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Letter

NaCl as Catalyst and Water as Solvent: Highly *E*-Selective Olefination of Methyl Substituted *N*-Heteroarenes with Benzyl Amines and Alcohols

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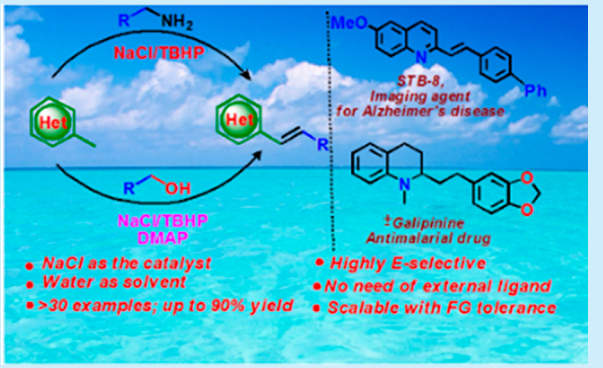
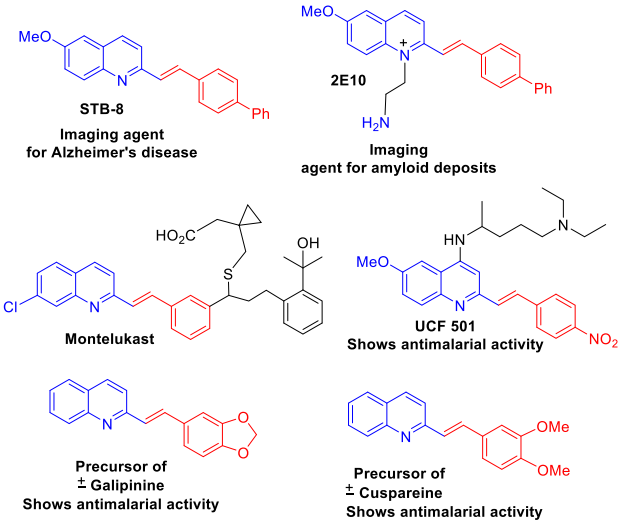
ABSTRACT: Oxidative coupling of benzylamines and alcohols with methyl substituted *N*-heteroarenes such as quinolines and quinoxalines has been achieved using chloride, a sea abundant anion as the catalyst for practical synthesis of a wide range of *E*-disubstituted olefins in aqueous medium. Detailed mechanistic studies and control experiments were carried out to deduce the reaction mechanism which indicated that *in situ* formed ClO_2^- is the active form of the catalyst. We have successfully carried out a 1 g scale reaction using this methodology, and five pharmaceutically relevant conjugated olefins were also synthesized by this method in moderate to good yields.



E-Selective conjugated olefins are considered as valuable building blocks due to their diverse applications in the synthesis of agrochemicals, pharmaceuticals, and fine chemicals, and they are also structural entities present in several bioactive natural products (Scheme 1).[1,2] There are well-known methods for the synthesis of regioselective alkenes such as the Wittig reaction, Julia olefination, Peterson olefination, etc., where a suitable leaving group is present.[3] Heck or Suzuki couplings and olefin metathesis are also standard methods for realizing conjugated olefins.[4]

Scheme 1. Some Selected Examples of Pharmaceutically Important Conjugated Olefins and Olefin Precursors



The synthesis of conjugated olefins was also carried out by the condensation of aldehydes with *N*-heteroarenes in the presence of a strong acid or base.[5] However, these methods often suffer from (i) requirement of prefunctionalized starting materials, (ii) multistep reaction sequences, (iii) use of organic solvents, (iv) generation of stoichiometric waste, (v) harsh reaction conditions, (vi) poor selectivity, and (vii) poor atom economy.[3−5] Therefore, the development of green and economical methods for the sustainable synthesis of highly *E*-selective olefins conjugated with *N*-heteroarenes is highly demanding and constitutes a new challenge.

In this context, the dehydrogenative coupling of alcohols was widely applicable for realizing value-added alkenes using various precious metal based catalysts.[6−8] The α-olefination of *N*-heteroarenes with alcohols was also achieved by using earth abundant metal catalysts stabilized by triazinyl-core PN^5P or NNN pincer ligands and the 1,10-phenanthroline ligands.[9−12] However, in addition to the use of metals, the multistep synthesis, highly expensive nature of pincer-based ligands, use of organic solvents, and strong bases are major

