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Rational Design of Sterically and Electronically Easily Tunable Chiral Bisimidazolines and Their Applications in Dual Lewis Acid/Brønsted Base Catalysis for Highly Enantioselective Nitroaldol (Henry) Reactions

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Abstract: A new addition to the rational design of sterically and electrically easily tunable chiral bis(imidazoline) ligands from chiral amino alcohols has been developed. Vast structural variation of chiral bis(imidazoline) ligands can be simply achieved by the choice of both the 1,2-amino alcohol and its N-1 R^1 substituent. A small library of chiral bisimidazolines (**1a–h**) has been constructed. The method has provided an easy and simplified route to a diverse set of air-stable and water-tolerant chiral bis(imidazoline) ligands on 10 g scales. The dual Lewis Acid/Brønsted base catalytic system generated from the (*S*)-**1a**/$Cu(OTf)_2$ complex and Et_3N was able to catalyze Henry reactions between aldehydes and nitromethane effectively at room temperature, and also to tolerate a wide scope of aldehydes with excellent enantiomeric excesses. Not only aromatic aldehydes but also aliphatic aldehydes afforded the nitroalcohol products, with enantiomeric excesses in the 93–98% range. This dual catalytic system is among the most effective systems so far reported for the asymmetric parent Henry reactions. This work also represents the first members of the class of chiral bisimidazolines to have been demonstrated to achieve excellent enantioselectivities.

Keywords: asymmetric catalysis · dual acid/base catalysis · Henry reaction · ligand design · N ligands

Introduction

Asymmetric catalysis is undoubtedly a powerful and economically viable tool for the synthesis of optically active organic compounds, and the design and synthesis of new and improved chiral ligands and their application in asymmetric catalysis continue to be research foci in both academic and industrial laboratories. The ideal ligand should be easily prepared, cheap, stable under the reaction conditions, and very selective for a large number of processes, hence very flexible.[1] It has not yet been discovered (and probably never will be), but *bis(oxazoline)* ligands have proved to be a privileged class of chiral ligands, being capable of forming a broad variety of metal complexes that are able to catalyze a great number of reactions with unparalleled enantioselectivity.[2]

It is reasonable to assume that the oxazoline ring should be structurally modifiable by the replacement of the O atom with a substituted N atom to provide a new class of imidazoline ligands, which should maintain the basic framework of oxazoline but also be further tunable electronically and conformationally over a wide range through judicious selection of the substituted R^1 group at the amine N atom (Figure 1). The highly modular nature of the construction of these ligands should therefore easily allow better matching of chiral ligand, metal ion, and substrate than are attainable with the analogous oxazoline ligands, and thus facilitate the achievement of excellent catalytic performance (activity and enantioselectivity). Surprisingly, however, imidazolines have not

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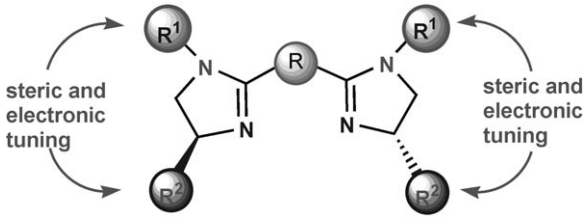


Figure 1. Chiral bis(imidazoline) ligands.

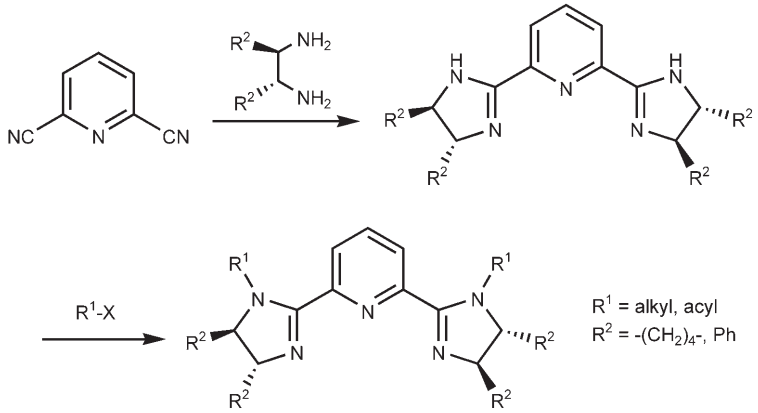
yet been applied as ligands in catalysis to any great extent.[3] More surprisingly, as far as we know, only a very few examples describing asymmetric catalysis versions have appeared in the literature to date.[4] Can this class of chiral imidazolines serve as efficient and useful ligands in asymmetric catalysis? This possibility prompted us to explore the synthesis of a series of *chiral bis(imidazoline)* ligands and to evaluate their scope as ligands in asymmetric reactions.

Nitroaldol (Henry) reactions between nitroalkanes and carbonyl compounds are important carbonyl addition processes that afford an atom-economic approach to α-hydroxynitroalkanes, which serve as valuable synthetic intermediates. It is therefore not surprising that great efforts have recently been directed towards the development of a catalytic asymmetric version of this reaction. In comparison with their closely related catalytic asymmetric aldol reaction counterparts, however, very few examples of efficient catalytic enantioselective Henry reactions are known to date,[5–6] and no significant success had been achieved until the current contributions to this area illustrated by the recent studies by the groups of Shibasaki,[7] Trost,[8] Evans,[9] and Palomo.[10] Typically, among the most outstanding examples, an aldehyde is treated with a nitroalkane (usually nitromethane) in the presence of a chiral metal complex and other additives to produce nitroalcohols with good to excellent optical purities. Some limitations have normally been encountered, however: a high catalyst loading (30 mol%) may be required,[10] for example, or the substrate scope may be limited to aromatic or aliphatic aldehydes,[6d–e,7–8] or a lower temperature may be needed.[6d,7–8,10] Environmentally friendly organocatalysts have notably begun to surface in the literature,[11] but these methods have also featured some important restrictions in terms of substrate scope, selectivity, and/or the need for a low reaction temperature. Very recently, two excellent examples of highly enantioselective Henry reactions between nitromethane and *aromatic aldehydes*[12] or *relatively active a-keto esters* in the presence of modified cinchona alkaloids have appeared.[13]

Because Henry reactions are still among the more challenging enantioselective reactions, and controlling the stereochemistry is still difficult, a catalyst that would overcome those limitations discussed above would be advantageous. We therefore chose to focus initial studies on evaluation of the behavior of chiral bis(imidazoline) ligands in asymmetric Henry reactions and wish to describe here our results in the application of new *chiral bis(imidazoline)* ligands for highly enantioselective parent Henry reactions with a broad range of substrates.

