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Asymmetric Friedel–Crafts Addition of Indoles to *N*-Sulfonyl Aldimines: A Simple Approach to Optically Active 3-Indolyl-methanamine Derivatives

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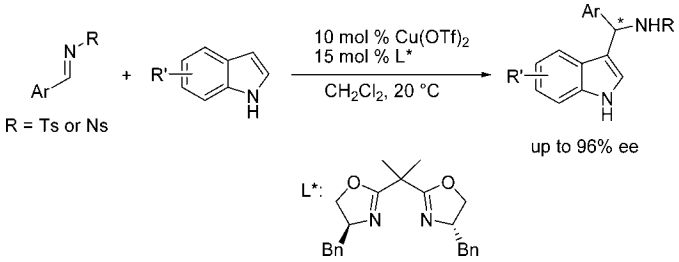
ABSTRACT



The enantioselective copper(II)-catalyzed Friedel–Crafts addition of indoles to *N*-sulfonyl aldimines was developed using chiral bisoxazoline as ligands, and high enantioselectivities (up to 96% ee) were achieved.

The Lewis acid-catalyzed Friedel−Crafts (F−C) alkylation reaction is a powerful carbon−carbon bond-forming process in organic chemistry.[1] The asymmetric version of this reaction can provide a very useful approach to the enantiomerically enriched alkylated arene products.[2] However, despite its importance, the catalytic asymmetric F−C reaction has not been explored until 1990, when the first example of the asymmetric addition of 1-naphthol to pyruvic esters using a chiral zirconium complex was reported.[3] Since this pioneering work, the research of catalytic asymmetric F−C reactions gained much attention, and the reactions of active carbonyl compounds,[4] expoxides,[5] and electron-deficient olefins [6] as substrates have been extensively studied.

The asymmetric F−C reaction of imine substrates is a completely atom-economical access to optically active functionalized benzylic amines, which are potential starting materials for many biologically active compounds. However, the study of the chiral Lewis acid-catalyzed F−C reaction of imines is only limited to the highly active *N*-protected α-imino esters. Johannsen[7] and Jørgensen[8] reported, respec-

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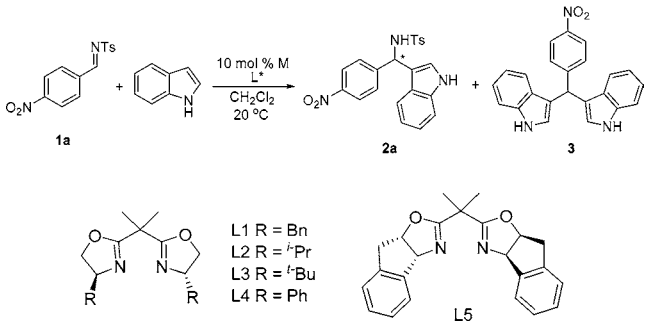
tively, the F−C reactions of *N*-tosyl α-imino esters and *N*-alkoxycarbonyl α-imino esters using chiral Tol-Binap/Cu(I) catalysts in high enantioselectivities. In this reaction, the substrate coordinated to copper by a 1,4-binding model of the N atom of α-imine and the carbonyl O atom of ester.[8b] In contrast, there was no report in the literature, to our best knowledge, on the chiral Lewis acid-catalyzed asymmetric F−C reaction of aryl aldimines,[9] although the non-enantioselective version of this reaction has been well-explored by several groups.[10]

In recent years, much interest has been attracted to the synthesis of 3-substituted indoles due to their numerous biologically significant activities.[11] The 3-indolylarylmethanamine derivatives were the important intermediates of the natural and natural-like products, such as hydro-γ-carboline and pyrido[4,3-b]indole derivatives.[12] The asymmetric F−C addition of indole to aryl aldimines will provide a straightforward access to the optically active 3-indolylarylmethanamines. In this letter, we would like to present our primary results in the reaction of indole with aryl aldimines catalyzed by $Cu(OTf)_2$/bisoxazoline complexes, providing chiral 3-indolylarylmethanamines in excellent enantioselectivities.

