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Three-component procedure for the synthesis of new 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 spiropyrrolizidineoxindoles *via* a four-component 1,3-dipolar cycloaddition reaction of azomethine ylides, derived from isatin, with electron-deficient dipolarophile was described. The process occurs at room temperature in aqueous ethanol as a green solvent and in the presence of a bidendatebis(imine)–Cu(II)triflate complex as efficient catalyst.

Keywords: Chiral auxiliaries; chiral spiro-oxindolopyrrolizidines; asymmetric 1,3-dipolar; azomethineylide; three-component reaction; MCRs; proline; sarcosine.

Introduction

Catalytic asymmetric multicomponent reaction (CAMCR) is one of the most efficient processes in terms of chirality economy and environmental benignity. In addition, this strategy has been manifested as 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 spirooxindolpyrrolizidines and spirooxindolprolines like horsfiline [2], elacomine [3], and rychnophylineexhibit significant biological activities [4]. Asymmetric multicomponent 1,3-dipolar cycloaddition of azomethineylides with alkenes can be a great interest and useful strategies for stereoselective synthesis and develop of this class of molecules and compounds has similar structure [5]. We recently reported the enantiomerically pure novel spirooxindolpyrrolizidines [6] by applying optically active cinnamoyloxazolidinone as chiral auxiliary and the enantioselectivities were exceptionally high. 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 [7], we applied copper complex of cyclohexane-1,2-bis(arylmethyleneamine) ligands (1) as a catalyst to synthesize a small library of this important class of spirooxindols [8] (Figure 1). Herein, we are going to report a highly exo- and

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enantioselective 1,3-dipolar cycloaddition reaction of azomethineylides, derived from isatin, with electron-deficient dipolarophile by using bidendate bis(imine)-Cu(II) complex **1**, that can be readily collected 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 [9], initially, the effects of substituents of bis (imines) ligands were examined using 10 mol% $[Cu(OTf)_2]$ as catalyst in a typical reaction of azomethineylide **2a** with dipolarophile **3a** at room temperature in aqueous ethanol as a solvent (Scheme 1). Results are summarized in Table 1.

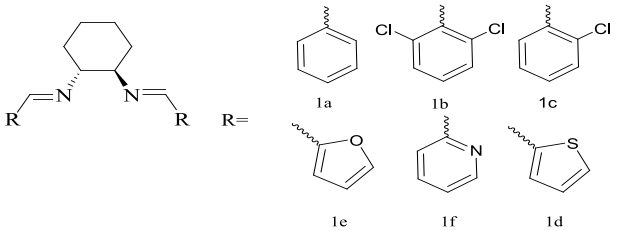
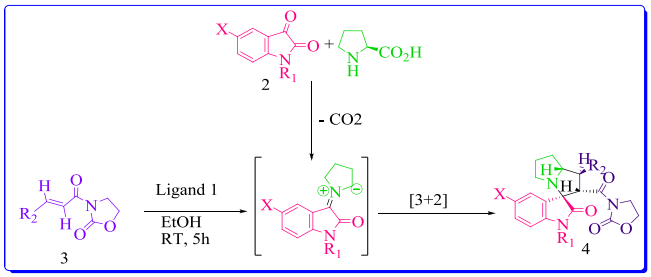


Figure 1. Cyclohexane-1,2-bis(arylmethyleneamine) ligands **1**(**a-f**)



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

Results and discussion

The ligands **1b** and **1c** bearing the electron-withdrawing and relatively bulky Cl substituents at the 2- or/and 6-positions of the benzene ring resulted in considerably higher yields and enantioselectivities in comparison with the other ligands[10]. The highest enantioselectivity (95%) and yield in high selectivity 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 ^{o}C to -40 ^{o}C greatly decreased the reaction yield and enantioselectivity (Entries 2, 7 and 8). Considering the **1b** as the best ligand, we tested the effect of Cu salts (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 by 34–90% and longer reaction times (Entries 3-4 *vs.*2). The use of $Zn(OTf)_2$ instead of $Cu(OTf)_2$ 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 20mol % of ligand was investigated under the similar conditions and the isolated yields and enantioselectivity remained the same at 95% respectively. Lowering the catalyst loading to less than 10 mol % led to a sharp decrease in the results. It should be noted that the addition of additives such as MS 4A, 3A did not give any observable changes in the results of the reaction and even lead to decreasing yields.

