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Enantioselective Friedel–Crafts alkylation of indoles with nitroalkenes catalyzed by a bis(oxazoline)–Cu(II) complex

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Abstract—The catalytic enantioselective Friedel–Crafts reaction of indole with *trans*-β-nitrostyrene is reported in the presence of copper triflate–bisoxazoline complexes. The reaction furnished nitroalkylated indoles in excellent yields (up to 95%) and high enantioselectivities up to an 86% ee.

The Friedel–Crafts (F–C) alkylation is an extremely efficient reaction in synthetic organic chemistry for the formation of new C–C bonds.[1] While Casiraghi described the first asymmetric Friedel–Crafts reaction,[2] the first example of a catalytic enantioselective F–C reaction was reported by Erker and van der Zeijden.[3] In the last few years, a variety of chiral Lewis acid catalysts have been used for this reaction.[4,5] The addition of indole to nitroalkenes[6] has typically been used as a test reaction to explore the feasibility of new catalyst systems. We earlier reported the synthesis and application of the copper complexes of chiral pyridine bis(diphenyloxazoline) **1** (Fig. 1) in the enantioselective allylic oxidation of olefins,[7] cyclopropanations[8] and propargylation of imines.[9] Thus, it occurred to us to evaluate these types of ligands for enantioselective F–C alkylation and report our results herein.

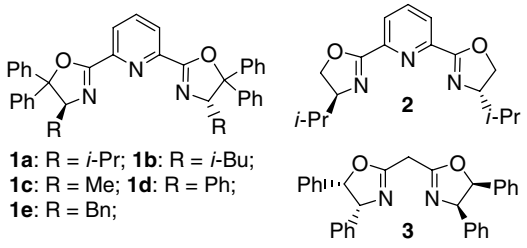
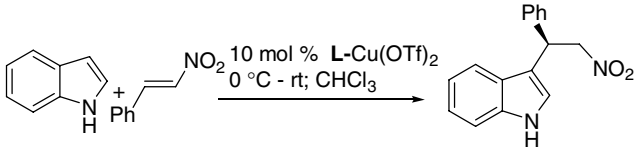


Figure 1. Examples of chiral ligands.

At the outset, the Cu(II) complexes of chiral ligands **1a–e** (10 mol %) were used for the addition of indole to *trans*-β-nitrostyrene in chloroform (Table 1). We achieved a maximum of 51% ee in this reaction with ligand **1e**. Although ees were poor to modest, it was satisfying that these ligands were working as catalysts as no product was obtained with the Zn complex of the original pybox ligand **2**.[4a] Since in our earlier study we had obtained excellent ee's in the enantioselective carbonylene reaction with ligand **3**,[10] we investigated its use in the enantioselective F–C reaction. The desired product was obtained in a 79% yield and an 81% ee (Table 1, entry 6). Among the Lewis acids used, $Cu(OTf)_2$ gave the best result in terms of enantioselectivity (Table 2). Using

Table 1. Enantioselective Friedel–Crafts reaction of indole with *trans*-β-nitrostyrene in the presence of different ligands



Entry	L	Time (h)	Yield[a] (%)	ee[b] (%)
1	**1a**	24	61	20
2	**1b**	24	62	7
3	**1c**	24	76	33
4	**1d**	24	53	1
5	**1e**	24	70	51
6	**3**	12	79	81

[a] Isolated yield.
[b] Determined by HPLC using a Chiralcel OD-H column.

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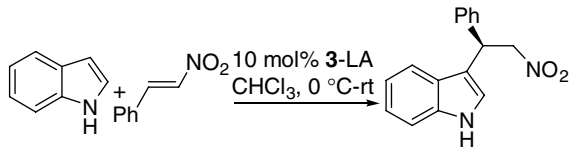
Table 2. Effect of Lewis acids



