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Enantioselective Friedel–Crafts Alkylation of Indoles with Nitroalkenes Catalyzed by Bifunctional Tridentate Bis(oxazoline)–Zn(II) Complex

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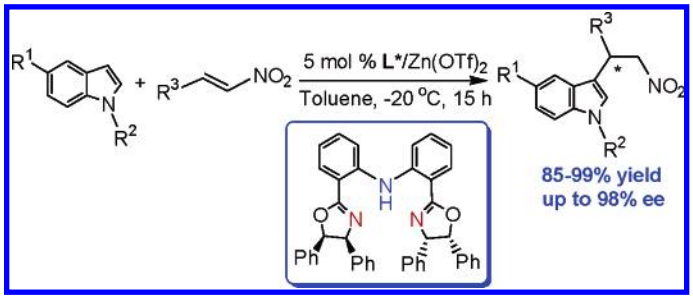
ABSTRACT



A more practical and efficient catalytic asymmetric Friedel–Crafts alkylation of indoles with nitroalkenes using bifunctional tridentate bis(oxazoline)–Zn(OTf)$_2$ as catalyst has been developed. Various types of the nitroalkylated indoles were obtained in excellent yields (85–99%) and high enantioselectivities (up to 98% ee).

The Friedel−Crafts reaction is one of the most powerful carbon−carbon bond-forming reactions in synthetic organic chemistry.[1] Recently, using nitroalkenes as substrates to achieve asymmetric Friedel−Crafts alkylation of indoles has been paid considerable attention.[2] It is the result of chemists' effort to develop new types of substrates for the enantioselective version of the Friedel−Crafts reaction,[3] which has suffered from significant restrictions that α,β-unsaturated carbonyl compounds were overwhelmingly investigated.[4] In addition, nitroalkenes are very active Michael acceptors,[5] and the easy transformation of the nitro group into a range of different functionalities[6] makes this methodology more attractive. In fact, the products of alkylations of indoles with nitroalkenes can be applied to the synthesis of many biologically active compounds such as physostigmine,[7] which serves as a useful clinical anticholinergic drug.[8]

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However, the enantioselective Friedel−Crafts alkylation of indoles with nitroalkenes needs to undergo continuous development. In these pioneer reports, relatively high catalyst loading was used[2a,c,d] and long reaction time was needed.[2a,b] Surprisingly, N-alkylated indole gave the product in dramatically decreased enantioselectivity versus the free indole,[2a,c] whereas in another case the result was the opposite.[2b] Normally, alkyl substituents at the β-position of the nitroalkene obtained lower enantioselectivity than aryl-substituted analogues. Herein, we present our new results of using bifunctional tridentate bis(oxazoline)−$Zn(OTf)_2$ complex to catalyze enantioselective Friedel−Crafts alkylation of indoles with nitroalkenes.

We have recently reported the preparation of a series of chiral C_2-symmetric tridentate bis(oxazoline) **1** and bis(thiazoline) **2**,[9] in which a diphenylamine unit links the two chiral oxazoline or thiazoline rings (Figure 1). The simply

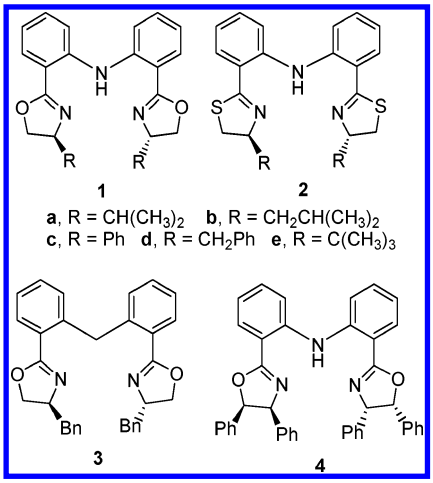
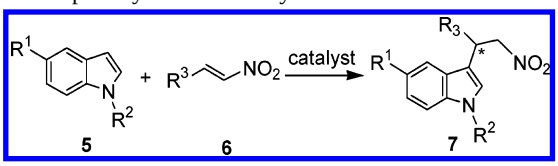


Figure 1. C_2-Symmetric bis(oxazoline) and bis(thiazoline) ligands.

synthetic approach of bis(oxazoline) **1** is directly employing 2,2′-dicarboxyl diphenylamine, unlike a palladium-catalyzed aryl amination coupling reported by Guiry.[10] Meanwhile, our laboratory has demonstrated that a dinuclear Lewis acid complex of tridentate bis(oxazoline) **1** and bis(thiazoline) **2** can catalyze the asymmetric Henry reaction of nitromethane with α-keto esters.[11] C_2-symmetric bis(oxazoline) ligand **3**, in which the NH group was replaced by a methylene group, has also been synthesized to elucidate the crucial role of the NH group in ligands **1** and **2**.[11] For the asymmetric Friedel−Crafts alkylation of indoles **5** with nitroalkenes **6** (Scheme 1), we assumed that ligands **1** and **2** with Lewis acid could

