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Novel nitrogen ligands based on imidazole derivatives and their application in asymmetric catalysis

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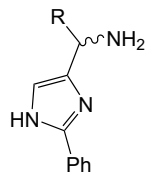
Abstract—Recently prepared chiral amines have been used in the preparation of novel tridentate ligands based on an imidazole ring with an additional (hetero)ring. The synthesis was carried out by the reaction of chiral amines with suitable aldehydes (2-phenylimidazole-4-carbaldehyde, 2-hydroxybenzaldehyde or pyridine-2-carbaldehyde) under reductive conditions (H_2/Pd or $NaBH_4$). All ligands prepared showed strong hydrogen bonds in d_6-DMSO solution, which resulted in hindered imidazole tautomerism. The observed hindered tautomerism was studied by ^{1}H NMR spectroscopy. The structures of the prepared ligands were also confirmed by APCI mass spectroscopy. Both chiral amines and tridentate compounds have been applied as ligands in copper (II)-catalyzed nitroaldol reactions (Henry reaction). Various reaction conditions for the Henry reaction have been studied (influence of temperature, molar ratio, solvent or copper (II) precursors). The compounds prepared with the two imidazole rings showed fast reaction times and a reversal in enantioselectivity compared to other chiral amines.

1. Introduction

Recently we have published[1] the synthesis of chiral derivatives of 2-fenylimidazole (Scheme 1) by the condensation of α-bromoketones with benzamidine in the solvent/base system THF/water/K_2CO_3. The application of the resulting amines as heterocyclic chiral intermediates in further organic syntheses or in asymmetric catalyzed reactions is currently of interest.



1

1a — CH_3- (*S*)
1b — CH_3- (*R*)
1c — $(CH_3)_2CH$- (*S*)
1d — $(CH_3)_2CHCH_2$- (*S*)
1e — $CH_3CH_2CH(CH_3)$- (*S*)
1f — $PhCH_2$- (*S*)

Scheme 1. Chiral amines.

The nitroaldol reaction (Henry reaction[2]) is one of the oldest carbon–carbon bond forming reactions in organic synthesis. It has been shown that five-membered heterocycles,[3,4] guanidine-based compounds[5,6] or amino alcohols promoted by diethylzinc,[7–9] can be used as ligands in the copper-catalyzed modification of this reaction. The reaction provides 2-nitroalcohols as products, which are versatile building blocks and intermediates in organic synthesis.

Novel tridentate ligands with two heterocyclic rings have been proposed and synthesized as suitable ligands (Scheme 2). The synthesis starts from the previously prepared chiral amines that were condensed with aromatic aldehydes. Isolation of the formed imine intermediates was unsuccessful and therefore the imines were reduced directly. The reduction was carried out by hydrogen in the presence of a palladium catalyst[10] or by using sodium borohydride.[11]

2. Results and discussion

The tridentate ligand synthesis is a simple reductive amination. The commercially available products have been used

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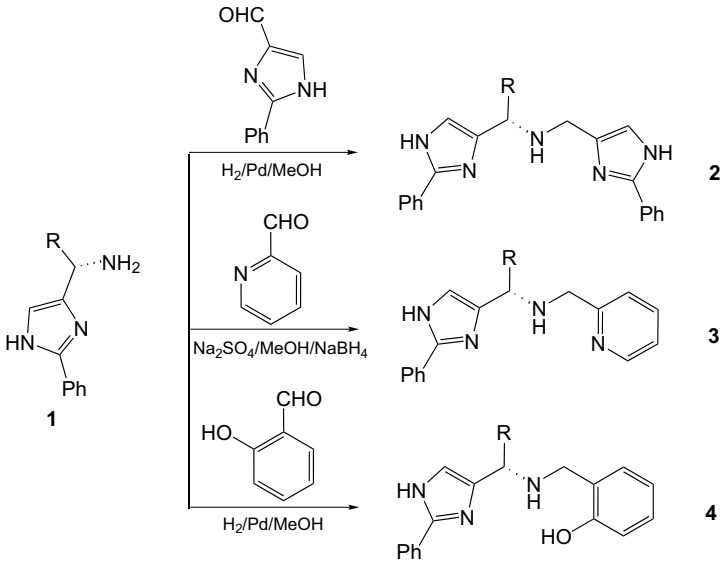


Scheme 2. Tridentate ligand synthesis.

as suitable aldehydes (2-hydroxybenzaldehyde or pyridine-2-carbaldehyde). 2-Phenylimidazole-4-carbaldehyde was prepared from dihydroxyacetone following the literature procedure.[12] The first and the last aldehydes named above were condensed with chiral amines in the presence of hydrogen (Method A). Reductive amination under hydrogenation conditions was unsuccessful in the case of pyridine-2-carbaldehyde. Hence, the reaction was carried out in methanol in the presence of a drying agent (sodium sulfate) and completed by reduction with sodium borohydride (Method B). Method A provided better yields than method B. Some of the properties of the compounds prepared are summarized in Table 1.

Table 1. Properties of tridentate ligands (see Scheme 2)

Ligand	Structure (R)	Yield (%)	mp (°C)	Configuration/$[\alpha]_D^{20}$ (c 0.5, CH_3OH)
2a	CH_3–	87	110–112	(*S*)/−43.0
2b	$(CH_3)_2CH$–	89	119–120	(*S*)/−66.2
2c	$(CH_3)_2CHCH_2$–	88	120–121	(*S*)/−30.8
2d	$PhCH_2$–	78	118–119	(*S*)/−10.0
3a	$(CH_3)_2CH$–	62	67–69	(*S*)/−49.8
3b	$(CH_3)_2CHCH_2$–	65	67–68	(*S*)/−29.4
3c	$PhCH_2$–	69	60–61	(*S*)/+34.0
4	$(CH_3)_2CHCH_2$–	60	160–162	(*S*)/−28.0

The NMR structural analyses of the tridentate ligands showed the presence of strong hydrogen bonds in d_6-DMSO solution, which resulted in hindered imidazole tautomerism. ^1H and ^{13}C spectra showing broad signals without estimated spin–spin interactions were obtained. The strong hydrogen bonds and hindered imidazole tautomerism were observed for each prepared compound, independent of the sample concentration, pH value or addition of water into the sample. The hindered imidazole tautomerism disappeared under high temperature conditions. Figure 1 depicts the dependence of the ^1H NMR spectra on temperature (ligand **2b**). At 300 K, nearly four broad signals of imidazole hydrogens (H-6,7) are visible in the aromatic area (6.8–7.1 ppm). At 350 K, the ^1H NMR spectrum was recorded with estimated spin–spin interactions due to a restored fast proton exchange. There are only two broader signals of the imidazole hydrogens (H-6,7) visible. The hindered imidazole tautomerism was not observed if the sample was measured in deuterated methanol (see Fig. 2, ligand **2b**). Hence, the ^1H and ^{13}C NMR spectra listed in Experimental were measured in CD_3OD.

