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Enantioselective Henry reaction catalyzed with copper(II)–iminopyridine complexes

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Abstract—Copper complexes of chiral iminopyridines prepared from camphane-derived ketones and picolylamine catalyzed the enantioselective Henry (nitroaldol) reaction between nitromethane and a number of aromatic and aliphatic aldehydes with high yields and good enantioselectivities. Iminopyridines derived from (1*R*)-(+)-camphor and (1*S*)-(+)-ketopinic acid gave the best results to afford the opposite enantiomers in each case, despite the fact they have the same stereochemical pattern at the camphane skeleton. The reactions were carried out without air or moisture exclusion.

1. Introduction

The addition of a nitroalkane to a carbonyl compound to give a β-nitroalkanol, known as the Henry or nitroaldol reaction, constitutes as one of the most useful methodologies for generating C–C bonds and obtaining polyfunctionalized molecules.[1] Due to the versatile chemistry of the nitro group,[2] the β-nitroalkanols that are obtained can be transformed into a plethora of key molecular frameworks, such as 1,2-amino alcohols, α-hydroxyacids, and others, by reduction, Nef reaction or nucleophilic displacement,[3] respectively. Consequently, considerable effort has been directed over the last few years towards development of the catalytic asymmetric version of this reaction.[4] This goal has been achieved with a number of organocatalytic methods,[5] and most often with the use of metal complexes with chiral ligands. Examples include rare-earth-BINOL,[6] zinc–aminoalcohol,[7] or cobalt–ketoimine[8] complexes, although copper complexes with nitrogenated ligands have attracted most attention as catalysts for this reaction.[9] Despite all the advances produced in this area, some of these catalytic systems still show limitations such as moisture or air sensitivity, high catalyst loading, low enantioselectivity, or a difficult preparation of the catalyst. In a previous communication,[10] we reported that complexes of Cu(II) with iminopyridine ligands derived from monoterpene ketones and pyridylalkylamines catalyzed the Henry reaction between nitromethane and *o*-anisaldehyde, without the need for air or moisture exclusion. Herein we report in detail the development of the enantioselective Henry reaction between nitromethane and aromatic and aliphatic aldehydes catalyzed by copper(II) salts in combination with iminopyridines.

2. Results and discussion

2.1. Design and synthesis of iminopyridine ligands

A set of ligands **5**–**7**, **9**, **11**, **13** and **15** with two coordinating *N* atoms with sp^2 hybridization were synthesized according to the design in Figure 1. *N*,*N*-Ligands have been extensively used in Lewis-acid catalyzed enantioselective reactions. Thus, besides bis-imines[11] and the omnipresent group of C_2-symmetric bis-oxazolines (BOX),[12] a number of ligands, which incorporate a coordinating pyridine ring have been described. This class includes C_2-symmetric bis-pyridines,[13] but also C_1-symmetric oxazolinylpyridines[14] and iminopyridines derived from aldehydes and chiral

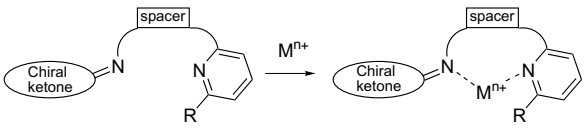

Figure 1. Design of chiral iminopyridine ligands.

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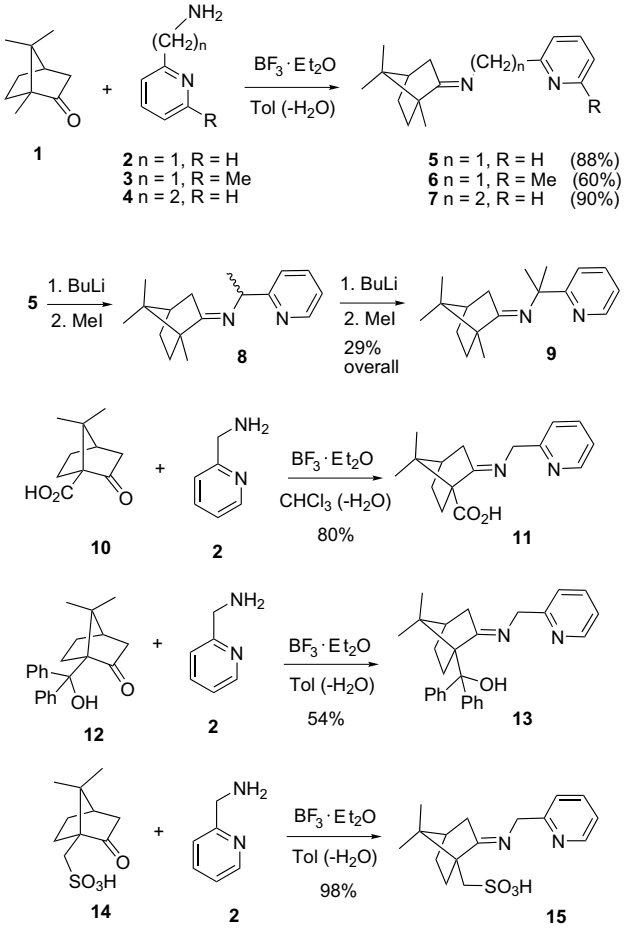
amines.[15] Three factors have been considered in our design. A monoterpene ketone with a camphane skeleton was used as the source of chirality.[16] A spacer of variable length and substitution is used to modify the bite angle of the ligands, and finally, different ketones or substituted pyridylamines can be used to modify the steric hindrance around the proximities of the metal ion.

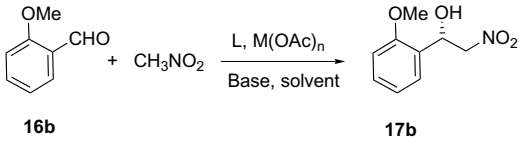
In general, the synthesis of these ligands involved short synthetic sequences (only one step in most cases) starting from commercial or readily available materials. Ligands **5**–**7** were prepared by condensation between (1*R*)-(+)-camphor **1** and the corresponding pyridylalkylamines **2**–**4** in the presence of a catalytic amount of $BF_3{\cdot}Et_2O$ with azeotropic removal of toluene–water (Dean–Stark). Ligand **9**, which has a double alkylated spacer chain was prepared in two steps from ligand **5** via a double alkylation at the benzylic position with BuLi and MeI in 29% overall yield Ligands **11** and **15** were prepared in a similar way as **5**–**7** starting from (1*S*)-(+)-ketopinic acid (**10**) and (1*S*)-(+)-camphorsulfonic acid (**14**), respectively. In these cases the reaction proceeded faster than with camphor, probably as a result of an intramolecular acid catalysis by the carboxylic or sulfonic acid during imine condensation. Finally, ligand **13** was prepared starting from alcohol **12**, which can be prepared by addition of 2 equiv of phenylmagnesium bromide to ketopinic acid methyl ester[17] (Scheme 1).



Scheme 1. Synthesis of iminopyridine ligands.

2.2. Nitroaldol reaction between nitromethane and aldehydes

2.2.1. Optimization of the reaction conditions. The reaction between nitromethane and *o*-anisole **16b** was used to test the ability of these ligands to induce enantioselectivity in the metal catalyzed Henry reaction (Scheme 2).



Scheme 2.

2.2.1.1. Screening of Lewis acids and ligands. Using the reaction conditions described by Evans[9a] for the copper–BOX catalyzed Henry reaction as a starting point, the reaction was initially carried out at room temperature in ethanol as the solvent and in the presence of 11 mol % of ligand **5** and 10 mol % acetate as the source for the metal ion. The reactions were performed in test tubes stopped with a septum with no special attention given for air or moisture exclusion (Table 1). A screening of some late transition metal acetates showed copper acetate to be the best promoter for this reaction (entry 5). Copper(II) triflate was also tested, but under these conditions, the nitroaldol reaction took place with concomitant dehydration to give *ortho*-methoxynitrostyrene as the main product (Table 1, footnote f). The reaction was also tested in different protic and aprotic solvents. Ethanol was found to be the best solvent for this reaction. Quite surprisingly, the use of nitromethane as the solvent, resulted in a slower reaction than with ethanol.

