Highly Efficient Friedel–Crafts Alkylation of Indoles and Pyrrole Catalyzed by Mesoporous 3D Aluminosilicate Catalyst with Electron-Deficient Olefins

T. Siddulu Naidu,[a] V. V. Balasubramanian,[b] M. A. Chari,[b] T. Mori,[a,b,e] S. M. J. Zaidi,[c] Salem S. Al-Deyab,[d] B. V. Subba Reddy,*[b,e] A. Vinu*[a,b,e]

[a] Ionics Materials Chemistry Group, Department of Chemistry, Hokkaido University, E-mail: Sapporo 060-0810, Japan

[b] International Center for Materials Nanoarchitectonics, WPI Research Center, National Institute for Materials Science, 1-1 Namiki, Tsukuba, 305-0044, Japan
Fax +81(29)8604706; E-mail: vinu.ajayan@nims.go.jp

[c] Department of Chemical Engineering, King Fahd University of Petroleum & Minerals, Dhahran 31261, Saudi Arabia

[d] Department of Chemistry, Petrochemicals Research Chair, Faculty of Science, King Saud University, P.O. Box 2455 Riyadh 11451, Kingdom of Saudi Arabia

[e] NIMS-IICT Materials Research Center, Indian Institute of Chemical Technology, Hyderabad 500007, India

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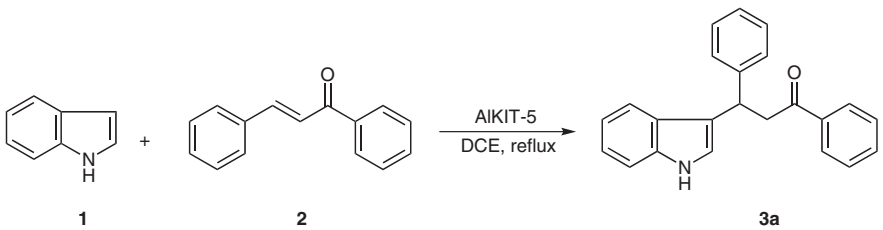
Abstract: The C3-selective Friedel–Crafts alkylation of indoles with electron-deficient olefins has been achieved using a mesoporous aluminosilicate catalyst with 3D cage-type porous structure to furnish the 3-alkylindole derivatives in excellent yields due to its high surface area, large pore volume and high acidity. Pyrrole also reacted efficiently under similar reaction conditions to give the corresponding 2-alkylated pyrrole derivatives in good yields.

Key words: nanoporous aluminosilicate, conjugate addition, electron-deficient olefins, C3-alkylation of indoles, C2-alkylation of pyrrole

The C3-selective Friedel–Crafts alkylation of indoles is one of the most important organic transformations and plays a key role in the total synthesis of complex natural products such as diolmycins[1] and hapalindole.[2] The hapalindole alkaloids are mostly obtained from the blue-green algae *Hapalosiphon fontinalis*[2] and exhibit potent antibacterial and antimycotic activity.[3] Therefore, the synthesis of 3-substituted indoles has been receiving significant interest in medicinal chemistry. The 3-alkylated indoles are generally prepared by the simple conjugate addition of indoles with electron-deficient olefins in the presence of either protic[4] or Lewis acids.[5–7] Recently, some Lewis acids also became known to be effective in promoting this reaction under mild reaction conditions.[7] Asymmetric version of conjugate addition of indole has also been reported using proline-derived chiral amines to produce enantiomerically enriched indole derivatives.[6] However, the acid-catalyzed addition of indoles on olefin often requires careful control of the acidity to prevent side reactions such as dimerization of indoles or polymerization of pyrroles. Thus, the development of an effective catalyst for the preparation of the alkyl derivatives of indole or pyrrole is highly critical as they have become increasingly useful and important in the field of drugs and pharmaceuticals. Recently we have found that the mesoporous aluminosilicate catalyst with 3D mesoporous cage-type porous structure, high surface area and large pore volume (AlKIT-5) has been highly active and efficient for various acid-catalyzed multicomponent organic transformations due to its excellent structural order and high acidity.[8,9]

In continuation of our research on the application of AlKIT-5 catalyst in various organic transformations, we herein report a simple and efficient method for the C3-alkylation of indoles with electron-deficient olefins using a highly acidic 3D mesoporous aluminosilicate nanocage catalyst. In a test experiment, 1 mmol of indole was treated with 1 mmol of chalcone in 1,2-dichloroethane at room temperature in the presence of 100 mg of AlKIT-5(10) where the number in the parenthesis indicates the n_{Si}/n_{Al} ratio of the final product. Even though the reaction proceeded at room temperature, the yield of the desired product **3a** was low even after 12 hours. However, the reaction was completed within 8.5 hours under reflux conditions and the final product **3a** was obtained in 87% yield (Scheme 1).