Results and Discussion

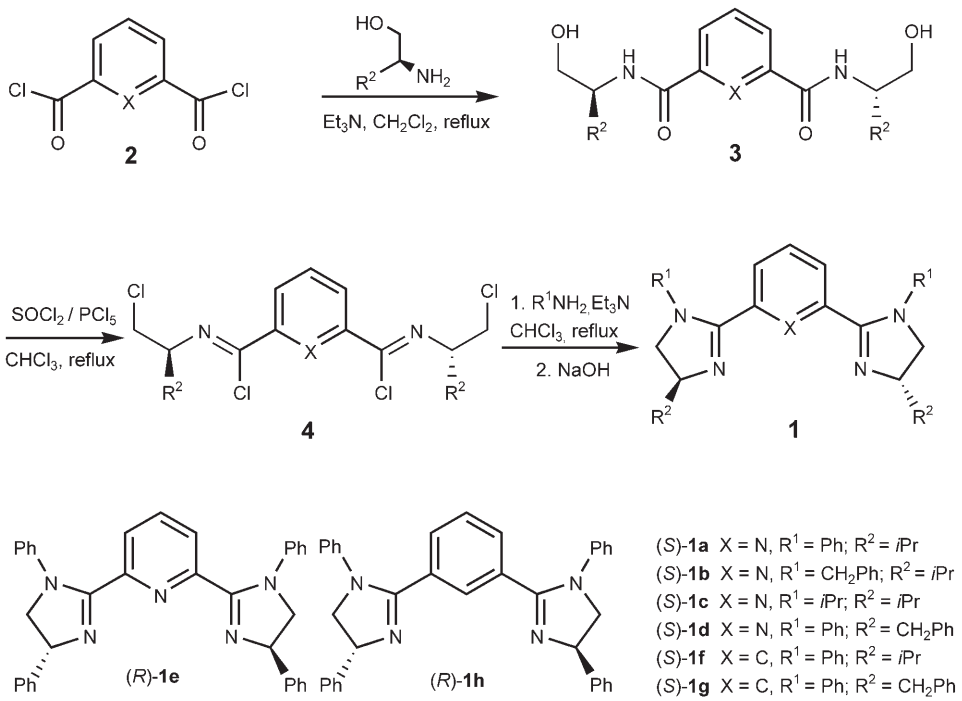
Although several different approaches to imidazoline rings are conceivable,[14] enantiopure 4-substituted imidazolines are generally prepared from chiral 1,2-diamines.[4,15,16] Very recently, Beller and his co-workers reported the first synthesis of chiral pyridinebisimidazolines derived from pyridine-2,6-dinitrile and chiral diamines (Scheme 1),[17] the obtained ligands being used in ruthenium-catalyzed asymmetric epoxidations with hydrogen peroxide as oxidant, albeit with only moderate *ee* values (up to 71% *ee*). Notably, the methodology based on chiral 1,2-diamines somewhat restricts convenient variation of the C-4-substituent R^2 groups on the imidazoline ring, because the range of chiral diamines easily commercially available in the forms of enantiomerically pure building blocks is currently not wide. Moreover, steric and electronic circumstances around the C-4-position should be one of the crucial factors governing the enantioselectivity and activity in the catalytic asymmetric reaction. In other words, further steric and electronic regulation solely through remote functionalization at the N-1 position is difficult. Furthermore, variations in the substituent at the N-1 position on the imidazoline ring might be easily carried out by *N*-alkylation and *N*-acylation, whereas analogous *N*-aryl groups were not introduced at the N-1 position.



Scheme 1. Beller's synthetic route to chiral bis(imidazoline) ligands.[17]

In contrast, our strategy to develop enantiopure bis(imidazoline) ligands from chiral amino alcohols is based on practical considerations, because the ease with which natural α-amino acids, the least expensive chiral starting materials, can be transformed into 1,2-amino alcohols opens up a wide variety of building blocks available in the chiral pool, so a vast structural variety of chiral bis(imidazoline) ligands can be simply achieved through the choice of both 1,2-amino alcohol and the N-1 R^1 substituent.

To illustrate our concept, a small library of chiral bisimidazolines (**1a–h**) has been constructed.[18] As shown in Scheme 2, the synthesis of bisimidazolines **1** is a straightforward process, starting from the bis-amido alcohols **3**, which are easily prepared from readily available amino alcohols.[19]

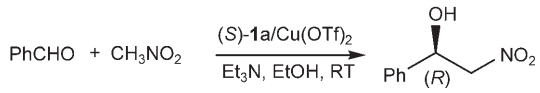


Scheme 2. Synthetic route to chiral bis(imidazoline) ligands.

Treatment of bis-amido alcohols **3** with $SOCl_2$ and/or PCl_5 afforded chloroethyl imidoyl chlorides **4**, and this was followed by two chloride displacements with amines or anilines. A wide variety of sterically and electronically different ligands could thus be prepared by structural variation of the bridging group and the imidazoline ring. It is noteworthy that the preparations of chiral bisimidazolines have been performed without problems on 10 g scales. These compounds were isolated in analytically pure form as white or pale yellow solids in moderate to good yields, depending on the natures of the substituents on the imidazoline rings and the bridging groups. These ligands are stable enough in air to be purified by means of column chromatography on silica gel without special precautions against water or air.

Our initial exploration of catalytic asymmetric Henry reactions focused on couplings between aldehydes and nitromethane in the presence of bis(imidazoline) ligands in combination with $Cu(OTf)_2$ (OTf: trifluoromethanesulfonyl). Unfortunately, though, the reactions were often low-yielding: benzaldehyde, for example, was treated with nitromethane in the presence of the (*S*)-**1a**/$Cu(OTf)_2$ complex—generated in situ from 10.5 mol% of (*S*)-**1a** and 10 mol% of $Cu(OTf)_2$ in ethanol at room temperature—to afford the nitro alcohol product in only 40% yield even after four days, but, excitingly, with an excellent enantioselectivity of up to 97% *ee* (Table 1, entry 3). Efforts to optimize asymmetric Henry reactions to improve the product yields under these conditions proved to be frustrating. For example, a series of solvents (e.g., methanol, ethanol, isopropanol, *n*-butanol, nitromethane, THF, dichloromethane, DMF, and DMSO) were first tested in the catalytic enantioselective Henry reaction between nitromethane and benzaldehyde, but ethanol was found to be the best one. In addition to solvent effects, we also tried to optimize other reaction conditions such as catalyst loading, ratio of ligand to $Cu(OTf)_2$, reaction time, and temperature, but these factors had little effect on improving of yields. Attempts to raise the product yields through the use of different copper salts in the presence of (*S*)-**1a** in ethanol were also unsuccessful: $Cu(OAc)_2 \cdot H_2O$ and $Cu(ClO_4)_2$ were capable of affording good yields (84% and 90%, respectively), but very low *ee* values (12% and 20%, respectively), whereas $Cu(NO_3)_2 \cdot 3H_2O$ and $CuCl_2 \cdot 2H_2O$ provided very low yields (less than 10%).

Table 1. The effect of the quantity of Et_3N on the enantioselective Henry reaction between benzaldehyde and nitromethane catalyzed by (*S*)-**1a**/$(OTf)_2$.[a]



Entry	(*S*)-**1a**/$(OTf)_2$ [mol%]	Et_3N [mol%]	Yield [%][b]	*ee* [%][c]
1	–	–	trace	–
2	–	10	98	–
3[d]	10	–	40	97
4	10	2	43	95
5	10	5	52	95
6	10	10	94	96
7	10	20	76	83
8	10	50	76	74
9	10	100	95	53

[a] Reactions were performed on a 0.5 mmol scale with $Cu(OTf)_2$ (10 mol%) and ligand (*S*)-**1a** (10.5 mol%) in the presence of Et_3N with nitromethane (10 equiv) in ethanol (1.5 mL) under N_2 at room temperature for 24 h. [b] Yield of isolated product based on aldehyde after chromatographic purification. [c] Enantiomeric excess was determined by HPLC on Chiracel OD-H. [d] This reaction was run for four days under identical conditions.

Recently, the concept of dual acid/base catalysis has been introduced for asymmetric catalytic reactions.[20–21] Base-catalyzed, nonselective Henry reactions are long known, so we reasoned that Et_3N might meet the requirement as a Brønsted base to facilitate the deprotonation of nitromethane as a prelude to the aldol addition process to improve the yields of enantioselective reactions, as we had observed that benzaldehyde was able to react smoothly with nitromethane with

the assistance of 10 mol% of Et_3N at room temperature with the formation of the racemic nitroaldol product in over 98% yield (Table 1, entry 2).[6a,b,9–10] As expected, the yields of nitroaldol products were improved dramatically when Et_3N was added to generate a binary Lewis acid/Brønsted base catalytic system, although the quantity of Et_3N was crucial to the outcome of the reaction, the effect of the chiral Lewis acid/Brønsted base ratio being described in Table 1, which shows a clear maximum at 10 mol% of Et_3N, indicating that equimolar amounts of chiral Lewis acid and Et_3N constitute the best catalytic system in terms of both enantioselectivity and yield (Table 1, entry 6). This shows that our optimized catalytic system significantly overcomes troubles potentially arising from the chemical incompatibility of Lewis acids and Brøsted bases and suppresses the Et_3N-initiated background reaction. When Et_3N is in excess in relation to the chiral Lewis acid, the Cu^{2+} center is likely to be coordinated by Et_3N to give the inactive $Cu(Et_3N)(OTf)_2$-bisimidazoline complex, hence trapping the chiral Lewis acid and resulting both in diminished yields and in poorer enantioselectivities. Moreover, the remaining uncoordinated Et_3N further promotes the racemic reaction path, affording only racemic nitroaldol product, so the combination of the $Cu(OTf)_2$/**1a** complex (10 mol%) and Et_3N (100 mol%) gave a 95% yield but only 53% *ee* (Table 1, entry 9).

