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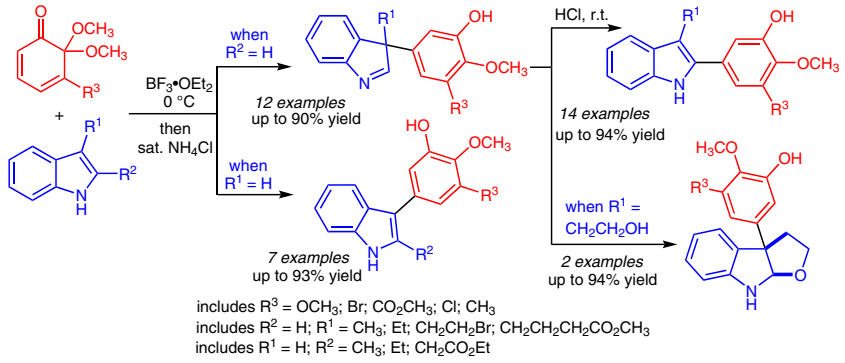
Facile Synthesis of 2-Arylindoles through Plancher-Type Rearrangement of 3-Alkyl-3-Arylindolenines

Santhosh Kumar Chittimalla*
Chennakesavulu Bandi
Vinod Kumar Gadi
Siva Ramakrishna Gunturu

Medicinal Chemistry Department, AMRI Singapore Research Centre, 61 Science Park Road, #05-01, The Galen, Science Park II, Singapore 117525, Singapore
santhosh.chittimalla@amriglobal.com
chemcsk@gmail.com



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Abstract 3-Alkylindoles on reaction with a cyclohexa-2,4-dien-1-one catalyzed by BF_3·OEt_2 gave the corresponding 3-alkyl-3-arylindolenines in high yields through a tandem Michael addition/aromatization sequence. In the presence of HCl, these indolenine derivatives underwent a facile Plancher-type C-3 to C-2 aryl rearrangement to deliver the corresponding 2-arylindoles.

Key words arylindoles, indolenines, Plancher rearrangement, cyclohexadienone, tandem reaction

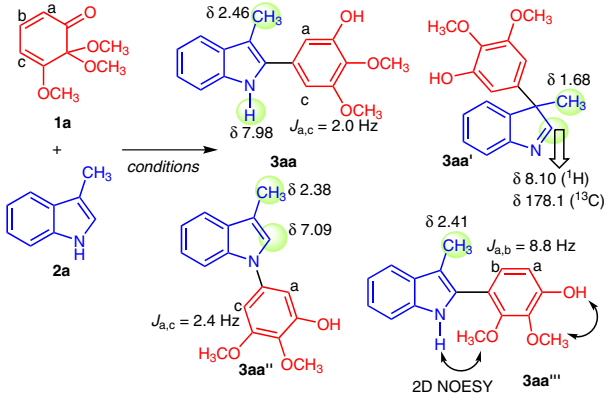
The indole nucleus is a renowned pharmacophore in medicinal chemistry.[1] Because of the indisputable importance of the indole core, the synthetic community continues to explore novel methods either to construct indole rings[2] or to functionalize them selectively at various positions.[3] Arylindole structures appear in several natural products as well as in pharmacologically active compounds. For this reason, protocols for installing an aryl group directly onto an indole ring are likewise a focus of current research. These endeavors have paved the way to plethora of metal-catalyzed or nonmetal-mediated procedures for the selective arylation of indoles at the C-3,[4] C-2,[5] or N-1 position.[3a,4a,b,6] Towards this objective, a variety of aryl precursors, including diaryliodonium salts,[7] aryl halides,[8] arylboronic acids,[9] potassium aryltrifluoroarylborates,[10] arylphosphines,[11] arylsiloxanes,[12] arylsulfonyl hydrazides,[13] arylsulfinic acids,[14] and cyclohexadienones[15] have been successfully employed.

In general, the indole molecule is well known to be susceptible to electrophilic attack at the C-3, C-2, and N-1 positions as a result of the electronic nature of the ring. Recently, we reported a Brønsted-acid-catalyzed tandem protocol involving a Michael addition reaction of a C-3 unsubstituted indole to a cyclohexa-2,4-dien-1-one (an electrophilic aryl equivalent) to furnish a 3-arylindole.[15d] However, under the optimized conditions ($HClO_4$·SiO_2 as catalyst) no reaction occurred between the C-3-substituted indole skatole (**2a**; 3-methyl-1*H*-indole) and 5,6,6-trimethoxycyclohexa-2,4-dien-1-one (**1a**). We wondered whether a Lewis acid as a catalyst[16] instead of a Brønsted acid might facilitate a possible reaction between such 3-alkylindoles and a cyclohexa-2,4-dien-1-ones. Consequently, we explored this speculation, and our preliminary results are presented here.

