1-(Chloromethyl)-4-fluoro-1,4-diazoniabicyclo-[2,2,2]octane Bis(tetrafluoroborate) as Novel and Efficient Reagent for the Conjugate Addition of Indoles to α,β-Unsaturated Ketones

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Indoles undergo smooth conjugate addition with α,β-unsaturated ketones in the presence of 10 mol % Selectfluor™ under extremely mild conditions to afford the corresponding Michael adducts in high to quantitative yields with 1,4-selectivity.

The conjugate addition of indoles to α,β-unsaturated ketones constitutes a key reaction in the total synthesis of complex natural products such as hapalindole. The hapalindole alkaloids isolated from the blue-green algae *Hapalosiphon fontinalis*. They exhibit potent antibacterial and antimycotic activity.[1] Consequently, numerous methods have been reported for the conjugate addition of indoles to electron-deficient olefins through the activation of enones by Lewis acids.[2,3] Asymmetric version of Michael addition of indole to α,β-unsaturated ketones has also been reported using proline-derived chiral amines to produce enantiomerically enriched indole derivatives.[4] Typically, these Michael reactions are performed under the influence of strong bases such as alkali metal alkoxides or hydroxides.[5] The strong basic conditions often lead to a number of undesirable side reactions such as aldol reaction, ester solvolysis, base-induced rearrangements such as retro-Claisen or retro-Michael reactions and polymerization reactions. Subsequently, Lewis acids are found to catalyze the Michael reactions under mild conditions.[6,7] Since indoles and their derivatives have become increasingly useful and important in the field of drugs and pharmaceuticals, the developments of simple and efficient approaches are desirable.

Recently, Selectfluor™ has been introduced commercially as a user-friendly electrophilic fluorinating agent (Figure 1).

Selectfluor™ is readily available at low cost and is easy to handle and also retains its activity even in the presence of amines.[8] More recently, Selectfluor™ has been employed as an efficient Lewis acid catalyst for the one-pot allylation of imines and for the hydrolysis of acetals, dithia-acetals and tetrahydropyranyl ethers[9] and also for the cleavage of epoxides with thiocyanates.[10] However, there have been no examples of the use of Selectfluor™ as a catalyst for the conjugate addition of indoles to α,β-unsaturated ketones.

As part of our on going programme in developing new synthetic methodologies for the functionalization of indoles,[11] herein we report the use of Selectfluor™ as a novel and efficient

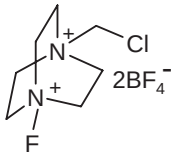
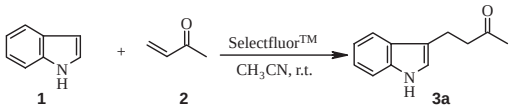


Figure 1.



Scheme 1.

catalyst for the conjugate addition of indoles to α,β-unsaturated ketones to produce 3-substituted indoles in high to quantitative yields under mild conditions.[12] Accordingly, treatment of indole (1) with methyl vinyl ketone (2) in the presence of 10 mol % Selectfluor™ resulted in the formation of 4-(3-indolyl)-2-butanone (**3a**) in 90% yield (Scheme 1).

The reaction proceeded efficiently in acetonitrile at room temperature with high 1,4-selectivity. The reaction went to completion in a short time (3.0 h). Encouraged by the results obtained with indole and methyl vinyl ketone, we turned our attention to various indoles and electron-deficient alkenes. Interestingly, various enones including chalcones underwent 1,4-addition with a range of indoles under these reaction conditions to afford the corresponding 3-alkylated indoles, the yields were generally high to quantitative in few hours. Like enones, other electron-deficient alkenes such as 1-[2-nitro-(*E*)-1-ethenyl]benzene also afforded the Michael adduct in excellent yields (Entry **N**). In the absence of catalyst, the reactions did not proceed even after long reaction times (10–20 h). No by-products arising from 1,2-addition or bis-addition was observed. Moreover, the reactions were clean and high yielding in some cases quantitative. It is well known that chiral quaternary ammonium salts activate the enones effectively to promote the Michael reaction.[13] Similarly, enones may be activated by quaternary nitrogen of the Selectfluor™. However, α,β-unsaturated nitriles and esters failed to undergo Michael addition with indoles under identical conditions. Furthermore, the reaction of indole with sterically hindered 3-methylcyclohexenone in the presence of 10 mol % of Selectfluor™ in refluxing acetonitrile gave low yield (10%). The scope and generality of this process is illustrated with respect to various enones and indoles and the results are summarized in Table 1.

