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Indoles

Regioselective Hydroarylation Reactions of C3 Electrophilic *N*-Acetylindoles Activated by $FeCl_3$: An Entry to 3-(Hetero)arylindolines

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Abstract: A method for the direct and rare umpolung of the 3 position of indoles is reported. The activation of *N*-acetylindole with iron(III) chloride allows the C–H addition of aromatic and heteroaromatic substrates to the C2=C3 double bond of the indole nucleus to generate a quaternary center at C3 and leads regioselectively to 3-arylindolines. Optimization, scope (50 examples), practicability (gram scale, air atmosphere, room temperature), and mechanistic insights of this process are presented. Synthetic transformations of the indoline products into drug-like compounds are also described.

Introduction

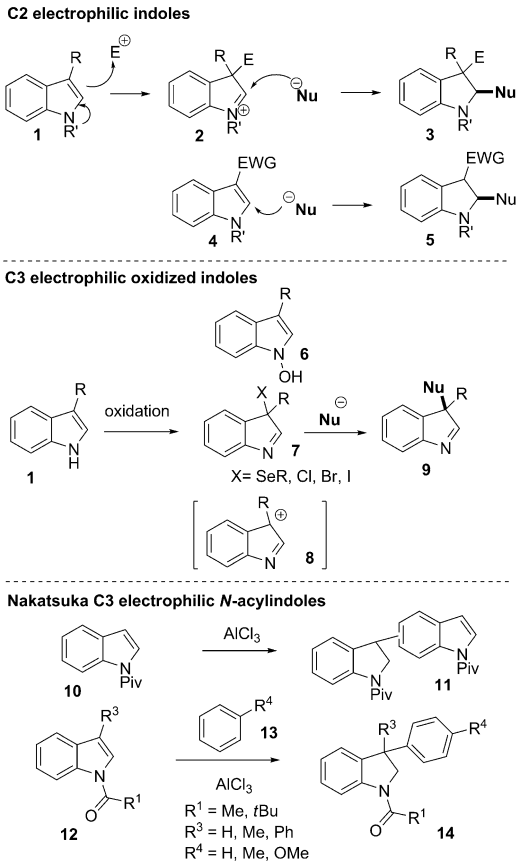
The nucleophilicity of the indole nucleus at C3 is well established.[1] In contrast, the electrophilic character of indoles has been less studied but is a fascinating emerging topic.[2]

Nucleophiles can be added to the benzene portion of indoles,[3] however, we are particularly interested in the generation of sp^3 carbon centers through the reaction of the C2=C3 bond of indoles **1**. Logically it has been reported that the addition of an electrophile at C3 results in the generation of a C2 electrophilic imine or iminium species **2**.[4] Indoles **4**, which contain a C3 electron-withdrawing group, are also electrophilic at C2 through 1,4-addition (Scheme 1).[5]

In contrast, the introduction of nucleophiles at C3 requires the umpolung of this position. Strategies to effect such a transformation rely on oxidation of the indole nucleus to generate *N*-hydroxyindoles **6**,[6] 3-halogeno- or 3-seleno-indolines **7**,[7] or indolenium ions **8**,[8] which are all electrophilic at C3 (Scheme 1).[9]

The latter C3 functionalization delivered indole derivatives at a higher oxidation state than the indolines obtained by C2-functionalization methods. If one wishes to obtain similar C3-functionalized indolines, an umpolung that does not require the preoxidation of indoles is needed.

In a seminal report, Nakatsuka and co-workers observed the oligomerization of *N*-pivaloylindole (**10**) in the presence of excess of $AlCl_3$ by the formation of a C–C bond between the benzene portion of one molecule and the C3 position of another indole molecule (Scheme 1).[10a] The authors were able to extend this observation to the addition of electron-rich benzene derivatives **13** to the C3 position of *N*-acylindoles **12** in the presence of $AlCl_3$, which is a very unusual hydroarylation reaction of the electron rich C2=C3 bond of indoles.[10b,11] However, the substrate scope reported was very limited.



Scheme 1. Electrophilic indoles for the generation of sp^3 carbon centers.

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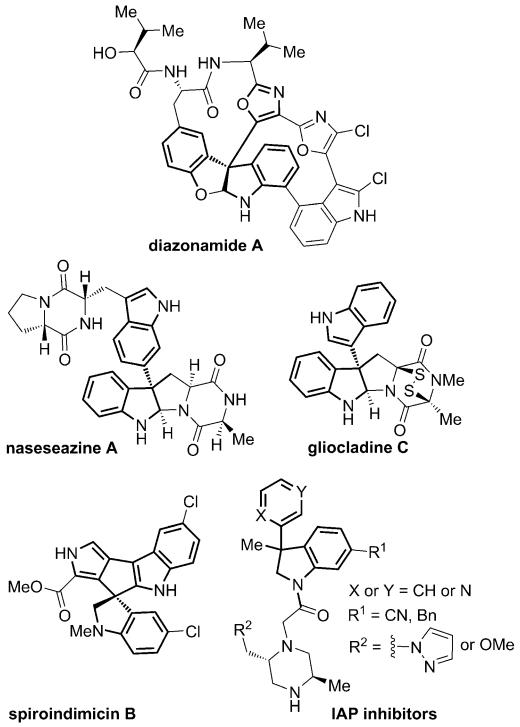
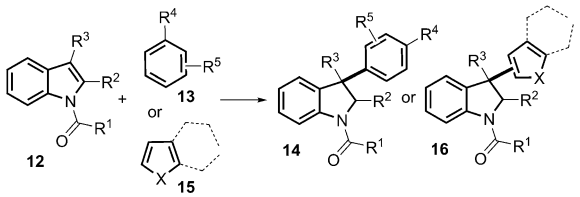


Figure 1. Biologically active and/or natural products that contain the 3-arylindoline moiety.

