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ACCEPTED MANUSCRIPT

Enantioselective Insertion of Carbenoids into N-H Bonds Catalyzed by Chiral Bicyclo Bisoxazoline Copper(I) Complexes.

Paul Le Maux* and Gérard Simonneaux*

Institut des Sciences Chimiques de Rennes, UMR CNRS 6226, Ingénierie Chimique et Molécules pour le Vivant, Campus de Beaulieu, 35042 Rennes Cedex, France

Abstract

Chiral copper(I)-bicyclobisoxazoline complexes were found to catalyse the insertion of α-diazocarbonyl compounds into N-H bonds of aniline derivatives. The insertion reactions proceeded with high yields (78-99%) and enantioselectivities of up to 81% for the different α-diazopropionates. A predominant effect of the nature and the position of the substituents on the enantiocontrol of the reaction was observed.

Keywords: N-H insertion catalysis; Copper; Chiral bisoxazoline ; Enantioselectivity.

* Corresponding author. E-mail address: paul.lemaux@univ-rennes1.fr (P. Le Maux).

1. Introduction

The transition-metal-catalyzed insertion of carbenoid species derived from α-diazocarbonyl compounds into X-H bonds (X = C, N, O, S, Si, etc.) has been widely recognized as a direct and efficient method for the construction of carbon-carbon and carbon-heteroatom bonds.[1-6] Among the insertion reactions, metal-catalyzed N-H insertions are of great importance, because they lead to the formation of various bioactive molecules such as α-amino acid derivatives, α-amino ketones, and pharmaceutically useful compounds.[7-16] The earliest example of an asymmetric N-H insertion is the chiral auxiliary approach of Kagan who developed a diastereoselective CuCN-catalyzed reaction with chiral amines or chiral diazoester acetates resulting in up to 26% de.[17] The first significant progress was realized in 1996 by McKervey in an intramolecular N-H insertion reaction, catalyzed by chiral rhodium (II) carboxylates leading to pipecolic acid derivatives with up to 45% ee.[18] Jørgensen and coworkers reported the first asymmetric intermolecular N-H insertion reactions by means of chiral copper(I)/silver(I) bisoxazoline.[19] Although only low to moderate yields and ee values were obtained, this study has actually opened the doors to new developments in the area of asymmetric N-H insertion reactions with copper. Chiral rhodium complexes can also be good catalysts for such reaction but the facility with which rhodium carbenoids undergo C-H insertion[20] and β-elimination[21] remains a problem with certain substrates. Since then developments with copper(I) have been rapid and high enantioselectivities have been achieved.[22-24] Zhou and coworkers[22] reported excellent ee values (98%) and yield (96%) using a catalytic system consisting of a spirobisoxazoline ligand, CuCl, and NaBARF (BARF = $[B[3,5-(CF_3)_2C_6H_3]_4]^-$) in the insertion of $MeC(N_2)CO_2R$ into aniline derivatives. Other chiral bisoxazolines with different backbones, such as Box, Pybox, and Binabox exhibited low enantioselectivity (0-12% ee).[5] This clearly demonstrates in these studies that the chiral spirobiindane structure of bisoxazoline was essential for obtaining high enantioselectivity in

Cu-catalyzed asymmetric N-H insertion reaction. Two other systems, using Cu(I) complexes of bis (azaferrocene) and binol derivatives as catalysts, have also been developed, they exhibited excellent enantioselectivities (up to 98%).[15,25]

In view of the great utility of this N-H insertion reaction, the exploration of alternative efficient catalytic system is still desirable. Our group has first demonstrated that ruthenium porphyrin complexes catalyze the ethyl diazoacetate insertion into N-H and S-H bonds in 1997.[26,27] Recently, we reported the application of a bisoxazoline ligand (Fig. 1), previously introduced by Takacs et al.[28] for the asymmetric copper-catalyzed Diels-Alder reaction.[29] Herein, we describe a readily available copper(I) catalytic system generated from bisoxazoline ligands bearing a chiral dihydroethanoanthracene backbone (L*) (Fig. **1**) and CuOTf for asymmetric N-H insertion of α-alkyl-α-diazoesters with aniline derivatives.

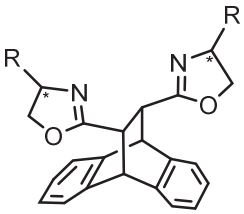


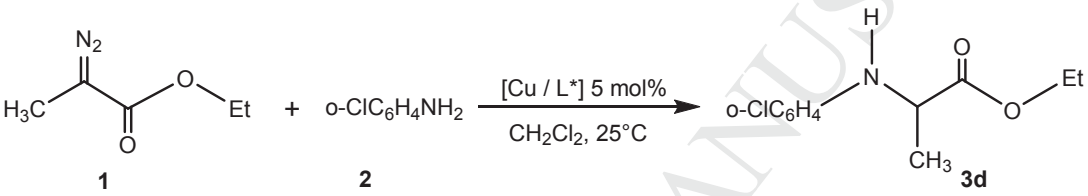
Fig.1. Structures of the chiral bicyclobisoxazoline ligands.

2. Results and discussion

Studies realized on the copper-catalyzed asymmetric N-H insertion of ethyl α-diazopropionate with aniline have demonstrated that the enantioselectivity was directly related to the anion of the copper precursor.[19,22] The smaller and stronger coordinating anions were found to be inferior to the larger and weaker coordinating anions for chiral induction. On this basis, various copper catalyst precursors were tested with different counterions (OTf^-, $BARF^-$, PF_6^-). We can see in Table **1** that the nature of the counterion had a significant effect on the enantioselectivity. The catalytic system with the smaller and stronger coordinating

OTf^- was the most efficient in the N-H insertion reaction of *o*-chloraniline with ethyl α-diazopropionate, 77% ee (entry 1). The weakly coordinating PF_6^- gave the insertion product in only 22% ee (entry 2), while with the larger and non-coordinating ion $BARF^-$ the enantioselectivity was in the range of 54-57% ee (entries 3 and 4). These results are in contrast with those reported by Zhou where excellent ee values (up to 98%) were obtained using a catalytic system consisting of a spirobisoxazoline ligand, CuCl, and NaBARF, but only 5% ee with CuOTf.[22]

