Enantioselective Henry reaction catalyzed by a C_2-symmetric bis(oxazoline)–$Cu(OAc)_2 \cdot H_2O$ complex†

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A C_2-symmetric diethyl ^{i}Pr-bis(oxazoline)–$Cu(OAc)_2 \cdot H_2O$ was found to be an efficient catalyst for catalyzing an enantioselective Henry reaction between nitromethane and various aldehydes to provide β-hydroxy nitroalkanes with high chemical yields (up to 95%) and enantiomeric excesses (up to 97%).

Introduction

The Henry[1] (nitroaldol) reaction is one of the classical C–C bond formation reactions in organic synthesis for the formation of β-hydroxynitroalkanes.[2] The diverse range of chemical transformations of the newly formed β-nitroalkanol functionality such as reduction, oxidation, dehydration, Nef reaction to carbonyl compounds,[3] or nucleophilic displacement,[4] *etc.* make it a very useful reaction. The enantioselective addition of nitroalkanes to carbonyl compounds provides optically active β-nitroalkanols, which are useful intermediates in the asymmetric synthesis of the β-receptor agonists (−)-denopamine[5] and (−)-arbutamine,[5] the β-blockers (*S*)-metoprolol,[6a] (*S*)-propanolol[6b] and (*S*)-pindolol,[6c] and pharmacologically important β-amino alcohol derivatives, such as chloroamphenicol,[7a] ephedrine,[7a] sphingosine,[7b] *etc.* Due to its significance in organic syntheses, a variety of chiral catalysts[8] have been used in the development of the catalytic enantioselective variant of this reaction, but successes are limited to a few cases.

Shibasaki *et al.* were the first to report the asymmetric version of this reaction using heterobimetallic lanthanide BINOL-based complexes with high enantioselectivity.[9] Trost and co-workers reported novel dinuclear zinc chiral semi-aza-crown complexes, which are found to be effective catalysts for inducing high enantioselectivity in the addition of nitromethane to various aldehydes.[5,10] Several other efficient metal-based catalysts such as salen–Co complexes,[11] chiral bis(oxazoline)–Cu complexes,[12–14] and Zn triflate–chiral amino alcohol complexes,[15] *etc.* have also been developed for this reaction.[16] Some of these catalytic systems have certain limitations such as lower substrate scope (limited to aromatic or aliphatic aldehydes), low reaction temperatures, the need for organic bases and 4 Å molecular sieves as additives, relatively high catalyst loading or use of expensive catalysts such as indabox or *tert*-butyl bis(oxazoline). Apart from chiral Lewis acid catalysts, environmentally friendly chiral Brønsted bases such as guanidine bases[17] and modified *Cinchona* alkaloids[18] have been reported to promote the direct asymmetric Henry reaction, but these also lack broader substrate scope. Hence, it is desirable to put more effort into this area to develop a catalytic system that can overcome the limitations associated with the existing methodologies. In this paper we wish to report some progress towards achieving this goal.

Results and discussion

Earlier we reported the use of copper complexes of chiral pyridine 2,6-bis(4′-isopropyl-5′,5′-diphenyloxazoline) (ip-pybox-diph) **1b** in enantioselective allylic oxidation of olefins,[19] cyclopropanations,[20] propargylation of imines[21] and Friedel–Crafts alkylation of indoles.[22] Continuing our efforts in this direction, we intended to evaluate these types of ligands for the enantioselective Henry reaction. At the outset, complexes of copper acetate with ip-pybox **1a** and ip-pybox-diph **1b** were investigated for the reaction of nitromethane and *p*-nitrobenzaldehyde in methanol. Although the reaction was complete in 24–36 h with good yields, the product was racemic (Table 1, entries 1 and 2). As expected, the ligand **1c** gave a similar result (entry 3). Then, we turned our attention towards other bis(oxazoline) (box) ligands (Fig. 1).[23] The 4,5-diphenyl-substituted box ligands **2a** and **2b**, which have successfully been used in our laboratory for the enantioselective Friedel–Crafts alkylation of indoles[22] and the carbonyl-ene reaction,[24] gave disappointing results, as the enantioselectivity was poor (entries 4 and 5). However, the ligands **3** were found to give encouraging results. A complex of **3** with $Cu(OAc)_2 \cdot H_2O$ was evaluated as

