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C_1-Symmetric 1,2-diaminobicyclo[2.2.2]octane ligands in Copper-catalyzed asymmetric Henry Reaction: catalyst development and DFT studies

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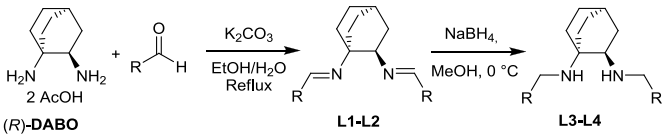
Abstract: New chiral tetra- and bidentate ligands derived from the (*R*)-1,2-diaminobicyclo[2.2.2]octane scaffold have been synthesized and the influence of ligand N,N'-substituents on the catalytic activity of their corresponding copper(II) complexes toward nitroaldol reaction have been investigated. Among them, the complex generated *in situ* by the interaction of the (*R*)-N,N'-Bis(1-naphthylmethyl)-1,2-diaminobicyclo[2.2.2]octane ligand **L10** with $Cu(OAc)_2$ proved to be the most effective for the asymmetric Henry reaction of nitromethane with various aldehydes, providing β-nitroalcohols in moderate to good yields, and enantioselectivity (up to 86%). In an attempt to rationalize the factors that control enantiodifferentiation, the most stable geometries of this C_1-symmetric bicyclic copper ligand complex, as well as plausible transition structures of the nitroaldol reaction, were investigated by DFT calculations.

Introduction

Chiral diamine ligands are widely used as catalyst precursors for quite a number of transition-metal-catalyzed asymmetric transformations.[1] Among them, the use of chiral copper complexes with chiral tetradentate and bidentate ligands have proven to be one of the most effective in the asymmetric nitroaldol (Henry) reaction of aldehydes with nitroalkanes.[2] This reaction provides the elaboration of polyfunctionalized chiral molecules. In particular, the resulting nitroaldol adducts constituted attractive building blocks to generate vicinal amino alcohol motifs often included in many natural or synthetic complex compounds.[3,4] Since the pioneering work of Shibasaki in 1992,[5] several studies on the asymmetric copper-catalyzed Henry reaction have focused on the development of chiral C_2-symmetric ligands that have often proved to possess an excellent asymmetric induction ability.[6] Thus, high stereoselectivities have been obtained using BOX-type,[6a,b,m] tetrahydrosalen (salan),[4d,6c,6h,i] diamines[6d,e,6j,k] and aminosulfonamide[6f,g] C_2-symmetric ligands, for example. Some catalytic systems based on other transition metals, such as Co- and Cr-complexes have also been developed inducing moderate to high stereoselectivity.[7] More recently chiral C_1-symmetric ligands based on unsymmetrical substitutions of previously described scaffolds[2f,8b,8d,8h,8n,8o] and on natural[8a,8g] and new synthetic systems,[8c,8e,f,8i-m,8p] have also proved to be effective in the copper-catalyzed Henry reaction. To synthesize efficient C_1-symmetric catalysts that do not possess any symmetry axis reducing the possible diastereoisomeric reaction pathways, it is important to focus on electronic and steric controlling factors in the design of new ligands.

Results and Discussion

We recently reported on the synthesis of a bicyclic C_1-symmetric chiral 1,2-diamine [(*R*)-DABO], containing a bicyclo[2.2.2]octane motif with one amine function at the bridgehead position.[9] This bridged bicyclic skeleton was recently proved to highly restrict the conformation of (*R*) and (*S*)-1-aminobicyclo[2.2.2]octane-2-carboxylic acid (ABOC) useful as potent helix inducers in homo- and mixed oligoureas,[10a] and in 1:1 or 2:1 α,β-hybrid peptides,[10b,c] or as part of α,β-peptide organocatalysts used in asymmetric aldol reactions.[11] Considering the significance of steric factors in chiral catalyst systems based on C_1-symmetric ligands, and the high constraint capacity of DABO, we investigated a series of its copper-diamine ligand derivatives for the asymmetric Henry reaction.



Scheme 1. Synthesis of the 1,2-diaminobicyclo[2.2.2]octane ligands **L1-L4**.

Synthesis of DABO tetradentate ligands, and their use in the Cu-catalyzed asymmetric Henry reaction. We first considered (*R*)-DABO as a potential precursor of chiral tetradentate ligands for the synthesis of copper salen and salan complexes. Chiral **L1** and **L2** salen ligands were prepared by condensation of the diacetate salt of (*R*)-DABO with either 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde or 2-hydroxybenzaldehyde respectively, in an ethanol/water potassium carbonate solution (Scheme 1, Figure 1). Suitable crystal obtained in ethanol by slow evaporation allowed characterization of the **L1** ligand structure by X-ray analysis (Figure S1). Reduction of **L1** and **L2** Schiff bases with sodium borohydride yielded the two corresponding **L3** and **L4** salan ligands (Scheme 1, Figure 1).

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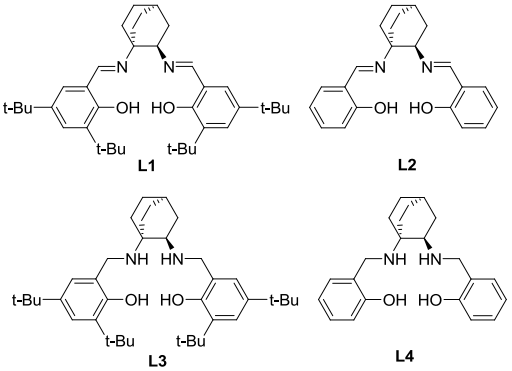
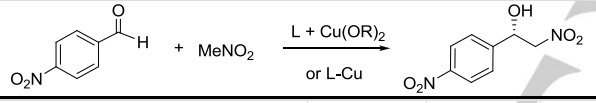


Figure 1. Tetradentate ligands **L1**-**L4**.

In first attempts, we selected as the model reaction the Henry reaction of 4-nitrobenzaldehyde with nitromethane, at room temperature, to investigate the potential of **L1-L4** ligands using either in situ formation of the copper-ligand complex in methanol or the preformed stable Copper complex in toluene (Table 1). Stable copper(II) salen and salan complexes (**L1**-Cu, **L2**-Cu, **L3**-Cu and **L4**-Cu) were obtained after treatment of **L1-L4** ligands with copper(II) acetate in refluxing methanol. A crystal structure of the **L1**-Cu complex was obtained that revealed the almost planar structure of the aromatic rings with the expected square planar geometry around the copper center (Figures S2 and S3).

Table 1. Tetradentate ligand's evaluation in the Henry reaction.



Entry	Catalyst	Solvent	Time (d)[b]	Yield[c](%)	ee (%)[d]
1	**L1**+Cu(OAc)$_2$	MeOH	10[e]	13	0
2	**L1**-Cu	Toluene	10[e]	16	0
3	**L2**+Cu(OAc)$_2$	MeOH	10[e]	60	0
4	**L2**-Cu	Toluene	10[e]	58	0
5	**L3**+Cu(OAc)$_2$	MeOH	5	68	0
6	**L3**-Cu	Toluene	7	60	60
7	**L4**+Cu(OAc)$_2$	MeOH	4	80	0
8	**L4**-Cu	Toluene	6	78	5

[a] Reactions were carried out on a 0.15 mmol scale of 4-nitrobenzaldehyde with 10 equiv of nitromethane at room temperature, and 10 mol % of copper salt. [b] The reaction time corresponds to complete conversion, except mention note e. [c] Isolated yield. [d] Enantiomeric excess was determined by chiral HPLC (OD-H, see SI). [e] Incomplete conversion.

