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# Facile Synthesis of Azaarene-Substituted 3-Hydroxy-2-oxindoles via Brønsted Acid Catalyzed $sp^3$ C–H Functionalization

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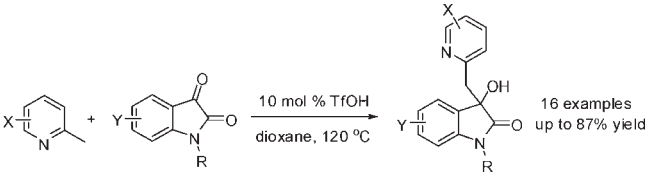
## ABSTRACT




**Brønsted acid catalyzed functionalization of $sp^3$ C–H bonds in 2-methyl azaarenes has been achieved in the reaction with isatins. This method provides facile synthesis of biologically important azaarene-substituted 3-hydroxy-2-oxindoles in one step in moderate to good yields.**

3-Substituted-3-hydroxy-2-oxindoles are key structural motifs which recurrently appear in a large array of alkaloids and natural products with diverse biological activities such as potent antioxidant, anticancer, anti-HIV, and neuroprotective properties.[1] Representative examples are convolutamydines, maremycins, donaxaridine, SM-130686, dioxibrassinine, and welwitindolinone C (Figure 1). Consequently, the 3-substituted-3-hydroxy-2-oxindole framework has been an intensively investigated synthetic target, and some elegant methods emerged such as transition-metal-catalyzed cyclization of ortho-prefunctionalized α-ketoanilides[2] (boronate or halide) or α-ketoamides[3] as well as direct hydroxylation of oxindoles.[4] In contrast, direct addition of nucleophiles to isatins represents the most straightforward manner to construct this motif. Thus direct catalytic arylation,[5] alkylation,[6] Friedel–Crafts reactions,[7] and organocatalyzed aldol[8] or Morita–Baylis–Hillman[9] reactions have been employed using isatins as electrophiles. However, all the known methods deal with the synthesis of aryl or alkyl substituted 3-hydroxy-2-oxindoles. As far as we know, no method for the synthesis of azaarene-substituted 3-hydroxy-2-oxindoles has been reported, although

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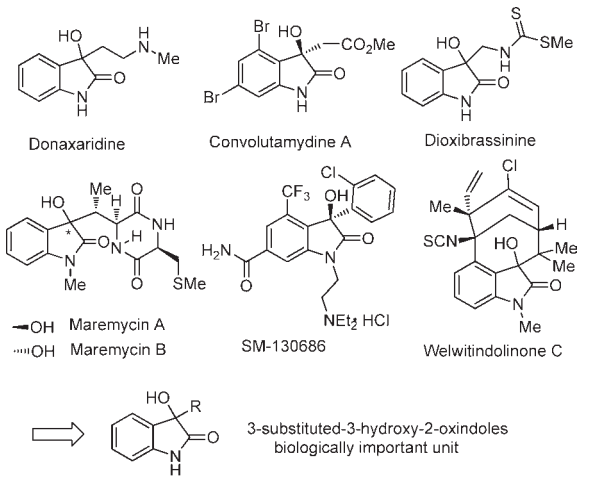



**Figure 1.** Representative natural products and pharmaceuticals possessing 3-substituted 3-hydroxy-2-oxindoles.

azaarene-substituted 3-hydroxy-2-oxindoles hold great potential for biological activities and pharmaceutical utility.[10] The biological effects are known to vary with the substituent at the C3 position of oxindoles.[1e] Thus development of an efficient synthetic route to this architecture is highly desirable.