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

Entry	Ligad	T (C)	Time(h)	4	
				Yield (%)	Ee (%)
1	**1a**	25	24	84	55
2	**1b**	25	22	93	95
3	**1c**	25	20	89	63
4	**1d**	25	29	79	Race
5	**1e**	25	29	73	Race
6	**1f**	25	32	83	Race
7	**1b**	0	35	35	93
8	**1b**	-40	48	<10	n.d

Table 2. Dependence of synthesis of new chiral spirooxindolopyrrolizidines with Lewis acid

Entry	Lewis acid	Time(h)	4[a]	
			Yield (%)[b]	Ee(%)[c]
1	$Zn(OAc)_2$	12	>99	Race
2	$Cu(OTf)_2$	22	93	95
3	$Cu(OAc)_2$	23	92	66
4	$Cu(Cl)_2$	28	76	Race
5	$Cu(OTf)_2$[d]	22	96	90

[a]reaction of 2a (0.22mmol) with 3a (0.20mmol) was carried out in 3ml of $EtOH/CH_2Cl_2$ at room temperature in the presence of 10% catalyst [Lewisacid-1=1.0:1.1], unless otherwise noted.
[b]Isolated yield
[c]Determined by chiral HPLC analysis
[d]20% catalyst is used

Considering the optimized reaction conditions, we next examined the scope and generality of this reaction with various types of azomethine ylides and numerous 3-(2-alkenoyl)-1,3-oxazolidin-2-ones (3) and synthesized a small library of new chiral spirooxindolopyrrolizidines **4a–j** (Table 3).

Table 3. Asymmetric synthesis of new chiral spirooxindolopyrrolizidines derivaitives **4**

Entry	X	R_1	R_2	Product	Yield	ee
1	H	H	Me	**4a**	93	95
2	H	H	Ph	**4b**	95	93
3	H	Me	Me	**4c**	93	89
4	H	Et	Ph	**4d**	92	87
5	H	Bn	Me	**4e**	92	91
6	Br	H	Me	**4f**	99	89
7	Br	Me	Me	**4g**	92	87
8	Br	Et	Me	**4h**	94	90
10	Br	Me	Ph	**4i**	91	89
11	NO_2	H	Me	**4j**	88	83

The structures of cycloadducts were assigned from their elemental and spectroscopic analyses including IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data. The observation of two characteristic triplets and one doublet in the ^{1}H NMR spectra of products **4** confirmed, unambiguously, the formation of a new pyrrolizidine ring. 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. The ORTEP view of single crystal X-ray analysis of **4g** with atomic numbering is shown in Figure 2. On the basis of X-ray structure of 4, we can now assign the four chiral centers in spiropyrrolizidineoxindole 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.

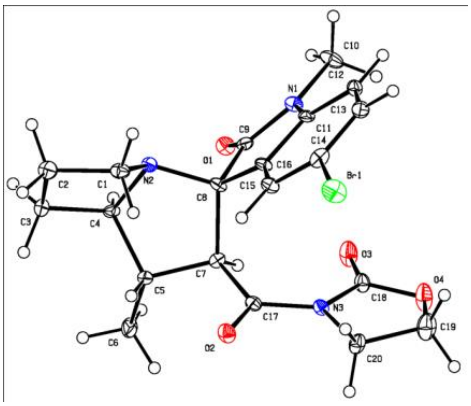
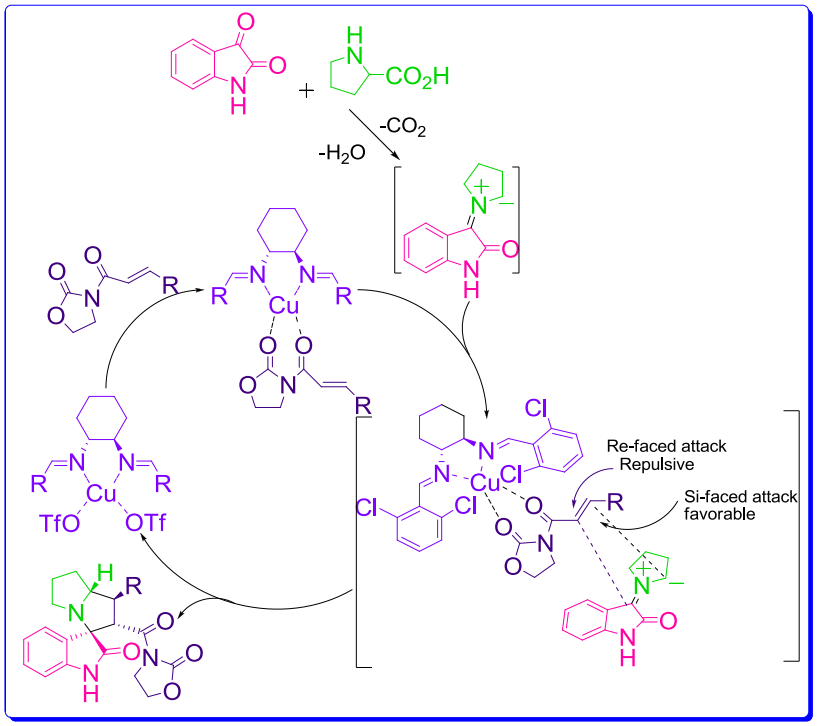


