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Article

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/jo402631u • Publication Date (Web): 18 Jan 2014

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

Synthesis of Tuneable Diamine Ligands with Spiro Indane-2,2'-pyrrolidine Backbone and Their Applications in Enantioselective Henry Reaction

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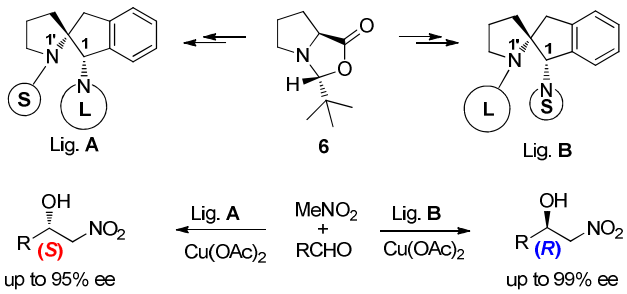
Abstract



Novel diamine ligands with spiro indane-2,2'-pyrrolidine scaffold were synthesized starting from Seebach's oxazolidinone **6** and were subsequently employed in asymmetric Henry reaction. Following the initial experimental findings, further synthesis resulted in two types of spiro diamines, with varying substituents at both nitrogen atoms. Ligands of type **A**, containing a small substituent at N-1' atom, and a large group at N-1 atom gave predominantly the *S*-configured β-nitroalcohol, while ligands of type **B**, with the reversed location of small and large substituents furnished the *R*-configured product. Both types of ligands turned out to be versatile catalysts for the Henry reaction between nitromethane and assortment of aryl as well as alkyl aldehydes offering either *S*- (lig. **A**) or *R*-configured (lig. **B**) nitroalcohols in a good to high chemical yield and an excellent enantioselectivity up to 99% ee.

Introduction

The chiral ligands with spiro-backbone, owing to their excellent catalytic efficiency in a variety of mechanistically dissimilar reactions[1] fulfill the requirements for "privileged" ligands, a term coined by Jacobsen.[2]

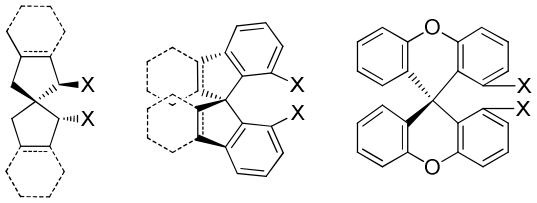


Figure 1. Representative example of privileged spiro ligands, where X = metal coordination groups such as -PAr_2, -$OPAr_2$, -$NHPAr_2$, oxazoline, etc.

The most prominent and successful spiro ligands have rigid C_2-symmetrical skeleton and metal coordination groups attached to the phenyl ring (predominantly) or to the spiro[4.4]nonane moiety (Figure 1). These mono or bidentate privileged ligands typically contain either phosphorus or/and sp^2-hybridized nitrogen donor atoms. Chiral amines, in comparison with phosphorus ligands, hold several well-known advantages such as easy availability in enantiomerically pure form, chemical robustness, particularly a substantially higher resistance to air oxidation, and ability to form stable complexes with transition as well as alkali metals. Although, for the reasons given above, the primary, secondary, and tertiary diamines are widely applied in the catalytic asymmetric syntheses,[3,4] the diamine ligands that contain spiro-backbone are relatively uncommon and have only been reported recently.[5]

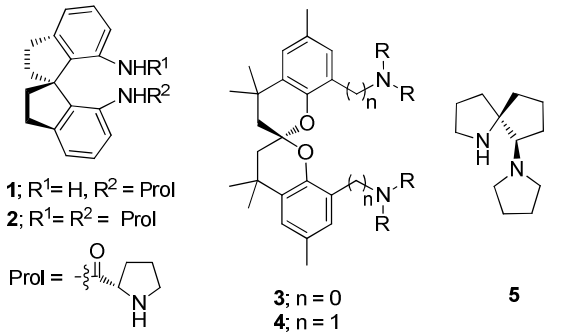


Figure 2. Spiro diamine ligands currently known.

The synthesis of proline derived diamines **1** and **2** with C_2-symmetric spirobi(indane) skeleton[5b] was reported by Zhou in 2006 (Figure 2). These diamines were shown to be a promising organocatalysts for the asymmetric aldol reaction. The preparation of spirobi(chromane) diamines **3** and **4** and isolation of their enantiopure forms were presented by Frexia.[5c] The catalytic effectiveness of ligands **3** and **4** was tested in palladium catalyzed oxidative kinetic resolution of 1-phenylethanol, displaying a low to moderate stereo-selectivity. The last example of spirodiamine ligand comes from Royer's group: an eleven steps synthesis, employing (S)-naphthylethylamine as a chiral auxiliary, furnished diamine **5** with the C_1-symmetrical 1-azaspiro[4.4]nonane scaffold in 19% overall yield.[5a] The rigid diamine **5** was demonstrated to be an effective catalyst for the asymmetric Michael addition to nitroolefines.

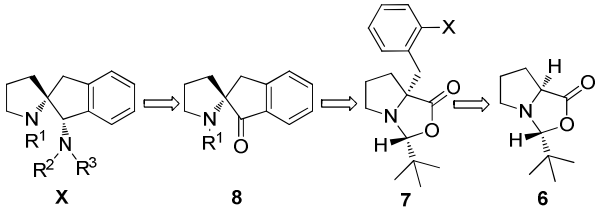
The presented above three examples of literature reports concerning the synthesis and applications of asymmetric spiro-diamines show that this field remains mostly unexplored. Moreover, the limited number of compounds with spiro-backbone used for the preparation of efficient ligands or organocatalysts indicates that the continuation of research in this area may lead to further progress.

Herein, we report our work targeting the design and synthesis of novel diamines that contain the C_1-symmetrical spiro[indane-2,2'-pyrrolidine] core.

Results and Discussion

In a continuation of our study on design and synthesis of diamine ligands for asymmetric catalysis,[6] we focused our efforts on the preparation of new compounds with a rigid spiro-backbone. Additionally, we anticipated that such spiro-diamines must fulfill the following requirements: their synthesis as well as further structure diversification must be simple, efficient, and provide a variety of derivatives in enantiopure form. A literature search for the suitable scaffold revealed Crooks' report, presenting the synthesis of racemic aminoketone with the spiro[indane-2,2'-pyrrolidine] backbone.[7] To the best of our knowledge, spirodiamine ligands with such skeleton were never previously described.

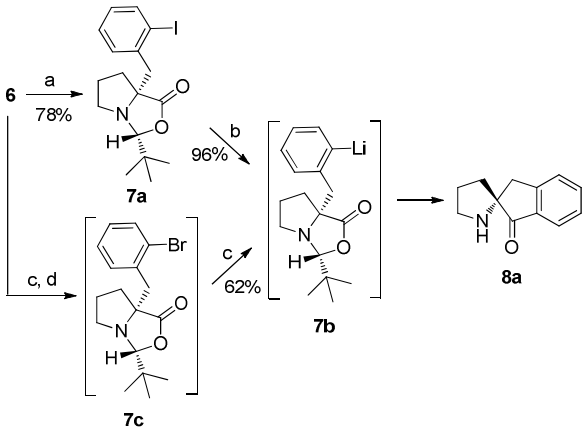
Inspired by this work, we proposed the asymmetric synthesis of spiro-diamines of general structure **X** starting from the easily available Seebach's oxazolidinone **6**[8] (Scheme 1). Such diamines with cis-arrangement of amino groups with respect to the indane parent, should offer a good metal chelation ability, while the chiral spiro-skeleton should assure an effective asymmetric induction.



Scheme 1. Retrosynthesis of diamines of type **X** from Seebach's oxazolidinone **6**.

We expected that the highly stereoselective alkylation (self-reproduction of chirality)[8] of compound **6** with *o*-iodo benzyl bromide**,** followed by Parham's cyclization[9] of **7** should provide aminoketone **8**, a suitable starting material for the preparation of diamines of type **X** *via* standard carbonyl group transformation.[10]

To verify this idea, the oxazolidinone **6** was alkylated with *o*-iodobenzyl bromide using Seebach procedure.[8] (Scheme 2).

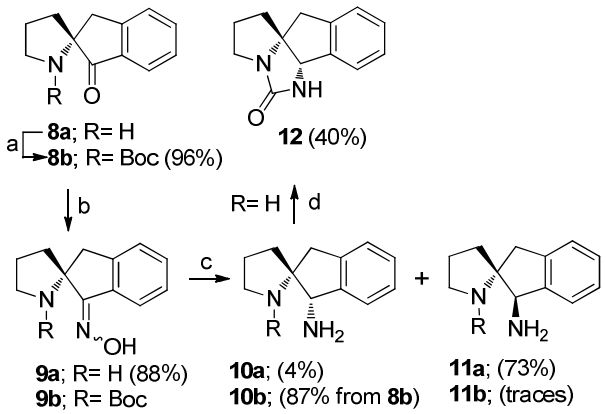


Scheme 2. Synthesis of aminoketone **8a** from oxazolidinone **6**. *Reagents and conditions:* a) LDA, THF, -78°C, 0.5 h, then *o*-iodobenzyl bromide, -78 →-30°C, 3 h; b) *n*-BuLi, THF, -78°C, 0.5 h; c) *t*-BuLi, THF, -78°C, 0.5 h; d) *o*-bromobenzyl bromide, THF -78 → -30°C.

The isolated product **7a** was treated with *n*-BuLi to generate organolithium species **7b**, which spontaneously cyclized furnishing aminoketone **8a** in an excellent yield (96%) and a high optical purity (~99% ee).[11] In order to simplify the preparation of **8a**, we examined also a one-pot two-step procedure with the sequential addition of organolithium reagent. The first equivalent of *t*-BuLi deprotonated oxazolidinone **6** to facilitate the alkylation with *o*-bromobenzyl bromide, then the *in situ* generated derivative **7c** was treated with another equivalent of *t*-BuLi to effect the bromine-lithium exchange, thus enabling cyclization step, leading to final aminoketone **8a.** Although the overall yield of **8a**, using unoptimized one pot synthesis (62%) is lower than that of the original two-step preparation (75%), the use of an inexpensive *o*-bromobenzyl bromide and a simplified procedure makes the one-pot synthesis a reasonable alternative.

The initial effort to prepare diamines from aminoketone **8a** using reductive amination[10] was unsuccessful. Consequently, we focused our attention on the alternative oxime approach for the

generation of amine. Thus, we converted the aminoketone **8a** into corresponding oxime **9a** and examined its palladium-catalyzed hydrogenation (Scheme 3).



Scheme 3. Synthesis of spiro-diamine **10.** *Reagents and conditions:* a) Boc_2O, 50°C, 0.5 h, 96%; b) NH_2OH, Py/EtOH, reflux, 1-3 days; c) H_2, Pd/C, MeOH/AcOH, 24 h; d) $COCl_2$, DIEPA, DCM, 0 → RT, 3h.

An initial testing led to a mixture of epimeric diamines **10a** (cis) and **11a** (trans), isolated in about 1:18 ratio, respectively. The *cis*-configuration of amine **10a** was corroborated by an easy formation of cyclic derivative **12** in reaction with phosgene. The major reduction product, *trans*-isomer **11a** did not react with phosgene.

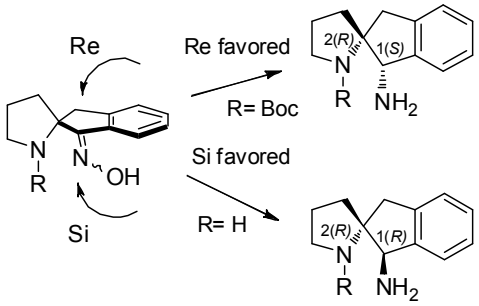
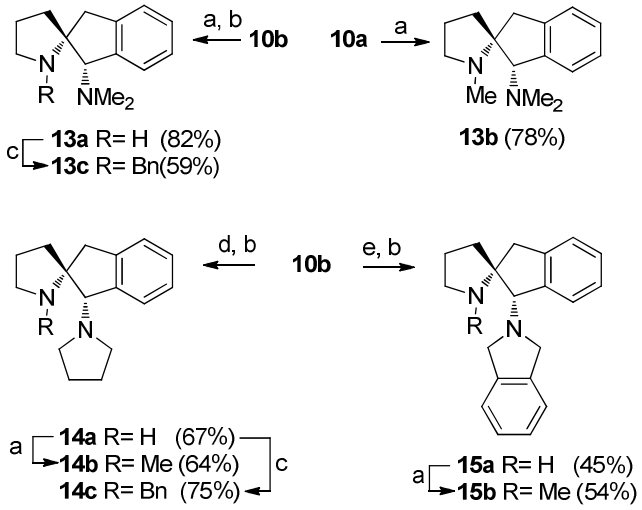


Figure 3. Palladium-catalyzed hydrogenation of spiro-oxime. The dependence of amine R-substituent size and reduction product stereochemistry

Based on the Crooks report that the reduction of *N*-benzoylated racemic spiro-ketone **8** yields predominantly the respective α-alcohol[7], we speculated that the protection of pyrrolidine nitrogen

atom with a bulky protective group will shield the *Si*-face of oxime, and the *Re*-face addition of hydrogen should be favored (Figure 3). In order to examine this assumption, we prepared the *N*-Boc protected oxime **9b** in two steps from ketone **8a** (Scheme 3). The catalytic hydrogenation of **9b** furnished the expected *cis*-amine **10b** in 87% yield. The unwanted *trans*-isomer **11b** was barely detectable by TLC, in agreement with our expectation. With enantiopure mono-protected diamine **10b** in hand, we synthesized several diamine derivatives with various substituents at both nitrogen atoms (Scheme 4). All syntheses were executed using standard reactions such as reductive amination with mono and dialdehydes, amine alkylation and Boc removal.

