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Silver-catalyzed one-pot cyclization/fluorination of 2-alkynylanilines: highly efficient synthesis of structurally diverse fluorinated indole derivatives†

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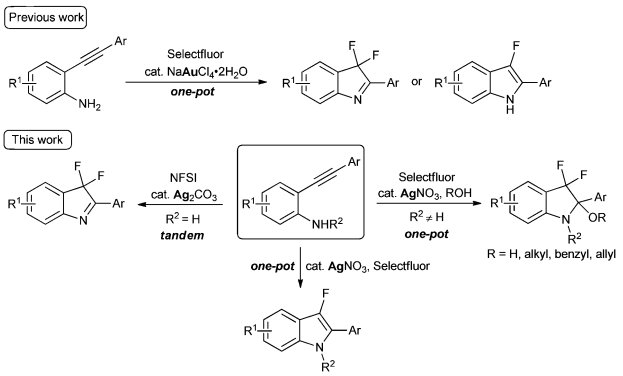
Highly efficient approaches to obtain structurally diverse fluorinated indole derivatives have been realized through the Ag-catalyzed one-pot cyclization/fluorination of 2-alkynylanilines in the presence of NFSI or Selectfluor.

Indole derivatives are widely found in naturally occurring products, bioactive compounds and pharmaceuticals.[1] Consequently, the synthesis and functionalization of indoles have attracted significant attention of chemists.[2,3] On the other hand, the fluorine atom is one of the most important groups in the area of organic chemistry. Fluorinated compounds often exhibit remarkably different chemical, physical and pharmacological properties in comparison with their fluorine-free analogues,[4] which make them widely applied in diverse areas ranging from pharmaceuticals to materials science.[5] Moreover, the introduction of fluorine atoms into bioactive heterocycles such as indoles would bring about enhanced and/or altered biological activities and lead to the discovery of novel biomolecules and potential therapeutic agents.[4b,d,5a]

Over the past decades, a large number of methods have been developed for the synthesis of fluorinated indole derivatives,[6,7] which mainly rely on the direct fluorination of the "preformed" indole ring. Given that indoles can be conveniently synthesized through the transition metal-catalyzed cyclization of readily available 2-alkynylanilines,[2a–c] the combination of cyclization and fluorination reaction in a single operation would provide highly efficient approaches to obtain fluorinated indole derivatives, which obviates the isolation and purification of the indole intermediates. Very recently, Michelet and co-workers reported a $NaAuCl_4 \cdot 2H_2O$-catalyzed aminofluorination of *N*-unprotected 2-alkynylanilines to afford 3-fluoroindoles and 3,3-difluoro-3*H*-indoles by using a one-pot, two-step procedure (Scheme 1).[8] Arguably, it is still highly desirable to develop new methods that can employ inexpensive metal salts as the catalyst and get rapid access to structurally diverse fluorinated indole derivatives. Following our continued interest in the synthesis of functionalized indoles,[9] we herein wish to report the efficient synthesis of various fluorinated indole derivatives (3,3-difluoro-3*H*-indoles, 3-fluoroindoles, 2-hydroxy-3,3-difluoroindolines and 2-alkoxy-3,3-difluoroindolines) through the sequential cyclization/fluorination reaction of 2-alkynylanilines catalyzed by the air-stable and low-cost silver salts (Scheme 1).



Scheme 1 Synthesis of fluorinated indole derivatives from 2-alkynylanilines.

Obviously, it is operationally more convenient to realize the aminofluorination of 2-alkynylanilines through a tandem process rather than the previously reported one-pot, two-step method.[8] Thus, we initially investigated the tandem cyclization/fluorination reaction of 2-(phenylethynyl)aniline **1a** with *N*-fluorobenzenesulfonimide (NFSI) by using relatively cheap metal salts as the catalyst (ESI,† Table S1). After screening various parameters, the desired **2a** was obtained in 81% yield by using 10 mol% Ag_2CO_3 as the catalyst in combination with 2.0 equiv. of NFSI as the fluorinating reagent in 1,4-dioxane at 60 °C (ESI,† Table S1, entry 12).[10] Other silver salts such as $AgNO_3$, AgOAc, and AgOTs showed comparable reactivity to Ag_2CO_3 (ESI,† Table S1, entries 17–20). However, $NiCl_2 \cdot 6H_2O$, CuCl, $Cu(OAc)_2 \cdot H_2O$, and $FeCl_3 \cdot 6H_2O$ all resulted in the decomposition of **1a** (ESI,† Table S1, entries 1–4). It is worth noting that this protocol does not require the exclusion of light, air or moisture.

