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An Efficient and One-pot Procedure for the Synthesis of Chiral Isoxazolidine *via* Catalytic Highly Enantioselective 1,3-dipolar cycloaddition

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Abstract

Synthesis of enantiomerically pure isoxazolidine *via* an asymmetric 1,3- dipolar cycloaddition reaction of nitrone 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 bidendate bis(imine)–Cu(II)triflate complex as catalyst. The reaction mechanism is discussed on the basis of the assignment of the absolute configuration of the cycloadducts.

Keywords: *Asymmetric 1,3-dipolar, Chiral auxiliaries, Chiral isoxazolidine, Nitrone .*

Introduction

Chiral isoxazolidines are important building blocks for the construction of biologically active compounds [1]. One of the most efficient approaches for the preparation of such isoxazolidines is the enantioselective 1,3-dipolar cycloaddition of nitrones with olefins, catalyzed by various chiral metal-containing complexes [2-4]. Since the early 1970s when proline was found to catalyze intramolecular aldol reactions,[5] a range of other metal-free organic compounds have been applied as catalysts in a variety of organic reactions [6]. One example is the highly enantioselective 1,3-dipolar cycloaddition reaction of nitrones with α,β- unsaturated aldehydes catalyzed by chiral imidazolidinone salts [7]. The catalytic effect of these salts has been described as being due to a reversible reaction between the catalyst and the starting aldehyde leading to an activation of the α,β-unsaturated aldehyde by iminium ion formation [7].

We reported the enantiomerically pure novel spirooxindole by applying optically active cinnamoyloxazolidinone as chiral auxiliary

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and the enantioselectivities were exceptionally high [8]. 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 spirooxindole [9], we applied copper complex of cyclohexane-1,2-bis(arylmethyleneamine) ligands (Fig 2) as a catalyst to synthesis of a spirooxindole [10]. In this paper, a new derivative of chiral ligand 1 (containing imine group) in 2 steps from a cheap and readily available substrate (1,2-diaminocyclohexane) were synthesized in good yield (Fig 1) [11-19]. We wish to report a highly endo- and enantioselective 1,3-dipolar cycloaddition reaction of nitrone, derived from benzaldehyde, with electron-deficient dipolarophile by using bidendate bis(imine)-Cu(II) complex 5, that can be readily assembled from commercially available trans 1,2-cyclohexanediamine and a variety of suitable benzaldehyde precursors, in optimized reaction condition. Based on experiences in our previous works and literature survey [20], Initially, the effects of substituents of bis (imines) ligands 5(a-g) were examined using 10 mol% [$Cu(OTf)_2$] as catalyst in a typical reaction of nitrone 6 with dipolarophile 7 at various temperature and solvent (Scheme 1). Results are summarized in Table 1.

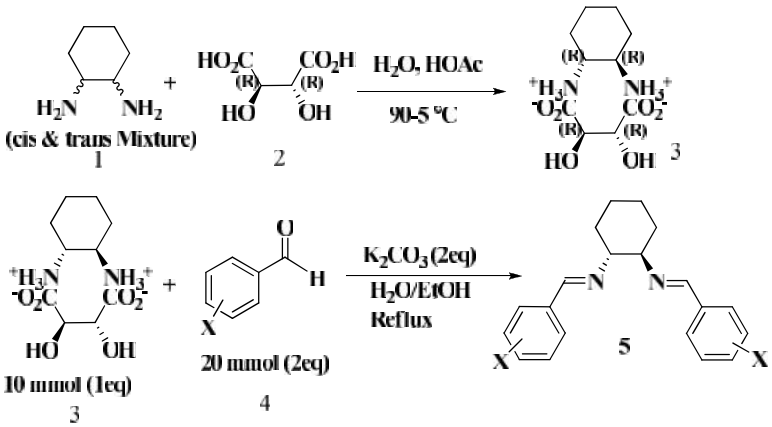


Figure 1. synthesis of chiral cyclohexane-1,2-bis(arylmethyleneamine) ligands **5.**