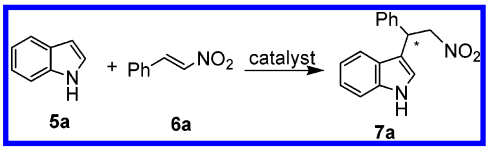
Scheme 1. Alkylation of Indole **5** with Nitroalkene **6** To Give Optically Active 3-Alkyl Indole Derivatives **7**



catalyze the reaction in a bifunctional way. On one hand, the chelated Lewis acid could activate nitroalkenes; on the other hand, the NH group in ligands **1** and **2** could interact with indoles and orient them in the intermediate. Then we performed the alkylation of indole with *trans*-β-nitrostyrene in toluene at room temperature using 10 mol % **1d**−$Zn(OTf)_2$ or **3**−$Zn(OTf)_2$ as the catalyst, respectively. Interestingly, the catalyst **1d**−$Zn(OTf)_2$ furnished overwhelmingly better result than the latter in enantioselectivity (66% vs 6% ee), while both gave nearly quantitive yield.

To further investigate the reaction conditions, ligand **1c** was first chosen to explore Lewis acids under 10 mol % catalyst loading, and the results are summarized in Table 1.

Table 1. Asymmetric Friedel−Crafts Alkylation of Indole **5a** with *trans*-β-Nitrostyrene **6a** Catalyzed by Chiral **1c**−Lewis Acid Complex[a]



entry	Lewis acid	time (h)	yield[b] (%)	ee[c] (%)
1	$Zn(OTf)_2$	13	99	85 (*R*)[d]
2	$Yb(OTf)_3$	42	51	4
3	$In(OTf)_3$	48	60	0
4	$Sc(OTf)_3$	48	59	2
5	$La(OTf)_3$	25	73	0
6	$Cu(OAc)_2$	122	53	1
7	$InBr_3$	122	64	0
8	$NiCl_2$	116	87	53
9[e]	$Zn(OTf)_2$	8	99	83 (*R*)[d]

[a] Reaction conditions: indole **5a** (0.50 mmol) with *trans*-β-nitrostyrene **6a** (0.50 mmol) in 2 mL of toluene under 10 mol % **1c**−Lewis acid complex. [b] Isolated yield by column chromatography. [c] Determined by HPLC on Daicel Chiracel OD-H column (hexane/2-propanol 70:30, 0.9 mL/min).[d] The absolute configurations of the products were assigned by comparison with literature values.[2c] [e] 5 mol % catalyst loading.

Except for $Zn(OTf)_2$ and $NiCl_2$, other Lewis acids gave nearly no enantioselectivity. With $Zn(OTf)_2$ as Lewis acid, both high yield and enantioselectivity were achieved (Table 1, entry 1). When the catalyst loading was reduced from 10 to 5 mol %, the enantioselectivity decreased slightly (Table 1, entry 9).

A series of chiral bis(oxazoline) and bis(thiazoline) ligands were subsequently investigated in the reaction under 5 mol % catalyst loading with $Zn(OTf)_2$ as the Lewis acid (Table

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Table 2. Effect of Ligands in the $Zn(OTf)_2$-Catalyzed Friedel−Crafts Alkylatin of Indole **5a** with *trans*-β-Nitrostyrene **6a**[a]

entry	ligand	yield[b] (%)	ee[c] (%)
1	**1a**	94	30
2	**1b**	85	71
3	**1c**	99	83
4	**1d**	99	66
5	**1e**	95	68
6	**2a**	93	11
7	**2b**	95	46
8	**2c**	99	78
9	**2d**	99	59
10	**2e**	87	2
11	**4**	99	90

[a] Reaction conditions: indole **5a** (0.50 mmol) with *trans*-β-nitrostyrene **6a** (0.50 mmol) in 2 mL of toluene under 5 mol % ligand−$Zn(OTf)_2$ complex. [b] Isolated yield by column chromatography. [c] Determined by HPLC on Daicel Chiracel OD-H column (hexane/2-propanol =70:30, 0.9 mL/min).

2). The bis(oxazoline) ligands **1** (entries 1−5) gave better enantioselectivities than their analogues bis(thiazoline) **2** (entries 6−10). The ligands **1c** and **2c**, which have phenyl substituents on their hetereocycles, gave the best results (entries 3 and 8). Apparently, the phenyl groups on the hetereocycles are critical for obtaining high enantioselectivity. Thus we further synthesized bis(oxazoline) ligand **4**,[12] which has *cis*-phenyl groups at both the 4- and 5-positions of oxazoline rings, and carried out the reaction with **4**−$Zn(OTf)_2$ complex as the catalyst. To our delight, the enantiomeric excess of the product was dramatically enhanced to 90% (entry 11).

