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$ZrCl_4$ catalyzed highly selective and efficient Michael addition of heterocyclic enamines with α,β-unsaturated olefins

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Abstract—Highly selective and efficient Michael additions of heterocyclic enamines, viz. indoles, pyrroles, and pyrazoles with α,β-unsaturated olefins using 2 mol % of $ZrCl_4$ has been achieved.

Michael addition and Friedel–Crafts type alkylation of heteroaromatics with electron-deficient α,β-unsaturated carbonyl compounds constitute powerful methods for direct C–C bond formation for functionalization of these biologically important motifs.[1] Recently, the Michael addition of electron-rich heteroaromatics, especially indoles to enones in the presence of catalytic or stoichiometric amounts of various Bronsted[2] and Lewis acids[3] have been reported. The protic acid catalyzed versions of these reactions require careful control of the acidity of the reaction medium and are often plagued with side reactions, particularly polymerization of unsaturated Michael acceptors, lower overall yields and eroding atom economy of the process. Lewis acids, viz. $InBr_3$, $InCl_3$, $Yb(OTf)_3$, $Bi(OTf)_3$, $Bi(NO_3)_3$, etc. have been exploited with various degrees of success. However, the reaction usually demands high catalyst loadings (>10 mol %), long reaction times ranging from several hours to days in some cases, strong acidic conditions, expensive and hazardous reagents, special reaction conditions to enhance reactivity such as heating, microwave irradiation or ionic liquids. Also, most of these reactions have been studied using highly nucleophilic indoles and even in the case of electron poor indoles, yields are sometimes unsatisfactory. Thus, an efficient, economical and environmentally benign Lewis acid catalyst is highly desirable for this process.

In continuation of our efforts in developing selective, efficient and mild synthetic methodologies in heterocyclic enamine chemistry,[4] herein, we report the $ZrCl_4$ catalyzed Michael addition of biologically and chemically important heterocyclic enamines, viz. indoles, pyrroles and pyrazoles to various α,β-unsaturated carbonyl compounds. Recently, there has been an increase in $ZrCl_4$ chemistry which has emerged as a safe, economical, air and moisture tolerant alternative Lewis acid in various organic transformations.[5] The reaction of indole **1** and methyl vinyl ketone using 2 mol % $ZrCl_4$ in CH_2Cl_2 at ambient temperature proceeded smoothly and after aqueous work-up and chromatography gave the pure conjugated addition product in 92% yield (Table 1, Scheme 1).[6] The use of THF or CH_3CN did not affect the efficiency of this reaction. In contrast[7] to the formation of triindolyl products arising from both double 1,2-addition and 1,4-addition with $Zr(OTf)_4$; on using $ZrCl_4$ only the 1,4-addition product was formed. This clearly demonstrates the effect of a conjugate anion on Lewis acidity and thus regioselectivity in Michael addition reactions.

The presence of a substituent either on the indole nitrogen or the aromatic ring did not affect the Michael addition as indoles with a wide variety of functionalities reacted with various cyclic and acyclic enones to provide the respective conjugate addition products in excellent yields (Table 1).

In the case of 3-methyl indole **6**, the reaction occurred at C-2 carbon although a longer reaction time was required for completion (Table 1, entry 16). To extend the

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Keywords: Zirconium tetrachloride; Michael addition; Heterocyclic enamines; α,β-unsaturated olefins.

