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New Highly Asymmetric Henry Reaction Catalyzed by Cu^{II} and a C_1-Symmetric Aminopyridine Ligand, and Its Application to the Synthesis of Miconazole

Gonzalo Blay,* Luis R. Domingo, Victor Hernández-Olmos, and José R. Pedro*[a]

Abstract: A new catalytic asymmetric Henry reaction has been developed that uses a C_1-symmetric chiral aminopyridine ligand derived from camphor and picolylamine. A variety of aromatic, heteroaromatic, aliphatic, and unsaturated aldehydes react with nitromethane and other nitroalkanes in the presence of DIPEA (1.0 equiv), $Cu(OAc)_2 \cdot H_2O$ (5 mol %), and an aminopyridine ligand (5 mol %) to give the expected products in high yields (up to 99 %), moderate-to-good diastereoselectivites (up to 82:18), and excellent enantioselectivities (up to 98 %). The reaction is air-tolerant and has been used in the synthesis of the antifungal agent miconazole.

Keywords: aldol reaction · antifungal agents · asymmetric catalysis · copper · nucleophilic addition

Introduction

The Henry or nitroaldol reaction constitutes one of the most useful methodologies for carbon–carbon bond formation.[1] Owing to the chemical versatility of the nitro group,[2] the resulting β-hydroxynitroalkanes, especially in an optically active form, are valuable intermediates for the synthesis of polyfunctionalized molecules and biologically active compounds.[3] Consequently, considerable effort has been directed towards the development of catalytic asymmetric versions of this reaction.[4] However, with the exception of earlier work by Shibasaki et al. with lanthanide–BINOL complexes (BINOL = 1,1′-bi-2-naphthol),[5] highly enantioselective Henry reactions have not been implemented until very recently. These reactions use metal complexes with chiral ligands. Examples include dinuclear zinc (Trost),[6] zinc triflate–amino alcohol (Palomo),[7] and cobalt–ketoimino (Yamada)[8] complexes, the last two were used in combination with Brønsted bases. Choudary et al. have also described the use of nanocrystalline MgO for asymmetric Henry and Michael reactions.[9] The most outstanding achievements have been obtained, however, with copper complexes. Evans et al. reported the copper acetate/bisoxazoline-catalyzed addition of nitromethane to aldehydes and obtained enantiomeric excess (*ee*) values up to 94 %.[10] Jørgensen et al. used a related Cu^{II}–BOX (BOX = bisoxazoline) system for the addition of silyl nitronates to aldehydes with moderate enantioselectivity.[11] Maheswaran et al. have used the dichloro[(−)-sparteine-*N*,*N*′]copper(II) complex for the Henry reaction with nitromethane and obtained *ee* values from 73 to 97 %.[12] You and Ma[13] have reported the synthesis of new chiral bisimidazoline ligands and their application to the copper(II)-catalyzed Henry reaction with which very high *ee* values (up to 98 %) were obtained. Highly enantioselective Henry reactions catalyzed by copper(II) complexes with diamino ligands have been described very recently by the groups of Bandini[14] and Arai.[15] Finally, Feng and co-workers have described the use of copper(I) complexes with tetrahydrosalen and *N*,*N*′-dioxide ligands.[16] In addition to these metal-based procedures, a number of organocatalytic methods have been recently described.[17] However, despite the recent advances in this reaction and the high enantioselectivities obtained, some limitations are still encountered: high catalyst loading (40–100 %),[7] activation of nitroalkanes as silyl nitronates,[11,17e] the substrate scope is limited to aliphatic or aromatic aldehydes,[5,9,16b,17c,f,h] difficulties in obtaining the catalyst in both enantiomeric forms,[12] and so forth. Moreover, with the exception of a few procedures,[5,11,15,16a,17f,h] these methods do not work or have not been tested with nitroalkanes other than nitromethane. Finally, some of the ligands employed are prepared in

[a] Dr. G. Blay, Dr. L. R. Domingo, V. Hernández-Olmos, Prof. Dr. J. R. Pedro
Departament de Química Orgànica
Facultat de Química, Universitat de València
Dr. Moliner 59, 46100 Burjassot (València) (Spain)
Fax: (+34) 963-544-328
E-mail: gonzalo.blay@uv.es
jose.r.pedro@uv.es

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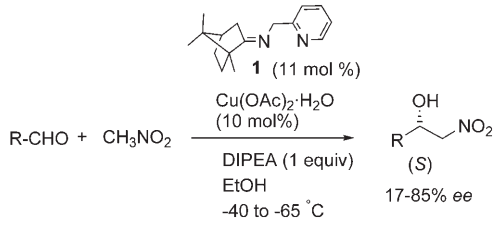
long synthetic sequences, some of which involve racemic resolution, use expensive starting materials and have a very high molecular weight.

