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# Monodentate N-Ligand-Directed Bifunctional Transition-Metal Catalysis: Highly Enantioselective Friedel–Crafts Alkylation of Indoles with Nitroalkenes

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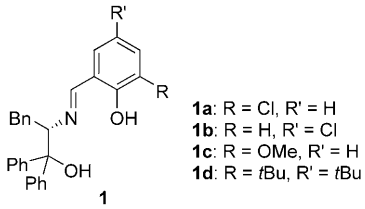
Recently, combinatorial transition-metal catalysis has been shown to be a promising way to enhance the enantio-, diastereo-, or regioselectivity of many reactions.[1] By applying this concept, structurally diverse catalysts can easily be generated by mixing ligands, without the need to synthesize any new compounds. Over the past two decades, numerous well-designed chiral and achiral compounds have been successfully applied as combinatorial ligands in many reactions.[1,2] However, the use of simple monodentate N ligands, such as piperidine, as combinatorial ligands has been less well explored.[3] Furthermore, understanding the origin of the enhanced reactivity and selectivity is still a challenge.[1a]

Tridentate Schiff bases **1** (Scheme 1), prepared from a chiral amino alcohol and 2-hydroxybenzaldehyde derivatives, are considered to be excellent chiral ligands for many asymmetric transformations, especially those with vanadium, chromium, aluminum, iron, titanium, and copper.[4] To maintain the saturated coordination modes of the central metals, dimeric structures[4g,h,n] or counteranions that bind directly to the central metal are generally required in the scaffolds of complexes. Encouraged by these combinatorial strategies, we anticipated that the addition of specific N ligands into the Schiff base metal system could disassemble the dimeric structure and perhaps provide some new active heterocomplexes for use in asymmetric catalysis. Herein, we describe a highly enantioselective Friedel–Crafts alkylation[5] of indoles with nitroalkenes that is catalyzed by novel Schiff base zinc(II) complexes which use piperidine as a crucial combinatorial ligand.[6,7]




**1a**: R = Cl, R' = H
**1b**: R = H, R' = Cl
**1c**: R = OMe, R' = H
**1d**: R = *t*Bu, R' = *t*Bu

Scheme 1. Chiral 2-hydroxybenzaldehyde derivatives used as ligands in this study. Bn = Benzyl.

Initially, we selected the Friedel–Crafts alkylation of indole with *trans*-β-nitrostyrene as the model reaction, which would readily give access to many bioactive indole derivatives.[7g] The catalyst was formed in situ by mixing Schiff base **1a** and $Zn(OTf)_2$ (OTf = triflate) in a 1:1 ratio, in toluene, at room temperature, which gave the product in 88% isolated yield with 52% *ee* (Table 1, entry 1). Notably, partial decomposition of **1a** was observed due to the strongly acidic HOTf generated during the coordination.[8] This result provided us with a possible method of further enhancing the enantioselectivity by using an extra base as an acid scavenger. However, no increase in *ee* was obtained after careful screening of various bases as additives (ratio: Schiff base **1a**/$Zn(OTf)_2$/base = 1:1:1). In contrast, a reduction in *ee* generally occurred (Table 1, entries 2–10).

With a combinatorial ligand strategy in mind, a library of achiral monodentate N ligands was introduced to the catalytic system and the ratio of Schiff base **1a**, $Zn(OTf)_2$, and achiral ligand was chosen to be 1:1:2. We expected that, in addition, the nitrogen compounds here could also play a crucial role as ligands as well as their traditional role as acid scavengers. Surprisingly, the absolute configuration of the product was reversed in all cases and significant improvements in reactivity and enantioselectivity were observed. As shown in Table 2, six-membered ring achiral ligands gave better selectivities than five-membered ring ligands, al-

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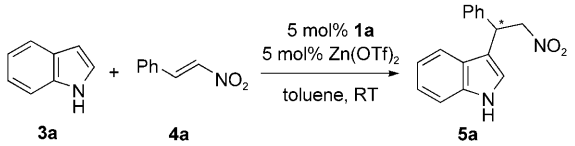
Table 1. Effect of bases on the reaction of indole (**3a**) with *trans*-β-nitrostyrene (**4a**).[a]




