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Merging hypervalent iodine and sulfoximine chemistry: a new electrophilic trifluoromethylation reagent†

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Electrophilic trifluoromethylation is at the forefront of methodologies available for the installation of the CF_3 moiety to organic molecules; research in this field is largely spurred by the availability of stable and accessible trifluoromethylation reagents, of which hypervalent iodine and sulfoximine based compounds have emerged as two prominent reagent classes. Herein, we describe the facile synthesis of an electrophilic trifluoromethylation reagent which merges these two scaffolds in a novel hypervalent iodosulfoximine compound. This presents the first analogue of the well-known Togni reagents which neither compromises stability or reactivity. The electronic and physical properties of this new compound were fully explored by X-ray crystallography, cyclic voltammetry, TGA/DSC and DFT analysis. This solution stable, crystalline reagent was found to be competent in the electrophilic trifluoromethylation of a variety of nucleophiles as well as a source of the trifluoromethyl radical. Furthermore, the possibility of enantioinductive transformations could be probed with the isolation of the first enantiopure hypervalent iodine compound bearing a CF_3 group, thus this new reagent scaffold offers the opportunity of structurally diversifying the reagent towards asymmetric synthesis.

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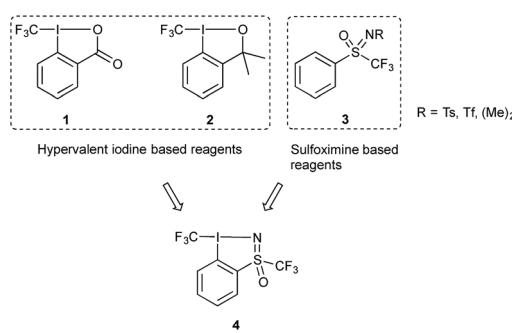
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Introduction

The unique properties imbued by the trifluoromethyl group to organic molecules has made this motif ubiquitous in compounds of interest in pharmaceutical, agrochemical and materials research.¹ Its introduction often leads to changes in the chemical, biological and physical properties of a given compound; for example, lipophilicity and membrane permeability of drug candidates are improved. Furthermore, the energetic cost of breaking the C–F bond compared to other C–heteroatom bonds means that fluorinated compounds display enhanced chemical stability. The accessibility of this group is largely dependent on the development of CF_3 transfer reagents, which can be classified according to their nucleophilic, electrophilic or radical character. The utility of

nucleophilic trifluoromethylation reagents, exemplified by trifluoromethyltrimethylsilane (TMSCF_3), has been expansively studied, however the need for differential functional group tolerance has spurred extensive research in the development of electrophilic trifluoromethylation reagents.²

One prominent class of electrophilic trifluoromethylating reagents are hypervalent iodine compounds **1** and **2** (Fig. 1), first reported by one of our groups in 2006.³ Reagents **1** and **2**, have been used to transform a wide variety of nucleophiles, for the generation of new C–, N–, O–, P–, or S– CF_3 bonds. In many cases this process corresponds to a substitution of a hydrogen atom by the CF_3 group. Synthetically and commercially, reagents **1** and **2**



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Fig. 1 Known electrophilic fluoroalkylation reagents, **1**, **2** and **3** and newly designed hypervalent iodosulfoximine reagent **4**.



are readily accessible as crystalline shelf-stable compounds, resulting in vigorous research efforts by one of our groups and others towards utilizing them in disparate applications. This research has received particular attention, given the increasing interest of the synthetic community for new methodologies in organofluorine chemistry. The activation of **1** and **2** can be achieved using Brønsted or Lewis acids which increases their electrophilic or iodonium-like character, thus matching the electrophilic character of the reagent to the nucleophile.^{3c,4} One of our groups recently reported the activation of reagent **2** with TiCl_4 which enabled the trifluoromethylation of sulfonate salts, a transformation which is otherwise difficult to achieve.^{4b}

Another class of electrophilic fluoroalkylating reagents are sulfoximine based compounds of type **3** (Fig. 1).⁵ They have been successfully employed for the introduction of trifluoro- and monofluoromethyl groups by Shibata and coworkers,⁶ difluoromethyl by the groups of Hu⁷ as well as Olah and Prakash,⁸ and for bromodifluoro- and dichlorofluoromethyl by one of our groups.⁹ In 2012, Hu and coworkers greatly expanded the field of application of perfluoroalkylated sulfoximine reagents by showing that mono- and difluoromethyl derivatives can also be efficient reagents for the nucleophilic transfer of perfluorinated entities.¹⁰ More recently, Akita and coworkers have published the use of the same reagent as a source for generating difluoromethyl radicals.¹¹ One year later, one of our groups extended this methodology to other perfluoroalkyl radicals including the trifluoromethyl group.¹² One important property of these compounds is the ease with which they can be structurally diversified and their properties finely tuned for targeted applications.

