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TEMPO-Mediated Cross-Dehydrogenative Coupling of Indoles and Imidazo[1,2-*a*]pyridines with Fluorinated Alcohols

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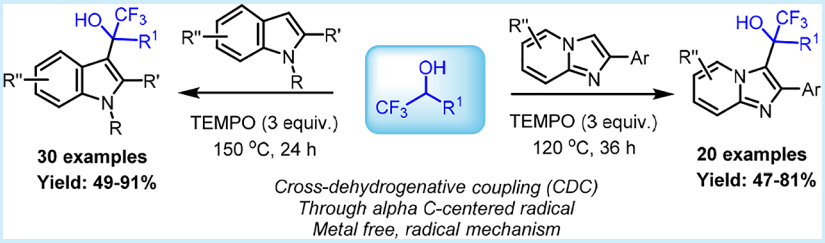

ABSTRACT: A simple and highly efficient metal-free method has been developed for hydroxyfluoroalkylation of indoles and imidazo[1,2-*a*]pyridines via TEMPO-mediated C(sp^3)−H and C(sp^2)−H bond cross-dehydrogenative coupling of fluorinated alcohols and indoles. The protocol showed broad substrate scope, afforded good yields of hydroxyfluoroalkylated products, and was amenable for scale-up. Mechanistic investigation indicated involvement of the radical pathway.

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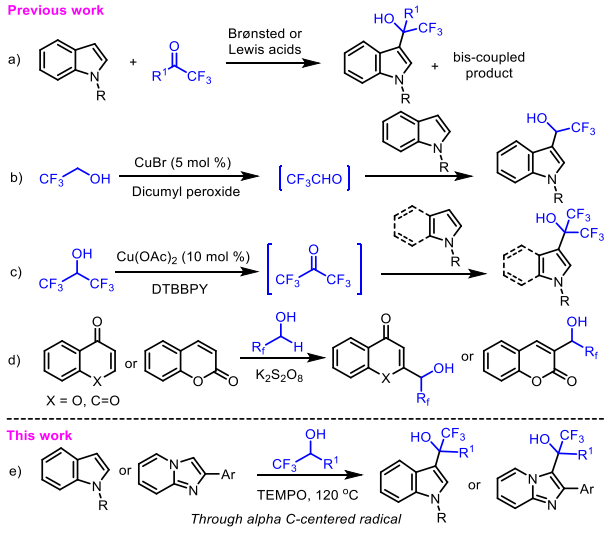
Indole and imidazo[1,2-*a*]pyridine skeletons functionalized at C3-positions are found in a wide variety of synthetic bioactive compounds.[1] Thus, functionalization of these heterocycles has aroused much attention from the synthetic community.[2] Introduction of fluoroalkyl groups at the C3-position of these heterocycles can further enhance their drug-like potential as the relatively small size and high electronegativity of fluorine atoms lead to dramatic modifications in the physicochemical properties and biological activities of organic molecules.[3] Friedel−Crafts alkylation of indoles with fluorocarbonyls is one of the most straightforward methods used for introducing a hydroxyfluoroalkyl moiety at the C3-position of indole (Scheme 1a).[4] However, formation of bis-coupled adducts and harsh reaction conditions are the drawbacks associated with these methods. On the other hand, hydroxyfluoroalkylation of imidazo[1,2-*a*]pyridines has not been reported so far. Thus, a practical synthetic method for the hydroxyfluoroalkylation of these heteroarenes is of great interest and highly desirable.

Direct C−H bond functionalization through various cross-dehydrogenative coupling (CDC) reactions has promoted a paradigmatic change in the field of organic synthesis in recent years.[5] The CDC of C(sp^3)−H bonds offers an excellent starting point for the functionalization of organic compounds due to its abundance. Among various strategies, free-radical-triggered CDCs of the C(sp^3)−H bond adjacent to heteroatoms has attracted special attention as they allow functionalization in a step- and atom-economical fashion and high efficiency. Functionalization of the C(sp^3)−H bond adjacent to a heteroatom is of particular synthetic value as it generates a new bond with concomitant retention of a functional group in the product, which can be used for subsequent reactions.[6] Considerable efforts have been made toward functionalization of alcohols through radical-triggered

