

Zinc-Mediated Formation of Trifluoromethyl Ethers from Alcohols and Hypervalent Iodine Trifluoromethylation Reagents**

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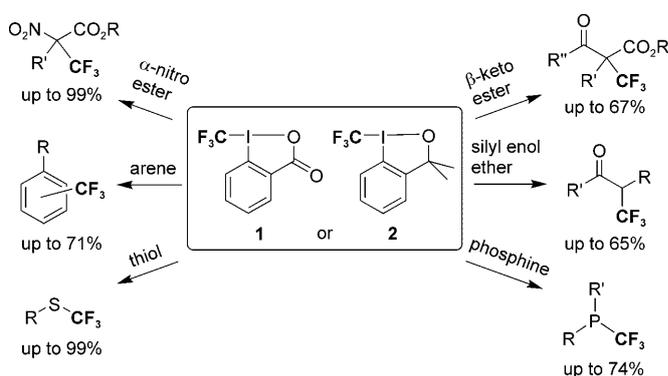
The incorporation of fluorine atoms into biologically active organic molecules has become an increasingly important tool in the life science industry.^[1] Properties such as the metabolic stability, lipophilicity, and bioavailability of drug candidates and crop protection agents^[2] may be drastically improved by the presence of just one fluorine atom, or by a trifluoromethyl group. The trifluoromethoxy substituent is less often encountered. However, the drug Riluzole^[3] and the pesticide Triflumuron^[4] are prominent examples of compounds containing the OCF₃ group at an aromatic position, and aliphatic trifluoromethyl ethers have been incorporated, for example, into liquid crystalline materials.^[5]

None of the trifluorohalomethane compounds react with alcohols or their deprotonated form to afford the corresponding trifluoromethyl ethers. The syntheses of these compounds require special reagents and equipment. Thus, anisoles are converted into the corresponding trifluoromethoxy derivatives by a chlorination/fluorination sequence using PCl₅/Cl₂ and anhydrous HF.^[6] Similar considerations apply for the in situ sequence starting from the aryl alcohol, HF, and CCl₄.^[7] Moreover, concentrated HF solutions are needed in the oxidative desulfurization/fluorination of xanthates.^[8] Recently, Umemoto et al. reported a conceptually important approach for the direct, electrophilic trifluoromethylation of both alcohols and amines using *O*-(trifluoromethyl)dibenzofuranium salts.^[9] However, these highly reactive species need to be generated in situ from diazonium salts already containing a trifluoromethoxy group.

From the above considerations it is safe to say that a mild, reliable, and broadly applicable method for the formation of trifluoromethyl ethers starting from alcohols is still lacking. The synthesis of relatively complex target molecules containing a trifluoromethoxy fragment has to rely heavily upon the use of small building blocks already containing this entity.

Generally speaking, this is very true for any trifluoromethyl group.

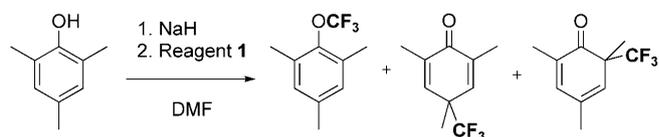
Recently, our group developed a new class of electrophilic trifluoromethylation reagents based on hypervalent iodine(III) derivatives (**1** and **2**; Scheme 1). Both reagents are easily



Scheme 1. Applications of hypervalent iodine trifluoromethylation reagents **1** and **2**.

accessible from commercially available 2-iodobenzoic acid.^[10] As outlined in Scheme 1, various substrates, such as thiols, phosphines, active methylene compounds, or aromatic compounds can be trifluoromethylated under mild reaction conditions in good to excellent yields.^[11]

However, the direct *O*-trifluoromethylation of phenols remains an unsolved problem. For the model substrate, 2,4,6-trimethylphenol, the desired product was obtained in only 15% yield after tedious variation of the reaction parameters (Scheme 2). The major products are a mixture of *C*-trifluoromethylated derivatives,^[12] the formation of which may be explained by an oxidation/trifluoromethylation sequence of the starting phenol.^[13]



Scheme 2. Trifluoromethylation of 2,4,6-trimethylphenol using **1**.