3,3-Disubstituted indoline derivatives that incorporate an aryl group at the 3 position are found in various families of biologically relevant natural products or potential drugs[12–19] (Figure 1). Examples include the antitumoral natural product diazonamide A[12,13] of the benzofuroindoline family,[14,15] pyrroloindolines (such as the naseseazines or gliocladine C, which contain a 3-indolylindoline framework), the recently isolated spiroindimicin B, which features a rare 3,3-spiro-pyrrolylindolylindoline core, and 3-aryl-*N*-acylindolines, which have recently been reported to target the family of inhibitors of apoptosis (IAP) proteins, over expressed in several cancers.[18]

The C3 regioselective hydroarylation of electrophilic *N*-acylindoles **12** appeared very attractive to us to devise a general access to relevant 3-arylindolines **14** and **16** (Scheme 2). This Friedel–Crafts-type cross-coupling reaction does not require the prefunctionalization of both partners and is formally the addition of a C–H bond into the indole C2=C3 double bond.

In the context of an ongoing project to target the benzofuranoindoline core, we embarked on a general research program directed towards the C3 umpolung of indoles.[20] We report our efforts to make this reaction practical and useful to the synthetic community by showcasing its broad scope and the subsequent access to natural product-like and drug-like motifs. Particular attention was paid to the introduction of heteroaryl groups **15**.

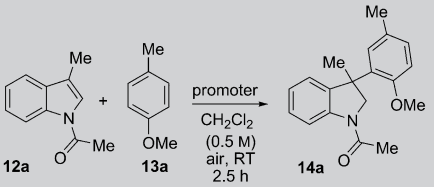


Scheme 2. Hydroarylation of *N*-acylindoles.

Results and Discussion

We initiated our investigation of the hydroarylation of *N*-acylindoles **12** by the study of the reaction between *N*-acetylskatole (**12a**) and 4-methylanisole (**13a**); the results are compiled in Table 1.

Table 1. Screening of promoters for the hydroarylation of *N*-acetylskatole (**12a**) by 4-methylanisole (**13a**).



Entry	Promoter	[Equiv]	**13a** [equiv]	Yield [%]
1	**$AlCl_3$**	4.5	5.0	**78**
2	**$AlCl_3$**	2.6	2.0	**23**
3	$Al(OTf)_3$	2.6	2.0	0
4	$CuCl_2$	2.6	2.0	0
5	$Cu(OTf)_2$	2.6	2.0	0
6	$MgCl_2$	2.6	2.0	0
7	$InCl_3{\cdot}2H_2O$	2.6	2.0	0
8	$In(OTf)_3$	2.6	2.0	0
9	$Sc(OTf)_3$	2.6	2.0	0
10	$BF_3{\cdot}OEt_2$	2.6	2.0	trace
11	BBr_3	2.6	2.0	0
12	$PdCl_2$	2.6	2.0	0
13	$SiCl_4$	2.6	2.0	0
14	**$TiCl_4$**	2.6	2.0	**38**
15	**$GaCl_3$**	2.6	2.0	**17**
16	**$FeCl_3$**	**2.6**	**2.0**	**94**
17	$FeCl_3$	1.0	2.0	0
18	**$FeBr_3$**	2.6	2.0	**88**
19	FeF_3	2.6	2.0	0
20	$FeCl_2$	2.6	2.0	0
21	K_3FeCN_6	2.6	2.0	0
22	$Fe(acac)_3$	2.6	2.0	0
23	$Fe(OTf)_3$	2.6	2.0	0
24	MsOH	2.6	2.0	0
25	CF_3CO_2H	2.6	2.0	0
26	HCl[a]	3.0	2.0	0

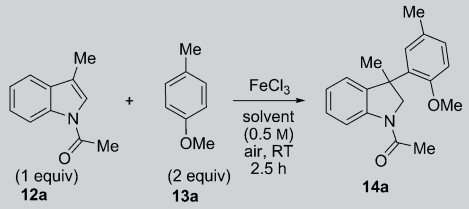
[a] 4.0 M solution in dioxane. Tf = trifluoromethanesulfonyl, acac = acetylacetonate, Ms = methanesulfonyl.

First we evaluated the conditions reported by Nakatsuka, which involved a large excess of $AlCl_3$ and electron-rich benzene derivatives. Very promisingly, the reaction with $AlCl_3$ (4.5 equiv) and **13a** (5 equiv) in CH_2Cl_2 yielded 78% of the 3-hydroarylated indoline **14a** (Table 1, entry 1). When we tried to lower the amounts of $AlCl_3$ and **13a** (2.6 and 2.0 equiv, respectively) the yield of the reaction dropped to 23% (Table 1, entry 2). Interestingly, replacement of aluminum chloride with

aluminum triflate resulted in a loss of reactivity (Table 1, entry 3). We next screened various Lewis acids to identify a more-efficient promoter. Disappointingly, almost all of the promoters evaluated under the typical conditions (Lewis acid (2.6 equiv), **13a** (2.0 equiv), 0.5 M CH_2Cl_2) were ineffective (Table 1, entries 4–13). $TiCl_4$ and $GaCl_3$ were able to promote the reaction in modest yields of 38 and 17%, respectively (Table 1, entries 14 and 15). Very rewardingly, $FeCl_3$ demonstrated a unique and very high activity: 94% of indoline **14a** was isolated (Table 1, entry 16). The stoichiometry of $FeCl_3$ was important because with only one equivalent, the reaction did not occur (Table 1, entry 17). $FeBr_3$ also mediated the hydroarylation in a useful yield of 88% (Table 1, entry 18). These iron(III) halides[21] seemed very exclusive in this context because other iron species, such as FeF_3, $FeCl_2$, K_3FeCN_6, $Fe(acac)_3$ (acac = acetylacetonate), and $Fe(OTf)_3$ did not mediate the reaction (Table 1, entries 19–23). Brønsted acids were also unable to promote the reaction (Table 1, entries 24–26).