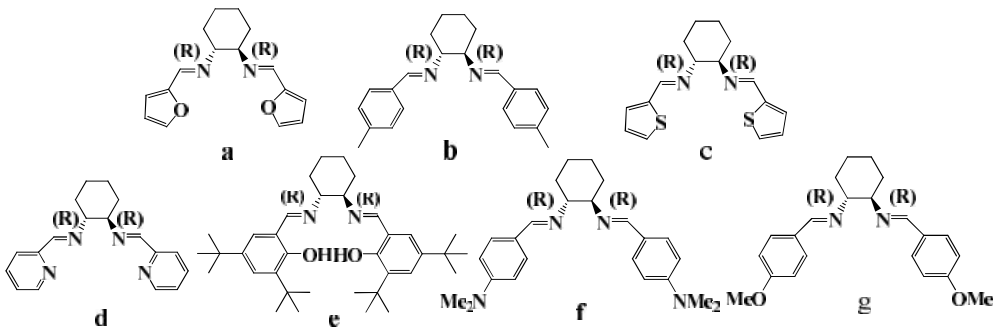
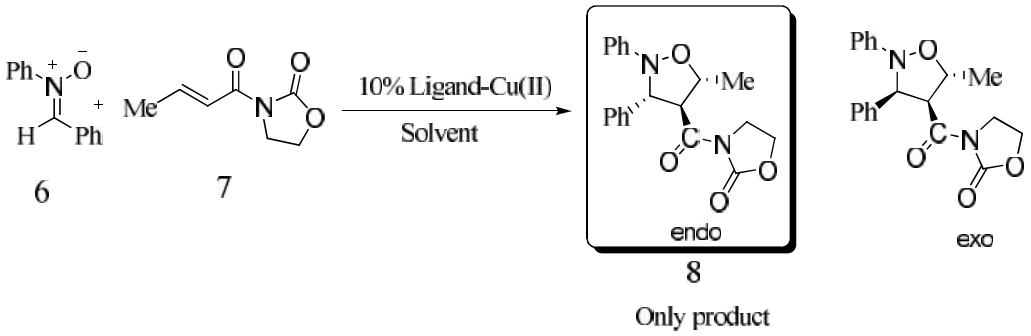


Figure 2. chiral cyclohexane-1,2-bis(arylmethyleneamine) ligands 5(a-g).



Scheme 1. Asymmetric synthesis of chiral isoxazolidine **8** with ligand of **5.**

Experimental

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 CDCl3 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. benzaldehyde, n-phenylhydroxylamine, were obtained from Fluka (Buchs, Switzerland) and were used without further purification, and trans-crotonic acid derived from the oxazoline were obtained via synthesized.

General procedure

General procedure for synthesis of (1R,2R)-cyclohexane-1,2-diaminium (2R,3R)-2,3-dihydroxysuccinate (3)

150 g (1000 mmol) L-tartaric acid was solved in a beaker containing 500 ml of water with a mechanical stirrer. Then, while the solution was stirred, 240 ml (2000 mmol) racemic mixture of cis and trans diamino-cyclohexane was added so that the temperature is not greater than 70 C°. After complete dissolution, 100 ml analytical grade acetic acid was added slowly so that the temperature of 90 C° remained unchanged. The mixture was allowed to cool for 2 h in an ice bath. The reaction mixture was filtered and white precipitate washed with water and methanol.

General procedure for synthesis of (1R,2R)-N1,N2-bis(arylomethylene)cyclohexane-1,2-diamine (5)

A mixture of tartrate salt (R_2,R_1)-trans-diamino cyclohexane (10 mmol, 2/64 g) and potassium carbonate (20 mmol, 2/76 g) was solved in water (3 mL). Then 20 mmol aldehyde dissolved in 5 ml ethanol was added and reflux for 2 h. The solvent is evaporated and compounds 5(a-g) were obtained.

(5a); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) =1.46 (2H, m, $2CH_2$), 1.85 (6H, m, $3CH_2$), 3.33 (2H, m, 2CH), 6.98 (2H, t, ^{3}J = 4.5 Hz, 2CH), 7.15 (2H, d, ^{3}J = 4.2 Hz, 2CH), 7.30 (2H, d, ^{3}J = 5.1 Hz, 2CH), 8.28 (2H, s, 2CH=N); 13C

NMR (75 MHz, $CDCl_3$): δ_C (ppm)= 24.2, 32.8 (4C, $4CH_2$), 73.7(2C, 2CH), 128.7, 129.0, 134.6 (10C, 10CH), 136.2 (2C), 159.7 (2C, 2CH=N); MS (m/z %): 359 (M^+, 6), 186 (44), 221 (100), 140 (100), 125 (45), 89 (53).