1 2 3a

Scheme 1 C3-Alkylation of indole with chalcone

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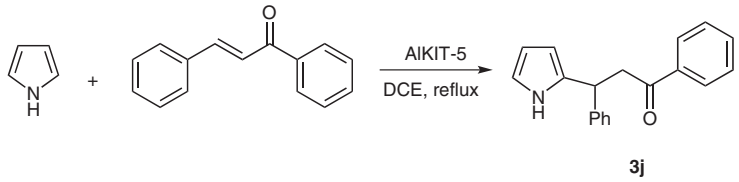
The effect of n_{Si}/n_{Al} ratio of the AlKIT-5 catalyst on the alkylation of indole has also been investigated. It has been found that the catalytic activity of the materials increases with increasing the Al content of the sample as each Al atom in the aluminosilicate matrix of the catalyst offers an active site. Among the catalysts with different n_{Si}/n_{Al} ratio studied, AlKIT-5(10) was found to be the best, affording a high yield of the final product. The high activity of the AlKIT-5(10) catalyst is mainly due to the fact that the acidity, surface area, pore diameter and pore volume of the catalyst are higher as compared to those of other catalysts used in the study.[8,9] These factors are highly critical for the adsorption, diffusion, and the activation of the reactant molecules in the pore channels of the catalyst.

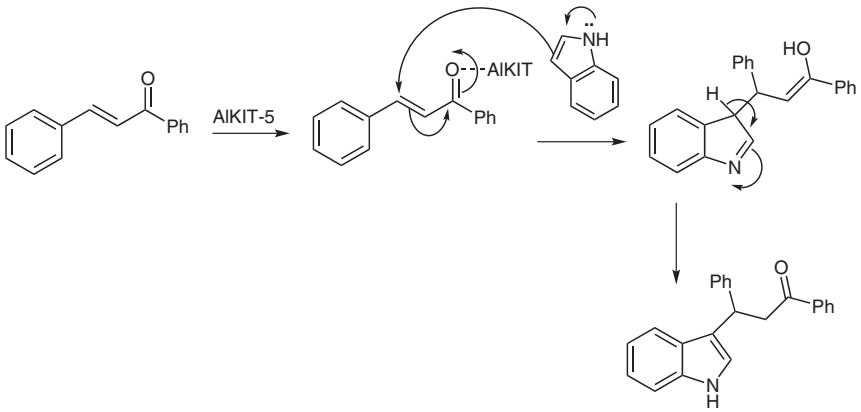
Inspired by the results obtained from indole and chalcone, we turned our attention to various indoles. Substituted indoles such as 2-methyl, 5-methoxy, 5-bromo, and *N*-methyl derivatives participated well in this reaction (entries **b**–**e**, Table 1). In addition, various electron-deficient olefins such as 1,3-diphenyl-2-propen-1-one, 4-chlorochalcone, *trans*-β-nitrostyrene, 1-cyclohex-2-enone and 1-cyclopent-2-enone were examined for this transformation. In all the cases, the reactions were highly selective and the catalyst afforded the corresponding Michael adducts in excellent yields (entries **a**–**i**, Table 1). Next, we have attempted the Friedel–Crafts alkylation of pyrrole with various electron-deficient olefins. To our surprise, the reaction of pyrrole with chalcone (Scheme 2) under similar reaction conditions underwent smoothly to furnish the C2-alkylated pyrrole in 65% yield (entry **j**, Table 1).

