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Pyrrole Macrocyclic Ligands for Cu-Catalyzed Asymmetric Henry Reactions

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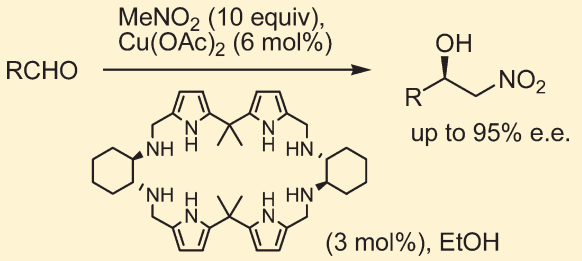
Supporting Information

ABSTRACT: New chiral perazamacrocycles containing four pyrrole rings have been synthesized by the [2 + 2] condensation of (*R*,*R*)-diaminocyclohexane and 5,5′-(alkane-2,2-diyl)bis(1*H*-pyrrole-2-carbaldehydes). These macrocycles, differing for the alkyl/aryl *meso*-substituents, were used as ligands in the copper-catalyzed Henry reactions of aromatic and aliphatic aldehydes with nitroalkanes. In the optimized experimental conditions, the condensations of nitromethane and aromatic and aliphatic aldehydes in the presence of catalytic amounts of copper diacetate and methyl-substituted macrocyclic ligand (2:1 ratio) in ethanol at room temperature provided products often with high enantiomeric excesses (up to 95% ee). The positive influence of the macrocyclic structure on the efficiency/enantioselectivity of the catalytic system was demonstrated by comparison with the outcomes of Henry reactions performed using analogous macrocyclic ligands (trianglamines) and open-chain ligands derived from (*R*,*R*)-diaminocyclohexane.



INTRODUCTION

Among the many synthetic tools of organic chemists, the Henry reaction is prominent because of the versatile chemistry of the nitro group. In particular, the asymmetric version of the reaction affords enantiomerically enriched β-hydroxy nitroalkanes which are precursors of valuable bifunctional compounds, such as β-amino alcohols and α-hydroxy carboxylic acids.[1] Metal complexes with chiral ligands are widely used as catalysts for Henry reactions. Among these enantioselective protocols, those exploiting copper complexes with a variety of ligands have provided remarkably high levels of enantioselectivity.[2]

In the realm of chiral ligands participating in metal complexes which are catalytically active in enantioselective organic reactions, polyazamacrocycles[3,4] and poly(oxaza)-[5] and poly(thiaza)macrocycles[6] have heretofore found a limited use. A simple and efficient way to synthesize nitrogen-containing macrocycles relies on the condensation of chiral diamines and aromatic dialdehydes both having a rigid structure, such as *trans*-1,2-diaminocyclohexane and aromatic dialdehydes (Scheme 1). Cyclic polyimines **1** (n = 1, 2, 3...) can be obtained by [n + n] cyclization of the reaction partners,[3,7] often with high selectivity depending on the structure of the dialdehyde and the experimental conditions, particularly the use of metal templates. The compounds **1** can be simply reduced to the corresponding saturated compounds **2** but are also capable of undergoing diastereoselective addition of carbon nucleophiles, so forming more complex compounds with defined stereochemistry.[8] Moreover, substituents at the nitrogen atoms can be routinely introduced.

The inherent symmetry of these chiral peraza macrocycles has induced investigation of their potential as ligands of metal species which are active as catalysts in several organic reactions. Several chiral ligands have been heretofore studied with this aim. For example, the trianglamines **3** and **4** are comparably effective ligands in $Cu(OAc)_2$-catalyzed Henry reactions (Scheme 2) of nitromethane with aromatic aldehydes (up to 87% ee with **4**) and aliphatic aldehydes (up to 93% ee with **3**) in solvent-free conditions. Analogous macrocycles with larger rings provided lower ee's.[4c] The complex formed by addition of 3 equiv of Et_2Zn to the same ligand **3**, formed in situ from its salt **3**·$(HBr)_6$ and 6 equiv of triethylamine, catalyzed the enantioselective condensation of acetone and *p*-nitrobenzaldehyde in DMSO providing a moderate 56.7% ee.[4b] Moreover, a 75% ee was obtained in the zinc-catalyzed Henry reaction (PhCHO−$MeNO_2$, MS, THF, −20 °C) using the ligand **6**.[6] We have recently demonstrated that added steric complexity in the molecular structure of the macrocycle was not useful, as the hexamethyl- and hexaphenyl-substituted macrocycles **5** displayed a lesser degree of asymmetric induction as compared to ligand **3** in the Cu-catalyzed Henry reaction.[8]

We were surprised to observe that although a large number of aromatic and heteroaromatic dialdehydes including pyridine, furan- and thiophenedialdehydes had been used for the construction of chiral macrocycles by condensation with optically pure *trans*-1,2-diaminocyclohexane, the synthesis of analogous chiral macrocycles from pyrroledialdehydes has been neglected.[9] This contrasts with the ubiquitous presence of pyrrole rings in

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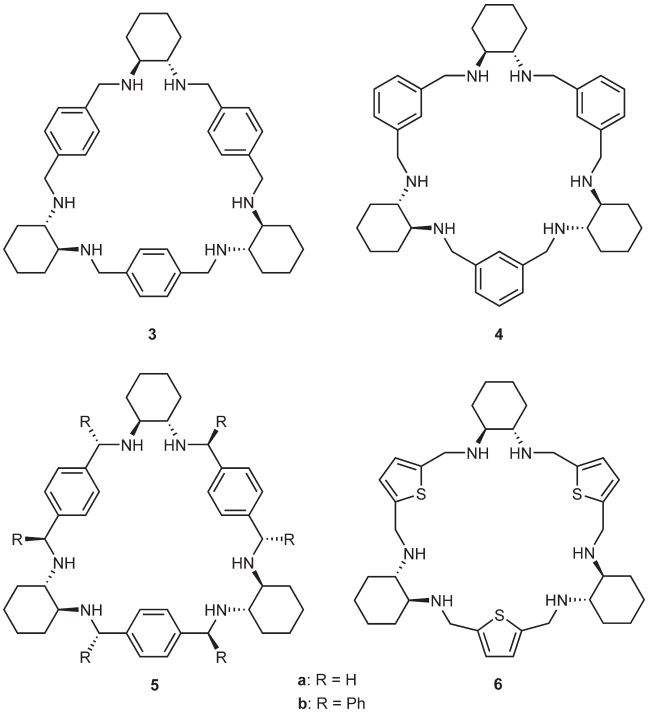
biologically active macrocycles as well as unnatural macrocyclic compounds, including porphyrins, expanded porphyrins, cryptophyrins, calyxpyrroles, calyxphyrins, and sapphyrins, which are mostly useful as ligands of metal ions and as receptors, carriers and sensors of inorganic and organic anions.[10] For example, the anion-binding capabilities of calyxpyrroles[7,11] and the partially reduced calyxpyrrole[12] have been documented.

As a continuation of our ongoing research on the synthesis of (chiral) peraza macrocycles and on the use of chiral 2-pyrroleimines for the synthesis of stereochemically defined molecules,[13] we now report the first preparation of C_2-symmetric, optically pure macrocycles containing pyrrole rings and their application as ligands in enantioselective Henry reactions.

