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An $FeCl_3$-catalyzed highly C3-selective Friedel–Crafts alkylation of indoles with alcohols

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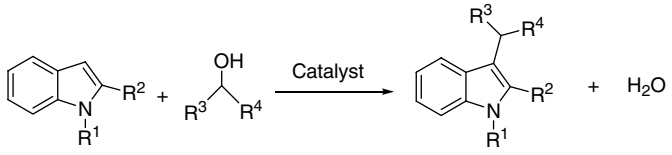
Abstract—The $FeCl_3$-catalyzed C3-selective Friedel–Crafts alkylation of indoles using allylic, benzylic and propargylic alcohols has been developed. The reaction was performed in the presence of a catalytic amount of inexpensive anhydrous $FeCl_3$ (10 mol %) in nitromethane under mild conditions. This method can also be used for the alkylation of pyrrole.

The indole framework is a versatile and important structural motif frequently found in natural products, pharmaceuticals, and other synthetic compounds.[1] Modification of the indole structure is an emerging field of research. Among the various methods to synthesize substituted indoles, substitution at C-3 with alcohol derivatives is important.[2] However, the substitution with derivatives of alcohols produces large amounts of salt waste as a by-product and many reactions require stoichiometric amounts of base or Lewis acids. Thus, in view of the demand for efficient, atom-economic[3] and economically valuable processes, the direct catalytic substitution of indoles with alcohols is highly desirable, as water is the only by-product (Scheme 1).

Recently, a few reports[4–6] have appeared on the direct catalytic substitution of indole with alcohols. However, the harsh reaction conditions and the use of expensive, toxic and moisture sensitive reagents in most of the above methods limits their practical utility in large-scale synthesis. Moreover, these methods are not general for substrates such as benzylic, allylic and propargylic alcohols. Therefore, the development of a more general and practical method under mild conditions and preferably using environmentally friendly and inexpensive reagents is highly desirable.

During the course of our investigations on the catalytic activation of alcohols using $FeCl_3$,[7] as an inexpensive and environmentally friendly Lewis acid, we herein report the direct regioselective C-3 alkylation of indoles using alcohols.

First, we investigated the Friedel–Crafts allylic alkylation between indole **1a** and allyl alcohol **2a** in order to develop the reaction conditions. We found that in the presence of $FeCl_3$ (10 mol %) at room temperature in nitromethane as solvent, the reaction proceeded efficiently to afford the allylated product **3a**[8] in 70% yield. The reaction was clean and complete within 2 h without the need for an inert atmosphere, and gave the C3-substitution product exclusively. Among various solvents, nitromethane was found to be the best in terms of the efficiency of the reaction.



Scheme 1. Catalytic substitution of indoles.

Keywords: Indole; Ferric chloride; Alkylation; Alcohols; Atom-economical.
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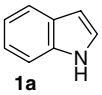
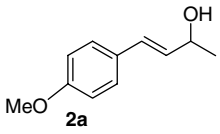
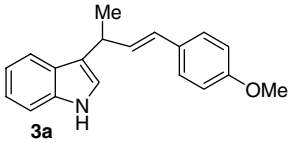
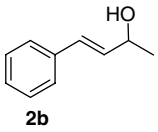
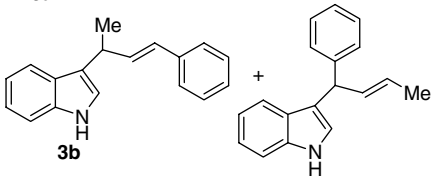
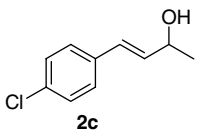
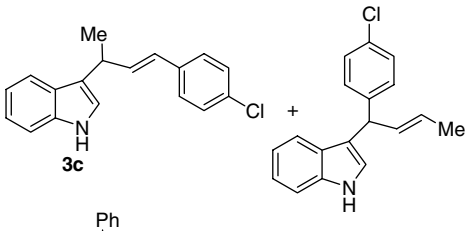
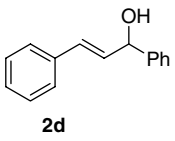
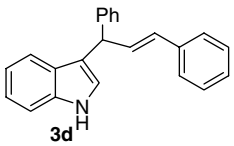
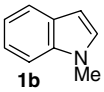
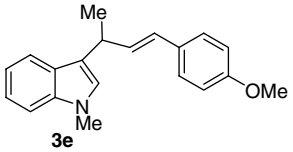
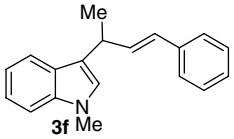
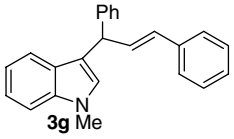
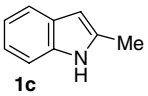
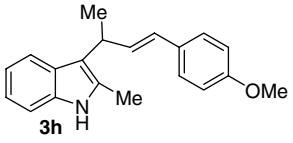
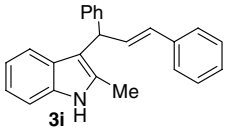
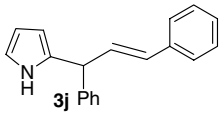
Table 1. $FeCl_3$-catalyzed substitution of indoles **1** with allylic alcohols **2**[a]