The nitroaldol Henry reaction (Scheme 3) was chosen as a model reaction for an enantioselectivity test of the prepared compounds, and chiral amines as well as tridentate ligands were tested. The catalysts were prepared in situ by stirring a copper (II) precursor with the chiral ligands and then nitromethane after which the aldehyde was added. The reaction was followed by TLC. The yields, reaction times and the enantiomeric excesses obtained are reported in Tables 2 and 3. All reactions were carried out in a Teflon coated flask using copper (II) complex catalysis to minimize the formation of styrene derivatives (Table 2, compare with entry 2.1). There have been some changes of the reaction conditions and we made several observations. Decreasing the temperature resulted in a longer reaction time with a small effect on ee (Table 2, entry 2.9). Replacement of the ethanol by THF resulted in a lower yield and ee (Table 2, entry 2.12). Preparation of the catalyst in a 2:1 ratio (ligand:precursor) and a change of the nitromethane concentration did not cause any significant changes (Table 2, entries 2.11 and 2.13). Application of copper (II) chloride as metal precursor and an external base (triethylamine) under standard reaction conditions were carried out as well (Table 2, entry 2.18). Application of copper (II) benzoate provided sufficient yield (moderate reaction time) but higher enantiomeric excess (Table 2,

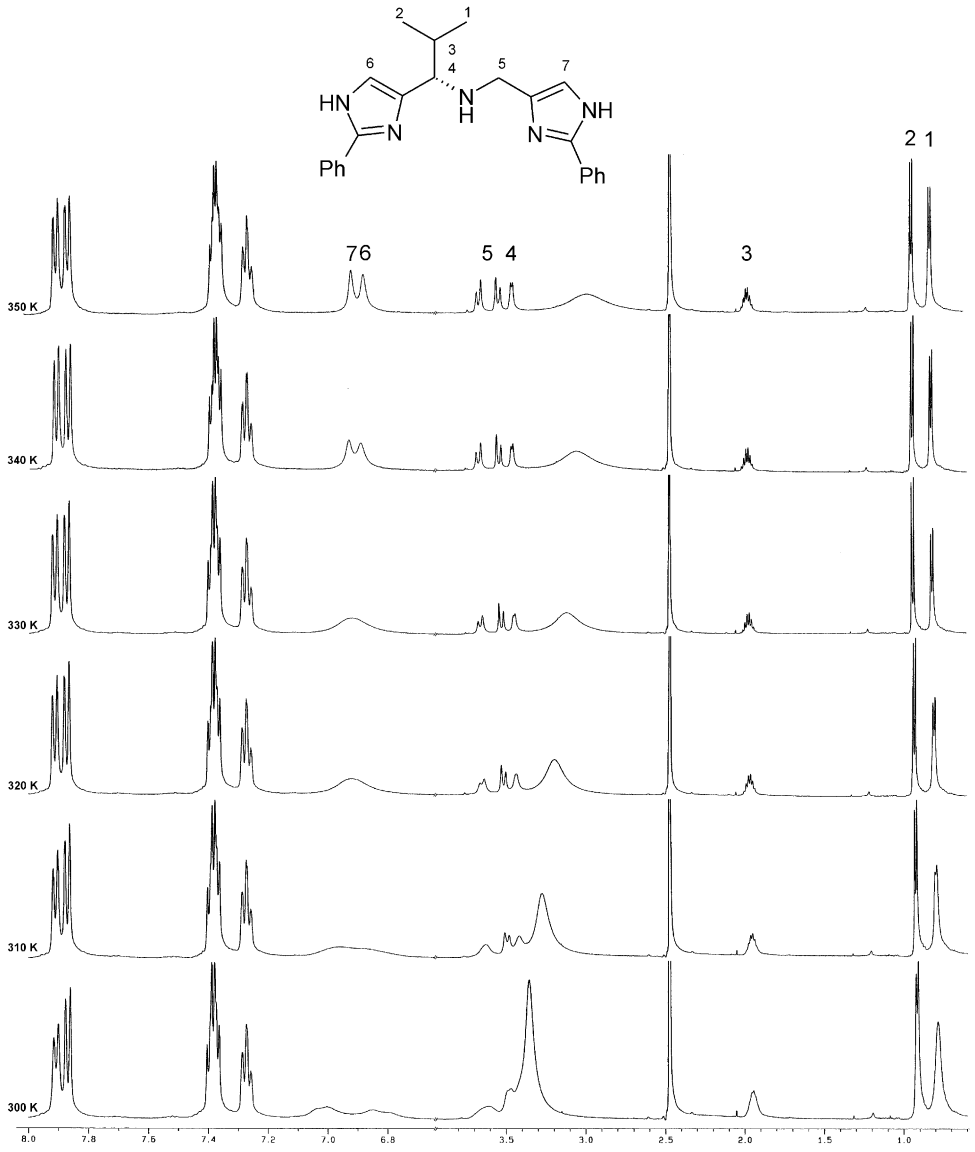


Figure 1. Dependence of ^{1}H NMR spectrum on temperature—ligand **2b** (d_6-DMSO).

