Synthetic Methods

International Edition: DOI: 10.1002/anie.201511149
German Edition: DOI: 10.1002/ange.201511149

Metal-Free Synthesis of Fluorinated Indoles Enabled by Oxidative Dearomatization

*Edon Vitaku, David T. Smith, and Jon T. Njardarson**

Abstract: *Nitrogen heterocycles are found in a majority of approved small-molecule pharmaceuticals, and the number of approved fluorinated drugs is increasing each decade. Therefore, new approaches for accessing fluorinated nitrogen heterocycles are of great significance. A novel, scalable, and metal-free method for accessing a wide range of fluorinated indoles is described. This oxidative-dearomatization-enabled approach assembles 2-trifluoromethyl NH-indole products from simple commercially available anilines with hexafluoroacetylacetone in the presence of an organic oxidant. The nature of the aniline N-capping group is critical for the success of this new reaction. Furthermore, the indole products contain a 3-trifluoroacetyl group, which can be exploited to access a plethora of useful functional groups.*

Nitrogen heterocycles are structural components of a large number of bioactive natural and unnatural compounds. Our recent analysis revealed that 59% of all US FDA (FDA = Food and Drug Administration) approved small-molecule drugs contain at least one nitrogen heterocycle.[1] Additionally, the fluorine atom is undoubtedly one of the most successful additions to the drug discovery toolkit in the last few decades, as its incorporation impacts solubility, lipophilicity, and metabolic activity, among other drug properties.[2] Fluorinated drugs make up 11% of small-molecule drugs, and around 20% of drugs in the current decade.[3] The combination of fluorine substituents with nitrogen heterocycles has resulted in numerous blockbuster drugs, five of which are shown in Figure 1. As such, we are interested in the development of robust methods for forming fluorinated nitrogen heterocycles from simple building blocks.

Indoles[4] are one of the most common nitrogen heterocycles found in pharmaceuticals,[1] and they have been referred to as "privileged structures" in drug discovery.[5] Inspired by the oxidative dearomatization[6] reaction used in our synthesis of vinigrol,[7] we decided to apply this approach to the synthesis of 2-trifluoromethyl substituted indoles.[8] Recently, our group has been interested in using strategic dearomatization/rearomatization cascades to result in a net C–H functionalization, a strategy we used to form fused oxygenated aromatic heterocycles.[9] Based on the insights of the hypervalent iodine[10] mediated oxidative dearomatization

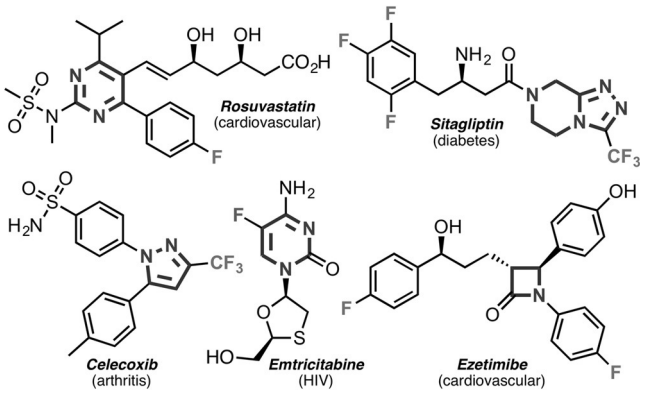
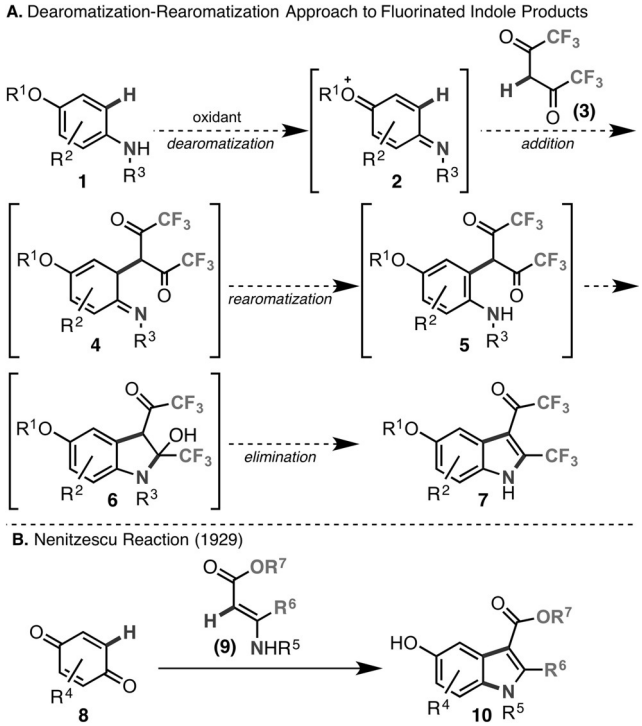


Figure 1. Blockbuster drugs containing nitrogen heterocycles and fluorinated substituents.