**3a** **4a** **5a**

| Entry | Base | Loading [mol %][b] | Yield [%][c] | *ee* [%][d] |
|---|---|---|---|---|
| 1 | – | – | 88 | 52 (*S*) |
| 2 | $Et_3N$ | 5 | 73 | 52 (*S*) |
| 3 | DIPEA[e] | 5 | 57 | 33 (*S*) |
| 4 | DBU[e] | 5 | 49 | 30 (*S*) |
| 5 | *t*BuOK | 5 | 68 | 20 (*S*) |
| 6 | PhCOONa | 5 | 52 | 23 (*S*) |
| 7 | pyrrolidine | 5 | 44 | 34 (*S*) |
| 8 | piperidine | 5 | 45 | 50 (*S*) |
| 9 | hexamethyleneimine | 5 | 46 | 31 (*S*) |
| 10 | 2-methylpiperidine | 5 | 41 | 33 (*S*) |

[a] Reaction conditions: indole (**3a**; 0.3 mmol) and *trans*-β-nitrostyrene (**4a**; 0.3 mmol) in toluene (2 mL) at room temperature for 24 h. [b] Amount of base. [c] Isolated yield. [d] The *ee* values were determined by chiral HPLC analysis and the absolute configuration of the products (in parentheses) was determined by comparison of the optical rotation with the literature.[6a] [e] DIPEA = ethyldiisopropylamine, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

Table 2. Screening of chiral and achiral ligands.[a]

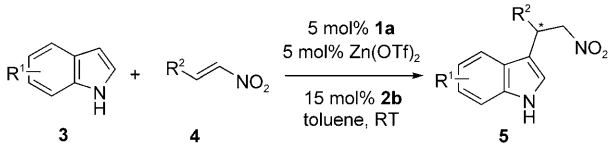
| Entry | Chiral ligand | Achiral ligand | Ratio[b] | Yield [%][c] | *Ee* [%][d] |
|---|---|---|---|---|---|
| 1 | **1a** | pyrrolidine (**2a**) | 1:2 | 87 | 76 (*R*) |
| 2 | **1a** | piperidine (**2b**) | 1:2 | 94 | 86 (*R*) |
| 3 | **1a** | hexamethyleneimine (**2c**) | 1:2 | 62 | 91 (*R*) |
| 4 | **1a** | 2-methylpiperidine (**2d**) | 1:2 | 43 | 68 (*R*) |
| 5 | **1a** | 3-methylpiperidine (**2e**) | 1:2 | 46 | 66 (*R*) |
| 6 | **1a** | 4-methylpiperidine (**2f**) | 1:2 | 54 | 72 (*R*) |
| 7 | **1a** | **2a** | 1:3 | 90 | 86 (*R*) |
| 8 | **1a** | **2b** | 1:3 | 96 | 96 (*R*) |
| 9 | **1a** | **2c** | 1:3 | 60 | 89 (*R*) |
| 10 | **1a** | **2d** | 1:3 | 43 | 60 (*R*) |
| 11 | **1a** | **2e** | 1:3 | 70 | 92 (*R*) |
| 12 | **1a** | **2f** | 1:3 | 86 | 96 (*R*) |
| 13 | **1a** | **2a** | 1:4 | 91 | 91 (*R*) |
| 14 | **1a** | **2b** | 1:4 | 93 | 94 (*R*) |
| 15 | **1b** | **2b** | 1:3 | 87 | 65 (*R*) |
| 16 | **1c** | **2b** | 1:3 | 91 | 57 (*R*) |
| 17 | **1d** | **2b** | 1:3 | 96 | 56 (*R*) |

[a] Reaction conditions: indole (**3a**; 0.3 mmol) and *trans*-β-nitrostyrene (**4a**; 0.3 mmol) in toluene (2 mL) at room temperature for 24 h. [b] Ratio of chiral ligand to achiral ligand. [c] Isolated yield. [d] The *ee* values were determined by chiral HPLC analysis and the absolute configuration of the products (in parentheses) was determined by comparison of the optical rotation with the literature.[6a]

though a low yield was obtained if hexamethyleneimine was utilized (Table 2, entries 1–3). More sterically hindered ligands gave lower yields and moderate enantioselectivities (Table 2, entries 4–6). Interestingly, if the ratio of chiral ligand to achiral ligand was increased to 1:3, higher reactivity and enantioselectivity was obtained (Table 2, entries 7–12). A further increase in the amount of achiral ligand proved to be less effective (Table 2, entries 13 and 14). These results suggest that the combination of Schiff base **1a**/$Zn(OTf)_2$/achiral ligand in a 1:1:3 ratio generates rather active heterocomplexes for the asymmetric Friedel–Crafts alkylation of indole (**3a**) with *trans*-β-nitrostyrene (**4a**) with **2b** being the best achiral ligand (Table 2, entry 8).[9] Next we examined the combination of **2b** with different Schiff bases, **1a**–**d**, under the same conditions (Table 2, entries 15–17). Alteration of the Schiff base by changing the substituents on the 2-hydroxybenzaldehyde structural motif revealed that the enantioselectivity highly depends upon the electronic nature and size of the substituents with Schiff base **1a** proving to be the best (Table 2, entry 8).