Among the **L1-L4** copper complexes, only the preformed **L3**-Cu complex was found as a potential catalyst for the asymmetric Henry reaction (Table 1, entry 6). Indeed, when using the **L1-L2** salen ligands, an incomplete conversion was observed even after 10 days, with formation of the racemic nitroaldol product in all cases (Table 1, entries 2-4). For **L3-L4** salan ligands, a full conversion was obtained in all cases after 4-7 days (Table 1, entries 5-8). However, the use of the preformed copper complex and the presence of *t*-butyl groups on the salan aromatic ring, were essential to afford an acceptable enantioselectivity (Table 1, entry 6). A similar superiority of copper salan catalysts over their corresponding salen derivatives in terms of both the conversion rate and the stereoselectivity has already been described,[4d,6c,6h,i] and has been rationalized in terms of increased N-basicity and backbone flexibility around the copper, favouring the reaction rate and the induction ability. Optimization of the reaction conditions has been investigated using the most efficient **L3**-Cu complex (Table 2). The use of isopropanol instead of toluene at room temperature induced an increase in the selectivity of the reaction without increasing the reaction rate (Table 2, entry 1) that prevented the use of a lower temperature. At 45°C, although the reaction rate was improved, the induced stereoselectivity was strongly affected. The reaction rate was also improved by adding a small amount of organic base to the reaction mixture. However, under these conditions, no increase in stereoselectivity was observed (Table 2, entries 3-4) except when using the weak tertiary N-methyl morpholine base. In this case, the stereoselectivity was slightly increased (Table 2, entry 5). When the toluene complex of copper(I) triflate[12] was used for the *in situ* generation of the chiral copper catalyst, a deleterious effect on the reaction rate without any enhancement of the stereoselectivity was observed, affording the nitroaldol product in only 17-25% yield with a moderate enantioselectivity after 14 days (Table 2, entries 6 and 7).

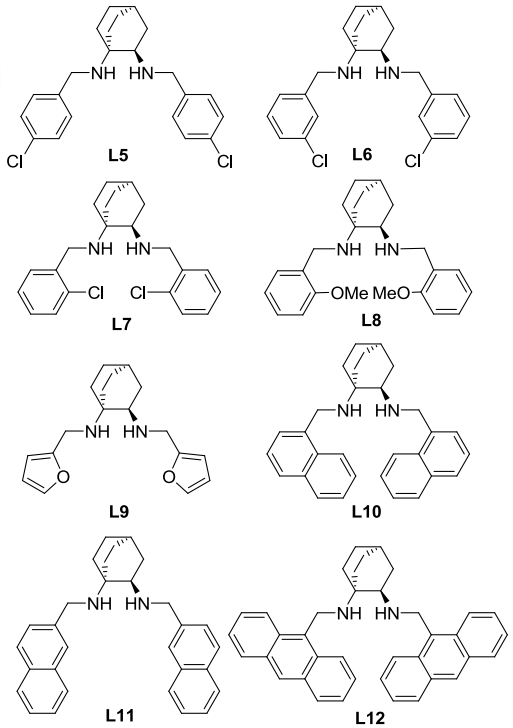


Figure 2. Bidentate ligands **L5**-**L12**.

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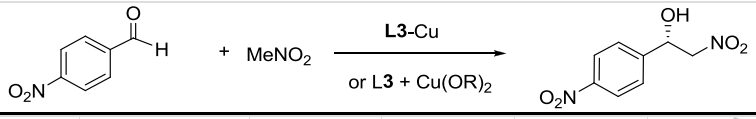
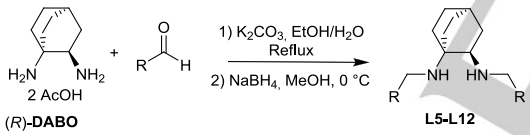
Table 2. Effect of solvent and base in the asymmetric Henry reaction catalysed by **L3**-Cu or **L3**+$(CuOTf)_2$.Tol.



Entry	Catalyst	Base	Solvent	T (°C)	Time (d)[b]	Yield[c] (%)	ee (%)[d]
1	**L3**-Cu	-	*i*-PrOH	RT	7	88	69
2	**L3**-Cu	-	*i*-PrOH	45°C	2	82	12
3	**L3**-Cu	Py 0,1 mol%	*i*-PrOH	RT	7	60	56
4	**L3**-Cu	Py 1 mol%	*i*-PrOH	RT	3	81	60
5	**L3**-Cu	NMM 0.5 mol%	*i*-PrOH	RT	4	73	70
6	**L3**+$(CuOTf)_2$.Tol	-	*i*-PrOH	RT	14[e]	25	60
7	**L3**+$(CuOTf)_2$.Tol	-	MeOH	45°C	14[e]	17	60

[a], [b], [c], [d] and [e] see Table 1 (notes a, b, c, d and e respectively).

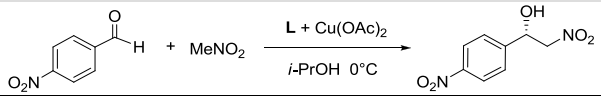
Synthesis of DABO bidentate ligands, and their used in the Cu-catalyzed asymmetric Henry reaction. The first moderate results of this study, and the previous successful application of bidentate diamine ligands in the copper catalyzed asymmetric Henry reaction,[6d,6i,j,8i,8h-j,8l,m] prompted us to investigated the preparation of bidentate ligands using (*R*)-DABO and various *ortho*-, *meta*- or *para*-monosubstituted aromatic moieties, as well as hetero or fused aromatic moieties (Figure 2).



Scheme 2. Synthesis of the 1,2-diaminobicyclo[2.2.2]octane ligands **L5-L12**.

Compounds **L5-L12** were easily prepared by a two-step synthesis starting from (*R*)-DABO diacetate and the selected aldehyde, without isolation of the diimine intermediates (Scheme 2). **L5**-**L12** ligand complexes with $Cu(OAc)_2$ generated *in situ* were evaluated in the Henry reaction of 4-nitrobenzaldehyde with nitromethane, in *i*-PrOH at 0°C, to define the influence of both the electronic nature and the size of the aromatic moieties in the diamine ligands (Table 3). As a general remark, **L5**-**L12** ligand copper complexes were globally more efficient catalysts than the previously tested complexes derived from **L1**-**L4** ligands, in terms of yield and induced stereoselectivity of the Henry reaction. Among them, **L5** ligand with a *para*-chloro substituent on the aromatic moiety allowed a large increased in the reaction rate (Table 3, entry 1). On the other hand, when the chlorine atom was closer to the copper, in both *meta* or *ortho*-position of the aromatic moiety increasing the steric hindrance around the metal, the stereoselectivity was slightly increased with however a decrease of the reaction rate (Table 3, entries 2 and 3). A comparison between complexes derived from **L7** and **L8** ligands also demonstrated that a bulkier *ortho* substituent, led to a slower reaction rate without improving stereoselectivity (Table 3, entries 3 and 4). Introduction of heteroaromatic moieties (ligand **L9**), resulting in two additional heteroatoms close to the metal in the complex without adding steric constraints, had a beneficial effect since a total conversion was observed after 12 hours with a slightly increased enantiomeric excess (Table 3, entry 5). In terms of enantioselectivity, the best result was obtained when the **L10** ligand copper-complex was used as catalyst (Table 3, entry 6). The two fused aromatic pendants of **L10** appeared to play an important positive role in the transition state complex, which was not the case when using the two **L11** and **L12** ligands that also possess fused aromatic rings (Table 3, entries 7 and 8).

Table 3. Bidentate ligand's evaluation in the asymmetric Henry reaction.



Entry	Ligand	Time (h)[b]	Yield[c](%)	ee (%)[d]
1	**L5**	7	66	50
2	**L6**	48[e]	50	56
3	**L7**	60	78	64
4	**L8**	240	72	64
5	**L9**	12	77	72
6	**L10**	72	95	80
7	**L11**	60	74	64
8	**L12**	48[e]	66	30

[a], [b], [c], [d] and [e] see Table 1 (notes a, b, c, d and e respectively).

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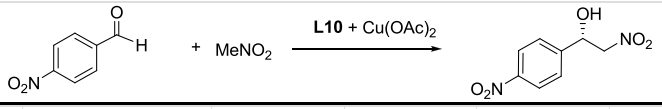
Table 4. Effect of solvents and bases in the asymmetric Henry reaction catalysed by **L10/**$Cu(OAc)_2$.