Scheme 1. a) Oxidative dearomatization inspired approach to indoles. b) Nenitzescu indole reaction.

mechanism, we postulated that strategically substituted anilines (Scheme 1a) could be dearomatized to create quinone imines (**2**). We then expected that these cationic acceptors would electronically guide soft nucleophiles, such as hexafluoroacetylacetone (hfacac; **3**), to add *ortho* to the resulting

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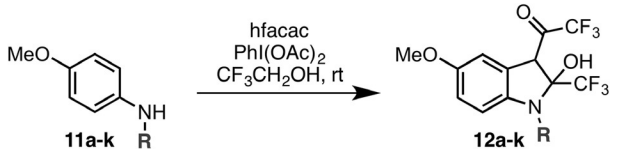
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201511149.

quinone imine. The nucleophilic addition product (**4**) would then rearomatize, thus resulting in a net C–H functionalization (**5**). Furthermore, we anticipated that this aromatic intermediate would undergo a cyclization event (**6**), with the expectation that the nitrogen atom substituent could be removed in the same pot to afford 2-trifluoromethyl-3-trifluoroacetyl NH-indole products (**7**). From a mechanistic perspective, the Nenitzescu reaction[11] is the closest of the indole syntheses to our proposal. However, in the Nenitzescu reaction (Scheme 1 b), *para*-benzoquinones (**8**) are used as electrophiles, and 3-aminocrotonates (**9**) are used as nucleophiles. Consequently, the indole nitrogen atom is a part of the nucleophile, whereas in our approach it is built into the electrophile.

We soon established that Boc-functionalized aniline (Table 1) could be dearomatized[12] as proposed by employing phenyliodine(III) diacetate (PIDA) as our hypervalent iodine oxidant, and hfacac as our nucleophile in the polar non-nucleophilic solvent trifluoroethanol (TFE).[13] When structurally similar 1,3-dicarbonyl compounds (acetylacetone, trifluoroacetylacetone, methyl acetoacetate, and dimethyl malonate) were used instead of hfacac, we either observed reactions between the oxidant and the nucleophile, or oligomerization of the quinone imine intermediates.[14] Thus, it is remarkable how well-matched hfacac is as a nucleophile in this novel indole approach.[15] To better understand the electronic and steric impacts of the aniline nitrogen substituent, we evaluated ten commonly used nitrogen-capping groups (Table 1) using our optimized reaction conditions (see the Supporting Information).[16] Our studies revealed that carbamate substituents (entries 1–3) and phosphoramidate (entry 11) were best suited for this reaction. Sulfonamides (entries 9 and 10) were compatible, but suffered lower conversion. Hydrogen or alkyl substituents (entries 4–6) failed to give any desired product, as did acylated anilines (entries 7 and 8).

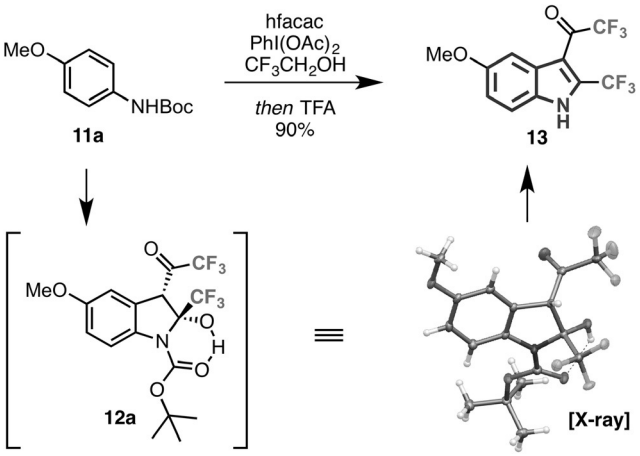
Table 1: Critical nature of the nitrogen-capping group.



