ORGANIC LETTERS

2008
Vol. 10, No. 18
4121−4124

Highly Enantioselective Friedel−Crafts Reaction of Indoles with 2-EnoylPyridine 1-Oxides Catalyzed by Chiral Pyridine 2,6-Bis(5′,5′-diphenyloxazoline)−Cu(II) Complexes†

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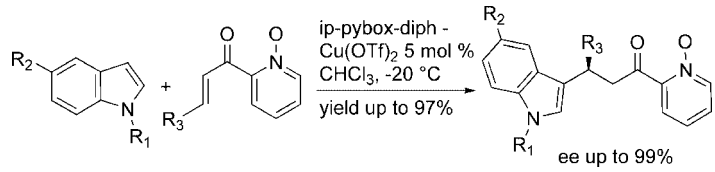
Received July 24, 2008

ABSTRACT



The catalytic enantioselective Friedel−Crafts reaction of indoles with 2-enoylpyridine 1-oxides has been studied in the presence of chiral pyridine 2,6-bis(5′,5′-diphenyloxazoline)−Cu(II) complexes. The reaction furnished alkylated indoles in excellent yields (up to 97%) and enantioselectivities (up to 99% ee).

The Friedel−Crafts (F−C) alkylation is one of the most efficient methods in synthetic organic chemistry for the formation of new C−C bonds. The asymmetric version of this reaction can afford important enantiomerically enriched alkylated arene products.[1] In recent years, enantioselective F−C reaction has attracted significant attention.[2,3] Several bidentate chelating substrates such as nitrostyrenes,[4] β,γ-unsaturated α-ketoesters,[5] alkylidene malonates,[6] glyoxylates and pyruvates,[7] acyl phosphonates,[8] 2-acyl imidazoles,[8] α′-hydroxy enones,[9] and thioesters[10] have been used in the metal-catalyzed enantioselective F−C reaction. In order to develop a new template for the enantioselective F−C reaction, we chose 2-enoylpyridines as a bidentate chelating electrophile. We have previously shown the potential utility of chiral pyridine 2,6-bis(5′,5′diphenyloxazoline)−Cu(II)

† This paper is dedicated to Prof. E. J. Corey on his 80th birthday and Prof. G. Mehta on his 65th birthday.

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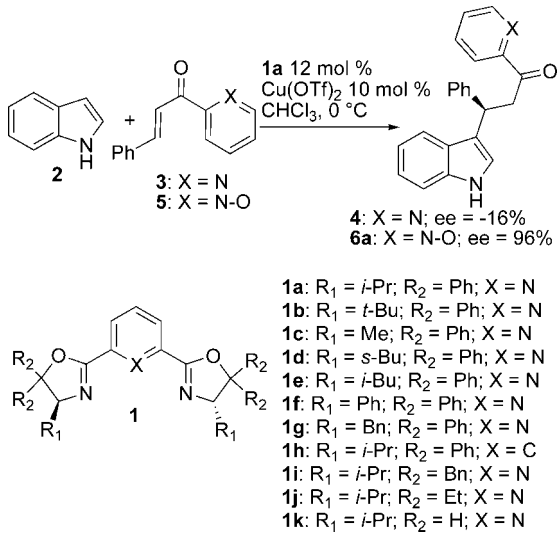
10.1021/ol8016929 CCC: $40.75
Published on Web 08/23/2008

complexes in the enantioselective allylic oxidation of olefins,[11] cyclopropanation reactions,[12] and propargylation of imines.[13] We observed that the diphenyl groups at the C-5 of the oxazoline rings played a crucial role in enhancing the enantioselectivity. To further explore the efficiency of the catalyst, we thought to extend the use of chiral pyridine 2,6-bis(5′,5′diphenyloxazoline)− Cu(II) complexes in enantioselective F−C reaction of indole with 2-enoylpyridines. The Cu(II) complex of ligand **1a** catalyzed the Friedel−Crafts reaction of indole and benzylidene-2-acetylpyridine to give the product in 89% yield and 16% ee (Scheme 1) after 24 h.

