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Alkene *Syn*- and *Anti*-Oxyamination with Malonoyl Peroxides

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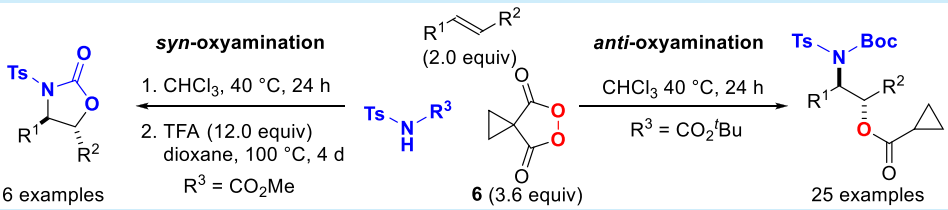
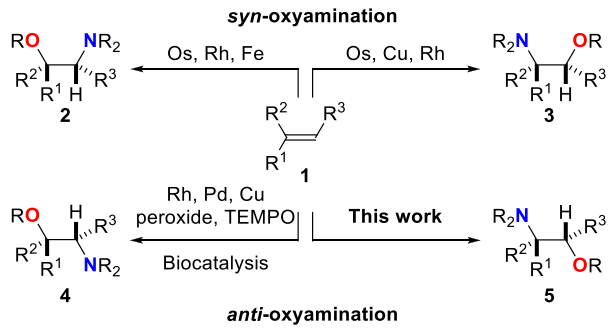


ABSTRACT: Malonoyl peroxide **6** is an effective reagent for the *syn*- or *anti*-oxyamination of alkenes. Reaction of **6** and an alkene in the presence of *O*-*tert*-butyl-*N*-tosylcarbamate ($R^3 = CO_2{}^tBu$) leads to the *anti*-oxyaminated product in up to 99% yield. Use of *O*-methyl-*N*-tosyl carbamate ($R^3 = CO_2Me$) as the nitrogen nucleophile followed by treatment of the product with trifluoroacetic acid leads to the *syn*-oxyaminated product in up to 77% yield. Mechanisms consistent with the observed selectivities are proposed.

The β-amino alcohol functionality is an important motif present in natural products, agrochemicals, pharmaceuticals, and ligands for catalysis. Many methods exist for the introduction of this functionality with the difunctionalization of alkenes representing a particularly efficient process.[1] In the reaction of an alkene **1**, the oxyamination presents significant challenges with regard to regioselectivity and stereoselectivity with up to four possible products **2**−**5** (Scheme 1).

Scheme 1. Challenges of Oxyamination



Considerable attention has been devoted to the intramolecular (tethered) oxyamination of alkenes, which can circumvent regiochemistry issues;[2] however, there are substantially fewer reports of intermolecular procedures which meet the regio- and diastereochemical challenges of the process.[3]

For the preparation of the *syn*-products **2** and **3** through an intermolecular oxyamination the osmium catalyzed asymmetric aminohydroxylation developed by Sharpless represents the gold standard within the field.[1,4] Loss of selectivity for some alkene substrates along with deficiencies in regioselectivity and the desire to prepare the *anti*-products **4** and **5** have driven further investigation. Important advances have been made with a variety of transition metals including osmium,[5] rhodium,[6] palladium,[7] copper,[8] and iron.[9] Metal-free methods for the intermolecular oxyamination of alkenes have also been developed which include the use of TEMPO[10] or peroxides.[11] In addition, Arnold reported a biocatalytic method for *anti*-oxyamination using a hemoprotein.[12] While these recent developments represent excellent progress, diastereoselectivity in the majority of these transformations is not well explored and provides the impetus for additional research efforts. It is also noteworthy that stereoselective intermolecular methods to access *anti*-oxyamination product **5** are particularly limited.[13] Within this manuscript, we report the development of an intermolecular metal-free *anti*-oxyamination through the reaction of an alkene **1**, malonoyl peroxide **6** and a nitrogen nucleophile and show how the product can be converted directly into the *syn*-oxyaminated product by treatment with TFA.

