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Steric Tuning of Sulfinamide/Sulfoxides as Chiral Ligands with C_1, Pseudo-*meso*, and Pseudo-C_2 Symmetries: Application in Rhodium(I)-Mediated Arylation

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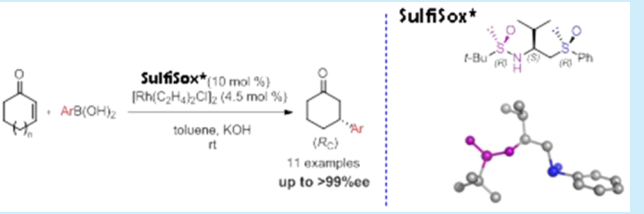
Supporting Information

ABSTRACT: A new family of sulfinamide/sulfoxide derivatives was synthesized as chiral bidentate ligands by stereoselective additions of methylsulfinyl carbanions to *N*-*tert*-butylsulfinylimines. The new ligands, with C_1, pseudo-*meso*, and pseudo-C_2 symmetries, were successfully assayed in Rh-catalyzed additions of arylboronic acids to activated ketones. The sterically dissymmetric C_1 ligand (R_S,S_C,R_S)-*N*-[1-(phenylsulfinyl)-3-methylbut-2-yl] *tert*-butylsulfinamide turned out to be the optimal one, allowing the 1,4-additions of diverse arylboronic acids, on different α,β-unsaturated cyclic ketones with high chemical yields and enantioselectivities up to >99% ee.



Transition metal enantioselective catalysis remains an active area of development in synthetic methodology.[1−4] Despite the great progress made in this field, one of the aspects that has been and remains a cardinal challenge in this area is the design and development of new effective ligands.[5] The steric, electronic, and overall symmetry of the ligands are important elements to be considered in their design and preparation. Ligands with C_2 symmetry dominated the field at its birth, while electronically dissymmetric C_1 ligands gained importance over the years. Otherwise, modern asymmetric catalysis requires ligands that are not only highly enantioselective but also structurally simple and chemically stable, and both enantiomers could be easily accessed by practical and cost-effective synthetic approximations. Of the few ligands that meet these characteristics, those derived from sulfinyl compounds occupy a preponderant place in asymmetric catalysis.[6−9] Indeed sulfinyl-based ligands are air-, oxygen-, moisture-, and shelf-stable, and in addition, currently a number of highly efficient and modular approaches allow their rapid synthesis in both enantiomeric forms.[10−13] Moreover, like the synthetically challenging P-chiral phosphines, they are ideally suited for the construction of diverse metal−ligand complexes with a well-defined chiral environment due to the proximity of the chiral sulfur atom to the coordination sphere of the metal.[6,13,14].

Within our interest in the development of new efficient chiral catalysts[15−17] with the aforementioned advantages, our research group focused on the study of structurally varied, symmetric, and nonsymmetric sulfinyl derivatives as chiral ligands in enantioselective organic[18] and organometallic catalysis.[19] Within the C_2-symmetric ligands developed, Ferbisox (Figure 1), a 1,2-bis(ferrocenylsulfinyl) ethane, has proven to be an excellent chiral ligand in the enantioselective rhodium-catalyzed 1,4-addition of boronic acids to electron-deficient alkenes.[20,21] In the case of the most interesting C_1-symmetric ligands, we have recently found that mixed sulfinamido−olefin ligands, Sulfolefin[17,22,23] and Metsulfolefin[24] (Figure 1), enclosing a chiral sulfur atom as the sole

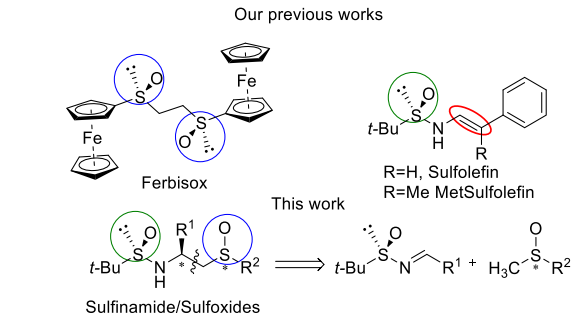


Figure 1. Homo and hybrid-bidentate sulfinyl-based ligands.