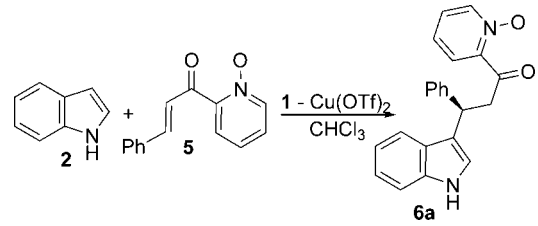
Scheme 1. Enantioselective Friedel−Crafts Reaction of Indole Catalyzed by pybox-diph−Cu(II) Complex



The poor enantioselectivity and reactivity could be due to an inappropriate coordination between substrate and catalyst. Pedro has reported that 2-enoylpyridine 1-oxides provide better coordination than the 2-enoylpyridines with Cu(II) metal.[14] In this paper, we wish to report the use of 2-enoylpyridine 1-oxides in enantioselective F−C reaction.

The initial study was carried out by using indole and benzylidene-2-acetylpyridine *N*-oxide as the substrates in the presence of chiral Cu(II) complex of ligand **1a** (10 mol %) in chloroform at 0 °C. To our delight, the F−C reaction was efficient with excellent enantioselectivity (96%) (Scheme 1). Various pybox-diph ligands with different substituents at chiral center (**1a**−**g**) were used in the above reaction, and the results are summarized in Table 1. It was observed that the ligand **1a** having an isopropyl group at the chiral center (C-4) of oxazoline rings was optimum (Table 1, entry 2). However, bulkier substituents such as *t*-Bu and *s*-Bu groups

Table 1. Friedel−Crafts Alkylation of Indole with Benzylidene−2-Acetylpyridine *N*-Oxide Catalyzed by Various Catalysts



entry	1	catalyst (mol %)	T (°C)	time	yield (%)[a]	ee (%)[b]
1	**1a**	10	rt	15 min	90	88
2	**1a**	10	0	15 min	96	96
3	**1b**	10	0	15 min	95	94
4	**1c**	10	0	15 min	89	17
5	**1d**	10	0	15 min	86	94
6	**1e**	10	0	15 min	98	5
7	**1f**	10	0	15 min	65	6
8	**1g**	10	0	15 min	87	1
9	**1h**	10	0	12 h	84	1
10	**1i**	10	0	15 min	97	65
11	**1j**	10	0	8 h	93	59
12	**1k**	10	0	48 h	92	25
13	**1a**	10	−20	15 min	97	99
14	**1a**	5	−20	15 min	96	99
15	**1a**	2	−20	5 h	94	96
16	**1a**	1	−20	12 h	89	82

[a] Isolated yield. [b] Determined by chiral HPLC using a Chiralpak AD-H column (see the Supporting Information).

(**1b** and **1d**) gave slightly lower enantioselectivity (94% ee) (Table 1, entries 3 and 5). Lack of asymmetric induction with the ligand **1h** indicated that the pyridine nitrogen was important for chelation with Cu(II). In order to find out the role of the *gem*-diphenyl groups of the ligands on enantioselectivity, we studied the reaction with ligands **1i**−**k**. The poor enantioselectivity with these ligands indicated that the

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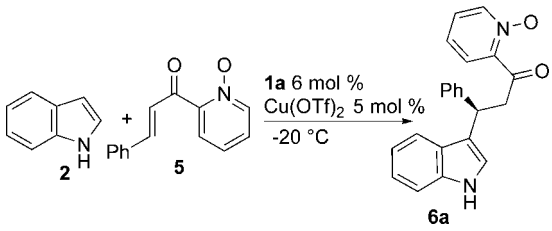
Table 2. Screening of Solvents for Enantioselective Friedel−Crafts Alkylation of Indole

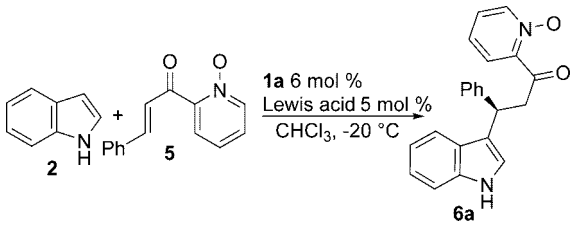


entry	solvent	time	yield[a] (%)	ee[b] (%)
1	$CHCl_3$	15 min	97	99
2	CH_2Cl_2	15 min	92	95
3	$(CH_2Cl)_2$	15 min	96	92
4	THF	15 min	95	98
5	CH_3CN	5 h	94	64
6	Toluene	24 h	91	94
7	CCl_4	7 d	nr	nr

