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Synthesis of Sulfinamidines and Sulfinimidate Esters by Transfer of Nitrogen to Sulfenamides

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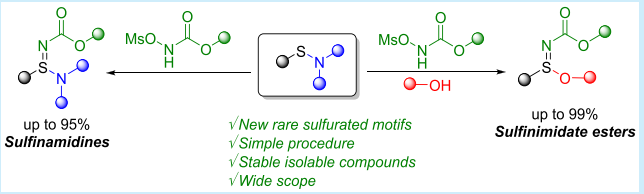
ABSTRACT: In this work we report a new synthetic tactic for the straightforward preparation of hardly accessible sulfinamidines and sulfinamide esters, by using a simple metal-free protocol. The process is robust and uses readily available sulfenamides as the S-donor and sulfonyloxycarbamates as the N-source. The scope and mechanism have also been investigated.



The development of novel synthetic strategies for the installation of sulfur-bearing functional groups has great impact in drug discovery, since these motifs can be found in several biologically active molecules and natural products, and their preparation allows the assessment of interesting bioisosteres.[1] Tetravalent sulfur motifs as sulfones and sulfonamides are well established in pharmaceutics, and recently there has been growing interest in the development of synthetic methodologies for the preparation of their aza analogues such as sulfoximines and sulfonamidamides.[2] In particular, the replacement of the oxygen atom with nitrogen is crucial to the efficient modulation of physicochemical properties and to the introduction of molecular diversity. In striking contrast, the landscape of trivalent sulfur motifs is dominated by sulfoxides, sulfinate esters, and sulfinamides while the preparation of other potentially important trivalent sulfur aza-analogues, such as sulfinimidate esters and sulfinamidines, remains a very poorly explored topic (Figure 1). In fact, synthesis of either sulfinimidate esters or sulfinamidines represents a challenge, and the very few methods available for their preparation have several limitations. Sulfinamidines have been prepared by reaction of sulfurdiimide with conjugated dienes or alkenes (Scheme 1a),[3,4] or by using sodium arylsulfonylchloroamide and disulfides (Scheme 1b).[5] Other strategies with limited scope and versatility have been reported.[6−8]

Ferry reported the use of dialkylaminosulfur trifluorides, amines, and trifluoromethyltrimethylsilane for a specific synthesis of trifluoromethyl-substituted sulfinamidines (Scheme 1c).[9] In spite of their application as ligands, synthetic intermediates, and additives for lithium power sources,[5,6,10] no relevant advances have been reported during the past decades for a general synthesis of sulfinamidines. Furthermore, the preparation and chemistry of sulfinimidate esters remains still severely underdeveloped. Interestingly, only a single case of *N*-tosylmethyloxysulfinimidate, relying on the reaction of *N*-tosyl sulfinamide with diazomethane, has been reported (Scheme 1d).[11] Sulfinimidate esters have been reported as byproducts or as sulfonium salts.[12,13]

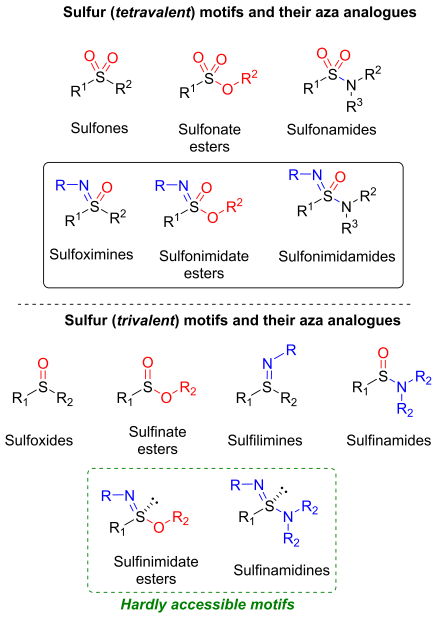


Figure 1. Sulfur-bearing functional groups and their aza analogues.

