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Regioselectivity Control in the Oxidative Formal [3 + 2] Annulations of Ketoxime Acetates and Tetrohydroisoquinolines

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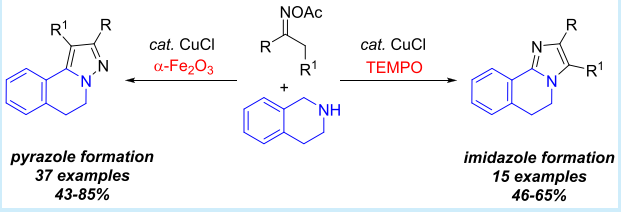
Supporting Information

ABSTRACT: A novel copper-catalyzed oxidative formal [3 + 2] annulations of ketoxime acetates and tetrohydroisoquinolines for the synthesis of fused pyrazoles and imidazoles has been developed. A broad range of important isoquinoline-fused pyrazole and imidazole products were selectively generated by the key control of oxidant.



Oximes have been widely employed both in academic and industrial fields.[1] Consequently, the studies on the transformation of ketoximes have attracted considerable interest in molecular synthesis. In this regard, for example, Narasaka and co-workers have pioneered the viable palladium-catalyzed intramolecular aza-Heck cyclization of vinylketoximes.[2] Alternatively, methyl ketoximes have been found to be versatile building blocks to construct nitrogen heterocycles such as pyridines,[3] pyrroles,[4] pyrazoles,[5] imidazole,[6] isoxazoles,[7] and thiazoles.[8] Formal [3 + 2] annulations of methyl ketoximes (N−C−C building block) with unsaturated compounds possessing unsaturation such as alkenes[4d−f] and alkynes,[4a] imines,[5a,b] pyridines,[6a] and even indoles[5c] provide an effective access to the corresponding nitrogen heterocycles (Scheme 1a,b). In spite of the advancement, the regioselectivity control in the annulations of oximes with imines has not been realized. For example, imidazolannulation exclusively occurred when using pyridines, while pyrazoles were formed when imines were employed as the coupling partners. Considering that regioselective formation of two isomer products from the same reactants is of great significance for method development, herein we disclose the first copper-mediated oxidative formal [3 + 2] annulations of ketoxime acetates and tetrohydroisoquinolines to form important isoquinolines[9] fused with pyrazole and imidazole moieties, selectively generated by the key control of reaction conditions (Scheme 1c).

Initially, we employed 4-methylacetophenone oxime acetate (**1a**) and 1,2,3,4-tetrahydroisoquinoline (**2a**) as the model substrates in the reaction with different copper salts, additives, and solvents under air atmosphere (Table 1). When CuCl was used as the catalyst in CH_3CN, the pyrazole (**3a**) and imidazole (**4a**) products were observed in 35% and trace amounts, respectively (entry 1). The screening of other copper salts including CuBr, CuI, $CuCl_2$, and $CuBr_2$ resulted in the product **3a** as the major product with lower yields (entries 2−5). A series of oxidants such as Fe_2O_3, γ-Fe_2O_3, α-Fe_2O_3, Fe_3O_4, Al_2O_3, and MnO_2 were systematically studied, and the results revealed that all additives could promote the formation of **3a** (entries 6−11), while the reaction performed under an oxygen atmosphere had no beneficial effect on the yield (entry 12). Among them, α-Fe_2O_3 was proved to be the best oxidant for the generation of **3a**. In addition, the use of TEMPO as the