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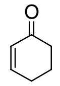
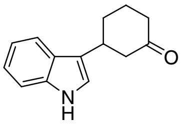
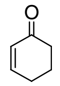
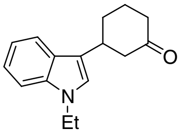
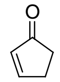
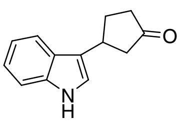
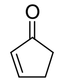
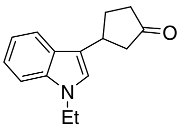
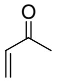
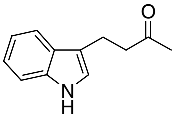
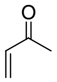
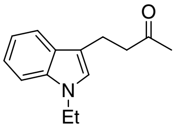
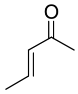
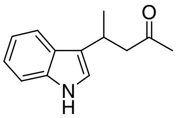
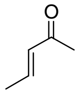
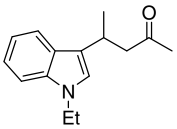
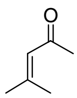
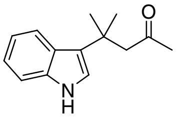
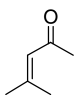
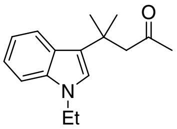
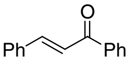
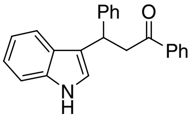
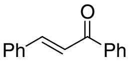
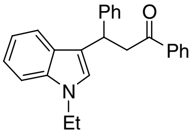
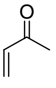
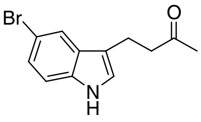
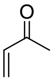
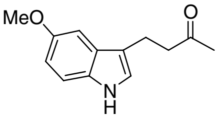
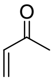
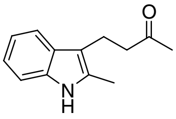
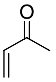
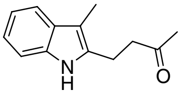
Table 1. $ZrCl_4$ catalyzed Michael addition of indoles to enones

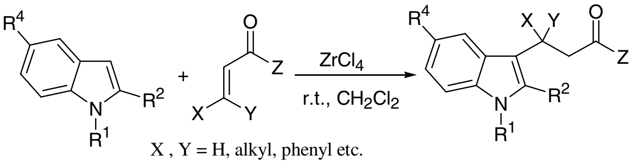
Entry	Indole	Enone	Product[a] time (min), yield (%)[b]
1	**1**		 5 (96)
2	**2**		 5 (96)
3	**1**		 5 (94)
4	**2**		 5 (95)
5	**1**		 8 (92)
6	**2**		 10 (93)
7	**1**		 5 (96)
8	**2**		 5 (96)
9	**1**		 8 (92)
10	**2**		 10 (91)
11	**1**		 5 (96)
12	**2**		 5 (96)
13	**3**		 8 (90)
14	**4**		 5 (96)
15	**5**		 8 (96)
16	**6**		 120 (73)[c]

[a] All products were characterized using standard spectroscopic methods (IR, ^1H and ^{13}C NMR, HRMS).

[b] Yield refer to pure isolated products from silica gel column chromatography.

[c] Based on recovered starting material with an overall conversion of 46%.

generality of this method, the reactions of other heterocyclic enamines, pyrroles and pyrazoles, were also investigated (Table 2). Again the reactions proceeded to completion with only 2 mol % of $ZrCl_4$.

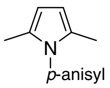
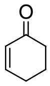
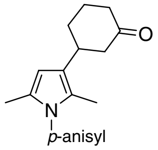
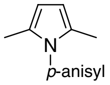
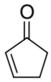
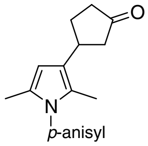
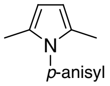
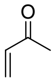
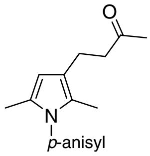
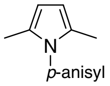
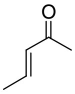
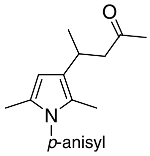
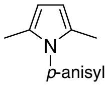
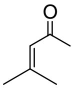
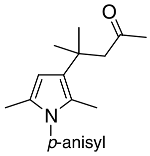
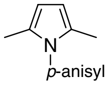
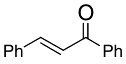
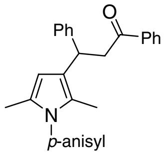
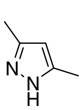
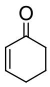
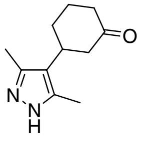
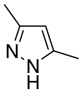
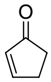
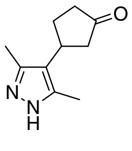
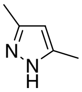
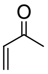
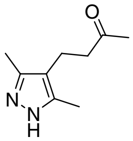
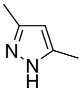
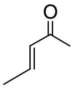
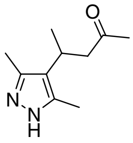
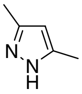
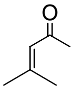
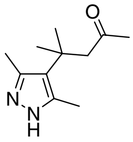
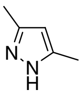
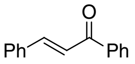
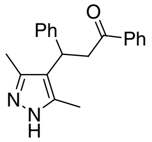