To explore the generality and scope of the pyrrole alkylation catalyzed by AlKIT-5(10), the reaction was carried out with various electron-deficient olefins. It has been found that the pyrrole reacted well with cyclopentenone, 4-chlorochalcone, and *trans*-β-nitrostyrene to afford the corresponding C2-alkylated pyrrole derivatives in good yields (entries **k**–**m**, Table 1). It should be noted that no by-products arising from 1,2-addition or bisaddition were observed. The reaction was also carried out with α,β-unsaturated esters and nitriles using AlKIT-5 which failed to undergo Michael addition with indoles or pyrroles under identical conditions. In order to confirm the effectiveness of the AlKIT-5 catalyst, the reaction was carried out at room temperature or reflux conditions without catalyst. Unsurprisingly, no product was formed even after long reaction times (10–20 h) in the absence of a catalyst, revealing the effectiveness of the AlKIT-5 catalyst for this particular reaction. It is noteworthy to highlight that this method is useful for the alkylation of both pyrrole and indoles. Various electron-deficient olefins have been used with similar success to provide the corresponding C3-alkylated indoles in high yields, which are also of much interest with respect to biological activity. In all the cases, the corresponding products were obtained in high yields (60–91%). The structure of the products was determined from their spectral data (NMR, IR, and MS) and also by comparison with authentic samples.[5,7]

Mechanistically, the reaction proceeds via the activation of enone by AlKIT-5 followed by indole addition on olefin. The resulting intermediate undergoes subsequent tautomerization to give the C3-alkylated product as shown in Scheme 3. The catalyst was easily separated by filtration and reused after activation at 500 °C for three to four hours. The efficiency of the recovered catalyst was verified in the alkylation of indole with chalcone (entry **a**, Table 1). Using the fresh catalyst, the yield of product **3a** was 87%, while the recovered catalyst gave the yield of 87%, 85% and 82% over three cycles, respectively. The scope and generality of this process is illustrated with respect to various electron-deficient olefins and indoles and the results are summarized in Table 1.[10]



Scheme 2 C2-Alkylation of pyrrole with chalcone



Scheme 3 A plausible reaction mechanism

Table 1 AlKIT-5-Catalyzed Conjugate Addition of Indoles and Pyrrole with Electron-Deficient Olefins

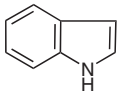
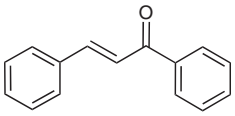
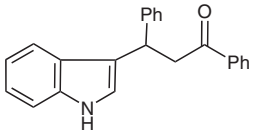
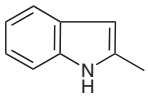
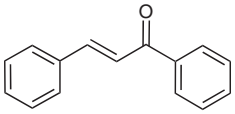
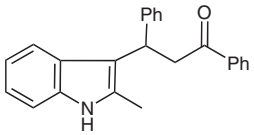
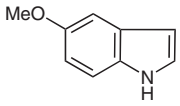
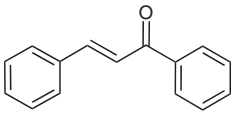
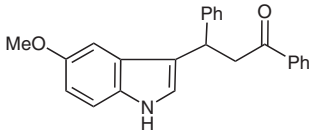
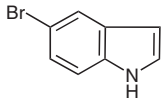
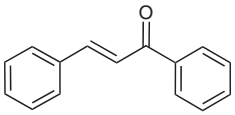
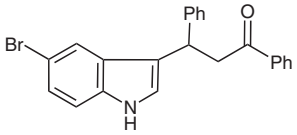
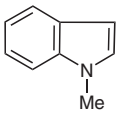
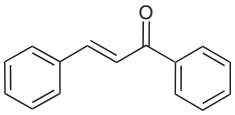
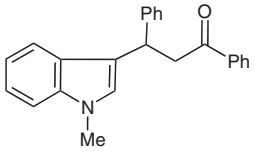
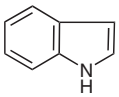
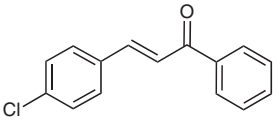
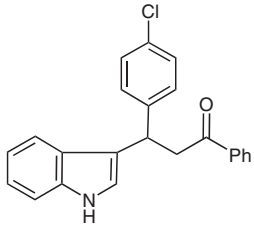
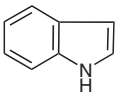
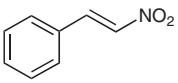
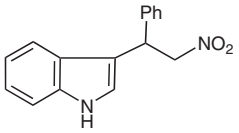
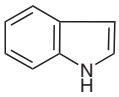
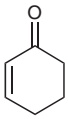
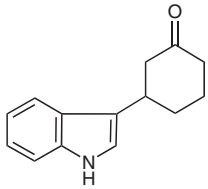
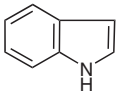
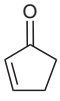
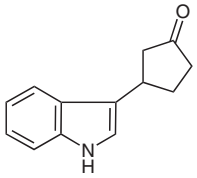
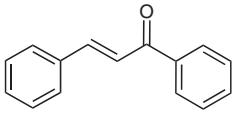
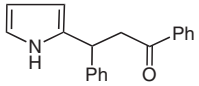
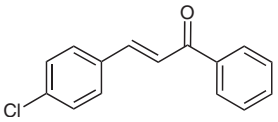
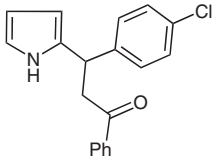
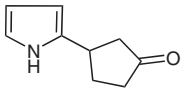
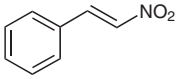
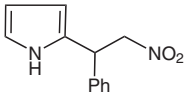
Entry	Indole **1**	Enone **2**	Product **3**[a]	Time (h)	Yield (%)[b]
a				8.5	87
b				9.5	85
c				8.0	91
d				9.0	82
e				10.0	80
f				9.0	89
g				8.0	91
h				11.0	82
i				10.5	85
j				10.0	65