To get the most optimized reaction conditions, we further screened different solvents, temperature, and catalyst loading. Some typical results are presented in Table 3. First, a number of solvents were successfully applied to the catalytic enantioselective Friedel−Crafts reaction (entries 1−5). Toluene

Table 3. Further Optimization of Reaction Conditions for the Friedel−Crafts Alkylation of Indole **5a** with *trans*-β-Nitrostyrene **6a**[a]

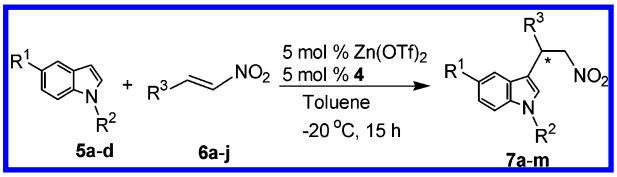
entry	solvent	T (°C)	catalyst (mol %)	yield[b] (%)	ee[c] (%)
1	toluene	10	5	99	90
2	CH_2Cl_2	10	5	91	67
3	$ClCH_2CH_2Cl$	10	5	90	69
4	THF	10	5	67	16
5	hexane	10	5	94	30
6	toluene	0	5	99	93
7	toluene	−20	5	99	94
8	toluene	−20	20	99	95
9	toluene	−20	10	99	94
10	toluene	−20	2	95	92
11	toluene	−20	1	94	90

[a] Reaction conditions: indole **5a** (0.50 mmol) with *trans*-β-nitrostyrene **6a** (0.50 mmol) in 2 mL of toluene using ligand−$Zn(OTf)_2$ complex as the catalyst. [b] Isolated yield by column chromatography. [c] Determined by HPLC on Daicel Chiracel OD-H column (hexane/2-propanol 70:30, 0.9 mL/min).

was the best choice (entry 1). Using alkyl halides as the solvent gave **7a** in high yield with moderate enantioselectivity (entries 2 and 3). Etheral solvents such as THF had a negative influence on the catalytic activity of the catalyst (entry 4). The use of a nonpolar solvent such as hexane produced **7a** in high yield with low enantioselectivity (entry 5). Then we were pleased to find that cooling the reaction led to a slight improvement in the enantioselectivity (entries 6 and 7). When the reaction was performed at −20 °C, **7a** was obtained in 94% ee (entry 7). Enhancement of the catalyst loading improved the enantioselectivity only very slightly (entries 8 and 9), while satisfactory yield and enantioselectivity was obtained even using only 2 or 1 mol % catalyst (entries 10 and 11). Finally, we determined that using 5 mol % **4**−$Zn(OTf)_2$ in toluene at −20 °C to catalyze the reaction was the most practical.

The scope of the enantioselective Friedel−Crafts alkylation of indoles with nitroalkenes under the optimized reaction conditions was explored, and the results are summarized in Table 4. We first tested a few indoles **5a**−**d** bearing different

Table 4. Friedel−Crafts Alkylation of Indoles **5** with Nitroalkene **6** Catalyzed by **4**−$Zn(OTf)_2$ Complex[a]



entry	indole	R^1	R^2	nitroalkene	R^3	product	yield[b] (%)	ee[c] (%)
1	**5a**	H	H	**6a**	Ph	**7a**	99	94 (*R*)[d]
2	**5b**	MeO	H	**6a**	Ph	**7b**	96	98
3	**5c**	Cl	H	**6a**	Ph	**7c**	88	81
4	**5d**	H	Me	**6a**	Ph	**7d**	93	90 (*R*)[d]
5	**5a**	H	H	**6b**	2-MeO-Ph	**7e**	99	77
6	**5a**	H	H	**6c**	2-Cl-Ph	**7f**	99	73
7	**5a**	H	H	**6d**	2-naphthyl	**7g**	99	89
8	**5a**	H	H	**6e**	2-furyl	**7h**	85	81
9	**5a**	H	H	**6f**	$CH_3(CH_2)_2$	**7i**	91	92
10	**5a**	H	H	**6g**	$CH_3(CH_2)_8$	**7j**	91	89
11	**5a**	H	H	**6h**	$Ph(CH_2)_2$	**7k**	88	93
12	**5a**	H	H	**6i**	cyclohexyl	**7l**	92	84
13	**5a**	H	H	**6j**[e]	$(CH_3)_3C$	**7m**	85	87