The reaction of *N*-(4-nitrobenzylidene)-4-methylbenzenesulfonamide (**1a**) with indole catalyzed by $Cu(OTf)_2$/(*S*)-Bn-bisoxazoline (**L1**) complex was performed to optimize the reaction conditions (Scheme 1). The catalyst was prepared

Scheme 1



in situ by mixing $Cu(OTf)_2$ with **L1** in CH_2Cl_2 at room temperature. After adding aldimine **1a** and indole, the mixture was stirred at room temperature for 3 days. The addition product *N*-(indol-3-yl-4-nitrophenylmethyl)-4-methylbenzenesulfonamide (**2a**) was isolated in 58% yield with 95% ee (Table 1, entry 1). The reaction also can be carried

Table 1. Asymmetric Friedel−Crafts Reaction of **1a** with Indole[a]

entry	L*	M	indole/imine	yield of **2a**[b] (%)	ee[c] (%)
1	L1	$Cu(OTf)_2$	1:1	58	95
2	L1	$Zn(OTf)_2$	1:1	n.r.[d]	
3	L1	$Mg(OTf)_2$	1:1	n.r.[d]	
4	L1	$Fe(ClO_4)_2$	1:1	44	−3
5	L1	$Ni(OTf)_2$	1:1	78	0
6	L1	$(CuOTf)_2C_6H_6$	1:1	n.r.[d]	
7	L1	$Cu(OTf)_2$	2:1	72	95
8	L2	$Cu(OTf)_2$	2:1	50	32
9	L3	$Cu(OTf)_2$	2:1	33	−6
10	L4	$Cu(OTf)_2$	2:1	39	0
11	L5	$Cu(OTf)_2$	2:1	25	−17
12	L1	$Cu(OTf)_2$	5/1	86	95
13[e]	L1	$Cu(OTf)_2$	5/1	94	95
14[e,f]	L1	$Cu(OTf)_2$	5/1	92	92

[a] The reactions were performed with 10 mol % M, 15 mol % L*, and 5 mL CH_2Cl_2 under N_2 at 20 °C for 3 days. [b] Isolated yield. [c] Determined by chiral HPLC using a Chiralcel OD column (25 cm × 0.46 cm i.d.). [d] No reaction. [e] 100 mg 4 Å molecular sieves were added. [f] 5 mol % catalyst, 6 days.

in CH_2ClCH_2Cl (58% yield and 92% ee), but not in THF and dioxane. Screening of the metal in chiral Lewis acids under the same reaction conditions showed that only copper(II) triflate had high enantioselectivity, and all other tested catalysts gave either no reaction or racemic product (Table 1, entries 2−6). The comparison of ligands indicated that the (*S*)-Bn-bisoxazoline (**L1**) was the best choice of ligand in terms of enantioselectivity and yield (Table 1, entries 7−11).

There are generally two main side-reactions affecting the yield of the F−C reaction of aryl aldimines, namely, the formation of double-alkylation product, like **3** and the hydrolysis of aryl aldimine substrates.[2b,8d] It was delightful to find that only a trace amount of achiral product **3** (<5%) was detected in all cases of the reactions of aldimine **1a** using $Cu(OTf)_2$/(*S*)-Bn-bisoxazoline catalyst. The hydrolysis of aryl aldimines can be reduced by increasing the amount of indole. For example, when the molar ratio of indole to aldimine **1a** was raised from 1:1 to 2:1 and 5:1, the yield of **2a** was remarkably improved from 58% to 72% and 86% (Table 1, entries 7 and 12). The influence of additives to the reaction was also examined. It was found that the addition of 4 Å molecular sieve could further increase the yield of F−C product to 94%, leaving the ee value unchanged (Table 1, entry 13), while HFIP (1,1,1,3,3,3-hexafluoropropan-2-ol) lowered the enantioselectivity of the reaction to 88% ee. Interestingly, when 1.2 equiv TMSCl was added, aldimine **1a** was consumed completely within 0.5 h, and the achiral double-alkylation product **3** was obtained quantitatively. The catalyst loading could be reduced to 5 mol %, and the results were comparable with that using 10 mol % catalyst, though a longer reaction time was needed (Table 1, entry 14).

