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Atroposelective Haloamidation of Indoles with Amino Acid Derivatives and Hypohalides

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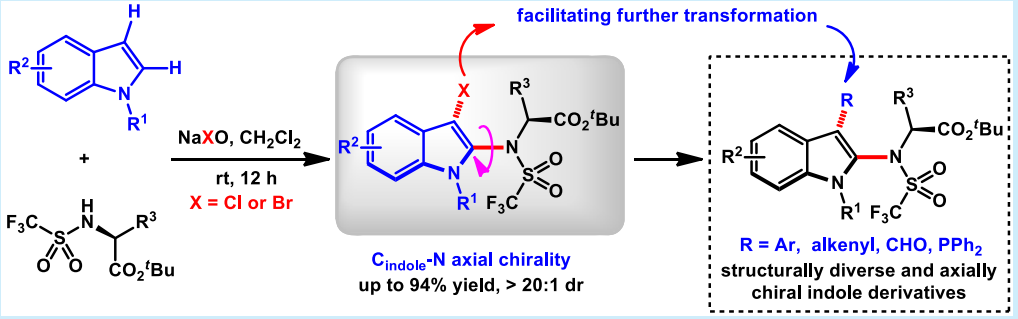
Supporting Information



ABSTRACT: An atroposelective coupling of indoles with chiral amino acid-based sulfonamides mediated by hypohalides is described. A series of 2-amido-3-haloindoles with a C−N chiral axis are delivered using this strategy. The C3 halogen atoms can facilitate further transformation. Various functionalities, such as carbonyl, phosphine, aryl, and alkenyl groups, can be introduced into the C3 position of indoles. These structurally diverse and axially chiral indole derivatives can find further synthetic utilities. It can be exemplified with an axially chiral phosphine, which serves as a ligand in Pd-catalyzed cross couplings.

Atropisomers around the C−N chiral axis, which have a typical chiral axis connecting an aryl substituent and the nitrogen-related hindrance, are one of the most important classes of nonbiaryl axially chiral compounds.[1] Representative examples with an axially chiral C−N bond are amide-type C−N axially chiral compounds[2] and nitrogen containing aromatic heterocyclic framework C−N axially chiral compounds[3] (Figure 1a). Investigation of these C−N axially chiral compounds has received increasing attention from the chemical community due to their widespread appearance in naturally occurring biologically active compounds[4] and applications toward chiral ligands for asymmetric catalysis.[5] Catalytic asymmetric syntheses of these N−C axially chiral compounds and their applications to asymmetric transformations are of current research interest.[6]

The indole skeleton is widely apparent in many natural products and drug molecules.[7] Therefore, it is interesting to introduce axial chirality into the indole skeleton. Uemura[3b,c] and Kitagawa[3e] reported the stereoselective synthesis of axially chiral indole derivatives possessing a sterically hindered phenyl group on the nitrogen atom. Catalytic asymmetric synthesis of indole-based heterobiaryl axially chiral compounds was also disclosed by the Shi,[8] Tan,[9] and Gu[10] groups. Despite these elegant achievements, asymmetric synthesis of indole-based atropisomers, especially with a C−N chiral axis, is still a synthetic challenge and remains largely unexplored because the indole-based atropisomers are expected to have less steric congestion and relatively lower rotation barriers than their benzene counterparts.[11]

Recently, we have succeeded in constructing a new class of C−N axial chirality based on *N*-indole sulfonamides by the atroposelective coupling of 3-substituted indoles with chiral amino acid-based sulfonamides (Figure 1b).[12] However, the substituents on the C3 position are mainly limited to alkyl groups, which are difficult to be functionalized and hamper the synthesis of these novel, axially chiral indole derivatives in a structurally diverse manner. We also reported chloroamidation of indoles with sulfonamides.[13] Sulfonamide and chloride were introduced into the C2 and C3 position, respectively. Using this 2,3-difunctionalization strategy, we envisage that atroposelective halosulfonamidation of indoles could be achieved using chiral amino acid-based sulfonamides as the coupling partners (Figure 1c). The halogen atoms are introduced into the C3 position of indoles, which is expected to increase the steric hindrance to ensure the thermodynamic stability of the chiral axis and also facilitate further transformation.