The proposed transition state model is consistent with experimental observations and accounts for the absolute configurations of some selected products. A complex that simultaneously binds the two reaction partners should position the nucleophile perpendicular to the ligand plane, while the electrophile, for maximum activation, should be positioned in one of the more Lewis acidic equatorial sites in the ligand plane, which is in accord with previously reported steric and electronic considerations (Figure 2).[6b,9,10]

A series of Brønsted bases were also tested in the reaction

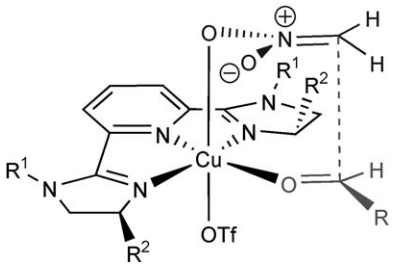
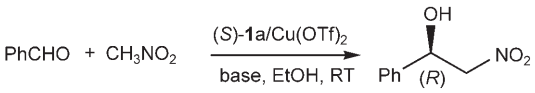


Figure 2. Proposed transition state model for the Henry reaction.

between benzaldehyde and nitromethane in the presence of 10 mol% of (*S*)-**1a**/$Cu(OTf)_2$ and 10 mol% of base, as shown in Table 2. After screening a variety of bases (e.g., Et_3N, pyridine, DBU, $Et(iPr)_2N$, 1-methyl-1*H*-imidazole, DMAP, and K_2CO_3), we found that Et_3N gave the best result (Table 2, entry 1). $Et(iPr)_2N$ is much more bulky than Et_3N but has the same basicity, and it was expected that the bulkiness of the base would retard coordination to the chiral Lewis acid, reducing levels of the inactive $Cu(R_3N)(OTf)_2$-bisimidazoline complex. However, the enantioselectivity and yield were significantly reduced in relation to those achieved with Et_3N (Table 2, entry 4). Furthermore, the bulkier and more basic DBU afforded a lower yield of the nitroaldol adduct than obtained with $Et(iPr_2)N$, with similar enantioselectivity (Table 2, entry 3). Pyridine, DMAP, and 1-methyl-1*H*-imidazole were also tested as bases, but lower yields of nitroaldol product were again formed, probably as a result of strong coordination of pyridine and imidazole to the copper complex (Table 2, entries 2, 5, and 6). The inorganic base K_2CO_3 was a good base in terms of yield, but the enantioselectivity was disappointing (Table 2, entry 7).

Table 2. Enantioselective Henry reaction between benzaldehyde and nitromethane catalyzed by (*S*)-**1a**/$Cu(OTf)_2$ (10 mol%) and base (10 mol%).[a]



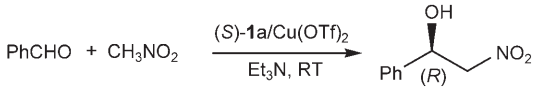
Entry	Base	Yield [%][b]	*ee* [%][c]
1	Et_3N	94	96
2	pyridine	5	77
3	DBU	54	86
4	$Et(iPr)_2N$	80	86
5	1-methyl-1*H*-imidazole	6	22
6	DMAP	52	28
7	K_2CO_3	82	22

[a] Reactions were performed on a 0.5 mmol scale with $Cu(OTf)_2$ (10 mol%) and ligand (*S*)-**1a** (10.5 mol%) in the presence of base with use of nitromethane (10 equiv) in ethanol (1.5 mL) under N_2 at room temperature for 24 h. [b] Yield of isolated product based on aldehyde after chromatographic purification. [c] Enantiomeric excess was determined by HPLC on Chiracel OD-H.

In addition, a series of reaction solvents (e.g., methanol, ethanol, isopropanol, *n*-butanol, nitromethane, THF, toluene, dichloromethane, acetonitrile, diethyl ether, DMF, and DMSO) were also tested in the catalytic enantioselective Henry reaction between benzaldehyde and nitromethane in combination with ligand (*S*)-**1a,** $Cu(OTf)_2$, and Et_3N (Table 3). The protonic solvents were found to be superior to the nonprotonic ones, and of the different solvents tested, ethanol was clearly the best choice for this reaction, with 94% yield and 96% *ee*.

Table 4 illustrates the impact of a variety of reaction parameters on the course of the asymmetric catalysis process. A series of copper salts were first screened in combination with (*S*)-**1a** and Et_3N in ethanol. In each instance the reaction was performed at ambient temperature over 24 h (Table 4, entries 1, 4–8), and as the data collected in Table 4 show, the enantioselectivity was dependent on the counterions. $Cu(OTf)_2$ proved to be the best choice, affording the nitroaldol adduct both in high yield and with an excellent *ee* value. Although $Cu(NO_3)_2{\cdot}3H_2O$ and $Cu(ClO_4)_2{\cdot}6H_2O$, when used in place of $Cu(OTf)_2$, gave very similar enantioselective results (94% and 94% *ee*, respectively), the reactions were notably sluggish (Table 4, entries 6 and 8). In contrast, $Cu(OAc)_2{\cdot}H_2O$ and $CuCl_2{\cdot}2H_2O$ were capable of providing very high yields, but the enantiomeric excesses

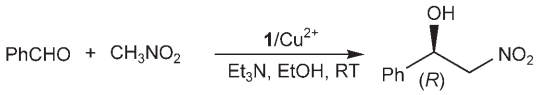
Table 3. Effect of solvents on the enantioselective Henry reaction between benzaldehyde and nitromethane catalyzed by (*S*)-**1a**/$Cu(OTf)_2$.[a]



Entry	Solvent	Yield [%][b]	*ee* [%][c]
1	methanol	60	92
2	ethanol	94	96
3	2-propanol	56	92
4	*n*-butanol	50	95
5	nitromethane	85	91
6	THF	24	80
7	toluene	20	81
8	dichloromethane	34	78
9	acetonitrile	25	81
10	diethyl ether	40	90
11	DMF	–	–
12	DMSO	–	–

[a] Reactions were performed on a 0.5 mmol scale with $Cu(OTf)_2$ (10 mol%) and ligand (*S*)-**1a** (10.5 mol%) in the presence of Et_3N with use of nitromethane (10 equiv) in solvent (1.5 mL) under N_2 at room temperature for 24 h. [b] Yield of isolated product based on aldehyde after chromatographic purification. [c] Enantiomeric excess was determined by HPLC on Chiracel OD-H.

Table 4. Some representative results from the screening of reaction conditions for the catalytic enantioselective Henry reaction between benzaldehyde and nitromethane in the presence of Et_3N (10 mol%) as base.[a]



Entry	**1**/Cu^{2+} (10 mol%)	Yield [%][b]	*ee* [%][c]
1	(*S*)-**1a**/$Cu(OTf)_2$	94	96
2[d]	(*S*)-**1a**/$Cu(OTf)_2$	91	98
3[e]	(*S*)-**1a**/$Cu(OTf)_2$	46	91
4	(*S*)-**1a**/$Cu(OAc)_2 \cdot H_2O$	98	11
5	(*S*)-**1a**/$Cu(ClO_4)_2$	95	2
6	(*S*)-**1a**/$Cu(NO_3)_2 \cdot 3H_2O$	51	94
7	(*S*)-**1a**/$CuCl_2 \cdot 2H_2O$	94	43
8	(*S*)-**1a**/$Cu(ClO_4)_2 \cdot 6H_2O$	50	94
9	(*S*)-**1b**/$Cu(OTf)_2$	64	58
10	(*S*)-**1c**/$Cu(OTf)_2$	85	93
11	(*S*)-**1d**/$Cu(OTf)_2$	22	91
12	(*R*)-**1e**/$Cu(OTf)_2$	23	−91
13	(*S*)-**1f**/$Cu(OTf)_2$	48	−8
14	(*S*)-**1g**/$Cu(OTf)_2$	34	−14
15	(*R*)-**1h**/$Cu(OTf)_2$	46	7

[a] Reactions were performed on a 0.5 mmol scale with nitromethane (10 equiv) in ethanol (1.5 mL) under N_2 at room temperature for 24 h. [b] Yield of isolated product based on aldehyde after chromatographic purification. [c] Enantiomeric excess was determined by HPLC on Chiracel OD-H. [d] The reaction was performed at 0 °C. [e] The reaction was performed at 40 °C.