With $FeCl_3$ in hand as the optimal promoter, under air atmosphere at room temperature, we decided to study the influence of the solvent (Table 2).

Table 2. Solvent effect in the hydroarylation of *N*-acetylskatole (**12a**) by 4-methylanisole (**13a**) with $FeCl_3$.

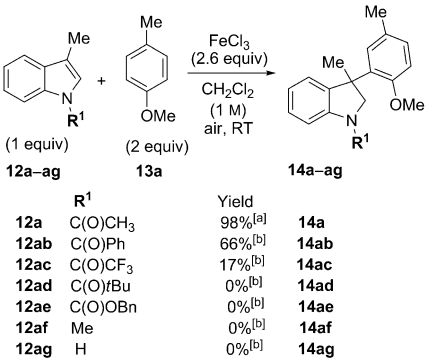


Entry	Solvent	$FeCl_3$ [equiv]	Yield [%]
1	CH_2Cl_2	2.6	94
2	acetone	2.6	0
3	THF	2.6	0
4	EtOAc	2.6	0
5	MeOH	2.6	0
6	CH_3CN	2.6	0
7	$EtNO_2$	2.6	15
8	heptane	2.6	15

Dichloromethane proved to be the most efficient solvent for the reaction (Table 2, entry 1). No conversion was observed in solvents that might coordinate $FeCl_3$ (acetone, THF, EtOAc, MeOH, CH_3CN; Table 2, entries 2–6), and low yields of **14a** were recovered in nitroethane or heptane (Table 2, entries 7 and 8).

We also noticed that the reaction could be run at a concentration of 1 M in dichloromethane, which allowed the reaction time to be reduced and gave an improved yield (Scheme 3).

With the optimized conditions in hand (**13a** (2.0 equiv), $FeCl_3$ (2.4 equiv), 1 M in CH_2Cl_2, rt), we evaluated the influence of the N-acyl group (Scheme 3). The initial acetyl group (**12a**) was the best choice. The more electron-withdrawing benzoyl (**12ab**) and trifluoroacetyl groups (**12ac**) resulted in reduced yields of 66 and 17%, respectively, whereas pivaloyl (**12ad**) or



Scheme 3. Effect of the nitrogen substituent. [a] 1.5 h, [b] 12 h. Bn = benzyl.

Cbz (**12ae**) substrates did not lead to the expected hydroarylated products because the nitrogen substituent was rapidly removed under the reaction conditions. The reaction of *N*-methyl (**12af**) or N–H skatole (**12ag**) resulted in unidentified oxidation products.

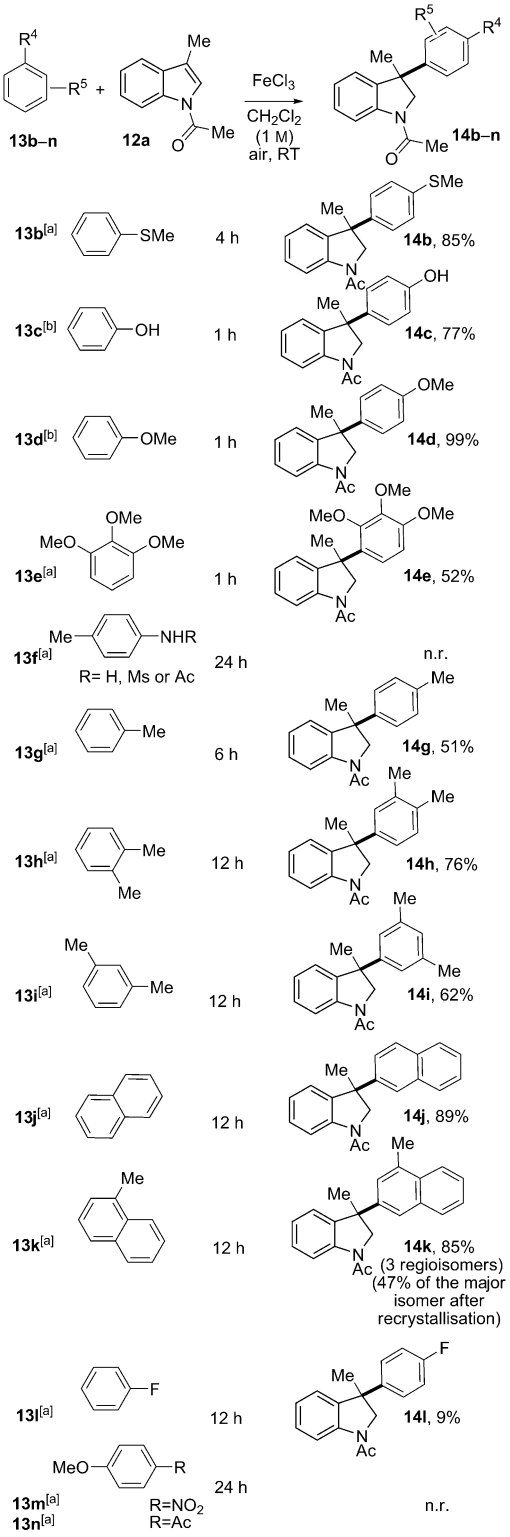
Having discovered a suitable combination of nitrogen substituent and Lewis acid promoter, we progressed to study the range of aromatic derivatives that could be added to the electrophile **12a** (Scheme 4).

