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Imidazolethiones: novel and efficient organocatalysts for asymmetric Friedel–Crafts alkylation

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ABSTRACT

Imidazolethiones organocatalyzed the asymmetric Friedel–Crafts alkylation of pyrroles with α,β-unsaturated aldehydes was achieved to afford the corresponding adducts in moderate to good yields and good to excellent enantioselectivities. The possible mechanism was proposed.

The asymmetric Friedel–Crafts alkylation of arenes with electron-deficient alkenes is a powerful C–C bond-forming process in organocatalytic chemistry.[1] The first enantioselective Friedel–Crafts reaction of pyrrole with α,β-unsaturated aldehydes was reported by MacMillan using the chiral imidazolidinone catalysts in 2001.[2] Chiral Lewis acid complexes[3] and other organocatalysts[4] have also been explored as the efficient catalysts for the enantioselective Friedel–Crafts reaction of pyrrole derivatives with α,β-unsaturated systems.

Among theses catalysts, the effectiveness of imidazolidinone[5] has attracted our considerable interest. In 1995, Wiberg groups[6] indicated the larger barrier of C–N rotating in thioamide by comparing with amide due to the much greater change in charge density at sulfur, which formed more appropriate resonance structure **I** for thioamide (Fig. 1). Initiated by these protocols, we designed a novel chiral organocatalyst imidazolethione to increase the rigidity of catalyst structures. We anticipated the more 'stiffer' imidazolethiones to help contribute to improving the reaction of stereoselectivity as chiral organocatalysts.

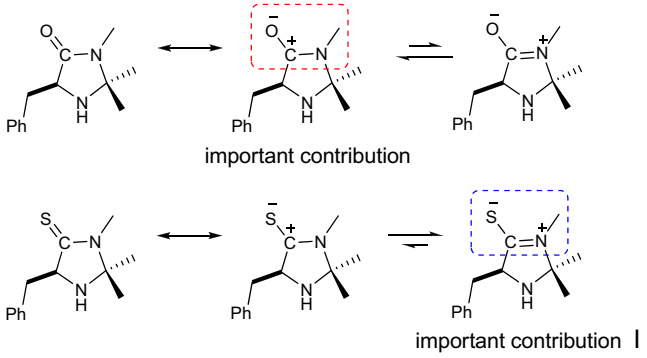
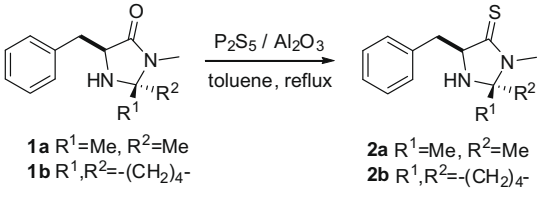


Figure 1.

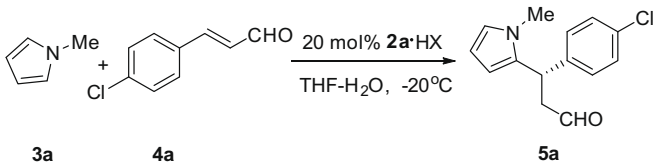
In our initial work, a series of novel imidazolethiones were easily prepared from the corresponding imidazolidinones with good yields using P_2S_5/Al_2O_3 as a sulfuration agent (Scheme 1). Among these organocatalysts, the imidazolethiones **2a** and **2b** exhibited excellent catalytic activities for the asymmetric Friedel–Crafts alkylation reaction of pyrroles with α,β-unsaturated aldehydes.



Scheme 1.

A mixture of *N*-methyl pyrrole **3a** and (*E*)-3-(4-chlorophenyl)acrylaldehyde **4a** was performed as a model reaction in the presence of catalytic amount (20 mol %) of imidazolethione **2a** (Scheme 2). Various factors including the kinds of catalysts, additives, solvents, and temperature were investigated for this reaction.

As revealed in Table 1, the effect of additive acids loading on reaction efficiency was first evaluated. Negligibly target adducts



Scheme 2.