[a] Isolated yield. [b] Determined by chiral HPLC using a Chiralpak AD-H column (see the Supporting Information). nr = no reaction.

diphenyl group is crucial for getting high ees in the reaction. In view of this study, **1a** was selected for further study. Lowering the temperature to −20 °C improved the enantioselectivity to 99% without any loss in reactivity (Table 1, entry 13). The catalyst was equally efficient at a loading of 5 mol % (Table 1, entry 14). Further, lowering the catalyst loading led to depletion in enantioselectivity with prolonged reaction time (Table 1, entries 15 and 16).

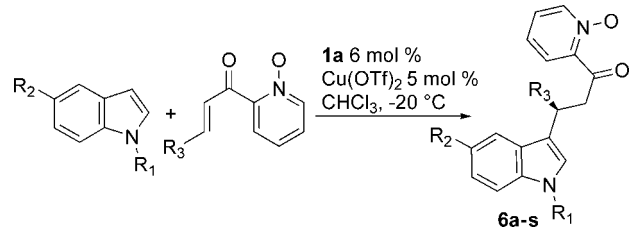
Table 3. Screening of Lewis Acids for Enantioselective Friedel−Crafts Alkylation of Indole



entry	Lewis acid	time	yield[a] (%)	ee[b] (%)
1	$Cu(OTf)_2$	15 min	97	99
2	$Cu(ClO_4)_2{\cdot}6H_2O$	15 min	95	99
3	$Cu(BF_4)_2{\cdot}xH_2O$	15 min	94	99
4	$Cu(CH_3CN)_4{\cdot}PF_6$	7 d	nr	nr
5[c]	$Cu(CH_3CN)_4{\cdot}PF_6$	36 h	90	33
6	$(CuOTf)_2{\cdot}PhH$	3 d	88	96
7	$Zn(OTf)_2$	36 h	91	96
8	$Sc(OTf)_3$	15 min	91	8
9	$In(OTf)_3$	30 min	96	3
10	$Yb(OTf)_3$	1 h	97	3
11	$Sn(OTf)_2$	2 h	95	10
12	$Mg(OTf)_2$	5 d	nr	nr
13	$CuCl_2$	5 d	nr	nr

[a] Isolated yield. [b] Determined by chiral HPLC using a Chiralpak AD-H column (see the Supporting Information). [c] Reaction was carried out at 0 °C. nr = no reaction.

Table 4. Enantioselective Friedel−Crafts Reaction of Indoles with Various 2-Enoylpyridine 1-Oxides



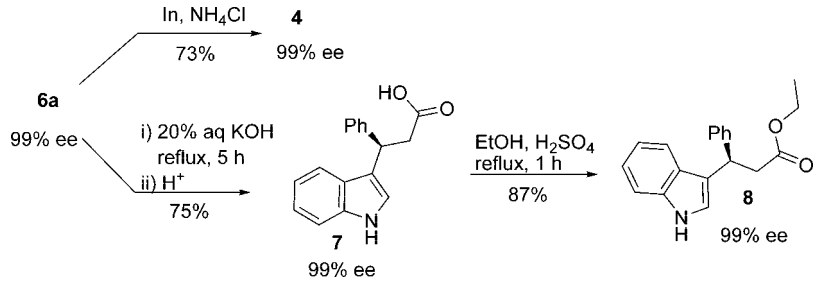
entry	R_1	R_2	R_3	6	time	yield[a] (%)	ee[b] (%)
1	H	H	Ph	**6a**	15 min	97	99
2	H	F	Ph	**6b**	1 h	97	97
3	H	Cl	Ph	**6c**	1 h	92	96
4	H	Br	Ph	**6d**	6 h	93	97
5	H	OMe	Ph	**6e**	15 min	98	95
6	H	CN	Ph	**6f**	7 d	86	83
7	Me	H	Ph	**6g**	30 min	97	86
8	Bn	H	Ph	**6h**	3 h	94	87
9	H	H	4-F-C_6H_4	**6i**	15 min	96	95
10	H	H	4-MeO-C_6H_4	**6j**	3 h	97	94
11	H	H	4-NO_2-C_6H_4	**6k**	15 min	95	99
12	H	H	3-NO_2-C_6H_4	**6l**	15 min	97	98
13	H	H	2-NO_2-C_6H_4	**6m**	15 min	96	97
14	H	H	4-Cl-C_6H_4	**6n**	15 min	97	94
15	H	H	3-Cl-C_6H_4	**6o**	15 min	98	93
16	H	H	2-Cl-C_6H_4	**6p**	15 min	96	91
17	H	H	1-naphthyl	**6q**	2 h	83	89
18[c]	H	H	2-furyl	**6r**	3 h	97	87
19	H	H	cyclohexyl	**6s**	3 d	75	5

