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First example of $FeCl_3$-catalyzed alkylation of indoles with pinenes

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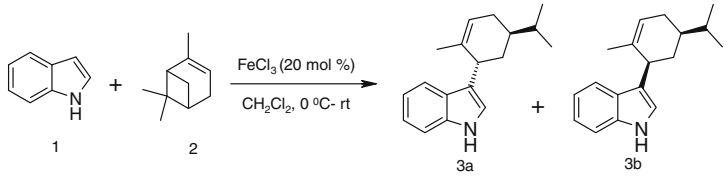
ABSTRACT

Indoles undergo smooth alkylation with α- and β-pinenes in the presence of 20 mol % of anhydrous $FeCl_3$ under mild reaction conditions to produce a wide range of the corresponding 3-alkylated indoles in excellent yields with high trans-selectivity. This is the first example of alkylation of indoles with monoterpenes.

Indole and its derivatives are found abundantly in nature and are known to exhibit potent physiological properties.[1] Substituted indoles are capable of binding to many receptors with high affinity. Therefore, the synthesis and selective functionalization of indoles have been the focus of active research over the years.[2–4] In particular, 3-substituted indoles have contributed a major role in the synthesis of various biologically active molecules. Consequently, there is a continuous demand for the development of improved methods for the synthesis of 3-substituted indoles.[5] Typically, organometallic couplings require that one or both entities are prefunctionalized as halides or with another disposable functionality.[6] In this context, particular focus was devoted for developing new methods to couple indoles with olefins directly without the modification of either of the coupling partners. For instance, electrophilic substitution of indoles at C-3 position with olefins has been reported by transition metal catalysis.[7] Recently, we have reported alkylation of indoles at C-3 position with activated cyclopropanes using $CeCl_3 \cdot 7H_2O$[8] and also from 1,3-dicarbonyl compounds using a catalytic amount of $FeCl_3$.[9]

Lewis acid-catalyzed carbon–carbon bond forming reactions are of great importance in organic synthesis because of their high reactivity, selectivity and mild reaction conditions.[10] In particular, iron(III) chloride has emerged as a powerful Lewis acid catalyst and performs many useful organic transformations under mild reaction conditions.[11] Moreover, iron salts are inexpensive, easy to handle and are environmentally friendly. To the best of our knowledge, there have been no previous reports on the direct coupling of indoles with α-pinene using $FeCl_3$ as a catalyst.

In this Letter, we report the direct $FeCl_3$-catalyzed alkylation of indoles with monoterpenes under mild conditions to produce a wide range of the corresponding 3-alkylated indoles in excellent yields with high trans-selectivity. We first attempted the alkylation of indole (**1**) with α-pinene (**2**) using 20 mol % of anhy-



Scheme 1.

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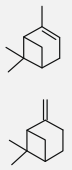
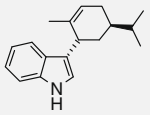
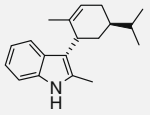
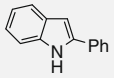
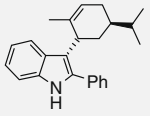
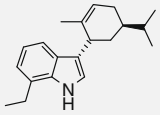
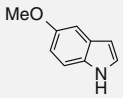
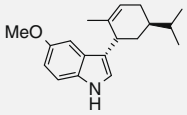
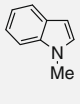
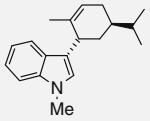
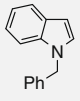
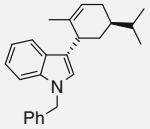
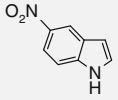
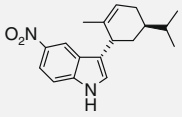
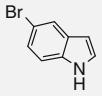
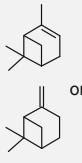
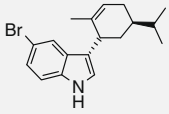
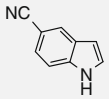
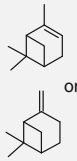
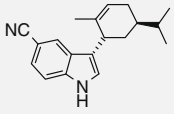
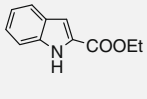
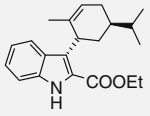
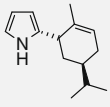
Table 1
$FeCl_3$-catalyzed alkylation of indoles