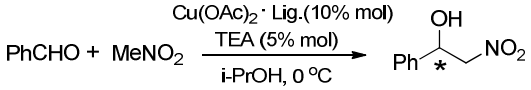


Scheme 4. Synthesis of spiro-diamine derivatives **13-16.** *Reagents and conditions:* a) HCHO, $NaBH_3CN$, DCM/AcOH, RT; b) TFA, DCM; c) PhCHO, $NaBH_3CN$, DCM/AcOH, MeOH/AcOH, 24 h; d) 1,4-dibromobutane, Na_2CO_3, NaI, MeCN, reflux; e) Benzene-1,2-dicarbaldehyde, $NaBH_3CN$, DCM/AcOH, 24 h;

Complexes of chiral diamines with copper salts are widely utilized in asymmetric Henry reaction, a useful C–C bond-forming process with a strong industrial relevancy.[12] We have selected this process to evaluate the catalytic efficiency of new ligands **13a-c**, **14a-c**, and **15a-b**. Until now, many catalytic systems for the Henry reaction have been developed. A literature search revealed, that screening the catalytic performance of a new ligands in nitroaldol reactions, the catalyst (Cu-diamine complex) is used at first in 5,[13a] 10[12f, 12g] or even 20[12i] mol%. For the most effective ligands,

optimization of the reaction conditions allows to reduce the amount of catalyst down to 2.5 mol%.[13c-d] The reactions are performed mainly in an alcohol solution using iso-propanol,[12p] n-propanol[13a] or ethanol.[12q] However, other solvents as THF[13c] or diethyl ether[13d] are also suitable for this process. Depending on copper complex, nitroaldol reaction proceeds smoothly without an external base,[12p, 13a] or the base, typically tertiary amine is required to activate the nitromethane, thus increasing the reaction rate.[12q, 13c] In certain catalytic systems, tertiary amine is applied up to equimolar amount without effecting the stereoselectivity.[12m, 13c] However, a large amount of a base can decrease stereoselectivity, therefore it is used in the same as a catalyst amount or lower.[12f] Taking into account the above literature information, we carried out a model reaction between nitromethane and benzaldehyde in iso-propanol solution at 0°C, using complexes of copper(II) acetate with a series of new ligands (10 mol% each) and triethylamine (5 mol%). In result, corresponding nitroalcohol was isolated in good chemical yield and with a low to moderate enantioselectivity (ee 13-45%; Table 1) with notable exception of ligand **14a** that offered a substantially higher enantioselectivity (ee 77%, entry 4).

Table 1. Asymmetric Henry reaction catalyzed by $Cu(OAc)_2$ complexes with diamines **13-15**.[a]



Entry	Ligand	R	Time [h]	Yield [%]	Ee[b] [%]	Conf.
1	**13a**	H	24	78	45	***S***
2	**13b**	Me	6	82	13	***R***
3	**13c**	Bn	24	81	47	***R***
4	**14a**	H	3	78	77	***S***
5	**14b**	Me	4	80	18	***S***
6	**14c**	Bn	16	78	32	***R***
7	**15a**	H	4	76	38	***S***
8	**15b**	Me	24	85	33	***R***

[a)] Reaction conditions: $Cu(OAc)_2$·Lig generated in DCM from $Cu(OAc)_2$·H_2O (0.05 mmol, 10 mol%), benzaldehyde (0.5 mmol), *i*-PrOH (2 mL)**,** nitromethane (5 mmol), TEA (0.025 mmol, 5 mol%), 0 °C. [b)] The ee's and absolute configurations were determined by chiral HPLC analysis using OD-H Chiralpack column as described in the literature**.** [12n]

Considering the fact that new ligands possess both the same spiro-skeleton and configuration (*1S,2R*), we noticed interesting changes in the direction of asymmetric induction in a standard test reaction. A thorough analysis of reaction results has shown an intriguing regularity in the product configuration that could be reasonably associated with the characteristics of substituents at both nitrogen atoms within the ligand. For example, in the reaction catalyzed by diamines with unsubstituted pyrrolidine nitrogen atom (**13a**, **14a**, **15a**), the *S*-configured product dominated in all cases. The enantiomeric excess observed in each case depends, however, on the bulkiness of

substituent on the second nitrogen atom (entry 1, 4, 7). When *N*-1'-methyl or benzyl analogues were used, the *R* nitro alcohol was obtained (entry 2, 3, 6, 8). Only in the case of diamine **14b**, the *S*-enantiomer still dominated, but in comparison with ligand **14a**, the enantiomeric excess was considerably reduced from 77% ee (*S*) to 18% ee (*S*), (entry 4 and 5). Considering the above results we formulated a working hypothesis correlating the relationship between the steric bulkiness of substituents at both nitrogen atoms within ligand and the configuration of product as well as the extent of observed enantiomeric excess.

Our proposed hypothesis is that ligands **A** with a small substituent at *N*-1'atom, and a large group at *N*-1 atom should furnish predominantly the *S*-configured β-nitroalcohol (Figure 4).

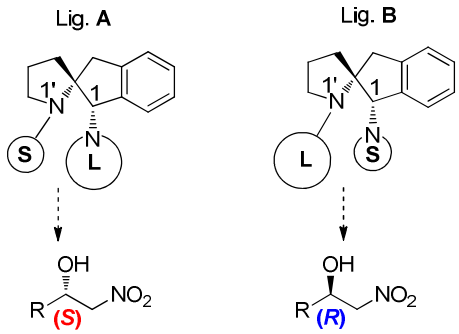
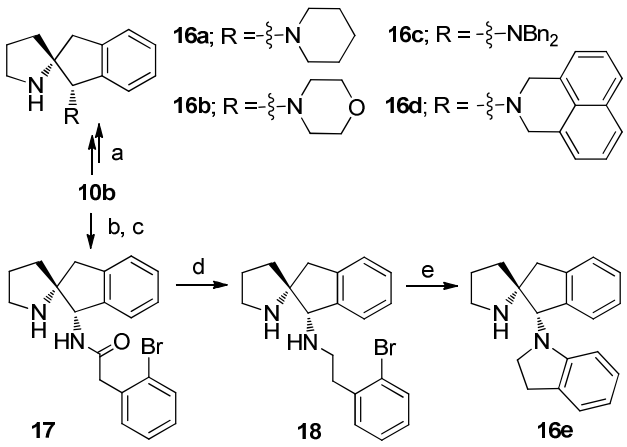


Figure 4. The relationship between ligand structure and product configuration in Henry reaction.

On the other hand, ligands **B** with the reverse location of small and large substituent favour the formation of *R*-configured product. The extent of observed enantiomeric excess depends to some degree on the relative difference of steric bulkiness of substituents at both nitrogen atoms. This hypothesis is strongly supported by the results of test reaction using ligands **13c** (47% ee, *S*) and **14a** (77% ee, *R*), (Table 1, entry 3, and 4).

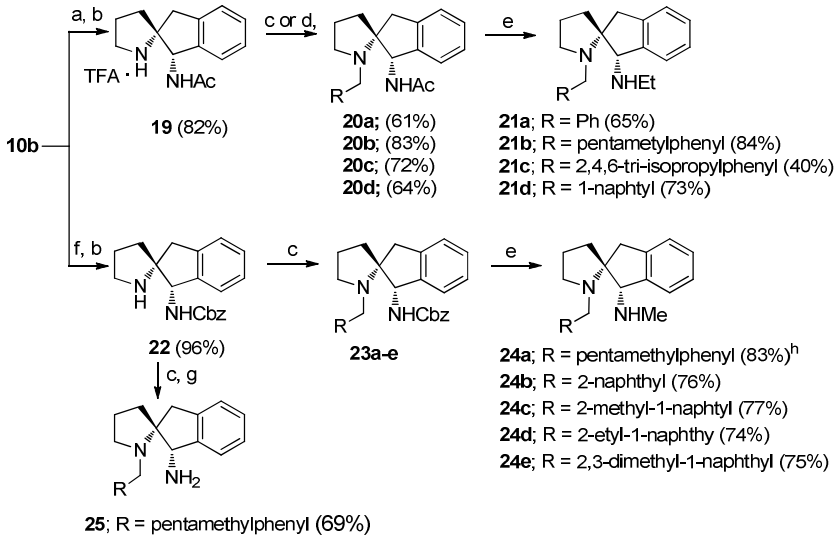
To verify the above hypothesis we decided to synthesize an array of diamines of type **A** and **B**, then explore in-depth their structure-properties relationship. The ligands of type **A** (compounds **16a-d**) were prepared by analogy to compounds **13-15** (Scheme 5). The *N*-Boc-protected diamine

10b was subjected either to the alkylation with appropriate terminal di-bromide (**16a**, **16b, 16d**), or benzyl bromide (**16c**). Finally, the Boc group was removed to give ligands **16a-d**. The diamine **16e** was obtained from **10b** in four step reaction sequence: acylation with 2-(2-bromophenyl)acetyl chloride, deprotection of secondary amine followed by the aluminium hydride reduction of amide group, and finally intramolecular palladium catalyzed amine arylation to give the title compound.



Scheme 5. Synthesis of spiro-diamines type **A**, **16a-e.** *Reagents and conditions:* a) ligands **16a-d** were obtained as shown in Scheme 4. b) 2-(2-bromophenyl)acetyl chloride, TEA, DCM, -30°C → RT, 0.5 h, 83%; c) TFA; d) AlH_3, THF/E_2O, 0°C → RT, 3h; e) $Pd(PPh)_4$ (10 mol%), K_2CO_3, *t*-BuONa, toluene, 100°C.

The initial ligand screening indicated that the highest enantiomeric excess (47% ee) of *R*-configured nitroalcohol was obtained when ligand **13c** with benzyl substituent at *N*-1'atom and dimethylamine at C-1 carbon atom was used (Table 1, entry 3). Consequently, hoping to improve the *R*-selectivity of type **B** ligands, we decided to prepare several similar diamines with a bulky substituent at *N*-1'atom, and ethyl or methyl group at the second nitrogen atom.



Scheme 6. Synthesis of spiro-diamines type **B**, **21a-d**, **24a-e and 25**. *Reagents and conditions:* a) Ac_2O, Py; b) TFA, RT, 0.5 h; c) RCH_2Cl, Na_2CO_3, NaI, MeCN, reflux; d) RCHO, $NaBH_3CN$, MeOH, AcOH; e) $LiAlH_4$, THF, reflux; f) CbzCl, TEA, DCM; g) H_2, Pd/C, MeOH, AcOH. h) Yield calculated for two steps from **22**.

The synthesis of type **B** ligands is shown on Scheme 6. Amine **10b** was acetylated and crude amide was treated with TFA. The pure product was isolated *via* crystallization as an easy to handle trifluoroacetate salt **19**. The initial attempts to introduce bulky substituents at *N*-1' atom by alkylation with active secondary bromides such as benzhydryl bromide, or by reductive amination with pivaloyl aldehyde or several ketones were unsuccessful, probably due to the steric hindrance. An alkylation of pyrrolidine nitrogen atom in **19** was accomplished by either the use of apropriate benzyl chloride or by applying reductive amination with aromatic aldehyde (For details see experimental section). Finally, the reduction of acetamide **20a-d** with $LiAlH_4$ led to a series of ethylamine substituted ligands **21a-d**. A number of corresponding diamines with methylamine group at C-1 carbon atom, i.e., compounds **24a-e**, were prepared following a similar strategy. The reaction sequences differ only at the first step, namely the Cbz protection of primary amine in common substrate **10b**. A newly synthesized ligands of type **A** and **B** were subsequently examined in a model reaction between nitromethane and benzaldehyde, carried out under the same conditions as described above (see Table 1). The collected results are listed in Table 2.

Table 2. Asymmetric Henry reaction catalyzed by $Cu(OAc)_2$ complexes with diamines **16, 21** and **24**[a]

Entry	Ligand	Time [h]	Yield [%]	Ee [%]	Conf.
1	**16a**	24	85	92	***S***
2[b]	**16a**	48	68	93	***S***
3[c]	**16a**	72	33	97	***S***
4	**16b**	8	78	83	***S***
5[d]	**16c**	24	0	-	-
6	**16d**	8	80	30	***S***
7	**16e**	24	70	82	***S***
8	**21a**	6	79	74	***R***
9	**21b**	3	85	91	***R***
10	**21c**	24	84	90	***R***
11	**21d**	8	80	87	***R***
12	**24a**	3	86	93	***R***
13[c]	**24a**	24	84	99	***R***
14	**25**	8	72	94	***R***
15	**24b**	24	73	81	***R***
16	**24c**	24	82	96	***R***
17[c]	**24c**	48	81	98	***R***
18	**24d**	24	85	96	***R***
19	**24e**	24	74	91	***R***

[a] Reagents, reaction conditions, and ee assignment are as described in Table 1 unless otherwise noted. [b] Reaction was run at -20 °C. [c] Reaction was run at -40 °C. [d] A fast decomposition of copper complex was observed.