Figure 2. ORTEP diagram of one of the four crystallographic independent molecules in the asymmetric unit of **4g**. Thermal ellipsoids are at 30% probability level.

Because reactions of most non-stabilised azomethineylides with electron-deficient dipolarophiles are HOMO(dipole)-LUMO(dipolarophile) controlled [11], thus, in order to obtain an increased reaction rate, the **3**-$Cu(OTf)_2$was coordinated to the electron-deficient dipolarophileto formsquare planner geometry[12]. On the other hand, condensation of isatin derivative **1** and (S)-proline, after decarboxylation, led to the non- stabilized azomethineylide **2**. The [3+2] cycloaddition of activated dipolarophiles with azomethineylide **2** resulted in the formation of chiral spirooxindolopyrrolizidine **4** which contain contiguous stereogeniccenters. Despite the fact that sixteen different stereoisomerscould can be prepared theoretically, only diastereoisomer **4** was obtained in high yield in all the cases that we present in this article (Scheme 2). Based on the stereochemistry of the cycloadduct clarified by single-crystal X-ray analysis and 2D NMR spectroscopic techniques, the transition state and the reaction pathway were proposed as below:



Scheme 2. Propose of the transition state and the reaction pathway

Experimental

General

General melting points were recorded on an electrothermal digital melting point apparatus. Infrared spectra were recorded on a mattson 1000 FTIR. ^{1}H, ^{13}CNMR spectra were measured with a Bruker DRX-300 AVANCE instrument with $CDCl_3$ as solvent at 300.1 MHz. Mass spectra were recorded on a Finnigan MAT 8430 mass spectrometer operating at an electron energy of 70 eV. Isatin derivatives, proline, were obtained from Fluka (Buchs, Switzerland) and used without further purification, and *trans*-cinnamicacid derived from the menthol was obtained *via* synthesis.

Experimental details and spectra data for new chiral spirooxindolopyrrolizidines 4a-i

General methods: At 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 the 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 $MgSO_4$. The organic layer was concentrated in vacuum to furnish the products, which were recrystallized from ethanol.

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%, [α]D+267.5 (c 0.01, CH_2Cl_2), IR(KBr)(υmax, cm^{-1}): 1694(C=O), 1745(C=O), 1800(C=O), 3420(NH); ^{1}HNMR (300.1 MHz, $CDCl_3$); 1.17 (3H, d, ^{3}JHH=6.3 Hz, CH_3), 1.73-1.93 (4H, m, $2CH_2$), 2.07-2.16 (1H, m, CH), 2.56 (1H, m, CH), 2.83-3.00 (2H, m, CH_2), 3.53-3.62 (1H, m, CH), 3.87-3.96 (3H, m, CH and CH_2), 4.13-4.21 (1H, m, CH), 4.31 (1H, d, ^{3}JHH=9.6 Hz, CH), 6.83-7.23 (4H, m, Ar-H), 7.55 (1H, s, NH); ^{13}CNMR (300.1 MHz, $CDCl_3$); 15.9(1C, CH_3), 24.8, 27.6, 41.3, 42.7, 62.1 (5C, $5CH_2$), 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++2, 30), 69 (100), 131 (45).