Entry	Substrate	R	Consumption [%]	Yield [%][a–c]
1	**11a**	Boc	100	>99 (64)
2	**11b**	Troc	100	>99 (55)
3	**11c**	Fmoc	100	>99 (47)
4	**11d**	H	100	0
5	**11e**	Me	100	0
6	**11f**	Bn	100	0
7	**11g**	$COCH_3$	14	0
8	**11h**	$COCF_3$	0	0
9	**11i**	Ms	34	34 (30)
10	**11j**	Ts	75	75 (46)
11	**11k**	$P(O)(OEt)_2$	100	>99 (73)

[a] Reaction conditions: substrate (0.25 mmol, 1.0 equiv), PIDA (0.50 mmol, 2.0 equiv), hfacac (0.75 mmol, 3.0 equiv), TFE (1.0 mL). [b] Yield is based on conversion as determined by ^{1}H NMR spectroscopy. [c] Yield within parentheses is that of the product isolated after chromatography. Boc = *tert*-butoxycarbonyl, Fmoc = 9-fluorenylmethoxycarbonyl, Ms = methanesulfonyl, Troc = 2,2,2-trichloroethoxylcarbonyl, Ts = 4-toluenesulfonyl.

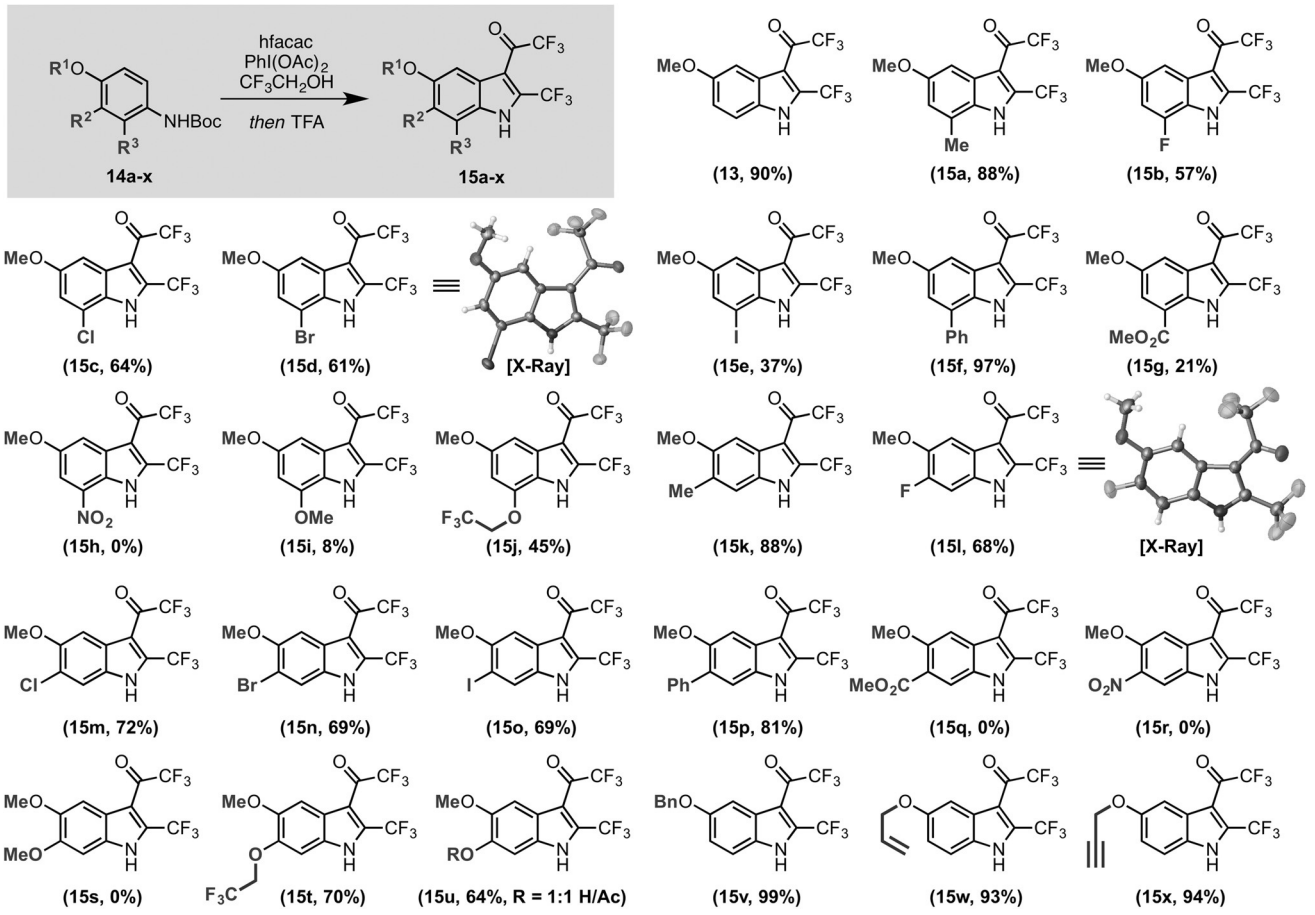
Since our goal was to access indoles in one pot, we were pleased that the carbamates worked great, as they can be installed easily and be removed cleanly using a variety of industrially attractive approaches. Therefore, Boc was chosen as the ideal capping group for all investigations. We obtained an X-ray crystal structure of the Boc-dihydroindole (**12a**; Scheme 2), which reveals that the trifluoroacetyl and the trifluoromethyl groups are oriented *anti* to each other and the hydroxy group of the aminal is engaged in a hydrogen bond with the carbonyl group of the Boc substituent. Addition of trifluoroacetic acid (TFA) to the crude reaction mixture at room temperature afforded the desired fluorinated NH indole in an excellent yield upon isolation.



