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# An efficient, one-pot, three-component procedure for the synthesis of chiral spirooxindolopyrrolizidines via catalytic highly enantioselective 1,3-dipolar cycloaddition

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ABSTRACT

The catalytic, highly regio-, diastereo-, and enantioselective synthesis of a small library of chiral spirooxindolopyrrolizidines via a three-component 1,3-dipolar cycloaddition reaction of azomethine ylides, derived from isatin, with electron-deficient dipolarophiles, 3-(2-alkenoyl)-1,3-oxazolidin-2-ones, is described. A chiral copper(II) complex of cyclohexane-1,2-bis(arylmethyleneamine) catalyzed this process at room temperature. The reaction mechanism is discussed on the basis of the assignment of the absolute configuration of the cycloadducts.



Catalytic asymmetric multicomponent reactions (CAMCR) are efficient processes in terms of chirality economy and environmental impact. In addition, this strategy is a powerful tool for the rapid introduction and expansion of molecular diversity.[1] It is therefore desirable to utilize and develop this method for the synthesis of important heterocycles such as chiral spirooxindolopyrrolizidines and spirooxindoloprolines, for example, horsfiline,[2] elacomine[3] and rhynchophylline, which exhibit significant biological activities[4] (Fig. 1). Asymmetric multicomponent 1,3-dipolar cycloadditions of azomethine ylides with alkenes represent a useful strategy for stereoselective synthesis and the development of compounds having similar structures.[5]

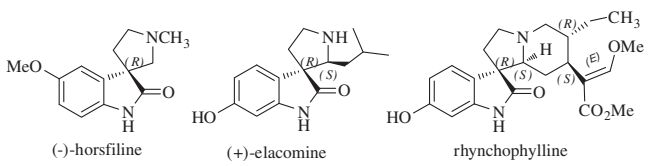


**Figure 1.** Spiropyrrolidine oxindole alkaloids.

We previously reported the synthesis of enantiomerically pure novel spirooxindolopyrrolizidines by applying an optically active cinnamoyl oxazolidinone as a chiral auxiliary and the obtained diastereoselectivities were very high.[6] However, this protocol required the use of at least one equivalent of an enantiopure auxiliary which represents a major drawback. To resolve this problem, and in continuation of our previous work on the synthesis of spirooxindoles,[7] herein, we have utilized a copper complex of cyclohexane-1,2-bis(arylmethyleneamine) **1** as a catalyst to synthesize a small library of this important class of spirooxindoles.[8] We report a highly regio-, diastereo-, and enantioselective 1,3-dipolar cycloaddition reaction of azomethine ylides, derived from isatin, with an electron-deficient dipolarophile by using bidentate bis(imine)-Cu(II) complex **1**, that can be readily assembled from commercially available *trans* 1,2-cyclohexanediamine and a variety of suitable aldehyde precursors,[9] under optimized reaction conditions. Based on our previous experience and a literature survey,[10] initially, the effects of substituents on the bis(imine) ligands **1** were examined using 10 mol % of $Cu(OTf)_2$ as the catalyst in the three-component reaction of isatin, (*S*)-proline, and dipolarophile **2a** at room temperature. The results are summarized in Table 1.

The ligands **1b** and **1c** bearing the electron-withdrawing and relatively bulky Cl-containing substituents at the 2- and/or 6-positions of the benzene ring resulted in considerably higher yields and enantioselectivities in comparison with the other ligands.[11] The

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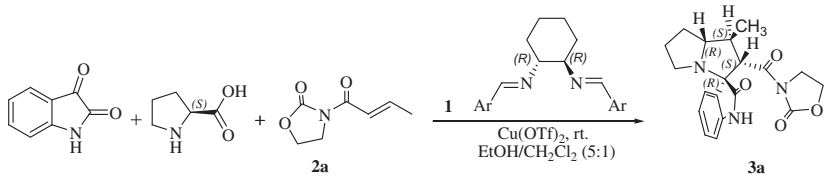
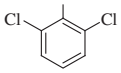
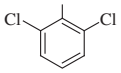
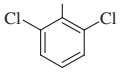
**Table 1**
Asymmetric synthesis of new chiral spirooxindolopyrrolidine **3a** with chiral ligands **1a–f**




| Entry[a] | Ligand | Ar | Temp (°C) | Time (h) | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|---|
| 1 | **1a** |  | 25 | 24 | 84 | 55 |
| 2 | **1b** |  | 25 | 22 | 93 | 95 |
| 3 | **1c** |  | 25 | 20 | 89 | 63 |
| 4 | **1d** |  | 25 | 29 | 79 | racemic |
| 5 | **1e** |  | 25 | 29 | 73 | racemic |
| 6 | **1f** |  | 25 | 32 | 83 | racemic |
| 7 | **1b** |  | 0 | 35 | 35 | 93 |
| 8 | **1b** |  | −40 | 48 | <10 | n.d. |

