Catalysis Science & Technology

PAPER

View Article Online
View Journal | View Issue

Cite this: *Catal. Sci. Technol.*, 2014, **4**, 548

Chiral Cu(II)-amino alcohol based complexes for asymmetric aza-Henry reaction of *N*-Ts imines†

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Received 4th October 2013,
Accepted 4th November 2013

DOI: 10.1039/c3cy00774j

www.rsc.org/catalysis

A series of chiral dimeric ligands **1A–C**, **2A–B**, **3A–B** and **4A** derived from (*S*)/(*R*) 1,1′-bi(2-naphthol)-bis-aldehyde/piperazine-bis-aldehyde and various aminoalcohols *viz.*, (1*R*,2*S*)-(–)-2-aminodiphenylethanol, (1*S*,2*R*)-(–)-2-aminodiphenylethanol, (1*R*,2*S*)-1-amino-2,3-dihydro-1*H*-inden-2-ol and (*R*)-valinol were synthesized. *In situ* generated complexes **1A–C–**, **2A–B–**, **3A–B–**, **4A–Cu(II)/Cu(I)** of dimeric chiral ligands with different copper salts were used as catalysts for the asymmetric aza-Henry reaction of a variety of *N*-tosylimines as substrates with different nitroalkanes at RT to afford good yields of aza-Henry products (80% with respect to the imines) with excellent enantioselectivity (ee > 99%) in 24 h with nitromethane and high *syn* selective products with excellent enantioselectivity with nitroethane. The dimeric chiral Cu(II) complex **1A–Cu(II)** retained its performance at the gram level and was expediently recycled for a number of times. The enantio-pure aza-Henry product was further used for the synthesis of (*S*)-levamisole (an anthelminthic agent) in good yield and ee in three steps.

Introduction

The aza-Henry, or nitro-Mannich, reaction is a fundamental C–C bond forming reaction in organic chemistry that involves the addition of nitroalkanes to several types of imines. Nowadays, this reaction has drawn much attention, because the end products of the aza-Henry reaction can easily be transformed into many value added products *viz.*, vicinal diamines *via* reduction of the nitro group[1,2] and α-amino carbonyl compounds by the Nef oxidation.[3–6] Several natural products comprising of vicinal diamine moieties have valuable biological[7] and medicinal properties[8] like antiarrhythmic,[9] antidepressant,[10] antihypertensive,[11] analgesic,[12] anticancer, antiviral drugs[13] and antiparasitic agents.[14] Apart from the applications in the field of medicinal chemistry, the use of diamines has also gained considerable interest in the synthesis of ligands for metal based catalysts[15–19] and organo-catalysts.[20–22] Due to the extensive applications of the enantio-pure product of the asymmetric aza-Henry reaction, several catalytic systems based on both metal and metal-free (organo-catalyst) have been explored in recent years.[23] Among them, BINOL,[24,25] bis-oxazolines,[26,27] phenyl bis oxazoline[28] and salen ligands with various metals (Cu, Zn, La, Ni, Yb)[29–39] and organo-catalysts[40–54] have shown good catalytic activity in asymmetric aza-Henry reactions both in terms of yield and enantio-selectivity at lower temperature, but there is a nagging issue of separation and recycling of the catalyst. Chiral catalysts are very expensive; hence their recyclability is of prime concern in off-setting the catalyst cost. Consequently, we report here a couple of modifications in the catalyst design. First, in order to improve the efficiency two catalytic sites were incorporated in one and thereby increase the molecular weight of the catalyst to facilitate its recyclability.[37,38] Second, incorporate basic sites in the catalyst which might assist abstraction of the proton from nitromethane to generate a nitronate ion as a nucleophile. Finally, often an extra element of chirality helps in improving enantioselectivity as demonstrated earlier in the C–C bond forming reaction.[55] Accordingly, we incorporated the above features and prepared dimeric ligands **1A–C**, **2A–B**, **3A–B** and **4A**, where chiral salen units are suitably linked through chiral (*R*)/(*S*)-BINOL as an extra element of chirality or through the piperazine group as base functionality by following simple synthetic steps. The chiral dimeric complexes **1A–C–**, **2A–B–**, **3A–B–** and **4A–Cu(II)/Cu(I)** were generated *in situ* derived from ligands **1A–C**, **2A–B**, **3A–B** and **4A**, respectively, with different copper salts and examined their catalytic efficacy in aza-Henry reaction for a wide range of *N*-tosylimines with various nitroalkanes notably at RT. Chiral β-nitroamines were obtained in high yield and enantioselectivity particularly with the catalyst generated from ligand **1A** and copper acetate henceforth designated as **1A–Cu(II)**. The complex **1A–Cu(II)** was easily isolated

