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Communication

Radical Aryl Migration from Boron to Carbon

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ABSTRACT: Radical aryl migration reactions represent a unique type of organic transformations that involve the intramolecular migration of an aryl group from a carbon or heteroatom to a C- or heteroatom-centered radical through a spirocyclic intermediate. Various elements, including N, O, Si, P, S, Sn, Ge, and Se, have been reported to participate in radical aryl migrations. However, radical aryl migration from a boron center has not been reported to date. In this communication, radical 1,5-aryl migration from boron to carbon in aryl boronate complexes is presented. C-radicals readily generated through radical addition onto alkenyl aryl boronate complexes are shown to engage in 1,5-aryl migration reactions to provide 4-aryl-alkylboronic esters. As boronate complexes can be generated *in situ* by the reaction of alkenylboronic acid esters with aryl lithium reagents, the aryl moiety is readily varied, providing access to a series of arylated products starting from the same alkenylboronic acid ester via divergent chemistry. Reactions proceed with high diastereoselectivity under mild conditions, and also the analogous 1,4-aryl shifts are feasible. The suggested mechanism is supported by DFT calculations.

Radical aryl migration reactions are valuable transformations involving the intramolecular translocation of an aryl group from a carbon or heteroatom to a radical center through a three-, four-, five-, or six-membered spirocyclic intermediate or transition state.[1−6] Various synthetic methods have been developed for C−C σ-bond formation through radical 1,2-,[7−13] 1,3-,[14,15] 1,4-,[16−24] and 1,5-aryl[19,24−26] migration. Such reactions are not restricted to the "all-carbon" case, and various elements, such as N,[27,28] O,[29−31] Si,[32−36] P,[37] S,[38−46] Sn,[47] Ge, and Se,[39] have been reported as origins in radical aryl migrations (Scheme 1, a). Although intensively studied and applied in synthesis, radical aryl migration generally[19−23,26,45,46] suffers from the need to preinstall the transferable aryl group onto the substrate. Considering the aryl translocation step, only one aryl migration product is accessible from the functionalized starting material. In that regard, a divergent approach would be desirable.

Organoboron compounds are important intermediates,[48−51] and their radical chemistry has gained great attention recently.[52,53] Surprisingly, aryl migration from a boron center to a C-radical has not yet been reported. Considering an sp^2-hybridized boron compound bearing an aryl moiety, it is more likely that the whole boron group migrates rather than the aryl group, due to the interaction of the empty p orbital at boron with the C-radical. Indeed, 1,2-boron shifts of β-boryl radicals of type **1** were recently reported by Aggarwal's group[54] and us[55] (Scheme 1, b-i). We envisioned that aryl migration from sp^3 boron intermediate **2** would be feasible, as the p orbital of boron is no longer vacant, rendering a radical−aryl interaction possible (Scheme 1, b-ii). Accordingly, we assumed that boronate complexes should be eligible substrates for radical aryl migration from an sp^3 boron center, as they can be easily generated by the reaction of organoboronic acid esters with organometallic reagents.[56−59]

Radical chemistry on boronate complexes is an emerging area in synthesis.[59] For example, radical-induced 1,2-aryl migrations of boronate complexes to access benzylic boronic acid esters **5** in radical/polar crossover processes were reported by us,[60−62] Aggarwal,[63,64] and Renaud.[65] In such transformations, the α-C-radical anion intermediate **3** is oxidized by single electron transfer (SET) to generate the zwitterion **4** (Scheme 1, c).[60] An ionic 1,2-aryl migration eventually provides the product **5**. We supposed that the interaction of a distal C-radical and an aryl group in a boronate complex[66] would allow for an unprecedented radical aryl migration (Scheme 1, b-ii). First, the reaction of an alkenylboronic acid ester **6** with an aryl lithium compound will give boronate complex **7** (Scheme 1, d). Radical addition of $\mathbf{R}^{\bullet}$ to **7** will generate the distal radical anion **9**. Intramolecular radical 1,5-aryl migration should lead to the radical anion **10**, which could finally be SET oxidized to the targeted product **8** by the radical precursor **R**−**X** sustaining the chain reaction. Initiation could be achieved by LED irradiation of the corresponding halide **R**−**X**. As the boronate complex **7** is formed *in situ* and various aryl lithium reagents can be accessed by lithium/halogen exchange reaction of aryl halides and *n*-BuLi or deprotonation of heteroarenes with a strong base, various arylated products could be formed from a single starting alkenylboronic acid ester in a divergent manner. Moreover, also the radical precursor **R**−**X** should be varied, further enlarging the number of potential products from the same substrate.

