Preprint Title	Asymmetric Synthesis of CF_2-Aziridines Enabled by Combined Strong Brønsted Acid Catalysis
Authors	Xing-Fa Tan, Fa-Guang Zhang and Jun-An Ma
Publication Date	17 Feb 2020
Article Type	Full Research Paper
Supporting Information File 1	Checkcif for compound 5c.pdf; 121.5 KB
Supporting Information File 2	Checkif for compound 4a.pdf; 118.2 KB
Supporting Information File 3	Supporting Information.pdf; 3.2 MB
Supporting Information File 4	X-ray data for compound 4a.cif; 17.6 KB
Supporting Information File 5	X-ray data for compound 5c.cif; 278.0 KB
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Asymmetric Synthesis of CF_2-Aziridines Enabled by Combined Strong Brønsted Acid Catalysis

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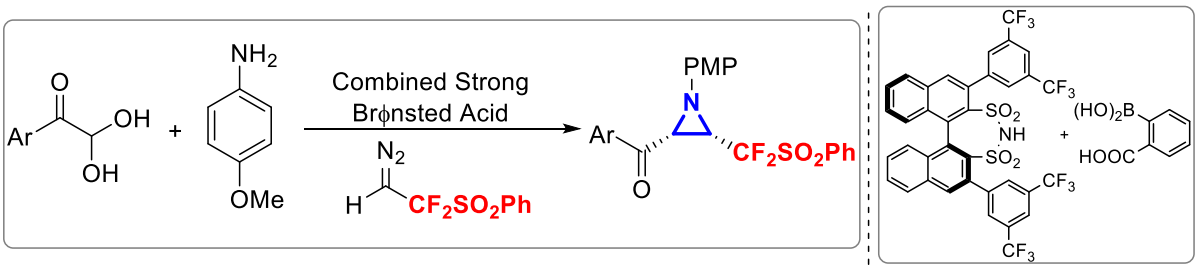
Abstract

A diastereo- and enantioselective approach to access chiral CF_2-functionalized aziridines from phenylsulfone difluorodiazoethane ($PhSO_2CF_2CHN_2$) and *in-situ* formed aldimines is described. This multicomponent reaction is enabled by a combined strong Brønsted acid catalytic platform consisting of a chiral disulfonimide and 2-carboxyphenylboronic acid. The optical purity of obtained CF_2-aziridines could be further improved by a practical dissolution-filtration procedure.



Keywords

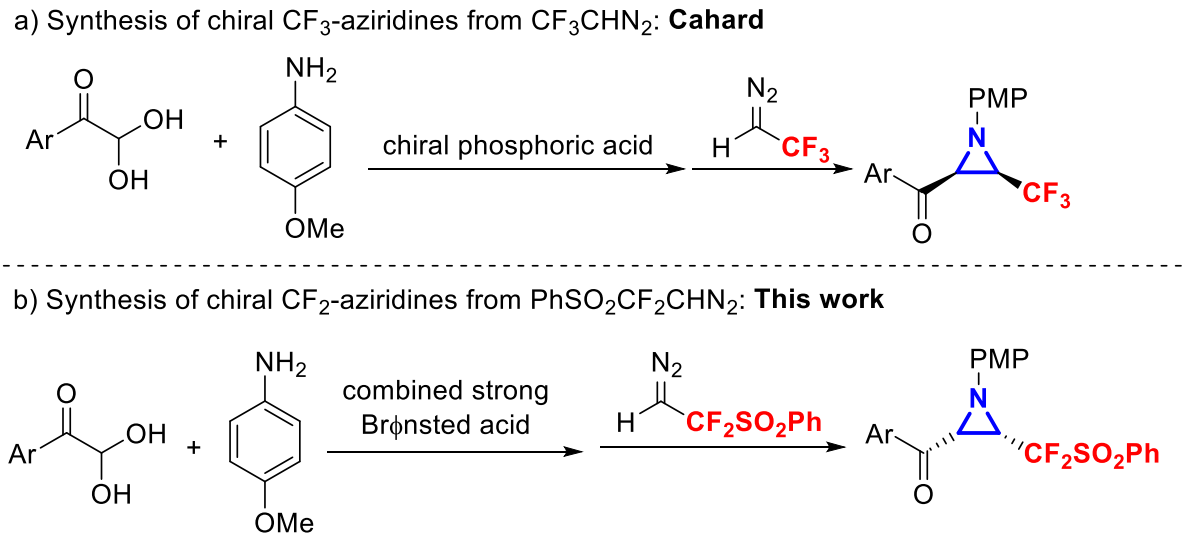
difluoromethyl compounds; aziridines; fluorinated diazo reagents; chiral disulfonimides; strong Brønsted acids

This article is part of the Thematic Series "Organo-fluorine chemistry V".