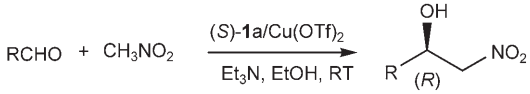
were significantly lower (Table 4, entries 4 and 7). Notably, $Cu(ClO_4)_2$ gave a very high yield, but of almost racemic product (Table 4, entry 5).

The results from the ligand survey in combination with $Cu(OTf)_2$ are also summarized in Table 4. First, after screening the tridentate valine-derived (*S*)-**1a–c**, we found that the enantioselectivities and reactivities of the ligands were largely dependent on the R^1 substituents at the N-1 position of the imidazoline ring. Our results indicate that the catalytic performances of chiral imidazolines with *N*-aryl groups at their N-1 positions may be superior to those obtained with *N*-alkyl groups (Table 4, entries 1, 9, and 10). The (*S*)-**1a**/$Cu(OTf)_2$ complex afforded the nitroaldol adduct in 94% yield and with 96% *ee*. Notably, with chiral pyridinebisimidazolines derived from pyridine-2,6-dinitrile and chiral diamines as reported by Beller and his co-workers, analogous *N*-aryl groups could not easily be introduced at the N-1 position in the imidazoline ring.[17] On the other hand, the R^2 substituents at the C-4-positions in the imidazoline rings have a distinct influence on catalytic performance (Table 4, entries 1, 11, and 12). Excellent enantioselectivities could be obtained with the phenylalanine-derived (*S*)-**1d** or the phenylglycine-derived (*R*)-**1e**, but the lower yields were only in the 20–30% range. These are clear validations of our strategy, in that the catalytic performances of chiral bisimidazolines may be sterically and electrically easily tuned both by remote functionalizations at their N-1 positions and through the associated steric and electronic conditions at their C-4-positions. Additionally, the bidentate ligands **1f**, **1g**, or **1h** gave lower yields and enantioselectivities of nitroalcohol product (Table 4, entries 13–15), this observation clearly indicating that the stereochemical course of this Henry reaction depends not only on the stereo- and electronic situation of the bisimidazoline backbone but also on that of the bridging scaffold. Of the eight chiral bisimidazolines with the illustrated absolute configurations, the tridentate valine-derived (*S*)-**1a** with a phenyl group at the N-1 position proved to be the ligand of choice. In contrast, excellent enantioselectivity could in most cases be achieved only when *tert*-butyl bisoxazoline derived from high-priced, non-natural *tert*-leucine or from indabox—prepared from the quite expensive *cis*-1-amino-2-indanol—was used.[6a–b,9,22]

In the most outstanding examples,[7–10] the reaction temperature typically played a significant role in determining the *ee* values of the nitroalcohol products. Lowering the temperature of the reaction could significantly increase the *ee* value, and the catalytic systems reported by Shibasaki, Trost, and Palomo and their co-workers even needed much lower temperatures (−30/−78 °C) to achieve high enantioselectivities.[7–8,10] In sharp contrast, in our catalytic system generated from (*S*)-**1a**, $Cu(OTf)_2$, and Et_3N the enantioselectivity was not very sensitive to the temperature, although the temperature could significantly effect the yield of nitroaldol adduct. When carried out at 0 °C, for example, the reaction afforded the corresponding aldol adduct in 91% yield and with 98% *ee* within 24 h (Table 4, entry 2), whereas when the same reaction was performed at 40 °C, a large rate acceleration was observed but with an accompanying increase in elimination byproduct, resulting in a drop in the yield of the corresponding nitroaldol adduct to 46%, though without any significant loss of enantioselectivity (Table 4, entry 3).

With optimized conditions now to hand, the scope of the catalytic enantioselective Henry reaction was demonstrated by treatment of aldehydes with nitromethane in the presence of 10 mol% of the (*S*)-**1a**/$Cu(OTf)_2$ complex and 10 mol% of Et_3N in ethanol at room temperature for 24 h. *We were delighted to find that our catalytic system was able to tolerate a wide scope of aldehydes. Not only aromatic aldehydes but also aliphatic aldehydes afforded the nitroalcohol products with enantiomeric excesses in the 93–98% range.* As is evident in Table 5, regardless of whether the aromatic aldehydes were electron-rich (Table 5, entries 3 and 7), electron-poor (Table 5, entries 4, 8, and 9), electron-neutral (Table 5, entries 2, 5, and 6), or sterically hindered (Table 5, entries 2–5), all of them smoothly underwent catalytic enantioselective Henry reactions with reasonable product yields and excellent enantioselectivities under our conditions. Most remarkably, the examined aliphatic unbranched and even branched or sterically hindered aldehydes also reacted with nitromethane to give the optically active Henry adducts in excellent yields (85–98%) and enantiomeric excesses (93–96% *ee*) (Table 5, entries 10–14).

Table 5. Range of aldehydes used in Henry reactions with nitromethane in the presence of (*S*)-**1a**/$Cu(OTf)_2$ (10 mol%).[a]

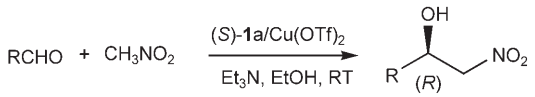


Entry	Aldehyde (R)	Yield [%][b]	*ee* [%][c]
1	Ph	94	96
2	2-MeC_6H_4	78	97
3	2-$MeOC_6H_4$	65	96
4	2-ClC_6H_4	92	95
5	1-naphthyl	74	97
6	4-MeC_6H_4	60	95
7	4-$MeOC_6H_4$	45	94
8	4-ClC_6H_4	82	98
9	4-FC_6H_4	76	97
10	$PhCH_2CH_2$	95	93
11	*i*Pr	91	96
12	*i*Bu	88	96
13	*n*Bu	85	94
14	cyclohexyl	98	95

[a] Reactions were performed on a 0.5 mmol scale with $Cu(OTf)_2$ (10 mol%), ligand (*S*)-**1a** (10.5 mol%), and Et_3N (10 mol%) with use of nitromethane (10 equiv) in ethanol (1.5 mL) under N_2 at room temperature for 24 h. [b] Yield of isolated product based on aldehyde after chromatographic purification. [c] Enantiomeric excess was determined by HPLC on Chiracel OD-H, OD, OJ, or AD-H columns. The absolute configurations of nitroaldol adducts were assigned by comparison with literature compounds.

Although not yet investigated in detail, the asymmetric Henry reactions also took place with substantially lower catalyst loadings than under our standard conditions of 10.5 mol% of (*S*)-**1a**. As shown in Table 6, treatment of both aromatic and aliphatic aldehydes with nitromethane at room temperature in the presence of 2 mol% of (*S*)-**1a**/$Cu(OTf)_2$ and 2 mol% of Et_3N gave the corresponding nitroalcohol products with enantiomeric excesses in the 90–97% range, although slightly low yields of products were observed.

Table 6. Range of aldehydes used in Henry reactions with nitromethane in the presence of (*S*)-**1a**/$Cu(OTf)_2$ (2 mol%) either under N_2[a] or under air.[b]



Entry	Aldehyde (R)	Yield [%][c]	*ee* [%][d]
1[a]	Ph	80	94
2[a]	4-ClC_6H_4	82	91
3[a]	1-naphthyl	63	90
4[a]	2-$MeOC_6H_4$	53	97
5[a]	cyclohexyl	61	90
6[b]	Ph	78	95
7[b]	4-ClC_6H_4	80	91
8[b]	1-naphthyl	65	94
9[b]	2-$MeOC_6H_4$	56	95
10[b]	cyclohexyl	59	91

[a] Reactions were performed on a 1.0 mmol scale with $Cu(OTf)_2$ (2 mol%), ligand (*S*)-**1a** (2.1 mol%), and Et_3N (2 mol%) with use of nitromethane (10 equiv) in ethanol (3.0 mL) under N_2 at room temperature for 24 h. [b] Reactions run under air at room temperature for 24 h. [c] Yield of isolated product based on aldehyde after chromatographic purification. [d] Enantiomeric excess was determined by HPLC on Chiracel OD-H or AD-H columns. The absolute configurations of nitroaldol adducts were assigned by comparison with literature compounds.

In addition, we were delighted to find that the (*S*)-**1a**/$Cu(OTf)_2$ complex is an air- and water-stable compound. While we routinely conduct the reactions under inert atmospheres, we have determined that the reactions are not highly oxygen- or moisture-sensitive; under identical conditions, even with 2 mol% of (*S*)-**1a**/$Cu(OTf)_2$, the reactions run under an atmosphere of air proceed in comparable enantiomeric excesses and yields (Table 6, entries 6–10).