While considering the fundamental question as to whether the direct and synthetically efficient transfer of an intact CF₃ group from an electrophilic source to an alcohol oxygen atom would be possible, we focused on aliphatic alcohols, thereby

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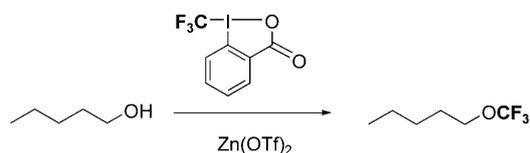
[†] R. Aardoom and K. Niedermann carried out the X-ray crystal structural study of compound **5**.

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most likely circumventing potential problems associated with oxidations.

While investigating the activation of alkynes with zinc triflate towards possible trifluoromethylation with reagent **1** we observed the unexpected formation of trifluoromethyl triflate (TFMT).^[14] Similar experiments with sodium, potassium, or copper(II) triflate did not afford any conversion into TFMT, as indicated by ¹⁹F NMR spectroscopy. However, the addition of one equivalent of zinc bromide to such reaction mixtures triggered the formation of TFMT, indicating the crucial role of zinc(II). The trifluoromethylation of triflate per se does not seem to be a particularly relevant reaction. However, it clearly indicates that our reagent is capable of trifluoromethylating an oxygen-centered nucleophile, despite the fact that it had been identified as being too soft of a reagent for this purpose.^[15] At this point we focused on the direct trifluoromethylation of alcohols. Preliminary studies were carried out in 1-pentanol as both the solvent and the substrate, using Zn(OTf)₂ as zinc source and **1** as electrophilic CF₃-transfer reagent (Scheme 3).



Scheme 3. Zn(OTf)₂-assisted direct trifluoromethylation of 1-pentanol.

By using one equivalent of Zn(OTf)₂, the trifluoromethylation took place under very mild reaction conditions, giving the desired trifluoromethyl ether in 83% yield, based on **1** (Table 1, entry 1). Better results were obtained with substoichiometric amounts of Zn(OTf)₂ (Table 1, entries 2 and 3). Therefore, by using 20 mol % of Zn(OTf)₂ the formation of the undesired side product TFMT was suppressed completely. When the amount of alcohol used was reduced to 10 equivalents, in either chloroform or toluene as the solvent, the reaction became slow and larger amounts of TFMT were formed (Table 1, entries 4 and 5).

To exclude the formation of TFMT we screened various zinc sources. Zinc(II) halides (Cl⁻, Br⁻, I⁻) also assisted the alcohol trifluoromethylation, but the major product was always the corresponding trifluoromethyl halide. If basic anions such as CO₃²⁻ or acac⁻ (acac = acetylacetonate) were

used, the reaction did not afford the desired product. At last, zinc(II) bis(trifluoromethylsulfonyl)imide, Zn(NTf₂)₂, was chosen because of its satisfactory solubility in polar and chlorinated solvents, and the non-nucleophilic and nonbasic character of the anion. These characteristics are partly illustrated by (CF₃SO₂)₂NH being one of the strongest acids known in the gas phase.^[16] Moreover, DesMarteau and co-workers recently reported the synthesis of hypervalent iodonium salts bearing NTf₂⁻ as a counter ion, which displayed remarkable arylating and alkylating powers.^[17a-c]

We found that Zn(NTf₂)₂ gave better yields and generated fewer side products than all other zinc(II) salts. By using a stoichiometric amount of Zn(NTf₂)₂ (with respect to reagent **1**) 1-trifluoromethoxypentane was obtained in a yield of 93% instead of 83% (Table 2, entry 1). Again, catalytic amounts of zinc(II) did not significantly lower the yield of the ether. When the amount of the alcohol was reduced to 10 equivalents, using chloroform as the solvent, the yield fell to 67% (Table 2, entry 3), representing a significant improvement compared to the 25% yield obtained with Zn(OTf)₂. Further reduction of the amount of alcohol used to 5 equivalents slowed down the reaction and resulted in only 17–19% yield of the desired trifluoromethyl ether (Table 2, entry 4). By using Zn(NTf₂)₂ in catalytic amounts (34 mol %) the trifluoromethyl ether was afforded in significantly improved yields of up to 61% (Table 2, entry 5). Notably, the NTf₂⁻ anion can undergo trifluoromethylation at the oxygen atom to give TfN=SO(OCF₃)CF₃ (**3**), despite its extremely low nucleophilicity. However, the formation of this side product can be minimized by reducing the amount of Zn(NTf₂)₂. Furthermore, 2-iodobenzoic acid is O-trifluoromethylated giving

Table 1: Trifluoromethylation of 1-pentanol using **1** and Zn(OTf)₂.