Once we had determined the best solvent and metal ion, we screened the different iminopyridines **6**, **7**, **9**, **11** and **13** as chiral ligands in combination with copper(II) acetate. None of these ligands gave better results than ligand **5**. Thus, it was observed that the elongation (ligand **7**, entry 11) and the introduction of substituents (ligand **9**, entry 12) on the spacer, which alter the bite angle of the ligand had a deleterious effect. Similarly, the introduction of steric hindrance in the proximities of the pyridine nitrogen as in ligand **6** (entry 10) or in the proximities of the imine as in ligand **13** (entry 14), brought about a decrease in the enantioselectivity, these ligands being less effective than ligand **5**. Only iminopyridine **11** (entry 13), which derives from (+)-ketopinic acid, was able to induce a considerable level of enantioselectivity (50%) in this reaction, although it was lower than that obtained with ligand **5**. An important aspect of the reaction catalyzed with **11** is that, unlike the other ligands that yielded (*S*)-(+)-**17b** as the product, the reaction with ligand **11** afforded the opposite enantiomer (*R*)-(−)-**17b**. This was quite surprising, considering that all ligands share the same stereochemical pattern in the chiral ketone. Therefore, the optimization process was continued with ligands **5** and **11**.

2.2.1.2. Lewis acid–Brønsted base dual activation. To increase the enantiomeric excess of the reaction product, we decided to lower the reaction temperature. Using the

Table 1. Henry reaction between nitromethane and *o*-anisole according to Scheme 2[a]: Lewis acid and ligand screening

Entry	L	Metal salt	Solvent	*t* (h)	Yield[b] (%)	ee[c] (%)
1	**5**	$Co(OAc)_2{\cdot}4H_2O$	EtOH	24	94	*rac*
2	**5**	$Ni(OAc)_2{\cdot}4H_2O$	EtOH	24	94	*rac*
3	**5**	$Zn(OAc)_2{\cdot}2H_2O$	EtOH	93	77	10[d]
4	**5**	$Pd(OAc)_2$	EtOH	70	40[e]	37
5	**5**	$Cu(OAc)_2{\cdot}H_2O$[f]	EtOH	24	93	61
6	**5**	$Cu(OAc)_2{\cdot}H_2O$	MeOH	24	95	53
7	**5**	$Cu(OAc)_2{\cdot}H_2O$	$MeNO_2$	70	90	48
8	**5**	$Cu(OAc)_2{\cdot}H_2O$	CH_2Cl_2	70	62[e]	49
9	**5**	$Cu(OAc)_2{\cdot}H_2O$	DMF	24	54[e]	52
10	**6**	$Cu(OAc)_2{\cdot}H_2O$	EtOH	64	47[e]	16
11	**7**	$Cu(OAc)_2{\cdot}H_2O$	EtOH	26	62	19
12	**9**	$Cu(OAc)_2{\cdot}H_2O$	EtOH	64	45[e]	21
13	**11**	$Cu(OAc)_2{\cdot}H_2O$	EtOH	24	70	50[d]
14	**13**	$Cu(OAc)_2{\cdot}H_2O$	EtOH	70	95	7

[a] All reactions carried out at 0.5 mmol scale, using 11 mol % L, 10 mol % $M(OAc)_n$ at rt.
[b] Yields refer to isolated product after column chromatography.
[c] Determined by HPLC analysis using a Chiralcel OD–H column. The (*S*)-enantiomer was obtained unless if otherwise stated.
[d] The (*R*)-enantiomer was obtained.
[e] Uncompleted reaction after the indicated time.
[f] Under similar reaction conditions, $Cu(OTf)_2$ gave *ortho*-methoxynitrostyrene.

catalyst formed by **5**–$Cu(OAc)_2$ at 0 °C, the enantiomeric excess of the product increased up to 67% (Table 2, entry 1). Unfortunately, when we attempted a further decrease of the reaction temperature to −20 °C, it resulted in impractical reaction times.

The concurrent activation of the aldehyde and nitromethane in the Henry reaction by the combined use of discrete Lewis acids and Brønsted bases as independent entities has some precedent in the literature, and the combined use of amines with copper or zinc complexes has been described.[7d,8,9c,18] Accordingly, the use of different amines as additives was tested using complex **5**–$Cu(OAc)_2$ as the Lewis acid (Table 2). The use of the heterocyclic amine 2,6-lutidine (entry 2) decreased the reactivity with respect to the amine-free reaction, to afford the expected product in similar ee. The use of alkylamines was tested next (entries 3–9). With these additives, the reaction temperature could be lowered to −65 °C, while maintaining acceptable reaction times. Under these conditions, a noticeable increase in the ee of the product could be attained.

Diisopropylethylamine (DIPEA) gave the best results (up to 86% ee) either when used in stoichiometric (entry 6) or catalytic amounts (entry 7), although in this case, the reaction required higher temperature to start. Finally, variations in the catalyst load (entries 8 and 9) did not give a significant variation on the result of the reaction.

The results obtained with ligand **5** were used as a starting point for the optimization with ligand **11**, which affords the opposite enantiomer. When DIPEA (1 equiv) was used as an additive with the catalyst formed by **11** and $Cu(OAc)_2$, the reaction could be carried out at −65 °C. However, the product obtained under these conditions showed an ee similar to that obtained with the amine-free system at rt (Table 1, entry 13 vs Table 2, entry 11). Since ligand **11** bears a carboxylic acid functionality, which can form hydrogen bonds with EtOH, we decided to test the use of aprotic solvents with ligand **11**. Diethyl ether, which can act as an acceptor for hydrogen bond formation gave a sluggish reaction at −45 °C affording the expected product in very low yield and only 30% ee. However, with the use of chlorinated solvents, increased enantiomeric excesses could

Table 2. Henry reaction between nitromethane and *o*-anisole according to Scheme 2 in the presence of amines[a]

Entry	L	Solvent	Base	*T* (°C)	*t* (h)	Yield[b] (%)	ee[c] (%)
1	**5**	EtOH	—	0	88	98	67
2	**5**	EtOH	2,6-Lutidine	0[d]	117	90	66
3	**5**	EtOH	*i*-$PrNH_2$	−65	45	85	77
4	**5**	EtOH	Cy_2NH	−65	45	84	80
5	**5**	EtOH	Et_3N	−65	88	56	83
6	**5**	EtOH	DIPEA	−65	48	90	85
7	**5**	EtOH	DIPEA (0.1 equiv)	−55	70	92	83
8	**5**[e] (22 mol %)	EtOH	DIPEA	−65	70	96	86
9	**5**[f] (6 mol %)	EtOH	DIPEA	−65	70	94	84
10	**5**	$CHCl_3$	DIPEA	−40	46	94	78
11	**11**	EtOH	DIPEA	−65	20	76	54[g]
12	**11**	Et_2O	DIPEA	−45	144	5	30[g]
13	**11**	CH_2Cl_2	DIPEA	−45	74	88	73[g]
14	**11**	$(ClCH_2)_2$	DIPEA	−45	46	83	67[g]
15	**11**	$CHCl_3$	DIPEA	−45	22	83	79[g]
16	**11**	$CHCl_3$	DIPEA	−65	46	98	84[g]
17	**15**	$CHCl_3$	DIPEA	−45	48	90	68