The discovery and development of novel chiral ligands are of significant importance in asymmetric catalysis. The ideal ligand should be easily prepared, cheap, stable under the reaction conditions, storable, and highly selective for a large number of processes. Ligands with two N (sp^2) coordinating atoms have found wide application in enantioselective metal-catalyzed reactions.[18] BOX ligands have proved to be a privileged class of chiral ligands that are capable of forming a broad variety of metal complexes that can catalyze a great number of reactions with outstanding enantioselectivity. High enantioselectivities have also been achieved with other C_2-symmetric *N,N*-ligands, such as bisimines,[19] and bispyridines.[20] Application of the desymmetrization concept to these ligands has also led to C_1-symmetric ligands with two differentiated N (sp^2) atoms, such as oxazolinyl pyridines[21] and iminopyridines.[22] According to this last strategy, we developed a new family of modular C_1-symmetric iminopyridine ligands, which are easily prepared (one step) from readily available monoterpene ketones and pyridylalkylamines. These ligands were used in a copper(II)-catalyzed Henry reaction to give the corresponding products in high yields, albeit with moderate enantioselectivity (Scheme 1).[23] In this article, we report a highly enantioselective Henry reaction with aldehydes that uses a new aminopyridine ligand based on our previous design for iminopyridine ligands.



Scheme 1. Henry reaction catalyzed by Cu^{II} and iminopyridine ligand **1**.

Results and Discussion

Studies carried out with unsymmetrical bidentate ligands have shown that the electronic and steric differentiation of the two opposite equatorial coordination sites of the metal by the ligand has a profound effect on both the catalyst activity and the enantioselectivity.[24,25] Iminopyridine ligands, such as **1**, provide highly sterically differentiated surroundings for both equatorial coordination sites of the copper ion. However, because both nitrogen atoms have the same hybridation (although with different functional groups), the two equatorial coordination sites of copper should have similar electronic features, that is, similar acidity and coordinating ability. On the other hand, the *Z* geometry of the imine places C_1-Me of the camphor skeleton very close to the copper coordination site *trans* to the pyridine, which may hinder the reaction partners from accessing the metal center. To increase electronic differentiation between the two equatorial coordination sites and to provide the ligand with bigger flexibility, we decided to reduce the C=N bond of the iminopyridine ligands. The new ligands should coordinate to the copper ion with a strongly basic amine N (sp^3) atom and a weekly basic pyridine N (sp^2) atom, to form a square-planar complex, in which both equatorial coordinating positions of the hypothetical square-planar complex would have greater electronic differentiation. Furthermore, the possibility of rotation around the C–N bond would allow better accommodation of the camphor skeleton in the metal complex (Figure 1).

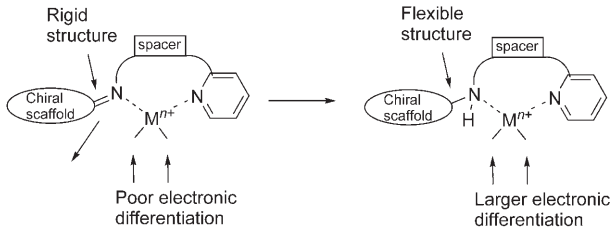
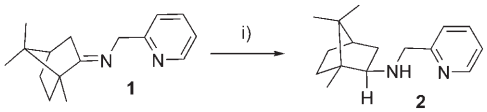


Figure 1. Design of aminopyridine ligands from iminopyridine ligands.