Unsurprisingly, electron-rich benzene derivatives, such as thioanisole (**13b**), phenol (**13c**), and anisole (**13d**) afforded high yields of coupling products **14b–d**, respectively, linked at the *para* position of the benzene derivatives. 1,2,3-Trimethoxybenzene (**13e**) delivered the 3-(2,3,4-trimethoxyphen-1-yl)indoline **14e**. Unfortunately, aniline derivatives **13f** did not react with **12a**.

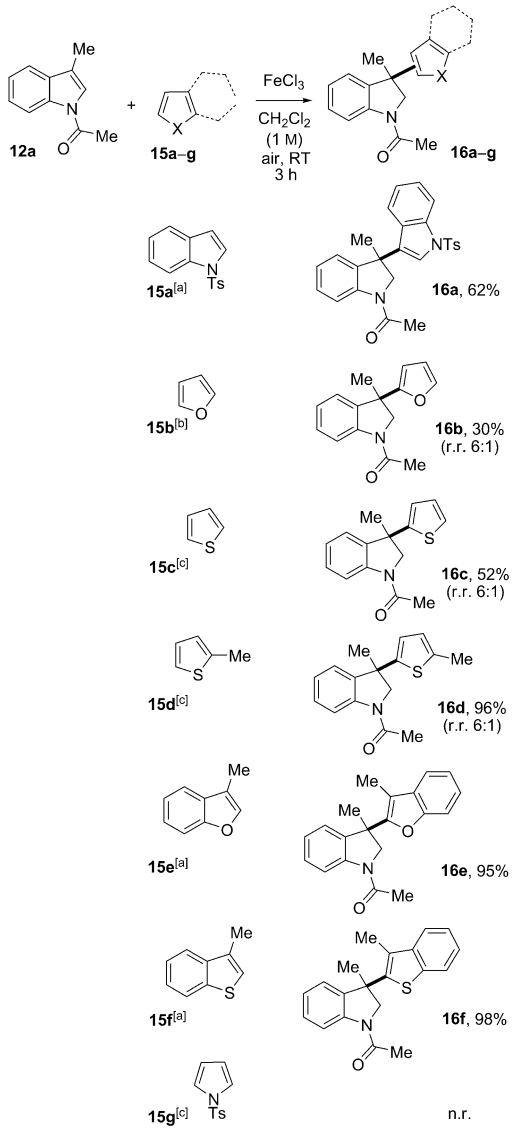
Toluene, xylenes, and naphthalenes were also prone to efficiently realize the hydroarylation. Indeed, toluene (**13g**) reacted at the *para* position and *ortho*-xylene (**13h**) delivered the 3-(3,4-dimethylphen-1-yl)indoline **14h**. *Meta*-xylene (**13i**) led to the 3-(3,5-dimethylphen-1-yl)indoline **14i**; the regioselectivity on the xylene ring is governed by steric rather than electronic effects. Naphthalene (**13j**) reacted at the 2 position, whereas 1-methylnaphthalene (**13k**) furnished a mixture of regioisomers but 3-(1-methylnaphthalen-3-yl)indoline **14k** was isolated as the major isomer after recrystallization. On the other hand, electron-deficient rings were significantly less reactive. Fluorobenzene (**13l**) led to indoline **14l** in 9% yield; 4-nitroanisole (**13m**) and 4-acetylanisole (**13n**) were unreactive.

Heterocycles are widely present in the context of drug discovery. Therefore, the formation of 3-heteroarylindolines by our method would be highly desirable (Scheme 5).

Rewardingly, several heterocycles are efficient nucleophiles for this reaction (Scheme 5). Indeed *N*-tosylindole (**15a**) delivered the C3–C3′ connected bis-indoline derivative **16a**. Furan (**15b**), thiophene (**15c**), and 2-methylthiophene (**15d**) reacted predominantly at the C2 position. The moderate yield of the furan–indoline adduct **16b** could be explained by partial polymerization of furan under the reaction conditions. Utilization of 3-methylbenzofuran (**15e**) and 3-methylbenzothiophene (**15f**) significantly improved the yield. However, *N*-tosylpyrrole (**15g**) was not a suitable partner for the hydroarylation.



Scheme 4. $FeCl_3$-promoted hydroarylation of *N*-acetylskatole (**12a**) with benzene derivatives. [a] **13** (3 equiv), $FeCl_3$ (3.4 equiv). [b] **13** (2 equiv), $FeCl_3$ (2.4 equiv). n.r. = no reaction of **12a**. Ac = acetyl.



Scheme 5. $FeCl_3$-promoted hydroarylation of *N*-acetylskatole (**12a**) with heterocycles. [a] **13** (2 equiv), $FeCl_3$ (2.4 equiv). [b] **13** (7.2 equiv), $FeCl_3$ (7.6 equi). [c] **13** (3 equiv), $FeCl_3$ (3.4 equiv). r.r. = regioisomeric ratio; n.r. = no reaction of **12a**.

