

## Enantioselective Synthesis of Spirooxindolopyrrolizidines via Catalytic 1,3-dipolar Cycloaddition of Azomethine Ylides and 3-(2-Alkenoyl)-1,3-oxazolidin-2-ones

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### INTRODUCTION

The ability of controlling the selectivity is an important aspect in organic synthesis. Compounds that differ in the position of a substituent are known as regioisomers. Although the regioisomers look very alike, they might possess different properties. Since Padwa and co-workers performed the first diastereoselectivity of 1,3-dipolar cycloaddition reaction in 1985, by applying a chiral non-racemic azomethine ylide,<sup>1</sup> their applications has been developed as a cornerstone in organic synthesis.<sup>2</sup> One of today's challenges in this field is to control the regio-, diastereo- and enantioselectivities of these reactions. Asymmetric 1,3-dipolar cycloaddition reactions of azomethine ylides offer an effective means to access chiral pyrrolidines substructures containing up to four new stereogenic centres that found in many biologically active compounds.<sup>3</sup> Asymmetric multicomponent 1,3-dipolar cycloaddition of azomethine ylides with alkenes can be a great interest and useful strategies for stereoselective synthesis and develop of these class of molecules and compounds having similar structure.<sup>4</sup> We reported the enantiomerically pure novel spirooxindolopyrrolizidines by applying optically active cinnamoyloxazolidinone as chiral auxiliary and the enantioselectivities were exceptionally high.<sup>5</sup> However, it requires the use of at least one equivalent of enantiopure auxiliary. To resolve this problem and in continuation of our previous work on the synthesis of spirooxindoles,<sup>6</sup> we applied copper complex of cyclohexane-1,2-bis(arylmethyleneamine) ligands (Fig. 1) as a catalyst to synthesis of a small library of this important class of spirooxindols.<sup>7</sup> In this paper, we wish to report a highly endo- and enantioselective 1,3-dipolar cycloaddition reaction of azomethine ylides, derived from isatin, with 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, in optimized reaction condition. Based on experiences in our previous works and literature survey.<sup>8</sup> Initially, the effects of substituents of bis(imines) ligands **1(a-f)** were examined using 10 mol% [Cu(OTf)<sub>2</sub>] as catalyst in a typical reaction of azomethine ylide **2a** with dipolarophile **3a** at room temperature in aqueous ethanol as a solvent (Scheme 1). Results are summarized in Table 1.

### EXPERIMENTAL

#### General Procedure

At the first, a mixture containing (10% mol) aimin base ligand and transition metal salts (10% mol) was prepared in 10 ml dichloromethan. Then a mixture of isatin derivatives (1 mmol) and (S)-proline (1.1 mmol), in 10 mL ethanol was added to mixture. After completion of the reaction (monitored by TLC), the reaction mixture was extracted with dichloromethane (15 mL). The combined organic layer dried over anhydrous MgSO<sub>4</sub>. The organic layer was concentrated in vacuum to furnish the products, which were recrystallized from ethanol.

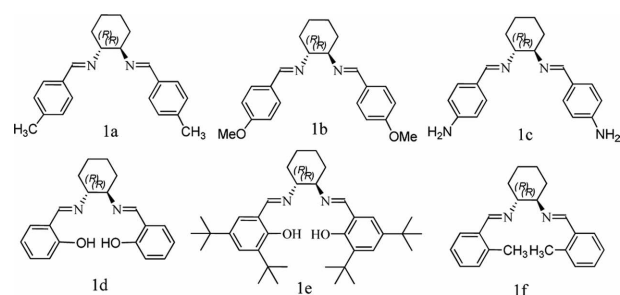
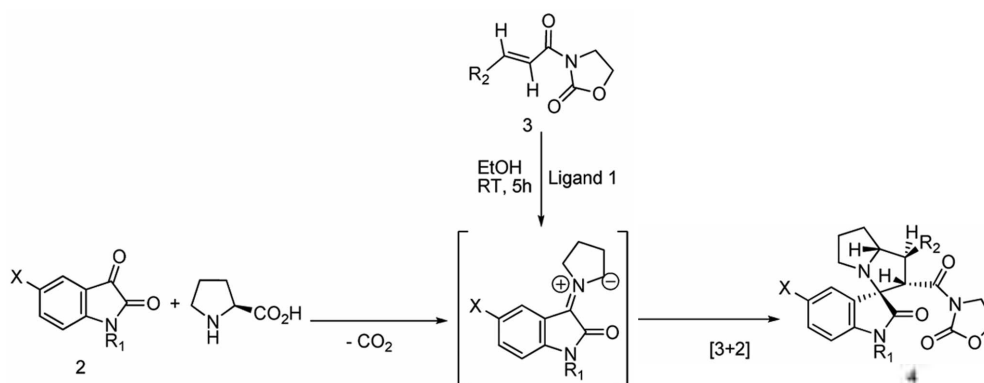