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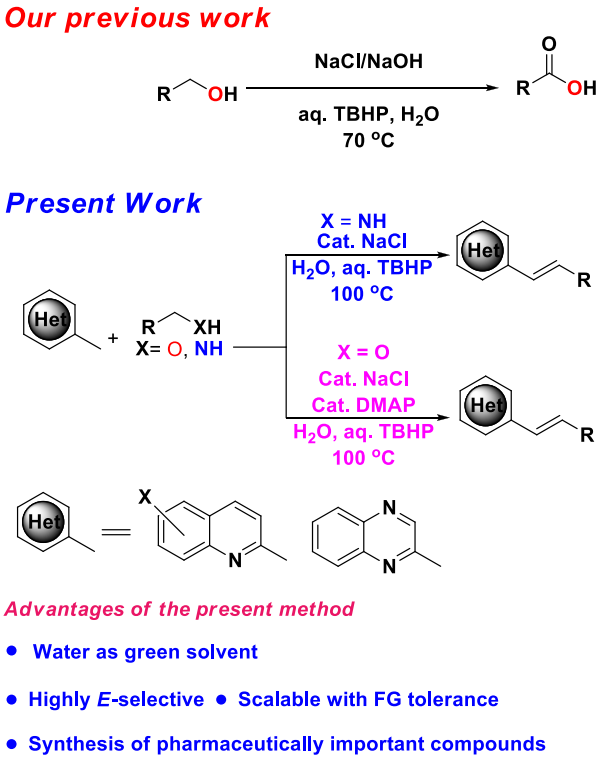
limitations of these methods.[9−12] Although I_2 and NBS have been used as metal-free catalysts in oxidation reactions, cross dehydrogenative coupling (CDC) reactions,[13,14] and even in olefination reactions using benzylamines,[13e,14b] they cannot be considered as "abundant", as their natural abundance is poor.[15] In sharp contrast, catalysis using chloride, the most abundant anion present in seawater, has rarely been explored.[16] In addition, carrying out organic reactions using water as a green, economical, nontoxic, and nonflammable solvent has become one of the prime goals in sustainable organic synthesis in the last two decades.[17] Therefore, utilization of the ubiquitous NaCl as the catalyst and water as the solvent for key organic transformations is an attractive, sustainable, and inexpensive alternative.

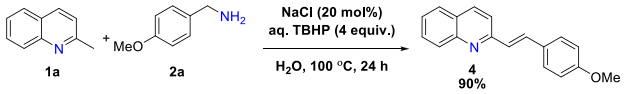
Herein, we report the highly *E*-selective olefination of methyl substituted *N*-heteroarenes with benzyl amines and alcohols in water using NaCl as the catalyst and aq TBHP as the oxidant. The study has been extended to the synthesis of five pharmaceutically important conjugated olefins which have been carried out using water as the only solvent.

In our previously reported work on NaCl catalyzed oxidation of aromatic amines and alcohols to imines and carboxylic acids, we observed that aldehydes were generated *in situ* and subsequently converted to the corresponding imines and carboxylic acids (Scheme 2).[16] We were therefore keen to study whether the *in situ* generated aldehydes could be coupled with *N*-containing heteroarenes under mild reaction conditions to obtain the desired olefinic compounds.[9−12] This method would be highly sustainable and advantageous for several reasons: (i) the alcohols and amines are readily available from several industrial processes; (ii) NaCl is inexpensive and is a readily available commodity; (iii) water is the greenest and most sustainable solvent; (iv) no requirement of an external ligand; (v) the method is base-free or requires only catalytic amount of base; and (vi) the byproduct is *t*-BuOH which can be reused if necessary (Scheme 2). We began our investigation by examining the oxidative coupling of 4-methoxybenzylamine **2a** with 2-methylquinoline **1a** in aqueous medium using NaCl as catalyst and aq TBHP as oxidant at 70 °C. The reaction was carried out for 24 h, and we were able to isolate *E*-2-(4-methoxystyryl) quinoline **4** in 42% yield. This result encouraged us to study the effect of varying the reaction parameters to improve the yields. To explore the role of the cation, different chloride salts were tried such as NaCl, KCl, $MgCl_2$, and Et_4NCl and the maximum yield was obtained with NaCl. After detailed studies (see the Supporting Information, Tables S1−S5), the yields of olefins were improved up to 90% using sodium chloride (20 mol %) and aq TBHP (4 equiv) at 100 °C (Scheme 3).

Scheme 2. Advantages of NaCl as Catalyst for Olefination Reaction in Water



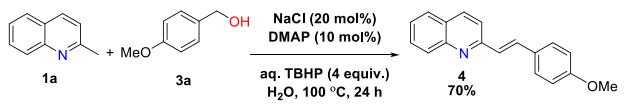
Scheme 3. Oxidative Coupling of 4-Methoxybenzylamine with 2-Methylquinoline[a]



[a]Reaction conditions: 2-methylquinoline **1a** (143 mg, 1 mmol), 4-methoxybenzylamine **2a** (240 mg, 1.75 mmol), NaCl (11.6 mg, 0.2 mmol), TBHP (70% in water, 360 mg, 4 mmol), and water (0.3 mL), 100 °C oil bath for 24 h.