We began our investigation by selecting skatole (**2a**) as representative substrate in Lewis-acid-mediated reaction with 5,6,6-trimethoxycyclohexa-2,4-dien-1-one (**1a**) as an electrophilic aryl equivalent. At the outset, when a solution of skatole (**2a**) and dienone **1a** at –78 °C was treated with BF_3·OEt_2, three products, namely **3aa** (27%), **3aa′** (13%) and **3aa″** (24%), were obtained (Table 1, entry 1). Obviously, under these reaction conditions skatole (**2a**) and dienone **1a** could be coupled, but various products from competing reaction pathways were isolated. Remarkably, however, the BF_3·OEt_2-catalyzed reaction at 0 °C, after silica-gel column chromatography, provided the 2-arylindole **3aa** as the only product in 82% yield (entry 2). As expected, the reaction time had to be prolonged when a catalytic amount of BF_3·OEt_2 was used; nevertheless, the yield of 2-arylindole **3aa** (entry 3) was unaffected. A possible reaction pathway for the formation of all the observed isomeric products is rationalized in Scheme 3 (see below).[17] Subsequently, we explored various Lewis acids as catalysts for this reaction and we found that the $Sc(OTf)_3$- and $Bi(OTf)_3$-catalyzed reactions were complete in 16 hours and gave the 2-arylindole **3aa** and the *N*-arylindole **3aa″** in ~70% total yield and a ~1:1 ratio (entries 4 and 5). Interestingly, $Yb(OTf)_3$, $Gd(OTf)_3$, and $In(OTf)_3$ were not efficient catalysts for this reaction (entries 6–8); under these conditions, selectivity was poor and three products, the 2-arylindoles **3aa** and

3aa‴, and the *N*-arylindole **3aa″**, were obtained in 25–30% total yield. It should be noted that the reaction of skatole (**2a**) with dienone **1a** catalyzed by metal triflates at elevated temperature became complex. In a nutshell, of the Lewis acids that we examined (Table 1), BF_3·OEt_2 was the best catalyst in terms of selectivity and product yield.

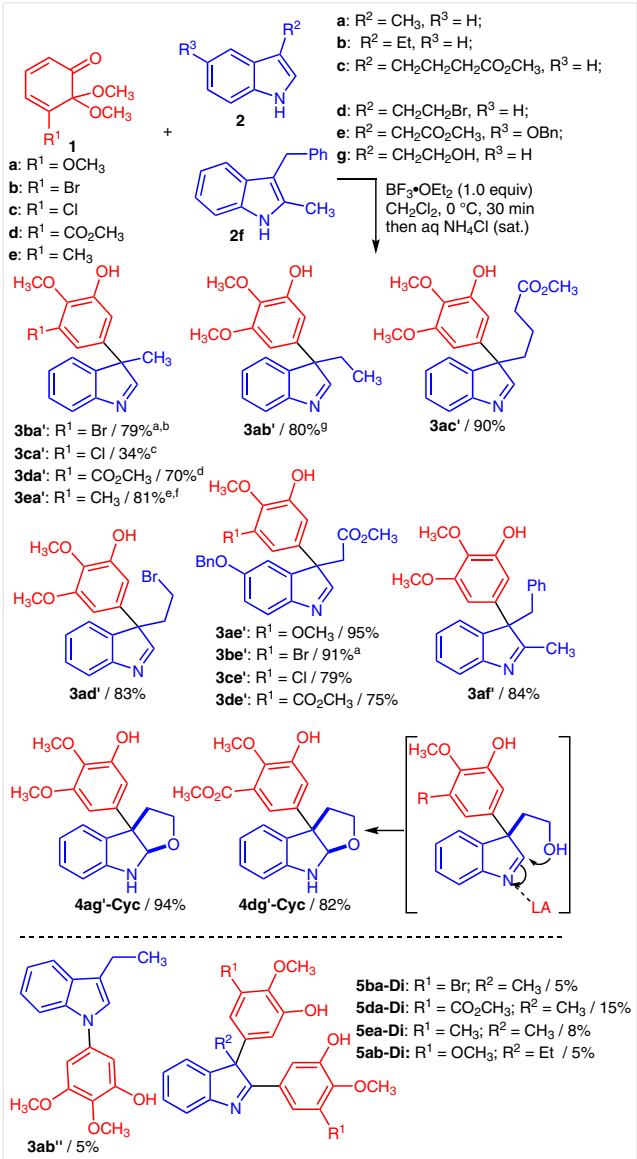
Table 1 Reaction of Skatole (**2a**) with Dienone **1a** in the Presence of Various Lewis Acids[a]