Conclusion

In summary, we have developed a new addition to the rational design of sterically and electrically easily tunable chiral bisimidazoline ligands, which are readily synthesized in a straightforward fashion from commercially available, inexpensive α-amino acids. Moreover, our method provides an easy and simplified route to a diverse set of air-stable and water-tolerant chiral bis(imidazoline) ligands on 10 g scales. Our methodology is more versatile than the route reported by Beller and co-workers,[17] offering fewer restrictions in the R^2 group substituent at C-4 and in the substituent at the N-1 position in the imidazoline ring. We have further demonstrated the use of (*S*)-**1a** in asymmetric Henry reactions, in which it is the first member of the class of *chiral bisimidazolines* to have been demonstrated to achieve excellent enantioselectivities. To the best of our knowledge, our dual catalytic system is among the most effective systems so far reported for the asymmetric parent Henry reactions. Further investigations into other versions of asymmetric catalysis are

currently underway and will be reported in due course. In particular, because their modular natures enable easy tuning of steric and electronic properties, it is reasonable to suggest that this class of ligands should be widely applicable in asymmetric catalysis.

Experimental Section

General remarks: ^{1}H NMR spectra were obtained with a Bruker AV-300 (300 MHz) or a Varian Inova-600 (600 MHz) spectrometer, while ^{13}C NMR spectra were also recorded with a Bruker AV-300 (75 MHz) or a Varian Inova-600 (150 MHz). The ^{1}H chemical shifts were measured relative to tetramethylsilane as the internal reference, while the ^{13}C NMR chemical shifts were recorded with $CDCl_3$ as the internal standard. Elemental analyses were performed with a Heraeus CHN-O-RAPID instrument. The high-resolution FAB-mass spectra and EI-mass spectra were obtained with a JEOL JMS-SX/SX 102 A spectrometer, and the GC-MS spectra were obtained with an Agilent 6890—5973 machine. Optical rotations were determined on a WZZ-2B polarimeter. Melting points were determined and are uncorrected.

Materials: L-Phenylalanine and L-valine were purchased from ChengDu Chempep New Technology Co., Ltd, while D-phenylglycine was purchased from Lancaster. Aldehydes were purchased from Aldrich, Lancaster, Acros, and AstatTech in China: all liquid aldehydes were distilled before use, while the others were used without further purification. Solvents were dried by heating at reflux for at least 24 h over CaH_2 (dichloromethane or chloroform), sodium/benzophenone (THF), or sodium (C_2H_5OH or CH_3OH) and freshly distilled prior to use. Triethylamine (Et_3N) was dried over P_2O_5, while nitromethane (CH_3NO_2) was dried over $CaCl_2$ and was freshly distilled prior to use. Except as noted, commercial reagents were used as received without further purification. Unless otherwise indicated, all syntheses and manipulations were carried out under dry dinitrogen. Amino alcohols were prepared by the procedure described by Meyers and McKennon.[19] Isophthaloyl dichloride and pyridine-2,6-dicarbonyl dichloride were prepared by the procedure described by Cram et al.[23]

Procedure for the preparation of chiral bis(imidazoline) ligands 1a–h—2,6-bis[(*S*)-4-isopropyl-1-phenyl-4,5-dihydro-1*H*-imidazol-2-yl]pyridine [(*S*)-1a)]: A solution of pyridine-2,6-dicarbonyl dichloride (8.16 g, 40 mmol) in CH_2Cl_2 (50 mL) was added dropwise at 0 °C to a stirred solution of L-valinol (8.24 g, 80 mmol) and triethylamine (11.0 mL, 80 mmol) in CH_2Cl_2 (150 mL). The reaction mixture was then allowed to warm to room temperature and stirring was continued for 12 h, after which water (200 mL) was added. The layers were separated, the organic layer was dried over Na_2SO_4, and the removal of the solvent in vacuo gave a white solid, which was recrystallized from CH_2Cl_2 to afford **3a** as white crystals (12.4 g, 92%).

$SOCl_2$ (4.20 mL, 57.5 mmol) was added at 0 °C to a mixture of **3a** (3.37 g, 10.0 mmol) and $CHCl_3$ (70 mL), which was then stirred at reflux for 5 h. PCl_5 (4.37 g, 21 mmol) was then added, the mixture was stirred at reflux for a further 6 h, and volatiles were removed under reduced pressure to afford **4a**. $CHCl_3$ (70 mL), Et_3N (10.2 mL, 72.9 mmol), and aniline (2.0 mL, 21.8 mmol) were added to the residue at 0 °C and the resulting mixture was stirred at room temperature for 2 h, followed by heating at reflux for 24 h. The solution was then washed with NaOH (20%, 50 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried over Mg_2SO_4, and the solvent was removed under reduced pressure to give a brown solid, which could be purified by column chromatography on silica gel with elution with ethyl acetate/methanol/Et_3N (9:1:0.01) to afford (*S*)-**1a** as a pale yellow solid (3.97 g, 88%). m.p.: 121–123 °C; $[\alpha]_D^{25} = -20.0$ (c = 0.5 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.88 (d, J = 6.6 Hz, 6H), 0.98 (d, J = 6.6 Hz, 6H), 1.87–1.92 (m, 2H), 3.59–3.61 (m, 2H), 3.99–4.06 (m, 4H), 6.60–6.62 (m, 4H), 6.92–6.94 (m, 2H), 7.08–7.11 (m, 4H), 7.58–7.64 ppm (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 17.71, 18.79, 32.81, 55.82, 70.33, 122.30, 122.97, 124.42, 128.24, 136.63, 142.68, 150.03, 159.66 ppm; HRMS (FAB) calcd for $[C_{29}H_{33}N_5+H]^+$: 452.2814; found: 452.2817; elemental analysis calcd (%) for $C_{29}H_{33}N_5$: C 77.13, H 7.37, N 15.51; found: C 76.98, H 7.47, N 15.37.

2,6-Bis[(*S*)-4-isopropyl-1-benzyl-4,5-dihydro-1*H*-imidazol-2-yl]pyridine [(*S*)-1b]: This compound was prepared by the same procedure as described above (for (*S*)-**1a**). Starting materials were (*S*)-2-amino-3-methylbutan-1-ol and benzylamine. Compound (*S*)-**1b** was obtained in 78% yield as a pale yellow semi-solid after purification by column chromatography on silica gel with elution with ethyl acetate/methanol/Et_3N (5:1:0.02). $[\alpha]_D^{25} = -133.5$ (c = 0.39 in $CHCl_3$); ^{1}H NMR (600 MHz, CD_3OD): δ = 0.86 (2×d, J = 7.2 Hz, 7.2 Hz, 12H), 1.80–1.83 (m, 2H), 3.19 (t, J = 9.0 Hz, 2H), 3.51 (t, J = 11.4 Hz, 2H), 3.95–3.99 (m, 2H), 4.42 (2×d, J = 15.6 Hz, 15.6 Hz, 4H), 7.19–7.26 (m, 10H), 7.95 (d, J = 7.8 Hz, 2H), 8.09 ppm (t, J = 7.2 Hz ,1H); ^{13}C NMR (150 MHz, CD_3OD): δ = 18.07, 18.76, 34.20, 51.97, 53.17, 69.89, 127.22, 128.58, 128.81, 129.63, 138.46, 139.76, 150.41, 164.65 ppm; HRMS (FAB) calcd for $[C_{31}H_{37}N_5+H]^+$: 480.3127; found: 480.3133; elemental analysis calcd (%) for $C_{23}H_{37}N_5$: C 77.62, H 7.78, N 14.60; found: C 76.61, H 8.04, N 13.97.