Unlike aromatic amines, aromatic alcohols were not found to oxidize to acids in the absence of a base such as NaOH. Therefore, we carried out the olefination reaction of 4-methoxybenzyl alcohol **3a** with 2-methylquinoline **1a** in aqueous medium using NaCl as catalyst and aq TBHP as oxidant at 70 °C in the presence of 50 mol % NaOH. Unfortunately, 4-methoxybenzyl alcohol was mostly converted to the corresponding 4-methoxybenzoic acid and we isolated the olefin **4** in only 5% yield. After detailed studies (see the Supporting Information, Tables S6−S9), we found that a catalytic amount of an organic base such as 4-dimethylamino-pyridine (DMAP) increases the yield of the olefin up to 70% using sodium chloride (20 mol %) and aq TBHP (4 equiv) at 100 °C (Scheme 4). While electrophilic halogenating reagents such as NBS in organic solvent have been used for the olefination of benzylamines, no reports indicating the use of anionic halogens are reported in the literature.[14b] Our attempts to explore other halides such as Br^- and I^- for this reaction resulted in lesser yields of the products (see the Supporting Information, Table S1).

Scheme 4. Oxidative Coupling of 4-Methoxybenzylalcohol with 2-Methyl Quinoline[a]



[a]Reaction conditions: 2-methylquinoline **1a** (143 mg, 1 mmol), 4-methoxybenzyl alcohol **3a** (241 mg, 1.75 mmol), NaCl (11.6 mg, 0.2 mmol), 4-dimethylaminopyridine (12.2 mg, 0.1 mmol), TBHP (70% in water, 360 mg, 4 mmol), and water (0.3 mL), 100 °C oil bath for 24 h.

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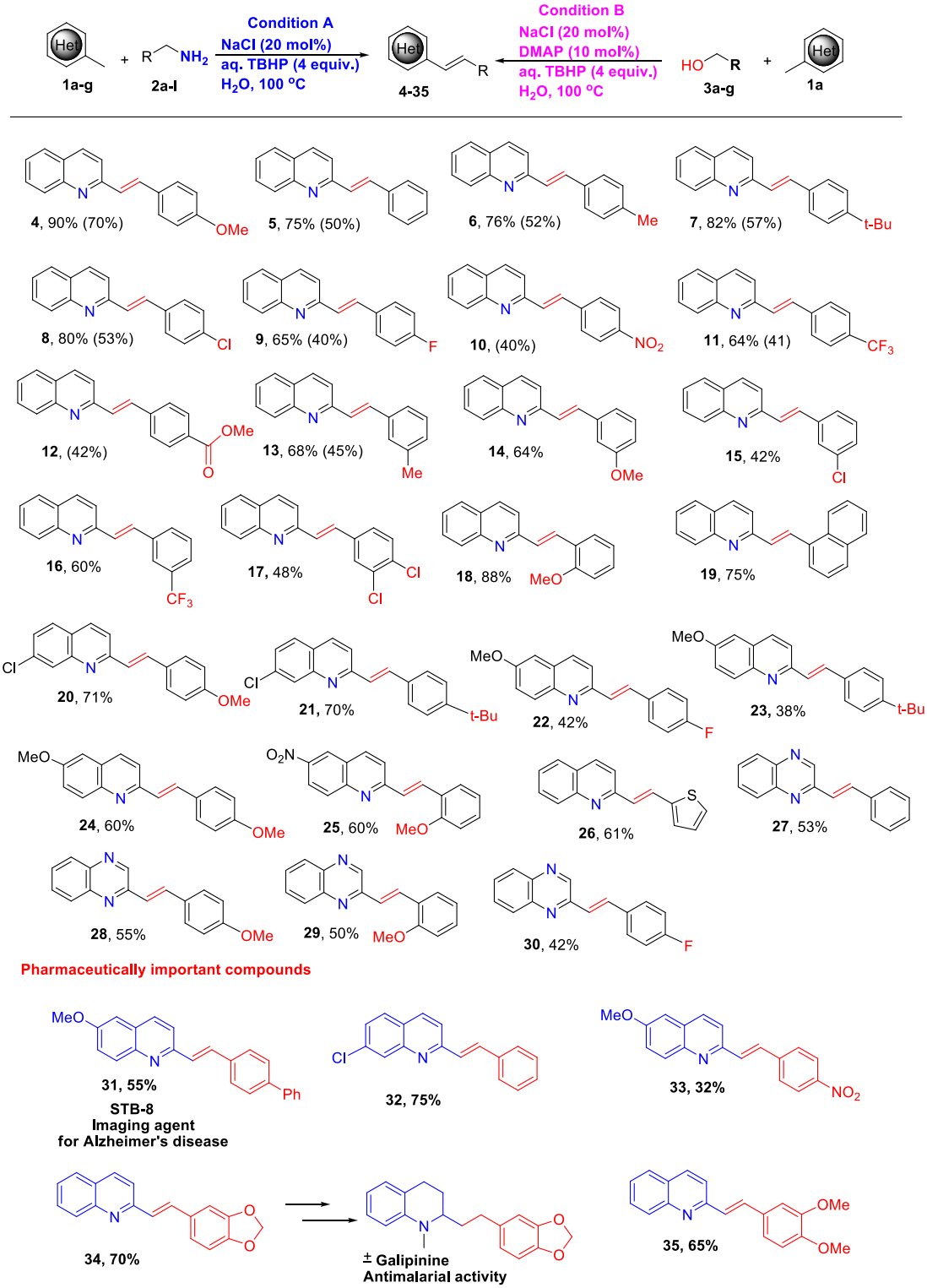
Table 1. Substrate Scope for the Olefination and for the Synthesis of Pharmaceutically Important Compounds in Water[a]