Entry	Conditions	Product(s)	Yield[b] (%)
1[b]	BF_3·OEt_2 (1.0 equiv), CH_2Cl_2, –78 °C, 3 h	**3aa** **3aa′** **3aa″**	27 13 24
2	BF_3·OEt_2 (1.0 equiv), CH_2Cl_2, 0 °C, 20 min	**3aa**	82
3	BF_3·OEt_2 (0.1 equiv), CH_2Cl_2, 0 °C to rt, 16 h	**3aa**	84
4	$Bi(OTf)_3$ (0.1 equiv), MeCN, rt, 16 h	**3aa** **3aa″**	35 31
5	$Sc(OTf)_3$ (0.1 equiv), MeCN, rt, 16 h	**3aa** **3aa″**	36 35
6[c,d]	$Yb(OTf)_3$ (0.1 equiv), MeCN, rt, 20 h	**3aa** **3aa″** **3aa‴**	1:1:1[e]
7[c,d]	$Gd(OTf)_3$ (0.1 equiv), MeCN, rt, 20 h	As above	
8[c]	$In(OTf)_3$ (0.1 equiv), MeCN, rt, 20 h	As above	

[a] *Reaction conditions*: dienone **1a** (1.0 mmol), skatole (**2a**; 1.0 mmol). Diagnostic ^{1}H & ^{13}C NMR chemical shifts (in ppm), *J*-couplings, and 2D-NOESY cross-peaks are indicated for the respective structures.
[b] An inseparable mixture of other products (~15%) was also formed.
[c] The reaction did not proceed to completion [~50% conversion based on recovery of skatole (**2a**)].
[d] The reaction performed at 70 °C produced a complex mixture.
[e] Ratio determined from diagnostic peak integration in the ^{1}H NMR of the crude reaction mixture. 9–11% each of **3aa**, **3aa″** and **3aa‴** were isolated.

