

Iron Catalysis of C(sp³)-H Azidation Using a Heteroarene Radical Cation Strategy

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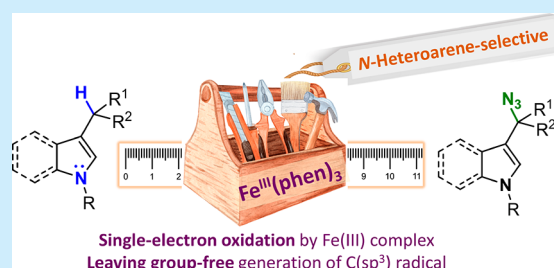
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ABSTRACT: The Fe^{III}(phen)₃ catalysis of the benzylic C(sp³)-H azidation of indoles has been investigated. The Fe(III) complex can selectively oxidize indoles to form arene radical cations, which are transformed into benzylic C(sp³) radical intermediates. This strategy exhibits a difference in reactivity between *N*-heteroarenes and benzene, which is difficult to achieve via direct hydrogen abstraction approaches. Various biorelevant azide precursors were constructed, highlighting the utility of this mild first-row transition-metal catalyst system.



C(sp³)-H bond functionalization has received considerable attention as an atom-economical method for increasing the molecular complexity with simple modifications. Although the selective activation of C(sp³)-H over other ubiquitous C-H bonds is highly challenging, the benzylic C(sp³)-H bond exhibits potential for the generation of reactive radical intermediates because of its smaller bond dissociation energy (90 kcal/mol) compared to that of unactivated C(sp³)-H bonds (105 kcal/mol).^{1,2} The regioselectivity of the reaction primarily relies on the physicochemical properties, i.e., the C-H bond dissociation energy and electronic properties, of the intermolecular hydrogen atom transfer (HAT) reagents or oxidants used.³ Based on this outer-sphere radical initiation mechanism, precisely predicting the reaction regioselectivity, particularly for complex arenes and heteroarenes bearing benzylic-type C(sp³)-H bonds, is difficult.

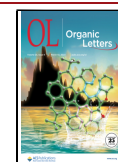
Organic azides are a versatile class of compounds found in biologically active pharmaceuticals and nitrogen-based scaffolds for therapeutic drugs and functional materials. Synthetic strategies for aliphatic azides have been mainly developed with the azidation of C-C multiple bonds, azidation of C-H bonds, and conversion of vinyl azides to aliphatic azides.⁴ Direct C-H azidation is one of the most straightforward strategies to convert hydrocarbons into azides; however, the selectivity for benzylic over aliphatic C(sp³)-H bonds is relatively low. Therefore, the selective azidation of benzylic and heterobenzylic C-H bonds could have a broad impact, and the oxidative and radical means of introducing azide groups have been investigated.⁵ Previously, a Cu(dap)₂-catalyzed photoredox reaction with a Zhdankin azidoiodinane (1-azido-1,2-benziodoxol-3(1H)-one, ABX) reagent was developed by Greaney et al. to generate azide radicals, which can abstract a benzylic hydrogen and initiate benzylic azidation through a