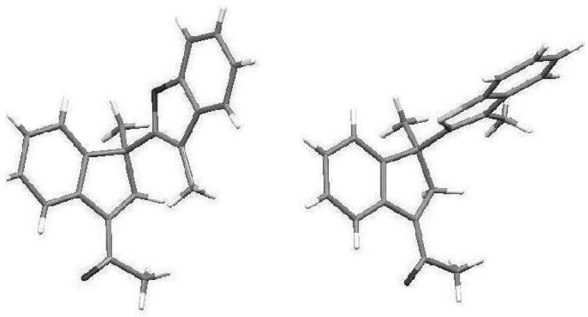
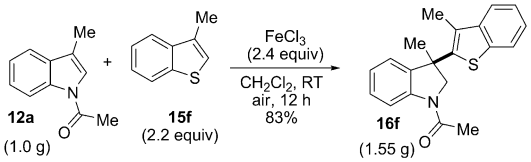


Figure 2. Crystal structures of hydroarylated indolines **16e** (left) and **16f** (right).

We were able to obtain crystals of some of the hydroarylated adducts of **12a** and to resolve their structure by X-ray crystallography (Figure 2).[22] Interestingly, in the case of the 3-methylbenzofuran adduct **16e**, the oxygen atom of the benzofuran unit points in the opposite direction to the C2–C3 bond of the indoline, whereas in sulfur analogue **16f**, the sulfur atom points towards the benzene ring of the indoline.

The scalability of this process was ascertained by the reaction of **12a** (1 g, 5.77 mmol) and **15f** (1.88 g, 12.8 mmol), which yielded indoline **16f** (1.55 g, 4.82 mmol, 83%; Scheme 6).



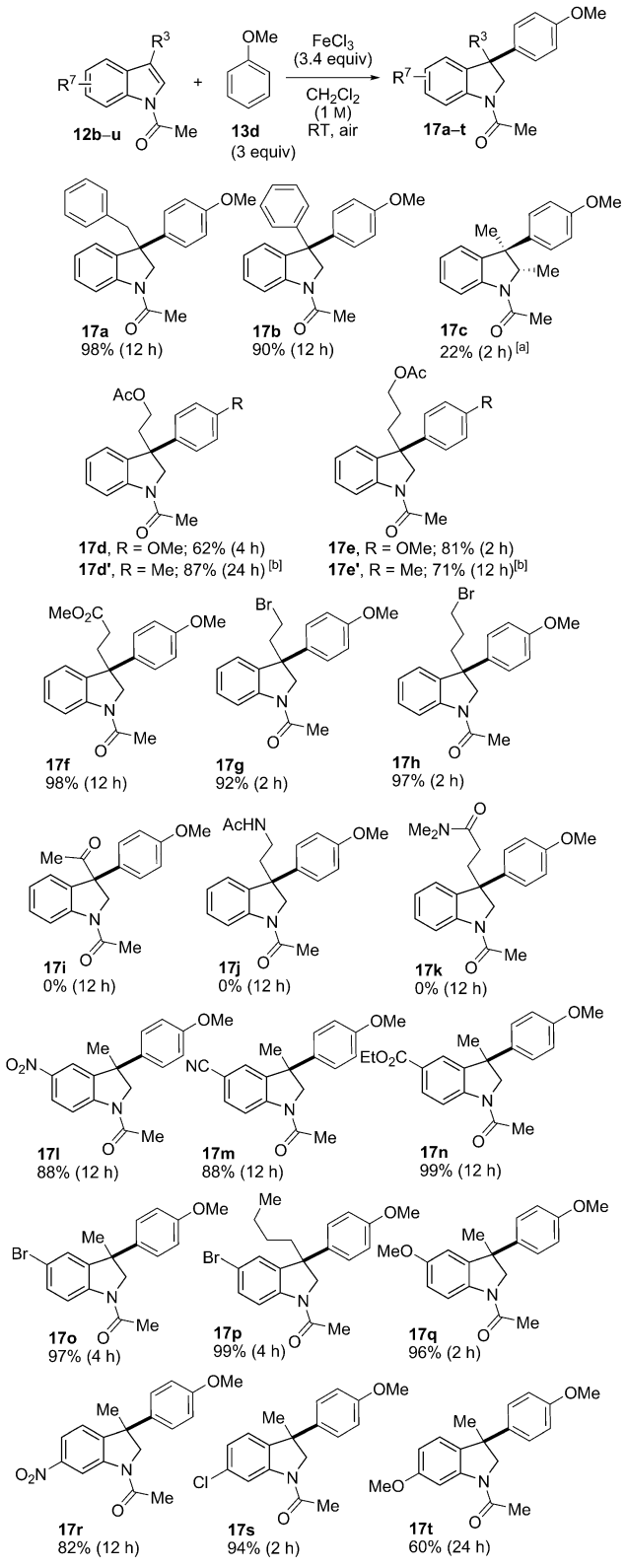
Scheme 6. Gram-scale hydroarylation.

After evaluation of the aromatic nucleophiles, the reactions of electrophilic *N*-acetylindole **12** were surveyed with anisole **13d** as the arylating agent (Scheme 7). The substitution at C3 was the first point under scrutiny. Increasing the steric hindrance slowed down the reaction but a good overall yield of 3-benzyl- and 3-phenylindolines **17a** and **17b** was obtained. 3,3,2-Trisubstituted-*N*-acetylindoline **17c** was isolated with a modest yield of 22% from 2,3-dimethyl-*N*-acetylindole, which could be explained by partial deacylation of the starting *N*-acetylindole by anisole (as a result, 4-methoxyacetophenone was isolated in 35%).

