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Magnesium-Catalyzed Electrophilic Trifluoromethylation: Facile Access to All-Carbon Quaternary Centers in Oxindoles

Dmitry Katayev,* Harutake Kajita, and Antonio Togni

Dedication ((optional))

Abstract: The first example of a magnesium-catalyzed direct trifluoromethylation of 3-substituted oxindoles using an electrophilic hypervalent iodine reagent is reported. The reaction proceeds under unprecedented mild conditions leading to the formation of an all-carbon quaternary center in oxindoles in high chemical yield and demonstrates excellent functional group tolerance. In addition to trifluoromethyl, other perfluoroalkyl groups can be introduced with similar level of efficacy. Mechanistic investigations are consistent with the involvement of a radical pathway. The chemical versatility of the obtained products is further illustrated through their conversion *in situ* into valuable organofluorine building blocks, making the protocol more widely practical.

Organofluorine compounds have substantially changed the fields of medicinal chemistry,[1] agrochemistry[2] and material science,[3] owing to their unique physico-chemical properties. For example, in drug design, the exchange of hydrogen for fluorine or trifluoromethyl can significantly enhance the activity, lipophilicity, and bioavailability of important lead compounds. Thus, the development of straightforward protocols for efficient and selective perfluoroalkylation of various organic frameworks has become a widespread topic of research in the chemical community.[4] During the past few decades, a variety of bench-stable trifluoromethylating reagents have been developed and successfully utilized in organic synthesis.[5] In particular, the previously reported λ^3-iodane-based compounds **1** and **2**[6] from our laboratory have become important reagents in the preparation of trifluoromethylated molecules (Figure 1). Their electronic and structural properties lead to distinct reactivity through electrophilic transfer of a CF_3 unit to a vast class of *C-, O-, N-, P-* and *S-*nucleophiles.[7]

Figure 1. Hypervalent iodine-based reagents **1** and **2**.

3,3-Difunctionalized oxindoles are widely recognized as valuable synthetic intermediates forming the core of many natural products and synthetic analogues.[8] It was recently demonstrated that introduction of a fluorine or a trifluoromethyl group at the C3 position of an oxindole improved its pharmaceutical properties.[9] As a part of ongoing research in our laboratory focused on the development of novel methodologies to access organofluorine compounds *via* electrophilic trifluoromethylation, we expect that the incorporation of fluoroalkyl group into oxindole moiety will provide access to new drug candidates with unique biological properties. Transformations leading to the formation of quaternary carbon centers upon trifluoromethylation by **1** or **2** are particularly challenging, and only a few examples are available in the literature.[10] To the best of our knowledge, the direct catalytic trifluoromethylation of oxindoles remains an unexplored field.

Herein we report the first example of direct electrophilic perfluoroalkylation of 3-substituted oxindoles under $MgBr_2$•Et_2O catalysis using hypervalent iodine reagents as a source of fluoroalkyl groups. As such, $MgBr_2$•Et_2O was discovered to be capable of activating both the λ^3-iodane-based compound **2** and the substrate. Furthermore, this Lewis acid is commercially available, is inexpensive, and generates non-toxic by-products while retaining its activity even in the presence of *O-* and *N-*containing compounds. Reagent **2** acts simultaneously in this transformation as a source of CF_3 species and as an internal base

