile to enable catalysis. This was facilitated by maximizing the ligand field stabilization energy by combining a strongly $\sigma$-donating NHC ligand with a $\pi$-accepting pyridine. At the same time, the acetonitrile ligands positioned trans to $\sigma$-donating NHC ligands are labilized due to the established trans-effect. Following this design, we achieved surprisingly robust configurational stabilities. Despite several modifications of the pyridyl substituents and changes in the mesityl group of the $N$-heterocyclic carbene, we observed that certain noncoordinating solvents, the presence of water, or the presence of air resulted in significant racemizations of the stereogenic iron center over time. We therefore became interested in under-

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standing the parameters that determine the configurational stability of such chiral-at-iron complexes. Herein, we demonstrate the influence of the π-acceptor properties of the NHC ligands on the configurational stability. Replacing the imidazol-2-ylidene carbene moieties with benzimidazol-2-ylidenes provides a significantly more configurationally robust chiral-at-iron catalyst, which catalyzes an asymmetric hetero-Diels–Alder reaction with high stereoselectivity under open-flask conditions (Figure 1).

■ RESULTS AND DISCUSSION

Synthesis of Benzimidazol-2-ylidene Iron Complexes. Previously, we accomplished the synthesis of the chiral-at-iron complexes under electrochemical conditions using a sacrificial iron anode in the presence of Ag₂O to generate silver carbene species and iron(II) in situ.¹² We aimed to develop a more convenient procedure without using expensive silver salts and a complicated electrochemical setup. Accordingly, the racemic complexes \( \text{rac-Fe}1 \) were generated by deprotonation of the imidazolium salt \( 1\text{a} \) or the benzimidazolium salts \( 1\text{b}, \text{c} \) with Hünig's base (diisopropylethylamine, DIPEA) in MeCN using FeCl₂ as the iron source (Scheme 1). Using this protocol and a reaction time of 72 h, \( \text{rac-Fe}1 \) was obtained in 81% yield compared to a yield of 70% following the previous electrochemical method.¹² The synthesis of the benzimidazol-2-ylidene complex \( \text{rac-Fe}2 \) was achieved in 70% yield with a reaction time of 60 h, and the dichloro-substituted benzimidazol-2-ylidene complex \( \text{rac-Fe}3 \) was provided in 86% yield after only a reaction time of 4 h. These results demonstrate that for achieving high yields, longer reaction times are required for less acidic imidazolium or benzimidazolium salts.

The racemic complexes \( \text{rac-Fe}2 \) and \( \text{rac-Fe}3 \) were resolved into their single enantiomers following our established chiral auxiliary method.¹⁴ (Scheme 2). Treatment of \( \text{rac-Fe}2 \) or \( \text{rac-Fe}3 \) with \((S)\)-salicyloxazoline in the presence of Et₃N provided the complexes \( \Lambda-\text{(S)}-\text{Fe}2 \) (41% yield) and \( \Lambda-\text{(S)}-\text{Fe}3 \) (42% yield) as single diastereomers. Likewise, using \((R)\)-salicyloxazoline instead provided the mirror-imaged complexes or \( \Delta-\text{(R)}-\text{Fe}3 \) (47% yield) after silica gel chromatography. Under the reaction conditions, \((S)\)-salicyloxazoline does only form isolable complexes with \( \Lambda-\text{Fe}2 \) or \( \Lambda-\text{Fe}3 \), while \((R)\)-salicyloxazoline does only form isolable complexes with \( \Delta-\text{Fe}2 \) or \( \Delta-\text{Fe}3 \). Indeed, unreacted enantioenriched complexes were isolated in the course of the silica gel chromatography but were not utilized further. Next, the diastereomerically pure iron auxiliary complexes were treated with NH₄PF₆ at 40 °C to replace the chiral bidentate ligands with acetonitriles to afford the individual enantiomers \( \Lambda-\text{Fe}2 \) (86% yield), \( \Delta-\text{Fe}2 \) (91% yield), \( \Lambda-\text{Fe}3 \) (80% yield), and

![Scheme 1. New Method for the Synthesis of Racemic Chiral-at-Iron Complexes](https://pubs.acs.org/suplementos/organometallics/2022/41/S055/00492/S055_00492_supplement.pdf)
and $\Delta$-Fe3 (91% yield). The enantiopurity of these chiral-at-iron complexes was determined by converting them to their corresponding auxiliary complexes using the methyl instead of isopropyl substituted (S)- or (R)-salicyloxazoline. This allowed for both enantiomers to convert to stable diastereomeric metal complexes and diastereomeric excess and in turn enantiomeric excess was conveniently determined via $^{19}$F NMR. As a result, for all of the nonracemic complexes, an ee of >99% was determined. CD spectra of the mirror-imaged complexes $\Lambda$- and $\Delta$-Fe2 are displayed in Figure 2.