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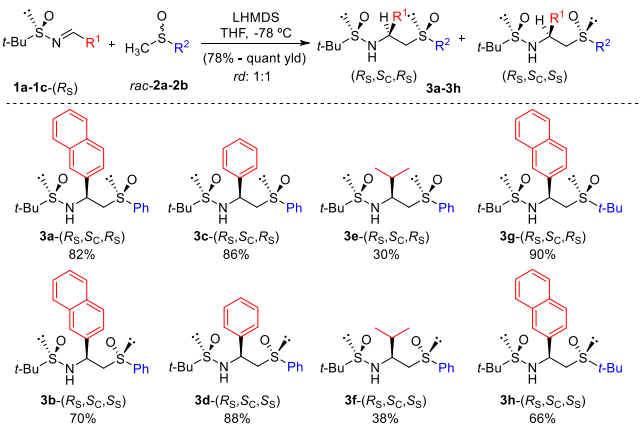
stereogenic center, are excellent precursors for Rh-catalyzed addition of arylboronic acids to activated ketones, including trifluoromethyl ketones.

Herein, we wished to explore the behavior of electronically dissymmetric C_1 ligands, comparing and contrasting the sterically symmetric (pseudo-*meso*- and pseudo-C_2-symmetric) with the sterically disymmetric ones. Ligands fulfilling our needs are those that belong to the unprecedented family of sulfinamide/sulfoxide ligands (Figure 1). The target ligands are accessible in a short, effective, and low-cost synthetic way, by nucleophilic addition of a methylsulfinyl carbanion to the corresponding *N-tert*-butylsulfinylaldimine (Figure 1). The approach presents the advantage of allowing the modulation of the stereochemistry of both sulfurs and the structure of the R1 and R2 groups in the nucleophile and electrophile.

The stereoselective synthesis of these ligands is based on the known sterochemical control of the *tert*-butylsulfinyl group of chiral *N-tert*-butylsulfinylimines in the nucleophilic additions to the imino double bond.[25] However, it must be taken into account the fact that the methylsulfinyl carbanion used as a nucleophile also has a stereogenic sulfur that could also influence (matched and mismatched pairs), or even control, the stereochemistry of the new stereogenic center generated in the process, as it has been previously demonstrated in the case of *N-p*-tolylsulfinylimines as substrates.[30] The additions of the corresponding racemic *tert*-butyl and phenyl methyl sulfoxides, *rac*-**2a** or *rac*-**2b**, on different (*R*)-*N-tert*-butylsulfinilimines, **1a**(R_S)−**1c**(R_S), were carried out at −78 °C, adding LHMDS (300 mol %) to a solution of both reagents in THF (Scheme 1). In all cases, the reactions were completed in <0.5 h, yielding high to quantitative chemical yields, a 1:1 mixture of two of the four possible diastereoisomers (Scheme 1).

Scheme 1. Synthesis of Sulfinamide/Sulfoxide Ligands 3a−3h



In general, the pairs of diastereoisomers obtained had different chromatographic resolution factors, allowing their isolation in diastereomerically pure form by column chromatography. Exceptions to this behavior are isopropyl diastereoisomers **3e** and **3f**, which despite being obtained with an 84% global yield are isolated in pure form in only 30% and 38% yields, respectively, due to their difficult separation by column chromatography. The configurational assignment, based on NMR spectroscopy, X-ray diffraction analysis, and chemical correlations (see the Supporting Information), showed that the induced stereochemical configuration of the new stereogenic center is independent of the chirality of the sulfinyl group of the nucleophile, unlike the analogous *N-p*-tolysulfinilimines.[26] Thus, each pair of diastereoisomers have identical configurations on the sulfinamide and the stereogenic carbon and opposite configurations in the sulfoxide.