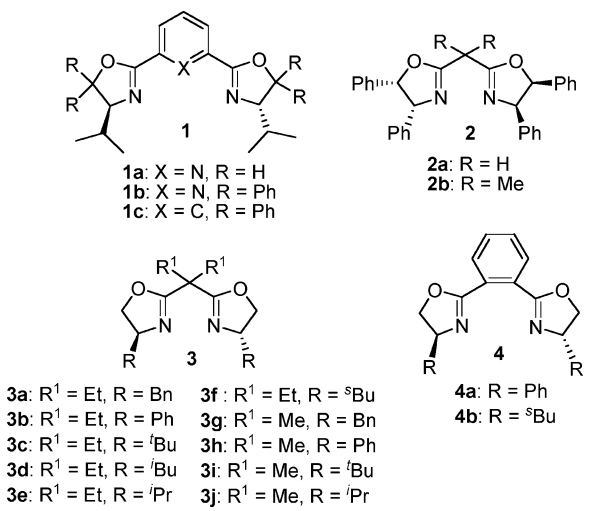

Fig. 1 Chiral ligands.

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† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR for new ligands, and ^{1}H NMR and HPLC data for the products of the Henry reactions. See DOI: 10.1039/b714153j

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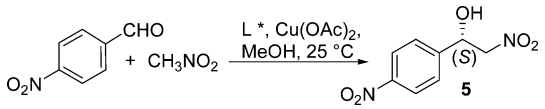
Table 1 Enantioselective Henry reaction of *p*-nitrobenzaldehyde with nitromethane in the presence of different ligands[a]



Entry	Ligand	Time/h	Yield (%)[b]	ee (%)[c]
1	**1a**	24	99	0
2	**1b**	36	98	2
3	**1c**	72	50	0
4	**2a**	72	59	11
5	**2b**	72	92	31
6	**3a**	24	88	69
7	**3b**	36	85	71
8	**3c**	36	87	25
9	**3d**	36	94	57
10	**3e**	36	93	72
11	**3f**	36	92	63
12	**3g**	36	95	65
13	**3h**	36	97	42
14	**3i**	36	60	47[d]
15	**3j**	24	91	67
16	**4a**	72	93	13
17	**4b**	72	87	28

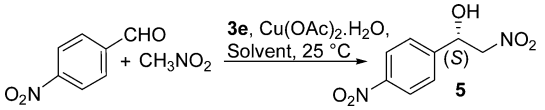
[a] Ratio of $Cu(OAc)_2 \cdot H_2O$, ligand, *p*-nitrobenzaldehyde and nitromethane was 0.05 : 0.06 : 1 : 0.1. [b] Isolated yield after column chromatography. [c] The enantiomeric excess was determined by HPLC using a Chiralcel OD-H column, and the absolute configuration assigned according to the literature data. [d] The reaction was not complete after 36 h.

a catalyst (5 mol%) by using *p*-nitrobenzaldehyde as a model substrate and 10 equivalents of nitromethane in methanol at rt. The ligands **3a**, **3b**, and **3e** (entries 6, 7, and 10) gave good enantioselectivity (69–72% ee). This indicated that diethyl box ligands with benzyl, phenyl, and isopropyl groups at the C(4) stereogenic center are more effective than isobutyl and *tert*-butyl groups. It was also observed that dimethyl box ligands were inferior to their diethyl counterparts (Table 1).