Given the growing body of research in new trifluoromethylating reagents based on compounds of the type shown in Fig. 1, we were interested in merging these two scaffolds to generate a new reagent, resulting in the design of compound **4**. Vastly altering the scaffold of **1** and **2** has been investigated in our labs and others, however in most cases these modifications either resulted in diminished reactivity, product instability, or proved difficult to synthetically access.¹³ One such example saw the introduction of a *para*- NO_2 group on compound **1**, which resulted in reduced solubility and instability under acidic reaction conditions.^{13d} In 2018 an acyclic chloro(phenyl)trifluoromethyliodane reagent was reported, which showed similar reactivity to **1** and **2**.^{13e} Previous attempts at synthesising this compound by Yagupolskii and Umemoto proved challenging, presumably due to the lack of stability of the acyclic structure.¹⁴ The reported compound was found to be stable as a solid, but substantial degradation was observed in commonly used solvents, for example 65% decomposition in $\text{MeCN-}d_3$ after 1 day. This finding suggests cyclic hypervalent iodine compounds such as **1** and **2** are more stable in solution compared to acyclic analogues. A further challenge in trifluoromethylation chemistry that has yet to be addressed is the introduction of chirality onto the reagent scaffold,^{13b} in order to enable the synthesis of enantioenriched trifluoromethylated substrates. Given the chirality of the sulfoximine group in **3**, we anticipated that reagent **4** could be used to investigate enantioinductive transformations.

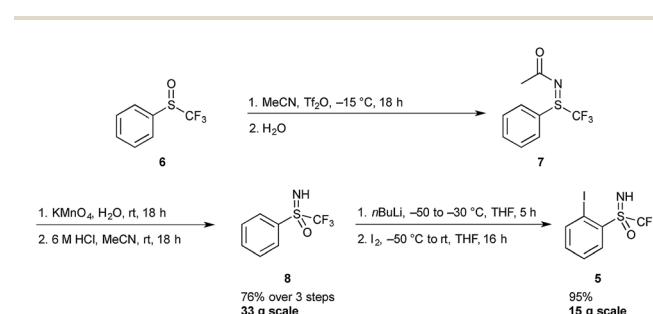
In this paper we describe the synthesis and characterization of an enantiopure, hypervalent iodosulfoximine compound **4** which is also an efficient trifluoromethylating reagent. To the best of our knowledge, this is the first example of a hypervalent iodine bonded to the nitrogen of a sulfoximine moiety incorporated into the 5-membered heterocyclic ring. The properties of compound **4** were investigated by X-ray crystallography, cyclic voltammetry, TGA/DSC and DFT. We conducted a comparative reaction screening which shows that in most cases reagent **4** reacts in a very similar fashion to reagent **1** and **2**, a very gratifying finding as this is the first successful modification of the original iodine(III) reagents which does not significantly impact reactivity or reduce stability.

Results and discussion

Reagent design and synthesis

A sulfoximine substituent on the aromatic ring *ortho* to the iodine center was expected to have a strong enough electron withdrawing character to stabilize the 3-centre 4-electron hypervalent iodine bond. Hypervalent iodine compounds bearing a sulfoximine group have previously been reported by Bolm and co-workers, however the reported compounds were designed for the transfer of the sulfoximine moiety, and hence not a part of the 5-membered heterocycle.¹⁵

Synthetic accessibility to iodine(I) reagent precursor **5** has previously been reported by the Versailles lab, starting from phenyl trifluoromethyl sulfoxide **6** (Scheme 1).¹⁶ This three-step procedure involves the preparation of a sulfilimine **7** (*via* a Ritter-like process), its subsequent oxidation and final N-deprotection sequence to deliver the sulfoximine **8**. This protocol can be safely followed on a multi-gram scale, allowing for the preparation of 33 g of **8**.¹⁷ In the next step, the trifluoromethylsulfoximine group acts as an *ortho*-directing substituent and various electrophiles can be introduced. Thus, *ortho*-lithiation followed by quenching with excess iodine gave the iodoarene **5** in excellent yields on a 15 g scale.¹⁸ In a more recent report, sulfoximine **8** could be accessed *via* a one-pot protocol starting from commercially available phenyl trifluoromethyl sulfide, using phenyliodine diacetate and ammonium carbamate followed by acid hydrolysis. Application of this method gives compound **5** in two steps as opposed to three, however large scale synthesis *via* this route has not yet been established.¹⁹