Entry	Solvent	T (°C)	Time (h)[b]	Yield[c] (%)	ee (%)[d]
1	EtOH	rt	1.5	81	60
2	EtOH	0	36	77	42
3	*i*-PrOH	rt	12	90	68
4	*i*-PrOH	0	72	95	80
5	*n*-BuOH	0	24	67	33
6	*t*-BuOH	rt	2	80	68
7	Toluene	0	72	70	52
8	CH_2Cl_2	0	96	72	50
9	THF	0	96	70	75
10	CH_3CN	0	96	60	42
11	Et_2O	0	168[e]	20	70

[a], [b], [c]' [d] and [e] see Table 1 notes a, b, c, d and e respectively.

Optimization of the experimental reaction conditions. To find optimized reaction conditions using the most efficient chiral **L10** ligand, several experiments were carried out involving modification of the solvent, the reaction temperature, the copper salt, and testing various base additives. The different tested alcohols (EtOH, *i*-PrOH, *t*-BuOH) as solvents afforded good yields and comparable enantiomeric excesses when the reaction was performed at room temperature (Table 4, entries 1, 3 and 6). Lowering the temperature to 0° C, linear alcohols such as EtOH and n-BuOH resulted in a decrease in both the reaction rate, the stereoselectivity and the yield (Table 4, entries 2 and 5). When the reaction was carried out in aprotic solvents, at 0 °C, moderate enantioselectivities and yields were generally obtained that could be mostly compared to linear alcohols. It can be noted furthermore that higher enantioselectivities were observed when using oxygenated aprotic solvent such as THF and diethyl ether (Table 4, entries 9 and 11). Finally, branched *i*-PrOH proved to be the most suitable solvent at 0 ° C for this reaction.

Several divalent copper salts were then evaluated in combination with **L10** ligand in *i*-PrOH at 0°C (table 5). The presence of water in the copper diacetate salt was not beneficial for the reaction (Table 5, entry 2) and could compare with the use of the copper acetyl acetonate salt (Table 5, entry 3). Likewise, copper(II) triflate was not effective affording only 5% yield after 96 hours (Table 5, entry 4). As a consequence of the high enantiomeric excess (88% ee) but incomplete conversion observed when using $CuCl_2$, $2H_2O$, further optimization of the reaction conditions have been investigated with this copper salt. Although improvement in the conversion rate occurred by changing the solvent, the temperature and by using organic bases as additives, the enantiomeric excess obtained was always lower than when obtained using copper acetate (Table 5, entries 6-15). Finally, the use of copper(I) salts, such as CuCl or $(CuOTf)_2$.tol, only afforded the racemic nitroaldol product (Table 5, entries 16 and 17).

Aldehyde scope of the L10/Cu(OAC)$_2$ system. On the basis of the optimized reaction parameters, the **L10**-$Cu(OAc)_2$ catalyst was then applied to the enantioselective Henry reaction using various aromatic aldehydes and nitromethane (Table 6). The first general observation was that both the conversion rate and the enantioselectivity were dependent on electronic and steric properties of the substituents on the aldehyde aromatic ring. The reaction of nitromethane with benzaldehydes bearing one electron-withdrawing substituent in 2- and 3-position proceeded faster than with benzaldehyde substituted in 4-position (Table 6, entries 2, 4-8). In term of stereoselectivity, divergent results were observed depending on the nature/position of the electron-withdrawing substituent. Higher enantiomeric excesses were obtained with the 2- and 4-nitro substituted aldehydes (Table 6, entries 2, 3 and 5) while the best results were obtained with the 3- and 4-chloro derivatives (Table 6, entries 7 and 8). The use of 4-trifluorobenzaldehyde led to the full conversion into the nitroaldol product faster than the 4-substituted aldehydes but with a slightly lower enantiomeric excess (Table 6, entry 9). Curiously, aromatic aldehydes bearing two electron-withdrawing groups at 2,4- and 3,4-position of aromatic ring did not exhibit any difference in reactivity yielding both good conversion rates and enantioselectivities (Table 6, entries 11 and 12).

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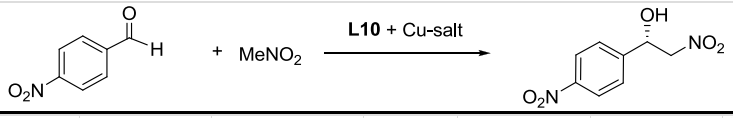
Table 5. Effect of varying metal ion source, solvent, temperature and base in the asymmetric Henry reaction catalysed by **L10**.



Entry	Copper salt	Solvent	Base (mol%)	T (°C)	Time (h)[b]	Yield[c] (%)	ee (%)[d]
1	$Cu(OAc)_2$	*i*-PrOH	-	0	72	95	80
2	$Cu(OAc)_2$, H_2O	*i*-PrOH	-	0	96	95	72
3	$Cu(acac)_2$	*i*-PrOH	-	0	96	91	60
4	$Cu(OTf)_2$	*i*-PrOH	-	0	96[e]	5	nd
5	$CuCl_2$, $2H_2O$	*i*-PrOH	-	0	96[e]	33	88
6	$CuCl_2$, $2H_2O$	EtOH	-	rt	96[e]	traces	nd
7	$CuCl_2$, $2H_2O$	THF	-	rt	84[e]	50	46
8	$CuCl_2$, $2H_2O$	*i*-PrOH	Pyridine (10)	rt	12	75	44
9	$CuCl_2$, $2H_2O$	*i*-PrOH	Pyridine (1)	rt	12	85	56
10	$CuCl_2$, $2H_2O$	*i*-PrOH	NMM (10)	rt	12	85	66
11	$CuCl_2$, $2H_2O$	*i*-PrOH	NMM (1)	rt	96	87	70
12	$CuCl_2$, $2H_2O$	*i*-PrOH	NMM (1)	0	96	94	70
13	$CuCl_2$, $2H_2O$	*i*-PrOH	AcONa (20)	0	48	91	71
14	$CuCl_2$, $2H_2O$	*i*-PrOH	AcONa (10)	0	96	82	52
15	$CuCl_2$, $2H_2O$	*i*-PrOH	AcONa (1)	0	240[e]	38	68
16	CuCl	*i*-PrOH	-	0	12	54	0
17	$(CuOTf)_2$, tol	*i*-PrOH	-	0	96[e]	23	0

[a], [b], [c], [d] and [e] see Table 1 (notes a, b, c, d and e respectively).

A drastic decrease in the conversion rate was observed for aromatic aldehydes bearing electron-donating groups in both 2,4- and 3,5-position, affording incomplete conversion after 96 hours, with low and moderate enantiomeric excess respectively (Table 6, entries 13 and 14). In an attempt to increase the stereoselectivity, experiments involving the two most reactive aldehydes (R = 2-$NO_2C_6H_4$ and 4-$CF_3C_6H_4$) were carried out at lower temperature (-20°C) (Table 6, entries 3 and 10). In these conditions, full conversion was observed after 60 hours, instead of 24 hours at 0°C, with no positive effect on the enantiomeric excess. The Henry reaction of the two 1- or 2-fused aromatic ring aldehydes with nitromethane resulted in similar reactivity and stereoselectivity, indicating no significant effect of the steric hindrance of the substrate (Table 6, entries 15 and 16). Finally, the reaction of furyl aldehyde and of some aliphatic aldehydes with nitromethane was investigated under the same experimental conditions, affording low to moderate yields of the corresponding nitroaldols, with stereoselectivities in a range of those of the aromatic analogues (Table 6, entries 17-20). Interestingly, it can be noted that in all cases investigated in this study, and using the *in situ* generated copper (*R*)-**L10** complex, the nucleophilic addition of the nitromethane proceeded mainly from the *Re* face of the aldehydes affording the corresponding (*S*) nitro alcohols with moderate to high enantioselectivities (up to 86%).

DFT calculations. Optimized geometries of the L3-Cu and L10-Cu(OAc)$_2$ complexes. Suitable crystals of the **L3**-Cu and **L10**-$Cu(OAc)_2$ complexes could not be obtained for X-ray analysis. However, to gain information about these complexes, their geometries were optimized at the DFT level of theory by employing the B3LYP functional[13] (completed with Grimme D3 dispersion correction[14]), and the 6-311G(d,p) basis set. The optimized **L3**-Cu conformation (figure S4 A and B) revealed a non-coplanar position of the aromatic rings, a slightly distorted square planar geometry around the metal, and an orientation toward opposite directions of the two NH groups. Compared to the **L1**-Cu crystal structure, these structural outcomes showed that **L3**-Cu complex possessed a more hindered coordination

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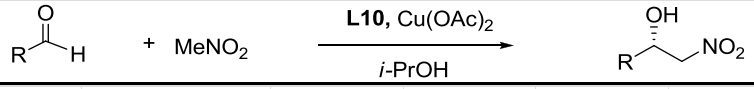
Table 6. Aldehyde scope of the **L10**/$Cu(OAC)_2$ system.