Figure 1. Cyclohexane-1,2-bis(arylmethyleneamine) ligands **1(a-f)**.



**Scheme 1.** Asymmetric synthesis of new chiral spirooxindolopyrrolizidines **4** with ligand of **1**.

**Table 1.** Asymmetric synthesis of new chiral spirooxindolopyrrolizidines with ligand of **1(a-f)**

Entry	Ligand	T(°C)	Time(h)	Yield (%) <sup>a</sup>	ee(%) <sup>b</sup>
1	1a	25	32	88	63
2	1b	25	28	90	55
3	1c	25	32	85	83
4	1d	25	28	93	74
5	1e	25	16	90	92
6	1f	25	32	85	rac
7	1e	0	48	25	rac
8	1e	-20	48	<15	n.d

<sup>a</sup>Temperature in the presence of 10% catalyst [Cu(OTf)<sub>2</sub>-1=1.0: 1.1], unless otherwise noted.

<sup>b</sup>Determined by chiral HPLC analysis.

### Selected Characterization Data

**3-((1'S,2'S,3R,7a'R)-1'-methyl-2-oxo-1',2',5',6',7',7a' hexahydrospiro[indoline-3,3'-pyrrolizine]-2'-ylcarbonyl) oxazolidin-2-one (4a):** white powder, mp 137–140 °C, yield 93%, [ $\alpha$ ]<sub>D</sub><sup>20</sup>+240.5 (c 0.01, CH<sub>2</sub>Cl<sub>2</sub>), IR(KBr)( $\nu_{\text{max}}$ , cm<sup>-1</sup>): 1694(C=O), 1745(C=O), 1800(C=O), 3420(NH); <sup>1</sup>H NMR (300.1 MHz, CDCl<sub>3</sub>): 1.17 (3H, d, <sup>3</sup>J<sub>HH</sub>=6.3 Hz, CH<sub>3</sub>), 1.73–1.93 (4H, m, 2CH<sub>2</sub>), 2.07–2.16 (1H, m, CH), 2.56 (1H, m, CH), 2.83–3.00 (2H, m, CH<sub>2</sub>), 3.53–3.62 (1H, m, CH), 3.87–3.96 (3H, m, CH and CH<sub>2</sub>), 4.13–4.21 (1H, m, CH), 4.31 (1H, d, <sup>3</sup>J<sub>HH</sub>=9.6 Hz, CH), 6.83–7.23 (4H, m, Ar-H), 7.55 (1H, s, NH); <sup>13</sup>C NMR (300.1 MHz, CDCl<sub>3</sub>): 15.9(1C, CH<sub>3</sub>), 24.8, 27.6, 41.3, 42.7, 62.1 (5C, 5CH<sub>2</sub>), 49.3, 59.9, 69.4 (3C, 3CH), 71.9(1C), 110.5, 121.1, 126.0, 129.8 (4C, 4CH), 125.6, 142.7 (2C) 153.0, 172.3, 179.7 (3C, 3C=O); MS, 355 (M<sup>+</sup>+2, 30), 69 (100), 131 (45).