Entry ^[a]	1-Pentanol ^[b] (equiv)	Zn(OTf) ₂ (equiv)	Solvent ^[c]	Yield [%] (conv.) ^[d]	Side products ^[e]
1	75	1.00	1-pentanol	83 (quant.)	2% TFMT
2	75	0.50	1-pentanol	89 (quant.)	2% TFMT
3	75	0.20	1-pentanol	84 (quant.)	–
4	10	0.50	toluene	25 (63%)	8% TFMT
5	10	0.50	CHCl ₃	26 (59%)	22% TFMT

[a] Reaction conditions: **1** was stirred with 1-pentanol in the solvent at RT for 48 h. [b] Distilled prior to use. [c] The concentration of **1** was approximately 0.15 M in all experiments. [d] The conversion of **1** and the product yield were calculated based on ¹⁹F NMR methods using C₆H₅CF₃ as an internal standard. [e] Observed by ¹⁹F NMR methods.

Table 2: Trifluoromethylation of 1-pentanol using **1** and Zn(NTf₂)₂.

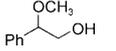
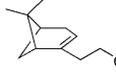
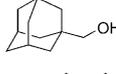
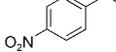
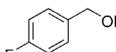
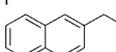
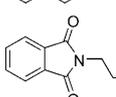
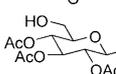
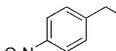
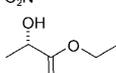
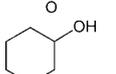
Entry ^[a]	1-Pentanol ^[b] (equiv)	Zn(NTf ₂) ₂ (equiv)	Solvent ^[c]	Yield [%] (conv.) ^[d]	Side products ^[e]
1	75	1.00	1-pentanol	93 (quant.)	–
2	75	0.20	1-pentanol	89 (quant.)	–
3	10	1.00	CHCl ₃	67 (quant.)	3% 4
4	5	1.00	CHCl ₃	19 (45%)	18% 3
5	5	0.34	CHCl ₃	61 (quant.)	3% 4
6	1.5	0.34	CHCl ₃	21 (86%)	–

[a] Reaction conditions: **1** was stirred with 1-pentanol in the solvent at RT for 48 h. [b] Distilled prior to use. [c] The concentration of **1** was approximately 0.15 M in all experiments. [d] The conversion of **1** and the product yield were calculated based on ¹⁹F NMR methods using C₆H₅CF₃ as an internal standard. [e] Observed by ¹⁹F NMR methods.

trifluoromethyl 2-iodobenzoate (**4**) as the second side product.

After optimization of the reaction conditions for 1-pentanol, we focused our attention on more challenging substrates. As shown in Table 3, excellent results were obtained using less volatile alcohols, which can be used as both the solvent and the substrate (Table 3, entries 1–3). The

Table 3: Trifluoromethylations of alcohols using **1** and Zn(NTf₂)₂.

Entry	Substrate	Zn(NTf ₂) ₂ (equiv)	Yield ^[c] [%]
1 ^[a]		1.0	99 (81)
2 ^[a]		1.0	92 (75)
3 ^[a]		1.0	62 ^[d]
4 ^[b]		0.50	55 (39)
5 ^[b]		0.50	49 (37)
		0.33	48
		0.25	44
6 ^[b]		0.50	43 ^[d]
7 ^[b]		0.50	28 (12)
8 ^[b]		0.50	27 (19)
		0.30	26
9 ^[b]		0.50	18 (2)
10 ^[b]		0.30	12
11 ^[a]		1.0	62 ^[d]
12 ^[a]		1.0	74 ^[d]

[a] Reaction conditions: reagent **1** was stirred with 1 equiv of Zn(NTf₂)₂ in the alcohol as the solvent (75 equiv) for 24 h. [b] Reaction conditions: **1** was stirred with Zn(NTf₂)₂ and 5 equiv of alcohol in CDCl₃ at RT for 2–3 days. [c] Yields were calculated based on reagent **1** as determined from ¹⁹F NMR integrals using C₆H₅CF₃ as an internal standard. Yields of isolated products are given in brackets. [d] Not isolated in pure form.