3-((1'R,2'S,3R,7a'R)-2-Oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-2'-ylcarbonyl)oxazolidin-2-one (4b): white powder, mp 145-148 C, yield 95%, [α]D+247.2 (c 0.01, CH_2Cl_2), IR(KBr)(υmax, cm-1): 1682(C=O), 1724(C=O), 1788(C=O), 3210(NH); ^{1}HNMR (300.1 MHz, $CDCl_3$); 1.77-2.02 (4H, m, $2CH_2$), 2.67 (1H, m, CH), 3.15 (1H, m, CH), 3.62 (1H, m, CH), 3.80-4.11 (4H, m, OCH_2, 2CH), 4.46 (1H, m, CH), 4.81 (1H, d, ^{3}JHH=9.3 Hz, CH), 6.87-7.63 (9H, m, Ar-H), 7.68 (1H, s, NH); ^{13}CNMR (300.1 MHz, $CDCl_3$); 24.4, 27.4, 29.7, 42.7 (4C, $4CH_2$), 49.3, 53.3, 61.8 (3C, 3CH), 57.9 (1C, OCH_2), 272.1(1C), 110.6, 121.1, 126.1, 126.8, 129.8 (5C, 5CH), 128.7, 129.1 (4C, 4CH), 125.8, 138.2, 143.0 (3C), 153.0, 172.2, 179.9 (3C, 3C=O); MS, 418 (M+ +1, 50), 200 (100), 131 (95), 275 (93).

3-((1'S,2'S,3R,7a'R)-1,1'-Dimethyl-2-oxo-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3' pyrrolizine]-2'-ylcarbonyl)oxazolidin-2-one (4c): white powder, mp 189 C, yield 93%, [α]D+223.1 (c 0.01, CH_2Cl_2), IR(KBr)(υmax, cm-1): 1686(C=O), 1720(C=O), 1778 (C=O); ^{1}HNMR (300.1 MHz, $CDCl_3$); 1.16 (3H, d, ^{3}JHH=6.3 Hz, CH_3), 1.72-2.13 (4H, m, $2CH_2$), 2.57 (1H, m, CH), 2.88 (1H, m, CH), 2.99 (1H, m, CH), 3.16 (3H, s, NCH_3), 3.55 (1H, m, CH), 3.80-3.98 (3H, m, CH and CH_2), 4.11 (1H, m, CH), 4.21 (1H, m, ^{3}JHH=9.3 Hz, CH), 6.78 (1H, d, ^{3}JHH=7.8 Hz, CH), 6.92 (1H, m, CH), 7.14 (1H, d, ^{3}JHH=7.8 Hz, CH), 7.28 (1H, m, CH); ^{13}CNMR (300.1 MHz, $CDCl_3$); 16.4(1C, CH_3), 24.7, 26.4, 27.6, 43.1, 62.7 (5C, $5CH_2$), 41.2(1C, NCH3), 49.3, 60.0, 69.2 (3C, 3CH), 71.5(1C), 108.9, 121.6, 125.7, 130.1 (4C, 4CH), 125.5, 145.4 (2C) 153.3, 172.2, 178.1 (3C, 3C=O); MS: 369 (M+, 9), 214 (100), 131 (59).