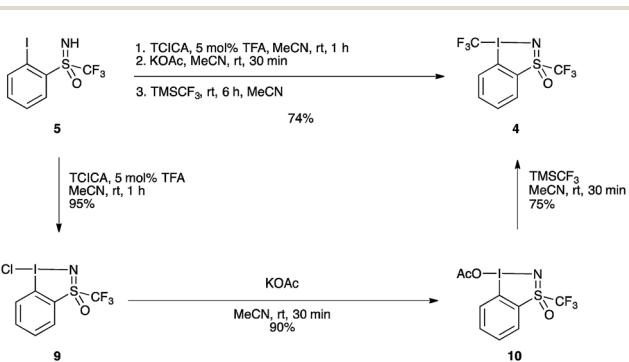
Scheme 1 Synthesis of iodosulfoximine compound **5**. Tf_2O = trifluoromethanesulfonic anhydride.



The improved one-pot procedure for the synthesis of reagent **1** was then successfully applied to iodosulfoximine **5** (Scheme 2), allowing for the isolation of reagent **4**.²⁰ Oxidation is first achieved using trichloroisocyanuric acid (TCICA) and 5 mol% trifluoroacetic acid (TFA) as a Brønsted acid catalyst,²¹ which facilitated the reaction at room temperature. After one hour, complete conversion to the chloroiodane **9** was confirmed by ¹⁹F NMR, and a subsequent ligand exchange at the iodine atom with potassium acetate was also found to be facile at room temperature with full conversion in 30 minutes. This is in contrast to the conditions reported for the synthesis of **1**, which involved heating at reflux for both the oxidation and ligand exchange steps. Finally, a second ligand exchange with TMSCF₃ gave **4** in excellent yield (74%) over the three steps. Reagent **4** could be purified by recrystallization from a mixture of pentane/MeCN/Et₂O (see ESI for details†), a simplified protocol compared to that reported previously for **1** and **2**.²⁰ The one-pot protocol could also be applied on a 10 g scale to give compound **4** in 75% (see ESI for detailst†). This yield compares well with that of the synthesis of **1**, which can be obtained in 72% over three-steps from 2-iodobenzoic acid, and is improved compared to the four-step protocol for the synthesis of **2** which can be obtained in 67% yield from methyl 2-iodobenzoate.²⁰

Additionally, the intermediate chlorinated and acetylated iodine(**iii**) precursors could be isolated in excellent yields, 95% for chloroiodane **9** and 90% for **10** (starting from **9**) following the standard procedures (see ESI for details[†]).²⁰ Reagent **4** could be accessed from isolated compound **10**, albeit with no improvement of yield compared to the one-pot protocol starting from **5**. It is worth noting the presence of a trifluoromethyl group linked to the sulfur atom is crucial as the same transformation with the S-methyl sulfoximine failed (see ESI, Scheme S1[†]).

Given the chirality of the sulfoximine group on the reagent scaffold, we envisaged taking advantage of this property for the preparation of an enantiopure reagent. We were pleased to find that the iodosulfoximine 5 could be separated by preparative chiral HPLC using a Chiralpak AS-H column and hexane/isopropanol (80/20) as mobile phase on a 2 g scale. The separated enantiomers were configurationally stable on the bench as confirmed by analytical chiral HPLC after several weeks. With the stable enantiomeric form of (+) and (-)-5 in hand we proceeded to synthesize the enantiopure form of (-) and (+)-4



Scheme 2 Synthesis of hypervalent iodosulfoximine reagent 4. TCICA = trichloroisocyanuric acid, TFA = trifluoroacetic acid.

respectively (see ESI for optical rotation values†). Gratifyingly, the one-pot protocol for the preparation of reagent 4 preserved the absolute configuration of the sulfur atom as confirmed by analytical chiral HPLC, which gave a single peak suggesting no epimerization had occurred. Furthermore, good quality single crystals that were used for an X-ray diffraction study of the structure of chloroiodane $(-)$ -9 could be obtained by slow evaporation of a dichloromethane solution, thereby determining the absolute configuration to be (S) - $(-)$ -9 (Fig. 2).