(5b); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm)=1.49-1.88 (8H, m, $3CH_2$), 2.52 (6H, s, $2CH_3$), 3.39 (2H, m, 2CH), 7.12 (4H, t, ^3J=9Hz, ArH), 7.49 (4H, t, ^3J=9Hz, ArH), 8.18 (2H, s, 2CH=N); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm)= 21.4 (2C, $2CH_3$), 24.5, 33.0 (4C, $4CH_2$), 73.8 (2C, 2CH), 127.9, 129.0 (8C, 8CH), 133.7 (2C), 140.3 (2C), 160.9 (2C, 2CH=N).

(**5c**); 1H NMR (300 MHz, $CDCl_3$): δ_H (ppm) =1.46 (2H, m, $2CH_2$), 1.85 (6H, m, $3CH_2$), 3.33 (2H, m, 2CH), 6.98 (2H, t, ^3J = 4.5 Hz, 2CH), 7.15 (2H, d, ^3J = 4.2 Hz, 2CH), 7.30 (2H, d, ^3J = 5.1 Hz, 2CH), 8.28 (2H, s, 2CH=N); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm)= 24.3, 32.7 (4C, $4CH_2$), 73.9 (2C, 2CH), 128.7, 129.0, 134.2 (10C, 10CH), 136.1 (2C), 158.8 (2C, 2CH=N); MS (m/z %): 375 (M^+, 6), 110 (74), 98 (100), 84 (53).

(**5d**); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) =1.45 (2H, m, $2CH_2$), 1.78 (6H, m, $3CH_2$), 2.10 (2H, s, 2CH), 3.48 (2H, m, 2CH), 7.14 (2H, t, ^3J = 6.6 Hz, 2CH), 7.57 (2H, t, ^3J = 7.5 Hz, 2CH), 7.82 (2H, d, ^3J = 7.8 Hz, 2CH), 8.26 (2H, s, 2CH=N), 8.47 (2H, s, 2CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) =24.3, 32.6 (4C, $4CH_2$), 73.5 (2C, 2CH), 121.3, 124.4, 149.1, 154.5 (8C, 8CH), 136.4 (2C), 161.3 (2C, 2CH=N).

(**5e**); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm)=1.27 (18H, s, $6CH_3$), 1.56 (18H, s, 6 CH_3), 1.86 (2H, m, 2CH), 2.03 (6H, m, $3CH_2$), 3.42 (2H, m, 2CH), 7.13 (2H, s, 2CH), 7.45 (2H, s, 2CH), 8.44 (2H, s, 2CH=N), 13.86 (2H, s, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm)=24.4, 31.5(4C, $4CH_2$), 29.6, 33.3 (12C, $12CH_3$), 34.1, 35.0 (2C), 72.5 (2C, 2CH), 117.9 (2C, 2CH), 126.1 (2C, 2CH), 126.8 (2C), 136.4 (2C), 139.9 (2C), 158.1 (2C), 165.9 (2C, 2CH=N).

(**5f**); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm)=1.47-1.83 (8H, m, $3CH_2$), 2.95 (12H, s, $4NCH_3$), 3.32 (2H, m, 2CH), 6.60 (4H, t, ^3J=9Hz, ArH), 7.48 (4H, t, ^3J=9Hz, ArH), 8.10 (2H, s, 2CH=N); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm)= 24.7, 33.3 (4C, $4CH_2$), 40.2 (2C, $2CH_3$), 73.9 (2C, 2CH), 111.5, 129.3 (8C, 8CH), 124.8 (2C), 151.7 (2C), 160.8 (2C, 2CH=N).

(**5g**); ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm)=1.48-1.87 (8H, m, $3CH_2$), 3.34 (2H, m, 2CH), 3.85 (6H, s, $2OCH_3$), 6.83 (4H, t, ^3J=9Hz, ArH), 7.53 (4H, t, ^3J=9Hz, ArH), 8.13 (2H, s, 2CH=N); 13C NMR (75 MHz, $CDCl_3$): δ_C (ppm)= 24.5, 33.1 (4C, $4CH_2$), 55.2 (2C, $2CH_3$), 73.7 (2C, 2CH), 113.7, 129.4

(8C, 8CH), 133.7 (2C), 160.3 (2C), 161.2 (2C, 2CH=N).