Regarding the synthesis of aza analogues of sulfurated compounds, the direct imination of the sulfur atom represents

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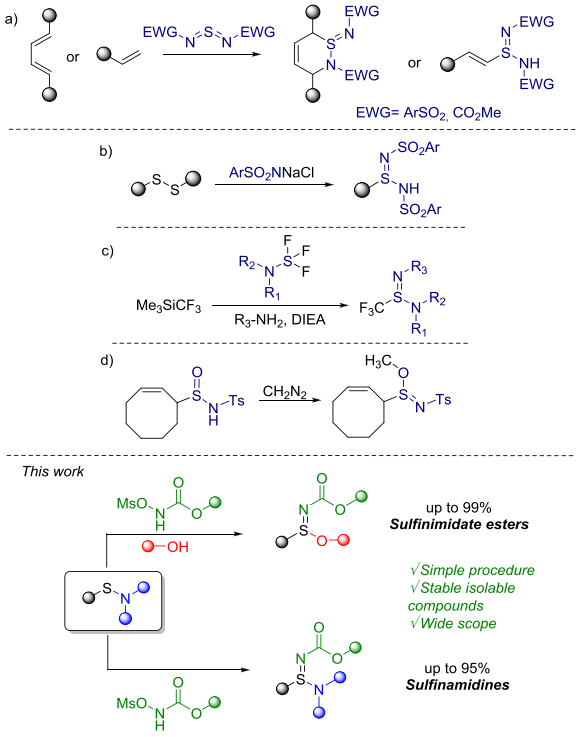
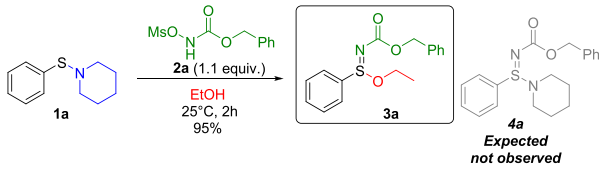
Scheme 1. Strategies To Access Sulfinamidines and Sulfinimidate Esters



an interesting transformation, and important advances have been achieved over the past few years by several research groups.[14] Most of the reported strategies for the imination of thioethers and sulfoxides involve the use of electrophilic aminating reagents, with or without metal catalysis.[14a,15] Moreover, several imination strategies have been developed for the nitrogen transfer on other sulfurated compounds such as sulfenamides, sulfinamides, and thiols.[14g,f,16] In continuation of our interest in the development of strategies for the electrophilic *N*-transfer to the sulfur atom, we became interested in the development of an efficient strategy for accessing extremely rare sulfinamidines and sulfinimidate esters. Herein, we present a robust synthetic methodology to streamline the preparation of such sulfurated motifs offering, for the first time, a widely applicable tactic, overcoming concerns related to the old procedures. Inspired by recent contributions by Lebel and Amstrong, on the use of sulfonyloxycarbamates as nitrene sources for the imination of thioethers, we wanted to explore the reaction of such *N*-donor species with sulfenamides en route to the corresponding sulfinamidines.[15e,17]

Our investigation started with the reaction of methylsulfonyloxycarbamate **2a** with sulfenamide **1a** in EtOH (Scheme 2). With our surprise, we observed a quantitative

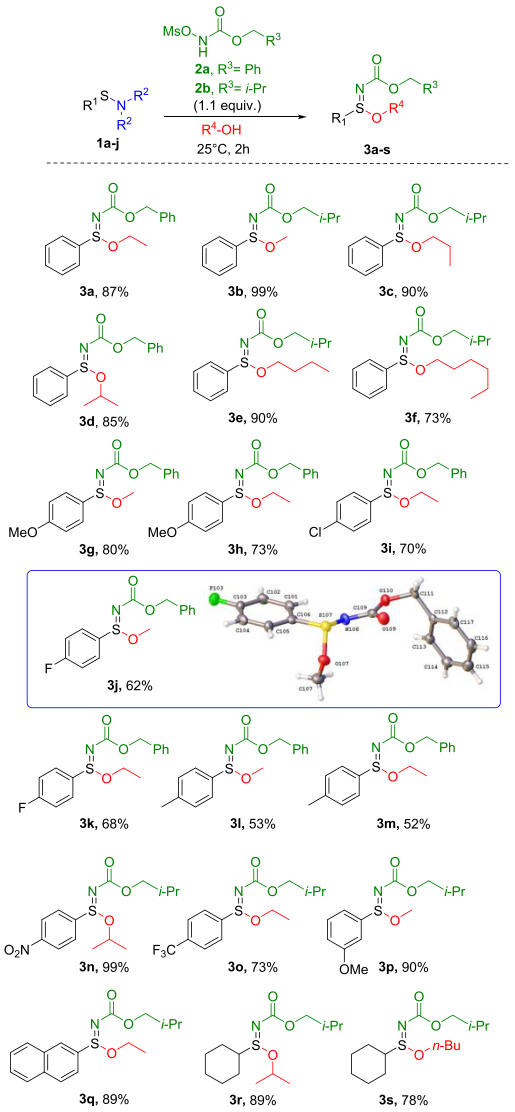
Scheme 2. Preparation of *N*-[(Benzyloxy)carbonyl]phenylsulfinimidate 3a