Table 1. Cu-catalyzed asymmetric insertion of ethyl α-diazopropionate into N-H bond of *o*-Cl aniline[a]



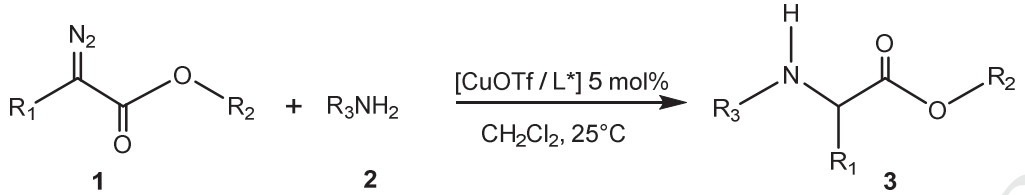
Entry	[Cu]	Product	Yield (%)	Ee (%)
1	CuOTf $(C_6H_6)_{1/2}$	**3d**	97	77
2	$Cu(CN)_4PF_6$	**3d**	97	22
3	$Cu(CN)_4PF_6$/NaBARF[b]	**3d**	97	57
4	CuCl/NaBARF[b]	**3d**	78	54

[a] Reaction conditions: [Cu] (5 μmol) and ligand (6 μmol) were mixed in CH_2Cl_2 (1 ml) for 1 h at 25°C, then o-Claniline (100 μmol) and ethyl 2-diazopropionate (100 μmol) were introduced and stirred for 1 h at 25°C. [b] NaBARF (6 μmol).

With the optimized conditions in hand, our catalytic system has been applied to a variety of substituted anilines. The N-H insertion reaction of different alkyl-α-diazoester compounds in the presence of catalysts derived from the chiral ligand bicyclobisoxazoline (L*) and Cu(I) triflate was investigated. As shown in Table **2**, the reactions with ethyl and benzyl α-diazopropionate afforded the corresponding insertion products in one hour with high yields (>95%) and in the range of 78-81% with *t*-butyl α-diazopropionate. The presence of halogen substituents at the *ortho*-position of aniline derivatives led to a significant increase in

enantioselectivity relative to *meta* and *para*-position, probably because of steric hindrance and electronic effect. Both effects appear favorable in controlling the enantioselectivity (entries 3, 4, 5, 19, and 20). The substitution of aniline with the chloro group in the *ortho*-position gave the major improvement of enantioselectivity with ethyl α-diazopropionate, 46% *vs* 77% ee (entries 1 and 4). No such stereoelectronic effect has already been reported. Zhou had rather observed a slightly diminution of the enantioselectivity when a halogen atom was introduced in the *ortho* position of aniline but the enantioselectivity remains high (85-91%).[22] The enantioselectivity decreased with *m*-Cl and *p*-Cl aniline, 66 and 48% ee respectively (entries 8 and 10). Electron-donor methyl group at the *ortho*, *meta* and *para*-positions afforded lower enantioselectivities, 42%, 33% and 31% ee respectively (entries 2, 7 and 9). In order to optimize the enantioselectivity of the reaction, the influence of the steric hindrance of ester group of diazo compound was examined. The enantioselectivity was increased when the ester group was changed from ethyl to *t*-butyl group in the reaction with aniline, ee up to 53% (entrie 11), and also with *o*, *m* and *p*-Me aniline, ee up to 56, 44 and 47% respectively (entries 12, 13 and 14). In contrast, the enantioselectivity decreased with *o*-Cl aniline to 67 % ee (entry 15). The reason for the negative effect of the chloro substituent is unclear. With a benzyl group on the diazoester, the highest enantioselectivity was obtained in the reaction with *o*-Cl aniline, 81% ee (entry 19). In the reaction of ethyl α-phenyl diazoacetate (R_1 = Ph) with *o*-Cl aniline, the insertion product was formed in 84% yield and 50% ee (entry 21). From observation of these results, the steric bulks of the substituents on the diazoester modify weakly the enantioselectivity, compared to the effect of the electron-withdrawing substituent in the *ortho*-position of the aniline. Increase of the steric bulk by using 1-naphtylamine as the substrate, which is a disubstituted aniline, the reaction provided 85% yield and 43% ee (entry 22). The alkylamines, *n*-butylamine and *t*-butylamine (entries 23 and 24) did not react.

Table 2. Catalytic asymmetric N-H insertion of amines with α-diazoesters[a]



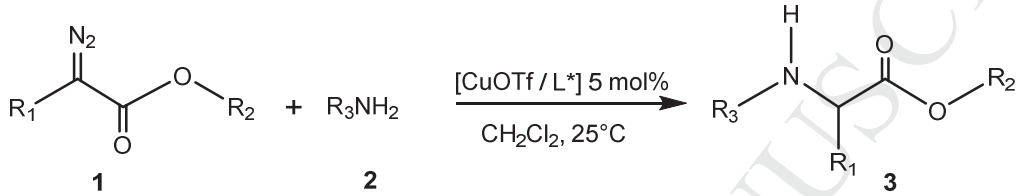
Entry	R_1	R_2	R_3	Product	Yield (%)	Ee (%)
1	Me	Et	C_6H_5	**3a**	98	46[b]
2	Me	Et	*o*-MeC_6H_4	**3b**	97	42
3	Me	Et	*o*-FC_6H_4	**3c**	98	72
4	Me	Et	*o*-ClC_6H_4	**3d**	97	77
5	Me	Et	*o*-BrC_6H_4	**3e**	98	74
6	Me	Et	*o*-I C_6H_4	**3f**	98	67
7	Me	Et	*m*-MeC_6H_4	**3g**	98	33
8	Me	Et	*m*-ClC_6H_4	**3h**	98	66
9	Me	Et	*p*-MeC_6H_4	**3i**	98	31
10	Me	Et	*p*-ClC_6H_4	**3j**	99	48
11	Me	*t*-Bu	C_6H_5	**3k**	86	53
12	Me	*t*-Bu	*o*-MeC_6H_4	**3l**	83	56
13	Me	*t*-Bu	*m*-MeC_6H_4	**3m**	78	44
14	Me	*t*-Bu	*p*-MeC_6H_4	**3n**	92	47
15	Me	*t*-Bu	*o*-ClC_6H_4	**3o**	89	67
16	Me	*t*-Bu	*m*-ClC_6H_4	**3p**	88	67
17	Me	*t*-Bu	*p*-ClC_6H_4	**3q**	91	55
18	Me	CH_2Ph	C_6H_5	**3r**	98	52
19	Me	CH_2Ph	*o*-ClC_6H_4	**3s**	98	81
20	Me	CH_2Ph	*o*-BrC_6H_4	**3t**	97	73
21	Ph	Et	*o*-ClC_6H_4	**3v**	84	50
22	Me	Et	1-Naphtyl	**3w**	85	43
23	Me	Et	*n*-Bu	**3x**	0	-
24	Me	Et	*t*-Bu	**3y**	0	-