[a] Reaction conditions: indole **5** (0.50 mmol) with nitroalkene **6** (0.50 mmol) in 2 mL of toluene using 5 mol % **4**−$Zn(OTf)_2$ complex as the catalyst at −20 °C for 15 h. [b] Isolated yield by column chromatography. [c] Determined by HPLC. [d] Determined to be *R* by comparison of optical rotation with that in ref 2c. [e] The reaction was carried out at 30 °C for 144 h.

substituents in the reaction with *trans*-β-nitrostyrene **6a** catalyzed by 5 mol % **4**−$Zn(OTf)_2$. The Friedel−Crafts alkylation of indole **5a** proceeded very smoothly at −20 °C to furnish the product **7a** in nearly quantitive yield with excellent enantioselectivity (entry 1). When electron-rich 5-methoxyindole **5b** was used, the enantiomeric excess of

(12) For the synthesis of ligand **4**, see Supporting Information.

the product **7b** was up to 98% (entry 2). An electron-withdrawing substituent such as chlorine in the 5-position of the indole ring in **5c** caused moderate decrease in both yield and enantioselectivity (entry 3). When we introduced a methyl substituent to the indolic nitrogen atom, to our delight, the reaction proceeded very well, giving the corresponding derivatives **7d** in high yield and enantioselectivity (entry 4). The enantioselectivity was enhanced by 40% compared with previous reports.[2]

The generality of the reaction was further demonstrated by variation of the nitroalkene partner. Aromatic-, heteroaromatic-, and aliphatic-substituted nitroalkenes all reacted well with indole to afford alkylated indoles in excellent yields and high enantioselectivities (entries 5−12). The *ortho*-substitution on the phenyl in nitrostyrene, either electrodonating or electron-withdrawing groups, lowered the enantiomeric excess of products, perhaps due to the steric effect of *ortho*-substituents (entries 5 and 6). Naphthyl- and heteroaryl-substituted nitroalkenes **6d** and **6e** could also react smoothly, affording the corresponding products **7g** and **7h** in good yields and enantioselectivities (entries 7 and 8). Interestingly, the reaction could be easily extended to aliphatic nitroalkenes while neither the reaction rate nor the enantioselectivity suffered (entries 9−12). When unbranched alkyl substituents were investigated, the number of the carbon atoms of the chain had little effect on the reaction (entries 9 and 10). A terminal phenyl substituent on the alkyl chain enhanced the enantioselectivity slightly in our experiment (entry 11). The alkylation of indole **5a** with the more hindered cyclohexyl-substituted nitroalkene **6i** could occur smoothly in high enantioselectivity (entry 12). Even the very bulky *tert*-butyl-substituted nitroalkene **6j** could react with indole in good yield and enantioselectivity, although the reaction needed to be performed at 30 °C for 144 h (entry 13).

By comparison of ligands **3** and **1** in the $Zn(OTf)_2$-catalyzed alkylation of indole with *trans*-β-nitrostyrene, we assumed that the NH group in ligands **1**, **2**, and **4** is crucial.[11] When we mixed the ligand with $Zn(OTf)_2$ in toluene, the mixture became clear in 0.5 h. We supposed that the tridentate ligand and $Zn(OTf)_2$ formed a 1:1 complex. This complex could activate the nitroalkene through the coordination of the nitro group to the Lewis acid center.[2c] We envisioned that the **4**−$Zn(OTf)_2$ complex would act in a bifunctional fashion (Figure 2). The NH group between the two phenyl groups in the ligand could act as a donor for the NH···π (indole) interaction,[13] which would direct the indole to attack the nitroalkene preferably from *si* face as depicted in Figure 2. Thus, we obtained the product with *R* configuration excessively, and even with N-protected indole the enantioselectivity was kept at a high level.

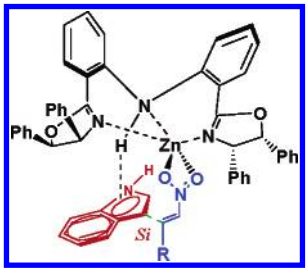


Figure 2. Possible bifunctional mode in transition state of the catalyst **4**−$Zn(OTf)_2$.

In conclusion, we have developed a more practical catalytic asymmetric Friedel−Crafts alkylation of indoles **5** with a variety of nitroalkenes **6** using tridentate bis(oxazoline) **4**−$Zn(OTf)_2$ complex as catalyst, which can activate nitroalkenes and orient indoles effectively at the same time. Various types of the nitroalkylated indoles were obtained in excellent yields and high enantioselectivities (up to 98% ee). These chiral tridentate ligands **1**, **2**, and **4** contaning a diphenylamine unit would have further applications in other Lewis acid catalyzed asymmetric transformations. Studies are in progress in our laboratory.

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Supporting Information Available: Experimental procedures and characterization, copies of ^{1}H NMR and ^{13}C NMR of new compounds, and HPLC profiles. This material is available free of charge via the Internet at http://pubs.acs.org.

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