excess alcohol allowed preparation of the corresponding trifluoromethyl ethers in yields up to 99% with only traces of the side product **3**. Notably, from a practical point of view, the trifluoromethylated products can be easily separated from the much more polar alcohols by simple flash column chromatography. Since an excess of alcohol is necessary to obtain good yields, a molar ratio of 5:1 between the alcohol and reagent **1** is a tenable compromise, even in the case of using solid and expensive substrates; higher ratios are likely to give better yields (Table 3, entries 4–10). We tried a series of primary alcohols in chloroform and found that all could be trifluoromethylated in fair yields (up to 55%). Although both side products **3** and **4** were formed in the trifluoromethylation

of 1-adamantyl methanol, the corresponding CF₃ ether could be isolated in 39% yield (Table 3, entry 4). However, some substrates were less tolerant to the acidic reaction conditions, giving the desired products in less than 20% yield. Therefore, the trifluoromethylation of a tetra-acetylated glucose derivative was rather sluggish, affording the desired product in low yield along with four minor, uncharacterized side products, possibly arising from deacylation reactions or epimerization (Table 3, entry 9). Finally, we were pleased to find that secondary alcohols also undergo trifluoromethylation quite cleanly; the CF₃ ether of ethyl lactate forms in 62% yield, whereas trifluoromethoxycyclohexane is obtained from cyclohexanol in 74% yield (Table 3, entries 11–12). Alcohols such as *t*-BuOH, as well as phenols, still cannot be O-trifluoromethylated.

¹⁹F NMR and ESI-MS measurements of the reaction mixture of reagent **1**, *p*-nitrobenzyl alcohol, and Zn(NTf₂)₂ provided the first important mechanistic insights. The corresponding ¹⁹F NMR spectra showed a shift of the CF₃ signal of our hypervalent iodine species from $\delta = -33.0$ ppm to $\delta = -26.9$ ppm after a few minutes at room temperature, indicating the formation of a relatively stable intermediate which subsequently decayed under reaction conditions. The major peak in the ESI-MS spectrum depicted in Figure 1 corresponds to a cationic species of stoichiometry [Zn(**1**)₂(NTf₂)⁺]. We tentatively assign the structure of a zinc(II) dicarboxylato complex to this cation. This assignment reveals the very nature of the activation process of reagent **1** by Zn²⁺, consisting of the cleavage of the I–O bond, thus generating a more reactive (harder) trifluoromethyl iodonium derivative (Figure 1).

Although several attempts to prepare an aryl trifluoromethyl iodonium salt have been already reported in the literature, so far none have succeeded.^[18] The reported approach starting from bis(trifluoroacetoxy)-iodoperfluoroalkanes was restricted to perfluoroalkyl groups larger than CF₃. Our experiments indicate a possible new avenue which relies on the sequestration of the carboxyl group from iodine by coordination to an appropriate metal center, in this case Zn²⁺. Pulsed-field gradient spin echo (PGSE) diffusion measurements^[19] of the same solution supported the formulation of a 1:2 adduct of Zn²⁺ with the reagent. This intermediate showed a strong interaction with the NTf₂[−] anion, displaying a very similar diffusion constant. This was not the case for the alcohol (see the Supporting Information).

A systematic variation of the crystallization conditions allowed the isolation and analysis by X-ray diffraction of a crystalline material in the form of very thin platelets, corresponding to the bis(triflimide) salt of the dicationic octahedral complex [Zn(**1**)₂(4-NO₂C₆H₄CH₂OH)₂(H₂O)₂]²⁺ (**5**). An ORTEP view of the asymmetric unit is shown in Figure 2.

