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Aerobic Catalyzed Oxidative Cross-Coupling of *N,N*-Disubstituted Anilines and Aminonaphthalenes with Phenols and Naphthols

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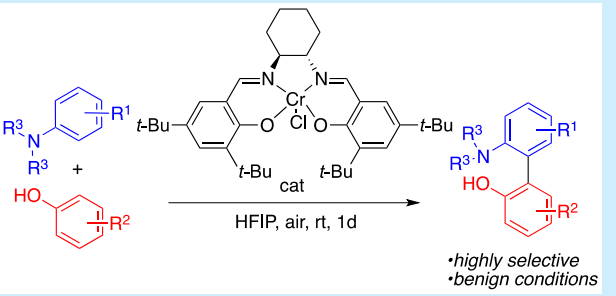
ABSTRACT: The cross-coupling of *N,N*-dialkyl aniline and aminonaphthalenes with phenols and naphthols using a Cr−salen catalyst under aerobic conditions was developed. Notably, air serves as an effective oxidant affording products in high selectivity. Initial mechanistic studies suggest an outer-sphere oxidation of the aniline/aminonaphthalene partner, followed by nucleophilic attack of the phenol/naphthol. Single products were observed in most cases, whereas mixtures of C−C and C−O coupled products arose from reactions involving aminonapthalene and sterically unencumbered phenols.



Unsymmetrical biaryls are found in organometallic chemistry,[1] natural product synthesis,[2] pharmaceutical synthesis,[3] and materials chemistry.[4] The ability to generate such structures selectively from simple precursors is an important challenge in organic synthesis. These motifs are classically synthesized through the metal-catalyzed cross-coupling of prefunctionalized partners.[5] Dehydrogenative cross-coupling of arenes,[6] in particular of phenols,[7,8] has been developed recently to overcome the need for prefunctionalization.

The 2′-aminobiphenyl-2-ol structural motif is an interesting unsymmetrical biaryl with examples found in active natural products[9] (Figure 1). Most routes to access these structures

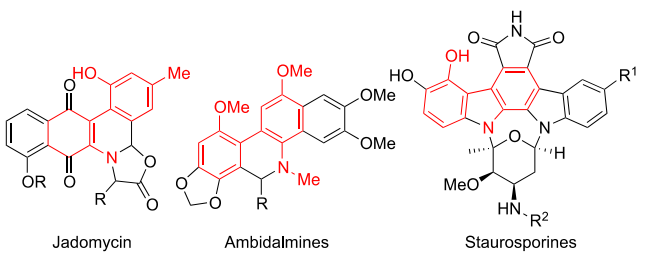
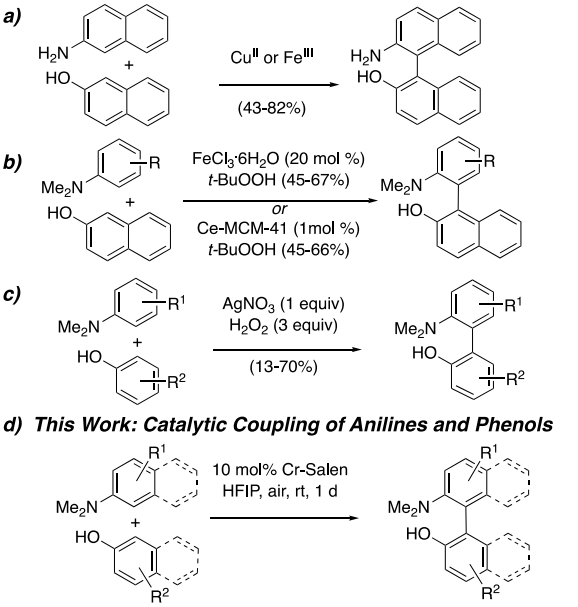


Figure 1. Natural products with 2′-aminobiphenyl-2-ol motif.

involve prefunctionalization. Oxidative methods for direct C−H activation to construct this motif have been developed in the past decades.[10] Seminal work centers on the coupling of 2-aminonaphthalene with 2-naphthol (Scheme 1a), which was complicated by the high reactivity of the amino group. More recently, oxidative couplings of *N,N*-disubstituted aniline derivatives with naphthols have been studied using Fe and Ce catalysts (Scheme 1b).[11a,b] The scope was confined to 2-naphthol and *t*-BuOOH was needed, and in the latter case,