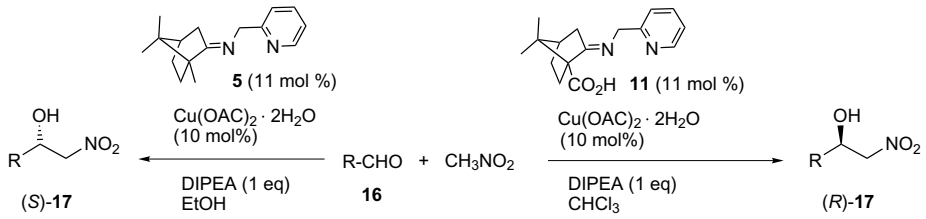
[a] All reactions carried out at 0.5 mmol scale, using 11 mol % L, 10 mol % $Cu(OAc)_2{\cdot}2H_2O$, and 0.5 mmol of base, unless if otherwise stated.
[b] Yields refer to isolated product after column chromatography.
[c] Determined by HPLC analysis using a Chiralcel OD–H column. The (*S*)-enantiomer was obtained unless if otherwise stated.
[d] No reaction was observed at −20 °C.
[e] 20 mol % of $Cu(OAc)_2{\cdot}2H_2O$.
[f] 5 mol % of $Cu(OAc)_2{\cdot}2H_2O$.
[g] The (*R*)-enantiomer was obtained.

be obtained. Chloroform was found to be the most effective solvent, which allowed us to decrease the reaction temperature to −65 °C and afforded the reaction product almost quantitatively with 84% ee (entry 16).

A last assay was made using ligand **15** derived from (1*S*)-(+)-camphorsulfonic acid, which incorporates a sulfonic acid instead of a carboxylic acid moiety. Under the optimized reaction conditions developed for ligand **11**, the reaction in the presence of **15** afforded (*S*)-(+)-**17b** in 68% ee, showing that the presence of an acidic function at this particular position of the terpene ketone is not responsible for the inversion of the enantioselectivity observed with ligand **11**.

2.2.2. Substrate scope. A representative selection of aldehydes were evaluated under the optimized conditions: 11 mol % L, 10 mol % $Cu(OAc)_2{\cdot}H_2O$ in EtOH for ligand **5** and $CHCl_3$ for ligand **11**. The reaction temperature was adjusted according to the reactivity of the aldehyde. The results are summarized in Table 3 (Scheme 3).

As already noticed during the optimization process, both ligands **5** and **11** yielded the opposite enantiomers with all the aldehydes tested. Thus, while ligand **5** primarily afforded the (*S*)-enantiomer, the opposite (*R*)-enantiomer of the nitroaldol products were obtained with ligand **11**. The reaction was carried out with several substituted benzaldehydes (entries 1–17 and 21–37). With both catalysts, the best results were obtained with *ortho*-substitued benzaldehydes bearing electron-releasing substituents with lone electron pairs (RO– and RS–, entries 2–4 and 22–24) or simple alkyl groups (Me, Et, entries 5, 6 and 25, 26). The presence of electron-withdrawing atoms, such as halogens at this position, brought about a decrease in the enantioselectivity of the reaction (entries 7–9 and 27–29), which was especially important with the strongly electron-withdrawing nitro group (entries 10 and 30). Benzaldehydes substituted at the *para*- and *meta*-positions followed a similar behaviour and the products were obtained with somehow lower enantiomeric excesses than their *ortho*-substituted analogues (entries 11–17 and 31–37). With aliphatic aldehydes, both catalysts showed significant differences. Thus the reaction of nitromethane with 3-phenylpropanal catalyzed by the Cu(II)–**5** complex (entry 18) was very sluggish and was still incomplete after 10 days at −20 °C, affording the expected nitroaldol product with low yield (44%) and ee (43%). On the other hand, the Cu(II)–**11** complex was able



Scheme 3. Henry reaction between nitromethane and aldehydes in the presence of $Cu(OAc)_2{\cdot}2H_2O$ and ligands **5** or **11**.

Table 3. Henry reaction between nitromethane and aldehydes according to Scheme 3: Substrate scope

Entry	Aldehyde **16**		Reaction with ligand **5**				Entry	Reaction with ligand **11**			
			T (°C)	*t* (h)	Yield[a] (%) (*S*)-**17**	ee[b] (%)		*T* (°C)	*t* (h)	Yield[a] (%) (*R*)-**17**	ee[b] (%)
1	Benzaldehyde	**a**	−40	90	81	72	21	−65	140	84	80
2	2-Methoxybenzaldehyde	**b**	−65	50	90	85	22	−65	46	98	84
3	2-(Benzyloxy)benzaldehyde	**c**	−65	64	97	85	23	−65	90	96	83
4	2-(Methylthio)benzaldehyde	**d**	−65	72	89	79	24	−50	67	83	83
5	2-Methylbenzaldehyde	**e**	−65	96	95	82	25	−65	50	97	83
6	2-Ethylbenzaldehyde	**f**	−65	114	80	84	26	−65	115	82	84
7	2-Chlorobenzaldehyde	**g**	−65	141	54	65	27	−65	140	90	75
8	2-Bromobenzaldehyde	**h**	−65	90	65	68	28	−65	50	98	78
9	2-Iodobenzaldehyde	**i**	−65	90	75	71	29	−65	46	95	77
10	2-Nitrobenzaldehyde	**j**	−40	70	70	27	30	−50	20	89	31
11	4-Methoxybenzaldehyde	**k**	−40	120	75	78	31	−50	120	80	78
12	4-Methylbenzaldehyde	**l**	−50	67	81	73	32	−65	67	80	81
13	4-Chlorobenzaldehyde	**m**	−45	69	76	56	33	−50	90	90	74
14	4-Nitrobenzaldehyde	**n**	−25	93	85	17	34	−50	67	99	27
15	3-Methoxybenzaldehyde	**o**	−40	90	81	76	35	−50	70	83	75
16	3-Methylbenzaldehyde	**p**	−40	74	88	72	36	−65	120	91	72
17	3-Chlorobenzaldehyde	**q**	−40	99	84	51	37	−40	93	95	63
18	3-Phenylpropanal	**r**	−20	200	44	43	38	−50	120	83	74
19	Cyclohexancarbaldehyde	**s**	—	—	—	—	39	−50	120	99	73
20	3-Methylbutanal	**t**	—	—	—	—	40	−50	120	94	79

[a] Yields refer to isolated product after column chromatography.
[b] Determined by HPLC analysis using chiral stationary phase columns.

to promote the reaction at −50 °C yielding the expected product with 74% ee (entry 38). Similar results were obtained with other branched or sterically hindered aliphatic aldehydes (entries 39 and 40) using ligand **11**.

2.2.3. Stereochemical considerations. As we have seen, ligands **5** and **11** lead to opposite enantiomers, although they have the same stereochemical pattern in the monoterpene ketone. Unfortunately, we have not been able to obtain crystals of the copper complexes with these ligands suitable for X-ray analysis. However, based on our experimental observations and the previously reported steric and electronic considerations,[9a] we propose two transition state models, which account for the absolute configuration of the products obtained with ligands **5** and **11**. The active species simultaneously binds the two reaction partners with the nucleophile positioned 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. With ligand **11**, the ligand plane should be defined by the two nitrogen atoms and the deprotonated carboxyl group, which would bind to the copper centre giving the expected distorted square planar complex (Fig. 2b). The fourth equatorial position should be occupied by the aldehyde and transfer of the nitronate from the less hindered apical position to the *Si* face of the carbonyl group would lead to the (*R*)-nitroaldol product. On the other hand, the complex with ligand **5** should have a more distorted geometry around the metal centre in order to avoid the repulsive interaction between the methyl group at C1 of the camphor skeleton and one of the acetate molecules, which occupies the vacant equatorial coordination site (Fig. 2a). In this distorted complex the C1-Methyl group would shield one of the apical positions of the copper complex and attack of the nitronate would take place preferentially to the *Re* face of the carbonyl group giving the nitroaldol product with the (*S*)-configuration.