[a] Reaction conditions: CuOTf (5 μmol) and ligand (6 μmol) were mixed in CH_2Cl_2 (1 ml) for 1 h at 25°C, then aniline (100 μmol) and alkyl α-diazopropionate(100 μmol) were introduced and stirred for 1 h at 25°C. [b] The absolute configuration (S) of **3a** was determined by comparison of the optical rotation with the reference.[22]

The influence of different substituent groups on the ligand was summarized in Table **3**. With aniline and *o*-Cl aniline as substrates, the yields were better with the ligand bearing

phenyl susbtituent, 97-98% (entries 1 and 2). The enantioselectivity was improved from an *i*-butyl (48% ee) to *t*-butyl (69% ee) and phenyl substituents (77% ee) (entries 6, 4 and 2 respectively) with *o*-Cl aniline as substrate. The ee values were lower with aniline. Other reaction condition such as excess of ligand did not significantly influence the enantioselectivity of the catalyst whereas lower temperature (0°C) decreased the yield and enantioselectivity.

Table 3. Catalytic asymmetric N-H insertion of arylamines with ethyl α-diazopropionate with different ligands[a]



Entry	Ligand R =	R_1	R_2	R_3	Product	Yield (%)	Ee (%)
1	**Ph**	Me	Et	C_6H_5	**3a**	98	46
2	**Ph**	Me	Et	*o*-ClC_6H_4	**3d**	97	77
3	***t*-Bu**	Me	Et	C_6H_5	**3a**	82	56
4	***t*-Bu**	Me	Et	*o*-ClC_6H_4	**3d**	75	69
5	***i*-Bu**	Me	Et	C_6H_5	**3a**	86	23
6	***i*-Bu**	Me	Et	*o*-ClC_6H_4	**3d**	77	48

[a] Reaction conditions: CuOTf (5 µmol) and ligand (6 µmol) were mixed in CH_2Cl_2 (1 ml) for 1 h at 25°C, then aniline (100 µmol) and ethyl α-diazopropionate (100 µmol) were introduced and stirred for 1 h at 25°C.

In order to obtain information on the reaction mechanism, investigations on the catalyst structure were undertaken by electrospray ionization mass spectrometry (ESI-MS) analysis. ESI-MS of CuL* prepared in situ from CuOTf and ligand L* revealed the presence of two species in solution (*m*/*z* 559.1445, $[CuL^*]^+$ and *m*/*z* 1055.3595, $[CuL_2^*]^+$). An analogy can be made with a previous study with copper complex bearing spirobisoxazoline ligand (L) prepared in situ from CuCl and the ligand (L).[23] Species of the type $[CuL]^+$ and $[CuL_2]^+$ have also been detected together with a dimeric species $[Cu_2Cl(L)_2]^+$. Formation of $[CuL_2]$ was

related to the fragmentation of the dimer. In our case, only traces of the dimeric species [$Cu_2OTf(L^*)_2$] (0.02%) were present, due to a possible instability in the ESI-MS conditions.

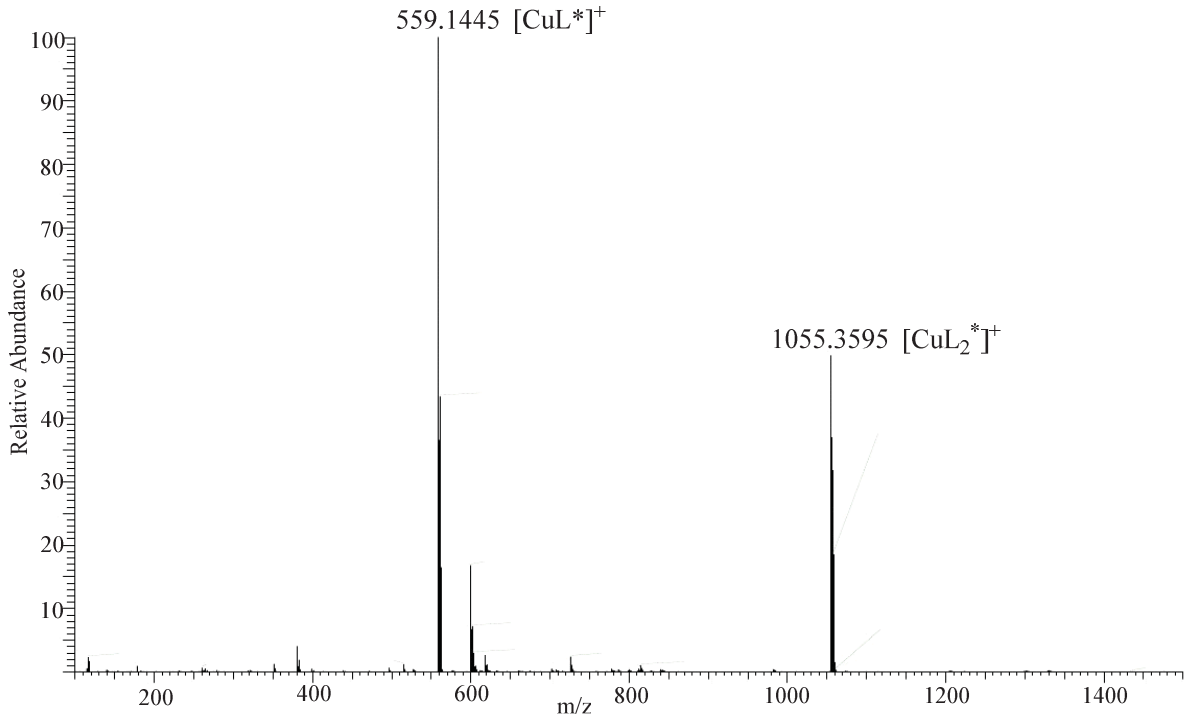
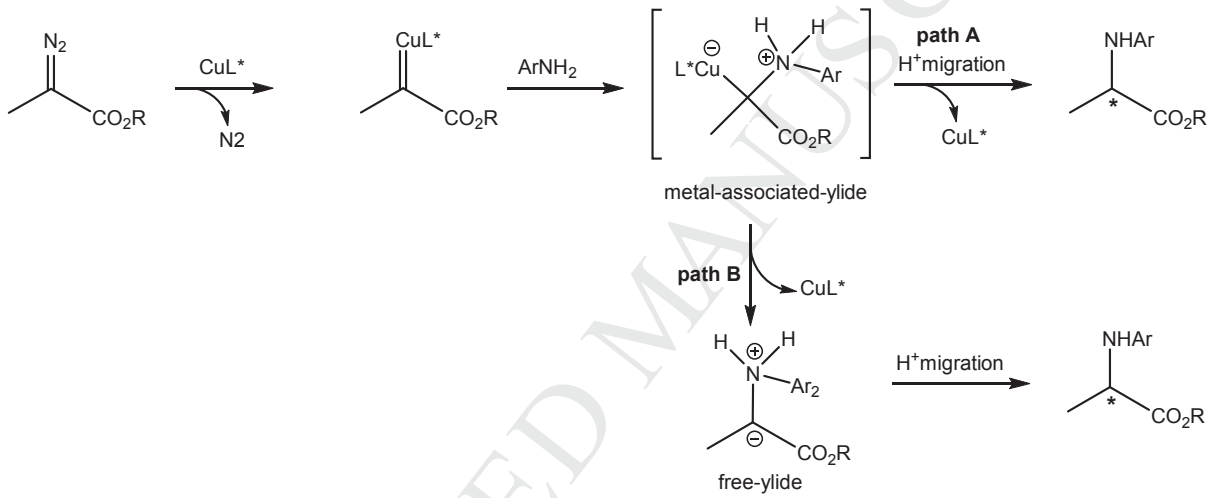