Scheme 1. Formal [3 + 2] Annulations of Methylketoximes

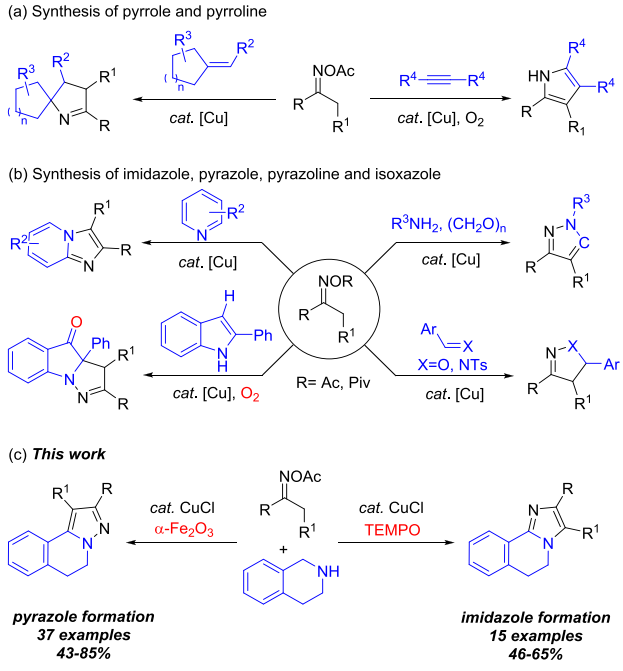


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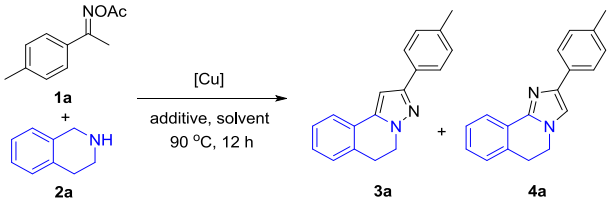
Table 1. Optimization of Reaction Conditions[a]



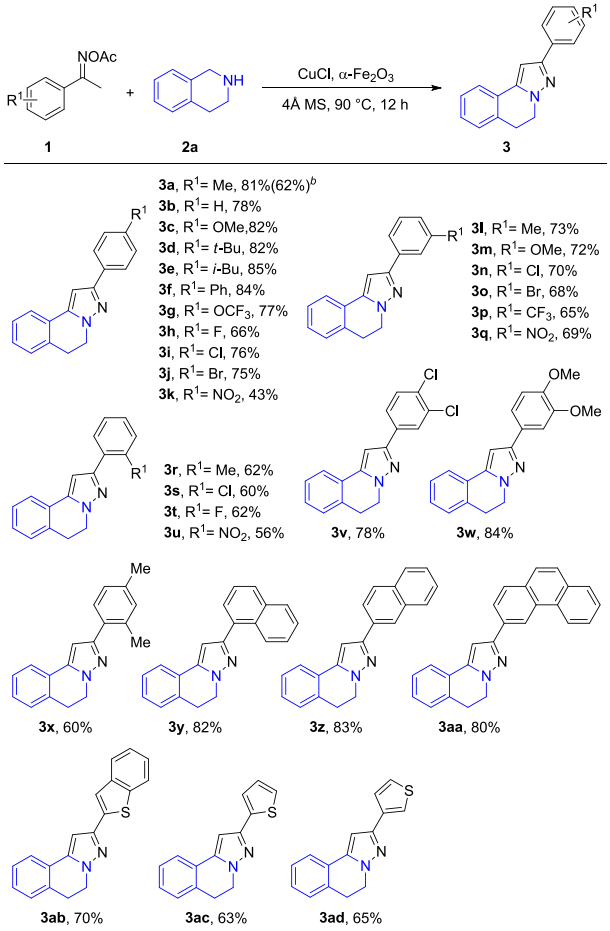
entry	[Cu]	oxidant	solvent	yield[b] (%) 3a	4a
1	CuCl		CH_3CN	35	trace
2	CuBr		CH_3CN	28	trace
3	CuI		CH_3CN	10	trace
4	$CuCl_2$		CH_3CN	24	trace
5	$CuBr_2$		CH_3CN	20	trace
6	CuCl	Fe_2O_3	CH_3CN	50	8
7	CuCl	γ-Fe_2O_3	CH_3CN	52	6
8	CuCl	α-Fe_2O_3	CH_3CN	59	7
9	CuCl	Fe_3O_4	CH_3CN	48	trace
10	CuCl	Al_2O_3	CH_3CN	43	trace
11	CuCl	MnO_2	CH_3CN	37	trace
12[c]	CuCl	O_2	CH_3CN	30	8
13	CuCl	TEMPO	CH_3CN	11	30
14	CuCl	α-Fe_2O_3	DMSO	34	trace
15	CuCl	α-Fe_2O_3	NMP	50	7
16	CuCl	α-Fe_2O_3	PhCl	trace	trace
17	CuCl	α-Fe_2O_3	$PhCH_3$	trace	trace
18	CuCl	α-Fe_2O_3	DMF	trace	0
19[d]	CuCl	α-Fe_2O_3	CH_3CN/NMP	63	9
20[e]	CuCl	α-Fe_2O_3	CH_3CN/NMP	72	7
21[e,f]	CuCl	α-Fe_2O_3	CH_3CN/NMP	81	trace
22[e,f]		α-Fe_2O_3	CH_3CN/NMP	0	0
23[e−g]	CuCl	α-Fe_2O_3	CH_3CN/NMP	41	trace
24[f,h,i]	CuCl	TEMPO	CH_3CN	trace	52