Tautomerization of chlorinated 5-

Interestingly, during our first attempts at oxidizing the iodine center with TCICA using the original conditions reported for the synthesis of **1** and **2** without use of a Brønsted acid catalyst, an unexpected product was obtained. We found that conducting the reaction at room temperature with 0.34 eq. of TCICA gave a mixture of products, the desired cyclic structure **9** and another product characterized by a new peak in the ^{19}F NMR spectrum at -63.89 ppm in $\text{MeCN-}d_3$. We assigned this new compound to an acyclic N-chlorinated structure **9'**. Furthermore, we found that conducting the reaction at -20 $^\circ\text{C}$ gave a mixture of $99 : 1$ of **9'** to **9**, and slow irreversible transformation of **9'** into **9** could be observed at room temperature over 12 hours. Hence, **9'** is the kinetic product for the chlorination with TCICA, with **9** being the thermodynamically favoured tautomer (Scheme 3).

The structure of N-chlorinated compound **9'** could be confirmed by NMR and HRMS analysis, crystal structural analysis was inaccessible as compound **9'** tautomerizes to **9** in solution at low temperatures as well as in the solid state. To further corroborate the acyclic structure of **9'** we compared the obtained NMR data with that of the newly synthesized and previously reported compounds (see ESI, Table S1†). The Versailles lab has recently reported the synthesis of an N-chlorinated sulfoximine analogue of **8** *via* the same method,²² and the ¹⁹F NMR signal of this compound was reported to be at -68.19 ppm in $\text{MeCN-}d_3$, which is a 4 ppm difference to that of **9'**. Analysis of the ¹⁹F NMR chemical shifts of the synthesized cyclic reagents **4**, **9** and **10** showed a 13 ppm difference between the signal of acyclic **9'** and that of the cyclic structures (which

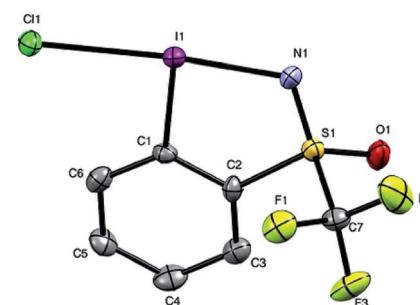
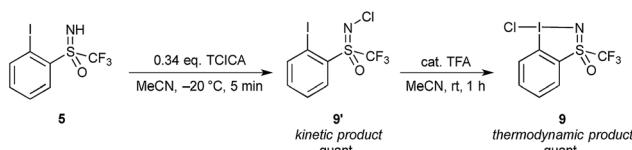


Fig. 2 Structure of (S)-(-)-chloriodane, **9**, as determined by X-ray diffraction. Selected bond lengths and angles: I1–Cl1: 2.576(2) Å; I1–N1: 2.102(6) Å; N1–S1: 1.498(8) Å; angle: Cl1–I1–N1: 174.9(2)°; C1–I1–Cl1: 89.5(2)°; C1–I1–N1: 85.4(3)°; torsion: C6–C1–I1–Cl1: 5.1(7)°; C2–C1–I1–N1: 3.3(6)°. H atoms are omitted for clarity; thermal ellipsoids given at 50% probability



Scheme 3 Oxidative chlorination of 5 with TCICA giving *N*-chlorinated compound 9' which tautomerizes to cyclic chloroiodane 9.

are in -77 ppm region). Additionally, to confirm this acyclic structure we examined the ^{13}C NMR shifts for the carbon atom bound to iodine on the aromatic ring, C_{ipso} (see ESI, Table S1 \dagger) which gives a distinct chemical shift depending on the oxidation state of the iodine atom. In iodine(i) compounds the $ipso$ -carbon is strongly shielded as a result of relativistic effects, which is reduced in iodine(III) and iodine(V) species. 23 This trend is observed in both cyclic and acyclic variants of oxidized iodine species and is not impacted strongly by the nature of the ligands at the iodine atom (see Table S1 in ESI \dagger). 23 When comparing the ^{13}C NMR shifts of the new and previously synthesized compounds we found that derivatives of iodine(i) gave a signal in the 95 ppm region, whilst iodine(III) species had a ^{13}C NMR chemical shift of 110 – 122 ppm for C_{ipso} , a significant difference of 15 – 27 ppm.