Crystal Structure. Figure 3 displays a crystal structure of the racemic catalyst Fe2, which confirms the presence of a stereogenic iron center with a helical topology of the coordinated bidentate PyNHC ligands. The crystal structure also reveals a $\pi-\pi$ stacking of the mesityl substituents of the individual NHC ligands against the pyridyl moieties of the neighboring bidentate PyNHC ligands, which should contribute to the high constitutional and configurational stability of this class of chiral-at-iron complexes. The catalytic site is composed of the two labile acetonitrile ligands, while one methyl group of each mesityl moiety reaches toward the catalytic site and thus affects the asymmetric induction.

Catalysis of a Hetero-Diels–Alder Reaction. With enantiomerically pure chiral-at-iron complexes in hand, we tested the benzimidazol-2-ylidene complexes $\Lambda$-Fe2 and $\Lambda$-Fe3 in the previously reported hetero-Diels–Alder reaction of $\beta,\gamma$-unsaturated $\alpha$-ketoester 3 with the dienophile 2,3-dihydrofuran 4 to afford the bicyclic dihydropyran 5 and compared with results obtained for the previously reported imidazol-2-ylidene catalyst $\Lambda$-Fe1. To investigate the robustness of the catalysts, the reactions were performed either under air or under nitrogen and in the presence or absence of water (Table 1). As a result, all conducted reactions displayed high diastereoselectivity (>98:2) which will be discussed further. Catalysis with $\Lambda$-Fe1 under nitrogen atmosphere provided the dihydropyran 5 in 88% yield with 89.4% ee (entry 1). The presence of air did not affect the enantioselectivity but lowered somewhat the yield (71% yield, 89.6% ee) (entry 2), while the presence of small amounts of water (10 equivalents) diminished both yield and enantioselectivity (78% yield, 74.6% ee) (entry 3). Executing the reaction both in the presence of air and water afforded the hetero-Diels–Alder product also...
Table 1. Comparison of Different Chiral-at-Iron Catalysts in a Hetero-Diels–Alder Reaction

| entry | catalyst | conditions | yield (%) | dr (%) | ee (%) |
|-------|----------|------------|-----------|--------|--------|
| 1     | Λ-Fe1    | N₂         | 88        | 97.3   | 89.4   |
| 2     | Λ-Fe1    | Air        | 71        | 97.3   | 89.6   |
| 3     | Λ-Fe1    | N₂ + H₂O (10 equiv) | 78 | 97.3 | 74.6 |
| 4     | Λ-Fe1    | Air + H₂O (10 equiv) | 67 | 98.2 | 81.2 |
| 5     | Λ-Fe2    | N₂         | 83        | 97.3   | 91.4   |
| 6     | Λ-Fe2    | Air        | 77        | 97.3   | 91.6   |
| 7     | Λ-Fe2    | N₂ + H₂O (10 equiv) | 83 | 98.2 | 93.6 |
| 8     | Λ-Fe2    | Air + H₂O (10 equiv) | 61 | 98.2 | 93.8 |
| 9     | Λ-Fe3    | N₂         | 64        | 95.5   | 70.8   |
| 10    | Λ-Fe3    | Air + H₂O (10 equiv) | 38 | 99.1 | 89.0 |
| 11    | Λ-Fe2    | Air + H₂O (10 equiv) | 75 | 98.2 | 93.9 |
| 12    | Δ-Fe2    | Air + H₂O (20 equiv) | 63 | 98.2 | 94.1 |

*Reaction conditions: Λ-Fe1-3 (3 mol %) or Δ-Fe2 (3 mol %), ketoester 3 (0.20 mmol), and dihydrofuran 4 (0.30 mmol) were dissolved in distilled CH₂Cl₂ (0.05 M) and stirred under indicated conditions at room temperature for 24 h. *Isolated yield. *Values dr and ee were determined by HPLC analysis on a chiral stationary phase. *Catalyst at 5 mol % was used instead.