Fig. 2. ESI-MS analysis of the solution of [CuL*] formed by CuOTf and L*(1:1 molar ratio) in CH_2Cl_2.

A generally accepted insertion mechanism includes the formation of an electron-deficient metal carbene intermediate and the insertion into the N-H bond according to a stepwise ylide-generation/proton-shift process (Scheme **1**).[23] High enantioselectivities can be achieved in the metal-associated-ylide pathway (path A) in which the copper complex remained bound to the substrate for transfer of chiral information during the proton migration. In the free ylide pathway (path B), the chiral catalyst is dissociated and thus low enantioselectivities would be obtained. During the experimental process of the reaction typical changes in the colour were observed and may offer insight on the mechanism. After the addition of *o*-Cl aniline, the colour of solution turned pale-green to violet, then yellow

after the addition of the diazo compound. We suspected that the aniline could coordinate to the central metal copper in the catalyst (violet colour), but not too strongly, in order to allow the formation of the copper carbene (yellow colour). The electron-deficient copper carbene is then attacked by the lone-pair electrons of the aniline nitrogen atom which lead to the metal-associated-ylide intermediate. With aniline derivatives bearing electron-withdrawing substituents, the degeneration of the catalyst-associated-ylide to a free ylide was probably less facilitated and thus leads to better enantioselectivity. Moreover, the greater steric hindrance of substituent at the *ortho*-position of aniline might also enhance the chiral induction.



Scheme 1. Proposed mechanism for copper-catalyzed N-H insertion

3. Conclusion

In summary, we have developed a new Cu(I)-bicyclobisoxazoline-catalyst system for the asymmetric insertion of α-diazocarbonyl compounds into the N-H bond of different substituted aniline derivatives under mild conditions. Excellent yields and good enantioselectivities of up to 81% can be obtained. Studies of the electronic properties of the substrates have demonstrated that electron-withdrawing substituents on the *ortho*-position of aniline gave the best enantioselectivities. In this work, it is clear that the aryl substituent is critically important, presumably via a combination of steric and electronic effect. A stepwise insertion mechanism involving simultaneous proton transfer and catalyst dissociation as major

pathway has been proposed. Studies on the application of the insertion reaction into O-H and S-H bond with Cu and Fe-catalyst systems are in progress.

4. Experimental

4.1. General

All reactions were performed under argon. Solvents were distilled from an appropriate drying agent prior to use: CH_2Cl_2 from CaH_2. Commercially available reagents were used without further purification unless otherwise stated. All reactions were monitored by TLC with Merck precoated aluminum foil sheets (Silica gel 60 with fluorescent indicator UV254). Compounds were visualized with UV light at 254 nm. Column chromatographies were carried out using silica gel from Merck (0.063−0.200 mm). ^{1}H NMR and ^{13}C NMR in $CDCl_3$ were recorded using Bruker (Advance 400dpx spectrometer) at 400 MHz and 125 MHz, respectively. High resolution mass spectra were recorded on a Thermo-Fisher Q-Exactive spectrometer in ESI positif mode at the CRMPO at Rennes. Aromatic amines were commercially available and were purified by distillation prior to use. All catalytic reactions were controlled on a Varian CP-3380 GC system that was equipped with a CP-Chirasil-Dex Column (25m, 0.25 mm I.D.) HPLC analysis was realized on a Varian Prostar 218 system equipped with a Chiralpak AS-H or a Chiralcel OJ-H column. The optical rotations were recorded on a PerkinElmer model 341 polarimeter. The bicyclobis(oxazoline) ligands L* were synthetized as we previously described.[29] The α-diazoesters **1** were prepared according to procedures described in the literature.[19,30,31]

4.2. General procedure for asymmetric N-H insertion reaction

A mixture of Cu(I)(OTf) (5μmol, 5 mol %) and ligand (6 μmol,) in dry CH_2Cl_2 (1 ml) was stirred for 1 h at 25°C under argon. The substrate (100 μmol) and the α-diazopropionate (100 μmol) were then respectively added. The solution was stirred at 25°C under the argon atmosphere for 1 h and purified by flash chromatography (ethyl acetate/hexane = 0.5/9.5).

The insertion yield was determined by GC analysis on the crude reaction mixture and the enantiomeric excess of the insertion product was determined by chiral HPLC analysis.