The most common activation mechanism for oxindoles relies upon the coordination of the carbonyl group to a Lewis acid or H-bond donor species. The corresponding enolate intermediate can then subsequently react with the electrophilic fluoroalkyl species. In order to test the viability of this transformation, we attempted to trap the *in situ* generated lithium enolate of oxindole **3a** with reagents **1** or **2**. The reaction proceeded smoothly with **1** leading to the formation of the desired product **4a** in 68%, while no product was detected with **2** (THF, –78 °C to rt, 5 h). Encouraged by these results, we turned our attention to a catalytic approach for the direct trifluoromethylation of oxindoles. Without a Lewis acid catalyst, the direct trifluoromethylation of **3a** using either **1** or **2** in CH_2Cl_2 at room temperature did not show any reactivity (Table 1, entry 1). The addition of catalytic amounts of $MgBr_2$•Et_2O (10 mol %) to the reaction mixture led to the formation of the desired product in less than 20% in the presence of reagent **2**, whereas reagent **1** was totally inactive (entries 2-3). Therefore, subsequent optimizations were performed only with iodane **2**. Reducing the reaction temperature to –78 °C increased the product yield to 58% (entry 4-5). No significant improvement was observed by using either different magnesium salts or Lewis acids (entries 6-12). When using different loading of $MgBr_2$•Et_2O (entries 13-14) we observed a decrease in the chemical yield of **4a**. Accordingly, an excess of the catalyst resulted in a background Boc-deprotection.[11] In contrast, using 1.5 equivalent of reagent **2** enhanced the yield to 72% (entry 15). It is well known, that reagents **1** and **2** are extremely reactive in the presence of an

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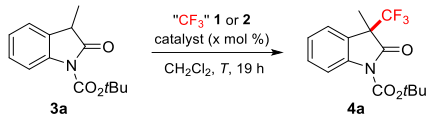
Table 1: Development of the catalytic trifluoromethylation of oxindole **3a**.



3a **4a**

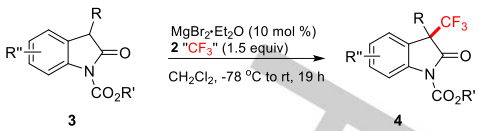
Entry[a]	"CF_3"	Catalyst (x mol %)	*T* [° C]	Yield [%][b]
1	1 or 2	–	RT	nd
2	1	$MgBr_2$•Et_2O (10)	RT	nd
3	2	$MgBr_2$•Et_2O (10)	RT	17
4	2	$MgBr_2$•Et_2O (10)	0	35
5	2	$MgBr_2$•Et_2O (10)	–78 to RT	58
6	2	$MgBr_2$ (10)	–78 to RT	<5
7	2	MgI_2 (10)	–78 to RT	36
8	2	$Mg(ClO_4)_2$ (10)	–78 to RT	19
9	2	$Zn(NTf_2)_2$ (10)	–78 to RT	<5
10	2	$Ti(OiPr)_4$ (10)	–78 to RT	6
11	2	$Cu(OTf)_2$ (10)	–78 to RT	<5
12	2	$AlCl_3$ (10)	–78 to RT	8
13	2	$MgBr_2$•Et_2O (5)	–78 to RT	38
14	2	$MgBr_2$•Et_2O (25)	–78 to RT	55
15[c]	2	$MgBr_2$•Et_2O (10)	–78 to RT	72
16[c,d]	2	$MgBr_2$•Et_2O (10)	–78 to RT	63
17[c,e,f]	**2**	**$MgBr_2$•Et_2O (10)**	**–78 to RT**	**82**

[a] **3a** (0.16 mmol, 0.08 M in CH_2Cl_2), "CF_3" (1.3 equiv), cat. (10 mol %), –78 °C to RT, Ar, 19 h. [b] Yields were determined by ^{19}F NMR using benzotrifluoride as an internal standard; nd – not determined. [c] With 1.5 equiv of **2**. [d] Slow addition of **2**. [e] Slow addition of **3a**. [f] Isolated compound. Boc – *tert*-Butyloxycarbonyl.