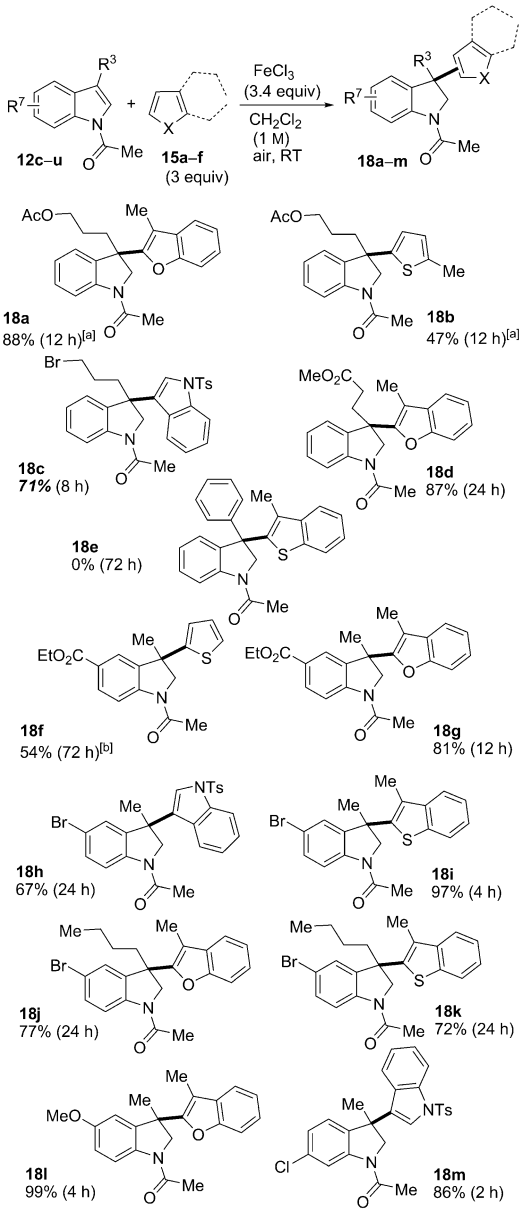
In terms of functional group tolerance, ester groups or halogens are tolerated in the C3 side chain, demonstrated by the isolation of indolines **17d**–**h**. A carbonyl group directly connected to the 3 position of indole (**17i**) suppressed the reactivity, as did the presence of amides on the C3 side chain (**17j** and **17k**); in all cases, the starting indoles were recovered. Electronic effects on the benzene portion of indoles **12** were then evaluated. Pleasingly, electron-withdrawing groups (NO_2, CN, CO_2Et), halides (Br), and electron-donating groups (OMe) at the 5 position efficiently delivered the expected indolines **17l**–**q**. Similarly, hydroarylation occurred with an electron-withdrawing group (NO_2; **17r**), halide (Cl; **17s**), or electron-donating group (MeO; **17t**) at the 6 position.

Having established that a vast array of functional groups on **12** are tolerated during the hydroarylation with **13d**, the reaction of diversely substituted *N*-acetylindole **12** and nucleophilic heterocycles **15** were next examined (Scheme 8). The goal is to show that this methodology is well suited for the rapid generation of building blocks for medicinal chemistry.

Heterocycles **15e** and **15d** could be efficiently added to 3-(3-acetoxyprop-1-yl)-*N*-acetylindole to afford **18a** and **18b**, respectively. Reaction of **15a** with 3-(1-bromopropyl)-*N*-acetylindole gave **18c**. Nucleophile **15e** reacted efficiently with 3-(2-(methoxycarbonyl)eth-1-yl)-*N*-acetylindole to give **18d**. Unfortunately, it was not possible to add heterocycle **15f** to hindered 3-phenyl-*N*-acetylindole and **18e** was not obtained, even after 72 h. *N*-Acetylindoles substituted at the 5 position were suitable acceptors for heterocycles. Heterocycles **15c** and **15e** delivered the electron-poor 5-ethylcarboxylateindolines **18f** and **18g**, respectively. Reaction of **15a**, **15f**, and **15e** with 5-bromo-*N*-acetylindole gave the 5-bromoindolines **18h**–**k**. 5-Methoxy-*N*-acetylindole and **15e** gave electron-rich 5-methoxyindoline **18l**. Finally, 6-chloro-*N*-acetylindole was successfully coupled with **15a** to yield **18m**.



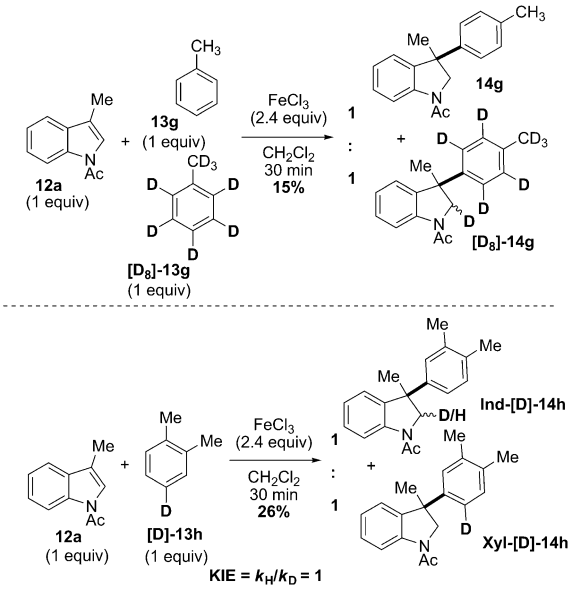
Scheme 7. $FeCl_3$-promoted hydroarylation of diversely substituted *N*-acetylindole with anisole. [a] **13d** (2 equiv), $FeCl_3$ (2.2 equiv). [b] **17d'** and **17e'** were obtained from reaction with **13g**.



