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Lewis Acid and Fluoroalcohol Mediated Nucleophilic Addition to the C2 Position of Indoles

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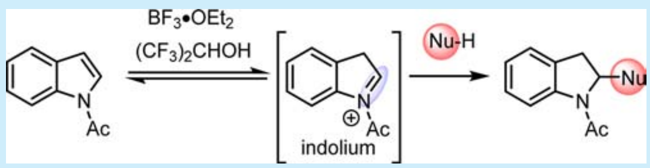
Supporting Information

ABSTRACT: Indole readily undergoes nucleophilic substitution at the C3 site, and many indole derivatives have been functionalized using this property. Indole also forms indolium, which allows electrophilic addition in acidic conditions, but current examples have been limited to intramolecular reactions. C2 site-selective nucleophilic addition to indole derivatives using fluoroalcohol and a Lewis acid was developed.

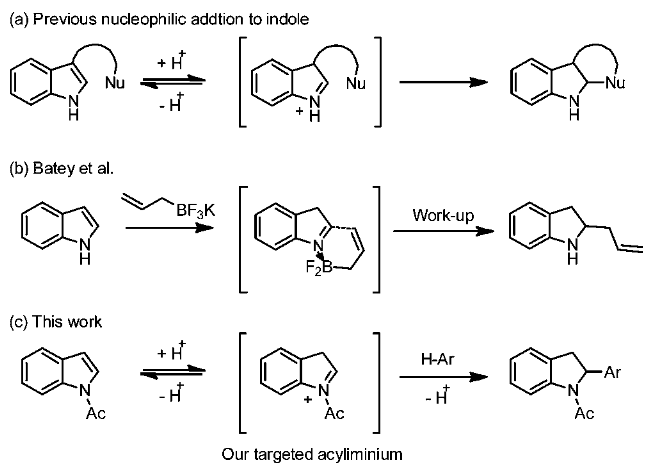


Heterocyclic compounds are the core structures in naturally and artificially available bioactive compounds, making efficient construction methods of them and their derivatives very much in demand in organic synthesis.[1] Two general strategies for the derivatization of heterocycles are used; one is the cyclization of heteroatom-containing compounds, and the other is the functionalization of existing heterocycles. The latter method is more facile when the desired heterocycle is readily available. Among various heterocycles, we have focused on indole because it is an important building block for organic synthesis,[2] easily synthesized,[3] and commercially available.

Indoles generally act as nucleophiles at the C3 position because of the conjugation to the lone pair on the N atom. This has resulted in many reports on the functionalization at the C3 position by a substitution reaction.[4] In contrast, electrophilic addition reactions toward indoles have been limited.[5] Addition of an aryl compound at the C3 position of 3-alkyl-*N*-acetylindole using $FeCl_3$ was reported.[6] The proposed mechanism for this reaction is via the formation of a cationic intermediate at the C3 position, which is subjected to nucleophilic attack by an electron-rich aromatic compound.

For transformations at the C2 position of indoles, dehydrogenative silylation using an earth-abundant metal catalyst was recently reported.[7] Generally, electrophilic addition reactions have been investigated via the formation of indolium intermediates to produce indoline derivatives.[8] Unfortunately, the latent nucleophilicity of indole at the C3 position facilitates dimerization.[9] Therefore, electrophilic C2 transformations of indole have been limited to intramolecular reactions (Scheme 1a). This means there is limited access to C2-functionalized indolines. To improve the availability of transformations at the C2 position, intermolecular reactions are much more desirable. Formally, intermolecular electrophilic additions of indolium intermediates have been achieved using triallylic boranes[10] or allylic trifluoroborates.[11] These reactions were promoted by formation of a N−B bond in the first step, meaning they are mechanistically intramolecular (Scheme 1b).

Scheme 1. Nucleophilic Addition to Indoles



To achieve true intermolecular electrophilic addition at the C2 position of indole, we focused on controlling the following factors: (1) nucleophilicity at the C3 position of indole, (2) formation and stabilization of the indolium intermediate, and (3) choice of an appropriate proton source for the C3 position.