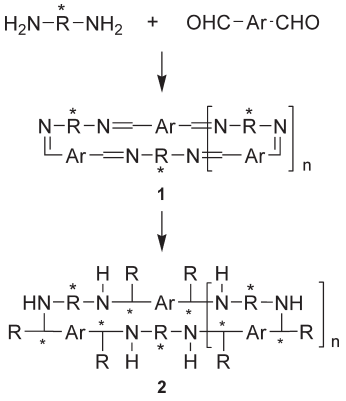
In this context, it is appropriate to note that chiral nonracemic pyrrole derivatives have found limited use in asymmetric catalytic reactions: 2-pyrroleimines provided low enantioselectivities in rhodium-catalyzed hydrosilylation of acetophenone,[14a,b] whereas excellent results were achieved with a 2-pyrrolethiazolidine.[14c] On the other hand, a 2-pyrrole-imidazolidinone was an efficient organocatalyst in a Mannich reaction leading to (+)-*epi*-cytoxazone with high levels of diastereo- and enantioselectivity.[15] Similarly, a racemic *trans*-10,20-disubstituted calyxpyrrole acted as an organocatalyst for a few regio- and diastereoselective reactions.[16] Lastly, in the domain of supramolecular chemistry, enantiomerically pure 2,5-bis(oxazolinyl)pyrroles, analogous to the classic Pybox ligands were prepared from (*R*)- and (*S*)-valinol and pyrrole-2,5-biscarbonitrile, lithiated and converted to enantiomerically pure double helical palladium complexes.[17]



RESULTS AND DISCUSSION

We chose to begin our research by preparing several macrocycles **10** (Scheme 2) from (*R*,*R*)-1,2-diaminocyclohexane and the *meso*-disubstituted diformyldipyrromethanes **8**. The condensation of the dialdehydes **8** with *o*-phenylenediamines has been previously used to synthesize achiral macrocyclic tetraimines,[18] which display binding properties toward transition-metal and uranyl salts[18a−c] or anions[18d] and metallo-macrocycles.[19]

Scheme 1. Synthesis of Chiral Perazamacrocycles from Chiral Diamines and Aromatic Dialdehydes



The choice of the dialdehydes **8** was dictated first of all by their easy preparation. Moreover, they allow the study of the effect of different substituents R in the macrocyclic ligand on the activity and enantioselectivity of the derived catalysts. The dialdehydes **8** were prepared by formylation of the pyrrole nuclei of the dipyrrole derivative **7**, in turn obtained by reaction of pyrrole with different ketones. Then, condensation of **8** with (*R*,*R*)-1,2-diaminocyclohexane, formed in situ by treatment of the corresponding L-tartrate salt with triethylamine, gave the expected macrocyclic tetraimines **9** with good yields. The subsequent reduction of the crude imines with sodium borohydride occurred without event to give the octadentate macrocyclic ligands **10** with good overall yields.

In order to evaluate the importance of the macrocyclic structure of the ligands **10** on the stereoselectivity of the catalytic system, we also synthesized the acyclic, tetraaza ligands **11** and **13**,[20] which feature different fragments present in the macrocyclic ligands (Scheme 3). The former was prepared from dipyrroledialdehyde **8a**, and the chirality was derived from (*S*)-1-phenylethylamine. On the other hand, the ligand **13** was formed from (*R*,*R*)-1,2-diaminocyclohexane and the two lateral pyrrole rings were introduced by condensation with 2-pyrrolecarboxaldehyde **12**, followed by routine reduction.

With all these ligands in hand, the prototypical Henry reaction between benzaldehyde and nitromethane was explored, first looking for the optimal metal salt/ligand combination. The reactions were carried out in ethanol as the solvent at room temperature using 10 molar equiv of nitromethane and were analyzed after 14 h (Scheme 4 and Table 1).

We observed that the methyl-substituted ligand **10a** (5 mol %) in the absence of a metal salt was an effective organocatalyst, as the nitro alcohol **14a** was produced with 90% yield by stirring overnight (14 h) but, unfortunately, as a racemic compound (entry 1). On the other hand, when the reaction was carried out with the same ligand in the presence of either $CuCl_2$ or $Cu(OTf)_2$ (10 mol %), no reaction took place (entries 2 and 3). However, the presence of a small amount of triethylamine had a dramatic effect on the copper-catalyzed reaction, as an almost complete formation of the product was observed. Therefore, since a weakly basic medium was required, we directed our attention to the use of zinc(II) and copper(II) acetates because the acetate anion is more basic than chloride and triflate anions,

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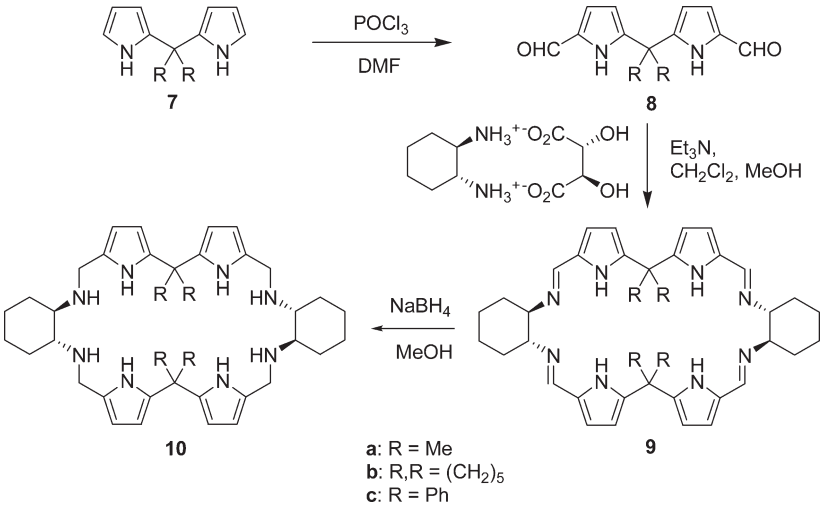
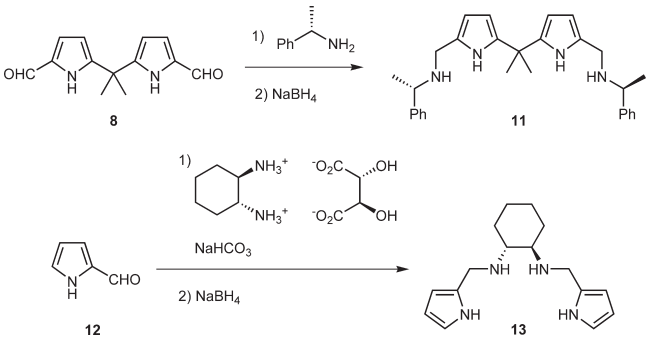
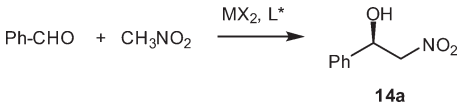
Scheme 2. Synthesis of Chiral Macrocyclic Ligands



Scheme 3. Synthesis of Acyclic Pyrrole Ligands



Scheme 4



so that the presence of triethylamine should have been avoided. As a matter of fact, the use of these salts enabled us to obtain excellent conversions to the nitro alcohol **14a** without the need to use added base (entries 5 and 6). A strikingly different degree of stereoocontrol was observed with the two salts, as only with copper acetate a remarkable degree of enantioselectivity was obtained (90% ee, entry 6). Moreover, when the reaction was performed in the presence of triethylamine the ee decreased to 64% (entry 7).[21]

On the basis of these results, the following experiments were carried out using the other ligands in the presence of $Cu(OAc)_2$. In this way, we assessed that increasing the size of the substituents R on the carbon tether linking the pyrrole nuclei had a detrimental effect on the enantioselectivity, which decreased down to 75% ee for ligand **10b** and 61% ee for ligand **10c** (entries 8 and 9). Successively, in order to verify the importance of the macrocyclic structure of the ligand on the enantioselectivity, we checked the acyclic ligands **11** and **13**, each of them featuring a different fragment of the macrocyclic ligands **10**. Ligand **11**, which lacks rigidity of the peripheral chiral moieties, gave an unsatisfactory performance, particularly in terms of enantioselectivity (3% ee, entry 11). On the other hand, ligand **13** with the rigid 1,2-diaminocyclohexane structure afforded **14a** with excellent yield and moderate stereocontrol (59% ee). Finally, we demonstrated that copper acetate in the absence of the ligand was unable to catalyze the reaction to a significant extent, as *rac*-**14a** was formed in 10% yield (entry 13). Overall, it was demonstrated that the combined use of copper acetate and the macrocyclic polydentate ligand **10a** was necessary for the efficient enantioselective catalysis.