[a]Reaction conditions: unless otherwise noted, all reactions were performed with **1a** (0.2 mmol), **2a** (0.4 mmol), [Cu] (50 mol %), oxidant (50 mol %), and CH_3CN (1 mL) at 90 °C under air atmosphere for 12 h. [b]Isolated yield. [c]Under O_2 atmosphere. [d]CH_3CN (0.8 mL) combined with NMP (0.2 mL). [e]Dry CH_3CN (0.8 mL) combined with dry NMP (0.2 mL). [f]4 Å MS (150 mg). [g]Under Ar. [h]TEMPO (0.4 mmol, 2.0 equiv). [i]Dry CH_3CN (1.0 mL).

additive provided the imidazole **4a** as the major product with 30% yield (entry 13), while the formation of **3a** was inhibited. The examination of solvents showed that CH_3CN and *N*-methylpyrrolidone (NMP) were superior to others for the formation of **3a** (entries 8 and 14−18). To our delight, the combination of CH_3CN with NMP was found to further improve the transformation of **3a** (entry 19). Moreover, the use of anhydrous solvents and the addition of 4 Å molecular sieves led to a significant yield enhancement of **3a** (entries 20 and 21). Control experiments revealed that no annulation products were obtained in the absence of CuCl (entry 22). Further, the reaction under argon atmosphere resulted in decrease of the yield of **3a** (entry 23). Surprisingly, the addition of 2 equiv of TEMPO with dry CH_3CN as solvent gave **4a** in 52% yields (entry 24).

As shown in Scheme 2, the substrate scope of pyrazole formation with respect to oxime acetates (**1**) was investigated under the optimized conditions. Thus, the copper-catalyzed oxidative formal [3 + 2] annulation reactions were proved to be a general method for the facile construction of 2-substituted

Scheme 2. Scope of Ketoxime Acetates for Pyrazole Formation[a]



[a]Conditions: **1** (0.2 mmol), **2a** (0.4 mmol), CuCl (50 mol %), α-Fe_2O_3 (50 mol %), 4 Å MS (150 mg), dry CH_3CN (0.8 mL) combined with dry NMP (0.2 mL), under air, 90 °C, 12 h. Isolated yields based on **1**. [b]8 mmol scale preparation (1.29 g).

5,6-dihydropyrazolo[5,1-*a*]isoquinolines with good functional-group tolerance. Aromatic ketoxime acetates with electron-donating groups such as methyl, methoxy, *tert*-butyl, isobutyl, phenyl, and trifluoromethoxy afforded the corresponding products (**3a−3g**, **3l−3m**) in excellent yields (72−85%). The ketoximes derived from acetophenones with electron-withdrawing substituents such as fluoro, chloro, bromo, nitro, and trifluoromethyl were well tolerated and afforded the desired products in good yields (**3h−3j**, **3n−3q**, 65−76%). Moreover, *p*-nitro-substituted ketoxime acetate worked well to generate the product **3k** in 43% yield. These results indicate that the electronic nature of the ketoxime acetates has little effect on the reaction yield. A steric hindrance effect was observed when the substituents were located at the ortho position of the aromatic ring, in which the desired products were obtained in lower yields (**3r−3u** and **3x**). Moderate to high yields were obtained when 3,4-disubstituted acetophenone oxime acetates were used (**3v−3x**). The oxime acetates from 1-acetylnaphthalene, 2-acetylnaphthalene, and 3-acetylphenanthrene underwent the desired transformation to give the corresponding products **3y-3aa** in 82%, 83%, and 80% yields, respectively. Heteroaryl ketoxime acetates were compatible to generate **3ab−3ad** in good yields. The