Entry	Indole	Alkene	Product[a]	Time (min)	Yield (%)[b]	*Trans:cis*
a				45 55	89 87	85:15 90:10
b				50	86	75:25
c				65	82	90:10
d				50	85	80:20
e				55	85	72:28
f				70	80	82:18
g				75	75	73:27
h				95	80	80:20
i				80 75	82 80	85:15 82:18
j				85 90	74 73	90:10 90:10
k				75	85	78:22
l				45	84	80:20

[a] All products were characterized by ^1H NMR, IR and mass spectrometry.
[b] Yield refers to pure products after chromatography.

drous $FeCl_3$ in dichloromethane. The reaction went to completion in 45 min at room temperature giving product **3a** in 89% yield. No improvement in yield or reaction time was achieved even by increasing the amount of the catalyst from 20 mol % to stoichiometric or by heating the reaction mixture (Scheme 1).

Similarly, α-pinene reacted smoothly with various indole derivatives such as 2-methyl, 2-phenyl, 7-ethyl, 5-methoxy, *N*-methyl, and *N*-benzyl-indoles to afford the corresponding 3-alkyl-substituted indoles (Table 1, entries b–g). Interestingly, electron-deficient indoles such as 5-nitro, 5-bromo, 5-cyano, and 2-ethoxy carbonyl were participated well with α-pinene to produce the corresponding 3-substituted indoles in good yields with trans-selectivity (Table 1, entries h–k). In case of electron-deficient indoles and N-substituted indoles, the reactions were sluggish compared to electron-rich counterparts. It is worthy mentioning that β-pinene also worked well in this reaction and the resulting products were the same (Table 1, entries a, i and j) as that of α-pinene.[12] Like indoles, pyrrole also was effective substrate to afford the corresponding 2-substituted pyrrole in high yield (Table 1, entry l).

The stereochemistry of **3j** was established using NOESY experiment (Fig. 1). Chemical shifts of the protons were assigned using DQFCOSY, TOCSY and decoupling methods, because of the multiplet structures of the peaks obtained in ^1H NMR. The presence of strong NOE between H_a–H_k, and H_a–CH_3 (isopropyl), clearly indicates the trans-conformation for Ha and Hc, which was further supported by NOE's between H_k–CH_3 (isopropyl), H_a–H_k and H_g–$H_{b'}$. Decoupling of H_b gave a large coupling to H_a indicating H_a and $H_{b'}$ are trans to each other. The NOE intensities were normalized with respect to that of geminal protons (H_d–$H_{d'}$) and taken as a reference 100%. Accordingly, the NOE intensities in Figure 1 are H_a–H_k (8.6%), H_a–CH_3 (12.7%, 24.3%), H_k–CH_3 (6.8%, 4.9%), and H_g–$H_{b'}$ (8.2%).

Mechanistically, the reaction may proceed via the activation of alkene by a metal catalyst followed by attack of indole and subsequent migration of the double bond towards four-membered ring leading to the formation of 3-substituted indole (Scheme 2). In the recent report of Duñach et al. on the alkoxylation of monoterpenes,[14] the alcohol was attacked at tertiary carbon whereas in the present case, the indole attacks on the double bond to induce the reaction. On the other hand, the reaction may also involve a Meerwein migration of a carbocation.[15]

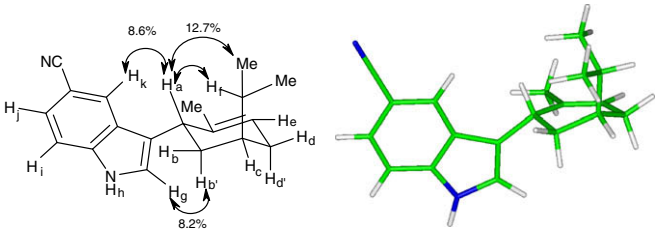
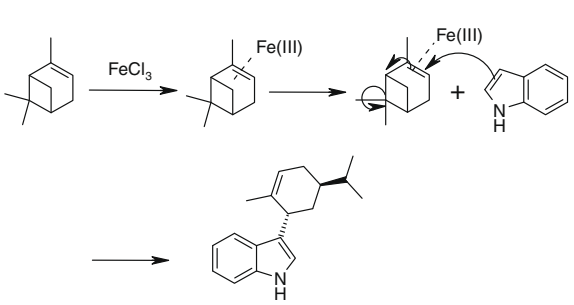


Figure 1. Characteristic NOE's and energy minimized structure of product **3j**.[13]



Scheme 2. A plausible reaction mechanism.