The instability of *N*-chloroamides and their use as oxidants in organic synthesis is well described; *N*-chloroamides such as TCICA and *N*-chlorosuccinimide are known to undergo reactions with amines *via* Cl^+ oxidation, hence it is unsurprising to find that TCICA reacts preferentially with the imine moiety. 24 To probe the mechanism of the tautomerization process we monitored the reaction profile by ^{19}F NMR spectroscopy (see ESI for details \dagger). The rate of decay of 9' and the rate of formation of 9 was found to be the same. Increasing the concentration or the temperature accelerates the tautomerization process, with the fastest reaction rates observed with the addition of TFA at room temperature. Furthermore, an induction period was seen at various temperatures and concentrations, with no intermediate observed and only traces ($<1\%$) of by-products identified in the ^{19}F NMR spectrum. Given the sigmoidal curve for the reaction profile, which is characteristic of autocatalytic processes, we could rule out such a mechanism by addition of 10 mol% of product 9 to a mixture of 5, which was found to have the same reaction profile as the same reaction mixture without the addition of compound 9 (see ESI for details \dagger). Since many chlorination reactions using *N*-haloamides have been proposed to occur *via* formation of radical species such as variations of the Hofmann–Löffler–Freytag reaction, 25 we explored this possibility by conducting the reaction in the absence of light, but found the reaction to proceed; EPR studies of the reaction mixture also gave no signal for radical intermediates. Kinetic studies conducted thus far have proved inconclusive. However, from these qualitative findings we could rule out covalent isomerization processes where the Cl atom migrates from nitrogen to iodine or bimolecular transition states involving two 9' molecules, where Cl atom transfer occurs in a concerted fashion, as these would show first or second order reaction

profiles respectively. One suggestion for the mechanism by which this occurs would be that the reaction proceeds *via* an ionic mechanism involving an iodonium [8-*I*-2] species, these intermediates have been previously reported to form *via* a dissociative mechanism from [10-*I*-3] compounds. 26 Further investigation of this unusual reaction mechanism is underway in our laboratories.

Structure and properties

In order to get a full understanding of the stability and reactivity of 4, we performed several analytical measurements. TGA/DSC analysis revealed no melting event to occur before the onset of rapid thermal decomposition at 146.3 °C within a short temperature window. A similar observation was made in previous reports for compound 1. 27 The solution stability of the reagent was checked in several solvents. After 1 day traces of decomposition products ($<5\%$) were observed in methanol- d_4 and 15% after 4 days, similarly 8% decomposition was observed after 4 days in CDCl_3 , but the compound was stable in $\text{MeCN-}d_3$ for 1 week, and only traces ($<5\%$) of decomposition products were observed in acetone- d_6 after 1 week. Thus, the reagent is stable in commonly used solvents for trifluoromethylation reactions for extended periods, and the minor decomposition observed is indicative of its reactivity.

Good quality single crystals of compound 4 for X-ray diffraction could be obtained by slow evaporation of a dichloromethane solution (Fig. 3). The structural features of this new reagent were compared with that of compounds 1 and 2 (Table 1). 3a,b The I1-N1 bond of compound 4 is elongated relative to the I1-O1 bond of reagent 2 ($2.284(2)$ in 4 *vs.* $2.1176(14)$ Å in 2) and is the same as that of compound 1 ($2.283(2)$ Å), indicating that the carboxylate and sulfoxime moieties have similar electron withdrawing properties. This trend is reversed when looking at the I1-CF_3 bond lengths, which is shortest in compound 1 (2.219 Å), with similar bond lengths observed for compounds 2 and 4 ($2.267(2)$ and $2.250(3)$ Å respectively). Interestingly, the lengthening of the I1-N1 bond in the sulfoxime reagent does not coincide with a significant shortening of the I1-CF_3 bond length which is typically

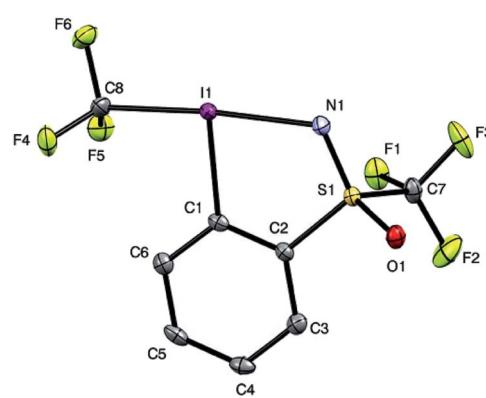
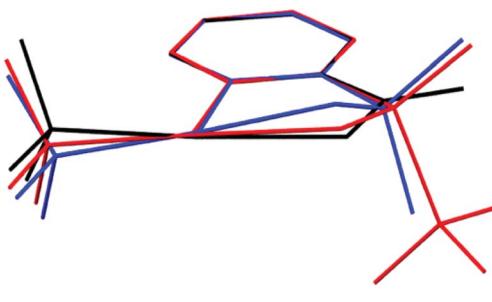


Fig. 3 Structure of hypervalent iodine compound 4 (see Table 1 for structural properties). H atoms are omitted for clarity; thermal ellipsoids given at 50% probability.



