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Difluoroisoxazolacetophenone: A Difluoroalkylation Reagent for Organocatalytic Vinylogous Nitroaldol Reactions of 1,2-Diketones

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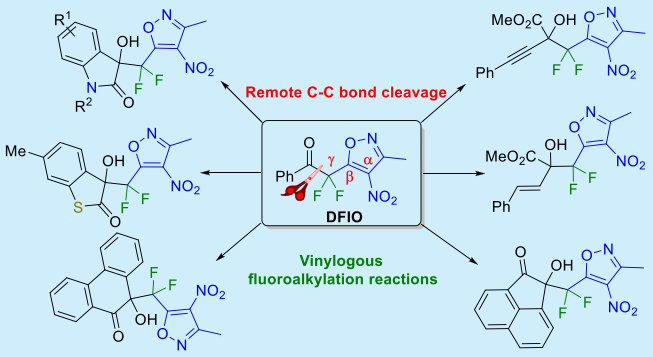
ABSTRACT: Difluoroisoxazolacetophenone (DFIO) is developed as a new difluoroalkylation reagent that can be easily prepared from inexpensive starting materials. In situ remote C−C bond cleavage of DFIO affords γ,γ-difluoroisoxazole nitronate that undergoes base-catalyzed vinylogous nitroaldol additions to isatins, benzothiophene-2,3-dione, unsaturated-α-ketoesters, and cyclic 1,2-diketones. This organocatalytic debenzoate vinylogous nitroaldol reaction provides a new and mild approach for the preparation of various difluoroisoxazole-substituted 3-hydroxy-2-oxindoles.



Fluorine-containing compounds are now widespread in medicinal chemistry and material sciences.[1] It is well established that the introduction of fluorine into bioactive compounds can significantly alter their lipophilicity, bioavailability, and metabolic stability.[2] Consequently, great efforts have been made to develop efficient strategies, methods, reagents, and catalysts for the preparation of various fluorine-containing compounds.[3] Recently, the introduction of a difluoromethylene group has been particularly interesting because it can serve as a bioisostere for an oxygen atom, an isopropyl group, or a carbonyl group.[4] Significant progress has been witnessed in the studies on transition-metal-catalyzed[5] or radical-mediated[6] difluoroalkylation for the formation of C−CF_2 bonds. However, reliable methods for the introduction of functionalized α,α-difluoroalkyl groups onto heteroarenes are limited. Therefore, the development of novel alternative methods for the preparation of heterocyclic compounds with a difluoromethylene group would be highly desirable.

The selective cleavage of carbon−carbon (C−C) bonds is quite challenging due to the inherent robustness of the C−C bond.[7] One of the most powerful of these methods is deacylation because of its efficiency in generating reaction intermediates under mild conditions.[8] In 2011, Colby and co-workers demonstrated that the trifluoroacetate release strategy was also applicable in furnishing α,α-difluoroenolates with the use of α,α-difluoro-β-ketone-*gem*-diols (I) as precursors (Scheme 1a).[9] Since then, the deacylative fluoroalkylation has been extensively studied for the synthesis of various organofluorine compounds.[10] Several new difluoroalkylation reagents including α,α-difluorodiaroylmethane (II),[11] α,α-difluoro-β-ketoesters (III and IV),[12] and difluoronitromethyl ketones (V)[13] have been developed for the in situ generation of α,α-difluoroenolates and α,α-difluoronitronates. As part of our research interest in the development of vinylogous reactions,[14] we envisioned that the deacylative fluoroalkylation can be extended in its vinylogous terms[15] by exploiting the cleavage of remote C−C bonds.[16] Herein, we describe the development of difluoroisoxazolacetophenone (DFIO) as a new vinylogous difluoroalkylation reagent. DFIO can be used to in situ generate γ,γ-difluoroisoxazole nitronates from the release of benzoate under mild conditions (Scheme 1b). The synthetic potency of DFIO is demonstrated by its vinylogous nitroaldol reactions in the presence of catalytic amounts of organic base.