From the results of Table 1, the ligand **3e** was selected and evaluated in several solvents for the catalytic enantioselective Henry reaction between *p*-nitrobenzaldehyde and nitromethane (Table 2). It is clear that protic alcoholic solvents are superior to aprotic solvents. It was found that the enantioselectivity increased from 72% to 81% as the size of the alcohol was increased; MeOH < EtOH< ^{n}PrOH < ^{i}PrOH (Table 2, entries 1–4).[25] On further increasing the size to ^{n}BuOH, ^{i}BuOH and ^{t}BuOH, the enantioselectivity remained the same (Table 2, entries 5–7). However, the enantioselectivity was enhanced to 85% on using *n*-heptanol as a solvent, but the reaction became sluggish (entry 8). It is possible that these alcoholic solvents might coordinate the copper metal, and this process might be help to enhance the enantioselectivity. A poor result (entry 9) in terms of chemical and optical yield by using a non-coordinating solvents such as CH_2Cl_2 strengthens the above hypothesis.

A series of copper salts and other metal acetates were screened for the enantioselective Henry reaction by using the chiral ligand **3e** in isopropanol (Table 3). $Cu(OAc)_2 \cdot H_2O$ was found to be the best metal salt for the reaction (Table 3, entry 1). Although $Cu(OTf)_2$ by itself was inert in initiating the reaction, its combination with triethylamine as a base did induce the reaction to give a nitroaldol product with 32% ee (Table 3, entries 2 and 3). Other metal acetates

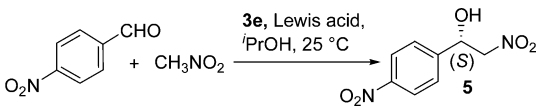
Table 2 Effect of solvent on the enantioselective Henry reaction



Entry	Solvent	Time/h	Yield (%)[a]	ee (%)
1	MeOH	36	95	72
2	EtOH	24	90	75
3	^{n}PrOH	12	93	79
4	^{i}PrOH	12	89	81
5	^{n}BuOH	12	85	77
6	^{i}BuOH	12	84	79
7	^{t}BuOH	10	88	72
8	Heptanol	48	94	85
9	DCM	120	45	47[b]
10	DCM + ^{i}PrOH	36	70	66[c]
11	MeCN	36	77	43

[a] Isolated yield after column chromatography. [b] The reaction was not complete after 120 h. [c] A mixture of DCM and ^{i}PrOH (1 : 1) was used.

Table 3 Effect of Lewis acid on the enantioselectivity[a]



Entry	Lewis acid	Time/h	Yield (%)[b]	ee (%)[c]
1	$Cu(OAc)_2 \cdot H_2O$	12	89	81
2	$Cu(OTf)_2$	48	—	—
3	$Cu(OTf)_2$	36	70	32[d]
4	$CuCl_2$	48	5	60[e]
5	$Zn(OAc)_2 \cdot 4H_2O$	36	85	8[f]
6	$Mg(OAc)_2 \cdot 4H_2O$	36	84	2

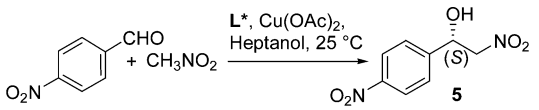
[a] The ratio of metal salt, ligand, *p*-nitrobenzaldehyde and nitromethane was 0.05 : 0.06 : 1 : 0.1. [b] Isolated yield after column chromatography. [c] The enantiomeric excess was determined by HPLC using an Chiralcel OD-H column. [d] 5 mol% triethylamine was used. [e] The reaction rate was very slow and starting material was recovered. [f] The *R* isomer was formed.

such as $Zn(OAc)_2 \cdot 4H_2O$ and $Mg(OAc)_2 \cdot 4H_2O$ were capable of providing good yields in reasonable times but the products were almost racemic (Table 3, entries 5 and 6).