The role of the solvent was investigated by performing the reaction in other protic, polar aprotic and apolar solvents using the $Cu(OAc)_2 \cdot H_2O$/**10a** (2:1 ratio) system (Table 2). It was demonstrated that the nature of the solvent affected to a limited extent the yield and the enantioselectivity. When the protic solvents MeOH, *i*-PrOH, and H_2O were used, comparable levels of ee were achieved, but a lower yield of **14a** was obtained in water. Among the polar aprotic solvents, CH_2Cl_2 gave an unsatisfactory performance in terms of both yield (81%) and ee (60%, entry 5), whereas in MeCN an almost complete conversion (99%) but a moderate ee (74%) were obtained (entry 6). On the other hand, either in THF and in $MeNO_2$ (entries 7 and 8, respectively) the levels of enantioselectivity were comparable to or slightly higher than those obtained in alcoholic solvents, but the yields were slightly lower. Finally, a 92% ee was obtained in toluene, but the yield was very low (entry 9). In conclusion, it appeared that the use of EtOH as the solvent gave a convenient balance of yield and enantioselectivity.

The effect of the ligand/metal ratio and catalyst loading on reaction rate and enantioselectivity was investigated next working in the previously established optimal conditions (Table 3). Working with a fixed amount of the ligand (5% molar equivalents), the loading of copper acetate was varied with respect to the 2-fold amount previously employed. Thus, it was observed that reducing to half the metal loading resulted in the decrease of the enantioselectivity to 80% ee (entry 2), although a comparable conversion was achieved. On the other hand, an increase of the metal loading to 15 mol % had no influence on ee (entry 3). Having so established the optimal ligand/metal ratio 1:2, we

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Table 1. Copper-Catalyzed Enantioselective Henry Reaction of Benzaldehyde with Nitromethane[a]

entry	L* (mol %)	metal salt (mol %)	base (mol %)	**14a** (yield, %)[b]	ee[c] (%)
1	**10a** (5)			90	0
2	**10a** (5)	$CuCl_2$ (10)		0	0
3	**10a** (5)	$Cu(OTf)_2$ (10)		0	0
4	**10a** (5)	$Cu(OTf)_2$ (10)	Et_3N (10)	98	8
5	**10a** (5)	$Zn(OAc)_2 \cdot 2H_2O$ (10)		99	5[d]
6	**10a** (5)	$Cu(OAc)_2 \cdot H_2O$ (10)		95	90
7	**10a** (5)	$Cu(OAc)_2 \cdot H_2O$ (10)	Et_3N (10)	99	64
8	**10b** (5)	$Cu(OAc)_2 \cdot H_2O$ (10)		99	75
9	**10c** (5)	$Cu(OAc)_2 \cdot H_2O$ (10)		85	61
10	**11** (10)	$Cu(OAc)_2 \cdot H_2O$ (10)		59	3
11	**13** (10)	$Cu(OAc)_2 \cdot H_2O$ (10)		99	59
12		$Cu(OAc)_2 \cdot H_2O$ (20)		10	0

[a] Conditions: 0.25 mmol of benzaldehyde, 2.5 mmol of nitromethane, 1.5 mL of EtOH, rt, 14 h. [b] Yield determined by ^{1}H NMR. [c] Determined by HPLC on chiral column. [d] A slight prevalence of the (*S*)-enantiomer was observed.

Table 2. Effect of Solvent in the Cu-Catalyzed Reaction of Benzaldehyde and Nitromethane in the Presence of Ligand 10a[a]

entry	solvent	**14a** (yield, %)[b]	ee[c] (%)
1	EtOH	95	90
2	MeOH	84	91
3	*i*-PrOH	92	89
4	H_2O	94	71
5	CH_2Cl_2	81	60
6	CH_3CN	99	74
7	THF	84	92
8	CH_3NO_2	79	91
9	Toluene	35	92

[a] Conditions: 0.25 mmol of benzaldehyde, 2.5 mmol of nitromethane, $Cu(OAc)_2 \cdot H_2O$ (0.025 mol), **10a** (0.012 mmol), 1.5 mL of solvent, rt, 14 h. [b] Yield determined by ^{1}H NMR. [c] Determined by HPLC on chiral column.

Table 3. Effect of Cu/10a Ratio, Catalyst Loading, and Temperature in the Henry Reaction[a]

entry	**10a** (mol %)	Cu (mol %)	**14a** (yield, %)[b]	ee[c] (%)
1	5	10	95	90
2	5	5	92	80
3	5	15	92	90
4	10	20	94	90
5	3	6	99 (92)[d]	92
6	1	2	93	90
7	0.2	0.4	56 (42)[d]	92
8	4	8[e]	97	92
9	1	2[e]	82[f]	86
10	5	10[g]	45[f]	83

[a] Unless otherwise stated, the reactions were performed using 0.25 mmol of benzaldehyde, 2.5 mmol of nitromethane, and copper acetate as the catalyst in 1.5 mL of EtOH at 22 °C for 14 h. [b] Determined by ^{1}H NMR. [c] Determined by HPLC on chiral column. [d] Isolated yield. [e] Reaction performed at 0 °C. [f] Reaction time: 48 h. [g] Reaction performed at −25 °C.

performed a set of reactions by varying the loading of the catalytic system. Using a 2-fold amount of the catalytic system **10a**/$Cu(OAc)_2 \cdot H_2O$ (10/20 mol %) did not change the outcome of the reaction (entry 4), although it is likely that a complete conversion should have been accomplished in a reduced time. In particular, reducing the L/Cu loading to 3/6 and then 1/2 mol % had no significant effect on the yield and enantioselectivity (entries 5 and 6), whereas a further reduction of the L/Cu loading to 0.2/0.4 mol % slowed the reaction and a moderate yield of **14a** was obtained after the canonical 12 h, although the same level of enantioselectivity was maintained (entry 7). At this point, we hoped that higher ee could have been obtained at a lower temperature, so we performed two tests at 0 °C using different catalyst loading. This allowed us to establish that the same high levels of reactivity and enantioselectivity were maintained using a L/Cu ratio of 4:8 mol % (entry 8), but a further decrease of the loading to L/Cu 1:2 reduced both the yield (82% after 48 h) and the ee (86%) (entry 9). This negative trend was confirmed when the reaction was carried out at −25 °C using a L/Cu loading of 5:10 mol %, when 45% yield (after 48 h) and 83% ee were obtained.

The study was then extended to other aldehydes to verify the full scope of the catalytic system. A number of aromatic and aliphatic aldehydes were screened in the reaction with nitromethane in the optimized experimental conditions: $Cu(OAc)_2 \cdot H_2O$ (6 mol %), **10a** (3 mol %), EtOH, 22 °C, 14 h (Scheme 5).