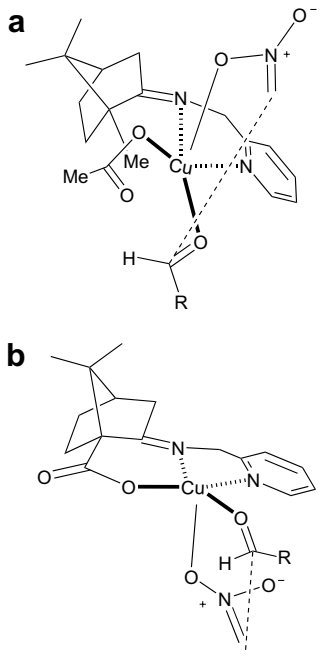


Figure 2. Proposed transition state models for the copper-catalyzed enantioselective Henry reaction with ligands **5** (a) and **l1** (b).

3. Conclusion

In conclusion, we have developed a new catalytic system for the copper(II)-catalyzed enantioselective Henry reaction between nitromethane and aldehydes. This system uses a new family of *N*,*N*-ligands, namely iminopyridines, which can be easily prepared in a modular way from readily available monoterpene ketones and pyridylalkylamines. Two iminopyridines **5** and **11** derived from picolylamine and (1*R*)-(+)-camphor and (1*S*)-(+)-ketopinic acid, respectively, showed the maximum efficiency providing the corresponding nitroalkanols with good yields and moderate to high ee values. Both ligands provide opposite enantiomers, despite the fact they have the same stereochemical pattern in the terpene ketone. Finally, the reaction is carried out without the need of air or moisture exclusion.

4. Experimental

4.1. General

Commercial reagents were used as purchased. Reagent quality EtOH and $CHCl_3$ were used for all enantioselective reactions, which were carried out in test tubes stopped with a septum. No special precautions were observed for air or moisture exclusion. Reactions were monitored by TLC analysis using Merck Silica Gel 60 F-254 thin layer plates. Flash column chromatography was performed on Merck silica gel 60, 0.040–0.063 mm. Optical rotations were measured using sodium light (D line 589 nm) on a Perkin Elmer 243 polarimeter. ^{1}H NMR (Bruker Avance 300 DPX spectrometer) were run at 300 MHz for ^{1}H and at 75 MHz for ^{13}C NMR, in $CDCl_3$ and referenced to the residual non-deuterated solvent as internal standard (δ 7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C NMR, respectively). The carbon type was determined by DEPT experiments. MS(EI) were run at 70 eV. MS(FAB) were carried out on a Fisons instruments VG autospec GC8000 series spectrometer at 30 kV in a MNBA matrix. Chiral HPLC analyses were performed in an Agilent 1100 series instrument equipped with a refraction index detector or in a Hitachi ELITE LaChrom L-2130 instrument equipped with a UV diode-array L-4500 detector. Retention times are given in min.

4.2. Synthesis of ligand 5

A solution of (+)-camphor **1** (6.0 g, 41.8 mmol), picolylamine **2** (4.27 mL, 41.8 mmol) and $BF_3{\cdot}Et_2O$ (0.24 mL) in toluene (95 mL) in a round bottom flask with a Dean–Stark system was refluxed overnight under nitrogen. The reaction mixture was diluted with EtOAc (50 mL), washed with saturated aqueous $NaHCO_3$ and dried over $MgSO_4$. Solvent removal was followed by column chromatography eluting with hexane–EtOAc (8:2) to give 8.9 g (88%) of ligand **5**: $[\alpha]_D^{25} = -24.2$ (*c* 0.91, $CHCl_3$), $[\alpha]_D^{25} = -30.4$ (*c* 0.81, MeOH); MS(EI) 242 (M^+, 58), 241 (100), 92 (78); HRMS 242.1772, $C_{16}H_{22}N_2$ required 242.1783; ^{1}H NMR

(300 MHz, $CDCl_3$) δ 8.50 (dd, $J = 5.0$, 1.8 Hz, 1H), 7.66 (td, $J = 7.5$, 1.8 Hz, 1H), 7.50 (d, $J = 7.5$ Hz, 1H), 7.14 (dd, $J = 7.5$, 5.0 Hz, 1H), 4.65 (d, $J = 16.2$ Hz, 1H), 4.61 (d, $J = 16.2$ Hz, 1H), 2.54 (dt, $J = 17.4$, 3.3 Hz, 1H), 2.03–1.83 (m, 3H), 1.74 (td, $J = 12.0$, 4.2 Hz, 1H), 1.44 (ddd, $J = 12.0$, 9.0, 4.2 Hz, 1H), 1.24 (ddd, $J = 12.0$, 9.0, 4.2 Hz), 1.11 (s, 3H), 0.95 (s, 3H), 0.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.5 (s), 160.6 (s), 148.8 (d), 136.4 (d), 121.4 (d), 121.4 (d), 57.5 (t), 53.9 (s), 47.2 (s), 43.8 (d), 35.9 (t), 32.1 (t), 27.3 (t), 19.5 (q), 18.9 (q), 11.3 (q).

4.3. Synthesis of ligand 6

By using the same procedure as for the synthesis of 5, from (+)-camphor (717 mg, 4.7 mmol) and amine **3** (593 mg, 4.9 mmol), after 21 h, and column chromatography eluting with hexane–EtOAc (4:6) were obtained 723 mg (60%) of ligand **6**: $[\alpha]_D^{25} = -23.9$ (c 0.92, $CHCl_3$); MS(EI) 256 (M^+, 75), 255 (100), 107 (70), 106 (81); HRMS 256.1901, $C_{17}H_{24}N_2$ required 256.1939; ^1H NMR (300 MHz, $CDCl_3$) δ 7.53 (t, $J = 7.8$ Hz, 1H), 7.25 (d, $J = 7.8$ Hz, 1H), 6.97 (d, $J = 7.8$ Hz, 1H), 4.56 (d, $J = 17.1$ Hz, 1H), 4.50 (d, $J = 17.1$ Hz, 1H), 2.50 (s, 3H), 2.40 (dt, $J = 17.4$, 4.2 Hz, 1H), 1.96–1.79 (m, 3H), 1.69 (td, $J = 12.9$, 4.2 Hz, 1H), 1.41 (ddd, $J = 12.9$, 9.0, 4.2 Hz, 1H), 1.26–1.16 (m, 1H), 1.04 (s, 3H), 0.93 (s, 3H), 0.76 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.6 (s), 159.9 (s), 157.3 (s), 136.7 (d), 121.0 (d), 118.3 (d), 57.5 (t), 54.0 (s), 47.2 (s), 43.8 (d), 36.0 (t), 32.1 (t), 27.3 (t), 24.4 (q), 19.6 (q), 18.9 (q), 11.4 (q).

4.4. Synthesis of ligand 7

By using the same procedure as for the synthesis of **5**, from camphor (1.0 g, 7.0 mmol) and amine **4** (890 mg, 7.35 mmol), after 27 h, and column chromatography eluting with hexane–EtOAc (2:8) were obtained 1.61 g (90%) of ligand **7**: $[\alpha]_D^{25} = -28.4$ (c 1.01, $CHCl_3$); MS(EI) 256 (M^+, 44), 106 (100); HRMS 256.1925, $C_{17}H_{24}N_2$ required 256.1939; ^1H NMR (300 MHz, $CDCl_3$) δ 8.49 (d, $J = 4.8$ Hz, 1H), 7.53 (td, $J = 6.0$, 1.2 Hz, 1H), 7.15 (d, $J = 7.8$ Hz, 1H), 7.09–7.05 (m, 1H), 3.71–3.53 (m, 2H), 3.11–3.07 (m, 2H) 2.19 (dt, $J = 17.1$, 3.6 Hz, 1H), 1.82–1.52 (m, 4H), 1.21–1.14 (m, 1H), 1.01–0.96 (m, 1H), 0.96 (s, 3H), 0.84 (s, 3H), 0.54 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.8 (s), 160.5 (s), 149.2 (d), 136.0 (d), 124.0 (d), 121.0 (d), 53.5 (s), 52.1 (t), 46.7 (s), 43.6 (d), 39.3 (t), 35.5 (t), 32.1 (t), 27.3 (t), 19.3 (q), 18.8 (q), 11.4 (q).