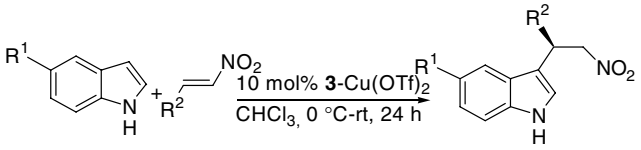
Entry	Lewis acid	Time (h)	Yield[a] (%)	ee[b] (%)
1	$Cu(OTf)_2$	12	79	81
2	$Zn(OTf)_2$	12	95	71
3	$Cu(CH_3CN)_4PF_6$	48	64	31
4	$(CuOTf)_2{\cdot}PhCH_3$	60	55	22
5	$In(OTf)_3$	48	68	5
6	$Yb(OTf)_3{\cdot}H_2O$	24	86	3
7	$Sc(OTf)_3$	36	73	0

[a] Isolated yield.
[b] Determined by HPLC using a Chiralcel OD-H column.

the Cu(II) complex of ligand **3**, the reaction was studied in different solvents, and based on the enantioselectivity given in brackets, chloroform was the best; $CHCl_3$ (81% ee), CH_2Cl_2 (67% ee), THF (10% ee), MeCN (nil), toluene (77% ee), Et_2O (46% ee), acetone (42% ee), *n*-hexane (21% ee), CCl_4 (63% ee).

In order to extend the scope of the reaction, different indoles were reacted with various β-nitroalkenes using the Cu(II) complex of chiral ligand **3** under the optimized

Table 3. Enantioselective Friedel–Crafts alkylation of various indoles with nitroolefins



Entry	R^1	R^2	Yield[a] (%)	ee[b] (%)
1	H	Ph	79	81
2	F	Ph	69	80
3	Cl	Ph	77	82
4	Br	Ph	62	82
5	OMe	Ph	58	79
6	CN	Ph	25	5[c]
7	H	4-Br–C_6H_4	77	78
8	F	4-Br–C_6H_4	59	83
9	Cl	4-Br–C_6H_4	89	83
10	Br	4-Br–C_6H_4	72	86
11	OMe	4-Br–C_6H_4	79	68
12	H	4-F–C_6H_4	67	76
13	F	4-F–C_6H_4	84	77
14	Cl	4-F–C_6H_4	75	81
15	Br	4-F–C_6H_4	58	86
16	OMe	4-F–C_6H_4	62	78
17	H	4-MeO–C_6H_4	80	72
18	F	4-MeO–C_6H_4	80	77
19	Cl	4-MeO–C_6H_4	78	75
20	Br	4-MeO–C_6H_4	58	79
21	OMe	4-MeO–C_6H_4	80	72
22	H	2-MeO–C_6H_4	35	69
23	F	2-MeO–C_6H_4	49	57
24	Cl	2-MeO–C_6H_4	68	70
25	Br	2-MeO–C_6H_4	44	74
26	OMe	2-MeO–C_6H_4	48	50
27	H	2-Cl–C_6H_4	94	73
28	F	2-Cl–C_6H_4	68	74
29	Cl	2-Cl–C_6H_4	68	78
30	Br	2-Cl–C_6H_4	41	78
31	OMe	2-Cl–C_6H_4	68	59
32	H	4-Cl–C_6H_4	73	75
33	Br	4-Cl–C_6H_4	50	79
34	H	4-^{i}Pr–C_6H_4	53	66
35	Br	4-^{i}Pr–C_6H_4	40	85
36	H	3-F–C_6H_4	80	75
37	Br	3-F–C_6H_4	59	84
38	H	4-CF_3O–C_6H_4	80	79
39	Br	4-CF_3O–C_6H_4	51	72
40	H	2-Furyl	56	68
41	Br	2-Furyl	68	73
42	H	2-Thienyl	77	72
43	Br	2-Thienyl	64	81

[a] Isolated yield.
[b] Determined by HPLC using a Chiralcel OD-H column or a Chiralpak AD-H column.
[c] Reaction time was 15 days.

reaction conditions (Table 3). The enantioselectivity in all the cases appeared consistent, the highest being 86% ee (entries 10 and 15).

In conclusion, chiral Cu(II)-**3** complex prepared from $Cu(OTf)_2$ and the C_2-symmetric box ligand **3** was found to be an effective catalyst for the enantioselective Friedel–Crafts reaction of indoles with nitroalkenes. The reaction can furnish a variety of nitroalkylated indoles in good to excellent yields (up to 95%) with high enantioselectivities (up to 86% ee).

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