Ligands of type **A**, i.e., compounds **16a-b** and **16d-e** gave predominantly the *S*-configured products in all cases. For diamine **16c** we did not observe any reaction, probably due to the fast decomposition of copper complex (Entry 5). The highest enantiomeric excess (92% ee) was achieved with piperidine derivative **16a**. The reaction catalyzed with morpholine analog **16b** proceeded much faster, but with a lower stereoselectively (only 83% ee). The last two examples (entry 1 and 4) clearly show that apart from the size of nitrogen substituent, also its electronic properties play an important role. The reaction catalyzed with the best ligand in this series, diamine **16a**, was run at -20 °C and -40 °C to give corresponding nitroalcohol with a high selectivity, 93% and 97% ee, respectively. However, both the reaction rate and its yield were reduced considerably (Entry 2 and 3). In agreement with the expectation, ligands of C-1-ethylamine series **21a-d** furnished exclusively the *R*-configured product in a high enantiomeric purity (Entry 8-11). The highest enantiomeric excess (91% ee) was achieved for the pentamethylbenzyl derivative **21b**. The use of a more sterically congested 2,4,6-triisopropylbenzyl analog **21c** led to the same level of selectivity (90% ee), but the reaction was much slower than that catalyzed with ligand **21b** (Entry 9 and 10). The methylamine analogs **24a-e** gave excellent results in terms of both the stereoselectivity and the yield of nitroaldol reaction. When the reaction was carried out at 0 °C, all ligands, with exception of compound **24b**, furnished 2-nitro-1-phenylethanol with enantiomeric excess between 91-96% ee. Considering the enantioselectivity of ligands with the same pentamethylbenzyl substituent at pyrrolidine nitrogen atom (**21b**, **24a**, **25**), we can clearly see a simple relationship: smaller *N*-1-substituent induces formation of *R*-configured product with a higher ee. For instance, for ethyl derivative the 91% ee was observed (entry 9), 93% for methyl (entry 12), and 94% for primary amine (entry 14). The best ligand in

terms of *R*-selectivity, the primary amine **25**, however, showed a slower reaction rate in comparison with its secondary amine analogs **21b**, **24a**, and the formation of unidentified side products was observed. For the best ligands in this series, we repeated the reaction at –40 ^{o}C, and observed an excellent stereoselectivity for pentamethylbenzyl derivative **24a** (99% ee), and 2-methyl-naphthyl **24c** (98% ee).

The high ee's achieved for several ligands in a test reaction (Table 2) indicate that initially selected reaction conditions were suitable, nonetheless we decided to undertake further optimization. The results are given in Table 3. Firstly, a series of copper salts (10 mol%) were evaluated in complexes with ligand **16a** (10 mol%) in iso-propanol at 0 °C for a specified time.

Table 3. Optimization of the enantioselective Henry reaction between benzaldehyde and nitromethane catalysed by Cu(II) complexes with diamines **16a**. The influence of copper(II) salt, solvent and amount of tiethylamine on the reaction yield and product ee.[a]

Entry	Copper salt	Solvent	TEA [mol%]	Time [h]	Yield [%]	Ee [%]
1	$Cu(OAc)_2$	i-PrOH	5	24	85	92
2	$Cu(OAc)_2 \cdot H_2O$	i-PrOH	5	24	83	92
3	$CuCl_2$	i-PrOH	5	48	7	<1
4	$CuBr_2$	i-PrOH	5	48	20	<1
5	$Cu(OAc)_2$	EtOH	5	24	89	88
6	$Cu(OAc)_2$	EtOH 96%	5	24	86	83
7	$Cu(OAc)_2$	MeOH	5	24	89	87
8	$Cu(OAc)_2$	THF	5	72	39	90
9	$Cu(OAc)_2$	DCM	5	72	45	79
10	$Cu(OAc)_2$	i-PrOH	10	24	85	91
11	$Cu(OAc)_2$	i-PrOH	20	24	86	89

[a] Reagents, reaction conditions, and ee assignment are as described in Table 1 unless otherwise noted

Copper(II)acetate, both hydrated and anhydrous, has shown the same level of stereoselecitity, 92%, (Entry 1, 2). Contrary to that, complexes of copper(II)chloride and bromide, yielded racemates in low yield (Entry 3, 4). Next, the solvent effects on enantioselectivity were examined (Entry 5-9). All tested solvents gave results inferior to these of iso-propanol. Only THF offered comparable enantioselectivity (90% ee), but product was isolated in 39% yield only, reflecting slow reaction rate. (Entry 8). Finally, the impact of the amount of triethylamine on nitroaldol reaction was evaluated. When TEA was applied in the same amount as catalyst, 10 mol%, the ee dropped by 1%. (Entry 10). However, when the quantity of a base was increased to 20 mol%, further reduction in stereoselectivity was observed. (Entry 11). The last two results indicate, that to achieve a high enantioselectivity in our catalytic system, a molar quantity of a base should not exceed that of the catalyst.

Table 4 presents the results of the catalyst loading optimization using ligands **16a** and **24a**. For both ligands, the decrease of the catalyst amount did not affected stereoselectivity significantly. The reduction of the amount of catalyst to 5 mol% and 2.5 mol% (Entry 2, 4, 6 and 8) resulted in a small increase of enantioselestivity, approximately by 1% ee, however, the reactions were slower.

Table 4. Optimization of reaction conditions.[a] Effect of the amount of the catalyst on the asymmetric Henry reaction.

Entry	ligand	Cat./TEA [mol%]	Time [h]	Yield [%]	ee [%]
1	**16a**	10/5	24	85	92
2	**16a**	5/2.5	26	83	92
3[b]	**16a**	5/2.5	72	73	94
4	**16a**	2.5/2	28	80	93
5	**24a**	10/5	3	85	93
6	**24a**	5/2.5	18	83	94
7[c]	**24a**	5/2.5	30	81	98
8	**24a**	2.5/2	24	76	94

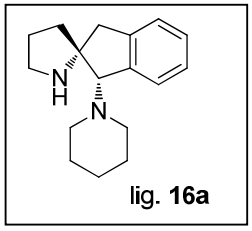
[a)] Reagents, reaction conditions, and ee assignment are as described in Table 1 unless otherwise noted. [b)] Reaction was run at -20 ^{o}C. [c)] Reaction was run at -40 ^{o}C. [d)]

The reaction catalysed with 5 mol% of ligand **16a** and **24a**, was run at -20 ^{o}C and -40 ^{o}C respectively. (Entry 3 and 7) Corresponding nitroalcohol was obtained with very high enantiomeric excess, 94% and 98% ee, respectively, however both the reaction rate and the yield were significantly lower.

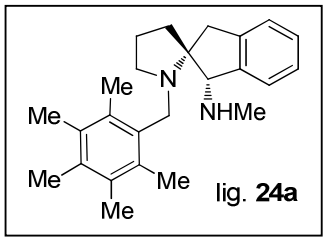
Finally, we decided to assess the scope of applicability of selected ligands of type **A** and **B** in Henry reaction with variety of aldehydes. Considering the fact that reduction of the catalyst loading resulted in the decrease of reaction rate and a small variation of stereoselectivity (~1% ee), the test reaction were conducted using 10 mol% of the catalyst and 5 mol % of TEA to avoid a long reaction time in low temperature. The experimental results of reactions with both aryl and alkyl aldehydes catalyzed with diamines **16a** and **24a** are collected in Table 5. As can be seen, both ligands turned out to be versatile catalysts, offering either *S*- (ligand **16a**) or *R*-configured (ligand

24a) nitroalcohols in a good to high chemical yield and with an excellent enantioselectivity up to 99% ee.

Table 5 Asymmetric Henry reaction catalyzed by $Cu(OAc)_2$ complexes with ligands **16a**[a,b] and **24a**[a,c]



lig. **16a**



lig. **24a**

Entry	Time [day]	Yield [%]	Conf.[d]	Ee[d] [%]	Aldehyde	Ee[d] [%]	Conf.[d]	Yield [%]	Time [day]	Entry
1	2	68	***S***	93	benzaldehyde	99	***R***	84	1	12
2	1	64	***S***	89	2-nitrobenzaldehyde	76	***R***	75	2	13
3	3	90	***S***	92	2-bromobenzaldehyde	96	***R***	89	1	14
4	1	86	***S***	94	2-methoxybenzaldehyde	99	***R***	88	1	15
5	2	78	***S***	94	3,4-dimethoxybenzaldehyde	95	***R***	96	1	16
6	2	72	***S***	95	2-furaldehyde	89	***R***	75	1	17
7	2	94	***S***	85	1-naphthaldehyde	98	***R***	90	1	18
8	3	63	***S***	93	3-phenylpropionaldehyde	98	***R***	65	1	19
9	4	51	***S***	93	2-methylpropionaldehyde	98	***R***	58	3	20
10	4	56	***S***	94	Valeraldehyde	90	***R***	78	2	21
11	4	50	***S***	91	cyclohexanecarboxaldehyde	97	***R***	66	1	22

[a] Reagents and reaction conditions are as described in Table 1 unless otherwise noted.

[b] Reactions with ligand **16a** were conducted at -20°C.

[c] Reactions with ligand **24a** were conducted at -40°C.

[d] The ee's and absolute configurations were determined by chiral HPLC analysis using OD-H, OJ-H and AD-H Chiralpack column as described in the literature. [12n]

Based on these experimental findings and in agreement with the commonly accepted mechanism of nitroaldol reaction,[14] we proposed a reasonable transition state model for the enantioselective Henry reaction (Figure 5). In the transition state TS-**16a**-*Si* (copper complex with ligand **16a**), the *Si* attack is impeded by the steric interaction of aldehyde R-substituent with piperidine ring. In TS-**16a**-*Re*, the R-group faces outside, avoiding the steric hindrance and the corresponding nitroaldol adduct is formed with the *S* configuration. In a case of ligand **24a** with the reverse location of small and large substituents, for the same reasons as above, *Si*-attack is favoured (TS-**24a**-*Si*) and the *R*-configured product is formed.

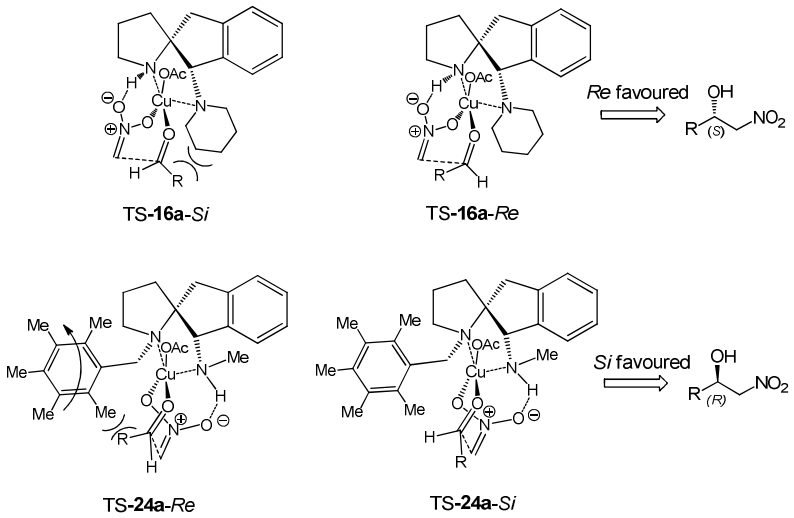


Figure 5. Proposed transition state models of Henry reaction for ligands of type **A** and **B.**

3. Conclusion

In summary, we developed a simple methodology for the preparation of novel, easily tuneable diamine ligands that are characterized by the presence of spiro[indane-2,2'-pyrrolidine] scaffold. The alkylation of Seebach's oxazolidinone **6** with *o*-iodo benzyl bromide, followed by the Parham's cyclization led to formation of spiro aminoketone **8a** in a high optical purity > 99% ee. Alternatively, ketone **8a** can be obtained in a one-pot reaction by the sequential addition of organolithium reagent. The catalytic hydrogenation of *N*-Boc protected oxime **9b**, prepared in two

steps from **8a**, furnished diamine **10b**, with *cis*-configuration in respect to the indane. Starting from the mono protected diamine **10b**, several ligands with different substituents at both nitrogen atoms were obtained and applied in asymmetric Henry reaction. Based on the initial experimental findings, further synthesis resulted in preparation of two types of ligands: type **A** ligands, containing a small substituent at *N*-1'atom, and a large group at *N*-1 atom that gives predominantly the *S*-configured β-nitroalcohol, and ligands type **B,** with the reverse location of small and large substituents that are furnishing the *R*-configured product. Ligands of both types turned out to be a versatile catalysts for Henry reaction between nitromethane and assortment of aryl as well as alkyl aldehydes offering either *S*- (ligands **A**, up to 95% ee) or *R*-configured (ligands **B**, up to 99% ee) nitroalcohols in a good to high chemical yield and with excellent enantioselectivity.

Considering the efficiency of presented enantioselective synthesis of spiro-diamine ligands as well as their ability to easily introduce substituent diversity, we expect that this methodology could be extended to the preparation of diverse range of similar spiro-scaffolds. Initial work in this direction is in progress in our research group.

Experimental Section

Preparation of 7a. Alkylation of oxazolidinone **6** (0.830 g, 4.54 mmol) with *o*-iodo benzyl bromide (1.423 g, 4.79 mmol) was performed according to reported Seebach's procedure.[8] Product was purified by flash chromatography on silica gel using ethyl acetate/hexane 3:97 v/v as an eluent. Yield 1.414 g (3.54 mmol, 78%); oil, $[\alpha]_D^{23}$ 9.2 (c 1.0, CH_2Cl_2); IR (CH_2Cl_2): 2962, 2872, 1775 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.83-7.81 (m, 1H), 7.52-7.49 (m, 1H), 7.26-7.21 (m, 1H), 6.91-6.86 (m, 1H), 4.22 (s, 1H), 3.25 (s, 2H), 3.11-3.04 (m, 1H), 2.80-2.74 (m, 1H), 2.14-2.08 (m, 1H), 1.94-1.87 (m, 1H), 1.80-1.67 (m, 2H), 0.72 (s, 9H); ^{13}C-NMR ($CDCl_3$, 125 MHz): 177.4, 140.1, 139.5, 131.2, 128.6, 128.2, 105.3, 104.3, 74.3, 57.7, 45.7, 36.4, 36.2, 24.9, 24.0; MS (ES, HR) m/z: ($M+Na^+$) calcd for $C_{17}H_{22}NO_2NaI$: 422.0587; found: 422.0572.