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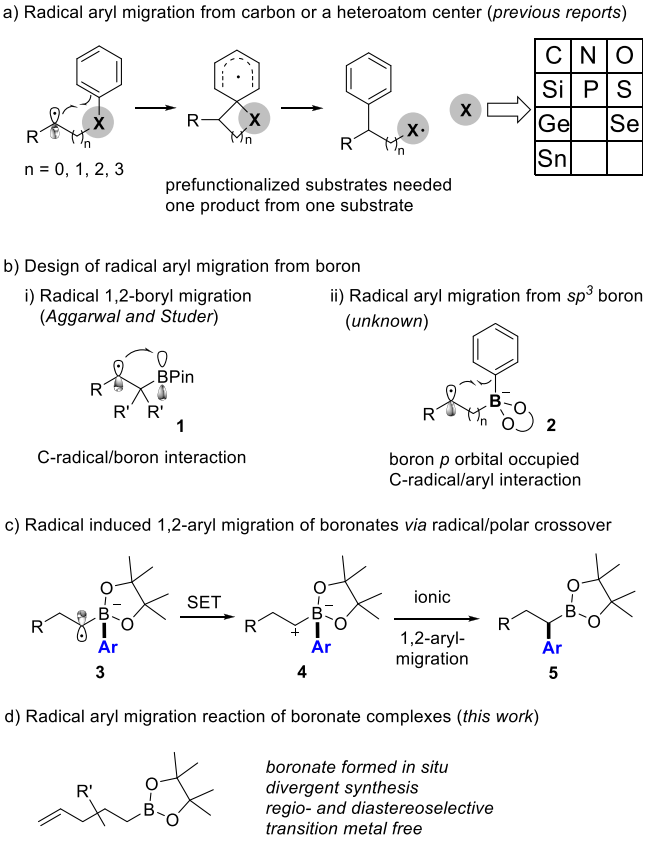
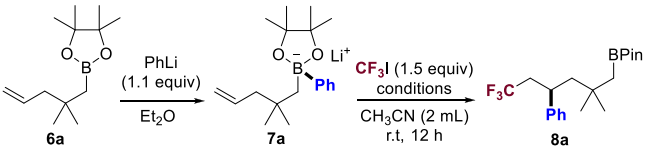
Scheme 1. Radical Aryl Migrations



Considering the prevalence of the CF_3 group in pharmaceutical compounds and bioactive molecules,[67−69] we first tested the CF_3-radical addition induced aryl migration reaction of boronate complex **7a**,[7,9,16,43,70−74,20,42,75−78] which was *in situ* generated by reaction of pinacol ester **6a** and PhLi. Pleasingly, upon 365 nm LED light irradiation of a solution of **7a** and CF_3I in acetonitrile, **8a** was obtained in 77% yield (Table 1, entry 1). With photocatalysts as smart initiators,[79] lower yields were noted (66−72%, entries 2−5), and 465 nm LED irradiation in the absence of a catalyst provided **8a** in a lower yield (42%, entry 6). Decreasing the reaction temperature to −20 °C also provided a worse result (64%, Table 2, entry 7). In all cases, the PhBpin (3−14%) was identified as the side product, which was likely formed by direct SET oxidation of **7a** by oxidizing species such as the CF_3-radical or CF_3I. No product was obtained upon conducting the reaction in the dark (Table 2, entry 8). Notably, the corresponding catechol boronic ester did not engage in the phenyl migration reaction.