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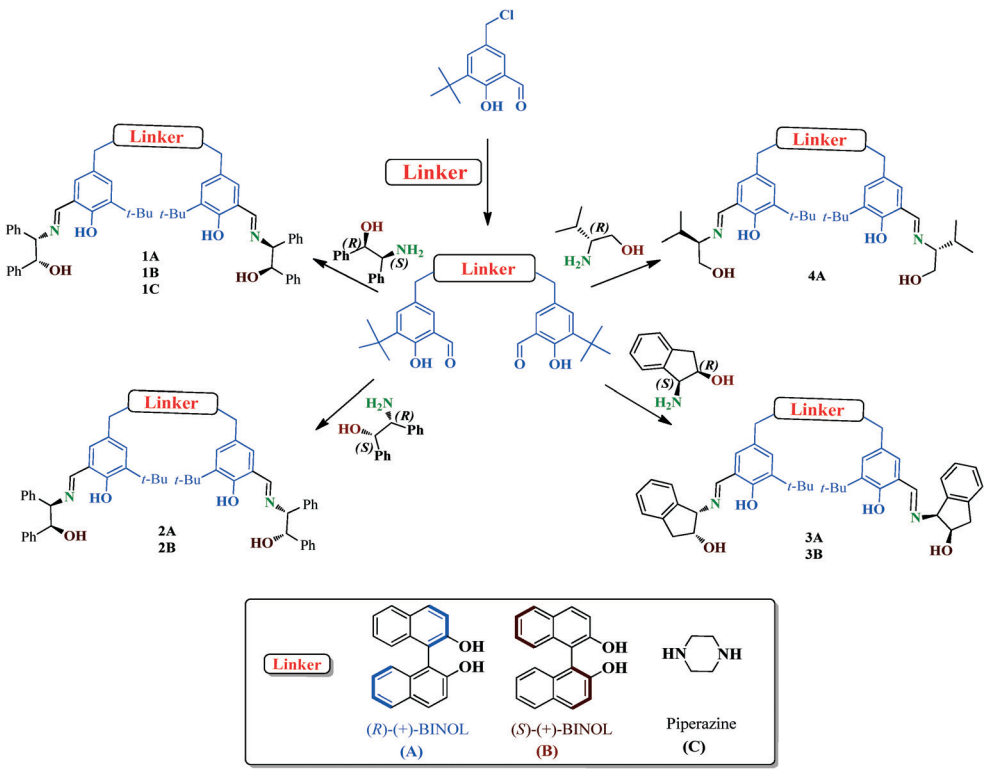
† Electronic supplementary information (ESI) available: ^{1}H & ^{13}C-NMR data, HPLC profiles of aza-Henry product. See DOI: 10.1039/c3cy00774j

from the catalytic mixture and recycled effectively up to five cycles. This protocol was also applied for the synthesis of anthelminthic (*S*)-levamisole[56,57] at 1.0 g scale.