Introduction

Chiral aziridines have been prevalently found in natural products and artificially-made bio-active molecules, thus receiving significant attention in the past decades [1-6]. Among them, the introduction of fluorine or fluoroalkyl groups into the three-membered *N*-heterocycles has emerged as an attractive direction owing to the unique fluorine effect in pharmaceuticals and biology [7-11]. In this context, it is not surprising that the synthesis of trifluoromethyl aziridines have been pursued from versatile precursors [12-25]. However, catalytic asymmetric access to chiral CF_3-aziridines have only been reported by Cahard in 2012, which utilized trifluorodiazoethane (CF_3CHN_2) as the nucleophile to react with aldimines catalyzed by chiral phosphoric acid (Scheme 1a) [26]. In comparison, there is a significant dearth of available synthetic approaches to CF_2-functionalized aziridines, particularly in a stereo-controlled manner. Indeed, a handful of reported methods document the employment of difluoromethyl imines, difluoromethyl phenylsulfone, and difluoromethyl vinyl sulfonium salt as the fluorinated

partner *en route* to various CF_2-aziridines [27-31], but a general protocol to chiral CF_2-aziridines remains an unsolved challenge. Thus, herein we report a diastereo- and enantioselective aza-Darzens reaction between *in situ*-generated aldimines and our recently developed difluorodiazo reagent-$PhSO_2CF_2CHN_2$ acting as the difluorinated nucleophile [32-35], providing access to a variety of chiral CF_2-aziridines under mild conditions (Scheme 1b). The key to this multicomponent transformation hinges upon the discovery of a combined strong Brønsted acid system comprised of a chiral disulfonimide and 2-carboxyphenylboronic acid.



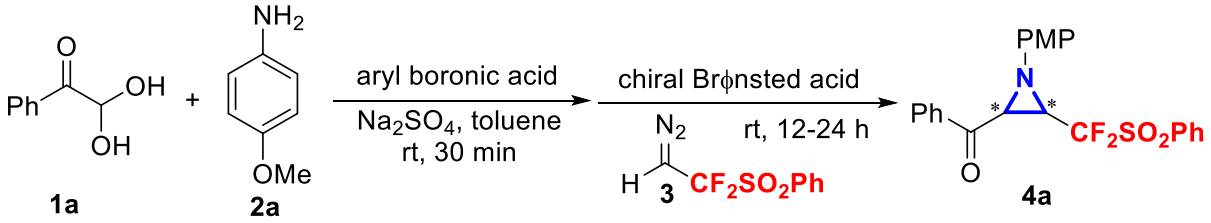
Scheme 1: Preparation of chiral aziridines from fluorinated diazo reagents.

Results and Discussion

We commenced the desired one-pot transformation by conducting the model reaction between phenyl glyoxal monohydrate **1a**, 4-methoxyaniline **2a**, and $PhSO_2CF_2CHN_2$ **3** (Ps-DFA). Initial screenings were focused on the evaluation of various chiral phosphoric acids which has proven effective in similar aza-Darzens reactions of diazo esters and trifluorodiazoethane [36-39]. Unfortunately, such endeavors resulted in either no conversion or no enantioselectivity at all. As aryl boronic acids have been