Scheme 1. Direct Hydroxyfluoroalkylation of Heterocycles



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CDC reactions,[7] but direct C(sp^3)−H bond functionalization of fluorinated alcohols has very rarely been achieved. Liu and co-workers developed a practical method for coupling of indoles and pyrroles with 2,2,2-trifluoroethanol (TFE) using a DCP/CuBr catalytic system (Scheme 1b).[8] Sun and Jiang developed a copper-catalyzed method for the direct C(sp^2)−H/C(sp^3)−H coupling of aza-heterocycles with fluorinated alcohols (Scheme 1c).[9] Both reactions proceed through a Friedel−Crafts reaction of electron-rich heteroarenes with in situ generated fluorocarbonyls by oxidation of fluorinated alcohols, thus limiting the scope of the reaction. Very recently, Liu et al. reported a $K_2S_2O_8$-mediated dehydrogenative coupling of quinones, chromones, and coumarins with polyfluorinated alcohols which proceeded through an α-carbon-centered radical intermediate (Scheme 1d).[10]

TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl) is a stable organic nitroxyl radical that has been extensively used as a reagent and/or catalyst in organic reactions.[11] The Han[12] and Chiba[13] groups independently reported TEMPO-mediated generation of radicals from hydrazones. In recent years, TEMPO has been used as a mild hydrogen acceptor for the oxidative functionalization of C(sp^3)−H bonds alpha to heteroatoms. For example, Jiao et al. reported TEMPO-catalyzed oxidative C−C coupling of dihydroacridines with nitromethane and other active methylene compounds using molecular oxygen as the oxidant.[14] Herein, we report a facile, metal-free, TEMPO-mediated method for the direct hydroxyfluoroalkylation of indoles and imidazo[1,2-*a*]pyridines through CDC of the alpha C(sp^3)−H bond of fluorinated alcohols with the C(sp^2)−H bond of indoles or imidazo[1,2-*a*]pyridines (Scheme 1e).

We commenced our studies for hydroxyfluoroalkylation with 2-phenylindole (**1a**) and 2,2,2-trifluoroethanol (TFE, **2a**) as the model substrates (Table 1). Initially, the reaction of **1a** (0.4 mmol) was carried out in TFE (2.0 mL) using (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO, 3 equiv) as the oxidant at 90 °C. We were delighted to observe the formation of 3-(2,2,2-trifluoro-1-hydroxyethyl)indole (**3aa**) in 36% yield within 12 h (entry 1). The molecular structure of **3aa** was fully characterized by spectral analysis. While in the absence of TEMPO, as expected formation of **3aa** was not observed (entry 2). Other oxidants such as $K_2S_2O_8$, TBHP, and DCP were found to be ineffective (entries 3−5). Increasing the reaction time slightly improved the reaction efficiency, and **3aa** was formed in 41% yield (entry 6). Further prolonging the reaction for 36 h did not improve the yield of **3aa** (entry 7). Significant improvement in the yield of **3aa** was observed by increasing the reaction temperature up to 150 °C (entries 8−10). Further increase in temperature showed a detrimental effect on the yield of **3aa** (entry 11). When the amount of TEMPO was increased to 3 equiv at 150 °C, **3aa** was formed in 89% yield (85% isolated) (entry 12). Subsequent increase in the amount of TEMPO to 3.5 equiv resulted in a lower yield of **3aa** (entry 13). Use of acetic acid as additive decreased the reaction time to 3 h with slightly lower yields (entry 14).

