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Enantioselective Friedel−Crafts Alkylations of α,β-Unsaturated 2-Acyl Imidazoles Catalyzed by Bis(oxazolinyl)pyridine−Scandium(III) Triflate Complexes

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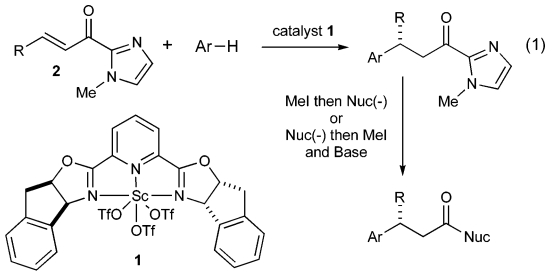
The Friedel−Crafts reaction and its enantioselective variants are powerful carbon−carbon bond forming processes,[1] and the application of these reactions to the alkylation of electron-rich heteroaromatic rings, such as indoles,[2,3] is a topic of ongoing interest.[4] Previous examples of Friedel−Crafts reactions of this type generally require cryogenic temperatures for high enantioselectivity and/or tolerate only a limited range of substituents at the enone β-position. Although α,β-unsaturated 1-acyl pyrazoles have been utilized as conjugate acceptors,[5] α,β-unsaturated 2-acyl imidazoles have not been reported as being used in this capacity. The purpose of this communication is to describe the enantioselective Friedel−Crafts reactions of α,β-unsaturated 2-acyl *N*-methylimidazoles **2** with electron-rich heterocycles catalyzed by the chiral bis(oxazolinyl)pyridine (pybox)−scandium(III) triflate complex **1**.[6] This reaction exhibits good enantioselectivities (>90% ee) over a broad range of substrates. In addition, the products may be easily transformed into synthetically useful amides, esters, carboxylic acids, ketones, and aldehydes.[7]



The pybox ligand, solvent, and reaction conditions were optimized with *N*-methylindole (**3**) as the nucleophile. A survey of $Sc(OTf)_3$−pybox complexes revealed that complex **1** was the most promising catalyst, and that acetonitrile was the solvent of choice. The use of 4 Å molecular sieves was also found to be advantageous. The desired alkylation products were formed in good yields and enantioselectivities. During this series of experiments, it was noted that the product enantiomeric excess is inversely proportional to the mole percent of catalyst employed (Table 1, first three entries).[8] The range of β-enone substituents (R) that may be tolerated is broad for reactions of this type.

A representative selection of indole derivatives was evaluated (Table 2). The reactions generally displayed the best selectivity with *N*-benzylindoles. 1,2-Dimethylindole is also a competent nucleophile for the reaction. Other substituted indoles are also well tolerated in the illustrated reaction.

2-Methoxyfuran and pyrrole are also competent nucleophiles for the illustrated reaction (eqs 4 and 5). These furan and pyrrole cases also highlight the point that the imidazole N-substituent may play a beneficial role in the level of reaction enantioselectivity. This trend was also noted in the indole alkylations. In general, the more sterically demanding *N*-isopropyl substituent affords a boost in enantioselection of 1−6% ee over its *N*-methyl counterpart. While this study has focused on the commercially available *N*-methylimidazole derivatives on the basis of economic considerations, improved enantioselectivities in marginal cases may be achieved by increasing the steric requirements of this moiety.

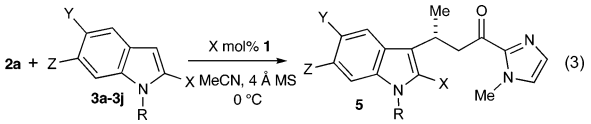
One intramolecular indole alkylation has been investigated to date (eq 6). The reaction proceeds in good yield and enantioselectivity. The absolute configuration of **11** has been assigned by analogy to the other cases included in this study.

Table 1. Scandium-Catalyzed Alkylations of α,β-Unsaturated 2-Acyl Imidazoles **2** with *N*-Methylindole **3**[a] (eq 2)

imidazole	R	mol % of **1**	*T* (°C)	time (h)	ee (%)[b]	yield (%)
2a	Me	1	−40	16	98	97 (**4a**)
2a	Me	5	−40	24	97	99 (**4a**)[c]
2a	Me	10	−40	24	90	99 (**4a**)[c]
2a	Me	1	20	5	96	99 (**4a**)[c]
2a	Me	1	65	3	90	99 (**4a**)[c]
2a	Me	2.5	0	3	93	93 (**4a**)
2b	Et	2.5	0	12	92	97 (**4b**)
2c	*i*-Pr	2.5	0	8	94	78 (**4c**)
2d	*n*-Bu	2.5	0	12	93	95 (**4d**)
2e	CO_2Et	2.5	0	12	96	95 (**4e**)
2f	Ph	2.5	0	8	91	94 (**4f**)

[a] All reactions were carried out at 0.26 M in substrate. [b] Enantiomeric excess determined by chiral HPLC. [c] Reported as conversion based on ^1H NMR spectroscopy.

Table 2. Scandium-Catalyzed Alkylations of α,β-Unsaturated 2-Acyl Imidazoles **2a** with Substituted Indoles **3**[a] (eq 3)



indole	R	X	Y	Z	mol % of **1**	time (h)	ee (%)[b]	yield (%)
3a	H	H	H	H	2.5	20	65	80 (**5a**)
3b	allyl	H	H	H	2.5	24	88	80 (**5b**)
3c	Bn	H	H	H	2.5	8	98	90 (**5c**)
3d	Me	Me	H	H	2.5	2	91	88 (**5d**)
3e	Me	Ph	H	H	5	90	66	43 (**5e**)
3f	Bn	H	OMe	H	2.5	20	97	99 (**5f**)
3g	Bn	H	Br	H	5	20	92	55 (**5g**)
3h	Bn	H	Cl	H	5	20	95	70 (**5h**)
3i	Bn	H	Me	H	5	20	93	91 (**5i**)
3j	Bn	H	H	OMe	5	20	95	99 (**5j**)

[a] All reactions were carried out at 0.26 M in substrate. [b] Enantiomeric excess determined by chiral HPLC.