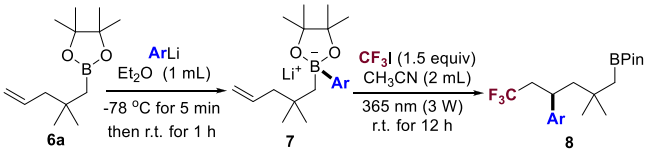
Table 1. Reaction Optimization[a]

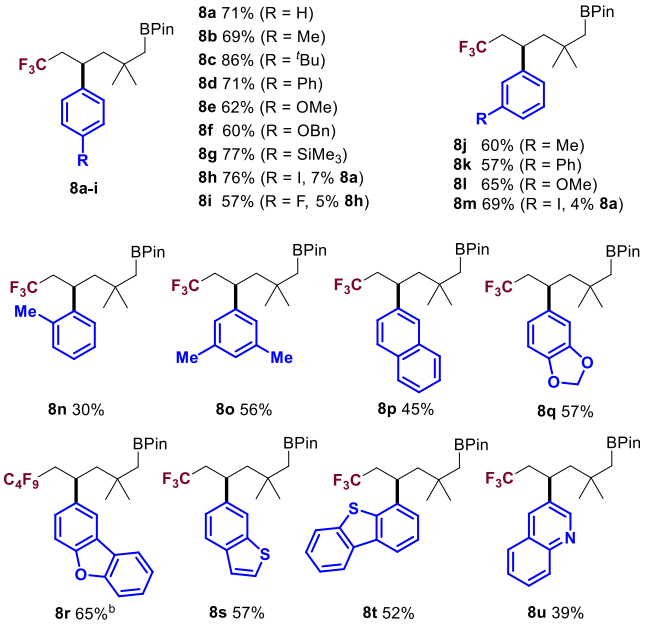


entry	variation from the standard condition	8a	Ph-Bpin	conv
1	365 nm LED (3 W)	77% (71%[b])	4%	100%
2	*fac*-Ir(ppy)$_3$, 465 nm LED (3 W)	72%	8%	100%
3	Ru(bpy)$_3$(PF$_6$)$_2$, 465 nm LED (3 W)	66%	13%	100%
4	rhodamine B base, 465 nm LED (3 W)	72%	11%	100%
5	eosin Y, 465 nm LED (3 W)	68%	14%	100%
6	no photo catalyst, 465 nm LED (3 W)	42%	3%	100%
7	−20 °C	64%	4%	100%
8	no light irradiation	0%	0%	100%

[a]Reactions conducted on a 0.2 mmol scale in CH_3CN (2 mL), conversion determined based on recovered **6a**, yields determined by GC analysis with *n*-tetradecane as the internal standard. [b]Isolated yield. Pin = pinacolato.

Table 2. Variation of the Aryl Lithium Reagent[a]





[a]Reactions conducted on a 0.2 mmol scale in CH_3CN (2 mL). [b]Reaction conducted with nonafluorobutyl bromide (1.5 equiv).

With the optimized reaction condition in hand, we first tested the scope with respect to the aryl lithium reagent, keeping **6a** as the acceptor and CF_3I as the C-radical precursor (Table 2). Aryl lithium reagents were generated *in situ* by lithium/halogen exchange of the corresponding aryl iodides/bromides and *n*-butyllithium. Boronate complexes derived