Having failed to enhance the ee beyond 85% in the above reaction, it occurred to us to vary the bite angle[26] in the complex with the hope of enhancing the enantioselectivity. Thus, several spiro box ligands **6a–f** were synthesized (Scheme 1). By using the Hyperchem program package, the geometries of the chiral ligands were energy-minimized at the MM+ level. The computational modeling of the ground state of the uncomplexed chiral ligand (**6**, **3a** and **3g**) was carried out in order to calculate the angle Φ, which directly affects the bite angle. The results from Table 4 indicated that there was no effect of bite angle on enantioselectivity. The poor enantioselectivity with ligand **7** (Table 4, entry 9) is obvious, as the five-membered chelate with copper keeps the stereogenic center away from the reactive metal (Fig. 2).

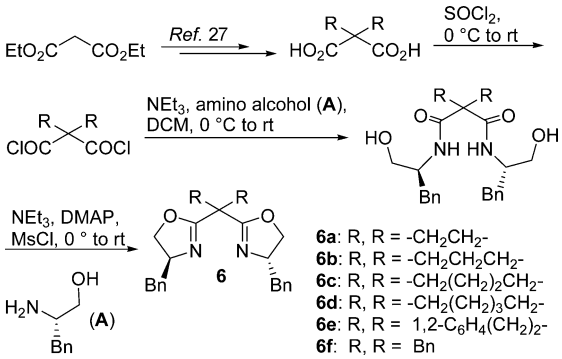
In order to extend the scope of the reaction, the reaction was carried on several substrates using the chiral ligand **3e** in isopropanol (Table 5). A variety of aromatic, heteroaromatic, aliphatic (branched, unbranched, sterically hindered) and α,β-unsaturated aldehydes provided nitroaldol products with enantiomeric excesses

Table 4 Effect of ligand bite angle on the enantioselective Henry reaction



Entry	Ligand	Φ/°	Time/h	Yield (%)[a]	ee (%)[b]
1	**6a**	115.6	12	97	77
2	**6b**	112.0	36	95	76
3	**6c**	107.5	48	96	77
4	**6d**	106.2	48	93	61
5	**6e**	107.0	24	85	75
6	**6f**	111.3	48	96	66
7	**3a**	107.0	24	98	83
8	**3g**	108.1	10	92	81
9	**7**	—	72	81	35

[a] Isolated yield after column chromatography. [b] The enantiomeric excess was determined by HPLC using a Chiralcel OD-H column.



Scheme 1 Synthesis of some other chiral ligands.

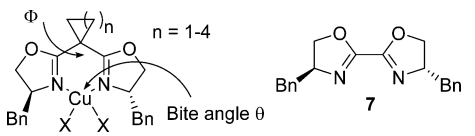
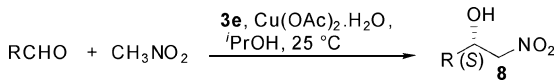


Fig. 2 Bite angle and ligand **7**.

in the range of 85 to 97% at room temperature. In some cases, along with the expected nitroaldol product, small amount (5–10%) of the corresponding elimination product was also detected. It was observed that the electronic nature and steric hindrance of the substituents at the aromatic rings does not have much effect on the enantioselectivity (Table 5, entries 1–9). Heteroaromatic aldehydes and enals gave nitroaldol product in good yield and good ee (Table 5, entries 10–13). Under these conditions even aliphatic aldehydes (branched, unbranched, sterically hindered) were shown to be good substrates, and these could be transformed into nitro alcohols in consistently high yields and enantiomeric excesses (94–97% ee, Table 5, entries 14–18).