Scheme 1. Oxidative Cross-Couplings of 2-Aminonaphthalenes/Anilines with Naphthols/Phenols



elevated temperatures were required. With chiral-auxiliary-derived aminonaphthalenes, catalytic oxidative conditions give rise to enantiopure axial chiral versions.[12] The coupling of

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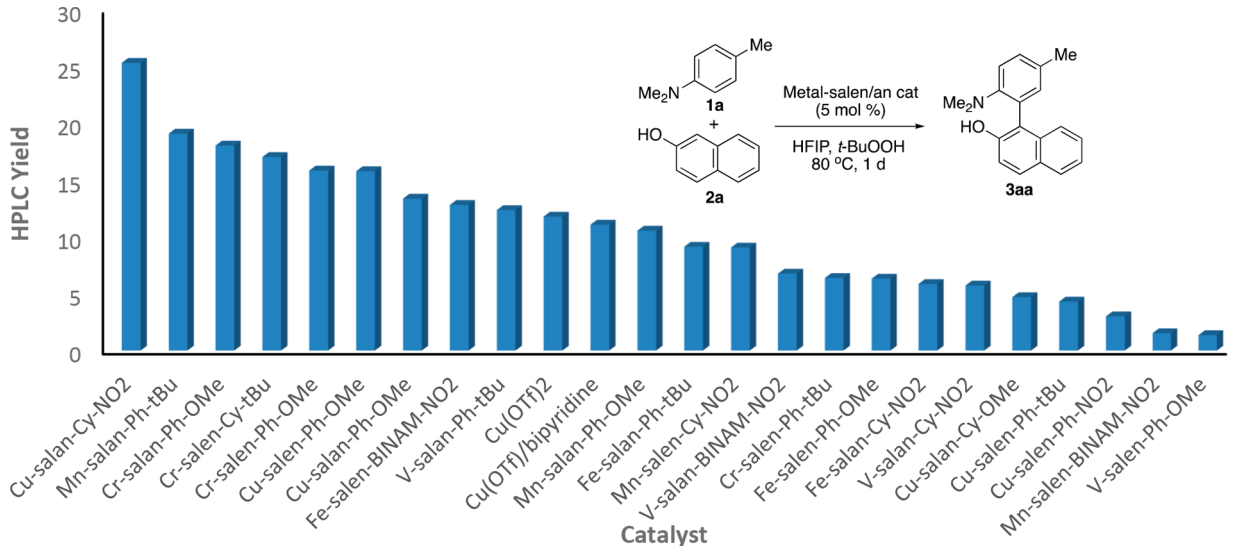


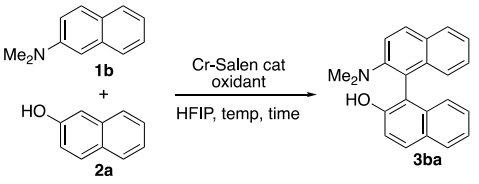
Figure 2. High-throughput experimentation results for the catalyst library screen (internal standard = 4,4′-di-*tert*-butylbiphenyl).

phenols with similar anilines is much more difficult, with the first report from Fotie et al. in 2016 (Scheme 1c).[13] This process required a super-stoichiometric Ag oxidant (3 equiv), with the highest yield of the aniline/phenol coupling being 70%. Further methods with a hypervalent iodine oxidant,[14] a periodic acid,[15] a Pd/Al_2O_3 catalyst,[16] and a heterogeneous Rh catalyst[17] have been reported but with very limited examples (three to six per report) or the requirement of amino-naphthalenes and naphthols versus anilines and phenols. For example, an electrochemical method only uses 2-amino-naphthalene.[18] Herein we describe the development of Cr−salen-catalyzed cross-coupling of *N*,*N*-substituted anilines/2-aminonaphthalenes with naphthols/phenols. This process utilizes benign conditions (room temperature (rt) air as oxidant, Scheme 1d). Interestingly, most reactions result in C−C coupling products, but some couplings of 2-amino-naphthalene with phenols lead to the formation of C−O coupled products as well.