Initially, DFIO (**2**) was designed and synthesized according to the procedure illustrated in Scheme 2.[17] The direct vinylogous Henry reaction of benzaldehyde with 3,5-dimethyl-4-nitroisoxazole gave the nitroaldol adduct,[14e] which was easily transformed to the corresponding nitroketone[18] in the presence of *o*-iodoxybenzoic acid (IBX). Subsequent electrophilic fluorination of nitroketone with selectfluor produced DFIO (**2**) in high yield. Isatin **1a** and DFIO (**2**) were then chosen as model substrates to study the debenzoate vinylogous nitroaldol reaction. As shown in Table

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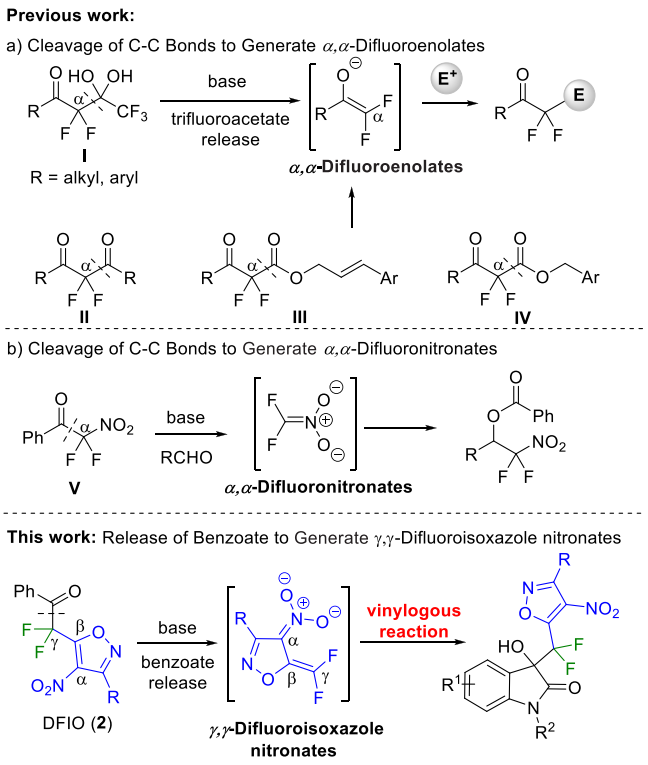
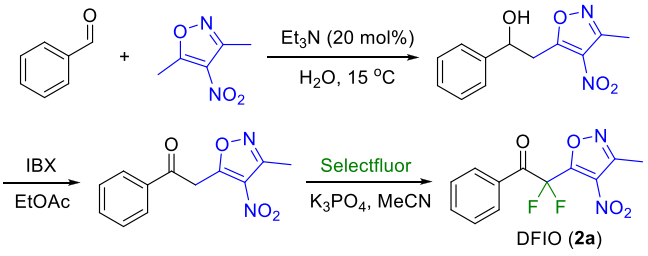
Scheme 1. Strategies for the in Situ Generation of Difluoroenolate and Nitronate

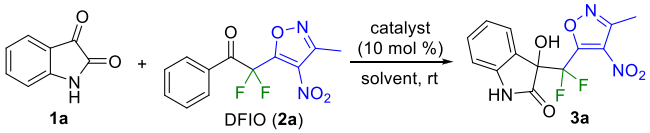


Scheme 2. Synthesis of Difluoroisoxazolacetophenone 2a



1, using THF as a solvent at room temperature for the reaction catalyzed with 10 mol % Et_3N gave product **3a** in 31% yield after 48 h. Other solvents such as MeCN, DMF, DMSO, DCM, and toluene gave inferior results (entries 1−6). To our delight, the formation of vinylogous nitroaldol product **3a** was almost quantitative when MeOH was used as the reaction solvent (entry 7). It is worth mentioning that the reaction can easily be monitored by the color change from dark reddish to pale orange. Methyl benzoate was detected as a byproduct in this reaction, which indicated that MeOH may serve as a nucleophile to facilitate the debenzoate process. Using other protic solvents such as EtOH and ^{i}-PrOH did not improve the reaction efficiency. These results promoted us to further investigate the role of base catalyst with MeOH as the solvent. As expected, formation of product **3a** was not observed in the absence of base catalyst (entry 10). The reaction with DABCO gave a similar result as Et_3N, while other bases led to lower yields (entries 11−17). Hence, the most available and inexpensive Et_3N was considered as the best catalyst for this reaction. Additional experimentation showed that the catalyst loading could be reduced to 5 mol % with only a slight effect on reaction efficiency (entry 18).