The different nature of both functional groups, sulfinamide and sulfoxide, with stereogenic sulfurs as metal coordination elements, implies a C_1 symmetry for all these ligands. However, by selecting the nature of the R^2 group and the stereochemistry of the starting sulfoxide, we could consider some of the obtained ligands as pseudo-C_2-symmetric (ligand type I, **3h**) or pseudo-*meso* (ligand type II, **3g**) (Figure 2). Such ligands are

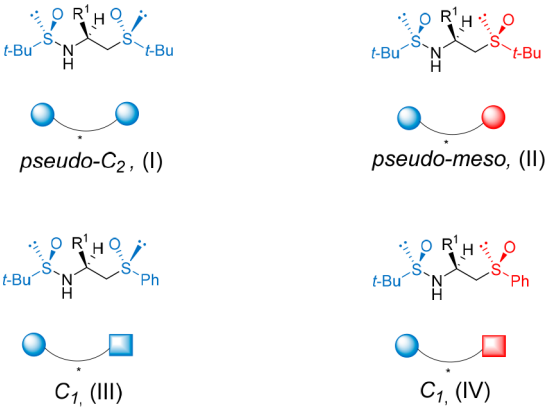


Figure 2. Sterically symmetric, pseudo-C_2 (I), pseudo-*meso* (II), and sterically dissymmetric (III and IV) sulfinamide/sulfoxide ligands.

of interest as they allow the determination of the role played by the steric and electronic factors on the stereochemical outcome of the catalysis. Pseudo-*meso*- and pseudo-C_2-symmetric ligands have previously been used in catalysis with success, but the ligands used were mostly mixed ligands with two different heteroatoms or bimetallic ligands.[27] To the best of our knowledge, no *pseudo-meso* or pseudo-C_2 ligands with a sole coordinating heteroatom have yet been reported.

With ligands **3a−3h** in hand, they were assayed as precursors of chiral Rh(I) catalysts in the 1,4-addition of arylboronic acids to α,β-unsaturated ketones and the results obtained are discussed below. To determine the optimal ligand, we used as a model reaction the addition of phenylboronic acid (**5a**) to 2-cyclohexen-1-one (**6a**) under the previously determined optimal conditions, i.e., 10 mol % of the chiral ligand **3a−3h**, 4.5 mol % of the rhodium precursor $[Rh(C_2H_4)_2Cl]_2$, and a previously deoxygenated 2.5 M aqueous solution of potassium hydroxide as the base, in different solvents (toluene and methanol), and the results are listed in Table 1.

The results obtained indicate that, in contrast to the sterically dissymmetric C_1-phenyl sulfoxide ligands **3a−3f** (entries 1−10, Table 1), sterically symmetric *tert*-butylsulfoxides, **3g** and **3h**, are not suitable chiral ligands for this reaction, because they yield the corresponding addition products with low chemical yields, in the absence of enantioselectivity (entries 11 and 12, Table 1). In the case of *tert*-butyl derivative **3g**-(R_S,S_C,R_S) (entry 11, Table 2), the absence of stereoselectivity could be justified considering its pseudo-*meso* symmetry. However, its epimer, **3h**-(R_S,S_C,S_S) (entry 12, Table 1) with a pseudo-C_2 symmetry, is also not suitable as a chiral ligand. In general, the C_1 dissymmetric phenyl sulfoxides **3a−3f** provided the addition product with

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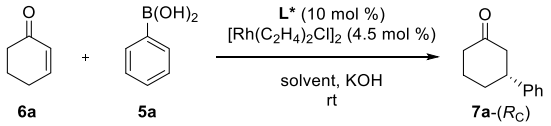
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Enantioselective Rhodium-Catalyzed Addition of Phenylboronic Acid 5a to Cyclohexen-2-one 6a, Using 3a–3h as Chiral Ligands[a]