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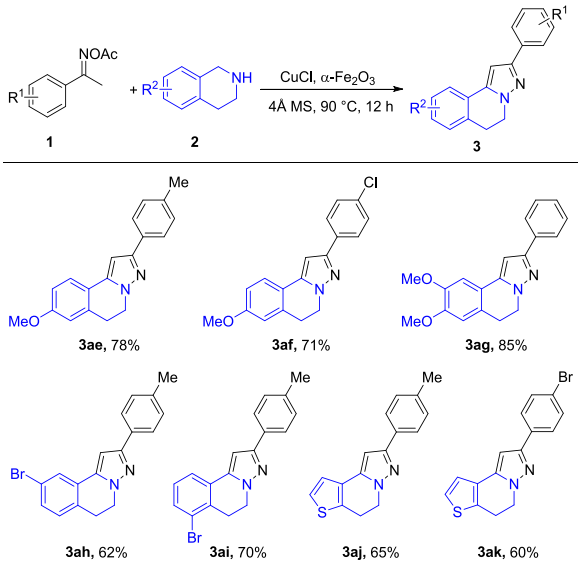
remarkable efficacy of the method was revealed by the effective gram-scale synthesis of the product **3a** in 62% yield. Unfortunately, when cyclohexanone and pentan-2-one oxime acetates were used as substrates, the corresponding pyrazole products were detected only in trace amounts.

Subsequently, several substituted 1,2,3,4-tetrahydroisoquinolines (**2**) were evaluated for their reactions with oxime acetates (**1**) (Scheme 3). Generally, the reactions with 1,2,3,4-tetrahydroisoquinoline bearing electron-donating groups and withdrawing groups proceeded smoothly to give the corresponding substituted products in moderate to good yields (**3ae**−**3ai**, 62−78%). 3,4-Disubstituted substrates also reacted well to give the desired **3ag** in 85% yield. In addition, heteroaromatic substrate (4,5,6,7-tetrahydrothieno[3,2-*c*]-pyridine) gave the products **3aj** and **3ak** in 65% and 60% yields, respectively.

Scheme 3. Scope of 1,2,3,4-Tetrahydroisoquinolines for Pyrazole Formation[a]



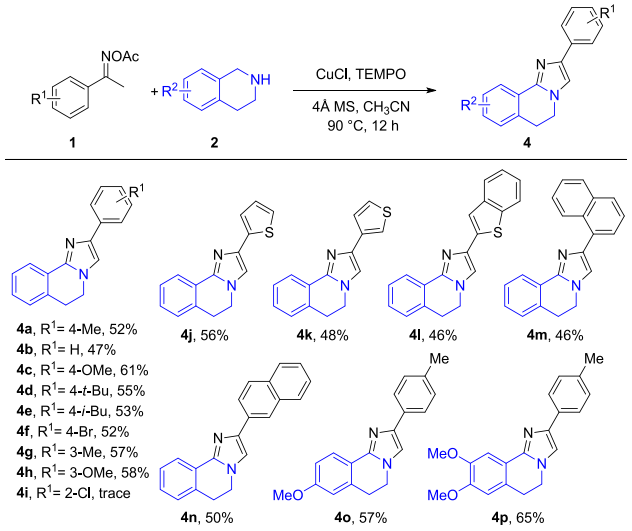
[a]Conditions: **1** (0.2 mmol), **2** (0.4 mmol), CuCl (50 mol %), α-Fe_2O_3 (50 mol %), 4 Å MS (150 mg), dry CH_3CN (0.8 mL) combined with dry NMP (0.2 mL), under air, 90 °C, 12 h. Isolated yields based on **1**.