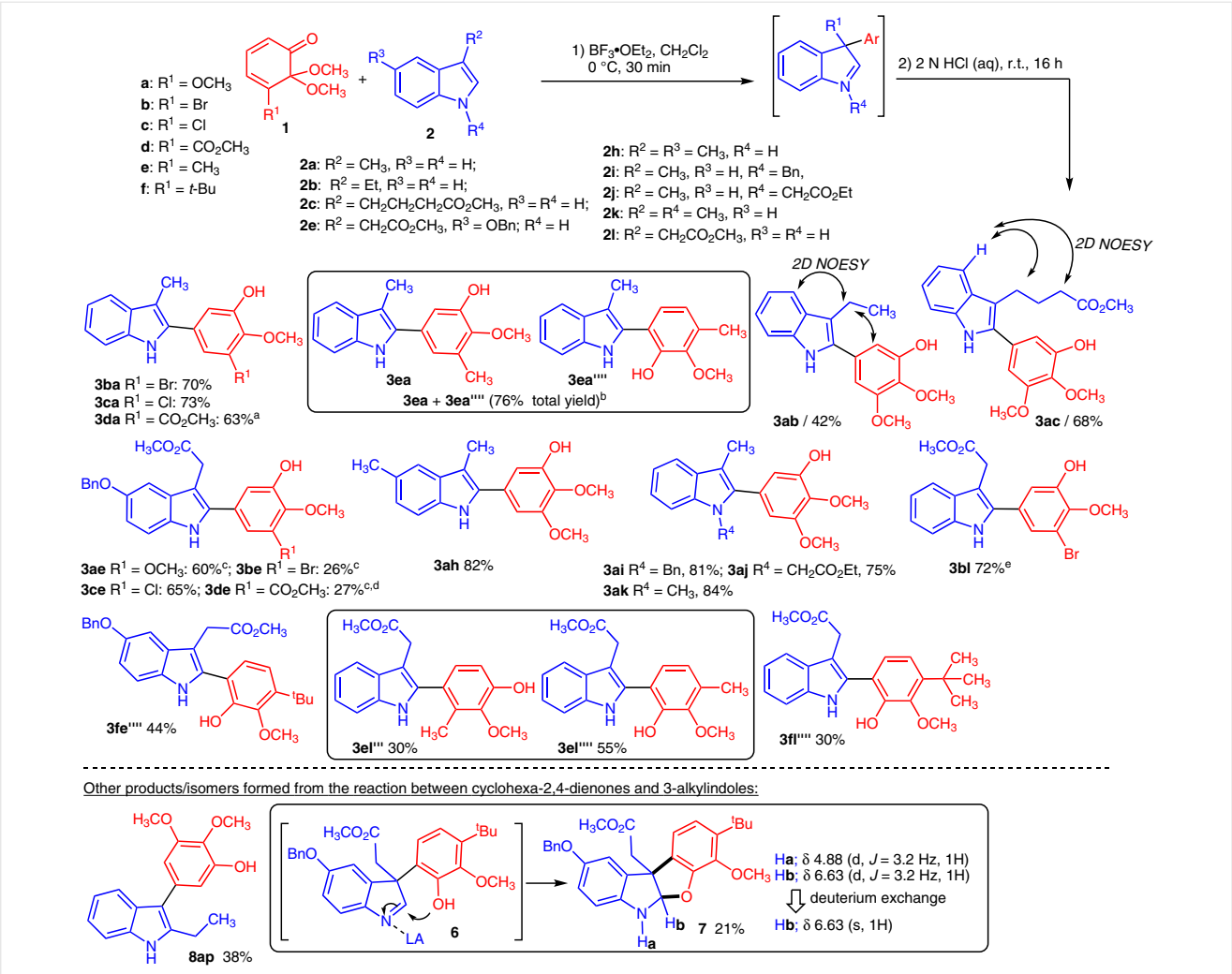
Intriguingly, TLC analyses of the BF_3·OEt_2-catalyzed reaction of skatole (**2a**) and dienone **1a** before and after silica-gel column chromatographic purification produced different results. Whereas TLC analysis of the reaction mixture showed a polar spot (R_f = 0.2; 30% EtOAc–hexanes) as the major reaction product, to our surprise, upon silica-gel column chromatography of the reaction mixture, a new nonpolar spot (R_f = 0.3) appeared exclusively. After close inspection, it became clear that the initially formed C-3 arylated indolenine **3aa′** (polar spot) underwent a facile C-3 to C-2 aryl migration (Plancher-type rearrangement)[18] during workup and silica-gel chromatography to give the 2-arylindole **3aa** (nonpolar spot). On a separate note, after the BF_3·OEt_2-catalyzed reaction of skatole (**2a**) with dienone **1a** at 0 °C for 30 min, when 2 N HCl was added and the mixture was stirred for 30 minutes at room temperature, the 2-arylindole **3aa**, was formed directly (see Scheme 3, Path a,



