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Enantioselective Friedel−Crafts Alkylation of Pyrroles Catalyzed by PYBOX-DIPH-Zn(II) Complexes

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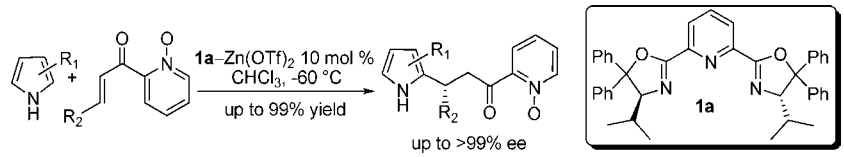
ABSTRACT



A highly enantioselective Friedel−Crafts alkylation of pyrroles with 2-enoylpyridine *N*-oxides catalyzed by chiral PYBOX-DIPH-Zn(II) complexes has been developed. The catalyst offers substantial substrate scope and furnished alkylated pyrroles in excellent yields (up to 99%) and enantioselectivities (up to >99% ee).

The Friedel−Crafts (F−C) reaction, first reported in 1877,[1] now 132 years later remains one of the most efficient procedures in synthetic organic chemistry for the formation of new C−C bonds. The asymmetric version of this reaction provides access to important enantiomerically enriched alkylated arene products and is a topic of ongoing research. Recently, there have been several reports of asymmetric F−C alkylation of indole derivatives for which excellent enantioselectivities have been achieved.[2] However, asymmetric F−C alkylation of pyrroles is less explored despite their prevalence in biologically active compounds.[3] Perhaps the tendency of dialkylation of pyrrole at both the 2- and 5-positions and instability toward acids have precluded the intensive research in this area. The first enantioselective F−C alkylation of pyrrole was reported by MacMillan using an iminium-catalysis strategy by chiral imidazolidinone.[4] After this poineering work, successful catalysts reported for enantioselective F−C alkylation of pyrrole include chiral bisoxazoline-metal complexes,[5] phosphoric acids,[6] BINOL-zirconium complex,[7] dinuclear zinc complex,[8] imidazoline-

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(1) (a) Friedel, C.; Crafts, J. M. C. R. *Hebd. Seances Acad. Sci.* **1877**, *84*, 1392. (b) Friedel, C.; Crafts, J. M. C. R. *Hebd. Seances Acad. Sci.* **1877**, *84*, 1450.

(2) For reviews, see: (a) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550. (b) Poulsen, T. B.; Jørgensen, K. A. *Chem. Rev.* **2008**, *108*, 2903. (c) You, S.-L.; Cai, Q.; Zeng, M. *Chem. Soc. Rev.* **2009**, *38*, 2190.

(3) (a) Fürstner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3582. (b) Hoffmann, H.; Lindel, T. *Synthesis* **2003**, 1753. (c) Balme, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 6238. (d) Jolicoeur, B.; Chapman, E. E.; Thompson, A.; Lubell, W. D. *Tetrahedron* **2006**, *62*, 11531.

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

(5) (a) Zhuang, W.; Gathergood, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2001**, *66*, 1009. (b) Palomo, C.; Oiarbide, M.; Kardak, B. G.; García, J. M.; Linden, A. *J. Am. Chem. Soc.* **2005**, *127*, 4154. (c) Evans, D. A.; Fandrick, K. R. *Org. Lett.* **2006**, *8*, 2249. (d) Evans, D. A.; Fandrick, K. R.; Song, H.-J.; Scheidt, K. A.; Xu, R. *J. Am. Chem. Soc.* **2007**, *129*, 10029. (e) Liu, H.; Lu, S.-F.; Xu, J.; Du, D.-M. *Chem. Asian J.* **2008**, *3*, 1111. (f) Yamazaki, S.; Kashima, S.; Kuriyama, T.; Iwata, Y.; Morimoto, T.; Kakiuchi, K. *Tetrahedron: Asymmetry* **2009**, *20*, 1224. (g) Cao, C.-L.; Zhou, Y.-Y.; Sun, X.-L.; Tang, Y. *Tetrahedron* **2008**, *64*, 10676.

(6) (a) Li, G.; Rowland, G. B.; Rowland, E. B.; Antilla, J. C. *Org. Lett.* **2007**, *9*, 4065. (b) Nakamura, S.; Sakurai, Y.; Nakashima, H.; Shibata, N.; Toru, T. *Synlett* **2009**, 1639. (c) Sheng, Y.-F.; Gu, Q.; Zhang, A.-J.; You, S.-L. *J. Org. Chem.* **2009**, *74*, 6899. (d) Sheng, Y.-F.; Li, G.-Q.; Kang, Q.; Zhang, A.-J.; You, S.-L. *Chem.—Eur. J.* **2009**, *15*, 3351.