conversion of **2a** into the corresponding ethyl *N*-((benzyloxy)carbonyl)phenylsulfinimidate **3a** as confirmed by NMR and MS analysis (see Supporting Information (SI)), without evidence of the expected sulfinamidine **4a**.

However, we considered this result remarkable. In fact, this simple procedure would have allowed the preparation of not easily accessible sulfinimidate esters. With the aim to further explore the reaction and validate the method, sulfenamides **1a–j** were reacted with *N*-mesyloxycarbamates **2a** and **2b** in various alcoholic solvents (Scheme 3). To our delight,

Scheme 3. Scope for Sulfinimidate Esters 3



sulfinimidate esters **3a–3s** were isolated in good to excellent yields. These results suggest that both **2a** and **2b** act as suitable electrophilic nitrogen sources in the reaction with sulfenamides.

Moreover, the method tolerated different substituents on the aromatic ring of the sulfenamide such as *p*-Cl (**3i**), *p*-F (**3j** and **3k**), *p*-NO_2 (**3n**), and *p*-CF_3 (**3o**). Similarly, the presence of electron-donating groups such as *p*-OMe (**3g** and **3h**), *p*-Me (**3l** and **3m**), and *m*-OMe (**3p**) allowed the preparation of the products in good yields. The method was also compatible with different aromatic and aliphatic S-substituents. The reaction

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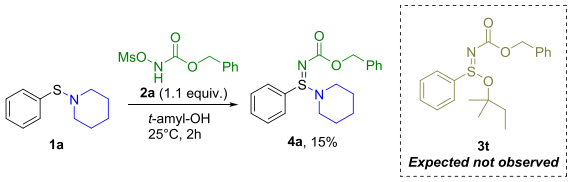
proceeds efficiently with naphthyl-substituted sulfenamide **1j**, giving sulfinimidate ester **3q** in 89% isolated yield, and with aliphatic sulfenamide **1j**, leading to derivatives **3r** and **3s** in good yields (Scheme 3). It should be noted that the reaction proceeds with piperidine-, pyrrolidine-, and morpholine-substituted sulfenamides, and several primary and secondary alcohols can proceed toward the formation of the corresponding sulfinimidate esters. The structures of these unusual sulfur derivatives were assigned on the basis of NMR and HMRS analysis, and in the case of **3j** the structure was confirmed by X-ray analysis. Interestingly, the crystal structure of sulfinimidate ester **3j** revealed an almost pyramidal sulfur atom, with bond angles in the range 99°−111° and bond lengths of 1.78 Å (C−S), 1.62 Å (S−O), and 1.59 Å (S═N) respectively.[18] However, the reaction must comply with steric requirements, since the use of *tert*-amyl alcohol did not allow for the preparation of the corresponding sulfinimidate ester **3t** from sulfenamide **1a** even in traces (Scheme 4). Much to our

Scheme 4. First Evidence for Sulfinamidine

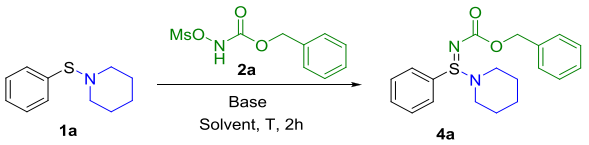


surprise, we were able to isolate the benzyl-(phenyl(piperidin-1-yl)-λ^4-sulfanylidene)carbamate **4a** in 15% yield. The structure of **4a** was initially assessed based on NMR, IR, and HRMS analysis.