Preparation of aminoketone 8a

Procedure 1. The *n*-BuLi (1.6 M/hexane, 3.32 mL, 5.31 mmol) was added dropwise to the stirred solution of **7a** (1.414 g, 3.54 mmol) in THF (20 mL) at -78°C. Stirring was continued at this temperature for 2 h, then the reaction mixture was poured into saturated aqueous NH_4Cl (20 mL), and extracted with DCM (3x40 mL). Collected extracts were washed with water (20 mL) and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by flash column chromatography using ethyl acetate/MeOH, 90/10 v/v as an eluent. Yield 636 mg (3.4 mmol, 96%).

Procedure 2. The *t*-BuLi (1.7 M/hexane, 18.7 mmol, 11 mL) was added dropwise to the stirred solution of oxazolidinone 6 (3.260 g, 17.81 mmol) in THF (90 mL) at -78°C. Stirring was continued at this temperature for 0.5 h, then 2-bromobenzyl bromide (4.878 g, 19.6 mmol) in THF (10 mL) was added. The temperature was slowly brought to -30°C and stirring was continued for 3h. The reaction mixture was cooled down to -78°C, *t*-BuLi (1.7 M/hexane, 21.37 mmol, 12.6 mL) was added dropwise and solution was stirred for another 2h. Further workup and purification as in procedure **1**. Yield 2.053 g (10.97 mmol, 62 %).

Oil; $[\alpha]_D^{23}$ 18.1 (c 1.0, CH_2Cl_2); IR (CH_2Cl_2): 2968, 2877, 1713 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.78-7.71 (d, 1H, *J*=5.0 Hz), 7.63-7.56 (m, 1H), 7.44-7.33 (m, 2H), 3.37-3.27 (m, 1H), 3.19-3.14 (s, 2H), 3.14-3.07 (m, 1H), 2.67 (br s, 1H), 2.08-2.00 (m, 1H), 2.00-1.90 (m, 2H), 1.82-1.72 (m, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz): 208.7, 151.8, 135.2, 135.0, 127.6, 126.5, 124.3, 72.1, 47.8, 43.5, 38.7, 26.3; MS (EI, HR) m/z: (M^+) calcd for $C_{12}H_{13}NO$: 187.0997; found: 187.1002.

Synthesis of *N*-Boc protected aminoketone 8b.

The mixture of aminoketone **8a** (1.05 g, 5.61 mmol) and Boc anhydride (1.35 g, 6.17 mmol) was heated at 50°C for 0.5 h. Reaction mixture was cooled to rt and filtered through a pad of silica gel (ethyl acetate/hexane, 30/70 v/v). The semisolid, obtained by removal of solvents under reduced pressure, was crystallized from hexane.

Yield 1.55 g (5.4 mmol, 96%); colourless crystals; mp 127-128°C (hexane); $[\alpha]_D^{23}$ -8.8 (c 1.0, CH_2Cl_2); IR (CH_2Cl_2): 3675, 2980, 1722, 1688 cm^{-1}; Spectral data (≈1:1.8 mixture of rotamers): ^{1}H-NMR (Tol-d_8, 500

MHz): 7.73-7.68 (m, 1H), 7.18-7.13 (m, 1H), 7.02-6.91 (m, 2H), 3.59 (d, 0.36H, *J*=17.0Hz), 3.56-3.48 (m, 1.28 H), 3.48-3.42 (m, 0.36H), 3.37-3.33 (m, 0.36H), 3.21 (d, 0.64H, *J*=17.0 Hz), 2.63-2.56 (m, 1H), 1.90-1.80 (m, 1H), 1.68-1.60 (m, 0.36H), 1.58-1.52 (m, 0.64H), 1.48-1.39 (m, 1H), 1.37 (s, 3.24H), 1.33-1.26 (m, 1H), 1.11 (s, 5.76H); ^{13}C-NMR (Tol-d_8, 125 MHz, major rotamer): 204.9, 204.1, 152.8, 150.7, 134.6, 127.7, 126.3, 124.2, 79.5, 69.6, 48.3, 41.7, 39.9, 28.0, 23.6; MS (EI, HR) m/z: (M^+) calcd for $C_{17}H_{21}NO_3$: 287.1521; found: 287.1526. Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87; found: C, 71.22; H, 7.34; N, 4.88.

General procedure ▌for the preparation of oximes 9a and 9b.

A mixture of aminoketone **8** (4.0 mmol), hydroxylamine hydrochloride (1.39 g, 20 mmol) and pyridine (8 mL) in anhydrous ethanol (8 mL) was refluxed until the reaction was complete (TLC control). The reaction mixture was cooled to rt, poured into saturated aqueous $NaHCO_3$, (20 mL) and extracted with DCM (3x20 mL). Combined extracts were washed with brine (20 mL), dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by flash column chromatography.

Oxime 9a.

Time to completion: 24h; eluent: DCM/MeOH/$NH_{3/aq}$, 95/5/1 v/v/v; compound **9a** was isolated as ≈3:1 mixture of E/Z isomers. Yield 715 mg (3.52 mmol, 88%).

White semisolid; ^{1}H-NMR (DMSO-d_6, 500 MHz): 11.14 (s, 1H), 8.25 (d, 1H, *J*=7.8 Hz), 7.51-7.48 (m, 0.29H), 7.40-7.25 (m, 3.87H), 3.18-3.12 (m, 0.29H), 3.12-3.07 (m, 1H), 3.03 (d, 1H, *J*=16.5 Hz), 2.97 (d, 1H, *J*=16.5 Hz), 2.89-2.83 (m, 1H), 2.83-2.80 (m, 0.29H), 2.26 (m, 0.29H), 1.93-1.74 (m, 4.58H), 1.71-1.68 (m, 0.29H); ^{13}C-NMR (DMSO-d_6, 125 MHz), major isomer: 161.0, 145.0, 132.7, 130.3, 128.4, 126.5, 125.2, 69.5, 45.8, 44.9, 38.2, 25.4, minor isomer: 161.4, 144.0, 136.0, 130.1, 127.0, 125.5, 120.5, 70.3, 46.2, 46.0, 35.7, 25.1; MS (ES, HR) m/z: ($M+H^+$) calcd for $C_{12}H_{15}N_2O$: 203.1184; found: 203.1184.

Reduction of oxime 9a.

Pearlman's catalyst ($Pd(OH)_2$/C, 20% wt loading, 100 mg) and acetic acid (2 mL) were added to the solution of oxime **9a** (600 mg, 2.97 mmol) in methanol (30 mL) and the mixture was stirred for 24h at rt under

hydrogen atmosphere (balloon). The solution was filtered through Celite and concentrated under reduced pressure. The residue was dissolved in DCM (10 mL), washed with aqueous NaOH (10%, 10 mL), dried over Na_2SO_4, filtered, and evaporated *in vacuo*. The crude product was purified by flash chromatography on silica gel (DCM/MeOH/$NH_{3/aq}$, 93/7/1 v/v/v) to give diamine **10a** and **11a**.

Cis-diamine **10a**: Yield 20 mg (0.106 mmol, 4%); oil; $[\alpha]_D^{23}$ -38.9 (c 1.0, CH_2Cl_2); IR (CH_2Cl_2): 3601, 3369, 2962, 1606 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.33-7.30 (m, 1H), 7.22-7.15 (m, 3H), 3.98 (s, 1H), 3.12-3.06 (m, 1H), 3.07 (d, 1H, *J*=15.5 Hz), 3.04-2.97 (m, 1H), 2.84 (d, 1H, *J*=15.5 Hz), 2.17 (br s, 3H), 1.90-1.75 (m, 4H); ^{13}C-NMR ($CDCl_3$, 125 MHz): 145.9, 140.9, 127.4, 126.7, 124.9, 124.1, 73.3, 62.5, 45.9, 43.6, 35.7, 25.4; MS (EI, HR) m/z: (M^+) calcd for $C_{12}H_{16}N_2$: 188.1313; found: 188.1321.

Trans-diamine **11a**: Yield 410 mg (2.18 mmol, 73%); oil; $[\alpha]_D^{23}$ -7.2 (c 1.0, CH_2Cl_2); IR (CH_2Cl_2): 3601, 3389, 2964, 2875, 1606 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.30-7.27 (m, 1H), 7.23-7.12 (m, 3H), 4.22 (s, 1H), 3.15-3.09 (m, 1H), 3.09-3.03 (m, 1H), 2.98 (d, 1H, *J*=15.0 Hz), 2.81 (d, 1H, *J*=15.0 Hz), 2.02 (br s, 3H), 1.92-1.80 (m, 3H), 1.45-1.39 (m, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz): 145.6, 140.3, 127.3, 126.7, 124.7, 123.1, 75.7, 63.1, 46.0, 44.0, 29.9, 24.9; MS (EI, HR) m/z: (M^+) calcd for $C_{12}H_{16}N_2$: 188.1313; found: 188.1308.

Preparation of compound 12.

The diisopropylethylamine (20 µl, 0.117 mmol) and phosgene (31 µl, 20% solution in toluene) were added to the solution of amine **10a** (11 mg, 0.0585 mmol) in DCM (1 mL) at -20°C. The solution was brought to rt and stirring was continued until disappearance of **10a**, (TLC control, ~3h). The reaction mixture was poured into aqueous NaOH (10%, 5 mL) and extracted with DCM (2x10 mL). The combined extracts were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by flash column chromatography using ethyl acetate/hexane, 80/20 v/v as an eluent. Yield 5 mg (0.023 mmol, 40%); oil; $[\alpha]_D^{23}$ -162.1 (c 1.0, CH_2Cl_2); IR (CH_2Cl_2): 1702 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz): 7.29-7.18 (m, 4H), 6.69 (br s, 1H), 4.88 (s, 1H), 3.73-3.66 (m, 1H), 3.22 (d, 1H, *J*=16.4 Hz), 3.17-3.12 (m, 1H), 2.98 (d, 1H, *J*=16.4 Hz), 2.14-2.05 (m, 1H), 2.05-1.89 (m, 3H); ^{13}C-NMR ($CDCl_3$, 150 MHz): 164.6, 142.1, 140.3, 128.5, 127.4, 125.2, 124.6, 76.3, 63.0, 43.9, 43.6, 34.3, 25.2; MS (EI, HR) m/z: (M^+) calcd dof $C_{13}H_{14}N_2O$: 214.1106; found: 214.1102.

Preparation of diamine 10b.

Oxime **9b** was obtained from aminoketone **8b** (1.753 g, 6.11 mmol) followed general procedure **I**. Time to completion: 72h; eluent DCM/MeOH/$NH_{3/aq}$, 98.5/1.5/0.5 v/v/v; semisolid; yield 1.642 g (5.44 mmol, 89%). The crude oxime **9b** was hydrogenated using the same procedure as used for oxime **9a**. Purification by flash chromatography on silica gel (MTBE/MeOH/$NH_{3/aq}$, 98.5/1.5/0.5 v/v/v) followed by crystallization (from MTBE) of solid obtained by solvent removal, gave enantiomerically pure amine **10b**. Yield 1.531 g (4.73 mmol, 87%); colourless crystals; mp 104-105°C (MTBE); $[\alpha]_D^{23}$ -4.3 (c 1.0, CH_2Cl_2); IR (CH_2Cl_2): 3387, 2978, 1680 cm^{-1}; ^{1}H-NMR (Tol-d_8, 70°C, 600 MHz): 7.31 (d, 1H, *J*=6.0 Hz), 7.11-7.04 (m, 2H), 7.00-6.96 (m, 1H), 3.77 (s, 1H), 3.48-3.40 (m, 2H), 2.64 (d, 1H, *J*=16.6 Hz), 1.70-1.60 (m, 2H), 1.58-1.49 (m, 3H), 1.45-1.38 (m, 1H), 1.23 (s, 9H); ^{13}C-NMR (Tol-d_8, 70°C, 150 MHz): 155.0, 146.5, 141.3, 127.7, 126.7, 124.2, 78.9, 71.9, 68.0, 49.4, 43.9, 28.6, 28.4, 22.3; MS (EI, HR) m/z: (M^+) calcd for $C_{17}H_{24}N_2O_2$: 288.1838; found: 288.1830. Anal. Calcd for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39; N, 9.71; found: C, 70.88; H, 8.37; N, 9.64.

Preparation of ligands 13-15.

General procedure II for *N*-Boc deprotection.

The *N*-Boc protected amine (1 mmol) was dissolved in TFA (4 mL) at rt and stirred until disappearance of the starting material, typically 0.5-1 h (TLC control). The solvent was evaporated *in vacuo* and residue was dissolved in DCM (20 mL), washed with aqueous NaOH (10%, 2x 5mL), dried and concentrated *in vacuo*. Crude product was directly used in the next step or was purified by flash chromatography.

General procedure III for reductive amination.

To the solution of amine (1 mmol) in MeOH (10 mL) either the monoaldehyde (3 equiv.) or dialdehyde (1.5 equiv.) were added at rt, followed by $NaBH_3CN$ (3 equiv.). The pH of the solution was adjusted to 6.0 with acetic acid, and the resulted mixture was stirred until the reaction was complete (TLC control). The reaction mixture was concentrated *in vacuo*, the residue was dissolved in DCM (20 mL), washed with aqueous NaOH

(10%, 2x 10 mL), dried and concentrated. Crude product was directly used in the next step or was purified by flash chromatography.

General procedure IV for amine alkylation.

Solid Na_2CO_3 (744 mg, 7.00 mmol), NaI (375 mg, 2.5 mmol) and alkyl halide were added to the solution of amine (1 mmol) in MeCN (10 mL). The resulted mixture was stirred at selected temperature until reaction was complete (TLC control). The reaction mixture was cooled to rt, poured into water (20 mL) and extracted with ethyl acetate (2x10 mL). Combined extracts were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. Crude product was directly used in the next step or was purified by flash chromatography.