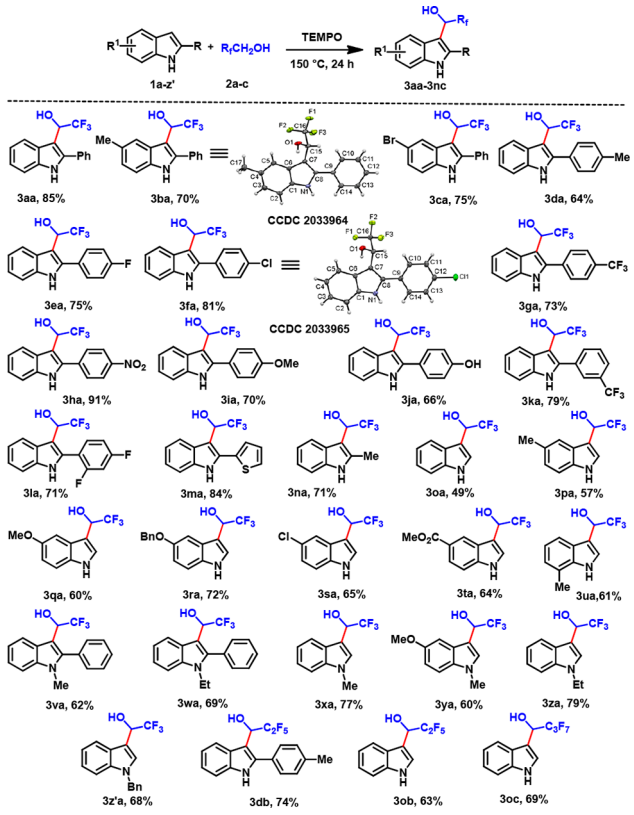
Table 1. Optimization of Reaction Conditions[a]

entry	oxidant	temp (°C)	time (h)	% yield (**3aa**)[b,c]
1	TEMPO	90	12	36 (30)
2		90	12	0
3	$K_2S_2O_8$	90	12	0
4	TBHP	90	12	0
5	DCP	90	12	0
6	TEMPO	90	24	41 (34)
7	TEMPO	90	36	40 (30)
8	TEMPO	110	24	55 (48)
9	TEMPO	130	24	60 (52)
10	TEMPO	150	24	65 (57)
11	TEMPO	160	24	50 (44)
12	TEMPO[d]	150	24	**89 (85)**
13	TEMPO[e]	150	24	85 (82)
14	TEMPO[f]	150	3	78 (72)

[a]Reaction conditions: **1a** (1 equiv, 0.4 mmol), oxidant (2 equiv), TFE (2 mL), sealed tube, heated in an oil bath. [b]Yield calculated based on ^{1}H NMR. [c]Values in parentheses refer to isolated yield after column chromatography. [d]3.0 equiv of TEMPO was used. [e]3.5 equiv of TEMPO was used. [f]Reaction performed in the presence of acetic acid (2 equiv).

With the optimized reaction conditions in hand (entry 12, Table 1), we examined the scope and limitations of this strategy against a variety of indoles (Scheme 2). Initially, 2-arylindoles (**1a−l**) were reacted with **2a** under standard conditions, and the corresponding hydroxyfluoroalkylated products **3aa−la** were obtained in good to excellent yields (64−91%). Interestingly, 2-arylindoles with electron-withdrawing groups on the C2-aryl ring produced a higher yield (compare **3ea−ha** vs **3ga**). 2-(Thiophen-2-yl)-1*H*-indole (**1m**) and 2-methyl-1*H*-indole (**1n**) also gave corresponding products **3ma** and **3na** in 84 and 71% yields, respectively. Indoles with a C2-unsubstituted position bearing either electron-donating or electron-withdrawing groups, such as

Scheme 2. Hydroxyfluoroalkylation of Indoles[a,b]



[a]Reaction conditions: **1** (1 equiv, 0.4 mmol), **2** (2 mL), TEMPO (3.0 equiv), 24 h, sealed tube, 150 °C in an oil bath. [b]Isolated yields.