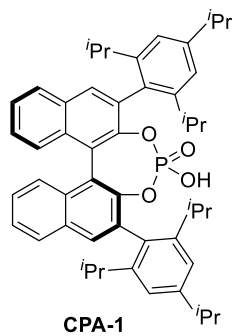
harnessed to enhance Brønsted acidity in asymmetric organocatalysis in combination with chiral diols or chiral amino-alcohols [40-44], we envisioned that the simultaneous use of aryl boronic acids and chiral Brønsted acid may bring with a complementary catalytic platform. Encouragingly, the targeted CF_2-aziridine **4a** was obtained in up to 51% ee with high diastereoselectivity, albeit in low yield (Table1, entries 1 and 2). Subsequently, a range of BINOL-derived disulfonimide were subjected as chiral additive in combination with 2-carboxyphenylboronic acid (**COOH-BA**) in the model reaction (entries 3–8) [45]. We were pleased to find that **CDSI-4** gave most promising result in terms of both yield and enantioselectivity (64% isolated yield with 73% ee, entry 6). An examination on various aryl boronic acids, solvent, temperature, and catalyst loadings resulted in no obvious improvement (entries 9–15). Removing boronic acid from the reaction system would lead to dramatic decrease in both yield and enantio-control (entry 16).

Table 1: Representative screening results for asymmetric aziridination reaction of $PhSO_2CF_2CHN_2$[a].

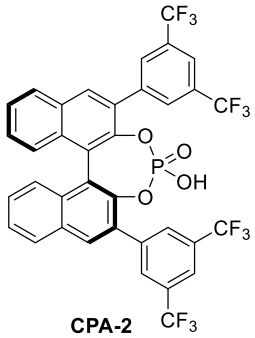


entry	aryl boronic acid (mol %)	chiral Brønsted acid (mol %)	yield of **4a** (%)[b]	ee (%) of **4a** and dr of crude mixture[c]
1	**COOH-BA** (8)	**CPA-1** (5)	24	51, 13:1
2	**COOH-BA** (8)	**CPA-2** (5)	28	25, 11:1
3	**COOH-BA** (8)	**CDSI-1** (5)	21	41, 19:1

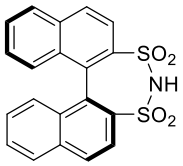
4	**COOH-BA** (8)	**CDSI-2** (5)	50	41, 9:1
5[d]	**COOH-BA** (8)	**CDSI-3** (5)	16	60, 5:1
6[d]	**COOH-BA** (8)	**CDSI-4** (5)	64	73, 13:1
7	**COOH-BA** (8)	**CDSI-5** (5)	34	33, 10:1
8	**COOH-BA** (8)	**CDSI-6** (5)	47	52, 9:1
9	**OH-BA** (8)	**CDSI-4** (5)	63	68, 28:1
10[d]	**SO_3H-BA** (8)	**CDSI-4** (5)	62	66, 16:1
11[d]	**NO_2-BA** (8)	**CDSI-4** (5)	45	62, 16:1
12	**CF_3-COOH-BA** (8)	**CDSI-4** (5)	81	67, 8:1
13[e]	**COOH-BA** (8)	**CDSI-4** (5)	60	47, 5:1
14[f]	**COOH-BA** (8)	**CDSI-4** (5)	trace	nd
15[d]	**COOH-BA** (8)	**CDSI-4** (10)	65	70, 12:1
16[d]	-	**CDSI-4** (5)	10	60, >20:1