X , Y = H, alkyl, phenyl etc.

1 $R^1 = R^2 = R^4 = H$, **2** $R^1 = Et$, $R^2 = R^4 = H$
3 $R^1 = R^2 = H$, $R^4 = Br$ **4** $R^1 = R^2 = H$, $R^4 = OMe$
5 $R^1 = R^4 = H$, $R^2 = Me$

Scheme 1.

Table 2. $ZrCl_4$ catalyzed Michael addition of pyrroles and pyrazoles to enones

Entry	Pyrrole	Enone	Product[a] time (min), yield (%)[b]
1			 5 (92)
2			 5 (96)
3			 8 (93)
4			 8 (90)
5			 10 (88)
6			 10 (93)
7			 40 (91)
8			 40 (92)
9			 50 (88)
10			 60 (85)
11			 60 (85)
12			 90 (87)

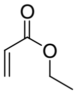
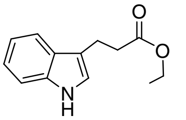
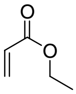
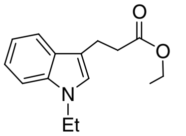
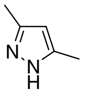
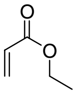
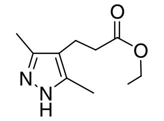
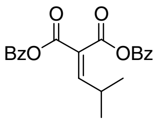
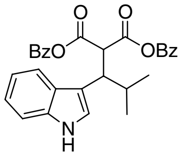
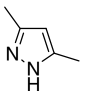
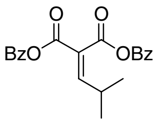
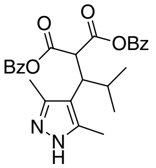
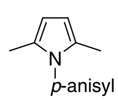
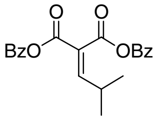
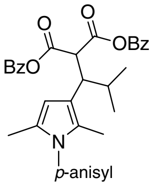
[a] All products were characterized using standard spectroscopic methods (IR, ^1H and ^{13}C NMR, HRMS).

[b] Yield refer to pure isolated products from silica gel column chromatography.

Most of the reported conjugate additions of heterocyclic enamines, especially indoles have been restricted to highly reactive Michael acceptor such as α,β-unsaturated ketones or nitroolefins. We were pleased to find that $ZrCl_4$ efficiently catalyzed the conjugate addition of these heterocyclic enamines to ethyl acrylate (Table 3, entries 1–3). Reactions were free from any side product but took longer reaction times for completion than for enones. As expected, the reactions of doubly activated alkenes also provided the required addition products in high yields (Table 3, entries 4–6).

In summary, $ZrCl_4$ has been demonstrated to be a highly selective and efficient catalyst for the Michael addition of heterocyclic enamines to a variety of electron-deficient olefins, providing the desired products in excellent yields. Of note is the fact that reactions do not need a dry solvent, inert atmosphere or special activation techniques such as microwave irradiation or ionic liquids.

Table 3. $ZrCl_4$ catalyzed Michael addition of enamines to α,β-unsaturated esters and alkylidene malonates

Entry	Enamine	Alkene	Product[a] time (min), yield (%)[b]
1	**1**		 180 (85)
2	**2**		 180 (86)
3			 360 (78%)
4	**1**		 240 (79)
5			 360 (77)
6			 240 (72)

[a] All products were characterized using standard spectroscopic methods (IR, ^1H and ^{13}C NMR, HRMS).