Under the optimized conditions (Table 2, entry 8), the scope of the Friedel–Crafts alkylation of indoles with nitroalkenes was explored. The results are summarized in Table 3. Various aromatic nitroalkenes with different substituents on the aromatic ring were examined. Electron-rich aromatic nitroalkenes usually gave the corresponding products in slightly better enantioselectivities than electron-poor ones (Table 3, entries 1–7). The enantioselectivity was found to be insensitive to the position of the substituent on the phenyl group of the nitroalkene (Table 3, entries 8–12). It is notable that the reaction can be extended to disubstituted, heterocyclic, and fused-ring nitroalkenes with excellent

Table 3. Scope of the enantioselective Friedel–Crafts alkylation of indoles with nitroalkenes.[a]




**3** **4** **5**

| Entry | $R^1$ | | $R^2$ | | Yield [%][b] | | *ee* [%][c] |
|---|---|---|---|---|---|---|---|
| 1 | H | **3a** | Ph | **4a** | 96 | **5a** | 96 |
| 2 | H | **3a** | 4-FPh | **4b** | 95 | **5b** | 91 |
| 3 | H | **3a** | 4-ClPh | **4c** | 97 | **5c** | 91 |
| 4 | H | **3a** | 4-BrPh | **4d** | 92 | **5d** | 92 |
| 5 | H | **3a** | 4-$CF_3$Ph | **4e** | 99 | **5e** | 90 |
| 6 | H | **3a** | 4-MePh | **4f** | 94 | **5f** | 96 |
| 7 | H | **3a** | 4-OMePh | **4g** | 90 | **5g** | 95 |
| 8 | H | **3a** | 3-ClPh | **4h** | 96 | **5h** | 92 |
| 9 | H | **3a** | 3-OMePh | **4i** | 97 | **5i** | 91 |
| 10 | H | **3a** | 3,4-$(OMe)_2$Ph | **4j** | 90 | **5j** | 97 |
| 11 | H | **3a** | 2-ClPh | **4k** | 96 | **5k** | 91 |
| 12 | H | **3a** | 2-OMePh | **4l** | 97 | **5l** | 95 |
| 13 | H | **3a** | 2-furyl | **4m** | 96 | **5m** | 95 |
| 14 | H | **3a** | 2-thienyl | **4n** | 99 | **5n** | 92 |
| 15 | H | **3a** | 1-napthyl | **4o** | 92 | **5o** | 94 |
| 16 | H | **3a** | 2-napthyl | **4p** | 91 | **5p** | 95 |
| 17 | 4-OMe | **3b** | Ph | **4a** | 96 | **5q** | 93 |
| 18 | 5-Br | **3c** | Ph | **4a** | 91 | **5r** | 93 |
| 19 | 5-OMe | **3d** | Ph | **4a** | 89 | **5s** | 96 |
| 20[d] | H | **3a** | Ph | **4a** | 90 | **5a** | 83 (>99)[e] |

[a] Reaction conditions: indole (**3**, 0.3 mmol) and nitroalkene (**4**, 0.3 mmol) in toluene (2 mL) at room temperature for 24 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Performed on a 5 mmol scale under 1 mol % catalyst in toluene (10 mL) at room temperature for 24 h. [e] The *ee* value after a single recrystallization is given in parentheses.

enantioselectivities (Table 3, entries 10 and 13–16). Several substituted indoles, containing either electron-withdrawing or electron-donating groups, have also been tested in the reaction with *trans*-β-nitrostyrene. In all cases, high yields and excellent enantioselectivities were achieved (93–96% *ee*, Table 3, entries 17–19). To our delight, this reaction can be performed, on a gram scale, with a lower catalyst loading (1 mol%), which results in the product in good yield with >99% enantiopurity after a single recrystallization (Table 3, entry 20).[10]

To get an insight into the reaction mechanism and a better understanding of the role of the achiral N ligands, we obtained the single-crystal X-ray structure of the optimum catalyst (Figure 1).[11] In the solid state, the catalyst exists in