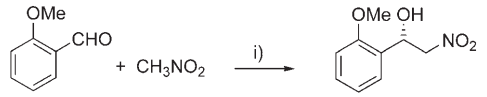
The imine C=N double bond in **1** was reduced upon treatment with $NaBH_4/NiCl_2$ to give **2** as only one diastereomer in a yield of 64% (Scheme 2).[26] The stereochemistry of the resulting amine was determined by NOE and NOESY experiments, which showed the spatial proximity of the CH_2-N methylene to the 1-Me ($\delta = 1.09$) and 7s-Me ($\delta = 0.95$) groups of the camphor framework, as well as the proximity between the 2-H ($\delta = 2.64$) and 5n-H ($\delta = 1.05$) protons.[27]



Scheme 2. Synthesis of aminopyridine ligand **2** from **1** (4.1 mmol). i) $NaBH_4$ (1.0 equiv), $NiCl_2$ (2.0 equiv), MeOH (60 mL), −30 °C, 3 h.

For purposes of comparison, we added nitromethane to benzaldehyde in the presence of $Cu(OAc)_2 \cdot H_2O$ (5 mol%) and **2** (5 mol%) in EtOH at 0 °C. We were very pleased to observe that the new catalyst showed enhanced catalytic activity and enantioselectivity with respect to **1**, and provided the expected product in a yield of 95% with an *ee* value of 91% after 51 h (Scheme 3), and proved the expected superiority of the amino ligands with respect to the related iminopyridines.

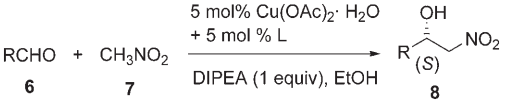
Based on our previous experience with iminopyridine ligands, further improvement was achieved by performing the reaction at a lower temperature and in the presence of diisopropylethylamine (DIPEA) to activate the nitromethane. In



Scheme 3. Comparative reaction of 2-anisole and nitromethane in the presence of ligands **1** (10 mol%) and **2** (5 mol%). i) L/$Cu(OAc)_2$, EtOH, 0°C. L = **1**: 88 h, 98% yield, 67% *ee*; L = **2**: 51 h, 95% yield, 91% *ee*.

this way, the expected product was obtained in an almost quantitative yield and with an excellent enantioselectivity (98% *ee*; Table 1, entry 1). We prepared three other aminopyridines **3–5** that differ in the spacer length, substitution on the pyridine ring, and the chiral scaffold (see the Supporting Information) and tested them with benzaldehyde under similar conditions. The resulting nitroalkanol had a lower enantioselectivity than with ligand **2** (Table 1, entries 1–4).

Table 1. Asymmetric addition of nitromethane to aldehydes catalyzed by copper(II) acetate and ligands **2–5**.



Entry[a]	L	Aldehyde	T [°C]	t [h]	Yield[b] [%]	*ee*[c] [%]
1	**2**	benzaldehyde (**6a**)	−50	22	99	98
2	**3**	benzaldehyde (**6a**)	−50	24	90	71
3	**4**	benzaldehyde (**6a**)	−50	24	90	44
4	**5**	benzaldehyde (**6a**)	−50	24	90	47
5	**2**	2-methoxybenzaldehyde (**6b**)	−50	3	99	98
6	**2**	2-methylbenzaldehyde (**6c**)	−50	2	99	98
7	**2**	2-chlorobenzaldehyde (**6d**)	−50	23	98	96
8	**2**	2-nitrobenzaldehyde (**6e**)	−40	35	82	86
9	**2**	3-methoxybenzaldehyde (**6f**)	−50	23	99	98
10	**2**	3-methylbenzaldehyde (**6g**)	−50	10	99	98
11	**2**	3-chlorobenzaldehyde (**6h**)	−50	10	94	97
12	**2**	4-methoxybenzaldehyde (**6i**)	−50	17	99	98
13	**2**	4-methylbenzaldehyde (**6j**)	−50	6	95	98
14	**2**	4-chlorobenzaldehyde (**6k**)	−50	22	99	97
15	**2**	4-nitrobenzaldehyde (**6l**)	−50	24	86	85
16	**2**	2,4-dichlorobenzaldehyde (**6m**)	−50	24	70	89 (98)[d]
17	**2**	thiophen-3-carbaldehyde (**6n**)	−50	21	99	98
18	**2**	decanal (**6o**)	−20	22	98	92
19	**2**	dihydrocinnamaldehyde (**6p**)	−20	23	79	94
20	**2**	cyclohexanecarbaldehyde (**6q**)	−20	22	95	90
21	**2**	isovaleraldehyde (**6r**)	−20	10	97	91
22	**2**	cinnamaldehyde (**6s**)	−50	24	97	96

[a] Reactions were carried out on a 0.5 mmol scale of aldehydes in a mixture of EtOH (2 mL) and nitromethane (0.27 mL). [b] Isolated yield. [c] Determined by HPLC analysis. The absolute configurations were established by comparison with literature data or with one another (see the Supporting Information). [d] *ee* value after a single crystallization.