2,6-Bis[(*S*)-1,4-diisopropyl-4,5-dihydro-1*H*-imidazol-2-yl]pyridine [(*S*)-1c]: This compound was prepared by the same procedure as described above ((*S*)-**1a**). Starting materials were (*S*)-2-amino-3-methylbutan-1-ol and isopropylamine. Compound (*S*)-**1c** was obtained in 94% yield as a white solid after purification by column chromatography on silica gel with elution with ethyl acetate/methanol/Et_3N (1:1:0.02) to methanol/Et_3N (1:0.01). m.p. 107–108 °C; $[\alpha]_D^{25} = -144.1$ (c = 0.51 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.94 (d, J = 6.6 Hz, 6H), 0.99 (d, J = 6.0 Hz, 6H), 1.03 (d, J = 7.2 Hz, 6H), 1.13 (d, J = 6.0 Hz, 6H), 1.84–1.90 (m, 2H), 3.18 (dd, J = 9.0 Hz, 9.6 Hz, 2H), 3.20 (dd, J = 9.6 Hz, 9.6 Hz, 2H), 3.88–3.92 (m, 2H), 4.40–4.44 (m, 2H), 7.77–7.86 ppm (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 17.99, 18.92, 19.44, 20.79, 33.41, 45.76, 45.86, 69.41, 125.04, 137.18, 150.20, 162.77 ppm; HRMS (FAB) calcd for $[C_{23}H_{37}N_5]^+$: 383.3049; found: 383.3047; elemental analysis calcd (%) for $C_{23}H_{37}N_5$: C 72.02, H 9.72, N 18.26; found: C 71.29, H 9.85, N 18.05.

2,6-Bis[(*S*)-4-benzyl-1-phenyl-4,5-dihydro-1*H*-imidazol-2-yl]pyridine [(*S*)-1d)]: This compound was prepared by the same procedure as described above ((*S*)-**1a**). Starting materials were (*S*)-2-amino-3-phenylpropan-1-ol and aniline. Compound (*S*)-**1d** was obtained in 85% yield as a pale yellow powder after purification by column chromatography on silica gel with elution with ethyl acetate/methanol (5:1). m.p. 55–57 °C; $[\alpha]_D^{25}$ = 24.5 (c = 0.5 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.75 (dd, J = 9.0 Hz, 4.8 Hz, 2H), 2.78 (dd, J = 9.0 Hz, 5.4 Hz, 2H), 3.65 (dd, J = 7.8 Hz, 9.6 Hz, 2H), 3.67 (dd, J = 7.8 Hz, 9.6 Hz, 2H), 4.50–4.55 (m, 2H), 6.50 (d, J = 7.8 Hz, 4H), 6.92 (t, J = 7.8 Hz, 2H), 7.05 (t, J = 7.8 Hz, 4H), 7.18–7.27 (m, 10H), 7.52 (d, J = 7.8 Hz, 2H), 7.62 ppm (t, J = 7.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 41.94, 57.83, 65.67, 122.10, 123.15, 124.58, 126.23, 128.28, 128.35, 129.31, 136.74, 138.17, 142.29, 150.14, 160.07 ppm; HRMS (FAB) calcd for $[C_{37}H_{33}N_5+H]^+$: 548.2814; found: 548.2806; elemental analysis calcd (%) for $C_{37}H_{33}N_5$: C 81.14, H 6.07, N 12.79; found: C 80.31, H 6.37, N 12.37.

2,6-Bis[(*R*)-1,4-diphenyl-4,5-dihydro-1*H*-imidazol-2-yl]pyridine [(*R*)-1e]: This compound was prepared by the same procedure as described above ((*S*)-**1a**). Starting materials were (*R*)-2-amino-2-phenylethanol and aniline. Compound (*R*)-**1e** was obtained in 75% yield as a brown powder after purification by column chromatography on silica gel with elution with ethyl acetate/methanol/Et_3N (15:1:0.02). m.p. 76–79 °C; $[\alpha]_D^{25}$ = 244.0 (c = 0.5 in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.85 (dd, J = 8.4 Hz, 9.6 Hz, 2H), 3.87 (dd, J = 8.4 Hz, 9.6 Hz, 2H), 5.29–5.32 (m, 2H), 6.66–6.68 (m, 4H), 7.01–7.03 (m, 2H), 7.14–7.17 (m, 4H), 7.26–7.30 (m, 6H), 7.34–7.36 (m, 4H), 7.70–7.73 (m, 1H), 7.76–7.78 ppm (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 61.46, 67.67, 122.91, 123.60, 124.94, 126.77, 127.23, 128.39, 128.56, 136.97, 142.35, 143.57, 149.46, 160.72 ppm; HRMS (FAB) calcd for $[C_{35}H_{29}N_5+H]^+$: 520.2501; found: 520.2511; elemental analysis calcd (%) for $C_{35}H_{29}N_5$: C 80.90, H 5.63, N 13.48; found: C 80.68, H 5.90, N 13.20.

(*S*)-4-Isopropyl-2-[3-((*S*)-4-isopropyl-1-phenyl-4,5-dihydro-1*H*-imidazol-2-yl)phenyl]-1-phenyl-4,5-dihydro-1*H*-imidazole [(*S*)-1 f]: A solution of isophthaloyl dichloride (4.06 g, 20 mmol) in CH_2Cl_2 (40 mL) was added dropwise at 0 °C to a stirred solution of L-valinol (4.12 g, 40 mmol) and triethylamine (5.5 mL, 40 mmol) in CH_2Cl_2 (70 mL). The reaction mixture was then allowed to warm to room temperature, stirring was continued for 12 h, and then water (100 mL) was added. The layers were separated, the organic layer was dried over Na_2SO_4, and the removal of the solvent in vacuo gave a white solid, which was recrystallized from CH_2Cl_2 to afford **3 f** as white crystals (6.4 g, 95 %).

A solution of **3 f** (3.67 g, 10.9 mmol) in $SOCl_2$ (5 mL) was stirred at reflux for 5 h, excess thionyl chloride was then removed under reduced pressure to afford **4 f**, and CH_2Cl_2 (60 mL), Et_3N (9.0 mL, 66 mmol), and aniline (2.2 mL, 24 mmol) were added to the residue at 0 °C. The mixture was then allowed to warm to room temperature and stirred for 24 h and then washed with NaOH (10 %, 50 mL), and the aqueous fraction was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried over Mg_2SO_4 and the solvent was removed in vacuo to give a brown solid, which could be purified by column chromatography on silica gel with elution with ethyl acetate/methanol (9:1) to afford (*S*)-**1 f** as a pale yellow semi-solid (4.07 g, 83 %). $[\alpha]_D^{25} = 91.5$ ($c = 0.55$ in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 0.91$ (d, $J = 6.6$ Hz, 6H), 0.99 (d, $J = 6.6$ Hz, 6H), 1.86–1.91 (m, 2H), 3.57 (dd, $J = 7.2$ Hz, 9.6 Hz, 2H), 4.02–4.06 (m, 2H), 3.59 (dd, $J = 7.2$ Hz, 9.6 Hz, 2H), 6.71–6.72, (m, 4H), 6.94–6.97 (m, 2H), 7.09–7.14 (m, 5H), 7.35 (2×d, $J = 1.8$ Hz, 1.8 Hz, 2H), 7.89 ppm (t, $J = 1.2$ Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta =$ 17.76, 18.73, 32.94, 56.11, 70.03, 122.59, 123.18, 127.71, 128.55, 129.18, 130.00, 131.59, 142.91, 160.67 ppm; HRMS (FAB) calcd for $[C_{30}H_{34}N_4+H]^+$: 451.2862; found: 451.2852; elemental analysis calcd (%) for $C_{30}H_{34}N_4$: C 79.96, H 7.61, N 12.43; found: C 79.85, H 7.74, N 12.23.

(*S*)-4-Benzyl-2-[3-((*S*)-4-benzyl-1-phenyl-4,5-dihydro-1*H*-imidazol-2-yl)-phenyl]-1-phenyl-4,5-dihydro-1*H*-imidazole [(*S*)-1 g]: This compound was prepared by the same procedure as described above ((*S*)-**1 f**). Starting materials were (*S*)-2-amino-3-phenylpropan-1-ol and aniline. Compound (*S*)-**1 g** was obtained in 90 % yield as a pale yellow powder after purification by column chromatography on silica gel with elution with ethyl acetate/methanol (9:1). m.p. 49–51 °C; $[\alpha]_D^{25} = 164.4$ ($c = 0.5$ in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 2.77$ (dd, $J = 9.0$ Hz, 5.4 Hz, 2H), 2.79 (dd, $J = 9.0$ Hz, 4.8 Hz, 2H), 3.64 (dd, $J = 6.6$ Hz, 9.6 Hz, 2H), 3.65 (dd, $J = 6.6$ Hz, 9.6 Hz, 2H), 4.48–4.53 (m, 2H), 6.57 (2×d, $J = 0.6$ Hz, 1.2 Hz, 4H), 6.93 (t, $J = 7.2$ Hz, 2H), 7.08–7.13 (m, 5H), 7.17–7.20 (m, 2H), 7.22–7.26 (m, 8H), 7.33 (2×d, $J = 1.2$ Hz, 1.2 Hz, 2H), 7.90 ppm (t, $J = 1.2$ Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 42.12$, 57.96, 65.14, 122.40, 123.33, 126.27, 127.81, 128.28, 128.55, 129.10, 129.35, 130.10, 131.39, 138.03, 142.44, 161.05 ppm; HRMS (FAB) calcd for $[C_{38}H_{34}N_4+H]^+$: 547.2862; found: 547.2865; elemental analysis calcd (%) for $C_{38}H_{34}N_4$: C 83.48, H 6.27, N 10.25; found: C 83.32, H 6.37, N 10.07.