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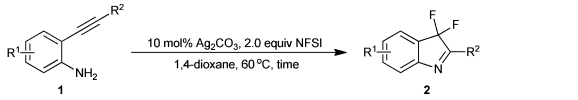
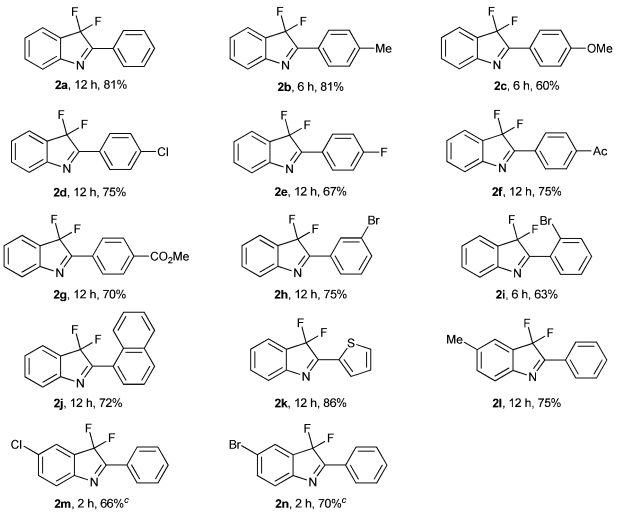
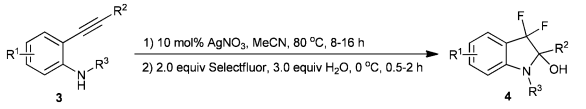
Table 1 Ag-catalyzed tandem cyclization/fluorination reaction of *N*-unsubstituted 2-alkynylanilines[a,b]

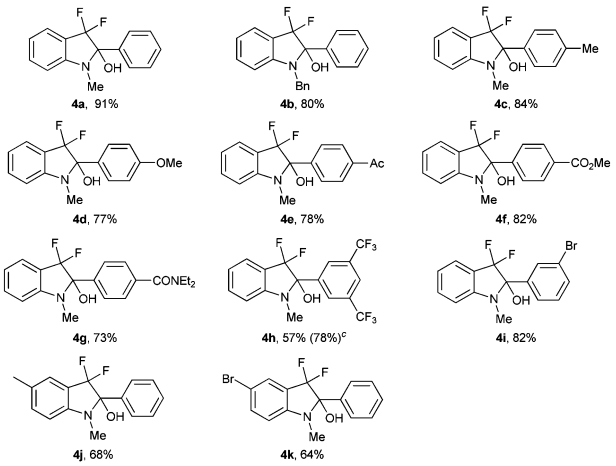




[a] Reaction conditions: **1** (0.3 mmol), Ag_2CO_3 (10 mol%), NFSI (2.0 equiv.), and 1,4-dioxane (3.0 mL, without degassing) at 60 °C under air. [b] Isolated yield. [c] At 100 °C.

Table 2 Ag-catalyzed one-pot synthesis of 3,3-difluoroindolin-2-ols from *N*-substituted 2-alkynylanilines[a,b]

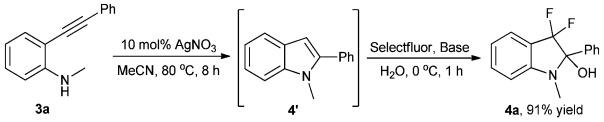




[a] The reaction was run on a 0.3 mmol scale under air. For details, see the ESI. [b] Isolated yield. [c] $NaHCO_3$ (1.0 equiv.) was added.