Table 1 Comparison of bond lengths and angles in reagents **1**, **2** and **4** obtained from single crystal X-ray diffractionStructural overlap of **1** (black), **2** (blue) and **4** (red)

	Reagent 1 ^a	Reagent 2 ^a	Reagent 4
I1-X1	2.283(2)	2.1176(14)	2.284(2)
I1-CF ₃	2.219(4)	2.267(2)	2.250(3)
I1-C1	2.113(3)	2.1211(19)	2.132(2)
X1-I1-CF ₃	170.49(12)	169.78(7)	173.35(9)
C1-I1-X1	76.79(11)	78.71(6)	82.73(8)
C1-I1-CF ₃	93.74(14)	91.11(8)	91.76(9)
X1-I1-C1-C2	0.3(2)	11.56(15)	4.6(2)
F3C-I1-C1-C6	0.7(3)	13.21(18)	10.1(2)

^a Data for reagent **1** and **2** taken from the literature.^{3a,b} X = O1 or N1.

observed in cyclic hypervalent iodine structures of this type. The CF₃-I1-N1 bond angle in the sulfoximine reagent (173.35(9) $^{\circ}$) is closer to 180 $^{\circ}$, compared to the I1-C8-O1 bond angles of reagents **1** and **2** which are around 170 $^{\circ}$, a consequence of the large N1-S1 bond length (1.482(2) \AA). Furthermore, structural overlap of the three compounds (Table 1) highlights the distortion of the torsion angles N1-I1-C1-C2 (4.6(2) $^{\circ}$) and C8-I1-C1-C6 (10.1(2) $^{\circ}$) in **4** out of plane of the phenyl group, which is not as pronounced as the corresponding angles in compound **2** (11.56(15) $^{\circ}$ and 13.21(2) $^{\circ}$), with **1** being essentially co-planar.

The structural properties of these hypervalent iodine reagents can be loosely related to their reactivity in that a lengthening of the I1-X1 bond length (usually coinciding with the shortening of the I1-CF₃ bond length) results in faster initial rates of reaction when toluene sulfonic acid is used as the model substrate, with **1** showing much faster reactivity than **2**.^{13b} However, this correlation only loosely holds as solid-state bond lengths may not truly reflect solution bond lengths due to crystal packing effects.

Given the novel structure of **4**, we aimed at gaining a deeper understanding of the electronic effects of the sulfoximine moiety on the hypervalent iodine scaffold and how this may compare to the existing reagents. Molecular electrostatic potential (MEP) surfaces were generated for the visualisation of electron density on all three compounds for comparison using the previously reported methods (Fig. 4, see ESI for details[†]).²⁸ Comparing the MEP electron density of the three reagents, a strong polarization towards the ligands is observed in all three compounds, with the calculated dipole moments following the trend: 5.2 D in **1**; 5.1 D in **4**; and 3.0 D in **2**. The electron density

on the heteroatom directly bound to iodine is similar in all three compounds at around –0.05 au. Larger differences are seen in the expression of the “ σ -hole” – a region of positive charge at the iodine atom,²⁸ the most strongly expressed region of positive potential is seen in compound **1** followed by that of compound **4**. These electronic properties have an impact on the strength and directionality of reagent–substrate or reagent–solvent interaction, wherein a nucleophile or polar solvent would be much more strongly coordinated to compounds **1** and **4** compared to **2**.

Finally, cyclic voltammetry experiments were conducted to compare the redox potentials of the new reagent **4** with that of **1** and **2** (see ESI for details[†]). The first cathodic peak potential for reagent **4** vs. [FeCp₂]/[FeCp₂]⁺ was found to be –2.02 V which is similar to that of **1** (–1.91 V vs. [FeCp₂]/[FeCp₂]⁺), compound **2** was found to be the most difficult to reduce with a first cathodic peak potential of –2.42 V under the same conditions. Hence, the cyclic voltammetry data further corroborates the similarity of compound **4** to **1**, both of which are more easily reduced compared to compound **2**.