4.5. Synthesis of ligand 9

BuLi (2 M) in cyclohexane (2.1 mL, 4.2 mmol) was added dropwise to a solution of ligand **5** (0.7 g, 2.73 mmol) in dry THF at −78 °C under nitrogen. After 5 min, a solution of MeI (0.77 g, 5.46 mmol) was added and the mixture stirred for 45 min. The reaction was quenched by the addition of water (10 mL), diluted with EtOAc (120 mL) and washed with brine (50 mL). After drying over $MgSO_4$, the solvent was removed under reduced pressure to give 673 mg (93%) of a mixture of diastereomers **8**. The procedure was repeated with this diastereomeric mixture for 5 h. The usual workup followed by column chromatography eluting with hexane–EtOAc (9:1) gave 214 mg (29%) of ligand **9**: $[\alpha]_D^{25} = -5.6$ (c 0.99, $CHCl_3$); MS(EI) 270 (M+, 11), 255 (100), 120 (57); HRMS 270.2085, $C_{18}H_{26}N_2$ required 270.2096; ^1H NMR (300 MHz, $CDCl_3$) δ 8.51 (d, $J = 3.6$ Hz, 1H), 7.58 (td, $J = 7.8$. 2.1 Hz, 1H), 7.45 (d, $J = 7.8$ Hz, 1H), 7.11–7.07 (m, 1H), 1.69–0.78 (m, 7H), 1.61 (s, 3H), 1.60 (s, 3H), 1.01 (s, 3H), 0.86 (s, 3H), 0.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.6 (s), 168.7 (s), 148.0 (d), 135.9 (d), 121.5 (d), 121.0 (d), 62.2 (s), 54.7 (s), 46.5 (s), 44.3 (d), 37.9 (t), 32.1 (t), 29.1 (q), 28.4 (q), 27.3 (t), 19.5 (q), 19.1 (q), 11.9 (q).

4.6. Synthesis of ligand 11

The same procedure as for the synthesis of **5**, in $CHCl_3$ instead of toluene was used. Starting from (1*S*)-(+)-ketopinic acid **10** (2.5 g, 13.7 mmol) and picolylamine **2** (1.5 mL, 14.6 mmol), after 4 h, the reaction mixture was concentrated under reduced pressure. Crystallization from hexane–CH_2Cl_2 afforded 2.99 g (80%) of ligand **11**: $[\alpha]_D^{25} = +64.8$ (c 1.11, $CHCl_3$); MS(EI) 272 (M^+, 55), 257 (49), 92 (100); HRMS 272.1425, $C_{16}H_{20}N_2O_2$ required 272.1525; ^1H NMR (300 MHz, $CDCl_3$) δ 8.53 (d, $J = 4.8$, 1H), 7.70 (td, $J = 7.5$, 1.8 Hz, 1H), 7.33 (d, $J = 7.5$ Hz, 1H), 7.21 (m, 1H), 4.79 (s, 2H), 2.76 (dt, $J = 18.0$, 3.3 Hz, 1H), 2.50 (td, $J = 12.3$, 3.9 Hz, 1H), 2.26–2.04 (m, 3H), 1.77 (ddd, $J = 13.8$, 9.0, 3.9 Hz, 1H), 1.41 (ddd, $J = 12.0$, 9.0, 3.9 Hz, 1 H), 1.31 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.3 (s), 173.2 (s), 157.2 (s), 149.3 (d), 137.0 (d), 122.4 (d), 121.7 (d), 60.7 (s), 56.5 (t), 50.6 (s), 43.9 (d), 35.7 (t), 31.4 (t), 28.0 (t), 20.2 (q), 19.9 (q).

4.7. Synthesis of ligand 13

By using the same procedure as for the synthesis of **5**, from ketone **12** (480 mg, 1.5 mmol) and picolylamine **2** (0.160 mL, 1.58 mmol), after 20 h and column chromatography eluting with hexane–EtOAc (6:4) were obtained 335 mg (54%) of ligand **13**: mp 172–176 °C; $[\alpha]_D^{25} = +163.7$ (c 0.97, $CHCl_3$); MS(EI) 410 (M+, 1.0), 341 (35), 318 (100); HRMS 410.2353, $C_{28}H_{30}N_2O$ required 410.2358; ^1H NMR (300 MHz, $CDCl_3$) δ 8.48 (d, $J = 4.2$, 1H), 7.56–7.46 (m, 5H), 7.28–7.09 (m, 8H), 6.98 (d, $J = 8.1$ Hz, 1H), 4.69 (d, $J = 17.4$ Hz, 1H), 4.58 (d, $J = 17.4$ Hz, 1H), 2.64–2.50 (m, 2H), 2.43–2.32 (m, 1H), 2.01 (d, $J = 17.4$ Hz, 1H), 1.91–1.79 (m, 1H), 1.66 (t, $J = 4.5$ Hz, 1H), 1.37–1.29 (m, 1H), 1.11 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.9 (s), 159.5 (s), 149.1 (s), 148.2 (d), 144.9 (s), 137.0 (d), 129.4 (d), 128.4 (d), 127.0 (d), 126.8 (d), 126.5 (d), 125.9 (d), 122.1 (d), 121.7 (d), 80.2 (s), 64.2 (s), 56.7 (t), 50.3 (s), 45.4 (d), 35.4 (t), 27.4 (t), 26.9 (t), 22.3 (q), 21.1 (q).

4.8. Synthesis of ligand 15

By using the same procedure as for the synthesis of **11**, from (1*S*)-(+)-camphorsulfonic acid **14** (2.5 g, 10.8 mmol) and picolylamine (**2**, 1.15 mL, 11.3 mmol), after 20 h, were obtained 3.4 g (98%) of ligand **15**: mp 172–176 °C; $[\alpha]_D^{25} = -39.6$ (c 1.03, $CHCl_3$); MS(FAB) 323 (M^++1, 45); HRMS 323.1421, $C_{16}H_{23}N_2O_3S$ required 323.1429; ^1H

NMR (300 MHz, $CDCl_3$) δ 8.60 (d, $J = 3.9$, 1H), 7.92 (td, $J = 7.5$, 2.1 Hz, 1H), 7.66 (d, $J = 7.5$ Hz, 1H), 7.45 (m, 1H), 5.11 (s, 2H), 3.45 (d, $J = 14.7$ Hz, 1H), 3.30–3.19 (m, 1H), 3.08 (d, $J = 14.7$ Hz, 1H), 2.73–2.05 (m, 5H), 1.56–1.51 (m, 1H), 1.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.7 (s), 151.9 (s), 149.7 (d), 137.5 (d), 123.7 (d), 123.1 (d), 58.4 (s), 53.2 (t), 52.8 (s), 49.2 (t), 43.0 (d), 38.0 (t), 28.8 (t), 26.2 (t), 19.9 (q), 18.7 (q).

4.9. General procedure for the enantioselective Henry reaction

$Cu(OAc)_2{\cdot}H_2O$ (9.9 mg, 0.05 mmol) was added to a solution of ligand **5** (13.3 mg, 0.055 mmol) in absolute EtOH (1.5 mL) and the mixture stirred for 1 h. To the resulting blue solution was added nitromethane (0.27 mL, 5 mmol) and the recipient introduced in a bath at the required temperature. Aldehyde **16** (0.5 mmol) dissolved in absolute ethanol (1.5 mL) was added followed by DIPEA (82 μL, 0.5 mmol) and the reaction mixture stirred until completion (TLC). The solvent was removed under reduced pressure and the residue chromatographed on silica gel to give nitroalkanol **17**. The same procedure was followed with ligand **11** (15.0 mg) but using $CHCl_3$ instead of EtOH. Yields and enantiomeric excesses for compounds **17** are shown in Table 3.