In the absence of catalyst, the reaction failed to give the desired product. The products were characterized by ^1H NMR, IR and mass spectrometry. No chlorination of α-pinene was observed under the reaction conditions. Other iron(III) salts such as $Fe(acac)_3$, $Fe(ClO_4)_3$ and $Fe(NO_3)_3$ were not so effective for this conversion. The reaction did not proceed with $CeCl_3{\cdot}7H_2O$ in acetonitrile even under reflux conditions. The scope and generality of this process is illustrated with respect to various indoles and monoterpenes such as α-pinene and β-pinene, and the results are presented in Table 1.[16] Thus, a large number of 3-terpenyl indole derivatives were prepared using this procedure.

In summary, anhydrous $FeCl_3$ has proved to be a useful and highly efficient catalyst for the alkylation of various indoles with pinenes such as α-pinene and β-pinene under mild conditions. In addition to its simplicity and efficiency, this method produces 3-terpenylindoles in excellent yields in short reaction time. This method is convenient and cost-effective and also provides the products with high trans-selectivity.

Acknowledgements

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12. (a) Optical rotation for product **3j** derived from α-pinene: $[\alpha]_D^{29}$ + 4.52 (*c* 1, $CHCl_3$) (b) Optical rotation for product **3j** derived from β-pinene: $[\alpha]_D^{29}$ + 4.53 (*c* 1, $CHCl_3$).
13. Energy minimization was performed on INSIGHT II-Discover program using 'Steepest descent' and 'Conjugate' methods for 1000 and 1,000,000 iterations, respectively, and dielectric constant value of 4.7 (for $CDCl_3$ solvent medium) was used during minimization.
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16. *General procedure*: To a stirred solution of α-pinene (163 mg, 1.2 mmol) and indole (117 mg, 1.0 mmol) in dichloromethane (4 mL) was added $FeCl_3$ (32 mg, 0.2 mmol) at 0 °C. The resulting mixture was stirred at room temperature for appropriate time (Table 1). After complete conversion as indicated by TLC, the reaction mixture was quenched with water (5 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The resulting product was purified by column chromatography to afford pure 3-substituted indole derivative. *Spectroscopic data for all products*: *3-(5-Isopropyl-2-methyl-cyclohex-2-enyl)-1H-indole* (**3a**): Semisolid; IR(KBr): *ν* 3414, 3054, 2957, 2925, 2870, 1682, 1617, 1456, 1338, 1300, 1218, 1155, 1092, 1011, 882, 844, 806, 741 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 7.79–7.68 (m, 1H), 7.53 (d, *J* = 7.7 Hz, 1H), 7.25 (d, *J* = 7.9 Hz, 1H), 7.15–6.96 (m, 2H), 6.85 (d, *J* = 2.0, 1H), 5.43–5.35 (m, 1H), 3.55–3.44 (m, 1H), 2.19–1.96 (m, 2H), 1.82–1.55 (m, 5H), 1.55–1.32 (m, 2H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.85 (d, *J* = 6.7 Hz, 3H); ESI-MS: *m/z*: 254 $(M+1)^+$, 181, 137, 101; HRMS calcd for $C_{18}H_{24}N$: 254.1908, found: 254.1906. *3-(5-Isopropyl-2-methyl-cyclohex-2-enyl)-2-methyl-1H-indole* (**3b**): Semisolid; IR(KBr): *ν* 