Quite recently, activation of the $sp^3$ C−H bond in 2-methyl azaarenes has been achieved using Lewis acids as the sole catalyst.[11] However, only sporadic examples were reported and functionalization of the $sp^3$ C−H bond in 2-methylazaarenes remains largely unexplored despite its synthetic utility.[12] To the best of our knowledge, no example of Brønsted acid catalyzed $sp^3$ C−H bond functionalization of azaarenes has been reported although Brønsted acids have been used to effect a wide variety of transformations.[13] As part of our ongoing interest in C−H bond activation as well as synthesis of diversity-oriented structures,[14] we now report the first Brønsted acid catalyzed $sp^3$ C−H functionalization of 2-methylazaarenes, leading to facile C−C formation.

**Scheme 1.** Proposed Brønsted Acid Catalyzed $sp^3$ Functionalization of 2-Methylazaarenes

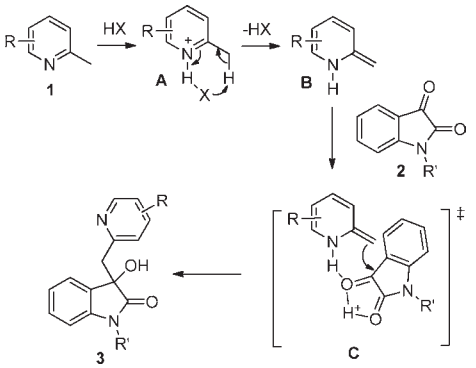
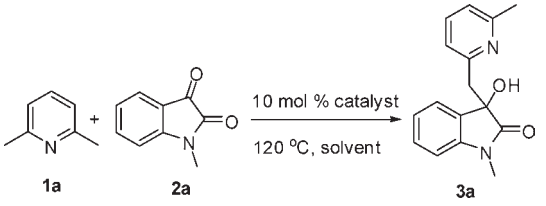



**Table 1.** Screening of the Catalyst[a]




| entry | catalyst | solvent | yield (%)[b] |
|---|---|---|---|
| 1 | $CH_3SO_3H$ | dioxane | 76 |
| 2 | $p$-$CH_3C_6H_4SO_3H$ | dioxane | 71 |
| 3 | $CF_3COOH$ | dioxane | 44 |
| 4 | $Tf_2NH$ | dioxane | 70 |
| 5 | TfOH | dioxane | 85 |
| 6 | TfOH | THF | 38 |
| 7 | TfOH | toluene | 41 |

[a] Reactions were conducted with **1a** (0.75 mmol), **2a** (0.3 mmol), catalyst **I** (0.03 mmol) in 1 mL of solvent at 120 °C for 48 h. [b] Isolated yield.

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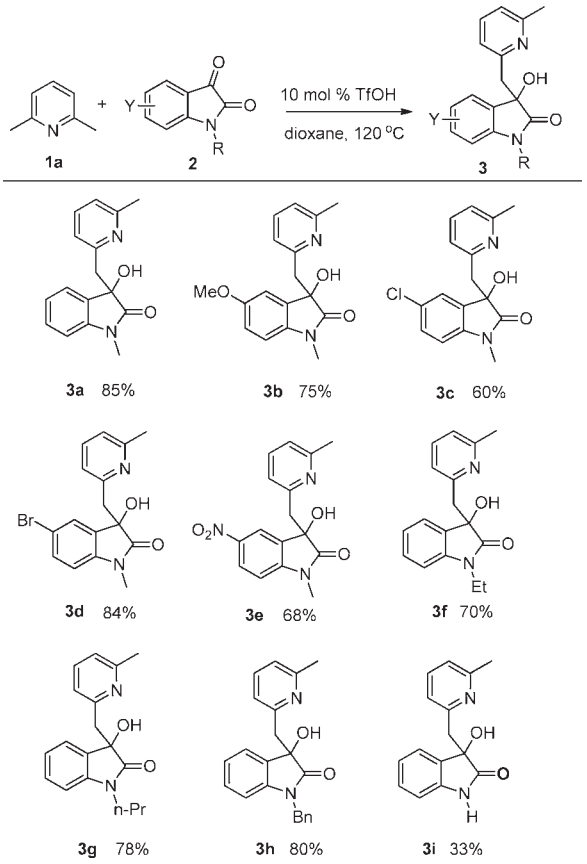
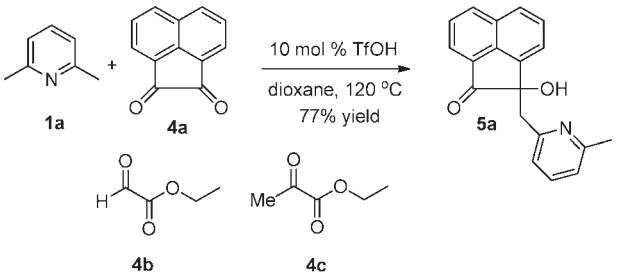
**Scheme 2.** Scope of Isatins[a]