4.9.1. (*S*)-(+)-2-Nitro-1-phenylethanol 17a. Purified by chromatography eluting with hexane–diethyl ether (9:1). Enantiomeric excess (72%) was determined by HPLC (Chiralcel OD–H), hexane–*i*-PrOH 90:10, 1 mL/min, major enantiomer (*S*) $t_r = 16.6$, minor enantiomer (*R*) $t_r = 14.1$; $[\alpha]_D^{25} = +33.7$ (*c* 1.05, CH_2Cl_2, ee 72%, obtained with ligand **5**); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.40 (m, 5H), 5.47 (dd, $J = 9.3$, 3.6 Hz, 1H), 4.62 (dd, $J = 13.8$, 9.3 Hz, 1H), 4.52 (dd, $J = 13.8$, 3.6 Hz, 1H), 2.77 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.0 (s), 129.0 (d), 128.9 (s), 125.9 (d), 81.1 (t), 70.9 (d).

4.9.2. (*S*)-(+)-1-(2-Methoxyphenyl)-2-nitroethanol 17b. Purified by chromatography eluting with hexane–diethyl ether (9:1). Enantiomeric excess (78%) was determined by HPLC (Chiralcel OD–H), hexane–*i*-PrOH 90:10, 1 mL/min, major enantiomer (*S*) $t_r = 13.6$, minor enantiomer (*R*) $t_r = 12.1$; $[\alpha]_D^{25} = +39.8$ (*c* 1.05, CH_2Cl_2, ee 85%, obtained with ligand **5**); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (dd, $J = 7.5$, 1.5 Hz, 1H), 7.33 (td, $J = 7.5$, 1.5 Hz, 1H), 7.04–6.99 (m, 1H), 6.91 (d, $J = 8.4$ Hz, 1H), 5.63 (dd, $J = 9.0$, 3.3 Hz, 1H), 4.65 (dd, $J = 13.2$, 3.3 Hz, 1H), 4.57 (dd, $J = 13.2$, 9.0 Hz, 1H), 3.88 (s, 3H), 2.87 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.9 (s), 129.7 (d), 127.1 (d), 125.9 (s), 121.0 (d), 110.5 (d), 79.8 (t), 67.7 (d), 55.3 (q).

4.9.3. (*R*)-(−)-1-(2-Benzyloxyphenyl)-2-nitroethanol 17c. Purified by chromatography eluting with hexane–diethyl ether (9:1). Enantiomeric excess (83%) was determined by HPLC (Chiralcel OD–H), hexane–*i*-PrOH 90:10, 1 mL/min, major enantiomer (*R*) $t_r = 13.8$, minor enantiomer (*S*) $t_r = 17.6$; mp 65–67 °C; $[\alpha]_D^{25} = -33.8$ (*c* 1.10, CH_2Cl_2, ee 83%, obtained with ligand **11**); MS(EI) 273 (M^+, 3), 91 (100). HRMS: 273.0985 $C_{15}H_{15}NO_4$ required 273.1001; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49–7.29 (m, 7H), 7.04 (t, $J = 7.8$ Hz, 1H), 6.99 (d, $J = 7.8$ Hz, 1H), 5.71 (dd, $J = 9.0$, 2.7 Hz, 1H), 5.17 (d, $J = 12.1$ Hz, 1H), 5.13 (d, $J = 12.1$ Hz, 1H), 4.68 (dd, $J = 12.9$, 2.7 Hz, 1H), 4.57 (dd, $J = 12.9$, 9.0 Hz, 1H), 3.03 (sample, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.0 (s), 136.1 (s), 129.7 (d), 128.8 (d), 128.3 (d), 127.2 (d), 127.1 (d), 126.3 (d), 121.4 (d), 111.9 (d), 79.8 (t), 70.2 (t), 67.6 (d).

4.9.4. (*R*)-(−)-1-(2-Methylthiophenyl)-2-nitroethanol 17d. Purified by chromatography eluting with hexane–diethyl ether (9:1). Enantiomeric excess (83%) was determined by HPLC (Chiralpak AD–H), hexane–*i*-PrOH 90:10, 0.5 mL/min, major enantiomer (*R*) $t_r = 27.8$, minor enantiomer (*S*) $t_r = 28.8$; $[\alpha]_D^{25} = -62.6$ (*c* 1.09, CH_2Cl_2, ee 83%, obtained with ligand **11**); MS(EI) 213 (M^+, 18), 151 (100), 91 (66); HRMS 213.0469, $C_9H_{11}NO_3S$ required 213.0460; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (dd, $J = 7.2$, 1.5 Hz, 1H), 7.34–7.29 (m, 1H), 7.20–7.14 (m, 2H), 5.81 (dd, $J = 9.6$, 2.4 Hz, 1H), 4.61 (dd, $J = 13.5$, 2.4 Hz, 1H), 4.44 (dd, $J = 13.5$, 9.6 Hz, 1H), 2.81 (br s, 1H), 2.49 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 135.9 (s), 135.5 (s), 129.2 (d), 126.3 (d), 126.1 (d), 125.8 (d), 79.6 (t), 67.9 (d), 16.1 (q).

4.9.5. (*S*)-(+)-1-(2-Methylphenyl)-2-nitroethanol 17e. Purified by chromatography eluting with hexane–diethyl ether (9:1). Enantiomeric excess (82%) was determined by HPLC (Chiralcel OD–H), hexane–*i*-PrOH 90:10, 1 mL/min, major enantiomer (*S*) $t_r = 17.1$, minor enantiomer (*R*) $t_r = 11.5$; $[\alpha]_D^{25} = +41.7$ (*c* 1.07, CH_2Cl_2, ee 82%, obtained with ligand **5**); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50–7.46 (m, 1H), 7.25–7.22 (m, 2H), 7.17–7.15 (m, 1H), 5.64 (dd, $J = 9.6$, 2.7 Hz, 1H), 4.51 (dd, $J = 13.5$, 9.6 Hz, 1H), 4.39 (dd, $J = 13.5$, 2.7 Hz, 1H), 2.79 (br s, 1H), 2.35 (s , 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 136.2 (s), 134.4 (s), 130.8 (d), 128.7 (d), 126.7 (d), 125.6 (d), 80.2 (t), 67.9 (d), 18.8 (q).

4.9.6. (*S*)-(+)-1-(2-Ethylphenyl)-2-nitroethanol 17f. Purified by chromatography eluting with hexane–diethyl ether (9:1). Enantiomeric excess (84%) was determined by HPLC (Chiralcel OD–H), hexane–*i*-PrOH 90:10, 1 mL/min, major enantiomer (*S*) $t_r = 13.3$, minor enantiomer (*R*) $t_r = 10.7$; $[\alpha]_D^{25} = +33.6$ (*c* 0.96, CH_2Cl_2, ee 84%, obtained with ligand **5**); MS(EI) 195 (M^+, 0.2), 133 (100), 131 (87), 91 (58), 79 (46); HRMS 195.0896, $C_{10}H_{13}NO_3$ required 195.0895; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (dd, $J = 9.0$, 2.4 Hz, 1H), 7.29–7.19 (m, 3H), 5.70 (dd, $J = 9.6$, 2.7 Hz, 1H), 4.56 (dd, $J = 13.2$, 9.6 Hz, 1H), 4.38 (dd, $J = 13.2$, 2.7 Hz, 1H), 3.02 (sample, 1H), 2.69 (m, 2H), 1.24 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 140.7 (s), 135.5 (s), 129.0 (d), 128.9 (d), 126.7 (d), 125.8 (d), 80.8 (t), 67.3 (d), 25.1 (t), 15.5 (q).