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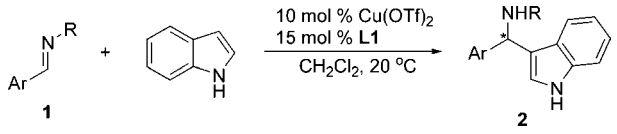
To extend the application of the reaction, variety of *N*-tosylarylimines were subjected to the reaction with indole under the optimal conditions. The data in Table 2 showed that the reactions of *N*-tosyl aldimines **1** bearing an electron-withdrawing group on the phenyl ring proceeded smoothly to provide corresponding F−C adducts in good yields and high ee values (93−96%) (Table 2, entries 1−10). However, the reaction of *N*-tosylphenylimine gave only 35% yield of the desired product in 88% ee. As for the substrates containing an electron-donating group, no F−C product was formed under the same reaction conditions, and most aldimines were hydrolyzed to aldehydes. Apparently, the electron-withdrawing substituent on the phenyl ring is critical to the Friedel−Crafts reaction of *N*-tosylarylimines with indole.

It was nice to find that, when the *p*-nitrobenzenesulfonyl (Ns) group, instead of tosyl group, was used as protecting group, the Friedel−Crafts addition of indole could be extended to the aldimine substrates contained electron-donating substituents. For instance, in the reaction of *N*-benzylidene-4-nitrobenzenesulfonamide (**1k**), the yield and the enantioselectivity reached to 86% and 94% ee (Table 2, entry 11), which were much better than those of the reaction of *N*-tosylphenylimine. Comparable results were obtained in the reaction of the substrates with a methyl or methoxy group (Table 2, entries 13−16). In addition to indole itself, 5-Br- and 5-MeO-indoles (**4** and **5**) could also react with aldimine **1k**, affording the corresponding indolyl-methanamine derivatives **6** and **7** in 50% yield with 77% ee and 93% yield with 92% ee, respectively (Scheme 2).

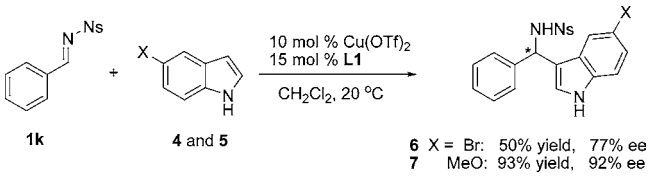
Table 2. Asymmetric Friedel−Crafts Reaction of *N*-Sulfonyl Aldimines with Indole[a]



entry	Ar	R	yield[b] (%)	ee (%)
1	4-$NO_2C_6H_4$ (**1a**)	Ts	**2a** (94)	95
2	3-$NO_2C_6H_4$ (**1b**)	Ts	**2b** (94)	94
3	4-ClC_6H_4 (**1c**)	Ts	**2c** (75)	94
4	3-ClC_6H_4 (**1d**)	Ts	**2d** (79)	95
5	2-ClC_6H_4 (**1e**)	Ts	**2e** (72)	94
6	4-BrC_6H_4 (**1f**)	Ts	**2f** (89)	96 (*S*)[c]
7	3-BrC_6H_4 (**1g**)	Ts	**2g** (87)	94
8	2-BrC_6H_4 (**1h**)	Ts	**2h** (78)	94
9	3,4-$Cl_2C_6H_3$ (**1i**)	Ts	**2i** (63)	95
10	2,6-$Cl_2C_6H_3$ (**1j**)	Ts	**2j** (47)	93
11	C_6H_5 (**1k**)	Ns	**2k** (86)	94
12	4-FC_6H_4 (**1l**)	Ns	**2l** (68)	92
13	4-MeC_6H_4 (**1m**)	Ns	**2m** (84)	94
14	3-MeC_6H_4 (**1n**)	Ns	**2n** (91)	95
15	2-MeC_6H_4 (**1o**)	Ns	**2o** (63)	89
16	4-$MeOC_6H_4$ (**1p**)	Ns	**2p** (47)	88
17	1-Naph (**1q**)	Ns	**2q** (85)	81

[a] Reaction conditions: 10 mol % $Cu(OTf)_2$, 15 mol % **L1**, 1.0 equiv aldimines, 5.0 equiv indoles, 100 mg 4 Å molecular sieves, 3−5 days. [b] Isolated yield. [c] Determined by single-crystal X-ray analysis.