Metal−salen complexes have been shown to be powerful catalysts in oxidative reactions.[8g] In particular, our group has previously reported the mechanism of a Cr−salen-catalyzed phenol cross-coupling.[19] To interrogate the potential of these metal−salen complexes in aniline/phenol cross-coupling, high-throughput experimentation screening was implemented with a library of catalysts. When using 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as the solvent, every catalyst screened resulted in some level of product formation (Figure 2). To identify the best catalyst, the top leads were run again on a larger scale (see the SI) which revealed that the Cr−salen complex results in the highest yield and minimizes the formation of undesired side products.

Optimization studies were performed on the cross-coupling of *N*,*N*-dimethyl-2-aminonaphthalene and 2-naphthol using this Cr−salen catalyst in HFIP (eq 1, Table 1). Lowering the temperature to rt provided higher yields (entries 1−3). Lower yields were observed at 0 °C, potentially due to the decreased solubility in HFIP (entry 4). Shorter reaction times led to a slight decrease in the yield, which was found to be more detrimental with less reactive coupling partners (entry 5). Different catalyst loadings (5, 10, and 20 mol %) had a small effect on the yield (entries 3, 6, and 7). Moving toward less harsh oxidants, O_2 was found to be beneficial (entry 8), with

Table 1. Optimization of Oxidative Cross-Coupling of *N*,*N*-Dimethyl-2-aminonaphthalene and 2-Naphthol[a]



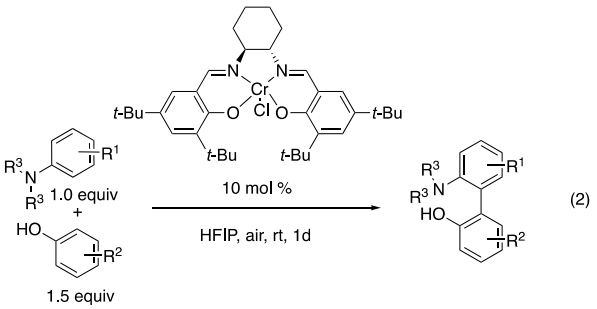
(1)

	1b:2a	cat (mol %)	oxidant	*T* (°C)	*t*	yield (%)
1	1:3	10	*t*-BuOOH	80	1 d	33
2	1:3	10	*t*-BuOOH	50	1 d	51
3	1:3	10	*t*-BuOOH	rt	1 d	55
4	1:3	10	*t*-BuOOH	0	1 d	23
5	1:3	10	*t*-BuOOH	rt	6 h	52
6	1:3	20	*t*-BuOOH	rt	1 d	59
7	1:3	5	*t*-BuOOH	rt	1 d	52
8	1:3	10	O_2	rt	1 d	78
9	1:3	10	air	rt	1 d	73
10	1:1.5	10	air	rt	1 d	74

[a]HFIP: 1,1,1,3,3,3-hexafluoro-2-propanol. Conditions: **1b** (0.10 mmol, 0.10 M), *t*-BuOOH (2.0 equiv), HFIP (1.0 mL). Yields were obtained by ^{1}H NMR using 4,4′-di-*tert*-butylbiphenyl as an internal standard.

even air being suitable for the reaction to proceed (entry 9). Finally, the reactant ratio was optimized to 1:1.5 aniline to phenol without a decrease in yield (entry 10).

With these optimized conditions, the scope of the method was investigated (eq 2). *N*,*N*-Dimethyl-2-aminonaphthalene



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was an effective coupling partner with a wide range of naphthols and phenols (Figure 3; blue compounds are new