Entry	R	T (°C)	Time (h)[b]	Yield[c] (%)	ee (%)[d]
1	C_6H_5	0	96	50	60
2	2-$NO_2C_6H_4$	0	24	78	82
3	2-$NO_2C_6H_4$	-20	60	85	74
4	3-$NO_2C_6H_4$	0	24	81	50
5	4-$NO_2C_6H_4$	0	72	95	80
6	2-ClC_6H_4	0	36	66	66
7	3-ClC_6H_4	0	36	70	84
8	4-ClC_6H_4	0	96	73	86
9	4-$CF_3C_6H_4$	0	24	82	75
10	4-$CF_3C_6H_4$	-20	60	74	48
11	2,4-diClC_6H_3	0	10	87	72
12	3,4-diClC_6H_3	0	10	87	72
13	2,4-di$MeOC_6H_3$	0	96[e]	12	10
14	3,5-di$MeOC_6H_3$	0	96[e]	50	66
15	1-naphtyl	0	96	75	73
16	2-naphtyl	0	96	75	69
17	2-furyl	0	48	62	70
18	*t*-Bu	0	48[f]	45	82
19	*n*-hexyl	0	48[g]	23	80
20	cyclohexyl	0	48	75	80

[a], [b], [c]' [d] and [e] see Table 1 (notes a, b, c, d and e respectively).

sphere that could be at the origin of the highest observed selectivity (figure S4 C).

In the case of **L10**-$Cu(OAc)_2$, various conformations (Table S2), were obtained due to the possible orientations of the naphthyl groups and the positions of the acetate groups. In each case, these acetate groups were found to be stabilized by hydrogen bonding with NH hydrogen atoms located in opposite positions, in addition to their coordination to the metal (Figures S5-S11). The most stable **L10**-$Cu(OAc)_2$-6 conformation (Figure S10) possessed the four atoms around the metal in a slightly deformed square plane, and the two naphthyl groups located on both side of the bicycle almost perpendicularly to the square plane.

DFT calculation. Stereochemical outcome of the nitroaldol reaction. To rationalize asymmetric induction transfer from **L10** chiral copper complex to the nitroaldol adduct, theoretical studies of transition structures were also undertaken by means of DFT calculations. Based on the modelled complex **L10**-$Cu(OAc)_2$-6 and on the previously reported steric and electronic considerations,[6a] various conformations/configurations of **L10**-Cu, one acetate group, the 4-nitrobenzaldehyde, and a nitronate anion, were considered. Various starting geometries leading to both *R* and *S* absolute configurations of the product were considered.

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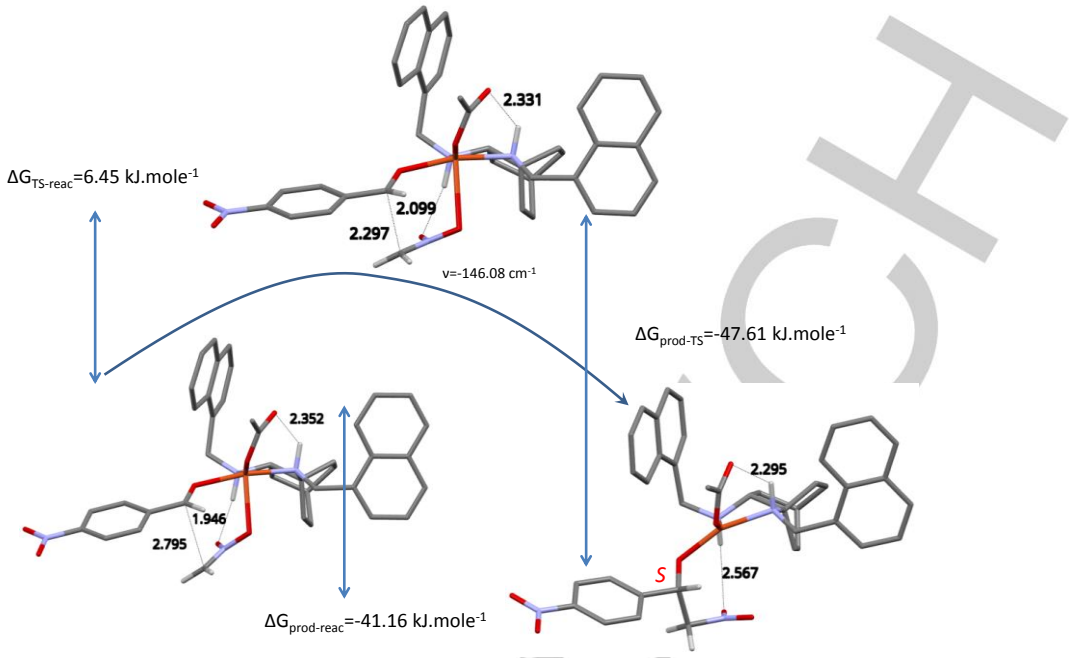

Figure 3. Optimized transition structures (reactants, transition state and products) of the **L10**-Cu(OAc, 4-nitrobenzaldehyde, nitronate anion) complex **Cplx5**. NH···O hydrogen bond and contacts, and $C_{aldeh.}\cdots C_{MeNO2}$ distances are indicated in Å. Most of the hydrogen atoms were omitted for clarity.

As for previous calculations, the B3LYP functional completed with Grimme D3 dispersion correction[14] was used with the 6-311G(d,p) basis set. The solvent effects (*i*-PrOH) were taken into account through the PCM model.[15] Frequency calculations confirmed the nature of the transition state (TS), which was characterized with only one imaginary frequency. Then, reactants and products were fully optimized starting from the TS geometry (slightly deformed according to the imaginary frequency normal mode). Frequency calculations on these last fully optimized geometry proved that true energy minima were obtained. Table S3 summarizes the obtained energies and energy barriers for the optimized transition structures (reactants, transition state and products) of the **L10**-Cu(OAc, 4-nitrobenzaldehyde, nitronate anion) complexes **Cplx1**-**Cplx9**.

As it can be seen from Table S3, the two most stable reactant complexes (**Cplx7** and **Cplx8**) were those leading to *R* products. However, these two conformations were associated to high-energy barriers toward the transition states (~45kJ.mol^{-1}) and the products formed were either destabilised (**Cplx8**) or moderately stabilized (**Cplx7**). The next two most stable reactants, about 10kJ.mol^{-1} less stable (**Cplx2**, and **Cplx5**) led to *S* products and were associated to most stable transition states (**Cplx5**), and corresponding products were the most stabilized. Thus, the lowest energy barrier toward transition state was associated to the *S* configuration (**Cplx5**), being only of 6.45kJ.mole^{-1} (Figures 3 and S13-S18). These calculations supported the preferential formation of *S* products with an approach of the nitronate by the *Re* face of the aldehyde, in agreement with the experimental results.

The four transition state structures having the lowest energy barriers (**Cplx5**, **Cplx4**, **Cplx1** and **Cplx2**; ΔG=6-17kJ.mol^{-1}) were characterized by the largest $C_{ald.}\cdot\cdot C_{MeNO2}$ interatomic distances (2.2 – 2.3Å), associated to the smallest Cu ·· $O_{ald.}$ bond distances (1.99 – 2.02 Å) (Tables S4-S6). By comparison, the other structures, having larger energy barriers (ΔG=28-63kJ.mol^{-1}), showed these two distances shorter and larger by about 0.2 – 0.3 Å, respectively. Thus, activation of the aldehyde carbon atom to favor the C-C bond formation was triggered by stabilization of the oxygen atom negative charge, and by the proximity of the latter with the central copper cation. Moreover, these most stable transition states were also stabilized by hydrogen bonding involving the NH diamine groups of the **L10** ligand, toward the uncoordinated oxygen atoms of the acetate and nitronate anions (Table S3). More specifically, stabilization of the nitronate by hydrogen bonding with **L10** appeared as a key characteristic since among the high energy barrier structure only one had such a hydrogen bond, which is rather long and thus not so stabilizing (**Cplx7**; 2.524 Å; 117.2°).