(*R*)-2-[3-((*R*)-1,4-Diphenyl-4,5-dihydro-1*H*-imidazol-2-yl)phenyl]-1,4-diphenyl-4,5-dihydro-1*H*-imidazole [(*R*)-1 h]: This compound was prepared by the same procedure as described above ((*S*)-**1 f**). Starting materials were (*R*)-2-amino-2-phenylethanol and aniline. Compound (*R*)-**1 h** was obtained in 78 % yield as a pale yellow powder after purification by column chromatography on silica gel with elution with ethyl acetate/petrol ether (2:1). m.p. 83–85 °C; $[\alpha]_D^{25} = -42.0$ ($c = 0.5$ in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 3.83$ (dd, $J = 7.8$ Hz, 9.6 Hz, 2H), 3.84 (dd, $J = 7.8$ Hz, 9.6 Hz, 2H), 5.29 (2×d, $J = 8.4$ Hz, 7.8 Hz, 2H), 6.77–6.79 (m, 4H), 6.99 (t, $J = 7.2$ Hz, 2H), 7.15–7.17 (m, 5H), 7.24–7.34 (m, 10H), 7.46 (2×d, $J = 1.2$ Hz, 1.2 Hz, 2H), 8.06 ppm (t, $J = 1.8$ Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 61.58$, 67.57, 122.84, 123.65, 126.67, 127.18, 127.84, 128.57, 128.70, 129.48, 130.37, 131.31, 142.56, 143.55, 161.77 ppm; HRMS (FAB) calcd for $[C_{36}H_{30}N_4+H]^+$: 519.2549; found: 519.2538; elemental analysis calcd (%) for $C_{36}H_{30}N_4$: C 83.37, H 5.83, N 10.80; found: C 83.11, H 6.01, N 10.59.

Preparation of the racemic nitroaldols:[24] A mixture of aldehyde (1.0 mmol), $MeNO_2$ (2.0 mmol), and Et_3N (3 drops) in ethanol (2.0 mmoL) was stirred at room temperature for 10 h. Volatiles were removed in vacuo and the residue was purification by column chromatography on silica gel with elution with ethyl acetate/petrol ether to afford the racemic nitroaldol adduct.

General procedure for the catalytic enantioselective Henry reaction: Cu(OTf)$_2$ (18.1 mg, 0.05 mmol), ligand (*S*)-**1** (0.0525 mmol), and ethanol (1.5 mL) were placed in a Schlenk tube fitted with a magnetic stirrer under N_2 at room temperature. After the mixture had been allowed to stir for 2 h, aldehyde (0.5 mmol) was added, and this was followed by the addition of dry freshly distilled nitromethane (0.26 mL, 5 mmol) and triethylamine (7 μL, 0.05 mmol). The reaction mixture was stirred at the same temperature for 24 h, volatiles were then removed in vacuo, and the residue was purified by column chromatography on silica gel with elution with ethyl acetate/hexane to afford the nitroaldol adduct.

The reported yields of asymmetric Henry reactions are isolated yields and are the averages of at least two runs. The Henry reaction products are known and their ^{1}H and ^{13}C NMR spectra agreed with those in the literature cited below.[6d,9] Enantiomeric excesses were determined by HPLC (LabTech 600 series) with Chiracel OD-H, OD, OJ, or AD-H columns. The absolute configurations of nitroaldol adducts were assigned by comparison with literature compounds.[6d,9]

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[1] T. P. Yoon, E. N. Jacobsen, *Science* **2003**, *299*, 1691–1693.
[2] For recent reviews, see: a) M. P. Sibi, S. Manyem, J. Zimmerman, *Chem. Rev.* **2004**, *104*, 3263–3295; b) G. Desimoni, G. Faita, P. Quadrelli, *Chem. Rev.* **2003**, *103*, 3119–3154; c) P. Braunstein, F. Naud, *Angew. Chem.* **2001**, *113*, 702–722; *Angew. Chem. Int. Ed.* **2001**, *40*, 680–699; d) K. A. Jørgensen, M. Johannsen, S. Yao, H. Audrain, J. Thornauge, *Acc. Chem. Res.* **1999**, *32*, 605–613; e) A. K. Ghosh, P. Mathivanan, J. Cappiello, *Tetrahedron: Asymmetry* **1998**, *9*, 1–45.
[3] For imidazolines as ligands in catalytic reactions, see: a) B. Çetinkaya, B. Alici, I. Özdemir, C. Bruneau, P. H. Dixneuf, *J. Organomet. Chem.* **1999**, *575*, 187–192; b) B. Çetinkaya, E. Çetinkaya, P. B. Hitchcock, M. F. Lappert, I. Özdemir, *J. Chem. Soc. Dalton Trans.* **1997**, 1359–1362; c) A. Bastero, A. Ruiz, C. Claver, S. Castillón, *Eur. J. Inorg. Chem.* **2001**, 3009–3011; d) A. A. Ruiz, C. Claver, *Organometallics* **2002**, *21*, 5820–5829; e) A. Bastero, C. Claver, A. Rui, S. Castillón, E. Daura, C. Bo, E. Zangrando, *Chem. Eur. J.* **2004**, *10*, 3747–3760.
[4] For imidazolines as ligands in enantioselective catalysis, see: a) C. Botteghi, A. Schionato, G. Chelucci, H. Brunner, A. Kürzinger, U. Obermann, *J. Organomet. Chem.* **1989**, *370*, 17–31; b) A. J. Davinport, D. L. Davies, J. Fawcett, D. R. Russell, *J. Chem. Soc. Perkin Trans. 1* **2001**, 1500–1503; c) J. Dupont, G. Ebeling, M. R. Delgado, C. S. Consorti, R. Burrow, D. H. Farrar, A. J. Lough, *Inorg. Chem. Commun.* **2001**, *4*, 471–474; d) C. A. Busacca, US Patent 6316620, **2001**; e) F. Menges, M. Neuburger, A. Pfaltz, *Org. Lett.* **2002**, *4*, 4713–4716.
[5] For an excellent short review, see: C. Palomo, M. Oiarbide, A. Mielgo, *Angew. Chem.* **2004**, *116*, 5558–5560; *Angew. Chem. Int. Ed.* **2004**, *43*, 5442–5444.
[6] a) C. Christensen, K. Juhl, K. A. Jørgensen, *Chem. Commun.* **2001**, 2222–2223; b) C. Christensen, K. Juhl, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2002**, *67*, 4875–4881; c) D.-M. Du, S.-F. Lu, T. Fang, J. Xu, *J. Org. Chem.* **2005**, *70*, 3712–3715; d) B. M. Choudary, K. V. S. Ranganath, U. Pal, M. L. Kantam, B. Sreedhar, *J. Am. Chem. Soc.* **2005**, *127*, 13167–13171; e) T. Purkarthofer, K. Gruber, M. G. Khadjawi, K. Waich, W. Skranc, D. Mink, H. Griengl, *Angew.*

Chem. **2006**, *118*, 3532–3535; *Angew. Chem. Int. Ed.* **2006**, *45*, 3454–3456.

[7] a) H. Sasai, T. Suzuki, S. Arai, T. Arai, M. Shibasaki, *J. Am. Chem. Soc.* **1992**, *114*, 4418–4420; b) T. Arai, Y. M. A. Yamada, N. Yamamoto, H. Sasai, M. Shibasaki, *Chem. Eur. J.* **1996**, *2*, 1368–1372; c) H. Sasai, S. Watanabe, T. Suzuki, M. Shibasaki, *Org. Synth.* **2004**, *10*, 571–577.