Further, we investigated the scope of the formation of imidazoles by TEMPO-mediated oxidative annulations of oxime acetates (**1**) and substituted 1,2,3,4-tetrahydroisoaquinolines (**2**) (Scheme 4). Generally, different substitutions on the aromatic ring of acetophenone oxime acetates such as methyl, methoxyl, *tert*-butyl, isobutyl, and bromo were well tolerated, and the corresponding products were formed in moderate yields (**4a**−**4h**). The ortho variant gave only trace amounts of the product (**4i**). Heteroaromatic ketoxime acetates with a thiophene moiety were compatible in this transformation (**4j**−**4l**). Naphthyl oxime acetates afforded the expected products **4m** and **4n** in moderate yields. Methoxy-substituted 1,2,3,4-tetrahydroisoquinolines reacted smoothly with oxime acetate, and the imidazoles **4o** and **4p** were formed in 57% and 65% yields, respectively.

In addition, we explored the reactions of ketoxime **1a** with other secondary amines (Scheme 5). The desired 2-*p*-tolyl-4,5-dihydropyrazolo[1,5-*a*]quinoline **5** was detected in trace amounts when 1,2,3,4-tetrahydroquinoline was used (Scheme 5a). Under the optimized reaction conditions, 4-phenyl-2,6-di-*p*-tolylpyridine **6** was obtained as the major product when N-substituted benzylamines were used, while the desired pyrazoles were not detected (Scheme 5b). When other cyclic secondary amines such as piperidine, 4-phenylpiperidine, morpholine, and pyrrolidine were used in the reaction, the corresponding pyrazole products were not formed.

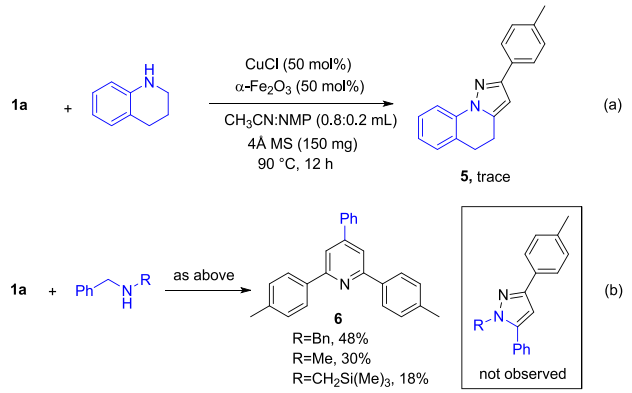
To understand the mechanism of the reaction, some control experiments were carried out, and the results are shown in Scheme 6. When the ketoxime **1ad** reacted with **2g** under the optimized reaction conditions, dihydropyrazole product **7** was formed in 24% yield, while the pyrazole product was generated only in trace amounts (Scheme 6a). In the reaction of **1b** and **2a**, besides the formation of **3a**, dihydropyrazole **8** was also detected under standard conditions within 6 h (Scheme 6b). Furthermore, pyrazole **3b** was almost quantitatively obtained when dihydropyrazole **8** was treated under air atmosphere at 120 °C for 3 h (Scheme 6c). These results indicate that dihydropyrazole product is a reaction intermediate and its dehydroaromatization proceeds under air. In the model reaction, the formation of 3,4-dihydroisoquinoline (**2a′**) and

Scheme 4. Synthesis of Imidazoles[a]



[a]Conditions: **1** (0.2 mmol), **2** (0.4 mmol), CuCl (50 mol %), TEMPO (0.4 mmol), 4 Å MS (150 mg), dry CH_3CN (1.0 mL), under air, 90 °C, 12 h. Isolated yields based on **1**.