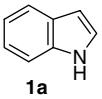
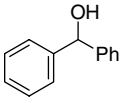
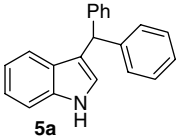
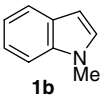
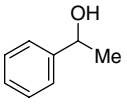
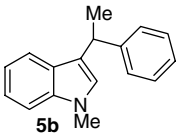
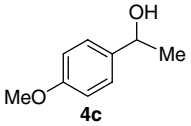
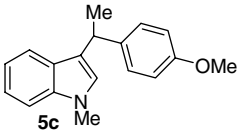
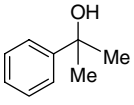
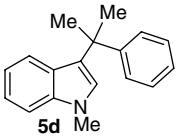
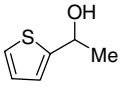
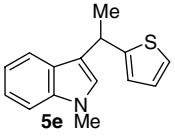
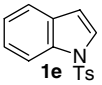
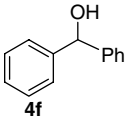
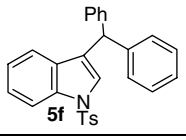
Entry	Nucleophile	Alcohol	Product	Time (h)	Yield[b] (%)
1	 **1a**	 **2a**	 **3a**	2	70
2	**1a**	 **2b**	 **3b**	3	56[c]
3	**1a**	 **2c**	 **3c**	2	60[c]
4	**1a**	 **2d**	 **3d**	3	58[d]
5	 **1b**	**2a**	 **3e**	2	72
6	**1b**	**2b**	 **3f**	2	65
7	**1b**	**2d**	 **3g**	3	72
8	 **1c**	**2a**	 **3h**	3	71
9	**1c**	**2b**	 **3i**	2	70
10	 **1d**	**2d**	 **3j**	2	60[e]

[a] Reaction conditions: Nucleophile **1** (1 mmol), alcohol **2** (1 mmol), $FeCl_3$ (0.1 mmol), nitromethane (3 mL), rt.
[b] The yield refers to pure isolated product characterized from spectral data.
[c] Mixture of regioisomers ~3:2 (^{1}H NMR).
[d] The reaction mixture was stirred at room temperature for 2 h, then alcohol **2** (0.3 mmol) was added and the reaction heated at 55 °C for 1 h.
[e] Toluene was used as the solvent at room temperature.

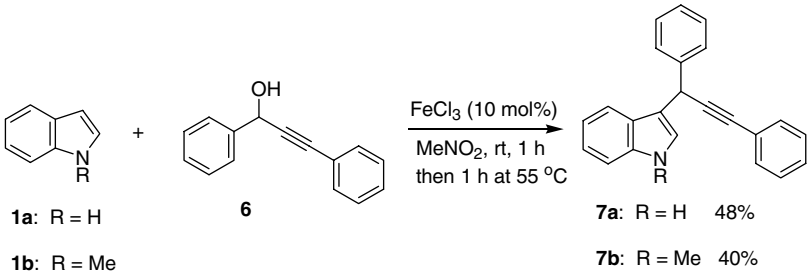
The reactions of various indoles with different alcohols were examined next and the results are summarized in Table 1. In general, the reactions proceeded smoothly with high selectivities for various secondary allylic alcohols **2a–d** with indole in very good yields within very short periods of time at room temperature. The process also worked efficiently for *N*-methylindole and afforded the desired products in good yields (Table 1, entries 5–7). This result differed from the allylation of indoles catalyzed by palladium in the presence of trialkylborane.[4a] The sterically demanding indole **1c** (Table 1, entries 8 and 9) reacted with alcohols **2a** and **2b** effectively under these conditions with excellent regioselectivity to give **3h** and **3j** in good yields. Unsymmetrical allylic alcohols without any activating group (Table 1, entries 2 and 3) produced mixtures of regioisomers. The acid and air sensitive pyrrole **1d** (Table 1, entry 10) could also be allylated using the present method in moderate yield without any side product formation. Allylation occurred selectively at the 2-position of pyrrole.[9] Although the present procedure is very useful for reaction with secondary allylic alcohols, unfortunately, primary allylic alcohols produced mixtures of products, therefore, these reactions were not persued further.