Initially, we tested this idea using 1-methylindole (**1a**) and *N*-triflyl-(L)-*tert*-leucine *tert*-butyl ester (**2a**) as the model substrates. When a solution of **1a**, **2a**, and aqueous NaClO solution with a ratio of 1:3:2.5 in $PhCF_3$ was stirred at room temperature for 12 h, the chloroamidation product **4a** was isolated in 11% NMR yield and >20:1 dr (entry 1, Table 1).

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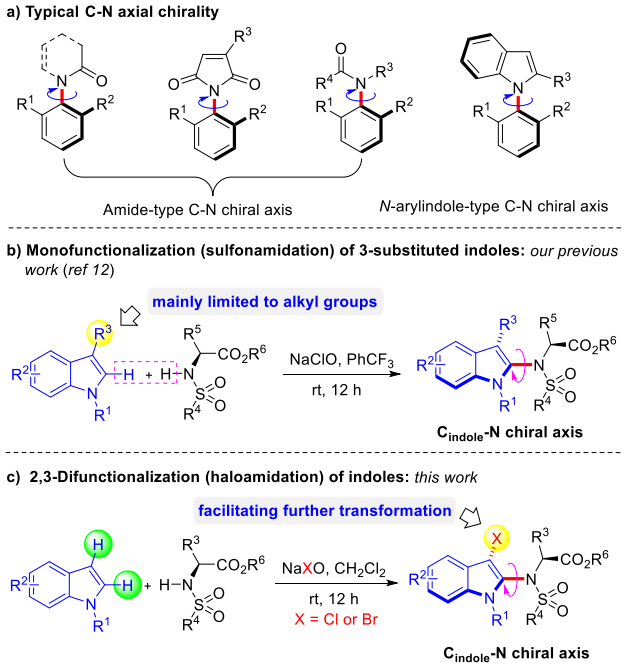
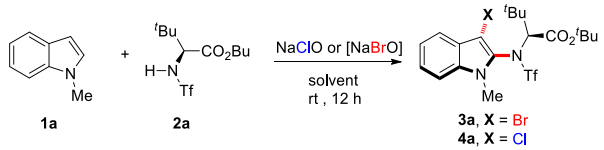


Figure 1. Establishment of a C−N chiral axis via amidation of indoles with amino acid derivatives.

Table 1. Reaction Conditions Optimization[a]



entry	1a:2a:NaClO	solvent	yield/%[b]	dr[d]
1	1:3:2.5	$PhCF_3$	11	> 20:1
2	1:3:2.5	CH_3CN	8	> 20:1
3	1:3:2.5	PhMe	14	> 20:1
4	1:3:2.5	MeOH	trace	-
5	1:3:2.5	CH_2Cl_2	59	> 20:1
6	1:3:2.5	DCE	45	> 20:1
7	**1:3:3**	**CH_2Cl_2**	**82 (76)[c]**	**> 20:1**
8	1:2:3	CH_2Cl_2	73	> 20:1
9[e]	**1:3:3**	**CH_2Cl_2**	**78 (65)[c]**	**> 20:1**

[a]Reaction conditions: a solution of **1a** (0.1 mmol), **2a**, and NaClO in the indicated solvent (2 mL) for 12 h under air. [b]The yields were determined by ^{1}H NMR. [c]Isolated yield in parentheses. [d]The dr values were determined by ^{19}F NMR. [e]Freshly prepared NaBrO aqueous solution (0.375 mol of NaOH and 0.125 mol of Br_2 formulated into 100 mL of aqueous solution at −5 °C) was used instead of NaClO, and **3a** was produced.