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

Entry	Catalysts	Additives HX	Time (h)	Yield[b] (%)	ee[c] (%)
1	**2a**	*p*-TSA	6	78	57
2	**2a**	F_3CSO_3H	32	75	58
3	**2a**	PhCOOH	32	Trace	—
4	**2a**	Cl_2CHCO_2H	48	79	90
5	**2a**	Cl_3CCO_2H	48	78	89
6	**2a**	TFA	48	85	91
7	**2b**	TFA	48	83	90
8	**1a**	TFA	48	80	86

[a] Reactions conditions: a mixture of **3a** (4.5 mmol), **4a** (2 mmol), 20 mol % catalysts and 20 mol % additives in THF (4 mL)/H_2O (0.6 mL) was stirred at −20 °C for the given time.
[b] Yields based upon isolation of the corresponding alcohol after $NaBH_4$ reduction.
[c] ee determined by chiral HPLC.

or poor enantioselectivities were obtained with **2a** in the presence of *p*-TSA, CF_3SO_3H, or $PhCO_2H$ (Table 1, entry 1–3), whereas Cl_2CHCO_2H, CCl_3CO_2H, and TFA showed significant activity (Table 1, entries 4–6). Most excitingly, the optimal yield (85%) and enantioselectivity (91%) were accomplished by using **2a**-TFA (Table 1, entry 6). In addition, catalyst **2b** gave a similar result (83% yield, 90% ee) under the same conditions (Table 1, entry 7). Compared to **2a** and **2b**, catalyst **1a** offered somewhat lower ee value (86% ee) (Table 1, entry 8).

Secondly, the influence of solvents and reaction temperature on this alkylation was examined (Table 2). The results indicated that CH_2Cl_2, *i*-PrOH, and THF were unsuitable for the reaction (Table 2, entries 1–3). A mixed solvent THF/H_2O (85:15) proved to be the most effective (Table 2, entry 6), while excess water (35%) resulted in decreasing yield (Table 2, entry 8). Moreover, lower ee was observed by elevating the reaction temperature (Table 2, entry 9).

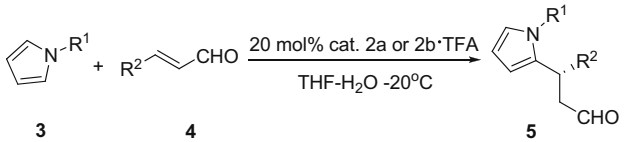
Encouraged by these initial results, the scope of α,β-unsaturated aldehydes and pyrroles was explored (Table 3, entries 1–17). Aromatic unsaturated aldehydes were well tolerated in the alkylation of *N*-metyl pyrrole (Table 3, entries 1–9), in which *para*-substitution offered higher yield and ee value (Table 3, entries 1–4) than *meta*- or *ortho*-substitution (Table 3, entries 6–9) on the aryl ring. More importantly, excellent levels of yields and enantioselectivities were observed for aliphatic unsaturated aldehydes (Table 3, entries 10 and 11), which were higher than that of MacMillan's imidazolidinone.[2] As far as alkylation of pyrrole was concerned, catalyst **2b** was used due to the difficult isolation of products with catalyst **2a**, giving moderate yields and enantioselectivities (Table 3, entries 12–16). In particular, crotonaldehyde offered excellent ee (Table 3, entry 17) compared with aromatic unsaturated aldehydes.

Table 2
The influence of solvents and temperature on the reaction[a]

Entry	Solvent (v/v)	Temp (°C)	Yield[b] (%)	ee[c] (%)
1	CH_2Cl_2	−20	31	50
2	*i*-PrOH	−20	trace	—
3	THF	−20	42	37
4	CH_2Cl_2/*i*-PrOH (85/15)	−20	76	89
5	THF/*i*-PrOH (90/10)	−20	80	80
6	THF/H_2O (85/15)	−20	85	91
7	THF/H_2O (95/5)	−20	84	91
8	THF/H_2O (65/35)	−20	64	88
9	THF/H_2O (85/15)	−5	83	76

[a] Reactions conditions: a mixture of **3a** (4.5 mmol), **4a** (2 mmol), 20 mol % catalyst **2a** and 20 mol % TFA in solvent (4.6 mL) was stirred at −20 °C for 48 h.
[b] Yields based upon isolation of the corresponding alcohol after $NaBH_4$ reduction.
[c] ee determined by chiral HPLC.