3-((1'R,2'S,3R,7a'R)-1-Ethyl-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-2'-ylcarbonyl)oxazolidin-2-one (4d): Yellow powder, mp 103 C, yield 92%, [α]D+224.5 (c 0.01, CH_2Cl_2) IR(KBr)(υmax, cm^{-1}): 1713(C=O), 1765(C=O), 1778 (C=O); ^{1}HNMR (300.1 MHz, $CDCl_3$); 1.38 (3H, t, ^{3}JHH=7.2 Hz, CH_3), 1.76-2.01 (4H, m, $2CH_2$), 2.67 (1H, m, CH), 3.13 (1H, m, CH), 3.61 (1H, m, CH), 3.78-4.11 (6H, m, 2CH, $2CH_2$), 4.46 (1H, m, CH), 4.81 (1H, d, ^{3}JHH=9 Hz, CH), 6.87-7.68 (9H, m, Ar-H); ^{13}CNMR (300.1 MHz, $CDCl_3$); 11.9 (1C, CH_3), 24.4, 27.4, 29.7, 42.7 (4C, $4CH_2$), 35.0 (1C, NCH_2), 49.3, 53.3, 61.8 (3C, 3CH), 57.9 (1C, OCH_2), 72.1(1C), 110.6, 121.1, 126.1, 126.8, 129.8 (5C, 5CH), 128.7, 129.1 (4C, 4CH), 125.8, 138.2, 143.0 (3C), 153.0, 172.2, 179.9 (3C, 3C=O); MS, 445 (M+, 7), 228 (100), 131 (90).

3-((1'R,2'S,3R)-1-Benzyl-2-oxo-1'-phenyl-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-2'-ylcarbonyl)oxazolidin-2-one (4e): white powder, mp 125-128 C, yield 92%, [α]D+253.9 (c 0.01, CH_2Cl_2), IR(KBr)(υmax, cm-1): 1611(C=O), 1719(C=O), 1775(C=O); ^{1}HNMR (300.1 MHz, $CDCl_3$); 1.80-2.04 (4H, m, $2CH_2$), 2.65(1H, m, CH), 3.16 (1H, m, CH), 3.57 (1H, m, CH), 3.76-3.89 (2H, m, CH_2), 3.99-4.11(2H, m, CH_2), 4.52(1H, m, CH), 4.76 (1H, d, ^{3}JHH=15.9 Hz, CH), 4.88 (1H, d, ^{3}JHH=9.3 Hz, CH), 5.13 (1H, d, ^{3}JHH=15.9 Hz, CH), 6.65-7.99 (14H, m, Ar-H); ^{13}CNMR (300.1 MHz, $CDCl_3$); 24.4, 27.4, 29.7, 42.7 (4C, $4CH_2$), 49.3, 53.3, 61.8 (3C, 3CH), 54.3 (1C, NCH_2), 57.9 (1C, OCH_2), 72.1(1C), 110.6, 121.1, 126.1, 126.8, 129.8, 133.8 (6C, 6CH), 127.7, 128.8, 129.5, 129.9 (8C, 8CH), 125.5, 139.8, 141.6 143.4 (4C), 153.1, 172.9, 181.2 (3C, 3C=O); MS, 507 (M+, 9), 290 (100), 131 (65), 91 (58).

3-((1'S,2'S,3R,7a'R)-5-Bromo-1'-methyl-2-oxo-1',2',5',6',7',7a' hexahydrospiro[indoline-3,3'-pyrrolizine]-2'-ylcarbonyl)oxazolidin-2-one (4f): Yellow powder, mp 169 C, yield 99%,[α]D+227.5 (c 0.01, CH_2Cl_2), IR(KBr)(υmax, cm^{-1}): 1620(C=O), 1708(C=O), 1760(C=O), 3428(NH); ^{1}HNMR (300.1 MHz, $CDCl_3$); 1.15 (3H, d, ^{3}JHH=6.7 Hz, CH_3), 1.76-1.96 (4H, m, $2CH_2$), 2.07-2.17 (1H, m, CH_2), 2.57 (1H, m, CH), 2.83-3.05 (2H, m, CH_2), 3.56 (1H, dt, ^{2}JHH=12 Hz, ^{3}JHH=6 Hz, CH), 3.88-3.96 (3H, m, CH and CH_2), 4.16 (1H, dt, ^{2}JHH=12 Hz, ^{3}JHH=6 Hz, CH), 4.31 (1H, d, ^{3}JHH=9 Hz, CH), 6.67 (1H, d, ^{3}JHH=8.0 Hz, Ar-H), 7.27 (1H, m,Ar-H), 7.47 (1H, d, ^{3}JHH=8.0 Hz, Ar-H), 8.06 (1H, s, NH); ^{13}CNMR (300.1 MHz, $CDCl_3$); 16.1(1C, CH_3), 24.2, 27.4, 41.2, 42.7, 62.5 (5C, $5CH_2$), 49.3, 59.9, 69.4 (3C, 3CH), 72.1(1C), 108.5, 122.3, 129.8 (3C, 3CH), 125.9, 142.3, 144.9 (3C) 153.1, 172.9, 179.9 (3C, 3C=O); MS, 434, 436 (M+, M++2, 6), 279, 281 (75), 131 (100).