The substrate scope was studied by using ligand **2**. A variety of aromatic and heteroaromatic aldehydes were found to be suitable substrates, with the Henry reaction providing the expected products in high-to-quantitative yields with excellent enantioselectivities, above *ee* values of 95% in most cases, regardless of the location of the substituent and its electronic nature (Table 1, entries 1 and 5–17). Only the presence of a strongly electron-withdrawing nitro group (Table 1, entries 8 and 15) or two electron-withdrawing chlorine atoms (Table 1, entry 16) brought about a small decrease in the enantioselectivity. Most remarkably, the reaction could also be performed with unbranched and even branched or sterically hindered aliphatic aldehydes (Table 1, entries 18–21). In these cases, the reaction was carried out at a higher temperature (−20°C), and the resulting products were obtained in high yields and enantiomeric excesses above 90% in all cases. Finally, the reaction with the **6s** exclusively afforded the 1,2-addition product in almost quantitative yield with an *ee* value of 96% (Table 1, entry 22).

Because of the good results obtained with the addition of nitromethane to aldehydes by using the $Cu(OAc)_2$/**2**/DIPEA system, we decided to extend the reaction to other nitroalkanes. As stated in the introduction, only a very small number of catalytic systems work or have been tested in the Henry reaction with nitroalkanes other than nitromethane. The results are shown in Table 2. Ligand **2** was again found to give better results than ligands **3–5** (Table 2, entries 1–4). The Cu^{II}/**2** system worked efficiently with nitroethane (**9**, R′ = Me; Table 2, entries 1 and 5–10), nitropropane (**9**, R′ = Et; Table 2, entries 11–17) and with the almost unstudied 2-phenylnitroethane (**9**, R′ = $PhCH_2$; Table 2, entry 18). With aromatic aldehydes, the reaction took place with good diastereoselectivity (from 61:39 to 82:18) favoring the *anti* product, which was obtained with *ee* values above 89% for the addition of nitroethane and nitropropane (Table 2, entries 1, 5–9, and 11–16), and an *ee* value of 83% for the addition of the bulkier 2-phenylnitroethane (Table 2, entry 18). On the other hand, reaction of nitroethane and nitropropane with **6p** (Table 2, entries 10 and 17, respectively) afforded chiefly the *syn* product, although with a lower diastereoselectivity and *ee* value than the reaction with aromatic aldehydes.

As a synthetic application of the procedure, we have achieved the enantioselective synthesis of (*S*)-miconazole (Scheme 4), a potent antifungal agent.[28] (*S*)-1-(2,4-

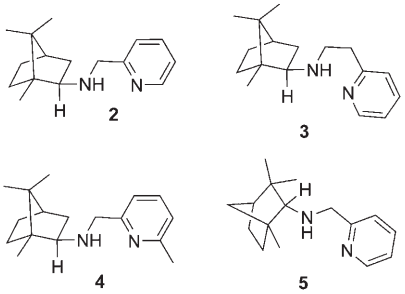
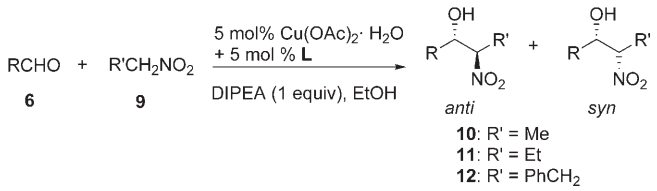


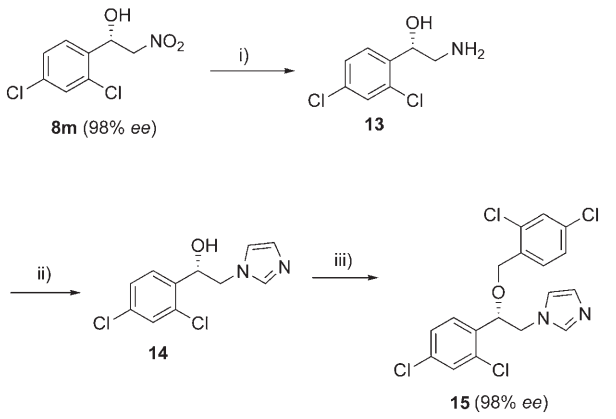
Table 2. Asymmetric addition of nitroalkanes to aldehydes catalyzed by copper(II) acetate and ligands **2**–**5**.