Table 3
Friedel–Crafts alkylation of pyrroles **3** with α,β-unsaturated aldehydes **4** catalyzed by **2a** or **2b**[a]

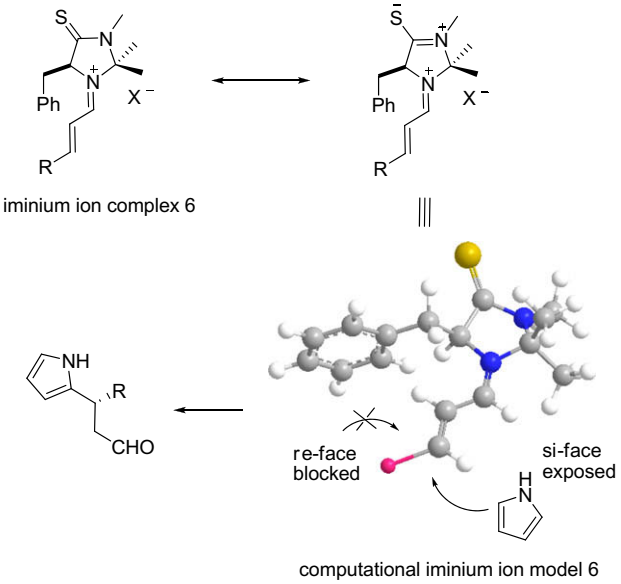


3 4 5

Entry	Product	R^1	R^2	Time (h)	Yield[a] (%)	ee[b] (%)
1	**5a**	Me	*p*-ClC_6H_4	48	85	91
2	**5b**	Me	*p*-FC_6H_4	48	80	93
3	**5c**	Me	*p*-$MeOC_6H_4$	48	74	94
4	**5d**	Me	*p*-MeC_6H_4	48	76	91
5	**5e**	Me	C_6H_5	48	85	92
6	**5f**	Me	*m*-ClC_6H_4	72	79	90
7	**5g**	Me	*m*-MeC_6H_4	72	75	89
8	**5h**	Me	*o*-$MeOC_6H_4$	72	73	84
9	**5i**	Me	*o*-$F_3CC_6H_4$	72	70	85
10	**5j**	Me	Me	56	82	98
11	**5k**	Me	$CH_3(CH_2)_2$	56	80	95
12[d]	**5l**	H	*p*-ClC_6H_4	48	62	63
13[d]	**5m**	H	*p*-FC_6H_4	48	65	60
14[c]	**5n**	H	*p*-MeC_6H_4	48	56	45
15[d]	**5o**	H	C_6H_5	48	65	53
16[d]	**5p**	H	*m*-MeC_6H_4	48	60	38
17[d]	**5q**	H	Me	48	71	97

[a] Reactions conditions: a mixture of **3** (4.5 mmol), **4** (2 mmol), 20 mol % catalyst **2a** and 20 mol % TFA in THF (4 mL)/H_2O (0.6 mL) was stirred at −20 °C for the given time.
[b] Yields based upon isolation of the corresponding alcohol after $NaBH_4$ reduction.
[c] ee determined by chiral HPLC.
[d] Using catalyst **2b**.

Based on the literatures[2,5j,7] and preliminary experimental findings, we assumed that the probable mechanism and transition states might be governed by imidazolethiones. As shown in computational modeling, the catalyst-activated iminium ion **6** formed selectively the (*E*)-iminium isomer[5b,j,8] to avoid nonbonding interactions with the *gem*-dimethyl group. Simultaneously, the benzyl group on the catalyst framework could effectively shield the *re*-face of the dienophile, led to stereoselective *si*-facial nucleophilic conjugate addition by pyrrole in its enol form (Scheme 3). The 'stiffer' imidazolethione was possibly attributed to the enhanced



Scheme 3.

catalytic activity and increased iminium geometry control in the transition state.