Ligand 13a.

Amine **10b** (202 mg, 0.70 mmol) was submitted to methylation with formaldehyde using the general procedure **III.** Next, Boc group was removed from crude product following the general procedure **II**. Purification by flash chromatography on silica gel (MTBE/MeOH/$NH_{3/aq}$, 90/10/1 v/v/v) gave diamine **13a.** Yield: 124 mg (0.574 mmol, 82%).

Oil; $[\alpha]_D^{23}$ 13.9 (c 0.960, CH_2Cl_2); IR (CH_2Cl_2): 3277, 2943, 2866, 1605, 1458 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz): 7.28-7.18 (m, 4H), 3.52 (s, 1H), 3.44 (br s, 1H), 3.19 (d, 1H, *J*=16.2 Hz), 3.13-3.08 (m, 1H), 3.07-3.02 (m, 1H), 2.87 (d, 1H, *J*=16.2 Hz), 2.21 (s, 6H), 1.93-1.85 (m, 1H), 1.78-1.66 (m, 3H); ^{13}C-NMR ($CDCl_3$, 150 MHz): 142.9, 139.1, 127.9, 126.3, 126.0, 124.9, 76.1, 69.8, 47.3, 47.1, 42.4, 41.7, 25.7; MS (EI, HR) m/z: (M+) calcd for $C_{14}H_{20}N_2$: 216.1626; found: 216.1634.

Ligand 13b.

Following the general procedure **II** Boc group was removed from diamine **10b** (160 mg, 0.555 mmol). The crude product was submitted to methylation with formaldehyde using the general procedure **III.** Purification by flash chromatography on silica gel (MTBE/MeOH/$NH_{3/aq}$, 93/7/0.5 v/v/v) gave diamine **13b**. Yield: 99.7 mg (0.433 mmol, 78%).

Oil; $[\alpha]_D^{23}$ 29.5 (c 1.0, CH_2Cl_2); IR (CH_2Cl_2): 2935, 1477, 1459 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.28-7.24 (m, 1H), 7.23-7.20 (m, 2H), 7.20-7.15 (m, 1H), 3.65 (s, 1H), 3.38 (d, 1H, *J*=15.5 Hz), 3.25-3.18 (m, 1H), 2.81-2.74 (m, 1H), 2.54 (d, 1H, *J*=15.5 Hz), 2.52 (s, 3H), 2.28 (s, 6H), 1.86-1.76 (m, 3H), 1.68-1.59 (m, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz): 142.2 140.2, 127.6, 126.2, 125.9, 124.9, 76.3, 74.0, 56.4, 43.1, 39.8, 38.4, 38.3, 29.7, 21.4; MS (EI, HR) m/z: (M_+) calcd for $C_{15}H_{22}N_2$: 230.1783; found: 230.1792.

Ligand 13c.

Amine **13a** (43 mg, 0.20 mmol) was submitted to reductive amination with benzaldehyde using the general procedure **III**. Purification by flash chromatography on silica gel (CH_2Cl_2/MeOH/$NH_{3/aq}$, 98/2/0.5 v/v/v) gave ligand **13c**. Yield: 36 mg (0.118 mmol, 59%).

Oil; $[\alpha]_D^{23}$ 18.6 (c 0.735, CH_2Cl_2); IR (CH_2Cl_2): 2961, 2931, 1478, 1458 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.44-7.40 (m, 2H), 7.33-7.27 (m, 3H), 7.25-7.22 (m, 3H), 7.22-7.16 (m, 1H), 4.20 (d, 1H, *J*=13.3 Hz), 3.73 (s, 1H), 3.68 (d, 1H, *J*=13.3 Hz), 3.43 (d, 1H, *J*=15.4 Hz), 3.07-3.00 (m, 1H), 2.70-2.66 (m, 1H), 2.63 (d, 1H, *J*=15.4 Hz), 2.37 (s, 6H), 1.88-1.76 (m, 3H), 1.69-1.62 (m, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz): 142.4, 141.4, 138.9, 128.5, 128.1, 127.5, 126.4, 126.4, 125.8, 124.8, 76.0, 74.5, 55.4, 52.6, 43.5, 40.0, 39.3, 21.3; MS (EI, HR) m/z: (M+) calcd for $C_{21}H_{26}N_2$: 306.2096; found: 306.2106.

Ligand 14a.

Amine **10b** (300 mg, 1.04 mmol) was alkylated with 1,4-dibromobutane (150 µl, 1.30 mmol) using the general procedure **IV**. The reaction mixture was heated at reflux for 16h**.** Next, Boc group was removed from crude product following the general procedure **II**. Purification by flash chromatography on silica gel (MTBE/MeOH/$NH_{3/aq}$, 90/10/1 v/v/v) gave ligand **14a**. Yield: 169 mg (0.70 mmol, 67%).

Oil; $[\alpha]_D^{23}$ 96.7 (c 1.0, CH_2Cl_2); IR (CH_2Cl_2): 3278, 2961 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.26-7.15 (m, 4H), 3.78 (s, 1H), 3.52 (br s, 1H), 3.18 (d, 1H, *J*=16.1 Hz), 3.13-3.03 (m, 2H), 2.85 (d, 1H, *J*=16.1 Hz), 2.74-2.67 (m, 2H), 2.37-2.31 (m, 2H), 1.93-1.85 (m, 1H), 1.81-1.59 (m, 7H); ^{13}C-NMR ($CDCl_3$, 125 MHz): 143.2, 139.5, 127.8, 126.4, 126.0, 124.7, 71.1, 70.3, 49.2, 47.0, 46.8, 40.8, 25.7, 23.3; MS (EI, HR) m/z: (M^+) calcd for $C_{16}H_{22}N_2$: 242.1783; found: 242.1781.

Ligand 14b.

Amine **14a** (68 mg, 0.28 mmol) was submitted to methylation with formaldehyde using the general procedure **III**. Purification by flash chromatography on silica gel (MTBE/MeOH/$NH_{3/aq}$, 90/10/1 v/v/v) gave diamine **14b**. Yield: 64 mg (0.25 mmol, 89%).

Oil; $[\alpha]_D^{23}$ 67.7 (c 1.0, CH_2Cl_2); IR (CH_2Cl_2): 2966, 2788, 1473, 1459 cm^{-1}; ^{1}H-NMR (Tol-d_8, 80°C, 500 MHz): 7.14-6.97 (m, 4H), 3.62 (s, 1H), 3.34 (d, 1H, *J*=14.9 Hz), 3.04-2.98 (m, 1H), 2.90-2.84 (m, 2H), 2.58-2.52 (m, 3H), 2.44 (s, 3H), 2.22 (d, 1H, *J*=14.9 Hz), 1.79-1.67 (m, 2H), 1.61-1.50 (m, 4H), 1.48-1.42 (m, 1H), 1.36-1.27 (m, 1H); ^{13}C-NMR (Tol-d_8, 80°C, 125 MHz): 142.6, 126.9, 126.0, 125.2, 124.5, 75.2, 74.0, 56.3, 51.7, 40.0, 37.3, 36.9, 23.7, 22.1; MS (EI, HR) m/z: (M^+) calcd for $C_{17}H_{24}N_2$: 256.1939; found: 256.1933.

Ligand 14c.

Amine **14a** (80 mg, 0.33 mmol) was submitted to reductive amination with benzaldehyde using the general procedure **III**. Purification by flash chromatography on silica gel (gradient CH_2Cl_2/MeOH, 97/3 to CH_2Cl_2/MeOH/$NH_{3/aq}$, 95/5/1 v/v/v) gave ligand **14c**. Yield: 82 mg (0.248 mmol, 75%).

Oil; $[\alpha]_D^{23}$ 37.7 (c 1.0, CH_2Cl_2); IR (CH_2Cl_2): 2964, 2929, 1453 cm^{-1}; ^{1}H-NMR (Tol-d_8, 80°C, 500 MHz): 7.41-7.37 (m, 2H), 7.21-7.17 (m, 2H), 7.15-7.11 (m, 1H), 7.09-6.96 (m, 4H), 4.33 (d, 1H, *J*=13.6 Hz), 3.78 (s, 1H), 3.69 (d, 1H, *J*=13.6 Hz), 3.35 (d, 1H, *J*=15.1 Hz), 3.02-2.97 (m, 1H), 2.77-2.71 (m, 2H), 2.60-2.52 (m, 3H), 2.40 (d, 1H, *J*=15.1 Hz), 1.77-1.72 (m, 1H), 1.70-1.63 (m, 1H), 1.60-1.47 (m, 6H); ^{13}C-NMR (Tol-d_8, 80°C, 125 MHz): 142.3, 142.1, 141.9, 128.0, 127.8, 127.2, 126.0, 126.0, 125.5, 124.6, 74.1, 74.0, 55.1, 52.5, 51.6, 40.3, 38.6, 23.6, 21.5; MS (EI, HR) m/z: (M^+) calcd for $C_{23}H_{28}N_2$: 332.2252; found: 332.2259.

Ligand 15a.

Amine **10b** (143 mg, 0.496 mmol) was submitted to reductive amination with benzene-1,2-dicarbaldehyde using the general procedure **III**. Next, Boc group was removed from crude product following the general procedure **II**. Purification by flash chromatography on silica gel (CH_2Cl_2/MeOH/$NH_{3/aq}$, 95/5/0.5 v/v/v) gave diamine **15a.** Yield: 64 mg (0.223 mmol, 45%).

Oil; $[\alpha]_D^{23}$ 174.8 (c 1.0, CH_2Cl_2); IR (CH_2Cl_2): 3286, 2958, 2942, 1678 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.30-7.27 (m, 1H), 7.26-7.20 (m, 2H), 7.17-7.11 (m, 5H), 4.18 (d, 2H, *J*=10.5 Hz), 3.96 (s, 1H), 3.85 (d, 2H, *J*=10.5

Hz), 3.22 (d, 1H, *J*=16.1 Hz), 3.13-3.01 (m, 2H), 2.91 (d, 1H, *J*=16.1 Hz), 1.96-1.88 (m, 1H), 1.85-1.77 (m, 2H), 1.75-1.68 (m, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz): 143.0, 140.0, 139.8, 128.0, 126.9, 126.6, 126.6, 124.9, 122.3, 71.3, 70.5, 55.1, 47.0, 46.7, 40.6, 25.7; MS (ES, HR) m/z: ($M+H^+$) calcd for $C_{20}H_{23}N_2$: 291.1856; found: 291.1844.

Ligand 15b.

Amine **15a** (35 mg, 0.12 mmol) was submitted to methylation with formaldehyde using the general procedure **III**. Purification by flash chromatography on silica gel (CH_2Cl_2/MeOH/$NH_{3/aq}$, 95/5/0.5 v/v/v) gave diamine **15b**. Yield: 20 mg (0.065 mmol, 54%).

Oil; $[\alpha]_D^{23}$ 72.3 (c 1.0, CH_2Cl_2); ^{1}H-NMR (Tol-d_8, 80°C, 500 MHz): 7.14-6.99 (m, 8H), 4.34 (d, 2H, *J*=11.1 Hz), 4.11 (d, 2H, *J*=11.1 Hz), 3.99 (s, 1H), 3.28 (d, 1H, *J*=15.1 Hz), 3.08-3.01 (m, 1H), 2.56-2.49 (m, 1H), 2.32 (s, 3H), 2.28 (d, 1H, *J*=15.1 Hz), 1.94-1.86 (m, 1H), 1.79-1.70 (m, 1H), 1.58-1.47 (m, 2H); ^{13}C-NMR (Tol-d_8, 80°C, 125 MHz): 142.5, 141.1, 129.2, 128.3, 126.7, 126.3, 125.5, 122.4, 75.2, 74.6, 57.7, 56.8, 39.8, 37.7, 37.5, 22.3; MS (ES, HR) m/z: ($M+H^+$) calcd for $C_{21}H_{25}N_2$: 305.2012; found: 305.2004.

Ligand 16a.

Amine **10b** (432 mg, 1.5 mmol) was alkylated with 1,5-dibromopentane (246 µl, 1.8 mmol) using the general procedure **IV.** The reaction mixture was heated at reflux for 24h. Next, Boc group was removed from crude product following the general procedure **II**. Purification by flash chromatography on silica gel (MTBE/MeOH/$NH_{3/aq}$, 90/10/1 v/v/v) gave ligand **16a**. Yield: 330 mg (1.29 mmol, 86%).

Semisolid; $[\alpha]_D^{23}$ 55.7 (c 0.545, CH_2Cl_2); IR (CH_2Cl_2): 3268, 2937, 1605 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 600 MHz): 7.29-7.27 (m, 1H), 7.25-7.22 (m, 1H), 7.21-7.17 (m, 2H), 3.47 (s, 1H), 3.27 (d, 1H, *J*=16.5 Hz), 3.15-3.10 (m, 2H), 2.94 (d, 1H, *J*=16.5 Hz), 2.60-2.53 (m, 2H), 2.24 (br s, 2H), 1.96-1.89 (m, 1H), 1.80-1.72 (m, 3H), 1.61-1.47 (m, 4H), 1.38-1.30 (m, 2H); ^{13}C-NMR ($CDCl_3$, 150 MHz): 142.5, 139.5, 127.9, 126.3, 126.1, 125.0, 77.3, 69.6, 47.2, 46.9, 41.5, 26.7, 25.5, 24.1; MS (EI, HR) m/z: (M^+) calcd for $C_{17}H_{24}N_2$: 256.1940; found: 256.1944.

Ligand 16b.