Entry[a]	L	Aldehyde	**9** R′	*t* [h]	Yield[b] [%]	*anti*/*syn*[c] [%]	*ee*[c] [%]
1	2	**6a**	Me	47	99	80:20	95/91
2	3	**6a**	Me	48	97	53:47	15/3
3	4	**6a**	Me	48	95	53:47	5/3
4	5	**6a**	Me	24	90	63:37	9/35
5	2	**6b**	Me	19	95	82:18	95/94
6	2	**6c**	Me	46	95	79:21	91/91
7	2	**6i**	Me	49	91	66:34	91/85
8	2	**6k**	Me	44	99	81:19	95/84
9	2	**6l**	Me	49	97	80:20	92/63
10[d]	2	**6p**	Me	53	75	47:53	77/80
11	2	**6a**	Et	64	97	71:29	94/92
12	2	**6b**	Et	64	96	70:30	93/95
13	2	**6c**	Et	45	96	75:25	89/90
14	2	**6i**	Et	40	90	61:39	89/93
15	2	**6k**	Et	46	96	65:35	91/87
16	2	**6l**	Et	48	95	74:26	91/75
17[d]	2	**6p**	Et	72	73	39:61	80/80
18	2	**6a**	$PhCH_2$	52	90	68:32	83/54

[a] Reactions were carried out on a 0.5 mmol scale of aldehydes in mixture of EtOH (2 mL) and the nitroalkane (10.0 equiv) at −40 °C. [b] Isolated yield. [c] Determined by HPLC analysis. The absolute configurations were established by comparison with literature data or with one another (see the Supporting Information). [d] Reaction carried out at −20 °C.

Dichlorophenyl)-2-nitroethanol (**8m**), obtained from the Henry reaction of nitromethane and **6m** was reduced in a yield of 82% to the corresponding hydroxyamine **13** by treatment with zinc/HCl. This transformation was not successful with other procedures, such as catalytic hydrogenation, because they caused hydrogenolysis of the C–Cl bond. The imidazole ring was synthesized from **13**, glyoxal, formaldehyde, and ammonium acetate,[29] to give **14** in a yield of 70%.[30] Finally alkylation of the hydroxyl group with 2,4-dichloro-1-(chloromethyl)benzene[31] afforded (*S*)-miconazole (**15**) in a yield of 76% with an *ee* value of 98%, without loss of optical purity in any of the steps of the synthetic sequence.



Scheme 4. Enantioselective synthesis of (*S*)-miconazole (**15**). i) Zn, HCl, $EtOH/H_2O$, reflux, 82%; ii) glyoxal, 38% aqueous formaldehyde, NH_4OAc, MeOH, reflux, 70%; iii) 1. NaH, THF/DMF, RT, 2. 2,4-dichloro-1-(chloromethyl)benzene, tetrabutylammonium iodide, RT, 76%.

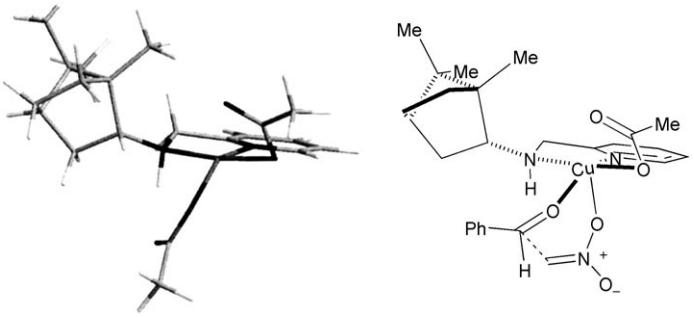


Figure 2. Optimized geometry for the $[Cu(\mathbf{2})(OAc)_2]$ complex (left) and a possible transition state (right) that shows the addition of the nitronate to the *Re* face of the aldehyde.