3-((1'S,2'S,3R,7a'R)-5-Bromo-1,1'-dimethyl-2-oxo-1',2',5',6',7',7a' hexahydrospiro[indoline-3,3'-pyrrolizine]-2'-ylcarbonyl)oxazolidin-2-one (4g): white powder, mp 142 C, yield 92%, [α]D+262.5 (c 0.01, CH_2Cl_2), IR(KBr)(υmax, cm^{-1}): 1686(C=O), 1722(C=O), 1778 (C=O);
^{1}HNMR (300.1 MHz, $CDCl_3$); 1.16 (3H, d, 3JHH=5.1 Hz, CH_3), 1.76-2.17 (4H, m, $2CH_2$), 2.56 (1H, m, CH), 2.93 (2H, m, CH_2), 3.14(3H, s, NCH_3), 3.66

(1H, m, CH), 3.04 (3H, m, CH and CH_2), 4.17 (1H, m, CH), 4.37 (1H, d, ^{3}JHH=9 Hz, CH), 6.67 (1H, d, ^{3}JHH=8.1 Hz, Ar-H), 7.27 (1H, s, Ar-H), 7.43 (1H, d, ^{3}JHH=8.1 Hz, Ar-H); ^{13}CNMR (300.1 MHz, $CDCl_3$); 16.4(1C, CH_3), 24.5, 27.7, 41.3, 42.9, 61.8 (5C, $5CH_2$), 42.4(1C, NCH_3), 49.3, 59.9, 69.8 (3C, 3CH), 72.8(1C), 109.9, 121.3, 130.5 (3C, 3CH), 125.7, 142.6, 144.2 (3C) 153.1, 172.9, 179.8 (3C, 3C=O); MS, 448, 450 (M+, M++2, 6), 292, 294 (M+, M++2, 67), 131 (100).

3-((1'S,2'S,3R,7a'R)-5-Bromo-1-ethyl-1'-methyl-2-oxo-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-2'-ylcarbonyl)oxazolidin-2-one (4h): Yellow powder, mp 135 C, yield 94%, [α]D+237.8 (c 0.01, CH_2Cl_2), IR(KBr)(υmax, cm^{-1}): 1691(C=O), 1709(C=O), 1783 (C=O); ^{1}HNMR (300.1 MHz, $CDCl_3$); 1.15 (3H, d, ^{3}JHH=6.8 Hz, CH_3), 1.39 (3H, t, ^{3}JHH=7 Hz, CH_3),1.76-1.96 (4H, m, $2CH_2$), 2.09-2.17 (1H, m, CH_2),2.56 (1H, m, CH), 2.83-3.05 (2H, m, CH_2), 3.80 (2H, q, ^{3}JHH=7 Hz, CH_2), 3.56 (1H, dt, ^{2}JHH=12 Hz, ^{3}JHH=6 Hz, CH), 3.88-3.96 (3H, m, CH and CH_2), 4.16 (1H, dt, ^{2}JHH=12 Hz, ^{3}JHH=6 Hz, CH), 4.31 (1H, d, ^{3}JHH=9 Hz, CH), 6.67 (1H, d, ^{3}JHH=8.0 Hz, Ar-H), 7.27 (1H, m, Ar-H), 7.47 (1H, d, ^{3}JHH=8.0 Hz, Ar-H); ^{13}CNMR (300.1 MHz, $CDCl_3$); 12.4 (1C, CH_3), 16.1(1C, CH_3), 24.6, 27.7, 41.3, 42.7, 62.8 (5C, $5CH_2$), 35.1 (1C, NCH_2), 49.2, 59.9, 69.4 (3C, 3CH), 72.1(1C), 108.7, 121.1, 129.9 (3C, 3CH), 125.8, 142.8, 144.7 (3C) 153.1, 172.9, 179.9 (3C, 3C=O); MS, 462, 464 (M+, M++2, 5), 307, 309 (M+, M++2, 60), 131 (100).