We next moved on to examine the substrate scope of this tandem reaction. As shown in Table 1, various *N*-unsubstituted-2-alkynylanilines with both electron-donating and electron-withdrawing functional groups (*e.g.*, ether, halogen, ester, and ketone) could participate in the reaction to afford the desired products in 60–81% yields (Table 1, **2b–2i**). 2-Alkynylanilines bearing aryl, heteroaryl, or bulky naphthyl groups all delivered the products in good yields (Table 1, **2a**, **2j**, and **2k**). However, the corresponding alkyl or TMS-substituted alkynylanilines led to the decomposition of the starting materials.

With the aim of obtaining 3,3-difluoroindolin-2-ols, we attempted to apply this Ag-catalyzed tandem protocol to the reaction of *N*-substituted 2-alkynylanilines with NFSI and H_2O.[7e] Unfortunately, the reaction of *N*-methyl-2-(phenylethynyl)aniline **3a** was always accompanied by side reactions and the desired product **4a** could only be obtained in the highest NMR yield of 56% after screening various parameters including the catalyst, solvent, base, and fluorinating reagent. Then we turned our attention to the one-pot, two-step cyclization/difluorohydroxylation manipulation. Pleasantly, the simple cyclization product of **3a** (1-methyl-2-phenyl-1*H*-indole **4′**) could be obtained in a quantitative yield by using 10 mol% $AgNO_3$ as the catalyst and MeCN as the solvent at 80 °C under air (ESI,† Table S2, entry 11). Finally, a one-pot protocol to obtain 3,3-difluoroindolin-2-ol **4a** was developed by the addition of 2.0 equiv. of Selectfluor and 3.0 equiv. of H_2O to the cyclization reaction mixture of **3a** (eqn (1); ESI,† Table S3).



(1)

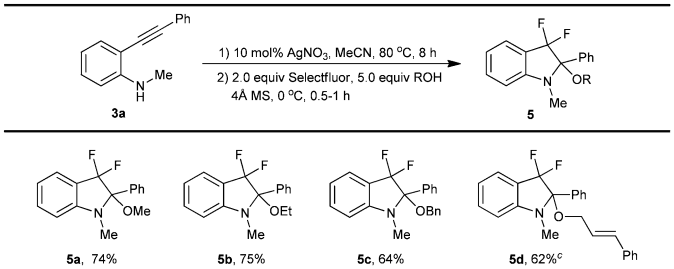
Subsequently, we were pleased to found that a variety of *N*-substituted 2-alkynylanilines could undergo the $AgNO_3$-catalyzed one-pot cyclization/difluorohydroxylation reaction to afford 3,3-difluoroindolin-2-ols in good to excellent yields under optimized conditions (Table 2). Like the above-mentioned tandem reaction of *N*-unsubstituted-2-alkynylanilines **1**, this one-pot protocol also tolerated a broad range of important functionalities such as methoxy, trifluoromethyl, halogen, ester, ketone, and amide (Table 2, **4d–4i**). When R^2 was the bis-trifluoromethyl-substituted phenyl group, 1.0 equiv. of $NaHCO_3$ was required to promote the full conversion of the 3-unsubstituted indole intermediate (Table 2, **4h**). We suspected that the basic conditions might facilitate the nucleophilic attack of the hydroxyl anions.[7e] When *N*-Boc, Cbz or Ac-2-(phenylethynyl)anilines were employed as the substrate, no reaction occurred under the standard conditions.

The intermolecular reaction of other nucleophiles with 2-alkynylanilines and Selectfluor was investigated next. It was found that various alcohols such as methanol, ethanol, benzyl alcohol, and allyl alcohol underwent cyclization/difluoroalkoxylation to afford the 2-alkoxy-3,3-difluoroindolines **5** in good yields (Table 3). In these cases, an N_2 atmosphere and 4 Å molecular sieves were beneficial to the reaction to prevent the competition reaction of H_2O.