Amine **10b** (86 mg, 0.30 mmol) was alkylated with bis(2-chloroethyl) ether (42 µl, 0.36 mmol) using modified general procedure **IV**. The reaction mixture in DMF solution was heated at 110°C for 16h. Next, Boc group was removed from crude product following the general procedure **II**. Purification by flash chromatography on silica gel (MTBE/MeOH/$NH_{3/aq}$, 90/10/1 v/v/v) gave ligand **16b**. Yield: 51 mg (0.198 mmol, 66%).

Oil; $[\alpha]_D^{23}$ 61.9 (c 0.945, CH_2Cl_2); IR (CH_2Cl_2): 3278, 2962, 2858 cm^{-1}; ^{1}H-NMR (C_6D_6, 600 MHz): 7.09-7.03 (m, 4H), 3.52-3.47 (m, 2H), 3.44-3.39 (m, 2H), 3.22 (s, 1H), 3.03 (d, 1H, *J*=16.3 Hz), 2.98-2.93 (m, 1H), 2.91-2.86 (m, 1H), 2.73 (d, 1H, *J*=16.3 Hz), 2.52-2.46 (m, 2H), 2.10-2.04 (m, 2H), 1.68-1.59 (m, 1H), 1.53-1.43 (m, 3H); ^{13}C-NMR (C_6D_6, 150 MHz): 143.0, 139.9, 127.8, 126.4, 126.0, 124.9, 77.1, 70.0, 67.1, 50.6, 48.3, 47.0, 41.9, 25.8; MS (EI, HR) m/z: (M^+) calcd for $C_{16}H_{22}N_2O$: 258.1732; found: 258.1721.

Ligand 16c.

Amine **10b** (58 mg, 0.20 mmol) was alkylated with benzyl chloride (54 µl, 0.45 mmol) using the general procedure **IV**. The reaction mixture was stirred at 50°C for 3h. Next, Boc group was removed from crude product following the general procedure **II**. Purification by flash chromatography on silica gel (MTBE/MeOH/$NH_{3/aq}$, 97/3/0.5 v/v/v) gave ligand **16c**. Yield: 68 mg (0.184 mmol, 92%).

Oil; $[\alpha]_D^{23}$ 136.8 (c 1.68, CH_2Cl_2); IR (CH_2Cl_2): 3279, 2957, 2931 cm^{-1}; ^{1}H-NMR (C_6D_6, 600 MHz): 7.39-7.36 (m, 1H), 7.35-7.30 (m, 3H), 7.18-6.98 (m, 10H), 3.80 (d, 2H, *J*=13.2 Hz), 3.78 (s, 1H), 3.34-3.25 (br d, 2H, *J*=13.2 Hz), 3.18 (d, 1H, *J*=16.3 Hz), 2.99-2.91 (m, 2H), 2.73 (d, 1H, *J*=16.3 Hz), 1.50-1.43 (m, 1H), 1.42-1.27 (m, 3H), 1.14-1.05 (m, 1H); ^{13}C-NMR (C_6D_6, 150 MHz): 143.2, 141.3, 140.2, 129.1, 128.8, 128.2, 127.8, 126.9, 126.1, 126.0, 125.1, 125.0, 70.4, 70.2, 55.5, 48.3, 47.3, 42.0, 25.8; MS (EI, HR) m/z: ($M+H^+$) calcd for $C_{26}H_{29}N_2$: 369.2325; found: 369.2326.

Ligand 16d.

Amine **10b** (86 mg, 0.30 mmol) was alkylated with 1,8-bis(bromomethyl)naphthalene[15] (113 mg, 0.36 mmol) using the general procedure **IV**. The reaction mixture was stirred at rt for 4h. Next, Boc group was

removed from crude product following the general procedure **II**,. Purification by flash chromatography on silica gel (CH_2Cl_2/MeOH/$NH_{3/aq}$, 96/4/0.5 v/v/v) gave ligand **16d**. Yield: 85 mg (0.249mmol, 83%).

Oil; $[\alpha]_D^{23}$ 146.3 (c 0.950, CH_2Cl_2); IR (CH_2Cl_2): 3283, 2958, 2929 cm^{-1}; ^{1}H-NMR (C_6D_6, 600 MHz): 7.48 (d, 1H, *J*=8.2 Hz), 7.14 (tr, 2H, *J*=8.2 Hz), 7.11-7.01 (m, 4H), 6.88 (d, 2H, *J*=6.8 Hz), 4.11 (d, 2H, *J*=14.1 Hz), 3.71 (s, 1H), 3.67 (d, 2H, *J*=14.1 Hz), 3.38 (d, 1H, *J*=16.4 Hz), 2.82 (d, 1H, J=16.4 Hz), 2.78-2.72 (m, 1H), 2.66-2.61 (m, 1H), 1.58-1.49 (m, 3H), 1.44-1.38 (m, 2H); ^{13}C-NMR (C_6D_6, 150 MHz): 143.1, 139.7, 134.7, 133.4, 128.5, 127.9, 126.6, 126.0, 125.8, 125.4, 125.1, 121.5, 76.6, 72.4, 53.8, 48.2, 46.7, 42.0, 25.7; MS (EI, HR) m/z: ($M+H^+$) calcd for $C_{24}H_{25}N_2$: 341.2012; found: 341.2018.

Ligand 16e.

Step 1: preparation of amide 17.

The solution of 2-(2-bromophenyl)acetyl chloride (117 mg, 0.5mmol) in DCM (1 mL) was added dropwise to the stirred solution of amine **10b** (144 mg, 0.5 mmol) and TEA (279 μl, 2 mmol) in DCM (10 mL) at -30^{o}C. Stirring was continued at this temperature for 0.5 h, the mixture was poured into aqueous NaOH (5%, 10 mL) and was extracted with DCM (3x10 mL). Combined organic extracts were washed with brine (20 mL), dried with $MgSO_4$ and concentrated *in vacuo*. Next, Boc group was removed from the crude product using the general procedure **II**. Purification by flash chromatography on silica gel (MTBE/MeOH/$NH_{3/aq}$ 95/5/0.5, v/v/v) furnished amide **17**. Yield: 161 mg (0.42 mmol, 84%).

Oil; $[\alpha]_D^{23}$ 32.3 (c 1.0, CH_2Cl_2); IR (CH_2Cl_2): 3314, 2956, 1662, 1497 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.60-7.54 (m, 1H), 7.41-7.37 (m, 1H), 7.33-7.28 (m, 1H), 7.19-7.09 (m, 4H), 6.94-6.86 (m, 1H), 5.17 (d, 1H, J=8.5 Hz), 3.84 (dd, 2H, *J*=16), 2.97 (d, 1H, *J*=16 Hz), 2.94-2.83 (m, 2H), 2.70-2.63 (m, 1H), 1.96-1.88 (m, 1H), 1.87-1.79 (m, 1H), 1.78-1.64 (m, 2H), 1.57 (bs, 2H); ^{13}C-NMR ($CDCl_3$, 125 MHz): 143.2, 140.2, 135.2, 133.0, 131.7, 128.9, 127.8, 127.4, 126.9, 125.1, 124.7, 124.6, 72.4, 60.0, 45.8, 45.0, 44.3, 34.5, 25.7; MS (ES, HR) m/z: ($M+H^+$) calcd for $C_{20}H_{22}N_2OBr$: 385.0910; found: 385.0929.

Step 2: preparation of amine 18.

Reduction of amide **17** was carried out analogously to reported procedure[16]

The solution of $AlCl_3$ (240 mg, 1.8 mmol) in diethyl ether (5 mL) was added dropwise into the suspension of $LiAlH_4$ (45.5 mg, 1.2 mmol) in diethyl ether (10 mL) at 0^{o}C. The mixture was stirred for 0.5 h and the solution of **17** (115 mg, 0.3 mmol) in diethyl ether (5 mL) was added. Stirring was continued at this temperature for 0.5 hr, then the mixture was allowed to warm up slowly to rt and was stirred for another 3 hr. The reaction was quenched by a slow addition of aqueous NaOH (20%, 20 mL). The mixture was extracted with DCM (3x20 mL), combined organic extracts were washed with brine (30 mL), dried with $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel (MTBE/MeOH/$NH_{3/aq}$, 85/55/0.5, v/v/v) furnished amine **18**. Yield: 79 mg (0.213 mmol, 71%).

Oil; $[\alpha]_D^{23}$ 19.6 (c 1.0, CH_2Cl_2); IR (CH_2Cl_2): 3290, 2926, 1470 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.55 (d, 1H, *J*=5.0Hz), 7.30-7.21 (m, 2H), 7.21-7.14 (m, 3H), 7.12-7.05 (m, 1H), 3.64 (s, 1H), 3.18 (d, 1H, J=15.5 Hz), 3.15-3.05 (m, 2H), 3.00-2.88 (m, 4H), 2.83 (d, 1H, J=15.5 Hz), 2.61 (bs, 2H), 1.93-1.83 (m, 1H), 1.82-1.70 (m, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz): 144.11, 141.4, 139.3, 132.9, 130.9, 127.9, 127.7, 127.4, 126.5, 125.1, 124.7, 124.6, 72.5, 68.7, 48.4, 46.0, 44.0, 37.5, 37.3, 25.2; MS (ES, HR) m/z: ($M+H^+$) calcd for $C_{20}H_{24}N_2Br$: 371.1117; found: 371.1123.

Step 3: preparation of diamine 16e.

The amine arylation was carried out analogously to Buchwald's procedure.[17]

The Schlenk tube was charged with K_2CO_3 (44 mg, 3.2mmol), NaOtBu (31 mg, 3.2 mmol), $Pd(PPh_3)_4$ (23 mg, 0.02 mmol), and amine **18** (74 mg, 0.2 mmol), followed by toluene (2.5 mL) and the solution was stirred at 100^{o}C for 4h. The reaction mixture was cooled to rt, poured into aqueous NaOH (5%, 5 mL) and extracted with DCM (3x5 mL). Combined organic extracts were washed with brine (15 mL), dried with $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel (MTBE/MeOH/$NH_{3/aq}$, 85/15/0.5 v/v/v) furnished ligand **16e**. Yield: 41 mg (0.142 mmol, 71%).

Oil; $[\alpha]_D^{23}$ 214.0 (c 1.0, CH_2Cl_2); IR (CH_2Cl_2): 2952, 2928, 1605, 1487 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.35-7.28 (m, 1H), 7.23-7.20 (m, 1H), 7.14-7.07 (m, 3H), 7.07-7.03 (m, 1H), 6.70-6.63 (m, 2H), 4.67 (s, 1H), 3.28-3.21 (m, 1H), 3.12 (d, 1H, J=16 Hz), 3.09-3.02 (m, 2H), 2.98-2.88 (m, 2H), 2.87-2.77 (m, 2H), 2.54 (bs, 1H), 1.99-1.86 (m, 3H), 1.86-1.78 (m, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz): 142.7, 139.4, 133.7, 129.5, 128.5, 128.3, 127.3, 126.7, 126.0, 124.8, 117.4, 106.2, 70.5, 67.6, 47.0, 46.8, 40.6, 29.7, 28.3, 25.6 ; MS (ES, HR) m/z: ($M+H^+$) calcd for $C_{20}H_{23}N_2$: 291.1856; found: 291.1853.

Preparation of 19.

Acetic anhydride (284 µl, 3.0 mmol) was added to a solution of **10b** (576 mg, 2.0 mmol) in pyridine (5 mL) at rt and the solution was stirred for 2h. The reaction mixture was poured into water (20 mL) and extracted with ethyl acetate (3x20 mL). Combined extracts were washed with water (20 mL), brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was dissolved in TFA (4 mL) and stirred at rt for 0.5 h. TFA was evaporated *in vacuo* and the residue was crystallized from ethyl acetate-hexane mixture. Yield: 565 mg (1.64 mmol, 82%).

Colourless crystals mp 100-110^{o}C (hexane/AcOEt), $[\alpha]_D$ 1.6 (c 1.0, MeOH); IR (KBr): 3225, 3049, 1666, 1183 cm^{-1}; ^{1}H-NMR (CD_3OD, 500 MHz): 7.38-7.29 (m, 4H), 5.4 (s, 1H), 3.51-3.46 (m, 1H), 3.46-3.39 (m, 2H), 3.17 (d, 1H, *J*=16 Hz), 2.28-2.20 (m, 2H), 2.20-2.14 (m, 1H), 2.07 (s, 3H); ^{13}C-NMR (CD_3OD, 125 MHz): 165.4, 152.2, 151.9, 130.8, 121.0, 119.7, 116.8, 116.6, 67.42, 51.0, 37.0, 31.5, 26.4, 13.8, 13.3.

Preparation of 20a.

Compound **19** (61 mg, 0.177 mmol) was submitted to reductive amination with benzaldehyde using the general procedure **III.** Purification by flash chromatography on silica gel (AcOEt/hexane, 40/60 v/v) furnished **20a**. Yield: 38 mg (0.194 mmol, 67%).

$[\alpha]_D^{23}$ 74.1 (c 0.795, CH_2Cl_2); IR (CH_2Cl_2): 3364, 2970, 1667 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.31-7.08 (m, 9H), 5.32 (d, 1H, *J*=6.4 Hz), 3.33-3.24 (m, 2H), 3.04-2.96 (m, 2H), 2.81 (d, 1H, *J*=16.3 Hz), 2.51-2.42 (m, 1H), 2.20-2.15 (m, 1H), 2.13 (s, 4H), 2.07-1.98 (m, 1H), 1.82-1.69 (m, 2H); ^{13}C-NMR ($CDCl_3$, 125 MHz): 170.8,

143.9, 140.3, 139.6, 128.4, 127.9, 127.7, 127.0, 126.9, 123.9, 123.7, 73.5, 58.8, 54.0, 51.5, 37.2, 36.8, 23.5, 21.6; MS (EI, HR) m/z: (M+) calcd for $C_{21}H_{24}N_2O$: 320.1889; found: 320.1886.