Encouraged by this promising result, we explored the solvent effect of this reaction. It was found that the solvent only affected the reactivity of this reaction and had no impact on the stereoselectivity (entries 2−6). Dichloromethane (CH_2Cl_2) proved to be the most efficient solvent, giving product **4a** in a 59% yield (entry 5). The ratio of **1a**:**2a**:NaClO was then investigated (entries 7 and 8). The optimal ratio of **1a**:**2a**:NaClO was determined to be 1:3:3, leading to 82% NMR yield (76% isolated yield) and >20:1 dr (entry 7). After succeeding in the chloroamidation of the indole **1a**, we turned our attention to bromoamidation of the indole **1a** with amino acid-based sulfonamide **2a** using bromine sources instead of aqueous NaClO solution. A series of common electrophilic bromine sources, such as NBS, DBDMH, NBP, and Br_2, were tested. However, only a trace amount of the bromoamidation product **3a** could be observed (not shown). Finally, freshly prepared aqueous NaBrO solution from Br_2 and sodium hydroxide in water was used as the bromine source;[14] the bromoamidation product **3a** was obtained in 78% NMR yield (65% isolated yield) and >20:1 dr (entry 9).

In order to show the generality of this 2,3-difunctionalization strategy, the couplings of various indoles with amino acid derivatives were investigated under chloroamidation and bromoamidation conditions, respectively. First, a series of substituted indole derivatives at different positions reacted with **2a** promoted by NaClO and NaBrO, respectively (Figure 2a). *N*-Benzyl indole was less active than its methylated counterpart. Both chloroamidation (**4b**, 26% yield) and bromoamidation (**3b**, 42% yield) resulted in lower yields. Substitutions at C4−C7 positions did not affect this transformation significantly, and chloroamidation (**4c**−**4i**, 36−64% yields) and

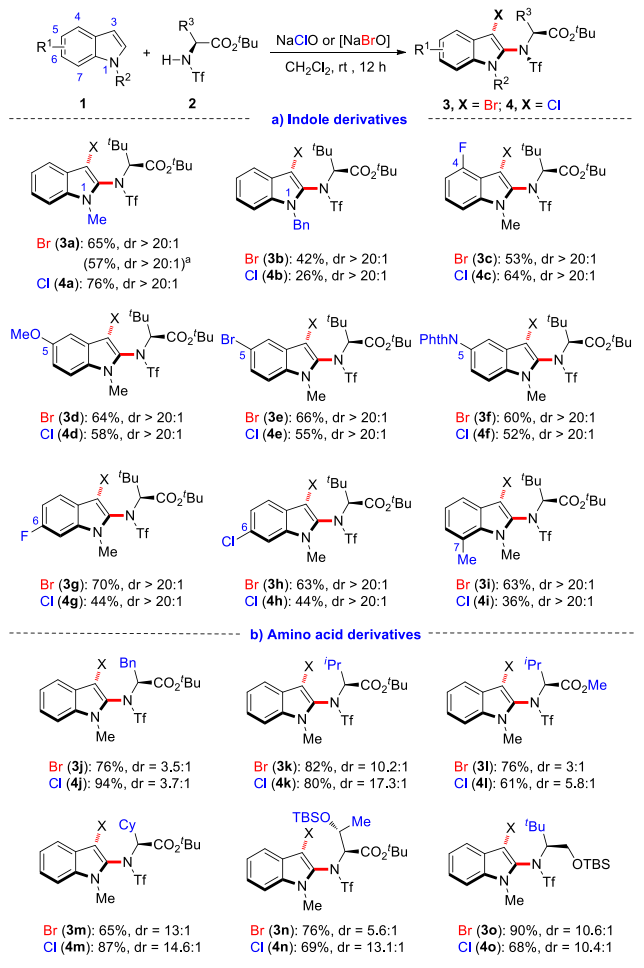


Figure 2. Substrate scope. Reaction conditions: a solution of **1** (0.1 mmol), **2a** (0.3 mmol), and NaClO or [NaBrO] (0.3 mmol, 3.0 equiv) in CH_2Cl_2 (2 mL) for 12 h under air. The yields were isolated yields, and the dr values were determined by ^{19}F NMR. [a]The reaction was run in a 4 mmol scale (**1a**).