The investigation began with the reaction of *trans*-stilbene **7** and malonoyl peroxide **6**[14,15] in the presence of different nitrogen nucleophiles. The aim was to find a nitrogen nucleophile that reacted with dioxonium **8** and not peroxide **6**.[16] From a total of 12 nitrogen nucleophiles examined, only saccharin **10** showed the desired activity (see the Supporting

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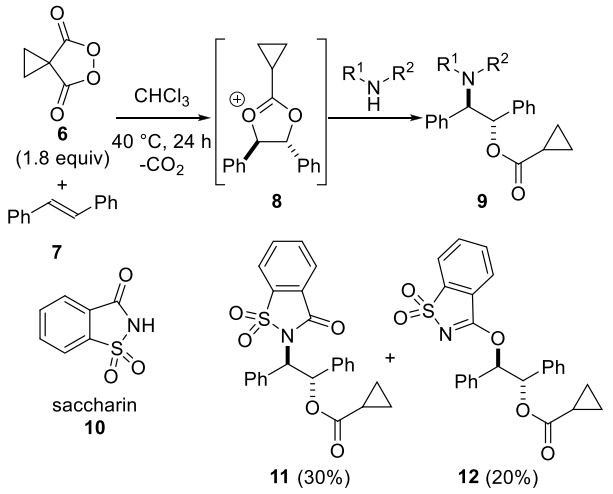
Information for full details of screen). Reaction of alkene **7** (1.0 equiv), peroxide **6** (1.8 equiv), and saccharin **10** (2.0 equiv) in chloroform at 40 °C for 24 h gave the *anti*-oxyaminated product **11** (30%) (Scheme 2). Saccharin **10** is an

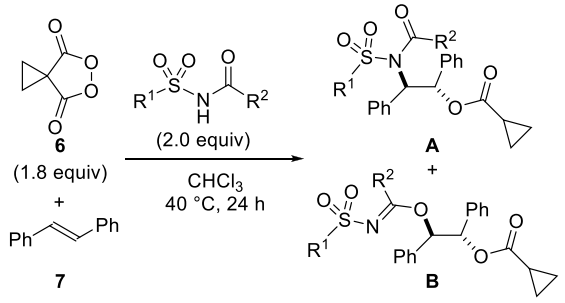
Scheme 2. Alkene Oxyamination in the Presence of Saccharin

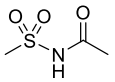
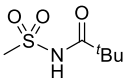
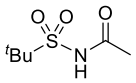
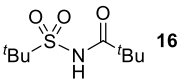
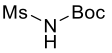
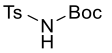
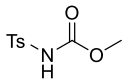


ambident nucleophile which can react through either its nitrogen or oxygen atom.[17] Along with the oxyaminated product **11** the *anti*-dioxygenated coproduct **12** was also isolated from the reaction mixture in 20% yield. The structures of both **11** and **12** were confirmed by single-crystal X-ray crystallography (see the Supporting Information for full details). In contrast to the related intramolecular oxyamination procedure,[2b] the product isolated has undergone decarboxylation. It is proposed that the low nucleophilicity of the amine nucleophile allows for decaboxylation of the initial adduct[16] to give **8** prior to trapping with saccharin. We believed synthesis of **11** represented a simple and effective *anti*-oxyamination which proceeded under mild conditions and warranted further investigation.

We sought to understand the ambident reactivity of saccharin **10** to improve the selectivity for *N*-alkylation over *O*-alkylation. Literature reports suggest the reactivity of ambident nucleophiles can be altered through changes in solvent and temperature;[18] however, despite extensive investigation we were unable to significantly alter the ratio of **11** and **12** obtained. We therefore turned our attention to modifying the structure of saccharin **10**. Seven acyl sulfonamide derivatives **13**−**19** were prepared by altering both the steric and electronic environments of the nitrogen atom, which were then reacted with stilbene **7** in the presence of malonoyl peroxide **6** ($CHCl_3$, 40 °C, 24 h) (Table 1). *N*-(Methylsulfonyl)acetamide **13** represents the simplest nucleophile to contain the acyl sulfonamide moiety and was found to produce the oxyaminated product **20A** and dioxygenated coproduct **20B** in a combined yield of 38% as a 1:1 mixture (entry 1). Nucleophiles **14**, **15**, and **16** were prepared to study the influence of the steric environment around the heteroatoms on the transformation. Under the reaction conditions examined, all three examples were selective toward *O*-alkylation, resulting in the *anti*-dioxygenated products **21B**−**23B** (entries 2−4; 22−60%). The added steric bulk clearly shielded the nitrogen atom, leading to the observed *O*-