Table 1 AlKIT-5-Catalyzed Conjugate Addition of Indoles and Pyrrole with Electron-Deficient Olefins (continued)

Entry	Indole **1**	Enone **2**	Product **3**[a]	Time (h)	Yield (%)[b]
k				10.0	62
l				10.5	60
m				9.5	70

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

In summary, we have demonstrated for the first time the Friedel–Crafts alkylation of indoles and pyrrole with electron-deficient olefins using a highly acidic 3D mesoporous aluminosilicate nanocage as the novel catalyst. The catalyst was highly active and selective, affording the alkylated indoles and pyrroles in a good to excellent yields. The high activity of the AlKIT-5 catalyst on the Friedel–Crafts alkylation is due to its high surface area, large pore volume, and high acidity. In addition, the catalyst is highly stable and can be recycled several number of times without much affecting the activity of the catalyst which makes this process simple, convenient and practical (Figure 1S and Table 1S, see Supporting Information).

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(10) **General Procedure**. A mixture of activated olefin (1.0 mmol), indole or pyrrole (1.0 mmol) and AlKIT-5 (100 mg) in DCE (5 mL) was stirred at reflux temperature for the appropriate time (Table 1). After completion of the reaction, as monitored by TLC, the reaction mixture was diluted with EtOAc (20 mL) and the catalyst was separated by filtration. The organic layer was concentrated under reduced pressure and the crude product was purified by silica gel column chromatography using EtOAc–*n*-hexane (1:9) as eluent to afford the pure 3-alkylindole or 2-alkylpyrrole. The spectral data are in full agreement with the data reported in the literature.[5] Spectral data for the selected products: 2-Phenyl-3-indolyl-1-nitroethane(**3g**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.91–5.12 (m, 2 H), 5.22 (t, *J* = 7.0 Hz, 1 H), 7.01 (d, *J* = 2.2 Hz, 1 H), 7.07–7.37 (m, 8 H), 7.47 (d, 1 H, *J* = 8.0 Hz, 1 H), 8.06 (br s, 1 H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.9, 78.4, 110.6, 118.7, 120.2, 121.9, 123.0, 126.3, 127.9, 128.2, 129.1, 135.8, 140.2. EIMS: *m/z* (%) = 266 (100) [M$^+$]. 2-Phenyl-2-pyrrolyl-1-nitroethane (**3m**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.76 (dd, *J* = 11.6, 7.4 Hz, 1 H), 4.86 (dd, *J* = 7.4, 7.1 Hz, 1 H), 4.96 (dd, *J* = 11.6, 7.1 Hz, 1 H), 6.03–6.05 (m, 1 H), 6.14 (dd, *J* = 6.0, 2.7 Hz, 1 H), 6.40 (dd, *J* = 4.0, 2.5 Hz, 1 H), 7.20–7.31 (m, 5 H), 7.85 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.9, 129.2, 128.9, 128.0, 127.9, 118.2, 108.6, 105.8, 79.2, 42.9. EIMS: *m/z* (%) = 216 (30) [M$^+$], 169 (100).