The results obtained showed that the protocol can be successfully applied to most aldehydes, although structural and electronic features of the substrate can affect significantly the reaction outcome (Table 4). The results obtained with aromatic aldehydes did not allow a rationalization of steric and electronic effects of the substituents. Methyl, methoxy, and fluoro *ortho*-substituents (entries 1−3) on the phenyl ring allowed to maintain or even increase the enantioselectivity observed with benzaldehyde, and the highest ee was observed with 2-methoxybenzaldehyde (95% ee). On the other hand, lower yield and enantioselectivity were obtained with 2-nitrobenzaldehyde (entry 4), and the 2-hydroxybenzaldehyde reacted efficiently but produced a racemic compound (entry 5). The variable effect of steric and electronic factors was confirmed when *para*- and *meta*-substituted benzaldehydes, bearing either electron-withdrawing and -donating substituents, such as 4-OH, 4-NO_2, 4-Cl, 4-OMe, 4-OBoc, and 3-OMe (entries 6−11), were converted to the

Scheme 5

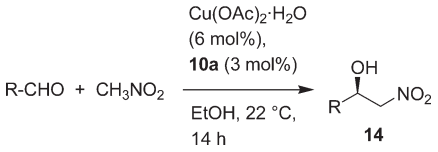


Table 4. Synthesis of β-Nitro Alcohols in the Optimized Conditions. Structural Effects on the Enantioselectivity[a]

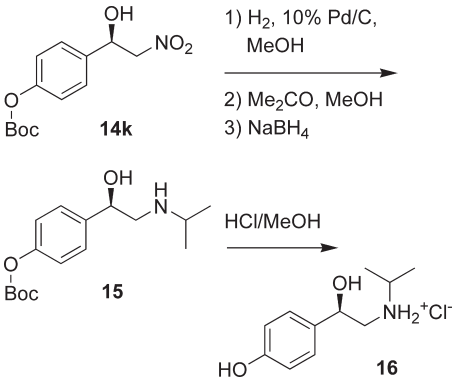
Entry	R	product, yield[b] (%)	ee[c] (%)
1	2-MeC_6H_4	**14b**, 91	91
2	2-$MeOC_6H_4$	**14c**, 90	95
3	2-F C_6H_4	**14d**, 80	90
4	2-$NO_2C_6H_4$	**14e**, 66	84
5	2-HOC_6H_4	**14f**, 87	0
6	4-HOC_6H_4	**14g**, 40	77
7	4-$NO_2C_6H_4$	**14h**, 96	71
8	4-ClC_6H_4	**14i**, 78	86
9	4-$MeOC_6H_4$	**14j**, 61[d]	83
10	4-$BocOC_6H_4$	**14k**, 81	87
11	3-$MeOC_6H_4$	**14l**, 75	86
12	4-MeC_6H_4	**14m**, 93	91
13	2-naphthyl	**14n**, 67	86
14	PhCH=CH	**14o**, 45	91
15	ferrocenyl	**14p**, 20	43
16	*N*-Boc-3-indolyl	**14q**, 60	73
17	3-Py	**14r**, 92	74
18	*i*-Bu	**14s**, 98[e]	85[f]
19	*t*-Bu	**14t**, 98[e]	89[f]
20	cyclohexyl	**14u**, 79	91
21	*rac*-PhMeCH	**14v**, 64[g]	*syn* 78, *anti* 90
22	*rac*-PhMeCH[h]	**14v**, 94[i]	*syn* 83, *anti* 87

[a] Conditions: aldehyde (0.25 mmol), nitroalkane (2.5 mmol), **10a** (3 mol %), $Cu(OAc)_2$ (6 mol %), EtOH (1.5 mL), 22 °C, 14 h. [b] Determined by ^1H NMR. [c] Determined by HPLC on chiral column. [d] Reaction time: 48 h. [e] Yield of crude product, which decomposed during purification. [f] Determined on the crude mixtures. [g] *Syn*/*anti* 61:39. [h] Reaction performed at 0 °C. [i] *Syn*/*anti* 67:33.

corresponding products with variable yields and lower ee's (in the range 74−86%), with the exception of *p*-tolualdehyde (93% yield and 91% ee, entry 12). In particular, the behavior of 4-hydroxybenzaldehyde (40% yield, 77% ee, entry 6) was opposite to that of 2-hydroxybenzaldehyde. Moderate to good yields and high ee's were obtained from 2-naphthylcarbaldehyde and cinnamaldehyde (entries 13 and 14), whereas ferrocenylcarbaldehyde proved to give a bad substrate yield and an especially poor enantioselectivity (entry 15). Among the heterocyclic aldehydes, *N*-Boc-3-indolylcarbaldehyde and 3-pyridinecarbaldehyde, which display opposite electronic effects, provided the same level of enantioselectivity (73−74% ee, entries 16 and 17).

Aliphatic aldehydes with primary, secondary, and tertiary alkyl substituents were efficiently converted to the expected products with high levels of enantioselectivity (85−91% ee, entries 18−20), but problems were often encountered during the isolation of the products, as previously observed.[2] As a matter of fact, extensive decomposition of the products **14s** (R = *i*-Bu) and **14t** (R = *t*-Bu) occurred during purification by chromatography on a silica gel column, and only the cyclohexyl derivative **14u** could be isolated.

Scheme 6



The reaction of nitromethane with racemic 2-phenylpropanal under the standard conditions gave the nitro alcohol **14v** as a mixture of diastereoisomers, with a moderate prevalence of the *syn* diastereoisomer, as the result of similar reactivities of the two enantiomers of the aldehyde (entry 21). The enantioselectivity for *anti*-**14v** (90% ee) was higher than for *syn*-**14v** (78% ee). For both diastereomers, we assume that the asymmetric induction is only slightly affected by the configuration of the starting aldehyde and the OH-substituted stereocenter is prevalently formed with the *R* configuration, by analogy with the reactions of achiral aldehydes. An almost complete conversion and a similar outcome was observed by performing the same reaction at 0 °C for 48 h, although increased yield and ee of *syn*-**14v** but slightly lower ee of *anti*-**14v** were obtained (entry 22).

The nitro-aldol derivative **14k** was then used to synthesize (*R*)-isopropylnorsynephrine, alias *N*-isopropyloctopamine[22] (Scheme 6), a member of the class of biologically active and pharmacologically active 1-aryl-2-amino alcohols[23] that have been prepared by a variety of asymmetric methods.[24] For that purpose, the nitro group of **14k** was reduced by heterogeneous hydrogenation to give the β-hydroxy amine **15**, and then reductive amination with acetone and sodium borohydride followed by removal of the Boc protection with a methanol solution of hydrochloric acid afforded the hydrochloride salt of (*R*)-isopropylnorsynephrine **16** with an overall yield of 47%.

Diastereoselectivity was further investigated by carrying out reactions of benzaldehyde with nitroethane using ligands **10a** and **10c** (5 mol %) in the presence of $Cu(OAc)_2$ (10 mol %), other conditions being the same. In both cases, mixtures of *syn* and *anti* β-nitro alcohols were obtained with almost no diastereoselectivity and only moderate enantioselectivity, with ee's falling in the range of 39−68%.

Crystals of the solvated macrocyclic imine **9a**·$(MeOH)_4$ were collected after slow evaporation of a methanolic solution of **9a**, and the structure was determined by X-ray crystallographic studies (see the Supporting Information). The macrocycle assumes a square geometry where at opposite corners are placed the cyclohexane rings and the methyl-substituted methylene carbons linking the pyrrole rings. The four MeOH molecules are symmetrically positioned in the inner space of the cavity, each of them forming two hydrogen

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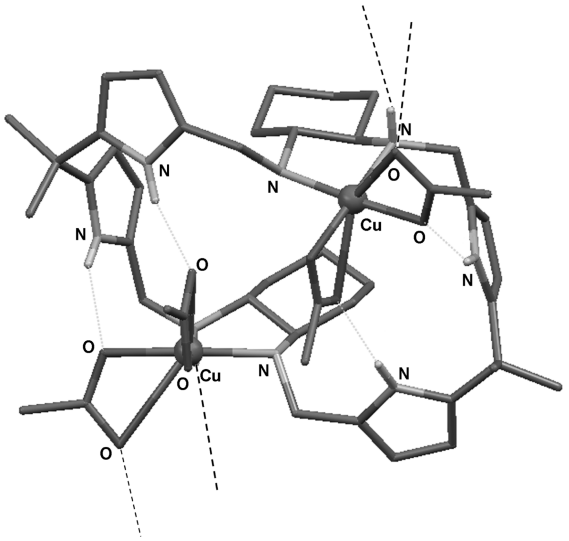