entry 2.15). A very quick reaction time was achieved by using copper (II) 4-methoxybenzoate as a metal precursor (Table 2, entry 2.17). On the other hand, the use of copper (II) 4-nitrobenzoate resulted in a longer reaction time, poor yield and ee (Table 2, entry 2.16). In general, the Henry reaction can be catalyzed or promoted by many different sets of conditions or catalysts, but the most frequently used are organic bases.[13] The electron rich 4-methoxybenzoate (pK_a of 4-methoxybenzoic acid in ethanol is 10.61)[14] is a stronger base than 4-nitrobenzoate (pK_a of 4-nitrobenzoic acid in ethanol is 8.91)[14] and, therefore, the deprotonation of nitromethane proceeds more easily. The analogous observation may be seen from the comparison of acetate and electron poor trifluoroacetate anions (Table 2, see entries 2.7 and 2.14). The application of trifluoroacetate anion showed a long reaction time with low conversion and ee. The formation of 1-(4-nitrophenyl)-2-nitroethene has also been observed. The electron poor and weaker fixed anions showed longer reaction times, and hence the probability of a nitroaldol condensation in the solution instead of on the active chiral catalyst is higher. The attained enantiomeric excesses obtained are then lower.

Tridentate ligands with two imidazole rings **2a**, **2b**, **2c** and **2d** showed fast reaction times and moderate enantiomeric excesses using copper (II) acetate as a metal precursor (Table 3, entries 3.1–3.4). The application of copper (II) 4-methoxybenzoate (Table 3, entry 3.5) caused a decrease in reaction time, similar to that observed in the case of ligands **1**. The nitrogen ligands based on the imidazole ring are stronger bases than the frequently published bisoxaline derivatives[3,4] and this fact furthermore facilitates deprotonation of nitromethane. For these reasons, the application of the electron rich copper (II) 4-methoxybenzoate and tridentate ligand **2d**, with a bulky benzyl group as the

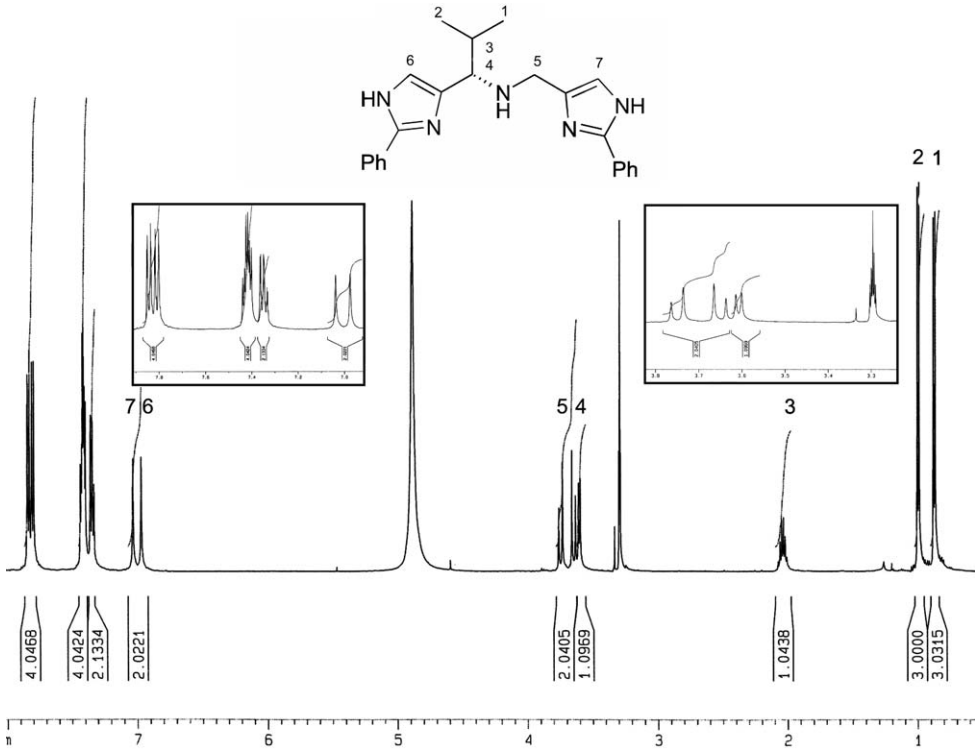
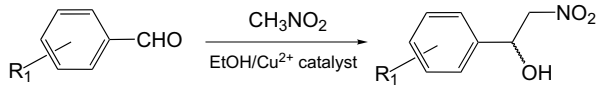


Figure 2. ^{1}H NMR spectrum—ligand **2b** (CD_3OD).



Scheme 3. Henry reaction.

substituent R, seems to be the most powerful combination (fast reaction time and the highest ee attained). These findings are in agreement with the reaction mechanism proposed by Evans et al.[3]

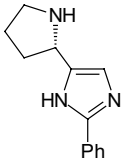
Although the absolute configuration of all chiral ligand prepared is (*S*) (except for **1b**), the tridentate ligands **2** and **3** showed a reversed enantioselectivity in the Henry reaction compared to the chiral amines **1**. According to the reaction mechanism proposed by Evans et al.,[3] the coordination and deprotonation of nitromethane occurs before the coordination of the aldehyde. In the case of tridentate ligands **2** and **3**, the second (hetero)ring may discriminate the addition of the aldehyde from the same side as in the case of ligands **1** and, therefore enantioselective reversal was observed. Other feasible explanation of the reversal of enantioselectivity could be due to another kind of complexation—coordination of copper to the second (hetero)ring and another complex formation. This supposition supports the application of a chiral amine with an additional pyrrolidine ring [Table 2, entry 2.22, prepared from (*S*)-proline[1]], where the reversed enantioselectivity has been observed as well. This is also supported by tridentate ligand **4** (Table 3, entry 3.9) with a hydroxyphenyl moiety, where the reversed enantioselectivity has not been observed. Unfortunately, the preparation of a suitable single crystal of ligands or copper (II) complex proved difficult and therefore X-ray analysis failed.

3. Conclusion

Recently prepared chiral amines have been applied as a starting material for tridentate ligands synthesis. The reductive amination was carried out using catalytic hydrogenation or reduction with sodium borohydride. All novel compounds prepared have been characterized by ^{1}H, ^{13}C NMR and APCI mass spectroscopy. Tridentate ligands showed strong hydrogen bonds, which resulted in hindered tautomerism if measured in dimethylsulfoxide. The measurements in deuterated methanol provided spectra with estimated spin–spin interactions.