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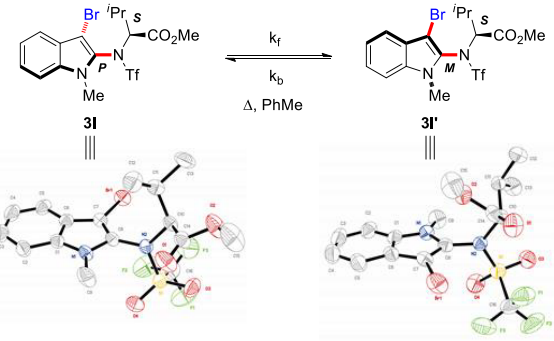
bromoamidation (**3c**−**3i**, 53−70% yields) products were produced in accepted yields. It is worthy to note that the diastereoselectivity was excellent (>20:1 dr) in all cases. This reaction could be scaled up to a gram scale. When 4 mmol of **1a** was subjected to the standard bromoamidation conditions, a comparable isolated yield of **3a** (1.2 g, 57% yield) was achieved without affecting the stereoselectivity (>20:1 dr). We next sought to investigate the reactivity and stereoselectivity of the reactions of 1-methylindole (**1a**) with various amino acid derivatives (Figure 2b). Generally, the steric hindrance of amino acid derivatives had a positive influence on the stereoselectivity without affecting the reactivity. The bulkier the amino acid derivatives, the better the stereoselectivity. The stereoselectivity of chloroamidation was better than that of bromoamidation. Chiral amino alcohol derivative was also explored and gave the corresponding products with good yield and stereoselectivity (90% yield and 10.6:1 dr for **3o** and 68% yield and 10.4:1 dr for **4o**).

All atropisomers prepared in this work are thermodynamically stable, and no obvious epimerization was observed at room temperature. However, upon heating, significant epimerization could be observed. In the case of **3l**, the half-lives and energy barriers for epimerization in toluene were measured experimentally at 50 °C (323.15 K) and 70 °C (343.15 K), respectively (Table 2; see the Supporting Information for more details). It was found that the half-lives for the epimerization of axially chiral indole **3l** were 3.45 h at 50 °C and 0.25 h at 70 °C, respectively. The rotational barriers for the forward and reverse directions were 26.98 kcal/mol ($\Delta G^{\ddagger}k_f$) and 25.29 kcal/mol ($\Delta G^{\ddagger}k_b$) at 50 °C and 26.78 kcal/mol ($\Delta G^{\ddagger}k_f$) and 25.12 kcal/mol ($\Delta G^{\ddagger}k_b$) at 70 °C. Chiral indole **3a** is thermodynamically more stable than **3l**. The half-lives for the epimerization of **3a** were 11.87 h at 50 °C, and the rotational barriers for the forward and reverse directions were 26.98 kcal/mol ($\Delta G^{\ddagger}k_f$) and 26.20 kcal/mol ($\Delta G^{\ddagger}k_b$) at 50 °C. The structures and stereochemistry of **3l** and **3l′** were confirmed unambiguously by single crystal X-ray diffraction analysis. The absolute stereochemistry of **3l** and **3l′** was assigned as (*S*, *P*) and (*S*, *M*), respectively.[15]

The C3 halogen atoms are expected to facilitate further transformation, which can generate structurally diverse indoles with a C−N chiral axis. Upon the treatment of bromide **3a** with *n*-BuLi leading to lithium−halogen exchange, the resultant anion was trapped by HCO_2Et and $ClPPh_2$, giving aldehyde (**5**, 58% yield, >20:1 dr)- and phosphine (**6**, 52% yield, >20:1 dr)-derived indoles, respectively (Figure 3a).

Table 2. Half-Lives and Energy Barriers for the Epimerization of 3l in Toluene



T	$\tau_{1/2rac}$ (h)	$\Delta G^{\ddagger}k_f$ (kcal/mol)	$\Delta G^{\ddagger}k_b$ (kcal/mol)	K_{eq}
323.15 K (50 °C)	3.45	26.98	25.29	0.072
343.15 K (70 °C)	0.25	26.78	25.12	0.088