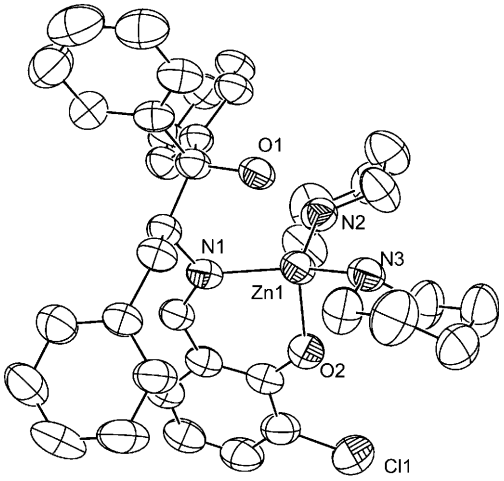



Figure 1. X-ray single-crystal structure of the catalyst **1a**/Zn(OTf)$_2$/**2b**. The triflate counteranion and all hydrogen atoms are omitted for clarity.

monomeric form as we proposed previously. Interestingly, the tridentate Schiff base ligand coordinates in a bidentate mode; the OH of the amino alcohol structural motif does not coordinate to zinc.[12] Two piperidine molecules occupy two of the coordination sites of the central metal, which generates a distorted-tetrahedral structure. We envision that the catalyst acts in a bifunctional fashion with the OH of the amino alcohol structural motif acting as a hydrogen-bond donor to direct the indole to attack the nitroalkene on the *Re* face,[13] while the nitroalkene is activated by zinc from its position within the tetrahedron (Figure 2). The heterocomplex does not split during the catalytic process, as no free piperidine was detected by $^1$H NMR analysis.[14]

In conclusion, we have developed a new, efficient combinatorial catalyst for the asymmetric Friedel–Crafts alkylation of indoles with nitroalkenes. A crucial achiral ligand effect was disclosed, which was further confirmed by single-crystal structural analysis of the catalyst. We also proposed a bifunctional mode of action for this catalytic process. To the best of our knowledge, this is the first example of a systematic evaluation of monodentate nitrogen compounds as combinatorial achiral ligands in asymmetric transition-metal catalysis. Efforts to apply a combinatorial strategy to other asymmetric transformations are underway in our group.

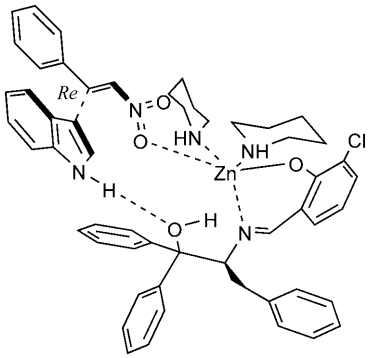



Figure 2. Proposed bifunctional mode of action in the transition state.

## Experimental Section

**General procedure**: Zn(OTf)$_2$ (5.4 mg, 0.015 mmol) and piperidine (**2b**; 4.5 μL, 0.045 mmol) were added to a solution of **1a** (6.7 mg, 0.015 mmol) in toluene (2 mL). The solution was stirred at room temperature for 30 min, before adding *trans*-β-nitrostyrene (**4a**; 44.7 mg, 0.3 mmol) and indole (**3a**; 35.1 mg, 0.3 mmol). After stirring for 24 h, the solvent was removed under vacuum. Column chromatography on silica gel (petroleum ether/ethyl acetate = 6:1) was performed to give the pure product **5a** as a white solid.

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**Keywords:** asymmetric catalysis · combinatorial chemistry · indoles · N ligands · Schiff bases

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[8] The amount of HOTf generated was proven to be one equivalent, with **1a** as the chiral ligand, by the fact that aging a mixture of **1a** and $Zn(OTf)_2$ in $Et_2O$ for two days gave crystals of the amino alcohol triflate as colorless needles.

[9] We anticipated that 1/3 of the achiral ligand added would act as an acid scavenger, while the other 2/3 might serve as ligands, which was further confirmed by the single-crystal structure of the catalyst.

[10] If 4-methyl-1-nitropent-1-ene was applied as an aliphatic nitroalkene under the standard conditions a relatively low yield (73%) and reduced enantioselectivity (60% *ee*) was obtained.

[11] Details of the crystal structure analysis are provided as Supporting Information. CCDC-763966 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[12] The distance between Zn**1** and O**1** was measured to be 2.519 Å and therefore an interaction between them can be ruled out.

[13] When *N*-methylindole was applied to the reaction very little product was formed under the standard conditions.

[14] By comparing the $^1$H NMR spectrum of the reaction mixture to the standard spectrum of piperidine, no characteristic signal at 2.80 ppm was observed.

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