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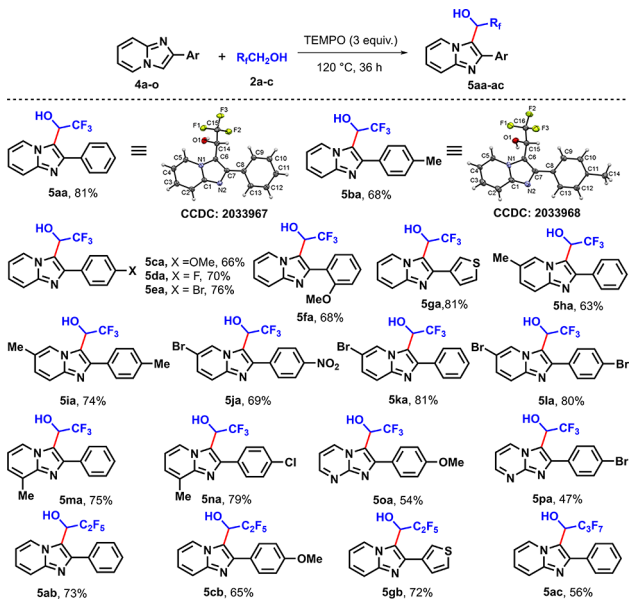
methyl, methoxy, benzyloxy, chloro, and carboxylate, at different positions (**1o**−**u**) reacted smoothly, generating the corresponding 3-(2,2,2-trifluoro-1-hydroxyethyl)indoles (**3oa**−**3ua**) in moderate to good yields (49−72%). Captivatingly, N-substituted indoles with methyl, ethyl, and benzyl groups (**1v**−**z′**) also afforded corresponding products **3va**−**3z′a** in good yields (60−79%). Notably, the tolerance of halogen substituents provided handles for late-stage functionalization. The structures of the products were confirmed by NMR (^{1}H, ^{19}F, and ^{13}C{^{1}H}) and HMRS data. The structures of **3ba** (CCDC 2033964) and **3fa** (CCDC 2033965) were unambiguously confirmed by single-crystal X-ray analysis.

After evaluating the substrate scope with respect to indoles, we explored the possibility of using different alcohols under optimal conditions. 2,2,3,3,3-Pentafluoropropan-1-ol (**2b**) and 2,2,3,3,4,4,4-heptafluorobutan-1-ol (**2c**) reacted with indole (**1o**) under optimized reaction conditions to afford the corresponding hydroxyfluoroalkylated products **3ob** and **3oc** in 63 and 69% yield, respectively. Similarly, 2-tolylindole (**1d**) upon reaction with **2b** produced hydroxyfluoroalkylated product **3db** in 74% yield. Unfortunately, hydroxyalkylated product could not be isolated from the reaction of **1a** with ethanol, butanol, and 2-hexafluoropropanol under these conditions.

To further extend the scope of this reaction, imidazo[1,2-*a*]pyridine (**4a**) was allowed to react with **2a**. A small change in the reaction conditions (increase in reaction time to 36 h and decreasing reaction temperature to 120 °C; see Table S1, Supporting Information) afforded 2,2,2-trifluoro-1-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)ethanol **5aa** in good yield (81%). We then evaluated the substrate scope for imidazo[1,2-*a*]pyridines (Scheme 3). Reaction of imidazo[1,2-*a*]pyridines having electron-donating as well electron-withdrawing substituents on the C2-phenyl ring and imidazo[1,2-*a*]pyridine nucleus (**4b**−**p**) with **2a** afforded the corresponding 2,2,2-trifluoro-1-hydroxyethyl derivatives **5ba**−**pa** in moderate to good yields (63−81%). 2-(Thiophen-3-yl)imidazo[1,2-*a*]-pyridine (**1m**) also successfully afforded the desired product **5ma** in 81% yield. Reaction of imidazo[1,2-*a*]pyrimidines (**1o** and **1p**) with **2a** provided the corresponding 2,2,2-trifluoro-1-hydroxyethyl derivatives **5oa** and **5pa** in 54 and 47%, respectively. Interestingly, reaction of **4a**, **4c**, and **4g** with **2b** afforded the corresponding products **5ab**, **5cb**, and **5mb** in good yields (65−73%). Reaction of **4a** with **2c** also gave the corresponding 2,2,2-trifluoro-1-hydroxyethyl derivative **5ac** in 56% yield. The NMR (^{1}H, ^{19}F, and ^{13}C{^{1}H}) and HRMS data of **5** were in good agreement with the structures, and the structures of **5aa** (CCDC 2033967) and **5ba** (CCDC 2033968) were unambiguously confirmed by single-crystal X-ray analysis.