General procedure for synthesis of isoxazolidine (8)

At the first, a mixture containing (10% mol) aimin base ligand and transition metal salts (10% mol) was prepared in 5 ml ethanol. Then a mixture of nitrone (1 mmol) and 3-(2-alkenoyl)-1,3-oxazolidin-2-ones (1 mmol), in 5 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 $MgSO_4$. The organic layer was concentrated in vacuum to furnish the products, which were recrystallized from ethanol.

^{1}H NMR ($CDC1_3$): 1.56 (3H, d, ^3J = 5. 9 Hz, CH_3), 3.97-4.03 (2H, m, CH_2), 4.03-4.38 (2H, m, OCH_2), 4.8 (lH, d, ^3J= 6 Hz, CH), 5. 19 (lH, d , 3J= 6 Hz, CH), 6.91-7.01 (3H, m, ArH), 7.22-7.5 (7H, m, ArH).

Result and discussion

The highest enantioselectivity (92%) and high yield were achieved by employing solvent of ethanol (Table 1, by comparison of entries 1-7). Considering the ethanol as the best solvent, we tested the effect of temperature. The yields and enantiomeric rations of the products showed the temperature dependence in this process. A decrease in the reaction temperature from 25 °C to 0 °C and -25 oC decreased the reaction yield and enantioselectivity (entries 5, 7 and 8) and increase in the reaction temperature from 25 °C to 40 °C increased the time reaction and decreased yield and enantioselectivity (entries 5and 8).

Table 1. Synthesis of chiral isoxazolidine **8.**

Entry	Ligand	T (C)	Time(h)	**8**	
				Yield (%)[a]	Ee(%)[b]
1	$CHCl_3$	25	32	88	63
2	EtOAC	25	28	90	55
3	CH_2Cl_2	25	32	85	83
4	n-Hexan	25	28	93	74
5	EtOH	25	16	90	92
6	CH_3CN	25	32	85	Race
7	EtOH	0	48	25	Race
8	EtOH	-20	48	<15	n.d
9	EtOH	40	36	<15	n.d

[a]Isolated yield.
[b]Determined by chiral HPLC analysis.

Considering the ethanol as the best solvent and the 25 oC as the best temperature, we tested the effect of ligands (Table 2).

Table 2. Asymmetric synthesis of chiral isoxazolidine **8.**

Entry	Solvent	Yield (%)	Ee(%)[c]
1	1a	93	82
2	1b	90	86
3	1c	93	88
4	1d	86	89
5	1e	90	92
6	1f	98	86
7	1g	92	91

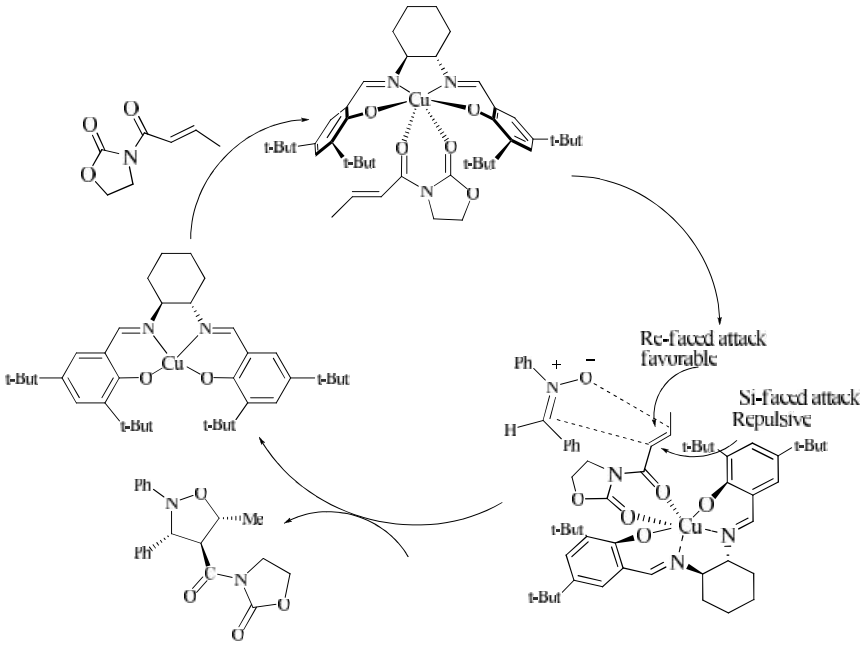
The ligand salen (1e) bearing the relatively bulky tert-butyl substituents at the 2- and 4-positions of the benzene ring resulted in considerably higher yields and enantioselectivities in comparison with the other ligands [21]. The highest enantioselectivity (92%) and yield in high selectivity were achieved by employing ligand 1e. Considering the 1e as the best ligand, we tested the effect of Cu salts (Table 3). 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 55–92% and longer reaction times (entries 3-4 vs.2). The use of $Zn(OAc)_2$ instead of $Cu(OTf)_2$ gave worse result in term of enantioselectivity (entry1). 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. It should be noted, 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 3. dependence of reaction with Lewis acid.