4.3. Analytical data for N-H insertion products

4.3.1. (-)-Ethyl-2-(phenylamino)propionate 3a. Yield: 98%; ^{1}H NMR ($CDCl_3$): δ = 1.18 (t, 3H), 1.39 (d, 3H), 4.05 (q, 1H), 4.11 (q, 2H), 6.53 (d, 2H), 6.68 (t, 1H), 7.10 (t, 2H); ^{13}C NMR ($CDCl_3$): 14.22, 18.96, 52.05, 61.14, 113.44, 118.28, 129.33, 146.64, 174.63; $[\alpha]^{20}_{D}$ = -17.6 (c 1.7, $CHCl_3$); ee = 38% (HPLC conditions: Chiralpak AS-H column, hexane/*i*-PrOH : 95/5, flow rate = 0.3 ml/min, wavelength = 220 nm, t_R = 25.42 min for minor isomer , t_R = 30.02 min for major isomer). HRESIMS (m/z) calculated for $C_{11}H_{16}NO_2$: 194.1175 $(M + H)^+$, found: 194.1175.

4.3.2. (-)-Ethyl-2-(o-toluidino)propionate 3b. Yield: 97%; ^{1}H NMR ($CDCl_3$): δ = 1.18 (t, 3H), 1.43 (d,3H), 2.12 (s, 3H), 4.12 (m, 3H), 6.45 (d, 1H), 6.60 (t, 1H), 7.01 (m, 2H); ^{13}C NMR ($CDCl_3$): 14.20, 17.48, 19.15, 52.00, 61.17, 110.34, 117.84, 122.67, 127.08, 130.39, 144.70, 174.78; $[\alpha]^{20}_{D}$ = -12.5 (c 2, $CHCl_3$); ee = 42% (GC conditions: CP-Chirasil-Dex column, 80°C (1 min), 1°C min^{-1} 80-180°C , t_R = 45.66 min for minor isomer , t_R = 46.34 min for major isomer). HRESIMS (m/z) calculated for $C_{12}H_{18}NO_2$: 208.1332 $(M + H)^+$, found: 208.1330.

4.3.3. (-)-Ethyl-2-(*o*-fluorophenylamino)propionate 3c. Yield: 98%; ^{1}H NMR ($CDCl_3$): δ = 1.27 (t, 3H), 1.53 (d,3H), 4.16 (q, 1H), 4.22 (q, 2H), 6.63-6.71 (m, 2H), 6.97-7.03 (m, 2H); ^{13}C NMR ($CDCl_3$): 14.17, 18.86, 51.86, 61.21, 112.73, 114.68, 114.86, 117.71, 117.78, 124.51, 174.09; $[\alpha]^{20}_{D}$ = -35.3 (c 1.3, $CHCl_3$); ee = 65% (GC conditions: CP-Chirasil-Dex column, 80°C (1 min), 1°C min^{-1} 80-180°C, t_R = 36.85 min for minor isomer , t_R = 37.92 min for major isomer). HRESIMS (m/z) calculated for $C_{11}H_{15}NO_2F$: 212.1081 $(M + H)^+$, found: 212.1079.

4.3.4. (-)-Ethyl-2-(*o*-chlorophenylamino)propionate 3d. Yield: 98%; ^{1}H NMR ($CDCl_3$): δ = 1.28 (t, 3H), 1.55 (d,3H), 4.18 (q, 1H), 4.23 (q, 2H), 6.61 (d, 1H), 6.69 (t, 1H), 7.13 (t, 1H), 7.29 (d, 1H); ^{13}C NMR ($CDCl_3$): 14.17, 18.79, 51.90, 61.29, 111.68, 118.16, 119.74, 127.75, 129.41, 142.59, 173.87; $[\alpha]^{20}_{D}$ = -14.5 (c 1.6, $CHCl_3$); ee = 77% (HPLC conditions: Chiralcel OD-H column, hexane/*i*-PrOH : 98/2, flow rate = 1 ml/min, wavelength = 220 nm, t_R = 6.30 min for major isomer , t_R = 17.93 min for minor isomer). HRESIMS (m/z) calculated for $C_{11}H_{14}NO_2ClNa$: 250.0605 $(M + Na)^+$, found: 250.0608.

4.3.5. (-)-Ethyl-2-(*o*-bromophenylamino)propionate 3e. Yield: 87%; ^{1}H NMR ($CDCl_3$): δ = 1.28 (t, 3H), 1.55 (d,3H), 4.19 (q, 1H), 4.23 (q, 2H), 6.58 (d, 1H), 6.62 (t, 1H), 7.17 (t, 1H), 7.45 (d, 1H); ^{13}C NMR ($CDCl_3$): 14.17, 18.78, 52.05, 61.30, 110.22, 111.70, 118.64, 128.45, 132.69, 143.62, 173.85; $[\alpha]^{20}_{D}$ = -1.0 (c 2.5, $CHCl_3$); ee = 75% (HPLC conditions: Chiralcel OB-H column, hexane/*i*-PrOH : 99/1, flow rate = 0.5 ml/min, wavelength = 220 nm, t_R = 15.52 min for major isomer , t_R = 21.30 min for minor isomer). HRESIMS (m/z) calculated for $C_{11}H_{15}NO_2Br$: 272.0286 $(M + H)^+$, found: 272.0290.

4.3.6. (+)-Ethyl-2-(*o*-iodophenylamino)propionate 3f. Yield: 82%; ^{1}H NMR ($CDCl_3$): δ = 1.29 (t, 3H), 1.56 (d,3H), 4.18 (q, 1H), 4.23 (q, 2H), 6.50 (t, 1H), 6.52 (d, 1H), 7.21 (t, 1H), 7.70 (d, 1H); ^{13}C NMR ($CDCl_3$): 14.20, 18.80, 52.41, 61.33, 85.88, 111.02, 119.45, 129.40, 139.34, 145.95, 173.87; $[\alpha]^{20}_{D}$ = +7.2 (c 2.9, $CHCl_3$); ee = 55% (HPLC conditions: Chiralcel OB-H column, hexane/*i*-PrOH : 99/1, flow rate = 0.5 ml/min, wavelength = 220 nm, t_R = 17.56 min for major isomer , t_R = 26.38 min for minor isomer). HRESIMS (m/z) calculated for $C_{11}H_{15}NO_2I$: 320.0147 $(M + H)^+$, found: 320.0158.

