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A New Type of Bis(sulfonamide)-Diamine Ligand for a $Cu(OTf)_2$-Catalyzed Asymmetric Friedel–Crafts Alkylation Reaction of Indoles with Nitroalkenes

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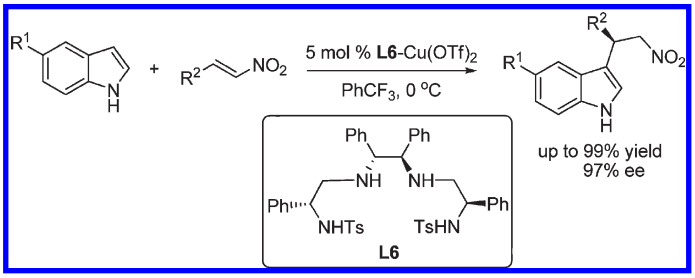
ABSTRACT



Chiral bis(sulfonamide)-diamine served as new type of ligand for a $Cu(OTf)_2$-catalyzed asymmetric Friedel–Crafts alkylation reaction of indoles with nitroalkenes. The desired products were obtained with up to 99% yield and 97% ee.

Indole derivatives are always considered to be attractive synthetic targets due to their prevalence in numerous natural products and pharmaceutical lead compounds.[1] Meanwhile, the catalytic asymmetric Friedel–Crafts alkylation reaction[2] opens up access to construct a new C–C bond directly on indoles with a new stereogenic center. In addition, nitroalkenes as active Michael acceptors have drawn considerable attention due to their versatility in further transformations. Over the past few years, significant efforts have been made for this asymmetric reaction and several successful catalytic systems have been developed including hydrogen-bond-based organocatalysts[3] and metal catalysts.[4–6] The organocatalysts were symbolized by chiral thioureas[3a–e] and chiral phosphoric acid,[3f] while the metals used for metal catalysts were mainly focused on Al,[4] Cu,[5] and Zn.[6] Efficient metal catalytic systems for this transformation were very rare. Impressive studies were reported by Du and Wang. Du[6b,h] developed bisoxazolines and bisimidazolines–$Zn(OTf)_2$ systems, affording high yields and enantioselectivities except in the case of

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nitroalkene substrates with *ortho* substituents on the phenyl group. It is worthy to note that these systems were also effective for aliphatic nitroalkenes and *N*-methyl indole. Recently, Wang[6g] noted that a Schiff base and piperidine performed as a combinational catalyst for aromatic nitroalkenes, including *ortho*-substituted substrates. Electron-rich *ortho*-substituted aromatic nitroalkenes gave the products in slightly better ee. However, we found that the ligands employed therein were limited to the ligands containing an oxazoline, an imidazoline, or a Schiff base. Thus, it is still highly desirable to explore efficient alternative ligands for metal catalysts because of the great utility of this reaction.

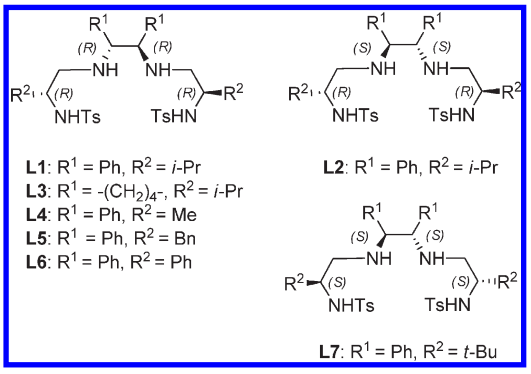


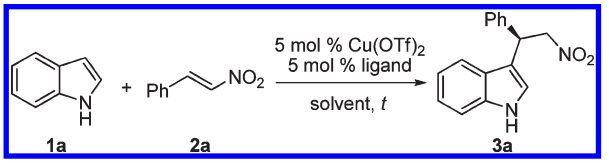
Figure 1. Bis(sulfonamide)-diamine ligands.

Very recently, we have developed a novel type of chiral bis-sulfonamide diamine ligand (Figure 1) with several chiral centers in the skeleton in favor of easily tuning the stereo and electronic effect. This type of ligands proved to be highly effective for a Cu-catalyzed enantioselective and diastereoselective Henry reaction.[7] Since Cu-catalyzed Friedel–Crafts alkylation of indole with nitroalkene has been reported, we envisioned that this type of ligands may be effective in this transformation. Herein, we describe that bis-sulfonamide diamine served as a new type of ligand for a Cu-catalyzed asymmetric Friedel–Crafts alkylation of indoles with nitroalkenes to provide the corresponding products with up to 99% yield and 97% ee. As far as we know, we obtained the best results of *ortho*-substituted electron-withdrawing aromatic nitroalkenes.