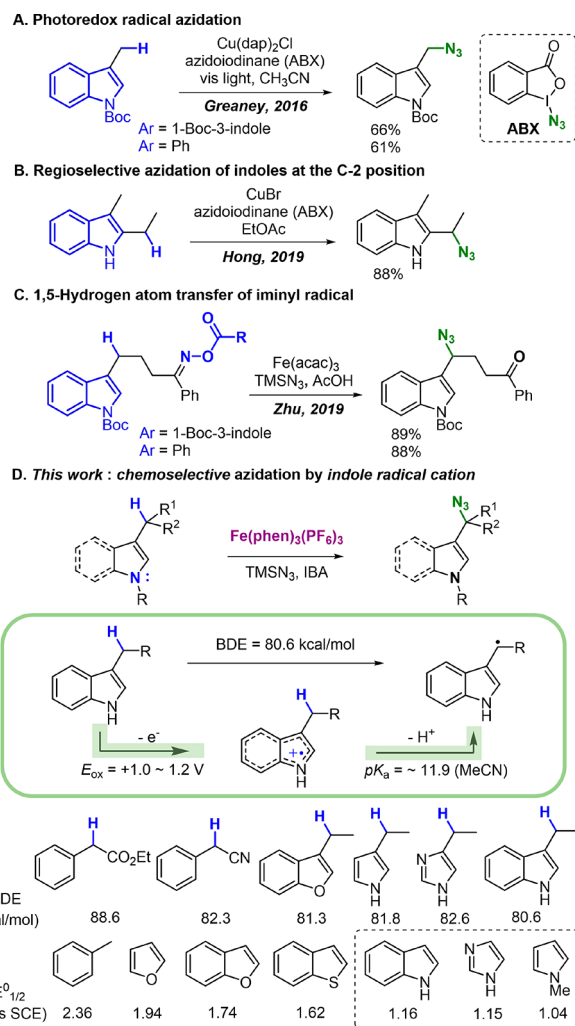
radical chain mechanism (Scheme 1A).⁶ A Cu(I)-catalyzed heterobenzylic azidation of alkyl substituents of indoles was reported by Hong et al., resulting in regioselective azide introduction at the C-2 position (Scheme 1B).⁷ Zhu et al. also reported the homolytic fission of oximes to prepare iminyl radicals, which further generate remote benzylic carbon radicals via intramolecular 1,5-HAT (Scheme 1C).⁸ Although these methods were successful in providing the corresponding azidation products, both the indolyl and benzyl moieties were identical in their reactivity and reaction efficiency. Unlike previous approaches for HAT-mediated direct benzylic radical formation, single-electron oxidation of arenes and heteroarenes to form radical cation intermediates, followed by deprotonation, may enable chemoselective radical formation.^{9,10} *N*-Heteroarenes such as indole, pyrrole, and imidazole have relatively low oxidation potentials (1.04–1.16 V vs SCE), which enables selective single-electron oxidation when these are treated with appropriate oxidants.¹¹ This oxidation results in considerable acidification of the corresponding benzylic-type C(sp³)-H bond; for example, the indole radical cation is estimated to be acidic in acetonitrile solution (pK_a = 12).¹²

In this study, we examined the iron-polypyridyl complex-mediated azidation of substituted indoles by generating *indolyl* C(sp³) radical species via single-electron oxidation and deprotonation, followed by coupling with azide radicals to afford various secondary and tertiary organic azides.¹³ Subsequently,

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Scheme 1. Radical Azidation Reactions of *N*-Heterobenzyl C(sp³)-H Bonds¹⁴

the role of the iron complex in this process was investigated, and the reaction mechanism was verified by UV-vis absorption, voltammetry, and regioselectivity experiments.

First, optimization of the benzylic C(sp³)-H azidation reaction conditions was performed (Table 1). 2-(1-Methyl-1H-indol-3-yl)propanoate (**1a**) was selected as the model substrate and initially reacted with Fe(phen)₃(PF₆)₃, trimethylsilyl azide (TMSN₃), and 2-iodosobenzoic acid (IBA) in 1,2-dichloroethane (DCE) at 25 °C for 12 h under an argon atmosphere (entry 1). This reaction afforded azide product **2a** in 73% yield without any azidation at the C-2 position.¹⁵ Subsequently, other polypyridyl Fe(II) and Fe(III) catalysts were tested (entries 2–6); these produced comparable yields of the desired product, with Fe(phen)₃(PF₆)₂ emerging as the optimal catalyst. However, replacement of the polypyridyl Fe complex with other iron salts, such as Fe(OAc)₂, Fe(OTf)₃, or FeCl₃, was detrimental to the reaction efficiency, resulting in reduced yields of 36, 30, and 44%, respectively (entry 7). The azidation reaction was tested with the commercially available Co(III) and Ru(III) catalysts having a phenanthroline ligand; however, the reaction efficiency of Co and Ru complexes was inferior to that of the Fe(III) catalyst (entries 8 and 9). In the absence of the Fe catalyst, a 24% yield is obtained, confirming the necessity of the Fe(phen)₃(PF₆)₂ complex for efficient