3368, 2958, 2927, 2872, 1695, 1617, 1523, 1367, 1300, 1242, 1159, 753 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): *δ* 7.59–7.51 (br s, 1H), 7.40 (d, *J* = 7.5 Hz, 1H), 7.15 (d, *J* = 7.5, 1H), 7.03–6.89 (m, 2H), 5.34–5.29 (m, 1H), 3.43–3.33 (m, 1H), 2.34 (s, 3H), 2.26–2.0 (m, 2H), 1.83–1.68 (m, 4H), 1.63–1.51 (m, 1H), 1.49–1.24 (m, 2H), 0.80 (t, *J* = 6.7, 13.6 Hz, 6H); LC–MS: *m/z*: 268 $(M+1)^+$, 245, 227, 217, 186, 157. *3-(5-Isopropyl-2-methyl-cyclohex-2-enyl)-2-phenyl-1H-indole* (**3c**): Semisolid; IR(KBr): *ν* 3403, 3055, 2956, 2925, 1881, 1674, 1605, 1484, 1452, 1368, 1306, 1241, 1151, 1071, 917, 848, 744, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): *δ* 7.92–7.78 (br s, 1H), 7.66–7.26 (m, 7H), 7.20–6.97 (m, 2H), 5.63–5.54 (m, 1H), 3.74–3.57 (m, 1H), 2.37–2.08 (m, 2H), 1.84–1.67 (m, 4H), 1.50–1.17 (m, 3H), 0.70 (d, *J* = 7.0 Hz, 3H), 0.31 (d, *J* = 7.0 Hz, 3H); LC–MS: *m/z*: 347 $(M+NH_4)^+$, 319, 303, 278, 235, 183, 139, 118. *7-Ethyl-3-(5-isopropyl-2-methyl-cyclohex-2-enyl)-1H-indole* (**3d**): Semisolid; IR(KBr): *ν* 3422, 3053, 2960, 2927, 2871, 1610, 1435, 1349, 1218, 1112, 1073, 990, 882, 797, 747 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 7.80–7.64 (br s, 1H), 7.45–7.34 (m, 1H), 6.99–6.90 (m, 2H), 6.86 (d, *J* = 2.2 Hz, 1H), 5.41–5.35 (m, 1H), 3.54–3.44 (m, 1H), 2.90–2.76 (m, 2H), 2.27–1.97 (m, 2H), 1.82–1.61 (m, 4H), 1.54–1.31 (m, 6H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.84 (d, *J* = 6.7 Hz, 3H); ESI-MS: *m/z*: 282 $(M+1)^+$, 146, 137, 102, 100, 81. *3-(5-Isopropyl-2-methyl-cyclohex-2-enyl)-5-methoxy-1H-indole* (**3e**): Semisolid; IR(KBr): *ν* 3448, 2958, 2924, 1712, 1462, 1432, 1376, 1305, 1181, 1099, 1071, 949, 834, 753, 712 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 7.78–7.66 (br s, 1H), 7.15 (d, *J* = 8.3 Hz, 1H), 6.97 (d, *J* = 2.2 Hz, 1H), 6.73 (dd, *J* = 2.2, 6.0 Hz, 1H), 6.16 (d, *J* = 2.2 Hz, 1H), 5.40–5.34 (m, 1H), 3.83 (s, 3H), 3.47–3.36 (m, 1H), 2.16–1.92 (m, 2H), 1.87–1.37 (m, 7H), 0.88 (d, *J* = 6.7 Hz, 3H), 0.83 (d, *J* = 6.7 Hz, 3H); ESI-MS: *m/z*: 301 $(M+NH_4)^+$, 282 $(M+1)^+$, 267, 236, 218, 200, 178, 163, 133. *3-(5-Isopropyl-2-methyl-cyclohex-2-enyl)-1-methyl-1H-indole* (**3f**): Liquid; IR (KBr): *ν* 3051, 2956, 2926, 2871, 1613, 1545, 1468, 1372, 1227, 1154, 1061, 1012, 918, 797, 737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 7.53 (d, *J* = 7.8 Hz, 1H), 7.22 (d, *J* = 7.8 Hz, 1H), 7.14 (t, *J* = 7.8, 6.8 Hz, 1H), 7.01 (t, *J* = 7.8, 6.8 Hz, 1H), 6.74 (d, *J* = 1.9 Hz, 1H), 5.41–5.36 (m, 1H), 3.77 (m, 3H), 3.53–3.46 (m, 1H), 2.12–1.99 (m, 2H), 1.83–1.57 (m, 6H), 1.52–1.40 (m, 1H), 0.95 (d, *J* = 6.8 Hz, 3H),0.87 (d, *J* = 6.8 Hz, 3H); LC–MS: *m/z*: 268 $(M+1)^+$, 254, 183, 132, 116, 102, 88. *1-Benzyl-3-(5-isopropyl-2-methyl-cyclohex-2-enyl)-1H-indole* (**3g**): Liquid; IR(KBr): *ν* 3027, 2956, 2926, 2869, 1605, 1492, 1457, 1359, 1176, 1026, 856, 733 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): *δ* 7.55 (d, *J* = 6.8 Hz, 1H), 7.35–6.93 (m, 8H), 6.81 (s, 1H), 5.48–5.36 (m, 1H), 5.25 (s, 2H), 3.59–3.44 (m, 1H), 2.16–1.90 (m, 2H), 1.83–1.32 (m, 7H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H); ESI-MS: *m/z*: 343 (M^+), 342, 296, 290, 259, 226, 193, 166, 149. *3-(5-Isopropyl-2-methyl-cyclohex-2-enyl)-5-nitro-1H-indole* (**3h**)*:* Liquid, IR(KBr): *ν* 3325, 2957, 1593, 1512, 1468, 1384, 1324, 1156, 1088, 890, 833, 776, 736, 670, 618 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 8.52 (br s, 1H), 7.89 (s, 1H), 7.40–7.33 (m, 2H), 7.04 (d, *J* = 2.2 Hz, 1H), 5.37–5.31 (m, 1H), 3.54–3.44 (dd, *J* = 5.2, 2.2 Hz, 1H), 2.13–1.99 (m, 2H), 1.81–1.35 (m, 7H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H); LC–MS: *m/z*: 321 $(M+Na)^+$, 301, 275, 231, 217, 186, 157, 130. HRMS calcd 321.1578; found: 321.1570; *5-Bromo-3-(5-isopropyl-2-methyl-cyclohex-2-enyl)-1H-indole* (**3i**): Colour: Brown; Solid, mp: 116–118 °C; IR (KBr): *ν* 3429, 2957, 2927, 2870, 1722, 1614, 1563, 1456, 1365, 1327, 1217, 1092, 1044, 1000, 884, 793 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): *δ* 7.92–7.71 (br s, 1H), 7.63 (s, 1H), 7.25–7.08 (m, 2H), 6.87 (d, *J* = 2.1 Hz, 1H), 5.38–5.28 (m, 1H), 3.51–3.36 (m, 1H), 2.18–1.97 (m, 2H), 1.82–1.33 (m, 7H), 0.94 (d, *J* = 7.2 Hz, 3H), 0.84 (d, *J* = 7.2 Hz, 3H); LC–MS: *m/z*: 332 $(M+1)^+$; HRMS calcd for $C_{18}H_{23}NBr$: 332.1013, found: 332.1022. *3-(5-Isopropyl-2-methyl-cyclohex-2-enyl)-1H-indole-5-carbonitrile* (**3j**): Liquid, IR(KBr): *ν* 3330, 2956, 2923, 2856, 2220, 1720, 1615, 1466, 1434, 1359, 1225, 1180, 1093, 919, 883, 805, 761, 636 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 8.39 (s, 1H), 7.95 (s, 1H), 7.40 (m, 2H), 7.08 (d, 1H, *J* = 2.2 Hz), 5.36 (m, 1H), 3.51 (m, 1H), 2.09 (m, 2H), 1.76 (m, 1H), 1.73 (s, 3H), 1.63 (m, 1H), 1.60 (m, 1H), 1.44 (m, 1H), 0.91 (d, 3H, *J* = 6.7 Hz), 0.83 (d, 3H, *J* = 6.7 Hz); LC–MS: *m/z*: 301 $(M+Na)^+$, 277, 261, 229, 217, 186, 171, 157, 138, 130.; HRMS calcd 279.1861; found: 279.1854. *Ethyl-3-(5-isopropyl-2-methyl-cyclohex-2-enyl)-1H-indole-2-carboxylate* (**3k**): Colourless solid, mp 194–196 °C; IR(KBr): *ν* 3346, 3057, 2955, 1889, 1676, 1535, 1445, 1377, 1324, 1245, 1183, 1092, 1019, 930, 863, 743 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): *δ* 8.96–8.67 (br s, 1H), 7.66 (d, *J* = 7.7 Hz, 1H), 7.39–7.17 (m,2H), 7.11–6.93 (m, 1H), 5.41–5.32 (m, 1H), 4.51–4.31 (m, 2H), 4.08–3.78 (m, 1H), 2.70–1.64 (m, 8H), 1.62–1.37 (m, 4H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.78 (d, *J* = 6.8 Hz, 3H); ESI-MS: *m/z*: 325 (M^+), 324, 317, 275, 262, 249, 223, 197, 167, 155, 144, 115. *2-(5-Isopropyl-2-methyl-cyclohex-2-enyl)-1H-pyrrole* (**3l**): Liquid; IR(KBr): *ν* 3404, 2958, 2923, 2854, 1716, 1460, 1379, 1154, 1066, 777, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 7.99–7.65 (br s, 1H), 6.60–6.52 (m, 1H), 6.06–5.98 (m, 1H), 5.88–5.80 (m, 1H), 5.31–5.22 (m, 1H), 3.36–3.17 (m, 1H), 2.26–1.43 (m, 7H), 1.40–0.64 (m, 8H),; ESI-MS: *m/z*: 204 $(M+1)^+$, 200, 183, 178, 164, 146, 134, 118, 115.