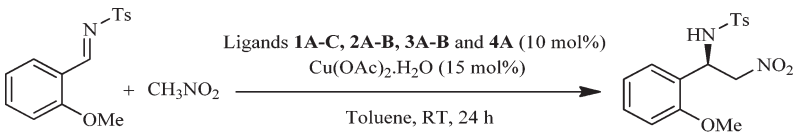
Results and discussion

In the quest of developing a highly active and enantioselective catalyst for aza-Henry reaction, new chiral dimeric ligands **1A–C**, **2A–B** and **4A** were prepared by the condensation of a bis-aldehyde having linker **A**, **B**, or **C** with various aminoalcohol *viz*., (1*R*,2*S*)-(−)-2-aminodiphenylethanol,(1*S*,2*R*)-(−)-2-aminodiphenylethanol, (1*R*,2*S*)-1-amino-2,3-dihydro-1*H*-inden-2-ol and (*R*)-valinol (Scheme 1). Meanwhile chiral dimeric Schiff base ligands **3A** and **3B** were prepared by the reaction of bis-aldehyde having linker **A** or **B** with (1*R*,2*S*)-1-amino-2,3-dihydro-1*H*-inden-2-ol by the reported method.[58] The catalytic activity and selectivity of catalysts generated *in situ* with the ligands **1A–C**, **2A–B**, **3A–B** and **4A** (10 mol%) with $Cu(OAc)_2{\cdot}H_2O$ (15 mol%) as a metal source and *N*-tosylimine **2b** as the substrate in toluene with nitromethane as the nucleophile at room temperature and data are summarized in Table 1. In the first set of screening of complexes of **1A–C**, **2A–B–Cu(II)** we altered the linker namely, (*S*)-BINOL/(*R*)-BINOL (chiral) and piperazine (achiral) at 5,5′-positions of the dimeric ligands, with (1*R*,2*S*)-(−)-2-aminodiphenylethanol and a (1*S*,2*R*)-(−)-2-aminodiphenylethanol collar. We observed that the dimeric complex **1A–Cu(II)** having a (1*R*,2*S*)-(−)-2-aminodiphenylethanol collar with (*R*)-BINOL as the linker (matching chirality element) generates a more active catalyst (yield 80% and ee 90%; Table 1, entry 1) than complexes of **1B–C–**, **2A–B–Cu(II)** having other permutations and combinations of aminoalcohols with (*R*)-BINOL/(*S*)-BINOL/piperazine as the chiral/achiral linker (entries 2–5). Such an effect of matching and mismatching of the chirality of an element, though not well understood, does exist in literature.[55] To further improve the activity of the present catalytic system, other aminoalcohol functionalities with one and two chiral centres *viz*., (1*R*,2*S*)-1-amino-2,3-dihydro-1*H*-inden-2-ol and (*R*)-valinol with both (*R*)-BINOL/(*S*)-BINOL as a chiral linker, referred as complexes **3A–B–**, **4A–Cu(II)** were used in aza Henry reaction, however, the yield and ee of the product declined sharply (entries 6–8). To assess the probable role of diverse stereogenic centers in the catalyst that govern the configuration of the product, CD spectra were recorded in THF for *in situ* generated complexes *viz*., **1A–Cu(II)**, **2A–Cu(II)** and **1B–Cu(II)** (Fig. 1). The complexes **1A–Cu(II)** and **1B–Cu(II)** derived from (*R*)-BINOL and (*S*)-BINOL, respectively, with a (1*R*,2*S*)-(−)-2-aminodiphenylethanol collar showed n → π* and d → π* bands at 400 and 650 nm with negative cotton effect and favored the (*S*) product formation (Table 1; entries 7 and 8). Whereas, the complex **2A–Cu(II)** having (*R*)-BINOL with (1*S*,2*R*)-(−)-2-aminodiphenylethanol showed n → π*and d → π* bands with a positive cotton effect in the same region and preferred the product with opposite configuration (*R*) (Table 1, entries 5 and 6). Based on these results it can be assumed that the enantio-induction in the product of the aza-Henry reaction of *N*-tosylimines **2b** is largely governed by the chirality originated from aminoalcohol functionality, but the