The above results have been rationalized by the transition state model shown in Fig. 3. An aldehyde and nitromethane coordinate to the copper center in such a way that there is a maximum activation for the reactive partners. Thus, the oxygen atom of the nitromethane approaches the metal center from the axial side and the carbonyl oxygen atom comes from the equatorial side.[12,13b] In the favorable transition state model, the nucleophilic carbon of the

Table 5 Enantioselective Henry reaction of various aldehydes with nitromethane[a]



Entry	R	Product	Time/h	Yield (%)[b]	ee (%)[c]
1	Ph	**8a**	96	72	95
2	2-$NO_2C_6H_4$	**8b**	12	95	92
3	4-ClC_6H_4	**8c**	96	81	91
4	4-FC_6H_4	**8d**	48	79	91
5	4-MeC_6H_4	**8e**	120	81	90
6	3-MeC_6H_4	**8f**	72	79	91
7	2-$MeOC_6H_4$	**8g**	48	76	85
8	3,5-$MeOC_6H_3$	**8h**	72	81	87
9	2-Naphthyl	**8i**	48	80	86
10	2-Thienyl	**8j**	48	71	87
11	PhCH=CH	**8k**	72	75	88
12	4-$NO_2C_6H_4CH$=CH	**8l**	24	82	88
13	2-$NO_2C_6H_4CH$=CH	**8m**	24	79	91
14	$PhCH_2CH_2$	**8n**	96	90	97
15	^{i}Pr	**8o**	144	85	94
16	^{n}Bu	**8p**	144	83	95
17	Cyclohexyl	**8q**	120	88	97
18	3-Pentyl	**8r**	120	82	94

[a] Ratio of $Cu(OAc)_2 \cdot H_2O$, ligand **3e**, aldehyde and nitromethane was 0.05 : 0.06 : 1 : 0.1. [b] Isolated yield after column chromatography. [c] Enantiomeric excess was determined by HPLC using Chiralcel OD-H and Chiralpak AD-H columns.

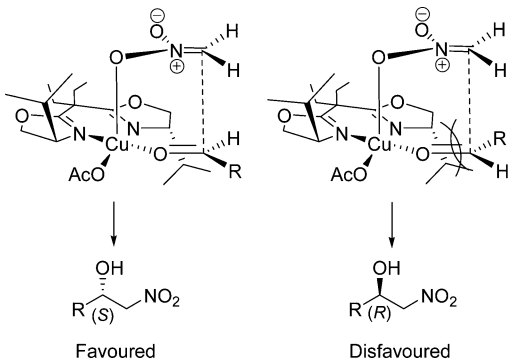


Fig. 3 Proposed transition state models for the enantioselective Henry reaction.

nitronate ion, formed *in situ* by the deprotonation of nitromethane with an acetate ion, approaches the aldehyde from the *Si* face to give *S* isomer as the major product. *Re* face attack is unfavored due to a severe non-bonding interaction between the aromatic group or long chain of the corresponding aldehyde with isopropyl substituents of the chiral bis(oxazoline) ligand.

Conclusions

In conclusion, the complex of the diethyl ^{i}Pr-bis(oxazoline) **3e** and $Cu(OAc)_2 \cdot H_2O$ was found to be an efficient catalyst for the catalytic enantioselective Henry reaction at ambient temperature. It showed a broad substrate applicability, giving products in high chemical and optical yields. The drawback of the method is that it is limited to aldehydes. The stereochemical outcome has been explained with the help of a transition state model.

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Experimental

General methods

^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-LA 400 MHz spectrometer. Chemical shifts are expressed in ppm downfield from TMS as an internal standard, and coupling constants are reported in Hz. Routine monitoring of reactions were performed by TLC, using 0.2 mm Kieselgel 60 F_{254} precoated aluminium sheets, commercially available from Merck. Visualization was done by fluorescence quenching at 254 nm, exposure to iodine vapor, and/or 2,4-dinitrophenylhydrazine solution. All the column chromatographic separations were done using silica gel (Acme, 60–120 mesh). HPLC was performed on a Daicel chiral column (0.46 cm internal diameter × 25 cm length). Petroleum ether used was of boiling range 60–80 °C. Reactions that needed anhydrous conditions were run under an atmosphere of nitrogen or argon using flame-dried glassware. The organic extracts were dried over *anhydrous* sodium sulfate. Evaporation of solvents was performed at reduced pressure. L-Phenylalaninol,[28] L-isoleucinol[28] and diacids[27] were prepared using literature procedures. Diethylmalonyl chloride was used as received from Aldrich. Diethylmalonate, mesyl chloride and triethylamine were distilled before use. CH_2Cl_2 and acetonitrile were distilled from CaH_2.