Table 1. Optimization of Nitrogen Nucleophile



entry	nucleophile	A	B
1	 **13**	**20A** (19%)	**20B** (19%)
2	 **14**	**21A** (0%)	**21B** (60%)
3	 **15**	**22A** (0%)	**22B** (33%)
4	 **16**	**23A** (0%)	**23B** (22%)
5	 **17**	**24A** (39%)	**24B** (0%)
6	 **18**	**25A** (49%)	**25B** (0%)
7	 **19**	**26A** (45%)	**26B** (0%)

selectivity. We therefore altered the electronic environment of the nitrogen nucleophile by preparing the *N*-sulfonyl carbamates **17**−**19**. Under standard reaction conditions, all three nucleophiles were *N*-selective, providing the *anti*-oxyaminated products **24A**−**26A** (entries 5−7; 39−49%). This remarkable switch in selectivity by changing the steric or electronic environment of the nitrogen nucleophile represents a powerful observation that presents an intriguing opportunity for further investigation.

O-*tert*-Butyl-*N*-tosylcarbamate **18** was selected as the preferred nucleophile. Further optimization of the reaction conditions failed to improve the yield of oxyamination product **25A** beyond 49%. However, the conversion of nucleophile **18** to oxyaminated product **25A** was an efficient process. Therefore, in examining the substrate scope of the reaction we employed the conditions outlined in Scheme 3 (entry 1, 97%), using the nitrogen nucleophile **18** as the limiting reagent.

Examination of a series of stilbene derivatives showed the reaction to proceed efficiently at room temperature with complete *anti*-diastereoselectivity (Scheme 3). The reaction was tolerant of substitution in the 2-, 3-, and 4-positions of the stilbene substrate (entries 2−4, 62−92%). In addition, fluorine (entry 6, 71%), chlorine (entry 7, 90%), and bromine (entry 8, 85%) substituents on the aromatic ring also led to the expected products, providing useful handles for further synthetic manipulation. Alternative *N*- and *O*-substituted carbamates

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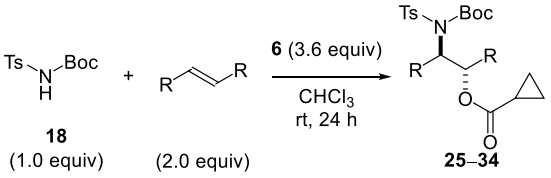
Scheme 3. Stilbene Substrate Scope[a]