[a]Reaction condition **A**: Heteroarenes **1a−g** (1 mmol, 1 equiv), amines **2a−l** (1.5 mmol, 1.5 equiv), NaCl (0.2 mmol, 20 mol %), TBHP (70% in water, 4 mmol, 4 equiv), 0.3 mL of water, 100 °C oil bath for 24−40 h. Reaction condition **B**: Heteroarenes **1a−e** (1 mmol, 1 equiv), alcohols **3a−g** (1.5 mmol, 1.5 equiv), NaCl (0.2 mmol, 20 mol %), DMAP (0.1 mmol, 10 mol %), aq TBHP (4 equiv), 0.3 mL of water, 100 °C oil bath for 24 h (% yields in parentheses are for alcohol substrates).

Keeping optimized reaction conditions in hand, we explored the substrate scope with the compounds having electron donating as well as electron withdrawing groups on the aryl ring of amines and alcohols as well as on the heterocyclic ring (Table 1). Both afforded the desired olefinated products in good to excellent yields. We have also carried out the reaction with various substituted quinolines **21−25** and quinoxazoline derivatives **27−30** using aromatic amines as the coupling

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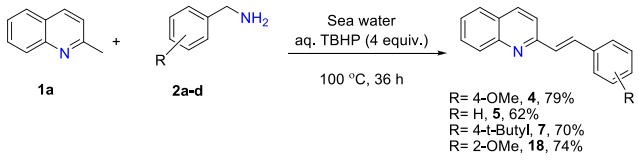
partner (Table 1). A series of functional groups such as halogens, $-CF_3$, $-NO_2$, and $-CO_2Me$ were compatible with the present catalytic system for alcohols and amines.

The applicability of our method was experienced by the synthesis of STB-8, an *in vivo* specific staining agent for *β*-amyloid plaques found in the brain cells of patients with Alzheimer's disease (Table 1). The STB-8 unit is also present in the core structure of 2E10, another imaging agent for amyloid deposits. The core structures of the drugs Montelukast and UCF 501, which are used for the treatment of asthma/seasonal allergies and malaria, respectively, were also synthesized using this present method (Table 1). In addition, we were able to isolate (±)-Galipinine in 53% overall yield using the olefin **34** followed by Ni catalyzed hydrogenation and *N*-methylation (see the Supporting Information, pp S12 and S13). These examples highlight the potential applications of this present work. We have also carried out a 1 g scale reaction of 4-methoxybenzylamine **2a** with 2-methylquinoline **1a** which resulted in the desired olefin **4** in 85% yield (see the Supporting Information, p S12). We have also attempted the possibility of performing the olefination reaction in seawater (Scheme 5). As given in Scheme 5, oxidative coupling of four different amines has been performed in seawater with excellent selectivity and yields.