General procedure for the synthesis of catalysts (Scheme 1)

General procedure for synthesis of acid chlorides. To ice-cold thionyl chloride (50.4 mmol, 8 eq.) the carboxylic acid[2] (6.3 mmol, 1 eq.) was added portionwise over 5–10 minutes, with evolution of gas. After complete addition of carboxylic acid, the ice bath was removed and the reaction mixture was heated to reflux for 3–8 hours. Excess thionyl chloride was distilled through short neck distillation assembly. The acid chloride formed was used without further purification.

General procedure for synthesis of amido alcohols. To a stirred solution of the corresponding (*S*)-amino alcohol (8.64 mmol) and Et_3N (2.41 mL, 17.4 mmol) in CH_2Cl_2 (30 mL) was added dropwise a solution corresponding acid chloride (4.34 mmol) in 5 mL of CH_2Cl_2 at 0 °C, and the mixture was stirred for 12 h (0 °C to rt). The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with 1 N HCl, and the aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$, water, and brine. The organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated *in vacuo.* Crude amido alcohol was used for the next step without further purification.

General procedure for cyclization of amido alcohols to bis-(oxazolines). Freshly distilled methanesulfonyl chloride (746 µL, 10 mmol) was added dropwise to a solution of amido alcohol (5 mmol), triethylamine (2.66 mL, 20 mmol), and 4-(dimethylamino)pyridine (58.6 mg, 0.5 mmol) in CH_2Cl_2 (70 mL) at 0 °C over a period of approximately 10 min under nitrogen. The reaction mixture was warmed to room temperature and stirred for 12 hours. After completion of the reaction, saturated aqueous ammonium chloride solution was added and stirred for another 10 min at room temperature. The organic layer was extracted with CH_2Cl_2 and washed with saturated aqueous Na_2HCO_3 solution. The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was evaporated *in vacuo* to afford crude product, which was purified by column chromatography.

(*S*,4*S*,4′*S*)-2,2′-(Pentane-3,3-diyl)-bis(4-*sec*-butyl-4,5-dihydro-oxazole) (3f). The compound was purified by silica gel column chromatography using EtOAc–pet ether. It was obtained in a maximum of 78% yield as a colorless oil. $[\alpha]_D^{25}$ −89.2 (*c* 1.73, $CHCl_3$). IR ν_{max}/cm^{-1} (film) 2963, 2934, 2877, 1737, 1659, 1460, 1381, 1221, 1131, 1105, 985; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.79–0.85 (m, 12H), 0.91 (t, J = 7.6 Hz, 6H), 1.13–1.20 (m, 2H), 1.41–1.48 (m, 2H) 1.63–1.66 (m, 2H), 1.92–2.06 (m, 4H), 3.94 (t, J = 7.1 Hz, 2H), 4.08–4.19 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.2, 11.7, 13.8, 25.0, 26.2, 38.5, 46.5, 68.7, 70.2, 167.1; HRMS (ES$^+$): Exact mass calcd for $C_{19}H_{34}N_2O_2$ [M + H]$^+$, 323.2699, Found 323.2695.