All compounds prepared have been tested as ligands in the copper (II) catalyzed Henry reaction. The best results were achieved by using chiral amines (Table 2, entry 2.21) or tridentate ligands (Table 3, entry 3.5) with the bulky benzyl group as the R substituent and copper (II) 4-methoxybenzoate as a metal precursor. Increasing bulkiness of the substituent R and the anion used resulted in increasing ee. Electron rich copper (II) 4-methoxybenzoate has been shown as the anion of choice (fast reaction times and higher ee). Conversely by using electron poor copper (II) 4-nitrobenzoate or trifluoracetate resulted in a longer reaction time and poor ee. The most frequently used copper (II) acetate showed moderate yields and enantiomeric excesses.

Table 2. Henry reaction (chiral amines as ligands **1**—see Schemes 1 and 3)

Entry	Aldehydes (R_1)	Ligand	Time (h)	Yield (%)	$[\alpha]_D^{25}$ (*c* 1, CH_2Cl_2)	Configuration/ee[a] (%)
2.1[b]	4-NO_2	—	72	98	—	—
2.2[c]	4-NO_2	—	144	52	0.0	(*R*,*S*)/0.0
2.3	4-NO_2	**1a**	12	92	−4.0	(*R*)/9.8
2.4	4-NO_2	**1b**	12	93	+4.1	(*S*)/10.6
2.5	4-NO_2	**1c**	12	96	−5.2	(*R*)/12.8
2.6	H	**1d**	24	68	−2.8	(*R*)/6.3
2.7	4-NO_2	**1d**	13	97	−4.9	(*R*)/12.1
2.8	Acetophenone	**1d**	24	0	—	—
2.9[d]	4-NO_2	**1d**	48	94	−5.6	(*R*)/13.9
2.10[e]	4-NO_2	**1d**	48	91	−3.8	(*R*)/9.4
2.11[f]	4-NO_2	**1d**	22	91	−4.2	(*R*)/10.4
2.12[g]	4-NO_2	**1d**	24	75	−2.4	(*R*)/5.4
2.13[h]	4-NO_2	**1d**	24	84	−4.2	(*R*)/10.4
2.14[i]	4-NO_2	**1d**	120	32	−1.1	(*R*)/2.7
2.15[j]	4-NO_2	**1d**	48	88	−6.5	(*R*)/16.1
2.16[k]	4-NO_2	**1d**	240	48	−1.4	(*R*)/3.5
2.17[l]	4-NO_2	**1d**	2.5	97	−5.5	(*R*)/13.6
2.18[m]	4-NO_2	**1d**	24	94	−5.1	(*R*)/12.5
2.19	4-NO_2	**1e**	14	94	−5.4	(*R*)/13.3
2.20	4-NO_2	**1f**	14	91	−9.1	(*R*)/22.5
2.21[l]	4-NO_2	**1f**	3	95	−11.3	(*R*)/27.9
2.22	4-NO_2		22	92	+3.1	(*S*)/7.7

[a] Determined by chiral HPLC analysis.
[b] Reaction of aldehyde with nitromethane without the presence of a catalyst in a glass flask (product is 1-(4-nitrophenyl)-2-nitroethene).
[c] Reaction of aldehyde with nitromethane in ethanol in the presence of $Cu(OAc)_2$.
[d] Temperature 5 °C.
[e] Half concentration of catalyst (formation of 1-(4-nitrophenyl)-2-nitroethene observed).
[f] Molar ratio of ligand:precursor 2:1.
[g] THF as solvent.
[h] Half concentration of nitromethane (0.25 ml; 0.5 mmol).
[i] Copper (II) trifluoroacetate as metal precursor (formation of 1-(4-nitrophenyl)-2-nitroethene observed).
[j] Copper (II) benzoate as metal precursor.
[k] Copper (II) 4-nitrobenzoate as metal precursor.
[l] Copper (II) 4-methoxybenzoate as metal precursor.
[m] Copper (II) chloride as metal precursor (with addition of Et_3N (1:1)).

Table 3. Henry reaction (tridentate ligands—see Schemes 2 and 3)

Entry	Aldehyde (R_1)	Tridentate ligand	Time (h)	Yield (%)	$[\alpha]_D^{25}$ (*c* 1, CH_2Cl_2)	Configuration/ee[a] (%)
3.1	4-NO_2	**2a**	6	94	+5.2	(*S*)/12.7
3.2	4-NO_2	**2b**	6	95	+5.4	(*S*)/13.3
3.3	4-NO_2	**2c**	6	96	+5.8	(*S*)/14.5
3.4	4-NO_2	**2d**	6	96	+7.9	(*S*)/19.4
3.5[b]	4-NO_2	**2d**	4	95	+12.9	(*S*)/31.8
3.6	4-NO_2	**3a**	72	94	+3.9	(*S*)/9.9
3.7	4-NO_2	**3b**	72	95	+4.1	(*S*)/10.1
3.8	4-NO_2	**3c**	48	89	+5.7	(*S*)/14.1
3.9	4-NO_2	**4**	120	54	−3.4	(*R*)/8.4

[a] Determined by chiral HPLC analysis.
[b] Copper (II) 4-methoxybenzoate as metal precursor.

The tridentate ligands showed a reversed enantioselectivity compared to other chiral amines.

Overall, the prepared ligands were applied in the Henry reaction and showed good yields/reaction times but the enantiomeric excesses were moderate (31.8% ee max).

4. Experimental

^1H and ^{13}C NMR spectra were recorded in CD_3OD or $CDCl_3$ at 500 MHz with Bruker AVANCE 500 instruments. NMR techniques, such as COSY, HMBC and HMQC were used for regular assignment of particular

signals. Chemical shifts are reported in parts per million and calibrated to the signal of hexamethyldisiloxane (0.05 ppm). *J* values are given in hertz.