In summary, we developed novel organocatalyst imidazolethiones which were efficient to promote the enantioselective Friedel–Crafts alkylation of pyrroles and α,β-unsaturated aldehydes with moderate to excellent yields and high enantioselectivities, especially for the aliphatic unsaturated aldehydes.[9] Further, thriving area of catalysis concepts and widely applicable reactions based on these catalysts are going in our studies.

Acknowledgment

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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.2010.02.160.

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9. *Typical procedure for the synthesis of imidazolethione* **2a**: A mixture of P_2S_5 (3.0 g, 13.5 mmol) and Al_2O_3 (5.0 g, 49.0 mmol) was ground continuously in a mortar until a fine, homogeneous powder was obtained. Then, P_2S_5/Al_2O_3 (2 g, 5 mmol) was added to the solution of imidazolidinone **1a** (1.1 g, 5 mmol) in 30 mL toluene. The reaction mixture was stirred at refluxing for the given time under nitrogen (monitored by TLC). The reaction mixture was filtrated, the solvent was evaporated under *vacuum*, and the residue was purified by flash column chromatography over silica gel (petroleum ether/CH_2Cl_2/AcOEt 4:1:1) to afford the corresponding imidazolethione **2a** in 89% yield.
(*S*)-5-Benzyl-2,2,3-trimethylimidazolidine-4-thione (**2a**): Yellow oil. Yield: 89%; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.30–7.22 (m, 5H), 4.15 (t, J = 6.8 Hz, 1H), 3.50 (dd, J_1 = 4.4 Hz, J_2 = 14.0 Hz, 1H), 3.17 (dd, J_1 = 6.8 Hz, J_2 = 14.0 Hz, 1H), 3.16 (s, 3H), 1.78 (br s, 1H), 1.31 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 200.0, 137.1, 129.4, 128.5, 126.8, 83.8, 70.0, 39.3, 30.9, 26.5, 24.7; MS (EI): m/z (%) = 234(96, M^+), 177(94), 176(81), 160(83), 143(100). HRMS (EI) exact mass calcd for [$C_{13}H_{18}N_2S$]: 234.1191; found: 234.1196. $[\alpha]_D^{20}$ −139.2 (c 0.87, $CHCl_3$).
General procedure for the synthesis of 3-(pyrrols-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 (4 mL) and H_2O (0.6 mL) was stirred for 5 min at room temperature. Then, the pyrroles (4.5 mmol) were added. The reaction mixture was stirred at −20 °C for the given time (monitored by TLC). The resulting solution was added to equal volume of absolute EtOH and excess of $NaBH_4$ and stirred for 15 min. The reaction 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 1:6) to provide products **5**.
(*S*)-3-(4-Chlorophenyl)-3-(1-methyl-1*H*-pyrrol-2-yl)propan-1-ol (**5a**): Yellow oil. Yield: 85%. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.22 (d, J = 8.4 Hz, 2H), 7.07 (d, J = 8.4 Hz, 2H), 6.52 (t, J = 2.0 Hz, 1H), 6.12–6.09 (m, 2H), 4.10 (t, J = 7.6 Hz, 1H), 3.70–3.64 (m, 1H), 3.58–3.54 (m, 1H), 3.28 (s, 3H), 2.34–2.26 (m, 1H), 2.07–1.99 (m, 1H), 1.54 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 142.0, 134.3, 132.0, 129.3, 128.7, 122.0, 106.4, 105.9, 60.3, 38.8, 38.7, 33.8; MS (EI): m/z (%) = 249 (22, M^+), 206(35), 204(100); HRMS (EI) exact mass calcd for [$C_{14}H_{16}ClNO$]: 249.0920, found: 249.0927. $[\alpha]_D^{20}$ +91.4 (c 0.51, $CHCl_3$). HPLC condition: Chiralcel AS-H column, isopropanol/hexanes 10:90, flow rate 1.0 mL/min, UV detection at 214 nm, t_{major} = 6.3 min, t_{minor} = 7.1 min, 91% ee.