3-((1'R,2'S,3R,7a'R)-5-Bromo-1-methyl-2-oxo-1'-phenyl-1',2',5',6',7',7a' hexahydrospiro[indoline-3,3'-pyrrolizine]-2'-ylcarbonyl)oxazolidin-2-one (4i): white powder, mp 122 C, yield 91%, [α]D+227.5 (c 0.01, CH_2Cl_2), IR(KBr)(υmax, cm^{-1}): 1614(C=O), 1711(C=O), 1785 (C=O); ^{1}HNMR (300.1 MHz, $CDCl_3$); 1.77-2.02 (4H, m, $2CH_2$), 2.67 (1H, m, CH), 3.15 (1H, m, CH), 3.24 (3H, s, NMe), 3.61 (1H, m, CH), 3.78-4.06 (4H, m, OCH_2, 2CH), 4.46 (1H, m, CH), 4.81 (1H, d, ^{3}JHH=9 Hz, CH), 6.87-7.68 (8H, m, Ar-H); ^{13}CNMR (300.1 MHz, $CDCl_3$); 24.4, 27.4, 29.7, 42.7 (4C, $4CH_2$), 42.1 (1C, NCH_3), 49.3, 53.3, 61.8 (3C, 3CH), 57.9 (1C, OCH_2), 72.1(1C), 110.6, 121.1, 126.1, 129.8 (4C, 4CH), 128.7, 129.1 (4C, 4CH), 125.8, 138.2, 141.5, 144.1 (4C), 153.0, 172.2, 179.9 (3C, 3C=O); MS, 510, 512 (M+, M++2, 90), 293, 295 (95), 131 (100).

3-((1'S,2'S,3R,7a'R)-1'-Methyl-5-nitro-2-oxo-1',2',5',6',7',7a'-hexahydrospiro[indoline-3,3'-pyrrolizine]-2'-ylcarbonyl)oxazolidin-2-one (4j): Yellow powder, mp 130-133 C, yield 88%, [α]D+243.7 (c 0.01, CH_2Cl_2), IR(KBr)(υmax, cm^{-1}): 1690(C=O), 1753(C=O), 1777(C=O), 3449(NH); ^{1}HNMR (300.1 MHz, $CDCl_3$); 1.19 (3H, d, ^{3}JHH=6.6 Hz, CH_3), 1.67-1.83 (2H, m,CH_2), 1.87-2.18 (2H, m, CH_2) 2.52 (1H, m, CH), 2.66 (2H, m, CH_2), 3.70 (1H, m, CH), 3.86 (1H, m, CH), 3.97-4.08 (1H, m, CH), 4.23 (2H, m, CH_2), 6.96 (1H, d, 3JHH=8.4 Hz, CH), 8.00 (1H, d, ^{4}JHH=3 Hz, CH), 8.22 (1H, dd, ^{3}JHH=8.4 Hz, ^{4}JHH=3 Hz, CH), 8.32 (1H, s, NH); ^{13}CNMR (300.1 MHz, $CDCl_3$); 15.9(1C, CH_3), 24.6, 27.7, 41.3, 42.8, 62.9 (5C, $5CH_2$), 49.3, 59.9, 69.4 (3C, 3CH), 71.9(1C), 110.5,

121.1, 129.8 (3C, 3CH), 125.9, 142.7, 144.8 (3C) 153.0, 172.3, 179.7 (3C, 3C=O); MS, 400 (M+, 8), 245 (100), 131 (57).

Conclusion

Simple cyclohexane-1,2-bis(arylmethyleneamine) ligands with copper(II) triflate catalyzed 1,3-dipolar cycloaddition reaction of azomethineylides with electron-deficient dipolarophile to give spiropyrrolizidineoxindoles in good yield with high regio-, diastereo-, and enantioselectivity (up to 93% ee) in optimized condition. The reaction was accomplished with 10% catalyst at room temperature in environmentally friendly aqueous ethanol. The structures of the products were elucidated using IR, mass, one and two dimensional NMR techniques, and X-ray single crystal diffraction. The reaction mechanism is briefly discussed on the basis of the assignment of the absolute configuration of the cycloadduct.

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