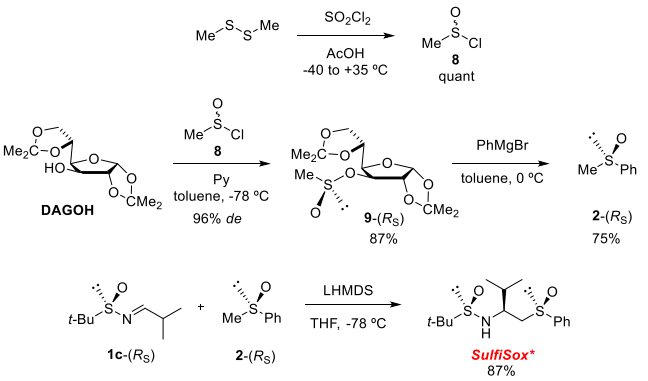
entry	L*	solvent	yield (%)[b]	ee (%)[c]
1	**3a**	toluene	61	95
2	**3a**	MeOH	74	85
3	**3b**	toluene	34	83
4	**3b**	MeOH	66	26
5	**3c**	toluene	73	96
6	**3c**	MeOH	66	80
7	**3d**	toluene	49	82
8	**3d**	MeOH	23	52
9	**3e**	toluene	85	99
10	**3f**	toluene	90	78
11	**3g**	toluene	27	0
12	**3h**	toluene	30	0

[a]All reactions were conducted using 10 mol % chiral ligand and 4.5 mol % $[Rh(C_2H_4)Cl]_2$ at rt for 18–60 h. [b]Isolated yield of pure compound **7a** after column chromatographic purification. [c]For HPLC conditions, see the Supporting Information.

yields and enantioselectivities ranging from good to excellent, always in favor of the *R* enantiomer, which results from the insertion of the aryl group of boronic acid on the *re* face of the olefin. Enantioselectivities are higher with toluene as a solvent (compare entries 1, 3, 5, and 7 and 2, 4, 6, and 8, respectively, in Table 1). Additionally, the higher chemical and stereochemical yields are obtained with the *R*-sulfoxide ligands **3a**, **3c**, and **3e** (compare entries 1, 5, and 9 and 3, 7, and 10, respectively). A comparison between the different homochiral ligands of the (R_S,S_C,R_S) series shows that an increase in the size of the aromatic ring of the stereogenic carbon, phenyl to naphthyl (**3c** to **3a**, respectively), does not improve the enantioselectivity of the process (96% and 95% ee for entries 5 and 1, respectively, Table 1). However, the enantioselectivity improves with isopropyl derivative **3e**, which we have named ***SulfiSox****, yielding the highest enantioselectivity, 99% ee, with a high chemical yield (entry 9, Table 1).

After establishing the sulfinamide/sulfoxide **3e**-(R_S,S_C,R_S) as the optimal chiral ligand, we achieved its stereoselective synthesis, using the DAG methodology[28] as the key reaction (Scheme 2). Condensation of racemic methylsulfinyl chloride

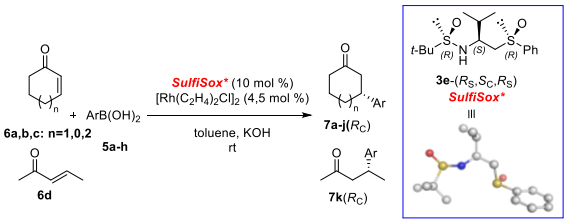
Scheme 2. Stereoselective Synthesis of Sulfinamide/Sulfoxide Ligand 3e (*SulfiSox)**



8 on diacetone-D-glucose (DAGOH) afforded R_S-DAG-methane sulfinate **9**-(R_S) in 87% yield and 96% diastereomeric excess, which after reaction with phenyl Grignard gave enantiopure (*R*)-methyl phenyl sulfoxide **2**-(R_S). Next, the addition of **2**-(R_S) to *N*-sulfinilimine **1c**-(R_S) afforded the corresponding ligand ***SulfiSox**** as a single diastereoisomer in 87% chemical yield.

We next set to examine the substrate scope with this ligand. The results obtained (Table 2) showed that ligand ***SulfiSox**** is