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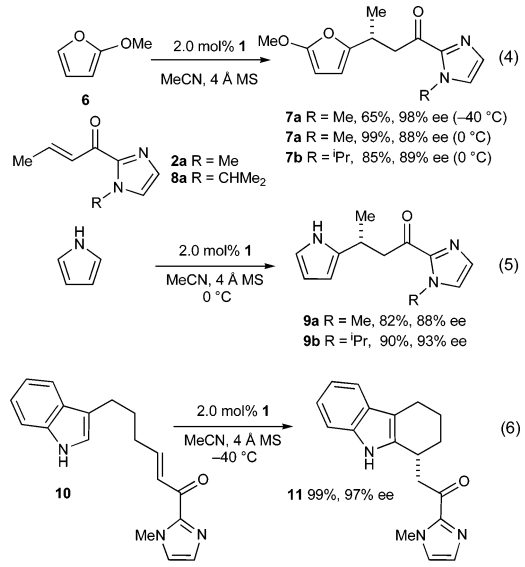
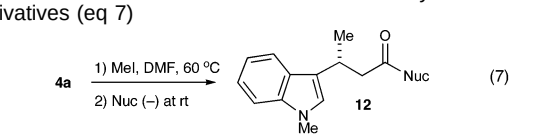
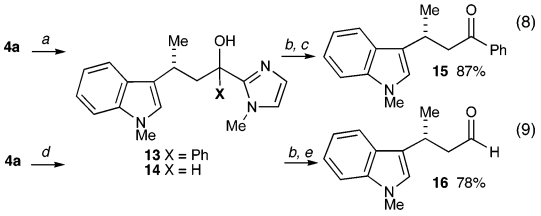


The 2-acyl imidazole residue may be transformed into a range of carboxylic acid derivatives.[7] Removal of the imidazole group can be accomplished in one of two ways (eqs 7−9). First, the imidazole group can be successively methylated then treated under a variety of nucleophilic conditions to acquire esters, amides, and carboxylic acids in good yields in one-pot operations (Table 3).

Table 3. Conversion of Imidazole **4a** to Carboxylic Acid Derivatives (eq 7)



entry	Nuc (–) conditions	Nuc	time	yield (%)
1	MeOH/DBU in CH_2Cl_2	-OMe	30 min	93 (**12a**)
2	EtOH/DBU in CH_2Cl_2	-OEt	30 min	86 (**12b**)
3	*i*-PrOH/DBU in CH_2Cl_2	-OCH$(CH_3)_2$	30 min	95 (**12c**)
4	H_2O/DBU in DMF	-OH	30 min	87 (**12d**)
5	*i*-PrNH_2 in DMF	-NHCH$(CH_3)_2$	20 min	77 (**12e**)
6	Morpholine in CH_2Cl_2	Morpholine	1 h	88 (**12f**)
7	Aniline in DMF	-NHPh	12 h	84 (**12g**)



[a] PhMgBr, THF, −78 to 0 °C. [b] MeI, EtOAc, 50 °C. [c] Benzene, 10 wt % Na_2CO_3, 50 °C. [d] $NaBH_4$, MeOH, rt. [e] Benzene, 0.1 M NaOH, $H_2N(CH_2)_5CO_2Na$, 80 °C.

Second, the initial ketone moiety in **4a** can be treated with a Grignard reagent to give the tertiary alcohol **13** or reduced to the secondary alcohol **14** with sodium borohydride (eqs 8 and 9). The resulting imidazole groups can be methylated and subsequently eliminated under basic conditions to liberate the ketone **15** or aldehyde **16** in good yields.

Next, we turned our attention to the issue of the effect of catalyst loading on enantioselectivity. As shown in Table 1, the addition of *N*-methylindole to **2a** afforded better selectivities with lower catalyst loadings. To further explore this phenomenon, we conducted a series of experiments with different catalyst loadings of **1** at −40 °C at 0.26 M in substrate (eq 2): 1 mol % (98% ee); 10 mol % (90% ee); 20 mol % (78% ee); 35 mol % (49% ee); 50 mol % (11% ee). This trend was most evident when a stoichiometric amount of catalyst **1** was used, resulting in a turnover in asymmetric induction (−31% ee).

Reaction enantioselection in the presence of 5 mol % of **1** (−40 °C) as a function of reaction molarity was also probed: 0.10 M (95% ee); 0.4 M (94% ee); 0.8 M (93% ee); 1.0 M (92% ee).

On the basis of these data and the fact that $Sc(OTf)_3$−pybox complexes can adopt seven-coordinate pentagonal-bipyramidal geometry,[6,9] we speculate that the reaction might proceed through a 1:1:1 substrate:product:catalyst complex that is favored at lower catalyst loadings and is more enantioselective than the corresponding 1:1 substrate:catalyst complex which would be favored at higher catalyst loadings.

In summary, α,β-unsaturated 2-acyl imidazoles are efficient substrates for Friedel−Crafts alkylations. These substrates are easily converted to a variety of useful functional groups and are easily synthesized. Further studies to explain the catalyst loading profile and expand the scope of the reactions of the α,β-unsaturated 2-acyl imidazoles are in progress.

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Supporting Information Available: Experimental procedures, spectral data for all new compounds, stereochemical determinations, synthesis of α,β-unsaturated 2-acyl imidazoles, and complete ref 3b (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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