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Highly stereoselective imidazolethiones mediated Friedel–Crafts alkylation of indole derivatives

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ABSTRACT

The asymmetric Friedel–Crafts alkylation of indoles with α,β-unsaturated aldehydes was promoted by the novel imidazolethiones to afford the corresponding adducts in moderate to excellent yields and high enantioselectivities under mild reaction conditions.

The indole framework has become widely identified as a 'privileged' structure or pharmacaphore[1] that could potentially be accessed by asymmetric Friedel–Crafts chemistry. Over the past decade, the chemistry and biological activity of novel indole derivatives, especially for chiral indole intermediates, have attracted much attention.[2] Several types of chiral amines[3] and metal catalysts[4] have been employed for the asymmetric Friedel–Crafts-type alkylation of indole derivatives. However, the techniques and methodologies for the asymmetric reaction of indole derivatives are still lagging behind.[5]

The first enantioselective Friedel–Crafts reaction of indole was reported by MacMillan in 2002 using imidizolidinone as catalyst which enriched the paths to indole derivatives.[6] However, the comparatively harsh conditions were needed for the reaction and only 56% *ee* value was obtained in the case of **1a** (Fig. 1) as activator at −40 °C. Still, hunting for good chiral catalysis which requests mild conditions, high selectivities, and yields is always the focus of great attention for asymmetric reaction.[7] In our continuous work on investigation of the novel chiral catalysts imidazolethiones,[8] the efficiency of imidazolethiones prompted us to further investigate the possibility of the Friedel–Crafts alkylation of indole derivatives with α,β-unsaturated systems.

Accordingly, the screening of the catalysts was conducted with several imidazolethiones (Fig. 1), using *N*-methylindole (**3a**) and (***E***)-3-(3-chlorophenyl) acrylaldehyde (**4a**) as a model reaction under suitable reaction conditions to give the corresponding adducts **5a** (Table 1). Due to the highly reactive chemical nature of aldehyde, all the aldehydes formed were converted to corresponding alcohols by $NaBH_4$ in situ.

To our delight, good yields (85%) and high level of stereoselectivities (96%) were achieved with imidazolethione **2a** (Table 1, entry 1), while poor results or nearly no product was obtained in the case of **2b** (Table 1, entry 2) or **2c** (Table 1, entry 3). In addition, imidazolidinone **1a** was also investigated under the same conditions, and compared to **2a**, the *ee* value was only 26% though with moderate yields (Table 1, entry 4).

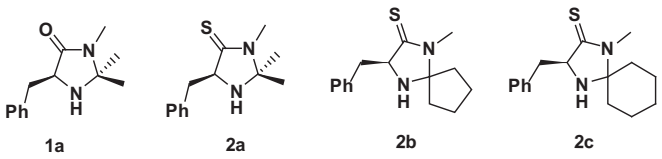
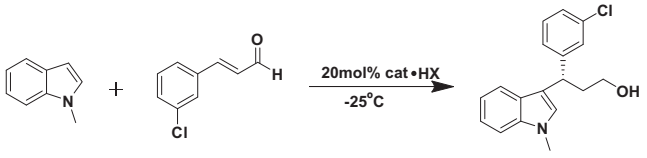


Figure 1. The imidazolethiones catalysts.

Table 1
Catalysts screening for the reaction of **3a** and **4a**[a]



Entry	Catalysts	Yield[b] (%)	*ee*[c] (%)
1	**2a**	85	96
2	**2b**	77	35
3	**2c**	/	/
4	**1a**	72	26

[a] Reagents and conditions: a mixture of **3a** (5 mmol), **4a** (2 mmol), 20%catalysts, and 20% TFA in THF (3 mL)/*i*-PrOH (3 mL) stirred at −25 °C for 48 h;
[b] Yields based upon isolation of the corresponding alcohol after $NaBH_4$ reduction.
[c] *ee* determined by chiral HPLC.