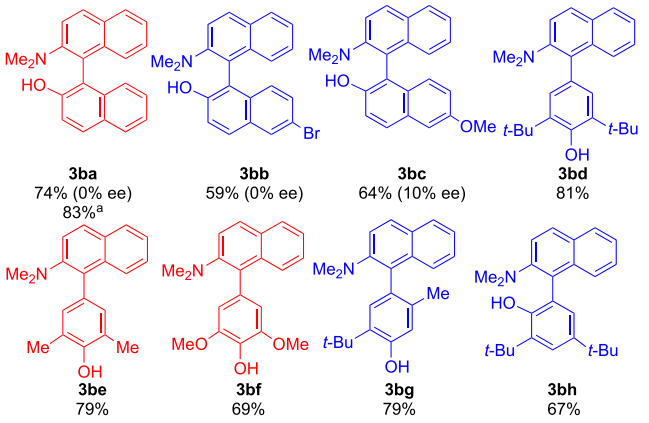

Figure 3. Couplings of *N,N*-dimethyl-2-aminonaphthalene using the conditions in eq 2. (Blue compounds are new compounds, not previously reported.) [a]Isolated yield on a 1.0 mmol scale.

compounds, not previously reported). Few byproducts were observed, and the efficiency was generally good. Bromo- and methoxynaphthols were well tolerated along with 2-naphthol (Figure 3, **3ba**–**bc**). Several substituted phenols coupled effectively as well (**3bd**–**bh**) and with very high regioselectivity (>50:1). On a larger scale, the reaction efficiency was even higher (**3ba**, 83%)

The catalyst system was sufficiently reactive that the couplings of the more difficult aniline derivatives could be accomplished (Figure 4). In addition to the *N,N*-dimethyl congener (**3aa**–**ab**), *para*-toluidines with *N,N*-diethyl substitution (**3ca**–**cb**) or with the incorporation of the nitrogen into pyrrolidine (**3da**–**db**), piperidine (**3ea**–**eb**), or morpholine (**3fb**) rings all coupled to naphthols with good to very good efficiency. The more electron-rich *para*-methoxyanilines were also effectively coupled (**3ga**–**ha**). Notably, the coupling of the aniline analogs with phenols also proceeded in moderate yield (**3dd**–**de**), even for a monosubstituted phenol (**3ai**) for which selective couplings are typically very difficult. In all of these cases, the reactions were fairly clean, giving only one product along with residual starting material or decomposition to baseline materials.

Coupling reactions of *N,N*-dimethyl-2-aminonaphthylene and phenols led to somewhat unexpected results in certain instances (Figure 5). Coupling using phenols with multiple unhindered reactive sites, such as 2-*tert*-butylphenol, led to a mixture of ortho- and para-substituted products (**3bj**, **3bj′**). The product ratio observed (1:2.2) is consistent with the calculated site nucleophilicities of the ortho and para positions of the phenolate anion (1.70:2.15)[19] showing a preference for the para-substituted product. When using a phenol with a sterically unencumbered −OH group, a mixture of C−C (**3bi**–**bn**) and C−O (**3bi′**–**bn′**) coupled products was observed. In para-substituted phenols (**3bi**–**bl**), a preference for the C−O product is observed, with product ratios of 1:1.5−3.1. For each of these cases, the site nucleophilicities (see the SI) of the phenolates predict that the oxygen is more reactive in accord with the observed trends. The greatest preference for C−O products is seen with an electron-donating methoxy group (**3bl**, **3bl′**). In contrast, increasing the steric bulk around the OH leads to more C−C coupled product (**3bm**). Furthermore,