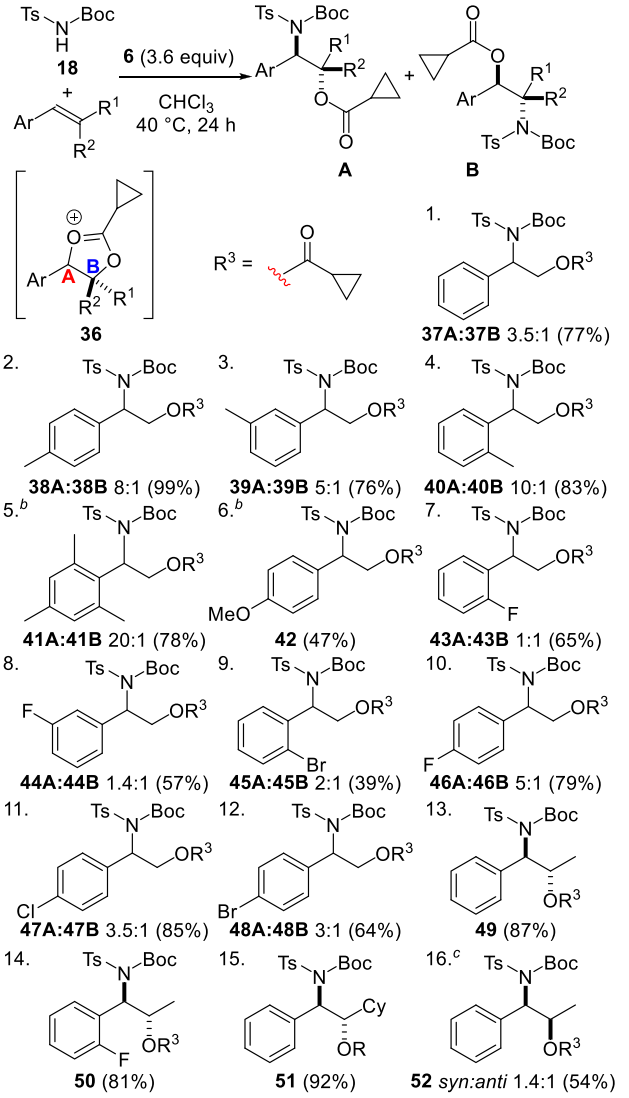
entry	R	product	% yield
1	Ph	**25A**	97
2	4-MeC_6H_4	**27**	62
3	3-MeC_6H_4	**28**	73
4	2-MeC_6H_4	**29**	92
5[b]	4-OMeC_6H_4	**30**	57
6	4-FC_6H_4	**31**	71
7	4-ClC_6H_4	**32**	90
8	4-BrC_6H_4	**33**	85
9[c]	Ph	**34**	94
10[d]	Ph	**26A**	71

[a]All reactions conducted in duplicate. [b]Reaction conducted at 0 °C. [c]*O-tert*-Butyl-*N*-((4-cyanophenyl)sulfonyl)carbamate **35** was used as nucleophile. [d]*O*-Methyl-*N*-tosylcarbamate **19** was used as nucleophile.

were also tolerated under the optimized reaction conditions. For example, *O-tert*-butyl-*N*-((4-cyanophenyl)sulfonyl)-carbamate **35** (entry 9, 94%) and *O*-methyl-*N*-tosylcarbamate **19** (entry 10, 71%) both gave the expected *anti*-oxyaminated products in excellent yields.

Our attention then turned to styrene substrates (Scheme 4). Reaction of styrene, peroxide **6**, and amine nucleophile **18** ($CHCl_3$, 40 °C, 24 h) gave oxyaminated product **37A** along with the regioisomer **37B** in a 3.5:1 ratio (Scheme 4, entry 1; 77%). The expected product **37A** is a result of the nucleophile **18** adding to the benzylic position **A** of dioxonium intermediate **36**. The minor regioisomer **37B** arises through addition of **18** to the more sterically accessible position **B**. The amount of the major regioisomer **A** can be increased by the introduction of electron-donating substituents to the aromatic ring. For example, a methyl group can increase the amount of the major isomer to up to 10:1 (Scheme 4, entries 2–4; 76–99%). This ratio increases further using mesityl styrene as the substrate (entry 5, 20:1; 78%). 4-Methoxystyrene provides the expected oxyaminated product **42** with complete selectivity for addition of the nucleophile at position **A** (entry 6, 47%). Using halogen-substituted styrenes lowers the ratio of products **A**/**B** observed as the substituent is moved from *para* (entries 10–12, up to 5:1) to *meta* (entry 8, 1.4:1) to *ortho* positions (entry 7, 1:1). We believe selectivity and reactivity are altered by a combination of lone pair stabilization and the electron-withdrawing nature of the substituents destabilizing any buildup of positive charge at position **A** of proposed intermediate **36**. Introducing substitution at the *β*-position of the styrene substrate results in complete stereoselectivity in the oxyamination process for addition of the nucleophile at position **A** (Scheme 4, entries 13–15; 81–92%). This steric factor completely overrides any electronic influence on the regiochemical outcome of the transformation (cf. entries 7 vs 14). The reaction of *cis-β*-methylstyrene proceeded with

Scheme 4. Styrene Substrate Scope[a]



[a]All reactions were conducted in duplicate, with combined yield of regioisomers quoted. [b]Reaction conducted at 25 °C. [c]*cis-β*-methylstyrene was used as the alkene substrate.

complete regioselectivity; however, considerable loss in stereoselectivity was observed, suggesting that *cis*-alkenes will be poor substrates within this transformation (entry 16).