4.9.7. (*S*)-(+)-1-(2-Chlorophenyl)-2-nitroethanol 17g. Purified by chromatography eluting with hexane–diethyl ether (9:1). Enantiomeric excess (65%) was determined by HPLC (Chiralcel OD–H), hexane–*i*-PrOH 95:5, 0.5 mL/min, major enantiomer (*S*) $t_r = 29.9$, minor enantiomer (*R*) $t_r = 28.2$; $[\alpha]_D^{25} = +40.3$ (*c* 1.10, CH_2Cl_2, ee 65%, obtained with ligand **5**); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (dd,

$J = 7.5$, 2.1 Hz, 1H), 7.40–7.27 (m, 3H), 5.85 (dd, $J = 9.6$, 2.4 Hz, 1H), 4.68 (dd, $J = 13.5$, 2.4 Hz, 1H), 4.45 (dd, $J = 13.5$, 9.6 Hz, 1H), 2.88 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ135.4 (s), 131.5 (s), 129.9 (d), 129.7 (d), 127.6 (d), 127.5 (d), 79.3 (t), 67.8 (d).

4.9.8. (*R*)-(−)-1-(2-Bromophenyl)-2-nitroethanol 17h. Purified by chromatography eluting with hexane–diethyl ether (9:1). Enantiomeric excess (78%) was determined by HPLC (Chiralcel OD–H), hexane–*i*-PrOH 95:5, 0.5 mL/min, major enantiomer (*R*) $t_r = 29.4$, minor enantiomer (*S*) $t_r = 33.3$; $[\alpha]_D^{25} = -29.2$ (*c* 1.06, CH_2Cl_2, ee 78%, obtained with ligand **11**); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (dd, $J = 7.8$, 1.8 Hz, 1H), 7.56 (dd, $J = 7.8$, 1.2 Hz, 1H), 7.41 (td, $J = 7.8$, 1.2 Hz, 1H), 7.23 (td, 7.8, 1.8 Hz, 1H), 5.81 (dd, $J = 9.6$, 2.4 Hz, 1H), 4.69 (dd, $J = 13.8$, 2.4 Hz, 1H), 4.32 (dd, $J = 13.8$, 9.6 Hz, 1H), 2.85 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 137.0 (s), 133.0 (d), 130.2 (d), 128.2 (d), 127.8 (d), 121.4 (s), 79.3 (t), 70.0 (d).

4.9.9. (*S*)-(+)-1-(2-Iodophenyl)-2-nitroethanol 17i. Purified by chromatography eluting with hexane–diethyl ether (9:1). Enantiomeric excess (71%) was determined by HPLC (Chiralpak AD–H), hexane–*i*-PrOH 95:5, 0.5 mL/min, major enantiomer (*S*) $t_r = 33.8$, minor enantiomer (*R*) $t_r = 35.6$; $[\alpha]_D^{25} = +24.2$ (*c* 1.08, CH_2Cl_2, ee 71%, obtained with ligand **5**); MS(EI) 293 (M^+, 72), 246 (100), 233 (72), 91 (95); HRMS 292.9539, $C_8H_8INO_3$ required 292.9549; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (dd, $J = 7.8$, 1.5 Hz, 1H), 7.62 (dd, $J = 7.8$, 1.2 Hz, 1H), 7.43 (td, $J = 7.8$, 1.5 Hz, 1H), 7.07 (td, 7.8, 1.2 Hz, 1H), 5.67 (dd, $J = 9.9$, 2.4 Hz, 1H), 4.65 (dd, $J = 13.5$, 2.4 Hz, 1H), 4.40 (dd, $J = 13.5$, 9.9 Hz, 1H), 2.97 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 139.9 (s), 139.7 (d), 130.5 (d), 129.0 (d), 127.6 (d), 96.7 (s), 79.4 (t), 74.3 (d).

4.9.10. (*S*)-(−)-2-Nitro-1-(2-nitrophenyl)ethanol 17j. Purified by chromatography eluting with hexane–diethyl ether (8:2). Enantiomeric excess (27%) was determined by HPLC (Chiralcel OD–H), hexane–*i*-PrOH 90:10, 0.8 mL/min, major enantiomer (*S*) $t_r = 19.6$, minor enantiomer (*R*) $t_r = 18.0$; $[\alpha]_D^{25} = -50.3$ (*c* 0.38, CH_2Cl_2, ee 27%, obtained with ligand **5**); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (dd, $J = 8.1$, 1.2 Hz, 1H), 7.95 (dd, $J = 8.1$, 1.2 Hz, 1H), 7.75 (td, $J = 7.8$, 1.2 Hz, 1H), 7.55 (td, $J = 7.8$, 1.2 Hz, 1H) 6.04 (dd, $J = 9.3$, 2.4 Hz, 1H), 4.86 (dd, $J = 13.8$, 2.4 Hz, 1H), 4.55 (dd, $J = 13.8$, 9.3 Hz, 1H), 3.28 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 147.1 (s), 134.3 (d), 134.0 (s), 129.7 (d), 128.7 (d), 125.0 (d), 80.0 (t), 66.7 (d).

4.9.11. (*S*)-(+)-1-(4-Methoxyphenyl)-2-nitroethanol 17k. Purified by chromatography eluting with hexane–diethyl ether (8:2). Enantiomeric excess (78%) was determined by HPLC (Chiralcel OD–H), hexane–*i*-PrOH 90:10, 1 mL/min, major enantiomer (*S*) $t_r = 25.2$, minor enantiomer (*R*) $t_r = 20.2$; $[\alpha]_D^{25} = +32.3$ (*c* 1.05, CH_2Cl_2, ee 78%, obtained with ligand **5**); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, $J = 8.7$, 2H), 6.92 (d, $J = 8.7$, 2H), 5.41 (dd, $J = 9.3$, 3.0 Hz, 1H), 4.60 (dd, $J = 13.2$, 9.3 Hz, 1H), 4.47 (dd, $J = 13.2$, 3.0 Hz, 1H), 3.81 (s, 3H), 2.35 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.9 (s), 130.2 (s), 127.2 (d), 114.3 (d), 81.2 (t), 70.6 (d), 55.3 (q).

4.9.12. (*R*)-(−)-1-(4-Methylphenyl)-2-nitroethanol 17l. Purified by chromatography eluting with hexane–diethyl ether (8:2). Enantiomeric excess (81%) was determined by HPLC (Chiralcel OD–H), hexane–*i*-PrOH 90:10, 1 mL/min, major enantiomer (*R*) $t_r = 14.1$, minor enantiomer (*S*) $t_r = 18.6$; $[\alpha]_D^{25} = -37.2$ (*c* 1.14, CH_2Cl_2, ee 81%, obtained with ligand **11**); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, $J = 7.8$ Hz, 2H), 7.26 (d, $J = 7.8$ Hz, 2H), 5.46 (dd, $J = 9.3$, 3.0 Hz, 1H), 4.64 (dd, $J = 13.2$, 9.3 Hz, 1H), 4.52 (dd, $J = 13.2$, 3.0 Hz, 1H), 2.82 (br s, 1H), 2.41 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.9 (s), 135.1 (s), 129.6 (d), 125.8 (d), 81.2 (t), 70.8 (d), 21.1 (q).