Encouraged by this preliminary result, we persevered in our search for an efficient synthetic strategy for the preparation of sulfinamidines. First, we initiated an optimization study for the reaction of sulfenamide **1a** with **2a** as the nitrogen source (Table 1).

Sulfinamidine **4a** was obtained in 20% yield when equimolar quantities of **1a** and **2a** were stirred in toluene at room temperature for 2 h (Table 1, entry 1). However, raising the

Table 1. Optimization Study for the Preparation of 4a

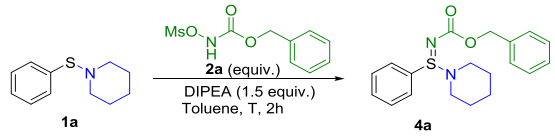


Entry	Solvent	T (°C)	Base (equiv)	**2a** (equiv)	**4a** yield[a]
1	toluene	25	–	1.0	20%
2	toluene	60	–	1.0	–
3	toluene	25	K_2CO_3 (1.5)[b]	1.0	35%
4	toluene	25	DIPEA (1.5)	1.0	38%
5	toluene	50	DIPEA (1.5)	1.2	53%
6	CH_2Cl_2	0	K_2CO_3 (1.5)[b]	1.0	21%
7	CH_2Cl_2	25	K_2CO_3 (1.5)[b]	1.0	35%
8	CH_2Cl_2	0	K_2CO_3 (1.5)[b]	1.3	29%
9	CH_2Cl_2	25	K_2CO_3 (1.5)[b]	1.3	43%
10	2-MeTHF	25	K_2CO_3 (1.5)[b]	1.0	–
11	MeOH	25	K_2CO_3 (1.5)[b]	1.0	traces

[a]Yields calculated by ^{1}H NMR analysis of the crude reaction mixture in the presence of internal standard. [b]An aqueous solution of K_2CO_3 was employed.

temperature up to 60 °C resulted in decomposition of the reactants (Table 1, entry 2). Assuming that a base would have been required in this process, we ran the reaction in the presence of 1.5 equiv of aqueous K_2CO_3 or DIPEA (diisopropylethylamine). Under these conditions (Table 1, entries 3−4), **4a** was obtained in 35% and 38% yield, respectively. The yield of **4a** improved up to 53%, using 1.2 equiv of **2a** at 50 °C in toluene (Table 1, entry 5). Similar results were obtained for the reaction in CH_2Cl_2 (Table 1, entries 6−9), while complex mixtures were observed in polar solvents such as 2-MeTHF or MeOH (Table 1, entries 10−11). With the aim to improve yields of **4a** and accelerate the optimization study, a Design of Experiment (DoE) approach was applied to this process. The equivalents of **2a** and the temperature were selected as the main variables, since such factors appeared to be critical for the reaction. Therefore, a full factorial 2^2 design (see SI. for details) was selected, and the reactions were performed in toluene in the presence of 1.5 equiv of DIPEA (Table 2).

Table 2. DoE Optimization Study for the Preparation of 4a



Entry	**2a** (equiv)	T (°C)	**4a** yield[a]
1	1.6	0	45%
2	1.9	0	53%
3	1.6	25	73%
4	**1.9**	**25**	**95%**

[a]Yields calculated by ^{1}H NMR analysis of the crude reaction mixture in the presence of internal standard.