4.3.7. (-)-Ethyl-2-(*m*-toluidino)propionate 3g. Yield: 98%; ^{1}H NMR ($CDCl_3$): δ = 1.17 (t, 3H), 1.38 (d,3H), 2.18 (s, 3H), 4.04 (q, 1H), 4.11 (q, 2H), 6.34 (d, 1H), 6.36 (s, 1H), 6.48 (d, 1H), 6.98 (t, 1H); ^{13}C NMR ($CDCl_3$): 14.23, 18.98, 21.62, 52.05, 61.10, 110.55, 114.33, 119.26, 129.18, 139.08, 146.81, 174.84; $[\alpha]^{20}_{D}$ = -12.7 (c 2.5, $CHCl_3$); ee = 33% (HPLC

conditions: Chiralpak AS-H column, hexane/*i*-PrOH : 99/1, flow rate = 0.3 ml/min, wavelength = 220 nm, t_R = 23.11 min for minor isomer , t_R = 27.40 min for major isomer). HRESIMS (m/z) calculated for $C_{12}H_{18}NO_2$: 208.1332 $(M + H)^+$, found: 208.1330.

4.3.8. (-)-Ethyl-2-(*m*-chlorophenylamino)propionate 3h. Yield: 98%; ^{1}H NMR ($CDCl_3$): δ = 1.29 (t, 3H), 1.49 (d, 3H), 4.12 (q, 1H), 4.23 (q, 2H), 6.51 (d, 1H), 6.62 (s, 1H), 6.73 (d, 1H), 7.10 (t, 1H); ^{13}C NMR ($CDCl_3$): 14.19, 18.72, 51.91, 61.34, 111.80, 113.23, 118.26, 130.29, 135.06, 147.56, 174.05; $[\alpha]^{20}_D$ = -23.7 (c 2.7, $CHCl_3$); ee = 66% (HPLC conditions: Chiralpak AS-H column, hexane/*i*-PrOH : 98/2, flow rate = 0.5 ml/min, wavelength = 220 nm, t_R = 17.13 min for minor isomer , t_R = 23.51 min for major isomer). HRESIMS (m/z) calculated for $C_{11}H_{15}ClNO_2$: 250.0605 $(M + H)^+$, found: 250.0608.

4.3.9. (-)-Ethyl-2-(*p*-toluidino)propionate 3i. Yield: 98%; ^{1}H NMR ($CDCl_3$): δ = 1.27 (t, 3H), 1.49 (d,3H), 2.26 (s, 3H), 4.12 (q, 1H), 4.4.20 (q, 2H), 6.61 (d, 2H), 7.01 (d, 2H); ^{13}C NMR ($CDCl_3$): 14.19, 18.81, 20.43, 52.74, 61.10, 114.09, 129.81, 174.48; $[\alpha]^{20}_D$ = -17.0 (c 1.5, $CHCl_3$); ee = 31% (HPLC conditions: Chiralpak AS-H column, hexane/*i*-PrOH : 99/1, flow rate = 0.5 ml/min, wavelength = 220 nm, t_R = 12.78 min for minor isomer , t_R = 14.77 min for major isomer). HRESIMS (m/z) calculated for $C_{12}H_{18}NO_2$: 208.1332 $(M + H)^+$, found: 208.1330.

4.3.10. (-)-Ethyl-2-(*p*-chlorophenylamino)propionate 3j. Yield: 99%; ^{1}H NMR ($CDCl_3$): δ = 1.27 (t, 3H), 1.47 (d, 3H), 4.08 (q, 1H), 4.20 (q, 2H), 6.54 (d, 2H), 7.12 (d, 2H); ^{13}C NMR ($CDCl_3$): 14.18, 18.77, 52.11, 61.25, 114.51, 122.86, 129.14, 145.24, 174.32; $[\alpha]^{20}_D$ = -26.1 (c 2.5, $CHCl_3$); ee = 48% (HPLC conditions: Chiralpak AS-H column, hexane/*i*-PrOH : 99/1, flow rate = 0.5 ml/min, wavelength = 220 nm, t_R = 32.79 min for minor isomer , t_R = 37.86 min for major isomer). HRESIMS (m/z) calculated for $C_{11}H_{15}ClNO_2$: 250.0605 $(M + H)^+$, found: 250.0608.

4.3.11. (-)-*t*-Bu-2-(phenylamino)propionate 3k. Yield: 75%; ^{1}H NMR ($CDCl_3$): δ = 1.46 (s, 9H), 1.47 (d, 3H), 4.05 (q, 1H), 6.66 (d, 2H), 6.76 (t, 1H), 7.20 (t, 2H); ^{13}C NMR ($CDCl_3$): 18.82, 27.98, 52.74, 81.50, 113.66, 118.28, 129.25, 146.59, 173.72; $[\alpha]^{20}_{D}$ = -26.6 (c 2.0, $CHCl_3$); ee = 53% (HPLC conditions: Chiralcel OJ-H column, hexane/*i*-PrOH : 99/1, flow rate = 0.5 ml/min, wavelength = 220 nm, t_R = 25.07 min for minor isomer , t_R = 27.26 min for major isomer). HRESIMS (m/z) calculated for $C_{13}H_{19}NO_2Na$: 244.1313 $(M + Na)^+$, found: 244.1314.

4.3.12. (-)-*t*-Bu-2-(*o*-toluidino)propionate 3l. Yield: 72%; ^{1}H NMR ($CDCl_3$): δ = 1.47 (s, 9H), 1.50 (d, 3H), 2.22 (s, 3H), 4.09 (q, 1H), 6.56 (d, 1H), 6.69 (t, 1H), 7.10 (m, 2H); ^{13}C NMR ($CDCl_3$): 17.48, 19.09, 28.00, 52.51, 81.47, 110.32, 117.60, 122.56, 127.01, 130.31, 144.86, 173.99; $[\alpha]^{20}_{D}$ = -15.3 (c 3.0, $CHCl_3$); ee = 56% (GC conditions: CP-Chirasil-Dex column, 80°C (1 min), 1°C min^{-1} 80-180°C, t_R = 50.15 min for minor isomer , t_R = 50.50 min for major isomer). HRESIMS (m/z) calculated for $C_{14}H_{21}NO_2Na$: 258.1470 $(M + Na)^+$, found: 258.1469.