Finally, this one-pot protocol was applied to the synthesis of 3-fluoroindoles. As illustrated in Table 4, 2-alkynylanilines with the electron-withdrawing groups delivered the desired products **6** in moderate yields. However, the addition of $NaHCO_3$ to the reaction mixture could not improve the product yield (Table 4, **6b**).

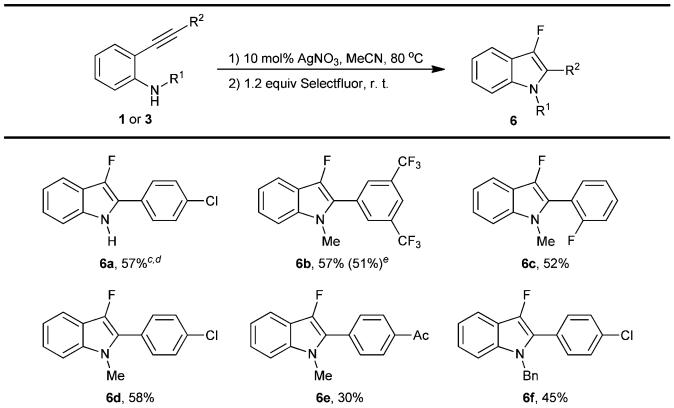
A tentative mechanism is proposed in Scheme 2. The silver first coordinates with the triple bond of 2-alkynylaniline to trigger the intramolecular nucleophilic addition. The resulting Ag(I) intermediate **IM2** is quenched by a proton to afford indole **IM3**, which undergoes monofluorination, difluorination, difluorohydroxylation and

Table 3 Ag-catalyzed one-pot two-step cyclization/difluoroalkoxylation of *N*-methyl-2-alkynylanilines[a,b]

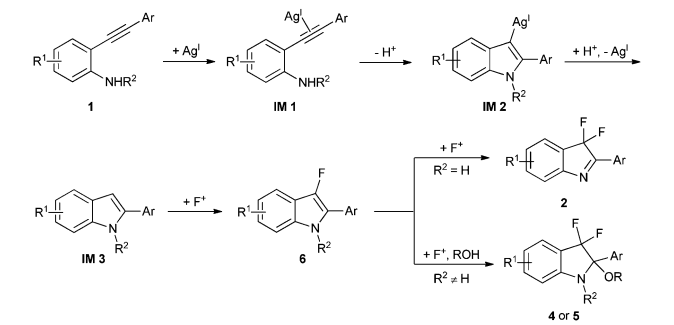


[a] The reaction was run on a 0.3 mmol scale under N_2. For details, see the ESI. [b] Isolated yield. [c] $NaHCO_3$ (1.0 equiv.) was added.

Table 4 Ag-catalyzed one-pot synthesis of 3-fluoroindoles[a,b]



[a] The reaction was run on a 0.3 mmol scale under N_2. For details, see the ESI. [b] Isolated yield. [c] 1.3 equiv. of Selectfluor was used. [d] 3,3-Difluoro-3*H*-indole **2d** was also obtained in 25% yield. [e] 1.0 equiv. of $NaHCO_3$ was added.



Scheme 2 Proposed mechanism.

difluoroalkoxylation with NFSI or Selectfluor to form 3-fluoroindoles, 3,3-difluoro-3*H*-indoles, 2-hydroxy-3,3-difluoroindolines and 2-alkoxy-3,3-difluoroindolines, respectively.[7e] The oxidation of **IM2** to Ag(II) species by NFSI and subsequent reductive elimination and electrophilic fluorination is also a possible pathway to obtain 3,3-difluoro-3*H*-indoles **2**.[11]

In conclusion, we have developed a highly efficient cyclization/fluorination reaction of 2-alkynylanilines with electrophilic fluorinating reagents in a single operation by employing inexpensive and air-stable silver salts as the catalyst. The current protocol conveniently affords structurally diverse fluorinated indole derivatives including 3-fluoroindoles, 3,3-difluoro-3*H*-indoles, 2-hydroxy-3,3-difluoroindolines and 2-alkoxy-3,3-difluoroindolines.

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