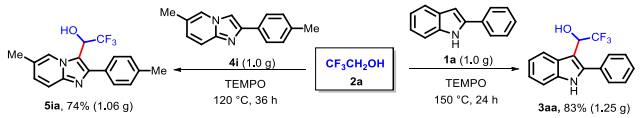
The robustness of this protocol was demonstrated by generating gram quantities of **3aa** and **5ia**. The gram-scale reaction of **1a** and **4i** with **2a** produced corresponding products **3aa** and **5ia** in 83% (1.25 g) and 74% (1.06 g) yield, respectively (Scheme 4).

Scheme 3. Hydroxyfluoroalkylation of Imidazo[1,2-*a*]pyridines[a,b]



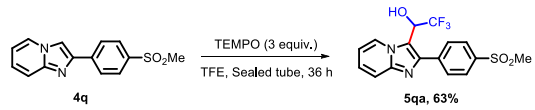
[a]Reaction conditions: **1** (1 equiv, 0.5 mmol), **2** (2.0 mL), TEMPO (3.0 equiv), sealed tube, 120 °C in an oil bath, 36 h. [b]Isolated yields.

Scheme 4. Gram-Scale Synthesis of 3aa and 5ia



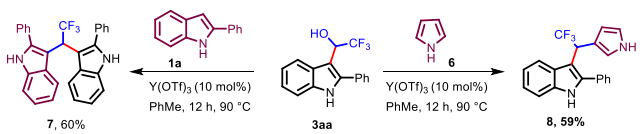
To demonstrate the synthetic utility of the developed protocol, late-stage functionalization of Zolimidine (**4q**), a gastroprotective drug, was performed. Delightfully, reaction of **4q** with TFE under standard conditions produced the hydroxyfluoroalkylated product **5qa** in 63% yield (Scheme 5).

Scheme 5. Late-Stage Functionalization of Zolimidine



Furthermore, the synthetic application of the synthesized products was demonstrated by converting **3aa** to trifluorinated 3-indolyl(heteroaryl)methanols via the Yb(OTf)$_3$-catalyzed Friedel−Crafts reaction (Scheme 6). Reaction of **3aa** with **1a**

Scheme 6. Yb(OTf)$_3$-Catalyzed Friedel−Crafts Reaction of 3aa



and pyrrole (**6**) in the presence of Yb(OTf)$_3$ (10 mol %) in toluene at 90 °C for 12 h gave 3,3′-(2,2,2-trifluoroethane-1,1-diyl)bis(2-phenyl-1*H*-indole) (**7**) and 2-phenyl-3-(2,2,2-trifluoro-1-(1*H*-pyrrol-3-yl)ethyl)-1*H*-indole (**8**) in 60 and 59% yields, respectively.

Some control experiments were performed to gain insights into the reaction mechanism of this CDC reaction (Scheme 7). First, the effect of a radical scavenger was studied by performing the reaction of **1a** with **2a** in the presence of butylated hydroxytoluene (BHT) (Scheme 7a). Formation of **3aa** was completely suppressed with concomitant formation of

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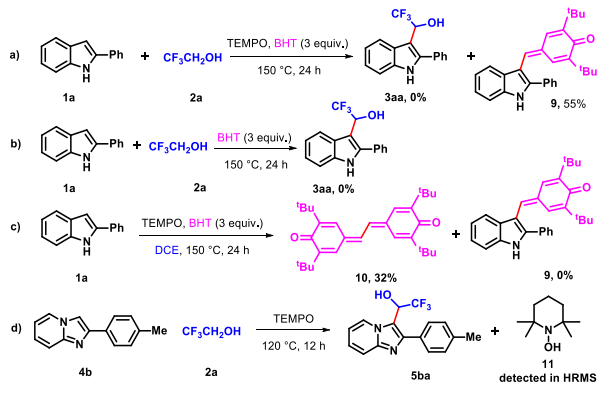
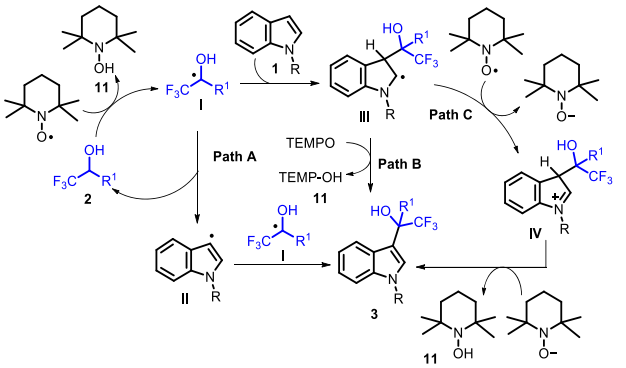
Scheme 7. Control Experiments