Conclusions

In conclusion, the synthesis of several chiral salen, salan and diamine ligands derived from the 1,2-diaminobicyclo[2.2.2]octane scaffold, as well as the catalytic activity of their corresponding copper(II) complexes toward the reaction of nitromethane with various aldehydes, have been described. It was found that the most efficient catalytic system involves the N,N'-bis(1-naphthylmethyl)diamine derivative to

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afford the corresponding β-nitroalcohols in moderate to good yield and enantioselectivity. In agreement with the experimental results, DFT calculations support the preferential formation of the S product with transfer of the nitronate anion to the *Re* face of the aldehyde.

Experimental Section

General experimental details, analytical data of nitroalcohol adducts, copies of ^{1}H, ^{13}C NMR spectra and HRMS analysis can be found in the Supporting Information, as well as Tables and Figures of DFT structural calculations. CCDC 1577508-1577509 contain the crystal structures of **L1** and **L1**-Cu. Data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

General procedure A for the synthesis of Schiff bases L1 and L2 (*R*)-1,2-diaminobicyclo[2.2.2]octane diacetate (R)-DABO (1 eq., 100 mg, 0.38 mmol) and potassium carbonate (2 eq., 106 mg, 0.76 mmol) were dissolved in a mixture of distilled water and ethanol (H_2O/EtOH : 0.6/2 mL), and the mixture was heated to reflux. A solution of the aldehyde (2 eq., 0.76 mmol) in ethanol (1 mL) was added dropwise with a syringe, and the mixture was stirred at reflux for 2 hours. The reaction was then cooled to 0°C and quenched with cold distilled water, leading to precipitation of the product. The precipitate was filtered and washed with cold ethanol to give the corresponding Schiff bases.

General procedure B for the synthesis of preformed copper complex L1-Cu, L2-Cu

The ligand (**L1** or **L2**) (1 eq., 0.018 mmol) was dissolved in methanol (2 mL). Copper diacetate (2 eq., 6.4 mg, 0.036 mmol) was added, and the solution was heated to reflux for 15 hours. The solution was concentrated under reduced pressure, dissolved with CH_2Cl_2 and filtered. The filtrate was concentrated under reduced pressure to give the corresponding copper complex.

General procedure C for the synthesis of preformed copper complex L3-Cu and L4-Cu

The ligand (**L3** or **L4**) (1eq., 0.07 mmol) was dissolved in ethanol (2 mL). Copper diacetate (2 eq., 12.4 mg, 0.14 mmol) was added, and the solution was stirred at room temperature overnight. The solution was concentrated under reduced pressure and the crude was purified by column chromatography on silica gel (elution gradient CH_2Cl_2 to CH_2Cl_2/MeOH, 8:2) yielding the expected copper complex.

General procedure D for the synthesis of ligands L3-L12

(*R*)-1,2-diaminobicyclo[2.2.2]octane diacetate (R)-DABO (1 eq., 40 mg, 0.15 mmol) and potassium carbonate (2 eq., 42.5 mg, 0.30 mmol) were dissolved in distilled water (0.2 mL), and ethanol (0.6 mL) was added. The mixture was heated to reflux. A solution of aldehyde (2 eq.) in ethanol (0.75 M) was added dropwise with a syringe and the mixture was stirred at reflux for 12 hours. The reaction was then cooled to 0°C, diluted with CH_2Cl_2 and quenched with cold distilled water. The product was extracted with CH_2Cl_2, the combined organic layers were washed with water, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was then dissolved in methanol (2 mL) at 0 °C. $NaBH_4$ (3 eq., 17.6 mg, 45 mmol) was added to the reaction mixture in 3 portions (1 every 10 min). Stirring at this temperature was maintained until gas evaporation was stopped and the mixture was allowed to reach room temperature. After complete conversion monitored by HPLC, the reaction media was quenched with distilled water, and all the volatiles were evaporated. The resulting aqueous mixture was extracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude was purified by column chromatography on silica gel (elution gradient CH_2Cl_2 to CH_2Cl_2/MeOH, 95:5) yielding the expected ligand.

(*R*)-Bis(3,5-di-*tert*-butyl-2-hydroxybenzylidene)-1,2-diaminobicyclo[2.2.2]octane L1 was obtained from 3,5-Di-*tert*-butyl-2-hydroxybenzaldehyde as yellow crystals in 91% yield according to the general procedure A. M.p. 176-178 °C; MS (ASAP): m/z = 573.4 $[M+H]^+$; $[\alpha]_D^{25}$ = +205.7°(c = 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.24 (s, 18H, 6CH_3), 1.38 (s, 9H, 3CH_3), 1.42 (s, 9H, 3CH_3), 1.71-1.86 (m, 7H, 3CH_2 and 4-*H*), 1.92-2.06 (m, 2H, CH_2), 2.20 (m, 2H, CH_2), 3.59 (d, *J* = 8.9 Hz, 1H, 2-*H*), 7.00 (dd, *J* = 7.3 Hz and 2.3 Hz, 2H, Ar-*H*), 7.30 (dd, *J* = 7.9 Hz and 2.3 Hz, 2H, Ar-*H*), 8.23 (s, 1H, 1-N=C*H*), 8.29 (s, 1H, 2-N=C*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 24.9 (*C*H_2), 25.1 (4-*C*H), 26.1 and 26.3 (*C*H_2), 29.6 and 31.6 (*C*H_3), 32.6 (*C*H_2), 34.2 and 35.1 (tBu-*C*), 36.3 (*C*H_2), 60.1 (1-*C*), 71.4 (2-*C*H), 118.0 and 118.2 (Ar-*C*), 126.2 and 126.9 (Ar-*C*H), 136.4 and 140.0 (Ar-*C*tBu), 158.1 and 158.6 (Ar-*C*OH), 163.1 and 165.9 (N=*C*H); HRMS (ESI-TOF) m/z $[M+H]^+$ calcd. for $C_{38}H_{57}N_2O_2$ 573.4420, found. 573.4422.

(*R*)-Bis(2-hydroxybenzylidene)-1,2-diaminobicyclo[2.2.2]octane L2 was obtained from 2-hydroxybenzaldehyde as yellow crystals in 80% yield according to the general procedure A. M.p. 88-90 °C; $[\alpha]_D^{25}$ = +4.2°(c = 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.63-2.01 (m, 9H, 3CH_2, *H*CH, 4-C*H*, 3-*H*CH); 2.15-2.26 (m, 2H, *H*CH, 3-*H*CH), 3.56, (m, 1H, 2-C*H*), 6.75-6.91 (m, 4H, Ar-*H*), 7.12-7.28 (m, 4H, Ar-*H*), 8.18 (s, 1H, 1-N=C*H*), 8.22 (s, 1H, 2-N=C*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 24.6 (*C*H_2), 25.0 (4-*C*H), 26.0, 26.1 and 32.5 (*C*H_2), 36.3 (3-*C*H_2), 60.4 (1-*C*), 71.4 (2-*C*H), 116.9, 117.1 and 118.5 (Ar-*C*H), 118.8 and 118.9 (Ar-*C*H, Ar-*C*), 131.7 and 132.3 (Ar-*C*H), 161.2 and 161.6 (Ar-*C*OH), 162.0 and 164.5 (N=*C*H), HRMS (ESI-TOF) m/z $[M+H]^+$ calcd. for $C_{22}H_{25}N_2O_2$ 349.1916, found 349.1913.