[a] Reactions were conducted with 2,6-lutidine **1** (0.75 mmol), isatins **2** (0.3 mmol), TfOH (0.03 mmol) in 1 mL of dioxane at 120 °C for 48 h. The yields indicated are the isolated yield by column chromatography.

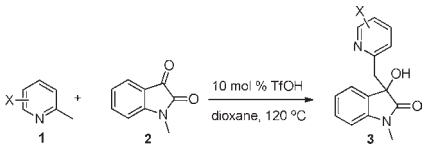
**Scheme 3.** Reaction of **1a** with Other Dicarbonyls

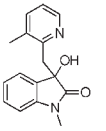
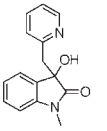
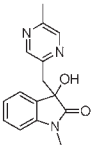
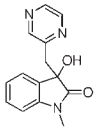
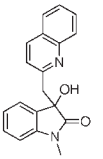
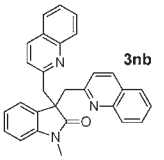
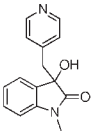
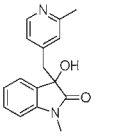
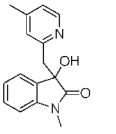



As outlined in Scheme 1, we envision that protonation of 2-methyl-substituted azaarenes **1** should give pyridinium **A**. As a result of the enhanced acidity of the benzylic protons and the endogenous proton abstraction, C−H cleavage should occur to give enamine **B**. Synergistically, protonation of the carbonyl group of isatin renders it more electrophilic such that enamine **B** can nucleophilically add via transition state **C** (Scheme 1) to afford the coupled product **3**.

To test this hypothesis, our initial studies were conducted on the reaction of 2,6-lutidine (**1a**) and

**Table 2.** Scope of 2-Methylazaarenes[a]




| entry | substrates | product | | yield (%)[b] |
|---|---|---|---|---|
| 1 |  |  | **3j** | 45 |
| 2 |  |  | **3k** | 64 |
| 3 |  |  | **3l** | 54 |
| 4 |  |  | **3m** | 38 |
| 5 |  |  | **3na** | n.d.[c] |
| 6 |  |  | **3nb** | 34 |
| 7 |  |  | **3o** | 58 |
| 8 |  |  | **3pa** | 37 |
| | |  | **3pb** | 31 |

[a] Reactions were conducted with **1** (1.2 mmol), **2** (0.3 mmol), TfOH (0.03 mmol) in 1 mL of dioxane at 120 °C for 48 h. [b] Isolated yield by column chromatography. [c] Not determined.

1-methylindoline-2,3-dione (**2a**) in 1,4-dioxane catalyzed by Brønsted acids (10 mol %) at 120 °C. It was found that

commonly used Brønsted acids such as methanesulfonic acid (MsOH) and *p*-toluenesulfonic acid gave good yields (Table 1, entries 1−2). A lower yield was obtained for trifluoroacetic acid, a weaker acid (Table 1, entry 3).