Scheme 1 BF_3·OEt_2-catalyzed reaction of 3-alkylindoles **2a–g** with cyclohexadienones **1a–e**. [a] 0.1 equivalents of BF_3·OEt_2 and a reaction time of 16 h were required for the reactions of dienone **1b**. [b] ~5% of indolenine **5ba-Di** was formed (isolated as a 1:1 inseparable mixture of **3ba′** and **5ba-Di**). [c] 38% of **3ca** was also isolated. [d] 15% of indolenine **5da-Di** was isolated. [e] the C-3-*ortho*-isomer was present in minor inseparable quantities. [f] 8% of indolenine **5ea-Di** was isolated. [g] Products **3ab′′** (5%) and **5ab-Di** (5%) were also isolated.

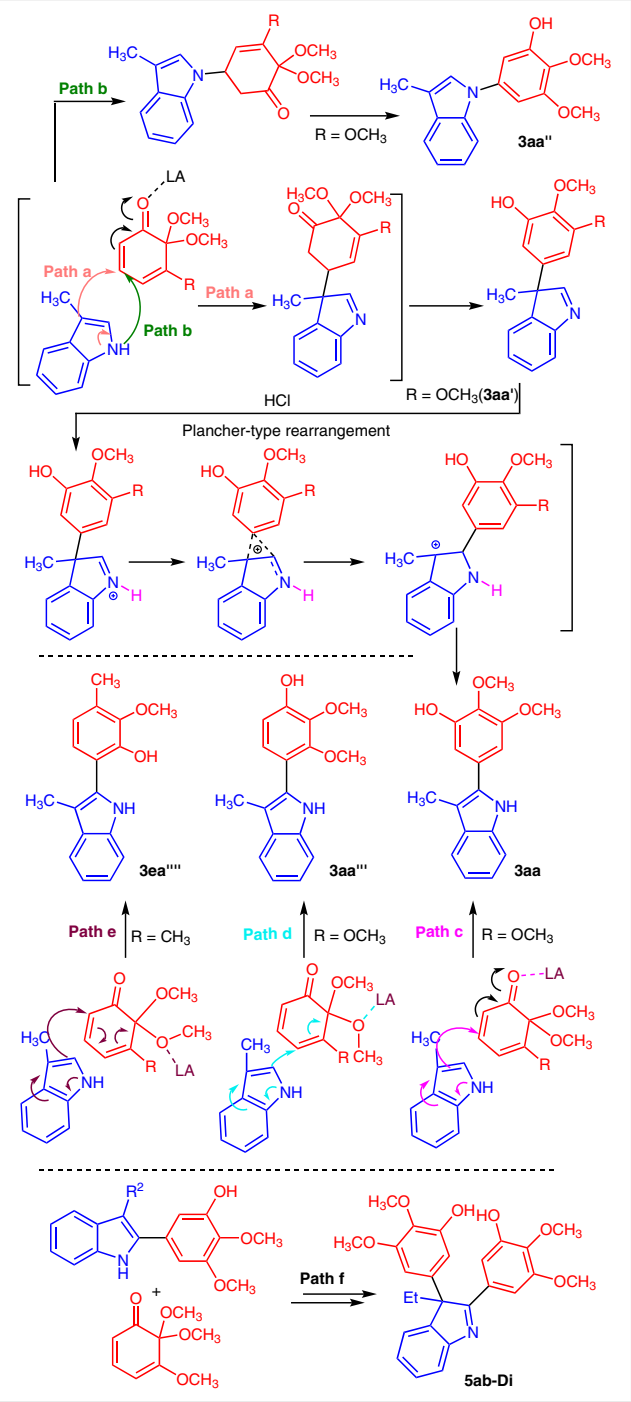
below). This result implied that C-3 arylated indolenine structures are prone to undergo acid-mediated Plancher-type rearrangement.

To extend the scope of the reaction we examined the reactions of indoles **2b–f** with cyclohexadienone **1a** under the general reaction conditions.[19] Intriguingly, the corresponding 3-alkyl-3-arylindolenines **3ab′–af′** formed from the reaction of indoles **2b–f** and dienone **1a** were stable to silica-gel purification and could be isolated in 80–95% yield (Scheme 1). Small quantities of *N*-arylindole **3ab″** (5%) and 2,3-diarylindolenine **5ab-Di** (5%) were also isolated from the reaction of 3-ethylindole (**2b**) and dienone **1a**. The formation of 2,3-diarylindolenine **5ab-Di** can be attributed to the reaction of the 2-arylindole **3ab**, generated in situ, with dienone **1a** (see Scheme 3, Path f, below). To broaden the scope of the reaction, we examined the reactions of dienones **1b–e** with indoles **2a** and **2e**. The reaction of skatole (**2a**) with dienones **1b–e** at 0 °C for 30 min in the presence of $BF_3{\cdot}OEt_2$ as catalyst followed by workup with saturated aqueous NH_4Cl, provided the corresponding indolenine derivative **3ba′–ea′** in up to 81% isolated yield. In these reactions, the corresponding 2,3-diarylindolenine **5ba-Di**, **5da-Di**, and **5ea-Di** were also isolated as minor reaction products (5–15%). 3-Alkyl-3-arylindolenine **3ca′** appeared to be sensitive to silica gel and gave 2-arylindole **3ca** (38%) during purification. The reaction of indole **2e** with dienones **1b–d** under the general reaction conditions gave the corresponding products **3be′–3de′** in good yields (up to 91%). Interestingly, the reactions of 2-(1*H*-indol-3-yl)ethanol (**2g**) with dienones **1a** and **1d** gave the cyclized products **4ag′-**



Scheme 2 A two-pot protocol for the synthesis of 2-arylindoles through a Plancher-type rearrangement of 3-alkyl-3-arylindolenine derivatives. [a] *Reaction conditions for Step 2*: 4 N HCl in 1,4-dioxane (25 equiv), r.t., 16 h. [b] An inseparable mixture of **3ea + 3ea**′′′′ in a 1:0.3 ratio (by 1 H NMR integration) was obtained. [c] *Reaction conditions for Step 2*: 4 N HCl in 1,4-dioxane (25 equiv), 50 °C, 8 h. [d] **3de**′ was also isolated in 30% yield. [e] 10% of a mixture of other isomers was formed.

Cyc and **4dg′-Cyc** exclusively in 94% and 82% yield, respectively. A possible reaction pathway leading to these products is shown in Scheme 1.