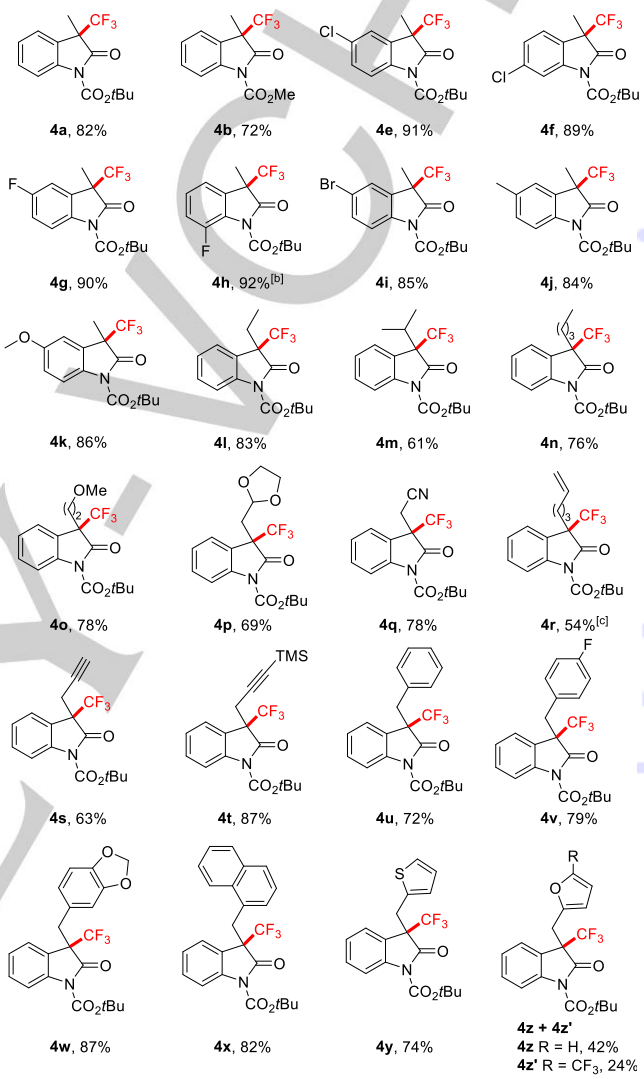
activator even at low temperature,[10,12] thus it was thought to control the reactivity by slow addition of one component (entries 16-17). The best yield of **4a** (82%) was achieved by slow addition of the substrate to the reaction mixture over 30 minutes (entry 17). We next investigated the effect of various *N*-protecting groups. However, at best, traces or no product were obtained using acetate (**4c**; <5%) or methoxymethyl acetal (**4d**; 0%) as protecting groups, while methyl carbamate (**4b**) exhibited a slightly lower reactivity providing the product in 72% yield. These experiments confirm that the bulky *N*-Boc protecting group is mandatory and is well tolerated.

With the optimized reaction conditions in hand, we next explored the generality of the protocol for various 3-substituted oxindoles and the results are summarized in Table 2. Oxindoles with either electron withdrawing or electron donating groups at the aromatic ring provided adducts with excellent chemical yields. Likewise, a chloro (**3e-f**), fluoro (3**g-h**) and bromo (**3i**) groups at the C4, C5, C6 and even at C7 of the oxindole are well tolerated giving the respective products in good yields, typically above 85%. Electron donating substituents such as methyl (**3j**) and methoxy (**3k**) groups at C5 of the aromatic ring elicited very similar reactivity. We were pleased to observe that oxindoles bearing both short and long alkyl chains (**3l**-**3o**) as well as functionalized alkyl chains **3p** and **3q** at position C3 are compatible affording the corresponding trifluoromethylated products in good yields (69-83%). However, the reaction was rather sensitive towards bulky substituents at C3 position, which often led to diminished yields. Functional C3-substituents such as 4-pentenyl (**3r**), propargyl (**3s**) and 3-TMS-propargyl (**3t**) are fully compatible with this method as well. Next, the reaction was carried out with a series of C3-benzyl-substituted oxidoles. As shown in Table 2, the electronic nature and the position of substituents on the C3-benzyl

Table 2: Substrate scope of the trifluoromethylation reaction.[a]



3 **4**



[a] All reactions were run on 1.0 mmol scale. Yields refer to isolated products [b] 15 mmol scale. [c] Formation of a cyclic product through the intramolecula radical cyclization reaction (below 10% yield) along with by-products via trifluoromethylation of a terminal double bond were observed.

ring (**3u-x**) had only little effect on the yields. Remarkably, variation of the C3-substituent to thienylmethyl (**3y**) and furfurylmethyl (**3z**) displayed good tolerance of the reaction conditions delivering the desired products in 66–74% yields. In the case of oxindole **3z**, trifluoromethylation of furfuryl ring takes place in addition to C3-trifluoromethylation leading to the formation of two separable products **4z** and **4z'** (24%, 42%). Direct trifluoromethylation of 3-phenylsubstituted oxindole was unsuccessful, and only trace amount of the product was detected. Such low reactivity might be explained by the depleted electron density of an enolate intermediate due to strong conjugation. To our delight, the reaction is adaptable to scale-up, and we were able to synthesise 4.6 g of C3-trifluoromethylated oxindole **4h**