Table 2 showed the influences of solvents, temperature, and additives on the reactions. Mixture of THF/*i*-PrOH (1:1) gave both higher yield and higher selectivity than CH_2Cl_2, [BMI][Br]IL, THF/H_2O, and CH_2Cl_2/*i*-PrOH. Temperature is essential to the selectivity of the reaction, and elevating the reaction temperature resulted in

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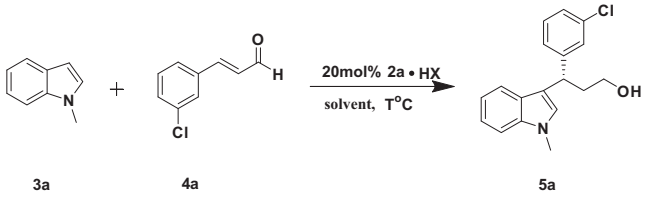
Table 2
Solvents and additives screening for the reaction of **3a** and **4a**[a]



3a 4a 5a

Entry	Solvent	Additives (HX)	Temp (°C)	Yield [c] (%)	*ee* [d] (%)
1	CH_2Cl_2	TFA	−25	75	30
2	[BMI][Br] IL	TFA	−25	90	/
3	THF/H_2O	TFA	−25	77	33
4	CH_2Cl_2/*i*-PrOH	TFA	−25	74	35
5[b]	THF/*i*-PrOH	TFA	−25	85	96
6[b]	THF/*i*-PrOH	*p*-TSA	−25	65	39
7[b]	THF/*i*-PrOH	PhCOOH	−25	73	46
8[b]	THF/*i*-PrOH	$Cl_2CHCOOH$	−25	78	52
9[b]	THF/*i*-PrOH	TFA	−10	88	56
10[b]	THF/*i*-PrOH	TFA	−50	56	99
11[e]	THF/*i*-PrOH	TFA	−25	73	76
12[f]	THF/*i*-PrOH	TFA	−25	69	78

[a] Reagents and conditions: a mixture of **3a** (5 mmol), **4a** (2 mmol), 20% catalysts **2a**, and 20% additives in solvent (6 mL) stirred for 48 h.
[b] THF/*i*-PrOH = 1:1.
[c] Yields based upon isolation of the corresponding alcohol after $NaBH_4$ reduction.
[d] *ee* determined by chiral HPLC.
[e] Using 10% additives in solvent stirred for 96 h.
[f] Using 10% catalysts.

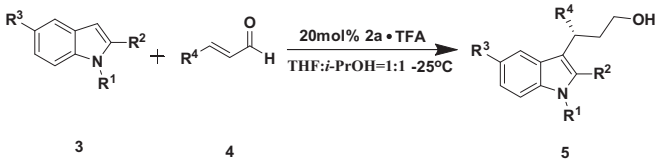
the decrease of *ee* value (Table 2, entry 9). Keeping the reaction at −50 °C would slightly increase *ee* value, but the yield decreased.

Additive acids and the amount of the catalysts loaded in the reaction also played dramatic roles both in the activation of the substrates and in the stability of the intermediates. Among the four additive acids TFA, *p*-TSA, $PhCO_2H$, and Cl_2CHCO_2H (Table 2, entries 5–8), TFA showed significant activity and gave the best result with excellent enantioselectivity. However, the attempt to reduce the amount of TFA (Table 2, entry 11) or catalysts (Table 2, entry 12) failed due to the lower yield and *ee* value even after 4 days reaction time.

With the optimized reaction conditions in hand, the scope of the enantioseletive Friedel–Crafts reaction of various aldehydes with indoles was investigated. Representative results were summarized in Table 3 and most aldehydes worked well with indole derivatives under the standard reaction conditions (Table 3, entries 1–17). As it can be seen, *N*-methylindole was very well tolerated in the alkylation with various aldehydes (Table 3, entries 1–11). As expected, the aliphatic α,β-unsaturated aldehydes showed higher reactivity and provided the corresponding product with the higher *ee* values (Table 3, entries 10–15). Particularly, crotonaldehyde was a very good reaction partner, moderate to excellent yields and *ee* values were obtained with several indole derivatives (Table 3, entries 12–15). However, **5r** and **5s** gave relatively poor enantioselectivities (after 72 h, 79% yield with 62% *ee* in **5r**, 83% yield with 60% *ee* in **5s**) (Table 3, entries 18 and 19) and the reversibility and racemization of the reaction might explain the low enantioselectivity.