Initially, the addition of indole **1a** to *trans*-*β*-nitrostyrene **2a** was selected as a model reaction for optimizing the conditions. A series of Lewis acid catalysts (Cu^{II}, Cu^{I}, Zn^{II}, Fe^{III}, Ag^{I} complexes) were first investigated. Preliminary studies revealed that only the complex generated in situ from $Cu(OTf)_2$ and ligand **L1** promoted the reaction with a promising result giving the product with 68% yield and 21% ee (Table 1, entry 1). Sequential investigations on modifying the structure of the bis-sulfonamide diamine ligands showed that the ligand derived from (1*R*,2*R*)-1,2-diphenylethylenediamine turned out to be better than the one derived from (1*S*,2*S*)-1,2-diphenylethylenediamine (Table 1, entries 1 and 2). Subsequently, the ligands derived from two chiral 1,2-diamines with different skeletons were compared. It was shown that the ligand linked with (1*R*,2*R*)-1,2-diphenylethylenediamine was superior to the one with (1*R*,2*R*)-cyclohexane-1,2-diamine (Table 1, compare entries 1 and 3). Furthermore, the substituent R^2 of the ligands could also greatly affect the reactivity and enantioselectivity of the reaction (Table 1, entries 4–7). Gratifyingly, significant enhancement of enantioselectivity was observed when **L6** with R^2 as a phenyl group was employed affording the corresponding adducts with 94% yield and 91% ee (Table 1, entry 6).

Further optimization of the reaction conditions focusing on the effect of the solvent (Table 1, entries 8–11) revealed

Table 1. Optimization of Reaction Conditions for the Enantioselective Friedel–Crafts Alkylation between **1a** and **2a**[a]



entry	ligand	solvent	*t* (°C)	yield (%)[b]	ee (%)[c]
1	**L1**	Toluene	rt	68	21
2	**L2**	Toluene	rt	91	5 (−)
3	**L3**	Toluene	rt	77	18
4	**L4**	Toluene	rt	58	18
5	**L5**	Toluene	rt	76	11
6	**L6**	Toluene	rt	94	91
7	**L7**	Toluene	rt	45	22 (−)
8	**L6**	CH_2Cl_2	rt	99	86
9	**L6**	$CHCl_3$	rt	99	85
10	**L6**	Benzene	rt	86	88
11	**L6**	$PhCF_3$	rt	99	92
12	**L6**	$PhCF_3$	0	99	94
13	**L6**	$PhCF_3$	−10	98	93
14[d]	**L6**	$PhCF_3$	0	99	95
15[e]	**L6**	$PhCF_3$	0	99	94
16[f]	**L6**	$PhCF_3$	0	78	0

[a] Unless otherwise noted, all reactions were performed with indole **1a** (0.25 mmol) and *trans*-*β*-nitrostyrene **2a** (0.375 mmol) with 5 mol % catalyst ($Cu(OTf)_2$:ligand = 1:1) in 1.5 mL of solvent under argon. [b] Isolated yields. [c] Determined by HPLC with chiral AD-H column. [d] 3 mL of solvent were used. [e] The reaction was performed in the open air. [f] Without addition of $Cu(OTf)_2$.

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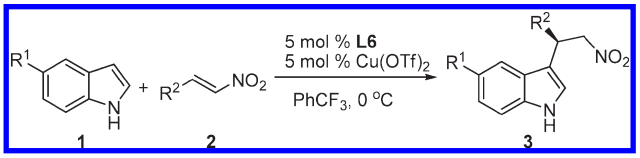
Table 2. Scope of the Asymmetric Friedel–Crafts Alkylation of Indoles with Various Nitroalkenes[a]



entry	R^1	R^2	yield (%)[b]	ee (%)[c]
1	H (**1a**)	Ph (**2a**)	99 (**3a**)	95 (*R*)[d]
2	H (**1a**)	4-ClC_6H_4 (**2b**)	96 (**3b**)	92
3	H (**1a**)	3-ClC_6H_4 (**2c**)	94 (**3c**)	94
4	H (**1a**)	2-ClC_6H_4 (**2d**)	99 (**3d**)	97
5	H (**1a**)	4-MeC_6H_4 (**2e**)	99 (**3e**)	93
6	H (**1a**)	4-$MeOC_6H_4$ (**2f**)	99 (**3f**)	88
7	H (**1a**)	2-$MeOC_6H_4$ (**2g**)	96 (**3g**)	93
8	H (**1a**)	2-BrC_6H_4 (**2h**)	97 (**3h**)	96
9	H (**1a**)	3-BrC_6H_4 (**2i**)	99 (**3i**)	93
10	H (**1a**)	4-BrC_6H_4 (**2j**)	96 (**3j**)	92
11	H (**1a**)	2-FC_6H_4 (**2k**)	98 (**3k**)	96
12	H (**1a**)	3-$CF_3C_6H_4$ (**2l**)	99 (**3l**)	94
13	H (**1a**)	2-furyl (**2m**)	98 (**3m**)	88
14	H (**1a**)	1-naphthyl (**2n**)	95 (**3n**)	95
15	H (**1a**)	2-naphthyl (**2o**)	90 (**3o**)	93
16[e]	H (**1a**)	*n*-Bu (**2p**)	65 (**3p**)	70
17	Me (**1b**)	Ph (**2a**)	99 (**3q**)	94
18	OMe (**1c**)	Ph (**2a**)	99 (**3r**)	95
19	F (**1d**)	Ph (**2a**)	88 (**3s**)	94
20	Br (**1e**)	Ph (**2a**)	99 (**3t**)	94