4.313. (-)-*t*-Bu-2-(*m*-toluidino)propionate 3m. Yield: 67%; ^{1}H NMR ($CDCl_3$): δ = 1.45 (d, 3H), 1.47 (s, 9H), 2.29 (s,3H), 4.04 (q, 1H), 6.44 (d, 1H), 6.46 (s, 1H), 6.57 (d, 1H), 7.08 (t, 1H); ^{13}C NMR ($CDCl_3$): 18.92, 21.59, 27.99, 52.57, 81.38, 110.56, 114.28, 118.99, 129.10, 138.98, 146.83, 174.01; $[\alpha]^{20}_{D}$ = -22.0 (c 1.4, $CHCl_3$); ee = 44% (HPLC conditions: Chiralcel OJ-H column, hexane/*i*-PrOH : 99/1, flow rate = 0.5 ml/min, wavelength = 220 nm, t_R = 18.82 min for minor isomer , t_R = 21.43 min for major isomer). HRESIMS (m/z) calculated for $C_{14}H_{22}NO_2$: 236.1651 $(M + H)^+$, found: 236.1651.

4.3.14. (-)-*t*-Bu-2-(*p*-toluidino)propionate 3n. Yield: 81%; ^{1}H NMR ($CDCl_3$): δ = 1.45 (d, 3H), 1.46 (s, 9H), 2.26 (s,3H), 4.01 (q, 1H), 6.58 (d, 2H), 7.01 (d, 2H); ^{13}C NMR ($CDCl_3$): 18.84, 20.42, 27.99, 53.10, 81.39, 113.91,127.55, 129.74, 144.25, 173.87; $[\alpha]^{20}_{D}$ = -17.5 (c 1.8, $CHCl_3$); ee = 47% (HPLC conditions: Chiralcel OD-H column, hexane/*i*-PrOH : 99/1,

flow rate = 0.3 ml/min, wavelength = 220 nm, t_R = 17.10 min for minor isomer , t_R = 20.22 min for major isomer). HRESIMS (m/z) calculated for $C_{14}H_{22}NO_2$: 236.1651 $(M + H)^+$, found: 236.1651.

4.3.15. (-)-*t*-Bu-2-(*o*-chlorophenylamino)propionate 3o. Yield: 76%; ^{1}H NMR ($CDCl_3$): δ = 1.46 (s, 9H), 1.51 (d, 3H), 4.07 (q, 1H), 6.61 (d, 1H), 6.67 (t, 1H), 7.13 (t, 1H), 7.28 (d, 1H); ^{13}C NMR ($CDCl_3$): 18.74, 27.95, 52.46, 81.70, 111.72, 115.87, 117.92, 127.68, 129.35, 142.84, 173.12; $[\alpha]^{20}_D$ = -8.3 (c 1.8, $CHCl_3$); ee = 67% (HPLC conditions: Chiralcel OJ-H column, hexane/*i*-PrOH : 99/1, flow rate = 0.1 ml/min, wavelength = 220 nm, t_R = 58.82 min for major isomer , t_R = 65.04 min for minor isomer). HRESIMS (m/z) calculated for $C_{13}H_{18}NO_2ClNa$: 278.0923 $(M + Na)^+$, found: 278.0924.

4.3.16. (-)-*t*-Bu-2-(*m*-chlorophenylamino)propionate 3p. Yield: 77%; ^{1}H NMR ($CDCl_3$): δ = 1.45 (d, 3H), 1.47 (s, 9H), 4.00 (q, 1H), 6.50 (d, 1H), 6.61 (s, 1H), 6.71 (d, 1H), 7.13 (t, 1H), 7.09 (t, 1H); ^{13}C NMR ($CDCl_3$): 18.63, 27.97, 52.46, 81.85, 111.90, 113.19, 118.05, 130.22, 135.00, 147.73, 173.27; $[\alpha]^{20}_D$ = -26.0 (c 2.1, $CHCl_3$); ee = 66% (HPLC conditions: Chiralcel OJ-H column, hexane/*i*-PrOH : 99/1, flow rate = 0.2 ml/min, wavelength = 220 nm, t_R = 49.19 min for minor isomer , t_R = 54.33 min for major isomer). HRESIMS (m/z) calculated for $C_{13}H_{18}NO_2ClNa$: 278.0923 $(M + Na)^+$, found: 278.0924.

4.3.17. (-)-*t*-Bu-2-(*p*-chlorophenylamino)propionate 3q Yield: 80%; ^{1}H NMR ($CDCl_3$): δ = 1.44 (d, 3H), 1.46 (s, 9H), 3.98 (q, 1H), 6.54 (d, 2H), 7.13 (d, 2H); ^{13}C NMR ($CDCl_3$): 18.73, 27.98, 52.64, 81.69, 114.50, 122.64, 129.09, 138.98, 145.42, 173.51; $[\alpha]^{20}_D$ = -25.6 (c 2.1, $CHCl_3$); ee = 55% (HPLC conditions: Chiralcel OJ-H column, hexane/*i*-PrOH : 99/1, flow rate = 0.5 ml/min, wavelength = 220 nm, t_R = 26.37 min for minor isomer , t_R = 28.06 min for major isomer). HRESIMS (m/z) calculated for $C_{13}H_{18}NO_2ClNa$: 278.0923 $(M + Na)^+$, found: 278.0924.

4.3.18. (-)-Benzyl-2-(phenylamino)propionate 3r. Yield: 98%; ^{1}H NMR ($CDCl_3$): δ = 1.52 (d, 3H), 4.24 (q, 1H), 5.20 (s, 2H), 6.65 (d, 1H), 6.79 (t, 1H), 7.21 (t, 2H), 7.31-7.41 (m, 5H); ^{13}C NMR ($CDCl_3$): 18.92, 52.14, 66.86, 113.52, 118.44, 128.16, 128.36, 128.60, 129.36, 135.59, 146.57, 174.49; $[\alpha]^{20}_{D}$ = -16.2 (c 2.4, $CHCl_3$); ee = 81% (HPLC conditions: Chiralcel OB-H column, hexane/*i*-PrOH : 99/1, flow rate = 0.5 ml/min, wavelength = 220 nm, t_R = 30.14 min for major isomer , t_R = 42.30 min for minor isomer). HRESIMS (m/z) calculated for $C_{16}H_{17}NO_2Na$: 278.1157 $(M + Na)^+$, found: 278.1156.