The positive-ion and negative-ion atmospheric pressure chemical ionization (APCI) mass spectra were measured on an Esquire 3000 ion trap analyzer (Bruker Daltonics, Bremen, Germany) within the mass range $m/z = 50$–600. Samples were dissolved in acetonitrile and analyzed by direct infusion at a flow rate of 40 μL/min. The ion source temperature was 300 °C, the APCI probe temperature was 350 °C; the flow rate and the pressure of nitrogen were 3 l/min and 25 psi, respectively. The tuning of the mass spectrometer was optimized for the target mass m/z 400. For MS/MS measurements, the isolation width of precursor ions was 4 m/z, and the collision amplitude was 1 V in all cases.

Optical rotation values were measured on a Perkin Elmer 341 instrument, concentration *c* is given in g/100 ml. The enantiomeric excesses of all the ligands prepared were determined by the ^{1}H NMR spectra measured with Mosher acid (comparison of enantiomerically pure products and racemates spectra, ee > 95% in all cases). The enantiomeric excesses of the Henry reaction products were determined by HPLC on a Daicel Chiracel OB column and simultaneously deduced from [α] values.[3] Hydrogenations were carried out in ROTH pressure vessel. The chiral amines[1] and 2-phenylimidazole-4-carbaldehyde[12] were prepared following literature procedures. Copper (II) benzoates were prepared by heating freshly prepared copper (II) hydroxide with the appropriate benzoic acid in aqueous solution. Copper (II) salts were isolated through filtration of the boiling reaction mixture and were purified by multiple washing with ether. The other compounds and solvents have been used as commercially available.

5. Tridentate ligands

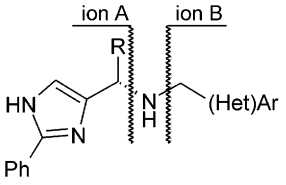
5.1. Method A

Into a solution of chiral amine **1** (0.87 mmol) and 2-phenylimidazole-4-carbaldehyde (0.87 mmol; 0.15 g) or 2-hydroxybenzaldehyde (0.87 mmol; 0.11 g) in dry methanol (10 ml), catalyst Pd/active carbon (0.5 g; 10%; Aldrich®) was added. The solution was degassed and saturated with hydrogen in an autoclave under 1 MPa pressure and 55 °C until TLC (methanol) showed reaction completion. The catalyst was then filtered off, the solvent evaporated and crude product **2** or **4** was purified by silica gel chromatography (methanol).

5.2. Method B

Into a solution of chiral amine **1** (0.87 mmol) and pyridine-2-carbaldehyde (0.87 mmol; 0.09 g) in dry methanol (10 ml), sodium sulfate (1 g) was added and the reaction mixture was stirred overnight. Sodium borohydride (0.9 mmol; 0.035 g) was added after cooling and filtration and the reaction mixture was stirred for further 5 h. Water (1 ml) was then added, methanol evaporated and crude product was purified by silica gel chromatography (methanol).

5.2.1. (1*S*)-1-(2-Phenyl-1*H*-imidazol-4-yl)-*N*-(2-phenyl-1*H*-imidazol-4-ylmethyl) ethanamine 2a. Prepared from chiral amine **1a** and 2-phenylimidazole-4-carbaldehyde by the method A to give title compound **2a** as a white solid, yield 87%, mp 110–112 °C, $[\alpha]_D^{20} = -43.0$ (*c* 0.5, CH_3OH), ee >95%. Found: C 73.9; H 6.1; N 20.2. $C_{21}H_{21}N_5$ requires C 73.4; H 6.2; N 20.4, molecular weight (MW) = 343. ^{1}H NMR (δ/ppm, 500 MHz, CD_3OD) 1.49 (3H, d, $J = 6.7$, CH_3), 3.77 (2H, s, $J = 6.7$, $NHCH_2$), 4.01 (1H, m, NH_2CH), 7.03 (1H, s, H_{im}), 7.08 (1H, s, H_{im}), 7.34 (2H, m, Ar*H*), 7.40 (4H, m, Ar*H*), 7.84 (4H, m, Ar*H*). ^{13}C NMR (δ/ppm, 125 MHz, CD_3OD) 21.7, 46.9, 51.6, 114.5, 120.2, 126.5, 126.6, 126.8, 127.1, 129.9, 130.0, 130.1, 130.2, 131.6, 131.7, 148.1, 148.2. Positive-ion APCI-MS (see Scheme 4 for the explanation of fragment ions A and B): m/z 344 $[M+H]^+$, 174 [ion B+NH_3]$^+$, 171 [ion A]$^+$ (100%), 157 [ion B]$^+$. Positive-ion APCI-MS/MS of m/z 344: m/z 186 [M−ion B]$^+$, 174 [ion B+NH_3]$^+$ (100%), 157 [ion B]$^+$. Negative-ion APCI-MS: m/z 342 $[M-H]^-$ (100%), 186 [M−ion B]$^-$, 172 [ion B+NH]$^-$, 169 [ion A−2H]$^-$, 156 [ion B−H]$^{-\cdot}$. Negative-ion APCI-MS/MS of m/z 342: m/z 325 [M−H−NH_3]$^-$, 186 [M−ion B]$^-$, 172 [ion B+NH]$^-$ (100%), 169 [ion A−2H]$^-$.



Scheme 4. Mass fragmentation.