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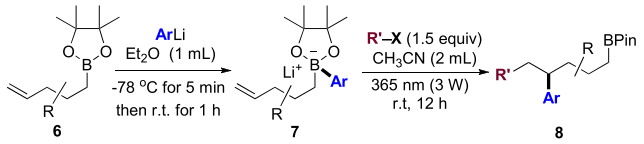
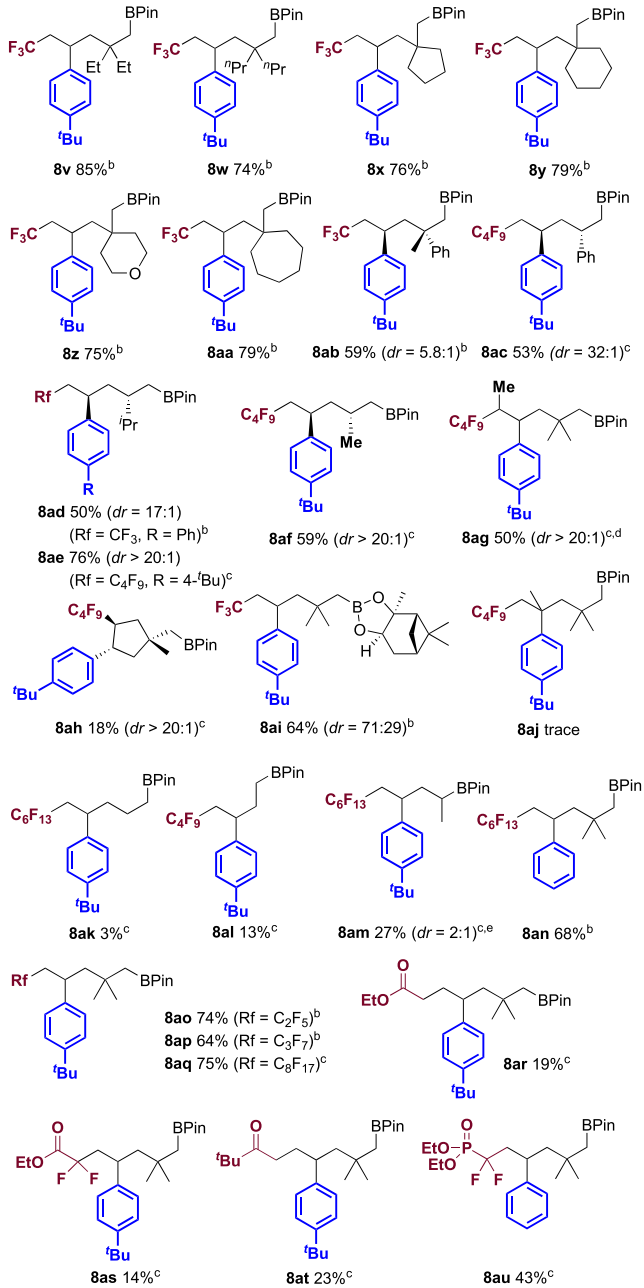
from *para*-substituted aryl lithium reagents reacted with moderate to good yields to the corresponding 4-arylalkyl boronic esters (57−86%). Various *para*-substituents are tolerated, such as methyl (**8b**), *tert*-butyl (**8c**), phenyl (**8d**), methoxy (**8e**), benzyloxy (**8f**), trimethylsilyl (**8g**), iodide (**8h**), and fluoride (**8i**). For the reaction of **7h**, 7% hydrodeiodination product **8a** was formed. Notably, both *para*-bromo and *para*-chloro phenyl lithium provided **8h** as the major product, likely derived from a halogen/iodide exchange in the targeted products (see SI for detailed discussion). Fluoride/iodide exchange was detected by crude GC analysis for the reaction of the F-substituted substrate **7i** (5% **8h**). *Meta*-substituted aryl lithium compounds were found to be eligible aryl donors, providing the products **8j−m** in 57−69% yield. Hydrodeiodination (4% **8a**) was also observed for **7m**. Migration of the *ortho*-tolyl group was less efficient (**8n**, 30%), likely for steric reasons. Reactions of boronate complexes generated with 3,5-dimethylphenyl lithium (**7o**), 3-naphthyl lithium (**7p**), and benzo[*d*][1,3]dioxol-5-yl lithium (**7q**) also worked (45−57%). Heteroarenes such as dibenzofuran (**8r**), benzothiophene (**8s**), dibenzothiophene (**8t**), and quinoline (**8u**) are compatible with the reaction conditions.

We then studied the scope with respect to the alkenylboronic acid pinacol ester and also varied the C-radical precursor (Table 3). These experiments were mostly conducted with *para-tert*-butylphenyl lithium as the aryl donor. The 2,2-diethyl and 2,2-dipropyl alkenyl boronic esters **6v** and **6w** delivered the trifluoromethylarylated products **8v** and **8w** in 85% and 74% yield, respectively. Substrates **6x−6aa**, bearing five- to seven-membered rings, also displayed good reactivity (76−79%). The boronic ester **6ab**, bearing a stereocenter, afforded the product **8ab** in 59% yield with good diastereoselectivity (dr = 5.8:1). The stereochemical outcome of the aryl migration will be discussed below. For the 2-isopropylalkenyl boronic ester **6ad**, the yield was lower (50%), but the diastereoselectivity was very high (17:1).