with a reduced yield and enantioselectivity (67% yield, 81.2% ee) (entry 4). From these experiments, we conclude that both water and air result in a slow decomposition and apparently water also leads to racemization of the iron catalyst Λ-Fe1 during the catalysis. Surprisingly, when we conducted the same set of experiments with the catalyst Λ-Fe2 (entries 5–8), the dihydrofuran 5 was provided with high enantioselectivities under all conditions (91.4–93.8% ee) and the presence of water did not diminish the enantiomeric excess. In fact, water even slightly increased the ee value (91.4 vs 93.6% ee under nitrogen, 91.6 vs 93.8% ee under air). We also tested the dichlorinated benzimidazol-2-ylidene complex Λ-Fe3 as a catalyst for the shown hetero-Diels–Alder reaction (entries 9 and 10), which showed a diminished performance compared to both Λ-Fe1 and Δ-Fe2.

Overall, these results reveal that the benzimidazol-2-ylidene complex Λ-Fe2 compared to the previously reported imidazol-2-ylidene complex Λ-Fe1 is a significantly improved catalyst for the investigated hetero-Diels–Alder reaction. It provides higher enantioselectivity (proposed transition state in Table 1; see ref 13 for a discussion) and enables to perform the reaction under open-flask conditions since it is not sensitive to air or water. While we do not understand the slight increase in enantioselectivity in the presence of water, the modest decrease in yield in the presence of air can be attributed to a slow air-induced decomposion of the iron catalysts. However, increasing the catalyst loading of Λ-Fe2 from 3 to 5 mol % could increase the yield of the dihydropyran product from 61 to 75% with no significant change in the stereoselectivity (entry 11). In addition, more water (20 instead of 10 equiv) using Δ-Fe2 instead of Δ-Fe2 (entry 12) gave a comparable reaction result to entry 8 (10 equivalents of water), providing the mirror-imaged product. Furthermore, the reduced catalytic performance of Λ-Fe3 compared to Λ-Fe2 in the hetero-Diels–Alder reaction indicates that additional electron-withdrawing groups on the benzimidazole, which further enhance the π-acceptor properties of the NHC, can ensure configurational robustness but also alter the catalytic behavior of the catalyst. Thus, if a certain degree of configurational stability is given, derivatization of the ligand could lead to a well-tailored catalyst for designated reactions.

**Testing the Configurational Stability of the Chiral-at-Iron Catalysts.** To experimentally verify the configurational stability of the chiral-at-iron complexes Fe1-3, enantiopure Δ-Fe1-3 (all >99% ee) were stirred in CH₂Cl₂ + H₂O (1% v/v) under air for 24 h. Subsequently, they were reacted with...
Figure 4. Evaluation of configurational stabilities. $^{19}$F NMR spectra are shown after conversion to diastereomeric $\Lambda$-$(R)$- and $\Delta$-$(R)$-FeAux complexes. (a) Auxiliary complexes obtained from racemic complexes Fe1-3. (b) Auxiliary complexes obtained from enantiopure complexes $\Delta$-Fe1-Fe3. (c) Auxiliary complexes obtained from complexes $\Delta$-Fe1-Fe3 after stirring them in CH$_2$Cl$_2$ + H$_2$O (1% v/v) for 24 h. Further experimental details are provided in the Supporting Information.

Scheme 3. Characterization of the $\pi$-Acceptor Properties of Carbene Ligands via $^{77}$Se NMR

$^\circ$ $^{77}$Se: 118.6 ppm

$^\circ$ $^{77}$Se: 140.6 ppm

$^\circ$ $^{77}$Se: 188.4 ppm

$p$-acceptor properties
methyl-substituted (R)-salicyloxazoline under basic conditions to obtain the corresponding auxiliary complexes FeAux, which are stable for both the Λ- and Δ-configured complexes and thus allow to determine the degree of racemization (Figure 4). This is demonstrated for a racemic (Figure 4a) and enantiomerically pure (Figure 4b) reference. In Figure 4c, the results of the racemization experiments are depicted, showing no racemization for Δ-Fe2 (dr > 99:1 of the auxiliary complexes) and Δ-Fe3 (dr > 99:1 of the auxiliary complexes) but a significant racemization for Δ-Fe1 (dr 93:7 of the auxiliary complexes). By further prolonging the time to 48 h, only Λ-Fe1 showed further racemization (dr 79:21 of the auxiliary complexes; see the Supporting Information for more information).