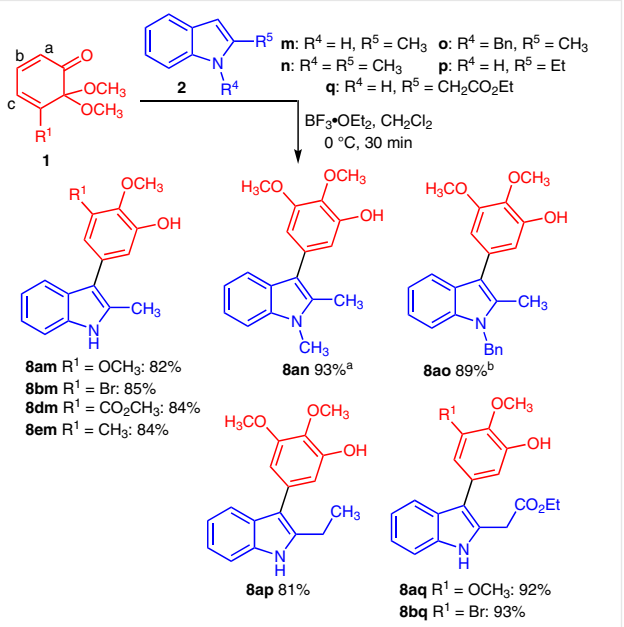
Scheme 3 Possible reaction pathways leading to the observed products from the Lewis-acid-mediated reactions of cyclohexa-2-4-dien-2-ones and 3-alkylindoles

From the above results, it was apparent that 3-alkyl-3-arylindolenines undergo an acid-mediated Plancher-type rearrangement to the corresponding 3-alkyl-2-arylindoles. Consequently, with the aim of simplifying the reaction procedure to obtain 3-alkyl-2-arylindoles, we decided to skip the purification at the 3-alkyl-3-arylindolenine stage. To this end, as shown in Scheme 2, after the initial $BF_3{\cdot}OEt_2$-mediated reaction of dienone **1a** and 3-alkylindole **2b**, **2c**, **2e**, or **2h–k** for 30 minutes, the solvent was removed to give a residue.[19,20] This residue was treated with 2 N aqueous HCl, and the mixture was stirred at room temperature to give the corresponding 2-arylindoles **3ab** (42%), **3ac** (68%), **3ae** (60%), **3ah** (82%), **3ai** (81%), **3aj** (75%), and **3ak** (84%), respectively. Among these 3-alkylindole substrates, a competing ethyl-versus-aryl migration from the C-3 position to the C-2 position was observed only in the case of 3-ethylindole (**2b**), which gave product **8ap** in 38% isolated yield. Next, to broaden the scope of the reaction, we examined the reactions of dienones **1b–d** with indoles **2a** and **2e**. By the general reaction procedure,[19] dienones **1b–d** reacted with indoles **2a** and **2e** to give the requisite 3-alkyl-2-arylindoles **3ba** (70%), **3ca** (73%), **3da** (63%), and **3ce** (65%), in acceptable yields, however, products **3be** (26%) and **3de** (27%) were produced in low yields. Attempts to improve the yields by increasing the reaction time led to complex reaction mixtures.

The reaction between 5-alkyl-substituted dienones **1e** and **1f** with 3-alkylindoles **2a**, **2e**, and **2l** were not regioselective. Thus, in these reactions regioisomers **3ea′′′′**, **3fe′′′′** (44%), **3el′′′** (30%), **3el′′′′** (55%), and **3fl′′′′** (30%) were isolated. The reason for this reversal in regioselectivity is not presently clear, but recently a reversal of regioselectivity was noticed when cyclohexa-2,4-dien-1-ones participated in a Friedel–Crafts-type reaction.[16] The production of product **7** can be rationalized in terms of its formation from the initially generated 3-arylindolenine **6**, which eventually undergoes cyclization by attack of the phenolic hydroxy group on the imine moiety in the molecule.

Plausible reactions pathways leading to the observed products are shown in Scheme 3.

In the present work, we identified $BF_3{\cdot}OEt_2$ as the catalyst of choice for the reaction between cyclohexa-2,4-dien-1-ones and 3-substituted indoles. We therefore extended the use of $BF_3{\cdot}OEt_2$ as catalyst to the reaction of cyclohexa-2,4-dien-1-ones and 3-unsubstituted indoles (Scheme 4).[15d] The reaction of dienones **1a**, **1b**, **1d**, and **1e** with 3-unsubstituted indoles **2m–q** gave the corresponding 3-arylindoles **8am–aq**, **8bm**, **8dm**, and **8em** in high isolated yields through a tandem Michael addition/aromatization sequence. Consequently, comparison of the analytical data for these products with those of the 3-alkyl-2-arylindole derivatives (Scheme 2), proved further proof that migration of the aryl group, and not the methyl group, occurred during the Plancher-type rearrangement of 3-alkyl-3-arylindolenines.