(7) (a) Blay, G.; Fernández, I.; Pedro, J. R.; Vila, C. *Org. Lett.* **2007**, *9*, 2601. (b) Blay, G.; Fernández, I.; Monleón, A.; Pedro, J. R.; Vila, C. *Org. Lett.* **2009**, *11*, 441.

(8) Trost, B. M.; Müller, C. *J. Am. Chem. Soc.* **2008**, *130*, 2438.

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aminophenol-CuOTf complex,[9] and secondary amine organocatalysts.[10] Most of the literature known F−C pyrrole alkylation methods lack substrate generality. Previous studies identified chiral pyridine 2,6-bis(5′,5′-diphenyloxazoline)-metal complexes as a potential catalyst for asymmetric synthesis.[11] We observed that the diphenyl groups at the C-5 of the oxazoline rings played a crucial role in enhancing the enantioselectivity. Meanwhile, 2-enoylpyridine *N*-oxides[12] proved to be a good template for enantioselective reactions. This led to enantioselective F−C alkylation of indoles with 2-enoylpyridine *N*-oxides catalyzed by chiral ip-pybox-diph-Cu(II) complexes.[11m] Herein, we report the application of this method to catalytic enantioselective F−C alkylation of pyrroles with 2-enoylpyridine *N*-oxides catalyzed by chiral ip-pybox-diph-metal complexes. The initial study was carried out by using a 1.5:1.0:0.1 mixture of pyrrole, benzylidene-2-acetylpyridine *N*-oxide, and chiral Cu(II) complex of ligand **1a** (Figure 1) in chloroform at −20 °C. The F−C reaction

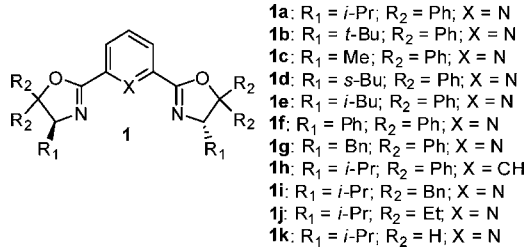


Figure 1. C_2 symmetric bisoxazoline ligands.

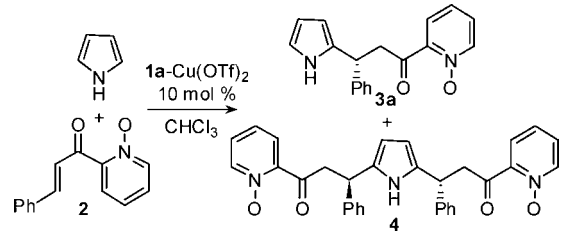
of pyrrole with benzylidene-2-acetylpyridine *N*-oxide catalyzed by **1a**-Cu(OTf)$_2$ was efficient and gave the product **3a** with excellent enantioselectivity (95% ee). However, the yield of the reaction was 48% and the monoalkylated product **3a** was accompanied by dialkylated product **4** (46% yield, Table 1, entry 1). We thought that lowering the temperature may reduce the dialkylated product formation. However, it was not the case, and the dialkylated product was obtained with the same yield at −40 and −60 °C (Table 1, entries 2 and 3). The increase in the amount of pyrrole had a beneficial effect on the suppression of dimer formation albeit at the expense of enantioselectivity of the product (Table 1, entries 4−6). To optimize the reaction conditions, various Lewis

(9) Yokoyama, N.; Arai, T. *Chem. Commun.* **2009**, 3285.

(10) (a) Bonini, B. F.; Capitò, E.; Comes-Franchini, M.; Fochi, M.; Ricci, A.; Zwanenburg, B. *Tetrahedron: Asymmetry* **2006**, *17*, 3135. (b) Hong, L.; Liu, C.; Sun, W.; Wang, L.; Wong, K.; Wang, R. *Org. Lett.* **2009**, *11*, 2177.