Suitable crystals of the $[Cu(\mathbf{2})(OAc)_2]$ complex could not be obtained for X-ray analysis. To account for the observed stereoselectivity, the geometry of $[Cu(\mathbf{2})(OAc)_2]$ was optimized at the UB3LYP/6-31G* level of theory[32] with the Gaussian 03 suite of programs[33] (Figure 2, left). The complex shows a large deviation from planar geometry with one of the acetate groups out of the N-Cu-N plane and forming a hydrogen bond with the N–H group. The acetate groups are oriented upwards and downwards, respectively, and the upper apical coordination site of the copper ion is shielded by the camphor framework. Based on this modeled complex, and the previously reported electronic considerations,[10] we propose a possible transition-state model that accounts for the absolute configuration of the obtained products (Figure 2, right). In the active species, the aldehyde will coordinate the copper(II) ion *trans* to the less electron-donating pyridine ligand for maximum electrophilic activation,[34] whereas the nitronate will occupy the less coordinating apical position for maximum nucleophilic activation. Transfer of the nitronate from the less hindered apical position to the exposed *Re* face of the aldehyde carbonyl group would yield products with an (*S*) configuration.

Conclusion

In conclusion, we have presented a new class of copper-aminopyridine catalysts for the highly enantioselective Henry reaction. A modular design of the catalyst is possible by varying the starting chiral ketone and the pyridylalkylamine. The most effective ligand for this reaction is readily prepared (two steps) from very cheap starting materials, and it can be obtained in both enantiomeric forms starting from the suitable camphor enantiomer, both of which are commercially available.

This Henry reaction is general in scope and provides the expected products with high-to-quantitative yields and ex-

cellent enantioselectivities with a broad range of aromatic, heteroaromatic, aliphatic, and unsaturated aldehydes, by using nitromethane and other nitroalkanes in the presence of a moderate catalyst loading (5 mol%). The operational procedure is very simple and does not require special care with respect to the exclusion of air or moisture. As a consequence of all these features, the present catalytic system is one of the most convenient procedures for the synthesis of nitroalkanols. The applicability of the procedure has been demonstrated with the synthesis of miconazole, a known antifungal agent.

Experimental Section

General methods: Commercial reagents were used as purchased. Reagent quality absolute EtOH without additional drying was used for all enantioselective reactions, which were carried out in test tubes stoppered with a septum. No special precautions were observed for the exclusion of air or moisture. Reactions were monitored by TLC analysis with Merck silica gel 60 F-254 thin-layer plates. Flash column chromatography was performed on Merck silica gel 60 (0.040–0.063 mm). Specific optical rotations were recorded by using a Perkin–Elmer 241 polarimeter with sodium light (D line 589 nm). NMR spectra were recorded by using Bruker Avance spectrometers in the deuterated solvents as stated. Residual non-deuterated solvent was used as the internal standard and $CFCl_3$ as the internal standard for ^{19}F NMR. *J* values are given in Hz. The carbon type was determined by DEPT experiments. Mass spectra were recorded by using a Fisons Instruments VG Autospec GC 8000 series spectrometer. EI mass spectra were run at 70 eV and FAB mass spectra were run at 30 kV in a *meta*-nitrobenzyl alcohol (MNBA) matrix. Chiral HPLC analyses were performed by using a Hitachi Elite Lachrom instrument equipped with a Hitachi UV diode array L-4500 detector with chiral stationary columns from Daicel. Retention times are given in min.

