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Catalytic Enantioselective Pyrrole Alkylations of α,β-Unsaturated 2-Acyl Imidazoles

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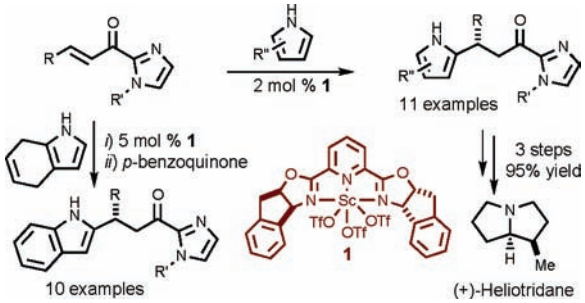
ABSTRACT



Enantioselective additions of pyrroles to α,β-unsaturated 2-acyl imidazoles catalyzed by the bis(oxazolinyl)pyridine−scandium(III) triflate complex (1) have been accomplished. The α,β-unsaturated 2-acyl imidazoles were synthesized in high yields through Wittig olefination. A short, enantioselective synthesis of the alkaloid (+)-heliotridane has been accomplished utilizing this methodology and a 2-acyl imidazole cleavage and cyclization. This methodology was then extended to the one-pot asymmetric synthesis of 2-substituted indoles.

The Friedel−Crafts reaction has been employed as a powerful carbon−carbon bond forming process in modern organic chemistry.[1] Even though considerable effort has been expended in the development of asymmetric Michael-type reactions between indoles and α,β-unsaturated carbonyl compounds,[2] the corresponding reaction with pyrroles has received less attention. MacMillan was the first to report catalytic asymmetric conjugate additions between pyrroles and α,β-unsaturated carbonyl compounds.[3] Palomo later showed that α′-hydroxy enones are competent electrophiles for the conjugate addition of pyrroles utilizing our previously reported Cu(II) bis(oxazoline) catalyst.[4] However, both of these examples focused on the use of *N*-alkyl-substituted pyrroles at subzero reaction temperatures. We previously reported that α,β-unsaturated 2-acyl imidazoles exhibit excellent enantioselectivity and yields for alkylations among indoles, pyrrole, and 2-methoxyfuran catalyzed by Sc complex **1** (Scheme 1).[5] Considering the value of pyrroles as useful synthons and as pyrrolidine surrogates,[6] we have expanded the reaction scope to include a range of pyrrole nucleophiles. In this letter, we report our studies in the enantioselective pyrrole Friedel−Crafts alkylation and the synthesis of the requisite α,β-unsaturated 2-acyl imidazoles.

The synthesis of β-substituted α,β-unsaturated 2-acyl imidazoles may be accomplished in a number of ways,[5] and

(1) For a review on the Friedel−Crafts reaction, see: Olah, G. A.; Krishnamurti, R.; Prakash, G. K. S. Friedel−Crafts Alkylations. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, pp 293−339.

(2) (a) For a review on the previous work on the Friedel−Crafts reaction between indoles and α,β-unsaturated carbonyl compounds, see: Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550−556. (b) For Sc(III)-catalyzed additions of indoles to α,β-unsaturated keto phosphonates, see: Evans, D. A.; Sheidt, K. A.; Fandrick, K. R.; Lam, H. W.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10780−10781.

(3) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370−4371.

(4) (a) Palomo, C.; Oiarbide, M.; Kardak, B. G.; Garcia, J. M.; Linden, A. *J. Am. Chem. Soc.* **2005**, *127*, 4154−4155. (b) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325−335.

(5) Evans, D. A.; Fandrick, K. R.; Song, H.-J. *J. Am. Chem. Soc.* **2005**, *127*, 8942−8943.

(6) For the hydrogenation of pyrroles to pyrrolidines, see: (a) Kaiser, H.-P.; Muchowski, J. M. *J. Org. Chem.* **1984**, *49*, 4203−4209. (b) Gilchrist, T. L.; Lemos, A.; Ottaway, C. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3005−3012.