(11) (a) DattaGupta, A.; Bhuniya, D.; Singh, V. K. *Tetrahedron* **1994**, *50*, 13725. (b) DattaGupta, A.; Singh, V. K. *Tetrahedron Lett.* **1996**, *37*, 2633. (c) Sekar, G.; DattaGupta, A.; Singh, V. K. *J. Org. Chem.* **1998**, *63*, 2961. (d) Lu, J.; Ji, S.-J.; Teo, Y.-C.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 159. (e) Lu, J.; Ji, S.-J.; Loh, T.-P. *Chem. Commun.* **2005**, 2345. (f) Lu, J.; Hong, M.-L.; Ji, S.-J.; Teo, Y.-C.; Loh, T.-P. *Chem. Commun.* **2005**, 4217. (g) Lu, J.; Ji, S.-J.; Teo, Y.-C.; Loh, T.-P. *Tetrahedron Lett.* **2005**, *46*, 7435. (h) Ginotra, S. K.; Singh, V. K. *Tetrahedron* **2006**, *62*, 3573. (i) Ginotra, S. K.; Singh, V. K. *Org. Biomol. Chem.* **2006**, *4*, 4370. (j) Bisai, A.; Singh, V. K. *Org. Lett.* **2006**, *8*, 2405. (k) Chen, W.-Y.; Li, X.-S. *Lett. Org. Chem.* **2007**, *4*, 398. (l) Dodda, R.; Zhao, C.-G. *Tetrahedron Lett.* **2007**, *48*, 4339. (m) Singh, P. K.; Singh, V. K. *Org. Lett.* **2008**, *10*, 4121.

Table 1. Enantioselective Friedel−Crafts Alkylation of Pyrrole with Benzylidene-2-acetylpyridine *N*-Oxide Catalyzed by **1a**-Cu(OTf)$_2$

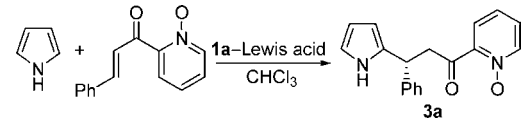


				yield (%)[a]		
entry	pyrrole (equiv)	temp (°C)	time	**3a**	4	ee **3a** (%)[b]
1	1.5	−20	15 min	48	46	95
2	1.5	−40	30 min	65	42	96
3	1.5	−60	3 h	42	40[c]	96
4	5	−60	2 h	69	17	93
5	10	−60	2 h	75	12	85
6	20	−60	2 h	90		85

[a] Isolated yields. [b] Determined by chiral HPLC, using a chiralcel OD-H column (see the Supporting Information). [c] Dimer consisted of a 77:23 mixture of C2-symmetric (>99% ee):meso isomer.

acids, solvents, and chiral ligands were screened. To our delight, a change in metal salt to Zn(OTf)$_2$ furnished the product in 96% enantioselectivity and 85% yield at −20 °C (Table 2, entry 1). Lowering the temperature to −60 °C

Table 2. Screening of Lewis Acids for Enantioselective Friedel−Crafts Alkylation of Pyrrole[a]



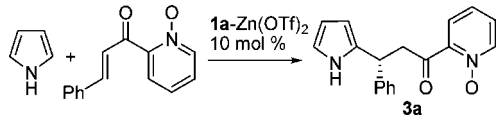
entry	Lewis acid	catalyst (mol %)	temp (°C)	time	yield[b] (%)	ee[c] (%)
1	$Zn(OTf)_2$	10	−20	30 min	85	96
2	$Zn(OTf)_2$	10	−40	1.5 h	84	98
3	$Zn(OTf)_2$	10	−60	9 h	95	>99
4	$Zn(OTf)_2$	5	−60	24 h	59	99
5	$Zn(OTf)_2$	2	−60	4 d	59	85
6	$Cu(ClO_4)_2{\cdot}6H_2O$	10	−60	30 min	51	96
7	$Cu(BF_4)_2{\cdot}xH_2O$	10	−60	30 min	67	95
8	$(CuOTf)_2{\cdot}PhCH_3$	10	−60	2.5 h	89	95
9	$(CuOTf)_2{\cdot}PhH$	10	−60	1 h	86	94
10	$Cu(MeCN)_4{\cdot}PF_6$	10	−20	60 h	46	51
11	$Sc(OTf)_3$	10	−60	3 h	38	0
12	$In(OTf)_3$	10	−60	30 min	34	6
13	$Yb(OTf)_3$	10	−60	30 min	38	37
14	$Sn(OTf)_2$	10	−60	2 h	29	2

[a] 1.5 equiv of pyrrole was used. [b] Isolated yields. [c] Determined by chiral HPLC, using a chiralcel OD-H column (see the Supporting Information).

improved the enantioselectivity to >99% and yield to 95% (Table 2, entry 3). Lowering the catalyst loading to 5 mol %

gave the product with the same enantioselectivity but reduced the reaction rate and yield of the product. So, the 10 mol % catalyst loading and temperature of −60 °C were selected, and various Lewis acids were screened. Cu(II) salt gave good enantioselectivity, but the yield of product was low because of the formation of dialkylated product (Table 2, entries 6 and 7). However, CuOTf gave good yields (86−89%, Table 2, entries 8 and 9). With other tested Lewis acids, the reaction was fast but yields and enantioselectivities were poor (Table 2, entries 11−14). From the results of Table 2, ligand **1a**-$Zn(OTf)_2$ was selected, and several solvents were evaluated. The reaction was sensitive to solvents as shown in Table 3.