(*R*)-N,N'-Bis(3,5-di-*tert*-butyl-2-hydroxybenzy)-1,2-diaminobicyclo[2.2.2]octane L3 was obtained from 3,5-Di-*tert*-butyl-2-hydroxybenzaldehyde as a colourless oil in 81% yield according to the general procedure D. t_R (HPLC) column A, gradient A = 3.50 min; MS (ESI): m/z = 219.32 [4-ditertbutyl-6-methylphenol+H]$^+$, 359.3 [M-(2,4-di-*tert*-butyl-6-methylphenol)+H]$^+$, 577.3 $[M+H]^+$; $[\alpha]_D^{25}$ = -10.4°(c = 1.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.27 and 1.29 (2s, 18H, 6CH_3), 1.39 (s, 18H, 6CH_3), 1.64-1.75 (m, 10H, 4CH_2, 4-C*H*, 3-*H*CH), 2.02 (m, 1H, 3-*H*CH), 2.95 (s, 1H, 2-C*H*), 3.92-3.75 (m, 3H, CH_2N, *H*CHN), 4.08 (d, *J* = 13.2 Hz, 1H, *H*CHN), 6.90 (br d, J = 2.4 Hz, 2H, Ar-*H*), 7.21 (br d, J = 2.4 Hz, 1H, Ar-*H*), 7.25 (m, 1H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 24.5 (4-*C*H), 25.6, 26.0, 26.2 and 29.1 (*C*H_2), 29.7 (*C*H_3), 31.7 (*C*H_3), 34.2 (3-*C*H_2), 34.9 and 35.0 (*C*-tBu), 45.5 (1-N*C*H_2), 51.0 (2-N*C*H_2), 53.6 (1-*C*), 55.8 (2-*C*H), 122.9, 123.0 and 123.2 (Ar-*C*H), 136.2 (Ar-*C*), 140.8 (Ar-*C*tBu), 154.4 (Ar-*C*OH); HRMS (ESI-TOF) m/z $[M+H]^+$ calcd. for $C_{38}H_{61}N_2O_2$ 577.4733, found 577.4739.

(*R*)-N,N'-Bis(2-hydroxybenzyl)-1,2-diaminobicyclo[2.2.2]octane L4 was obtained from 2-hydroxybenzaldehyde as a colourless oil in 66% yield according to the general procedure D. t_R (HPLC) column A, gradient A = 1.84 min; MS (ESI): m/z =141.3 [M-2(2-methylphenol)+H]$^+$, 247.2 [M-(2-methylphenol)+H]$^+$, 353.2 $[M+H]^+$; $[\alpha]_D^{25}$ = -24.1°(c = 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.60-1.74 (m, 10H, 4 CH_2, 3-*H*CH, 4-C*H*); 2.00 (t, J_1 = J_2 = 11.4 Hz, 1H, 3-*H*CH), 2.85 (d, *J* = 9.4 Hz, 1H, 2-C*H*), 3.72 (d, *J* = 13.7 Hz, 1H, 2-N*H*CH), 3.76 (d, *J* = 13.9 Hz, 1H, 1-N*H*CH), 3.85 (d, *J* = 13.9 Hz, 1H, 1-N*H*CH), 4.11 (d, *J* = 13.7 Hz, 1H, 2-N*H*CH), 6.75-6.87 (m, 4H, Ar-*H*), 6.95 (d, *J* = 7.0 Hz, 1H, Ar-*H*), 7.01 (d, *J* = 7.0 Hz, 1H, Ar-*H*), 7.13-7.21 (m, 2H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) =24.5 (4-CH), 25.7, 26.0, 26.4 and 29.1 (*C*H_2), 34.8 (3-*C*H_2), 44.9 (N-*C*H_2), 49.8 (N-*C*H_2), 53.8 (1-*C*), 55.4 (2-*C*H), 116.6, 116.7 and 119.4 (Ar-*C*H), 122.8, 123.6 (Ar-*C*), 128.4, 128.8, 128.9 and 129.2 (Ar-*C*H), 158.0 and 158.1 (Ar-*C*OH); HRMS (ESI-TOF) m/z $[M+H]^+$ calcd. for $C_{22}H_{29}N_2O_2$ 353.2229, found 353.2227.

Preformed copper complex L1-Cu was obtained as black cube shape crystals after recrystallization from CH_2Cl_2/MeOH (10 mg, 90 % yield) following the general procedure B. M.p. >200 °C; MS (ASAP): m/z = 634.36 $[M+H]^+$; FT-IR (neat) : 2943, 2905, 2864, 1608, 1525, 1463, 1423, 1384, 1357, 1328, 1253, 1169, 1077, 1021, 811, 788, 742.

Preformed copper complex L2-Cu was obtained as a purple powder (7 mg, 95% yield) following the general procedure B. M.p. >200 °C; MS (ASAP): m/z = 410.11 $[M+H]^+$; FT-IR (neat) : 2926, 2913, 2864, 1611, 1600, 1531, 1443, 1387, 1346, 1321, 1201, 1142, 1066, 1030, 909, 849, 751, 736.

Preformed copper complex L3-Cu was obtained as a dark green solid (44 mg, quant.) following the general procedure C. M.p. >200 °C; MS (ASAP): m/z = 638.36 $[M+H]^+$; FT-IR (neat) : 2945, 2901, 2863, 1618, 1461, 1437, 1412, 1358, 1296, 1262, 1234, 1199, 1168, 872, 827, 735.

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Preformed copper complex L4-Cu was obtained as a dark green solid following the general procedure C. M.p. >200 °C; MS (ASAP): m/z = 414.11 $[M+H]^+$; FT-IR (neat) : 2920, 2863, 1597, 1562, 1481, 1446, 1394, 1256, 1111, 1011, 877, 755.

(*R*)-N,N'-Bis(4-chlorobenzyl)-1,2-diaminobicyclo[2.2.2]octane L5 was obtained from 4-chlorobenzaldehyde as a colourless oil in 66% yield according to the general procedure D. t_R (HPLC) column A, gradient A = 2.50 min; MS (ESI): m/z = 265.3 [M-(4-chlorotoluene)+H]$^+$, 389.3 $[M+H]^+$; $[\alpha]_D^{25}$ = -16.9°(c = 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.34-1.40 (m, 1H, *H*CH), 1.48-1.51 (m, 1H, 3-*H*CH), 1.56-1.78 (m, 8H, *H*CH, 4-C*H*, 3CH_2), 1.87-1.92 (m, 1H, 3-*H*CH), 2.15 (br.s, 2H, 2N*H*), 2.64 (m, 1H, 2-C*H*), 3.36 (d, *J* = 13.0 Hz, 1H, 1-N*H*CH), 3.56 (d, *J* = 13.6 Hz, 1H, 2-N*H*CH), 3.57 (d, *J* = 13.0 Hz, 1H, 1-N*H*CH), 3.88 (d, *J* = 13.6 Hz, 1H, 2-N*H*CH), 7.19-7.28 (m, 8H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 24.8 (4-*C*H), 26.3, 26.4, 26.8 and 29.7 (CH_2), 35.3 (3-CH_2), 44.9 (1-NCH_2), 50.5 (2-NCH_2), 53.2 (1-*C*), 54.9 (2-*C*H), 128.6, 129.4 and 129.8 (Ar-*C*H), 132.6 and 132.7 (Ar-*C*Cl), 139.3 and 139.8 (Ar-*C*); HRMS (ESI-TOF) m/z $[M+H]^+$ calcd. for $C_{22}H_{27}N_2Cl_2$ 389.1551, found. 389.1552.