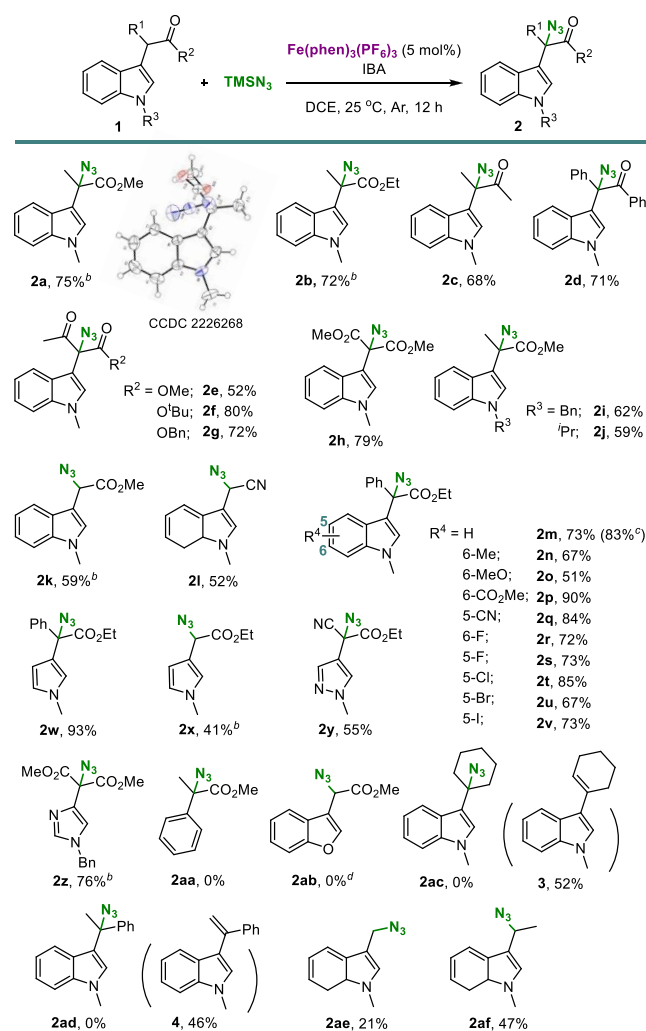
Table 1. Optimization of the Reaction Conditions^a

entry	Fe catalyst	oxidant	yield, % ^b
1	Fe(phen) ₃ (PF ₆) ₃	IBA	73
2	Fe(Me ₂ phen) ₃ (PF ₆) ₃	IBA	68
3	Fe(phen) ₃ (PF ₆) ₂	IBA	75
4	Fe(tpy) ₂ (PF ₆) ₂	IBA	69
5	Fe(bpy) ₃ (PF ₆) ₂	IBA	64
6	Fe(MeO ₂ bpy) ₃ (PF ₆) ₂	IBA	71
7	Fe(OAc) ₂ , Fe(OTf) ₃ , FeCl ₃	IBA	30–44
8	Co(phen) ₃ (PF ₆) ₃	IBA	54
9	Ru(phen) ₃ (PF ₆) ₃	IBA	29
10	—	IBA	24
11	Fe(phen) ₃ (PF ₆) ₂	—	—
12	Fe(phen) ₃ (PF ₆) ₂	TBHP	15
13	Fe(phen) ₃ (PF ₆) ₂	PhI(OAc) ₂	56
14	Fe(phen) ₃ (PF ₆) ₂	PhI(OPiv) ₂	44
15	Fe(phen) ₃ (PF ₆) ₂	PhI(OCOCF ₃) ₂	5

^aReaction conditions: **1a** (0.10 mmol), Fe catalyst (5.0 mol %), oxidant (0.15 mmol), TMSN₃ (0.30 mmol), DCE (0.10 M), 25 °C, Ar, 12 h. ^bIsolated yield. IBA = 2-iodosobenzoic acid; TBHP = *tert*-butyl hydroperoxide; phen = 1,10-phenanthroline; tpy = 2,2',6',2''-terpyridine; bpy = 2,2'-bipyridine; (MeO)₂bpy = 4,4'-dimethoxy-2,2'-bipyridine; Me₂phen = 4,7-dimethyl-1,10-phenanthroline.