(4*S*,4′*S*)-2,2′-(Cyclopropane-1,1-diyl)-bis(4-benzyl-4,5-dihydro-oxazole) (6a). The compound was purified by silica gel column chromatography using EtOAc–pet ether. It was obtained in a maximum of 73% yield as a colorless oil. $[\alpha]_D^{25}$ −21.9 (*c* 1.42, $CHCl_3$). IR ν_{max}/cm^{-1} (film) 3026, 2923, 1662, 1369, 1168, 1108, 979; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.32–1.41 (m, 4H), 2.65 (dd, J = 13.6, 8.6 Hz, 2H), 3.10 (dd, J = 13.6, 4.9 Hz, 2H), 4.02 (t, J = 7.6 Hz, 2H), 4.20 (t, J = 8.6 Hz, 2H), 4.36–4.44 (m, 2H), 7.17–7.31 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.4, 18.2, 29.6, 41.3, 67.0, 71.9, 126.4, 128.4, 129.3, 137.7, 165.8; HRMS (ES$^+$): Exact mass calcd for $C_{23}H_{24}N_2O_2$ [M + H]$^+$, 361.1916, Found 361.1913.

(4*S*,4′*S*)-2,2′-(Cyclobutane-1,1-diyl)-bis(4-benzyl-4,5-dihydro-oxazole) (6b). The compound was purified by silica gel column chromatography using EtOAc–pet ether. It was obtained in a maximum of 78% yield as a colorless oil. $[\alpha]_D^{25}$ −21.2 (*c* 1.12, $CHCl_3$). IR ν_{max}/cm^{-1} (film) 3027, 2951, 1657, 1452, 1353, 1120, 971; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.97–2.08 (m, 2H), 2.43–2.49 (m, 1H), 2.59–2.65 (m, 1H), 2.70 (dd, J = 13.7, 8.6 Hz, 2H), 3.12 (dd, J = 13.7, 4.9 Hz, 2H), 4.04 (dd, J = 8.5, 7.1 Hz, 2H), 4.22 (t, J = 8.5 Hz, 2H), 4.41–4.49 (m, 2H), 7.18–7.31 (m, 10H);^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.5, 30.0, 41.3, 41.9, 67.0, 72.2, 126.4, 128.4, 129.4, 137.6, 168.0; HRMS (ES$^+$): Exact mass calcd for $C_{24}H_{26}N_2O_2$ [M + H]$^+$, 375.2073, Found 375.2075.

(4*S*,4′*S*)-2,2′-(Cyclopentane-1,1-diyl)-bis(4-benzyl-4,5-dihydro-oxazole) (6c). The compound was purified by silica gel column chromatography using EtOAc–pet ether. It was obtained in a maximum of 81% yield as a colorless oil. $[\alpha]_D^{25}$ −15.4 (*c* 1.45, $CHCl_3$). IR ν_{max}/cm^{-1} (film) 3060, 3026, 2957, 1656, 1495, 1452, 1350, 1237, 1156, 998, 751; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.65–1.77 (m, 4H), 2.04–2.11 (m, 2H), 2.25–2.31 (m, 2H), 2.65 (dd, J = 13.7, 8.6 Hz, 2H), 3.08 (dd, J = 13.9, 4.9 Hz, 2H), 4.01 (dd, J = 8.6, 7.1 Hz, 2H), 4.18 (t, J = 8.8 Hz, 2H), 4.37–4.44 (m, 2H), 7.18–7.30 (m, 10H);^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.0, 35.3, 41.3, 49.0, 66.9, 72.0, 126.4, 128.4, 129.4, 137.7, 168.8; HRMS (ES$^+$): Exact mass calcd for $C_{25}H_{28}N_2O_2$ [M + H]$^+$, 389.2229, Found 389.2229.

(4*S*,4′*S*)-2,2′-(Cyclohexane-1,1-diyl)-bis(4-benzyl-4,5-dihydro-oxazole) (6d). The compound was purified by silica gel column chromatography using EtOAc–pet ether. It was obtained in a maximum of 80% yield as a colorless oil. $[\alpha]_D^{25}$ −13.6 (*c* 3.78,