Scheme 2



In most examples of asymmetric F−C reactions reported in the literature, the high enantioselectivity was only achieved when the substrates can coordinate to Lewis acid catalyst to form 1,4- or 1,5-chelating complexes.[4,6] However, in the reactions of *N*-tosyl and *p*-nitrobenzenesulfonyl aldimines, the 1,3-binding mode of the nitrogen atom of imine and the oxygen atom of the sulfonyl coordinated to Cu center is most likely. As shown in Figure 1, indole added to the 4-bromophenyl-*N*-tosylmethanimine (**1f**) from *Re* face to produce *N*-[indol-3-yl-(4-bromophenyl)methyl]-4-methylbenzenesulfonamide (**2f**). The configuration of compound **2f** was determined to be *S* by X-ray crystallography, which supported the proposed coordination mode of *N*-sulfonyl aldimine to Cu atom in Figure 1.[13]

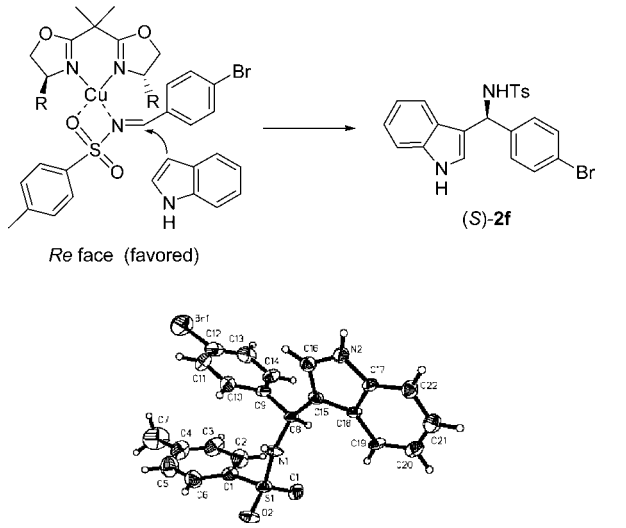
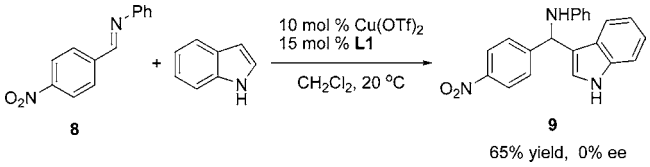


Figure 1. Proposed coordination mode of *N*-sulfonyl aldimine and X-ray crystallographic structure of (*S*)-**2f**.

To further prove this 1,3-coordination model, we carried out the reaction of (*E*)-*N*-(4-nitrobenzylidene)-benzenamine (**8**) with indole under the same conditions, and a completely racemic product **9** was obtained in 65% yield (Scheme 3).

(13) See Supporting Information for the crystal data and structure refinement of **2f**.

Scheme 3



The absence of enantioselectivity in the reaction of **8** conversely supported the presumption of the 1,3-coordination model of substrates in the F−C reaction of *N*-sulfonyl aldimines.

In conclusion, we have developed a copper-catalyzed asymmetric Friedel−Crafts reaction of *N*-sulfonyl aldimines with indoles to provide a simple approach to optically active 3-indolylmethanamine derivatives in high enantioselectivity. The 1,3-binding model of *N*-sulfonyl aldimine substrates to a copper center was the key point for enantiocontrol. This new coordination template has a potential for wide application of *N*-sulfonyl aldimines in the Lewis acid-catalyzed asymmetric transformations, which is in progress in this laboratory.

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Supporting Information Available: Experimental details, spectroscopic data for new compounds, and the determination of ee values of products (pdf). This material is available free of charge via the Internet at http://pubs.acs.org.

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