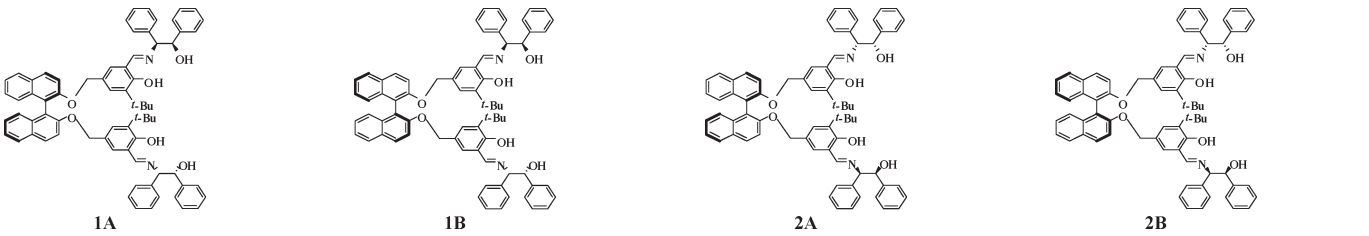


Scheme 1 Synthesis of chiral dimeric Schiff bases.

Table 1 Screening of *in situ* generated chiral salen complexes with ligands **1A–C**, **2A–B**, **3A–B** and **4A** and $Cu(OAc)_2{\cdot}H_2O$ as a source of metal used with nitromethane at RT[a]

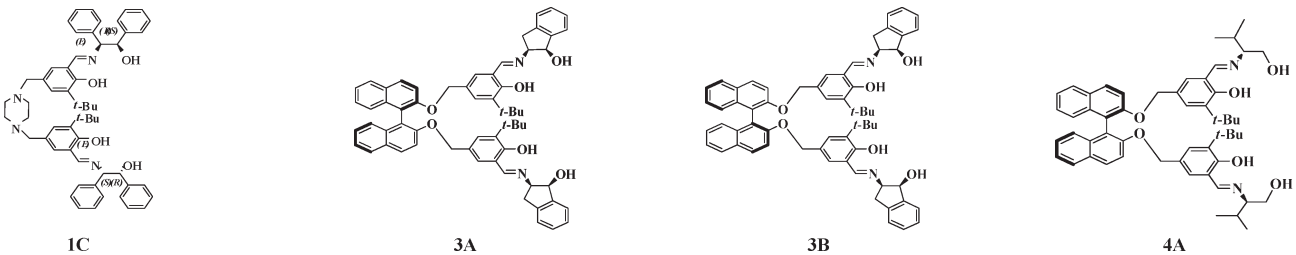


2b **3b**



1A **1B** **2A** **2B**

1A			1B			2A			2B		
Entry	Yield[b] (%)	ee[c] (%)	Entry	Yield[b] (%)	ee[c] (%)	Entry	Yield[b] (%)	ee[c] (%)	Entry	Yield[b] (%)	ee[c] (%)
1	80	90(*S*)	2	74	60(*S*)	3	77	80(*R*)	4	73	54



1C **3A** **3B** **4A**

1C			3A			3B			4A		
Entry	Yield[b] (%)	ee[c] (%)	Entry	Yield[b] (%)	ee[c] (%)	Entry	Yield[b] (%)	ee[c] (%)	Entry	Yield[b] (%)	ee[c] (%)
5	59	30	6	65	40	7	56	22	8	42	30

[a] All the reactions were performed with **2b** (0.2 mmol), nitromethane (5.0 mmol), ligands **1A–C**, **2A–B**, **3A–B** and **4A** (0.02 mmol), $Cu(OAc)_2{\cdot}H_2O$ (0.03 mmol) in toluene for 24 h. [b] Isolated yields after flash column chromatography. [c] Determined by HPLC (Chiralcel OD-H). Absolute configuration of the product was determined by compairing the HPLC profile and optical rotation value with reported literature data.

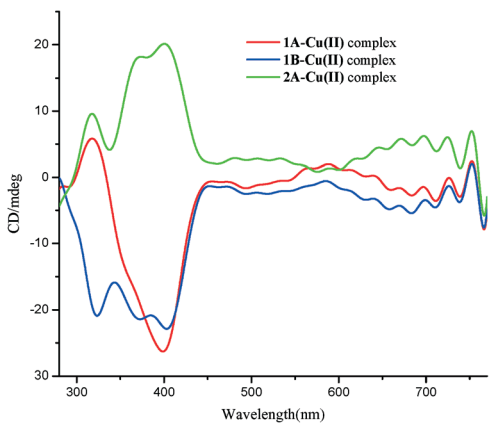


Fig. 1 CD spectra of **Cu(II)** complexes generated *in situ* derived from **1A**, **1B**, **2A** ligands in THF.