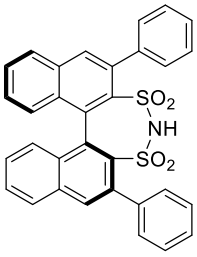
CPA-1



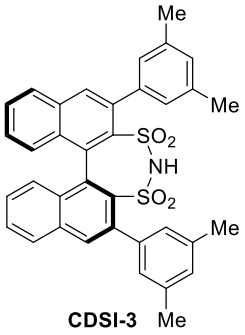
CPA-2



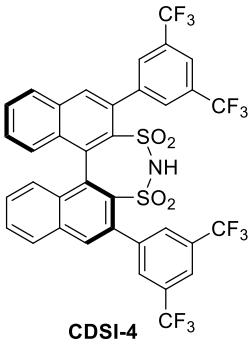
CDSI-1



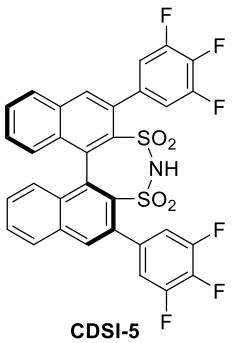
CDSI-2



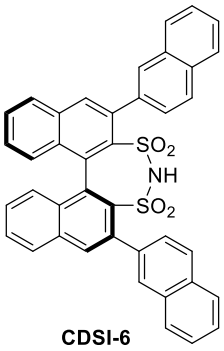
CDSI-3



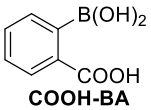
CDSI-4



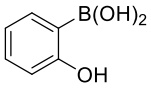
CDSI-5



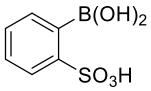
CDSI-6



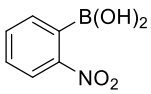
COOH-BA



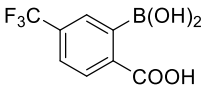
OH-BA



SO_3H-BA



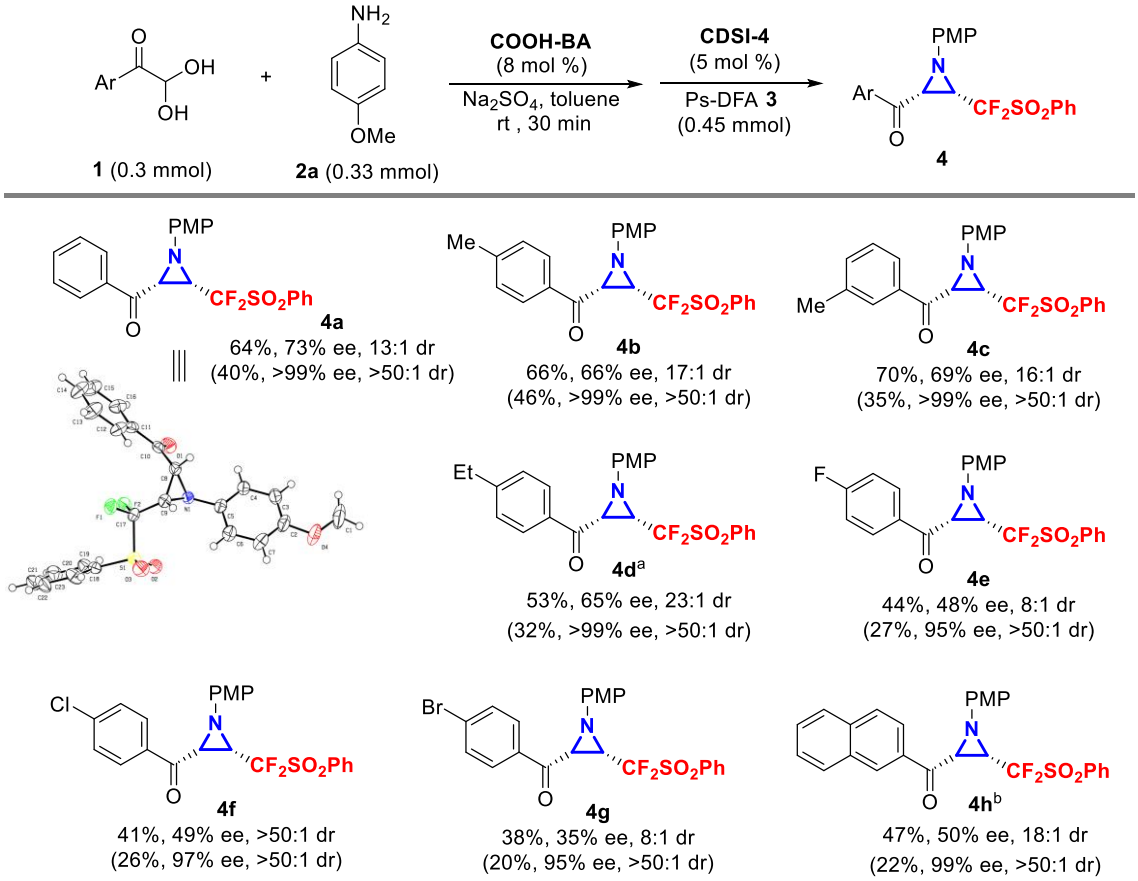
NO_2-BA



CF_3-COOH-BA

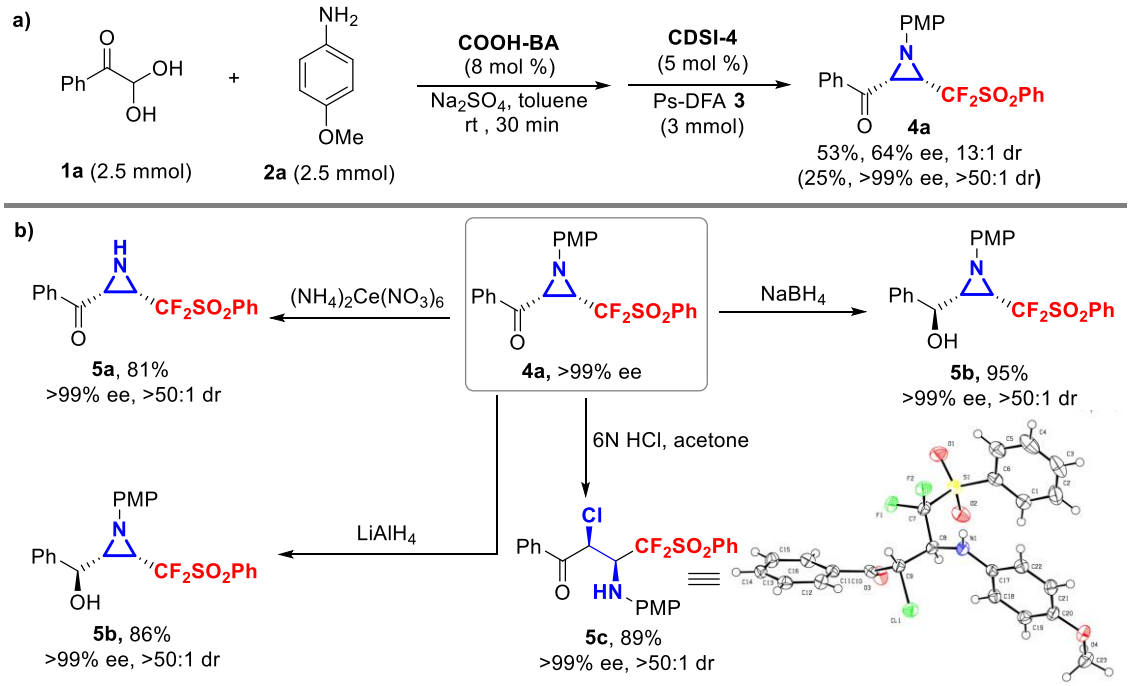
[a]General reaction conditions for entries labelled with d : **1a** (46 mg, 0.3 mmol, 1.0 equiv.), **2a** (41 mg, 0.33 mmol), aryl boronic acid (0.024 mmol), and Na_2SO_4 (200 mg) was stirred in toluene (2 mL) at rt for 30 min, then chiral Brønsted acid (0.015 mmol) and **3** (105 mg, 0.45 mmol) was added and the mixture was reacted at rt for 12-24 hours unless otherwise annotated; 0.05 mmol scale