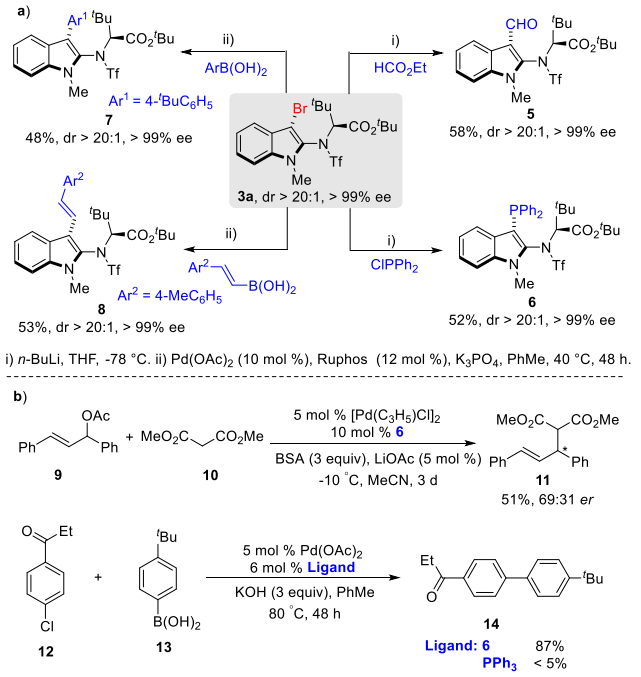


Figure 3. Synthetic application of axially chiral 3-bromoindole derivatives.

Bromide **3a** could also undergo a Suzuki−Miyaura coupling reaction with arylboronic acid and alkenylboronic acid to give arylation and alkenylation products **7** (48% yield, >20:1 dr) and **8** (53% yield, >20:1 dr), respectively (Figure 3a). All ee values of these compounds were determined to be more than 99%. No racemization was observed during these transformations.

These structurally interesting and novel axially chiral indole derivatives can find further synthetic utilities, which could be exemplified with the axially chiral phosphine **6** (Figure 3b). Phosphine **6** could serve as a chiral ligand in Pd-catalyzed asymmetric allylic alkylation of acetate **9** with malonate **10** to give the allylation product **11** in 51% yield and 69:31 er. Bulky and electron-rich phosphine **6** was also an effective ligand in the Pd-catalyzed Suzuki−Miyaura coupling reaction (87% yield for **14**) of the less reactive aryl chloride **12** with arylboronic acid **13**. As a contrast, PPh_3 was an ineffective ligand in the same reaction (<5% yield). These results showcased that these C−N chiral axes were a good skeleton as ligands in Pd-catalyzed cross couplings.

To obtain more details of these haloamidation reactions, a series of control experiments were conducted, as shown in Figure 4. It is known that *N*-chlorosulfonamides generated from sulfonamides and NaClO are good chlorinating reagents.[13] However, treatment of sulfonamide **2a** with NaClO could not provide *N*-chlorosulfonamide **15**, which ruled out *N*-chlorosulfonamide **15** serving as the chlorinating reagent (Figure 4a). 1-Methylindole **1a** reacted with NaClO could give chlorination product **16** and dichlorination product **17** but in low yields (8% yield for **16** and 6% yield for **17**). It was found that the overall yield for chlorination products **17**

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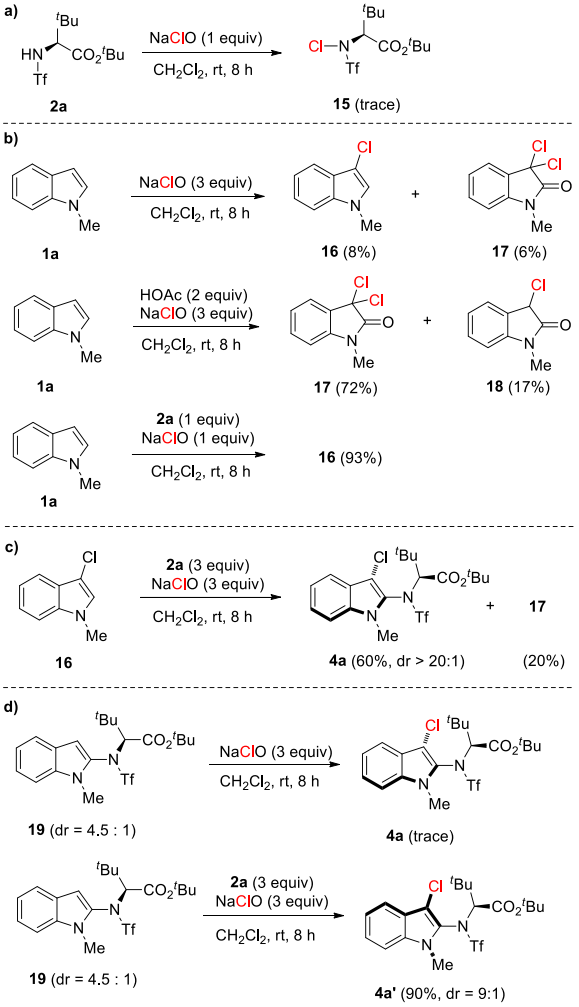