$CHCl_3$). IR ν_{max}/cm^{-1} (film) 3026, 2934, 2855, 1654, 1495, 1451, 1348, 1228, 1127, 980; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.45 (bs, 4H), 1.62 (bs, 2H), 1.92–2.07 (m, 4H), 2.64 (dd, J = 13.6, 8.5 Hz, 2H), 3.11 (dd, J = 13.7, 4.6 Hz, 2H), 3.99 (dd, J = 8.5, 7.1 Hz, 2H), 4.14 (t, J = 8.6 Hz, 2H), 4.38–4.46 (m, 2H), 7.19–7.30 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.5, 25.4, 32.4, 41.4, 43.1, 67.2, 71.5, 126.4, 128.4, 129.4, 137.8, 168.2; HRMS (ES^+): Exact mass calcd for $C_{26}H_{30}N_2O_2$ $[M + H]^+$, 403.2385, Found 403.2383.

(4*S*,4′*S*)-2,2′-(2,3-Dihydro-1*H*-indene-2,2-diyl)-bis(4-benzyl-4,5-dihydrooxazole) (6e). The compound was purified by silica gel column chromatography using EtOAc–pet ether. It was obtained in a maximum of 51% yield as a colorless oil. $[\alpha]_D^{25}$ +2.8 (c 1.75, $CHCl_3$). IR ν_{max}/cm^{-1} (film) 3026, 2923, 1658, 1492, 1454, 1352, 1233, 1155, 1029, 965; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.64 (dd, J = 13.7, 8.0 Hz, 2H), 2.98 (dd, J = 13.7, 4.9 Hz, 2H), 3.47 (d, J = 16.1 Hz, 2H), 3.70 (d, J = 16.4 Hz, 2H), 4.02 (dd, J = 8.6, 6.8 Hz, 2H), 4.20 (t, J = 8.8 Hz, 2H), 4.36–4.43 (m, 2H) 7.08–7.26 (m, 14H);^{13}C NMR ($CDCl_3$, 100 MHz) δ 41.1, 41.5, 48.8, 66.9, 72.2, 124.2, 126.3, 126.6, 128.3, 129.4, 137.4, 140.4, 168.0; HRMS (ES^+): Exact mass calcd for $C_{29}H_{28}N_2O_2$ $[M + H]^+$, 437.2229, Found 437.2227.

(4*S*,4′*S*)-2,2′-(1,3-Diphenylpropane-2,2-diyl)-bis(4-benzyl-4,5-dihydrooxazole) (6f). The compound was purified by silica gel column chromatography using EtOAc–pet ether. It was obtained in a maximum of 75% yield as a colorless oil. $[\alpha]_D^{25}$ −18.4 (c 1.35, $CHCl_3$). IR ν_{max}/cm^{-1} (film) 3027, 2927, 1656, 1452, 1176, 1082, 1031, 961; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.32 (dd, J = 13.6, 9.3 Hz, 2H), 2.99 (d, J = 13.6, 5.4 Hz, 2H), 3.37 (s, 4H), 3.89 (t, J = 8.6 Hz, 2H), 4.13 (t, J = 9.3 Hz, 2H), 4.28–4.36 (m, 2H) 7.11–7.32 (m, 20H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.3, 41.5, 48.2, 67.3, 71.9, 126.4, 126.8, 128.0, 128.5, 129.1, 130.5, 136.8, 138.0, 166.7; HRMS (ES^+): Exact mass calcd for $C_{35}H_{34}N_2O_2$ $[M + H]^+$, 515.2698, Found 515.2697.

General procedure for the enantioselective Henry reaction

To a oven-dried 5 mL round-bottomed flask a solution of appropriate ligand (0.06 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (10.0 mg, 0.05 mmol) in the appropriate solvent (2 mL) was stirred for 2 h at room temperature. To the resulting clear blue solution nitromethane (10 mmol) and the aldehyde (1 mmol) were added. The reaction mixture was left at room temperature until the reaction was complete (disappearance of aldehyde by TLC), during which time the color of the solution changed to green. After evaporation of the solvent, the residue was purified by column chromatography on silica gel (EtOAc–pet ether) to afford the nitroaldol product.

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