Scheme 2. One-pot synthesis of fluorinated indoles.[21] Thermal ellipsoids shown at 50% probability.

Further investigations revealed the scope of this new indole synthesis (Table 2). To best aid future users of this method we chose to investigate substrates containing halides (F, Cl, Br and I), alkyl (methyl), aryl (phenyl), electron-withdrawing groups (nitro and methyl ester) and electron-donating groups (alkoxy) in both *ortho*- and *meta*-positions, as well as phenol alkyl substituents (methyl, benzyl, allyl and propargyl). These studies revealed that alkyl, aryl, and halide substituents in both *ortho*- and *meta*-positions worked well (yields ranging from 57–88%), with the exception of *ortho*-iodo substitution (37% yield). Phenol alkyl substituents gave uniformly excellent yields (90–99%). Electron-withdrawing groups show a distinctive limitation to the method, with only the methyl ester in the *ortho*-position working, albeit in low yield (21%). In the latter cases, the starting *N*-Boc aniline underwent Boc-removal to give the corresponding free aniline, thus not undergoing dearomatization, because hfacac reacts with the oxidant instead. When stronger hypervalent iodine reagents (PIFA and iodosylbenzene) were used in hopes of alleviating this limitation, no improvements were observed.

Table 2: Substrate scope.[a,b]

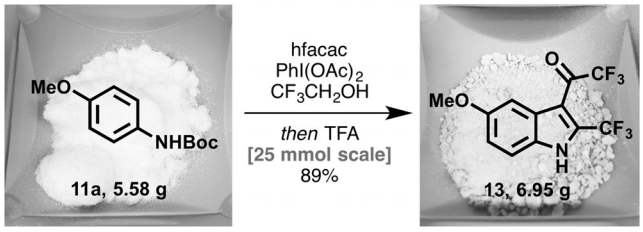


[a] Reaction conditions:[21] substrate (1.25 mmol, 1.0 equiv), PIDA (2.50 mmol, 2.0 equiv), hfacac (3.75 mmol, 3.0 equiv), TFE (5.0 mL), RT, 30 min, then TFA (12.50 mmol, 10.0 equiv), RT, 12 h. Thermal ellipsoids shown at 50% probability. [b] Yield of isolated product is given.

Methoxy-substituted substrates worked poorly, with only the *ortho* substitution working (8%), because of competing oligomerization of highly unstable quinone imines. To overcome the problem presented by alkoxy-substituted indoles, we used a trifluoroethoxy group,[17] which resulted in the formation of the desired indoles in good yields (45% and 70%, for *ortho*- and *meta*- substitution, respectively). The acetate group in the *meta*-position also works well, however, it gives a mixture of the desired indole and de-acetylated indole in a 1:1 ratio (64%).