The salient features of the structure of compound **5** are, firstly, the coordination of water (from an adventitious source), 4-nitrobenzyl alcohol, and reagent **1** as monodentate ligands, thus forming a slightly distorted octahedral ZnO₆ coordination environment. Secondly, and more importantly in view of understanding the activation mechanism of **1** by Zn²⁺, is the effect of the coordination to the metal center on the

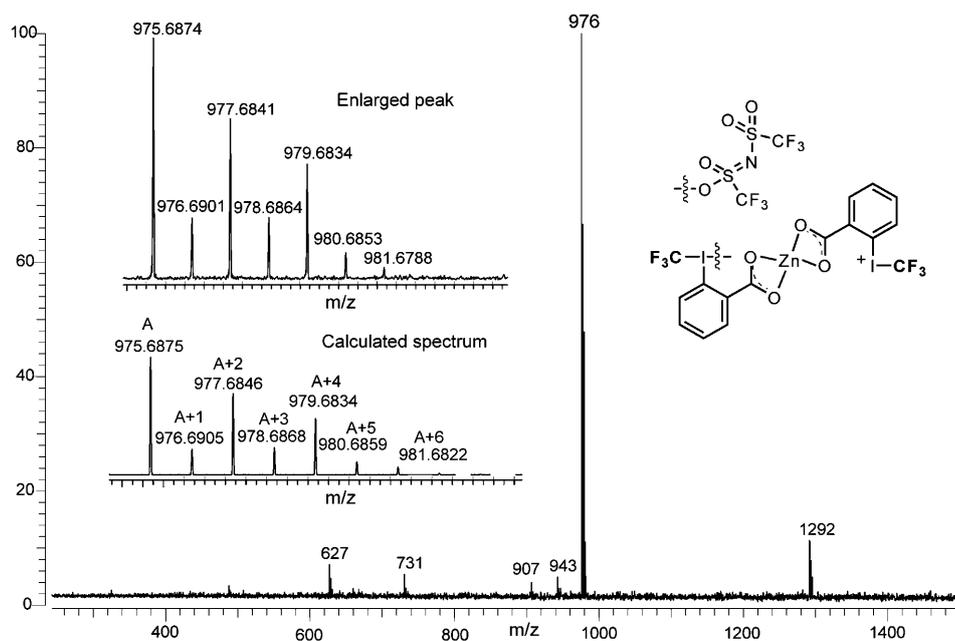


Figure 1. ESI-MS spectrum of a mixture of $\text{Zn}(\text{NTf}_2)_2$ with reagent **1** indicating the formation of a 1:2 adduct, tentatively formulated as a carboxylato complex/iononium ion.

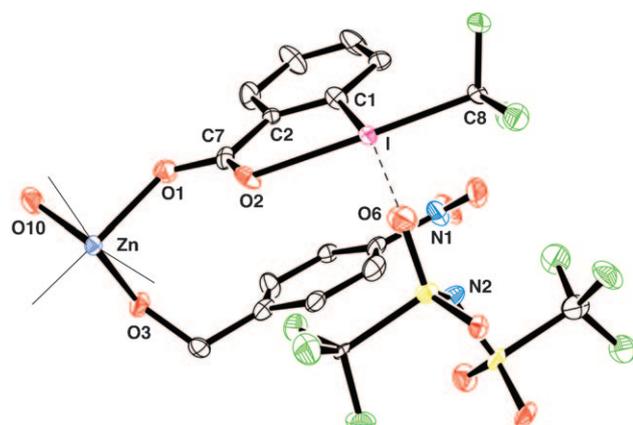
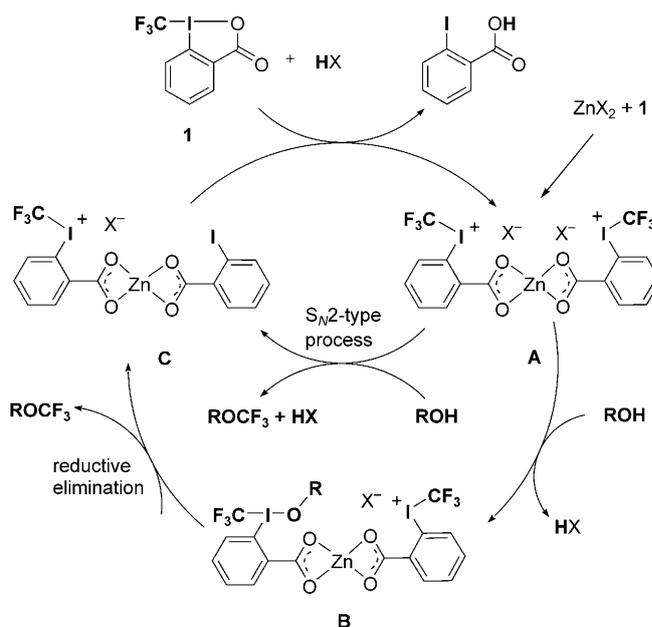