Investigation of π-Acceptor Properties of the NHC Ligands. To experimentally determine the electronic attributes, mainly the π-acceptor properties of the investigated ligands, Ganter's convenient 7Se NMR method was chosen.15 The imidazolium salts 1a–c were converted to their selenium-NHC 2a–c counterparts using a similar methodology as for the synthesis of the racemic iron(II) complexes (Scheme 3). Imidazolium salts 1a–c were deprotonated using DIPEA and stirred with an excess of selenium in MeCN at room temperature for 36 h. Generation of the selenium-NHC via the use K2CO3 or NaHMDS failed.16 The imidazolium-based PnNHC could be converted to the selenium analogue 2a in 57% yield. Transformation of the benzimidazol-2-ylidene complexes) and 99% yield for the dichloro-substituted congener (X = Cl, 2c). With the selenium-NHC compounds 2a–c in hand, 7Se NMR measurements were conducted and the chemical shifts were compared. As a result, it becomes apparent that with an extended π-system of the benzimidazol-2-ylidene carbene (140.6 ppm, 2b) and further addition of electron-withdrawing groups (188.4 ppm, 2c), the π-acceptor properties increase gradually compared to the imidazol-2-ylidene carbene (118.6 ppm, 2a).

**CONCLUSIONS**

In conclusion, we here reported an improved and very efficient reaction under open-flask conditions (presence of air and water). This design strategy paves the road for future structural motifs in the ligand sphere of chiral-at-iron catalysts providing distinct catalytic properties for applications in academia and industry, and still ensuring configurational robustness.

**EXPERIMENTAL SECTION**

General Methods and Materials. All reactions were carried out under a nitrogen atmosphere in oven-dried glassware unless noted otherwise. Solvents were distilled under nitrogen from calcium hydride (MeCN, CH2Cl2) prior to use. Reagents that were purchased from commercial suppliers were used without further purification. Flash column chromatography was performed with silica gel 60 M from Macherey–Nagel (irregular shaped, 230–400 mesh, pH 6.8, pore volume: 0.81 mL g−1, mean pore size: 66 Å, specific surface: 492 m2 g−1, particle size distribution: 0.5% < 25 µm and 1.7% > 71 µm, water content: 1.6%). 1H NMR, 13C (1H) NMR, 19F (1H) NMR, and 77Se (1H) NMR spectra were recorded on aBruker AV 300 MHz, AV II 500 MHz, or AV III HD 500 MHz spectrometer at ambient temperature. Chemical shift values δ are reported in ppm with the solvent resonance as internal standard. 19F (1H) NMR spectra were calibrated to trifluoroacetamide (CFCl3, δ = 0 ppm) as external standard. 77Se (1H) NMR spectra were calibrated to dimethyl selenide (SeMe2, δ = 0 ppm) as external standard. IR spectra were recorded on a Bruker Alpha Fourier transform infrared (FT-IR) spectrometer. Chiral HPLC was performed on an Agilent 1200 and 1260. CD spectra were acquired with a JASCO J-810 CD spectropolarimeter (parameters: 600–200 nm, 1 nm bandwidth, 50 nm min−1 scanning speed, accumulation of 3 scans). High-resolution mass spectrometry was performed on a Finnigan LTQ-FT Ultra mass spectrometer (Thermo Fisher Scientific) using ESI or APCI as ionization source.

**General Procedure for the Synthesis of Racemic Iron Complexes.** Under nitrogen atmosphere, ligand 1a–c (2.02 equiv), FeCl3 (1.00 equiv), and 4 Å molecular sieves (1.0 g/mmol of 1a) were dissolved in absolute and degassed acetonitrile (0.025 M based on 1a–c) at rt and stirred for 5 min. Then, dry DIPEA (2.50 equiv) was added to the reaction mixture, which turned the colorless solution orange-red, and the mixture was stirred at room temperature for 4–72 h. The suspension was filtered over a short plug of celite, and the crude product was purified over silica gel column chromatography (CH2Cl2/MeCN 10:1 – 1:1) with a pad of NH4PF6 on top, to ensure complete elution of the desired product. To completely remove the remaining NH4PF6 and DIPEA-HFPF6 salt, the complex was dissolved in CH2Cl2/MeCN (10:1) and washed with H2O (3×), dried over Na2SO4 and filtered over a short plug of celite. The solvent was removed under reduced pressure to afford the desired products rac-Fe1–Fe3. The iron complex rac-Fe1 has been reported previously, and the analytical data are in agreement with the literature.12