[8] a) B. M. Trost, V. S. C. Yeh, *Angew. Chem.* **2002**, *114*, 889–891; *Angew. Chem. Int. Ed.* **2002**, *41*, 861–863; b) B. M. Trost, V. S. C. Yeh, H. Ito, N. Bremeyer, *Org. Lett.* **2002**, *4*, 2621–2623.

[9] D. A. Evans, D. Seidel, M. Rueping, H. W. Lam, J. T. Shaw, C. W. Downey, *J. Am. Chem. Soc.* **2003**, *125*, 12692–12693.

[10] C. Palomo, M. Oiarbide, A. Laso, *Angew. Chem.* **2005**, *117*, 3949–3952; *Angew. Chem. Int. Ed.* **2005**, *44*, 3881–3884.

[11] a) T. Ooi, K. Doda, K. Maruoka, *J. Am. Chem. Soc.* **2003**, *125*, 2054–2055; b) Y. Sohtome, Y. Hashimoto, K. Nagasawaa, *Adv. Synth. Catal.* **2005**, *347*, 1643–1648; c) T. Marcelli, R. N. S. van der Haas, J. H. van Maarseveen, H. Hiemstra, *Synlett* **2005**, 2817–2819; d) T. Okino, S. Nakamura, T. Furukawa, Y. Takemoto, *Org. Lett.* **2004**, *6*, 625–627; e) T. P. Yoon, E. N. Jacobsen, *Angew. Chem.* **2005**, *117*, 470–472; *Angew. Chem. Int. Ed.* **2005**, *44*, 466–468.

[12] T. Marcelli, R. N. S. van der Haas, J. H. van Maarseveen, H. Hiemstra, *Angew. Chem.* **2006**, *118*, 943–945; *Angew. Chem. Int. Ed.* **2006**, *45*, 929–931.

[13] H. Li, B. Wang, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 732–733.

[14] a) T. Hayashi, E. Kishi, V. A. Soloshonok, Y. Uozumi, *Tetrahedron Lett.* **1996**, *37*, 4969–4972; b) Y.-R. Lin, X.-T. Zhou, L.-X. Dai, J. Sun, *J. Org. Chem.* **1997**, *62*, 1799–1834; c) D. H. Hunter, S. K. Sim, *Can. J. Chem.* **1972**, *50*, 669–677; d) E. Y. Borisova, N. V. Kropotova, E. M. Cherkasova, USSR Patent 466231, **1975**; *Chem. Abstr.* **1976**, *83*, 79277; e) R. Oi, K. B. Sharpless, *Tetrahedron Lett.* **1991**, *32*, 999–1002; f) J. Legters, J. G. H. Willems, L. Thijs, B. Zwanenburg, *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 59–68; g) P. Molina, I. Dïaz, A. Tárraga, *Synlett* **1995**, 1031–1032; h) C. Hulme, L. Ma, J. Romano, M. Morrissette, *Tetrahedron Lett.* **1999**, *40*, 7925–7928.

[15] a) R. C. F. Jones, I. Turner, K. J. Howard, *Tetrahedron Lett.* **1993**, *34*, 6329–6332; b) R. C. F. Jones, K. J. Howard, J. S. Snaith, *Tetrahedron Lett.* **1996**, *37*, 1707–1710; c) Y. Langlois, P. I. Dalko, *J. Org. Chem.* **1998**, *63*, 8107–8117; d) E. J. Corey, M. J. Grogan, *Org. Lett.* **1999**, *1*, 157–160; e) T. Isobe, K. Fukuda, Y. Araki, T. Ishikawa, *Chem. Commun.* **2001**, 243–244.

[16] A procedure providing enantiopure 4-substituted imidazoline rings from chiral 1,2-amino alcohols has recently been reported: N. A. Boland, M. Casey, S. J. Hynes, J. W. Matthews, M. P. Smyth, *J. Org. Chem.* **2002**, *67*, 3919–3922.

[17] While we were collecting data, Beller and his co-workers reported the first synthesis of chiral pyridinebisimidazolines derived from pyridine-2,6-dinitrile and chiral diamines: S. Bhor, G. Anilkumar, M. K. Tse, M. Klawonn, C. Döbler, B. Bitterlich, A. Grotevendt, M. Beller, *Org. Lett.* **2005**, *7*, 3393–3396.

[18] The configuration of (*S*)-**1a** was confirmed by X-ray structure analysis and these data are reported in: K. Ma, L. Cheng, H.-M. Gau, J. You, *Acta Crystallogr. Sect. E* **2006**, *62*, o1595–o1597). The crystal structure of **1a** shows no symmetry relationship between the two imidazoline rings, while the corresponding bond lengths reveal only small variations. In comparison with oxazoline compounds, the imidazoline imine C–N bond distances are slightly longer, by about 0.02 Å.

[19] For the preparation of α-chiral amino alcohols, see: M. J. McKennon, A. I. Meyers, *J. Org. Chem.* **1993**, *58*, 3568–3571.

[20] For reviews on the concept of dual acid/base catalysis, see: a) M. Shibasaki, N. Yoshikawa, *Chem. Rev.* **2002**, *102*, 2187–2209; b) M. Shibasaki, M. Kanai, K. Funabashi, *Chem. Commun.* **2002**, 1989–1999; c) G. J. Rowlands, *Tetrahedron* **2001**, *57*, 1865–1882; d) J.-A. Ma, D. Cahard, *Angew. Chem.* **2004**, *116*, 4666–4683; *Angew. Chem. Int. Ed.* **2004**, *43*, 4566–4583; e) H. Gröger, *Chem. Eur. J.* **2001**, *7*, 5247–5251.

[21] For selected dual acid/base catalytic systems, see: a) Y. Hamashima, D. Sawada, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **1999**, *121*, 2641–2642; b) E. Ichikawa, M. Suzuki, K. Yabu, M. Albert, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2004**, *126*, 11808–11809; c) R. Takita, K. Yakura, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 13760–13761; d) S. Lundgren, E. Wingstrand, M. Penhoat, C. Moberg, *J. Am. Chem. Soc.* **2005**, *127*, 11592–11593; e) C. Palomo, M. Oiarbide, R. Halder, A. Laso, R. López, *Angew. Chem.* **2006**, *118*, 113–116; *Angew. Chem. Int. Ed.* **2006**, *45*, 117–120..

[22] Selected recent excellent examples of catalysis with chiral bisoxazolines, see: a) J. S. Johnson, D. A. Evans, *Acc. Chem. Res.* **2000**, *33*, 325–335; b) D. M. Barnes, J. Ji, M. G. Fickes, M. A. Fitzgerald, S. A. King, H. E. Morton, F. A. Plagge, M. Preskill, S. H. Wagaw, S. J. Wittenberger, J. Zhang, *J. Am. Chem. Soc.* **2002**, *124*, 13097–13105; c) D. A. Evans, K. A. Scheidt, K. R. Fandrick, H. W. Lam, J. Wu, *J. Am. Chem. Soc.* **2003**, *125*, 10780–10781; d) M. P. Sibi, Z. Ma, C. P. Jasperse, *J. Am. Chem. Soc.* **2004**, *126*, 718–719; e) C. Palomo, M. Oiarbide, R. Halder, M. Kelso, E.-G. Bengoa, J. M. Garcia, *J. Am. Chem. Soc.* **2004**, *126*, 9188–9189; f) D. A. Evans, K. R. Fandrick, H.-J. Song, *J. Am. Chem. Soc.* **2005**, *127*, 8942–8943; g) D. A. Evans, J. Wu, *J. Am. Chem. Soc.* **2005**, *127*, 8006–8007; h) C. Palomo, M. Oiarbide, E. Arceo, J. M. García, R. López, A. González, A. Linden, *Angew. Chem.* **2005**, *117*, 6343–6345; *Angew. Chem. Int. Ed.* **2005**, *44*, 6187–6190.

[23] M. Newcomb, J. M. Timko, D. M. Walba, D. J. Cram, *J. Am. Chem. Soc.* **1977**, *99*, 6392–6398.

[24] X. Beebe, N. E. Schore, M. J. Kurth, *J. Org. Chem.* **1995**, *60*, 4196–4203.

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