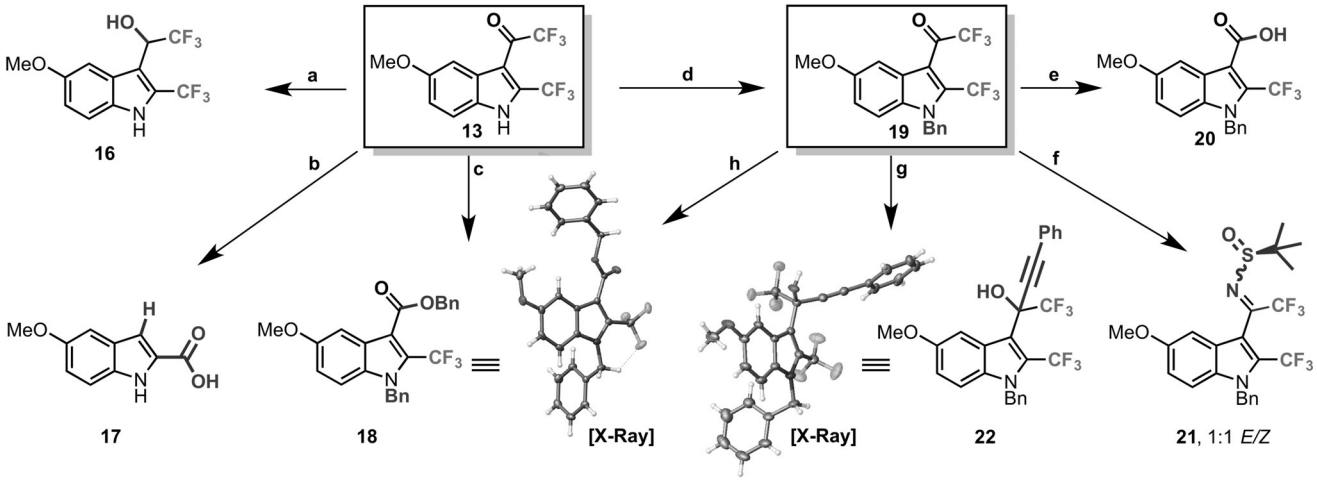
To demonstrate the scalability of this new methodology, we performed a 25 mmol scale reaction on our generic substrate (**11a**), thus giving the desired indole **13** in 89% yield (Scheme 3). This result is comparable to that obtained on 1.25 mmol scale as shown in Table 2.

An added benefit to this indole method is the resultant trifluoroacetyl functionality,[18] which can be utilized for a diverse variety of synthetic transformations.[19] This utility is showcased in Table 3, where the free (**13**) and N-benzyl (**19**) indoles are subjected to conditions which make possible reactivity associated with both ketones and esters. Reaction steps a, f, and g utilize the trifluoroacetyl group as a traditional ketone to give reduction, conversion into the chiral imine, and addition, respectively. When reaction conditions that utilize the trifluoromethyl component as a leaving group are applied, ester-like reactivity is observed. Highlighting this are esterifications in steps c and h, and hydrolysis in step e. It is remarkable that by changing the carbonate counterion from sodium to cesium (step d versus c), both N-alkylation and esterification occurred in one pot. Based on previous research,[20] along with our own observations, trace water mediates the reaction via a carboxylate intermediate, which then reacts with benzyl bromide to afford the ester. When **13** is subjected to the same hydrolysis conditions as **19**, all fluorines are lost and the indole-2-carboxylic acid (**17**) is generated. This serendipitous transformation provides a high-yielding metal-free route to indole-2-carboxylic acids.



Scheme 3. Large-scale synthesis of the indole **13**.

Table 3: Trifluoroacetyl group as a versatile synthon.



Reaciton consitions:[21] a) $NaBH_4$, $NaHCO_3$, MeOH, RT, 97%; b) NaOH, 1:10 THF/H_2O, reflux, 91%; c) BnBr, Cs_2CO_3, wet DMF, 90°C, 92%; d) BnBr, Na_2CO_3, DMF, 90°C, 86%; e) NaOH, 1:10 THF/H_2O, reflux, 97%; f) (*S*)-(−)-2-methyl-2-propanesulfinamide, $Ti(OiPr)_4$, THF, reflux, 98% (1:1 *E*/*Z*); g) Phenylacetylene, $Cu(OAc)_2$, K_2CO_3, DMSO, 70°C, 89%; h) BnBr, Cs_2CO_3, wet DMF, 90°C, 85%. Thermal ellipsoids shown at 50% probability. DMF = *N*,*N*-dimethylformamide, DMSO = dimethylsulfoxide, THF = tetrahydrofuran.

In summary, we report a new, one-pot, scalable and metal-free synthesis of 2-trifluoromethyl-3-trifluoroacetyl NH-indoles from N-Boc anilines and hfacac. This new reaction is regioselective, and works well with akyl, aryl, halide, and other moderately electron-donating groups as substituents on the parent aniline. We have further demonstrated the versatility of the trifluoroacetyl group, wherein it undergoes both ketone-like and ester-like chemistry.

Acknowledgements

Financial support for this work was provided by The University of Arizona. We thank Dr. Sue Roberts, Dr. Jonathan J. Loughrey, Isaac Chogii, Pradipta Das, and Brandon R. Smith for X-ray crystallographic collection and analysis.

Keywords: dearomatization · fluorine · indoles · nitrogen heterocycle · synthetic methods

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 2243–2247
Angew. Chem. **2016**, *128*, 2283–2287

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Received: December 1, 2015
Published online: January 8, 2016