reaction was conducted in other cases; [b]Yield of isolated product **4a** was given for entries labelled with d; Hexafluorobenzene was used as an internal standard to determine the yield in other cases; [c]Ee of **4a** was determined by chiral HPLC analysis, and the dr of the crude reaction mixture was probed by ^{19}F NMR analysis; [e]CH_2Cl_2 was used as the solvent; [f]Reaction was operated at 0 ℃.



Scheme 2: Substrate scope of chiral CF_2-aziridines from $PhSO_2CF_2CHN_2$. General reaction conditions: aryl glyoxal monohydrate **1** (0.3 mmol), **2a** (41 mg, 0.33 mmol), **COOH-BA** (4 mg, 0.024 mmol), and Na_2SO_4 (200 mg) was stirred in toluene (2 mL) at rt for 30 min, then **CDSI-4** (12 mg, 0.015 mmol) and Ps-DFA **3** (105 mg, 0.45 mmol) was added and the mixture was reacted at rt for 24 hours unless otherwise annotated; The yields are those of isolated products, and the dr was determined by ^{19}F-NMR analysis of crude mixture; The results in parentheses are those of isolated products after dissolution-filtration process: The corresponding CF_2-aziridine **4** was dissolved in isopropanol (0.05~0.2 mL/mg) with ultrasound, followed by filtration, and the obtained solution was concentrated to give **4** with increased ee and dr. [a]0.006 mmol of **COOH-BA** was employed. [b]The reaction was operated at 45 ℃ for 24 h.