Scheme 4 BF_3·OEt_2-catalyzed tandem Michael addition reaction and aromatization sequence for the synthesis of 3-arylindoles. [a] 6% of an inseparable mixture of an *ortho*-isomer was formed. [b] 8% of an inseparable mixture of an *ortho*-isomer was formed.

To conclude, we have shown that dearomatized C-3 arylated indole obtained through a BF_3·OEt_2-catalyzed reaction of a cyclohexa-2,4-dien-1-one with a 3-alkylindole effortlessly undergoes acid-mediated rearrangement to yield the corresponding 2-arylindole. The reaction provides access to 2-arylindole derivatives straightforwardly from readily available starting materials. We also found that BF_3·OEt_2 can also be successfully used in the synthesis of 3-arylindoles. Work towards improving the reaction protocol is being pursued, including expanding the substrate scope and improving the yields of 2-arylindoles. At the same time, studies on the application of these findings are underway.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588448.

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(19) **BF_3·OEt_2-Catalyzed Reaction of a Cyclohexadienone and an Alkylindole; Typical Procedure**

BF_3·OEt_2 (0.067 mL, 0.54 mmol) was added to a stirred solution of cyclohexadienone **1a** (100 mg, 0.54 mmol) and skatole (**2a**; 71 mg, 0.54 mmol) in CH_2Cl_2 (2.0 mL) at –78 °C, and the mixture was stirred at –78 °C for 3 h. MeOH (2 mL) was added and the mixture was stirred for 30 min. The solvent was removed by rotary evaporation, and the crude residue was purified by flash column chromatography (silica gel, 0–30% EtOAc–hexanes) to give **3aa** (62 mg, 27%), **3aa″** (55 mg, 24%) and **3aa′** (30 mg, 13%), along with inseparable mixture of other uncharacterized products.

2,3-Dimethoxy-5-(3-methyl-1*H*-indol-2-yl)phenol (3aa)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (br s, 1 H), 7.60–7.57 (m, 1 H), 7.37–7.34 (m, 1 H), 7.24–7.18 (m, 1 H), 7.17–7.12 (m, 1 H), 6.82 (d, *J* = 2.0 Hz, 1 H), 6.68 (d, *J* = 2.0 Hz, 1 H), 5.89 (br, s 1 H), 3.97 (s, 3 H), 3.93 (s, 3 H), 2.46 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.5 (C), 149.5 (C), 135.7 (C), 135.0 (C), 133.8 (C), 130.0 (C), 129.4 (C), 122.3 (CH), 119.5 (CH), 118.9 (CH), 110.6 (CH), 108.5 (C), 107.6 (CH), 104.0 (CH), 61.1 (CH_3), 56.0 (CH_3), 9.7 (CH_3). ESI-MS: *m/z* = 284 [$C_{17}H_{17}NO_3$ + H]$^+$.

2,3-Dimethoxy-5-(3-methyl-3*H*-indol-3-yl)phenol (3aa′)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (s, 1 H), 7.66 (app d, *J* = 8.0 Hz, 1 H), 7.40–7.34 (m, 1 H), 7.28–7.27 (m, 2 H), 6.56 (d, *J* = 2.0 Hz, 1 H), 5.79, (s, 1 H), 6.12 (d, *J* = 2.0 Hz, 1 H), 3.86 (s, 3 H), 3.73 (s, 3 H), 1.68 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.1 (CH), 154.3 (C), 152.5 (C), 149.6 (C), 144.5 (C), 135.0 (C), 134.0 (C), 128.1 (CH), 126.7 (CH), 122.5 (CH), 121.4 (CH), 106.4 (CH), 102.1 (CH), 61.1 (CH_3), 60.8 (C), 55.8 (CH_3), 20.2 (CH_3). ESI-MS: *m/z* = 284 [$C_{17}H_{17}NO_3$ + H]$^+$.

2,3-Dimethoxy-5-(3-methyl-1*H*-indol-1-yl)phenol (3aa″)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63–7.56 (m, 2 H), 7.25–7.14 (m, 2 H), 7.09 (app q, *J* = 1.2 Hz, 1 H), 6.74 (d, *J* = 2.4 Hz, 1 H), 6.60 (d, *J* = 2.4 Hz, 1 H), 5.93 (s, 1 H), 3.96 (s, 3 H), 3.89 (s, 3 H), 2.38 (d, *J* =1.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.8 (C), 149.8 (C), 136.2 (C), 136.0 (C), 133.7 (C), 129.7 (C), 125.5 (CH), 122.3 (CH), 119.7 (CH), 119.2 (CH), 112.6 (C), 110.5 (CH), 104.1 (CH), 100.7 (CH), 61.1 (CH_3), 56.1 (CH_3), 9.5 (CH_3). ESI-MS *m/z* 284 [$C_{17}H_{17}NO_3$ + H]$^+$.