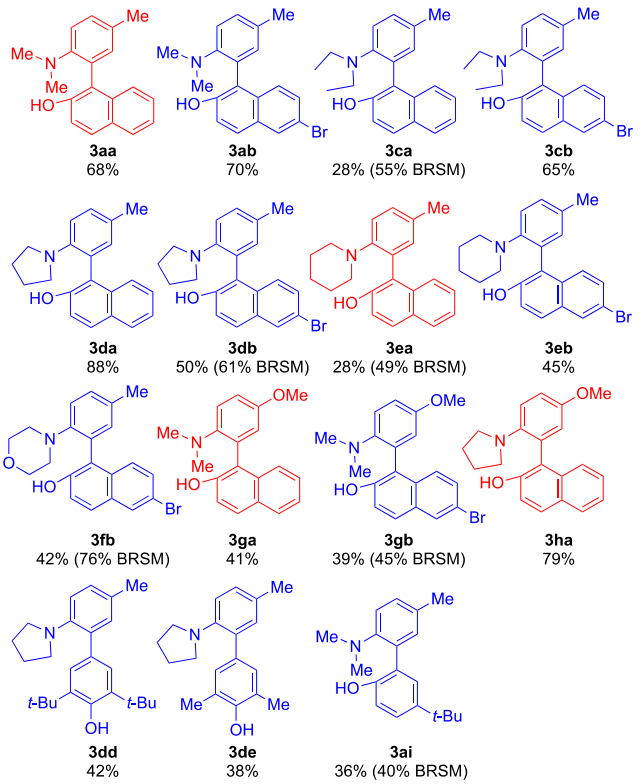

Figure 4. Couplings of anilines using the conditions in eq 2 (BRSM = based on recovered starting material; blue compounds are new compounds, not previously reported).

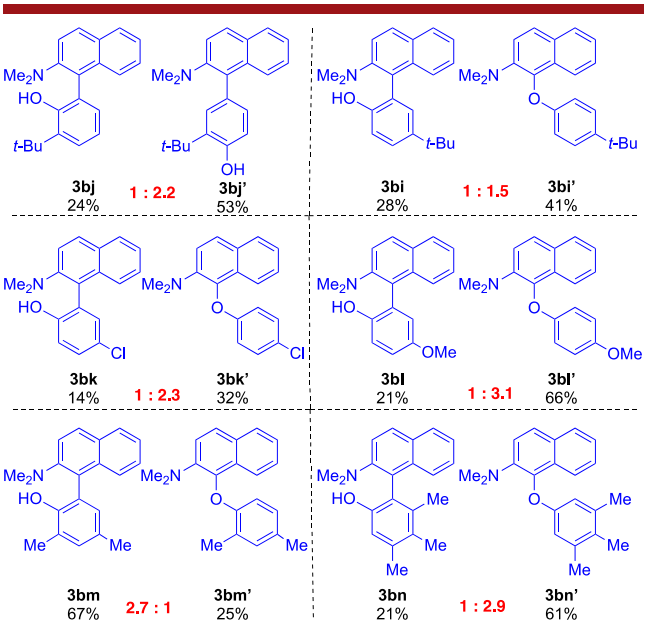

Figure 5. Couplings of *N,N*-dimethyl-2-aminonaphthalene with two outcomes (C−C_{ortho} vs C−C_{para} or C−C vs C−O; blue compounds are new compounds, not previously reported).

increased steric bulk around the ortho positions (by 3,5-substitution) leads to a greater preponderance of C−O product (**3bn′**).

This method required certain structural and electronic parameters in order for coupling to occur. Specifically, para substitution of the aniline derivative is required. *N,N*-Dimethylaniline as well as ortho-substituted *N,N*-dimethylani-

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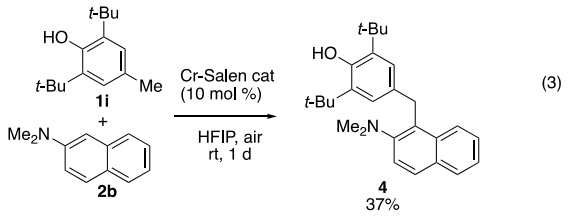
lines did not undergo coupling with this method. Furthermore, electron-withdrawing substituents on the aniline or phenol partner were not tolerated. The incorporation of the nitrogen into a ring (e.g., *N*-methylpyrrole or *N*-methylindole) did not afford cross-coupled product using this method.

To gain greater insight into the reaction, the active catalyst of the system was determined. The addition of 100 mol % *oxo*-Cr(V) was found to result in 100% conversion of starting material. The addition of sterically hindered base (2,6-di-*tert*-butyl-4-methylpyridine) increased the rate of loss of *oxo*-Cr(V) (1 min vs 20 s). This finding is consistent with the reported work on the cross-couplings of phenol with the same Cr−salen catalyst.[19]

Cyclic voltammetry and calculated nucleophilicities were used to probe which substrate likely initiates the reaction. The onset oxidation potential of *N*,*N*-dimethyl-2-aminonaphthalene (0.33 eV, relative to Fe/Fe^+) was found to be significantly lower than that of the most oxidizable phenolic partner, 2,6-dimethoxyphenol (0.89 eV),[19] suggesting that the aminonaphthalene was the more oxidizable species in the reaction. Support for this oxidation order is the rapid quantitative formation of a homodimer when *N*,*N*-dimethyl-2-aminonaphthalene alone is subjected to the catalyst.