The challenge in further improving the enantioselectivity promoted us to search for other practical solutions. Considering the poor solubility of **4a** in organic solvents, a dissolution-filtration process with isopropanol was found to be workable for increasing the final ee value. This simple procedure could afford **4a** in an excellent level of enantio-purity as a single diastereo-isomer (>99% ee, >50:1 dr, Scheme 2). By the aid of the developed one-pot aza-Darzens reaction and dissolution-filtration operation, a series of optically-pure CF_2-aziridines **4b**–**4h** were furnished in moderate total yields with uniformly excellent ee and dr values, including alkyl or halogen-substituted phenyl and 2-naphthyl ones (Scheme 2). Unfortunately, phenyl glyoxal monohydrates bearing strong electron-withdrawing groups are not compatible with current conditions. X-ray analysis of aziridine **4a** confirmed the absolute configuration of chiral centers, pointing to a *cis*-aziridination process [46].



Scheme 3: Scale-up experiment to **4a** and further synthetic transformations.

Scaled-up experiment with model substrate **1a** also proved to feasible, delivering chiral CF_2-aziridine **4a** with comparable results (Scheme 3a). The 4-methoxyphenyl

group of **4a** was cleaved with ceric ammonium nitrate smoothly, giving free aziridine **5a** in 81% yield with maintained ee value. Reduction of the carbonyl moiety with either $NaBH_4$ or $LiAlH_4$ produced hydroxyl-substituted CF_2-aziridine **5b** in excellent yield with exclusive diastereo-selectivity. Furthermore, ring-opening of **4a** under acidic conditions underwent well and gave rise to CF_2-functionalized α-chloro-β-amino ketone **5c** in 89% yield with >99% ee and >50:1 dr (X-ray confirmed) [46].

Conclusion

In summary, an array of chiral CF_2-functionalized aziridines were constructed from *in situ*-formed aldimines and phenylsulfone difluorodiazoethane under mild conditions rendered by a combined strong Brønsted acid system consisting of chiral disulfonimide and 2-carboxyphenylboronic acid. The optical purity of obtained CF_2-aziridines could be further improved by a practical dissolution-filtration procedure. Substrate expansion and mechanistic investigation are underway and will be reported in due course.

Experimental

General procedure for the preparation of chiral CF_2-aziridines 4: To a 25 mL Schlenk tube equipped with a stirring bar was added 2,2-dihydroxy-1-arylethan-1-one **1** (0.3 mmol, 1 equiv.), 4-methoxyaniline **2a** (40.6 mg, 0.33 mmol), 2-boronobenzoic acid **COOH-BA** (3.98 mg, 0.024 mmol), anhydrous Na_2SO_4 (200 mg) and toluene (1 mL) at room temperature under argon atmosphere. After reaction for 30 minutes at room temperature, the ((2-diazo-1,1-difluoroethyl)sulfonyl)benzene Ps-DFA **3** (104.5 mg, 77.4 uL, 0.45 mmol) was added with Micro syringe and **CDSI-4** (12.3 mg, 0.015 mmol) in toluene (1 mL) was added dropwise. The reaction was allowed to stir for 24 hours at room temperature under argon atmosphere until the consumption of substrates was completed (monitored by TLC). The reaction mixture was quenched with saturated aq. $NaHCO_3$ and extracted with ethyl acetate three times. The combined organic layer was washed with water and brine, and then dried over anhydrous Na_2SO_4, filtered and evaporated under vacuum. The residue was purified by neutral alumina column chromatography (eluting with dichloromethane/petroleum ether) to give CF_2-aziridine **4**. Enantiomeric excess was determined by chiral HPLC analysis.

See the Supporting Information for the dissolution-filtration procedure for each compound.

Supporting Information

Supporting Information File 1

Experimental procedures, compound characterisation, NMR spectra of all new compounds, and HPLC traces.

Acknowledgements

This work was supported by the National Key Research and Development Program of China (2019YFA0905100), National Natural Science Foundation of China (Nos. 21772142, 21901181, and 21961142015), and Tianjin Municipal Science & Technology Commission (19JCQNJC04700).

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46. CCDC 1983642 (**4a**) and 1983643 (**5c**) contain the supplementary crystallographic data. The crystallographic data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.