azidation (entry 10). IBA also exhibits a prominent effect on Fe(II)/Fe(III) catalysis, as demonstrated when other types of peroxide and hypervalent iodine oxidants are used (entries 12–15). Other azide sources (NaN₃, *p*-TosN₃, and *n*Bu₄NN₃) and base additives did not lead to the effective formation of the azide product.¹⁶

Next, we performed selective benzylic C(sp³)-H azidation of a wide range of indole derivatives (Scheme 2). Although Fe(phen)₃(PF₆)₂ was determined to be the optimal catalyst previously, subsequent substrate studies showed that Fe(phen)₃(PF₆)₃ also exhibited a comparable catalytic activity. The initial investigation examined the effect of the carbonyl substituents on the azidation reactions. Substrates bearing ester, ketone, ketoester, and diester functional groups undergo radical azidation and afford the corresponding products **2a–2h** in moderate to good yields. Notably, sterically hindered indole derivatives **1d–1h** are also compatible, furnishing indole derivatives containing functionalized quaternary centers under the optimized reaction conditions. These results indicate that carbonyl groups are an important motif for the formation of the radical intermediate; this can be attributed to the synergistic stabilization of the radical by the electron-donating (indole) and electron-withdrawing (carbonyl) substituents via the captodative effect.¹⁷ In addition to *N*-methyl substitution, substrates derived from *N*-benzyl and *N*-isopropyl indoles (**1i**, **1j**) were tested; these exhibited lower yields than those of **1a**.

Scheme 2. Substrate Scope of C(sp³)-H Azidation^a

^aReaction conditions: **1** (0.10 mmol), Fe(phen)₃(PF₆)₃ (5 mol %), IBA (0.15 mmol), TMSN₃ (0.30 mmol), DCE (0.1 M), 25 °C, Ar, 12 h. ^bFe(phen)₃(PF₆)₂ (5 mol %) was used as the catalyst. ^c1.5 mmol of **1m** was used. ^dBoth Fe(phen)₃(PF₆)₂ and Fe(phen)₃(PF₆)₃ were tested for 48 h, respectively, resulting in a byproduct mixture.

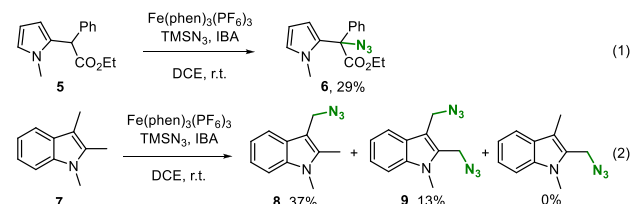
The susceptibility of tertiary C(sp³)-H activation may arise from the stability of the generated radical intermediate. Secondary C(sp³)-H azidation is less efficient than that of tertiary C(sp³)-H bonds, as demonstrated when indole derivatives **2k** and **2l** are afforded in moderate yields of 59 and 52%, respectively. When various substitutions at the 5- and 6-positions of the indole substrates are examined, this methodology exhibits a high functional group tolerance; methyl, methoxy, ester, nitrile, and halogen groups provide the corresponding azidation products **2m**–**2v**. Here, the potential scalability of this approach was also demonstrated by performing the reaction with **1m** on a 1.5 mmol scale; this gives an increased yield of 83%, thus showing the practical efficacy of this catalysis method. Next, the catalyzed azidation was examined with alternative heteroarenyl- and phenyl-derived substrates. Pyrrole derivatives **1w** and **1x** are predominantly transformed to **2w** and **2x**, while the pyrazole and imidazole precursors are also compatible, furnishing products **2y** and **2z**. When phenyl- and benzofuranyl-derived substrates are used, benzylic C–H azidation does not proceed

(**2aa** and **2ab**, 0%), thus highlighting the selectivity of this reaction toward N-heterocycles. This indicates that the N-heteroarene core is preferentially oxidized under Fe^{III}(phen)₃ catalysis, and the subsequent deprotonation of the C(sp³)-H bond furnishes a carbon radical. The incorporation of two alkyl groups or alkyl/aryl groups instead of a carbonyl substituent results in eliminated alkene products **3** and **4**; this may arise from the further oxidation and elimination of the alkyl radical intermediate in the absence of the carbonyl-mediated stabilization effect. When 3-methyl or 3-ethylindole was tested under the standard reaction conditions, primary C(sp³)-H azidation was far less efficient than that of secondary C(sp³)-H bonds, resulting in azide **2ae** and **2af** being produced in yields of 21 and 47%.