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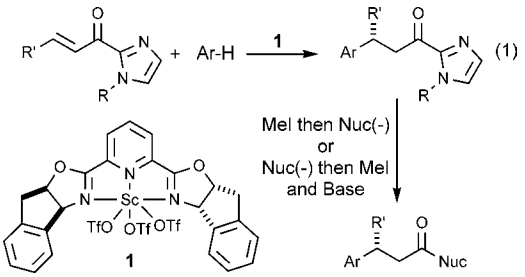
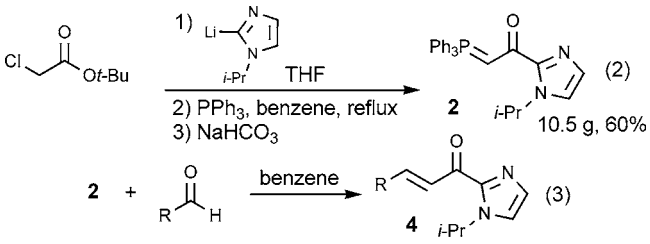
Scheme 1. Asymmetric Catalytic Friedel−Crafts Alkylations with α,β-Unsaturated 2-Acyl Imidazoles



the preferred method for the preparation of a given substrate will depend on the β-substituent. Direct acylation of the corresponding α,β-unsaturated carboxylic acids is the most direct route to substrates **4a** and **4b**. However, a more general method is needed to prepare more complex substrates, substrates with sensitive functional groups, or substrates where the corresponding carboxylic acid is not readily available. Shibasaki has shown that α,β-unsaturated *N*-acyl pyrroles may be effectively synthesized via Wittig olefination.[7] We chose to apply this methodology to the synthesis of α,β-unsaturated 2-acyl imidazoles. Preparation of Wittig reagent **2** proceeded cleanly starting from *tert*-butyl chloroacetate (Figure 1). Wittig reagent **2** was prepared on a multigram scale and was used without further purification. Wittig olefination between **2** and a variety of aldehydes **3** afforded the corresponding α,β-unsaturated 2-acyl imidazoles **4** in high yields and excellent *E:Z* selectivities.



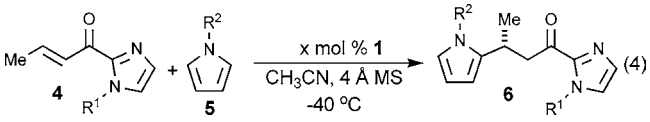
aldehyde	R	*E:Z*	yield (%)
3a	Me	>97:3[b,c]	93 (**4a**)
3b	Et	>98:2[b,d]	77 (**4b**)
3c	*i*-Pr	>99:1	99 (**4c**)
3d	CO_2Et	>99:1	77 (**4d**)
3e	Ph	>99:1	71 (**4e**)
3f	*p*-MeOPh	>97:3	96 (**4f**)
3g	*p*-CO_2MePh	>99:1	85 (**4g**)
3h	*p*-ClPh	>99:1	86 (**4h**)
3i	*o*-ClPh	>98:2	74 (**4i**)
3j	*p*-BrPh	>99:1	89 (**4j**)
3k	2-Furyl	>97:3	97 (**4k**)

[a]Typical Wittig conditions: 1.2-6 equiv of aldehyde at 0.5 M in benzene, rt to 80 °C for 12 h. [b]Required an isomerization with DMAP: 0.1-0.2 equiv of DMAP in CH_2Cl_2 at −5 to −10 °C overnight. [c]Before DMAP isomerization *E:Z* ratio was 85:15. [d]Before DMAP isomerization *E:Z* ratio was 96:4.

Figure 1. Synthesis of α,β-unsaturated 2-acyl imidazoles.[a]

As summarized in Table 1, more sterically demanding N-substituents on the imidazole moiety afford an increase in enantioselectivity. Even though the phenyl substituent was optimal with regard to overall yield (98%) and enantioselectivity (94% ee), we decided to employ the more readily prepared *N-iso*-propylimidazoles with a small sacrifice in yield.