Table 3. Effect of Solvents on Enantioselective Friedel−Crafts Alkylation of Pyrrole[a]



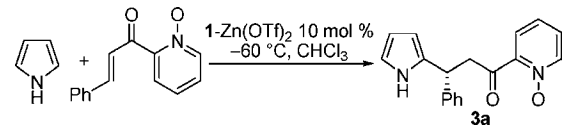
entry	solvent	temp (°C)	time	yield (%)[b]	ee (%)[c]
1	$CHCl_3$	−60	9 h	95	>99
2	CH_2Cl_2	−60	9 h	77	97
3	THF	−60	3 d	nr	nr
4	THF	−20	10 h	56	97
5	CH_3CN	−60	3 d	nr	nr
6	CH_3CN	−20	6 h	72	48
7	toluene	−60	3 d	nr	nr

[a] 1.5 equivalent pyrrole was used. [b] Isolated yields. [c] Determined by chiral HPLC using a chiralcel OD-H column (see the Supporting Information). nr = no reaction.

Chloroform was optimal in terms of both enantioselectivity and yield (Table 3, entry 1). Apart from chloroform, dichloromethane gave comperable enanantioselectivity (Table 3, entry 2). There was no reaction in THF at −60 °C. However, by increasing the temperature to −20 °C, the product was obtained in 56% yield and 97% enantiomeric excess (Table 3, entries 3 and 4). Not unexpectedly, the use of strong coordinating solvent (acetonitrile) has a detrimental effect on the asymmetric induction (Table 3, entries 5 and 6). To further investigate the reaction, various ligands were screened. Pybox-diph ligands with different substituents at the chiral center (**1a**−**g**) were used in the above reaction as shown in Table 4. It was observed that ip-pybox-diph (**1a**) gave the best results (Table 4, entry 1). The other ligands such as tb-pybox-diph (**1b**) and sb-pybox-diph (**1d**) gave comperable enantioselectivity (Table 4, entries 2 and 4). Poor enantioselectivity (5%) with **1h** indicated the importance of pyridine nitrogen in chelation with Zn(II) (Table 4, entry 8). Ligand **1k** gave the product with 79% ee (Table 4, entry 11), which clearly indicated the importance of *gem*-diphenyl substitutions at C5 of the oxazoline rings.

(12) (a) Barroso, S.; Blay, G.; Pedro, J. R. *Org. Lett.* **2007**, *9*, 1983. (b) Barroso, S.; Blay, G.; Muñoz, M. C.; Pedro, J. R. *Adv. Synth. Catal.* **2009**, *351*, 107.

Table 4. Friedel−Crafts Alkylation of Pyrrole with Benzylidene-2-acetylpyridine *N*-Oxide Catalyzed by Various Catalysts[a]

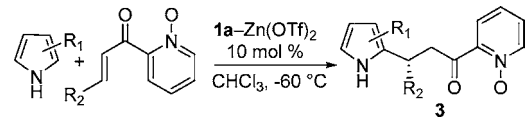


entry	ligand	time	yield (%)[b]	ee (%)[c]
1	**1a**	9 h	95	>99
2	**1b**	3 h	75	96
3	**1c**	24 h	82	44
4	**1d**	3 h	92	98
5	**1e**	5 d	61	78
6	**1f**	24 h	69	7
7	**1g**	36 h	72	74
8	**1h**	3 d	31	5
9	**1i**	24 h	75	92
10	**1j**	24 h	67	95
11	**1k**	40 h	79	79

[a] 1.5 equiv of pyrrole was used. [b] Isolated yields. [c] Determined by chiral HPLC, using a chiralcel OD-H column (see the Supporting Information).

After optimization of reaction conditions, the generality of the F−C reaction was explored. First substitution on the pyrrole ring was studied (Table 5, entries 1−3). *N*-Substitution of pyrrole reduced the reaction rate. In the case of *N*-methylpyrrole, the reaction took 3 days to complete at −30 °C with 95% enantioselectivity. However, a substituted pyrrole gave excellent enantioselectivity (>99%; Table 5,

Table 5. Enantioselective Friedel−Crafts Alkylation of Pyrroles with Various 2-Enoylpyridine *N*-Oxides[a]