Next, we attempted to synthesize 3-benzylated indoles using this method (Table 2). Both free indole (Table 2, entry 1) and *N*-methylindole (Table 2, entries 2–5) underwent smooth coupling with benzyl alcohol derivatives efficiently and selectively. In the presence of

Table 2. $FeCl_3$-catalyzed substitution of various indoles **1** with benzylic alcohols **4**[a]

Entry	Nucleophile	Alcohol	Product	Time (h)	Yield (%)
1	 **1a**	 **4a**	 **5a**	3	75[b]
2	 **1b**	 **4b**	 **5b**	4	80[b]
3	**1b**	 **4c**	 **5c**	1	92
4	**1b**	 **4d**	 **5d**	1	98
5	**1b**	 **4e**	 **5e**	1	95
6	 **1e**	 **4f**	 **5f**	3	89[b]

[a] Reaction conditions: Nucleophile **1** (1 mmol), alcohol **2** (1 mmol), $FeCl_3$ (0.1 mmol), $MeNO_2$ (3 mL), room temperature.
[b] Reaction was performed at 60 °C in the presence of alcohol (1.3 equiv).



Scheme 2. $FeCl_3$-catalyzed propargylation of indoles.

Brønsted or Lewis acid, secondary and tertiary benzylic alcohols possessing β-hydrogen atoms are very sensitive to dehydration, but the present method could also be applied to both secondary and tertiary alcohols (Table 2, entries 3–5). This reaction also proceeded smoothly with the thiophene derivative **4e** (Table 2, entry 5), affording a hybrid heterocycle in 95% yield. Moreover, this method could also be applied to *N*-tosylindole **1e** (Table 2, entry 6) and furnished product **5f** in 89% yield.

Finally, we investigated the $FeCl_3$-catalyzed propargylation of indoles with propargyl alcohol **6** (1.3 equiv) using the present method, which afforded alkynes **7a** and **7b** in moderate yields (Scheme 2).

In summary, we have developed an efficient and atom-economical method for the direct alkylation of indoles with various alcohols in the presence of the inexpensive and non-toxic Lewis acid $FeCl_3$, under mild conditions. Functional groups that could coordinate to the Lewis acid, such as an ether, chloride and tosyl remained unaffected under the reaction conditions. Sensitive molecules such as thiophene and pyrrole also survived under the reaction conditions. The reaction did not proceed at all without $FeCl_3$. Although the exact mechanism is uncertain at this moment, presumably, the reaction proceeded through an aromatic electrophilic substitution, where the alcohol is activated by coordination with $FeCl_3$. Further investigation on the reaction mechanism and the scope of this reaction are currently underway in our laboratory.