Reaction of *O*-methyl-*N*-tosylcarbamate **19** with stilbene **7** and malonoyl peroxide **6** under the standard reaction conditions provided the oxyaminated product **26A** (Scheme 3, entry 10, 71%). Treatment of this adduct with trifluoroacetic acid (12 equiv) in CH_2Cl_2 (40 °C, 5 h) led to the oxazolidinone **53** (77% over two steps), the product of a formal *syn*-oxyamination of the *trans*-stilbene substrate **7** (Scheme 5, entry 1). This provides a powerful and particularly useful complementary strategy to the *anti*-oxyamination procedure described above, allowing access to both diastereomeric oxyaminated products using the same alkene and malonoyl peroxide reagents. This strategy was also effective for styrene (entry 2) and *β*-substituted styrene derivatives (entries 3 and 4). Consistent with previous observations, 2-fluorostyrene provided the two regioisomeric products **57** and **58** after oxazolidinone formation (entry 5, 72%), the structures of which were confirmed by X-ray crystallography (see the

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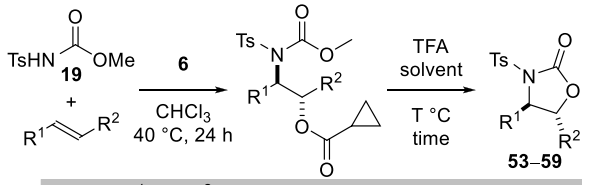
Scheme 5. *Anti*-Oxymaination of Alkenes



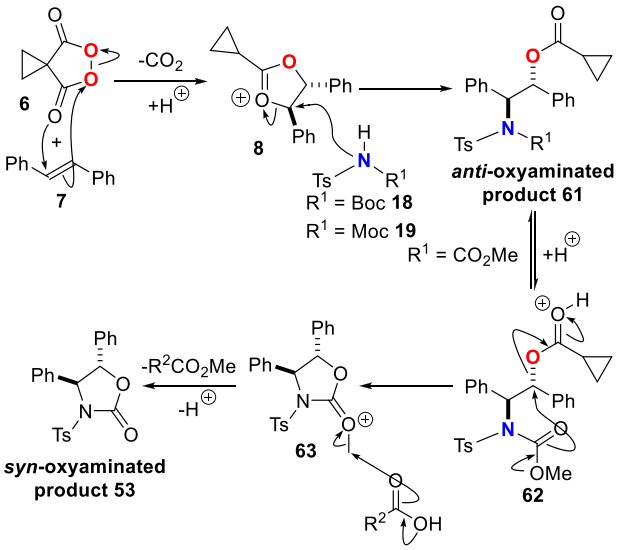
entry	R^1	R^2	solvent	temp (°C)	time	product (%)
1	Ph	Ph	CH_2Cl_2	40	5 h	**53** (77)
2	4-MeC_6H_4	H	Dioxane	100	4 d	**54** (73)
3	Ph	Me	Dioxane	100	4 d	**55** (59)
4	2-FC_6H_4	Me	Dioxane	100	3 d	**56** (63)
5[b]	2-FC_6H_4	H	Dioxane	100	4 d	**57** (50) **58** (22)
6[c]	Ph	Ph	CH_2Cl_2	40	5 h	**59** (56)

[a]All reactions conducted in duplicate. [b]**58** corresponds to the regioisomer. [c]Methyl ((4-cyanophenyl)sulfonyl)carbamate **60** used as nucleophile.

Supporting Information for full details). The alternative nitrogen nucleophile *O*-methyl-*N*-((4-cyanophenyl)sulfonyl)-carbamate **60** could also be used effectively within this synthetic sequence (entry 6, 56%).