Figure 4. Control experiments.

and **18** could be improved 89% when HOAc was added into the reaction mixture of **1a** and NaClO. Besides, 1-methylindole **1a** reacted with sulfonamide **2a** (1equiv) and NaClO (1 equiv), giving 3-chloroindole **16** in good yield (93%) (Figure 4b). Given that trifluoromethanesulfonamide is about 3 p*K* units more acidic than acetic acid in DMSO,[16] sulfonamide **2a** was believed to act not only as an amide source but also as an acid to promote the chlorine transfer from NaClO to indole **1a**.[17] When 3-chloroindole **16** replacing indole **1a** was subjected to the standard chloroamidation conditions, the desired chloroamidation product **4a** was isolated in a 60% yield (Figure 4c). However, C2 sulfomidated indole **19** could not be further chlorinated with the sole NaClO. Interestingly, when C2 sulfomidated indole **19** was treated with the combination of NaClO and sulfonamide **2a**, a new chloroamidation product **4a′** (90% yield, 9:1 dr), which was determined to be the diastereomer of **4a**, was produced (Figure 4d). These phenomena indicated that 3-chloroindole **16** was the key intermediate of this chloroamidation reaction.

Based on the aforementioned experimental phenomena as well as our previous works,[12,13] a plausible mechanism for this transformation is posited. As shown in Figure 5, electrophilic chlorination of indole **1a** with NaClO in the assistance of acidic sulfonamide **2a** gives the 3-chloroindole **16**. 3-Chloroindole **16** is further chlorinated with NaClO to give the dichlorinated iminium intermediate **20**. The iminium ion

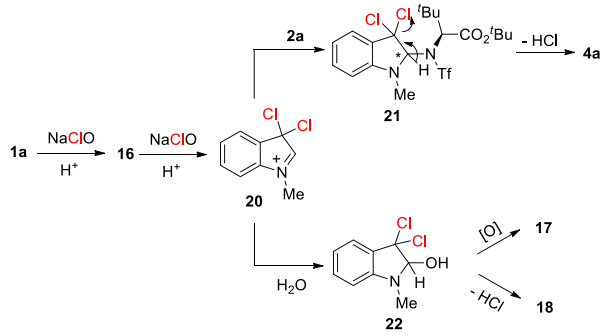

Figure 5. Plausible reaction mechanism.

20 is then trapped by sulfonamide **2a**. After antiperiplanar elimination of HCl with the help of a base, the chlorosulfonamidation product **4a** is finally afforded. The axial chirality is established by a point-to-axial chirality transfer process. Alternatively, the iminium intermediate **20** can be trapped by water in the absence of **2a** to provide the intermediate **22**. Intermediate **22** can either be oxidized to furnish the 3,3-dichloroindolinone **17** or lose HCl to give the 3-chloroindolinone **18**.

In summary, we have reported an atroposelective coupling of indoles with chiral amino acid-based sulfonamides mediated by hypohalides. This reaction delivers 2-amido-3-haloindoles with a C−N chiral axis. The C3 halogen atoms can facilitate further transformation, which can introduce various functionalities, such as carbonyl, phosphine, aryl, and alkenyl groups, into the C3 position of indoles. These structurally diverse and axially chiral indole derivatives can find further synthetic utilities. It can be exemplified with an axially chiral phosphine, which serves as a ligand in Pd-catalyzed couplings. Further investigation on the structural diversity and the application of these novel axially chiral indoles is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03456.

Experimental details, NMR spectra, and details of experiments (PDF)

Accession Codes

CCDC 1955748 and 1955749 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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