Compound 2: Sodium borohydride (1.59 g, 4.13 mmol) was added portionwise to a solution of **1** (1.00 g, 4.13 mmol) and $NiCl_2$ (1.09 g, 8.26 mmol) in MeOH (60 mL) at −30 °C under a nitrogen atmosphere over a period of 1 h. After 2 h, the solvent was evaporated under reduced pressure. Column chromatography (eluent = EtOAc) gave **2** as an oil (624 mg, 62%). $[\alpha]_D^{25} = -80.6$ ($c = 1.01$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.53$ (ddd, J(H,H) = 5.0, 1.8, 0.6 Hz, 1H; pyr), 7.63 (td, J(H,H) = 7.8, 1.8 Hz, 1H; pyr), 7.32 (d, J(H,H) = 7.8 Hz, 1H; pyr), 7.14 (ddd, J(H,H) = 7.5, 5.0, 0.6 Hz, 1H; pyr), 3.92 (d, J(H,H) = 14.4 Hz, 1H; CH_2N), 3.88 (d, J(H,H) = 14.4 Hz, 1H; CH_2N), 2.64 (dd, J(H,H) = 8.0, 4.3 Hz, 1H; 2n-H), 2.26 (brs, 1H; NH), 1.69 (s, 1H; 4-H), 1.70–1.56 (m, 3H; 3n-H, 3x-H, 5x-H), 1.09 (s, 3H; 1-Me), 1.05 (d, J(H,H) = 8.4 Hz, 2H; 5n-H, 6n-H), 0.95 (s, 3H; 7s-Me), 0.80 ppm (s, 3H; 7a-Me); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 160.4$ (C), 149.0 (CH), 136.3 (CH), 122.2 (CH), 121.7 (CH), 66.4 (CH), 53.9 (CH_2), 48.4 (C), 46.7 (C), 45.2 (CH), 38.5 (CH_2), 36.8 (CH_2), 27.3 (CH_2), 20.5 (CH_3), 20.5 (CH_3), 12.2 ppm (CH_3); MS (EI, 70 eV): m/z(%): 244 (0.8)$[M]^+$, 152 (100), 135 (29), 95 (41), 93 (92); HRMS: calcd for $C_{16}H_{24}N_2$ $[M]^+$: 244.1939, found: 244.1936.

General procedure for the catalytic enantioselective Henry reaction: A solution of **2** (6.7 mg, 0.025 mmol) in absolute EtOH (2 mL) was added to $Cu(OAc)_2{\cdot}H_2O$ (5.0 mg, 0.025 mmol) in a test tube. The test tube was stoppered with a septum, and the solution was stirred for 1 h to give a blue solution. The aldehyde (0.5 mmol) was added, and the tube was placed in a bath at the reaction temperature. After 5 min, the nitroalkane (5 mmol) was added followed by DIPEA (87.1 μL, 0.5 mmol). After the indicated time, the solvent was removed under reduced pressure and the product was isolated by column chromatography.

(*S*)-2-Amino-1-(2,4-dichlorophenyl)ethanol (13): Zn powder (314 mg, 4.78 mmol) was added to a solution of **8m** (100 mg, 0.212 mmol, 98% *ee*) in ethanol/H_2O (3.4:0.8 mL) followed by concentrated HCl (0.66 mL). The mixture was heated at reflux for 1 h. Aqueous saturated $NaHCO_3$ (10 mL) and water (10 mL) were added, and the mixture was extracted with EtOAc (3×25 mL). The organic phase was dried ($MgSO_4$), concentrated under reduced pressure, and the residue chromatographed on silica gel (EtOAc/EtOH 99:1 to 7:3) to give **13** (72 mg, 82%). $[\alpha]_D^{25} = +73.5$ ($c = 0.51$ in $CHCl_3$, 98% *ee*); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.51$ (d, J(H,H) = 8.4 Hz, 1H), 7.32 (d, J(H,H) = 2.1 Hz, 1H), 7.25 (dd, J-(H,H) = 8.4, 2.1 Hz, 1H), 4.98 (dd, J(H,H) = 7.8, 3.3 Hz, 1H), 3.07 (m, 4H), 2.66 ppm (dd, J(H,H) = 12.6, 7.8 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 138.5$ (C), 133.5 (C), 132.2 (C), 129.0 (CH), 128.3 (CH), 127.3 (CH), 69.9 (CH), 46.8 ppm (CH_2); MS (FAB, 30 kV): m/z (%): 206 (4) $[M+1]^+$; HRMS calcd for $C_8H_{10}NOCl_2$ $[M+1]^+$: 206.0139, found: 206.0147.