In summary, we have described a simple and highly efficient protocol for the conjugate addition of indoles to α,β-unsaturated ketones using Selectfluor™ as novel catalyst. This method offers several advantages including mild reaction conditions, high conversions, short reaction times, clean reaction profile, ease of handling, and ready availability of the catalyst at low cost, which makes it a useful and attractive process for the alkylation of indoles with α,β-unsaturated system.

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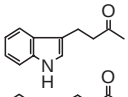
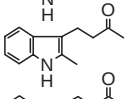
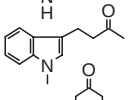
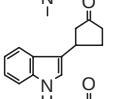
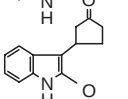
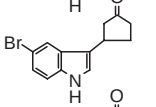
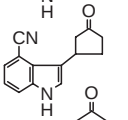
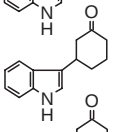
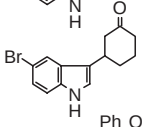
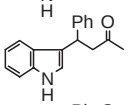
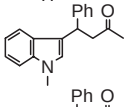
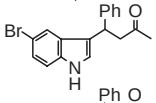
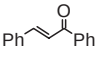
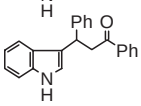
Table 1. Selectfluor™ catalyzed conjugate addition of indoles to enones

Entry	Indole (**1**)	Enone (**2**)	Product (**3**)[a]	Time/h	Yield/%[b]
A				3.0	90
B				2.5	92
C				3.5	90
D				4.0	89
E				4.0	90
F				4.5	91
G				3.5	88
H				4.0	90
I				4.0	90
J				3.0	90
K				3.0	91
L				4.0	90
M				3.5	95
N				3.0	92

[a]All products were characterized by ^{1}H NMR, IR, and mass spectrometry. [b]Isolated and unoptimized yield.

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12 General procedure. A mixture of indole (1 mmol) and α,β-unsaturated ketone (1 mmol) and Selectfluor™ (10 mol %) in acetonitrile (10 mL) was stirred at room temperature for the appropriate time (Table 1). After completion of the reaction, as indicated by TLC, The solvent was evaporated under reduced pressure. Then, the resulting product was directly charged onto a small silica gel column and eluted with a mixture of ethyl acetate: *n*-hexane (1.5:8.5) to afford pure 3-substituted indoles. Spectral data for selected products: **3a**. White solid, mp 94–95 °C; IR (KBr). ν 3329, 3047, 2936, 2841, 1702, 1595, 1503, 1437, 1361, 1227, 1159, 1061, 934, 859, 746 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.50 (s, 3H), 2.80 (t, 2H, $J = 7.5$ Hz), 3.04 (t, 2H, $J = 7.5$ Hz), 6.95 (d, 1H, $J = 2.5$ Hz), 7.00–7.18 (m, 2H), 7.22–7.32 (m, 1H), 7.50 (d, 1H, $J = 7.0$ Hz), 7.90 (brs, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.1, 30.5, 44.6, 113.8, 116.1, 118.2, 119.0, 120.6, 122.4, 127.6, 130.7, 208.3; EI-MS *m*/*z* (%). 187 (M^+ 32), 130 (100), 115 (10), 77 (12), 43 (48). **3n**. Yellow solid, mp 100–101 °C, IR (KBr). ν 3418, 3066, 2997, 2834, 1599, 1546, 1491, 1443, 1409, 1376, 1329, 1258, 1218, 1109, 1094, 1018, 967, 851, 743, 697 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.90–5.08 (m, 2H), 5.20 (t, 1H, $J = 7.0$ Hz), 6.96 (d, 1H, $J = 2.2$ Hz), 7.05–7.40 (m, 8H), 7.50 (d, 1H, $J = 8.0$ Hz), 8.00 (brs, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 40.8, 78.5, 110.9, 118.8, 120.1, 121.8, 123.0, 126.4, 127.8, 128.1, 129.2, 135.9, 140.1; EI-MS *m*/*z* (%). 266 (M^+ 100), 219 (37), 206 (21), 178 (11), 158 (47), 130 (16), 105 (24), 77 (31), 51 (26).

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