It is obvious that the aryl migration is slower for substrates lacking the two geminal substituents in the backbone (Thorpe Ingold effect). In these cases, iodine atom transfer outcompeted the aryl migration. To slow down the I atom transfer, we switched to the nonafluorobutyl bromide as the C-radical precursor. Pleasingly, the yield could be improved to 76% and **8ae** was obtained with complete stereoselectivity. Hence, switching from CF_3I to C_4F_9Br not only improved the yield but also led to an improved diastereoselectivity. Benefiting from these effects, **8ac** and **8af** were isolated in 53% and 59% yield and high diastereoselectivity (>20:1). As 1,6-aryl migration was not efficient, 1,5-aryl migration product **8ag** (50%) was the only isolated product with excellent diastereoselectivity (dr > 20:1) starting from the linear internal alkene **6ag** (*E*/*Z* = 3:1). As expected for the cyclic system **6ah**, an excellent diastereoselectivity was noted for the aryl migration (see **8ah**). Yield was low, likely due to non-diastereoselective initial addition of the C_4F_9-radical to the substituted cyclopentene. After having shown that stereoinduction can be high for acceptors with a chirality center in the backbone, we studied the aryl migration in the chiral boronate complex **7ai** bearing a chirality center at the diol moiety of the boronic ester. **7ai** was generated in diastereoisomerically pure form[80] from alkenylboronic acid (1*S*,2*S*,3*R*,5*S*)-(+)-pinanediol ester **6ai** and 4-*t*-BuC_6H_4Li. Reaction with CF_3I afforded **8ai** in 64% yield but moderate diastereoselectivity (71:29).

Table 3. Substrate Scope: Varying the Alkylboronic Acid Pinacol Ester and Carbon Radical Precursor[a]





[a]Reactions conducted on a 0.2 mmol scale in CH_3CN (2 mL). [b]Corresponding alkyl iodide (0.3 mmol, 1.5 equiv) was used. [c]Corresponding alkyl bromide (0.3 mmol, 1.5 equiv) was used. [d]Relative configuration could not be assigned. [e]Products isolated as corresponding alcohols after treatment with H_2O_2/NaOH.

Aryl migration to a tertiary C-radical is not efficient, likely for steric reasons (see **8aj**). We found a substituent in the backbone that renders the substrate conformationally less flexible to be important for getting acceptable yields. Thus, the unsubstituted boronic ester **6ak** provided the migration

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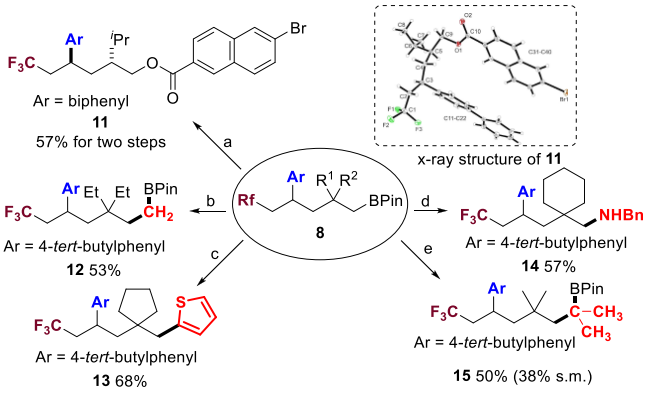
product **8ak** in 3% yield only. We also tested whether radical 1,4-aryl migration is feasible, by studying the lower homologues **6al** and **6am**. Both reactions worked, and as expected, a methyl substituent in the backbone increasing rigidity of the system improves the yield (**8al**–**8am**). However, as compared to the 1,5-aryl migration, the corresponding 1,4-translocation is far less efficient.

Other perfluoroalkyl halides also performed well in the radical addition/1,5-aryl migration sequence using acceptor **6a** and 4-*t*-BuC_6H_4Li as the reaction partners. Hence, pentafluoroethyl iodide (**8ao**, 74%), heptafluoropropyl iodide (**8ap**, 64%), perfluorohexyl bromide (**8an**, 68%), and perfluorooctyl bromide (**8aq**, 75%) engaged in this cascade. Less electrophilic alkyl halides reacted with significantly lower efficiencies (14–43% yield, **8ar**–**8au**).