Free-radical inhibitor butylated hydroxytoluene (BHT, 1.06 eV) was found to alter the reaction outcome dramatically. When *N*,*N*-dimethyl-2-aminonaphthalene (eq 3, no phenol



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present except BHT) was subjected to the Cr−salen catalyst under air with BHT, the aminonaphthalene homocoupling that was otherwise observed (see above) was completely suppressed, and compound **4** was formed instead.

On the basis of the above data, a catalytic cycle is proposed (Figure 6). Binding of the sterically hindered *N*,*N*-dimethyl-2-aminonaphthalene to the Cr−salen catalyst would be disfavored,[20] which suggests the possibility of an outer-sphere

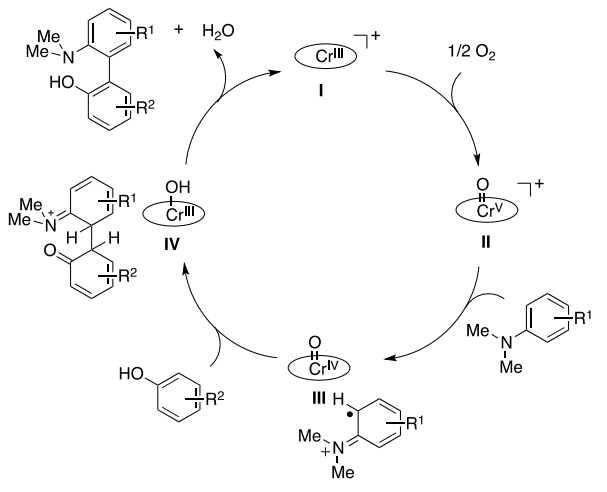

Figure 6. Proposed catalytic cycle for oxidative cross-coupling.

oxidation occurring in the reaction. Such an oxidation by the *oxo*-Cr(V) species **II** would yield a radical cation and Cr(IV) species **III**. A computational study of the site nucleophilicities[19] of the coupling partners revealed that the deprotonated phenol/naphthol (1.67−2.88; see the SI and previous work[19]) partner is considerably more nucleophilic at the *ortho*-carbon than *N*,*N*-dimethyl-2-aminonaphthalene (0.95). Thus, after deprotonation of the phenol by **III**, the attack of the more nucleophilic phenolate onto the radical cation accompanied by a one-electron oxidation would induce the selective cross coupling and yield **IV**. The addition of base suppresses the formation of the aminonaphthalene homodimer by ∼6% in the cross-coupling of *N*,*N*-dimethyl-2-aminonaphthalene and 4-chlorophenol, which further supports the role of the phenolate anion. No enantioselectivity was observed in the couplings of **3ba**, **3bb**, and **3bc** (see the SI), which is consistent with a mechanism where the coordination of the phenol does not occur. Ultimately, tautomerization and water release lead to the product and regenerate the Cr(III)−salen catalyst **I**. The complementary nature of the coupling partners (oxidizability vs nucleophilicity) is similar to that invoked in some phenol cross-couplings.[8d]

For some cases (i.e., unhindered phenols), phenol oxidation may involve coordination to the Cr(IV) species **III** and inner-sphere electron transfer; however, the dissociation of the resulting phenoxyl equivalent needs to be invoked to explain the C−O coupling outcomes (Figure 5). For more hindered phenols (e.g., 2,6-di-*tert*-butylphenol), outer-sphere electron transfer appears more likely.

In conclusion, we have developed an effective catalytic oxidative cross-coupling of *N*,*N*-disubstituted aniline derivatives with naphthols and phenols. The method proceeds under benign conditions, using O_2 in air as the oxidant at room temperature. Mechanism experiments suggest that oxidation of the aniline portion occurs first, which then engages in a coupling with the more nucleophilic species (naphthol/phenol) at the more nucleophilic site via a Cr(V) to Cr(III) redox couple.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00046.

Experimental and spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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