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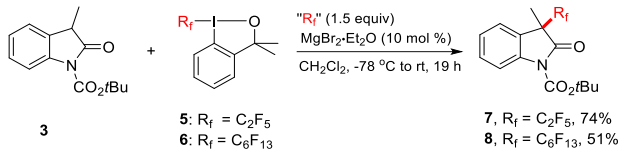
(92%) from 15.0 mmol of the corresponding starting material. In addition to the trifluoromethyl group, this procedure is also amenable to a range of C3-fluoroalkylations using various commercially available iodine(III)-R_f reagents. When subjected to the outlined protocol, oxindole **3a** underwent perfluoroalkylation (ethyl (**7**) and hexyl (**8**)) with good levels of chemical efficiency 75% and 51%, respectively (Scheme 1). Slow evaporation of a solution of **4i** in pure hexane gave single crystals suitable for X-ray structure determination (Figure 2). Closer inspection of this structure revealed that bond lengths and angles, especially at the C3-quaternary center, are in the expected ranges compared with other quaternary α-trifluoromethylated carbonyl compounds. The bulky *tert*-butoxide moiety of *N*-Boc protecting group adopts an antiperiplanar orientation with respect to the C_{Ar}–N bond and is coplanar with the carbonyl group of the oxindole.



Scheme 1. Perfluoroalkylation of oxindole **3a**.

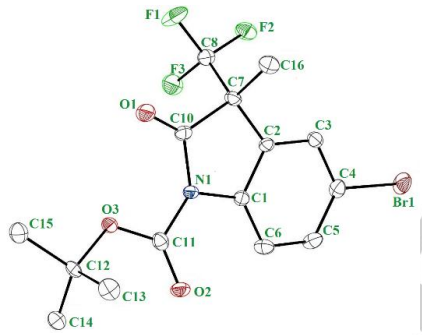
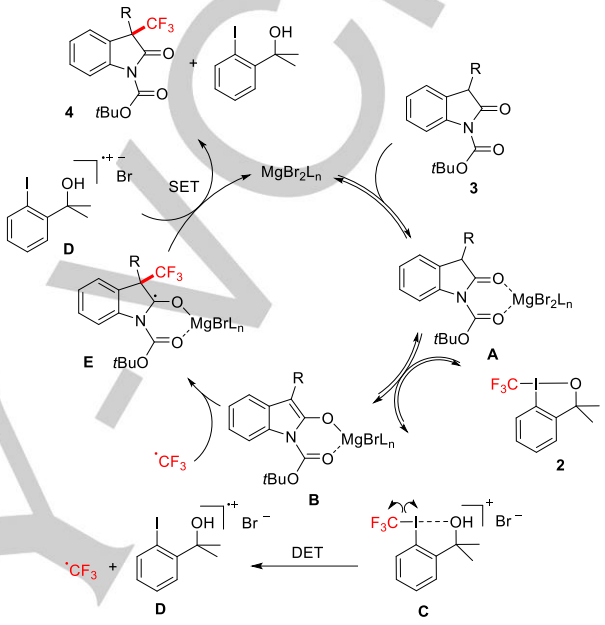


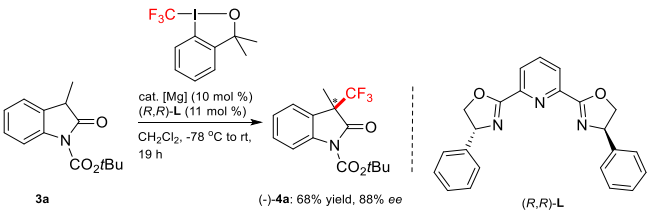
Figure 2. ORTEP representation of compound **4i**. Hydrogen atoms omitted for clarity (50% probability level for the thermal ellipsoids). CCDC 1526083.