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	solvent	time (h)	yield[b] (%)
1	Et_3N	THF	48	31
2	Et_3N	MeCN	48	20
3	Et_3N	DMF	48	26
4	Et_3N	DMSO	48	20
5	Et_3N	DCM	48	10
6	Et_3N	toluene	48	<10
7	Et_3N	MeOH	24	99
8	Et_3N	EtOH	24	75
9	Et_3N	^{i}-PrOH	48	74
10	none	MeOH	24	0
11	DBU	MeOH	10	83
12	DMAP	MeOH	24	85
13	DABCO	MeOH	24	99
14[c]	QD	MeOH	24	90
15	imidazole	MeOH	72	75
16	K_2CO_3	MeOH	24	72
17	KOH	MeOH	10	78
18[d]	Et_3N	MeOH	48	98

[a]Unless otherwise noted, the reaction was performed with 0.15 mmol of **1a**, 0.20 mmol of **2** and 10 mol % of catalyst in 0.75 mL solvent. [b]Isolated yield. [c]No enantioselectivity. [d]5 mol % of catalyst was used.

Under the optimal reaction conditions, a wide range of isatins were subsequently investigated (Scheme 3). Isatins bearing electron-withdrawing (5-F, 5-Cl, 5-Br, 5-I, 5-NO_2, and 5-OCF_3) or electron-donating (5-OMe and 5-Me) groups on the phenyl ring were well tolerated, and their reactions with DFIO (**2**) smoothly afforded the corresponding vinylogous products with good to excellent yields (**3b**−**3i**). Moreover, substitution was viable at the 4-position, 6-position, and 7-position of the isatin, and their corresponding products were formed in good to excellent yields (**3j**−**3p**). Furthermore, disubstituted isatins (3,5-dimethylisatin and 4,7-dichloroisatin) were also applicable for this reaction, affording the desired products in good yields. The scope of this debenzoate vinylogous procedure was further extended to *N*-protected isatins. It is shown that *N*-methylisatin, *N*-ethylisatin, *N*-benzylisatin, *N*-phenylisatin, and *N*-allylisatin were also compatible substrates with the formation of the desired products **3s**−**3w** in 85−99% yields. The structure of **3i** was confirmed by X-ray crystallographic analysis.

The scope of the difluoroisoxazolacetophenones was also briefly examined (Scheme 4). The reaction proceeded smoothly when the 3-position of isoxazole was substituted with a phenyl group, affording the desired product **4a** in good yield. Both electron-donating and electron-withdrawing groups on the benzene ring were tolerated, and their corresponding products **4b**−**4e** were formed in good to excellent yields.

To further demonstrate the synthetic utility of DFIO (**2a**), we applied it to the vinylogous nitroaldol reactions with several other electrophiles (Scheme 5). In the presence of DBU at 50 °C, the reaction of *β*,*γ*-unsaturated-*α*-ketoesters with **2a** proceeded smoothly to afford the desired products **5a** and **5b** in 62% yield and 93% yield, respectively. A heterocyclic electrophile such as benzothiophene-2,3-dione worked as well