Scheme 8. $FeCl_3$-promoted hydroarylation of diversely substituted *N*-acetylindole with heterocycles. [a] **15** (4 equiv), $FeCl_3$ (4.4 equiv). [b] **15** (5 equiv), $FeCl_3$ (5.4 equiv). Ts = *p*-toluenesulfonyl.

After demonstration of the large scope of the reaction, we wanted to gain some mechanistic insights. To this end, determination of a kinetic isotope effect (KIE) was sought. Therefore, we performed the competing hydroarylation of **12a** with **13g** and **[D_8]-13g** and interrupted the reaction at low conversion (Scheme 9). The ratio of hydroarylated compounds **14g** and **[D_8]-14g** was 1:1.

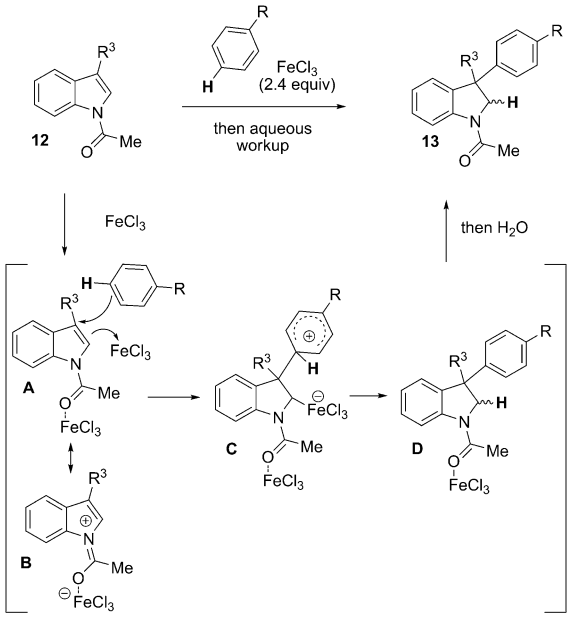
To complement this intermolecular experiment, an intramolecular competition experiment was done. The reaction of **12a** and 4-[D]-1,2-xylene (**[D]-13h**) delivered a 1:1 mixture of indolines **Ind-[D]-14h** and **Xyl-[D]-14h**, from cleavage of the C–D and C–H bonds of monodeuterated xylene **[D]-13h** (Scheme 9). The results of these inter- and intramolecular competition experiments are representative of a KIE of 1. This is indicative that cleavage of the C–H or C–D bond of the nucleophile is not the rate- or product-determining step.[23] Such behavior is observed for electrophilic substitution reactions in which C–H or C–D bond cleavage is very fast during the rearomatization of Wheland intermediates.[24]



Scheme 9. Determination of the KIE.

These experiments, and some previous observations, allowed us to propose a mechanistic hypothesis (Scheme 10).

We observed that over two equivalents of $FeCl_3$ are needed for the reaction to proceed to completion (Table 1, entries 16 and 17). It seems reasonable to think that two molecules of $FeCl_3$ are involved in the mechanism. One equivalent of $FeCl_3$



Scheme 10. Mechanistic hypothesis.

could undergo complexation by the oxygen atom of the carbonyl group (intermediate **A**). Consequently, the indole nitrogen lone pair could be delocalized in the carbonyl π system (intermediate **B**) and, thus, break the aromaticity of the pyrrole part of the indole. Therefore, the C2=C3 double bond should be less electron rich at C3. Activation of this double bond by a second molecule of $FeCl_3$ might generate an intermediate electrophile at C3 and trigger electrophilic substitution with an electron-rich aromatic compound via the formation of Wheland intermediate **C**, as suggested by the KIE of the reaction. The next event would be protonation of the C2 position by the proton released from rearomatization of **C**, illustrated by the reaction with [**D**]-**13g** (Scheme 9), in which the C2 position of the indoline product is deuterated. We have also run reactions with excess triethylamine or K_2CO_3 to neutralize conspicuous amounts of hydrogen chloride in solution and we observed complete shutdown of the reaction. We believe that these bases might neutralize the proton released from aromatization of Wheland intermediate **C**, which is necessary for the protonation of the C2 position. Finally, aqueous workup will decomplex iron(III) from the acetyl moiety of **D** to give indoline **13**.

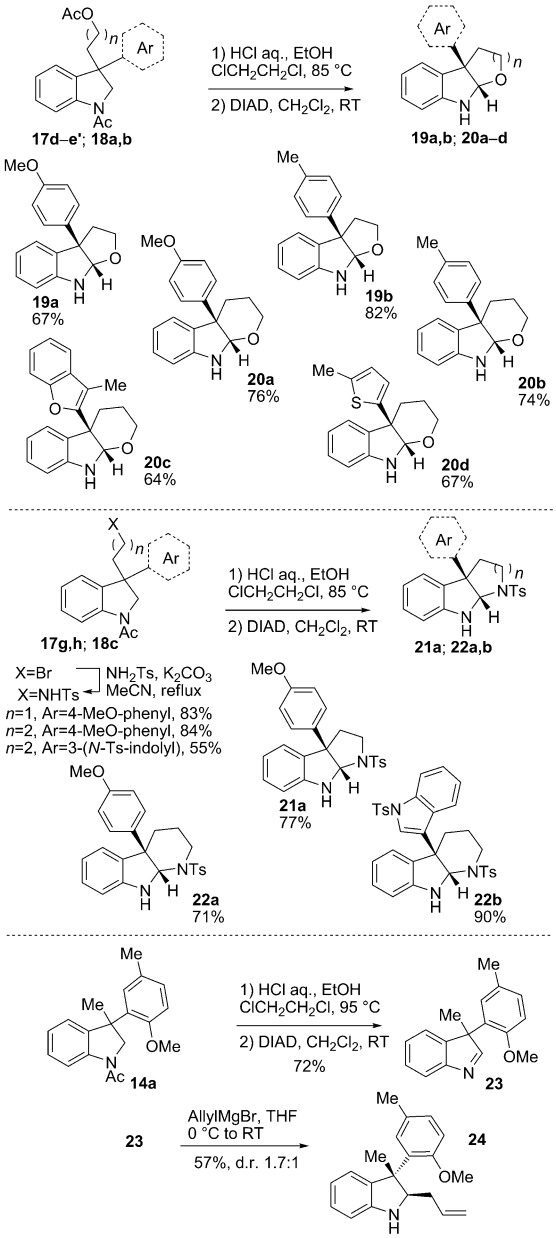
Alternatively to our mechanistic proposal, activation of the electron-rich aromatic partner could not be excluded. However, we do not believe that the iron promoter performs a C–H activation of the nucleophilic electron-rich arene because we would have expected a KIE greater than $k_H/k_D = 1$.[24b]