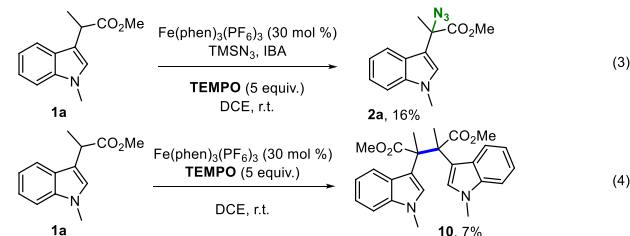
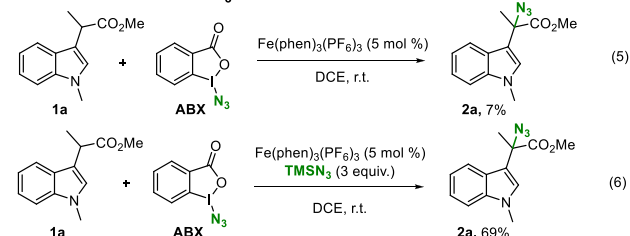
After the substrate scope of this reaction was established, several experiments were performed to clarify the reaction mechanism (Scheme 3). First, the regioselectivity of this

Scheme 3. Mechanistic Investigation

A. Investigation of regioselectivity



B. Observation of radical intermediate

C. Roles of IBA and TMSN₃

strategy was examined by using several substrates with alternative potential substitution sites. While azide **2w** was produced efficiently, as shown in Scheme 2, the regioisomer **6** was obtained with a reduced yield of 29% (eq 1). Next, 1,2,3-trimethyl-1H-indole **7**, which offers several sites for azidation, was treated under the optimized reaction conditions; here, the 3-methyl substituent **8** is preferentially obtained in 37% yield, along with the diazide **9** in 13% yield (eq 2).⁷ Monoazidation at the 2-methyl or N-methyl positions was not observed, thus indicating the dominant reactivity of the C-3 substituent of the indole substrate. Confirmation of the formation of the radical intermediate was then conducted via treatment of **1a** with (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO). Here, a considerable decrease in the yield of **2a** and the additional formation of dimer **10** indicates that the generation of the benzylic carbon radical is a key feature of the reaction (eqs 3

and 4). Next, the roles of IBA and TMSN_3 in the generation of the active azide intermediate were examined. 1-Azido-1,2-benziodoxol-3(1H)-one (ABX), which is formed from the reaction of IBA with TMSN_3 , was separately prepared and tested under the optimized conditions.¹⁸ When ABX is reacted with **1a** in isolation in the absence of TMSN_3 , an unsatisfactory yield of **2a** is obtained; however, when TMSN_3 is included, the expected activity is exhibited, thus indicating that TMSN_3 has a further role in the reaction mechanism (eqs 5 and 6).¹⁹

Based on the collective evidence from these observations, a reaction mechanism is proposed involving an initial electron transfer between the $\text{Fe}^{\text{III}}(\text{phen})_3$ complex and the indole substrate, as modeled here by **1a** (Figure 1). The activation

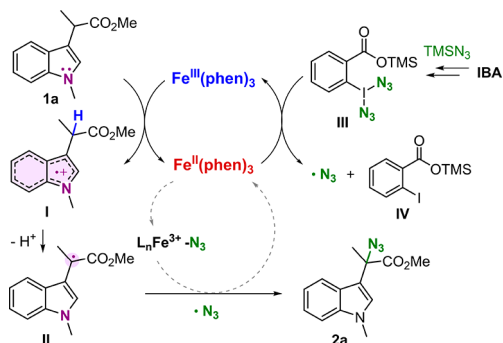
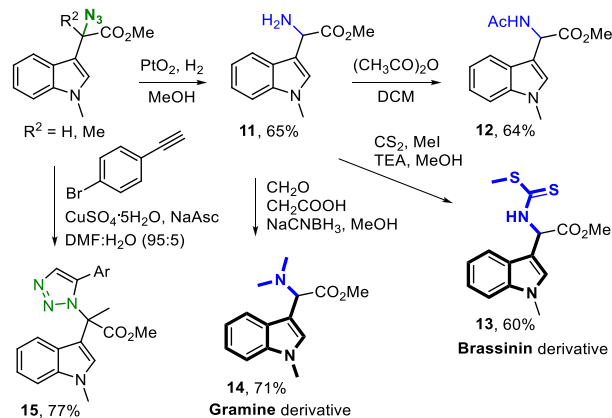