## RESULTS AND DISCUSSION

The ligand **1e** bearing the relatively bulky tert-butyl substituents at the 2- and 4-positions of the benzene ring

**Table 2.** Dependence of reaction with Lewis acid

Entry	Lewis acid	Time(h)	Yield (%) <sup>a</sup>	ee (%) <sup>b</sup>
1	Zn(OAc) <sub>2</sub>	12	>99	Race
2	Cu(OTf) <sub>2</sub>	16	90	92
3	Cu(OAc) <sub>2</sub>	23	92	55
4	Cu(Cl) <sub>2</sub>	28	76	Race
5	Cu(OTf) <sub>2</sub> <sup>c</sup>	22	96	65

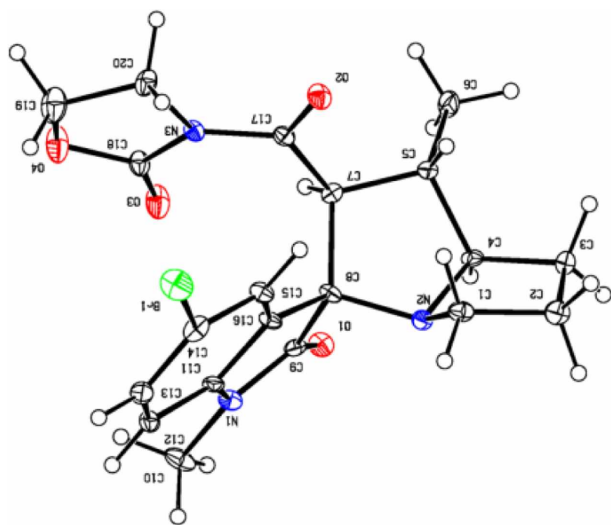
<sup>a</sup>Isolated yield.

<sup>b</sup>Determined by chiral HPLC analysis.

<sup>c</sup>20% catalyst is used.

resulted in considerably higher yields and enantioselectivities in comparison with the other ligands.<sup>9</sup> The highest enantioselectivity (92%) and yield in high selectivity were achieved by employing ligand **1e**. 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 -20 °C greatly decreased the reaction yield and enantioselectivity (entries 5, 7 and 8). Considering the **1e** as the best ligand, we tested the effect of Cu salts (Table 2). In all cases, Cu(OTf)<sub>2</sub> proved to be the best copper source while other Cu salts led to a decrease in the ee by 34–90% and longer reaction times (entries 3–4 vs. 2). The use of Zn(OTf)<sub>2</sub> instead of Cu(OTf)<sub>2</sub> gave worse result in term of enantioselectivity (entry 1). The effects of catalyst loading were also investigated and the best results were obtained when 10 mol% catalyst loading was used in the reaction. The ligand-to-metal ratio of 1.1:1 using 20 mol% of ligand was investigated under the similar conditions and the isolated yields and enantioselectivity remained the same at 92% respectively. Lowering the catalyst loading to less than 10 mol% led to a sharp decrease in the results.

Considering the optimized reaction conditions, we next examined the scope and generality of this reaction with various types of azomethineylides and synthesized a small

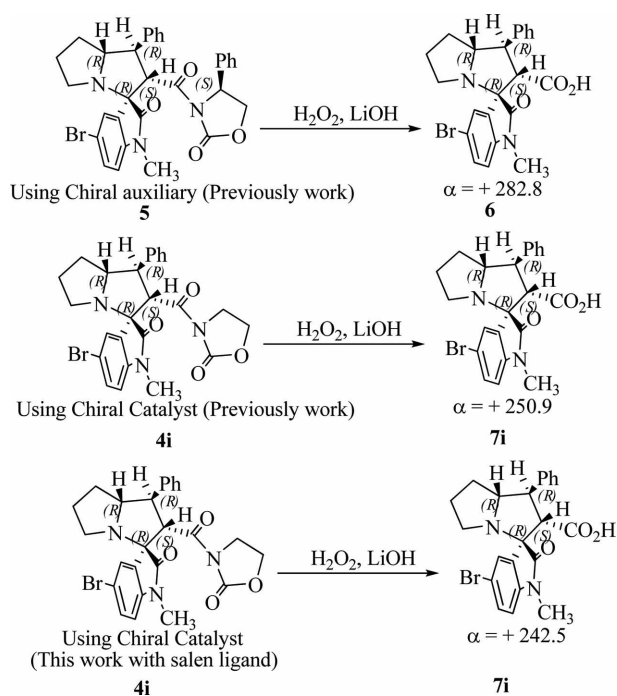


**Figure 2.** ORTEP diagram of one of the four crystallographic independent molecules in the asymmetric unit of **4g**; thermal ellipsoids are at 30% probability level.