[b] Yield refer to pure isolated products from silica gel column chromatography.

Acknowledgements

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References and notes

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6. General procedure: To a mixture of enamine (1 mmol), α,β-unsaturated olefin (1 mmol) in dichloromethane (5 ml) at room temperature was added $ZrCl_4$ (0.02 mmol) and the reaction mixture was stirred for the required period of time (see Tables). After completion of the reaction as indicated by TLC, the reaction mixture was diluted with H_2O and extracted with ethyl acetate. The organic phase was washed twice with saturated brine solution and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was column chromatographed on silica gel to give the pure product. Selected characterization data: (Table 1, entry 4) 95%, dense liquid. IR (neat) ν_{max}: 2934, 2870, 1735, 1650, 1489 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) $\delta = 1.45$ (t, $J = 7.2$ Hz, 3H), 2.05–2.19 (m, 1H), 2.26–2.57 (m, 4H), 2.76 (dd, $J = 15.6$, 6.8 Hz, 1H), 3.72 (quin, $J = 7.5$ Hz, 1H), 4.14 (q, $J = 7.2$ Hz, 2H), 6.90 (s, 1H), 7.12 (dd, $J = 7.9$, 6.8 Hz, 1H), 7.27 (dt, $J = 7.2$, 1.2 Hz, 1H), 7.33 (d, $J = 7.8$ Hz, 1H), 7.63 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 15.4, 30.0, 33.7, 38.2, 40.8, 45.4, 109.5, 118.8, 118.9, 119.2, 121.7, 122.9, 127.1, 136.4, 219.5; HRMS: (for $C_{19}H_{23}NO_2$) 297.1729 (calcd); 297.1742 (found). (Table 2, entry 1) 92%, dense liquid. IR (neat) ν_{max}: 2934, 1708, 1514, 1248 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) $\delta = 1.72$ (m, 2H), 1.91 (s, 3H, CH_3), 1.98–2.22 (m, 2H), 2.00 (s, 3H,CH_3), 2.23–2.58 (m, 4H), 2.91–3.03 (m, 1H), 3.85 (s, 3H, OCH_3), 5.83 (s, 1H), 6.97 (d, $J = 6$ Hz, 2H, ArH), 7.12 (d, $J = 6$ Hz, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): 10.7, 12.8, 31.4, 39.0, 43.3, 46.4, 55.4, 103.1, 114.1, 114.2, 120.2, 128.3, 129.2, 131.5, 158.8, 220.0; HRMS: (for $C_{19}H_{23}NO_2$) 297.1729 (calcd); 297.1742 (found). (Table 2, entry 8) 92%, dense liquid. IR (neat) ν_{max}: 2940, 1720, 1513, 1260 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) $\delta = 2.14$ (s, 3H, CH_3), 2.19 (s, 3H, CH_3) 2.23–2.49 (m, 3H), 2.56–2.71 (m, 2H), 2.88 (dd, $J = 19$, 9 Hz, 1H), 4.72–4.81 (m, 1H), 5.79 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): 10.9, 13.5, 29.8, 37.1, 44.3, 54.4, 105.2, 138.3,

147.5, 215.6; HRMS: (for $C_{10}H_{14}N_2O$) 178.1106 (calcd); 178.1113 (found). (Table 3, entry 3) 78%, dense liquid. IR (neat) ν_{max}: 2940, 1720, 1513, 1260 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) $\delta = 1.18$ (t, $J = 7.2$ Hz, 3H, CH_3), 2.14 (s, 3H, CH_3), 2.21 (s, 3H, CH_3) 2.81 (t, $J = 7$ Hz, 2H), 4.08 (q, $J = 7.2$ Hz, 2H), 4.17 (t, $J = 7.2$ Hz, 2H), 5.70 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): 10.8, 14.0, 14.1, 34.7, 43.5, 60.6, 104.8, 139.0, 147.6, 171.1; HRMS: (for $C_{10}H_{16}N_2O_2$) 196.1212 (calcd); 196.1218 (found).

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