Reactivity studies

After establishing the structural similarity of this new reagent **4** to the existing trifluoromethylation reagents **1** and **2**, we proceeded to investigate its reactivity. To this aim, we attempted the trifluoromethylation of various S-, C-, O-, and P-centered nucleophiles (Scheme 4), and compared the yields to the previously reported results for **1** and **2**. Trifluoromethylation of sulfonic acids was investigated first (entry 1), as this has been established as a clean and fast reference reaction in one of our labs for testing newly designed reagents.^{13b} To our satisfaction, we found that compound **4** performed comparatively to **1** when camphorsulfonic acid **11** is used as a substrate, giving 92% ¹⁹F NMR yield after 90 minutes for **12**.²⁹ Additionally, iodoarene **5** could be recovered from the reaction mixture, with 70% recovery after column chromatography in the case of entry 1 (Scheme 4), providing the opportunity to potentially re-use the material. Trifluoromethylation of chlorothiophenol **13** gave comparable results, and **14** was obtained in 73% ¹⁹F NMR yield (entry 2); typical yields for the trifluoromethylation of aromatic thiols with reagent **2** have been reported in 72–91% yield.^{3b} Diphenylphosphine **15** (entry 3) also proved to be a viable substrate giving the trifluoromethylated product **16** in 69% yield.³⁰ Oxytrifluoromethylation of styrene **17** (entry 4) gave satisfactory yields of 66% respectively, compared to 93% for the same transformation using reagent **1**.³¹

Inspired by the work of Akita and co-workers, we investigated the visible light induced electrophilic trifluoromethylation of trifluoroborates, **19** and **20**.³² We obtained very favourable results using 1 mol% of [Ru(bpy)₃](PF₆)₂ photocatalyst giving the trifluoromethylated alkene **21** in 86% yield when using 1.2 eq. of **4** for the potassium salt of styryl trifluoroborate (entry 5). The equivalent reaction with **1** is reported in the literature to give a yield of 81% with 5 mol% of the same photocatalyst, however in our hands the ¹⁹F NMR yield for this reaction was 35% after 5 h, and 56% after 15 h. We observed a similar trend



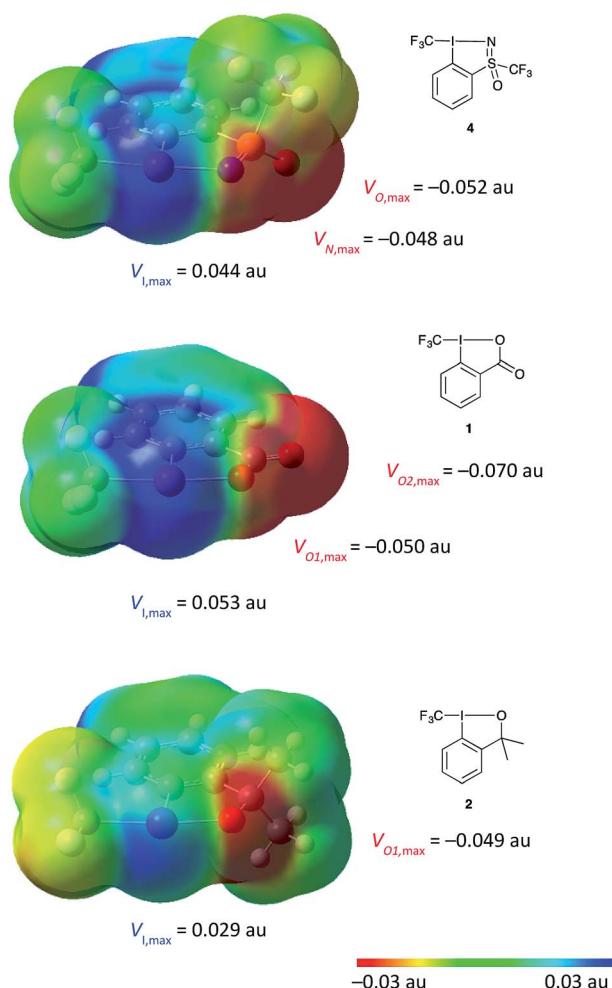
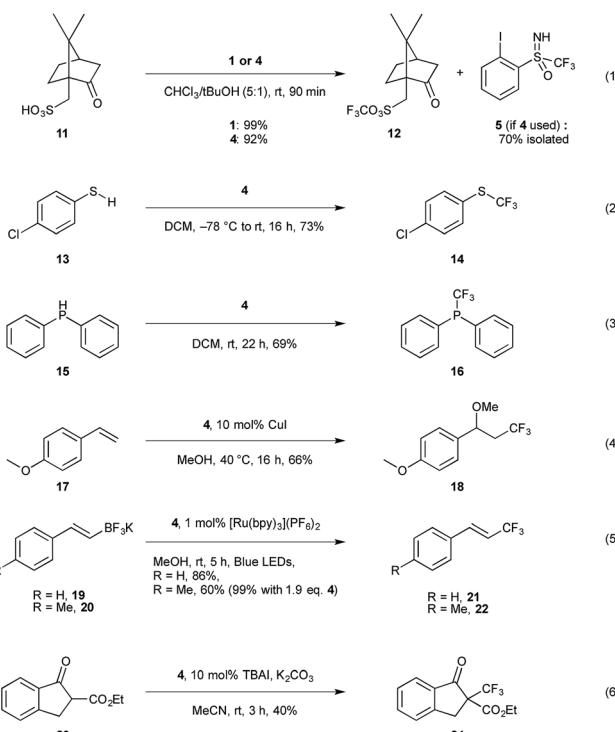