**Table 3.** Asymmetric synthesis of new chiral spiro-oxindolo pyrrolizidines derivatives **4**

Entry	X	R <sub>1</sub>	R <sub>2</sub>	Product	Yield	ee
1	H	H	Me	4a	93	82
2	H	H	Ph	4b	90	92
3	H	Me	Me	4c	93	88
4	H	Et	Ph	4d	86	89
5	H	Bn	Me	4e	88	90
6	Br	H	Me	4f	98	83
7	Br	Me	Me	4g	92	91
8	Br	Et	Me	4h	94	85
10	Br	Me	Ph	4i	85	86
11	NO <sub>2</sub>	H	Me	4j	88	91

library of new chiral spirooxindolopyrrolizidines **4a–j** (Table 3). We also were able to obtain suitable crystals of the **4g** for crystallography to confirm the assigned stereochemistry of products **4** that was carried out here using several NMR spectroscopy techniques. According to the stereochemistry of the cycloadducts, it can be suggested that the pathway of this reaction would be through the *endo* transition state. The absolute configuration of enantiomer of *endo-4g* can be assigned on the basis of our previous investigation and X-ray crystallographic analysis of compound **4g**. On the basis of X-ray structure of **4**, we can now assign the four chiral centers in spiropyrrolizidine-oxindole **4g** to be 5R (spiro carbon C7), 6S (C21), 7R (C14), 8R (C13). X-ray crystallographic analysis of compound **4g** also confirmed this absolute configuration (Fig. 2).<sup>6</sup>



**Scheme 2.** Determination of the absolute configuration *endo-4i*.

As described in our previous work, upon treatment of chiral spirooxindolopyrrolizidine **5** with hydrogen peroxide in the presence of lithium hydroxide produced product **6** with an optical rotation of +282.8.<sup>5</sup> In the other work procedure was performed with *endo-4i* (89% ee) to give compound **7i** with an optical rotation of +250.9.<sup>6</sup> The same procedure was performed with *endo-4i* (86% ee) to give compound **7i** with an optical rotation of +242.5. The reaction sequences are outlined in Scheme 2. The products **4** are identical in all respects (IR, NMR and mass spectral data) except in amount of optical rotation.

In conclusion, Simple Salen ligand with copper (II) triflate catalyzed 1,3-dipolar cycloaddition reaction of azomethine ylides with electron-deficient dipolarophile to give spiro-pyrrolizidineoxindoles in good yield with high regio-, diastereo-, and enantioselectivity (up to 92% ee) in optimized condition.

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**Supporting Information.** Supplementary data (included are general procedures and IR, Mass, <sup>1</sup>H and <sup>13</sup>C NMR spectra of all compounds) associated with this article can be found, in the online version.

## REFERENCES

1. Daly, J. W.; Spande, T. W.; Whittaker, N.; Highet, R. J.; Feigl, D.; Noshimori, N.; Tokuyama, T.; Meyers C. W. *J. Nat. Prod.* **1986**, *46*, 210.
  2. Carroll, W. A., Grieco, P.; Biomimetic, O. *J. Am. Chem. Soc.* **1993**, *115*, 1164.
  3. Shi, F.; Mancuso, R.; Larock, R. C. *Tetrahedron Lett.* **2009**, *50*, 4067.
  4. Ding, K.; et al. *J. Am. Chem. Soc.* **2005**, *127*, 10130.
  5. Taghizadeh, M. J.; Arvinnezhad, H.; Samadi, S.; Jadidi, K.; Javidan, A.; Notash, B. *Tetrahedron Lett.* **2012**, *53*, 5148.
  6. Salahi, F.; Taghizadeh, M. J.; Arvinnezhad, H.; Moemeni, M.; Jadidi, K.; Notash, B. *Tetrahedron Lett.* **2014**, *55*, 1515.
  7. Mehrdad, M.; Faraji, L.; Jadidi, K.; Eslami, P.; Sureni, H. *Monatsh. Chem.* **2001**, *142*, 917.
  8. Evans, D. A.; Lectkata, T.; Miller, S. *Tetrahedron Lett.* **1993**, *34*, 7027.
  9. Brandes, B. D.; Jacobsen, E. N. *Tetrahedron: Asymmetry* **1997**, *8*, 3927.
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