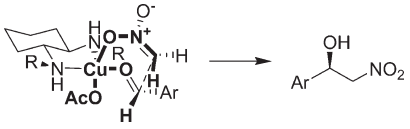
Figure 1. X-ray structure of the compound **10a**·2[Cu(OAc)$_2$]. Hydrogen bonds are depicted as dotted lines (intramolecular: gray, intermolecular: black) and copper atoms as spheres. Hydrogen atoms have been omitted for clarity.

bonds with adjacent imino and pyrrole NH groups. Crystals of the complex **10a**·2[Cu(OAc)$_2$] were then obtained by slow evaporation of a solution of the amine and copper acetate (1:2 molar ratio) in methanol. The X-ray structure of the complex (Figure 1) shows that both copper atoms assume the square planar geometry, where the *N*,*N*-bidentate diaminocyclohexane moiety and one oxygen of each carboxylate groups occupy *cis*-equatorial positions in the plane. The other two oxygens are oriented toward the vacant apical positions. Both cyclohexane rings have the chair conformation and the amino groups are equatorially disposed, and the dinuclear complex can be ideally split in two identical halves.

In both halves, the two acetate ligands are involved in intramolecular hydrogen bonding: one equatorial oxygen atom is linked to the adjacent pyrrole N−H group, and the axial-oxygen of the other acetoxy ligand is oriented toward the non-adjacent pyrrole N−H group. Moreover, intermolecular hydrogen-bonding interactions were observed between the oxygens of the carboxylate groups occupying the apical positions and the amino groups of adjacent macrocycles, thus determining the formation of a chain with a helicity feature (see the Supporting Information).

Concerning the mechanism, we are induced to think that the mechanism previously proposed by Evans for the analogous Henry reaction catalyzed by a chiral bis(oxazoline)−Cu(OAc)$_2$ complexes is also operative with our catalytic system.[2b] Hence, one acetate ligand is lost to leave room for coordination of both nucleophile and electrophile reagents to the copper center. The nitronate ion occupies the apical position, whereas the electrophilic carbonyl compound is more activated in the more Lewis acidic equatorial site. The model depicted in Scheme 7 appears to be favored by the reduced steric interactions of both reagents with the ligand backbone. Obviously, the sense of asymmetric induction is determined by the chirality of the 1,2-diaminocyclohexane moiety; however, the eventual role of dipyrrole moiety cannot be clearly evaluated at the moment, as different hypotheses can be advanced. In principle, it is possible that the copper-bound nitronate anion forms a hydrogen bond with the pyrrole ring

Scheme 7



closer to the copper-binding site and/or the more distant pyrrole similarly stabilizes the nitroalkoxide.

CONCLUSION

C_2-symmetric macrocycles containing two (*R*,*R*)-diaminocyclohexane moieties and four pyrrole nuclei have been synthesized for the first time by an efficient two-step sequence. These compounds exhibited enhanced usefulness as ligands in enantioselective copper-catalyzed Henry reactions, e.g., the reactions of nitromethane with aromatic and aliphatic aldehydes. Where up to 95% of ee has been reached. Such levels of enantioselectivity are superior to those obtained using analogous ligands, which contain benzene or thiophene rings in the macrocyclic structure, as well as acyclic ligands derived from 1,2-diaminocyclohexane and bearing pyrrole nuclei. However, unsatisfactory diastereoselectivities were obtained using nitroethane. Further studies are needed to understand the exact mechanism of the reaction and especially the role of the pyrrole nuclei on the enantioselectivity. This objective will be pursued by preparing modified macrocycles containing either pyrrole and/or different heteroaromatic rings. Hopefully, the thorough screening of new pyrrole-containing macrocyclic ligands will allow development of more efficient and stereoselective protocols for Henry reactions and perhaps expansion of their potential as ligands in other asymmetric reactions.

EXPERIMENTAL SECTION

General Methods. Chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard (deuterochloroform: δ 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = duplet, t = triplet, q = quartet, bs = broad singlet, m = multiplet), coupling constants (Hz). Chemical shifts are reported in ppm from TMS with the solvent as the internal standard (deuterochloroform: δ 77.0 ppm). GC−MS spectra were taken by EI ionization at 70 eV. They are reported as *m*/*z* (relative intensity). Chromatographic purification was done with 240−400 mesh silica gel. Determination of enantiomeric excess was performed on HPLC instrument equipped with a variable-wavelength UV detector, using a DAICEL Chiralpak columns (0.46 cm i.d. × 25 cm) and HPLC-grade 2-propanol and *n*-hexane were used as the eluting solvents. Optical rotations were determined in a 1 mL cell with a path length of 10 mm (Na_D line). Melting points are not corrected. Materials: All reactions were carried out under inert gas and under anhydrous conditions. Commercially available anhydrous solvents were used avoiding purification. *N*-Boc-3-indolecarbaldehyde,[25] 4-*tert*-butylcarbonate benzaldehyde, and 2-*tert*-butylcarbonate benzaldehyde,[26] compounds **7a**,[27] **7b**,[28] **7c**,[29] **8a**,[30] **8c**,[30] and **13**,[20] were prepared according to literature procedures. Spectroscopical details for compounds **14a**,[2f] **14b**,[31] **14c**,[2n] **14d**,[32] **14e**,[2n] **14f**,[2i] **14g**,[33] **14h**,[2n] **14i**,[2n] **14j**,[2n] **14l**,[2n] **14m**,[2n] **14n**,[2i] **14o**,[2n] **14p**,[34] **14r**,[2i] **14s**,[2i] **14t**,[2n] **14u**,[2n] and **14v**[2n] were already reported.

Synthesis of Dialdehyde 8b. $POCl_3$ (0.13 mL, 1.4 mmol) was added dropwise to a stirred solution of 2,2′-(cyclohexane-1,1-diyl) bis(1*H*-pyrrole) (150 mg, 0.7 mmol) in DMF (1 mL), which was cooled

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at 0 °C. The mixture was stirred at room temperature for 1 h and then cooled to 0 °C, and 10 N NaOH (10 mL) was added portionwise. The resultant precipitate was filtered and washed with water until pH = 7 was reached to obtain the crude product **8b** as a white amorphous solid: 162 mg, (86%). Mp = 208.4−209.7 °C dec. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.34 (m, 2 H), 1.61 (m, 4 H), 2.32 (t, J = 5.2 Hz, 4 H), 6.22 (d, J = 2.4 Hz, 2 H), 6.93 (d, J = 2.0 Hz, 2 H), 9.47 (s, 2 H), 10.45 (bs, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.5, 25.6, 34.9, 39.9, 108.7, 123.3, 132.6, 146.8, 179.5. IR (KBr): ν = 3281, 3198, 3131, 3109, 3093, 2925, 2856, 1679, 1472, 1269, 1193, 1052, 812, 776 cm^{-1}. ESI-MS m/z: 271.1 $[M + H]^+$, 293.1 $[M + Na]^+$, 541.3 $[2 M + H]^+$. Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.29; H, 6.74; N, 10.40.