Fig. 4 DFT calculation done at the B3LYP, aug-cc-pVTZ (for H, C, O, N), aug-cc-pV(T+d)Z (for S) and aug-cc-pVTZ-PP (for I). MEP mapped onto the isodensity surface at 0.001 au, within the vdW contact distances containing 96% of molecular electron density (see ESI for details†).²⁸

using *para*-methyl styryltrifluoroborate which, under the literature reported conditions gave only 45% yield for **22** when reproduced in our lab *vs.* 81% reported in the literature with compound **1**. Under the same conditions compound **4** gave 60% yield, which could be further improved to 99% when 1.9 eq. of **4** is used.

Considering reagent **4** is reminiscent of Shibata's fluorinated Johnson reagent on the sulfoximine moiety, we were curious to explore whether this could be a second reactive site on the scaffold.⁵ β -Keto ester **23** was chosen as a model substrate as this is known to react with Shibata's reagent to give the trifluoromethylated product **24** in 74% yield.^{5a} Using the literature reported conditions, with 1.5 eq. of **4**, DBU (1,8-diazabicyclo[5.4.0]undec-7) as base in CH_2Cl_2 and stirring for 2 h, only 29% ^{19}F NMR yield of **24** was obtained. The ^{19}F NMR of the reaction mixture showed 73% of unreacted **4** as well as 30% iodoarene **5** and 42% sulfoximine **8**. Thus, the CF_3 moiety at the iodine was transferred leaving the sulfoximine moiety intact. Stirring the reaction mixture longer did not lead to higher



Scheme 4 Reactivity screening of compound **4** with various nucleophiles. Yields determined by ^{19}F NMR using *o*,*o*,*o*-trifluorotoluene as an internal standard. TBAI = tetrabutylammonium iodide.

yields, however the yield could be improved by conducting the reaction under phase transfer conditions (entry 6), which gave moderate yields of 40%, whereas use of reagent **2** gives the desired product in 67% yield.^{3b}

Finally, we were curious to explore the possibility of using the enantiopure sulfoximine reagent for asymmetric transformations. We first turned our attention to trifluoromethylation of chiral sulfonic acids, as the mechanism for this is well established to occur *via* protonation of the reagent by the substrate and coordination of the sulfonate to the iodine center, followed by reductive elimination to give the corresponding trifluoromethylated sulfonic acid.³¹ In order to enable kinetic resolution, we took 2 eq. of racemic **4** and reacted it under the standard conditions with 1 eq. of (1*S*)-(+)10-camphor sulfonic acid (entry 1, Scheme 4). Once the reaction was complete, the remaining reagent was recovered after recrystallization of the reaction mixture, however no preferential reaction was observed, with 0% ee in recovered **4** observed by analytical chiral HPLC. Although this result was disappointing, we speculated that the stereogenic centre in camphorsulfonic acid was not close enough to the reactive centre to facilitate enantiodiscrimination. We next attempted the trifluoromethylation of β -keto ester **23** under phase transfer conditions (entry 6). However, chiral analytical HPLC analysis of the purified reaction mixture showed only racemic **24**. Although these results have so far proven unsuccessful, we aim to further investigate the possibility of asymmetric transformations by increasing the steric bulk on the sulfoximine group through

substitution of the CF_3 moiety or using Brønsted or Lewis acid catalysts.

Conclusions

In conclusion we have described the facile synthesis of the new hypervalent iodine trifluoromethylation reagent, **4**, which to our delight shows stability and reactivity comparable to those of the parent reagents **1** and **2**. Compound **4** could also be isolated in its enantiopure form and is, to the best of our knowledge, the first described enantiopure hypervalent iodine compound bearing a transferable CF_3 moiety. This is a promising start to explore the possibility of enantioselective trifluoromethylation of prochiral substrates, a longstanding challenge in electrophilic trifluoromethylation chemistry. Investigations towards this objective are currently underway in our laboratories.

Conflicts of interest

There are no conflicts to declare.

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