Remarkably, sulfinamidine **4a** could be obtained in 95% yield carrying out the reaction at 25 °C, and with the use of 1.9 equiv of **2a**. With the optimal conditions in hand, the scope of the reaction was explored (Scheme 5). Sulfenamides **1a−k** were reacted with N-sources **2a** and **2b** under the optimized conditions resulting in the formation of the corresponding sulfinamidines **4a−m** in good to excellent yields. The reaction leading to **4a** was scaled to 2 mmol, and the corresponding sulfinamidine crystallized. With our delight, X-ray analysis confirmed the structure of **4a** and revealed a pyramidal sulfur atom with angles in the range 99°−111° and bond lengths of 1.62 and 1.68 Å for S−N double and single bonds respectively, and 1.78 Å for the C−S bond.[19] The reaction tolerated both electron-withdrawing (i.e., **4d,f**, **4g,h**) and electron-donating groups (i.e., **4c**, **4i,j**) as well as the naphthyl group (**4k**) and aliphatic S-substituents (**4l,m**). However, the transformation of ((cyclohexyl)thio)morpholine **1j** required longer reaction times (24 h), affording the products in excellent yields. Similarly, when 1-((4-nitrophenyl)thio)piperidine **1f** was reacted, the reaction mixture was stirred for 24 h before the total consumption of sufenamide was observed. Remarkably, the use of commercially available NH-sulfenamide **1k** returned the corresponding sulfinamidines **4n** and **4o** in good yields. However, the preparation of this kind of scaffold would require multistep synthesis.[20]

After assessing the methods for the preparation of either sulfinimidate esters **3** and sulfinamidines **4**, we turned our attention to the mechanism of the reaction. To this end, we

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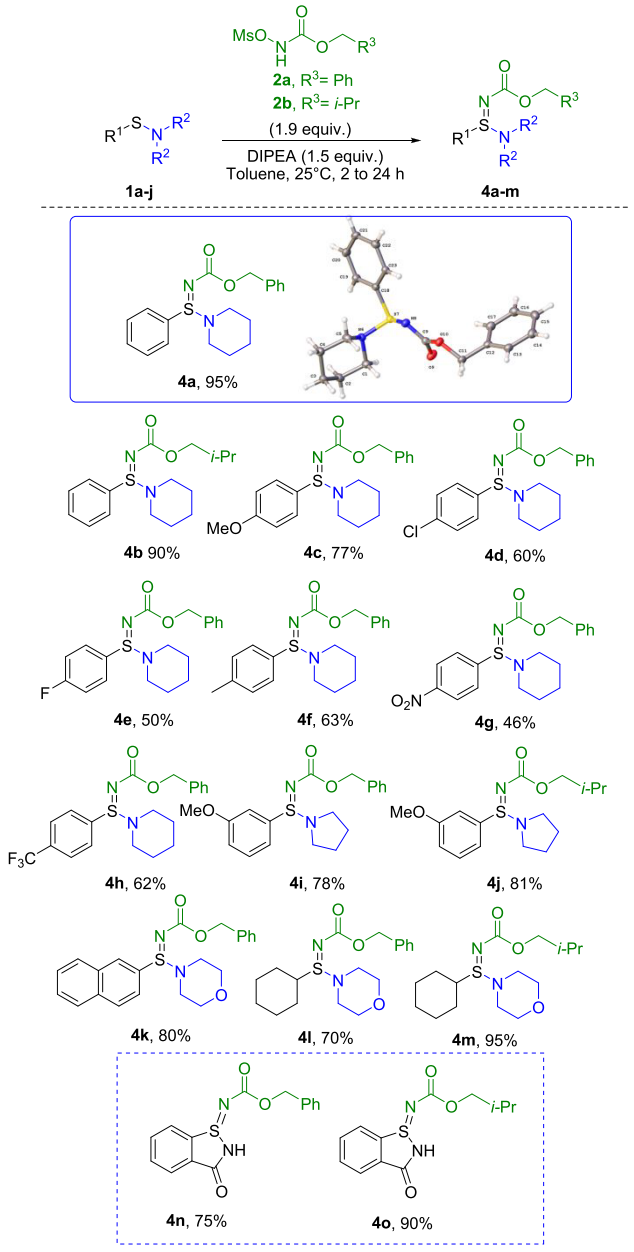
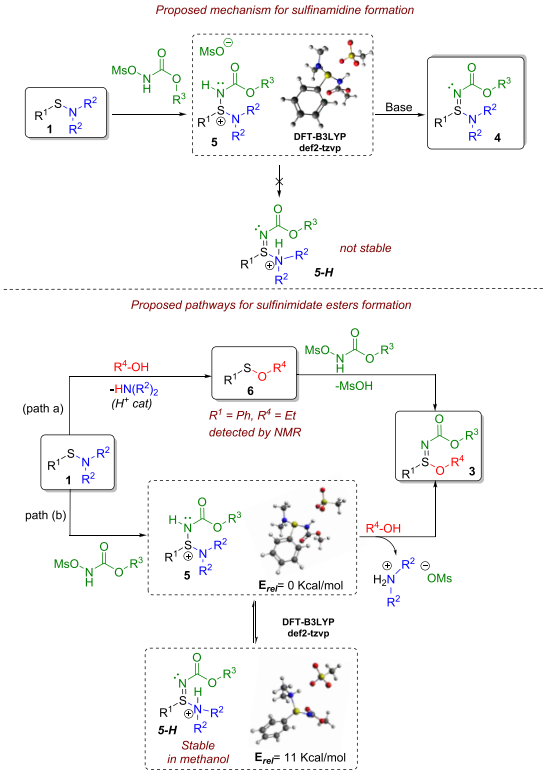
Scheme 5. Scope for Synthesis of Sulfinamidines 4