A mechanism consistent with the observed selectivities is outlined in Scheme 6. Reaction of malonoyl peroxide **6** with

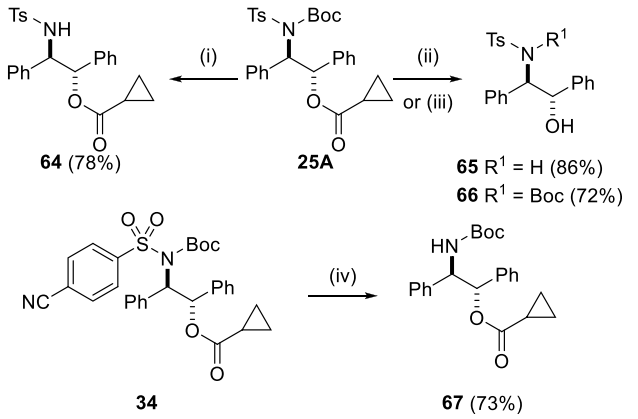
Scheme 6. Proposed Mechanism for the *Anti*- and *Syn*-Oxyamination



the alkene leads to the *syn*-dioxonium intermediate **8**.[16] Interception of **8** with the weak nitrogen nucleophile **18** (or **19**) via an S_N2 process leads to the *anti*-oxyaminated product **61** which can be isolated and purified. Subsequent reaction of **61** (R^1 = CO_2Me) under acidic conditions gives **62**, which can undergo a 5-*exo*-*tet* cyclization, inverting the relative stereochemistry of the oxygen substituent and leading to **63**. Reaction of intermediate **63** with either trifluoroacetic acid or cyclopropane carboxylic acid gives the *syn*-oxyaminated product **53**.[19] Doping experiments confirmed the presence of both methyl trifluoroacetate and methyl cyclopropane carboxylate within the crude reaction mixture (see the Supporting Information for full details) consistent with this proposal.

Selective removal of the oxygen and nitrogen protecting groups on the oxyaminated products was possible (Scheme 7),

Scheme 7. Removal of Nitrogen and Oxygen Protecting Groups[a]



[a]Reagents and conditions: (i) HCl (4 equiv), dioxane, 60 °C, 8 h; (ii) $MeNH_2$, EtOH, 40 °C, 18 h; (iii) K_2CO_3 (5 equiv), MeOH/CH_2C1_2 (1:1), rt, 18 h; (iv) 1-dodecanethiol (5 equiv), DBU (4.8 equiv), DMF, rt, 5 h.

providing the opportunity for further elaboration. Reaction of **25A** with HCl (4 equiv) in dioxane at 60 °C selectively removed the Boc group (**64**, 78%). Treatment of **25A** with K_2CO_3 in methanol removed the ester protecting group (**66**, 72%), whereas both the ester and carbamate could be removed by reaction with methylamine in ethanol (**65**, 86%). In addition, the 4-cyanobenzenesulfonamide group could be removed selectively using 1-dodecanethiol and DBU in DMF to give **67** (73%).[20] This sulfonamide protecting group could also be removed from the *syn*-oxyaminated product **59** (68%) (not shown, see the Supporting Information for full details).

In conclusion, we have shown that malonoyl peroxide **6** is an effective reagent for the intermolecular *anti*-oxyamination of a series of stilbene and styrene substrates in the presence of a nitrogen nucleophile. Optimization of the nitrogen nucleophile showed that *N*-sulfonyl carbamates formed the new C–N bond most efficiently. Stereoselectivity for the transformation was excellent with the reaction leading efficiently to the *anti*-oxyamination product. The regiochemcal outcome of the reaction is influenced by electronics, with the reaction of electron-rich alkenes proceeding with the highest regioselectivity; however, this subtle electronic influence is overridden by sterics. It also proved possible to convert the *anti*-oxyaminated product to the *syn*-diastereoisomer by treatment of the crude product with trifluoroacetic acid providing an effective method for the preparation of both the *syn*- and *anti*-oxyaminated product from reaction of the same alkene, nitrogen nucleophile, and peroxide. Effective methods for the selective or concomitant removal of substituents on both the nitrogen and oxygen atoms suggest this simple procedure, which extends recent advances in the chemistry of diacylperoxides,[21] should find broad use within synthesis.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00253.

Analytical data, experimental procedures, and NMR spectra for all compounds reported (PDF)

Accession Codes

CCDC 1951983−1951986 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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