5.2.2. (1*S*)-2-Methyl-1-(2-phenyl-1*H*-imidazol-4-yl)-*N*-(2-phenyl-1*H*-imidazol-4-ylmethyl) propanamine 2b. Prepared from chiral amine **1c** and 2-phenylimidazole-4-carbaldehyde by the method A to give title compound **2b** as a white solid, yield 89%, mp 119–120 °C, $[\alpha]_D^{20} = -66.2$ (*c* 0.5, CH_3OH), ee >95%. Found: C 74.1; H 6.8; N 18.9. $C_{23}H_{25}N_5$ requires C 74.4; H 6.8; N 18.9. MW = 371. ^{1}H NMR (δ/ppm, 500 MHz, CD_3OD) 0.87 (3H, d, $J = 6.8$, $(CH_3)_2CH$), 1.00 (3H, d, $J = 6.8$, $(CH_3)_2CH$), 2.04 (1H, m, $(CH_3)_2CH$), 3.61 (1H, d, $NHCHCH(CH_3)_2$), 3.70 (2H, 2 × d, $J = 14.0$, $NHCH_2$), 7.00 (1H, s, H_{im}), 7.03 (1H, s, H_{im}), 7.35 (2H, m, Ar*H*), 7.42 (4H, m, Ar*H*), 7.80 (2H, d, Ar*H*), 7.84 (2H, d, Ar*H*). ^{13}C NMR (δ/ppm, 125 MHz, CD_3OD) 19.5, 20.3, 34.4, 47.1, 62.5, 114.4, 120.1, 126.5, 126.6, 126.7, 126.8, 129.8, 129.9, 130.1, 130.2, 131.6, 131.8, 147.8, 148.1. Positive-ion APCI-MS: m/z 372 $[M+H]^+$, 215 [M+H−ion B]$^{+\cdot}$, 199 [ion A]$^+$ (100%), 174 [ion B+NH_3]$^+$, 157 [ion B]$^+$. Positive-ion APCI-MS/MS of m/z 372: m/z 215 [M+H−ion B]$^{+\cdot}$, 199 [ion A]$^+$, 174 [ion B+NH_3]$^+$ (100%), 157 [ion B]$^+$. Negative-ion APCI-MS: m/z 370 $[M-H]^-$ (100%), 353 [M−H−NH_3]$^-$, 214 [M−ion B]$^-$, 197 [ion A−2H]$^-$, 172 [M−ion A]$^-$, 156 [ion B−H]$^{-\cdot}$. Negative-ion APCI-MS/MS of m/z 370: m/z 353 [M−H−NH_3]$^-$, 214 [M−ion B]$^-$ (100%), 197 [ion A−2H]$^-$, 172 [M−ion A]$^-$.

5.2.3. (1*S*)-3-Methyl-1-(2-phenyl-1*H*-imidazol-4-yl)-*N*-(2-phenyl-1*H*-imidazol-4-ylmethyl) butanamine 2c. Prepared from chiral amine **1d** and 2-phenylimidazole-4-carbaldehyde by the method A to give title compound **2c** as a white solid, yield 88%, mp 120–121 °C, $[\alpha]_D^{20} = -30.8$ (*c* 0.5, CH_3OH), ee >95%. Found: C 74.3; H 7.2; N 18.1. $C_{23}H_{25}N_5$ requires C 74.8; H 7.1; N 18.2. MW = 385. ^{1}H NMR (δ/ppm, 500 MHz, CD_3OD) 0.87 (3H, d, $J = 6.6$, $(CH_3)_2CH$), 0.92 (3H, d, $J = 6.6$, $(CH_3)_2CH$), 1.54 (1H, m, $(CH_3)_2CH$), 1.67+1.78 (2 × 1H, 2 × m, $CH_2CH(CH_3)_2$), 3.70 (2H, 2 × d, $J = 14.0$, $NHCH_2$), 3.90 (1H, m, NHC*H*), 7.00 (1H, s, H_{im}), 7.01 (1H, s, H_{im}), 7.29–7.36 (2H, m, Ar*H*), 7.36–7.44 (4H, m, Ar*H*), 7.80 (2H, d, Ar*H*), 7.85 (2H, d, Ar*H*). ^{13}C NMR (δ/ppm, 125 MHz, CD_3OD) 23.1, 24.0, 26.7, 46.5, 48.4, 63.5, 114.5, 120.7, 125.0, 126.8, 127.0, 127.2, 129.1, 130.1, 130.2, 130.5, 131.9, 132.1, 148.5, 148.6. Positive-ion APCI-MS: *m*/*z* 386 $[M+H]^+$, 213 [ion A]$^+$ (100%), 174 [ion B+NH_3]$^+$, 157 [ion B]$^+$. Positive-ion APCI-MS/MS of *m*/*z* 386: *m*/*z* 228 [M−ion B]$^+$, 213 [ion A]$^+$, 174 [ion B+NH_3]$^+$ (100%), 157 [ion B]$^+$. Negative-ion APCI-MS: *m*/*z* 384 $[M-H]^-$, 367 $[M-H-NH_3]^-$, 228 [M−ion B]$^-$, 211 [ion A−2H]$^-$ (100%), 172 [M−ion A]$^-$, 156 [ion B−H]$^{-\bullet}$. Negative-ion APCI-MS/MS of *m*/*z* 384: *m*/*z* 367 $[M-H-NH_3]^-$, 228 [M−ion B]$^-$, 211 [ion A−2H]$^-$, 172 [M−ion A]$^-$ (100%).

5.2.4. (1*S*)-2-Phenyl-1-(2-phenyl-1*H*-imidazol-4-yl)-*N*-(2-phenyl-1*H*-imidazol-4-ylmethyl) ethanamine 2d. Prepared from chiral amine **1f** and 2-phenylimidazole-4-carbaldehyde by the method A to give title compound **2d** as a white solid, yield 88%, mp 120–121 °C, $[\alpha]_D^{20} = -10.0$ (*c* 0.5, CH_3OH), ee >95%. Found: C 77.3; H 6.1; N 16.5. $C_{27}H_{25}N_5$ requires C 77.3; H 6.0; N 16.7. MW = 419. ^{1}H NMR (δ/ppm, 500 MHz, CD_3OD) 3.16 (2H, m, CH_2Ph), 3.90 (2H, 2 × d, $J = 14.6$, $NHCH_2$), 4.12 (1H, t, $J = 7.2$, NH_2CH), 6.94 (1H, s, H_{im}), 7.04–7.44 (10H, m, Ar*H*), 7.69 (1H, t, Ar*H*), 7.80 (2H, d, Ar*H*), 8.42 (1H, m, Ar*H*). ^{13}C NMR (δ/ppm, 125 MHz, CD_3OD) 43.0, 52.6, 58.6, 121.1, 122.3, 124.0, 124.2, 126.6, 127.7, 129.5, 130.0, 130.1, 130.5, 131.6, 138.7, 139.5, 148.3, 150.0, 159.1. Positive-ion APCI-MS: *m*/*z* 420 $[M+H]^+$, 262 [M−ion B]$^+$, 247 [ion A]$^+$ (100%), 174 [ion B+NH_3]$^+$, 157 [ion B]$^+$. Positive-ion APCI-MS/MS of *m*/*z* 420: *m*/*z* 403 $[M+H-NH_3]^+$, 262 [M−ion B]$^+$, 247 [ion A]$^+$, 174 [ion B+NH_3]$^+$ (100%), 157 [ion B]$^+$. Negative-ion APCI-MS: *m*/*z* 418 $[M-H]^-$ (100%), 262 [M−ion B]$^-$, 245 [ion A−2H]$^-$, 172 [M−ion A]$^-$, 156 [ion B−H]$^{-\bullet}$. Negative-ion APCI-MS/MS of *m*/*z* 418: *m*/*z* 401 $[M-H-NH_3]^-$, 262 [M−ion B]$^-$(100%), 245 [ion A−2H]$^-$, 172 [M−ion A]$^-$.