4.9.13. (*S*)-(+)-1-(4-Chlorophenyl)-2-nitroethanol 17m. Purified by chromatography eluting with hexane–diethyl ether (9:1). Enantiomeric excess (56%) was determined by HPLC (Chiralcel OD–H), hexane–*i*-PrOH 90:10, 1 mL/min, major enantiomer (*S*) $t_r = 17.2$, minor enantiomer (*R*) $t_r = 14.1$; $[\alpha]_D^{25} = +24.7$ (*c* 1.13, CH_2Cl_2, ee 56%, obtained with ligand **5**); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.31 (m, 4H), 5.43 (dd, $J = 9.0$, 3.3 Hz, 1H), 4.56 (dd, $J = 13.2$, 9.0 Hz, 1H), 4.47 (dd, $J = 13.2$, 3.3 Hz, 1H), 3.11 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 136.5 (s), 134.7 (s), 129.2 (d), 127.3 (d), 80.9 (t), 70.2 (d).

4.9.14. (*R*)-(−)-2-Nitro-1-(4-nitrophenyl)ethanol 17n. Purified by chromatography eluting with hexane–diethyl ether (8:2). Enantiomeric excess (27%) was determined by HPLC (Chiralcel OD–H), hexane–*i*-PrOH 90:10, 1 mL/min, major enantiomer (*R*) $t_r = 26.7$, minor enantiomer (*S*) $t_r = 34.1$; $[\alpha]_D^{25} = -10.0$ (*c* 1.06, CH_2Cl_2, ee 27%, obtained with ligand **11**); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (d, $J = 8.7$ Hz, 2H), 7.62 (d, $J = 8.7$ Hz, 2H), 5.61 (dd, $J = 7.5$, 4.7 Hz, 1H), 4.59 (1H, d, $J = 7.5$ Hz, 1H), 4.58 (d, $J = 4.7$ Hz, 1H), 3.30 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 148.0 (s), 145.0 (s), 126.9 (d), 124.1 (d), 80.6 (t), 69.9 (d).

4.9.15. (*S*)-(+)-1-(3-Methoxyphenyl)-2-nitroethanol 17o. Purified by chromatography eluting with hexane–diethyl ether (8:2). Enantiomeric excess (76%) was determined by HPLC (Chiralcel OD–H), hexane–*i*-PrOH 90:10, 1 mL/min, major enantiomer (*S*) $t_r = 36.1$, minor enantiomer (*R*) $t_r = 25.2$; $[\alpha]_D^{25} = +26.6$ (*c* 0.97, CH_2Cl_2, ee 76%, obtained with ligand **5**); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (t, $J = 8.1$, 1H), 6.96 (m, 2H), 6.89 (dd, $J = 8.1$, 2.4 Hz, 1H), 5.44 (dd, $J = 9.3$, 3.3 Hz, 1H), 4.60 (dd, $J = 13.2$, 9.3 Hz, 1H), 4.51 (dd, $J = 13.2$, 3.3 Hz, 1H), 3.82 (s, 3H), 2.59 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 160.0 (s), 139.7 (s), 130.0 (d), 118.0 (d), 114.3 (d), 111.4 (d), 81.1 (t), 70.8 (d), 55.3 (t).

4.9.16. (*R*)-(−)-1-(3-Methylphenyl)-2-nitroethanol 17p. Purified by chromatography eluting with hexane–diethyl ether (8:2). Enantiomeric excess (72%) was determined by HPLC (Chiralcel OD–H), hexane–*i*-PrOH 90:10, 1 mL/min, major enantiomer (*R*) $t_r = 11.8$, minor enantiomer (*S*) $t_r = 14.2$; $[\alpha]_D^{25} = -36.8$ (*c* 1.09, CH_2Cl_2, ee 72%, obtained with ligand **11**); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (t, $J = 7.5$ Hz, 1H), 7.12–7.08 (m, 3H), 5.32 (dd, $J = 9.3$, 3.0 Hz, 1H), 4.50 (dd, $J = 13.2$, 9.3 Hz, 1H), 4.40 (dd, $J = 13.2$, 3.0 Hz, 1H), 2.79 (br s, 1H), 2.29 (s, 3H);

^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.8 (s), 138.0 (s), 129.6 (d), 128.8 (d), 126.5 (d), 122.9 (d), 81.2 (t), 71.0 (d), 21.3 (q).

4.9.17. (*R*)-(−)-1-(3-Chlorophenyl)-2-nitroethanol 17q. Purified by chromatography eluting with hexane–diethyl ether (9:1). Enantiomeric excess (63%) was determined by HPLC (Chiralcel OD–H), hexane–*i*-PrOH 90:10, 1 mL/min, major enantiomer (*R*) $t_r = 13.3$, minor enantiomer (*S*) $t_r = 16.6$; $[\alpha]_D^{25} = -27.2$ (*c* 1.05, CH_2Cl_2, ee 63%, obtained with ligand **11**); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (m, 1H), 7.35–7.26 (m, 3H), 5.44 (dd, $J = 9.3$, 3.6 Hz, 1H), 4.58 (dd, $J = 13.5$, 9.3 Hz, 1H), 4.50 (dd, $J = 13.5$, 3.6 Hz, 1H), 3.01 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 140.0 (s), 134.9 (s), 130.3 (d), 129.1 (d), 126.2 (d), 124.0 (d), 80.9 (t), 70.2 (d).

4.9.18. (*R*)-(+)-1-Nitro-4-phenyl-2-butanol 17r. Purified by chromatography eluting with hexane–diethyl ether (9:1). Enantiomeric excess (74%) was determined by HPLC (Chiralpak AD–H), hexane–*i*-PrOH 90:10, 1 mL/min, major enantiomer (*R*) $t_r = 12.0$, minor enantiomer (*S*) $t_r = 13.1$; $[\alpha]_D^{25} = +13.1$ (*c* 0.51, CH_2Cl_2, ee 74%, obtained with ligand **11**); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.10 (m, 5H), 4.33–4.30 (m, 2H), 4.26–4.20 (m, 1H), 2.83–260 (m, 3H), 1.80–1.69 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 140.6 (s), 128.6 (d), 128.4 (d), 126.3 (d), 80.5 (t), 67.7 (d), 35.1 (t), 31.3 (t).

4.9.19. (*R*)-(−)-1-Cyclohexyl-2-nitroethanol 17s. Purified by chromatography eluting with hexane–diethyl ether (9:1). Enantiomeric excess (73%) was determined by HPLC (Chiralpak AD–H), hexane–*i*-PrOH 95:5, 0.7 mL/min, major enantiomer (*R*) $t_r = 21.6$, minor enantiomer (*S*) $t_r = 23.3$; $[\alpha]_D^{25} = -14.7$ (*c* 1.03, $CHCl_3$, ee 73%, obtained with ligand **11**); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.48 (dd, $J = 12.9$, 3.3 Hz, 1H), 4.41 (dd, $J = 12.9$, 8.7 Hz, 1H), 4.11–4.05 (m, 1H), 2.68 (sample, 1H), 1.84–1.75 (m, 3H), 1.70–1.58 (m, 2H), 1.50–1.37 (m, 1H), 1.28–1.05 (m, 5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 79.3 (t), 72.8 (d), 41.3 (d), 28.8 (t), 27.9 (t), 26.0 (t), 25.8 (t), 25.7 (t).

4.9.20. (*R*)-(+)-4-Methyl-1-nitro-2-pentanol 17t. Purified by chromatography eluting with hexane–diethyl ether (9:1). Enantiomeric excess (79%) was determined by HPLC (Chiralpak AD–H), hexane–*i*-PrOH 95:5, 1 mL/min, major enantiomer (*R*) $t_r = 11.2$, minor enantiomer (*S*) $t_r = 15.6$; $[\alpha]_D^{25} = +1.4$ (*c* 1.01, CH_2Cl_2, ee 79%, obtained with ligand **11**); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.43–4.33 (m, 3H), 2.41 (sample, 1H), 1.87–1.78 (m, 1H), 1.53–1.45 (m, 1H), 1.26–1.17 (m, 1H), 0.96 (d, $J = 6.6$ Hz, 3H), 0.94 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 81.0 (t), 66.9 (d), 42.4 (t), 24.3 (d), 23.1 (q), 21.7 (q).

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