4.3.19. (-)-Benzyl-2-(*o*-chlorophenylamino)propionate 3s. Yield: 98%; ^{1}H NMR ($CDCl_3$): δ = 1.57 (d, 3H), 4.25 (q, 1H), 5.21 (s, 2H), 6.59 (d, 1H), 6.67 (t, 1H), 7.11 (t, 1H), 7.28-7.40 (m, 5H); ^{13}C NMR ($CDCl_3$): 18.75, 51.90, 51.93, 66.98, 111.73, 118.28, 119.75, 127.79, 128.15, 128.39, 128.60, 129.43, 133.50, 142.55, 173.77; $[\alpha]^{20}_{D}$ = -4.8 (c 2.7, $CHCl_3$); ee = 81% (HPLC conditions: Chiralcel OB-H column, hexane/*i*-PrOH : 99/1, flow rate = 0.5 ml/min, wavelength = 220 nm, t_R = 30.14 min for major isomer , t_R = 42.30 min for minor isomer). HRESIMS (m/z) calculated for $C_{16}H_{16}ClNO_2Na$: 312.0767 $(M + Na)^+$, found: 312.0766.

4.3.20. (+)-Benzyl-2-(*o*-bromophenylamino)propionate 3t. Yield: 97%; ^{1}H NMR ($CDCl_3$): δ = 1.58 (d,3H), 4.25 (q, 1H), 5.21 (s,1H), 6.57 (d, 1H), 6.63 (t, 1H), 7.15 (t, 1H), 7.32-7.48 (m, 5H); ^{13}C NMR ($CDCl_3$): 18.75, 52.09, 66.98, 110.23, 111.17, 118.77, 128.16, 128.39, 128.49, 128.61, 132.72, 135.50, 143.56, 173.72; $[\alpha]^{20}_{D}$ = +4.8 (c 3.1, $CHCl_3$); ee = 73% (HPLC conditions: Chiralcel OB-H column, hexane/*i*-PrOH : 99/1, flow rate = 0.5 ml/min, wavelength = 220 nm, t_R = 32.11 min for major isomer , t_R = 44.00 min for minor isomer). HRESIMS (m/z) calculated for $C_{16}H_{16}BrNO_2Na$: 356.0262$(M + Na)^+$, found: 356.0266.

4.3.21. (+)-Ethyl-2-phenyl-2-(*o*-chlorophenylamino)acetate 3u. Yield: 84%; ^{1}H NMR ($CDCl_3$): δ = 1.25 (t, 3H), 4.17-4.30 (m, 3H), 6.41 (d, 1H), 6.65 (t, 1H), 7.03 (t, 1H), 7.29-

7.41 (m, 4H), 7.53 (d, 2H); ^{13}C NMR ($CDCl_3$): 14.02, 29.72, 60.58, 61.99, 112.12, 118.00, 119.67, 127.12, 127.64, 128.38, 128.90, 129.25, 137.15, 141.95, 171.19; $[\alpha]^{20}_D$ = +7.0 (c 2.3, $CHCl_3$); ee = 50% (HPLC conditions: Chiralcel OJ-H column, hexane/*i*-PrOH : 99/1, flow rate = 0.3 ml/min, wavelength = 220 nm, t_R = 36.14 min for minor isomer , t_R = 40.12 min for major isomer). HRESIMS (m/z) calculated for $C_{16}H_{16}NO_2ClNa$: 312.0767 $(M + Na)^+$, found: 312.0766.

4.3.22. (+)-Ethyl-2-(naphtylamino)propionate 3w. Yield: 85%; ^1H NMR ($CDCl_3$): δ = 1.31 (t, 3H), 1.64 (d, 3H), 4.26 (q, 2H), 4.34 (q, 1H), 6.58 (d, 2H), 7.28-7.37 (m, 2H), 7.47-7.51 (m, 2H), 7.80-7.83 (m, 1H), 7.92-7.96 (m, 1H); ^{13}C NMR ($CDCl_3$): 14.22, 18.89, 52.15, 61.28, 105.15, 118.31, 120.14, 123.72, 124.91, 125.85, 126.36, 128.62, 134.43, 141.83, 174.67; $[\alpha]^{20}_D$ = +18 (c 1.2, $CHCl_3$); ee = 43% (HPLC conditions: Chiralpak OJ-H column, hexane/*i*-PrOH : 99/1, flow rate = 1.0 ml/min, wavelength = 220 nm, t_R = 27.56 min for minor isomer , t_R = 33.88 min for major isomer). HRESIMS (m/z) calculated for $C_{15}H_{18}NO_2$: 244.1338 $(M + H)^+$, found: 244.1336.

Legends

Fig.1. Structures of chiral bisoxazoline ligands

Fig. 2. ESI-MS analysis of the solution of [CuL*] formed by CuOTf and L*(1:1 molar ratio) in CH_2Cl_2

Scheme 1. Proposed mechanism for copper-catalyzed N-H insertion

Table 1. Cu-catalyzed asymmetric insertion of ethyl α-diazopropionate into N-H bond of *o*-Cl aniline

Table 2. Catalytic asymmetric N-H insertion of amines with α-diazoesters

Table 3. Catalytic asymmetric N-H insertion of arylamines with ethyl α-diazopropionate with different ligands

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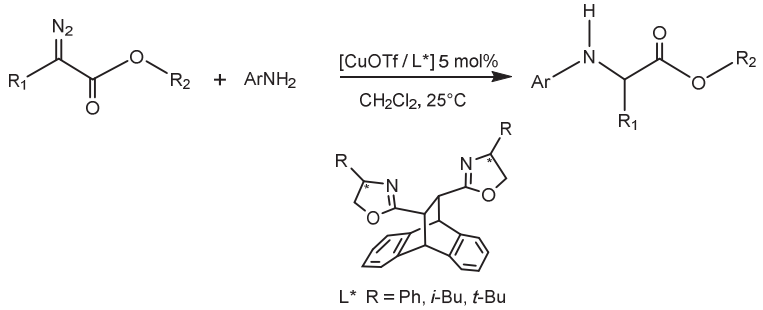

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