Synthesis of Imines 9a−c. *General Procedure.* To the suspension of (*R*,*R*)-1,2-diaminocyclohexane L-tartrate (0.580 g, 2.2 mmol) in MeOH (25 mL) were added aldehyde **8a** (0.51 g, 2.2 mmol) and triethylamine (0.67 mL, 4.8 mmol). The reaction mixture was stirred for 48 h, and the solvent was evaporated at reduce pressure. A saturated aqueous solution of $NaHCO_3$ (20 mL) was added, and the organic material was extracted with dichloromethane (3 × 30 mL). The collected organic layers were washed with brine (20 mL), dried over Na_2SO_4, and concentrated to leave a white solid, which was crystallized from MeOH to give pure **9a** (0.63 g, 1.0 mmol, 90%) as colorless crystals. Mp = 160−162 °C dec. $[\alpha]^{20}_D$ = +689.2 (c 0.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.34 (m, 4 H), 1.53 (m, 4 H), 1.64 (m, 4 H), 1.67 (s, 12 H), 1.78 (m, 4 H), 3.16 (m, 4 H), 6.11 (d, J = 3.6 Hz, 4 H), 6.29 (d, J = 3.6 Hz, 4 H), 7.90 (s, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.7, 27.9, 34.1, 35.2, 73.5, 105.1, 115.1, 129.6, 142.8, 151.4. IR (KBr): ν = 3296, 2971, 2925, 2855, 1633, 1561, 1486, 1270, 1216, 1042, 776 cm^{-1}. ESI-MS m/z: 617.3 $[M + H]^+$. Anal. Calcd for $C_{38}H_{48}N_8$: C, 73.99; H, 7.84; N, 18.17. Found: C, 74.28; H, 7.87; N, 18.09.

9b. Colorless crystals, 80%. Mp = 197−199 °C (MeCN). $[\alpha]^{20}_D$ = +379.5 (c 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.36−1.49 (m, 12 H), 1.52−1.52 (m, 4 H), 1.61−1.71 (m, 8 H), 1.78 (m, 4 H), 2.04 (m, 4 H), 2.25 (m, 4 H), 3.14 (m, 4 H), 6.08 (d, J = 3.6 Hz, 4 H), 6.26 (d, J = 3.6 Hz, 4 H), 7.85 (s, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.5, 24.6, 26.0, 33.3 35.3, 39.5, 73.5, 105.7, 115.6, 129.6, 142.1, 151.4. IR (KBr): ν = 3447, 2929, 1633, 1560,1476, 1044, 775 cm^{-1}. ESI-MS m/z: 697.4 $[M + H]^+$. Anal. Calcd for $C_{44}H_{56}N_8$: C, 75.82; H, 8.10; N, 16.08. Found: C, 76.10; H, 8.12; N, 16.03.

9c. Red amorphous solid, 40%. Mp = 158−160 °C. $[\alpha]^{20}_D$ = −498 (c 0.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.36 (m, 4 H), 1.57 (m, 4 H), 1.78−1.82 (m, 8 H), 3.05 (m, 4 H), 5.80 (d, J = 3.6 Hz, 4 H), 6.17 (d, J = 3.6 Hz, 4 H), 6.95−6.97 (m, 4 H), 7.21−7.23 (m, 16 H), 7.71 (s, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.5, 32.7, 56.4, 72.9, 112.2, 114.6, 127.1, 127.8, 129.4, 129.6, 140.2, 144.3, 152.5. IR (KBr): ν = 3439, 2924, 2853, 1632, 1445, 1182, 1044,734, 700 cm^{-1}. ESI-MS m/z: 865.4 $[M + H]^+$. Anal. Calcd for $C_{58}H_{56}N_8$: C, 80.52; H, 6.52; N, 12.95. Found: C, 80.22; H, 6.55; N 12.97.

Synthesis of amines 10a−c. *General procedure.* $NaBH_4$ (0.15 g, 4.1 mmol) was added to the solution of **9a** (0.50 g, 0.8 mmol) in MeOH (20 mL) and the reaction mixture was stirred during 20 h, then a 1 M NaOH solution (5 mL) was added and the solvent was evaporated at reduced pressure. The organic material was extracted with EtOAc (3 × 30 mL). The collected organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated to leave **10a** (0.47 g, 0.76 mmol, 95%) as a white solid: mp =166−167 °C; $[\alpha]_D^{20}$ = −23.7 (c 0.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.72−0.82 (m, 6 H), 1.03−1.11 (m, 4 H), 1.46 (s, 12 H), 1.61 (m, 6 H), 1.99−2.09 (m, 4 H), 3.37 (d, J = 14.7 Hz, 4 H), 3.62 (d, J = 14.7 Hz, 4 H), 5.72 (d, J = 2.4 Hz, 4 H), 5.89 (t, J = 2.4 Hz, 4 H), 10.82 (bs, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 25.2, 31.4, 33.0, 35.8, 42.9, 60.3, 103.4, 103.9, 130.1, 137.6. IR (KBr): ν = 3442, 2928, 2856, 1646, 1456, 1075 cm^{-1}. ESI-MS m/z: 625.4 $[M + H]^+$. Anal. Calcd for $C_{38}H_{56}N_8$: C, 73.04; H, 9.03; N, 17.93. Found: C, 73.26; H, 9.06;N, 17.88.

10b. White solid; 90%. Mp = 147.9−148.9 °C (MeCN). $[\alpha]^{20}_D$ = −52.0 (c 1.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.89−0.96 (m, 4 H), 1.15 (m, 8 H), 1.39−1.42 (m, 2 H), 1.45−1.53 (m, 8 H), 1.54−1.72 (m, 10 H), 1.86−1.93 (m, 8 H), 2.06−2.14 (m, 4 H), 3.60 (d, J = 13.7 Hz, 4 H), 3.81 (d, J = 13.7 Hz, 4 H), 5.82 (t, J = 2.8 Hz, 4 H), 5.90 (t, J = 2.8 Hz, 4 H), 8.78 (bs, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 22.8, 25.0, 26.2, 31.5, 36.2, 39.1, 43.7, 60.6, 103.1, 106.1, 129.2. IR (KBr): ν = 3439, 2929, 2854, 2361, 2342, 1636, 1448, 1105, 1036, 770 cm^{-1}. ESI-MS m/z: 705.5 $[M + H]^+$. Anal. Calcd for $C_{44}H_{64}N_8$: C, 74.96; H, 9.15; N, 15.89. Found: C, 75.11; H, 9.16; N, 15.87.

10c. Red amorphous solid; 80%. Mp = 230−231 °C dec. $[\alpha]^{20}_D$ = −44.8 (c 0.8, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.77−0.82 (m, 6 H), 1.15−1.21 (m, 4 H), 1.27−1.49 (m, 6 H), 1.74−1.86 (m, 4 H), 1.99−2.16 (m, 4 H), 3.16 (m, 8 H), 5.79 (d, J = 2.4 Hz, 4 H), 6.13 (d, J = 2.4 Hz, 4 H), 7.14−7.20 (m, 4 H), 7.21−7.30 (m, 4 H), 7.40−7.62 (m, 12 H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 24.7, 25.9, 46.3, 47.6, 60.7, 102.3, 104.6, 127.3, 127.8, 129.2, 138.3, 140.2, 151.4. IR (KBr): ν = 3442, 2923, 2853, 2363, 1635, 1445, 1384, 1109, 1039, 700 cm^{-1}. ESI-MS m/z: 873.3 $[M + H]^+$. Anal. Calcd for $C_{58}H_{64}N_8$: C, 79.78; H, 7.39; N, 12.83. Found: C, 79.99; H, 7.41; N, 12.80.

Synthesis of the Copper Complex (10a·2[Cu(OAc)$_2$]). To a solution of **10a** (0.075 g, 0.12 mmol) in CH_2Cl_2 (5 mL) was added $Cu(OAc)_2 \cdot H_2O$ (0.048 g, 0.024 mmol), and the solution was stirred for 1 h. The solvent was removed in vacuo, and the residue was washed with pentane/Et_2O 9/1 (2 × 10 mL) and dried under vacuum to obtain 0.113 g (95%, 0.11 mmol) of copper complex **10a**·2[$Cu(OAc)_2$] as a slightly green solid. $[\alpha]^{20}_D$ = −47.1 (c 1.1, $CHCl_3$). Mp = 180 °C dec. IR (KBr): ν = 3405, 3239, 3160, 2966, 2932, 2859, 1559, 1404, 1211, 1050, 1003, 778, 680 cm^{-1}. ESI-MS m/z: 747 $[M - 4\ CH_3COOH + H]^+$, 749 $[M - 4\ CH_3COOH + H]^+$.