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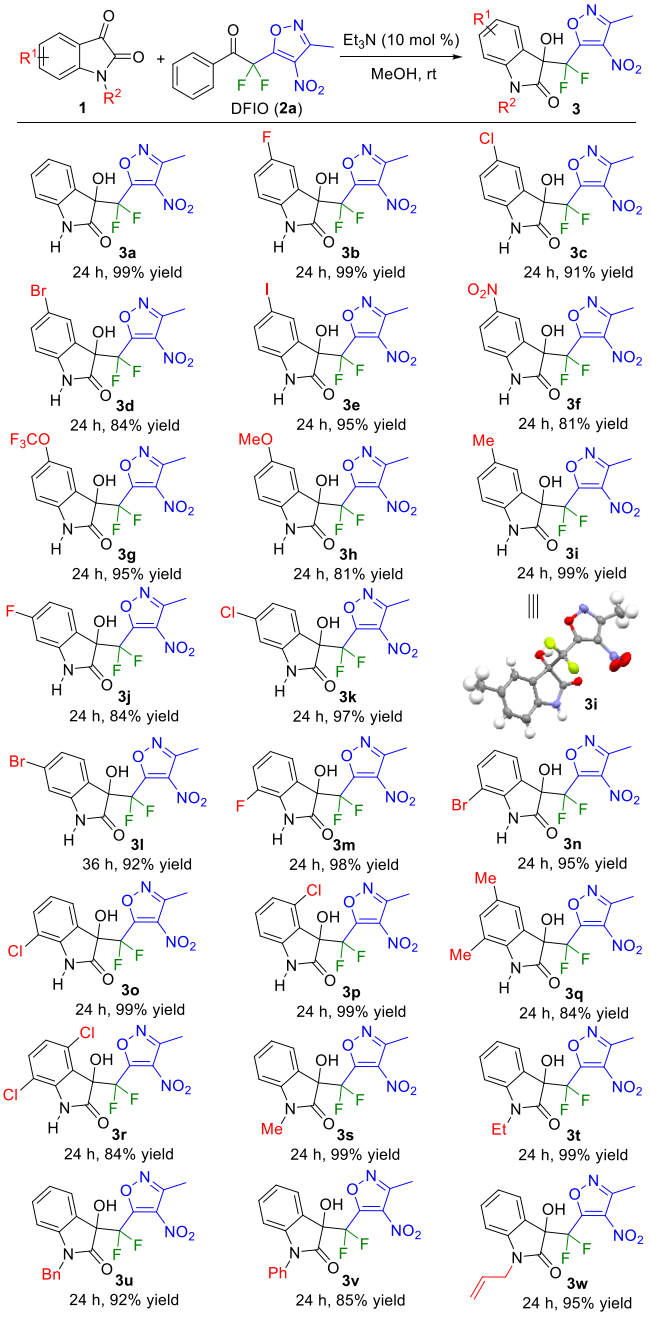
Scheme 3. Scope of Reaction of Isatins 1 and 2a[a,b]

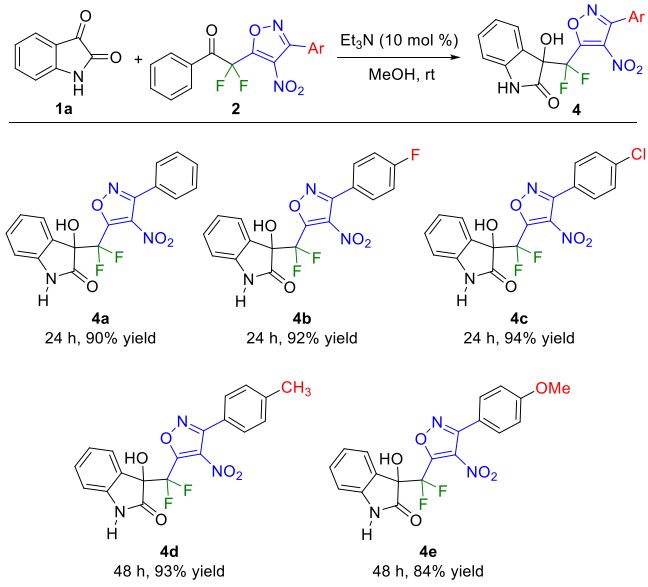


[a]Unless otherwise noted, the reaction was performed with 0.15 mmol of **1**, 0.20 mmol of **2a** and 10 mol % of catalyst in 0.75 mL of MeOH. [b]Isolated yield.

to afford **5c** in 81% yield. In addition, cyclic 1,2-diketones such as phenanthrenequinone and acenaphthenequinone also underwent efficient vinylogous nitroaldol reactions to furnish **5d** in 88% yield and **5e** in 95% yield. Disappointingly, aldehydes, trifluoromethyl ketones, and unactive ketones were not suitable for this reaction under the optimized conditions (Scheme S1).