The mechanism of the reaction was investigated by a series of control experiments. The reaction of oxindole **3a** with reagent **2** was carried out in the presence of an excess of radical acceptors such as 2,2,6,6-tetramethylpiperidine-*N*-oxide or styrene. In both cases, only trace amount of the product was found, suggesting that the reaction involves radicals. Functionalization of C(sp^3)-H bonds using hypervalent iodine-based reagents often operates *via* a radical chain mechanism.[13] To evaluate this hypothesis, we performed the reaction in the presence of CBr_4. However, the formation of C3-brominated oxindole was not observed spectroscopically, and only product **4a** was produced. At present stage we can propose the following mechanism for this trifluoromethylation reaction (Scheme 2). $MgBr_2$•Et_2O coordinates to oxindole *via* both carbonyl groups to form complex **A**, which further reacts with reagent **2** producing chelated magnesium-enolate **B** and cationic iodonium species **C**. In this step reagent **2** may also be activated by a Lewis acid. This activation mode has been shown by a separate experiment *via* mixing the catalyst and reagent **2** in CD_2Cl_2 in a 1:1 ratio. After 10 minutes, ^{19}F NMR revealed a full conversion of **2** to a new species with a clear shift of the CF_3 moiety from δ = -40.6 ppm to δ = -33.7 ppm. Subsequently, the highly reactive cationic iodonium species **C**, upon thermally induced internal dissociative electron transfer (DET), leads to the formation of CF_3 radical and radical cation species **D**.[14] The ensuing electrophilic CF_3 radical then rapidly reacts with nucleophilic intermediate **B** to furnish radical species **E**. The latter intermediate subsequently takes part in a single electron transfer (SET) with radical cation species **D** forming the trifluoromethylated oxindole **4** and regenerating the catalyst.



Scheme 2. Proposed catalytic cycle. [L] = Et_2O.

Based on our mechanistic assumptions, we commenced to investigate different types of chiral ligands in order to develop the corresponding enantioselective transformation. To our delight, after screening of several commercially available *N*-based chiral ligands, tridentate Py-Box type ligand (*R*,*R*)-**L** demonstrated excellent performance. Carrying out the reaction with oxindole **3a** under the established reaction conditions in the presence of chiral ligand in a ~1:1 ratio with the magnesium catalyst, the corresponding trifluoromethylated oxindole (-)-**4a** was obtained in 68% yield and a high level of enantioselectivity (88% ee) (Scheme 3).



Scheme 3. Mg-catalyzed enantioselective trifluoromethylation of **3a**. The *ee* value was determined by chiral HPLC analysis.

To highlight the utility of this catalytic trifluoromethylation protocol, we designed a one-pot, multi-step procedures in order

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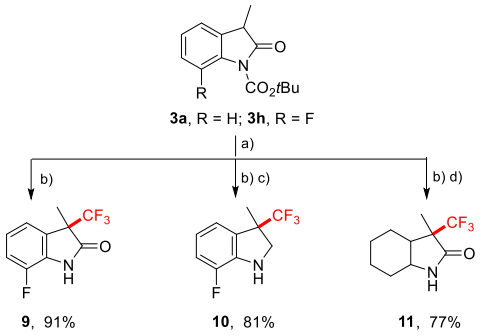
to prepare a wide range of organofluorine compounds. As shown in scheme 4, upon trifluoromethylation the *N*-Boc protecting group was rapidly cleaved *in situ* under acidic conditions giving free oxindole **9** in high 91% yield. The amide moiety can be subsequently reduced providing a straightforward access to 3-trifluoromethyl indoline structure **10** with excellent chemical efficiency (81%) despite the high complexity of this one-pot transformation. Alternatively, oxindole **3a** was successfully transformed into the corresponding 3-trifluoromethyl-substituted pyrrolidine **11** in overall 77% yield *via* three-step protocol including *in situ* trifluoromethylation, *N*-Boc cleavage and reduction steps.