CCDC numbers 803953 (**9a**(**MeOH**)$_4$) and 803954 (**10a**·2[Cu-$(OAc)_2$]) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Synthesis of Amine 11. The dialdehyde **8a** (200 mg, 0.87 mmol) and (*S*)-phenylethylamine (0.22 mL, 1.74 mmol) were dissolved in CH_2Cl_2 (10 mL), and then $MgSO_4$ (0.500 g) was added. The mixture was stirred at room temperature for 48 h and then filtered through a short pad of Celite, which was washed with CH_2Cl_2. The solvent was evaporated at reduced pressure. The crude product was dissolved in MeOH (10 mL), $NaBH_4$ (66 mg, 179 mmol) was added, and the mixture was stirred at room temperature overnight. Water (5 mL) was added, and the mixture was stirred 20 min and then concentrated at reduced pressure to remove MeOH. The organic phase was extracted with EtOAc (2 × 20 mL), and the collected organic layers were concentrated at reduced pressure to leave a yellowish oil. Column chromatography (SiO_2, CH_2Cl_2/MeOH, 9:1) gave **11** as a colorless oil, 340 mg (90%). $[\alpha]^{20}_D$ = −22.1 (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.36 (d, J = 6.6 Hz, 6H), 1.67 (s, 6 H), 1.88 (bs, 2 H), 3.48 (d, J = 13.6 Hz, 2 H), 3.57 (d, J = 13.6 Hz, 2 H), 3.73 (q, J = 6.6 Hz, 2 H), 5.94 (t, J = 2.7 Hz, 2 H), 6.00 (t, J = 2.9 Hz, 2 H), 7.25−7.41 (m, 10 H), 8.24 (bs, 2 H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 23.9, 29.2, 35.3, 44.3, 57.4, 103.3, 105.5, 125.6, 126.5, 126.9, 128.4, 129.8, 138.6. ESI-MS m/z: 439.3 $[M + H]^+$. Anal. Calcd for $C_{29}H_{36}N_4$: C, 79.05; H, 8.24; N, 12.72. Found: C, 79.22; H, 8.26; N, 12.69.

Enantioselective Henry Reaction. *Typical Procedure.* To a solution of $Cu(AcO)_2 \cdot H_2O$ (0.003 g, 0.015 mmol) in EtOH (1.5 mL) was added **10a** (0.004 g, 0.007 mmol), and the reaction mixture was stirred at room temperature for 30 min. Benzaldehyde (30 μL, 0.25 mmol) and nitromethane (134 μL, 2.5 mmol) were added. After 20 h, the reaction mixture was filtered through a small pad of silica,

which was washed with EtOAc. Column chromatography (SiO_2, cyclohexane/EtOAc, 9:1) gave (*R*)-**14a**: 0.181 g (92%). 92% ee was determined by chiral HPLC (Chiralpak OD; 2-propanol/hexane 1:9, 0.8 mL/min.; 214 nm; 40 °C): retention times 14.5 min (*S*, minor enantiomer) and 17.4 min (*R*, major enantiomer).

14b. The ee was determined by chiral HPLC (Chiralpak OD; 2-propanol/hexane 25:75, 0.5 mL/min; 214 nm; 40 °C): retention times 11.6 min (*S*, minor enantiomer) and 15.1 min (*R*, major enantiomer).

14c. The ee was determined by chiral HPLC (Chiralpak OD; 2-propanol/hexane 1:9, 0.8 mL/min; 214 nm; 40 °C): retention times 14.2 min (*S*, minor enantiomer) and 18.1 min (*R*, major enantiomer).

14d. The ee was determined by chiral HPLC (Chiralpak OJ; 2-propanol/hexane 2:98, 0.8 mL/min.; 214 nm; 40 °C): retention times 19.5 min (*S*, minor enantiomer) and 21.1 min (*R*, major enantiomer).

14e. The ee was determined by chiral HPLC (Chiralpak OD; 2-propanol/hexane 1:9, 0.5 mL/min.; 214 nm; 40 °C): retention times 22.1 min (*S*, minor enantiomer) and 23.2 min (*R*, major enantiomer).

14f. The ee was determined by chiral HPLC (Chiralpak OD; 2-propanol/hexane 1:9, 0.6 mL/min.; 214 nm; 40 °C): retention times 19.3 min (*S*, minor enantiomer) and 21.0 min (*R*, major enantiomer).

14g. The ee was determined by chiral HPLC (Chiralpak OJ; 2-propanol/hexane 3:7, 0.8 mL/min.; 214 nm; 40 °C): retention times 16.4 min (*S*, minor enantiomer) and 19.5 min (*R*, major enantiomer).

14h. The ee was determined by chiral HPLC (Chiralpak OD; 2-propanol/hexane 2:8, 0.5 mL/min.; 214 nm; 40 °C): retention times 17.0 min (*S*, minor enantiomer) and 21.1 min (*R*, major enantiomer).

14i. The ee was determined by chiral HPLC (Chiralpak OD; 2-propanol/hexane 2:8, 0.5 mL/min.; 214 nm; 40 °C): retention times 14.0 min (*S*, minor enantiomer) and 16.1 min (*R*, major enantiomer).

14j. The ee was determined by chiral HPLC (Chiralpak OD; 2-propanol/hexane 2:8, 0.8 mL/min.; 214 nm; 40 °C): retention times 18.8 min (*S*, minor enantiomer) and 22.3 min (*R*, major enantiomer).

14k. White solid. $[\alpha]^{20}_D = +25.3$ (*c* 0.8, $CHCl_3$). Mp = 85.4−86.0 °C dec. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.53 (s, 9 H), 3.29 (bs, 1 H), 4.48 (dd, *J* = 3.3 Hz, *J* = 13.2 Hz, 1 H), 4.51 (dd, *J* = 9.5 Hz, *J* = 13.1 Hz, 1 H), 5.36 (dd, *J* = 3.3 Hz, *J* = 9.3 Hz, 1 H), 7.13−7.17 (m, 2 H), 7.34−7.38 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 27.6, 70.3, 81.1, 84.0, 121.8, 127.1, 135.9, 151.1, 151.8. IR (neat): ν = 3489, 2990, 2935, 1732, 1556, 1286, 1221, 1149 cm^{-1}. ESI-MS *m*/*z*: 301.1 $[M + H_2O]^+$, 306.0 $[M + Na]^+$, 322 M + K]$^+$. Anal. Calcd for $C_{13}H_{17}NO_6$: C, 55.12; H, 6.05; N, 4.94. Found: C, 55.00; H, 6.10; N, 4.99. The ee was determined by chiral HPLC (Chiralpak OD; 2-propanol/hexane 1:9, 1.0 mL/min; 214 nm; 40 °C): retention times 11.9 min (*S*, minor enantiomer) and 13.71 min (*R*, major enantiomer).

14l. The ee was determined by chiral HPLC (Chiralpak OD; 2-propanol/hexane 3:7, 0.6 mL/min.; 214 nm; 40 °C): retention times 12.0 min (*S*, minor enantiomer) and 14.1 min (*R*, major enantiomer).

14m. The ee was determined by chiral HPLC (Chiralpak OD; 2-propanol/hexane 2:8, 0.8 mL/min.; 214 nm; 40 °C): retention times 11.9 min (*S*, minor enantiomer) and 13.8 min (*R*, major enantiomer).