5.2.5. (1*S*)-2-Methyl-1-(2-phenyl-1*H*-imidazol-4-yl)-*N*-(pyridine-2-ylmethyl) propanamine 3a. Prepared from chiral amine **1c** and pyridine-2-carbaldehyde by the method B to give title compound **3a** as a white solid, yield 62%, mp 67–69 °C, $[\alpha]_D^{20} = -49.8$ (*c* 0.5, CH_3OH), ee >95%. Found: C 74.3; H 7.1; N 18.4. $C_{19}H_{22}N_4$ requires C 74.5; H 7.2; N 18.3. MW = 306. ^{1}H NMR (δ/ppm, 500 MHz, CD_3OD) 0.92 (3H, d, $J = 6.8$, $(CH_3)_2CH$), 1.09 (3H, d, $J = 6.8$, $(CH_3)_2CH$), 2.25 (1H, m, $(CH_3)_2CH$), 3.83 (1H, d, $J = 7.1$, $NHCHCH(CH_3)_2$), 4.03 (2H, 2 × d, $J = 14.3$, $NHCH_2$), 7.14 (1H, s, H_{im}), 7.29–7.43 (5H, m, Ar*H*), 7.76–7.84 (3H, m, Ar*H*), 8.5 (1H, m, Ar*H*). ^{13}C NMR (δ/ppm, 125 MHz, CD_3OD) 19.3, 20.1, 33.4, 51.9, 63.2, 114.8, 124.4, 124.5, 126.6, 126.7, 130.0, 130.1, 131.3, 138.9, 148.5, 149.4, 150.1. Positive-ion APCI-MS: *m*/*z* 307 $[M+H]^+$, 215 $[M+H-\text{ion B}]^{+\bullet}$, 199 [ion A]$^+$ (100%), 109 [ion B+NH_3]$^+$. Positive-ion APCI-MS/MS of *m*/*z* 307: *m*/*z* 199 [ion A]$^+$, 109 [ion B+NH_3]$^+$ (100%). Negative-ion APCI-MS: *m*/*z* 305 $[M-H]^-$ (100%), 213 $[M-H-\text{ion B}]^{-\bullet}$, 197 [ion A−2H]$^-$, 183 [ion A−H−$CH_3$]$^-$. Negative-ion APCI-MS/MS of *m*/*z* 305: *m*/*z* 197 [ion A−2H]$^-$, 183 [ion A−H−CH_3]$^-$ (100%).

5.2.6. (1*S*)-3-Methyl-1-(2-phenyl-1*H*-imidazol-4-yl)-*N*-(pyridine-2-ylmethyl) butanamine 3b. Prepared from chiral amine **1d** and pyridine-2-carbaldehyde by the method B to give title compound **3b** as a white solid, yield 65%, mp 67–68 °C, $[\alpha]_D^{20} = -29.4$ (*c* 0.5, CH_3OH), ee >95%. Found: C 74.7; H 7.6; N 17.4. $C_{20}H_{24}N_4$ requires C 75.0; H 7.6; N 17.5. MW = 320. ^{1}H NMR (δ/ppm, 500 MHz, CD_3OD) 0.91 (3H, d, $J = 6.7$, $(CH_3)_2CH$), 0.93 (3H, d, $J = 6.6$, $(CH_3)_2CH$), 1.53 (1H, m, $(CH_3)_2CH$), 1.78+2.04 (2 × H, 2 × m, $CHCH_2CH(CH_3)_2$), 4.07 (2H, 2 × d, $J = 14.7$, $NHCH_2$), 4.21 (1H, dd, $J = 5.1$, NHC*H*), 7.22 (1H, s, H_{im}), 7.31 (1H, t, Ar*H*), 7.38 (2H, m, Ar*H*), 7.44 (2H, t, Ar*H*), 7.75 (1H, t, Ar*H*), 7.86 (2H, d, Ar*H*), 8.54 (1H, d, Ar*H*). ^{13}C NMR (δ/ppm, 125 MHz, CD_3OD) 22.1, 23.7, 26.3, 43.7, 51.2, 55.9, 119.1, 122.3, 124.3, 124.5, 126.7, 130.1, 130.2, 131.4, 137.1, 138.8, 149.0, 150.3. Positive-ion APCI-MS: *m*/*z* 321 $[M+H]^+$, 229 $[M+H-\text{ion B}]^{+\bullet}$, 213 [ion A]$^+$ (100%), 109 [ion B+NH_3]$^+$. Positive-ion APCI-MS/MS of *m*/*z* 321: *m*/*z* 213 [ion A]$^+$, 157 [ion A−butene]$^+$, 109 [ion B+NH_3]$^+$ (100%). Negative-ion APCI-MS: *m*/*z* 319 $[M-H]^-$, 227 $[M-H-\text{ion B}]^{-\bullet}$, 211 [ion A−2H]$^-$ (100%), 169 [ion A−2H−CH_3CHCH_2]$^-$. Negative-ion APCI-MS/MS of *m*/*z* 319: *m*/*z* 211 [ion A−2H]$^-$, 169 [ion A−2H−CH_3CHCH_2]$^-$ (100%).