(*R*)-N,N'-Bis(3-chlorobenzyl)-1,2-diaminobicyclo[2.2.2]octane L6 was obtained from 3-chlorobenzaldehyde as a colourless oil in 81% yield according to the general procedure D. t_R (HPLC) column A, gradient A = 2.49 min; MS (ESI): m/z = 265.2 [M-(4-chlorotoluene)+H]$^+$, 389.1 $[M+H]^+$;
$[\alpha]_D^{25}$ = -14.2°(c = 1.3, $CHCl_3$) ; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.38-1.80 (m, 10H, 4CH_2, 3-HC*H*, 4-C*H*), 1.89-1.95 (m, 1H, 3- HC*H*), 2.02 (br.s, 2H, 2N*H*), 2.68 (m, 1H, 2-C*H*), 3.38(d, J_1 = 13.8 Hz, 1H, 1-NHC*H*), 3.60 (d, $J_1 = J_2$ = 13.8 Hz, 2H, 1-NHC*H,* 2-NHC*H*), 3.93 (d, J_2 = 13.8 Hz, 1H, 2-NHC*H*), 7.15-7.25 (m, 6H, Ar-*H*), 7.28 (s, 1H Ar-*H*), 7.30 (s, 1H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 24.8 (4-*C*H), 26.3, 26.7 and 29.6 (CH_2), 35.0 (3-CH_2), 45.1(1-NCH_2), 50.6 (2-NCH_2), 53.4 (1-*C*), 54.9 (2-*C*H), 126.3, 126.7, 127.2, 127.3, 128.3, 128.6, and 129.8 (Ar-*C*H), 134.4 (Ar-*C*Cl),142.5 and 143.1 (Ar-*C*); HRMS (ESI-TOF) m/z $[M+H]^+$ calcd. for $C_{22}H_{27}N_2Cl_2$ 389.1551, found. 389.1552

(*R*)-N,N'-Bis(2-chlorobenzyl)-1,2-diaminobicyclo[2.2.2]octane L7 was obtained from 2-chlorobenzaldehyde as a colourless oil in 84% yield according to the general procedure D. t_R (HPLC) column A, gradient A = 2.58 min; MS (ESI): m/z = 389.3 $[M+H]^+$, 265.3 [M-(2-chlorotoluene)+H]$^+$, 125.1 [2-chlorotoluene+H]$^+$; $[\alpha]_D^{25}$ = -10.0°(c = 1.5, $CHCl_3$) ; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.41 (m, 1H, *H*CH),1.56-1.65 (m, 7H, *H*CH, 2CH_2, 3-*H*CH, 4-C*H*), 1.76 (m, 1H, *H*CH), 1.85 (m, 1H, *H*CH), 1.93 (m, 1H, 3-*H*CH), 2.36 (s, 2H, 2N*H*), 2.74 (m, 1H, 2-C*H*), 3.42 (d, *J* = 13.4 Hz, 1H, 1-N*H*CH), 3.72 (d, *J* = 13.4 Hz, 1H, 1-N*H*CH), 3.77 (d, *J* = 14.0 Hz, 1H, 2-N*H*CH), 4.04 (d, *J* = 14.0 Hz, 1H, 2-N*H*CH), 7.14-7.19 (m, 3H, Ar-*H*), 7.22 (td, *J* = 7.4, 1.5 Hz, 1H, Ar-*H*), 7.28-7.31 (m, 2H, Ar-*H*), 7.36 (dd, *J* = 5.6 Hz and 3.5 Hz, 1H, Ar-*H*), 7.43 (dd, *J* = 7.4 Hz and 1.7 Hz, 1H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 24.8 (4-*C*H), 26.3, 26.7 and 29.7 (CH_2), 35.1 (3-CH_2), 43.0 (1-NCH_2), 48.7 (2-NCH_2), 53.4 (1-*C*), 54.9 (2-*C*H), 126.8, 127.0, 128.2, 128.5, 129.4, 129.6, 130.0 and 130.7 (Ar-*C*H), 133.6 and 134.1 (Ar-*C*Cl), 137.9 and 138.3 (Ar-*C*); HRMS (ESI-TOF) m/z $[M+H]^+$ calcd. for $C_{22}H_{27}N_2Cl_2$ 389.1551, found 389.1552.

(*R*)-N,N'-Bis(2-methoxybenzyl)-1,2-diaminobicyclo[2.2.2]octane L8 was obtained from 2-methoxybenzaldehyde as a colourless oil in 78% yield according to the general procedure D. t_R (HPLC) column A, gradient A = 2.16 min; MS (ESI): m/z = 121.0 [2-methylmethoxyphenyl+H]$^+$, 261 [M-(2-methylmethoxyphenyl)+H]$^+$, 381.3 $[M+H]^+$; $[\alpha]_D^{25}$ = -53.6°(c = 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.59-2.12 (m, 11H, 5CH_2, 4-C*H*), 2.81 (m, 1H, 2-C*H*), 3.39 (s, 3H, OCH_3), 3.42 (d, *J* = 12.8 Hz, 1H, 1-NHC*H*), 3.61 (d, *J* = 12.8 Hz, 1H, 1-NHC*H*), 3.70 (s, 3H, OCH_3), 3.79 (d, *J* = 13.4 Hz, 1H, 2-NHC*H*), 4.39 (d, *J* = 13.4 Hz, 1H, 2-NHC*H*), 6.68 (d, *J* = 8.3 Hz, 1H, Ar-*H*), 6.81(d, *J* = 8.3 Hz, 1H, Ar-*H*), 6.93 (t, *J* = 7.4 Hz, 2H, Ar-*H*), 7.18-7.34 (m, 4H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 24.4 (4-*C*H), 25.4, 25.7, 26.0, 28.8 and 32.4 (CH_2), 40.9 and 46.4 (NCH_2), 53.6 (1-*C*), 55.1 (OCH_3), 55.2 (OCH_3), 55.5 (2-*C*H), 110.2, 110.4, 120.8, 128.8 and 129.6 (Ar-*C*H), 129.8 (Ar-*C*), 131.1 (Ar-*C*H), 157.4 and 157.9 (Ar-*C*OCH$_3$); HRMS (ESI-TOF) m/z $[M+H]^+$ calcd. for $C_{24}H_{33}N_2O_2$ 381.2542, found 381.2543.

(R)-N,N'-Bis(2-furanylmethyl)-1,2-diaminobicyclo[2.2.2]octane L9 was obtained from 2-furaldehyde as a light brown oil in 60% yield according to the general procedure D. t_R (HPLC) column A, gradient A = 1.80 min; MS (ESI): m/z = 221.2 [M-(2-methylfuran)+H]$^+$, 301.0 $[M+H]^+$; $[\alpha]_D^{25}$ = -11.8°(c = 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3CN): δ (ppm) = 1.29-1.35 (m, 1H, *H*CH), 1.37-1.41 (m, 1H, 3-*H*CH), 1.49-1.71 (m, 8H, 3CH_2, *H*CH, 4-C*H*), 1.83-1.89 (m, 1H, 3-*H*CH), 2.65 (m, 1H, 2-C*H*), 3.41 (d, *J* = 13.9 Hz, 1H, 1-NHC*H*), 3.58 (d, *J* = 13.9 Hz, 1H, 1-N*H*CH), 3.62 (d, *J* = 14.4 Hz, 1H, 2-NHC*H*), 3.80 (d, *J* = 14.4 Hz, 1H, 2-N*H*CH), 6.15 (m, 1H, Ar-*H*), 6.21 (m, 1H, Ar-*H*), 6.33 (m, 2H, Ar-*H*), 7.39 (m, 2H, Ar-*H*); ^{13}C NMR (100 MHz, CD_3CN): δ (ppm) = 25.7 (4-*C*H), 26.8, 26.9, 27.1 and 29.8 (*C*H$_2$), 35.5 (3-*C*H$_2$), 38.9 (1-N*C*H$_2$), 44.1 (2-N*C*H$_2$), 53.6 (1-*C*), 55.5 (2-*C*H), 107.0, 107.9, 111.2 and 111.3 (=*C*H), 142.6 and 142.8 (=*C*H-O), 155.6 and 156.3 (=*C*-O); HRMS (ESI-TOF) m/z $[M+H]^+$ calcd. for $C_{18}H_{25}N_2O_2$ 301.1916, found. 301.1917.