**rac-Fe1.** Following the general procedure, rac-Fe1 (185 mg, 0.17 mmol, 81%) was obtained as a red solid from the corresponding ligand 1a (0.20 g, 0.42 mmol). rac-Fe1 still contains some DIPEA-HFPF6-salt, since aq. work-up leads to some degradation of the complex. 1H NMR (300 MHz, CD2Cl2): δ = 8.37 (s, 2H), 8.29 (s, 2H), 8.07 (d, J = 8.6 Hz, 2H), 7.65 (d, J = 8.7 Hz, 2H), 7.21 (s, 2H), 6.71 (s, 2H), 6.62 (s, 2H), 2.16 (s, 3H), 1.99 (s, 3H), 1.46 (s, 3H) ppm. 19F NMR (282 MHz, CD2Cl2): δ = −62.86 (d, JCF = 706.4 Hz, PF6−) ppm. 13C NMR (125 MHz, CD2Cl2): δ = 200.15, 158.11, 150.99 (JCF = 4.5 Hz), 140.86, 137.53 (JCF = 3.2 Hz), 135.95, 134.69, 134.24, 132.60, 130.46, 130.39, 129.81, 124.94 (JCF = 34.9 Hz), 123.44 (JCF = 271.8 Hz), 120.43, 112.37, 20.81, 17.52, 17.40 ppm.

**rac-Fe2.** Following the general procedure, rac-Fe2 (158 mg, 0.13 mmol, 70%) was obtained as an orange solid from the corresponding ligand 1b (0.20 g, 0.38 mmol). 1H NMR (300 MHz, CD2Cl2): δ = 8.50 (s, 2H), 8.21 (t, J = 8.6 Hz, 2H), 8.10 (d, J = 8.9 Hz, 2H), 7.64 (t, J = 8.0 Hz, 2H), 7.43 (t, J = 7.7 Hz, 2H), 6.80 (s, 2H), 6.75 (d, J = 8.0 Hz, 2H), 6.71 (s, 2H), 2.24 (s, 3H), 1.96 (s, 3H, underneath the CD2CN-signal), 1.00 (s, 3H) ppm. 13C NMR (125 MHz, CD2Cl2): δ = 214.20, 158.66, 150.87 (JCF = 4.5 Hz), 141.75, 138.88, 137.90 (JCF = 3.2 Hz), 136.65, 135.18, 132.76, 132.59, 131.14, 130.95, 130.77, 127.06, 126.55, 124.73 (JCF = 34.7 Hz), 124.42 (JCF = 271.2 Hz), 113.41, 113.13, 111.74, 20.94, 17.48, 17.00 ppm. 19F NMR (282 MHz, CD2Cl2): δ = −62.72 (s, CF6), −72.94 (d, JCF = 706.3 Hz, PF6−) ppm. IR (neat): ν = 2925 (w), 2297 (w), 1623 (w), 1605 (w), 1557 (w), 1507 (w), 1473 (w), 1403 (m), 1324 (s), 1269 (w), 1218 (w), 1173 (w), 1137 (m), 1111 (w), 1085 (m), 1040 (w), 929 (w), 830 (s), 746 (m), 671 (w), 644 (w), 612 (w), 557 (s), 462 (w), 432 (w) cm−1.

HRMS ESI; m/z calculated for C67H49Fe2SeN6 [M+]: 1450.1388, found: 1450.1390.
**General Procedure for the Synthesis of Auxiliary Complexes.** Under nitrogen, a flame-dried Schlenk tube was charged with rac-Fe2-CF (31.0 mg, 0.029 mmol). The reaction was stirred at 40 °C for 16 h. Afterward, the mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (CH2Cl2/MeCN 95:5 → 1:1) to afford the desired auxiliary complex Λ(−)- or Δ(−)-Fe2-CF3.

**Following the general procedure, Δ(−)-Fe2 (35.4 mg, 0.029 mmol, 86%) was obtained as an orange solid from the corresponding Λ(−)-Fe2-CF3 (39.5 mg, 0.034 mmol).**

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Synthesis of ligands, NMR spectra, HPLC traces, and crystallographic data (PDF)

Accession Codes
CCDC 2209632 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, 1 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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