[a] Isolated yield. [b] Determined by chiral HPLC (see the Supporting Information). [c] ee was determined by cleavage of the N−O bond of the product.

Solvent study with the catalyst **1a**−$Cu(OTf)_2$ for enantioselective F−C reaction indicated that chloroform was the optimum (Table 2, entry 1). THF and dichloromethane also gave very good enantioselectivity in the reaction (Table 2, entries 4 and 2). In order to investigate the reaction further, various Lewis acids were screened. The results from $Cu(ClO_4)_2{\cdot}6H_2O$ and $Cu(BF_4)_2{\cdot}xH_2O$ were on par with $Cu(OTf)_2$ (Table 3, entries 1− 3). $(CuOTf)_2{\cdot}PhH$ and $Zn(OTf)_2$ gave good enantioselectivity, but the reaction was sluggish (Table 3, entries 6 and 7). With other selected Lewis acids, the reaction was slow and the enantioselectivity was poor. $Cu(OTf)_2$ was selected for rest of the study. Barring 5-cyanoindole, other indoles gave excellent enantioselectivity. 5-Cyanoindole and *N*-substituted indoles gave moderate enantioselectivity (Table 4, entries 6−8). The reaction was extended to various enoylpyridine 1-oxides. Aromatic substrates gave excellent yield and enantioselectivity regardless of the nature of substituent on the phenyl ring (Table 4, entries 9 −16). Heteroaromatic substrates gave slightly lower enantioselectivity (Table 4, entry 18).

The optically active product (**6a**) can easily be deoxygenated to the corresponding pyridine adduct (**4**) without any loss in enantioselectivity by treatment with In/NH_4Cl[14] (Scheme 2). The potential of this catalytic system was demonstrated by cleavage of the pyridine *N*-oxide ring. The

Scheme 2. Cleavage of the N−O Bond and Pyridine *N*-Oxide Ring



pyridine *N*-oxide ring of the product (**6a**) was cleaved by 20% aq KOH leading to the synthetically useful acid (**7**) without any loss in enantioselectivity (Scheme 2). The absolute stereochemistry of the product was determined by converting the acid to the corresponding ethyl ester (**8**).[6c]

In summary, the chiral Cu(II)−**1a** complex prepared from $Cu(OTf)_2$ and the C_2-symmetric ip-pybox-diph ligand **1a** was found to be an effective catalyst for the enantioselective Friedel−Crafts reaction of indoles with 2-enoylpyridine 1-oxides. The reaction time was short, and a variety of alkylated indoles were obtained in excellent yields (up to 97%) and enantioselectivities (up to 99% ee). It has been shown that the 2-enoylpyridine 1-oxides are better substrates than the corresponding 2-enoylpyridines. The product of 2-enoylpyridine 1-oxides can be deoxygenated to the corresponding pyridine adduct. The pyridine *N*-oxide ring of the product has been cleaved to give synthetically useful acid without any loss in enantiomeric purity. Extention of the reaction scope is currently underway in our laboratory.

Acknowledgment. V.K.S. thanks the Department of Science and Technology, Government of India, for a research grant through Ramanna Fellowship. P.K.S. thanks the Council of Scientific and Industrial Research, New Delhi, for a research fellowship.

Supporting Information Available: General experimental procedures, characterization data including ^{1}H NMR and ^{13}C NMR spectra, and an HPLC chromatogram for compounds **4**, **6a**−**s**, **7**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL8016929