Methyl 4-[3-(3-Hydroxy-4,5-dimethoxyphenyl)-3*H*-indol-3-yl]butanoate (3ac′); Typical Procedure

A freshly prepared stock solution of BF_3·Et_2O (0.3 mL, 0.54 mmol, 1 mL) in CH_2Cl_2 (4 mL) was added to stirred solution of cyclohexadienone **1a** (100 mg, 0.54 mmol) and methyl 4-(1*H*-indol-3-yl)butanoate (**2c**; 120 mg, 0.54 mmol) in CH_2Cl_2 (2.5 mL) at 0 °C, and the mixture was stirred for 30 min. The mixture was then diluted with sat. aq NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The extracts were concentrated by rotary evaporation and the crude product was purified by column chromatography (silica gel, 0–70% EtOAc–hexane) to give a brown solid; yield: 180 mg (90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (s, 1 H), 7.66 (d, *J* = 7.6 Hz, 1 H), 7.40–7.27 (m, 3 H), 6.58 (d, *J* = 2.0 Hz, 1 H), 6.22 (d, *J* = 2.0 Hz, 1 H), 5.82 (br s, 1 H), 3.85 (s, 3 H), 3.75 (s, 3 H), 3.62 (s, 3 H), 2.26–2.17 (m, 4 H), 1.53–1.47 (m, 1 H), 1.32–1.26 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.0 (CH), 173.3 (C), 154.9 (C), 152.6 (C), 149.7 (C), 142.0 (C), 135.0 (C), 133.2 (C), 128.2 (CH), 126.6 (CH), 123.2 (CH), 121.5 (CH), 106.8 (CH), 102.5 (CH), 65.2 (C), 60.8 (CH_3), 55.9 (CH_3), 51.5 (CH_3), 34.3 (CH_2), 33.8 (CH_2), 19.9 (CH_2). ESI-MS: *m/z* = 370 [$C_{21}H_{23}NO_5$ + H]$^+$.

5-(3,5-Dimethyl-1*H*-indol-2-yl)-2,3-dimethoxyphenol (3ah); Typical Procedure

A freshly prepared stock solution of BF_3·Et_2O (0.3 mL, 0.54 mmol, 1 mL) in CH_2Cl_2 (4 mL) was added to stirred solution of cyclohexadienone **1a** (100 mg, 0.54 mmol) and 3,5-dimethyl-1*H*-indole (**2h**, 79 mg, 0.54 mmol) in CH_2Cl_2 (2.5 mL) at 0 °C, and the mixture was stirred for 30 min, the solvent was removed to give a residue. The residue was then diluted with 2 N aq HCl (10 mL) and stirred for 2–6 h (16 h for reactions of indole **2e**). The mixture was extracted with EtOAc (3 × 20 mL), and the extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, 0–70% EtOAc–hexane) to give a reddish solid; yield: 131 mg (82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (br s, 1 H), 7.37 (br s, 1 H), 7.24 (d, *J* = 8.0 Hz, 1 H), 7.03 (dd, *J* = 8.0, 1.2 Hz, 1 H), 6.81 (d, *J* = 1.6 Hz, 1 H), 6.67 (d, *J* = 1.6 Hz, 1 H), 5.89 (br s, 1 H), 3.96 (s, 3 H), 3.93 (s, 3 H), 2.48 (s, 3 H), 2.44 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.5 (C), 149.5 (C), 134.9 (C), 134.0 (C), 133.9 (C), 130.0 (C), 129.6 (C), 128.8 (C), 123.9 (CH), 118.6 (CH), 110.3 (CH), 108.1 (C), 107.5 (CH), 104.0 (CH), 61.1 (CH_3), 56.0 (CH_3), 21.5 (CH_3), 9.6 (CH_3). ESI-MS: *m/z* 298 [$C_{18}H_{19}NO_3$ + H]$^+$.

(20) Even with *N*-substituted indoles **2i–k** as substrates, it appeared that C-3-arylation occurred first, and only after HCl treatment did these reaction mixtures become cleaner for isolation. We found that a prolonging reaction time under BF_3·OEt_2-catalyzed condition for the Plancher-type rearrangement was not suitable for delivering 2-arylindole derivatives. Under these conditions, 2-arylindoles were obtained in low yields together with uncharacterized product mixtures.