Entry	Lewis acid	Time(h)	**8**[a]	
			Yield (%)[b]	Ee(%)[c]
1	$Zn(OAc)_2$	12	>99	Race
2	$Cu(OTf)_2$	16	90	92
3	$Cu(OAc)_2$	23	91	50
4	$Cu(Cl)_2$	28	76	Race
5	$Cu(OTf)_2$[d]	22	93	55

[a]reaction of 6 (1 mmol) with 7 (1 mmol) was carried out in 10 ml of EtOH at room temperature in the presence of 10% catalyst [Lewis acid-1=1.0:1.1], unless otherwise noted.
[b]Isolated yield.
[c]Determined by chiral HPLC analysis.
[d]20% catalyst is used.

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 one characteristic triplet and two doublets in the ^{1}H NMR spectra of products 8 confirmed unambiguously the formation of a isoxazolidine ring. For example, the ^{1}HNMR spectrum of 8 for exhibits a doublet signal at δ = 1.56 ppm, a triplet at δ = 4.82 and a doublet at δ = 5.20 ppm. The absolute configuration of enantiomer of *endo*-8 can be assigned on the basis of our previous investigation. Based on the stereochemistry of the cycloadduct, the following reaction mechanism and the transition state for present work were proposed (scheme 2). Because reactions of most stabilised nitrone with electron-deficient dipolarophiles are HOMO(dipole)-LUMO(dipolarophile) controlled [22], thus, in order to obtain an increased reaction rate, the 5-$Cu(OTf)_2$ was coordinated to the electron-deficient dipolarophile to form square planner geometry [23]. On the other hand, condensation of N-phenylhydroxylamine and benzaldehyde, led to the stabilized nitrone 6. The [3+2] cycloaddition of activated dipolarophiles with nitrone 6 resulted in the formation of chiral isoxazolidine 8 which contain contiguous stereogenic centers. Despite the fact that nine different stereoisomers could be prepared theoretically, only diastereoisomer *endo*-8 was obtained in high yield in all the cases that we present in this article. On the basis of the absolute structure of the three chiral centers in the isoxazolidine ring, it is determined that the nitrone approaches *endo* to the Re-face of the dipolarophile in an S-cis conformation when coordinated to the Cu(II)-Salen. The transition state and the reaction pathway were proposed as below:



Scheme 2. A plausible reaction pathway for the enantioselective [3+2] cycloaddition of nitrone and dipolarophile.

Conclusion

Because of wide distribution in nature and variegated biological activities, chiral isoxazolidine alkaloids are very attractive synthetic targets. For the reason that a isoxazolidine can beviewed as a fused isoxazolidine, thus method employed for the formation of isoxazolidine rings can be used to construct the isoxazolidine ring system. So, the asymmetric 1,3-Dipolar cycloaddition reaction of nitrone, with olefins can be useful method for the synthesis of chiral isoxazolidine. In result of we have found a chiral synthetic method for the prepration of isoxazolidine of potential synthetic interest. The present method carries the advantage that not only is the reaction performed under neutral conditions, but also the starting materials and reagents can be mixed without any activation or modification.

Acknowledgments

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