14n. The ee was determined by chiral HPLC (Chiralpak OD; 2-propanol/hexane 1:1, 0.6 mL/min.; 214 nm; 40 °C): retention times 12.5 min (*S*, minor enantiomer) and 15.5 min (*R*, major enantiomer).

14o. The ee was determined by chiral HPLC (Chiralpak IC; 2-propanol/hexane 25:75, 0.5 mL/min.; 214 nm; 40 °C): retention times 22.6 min (*S*, minor enantiomer) and 24.8 min (*R*, major enantiomer).

14p. The ee was determined by chiral HPLC (Chiralpak IC; 2-propanol/hexane 5:95, 0.7 mL/min.; 214 nm; 40 °C): retention times 59.9 min (*S*, minor enantiomer) and 62.7 min (*R*, major enantiomer).

14q. Yellow oil. $[\alpha]^{20}_D = +15.5$ (*c* 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.65 (s, 9 H), 3.00 (bs, 1 H), 4.65 (dd, *J* = 3.1 Hz, *J* = 13.3 Hz, 1 H), 4.77 (dd, *J* = 9.4 Hz, *J* = 13.3 Hz, 1 H), 5.81 (dt, *J* = 3.0 Hz, *J* = 9.4 Hz, 1 H), 7.26 (ddd, *J* = 1.1 Hz, *J* = 7.3 Hz, *J* = 8.2 Hz, 1 H), 7.34 (ddd, *J* = 1.2 Hz, *J* = 7.3 Hz, *J* = 8.4 Hz, 1 H), 7.61 (dt, *J* = 0.9 Hz, *J* = 7.7 Hz, 1 H), 7.63 (s, 1 H), 8.15 (d, *J* = 8.6 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 28.1, 65.2, 80.0, 84.4, 115.6, 117.9, 119.0, 123.1, 125.1, 127.4, 135.7, 149.3. IR (neat): ν = 3468, 3054, 2979, 2928, 1735, 1555, 1373, 1155, 1097 cm^{-1}. ESI-MS *m*/*z*: 324.2 $[M + H_2O]^+$, 329.1 $[M + Na]^+$. Anal. Calcd for $C_{15}H_{18}N_2O_5$: C, 58.82; H, 5.92; N, 9.15. Found: C, 58.78; H, 5.97; N, 9.11. The ee was determined by chiral HPLC (Chiralpak OD; 2-propanol/hexane 1:9, 0.8 mL/min.; 214 nm; 40 °C): retention times 11.4 min (*S*, minor enantiomer) and 12.8 min (*R*, major enantiomer).

14r. The ee was determined by chiral HPLC (Chiralpak IC; 2-propanol/hexane 4:6, 0.5 mL/min.; 214 nm; 40 °C): retention times 14.3 min (*S*, minor enantiomer) and 17.5 min (*R*, major enantiomer).

14s. The ee was determined by chiral HPLC (Chiralpak OJ; 2-propanol/hexane 2:98, 0.5 mL/min.; 214 nm; 40 °C): retention times 35.1 min (*S*, minor enantiomer) and 39.2 min (*R*, major enantiomer).

14t. The ee was determined by chiral HPLC (Chiralpak OD; 2-propanol/hexane 2:98, 0.7 mL/min.; 214 nm; 40 °C): retention times 16.9 min (*S*, minor enantiomer) and 18.9 min (*R*, major enantiomer).

14u. The ee was determined by chiral HPLC (Chiralpak IC; 2-propanol/hexane 5:95, 0.7 mL/min.; 214 nm; 40 °C): retention times 24.7 min (*S*, minor enantiomer) and 25.9 min (*R*, major enantiomer).

14v. The ee was determined by chiral HPLC (Chiralpak OD; 2-propanol/hexane 1:9, 0.6 mL/min.; 214 nm; 40 °C): retention times 16.7 min (*anti*, *S*,*S*), 18.3 min (*anti*, *R*,*R*), 20.9 min (*syn*, *R*,*S*) and 22.9 (*syn*, *S*,*R*).

Preparation of Compound 16. To a solution of compound **14** (123 mg, 0.43 mmol) in EtOH (2 mL) was added 10% Pd/C (17 mg). The mixture was stirred under a hydrogen atmosphere (balloon) for 22 h. The mixture was filtered through a short pad of Celite to remove the catalyst. Removal of the solvent under reduced pressure afforded 73 mg (70%) of primary amine. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.52 (s, 9 H), 2.74 (dd, *J* = 8 Hz, *J* = 13.2 Hz, 1 H), 2.91 (dd, *J* = 3.6 Hz, *J* = 12.8 Hz, 1 H), 4.57 (dd, *J* = 4 Hz, *J* = 8 Hz, 1 H), 7.08 (d, *J* = 8.4 Hz, 2 H), 7.31 (d, *J* = 8 Hz, 2 H). A solution of amine (73 mg, 0.29 mmol), acetone (34 μL, 0.46 mmol), and $MgSO_4$ (40 mg) in EtOH (2 mL) was stirred at rt overnight. Then the reaction mixture was cooled to 0 °C (ice bath), and $NaBH_4$ (16 mg, 0.43 mmol) was added. After being stirred for 1 h, the reaction mixture was filtered through a small pad of Celite, which was washed with EtOAc and MeOH to give 80 mg (94%) of compound **15**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.05 (d, *J* = 6.4 Hz, 6 H), 1.58 (s, 9 H), 2.62 (dd, *J* = 10 Hz, *J* = 13.2 Hz, 1 H), 2.78−2.85 (m, 1 H), 2.91 (dd, *J* = 3.6 Hz, *J* = 12.4 Hz, 1 H), 4.63 (dd, *J* = 4 Hz, *J* = 9.2 Hz, 1 H), 7.12 (d, *J* = 8.8 Hz, 2 H), 7.35 (d, *J* = 8 Hz, 2 H). A solution of HCl in MeOH, prepared by addition of acetyl chloride (0.100 mL, 1.35 mmol) to MeOH (2 mL), was added dropwise to a solution of **15** (80 mg, 0.27 mmol) in MeOH (7 mL) at room temperature. After 6 h, the mixture was concentrated at reduced pressure. The solid was washed with Et_2O (3 × 3 mL) to give the crude salt **16** as a white solid, 0.04 g (0.22 mmol, 80%). Mp = 149−150 °C (lit. racemic compound, mp 151.5−152.5 °C). $[\alpha]^{20}_D = -32.1$ (*c* 1.2, MeOH). ^{1}H NMR ($CDCl_3$ with 10% DMSO, 400 MHz): δ = 1.41 (d, *J* = 6.4 Hz, 3 H), 1.44 (d, *J* = 6.4 Hz, 3 H), 2.89−2.98 (m, 1 H), 3.00−3.10 (m, 1 H), 3.35−3.42 (m, 1 H), 4.81 (dd, *J* = 2.4 Hz, *J* = 10 Hz, 1 H), 6.84 (d, *J* = 8.4 Hz, 2 H), 7.14 (d, *J* = 8.4 Hz, 2 H). ^{13}C NMR (DMSO, 100 MHz): δ = 18.5, 19.2, 49.8, 50.3, 56.1, 78.7, 115.9, 128.0, 128.5, 158.2. IR (KBr): ν = 3220, 2979, 1613, 1614, 1555, 1448, 1267, 1224, 1100, 838 cm^{-1}. ESI-MS *m*/*z*: 196.1 $[M + H]^+$. Anal. Calcd for $C_{11}H_{18}ClNO_2$: C, 57.02; H, 7.83; N, 6.04. Found: C, 56.86; H, 7.85; N, 6.03.

■ ASSOCIATED CONTENT

Supporting Information. X-ray crystallography details of **9a**$(MeOH)_4$ and **10a**·2$[Cu(OAc)_2]$; NMR spectra for all new

compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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