Preparation of 20b.

Compound **19** (86 mg, 0.25 mmol) was alkylated with 2,3,4,5,6-pentamethylbenzyl chloride using the general procedure **IV.** The reaction mixture was stirred at rt for 3h. Purification by flash chromatography on silica gel (AcOEt/hexane, 30/70 v/v) furnished **20b**. Yield: 81 mg (0.208 mmol, 83%).

Oil; $[\alpha]_D^{23}$ 45.7 (c 0.670, CH_2Cl_2); IR (CH_2Cl_2): 3373, 2931, 1667 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.40-7.36 (m, 1H), 7.22-7.14 (m, 3H), 7.11 (br d, 1H, *J*=6.4 Hz), 5.11 (d, 1H, *J*=6.4 Hz), 3.60 (d, 1H, *J*=12.8 Hz), 3.48 (d, 1H, *J*=16.1 Hz) 3.10 (d, 1H, *J*=12.8 Hz), 2.89 (d, 1H, *J*=16.1 Hz), 2.68-2.60 (m, 1H), 2.59-2.53 (m, 1H), 2.21 (s, 9H), 2.18 (s, 6H), 2.09 (s, 3H), 2.06-1.99 (m, 1H), 1.75-1.55 (m, 3H); ^{13}C-NMR ($CDCl_3$, 125 MHz): 170.6, 143.4, 140.8, 133.8, 132.9, 132.6, 127.6, 126.9, 124.5, 123.4, 74.4, 60.1, 49.8, 48.0, 38.5, 36.6, 22.4, 17.3, 17.0, 16.9; MS (EI, HR) m/z: (M+) calcd for $C_{26}H_{34}N_2O$: 390.2671; found: 390.2662.

Preparation of 20c.

Compound **19** (103 mg, 0.30 mmol) was alkylated with 2,4,6-triisopropylbenzyl bromide[18] using the general procedure **IV**. The reaction mixture was stirred at rt for 3h. Purification by flash chromatography on silica gel (AcOEt/hexane, 20/80 v/v) furnished **20c**. Yield: 96 mg (0.216 mmol, 72%).

Oil; $[\alpha]_D^{23}$ 32.7 (c 1.09, CH_2Cl_2); IR (CH_2Cl_2): 3374, 2964, 1666, 1490 cm^{-1}; ^{1}H-NMR (C_6D_6, 500 MHz): 7.64 (d, 1H, *J*=5.0Hz), 7.18-7.13 (m, 4H), 7.03-6.98 (m, 1H), 6.72 (d, 1H, *J*=6.7 Hz, -NH), 5.38 (d, 1H, *J*=6.7 Hz), 3.61 (d, 1H, *J*=12.6 Hz), 3.27 (sep, 2H, *J*=6.9 Hz), 3.23 (d, 1H, *J*=12.6 Hz), 3.14 (d, 1H, *J*=16.1 Hz), 2.79 (sep, 1H, *J*=6.9 Hz), 2.56-2.46 (m, 2H), 2.43 (d, 1H, *J*=16.1 Hz), 1.92 (s, 3H), 1.65-1.56 (m, 1H), 1.37-1.27 (m, 3H), 1.23 (d, 6H, *J*=6.9 Hz), 1.16 (d, 6H, *J*=6.9 Hz), 1.10 (d, 6H, J=6.9 Hz); ^{13}C-NMR (C_6D_6, 125 MHz): 169.3, 148.4, 148.1, 144.6, 141.1, 130.2, 128.3, 127.3, 124.7, 123.5, 121.2, 74.7, 60.9, 50.7, 45.7, 38.5, 36.8, 34.6, 29.5, 25.0, 24.3, 24.3, 23.8, 23.2, 22.9; MS (EI, HR) m/z: (M+) calcd for $C_{30}H_{42}N_2O$: 446.3297; found: 446.3292.

Preparation of 20d.

Compound **19** (89 mg, 0.257 mmol) was submitted to reductive amination with naphthalene-1-carbaldehyde using the general procedure **III.** Purification by flash chromatography on silica gel (AcOEt/hexane, 20/80 v/v) furnished **20d**. Yield: 61 mg (0.165 mmol, 64%).

Oil; $[\alpha]_D^{23}$ 78.9 (c 0.460, CH_2Cl_2); IR (CH_2Cl_2): 3372, 2970, 1666 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.82 (m, 1H), 7.73-7.69 (m, 1H), 7.66-7.62 (m, 1H), 7.48-7.37 (m, 2H), 7.34-7.14 (m, 6H), 6.80 (br d, 1H, *J*=7.0 Hz), 5.31 (d, 1H, *J*=7.0 Hz), 3.81 (d, 1H, *J*=13.7 Hz), 3.63 (d, 1H, *J*=13.7 Hz), 3.47 (d, 1H, *J*=16.7 Hz), 3.04-2.98 (m, 1H), 2.94 (d, 1H, *J*=16.7 Hz), 2.66-2.59 (m, 1H), 2.25-2.17 (m, 1H), 2.14-2.05 (m, 1H), 1.84 (s, 3H), 1.82-1.73 (m, 1H), 1.73-1.64 (m, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz): 170.6, 143.9, 140.7, 135.1, 133.8, 131.7, 128.8, 127.8, 127.7, 127.1, 126.3, 125.8, 125.6, 125.3, 124.2, 123.7, 123.6, 74.1, 60.1, 53.4, 52.1, 37.9, 37.6, 23.2, 22.3; MS (EI, HR) m/z: (M+) calcd for $C_{25}H_{26}N_2O$: 370.2045; found: 370.2049.

General procedure V for amide reduction. Preparation of ligands 21a-d.

The solution of amide **20** (0.3 mmol) in THF (3 mL) was added dropwise to suspension of $LiAlH_4$ (24 mg, 0.6 mmol) in THF (1 mL) at 0^{o}C. The reaction mixture was stirred and heated at reflux until completion (TLC control, 2-4h). The solution was cooled to rt and the reaction was quenched by slow addition of aqueous NaOH (20%, 2 mL). Stirring was continued for 0.5 h, mixture was poured into water (3 mL), extracted with DCM (3x15 mL), combined organic extracts were washed with brine (30 mL), dried with $MgSO_4$ and concentrated *in vacuo*. Crude product was purified using flash chromatography.

Ligand 21a.

Amide **20a** (38 mg, 0.12 mmol) was used. Eluent AcOEt/hexane, 65/35 v/v). Yield: 24 mg (0.078 mmol, 65%).

Oil; $[\alpha]_D^{23}$ -18.0 (c 0.405, CH_2Cl_2); IR (CH_2Cl_2): 3285, 2964, 2929 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.36-7.32 (m, 1H), 7.28-7.22 (m, 4H), 7.22-7.14 (m, 4H), 3.87 (s, 1H), 3.70 (d, 1H, *J*=13.1 Hz), 3.41 (d, 1H, *J*=16.1 Hz), 3.05 (d, 1H, *J*=13.1 Hz), 3.01-2.87 (m, 3H), 2.67 (d, 1H, *J*=16.1 Hz), 2.48-2.40 (m, 1H), 2.11-2.03 (m, 1H),

1.90-1.83 (m, 1H), 1.79-1.70 (m, 2H), 1.23 (t, 3H, *J*=7.1 Hz); ^{13}C-NMR ($CDCl_3$, 125 MHz): 141.0, 140.3, 128.4, 128.1, 127.0, 126.6, 126.3, 124.2, 124.1, 74.6, 69.0, 55.3, 51.6, 44.6, 38.6, 37.9, 21.7, 16.0; MS (EI, HR) m/z: (M+) calcd for $C_{21}H_{26}N_2$: 306.2096; found: 306.2091.

Ligand 21b.

Amide **20b** (58 mg, 0.149 mmol) was used. Eluent MTBE/hexane/$NH_{3/\,aq}$, 20/80/1 v/v/v. Yield: 47 mg (0.125 mmol, 84%).

Oil; $[\alpha]_D^{23}$ 0.5 (c 0.69, CH_2Cl_2); IR (CH_2Cl_2): 3278, 2959, 2928 cm^{-1}; ^{1}H-NMR (C_6D_6, 500 MHz): 7.38-7.34 (m, 1H), 7.16-7.10 (m, 3H), 3.65 (s, 1H), 3.60 (d, 1H, *J*=12.5 Hz), 3.57 (d, 1H, *J*=12.5 Hz), 3.53 (d, 1H, *J*=15.2 Hz), 2.89-2.74 (m, 2H), 2.66-2.60 (m, 1H), 2.55-2.49 (m, 1H), 2.49 (d, 1H, *J*=15.2 Hz), 2.33 (s, 6H), 2.07 (s, 9H), 1.87-1.80 (m, 1H), 1.65-1.58 (m, 1H), 1.57-1.49 (m, 1H), 1.49-1.40 (m, 1H), 1.14 (t, 3H, *J*=7.1 Hz); ^{13}C-NMR (C_6D_6, 125 MHz): 146.2, 141.7, 133.2, 133.2, 133.0, 131.9, 126.9, 126.1, 124.4, 123.9, 76.1, 68.9, 48.6, 48.1, 43.8, 38.9, 36.1, 21.9, 17.1, 16.6, 16.6, 15.8; MS (ES, HR) m/z: ($M+H^+$) calcd for $C_{26}H_{37}N_2$: 377.2957; found 377.2954.

Ligand 21c.

Amide **20c** (80 mg, 0.179 mmol) was used. The reduction was carried out using AlH_3 generated *in situ* from $LiAlH_3$ (21 mg, 0.538 mmol) and $AlCl_3$ (72 mg, 0.538 mmol). Reaction mixture was heated at reflux for 18 h. Workup and isolation as in general procedure **V**. Eluent: MTBE/hexane/$NH_{3/aq}$, 10/90/0.5 v/v/v. Yield: 31 mg (0.072 mmol, 40%).

Oil; $[\alpha]_D^{23}$ -12.9 (c 1.055, CH_2Cl_2); IR (CH_2Cl_2): 3282, 2963 cm^{-1}; ^{1}H-NMR (C_6D_6, 500 MHz): 7.38-7.33 (m, 1H), 7.18-7.12 (m, 5H), 3.70 (sep, 2H, *J*=6.8 Hz), 3.74-3.66 (m, 3H), 3.52 (d, 1H, *J*=15.2 Hz), 2.92-2.73 (m, 3H), 2.70-2.63 (m, 1H), 2.54-2.47 (m, 1H), 2.50 (d, 1H, J=15.2 Hz), 1.86-1.80 (m, 1H), 1.67-1.59 (m, 1H), 1.58-1.50 (m, 1H), 1.49-1.39 (m, 1H), 1.29 (dd, 12H, *J*=6.8 Hz), 1.25 (d, 6H, *J*=6.8 Hz), 1.18 (t, 3H, *J*=7.0 Hz); ^{13}C-NMR (C_6D_6, 125 MHz): 148.8, 147.8, 146.5, 142.0, 130.9, 127.3, 126.5, 124.6, 124.2, 121.2, 76.5, 69.2, 48.9, 45.5, 44.3, 39.1, 36.0, 34.7, 29.3, 25.4, 24.4, 24.3, 24.0, 22.2, 16.2; MS (EI, HR) m/z: (M+) calcd for $C_{30}H_{44}N_2$: 432.3504; found: 432.3494.

Ligand 21d.

Amide **20d** (50 mg, 0.135 mmol) was used. Eluent: MTBE/hexane/$NH_{3/aq}$, 20/80/1 v/v/v. Yield: 35 mg (0.0 99 mmol, 73%).

Oil; $[\alpha]_D^{23}$ -20.9 (c 0.650, CH_2Cl_2); IR (CH_2Cl_2): 3285, 2964, 2929 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): 8.25-8.18 (m, 1H), 7.78-7.71 (m, 1H), 7.69-7.63 (m, 1H), 7.43-7.34 (m, 3H), 7.34-7.30 (m, 1H), 7.29-7.25 (m, 1H), 7.21-7.17 (m, 1H), 7.15-7.08 (m, 2H), 4.13 (d, 1H, *J*=13.3 Hz), 3.77 (s, 1H), 3.56 (d, 1H, *J*=15.7 Hz), 3.53 (d, 1H, *J*=13.3 Hz), 2.91-2.79 (m, 2H), 2.76-2.67 (m, 2H), 2.57-2.49 (m, 1H), 2.01-1.93 (m, 1H), 1.86-1.79 (m, 1H), 1.78-1.70 (m, 1H), 1.69-1.61 (m, 1H), 1.12 (t, 3H, *J*=7.1 Hz); ^{13}C-NMR ($CDCl_3$, 125 MHz): 145.8, 141.3, 135.9, 133.7, 132.1, 128.4, 127.4, 127.1, 126.5, 126.3, 125.6, 125.4, 125.2, 124.6, 124.4, 124.3, 75.6, 69.2, 52.8, 51.5, 44.3, 38.3, 37.6, 21.6, 15.8; MS (ES, HR) m/z: ($M+H^+$) calcd for $C_{25}H_{29}N_2$: 357.2325; found: 357.2338.

Preparation of amide 22.

Benzyl chloroformate (149 µl, 1.041 mmol) was added dropwise to a stirred solution of **10b** (200 mg, 0.694 mmol) and Hünig's base (272 µl, 1.562 mmol) in DCM (15 mL) at rt and the solution was stirred for 2h. The mixture was poured into saturated aqueous $NaHCO_3$ (15 mL) and extracted with DCM (2x20 mL). Combined extracts were washed with water (20 mL), brine, dried over $MgSO_4$, and evaporated under reduced pressure. Next, Boc group was removed from the crude product following the general procedure **II**. Purification by flash chromatography on silica gel (MTBE/MeOH/$NH_{3\ aq}$, 98/2/0.5 v/v/v) furnished **22**. Yield: 214 mg (0.666 mmol, 96%).