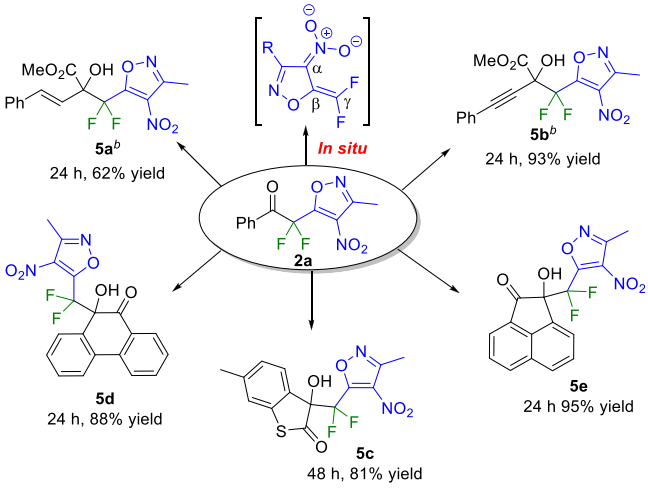
Inspired by the success with the catalysis summarized in Schemes 3−5, we wondered if this method can be extended to monofluoroisoxazolacetophenone **6** or other dihaloisoxazolacetophenones **7**. As shown in Scheme 6, the reaction of monofluoroisoxazolacetophenone **6** with isatin **1a** proceeded

Scheme 4. Scope of Reaction of Isatin 1a and 2[a,b]



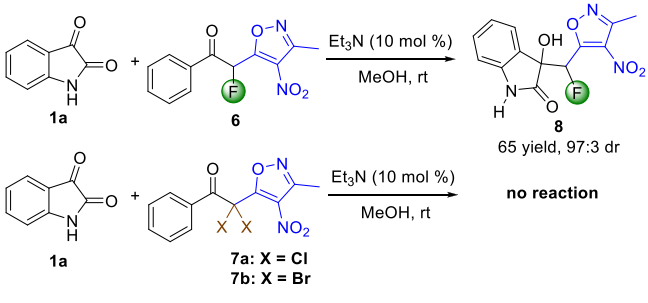
[a]Unless otherwise noted, the reaction was performed with 0.15 mmol of **1a**, 0.20 mmol of **2**, and 10 mol % of catalyst in 0.75 mL of MeOH. [b]Isolated yield.

Scheme 5. Scope of Other Electrophiles[a]



[a]Unless otherwise noted, the reaction was performed with 0.15 mmol of the corresponding electrophiles, 0.20 mmol of **2a**, and 10 mol % of Et_3N in 0.75 mL of MeOH at room temperature. Isolated yield. [b]The reaction was performed at 50 °C using DBU as the catalyst.

Scheme 6. Substrate Scope and Limitation



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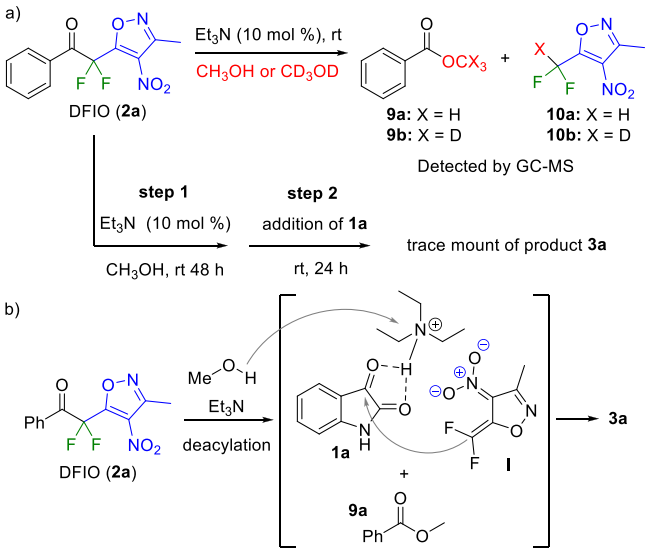
smoothly to afford the corresponding monofluoro substituted product **8** in moderate yield with excellent dr value, while no desired products were obtained when dichloroisoxazolacetophenone **7a** or dibromoisoxazolacetophenone **7b** were used, presumably due to steric hindrance. These experimental results indicate that the fluoro atom plays a significant role in this debenzoate vinylogous nitroaldol reaction.