To suppress the nucleophilicity of indole at the C3 position, which can result in dimerization, we decided to introduce an acyl group on the N atom of indole. This also suppresses the formation of the indolium intermediate because of the electron-withdrawing nature of the acyl group. Additionally, although

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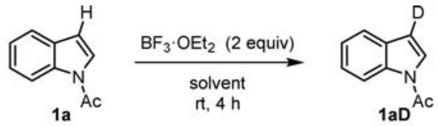
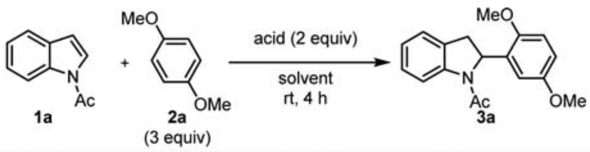
Table 1. H/D Exchange Optimization[a]



entry	solvent (D source)	deuteration ratio (%)[b]
1	$(CF_3)_2CHOD$	86
2[c]	$(CF_3)_2CHOD$	0
3	D_2O	3
4	CD_3OD	5
5	$(CH_3)_2CHOD$	2
6	CF_3COOD	77

[a]Reaction conditions: **1a** (0.3 mmol), solvent (0.5 mL), and BF_3·OEt_2 (0.6 mmol), rt, 4 h. [b]Determined by ^{1}H NMR. [c]Reaction carried out without BF_3·OEt_2.

Table 2. Optimization of the Reaction Conditions[a]



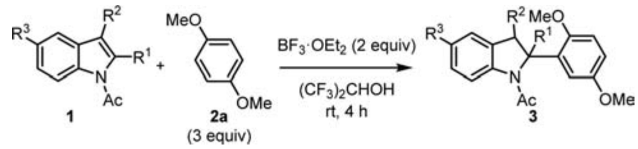
entry	acid	solvent	yield (%)[b]
1	BF_3·OEt_2	$(CF_3)_2CHOH$	79
2	$AlCl_3$	$(CF_3)_2CHOH$	67
3	$FeCl_3$	$(CF_3)_2CHOH$	61
4	$Sc(OTf)_3$	$(CF_3)_2CHOH$	40
5	TfOH	$(CF_3)_2CHOH$	56
6	BF_3·OEt_2	CF_3COOH	56
7[c]	BF_3·OEt_2	$(CF_3)_2CHOH$	N.D.[d]

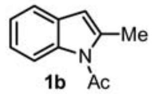
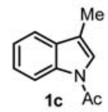
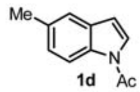
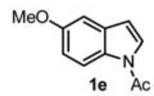
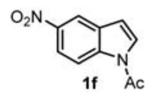
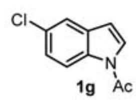
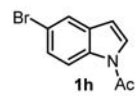
[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.9 mmol), solvent (0.5 mL), and BF_3·OEt_2 (0.6 mmol), rt, 4 h. [b]Isolated yield. [c]Reaction was carried out using indole instead of **1a**. [d]We recovered 20% of indole and >99% of **2a**.

acyliminium species can be formed from *N*-acylaminal in Lewis acidic conditions,[12] acylindolium intermediates have not been used in intermolecular electrophilic reactions because of the spontaneous transformation to *N*-acylindole.[13] Because of these factors, electrophilic attack at the C2 position of *N*-acylindoles has not been explored in the past.

We have focused on promoting the formation of a *N*-acylindolium intermediate using an additive and a proton source. To screen possible reaction conditions, the deuteration ratio of *N*-acetylindole (**1a**) at the C3 position was measured in the presence of a variety of Lewis acidic additives and a number of deuterated solvents (Table 1 and Supporting Information, SI). The highest H/D exchange was observed for the combination of $(CF_3)_2CHOD$ as the solvent and BF_3·OEt_2 as the additive (Table 1, entry 1). BF_3·OEt_2 is clearly important in the formation of the indolium intermediate, as no deuteration was observed without BF_3·OEt_2 (Table 1, entry 2). The pK_a of the solvent should be important because a conjugate base of a solvent with high pK_a would more strongly coordinate to BF_3·OEt_2 and suppress the Lewis acidity. Furthermore, the nucleophilicity of the solvent should also be optimized to avoid undesired addition of solvent

Table 3. Range of the Reaction with Various Substituted Indoles[a]



entry	1	yield (%)[b]
1 2[c]	 **1b**	trace trace
3 4[c]	 **1c**	trace 36
5	 **1d**	78
6	 **1e**	10
7	 **1f**	30
8	 **1g**	73
9	 **1h**	82

[a]Reaction conditions: **1a** (0.3 mmol), solvent (0.5 mL), and BF_3·OEt_2 (0.6 mmol), rt, 4 h. [b]Isolated yield. [c]Reaction was carried out at 60 °C.

to the indolium intermediate. Because of the lower pK_a and nucleophilicity, $(CF_3)_2CHOD$ performed better than other solvents, such as CD_3OD, D_2O, and $(CH_3)_2CHOD$.[14] When an aprotic solvent, such as dichloromethane or acetonitrile, was used with CF_3CO_2D and BF_3·OEt_2, no deuteration of *N*-Ac-indole was observed (see SI).