Figure 2. ORTEP-view (50% probability ellipsoids) of the asymmetric unit of $[\text{Zn}(\mathbf{1})_2(4\text{-NO}_2\text{C}_6\text{H}_4\text{CH}_2\text{OH})_2(\text{H}_2\text{O})_2](\text{NTf}_2)_2$ (**5**) in which the Zn atom lies on a crystallographic inversion center. Selected bond lengths [Å] and angles [°]: I–O2 2.403(12), I–C8 2.195(16), I–C1 2.103(19), I–O6 3.078(14), Zn–O1 2.029(13), Zn–O3 2.145(13), Zn–O10 2.090(15), C7–O1 1.27(2), C7–O1 1.26(2); C1–I–O2 75.0(6), C1–I–C8 95.4(7), O1–I–C8 169.9(5), O1–Zn–O5 92.1(5), O1–Zn–O10 87.7(5), O3–Zn–O10 92.2(5).

structural parameters of the reagent. Thus, a significant elongation of the I–O bond from 2.283(2) Å in free **1**^[10] to 2.403(12) Å and a larger C(1)–I–(CF₃) angle of 95.4(7)° (versus 93.7°) may be interpreted as distortions towards the formation of an iodonium species.^[20] Furthermore, a weak interaction between the proximal oxygen atom of an NTf₂[−] ion and the iodine atom is indicated by a relatively short O(6)–I distance of 3.078(14) Å.^[21]

With these results in hand it is possible to formulate a plausible working hypothesis for the reaction mechanism, as

illustrated in Scheme 4. We assume that reagent **1** reacts with the zinc salt under formation of the zinc dicarboxylato complex **A**, corresponding to the species detected by ESI-MS methods. This species then reacts with alcohols to form the intermediate **B**, resulting from the addition of an alcoholate to an iodonium moiety. A subsequent reductive elimination step^[22] is responsible for the formation of the trifluoromethyl ether product and species **C**. At the present stage we cannot exclude that, alternatively, the iodonium species **A** might undergo an intermolecular attack by the nucleophile leading to product formation via an S_N2-type process, enhanced by the exceedingly large nucleofugality of phenyliodonium deriv-



Scheme 4. Mechanistic hypothesis for the zinc-mediated electrophilic trifluoromethylation of alcohols using **1**, based on the postulated formation of trifluoromethyl iodonium salts.

atives.^[23] Intermediate **A** could also react with 2-iodobenzoate (accumulating in the course of the reaction) or with NTf₂[−] forming complexes analogous to **B**, which could explain the formation of the observed by-products **3** and **4**. Species **C** can undergo ligand exchange with reagent **1**, thus liberating 2-iodobenzoate and ending the catalytic cycle. It is reasonable to assume that this step is facilitated by the protonation of the carboxylate to 2-iodobenzoic acid. The latter can easily be

detected in the reaction mixture by NMR spectroscopy. In this context, the activation of **1** is not restricted to zinc salts. It is also possible to use other Lewis acids or even Brønsted acids such as HNTf₂ to trigger the formation of trifluoromethyl ethers, even though Zn(NTf₂)₂ is far superior; for example the maximum yield of 1-trifluoromethoxypentane is 35% (NMR) when using HNTf₂ instead of Zn(NTf₂)₂ (93% yield), under otherwise identical conditions.

In conclusion, we have shown that it is possible to trifluoromethylate aliphatic alcohols using the hypervalent iodine reagent **1**. In reactions with primary alcohols the trifluoromethyl ethers are obtained in yields up to 99% under very mild and easy to manipulate reaction conditions. Only a zinc(II) salt with an appropriate counter ion is the key to promoting the reaction. We are currently exploring other Lewis acidic metal complexes to additionally improve the generality of this unique reaction and to discover more effective catalytic conditions.

Experimental Section

Supporting Information available: Experimental procedures and characterization for selected new compounds, PGSE diffusion data, and ESI-MS spectra. CCDC 720606 (**5**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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