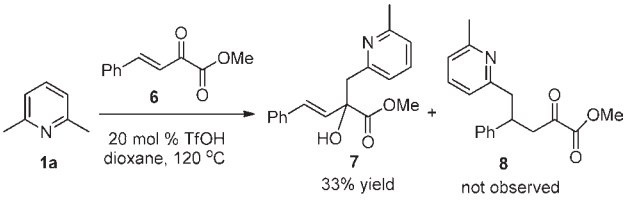
Trifluoromethanesulfonimide ($Tf_2NH$), a widely used strong Brønsted acid in synthetic organic chemistry,[15] also gave good yield (Table 1, entry 4). Eventually, the best result was obtained (85% yield) with trifluoromethanesulfonic acid (TfOH) in dioxane (Table 1, entry 5). However, other solvents gave inferior results (Table 1, entries 6−7).

With the optimized conditions in hand, we examined a variety of *N*-substituted isatins in the reaction with 2,6-lutidine (Scheme 2). Both electron-donating and -withdrawing substituents, including halogen groups, in the isatin phenyl ring are well-tolerated, affording the desired products in yields ranging from 60% to 84% (Scheme 2, **3a**−**3e**), where there seems no direct correlation between the efficiency of this reaction and the electronic effects of these substituents. Next, a range of *N*-alkylated isatins were allowed to react with 1-methylindoline-2,3-dione (**2a**). *N*-Ethyl, -propyl, and -benzyl isatins are suitable substrates, and **3f**−**h** were isolated in good yields (70−80%). However, the reaction of simple NH protic isatin afforded product **3i** in only 33% yield, which probably resulted from the decomposition of isatin. The scope of 2-methylazaarenes was then investigated, and the results are given in Table 2. The 2-methyl group in pyridine, quinoline, and quinoxaline rings can smoothly add to *N*-methylisatin to afford the corresponding 3-hydroxy-2-oxindoles in moderate to good yields (Table 2, **3j**−**3m**). Notably, when 2-methylquinoline was used as the substrate, the analogous product **3na** was not detected. Instead, the 1,2 addition product **3nb** was isolated in 34% yield. Thus in situ generated **3na** is proposed to undergo a subsequent acid-catalyzed dehydrative coupling reaction to furnish product **3nb**. In sharp contrast, this selectivity was not observed in the reported Lewis acid catalyzed addition of 2-methylquinoline to imines and enones.[12] Notably when 2,4-lutidine was employed as a substrate, two isometric products (**3pa** and **3pb**) were isolated in essentially the same yield. This implies that the 2- and 4-methyl groups are of comparable reactivity. Indeed, when only a 4-methyl group is present as in 4-picoline, product **3o** was also obtained in 58% yield.

Encouraged by the success in isatin substrates, we attempted to extend the scope to other 1,2-dicarbonyls. Gratifyingly, when diketone **4a** was allowed to react with **1a**, the corresponding product **5a** was isolated in 77% yield. However, other acyclic 1,2-dicarbonyls such as ethyl glyoxylate **4b** and methyl pyruvate **4c** failed to react under the same conditions (Scheme 3).

To probe the selectivity of 1,2 addition versus 1,4 addition of enones, the reaction of (*E*)-methyl 2-oxo-4-phenylbut-3-enoate (**6**) and **1a** was carried out (20 mol % TfOH). Interestingly, only the 1,2 addition product **7** was isolated (33% yield, Scheme 4). This observed exclusive 1,2 addition selectivity agrees with the proposed mechanism in Scheme 1.

**Scheme 4.** 1,2 Addition vs 1,4 Addition




In summary, we present the first Brønsted acid catalyzed $sp^3$ C−H functionalization of 2-methyl-substituted azaarenes for the efficient construction of substituted 3-hydroxy-2-oxindoles. A relatively broad scope of isatins and azaarenes has been defined, and the coupled products were isolated in moderate to good yields. This method provides an efficient and new protocol to construct this biologically important architecture in a single step. The success of this reaction should broaden the synthetic utility of Brønsted acids in the catalytic functionalization of $sp^3$ C−H bonds in organic synthesis.

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**Supporting Information Available.** Additional experimental procedures and spectroscopic data of new products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.