5.2.7. (1*S*)-2-Phenyl-1-(2-phenyl-1*H*-imidazol-4-yl)-*N*-(pyridine-2-ylmethyl) ethanamine 3c. Prepared from chiral amine **1f** and pyridine-2-carbaldehyde by the method B to give title compound **3c** as a white solid, yield 69%, mp 60–61 °C, $[\alpha]_D^{20} = 34.0$ (*c* 0.5, CH_3OH), ee >95%. Found: C 77.8; H 6.3; N 15.9. $C_{23}H_{22}N_4$ requires C 78.0; H 6.3; N 15.8. MW = 354. ^{1}H NMR (δ/ppm, 500 MHz, CD_3OD) 3.16 (2H, m, CH_2Ph), 3.90 (2H, 2 × d, $J = 14.6$, $NHCH_2$), 4.12 (1H, t, $J = 7.2$, NH_2CH), 6.94 (1H, s, H_{im}), 7.04–7.44 (10H, m, Ar*H*), 7.69 (1H, t, Ar*H*), 7.80 (2H, d, Ar*H*), 8.42 (1H, m, Ar*H*). ^{13}C NMR (δ/ppm, 125 MHz, CD_3OD) 43.0, 52.6, 58.6, 121.1, 122.3, 124.0, 124.2, 126.6, 127.7, 129.5, 130.0, 130.1, 130.5, 131.6, 138.7, 139.5, 148.3, 150.0, 159.1. Positive-ion APCI-MS: *m*/*z* 355 $[M+H]^+$, 263 $[M+H-\text{ion B}]^{+\bullet}$, 247 [ion A]$^+$ (100%), 109 [ion B+NH_3]$^+$. Positive-ion APCI-MS/MS of *m*/*z* 355: *m*/*z* 247 [ion A]$^+$ (100%), 109 [ion B+NH_3]$^+$. Negative-ion APCI-MS: *m*/*z* 353 $[M-H]^-$, 261 $[M-H-\text{ion B}]^{-\bullet}$, 245 [ion A−2H]$^-$ (100%). Negative-ion APCI-MS/MS of *m*/*z* 353: *m*/*z* 261 [M−H−ion B]$^-$ (100%), 245 [ion A−2H]$^-$.

5.2.8. 2-[(1*S*)-*N*-(3-Methyl-1-(2-phenyl-1*H*-imidazol-4-yl)-butyl)aminomethyl]phenol 4. Prepared from chiral amine **1d** and 2-hydroxybenzaldehyde by the method A to give title compound **4** as a white solid, yield 60%, mp 160–162 °C, $[\alpha]_D^{20} = -28.0$ (*c* 0.5, CH_3OH), ee >95%. Found:

C 75.0; H 7.3; N 12.5; O 4.8. $C_{21}H_{25}N_3O$ requires C 75.2; H 7.5; N 12.5; O 4.8. MW = 335. ^{1}H NMR (δ/ppm, 500 MHz, CD_3OD) 0.86 (3H, d, $J = 6.7$, $(CH_3)_2CH$), 0,89 (3H, d, $J = 6.6$, $(CH_3)_2CH$), 1.45 (1H, m, $(CH_3)_2CH$), 1.75+2.11 ($2 \times$H, $2 \times$m, $CHCH_2CH(CH_3)_2$), 4.01 (2H, s, $NHCH_2$), 4.26 (1H, d, $J = 6.4$, NHCH), 6.76–6.81 (2H, m, ArH), 7.12–7.18 (2H, m, ArH), 7.30 (1H, s, H_{im}), 7.35 (2H, t, ArH), 7.42 (2H, t, ArH), 7.86 (2H, d, ArH). ^{13}C NMR (δ/ppm, 125 MHz, CD_3OD) 21.8, 25.3, 26.3, 42.2, 46.9, 56.3, 116.4, 121.0, 126.7, 126.8, 130.1, 130.3, 131.4, 131.9, 132.4, 136.9, 149.1, 157.5. Positive-ion APCI-MS: m/z 336 $[M+H]^+$, 229 $[M+H-\text{ion B}]^{+\cdot}$, 213 $[\text{ion A}]^+$ (100%), 157 $[\text{ion A}-\text{butene}]^+$, 107 $[\text{ion B}]^+$. Positive-ion APCI-MS/MS of m/z 336: 229 $[M+2H-\text{ion B}]^+$, 213 $[\text{ion A}]^+$ (100%), 157 $[\text{ion A}-\text{butene}]^+$. Negative-ion APCI-MS: 334 $[M-H]^-$ (100%), 243 $[M-H-C_7H_7]^{-\cdot}$, 228 $[M-\text{ion B}]^-$, 211 $[\text{ion A}-2H]^-$, 122 $[\text{ion B}+NH]^-$. Negative-ion APCI-MS/MS of m/z 334: 228 $[M-\text{ion B}]^-$, 211 $[\text{ion A}-2H]^-$ (100%), 122 $[\text{ion B}+NH]^-$.

5.3. Asymmetric catalysis (*Henry reaction, standard experiment*)

A mixture of chiral ligand (55 μmol) and copper (II) precursor (50 μmol) in ethanol (5 ml) was stirred for an hour at room temperature in a Teflon coated flask. Nitromethane (0,54 ml; 10 mmol) and aldehyde (1 mmol) were then added and the reaction mixture stirred until TLC (ethyl acetate/hexane 1:4) showed reaction completion. Ethanol was evaporated under reduced pressure and replaced by ether. The precipitate was filtered off through a plug of silica and washed with ether. The ether extract was washed with sodium bisulfite, water and dried with sodium sulfate. Solvent was then removed under reduced pressure to give a pure product. Additional purification was possible to carry out on silica (ethyl acetate/hexane 1:4). 2-Nitro-1-(4-nitrophenyl)ethanol ^{1}H NMR (δ/ppm, 500 MHz, $CDCl_3$) 3.10 (1H, br d, $J = 4.1$, $CH(OH)CH_2NO_2$), 4.55–4.68 (1H, m, $CH(OH)CH_2NO_2$), 5.65 (1H, m, $CH(OH)CH_2NO_2$), 7.64 (2H, m, ArH), 8.30 (2H, m, ArH). ^{13}C NMR (δ/ppm, 125 MHz, $CDCl_3$) 70.0, 80.7, 124.4, 127.1, 145.2, 148.3.

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