Table 2. Enantioselective Addition of Arylboronic Acids 5a–5h to Enones 6a–6d, Using *SulfiSox as a Chiral Ligand**[a]



entry	*n*	ketone	Ar	boronic acid	product[a]	yield (%)[b]	ee (%)[c]
1	1	**6a**	Ph	**5a**	**7a**	85	99
2	1	**6a**	*p*-Tol	**5b**	**7b**	86	88
3	1	**6a**	1-Napht	**5c**	**7c**	73	93
4	1	**6a**	2-Napht	**5d**	**7d**	85	99
5	1	**6a**	*p*-F-C_6H_4	**5e**	**7e**	quant	>99
6	1	**6a**	*m*-Tol	**5f**	**7f**	67	99
7	1	**6a**	*o*-Tol	**5g**	**7g**	89	96
8	1	**6a**	*p*-OMe-C_6H_4	**5h**	**7h**	74	99
9	0	**6b**	*p*-F-C_6H_4	**5e**	**7i**	88	82
10	2	**6c**	*p*-F-C_6H_4	**5e**	**7j**	82	>99
11	–	**6d**	*p*-F-C_6H_4	**5e**	**7k**	64	34

[a]All reactions were conducted using 10 mol % ligand together with 4.5 mol % $[Rh(C_2H_4)Cl]_2$ at rt for 18 h. [b]Isolated yield of pure compound **7a–7k** after column chromatographic purification. [c]For HPLC conditions, see the Supporting Information.

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Org. Lett. XXXX, XXX, XXX–XXX

not specific to a single substrate but is also effective with different arylboronic acids and unsaturated systems.

First, several arylboronic acids with different steric and electronic characteristics of the aromatic ring were tested using 2-cyclohexen-1-one **6a** as the model substrate. As shown in Table 2, in all cases the corresponding 1,4-addition products were obtained with good to excellent chemical yields (64% quant) and high enantioselectivities (88−99% ee, entries 1−8, Table 2). The stereoselectivity of the process was independent of electronic factors, because boronic acids bearing both electron-withdrawing (entry 5, Table 2) and electron-donating (entries 2 and 6−8, Table 2) substituents in the aromatic ring rendered the addition products with very high chemical and stereochemical yields. With regard to steric factors, it should be noted that the position of the substituent in the aromatic ring (*ortho*, *meta*, or *para*) of the arylboronic acid does not significantly influence the chemical yield of the process. In this sense, upon comparison of the tolyl derivatives (entries 2, 6, and 7, Table 2), the lowest yields were obtained in the case of the *meta* substitution (67% yield, entry 6, Table 2), yielding similar chemical yields in the case of *ortho* and *para* derivatives (89% and 86% yields for entries 7 and 2, respectively). With regard to the enantioselectivity, upon comparison of the results obtained with 1- and 2-naphthylboronic acids (entries 3 and 4 for 93% and 99% ee, respectively), as a first interpretation it could be proposed that *ortho* substitution may erode the enantioselectivity. However, in the case of tolylboronic acids, the *ortho*- and *meta*-substituted derivatives (entries 7 and 6, respectively, Table 2) provided enantioselectivities (96% and 99% ee, respectively), which are similar to that of the unsubstituted phenyl derivative (99% ee, entry 1, Table 2) and higher than that of the *para*-substituted derivative (88% ee). Therefore, the differences in enantioselectivities cannot be attributed to steric factors.

The reaction scope was further explored by testing various cyclic ketones with different ring sizes (cyclohexenone **6a**, cyclopentenone **6b**, and cycloheptenone **6c**), as well as acyclic ketone [(*E*)-3-penten-2-one, **6d**], using *p*-fluorophenylboronic acid **5e**. A significant decrease in the enantioselectivity was observed in the special case of acyclic enone **6d** (entry 11, Table 2), to give addition product **7k** with low enantioselectivity. The conversion obtained in the case of other acyclic ketones, such as nitrostyrene and chalcone, was very low. This result is not surprising as the rhodium-catalyzed 1,4-addition of arylboronic acids to acyclic substrates is a very challenging process and most catalysts described in the literature render the addition product with only moderate enantioselectivities. Fortunately, the addition of **5e** to cyclopentenone **6b** yielded the corresponding 3-(4-fluorophenyl)cyclopentanone **7i** (entry 9, Table 2) with a high yield (88%) and good enantioselectivity (82% ee), although it was lower than that previously obtained with 2-cyclohexenone **6a** (>99% ee, entry 5, Table 2). Finally, in the case of the seven-membered enone **6c** (entry 10, Table 2), the addition product **7j** was also obtained with a high chemical yield and enantioselectivity (82% and >99% ee, respectively).