BHT-indole adduct **9**, resulting from substitution of a benzylic C−H bond,[15] indicating that the reaction involves a radical pathway which is contrary to the ionic mechanism reported by Jiang's group.[9] No product formation was observed from the reaction of **1a** and **2a** in the presence of BHT and absence of TEMPO (Scheme 7b), indicating the crucial role of TEMPO in initiating the reaction. Further, reaction of **1a** in the presence of TEMPO and BHT resulted in the formation of 4,4′-(ethane-1,2-diylidene)bis(2,6-di-*tert*-butylcyclohexa-2,5-dienone) (**10**) in 32% yield, and adduct **9** was not observed under these conditions (Scheme 7c). A peak at m/z 158.1523 corresponding to TEMP−OH (**11**) was observed along with peaks for **4b** and **5ba** in the HRMS analysis of the reaction mixture of the reaction between **4b** and **2a** after 12 h under standard conditions (Scheme 7d).

Based on the experimental results and literature reports,[8,14,16] a plausible mechanism of the developed CDC reaction is proposed in Scheme 8. First, α-hydrogen atom

Scheme 8. Plausible Mechanism for TEMPO-Mediated Hydroxyfluoroalkylation



abstraction by TEMPO generated the C-centered radical **I**, which abstracted C3-hydrogen from indole to generate the indole radical (**II**). Recombination of the radicals **I** and **II** produced product **3**. In another pathway, radical **I** upon addition to indole (**1**) produced radical intermediate **III**. Next, intermediate **III** either underwent hydrogen atom abstraction by TEMPO to produce product **3** (path B) or produced iminium ion **IV** with a single electron transfer process (path C). In path C, elimination of a proton from intermediate **IV** produced product **3**. Based on the control experiment, path A seems to be more probable; however, path B and path C cannot be ruled out.

In summary, TEMPO-mediated cross-dehydrogenative coupling of the C(sp^3)−H bond and the C(sp^2)−H bond has been developed for direct hydroxyfluoroalkylation of indoles and imidazo[1,2-*a*]pyridines by fluorinated alcohols under metal-free reaction conditions. The developed synthetic protocol is operationally simple and provides a wide range of C3-hydroxyfluoroalkylated indoles and imidazo[1,2-*a*]-pyridines in good to excellent yields. Broad substrate scope and high functional group tolerance are the silent features of the developed method. The synthetic utility of the protocol was showcased through gram-scale synthesis of **3aa** and **5ia**. Moreover, 2,2,2-trifluoro-1-(2-phenyl-1*H*-indol-3-yl)ethanol could be elegantly transformed to 3,3′-(2,2,2-trifluoroethane-1,1-diyl)bis(2-phenyl-1*H*-indole) and 2-phenyl-3-(2,2,2-trifluoro-1-(1*H*-pyrrol-3-yl)ethyl)-1*H*-indole. Mechanistic investigation revealed that the reaction involves a radical process. Further investigations on TEMPO-mediated hydroxyfluoroalkylation of other heterocycles are 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.1c00031.

Experimental procedure, ^{1}H, ^{19}F, and ^{13}C{^{1}H} NMR spectra, and copies of NMR data, HRMS of intermediate, crystal data for **3ba**, **3fa**, **5aa**, and **5ba** (PDF)

Accession Codes

CCDC 2033964−2033965 and 2033967−2033968 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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Notes

The authors declare no competing financial interest.

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