[a] Unless otherwise noted, all reactions were performed with indoles **1** (0.25 mmol) and nitroalkenes **2** (0.375 mmol) with 5 mol % catalyst ($Cu(OTf)_2$:**L6** = 1:1) in 3 mL of $PhCF_3$ under argon at 0 °C for 24–48 h. [b] Isolated yields. [c] The ee value was determined by HPLC analysis. [d] Determined to be *R* by comparison of optical rotation with that in ref 3d. [e] The reaction was performed with 20 mol % catalyst at room temperature.

that $PhCF_3$ was the best solvent leading to the quantitive conversion of the substrate in a shorter time and afforded the product with 99% yield and 92% ee (Table 1, entry 11). Decreasing the temperature to 0 °C slightly improved the enantioselectivity without affecting the yield (Table 1, entry 12). Further improvement of the enantioselectivity was observed with a lower concentration of the substrate (Table 1, entry 14). Importantly, the reaction was not sensitive to air and moisture and could be conducted in the open air without jeopardizing the yield and ee value (entry 15). In addition, the control reaction showed that the reaction could be catalyzed by the ligand **L6** in the absence of $Cu(OTf)_2$ giving the racemic product in moderate yield (entry 16).

Having found the optimized conditions, we set out to investigate the scope of the reaction. As shown in Table 2, regardless of steric hindrance or electronic properties of various aryl substituents, aromatic nitroalkenes reacted with indole **1a** smoothly and afforded the corresponding products in excellent yields and enantioselectivities (Table 2, entries 1–12). It was noteworthy that several catalytic systems suffered from lower enantioselectivities due to steric hindrance on *ortho* substitution of the phenyl group of aromatic nitroalkenes. On the contrary, in this system, the enantioselectivity increased rather than decreased when the *ortho* substitution exists (Table 2, entries 4, 7, 8, and 11). Furthermore, heteroaromatic nitroalkenes also served as good substrates for this reaction giving good results (Table 2, entries 13–15). However, to our disappointment, when aliphatic nitroalkenes were subjected to this reaction the results turned out to be not as good as the outcome of aromatic nitroalkenes. 20 mol % catalyst was needed when (*E*)-1-nitro-1-hexene **2p** was involved as the substrate, and only a moderate yield and ee were obtained (Table 2, entry 16). Meanwhile, the substituent effect of indole was also investigated (Table 2, entries 17–20). The electronic properties of the substituent at the 5-position of indole had little effect on enantioselectivities, but a longer reaction time was needed when electron-drawing groups were involved.

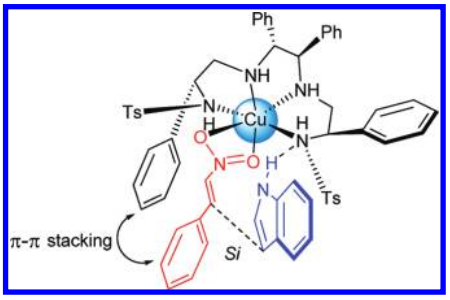


Figure 2. Proposed transition state model of catalyst **L6**–$Cu(OTf)_2$.

To gain some insight into the mechanism of this reaction, *N*-methyl indole was treated with nitroalkene under the optimized conditions. The corresponding product was obtained with only 51% yield and 17% ee. On the other hand, the phenyl group as R^2 was indispensable in the ligand to gain an excellent yield and enantioselectivity. Moreover, the poor results of aliphatic nitroalkenes were obtained as mentioned above (Table 2, entry 16). Based on these results, a plausible transition state was proposed as shown in Figure 2. We envision that catalyst **L6**–$Cu(OTf)_2$ acts in a bifunctional way. The nitroalkenes are activated by chelating to Cu(II), and a π–π stacking will exist between the phenyl group R^2 of the ligand and the phenyl group of nitroalkenes. In addition, an indolic proton will interact with the nitrogen atom which linked with the Ts substituent through a weak hydrogen bond[8] and the bulky Ts on the back directs the indole to attack nitroalkene on the *Si* face to afford the product with the configuration of *R*.

(8) Indole analogues carrying substituents in positions 2 and 7 were also tested. However, only racemic products were obtained with good yields. We surmised that the substituents in positions 2 and 7 were near the N–H bond of indole and the hydrogen bond cannot be generated because of the steric hindrance (see Supporting Information).

In conclusion, we have developed a highly enantioselective Friedel–Craft alkylation of indoles with nitroalkenes using a $Cu(OTf)_2$/bis(sulfonamide)-diamine catalytic system. The reaction performed well over a range of nitroalkenes, especially sterically hindered aromatic nitroalkenes with *ortho* substitution, giving the corresponding products with up to 99% yield and 97% ee. Further exploration of the mechanism and application of the ligands to other asymmetric reactions is currently underway in our laboratory.

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Supporting Information Available. General experimental procedures, synthesis of the ligands **L1**–**7**, characterization data, ^1H and ^{13}C NMR spectra, and HPLC analysis. This material is available free of charge via the Internet at http://pubs.acs.org.