(*S*)-1-(2,4-Dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethanol (14): 40% Aqueous glyoxal (73.2 μL, 0.64 mmol), ammonium acetate (50.9 mg, 0.64 mmol), and 38% aqueous formaldehyde (48.4 μL, 0.64 mmol) were added to a solution of **13** (66 mg, 0.32 mmol) in methanol (0.75 mL). The mixture was heated at reflux for 4 h. After this time, the volatile compounds were removed under reduced pressure and the residue was treated with 2 M aqueous KOH (15 mL). The mixture was extracted with CH_2Cl_2 (5×20 mL), and the organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (CH_2Cl_2/MeOH, 100:0 to 95:5) gave **14** (57.5 mg, 70%). $[\alpha]_D^{25} = +87.3$ ($c = 0.89$ in $CHCl_3$, 98% *ee*; lit.:[29] $[\alpha]_D^{25} = +83.8$); ^1H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.58 (d, J(H,H) = 8.4, 2.1 Hz, 1H), 7.39 (m, 2H), 7.29 (d, J(H,H) = 8.4 Hz, 1H), 6.89 (brs, 1H), 6.81 (brs, 1H), 5.21 (d, J(H,H) = 8.1 Hz, 1H), 5.20 (brs, 1H), 4.20 (d, J(H,H) = 14.1 Hz, 1H), 3.87 ppm (dd, J(H,H) = 14.1, 8.1 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 137.5$ (C), 137.3 (CH), 134.1 (C), 131.9 (C), 129.0 (CH), 128.7 (CH), 128.0 (CH), 127.7 (CH), 119.6 (CH), 69.5 (CH), 53.5 ppm (CH_2); MS (EI, 70 eV): m/z (%): 256 (2.8) $[M]^+$, 221 (30), 174 (38), 111 (25), 82 (100), 81 (39); HRMS: calcd for $C_{11}H_{10}N_2OCl_2$ $[M]^+$: 256.0170, found: 256.0174; the *ee* value (98%) was determined by HPLC on a Chiralpack AD-H column, hexane/*i*PrOH (90:10), flow rate = 1.0 mL min^{-1}, major enantiomer (*S*) $t_r = 10.1$ min, minor enantiomer (*R*) $t_r = 15.5$ min.

(*S*)-1-(2-(2,4-Dichlorobenzyloxy)-2-(2,4-dichlorophenyl)ethyl)-1*H*-imidazole (miconazole, 15): NaH (60% dispersion in mineral oil, 6.7 mg, 0.17 mmol) was added to a solution of **14** (17.3 mg, 0.067 mmol) in THF/DMF (1 mL, 10:1) at 0 °C, under nitrogen. After 15 min, 2,4-dichloro-1-(chloromethyl)benzene (14 μL, 0.10 mmol) was added followed by tetrabutylammonium iodide (2.5 mg, 0.0067 mmol). After stirring for 5 h at RT, water (10 mL) was added. The mixture was extracted with CH_2Cl_2 (3×15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Column chromatography (hexane/EtOAc, 5:5 to 1:9) gave **15** (21.1 mg, 76%). $[\alpha]_D^{25} = +57.9$ ($c = 1.3$ in $CHCl_3$, 98% *ee*); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.54$ (brs, 1H), 7.45 (d, J(H,H) = 1.8 Hz, 1H), 7.36 (d, J-(H,H) = 1.8 Hz, 1H), 7.31–7.29 (m, 2H), 7.24 (dd, J(H,H) = 8.4, 1.8 Hz, 1H), 7.18 (d, J(H,H) = 8.4 Hz, 1H), 7.05 (brs, 1H), 6.91 (brs, 1H), 5.02 (dd, J(H,H) = 7.2, 2.7 Hz, 1H), 4.49 (d, J(H,H) = 12.6 Hz, 1H), 4.34 (d, J-(H,H) = 12.6 Hz, 1H), 4.25 (dd, J(H,H) = 14.7, 2.7 Hz), 4.08 ppm (dd, J-(H,H) = 14.7, 7.2 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 137.8$ (CH), 135.0 (C), 134.3 (C), 133.68 (C), 133.64 (C), 133.24 (C), 133.21 (C), 130.0 (CH), 129.7 (CH), 129.3 (CH), 129.2 (CH), 128.3 (CH), 128.0 (CH), 127.3 (CH), 119.8 (CH), 77.6 (CH), 68.2 (CH_2), 51.3 ppm (CH_2); MS (EI): m/z (%): 414 (6.2) $[M]^+$, 334 (18), 161 (65), 159 (100); HRMS: calcd for $C_{18}H_{14}N_2OCl_4$ $[M]^+$: 413.9860, found: 413.9865; the *ee* (98%) was determined by HPLC on a Chiralcel OD-H column, hexane/*i*PrOH (90:10), flow rate = 1.0 mL min^{-1}, major enantiomer (*S*) $t_r = 20.8$ min, minor enantiomer (*R*) $t_r = 19.6$ min.

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