[a] The reaction of isatin (0.20 mmol), (*S*)-proline (0.21 mmol) with **2a** (0.20 mmol) was carried out in $EtOH/CH_2Cl_2$ (3 mL, 5:1) at rt in the presence of 10 mol % of the catalyst [$Cu(OTf)_2$–**1** = 1.0:1.1].
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.

highest enantioselectivity (95%) and yield (93%) were achieved by employing ligand **1b**. The yields and enantiomeric ratios of the products showed the temperature dependence of this process. A decrease in the reaction temperature from 25 °C to −40 °C significantly decreased the yield and enantioselectivity (entries 2, 7 and 8). We next tested the effect of different Cu salts in this process using **1b** as the ligand (Table 2).

In all cases, $Cu(OTf)_2$ proved to be the best copper source, while other Cu salts led to a decrease in the ee, and longer reaction times (entries 2 and 3 vs 1). The use of $Zn(OTf)_2$ instead of $Cu(OTf)_2$ gave a poorer result in terms of the enantioselectivity (entry 4). The effects of catalyst loading were also investigated and the best results were obtained when 10 mol % of the catalyst was used. The ligand-to-metal ratio of 1.1:1 using 20 mol % of ligand was investigated under similar conditions and the isolated yield and enantioselectivity remained the same at 96% and 90%, respectively. Lowering the catalyst loading to less than 10 mol % led to a decrease in the yield, reactivity and enantioselectivity. It should be noted that the addition of additives such as 3 or 4 Å molecular sieves did not give any noticeable changes in the results of the reaction, and even led to lower yields.

**Table 2**
Effect of the Lewis acid

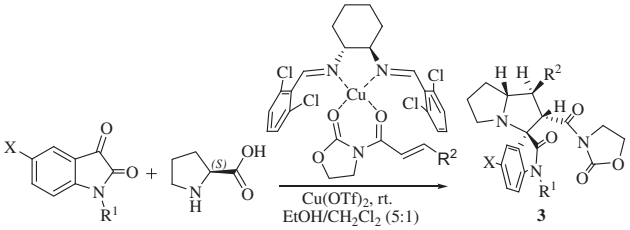
| Entry | Lewis acid (10 mol %) | Time (h) | Yield (%) | ee (%) |
|---|---|---|---|---|
| 1 | $Cu(OTf)_2$ | 22 | 93 | 95 |
| 2 | $Cu(OAc)_2$ | 23 | 92 | 66 |
| 3 | $CuCl_2$ | 28 | 76 | racemic |
| 4 | $Zn(OTf)_2$ | 12 | >99 | racemic |
| 5 | $Cu(OTf)_2$[a] | 22 | 96 | 90 |

[a] 20 mol % of catalyst was used.

Using the optimized reaction conditions, we next examined the scope and generality of this reaction with various types of azomethine ylides and two derivatives of 3-(2-alkenoyl)-1,3-oxazolidin-2-ones (**2**), and synthesized a small library of new chiral spirooxindolopyrrolizidines **3a–j** (Table 3).

The structures of the cycloadducts were assigned from their elemental and spectroscopic analyses including IR, $^1H$ NMR, $^{13}C$ NMR, and mass spectral data.

**Table 3**
Asymmetric synthesis of new chiral spirooxindolopyrrolizidines **3a–j**




| Entry | X | $R^1$ | $R^2$ | Cycloadduct | Yield (%) | ee (%) |
|---|---|---|---|---|---|---|
| 1 | H | H | Me | **3a** | 93 | 95 |
| 2 | H | H | Ph | **3b** | 95 | 93 |
| 3 | H | Me | Me | **3c** | 93 | 89 |
| 4 | H | Et | Ph | **3d** | 92 | 87 |
| 5 | H | Bn | Me | **3e** | 92 | 91 |
| 6 | Br | H | Me | **3f** | 99 | 89 |
| 7 | Br | Me | Me | **3g** | 92 | 87 |
| 8 | Br | Et | Me | **3h** | 94 | 90 |
| 9 | Br | Me | Ph | **3i** | 91 | 89 |
| 10 | $NO_2$ | H | Me | **3j** | 88 | 92 |