Table 1. Effects of N-Substitution on the Friedel−Crafts Reaction between 2-Acyl Imidazole **4** and Pyrrole (eq 4)[a]

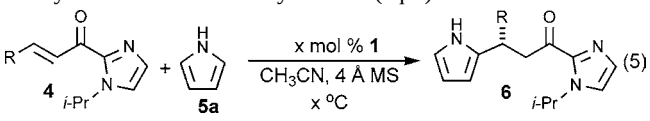


entry	R^1	R^2	mol % of **1**	ee (%)[b]	yield (%)
1	Me	H	5	87	69 (**6a**)
2	*iso*-Pr	H	5	94	91 (**6b**)
3	Ph	H	5	94	98 (**6c**)
4	Bn	H	5	91	84 (**6d**)
5[c]	Me	Me	5	77	69 (**6e**)
6	*iso*-Pr	Me	5	89	78 (**6f**)

[a] All reactions were carried out at 0.13 M in substrate. [b] Enantiomeric excess determined by chiral HPLC. [c] Reaction carried out at 0.26 M in substrate.

After a determination of the optimal *N*-substituent on the imidazole moiety **4**, the effects of temperature and catalyst loading on the illustrated reaction were evaluated (Table 2).

Table 2. Scandium-Catalyzed Alkylations of α,β-Unsaturated 2-Acyl Imidazoles **4** with Pyrrole **5a** (eq 5)[a]



entry	R	mol % of **1**	temp (°C)	time (h)	ee (%)[b]	yield (%)
1	Me (**4a**)	5	20	5	85	99 (**6b**)
2	Me (**4a**)	5	0	5	90	95 (**6b**)
3	Me (**4a**)	5	−40	15	94	96 (**6b**)
4	Me (**4a**)	2	−40	15	95	99 (**6b**)[c]
5	Me (**4a**)	10	−40	15	93	99 (**6b**)[c]
6	Me (**4a**)	20	−40	15	86	99 (**6b**)[c]
7	Me (**4a**)	30	−40	15	78	99 (**6b**)[c]
8	Me (**4a**)	50	−40	15	62	99 (**6b**)[c]
9	Me (**4a**)	2	0	18	93	90 (**6b**)
10	Et (**4b**)	2	0	18	86	91 (**6g**)
11	*i*-Pr (**4c**)	2	0	18	91	90 (**6h**)
12	CO_2Et (**4d**)	2	0	18	84	99 (**6i**)
13	Ph (**4e**)	2	0	18	96	99 (**6j**)
14	*p*-MeOPh (**4f**)	2	0	18	92	98 (**6k**)
15	*p*-CO_2MePh (**4g**)	2	0	18	96	99 (**6l**)
16	2-furyl (**4k**)	2	0	18	91	95 (**6m**)

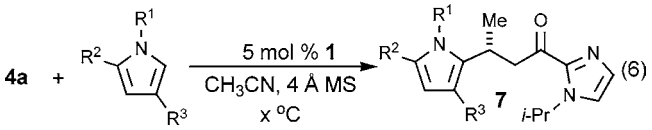
[a] All reactions performed at 0.13 M in substrate. [b] Enantiomeric excess determined by chiral HPLC. [c] Reported as conversion based on ^{1}H NMR spectroscopy.

As summarized, the reaction may be conveniently run at 0 °C with good enantioselectivities (90% ee) and yields (95%, entry 2). An increase in catalyst loading leads to lower enantioselectivities (entries 3−7). This inverse relationship between catalyst loading and ee was previously observed by us.[5] Finally, an increase in catalyst loading above 20 mol % leads to deleterious effects on facial selectivities (Table 2, entries 6−8).

The effect of the β-substituent on reaction enantioselection is also summarized in Table 2. Alkyl and aryl substitution are well tolerated in the illustrated reaction (entries 9−16).