performed an NMR investigation conducting the reaction in an NMR tube (see SI). First, we studied the formation of sulfinamidine **4a** by monitoring the reaction with sequential ^{1}H NMR analysis. This study revealed a quick reaction between **2a** and **1a** with an almost instantaneous formation of an intermediate species, likely the salt **5** (Scheme 6). Subsequently, the addition of DIPEA to the solution cleanly afforded sulfinamidine **4a**. A slightly different situation was observed in the case of sulfinimidate ester **3a**. In fact, the outcome of the experiments depended on the adopted reaction conditions. The NMR investigation revealed a competition in the formation either of **4a** or **3a** and that the presence of the alcohol was crucial to improve the reaction time and selectivity. It was observed that in the presence of the alcohol and traces of acid, sulfenamide **1a** was partially converted into a sulfenate ester (**6**, Scheme 6). Upon addition of the N-source **2a**, conversion of ester **6** into the sulfinamidate ester **3** occurred. Based on our mechanistic investigation, we proposed the

Scheme 6. Proposed Mechanisms



pathways depicted in Scheme 6 to explain the formation of derivatives **3** and **4**. To further support our hypotheses, the reaction was investigated computationally *in silico* on a model system using the DFT-B3LYP method with the def2-tzvp basis set (see SI).

Computational results suggested that the substitution reaction leading to intermediate **5** (Scheme 6) is an exothermic process, with a calculated enthalpy $\Delta H = -94.9$ kJ/mol (see SI). In addition, a proton transfer forming **5H** was ruled out by calculations. It is reasonable that adducts similar to **5** give sulfinamidines **4** when reacted under basic conditions. Our attention was subsequently focused on the elucidation of the mechanisms for the formation of sulfinimidate esters **3**. The NMR study suggested that the reaction can follow different pathways. Sulfinimidate esters may arise by direct immination of sulfenate ester **6** (path a, Scheme 6) or from a solvent-induced (R^4OH) displacement of the aminic portion on intermediate **5** or **5-H**, after proton exchange between the carbammic and aminic nitrogen, followed by the final deprotonation (path b, Scheme 6). On the other hand, the proton exchange may be promoted by the solvent proximity in a concerted transformation. Such hypotheses are supported by calculations that revealed a minimum for **5-H** in methanol, although this is less stable than **5**, while intermediacy of a tetrahedral intermediate was ruled out by calculations. In conclusion, in this work we reported a new synthetic route for the straightforward preparation of hardly accessible sulfinamidines and sulfinamide esters using a simple metal-free procedure. The mechanism has been investigated spectroscopically and computationally and proposed. The process is robust and provides stable trivalent sulfur derivatives that could be used as precursors of other interesting sulfur derivatives such as sulfonimidates, sulfoximines, and sulfonimidamides.[21] Further

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investigations are ongoing in our lab and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02471.

Characterization data for the prepared molecules, list of sulfenamides, optimization study by DoE, mechanistic study, DFT-calculations, Ortep views of crystal structures (PDF)

Accession Codes

CCDC 2016492−2016493 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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Author Contributions

⊥M.A. and M.S. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Prof. Saverio Florio on the occasion of his 80th birthday.

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