Acknowledgements

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6. Propargylation of indole catalyzed by $Sc(Otf)_3$, see: Yadav, J. S.; Reddy, B. V. S.; Raghavendra, K. V.; Kumar, C. G. K. S. N. *Tetrahedron Lett.* **2007**, *48*, 3295–3298.
7. Jana, U.; Biswas, S.; Maiti, S. *Tetrahedron Lett.* **2007**, *48*, 4065–4069.
8. *Representative experimental procedure*: To a stirred solution of indole **1a** (116 mg, 1 mmol) and allylic alcohol **2a** (178 mg, 1 mmol) in dry nitromethane (3 mL) was added anhydrous $FeCl_3$ (16 mg, 0.1 mmol). The resulting reaction mixture was stirred at room temperature for 2 h, and monitored by TLC. The reaction mixture was then concentrated under reduced pressure and the residue was purified by silica gel column chromatography to afford the alkylated indole **3a** (194 mg, 0.7 mmol) as a brown solid, mp 145 °C; $R_f = 0.5$ (petroleum ether/EtOAc, 9:1).
Spectral data for novel compounds are given below: 3-[3-(4-*Methoxyphenyl*)-1-*methyl-allyl*]-1*H-indole* (**3a**): IR (neat) 3409, 2959, 1608, 1512 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.56 (d, $J = 7.0$ Hz, 3H), 3.80 (s, 3H), 3.88–3.95 (m, 1H), 6.30–6.49 (m, 2H), 6.83 (d, $J = 8.7$ Hz, 2H), 7.03–7.39 (m, 6H) 7.69 (d, $J = 7.8$ Hz, 1H), 7.96 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 20.9, 34.3, 55.4, 111.3, 114.0, 119.3, 119.8, 120.5, 120.7, 123.0, 126.9, 127.4, 127.6, 130.8, 133.5, 136.7, 158.8; HRMS: *m*/*z* Calcd for $C_{19}H_{19}NO$: 277.1467; found, 277.1631.
3-[3-(4-*Chlorophenyl*)-1-*methyl-allyl*]-1*H-indole* (**3c**): Mixture of regioisomers (3:2); IR (neat) 3415, 2964, 1489, 1456 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.57 (d, $J = 7.10$ Hz, 1.8H), 1.73 (d, $J = 6.30$ Hz, 1.2H), 3.92–3.95 (m, 0.6H), 4.87 (d, $J = 3.68$ Hz, 0.4H), 5.48–5.57 (m, 0.5H), 5.89–5.97 (m, 0.5H), 6.44–6.45 (m, 1H), 6.89–7.42 (m, 8H), 7.66 (d, $J = 7.90$ Hz, 1H), 7.99 (br s, 1H); HRMS: *m*/*z* Calcd for $C_{18}H_{16}ClN$: 281.0971; found, 281.1708.
3-[3-(4-*Methoxyphenyl*)-1-*methyl-allyl*]-1-*methyl*-**1***H-indole* (**3e**): IR (neat) 3006, 1606, 1506, 1509, 1467 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.57 (d, $J = 7.0$ Hz, 3H), 3.77 (s, 3H), 3.81 (s, 3H) 3.91–3.96 (m, 1H), 6.30–6.51 (m, 2H), 6.83–6.90 (m, 3H), 7.10 (t, $J = 7.3$ Hz, 1H), 7.22–7.33 (m, 4H), 7.70 (d, $J = 7.9$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 32.7, 34.3, 55.4, 109.3, 113.8, 114.0, 118.8, 119.2, 119.8, 121.6, 125.4, 127.3, 127.5, 129.4, 130.8, 133.6, 137.4, 158.8; HRMS:*m*/*z* Calcd for $C_{20}H_{21}NO$: 291.1623; found 291.1679.
3-[3-(4-*Methoxyphenyl*)-1-*methyl-allyl*]-2-*methyl*-1*H-indole* (**3h**): IR (neat) 3407, 2963, 1680, 1606, 1510 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.57 (d, $J = 7.0$ Hz, 3H), 2.41 (s, 3H), 3.80 (s, 3H), 3.83–3.92 (m, 1H), 6.36–6.51 (m, 2H), 6.83 (d, $J = 8.6$ Hz, 2H), 7.06–7.18 (m, 2H), 7.29 (d, $J = 8.5$ Hz, 3H), 7.63 (d, $J = 7.7$ Hz, 1H), 7.75 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 12.3, 20.5, 33.7, 55.4, 110.4, 114.0, 119.0, 119.4, 120.8, 127.2, 127.3, 127.7, 130.9, 133.2, 135.4, 158.7; HRMS: *m*/*z* Calcd for $C_{20}H_{21}NO$: 291.1623; found, 291.0237.
2-(1,3-*Diphenylallyl*)-1*H*-pyrrole (**3j**): IR (neat) 3429, 3026, 1598, 1492, 1450 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 4.84 (d, $J = 7.4$ Hz, 1H), 5.96 (s, 1H), 6.16 (d, $J = 2.42$ Hz, 1H), 6.40–6.67 (m, 3H), 7.19–7.36 (m, 10H), 7.81 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 48.2, 106.9, 108.5, 117.4, 126.5, 126.9, 127.0, 127.6, 128.5, 128.7, 128.8, 131.2, 131.4, 133.1, 137.1, 142.2; HRMS: *m*/*z* Calcd for $C_{19}H_{17}N$: 259.1361; found, 259.3190.
3-*Benzhydrol*-1-(*toluene*-4-*sulfonyl*)-1*H-indole* (**5f**): IR (neat) 3059, 3024, 1598, 1494 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3H), 5.51 (s, 1H), 6.93 (s, 1H), 7.06–7.31 (m, 15H), 7.67 (d, $J = 8.14$ Hz, 2H), 7.96 (d, $J = 8.36$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.7, 48.6, 114.0, 120.6, 123.3, 124.9, 125.9, 126.9, 128.3, 128.7, 128.8, 128.9, 129.1, 129.6, 129.9, 142.2, 144.9; HRMS: *m*/*z* Calcd for $C_{28}H_{23}NO_2SNa$: 460.1347; found, 460.1363.
9. For allylation of pyrrole, see: Kimura, M.; Fukasaka, M.; Tamaru, Y. *Heterocycles* **2006**, *67*, 535–541.