Next, the effects of pyrrole substitution were evaluated (Table 3). N-substitution on the pyrrole heterocycle leads to

Table 3. Scandium-Catalyzed Alkylations of α,β-Unsaturated 2-Acyl Imidazole **4a** and Substituted Pyrroles (eq 6)[a]



(6)

R^1	R^2	R^3	temp (°C)	ee (%)[b]	yield (%)
H	H	H	−40	94	96 (**6b**)
Me	H	H	−40	78	89 (**6f**)
Bn	H	H	−40	11	67 (**7a**)
H	Et	H	−40	93	99 (**7b**)
H	Et	H	0	89	99 (**7b**)
H	Me	Me	−40	69	99 (**7c**)
H	Me	Me	0	78	99 (**7c**)

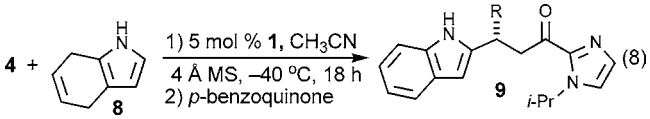
[a] All reactions performed at 0.13 M in substrate. [b] Enantiomeric excess determined by chiral HPLC.

a decrease in enantioselectivity. For example, *N*-benzylpyrrole is only poorly enantioselective (11% ee, Table 3), a result that is in sharp contrast to the Friedel−Crafts reactions with N-substituted indoles which afford the highest enantioselectivities.[5] The reaction is also not tolerant of substitution at the 3-position of the pyrrole nucleus; however, 2-ethylpyrrole was a competent nucleophile for the illustrated conjugate addition reaction (93% ee, 99% yield).

One may also access the 2-position of the indole nucleus if the dihydroindole is employed as the nucleophilic reaction component.[8] Saraçoglu has utilized this ploy in the racemic conjugate addition of 4,7-dihydroindole to enones followed by a *p*-benzoquinone oxidation to provide the 2-substituted indoles in moderate yields (30−49%).[8]

Initial attempts at the conjugate addition of 4,7-dihydroindole to enone **4a** were quite successful (90% ee, 99% yield); however, the subsequent aromatization to the indole nucleus with *p*-benzoquinone was sluggish when the oxidation was performed in dichloromethane as reported by Saraçoglu.[9] If this reaction is performed in acetonitrile, the yields improve

Table 4. Asymmetric Synthesis of 2-Substituted Indoles, 4,7-Dihydroindole Alkylations of α,β-Unsaturated 2-Acyl Imidazoles,[a] and Subsequent One-Pot Aromatization



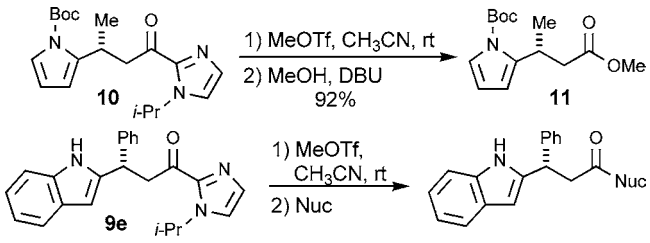
(8)

imidazole	R	ee (%)[b]	yield (%)
4a	Me	95	99 (**9a**)
4b	Et	77	97 (**9b**)
4c	*i*-Pr	72	62 (**9c**)
4e	Ph	96	98 (**9e**)
4f	*p*-MeOPh	90	97 (**9f**)
4g	*p*-CO_2MePh	97	85 (**9g**)
4h	*p*-ClPh	96	98 (**9h**)
4i	*o*-ClPh	93	90 (**9i**)
4j	*p*-BrPh	95	85 (**9j**)
4k	2-furyl	80	92 (**9k**)

[a] All reactions performed at 0.13 M in substrate. [b] Enantiomeric excess determined by chiral HPLC.

significantly (Table 4). We found that if the addition of 2 equiv of *p*-benzoquinone to the reaction occurs at the end of the conjugate addition a one-pot preparation of 2-substituted indoles from the enones **4** and 4,7-dihydroindole may be realized. This two-step sequence is well tolerant of β-substitution on the enone providing the 2-substituted indoles in good to excellent enantioselectivities and yields.