(*R*)-N,N'-Bis(1-naphthylmethyl)-1,2-diaminobicyclo[2.2.2]octane L10 was obtained from 1-naphthaldehyde as a colourless oil in 97% yield according to the general procedure D. t_R (HPLC) column A, gradient A = 2.75 min; MS (ESI): m/z = 141.1 [M-(2 methylnaphtalene)+H]$^+$, 281.3 [M-(methylnaphthalene)+H]$^+$, 421.1 $[M+H]^+$; $[\alpha]_D^{25}$ = -3.1°(c = 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3CN): δ (ppm) =1.43-1.51 (m, 1H, *H*CH), 1.59-1.77 (m, 7H, *H*CH, 3CH_2, 3-*H*CH, 4-C*H*), 2.06 (m, 1H, 3-*H*CH), 2.90 (m, 1H, 2-C*H*), 3.76 (d, *J* = 12.7 Hz, 1H,1-N*H*CH), 3.96 (d, *J* = 13.1 Hz, 1H,2-N*H*CH), 4.01 (d, *J* = 12.7 Hz, 1H, 1-N*H*CH), 4.39 (d, *J* = 13.1 Hz, 1H, 2-N*H*CH), 7.19 (d, *J* = 7.5 Hz, 1H, Ar-*H*), 7.26 (ddd, *J* = 8.3 Hz, 6.8 Hz and 1.3 Hz, 1H, Ar-*H*) 7.31-7.45 (m, 6H, Ar-*H*), 7.74 (t, *J* = 7.5 Hz, 2H, Ar-*H*), 7.83 (t, *J* = 8.3 Hz, 2H, Ar-*H*), 7.99 (d, *J* = 8.8 Hz, 1H, Ar-*H*), 8.14 (d, *J* = 8.3 Hz, 1H, Ar-*H*); ^{13}C NMR (100 MHz, CD_3CN): δ (ppm) = 25.9 (4-*C*H), 27.0, 27.2, 30.0 and 30.4 (*C*H$_2$), 35.9 (3-*C*H$_2$), 43.6 (1-NCH$_2$), 49.8 (2-N*C*H$_2$), 54.2 (1-*C*), 57.0 (2-*C*H), 125.0, 125.2, 126.4, 126.5, 126.8, 126.9, 127.4, 128.2, 128.4 and 129.4 (Ar-*C*H), 132.8, 132.9, 134.8, 134.9, 137.7,and 138.1 (Ar-*C*); HRMS (ESI-TOF) m/z $[M+H]^+$ calcd. for $C_{30}H_{33}N_2$ 421.2644, found 421.2638.

(*R*)-N,N'-Bis(2-naphthylmethyl)-1,2-diaminobicyclo[2.2.2]octane L11 was obtained from 2-naphthaldehyde as a white solid in 77% yield according to the general procedure D. M.p. 130-132 °C; t_R (HPLC) column A, gradient A = 2.86 min; MS (ESI): m/z = 141.1 [M-(2 methylnaphtalene)+H]$^+$, 281.2 [M-(methylnaphthalene)+H]$^+$, 421.3 $[M+H]^+$; $[\alpha]_D^{25}$ = +37.6°(c = 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.49-1.74 (m, 8H, 3CH_2, 4-C*H*, 3-*H*CH), 1.83 (m, 1H, *H*CH), 1.91-2.00 (m, 2H, *H*CH, 3-*H*CH), 2.83 (m, 1H, 2-C*H*), 3.53 (d, *J* = 12.9 Hz, 1H, 1-N*H*CH), 3.75 (d, *J* = 12.9 Hz, 1H, 1-N*H*CH), 3.84 (d, *J* = 13.6 Hz, 1H, 2-N*H*CH), 3.94 (br s, 2H, N*H*), 4.19 (d, *J* = 13.6 Hz, 1H, 2-N*H*CH), 7.39-7.47 (m, 6H, Ar-*H*), 7.66-7.79 (m, 8H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 24.6 (4-*C*H), 26.0, 26.1, 26.4 and 29.1 (*C*H$_2$), 34.1 (3-*C*H$_2$), 45.5 (1-NCH$_2$), 50.7 (2-N*C*H$_2$), 54.1 (1-*C*), 54.3 (2-*C*H), 125.8, 126.0, 126.1, 126.3, 126.8, 126.9, 127.5, 127.7, 127.8, 127.9, 128.2 and 128.5 (Ar-*C*H), 132.8, 132.9, 133.4, 133.5, 135.9 and 136.9 (Ar-*C*); HRMS (ESI-TOF) m/z $[M+H]^+$ calcd. for $C_{30}H_{33}N_2$ 421.2644, found 421.2645.

(*R*)-N,N'-Bis(9-anthracenylmethyl)-1,2-diaminobicyclo[2.2.2]octane L12 was obtained from 9-anthracenecarboxaldehyde as a yellow solid in 46% yield according to the general procedure D. M.p. 171-173 °C ; t_R (HPLC) column A, gradient A = 3.14 min; MS (ESI): m/z =521.3 $[M+H]^+$, $[\alpha]_D^{25}$ = +152.6°(c = 1.2, $CHCl_3$) ; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.63-1.68 (m, 2H, CH_2), 1.78-1.85 (m, 6H, 2CH_2, *H*CH, 4-C*H*), 1.91-1.96 (m, 1H, 3-*H*CH), 2.08-2.12 (m, 1H, *H*CH), 2.24 (m, 1H, 3-*H*CH), 2.98 (br d, 1H, 2-C*H*), 4.48 (d, *J* = 11.4 Hz, 1H, 1-NHC*H*), 4.53 (d, *J* = 11.4 Hz, 1H, 1-NHC*H*), 4.59 (d, *J* = 12.6 Hz, 1H, 2-NHC*H*), 4.91 (d, *J* = 12.6 Hz, 1H, 2-NHC*H*), 7.06-7.15 (m, 4H, Ar-*H*), 7.29-7.39 (m, 4H, Ar-*H*), 7.92 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.97 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 8.08 (d, *J* = 8.9 Hz, 2H, Ar-*H*), 8.22 (d, *J* = 8.9, 2H, Ar-*H*), 8.35 (d, *J* = 7.3 Hz, 2H, Ar-*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 25.1 (4-*C*H), 25.4, 26.4, 26.5 and 30.0 (*C*H$_2$), 35.9 (3-*C*H$_2$), 37.9 (1-NCH$_2$), 43.8 (2-NCH$_2$), 53.8 (1-*C*), 58.7 (2-*C*H), 124.3, 125.0, 126.0, 126.1 and 127.0 (Ar-*C*H), 127.3 (Ar-*C*), 129.0 (Ar-*C*H), 130.2, 130.5, 131.6 and 131.7 (Ar-*C*); HRMS (ESI-TOF) m/z $[M+H]^+$ calcd. for $C_{38}H_{37}N_2$ 521.2957, found. 521.2950.

General procedure E for the nitroaldol reaction (Henry reaction):
Ligand **L10** (12 mol%, 0.018 mmol, 7.6 mg) and $Cu(OAc)_2$ (10 mol%, 0.015 mmol, 2.1 mg) were dissolved in 2-propanol (0.5 mL) and stirred at room temperature for 10 min. The deep blue reaction mixture was cooled to 0 °C and aldehyde (1 equiv., 0.15 mmol) and nitromethane (10 equiv., 1.5 mmol, 80 µL) were added. The reaction mixture was left stirring at 0 °C for 10 to 72 h. Solvents were removed under reduced pressure and the residue was directly purified on a silica gel column eluting with cyclohexane/EtOAc (8:1-4:1, v/v) to yield the corresponding product.

Configuration assignment. The absolute configuration was assigned (*S*) for all the nitroalcohol adducts by comparison with previously published retention times in chiral HPLC.[4c,6a,6c,16]

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Keywords: Asymmetric catalysis • nitroaldol reaction • bicyclic 1,2-diamine • copper • DFT calculations

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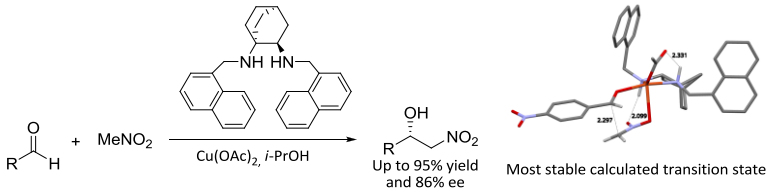

The C_1-symmetric (*R*)-N,N'-Bis(1-naphthylmethyl)-1,2-diaminobicyclo[2.2.2]octane ligand with $Cu(OAc)_2$ proved to be the most effective copper catalyst among those tested for the asymmetric Henry reaction of nitromethane with various aldehydes. DFT calculations of both the optimized copper complex conformations, and the most stable transition states of the reaction supported the preferential formation of *S* products in agreement with the experimental results.

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C_1-Symmetric 1,2-diamino bicyclo[2.2.2]octane ligands in Copper-catalyzed asymmetric Henry Reaction: catalyst development and DFT studies

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