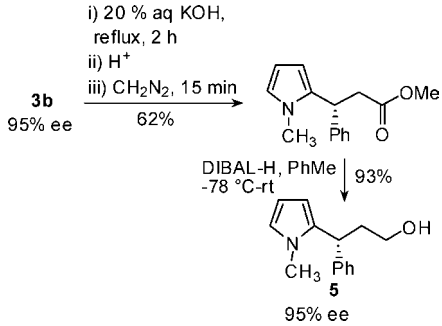
entry	R_1	R_2	**3**	time	yield (%)[b]	ee (%)[c]
1	H	Ph	**3a**	9 h	95	>99
2	1-Me	Ph	**3b**	3 d	87	95[d]
3	2,4-diMe,3-Ac	Ph	**3c**	20 h	97	>99
4	H	4-FC_6H_4	**3d**	3 h	90	98
5	H	4-$MeOC_6H_4$	**3e**	18 h	54	99
6	H	4-$NO_2C_6H_4$	**3f**	3 h	96	85
7	H	3-$NO_2C_6H_4$	**3g**	3 h	99	98
8	H	2-$NO_2C_6H_4$	**3h**	5 h	98	97
9	H	4-ClC_6H_4	**3i**	3 h	86	>99
10	H	3-ClC_6H_4	**3j**	5 h	96	98
11	H	2-ClC_6H_4	**3k**	5 h	88	98
12	H	1-naphthyl	***3l***	9 h	71	99
13	H	2-furyl	**3m**	18 h	82	95
14	H	cyclohexyl	**3n**	12 h	76	94
15	H	n-pentyl	**3o**	5 h	74	95

[a] 1.5 equiv of pyrrole was used. [b] Isolated yields. [c] Determined by chiral HPLC, using a chiral column (see the Supporting Information. [d] Reaction was carried out at −30 °C.

entry 3). The reaction was then extended to different β-substituted 2-enoylpyridine *N*-oxides (Table 5, entries 4−15). Aromatic substituted substrates gave excellent enantioselectivity, regardless of the electron density of the aromatic ring. Even substrates having an electron-donating group on the phenyl ring gave excellent enantioselectivity, although the reaction rate was slow (Table 5, entry 5).

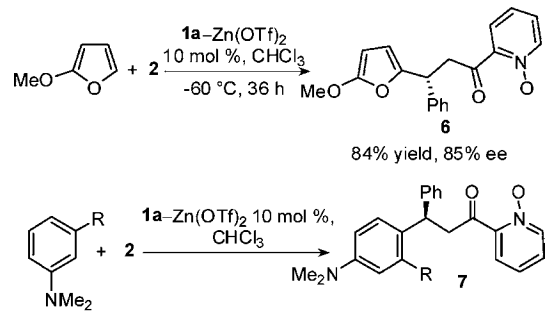
In the case of aliphatic substituted substrates, the catalyst system was efficient, and good enantioselectivity was obtained (Table 5, entries 14 and 15). The absolute stereochemistry in the reaction was determined by converting the product **3b** into a known compound **5**.[4] The pyridine *N*-oxide ring of **3b** was cleaved with 20% aq KOH to give the corresponding acid. The acid was esterified and reduced with DIBAL-H to give an alcohol **5** without any loss in enantioselectivity (Scheme 1). We have also evaluated the ip-pybox-diph-Zn(II) complex in enantioselective F−C alkylation of 2-methoxyfuran where the product was obtained in 85% ee. Our catalytic system was also extended to simple benzene derivatives, and to our delight, chiral F−C alkylated benzene derivatives were obtained in 93% ee (Scheme 2). The absolute stereochemistry of **6** and **7** is not known. However, we assume that the major isomer would have the same absolute stereochemistry as that observed with pyrrole F−C alkylation product **3**.

Scheme 1. Determination of Absolute Stereochemistry



In conclusion, we have developed an efficient method for highly enantioselective Friedel−Crafts alkylation of pyrrole with 2-enoylpyridine *N*-oxides utilizing the ip-pybox-diph-Zn(II) complex. Our catalytic system offers substantial substrate scope and excellent enantioselectivities were obtained in all cases. Even trisubstituted pyrrole underwent Friedel−Crafts alkylation with excellent enantioselectivity. Furthermore, the pyridine *N*-oxide ring of the product was cleaved to give the corresponding acid, allowing further transformations. The method also works well with 2-methoxyfuran and benzene derivatives. Further studies to extend the method to various phenols and related Friedel−Crafts reaction are underway.

Scheme 2. Enantioselective Friedel−Crafts Alkylation Catalyzed by Chiral ip-pybox-diph -Zn (II) Complex



R	7	temp (°C)	time	yield (%)	ee (%)
H	**7a**	10	7 d	87	93
OMe	**7b**	-30	3 d	88	93

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Supporting Information Available: General experimental procedures and full characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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