Justification of Enantioselectivity

To justify the enantioselectivity of the process, according to the established catalytic cycle for the rhodium-catalyzed additions of arylboronic acids to activated ketones, we propose that the addition of the aryl group to the double bond of the cyclohexenone occurs in a complex as shown in Figure 3,

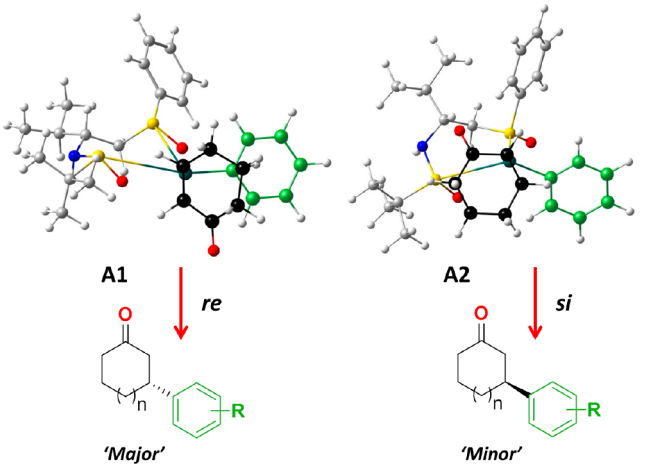

Figure 3. Transition states, A1 and A2, obtained theoretically at the M06/cc-pVDZ (for C, H, O, S, and N) and LANDL2DZ (for Rh) levels of theory for the enantioselective addition of arylboronic acids to α,β-unsaturated ketones.

where the aryl group is placed in an *anti* position to the sulfinyl sulfur of sulfinamide, due to its stronger *trans* effect. This hypothesis (*trans* effect, SON > SO) is based on the structural data of rhodium complexes derived from sulfoxide and sulfinamide ligands.[29−31]

Thus, considering the two possible intermediates, A1 and A2, generated when the substrate is coordinated to the transition metal, theoretical calculations were carried out using Gaussian 09,[32] and full geometry optimization of the molecules was performed using density functional theory in the context of the M06 functional[33] (see the Supporting Information). Theoretical results indicate that A1 is energetically more favorable than A2 (~8 kcal/mol), for steric reasons. In this sense, the square plane structure is lost in the A2 TS, while it is maintained in the most stable TS, that is, A1, with angles of ~170° (Figure 3). Therefore, the addition of the aromatic ring of the arylboronic acid to the double bond in A1, which implies an attack by the *re* face, followed by transmetalation, justifies the formation of the major enantiomer with high ee (Figure 3).

In conclusion, the addition of methylsulfinyl carbanions to different *N*-*tert*-butylsulfinylimines has allowed the synthesis of a new family of electronically dissymmetric bidentate ligands, with different types of symmetries, having two stereogenic sulfurs as coordination elements to the metal and an additional chiral center in the carbon backbone. The addition of the carbanions proceeds with total stereoselectivity and in the same sense with both enantiomeric sulfoxides, showing that the *N*-*tert*-butylsulfinyl group of the imine controls the stereochemical course of the addition. The sulfinamide/sulfoxide ligands were assayed in the Rh-catalyzed addition of arylboronic acids to activated ketones. From the ligands assayed, the sterically symmetric (pseudo-*meso* and pseudo-C_2-symmetric) ones were the least effective, while the sterically dissymmetric ligands gave better results. Among these last ligands, the (R_S,S_C,R_S)-*N*-[1-(phenylsulfinyl)-3-methylbut-2-yl] *tert*-butylsulfinamide (***SulfiSox****) has proven to be the optimum. It allows the 1,4-additions of arylboronic acids of a different nature, on different α,β-unsaturated cyclic ketones with high chemical yields and enantioselectivities, up to >99% ee.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02405.

Experimental data for the synthesis of ligands, substrates, and products; analytical data concerning the characterization of ligands, substrates, and products (NMR, HRMS, and chiral HPLC); and RX data of the ligands (PDF)

Accession Codes

CCDC 1912692−1912695 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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