To document the synthetic value of the method, various follow-up transformations on aryl migration products were conducted (Scheme 2). Oxidation of the C–B bond in **8ad**

Scheme 2. Follow-up Chemistry[a]



[a]a. (1) H_2O_2/NaOH in THF/H_2O, 0 °C, then rt; (2) DMAP, DCC, 6-bromo-2-naphthoic acid; b. CH_2Br_2, ^{n}BuLi; c. 2-thiophenyllithium, then NBS; d. BCl_3 in CH_2Cl_2, then BnN_3; e. isopropyl lithium, then CF_3I in CH_3CN/DMSO (10:1), 365 nm (3 W).

and esterification provided the ester **11** with overall 57% yield. X-ray structure analysis on **11** showed that the aryl and isopropyl groups in the backbone are *anti* to each other, which agrees with the relative configuration of the major aryl migration isomer deduced by DFT calculations (see below). Matteson homologation[50,81] of **8v** afforded the boronic ester **12** (53%). Oxidative coupling of **8x** with 2-thiophenyl lithium gave **13** (68%),[82] and oxidative amination[83] of the C–B bond in **8y** was achieved using standard protocols (**14**, 57%). Insertion of an isopropyl moiety into the C–B bond in **8c** was realized applying a radical homologation sequence (**15**, 50%).[62]

To get a better picture on the mechanism of the aryl migration reaction, the cascade was investigated by DFT (for details, see the SI). For the 1,5-aryl migration in the radical anion **9a** (R = CF_3, Ar = Ph, R′ = 2,2-Me,Me), we find a transition structure with chair conformation, in which the CH_2R_f group attains an equatorial position (Figure 1). The low barrier (10.9 kcal/mol) agrees with the facile transformation and can be rationalized with the spin delocalization in the aryl ring. In the intermediate radical anion then formed, the B atom/aryl interaction remains (see the SI). The subsequent SET-oxidation terminates the aryl translocation. The prevalent formation of *anti* products with a chiral precursor (e.g., **8ad**, R′ = *i*-Pr,H) is qualitatively confirmed by a barrier that is 0.5 kcal/mol lower than that of the *syn* pathway. This difference is determined by the equatorial position of the isopropyl group in the *anti* transition structure, which is axial in the *syn* TS (Figures S3–S5).

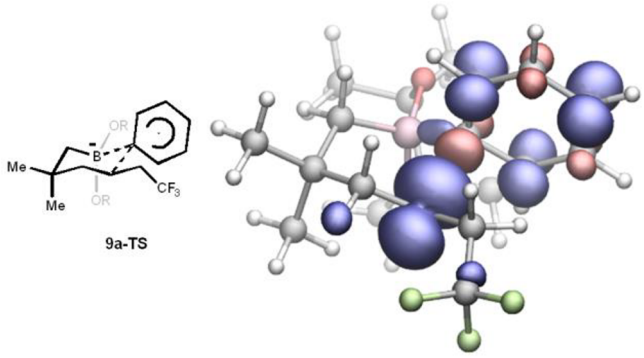


Figure 1. Transition structure (PBE0-D3/def2-TZVP) of Ph migration in **9a**. Spin density ($\rho_\alpha - \rho_\beta$) isosurface at ρ_{SD} = 0.005 au (PW6B95-D3/def2-TZVP).

In summary, radical aryl migration from boron in boronate complexes to carbon was introduced as an efficient route for arylation of secondary alkyl radicals that are generated by perfluoroalkyl radical addition onto alkenyl boronate complexes. These complexes derive from boronic esters by addition of aryl lithium reagents. The migrating aryl moiety is readily varied upon changing the aryl lithium reagent allowing for divergent chemistry. The 1,5-aryl shift occurs with high diastereoselectivity. The cascade also works on the lower homologous alkenylboronic esters comprising a 1,4-aryl migration step, albeit less efficiently. The potential of the method was convincingly documented by a series of valuable follow-up transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c04217.

Experimental details and characterization data, NMR spectra of new compounds, DFT calculations, X-ray data (PDF)

Accession Codes

CCDC 2078808 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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