Scheme 4. One-pot trifluoromethylation with follow-up, multi-step transformations of **3a** and **3h**. Reaction conditions: [a] **2**, $MgBr_2$•Et_2O (10 mol %), CH_2Cl_2, –78 °C to RT, 19 h. [b] TFA, CH_2Cl_2, RT, 4 h. [c] BH_3•Me_2S, THF, 3 h; HCl, reflux, 3 h. [d] AcOH, PtO_2 (10 mol %), 70 °C, 48 h.

In summary, we have found an unprecedented magnesium-catalyzed direct perfluoroalkylation of oxindoles using hypervalent iodine reagents as source of fluoroalkyl groups. The reaction can be performed with high chemical efficiency under very mild reaction conditions leading to all-carbon quaternary oxindoles and has a large functional group tolerance. The protocol can be also realized on a gram scale without compromising the yield. We have also demonstrated the first magnesium-catalyzed enantioselective trifluoromethylation of oxindoles. The unique synthetic utility of C3-trifluoromethylated oxindoles is demonstrated by their *in situ* interconversion into synthetically useful organofluorine building blocks. The new finding that simple magnesium salt can effectively activate λ^3-iodane-based compounds offers new venues towards discovering new trifluoromethylation methodologies. Further detailed mechanistic studies and applications based on this chemistry towards the formation of R_f-containing quaternary stereocenters are underway in our laboratory.

Experimental Section

Synthesis of **4a**: A flame-dried 50 mL Schlenk flask equipped with a magnetic stirring bar and rubber septum was charged under Ar subsequently with reagent **2** (495 mg, 1.5 mmol), $MgBr_2$×Et_2O (25.8 mg, 0.1 mmol) and anhydrous DCM (10 mL). The solution was cooled to -78 °C (dry ice/acetone bath) and stirred for 5 minutes. To the resulting well-stirred solution oxindole **3a** (247 mg, 1.0 mmol) in DCM (2.5 mL) was added dropwise via syringe during 30 minutes. The reaction mixture was allowed to reach room temperature overnight (19 h) with stirring. The crude material was purified by flash column chromatography on silica gel (eluting with EtOAc/Hexane 1:30) to afford **4a** in 82% yield (259 mg). Colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.65 (s, 9H), 1.70 (s, 3H), 7.13 – 7.31 (m, 1H), 7.34 – 7.49 (m, 2H), 7.93 (d, *J* = 8.1 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.6 (q, *J* = 2.1 Hz), 28.0, 52.6 (q, *J* = 27.5 Hz), 85.2, 115.35, 124.35, 124.36, 124.5 (q, *J* = 281.0 Hz), 124.9, 130.1, 139.8, 148.7, 170.38 (q, *J* = 2.5 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ -73.63. IR (ATR, neat): 2984, 1774, 1736, 1441, 1344, 1308, 1251, 1147, 1089, 838, 757. HRMS (ESI+) calcd (m/z) for $C_{15}H_{16}NNaF_3O_3$: $[M+Na]^+$ 338.0974, found 338.0981.

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Keywords: catalysis • magnesium • oxindole • quaternary carbon centers• trifluoromethylation

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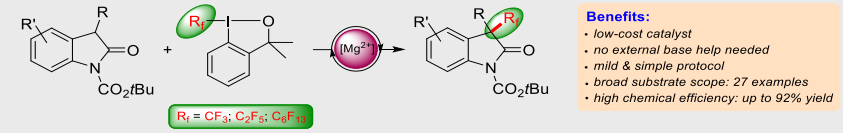

The first magnesium-catalyzed direct perfluoroalkylation of 3-substituted oxindoles using electrophilic hypervalent iodine reagent is described. This simple protocol offers rapid access to oxindoles containing an all-carbon quaternary center in high chemical yield and displays excellent functional group compatibility. Enantiomerically enriched C3-trifluoromethylated oxindoles can be also generated using chiral ligands. The trifluoromethylated products were further converted into a series of organofluorine building blocks *via* one-pot, multi-step transformations.

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Magnesium-Catalyzed Electrophilic Trifluoromethylation: Rapid Access to All-Carbon Quaternary Centers in Oxindoles