Having discovered the optimum reaction conditions for the indolium formation, we then investigated the intermolecular C2 transformation of **1a** using 1,4-dimethoxybenzene (**2a**) as the nucleophile.[15] As expected, the combination of $(CF_3)_2CHOH$ and BF_3·OEt_2 promoted nucleophilic addition at the C2 position of indole in 79% yield (Table 2, entry 1). Other Lewis and Brønsted acids promoted the reaction in moderate yields (Table 2, entries 2−5). The use of MeOH or *i*-PrOH as a solvent inhibited the reaction because the indolium intermediate did not form (see SI). CF_3CO_2H also worked as a solvent and gave the product in moderate yield (Table 1, entry 6). Unprotected indole was not suitable for this reaction system; no product was observed; 80% of indole was consumed by dimer formation, and >99% of **2a** was recovered (Table 2, entry 7).

Next, we investigated the effect of substituents on the *N*-acetylindole framework. When the C2 position had a methyl group (**1b**), trace amounts of product were observed by GC-MS

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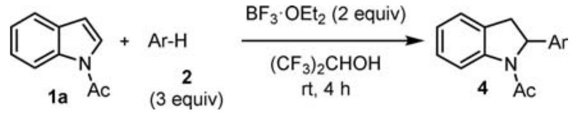
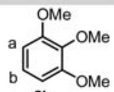
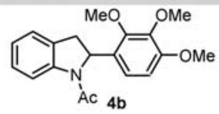
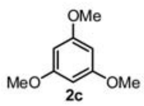
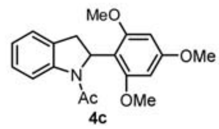
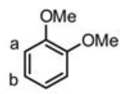
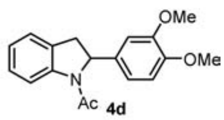
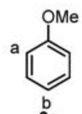
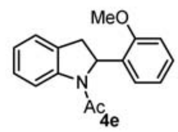
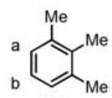
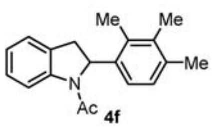
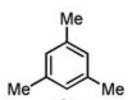
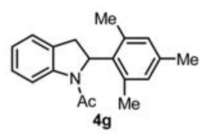
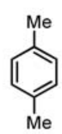
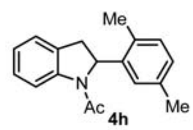
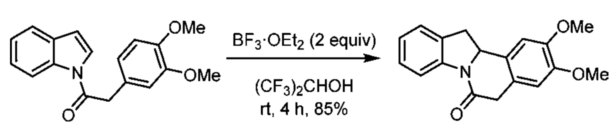
Table 4. Scope of the Reaction with Various Nucleophiles[a]



entry	Ar-H	yield (%)[b]	selectivity	main product
1	 2b	67	88 : 12	 4b
2	 2c	63	-	 4c
3	 2d	69	9 : 91	 4d
4	 2e	66	85 : 15	 4e
5	 2f	67	88 : 12	 4f
6	 2g	57	-	 4g
7	 2h	43	-	 4h

[a]Reaction condition: **1** (0.3 mmol), **2a** (0.9 mmol), solvent (0.5 mL), and $BF_3 \cdot OEt_2$ (0.6 mmol), rt, 4 h. [b]Isolated yield. [c]Selectivity was determined by ^1H NMR.

Scheme 2. Intramolecular Reaction To Give δ-Lactams



but could not be isolated (Table 3, entries 1 and 2). A methyl group at the C3 position also suppressed the reaction but gave **3c** at higher temperatures. Thus, the reaction was remarkably affected by steric hindrance (Table 3, entries 3 and 4). The electronic effect of indole was then investigated. The reaction proceeded without any loss of the activity with a methyl group at the C5 position (Table 3, entry 5). However, when a strongly electron-donating group, such as a methoxy group, was introduced, the yield was remarkably decreased with a commensurate increase in the dimerization of the indole (Table 3, entry 6). Nitro groups also suppressed the reactivity as an electron-withdrawing group is unlikely to facilitate the formation of the indolium intermediate (Table 3, entry 7). Chloro or bromo groups did not inhibit the reaction and gave the corresponding products in high yield (Table 3, entries 8 and 9).