Figure 1. Proposed mechanism for the $\text{Fe}^{\text{III}}(\text{phen})_3$ -catalyzed azidation reaction.

reaction is favorable, as inferred from the reduction potential of $\text{Fe}^{\text{III}}/\text{Fe}^{\text{II}}$ (1.14 V vs SCE) and the oxidation potential of indole (1.0–1.3 V vs SCE), respectively.^{11,13} This activation is also indicated by the UV–vis absorption spectra obtained for a solution of $\text{Fe}^{\text{III}}(\text{phen})_3$ and **1a** (Figure S2), where a gradual increase in the absorption intensity at 508 nm is observed with an increasing concentration of **1a**; this can be attributed to the increasing generation of the $\text{Fe}^{\text{II}}(\text{phen})_3$ species. After the electron transfer, the benzylic proton of oxidized indole radical cation **I** becomes sufficiently acidic ($\text{p}K_{\text{a}} = 12$ in MeCN) for deprotonation to occur, thus giving alkyl radical **II** (Figure 1). The reaction of IBA and TMSN_3 gives iodine-diazide intermediate **III**, which facilitates the $\text{Fe}^{\text{II}}(\text{phen})_3$ -catalyzed production of the azide radical.¹⁹ The resulting alkyl and azide radical intermediates then undergo radical coupling to produce the final azidation product. The formation of compound **IV** was detected by ^1H and ^{29}Si NMR analysis. Additionally, Fe-mediated azido transfer may be involved in furnishing the final azide product, followed by concomitant regeneration of the $\text{Fe}^{\text{II}}(\text{phen})_3$ catalyst.²⁰

Azides are versatile and valuable functional units in synthetic chemistry; thus, the newly synthesized products were subjected to several postmodification reactions (Scheme 4). Hydrogenation produces the corresponding amine **11**, which can then be further transformed to acetamide **12**, carbamodithioate **13**, and dimethylamine **14**. The latter two amino indoles are structurally similar to brassinin, a potent antimicrobial and anticarcinogenic substance, and gramine, a plant-based antibacterial agent. These indole alkaloids are important substances in secondary metabolism processes, and their structural modification has attracted increasing attention.²¹ Finally, the click reaction of the azide with an arylalkyne affords triazole heterocycle **15** in good yield.

Scheme 4. Synthetic Application



In conclusion, we have demonstrated the development of an $\text{Fe}^{\text{III}}(\text{phen})_3$ -catalyzed benzylic $\text{C}(\text{sp}^3)\text{—H}$ azidation of indoles under mild reaction conditions. This work represents the first use of a $\text{Fe}^{\text{III}}(\text{phen})_3$ complex for single-electron oxidation to afford an arene radical cation in which *N*-heteroarenes and benzene derivatives were differentiated according to their oxidation potential. The selective formation of the $\text{C}(\text{sp}^3)$ radical intermediate by deprotonation is enabled by the captodative effect of the electron-donating *N*-heteroarene and electron-withdrawing carbonyl groups. Various tertiary and secondary azides were constructed; furthermore, 2-azido-3-indolyl acetate derivatives can be elaborated to produce biologically active molecules. We anticipate that this sustainable Fe^{II} redox catalysis will be applicable in future diverse synthetic strategies, and the late-stage functionalization is expected to promote new protocols in Fe catalysis.

ASSOCIATED CONTENT

Data Availability Statement

Data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.3c00330>.

Experimental details, NMR spectra, and crystallographic methods (PDF)

Accession Codes

CCDC 2226268 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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