To gain insight into the mechanism of the debenzoate vinylogous nitroaldol reaction, we performed several control reactions to verify that the vinylogous nitroaldol reaction is not a stepwise process in which release of benzoate occurs first, followed by deprotonation of 5-(difluoromethyl)-3-methyl-4-nitroisoxazole, and then addition to the isatin. In fact, treatment of DFIO (**2a**) with Et_3N in MeOH (or CD_3OD) at room temperature produced smoothly the benzoate **9** as well as the difluoroisoxazole **10**, which was confirmed by GC−MS analysis (see the Supporting Information for details). Although we failed to isolate the difluoroisoxazole **10a**, a step by step experiment resulted only small amount of product. On the basis of the above results, we propose a plausible reaction mechanism, which is shown in Scheme 7b for the vinylogous

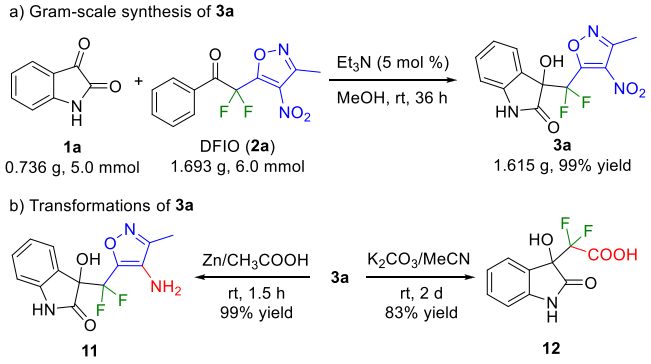
Scheme 7. Control Reactions and a Proposed Mechanism



addition of **2a** to **1a** in the presence of Et_3N. The deacylation of **2a** in the presence of Et_3N and MeOH results in γ,γ-difluoroisoxazole nitronate **I**, which is in situ stablized by Et_3N. The vinylogous addition is activated by the hydrogen bond between protonated Et_3N and two carbonyls in isatin. Nucleophilic addition of γ,γ-difluoroisoxazole nitronate **I** to isatin affords the desired vinylogous nitroaldol addition product **3a** (Scheme 7a).

To demonstrated the synthetic utility of this debenzoate process, a gram-scale reaction of isatin **1a** (0.736 g, 5.0 mmol) and DFIO **2a** (1.693 g, 6.0 mmol) was conducted in the presence of 5 mol % of Et_3N in 10 mL of MeOH (Scheme 8a). Gratifyingly, the reaction proceeded smoothly to afford **3a** (1.615 g) in 99% yield. It should be pointed out that in order to achieve excellent reactivity with 5 mol % of catalyst and only a slight excess of **2a** (1.2 equiv) a high concentration was required. In the presence of Zn dust and acetic acid, the nitro group of **3a** could be smoothly reduced, affording product **11** in almost quantitative yield. In addition, the isoxazole moiety

Scheme 8. Gram-Scale Synthesis of 3a and Its Transformations



of **3a** could be conveniently converted to acid **12** in high yield (Scheme 8b).

In conclusion, we have developed difluoroisoxazolacetophenone (DFIO) as a new and practical reagent for vinylogous difluoroalkylation reactions of isatins, benzothiophene-2,3-dione, unsaturated α-ketoesters, and cyclic 1,2-diketones. The key step of these vinylogous difluoroalkylation reactions is the release of benzoate for the cleavage of remote C−C bond by making use of DFIO as a synthetic equivalent of γ,γ-difluoroisoxazole nitronate. The resulting medicinally important difluoroisoxazole[19] substituted 3-hydroxy-2-oxindoles[20] were obtained in good to excellent yields. Further application of a debenzoate process for other (asymmetric) vinylogous fluoroalkylation reactions is currently 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.0c02873.

Experimental details and spectroscopic data (PDF)

Accession Codes

CCDC 1941387 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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