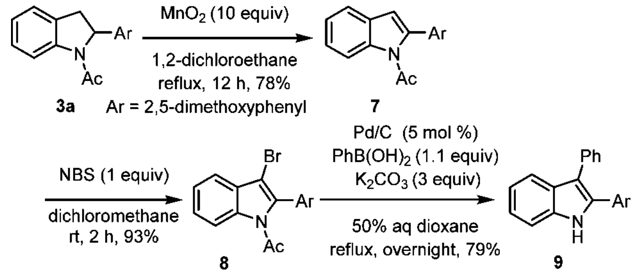
The scope of the reaction with aromatic compounds as nucleophiles is shown in Table 4. When 1,2,3-trimethoxybenzene (**2b**) was used, the reaction proceeded in 67% yield with high regioselectivity (Table 4, entry 1). 1,3,5-Trimethoxybenzene (**2c**) also gave the desired product with a similar yield (Table 4, entry 2). 1,2-Dimethoxybenzene (**2d**) reacted at the C4 position in good yield (Table 4, entry 3). Despite the steric hindrance, the C2 position of methoxybenzene (**2e**) gave the expected product in 66% yield with high selectivity (Table 4, entry 4). Reactions proceeded in moderate yield when a trialkylbenzene, such as **2f** or **2g**, was used (Table 4, entries 5 and 6). However, the yield decreased when dialkylbenzene (**2h**) was used, suggesting it is important that the substituents on nucleophile **2** be electron-donating (Table 4, entry 7). This was also observed when using toluene, furan, thiophene, pyrrole, or acetylacetone as **2** gave no or only a trace amount of product.

This C2 transformation of indoles was also applicable in intramolecular reactions to give δ-lactam compounds in high yield (Scheme 2). The resulting compound is an intermediate of the natural product, cryptaustoline.[16]

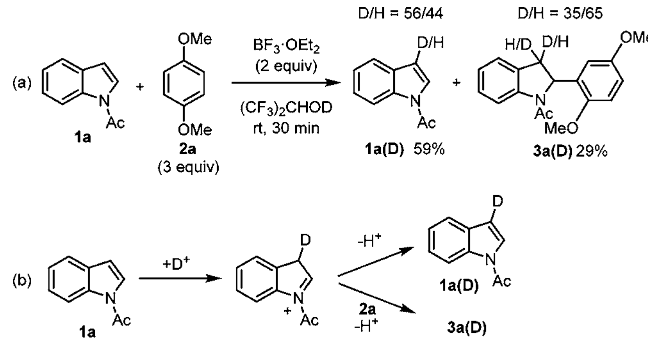
To make this method more useful, we synthesized a C2 and C3 diaryl-substituted indole (Scheme 3). **3a** was dehydrogenated in good yield using MnO_2 as the oxidant.[17] Selective bromination followed at the C3 site to give **8**.[18] The second aryl group was added by Suzuki coupling with simultaneous removal of the acetyl group due to the basic reaction conditions.[19]

We investigated the rate-determining step using $(CF_3)_2CHOD$ as a solvent and deuterium source at the C3 position of the product. The reaction was stopped at 30 min, and

Scheme 3. Synthesis of a C2 and C3 Diaryl-Substituted Indole 9 from 3a



Scheme 4. Determination of Rate-Determining Step of the Reaction



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the distribution of deuterium on **1a** and **3a** was evaluated. In these reaction conditions, 29% of **3a** was formed with a D/H ratio of 35:65 at the C3 position of **3a**, and 59% of **1a** was recovered with a D/H ratio of 56:44 at the C3 position (Scheme 4a). These results suggest that indolium is readily formed, and H/D exchange reaches equilibrium before the nucleophilic addition of **2a** (Scheme 4b). Therefore, we conclude that the nucleophilic addition by **2** was the rate-determining step.

In conclusion, we have exploited the formation of indolium from *N*-acetylindole using $BF_3 \cdot OEt_2$ in $(CF_3)_2CHOH$ to allow C2 site-selective intermolecular nucleophilic addition of an electron-rich aromatic compound. We believe that this approach opens a new synthetic strategy to produce more diverse indoline derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00629.

Experimental procedures and characterization of the product (PDF)

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Notes

The authors declare no competing financial interest.

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