Initial attempts to cleave the 2-acyl imidazole **6a** directly without pyrrole protection afforded the desired methyl ester in low yields ((a) MeOTf, CH_2Cl_2, rt; (b) MeOH, DBU). By utilizing acetonitrile as solvent and a Boc protection[9] of the pyrrole nitrogen (96% yield), a greatly increased yield of the cleavage process to the derived methyl ester was realized (92%, **11**, Figure 2). Cleavage of the 2-substituted



entry	Nuc conditions	Nuc	% yield
1	MeOH, DBU	-OMe	99 (**12**)
2	H_2O, DBU	-OH	71 (**13**)

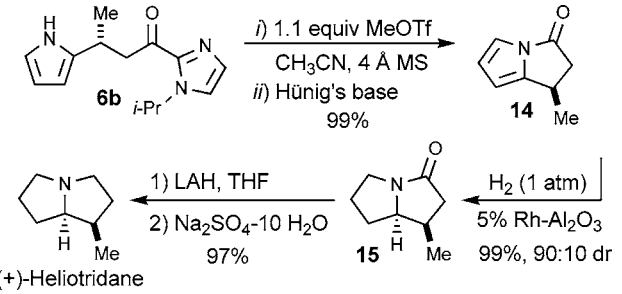
Figure 2. Cleavage of 2-acyl imidazoles **10** and **9e**.

indole product **9e** to the methyl ester (**12**, 99% yield) and the carboxylic acid (**13**, 71% yield, Figure 2) was effective using the modified methylation conditions described above. For the dihydroindole substrates, N-protection was not necessary.

(7) Matsunaga, S.; Kinosita, T.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 7559−7570.
(8) Çavdar, H.; Saraçoglu, N. *Tetrahedron* **2005**, *61*, 2401−2405.
(9) Davies, H. W.; Matasi, J. J.; Ahmed, G. *J. Org. Chem.* **1996**, *61*, 2305−2313.

If the imidazole cleavage in the pyrrole series was performed in the absence of an external nucleophile, the pyrrole nitrogen was internally acylated to give a 2,3-dihydro-1*H*-pyrrolizine (Scheme 2). We felt that this chemistry would be amenable to the synthesis of the hexahydro-1*H*-pyrrolizine alkaloids such as (+)-heliotridane.[10] Examination of the one-pot methylation and cyclization utilizing the known methods of 2-acyl imidazole cleavage[11] proved to be disappointing (excess MeOTf in CH_2Cl_2, <10% yield). The use of excess MeI in DMF, which effectively cleaved the 2-acyl imidazole in our previous work,[5] only provided trace amounts of product. We found that with acetonitrile as solvent we could use a slight excess (1.1 equiv) of methyl triflate to completely methylate the 2-acyl imidazole (Scheme 2). The use of DMAP or Hünig's base to promote acyl transfer provided the 2,3-dihydro-1*H*-pyrrolizine **14** in quantitative yield in a one-pot operation.

Scheme 2. One-Pot Methylation and Cyclization of **6b** to 2,3-Dihydro-1*H*-pyrrolizine **14** and the Synthesis of (+)-Heliotridane



With the 2,3-dihydro-1*H*-pyrrolizine **14** in hand, the completion of the synthesis of (+)-heliotridane was straightforward. The hydrogenation[6] of **14** afforded the hexahydropyrrolizin-3-one **15** in quantitative yield (90:10 dr), and the subsequent LAH reduction[8] (97% yield) provided (+)-heliotridane (Scheme 2). The material was purified and characterized as the picrate salt (optical rotation: $[\alpha]^{20}_D = +20.4°$ ($c = 0.77$, $CHCl_3$) lit.[11d] (−)-heliotridane, $[\alpha]^{20}_D = -22.4°$ ($c = 0.25$, $CHCl_3$)).

In summary, we have shown that a wide range of β-substituted α,β-unsaturated 2-acyl imidazoles are competent electrophiles for the Friedel−Crafts reaction with free pyrroles at noncryogenic temperatures. The use of 4,7-dihydroindole allowed for the one-pot asymmetric synthesis of a wide range of 2-substituted indoles. The α,β-unsaturated 2-acyl imidazoles are easily produced from the corresponding aldehydes and the Wittig reagent **2** in high yields and *E:Z* selectivity. With the synthesis of (+)-heliotridane, we discovered a more facile and efficient cleavage protocol for the 2-acyl imidazoles.

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Supporting Information Available: Complete experimental details, proton and carbon NMR spectra for all new compounds, and stereochemical determination are available in the Supporting Information document (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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