In summary, imidazolethiones were proven to be a kind of excellent activator in this work in the Friedel–Crafts reaction of indole derivatives with α,β-unsaturated systems with good achievements, which provided a practical method for the preparation of chiral indole derivatives.[9] Compared to MacMillan's imidazolidinones,[4] the corresponding adducts hold moderate to excellent

Table 3
Reaction of α,β-unsaturated aldehydes **4** with indoles **3** catalyzed by **2a**[a]



3 4 5

5a-5k: R^1=Me, R^2=H
5l: R^1=H, R^2=Me
5m-5s: R^1=R^2=H

Entry	Product	R^3	R^4	Time (h)	Yield[b] (%)	*ee*[c] (%)
1	**5a**	H	*m*-ClC_6H_4	48	85	96
2	**5b**	H	*m*-MeC_6H_4	48	83	95
3	**5c**	H	*p*-FC_6H_4	36	84	81
4	**5d**	H	*p*-ClC_6H_4	36	88	87
5	**5e**	H	*p*-$MeOC_6H_4$	48	80	96
6	**5f**	H	*p*-MeC_6H_4	48	78	88
7	**5g**	H	*o*-$MeOC_6H_4$	36	82	84
8	**5h**	H	*o*-$CF_3C_6H_4$	48	83	93
9	**5i**	H	C_6H_5	48	77	93
10	**5j**	H	Me	5	85	99
11	**5k**	H	Et	5	80	97
12	**5l**	H	Me	5	83	97
12	**5m**	H	Me	5	81	99
14	**5n**	Br	Me	5	87	98
15	**5o**	MeO	Me	5	82	97
16	**5p**	H	*p*-$MeOC_6H_4$	72	83	71
17	**5q**	MeO	*m*-ClC_6H_4	48	83	94
18	**5r**	H	*m*-MeC_6H_4	72	79	62
19	**5s**	Br	*m*-ClC_6H_4	72	83	60

[a] Reagents and conditions: a mixture of **6** (5 mmol), **4** (2 mmol), 20% catalysts **2a**, and 20% additives in THF (3 mL)/*i*-PrOH (3 mL) stirred at −25 °C for the given time.
[b] Yields based upon isolation of the corresponding alcohol after $NaBH_4$ reduction.
[c] *ee* determined by chiral HPLC.

yields and high enantioselectivities under less harsh conditions, especially for the aliphatic aldehydes. Based on this study, some researches organocatalyzed by imidazolethiones are now underway in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.11.007.

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9. *General procedure for the synthesis of 3-(indoles-2-yl)-3- arylpropanols* **5**: A mixture of catalyst **2a** (0.4 mmol), TFA (0.4 mmol), and α,β-unsaturated aldehydes (2 mmol) in THF (3 mL) and *i*-PrOH (3 mL) was stirred for 15 min at room temperature. Then, the indoles (5 mmol) were added. The reaction mixture was stirred at −25 °C for the given time (monitored by TLC). The resulting solution was stirred for 30 min after equal volume of absolute EtOH and excess of $NaBH_4$ was added. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, extracted with CH_2Cl_2 and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum, and the residue was purified by flash column chromatography over silica gel (AcOEt/petroleum ether 1:8) to provide products **5**.
(*R*)-3-(3-chlorophenyl)-3-(1-methyl-1*H*-indol-3-yl) propan-1 (**5a**): Yellow oil. Yield: 85%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 7.9 Hz, 1H), 7.26 (t, J = 4.1 Hz, 2H), 7.18 (m, J = 11.2, 4.8, 2.5 Hz, 2H), 7.15–7.08 (m, 2H), 6.99 (t, J = 7.4 Hz, 1H), 6.87 (s, 1H), 4.34 (t, J = 7.7 Hz, 1H), 3.71 (s, 3H), 3.66–3.54 (m, 2H), 2.39 (dq, J = 13.6, 6.8 Hz, 1H), 2.19 (dq, J = 8.2, 6.2 Hz, 1H), 1.61 (s, 1H).; ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 146.97, 136.92, 133.91, 129.32, 127.67, 126.80, 126.09, 125.79, 125.66, 121.54, 119.25, 119.05, 118.70, 117.09, 109.10, 60.89, 38.55, 32.78; MS (ESI): m/z (%) = 300.2 (28, M^+), 300.1 (100), 235.2 (39). HRMS (ESI) exact mass calculated for [$C_{18}H_{18}ClNONa$]: 322.0967, found: 322.0975. HPLC condition: Chiralcel OD-H column, isopropanol/hexane 18:82, flow rate 1.0 mL/min, UV detection at 214 nm, t_{minor} = 16.3 min, t_{major} = 24.4 min, 96% *ee*. $[\alpha]_D^{20} = -14.3$ (c 0.56, $CHCl_3$).