Oil; $[\alpha]_D^{23}$ 76.7 (c 0.801, CH_2Cl_2); IR (CH_2Cl_2): 3376, 2964, 1714 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.43-7.34 (m, 4H), 7.34-7.28 (m, 2H), 7.21-7.12 (m, 3H), 6.03 (br d, 1H, *J*=8.0 Hz), 5.21 (d, 1H, *J*=12.2 Hz), 5.16 (d, 1H, *J*=12.2 Hz), 4.95 (d, 1H, *J*=8.0 Hz), 3.03-2.96 (m, 1H), 2.96-2.88 (m, 3H), 2.02-1.92 (m, 1H), 1.89-1.77 (m, 3H), 1.48 (br s, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz): 157.1, 143.4, 140.2, 136.8, 128.5, 128.0, 127.5, 126.9, 124.7, 124.7, 72.5, 66.7, 61.5, 45.8, 44.6, 34.6, 25.5; MS (EI, HR) m/z: (M+) calcd for $C_{20}H_{22}N_2O_2$: 322.1681; found: 322.1671.

Preparation of ligands 24a-e

Compound **22** was alkylated with appropriate benzyl chloride or bromide using the general procedure **IV**. Crude products **23a-e** were reduced with $LiAlH_4$ following the general procedure **V** to give ligands **24a-e.**

Ligand 24a.

Compound **22** (370 mg, 1.15 mmol) was alkylated with 2,3,4,5,6-pentamethylbenzyl chloride. Reduction of amide **23a** followed by purification by flash chromatography on silica gel (MTBE/hexane/$NH_{3/aq}$, 30/70/0.5 v/v/v) furnished **24a**. Yield: 344 mg (0.955 mmol, 83%).

Colourless crystals; mp 164-166°C (hexane); $[\alpha]_D^{23}$ -0.5 (c 0.52, CH_2Cl_2); IR (CH_2Cl_2): 3603, 3299, 2929, 2881 cm^{-1}; ^{1H}NMR (C_6D_6, 500 MHz): 7.37-7.34 (m, 1H), 7.21-7.16 (m, 3H), 3.65 (s, 2H), 3.63 (d, 1H, *J*=14.8 Hz), 3.48 (s, 1H), 2.73-2.66 (m, 1H), 2.54 (s, 3H), 2.54 (d, 1H, *J*=14.8 Hz), 2.53-2.47 (m, 1H), 2.37 (s, 6H), 2.12 (s, 9H), 1.86-1.78 (m, 1H), 1.67-1.57 (m, 2H), 1.54-1.43 (m, 1H); ^{13}C-NMR (C_6D_6, 125 MHz): 145.5, 142.0, 133.3, 133.2, 133.1, 132.0, 127.0, 126.0, 124.7, 124.1, 76.5, 70.8, 48.6, 48.1, 39.1, 35.8, 35.7, 22.0, 16.9, 16.7, 16.6; MS (EI, HR) m/z: (M+) calcd for $C_{25}H_{34}N_2$: 362.2722; found: 362.2717. Anal. Calcd for: C, 82.80; H, 9.40; N, 7.70; found: C, 82.63; H, 9.56; N, 7.54.

Ligand 24b.

Compound **22** (97 mg, 0.3 mmol) was alkylated with 2-chloromethylnaphthalene. Reduction of amide **23b** followed by purification by flash chromatography on silica gel (MTBE/hexane/$NH_{3/aq}$, 20/80/0.5 v/v/v) furnished **24b**. Yield: 78.3 mg (0.228 mmol, 76%).

Oil; $[\alpha]_D^{23}$ -9.3 (c 1.0, CH_2Cl_2); IR (CH_2Cl_2): 3304, 3049, 2926, 1475, 1125 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): 7.81-7.73 (m, 3H), 7.66 (s, 1H), 7.48-7.44 (m, 1H), 7.44-7.40 (m, 2H), 7.37-7.33 (m, 2H), 7.24-7.16 (m, 2H), 3.91 (d, 1H, J=13.0 Hz), 3.75 (s, 1H), 3.49 (d, 1H, J=16 Hz), 3.29 (d, 1H, J=13 Hz), 2.93-2.87 (m, 1H), 2.75-2.68 (m, 4H), 2.55-2.48 (m, 1H), 2.40-2.18 (bs, 1H), 2.13-2.06 (m, 1H), 1.92-1.85 (m, 1H), 1.80-1.72 (m, 2H); ^{13}C-NMR ($CDCl_3$, 125 MHz): 145.4, 141.2, 138.0, 133.4, 128.5, 127.8, 127.6, 127.22, 127.0, 126.6, 126.3, 125.8, 125.3, 124.3, 74.7, 71.4, 55.7, 52.0, 38.6, 38.2, 37.0, 21.82 ; MS (EI, HR) m/z: (M+) calcd for $C_{24}H_{26}N_2$: 342.2096; found: 342.2091.

Ligand 24c.

Compound **22** (81 mg, 0.25 mmol) was alkylated with 1-chloromethyl-2-methylnaphthalene. Reduction of amide **23c** followed by purification by flash chromatography on silica gel (MTBE/hexane/$NH_{3/aq}$, 20/80/0.5 v/v/v) furnished **24c**. Yield: 68.6 mg (0.193 mmol, 77%).

Oil; $[\alpha]_D^{23}$ 14.0 (c 1.02, CH_2Cl_2); IR (CH_2Cl_2): 3307, 3046, 2927, 2786, 1470, 1064 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): 8.48-8.43 (m, 1H), 7.80-7.77 (m, 1H), 7.70-7.66 (m, 1H), 7.52-7.48 (m, 1H), 7.43-7.38 (m, 1H), 7.37-7.35 (m, 1H), 7.35-7.28 (m, 2H), 7.25-7.17 (m, 2H), 4.12-4.01 (m, 2H), 3.87 (d, 1H, *J*=14.9 Hz), 3.46 (s, 1H), 2.93 (d, 1H, *J*=15.0 Hz), 2.75-2.69 (m, 1H), 2.58 (s, 3H), 2.53 (s, 3H), 2.48-2.40 (m, 1H), 1.98-1.88 (m, 3H), 1.76-1.67 (m, 1H), 1.32-1.23 (m, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz): 144.6, 141.8, 140.9, 135.0, 133.4, 132.6, 129.1, 128.6, 128.2, 127.4, 127.0, 126.2, 125.9, 125.1, 124.8, 124.6, 70.8, 65.3, 49.2, 46.9, 39.5, 35.5, 35.4, 22.2, 20.8; MS (EI, HR) m/z: (M+) calcd for $C_{25}H_{28}N_2$: 356.2253; found: 356.2260.

Ligand 24d.

Compound **22** (97 mg, 0.3 mmol) was alkylated with 1-chloromethyl-2-ethylnaphthalene.[19] Reduction of amide **23d** followed by purification by flash chromatography on silica gel (MTBE/hexane/$NH_{3/aq}$, 20/80/0.5 v/v/v) furnished **24d**. Yield: 83 mg (0.222 mmol, 74%).

Oil; $[\alpha]_D^{23}$ 14.1 (c 0.99, CH_2Cl_2); IR (CH_2Cl_2): 3307, 3045, 2960, 2788, 1460, 819 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): 8.51-8.45 (m, 1H), 7.81-7.76 (m, 1H), 7.76-7.70 (m, 1H), 7.53-7.47 (m, 1H), 7.43-7.38 (m, 1H), 7.37-7.28 (m, 3H), 7.24-7.16 (m, 2H), 4.14-4.02 (m, 2H), 3.87 (d, 1H, *J*=14.5 Hz), 3.47 (bs, 1H), 3.06-2.93 (m, 3H), 2.77-2.70 (m, 1H), 2.52 (s, 3H), 2.48-2.40 (m, 1H), 1.97-1.88 (m, 3H), 1.76-1.65 (m, 1H), 1.35-1.20 (m, 4H); ^{13}C-NMR ($CDCl_3$, 125 MHz): 141.8, 141.4,140.9, 133.5, 132.5, 131.4, 128.6, 128.2, 127.8, 127.6, 127.0, 126.2, 125.9, 125.4, 124.9, 124.7, 71.0, 65.3, 49.0, 46.2, 39.5, 35.3, 29.7, 26.8, 22.2, 16.2; MS (ESI, HR) m/z: ($M+H^+$) calcd for $C_{26}H_{31}N_2$: 371.2481; found: 371.2494.

Ligand 24e.

Compound **22** (129 mg, 0.4 mmol) was alkylated with 1-chloromethyl-2,3-dimethylnaphthalene.[20] Reduction of amide **23d** followed by purification by flash chromatography on silica gel (MTBE/hexane/$NH_{3/aq}$, 20/80/0.5 v/v/v) furnished **24d**. Yield: 111 mg (0.3 mmol, 75%).

Oil; $[\alpha]_D^{23}$ 6.3 (c 1.06, CH_2Cl_2); IR (CH_2Cl_2): 3306, 3046, 2926, 2789,1461, 1063 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz): 8.37-8.31 (m, 1H), 7.73-7.69 (m, 1H), 7.58 (s, 1H), 7.47-7.42 (m, 1H), 7.41-7.37 (m, 1H), 7.41-7.28 (m, 3H), 7.25-7.15 (m, 1H), 4.68 (s, 1H), 4.17.4.07 (m, 2H), 3.88 (d, 1H, *J*=15.0), 3.48 (bs, 1H), 2.94 (d, 1H, *J*=15.0), 2.77-2.69 (m, 1H), 2.53-2.47 (m, 6H), 2.48-2.40 (m, 3H), 1.98-1.88 (m, 3H), 1.75-1.67 (m, 1H), 1.28-1.24 (m, 1H); ^{13}C-NMR ($CDCl_3$, 125 MHz): 144.4, 141.9, 140.9, 135.4, 135.3, 132.3, 132.1, 128.5, 127.7, 127.6, 126.9, 126.2, 125.1, 124.9, 124.8, 124.6, 79.5, 73.0, 65.3, 51.4, 49.2, 41.8, 37.7, 24.6, 24.0, 18.9; MS (EI, HR) m/z: (M+) calcd for $C_{26}H_{30}N_2$: 370.2409; found: 370.2413.

Ligand 25.

Compound **22** (78 mg, 0.242 mmol) was alkylated with 2,3,4,5,6-pentamethylbenzyl chloride. The Cbz protective group was removed using hydrogenation procedure analogical to that of oxime **9a** reduction. Purification by flash chromatography on silica gel (MTBE/hexane/$NH_{3/aq}$, 50/50/0.5 v/v/v) gave diamine **25**.Yield: 58 mg (0.167 mmol, 69%).

Colourless crystals; mp 127-128°C (hexane); $[\alpha]_D$ -52.5 (c 1.0, CH_2Cl_2); IR (CH_2Cl_2): 3380, 3288, 2928, cm^{-1}; ^{1}H-NMR (C_6D_6, 500 MHz): 7.55 (d, 1H, *J*=5Hz), 7.21- 7.14 (m, 3H), 3.91 (s, 1H), 3.59 (d, 1H, *J*=12.4 Hz), 3.33 (d, 1H, *J*=12.4 Hz), 3.31 (d, 1H, *J*=15.7 Hz), 2.65-2.56 (m, 2H), 2.49 (d, 1H, *J*=15.7 Hz), 2.25 (s, 6H), 2.10 (s, 3H), 2.08 (s, 6H), 1.85-1.78 (m, 1H), 1.68-1.60 (m, 1H), 1.52-1.41 (m, 2H), 1.32 (br s, 2H); ^{13}C-NMR (C_6D_6, 125 MHz): 147.2, 141.1, 133.1, 133.0, 132.9, 131.8, 127.0, 126.5, 123.6, 123.4, 75.7, 63.2, 49.2, 48.3, 38.1, 36.1, 22.1, 17.0, 16.6, 16.5; MS (EI, HR) m/z: (M+) calcd for dla $C_{24}H_{32}N_2$: 348.2565; found: 348.2573. Anal. Calcd for: C, 82.70; H, 9.20; N, 8.00; found: C, 82.97; H, 9.14; N, 7.93.

General procedure for the asymmetric Henry reaction

Ligand (0.05 mmol) and $Cu(OAc)_2 \cdot H_2O$ (10 mg, 0.05 mmol) were stirred in DCM (2 mL) until complete dissolution of copper salt (2–6 h). The resulted light to deep blue solution was filtered through a pad of Celite. The pad was washed with DCM (1 mL) and the combined filtrates were concentrated *in vacuo*. The

residue was dissolved in *i*-PrOH (2 mL), cooled to the appropriate temperature, and nitromethane (271 µL, 5 mmol), aldehyde (0.5 mmol) and triethylamine (0.025 mmol, 25 µL of 1 M TEA/i-PrOH) were successively added. The reaction mixture was stirred until the aldehyde was consumed (TLC control), and was quenched with saturated ammonium chloride (2 mL), stirred for 2 min, poured into water (5 mL) and extracted with DCM (3x 10 mL). The combined extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Flash chromatography purification of residue gave the known respective β-nitroalcohols. The ee's and absolute configuration were determined by chiral HPLC analysis using OD-H, OJ-H and AD-H Chiralpack column as described in the literature.[12n]

Acknowledgement

The authors are grateful to the National Science Centre (Grant NN 204 271538) for financial support.

Supporting Information Available: The general experimental methods as well as ^{1}H-NMR, ^{13}C-NMR spectra and selected HPLC chromatograms for the characterization of compounds are reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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