Scheme 5. Olefination of Heteroarenes with Benzylamines in Sea Water[a]

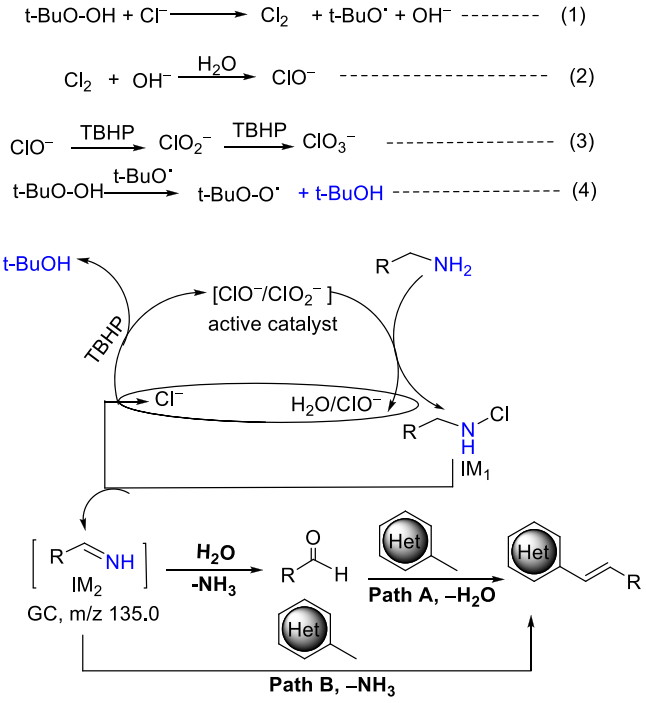


[a]Reaction conditions: 2-methylquinoline **1a** (143 mg, 1 mmol), benzylamines **2a–d** (1.75 mmol), TBHP (70% in water, 360 mg, 4 mmol), and seawater (0.4 mL), 100 °C oil bath for 36 h.

To understand the reaction mechanism and to identify the active chlorine species for the oxidative olefination, several control experiments were carried out (see the Supporting Information, p S14).

Using the results obtained from our control experiments and analysis of similar studies reported in the literature, a possible mechanism has been proposed in the catalytic cycle given in Scheme 6.[13,14,16] Initially, TBHP oxidizes the chloride ion to molecular chlorine (Cl_2) and *t*-BuO$^{\bullet}$ radical (eq 1, Scheme 6), which in the presence of water forms the hypochlorite.[16] This is followed by oxidation of hypochlorite (ClO^-) to chlorite (ClO_2^-) and chlorate (ClO_3^-) by TBHP (Scheme 6).[16] Primary amine reacts with hypochlorite or chlorite, resulting in the formation of the *N*-chloroamine IM1 (Scheme 6) which gets converted to imine IM2 readily. The formation of IM2 was confirmed by gas chromatographic analysis (*m*/*z* 135.0).[16] Hydrolysis of IM2 initiated by H_2O with the subsequent elimination of NH_3 results in benzaldehyde, which reacts with 2-methylazaarene to generate the desired olefin with the release of one molecule of H_2O (path A).[9−12,14b] In pathway B, imine IM2, which bears an electrophilic carbon atom, is attacked directly by 2-methylazaarene and loses a molecule of ammonia to generate product **4**.[14b] The isotope labeling experiments carried out suggest that *in situ* generated ammonia is acting as the base (pK_a 37, pK_a of substrate 14.5), which

Scheme 6. Proposed Reaction Mechanism for the Oxidative Coupling of Benzylamines with *N*-Heteroarenes



possibly assists in the formation of 2-methylene-1,2-dihydroquinoline from 2-methyl quinoline. This nucleophile attacks the aldehyde or imine intermediates to form the desired olefins. The reaction mixture becomes more basic in nature (from pH 9.84 to pH 10.04) after the completion of the reaction which supports the generation of NH_3 during the reaction. The selectivity for the *E*-isomers of the synthesized olefins was confirmed by single crystal X-ray diffraction and NMR studies (see the Supporting Information, pp S16−S21).

Conclusion

In conclusion, using Cl^- as catalyst, we report in this paper an efficient and easy catalytic method for the oxidative olefination of methyl substituted heteroarenes with benzyl amines and alcohols in water. Although base has been found to be essential for the olefination with alcohols, the olefination of amines has been found to occur even without the use of a base. A study of the mechanism of this reaction indicated that both radical and ionic mechanisms are responsible for oxidative coupling with benzyl alcohols. However, for benzyl amines, the mechanism seems to be purely ionic in nature. Simplicity in carrying out the reaction, broad substrate scope, and effortless scaling-up are additional features of this method, which is also both economical and metal-free. Five pharmaceutically significant conjugated olefins were also synthesized using this methodolgy in moderate to good yields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01851.

Experimental procedures, experimental data, and reaction kinetics (PDF)

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Accession Codes

CCDC 1984225 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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