Scheme 5. Reaction of Different Secondary Amines with 1a



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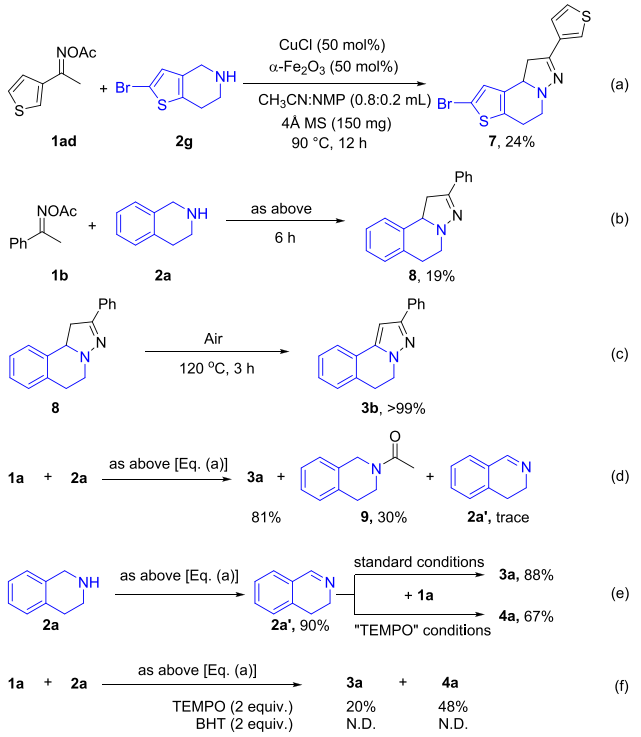
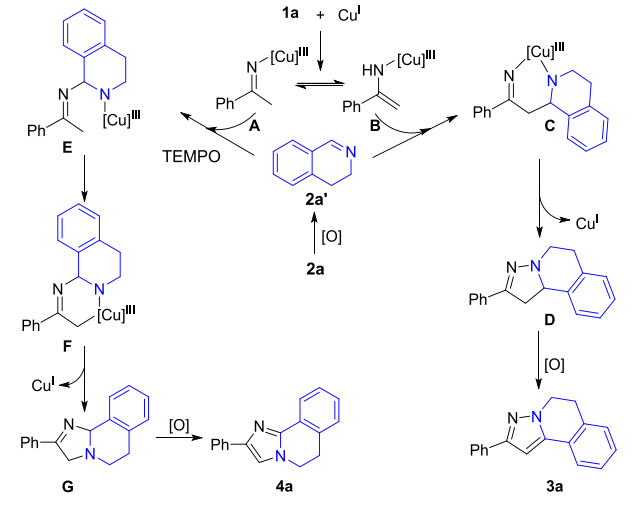
Scheme 6. Control Experiments



2-acetyl-1,2,3,4-tetrahydroisoquinoline (**9**) was observed (Scheme 6d). Then **2a′** was formed in 90% yield in the absence of ketoixme acetate, and further transformation of **2a′** with **1a** afforded the pyrazole product **3a** in excellent yield or else the imidazole **4a** in 67% yield under "TEMPO" conditions (Scheme 6e). Notably, **2a′** could not be further oxidized to isoquinoline under the optimized reaction conditions, probably due to the weak oxidizing capability of Cu(I)/α-Fe_2O_3. Finally, the addition of TEMPO turned the selectivity over the formation of imidazole **4a**, and BHT quenched the formation of both annulation products (Scheme 6f).

On the basis of experimental results and related literature reports, a possible mechanistic pathway is proposed (Scheme 7). For the pyrazole formation, oxime acetate **1a** is transformed

Scheme 7. Possible Reaction Mechanism



to the Cu(III)-imino species **A**. Tautomerization of **A** affords the intermediate **B**. Then the Cu(III) intermediate **C** is formed via nucleophilic addition of **B** to **2a′**, which is generated in situ via oxidation of **2a**. The pyrazole product **3a** is delivered by reductive elimination and subsequent dehydrogenative aromatization of the pyrazoline **D**, along with a copper(I) species released. With respect to imidazole synthesis, the intermediate **E** is formed by the migration insertion of **A** to **2a′** under the TEMPO conditions.[10] Then the six-membered copper ring intermediate **F** is furnished by the nucleophilic metalization. Analogously, reductive elimination followed by dehydrogenative oxidation affords the imidazole product **4a** via the imidazoline intermediate **G**.

In summary, we have documented the first copper-catalyzed oxidative regioselective formal [3 + 2] annulations of ketoxime acetates and tetrohydroisoquinolines toward divergent *N*-heterocycle synthesis. The reaction selectivity is well controlled under copper-mediated oxidative conditions to afford the corresponding pyrazoles and imidazoles in moderate to good yields. Mechanistic studies reveal that the copper catalyst enables the activation of the oxime N−O bond to form a highly active copper(III) species, which then induces the oxidative cyclization reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02978.

Experimental procedures, characterization data, and ^{1}H NMR and ^{13}C NMR spectra for all new products (PDF)

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Notes

The authors declare no competing financial interest.

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