Finally, to showcase the versatility of the arylated indolines **13** some synthetic transformations were investigated.

3-Arylfuranoindolines **19a** and **19b** and 3-arylpyrranoindolines **20a**–**d** were readily obtained by double deacetylation of the 3-aryl-3-acetoxyalkylindolines **17d** and **17d′** and **17e**, **17e′**, **18a**, and **18b**, respectively, followed by a diisopropylazodicarboxylate (DIAD) mediated oxidation (Scheme 11).[20,25] It should be noted that reports of pyranoindolines or furanoindolines that incorporate a 3-heteroaryl unit, such as compounds **20c** and **20d**, are very rare in the literature.[26]

To obtain nitrogen analogues of **19**, nucleophilic substitution of the bromide atoms on the C3 side chain in indole **17g** by *para*-toluenesulfonamide was first performed (Scheme 11). Then the hydrolysis–oxidation sequence yielded 3-(4-methoxyphenyl)pyrroloindoline **21a**, the core structure of the naseseazines. The nitrogen analogues of **20**, piperidinoindolines **22a** and **22b**, which incorporate a 3-(4-methoxyphenyl) and a 3-(3′-*N*-Ts-indolyl) group, respectively, were also synthesized efficiently through the same strategy from **17h** and **18c**.[27]

In the absence of a group for intramolecular trapping, the imine **23** could be isolated by hydrolysis of **14a** and oxidation. Allylation of **23** by the addition of a Grignard reagent delivered the 3,3,2-trisubstituted indoline **24** in a 1.7:1 diastereomeric ratio (d.r.) with attack of the allyl nucleophile from the less-hindered face as the major pathway.[19k]



Scheme 11. Synthesis of arylated furanoindolines, pyranoindolines, pyrroloindoline, piperidinoindolines, and trisubstituted indolines.

Conclusion

We have described the conception of a method for the regioselective hydroarylation of *N*-acetylindole activated by $FeCl_3$, which leads to functionalized indolines with an arylated quaternary carbon center at C3. The generation of electrophilic indoles represents the rare umpolung of the indole nucleus, which allows regioselective introduction of aryl and heteroaryl groups at the 3 position of *N*-acetylindole. This robust reaction employs cheap and nontoxic iron(III) chloride as promoter, proceeds at room temperature under air atmosphere, and is scalable. It tolerates a broad scope of indole electrophiles and electron-rich aromatic nucleophiles. Mechanistic insights and functionalization of the indolines obtained are also presented. We anticipate that this cross-coupling will find useful applications in natural product or medicinal chemistry because complexity may be rapidly introduced with only N-acylation of the indole as prefunctionalization.

Experimental Section

General procedure for the hydroarylation of *N*-acetylindole

In one portion, electron-rich arene (2 equiv) and $FeCl_3$ (2.6 equiv) were successively added to a solution of 3-substituted indole derivative **12** (1 equiv) in CH_2Cl_2 (1.0 M). The reaction was monitored by TLC from 1 h onwards. After complete consumption of **12**, the reaction was quenched with brine and diluted with EtOAc. The phases were separated and the aqueous phase was extracted with EtOAc (×2). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude oil was purified by flash column chromatography.

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FULL PAPER

Indoles

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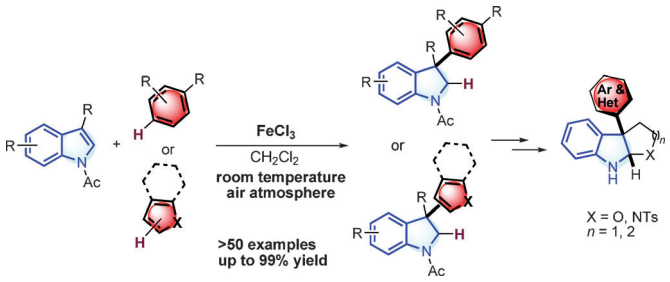
Regioselective Hydroarylation Reactions of C3 Electrophilic *N*-Acetylindoles Activated by $FeCl_3$: An Entry to 3-(Hetero)arylindolines



Indole electrophiles: A method for the direct and rare umpolung of the 3 position of indoles is reported. The activation of *N*-acetylindole with iron(III) chloride allows the C–H addition of aryl substrates to the C2=C3 double bond of the indole nucleus to regioselectively generate 3-arylindolines with a quaternary center at C3 (see scheme).