BINOL linker with matching chirality element also imparts a positive effect on catalytic activity and enantioselectivity of the corresponding aza-Henry product. To further confirm the role of the chiral BINOL linker in the catalytic aza-Henry reaction and to explore a comparative study of **1A–Cu(II)** with a chiral monomeric Schiff base complex, the monomeric ligand was synthesised by the interaction of (1*R*,2*S*)-(−)-2-amino-1,2-diphenylethanol with 3,5-di-*tert*-butylsalicylaldehyde. *In situ* generated monomeric complex from monomeric ligand with $Cu(OAc)_2{\cdot}H_2O$ in 1 : 1 molar ratio was used as a catalyst in the asymmetric aza-Henry reaction of **2b** with nitromethane under the same reaction conditions which gave 45% yield of aza-Henry product with 74% ee in 24 h. However, **1A–Cu(II)** gave 80% yield of aza-Henry product with 90% enantioselectivity under similar reaction conditions, inferring the significant role of BINOL in the present catalytic system. Further, the present catalytic system gave comparable results under milder reaction conditions (RT) as compared to the reported Schiff base systems with different metal ions where the catalytic systems need a very low reaction temperature (0 to −40 °C).[59]

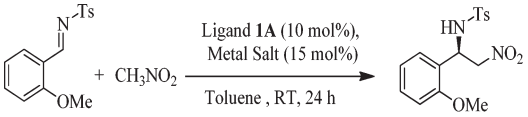
Invariably, in the asymmetric version of this reaction, the counter ions of the metal salt play an imperative role. Therefore, the dimeric ligand **1A** (most active and enantioselective) at 10 mol% loading in combination with a wide range of copper salts having different counter ions like Cl^-, OAc^-, OTf^-, I^- were screened for their effectiveness in the aza-Henry reaction of **2b** with nitromethane at RT in toluene as a solvent. Among these, $Cu(OAc)_2{\cdot}H_2O$ was found to be the most effective (ee, 90%; yield, 80%; Table 2, entry 2). Since the counter ion of the metal source helps to abstract the proton from the nitroalkane to generate active nucleophile, the basicity of the same is a key factor for the asymmetric aza-Henry reaction. Among the three Cu(II) salts with different counter ions, the basicity order is ($OAc^- > OTf^- > Cl^- > I^-$) and the yield of the product also follows the same order,[36] except for CuI which showed no catalytic activity possibly due to the formation of a complex with unfavourable geometry.

In order to improve the yield and enantioselectivity of chiral β-nitroamines, the catalyst **1A–Cu(II)** (most promising among screened) was subjected to optimization of catalytic reaction parameters like solvents, reaction temperature and catalyst loading. Since solvents have a decisive role in asymmetric reactions, so it was necessary to choose a suitable solvent for this reaction. A range of solvents like CH_3Cl, CH_2Cl_2, benzene, toluene and THF (Table 3, entries 1–7) were varied for the asymmetric aza-Henry reaction of **2b** with nitromethane at RT.

From the results of Table 3, it is clear that the non-polar solvents are more suitable than polar solvents in terms of both selectivity and activity and among them the non-polar toluene proved to be the best solvent (ee 90%, yield 80%, Table 3, entry 5). Since catalyst loading also plays an important role in achieving high yield and selectivity, hence this reaction was carried out with different catalyst **1A–Cu(II)** loading, ranging from 2–12 mol% (Table 3, entries 5, 8–11).

It is clear from the Table 3 that with decreasing catalyst loading, the enantioselectivity as well as activity of the reaction declines. Further, an increase in the catalyst loading beyond 10 mol% was of no advantage (Table 3, entry 11). So, 10 mol% catalyst was taken as ideal for the present system to get the best result with ee 90% and yield 80%. (Table 3, entry 5)

Table 2 Screening of counter ions of the metal source for an asymmetric aza-Henry reaction of **2b** using the ligand **1A** with different copper salts[a]

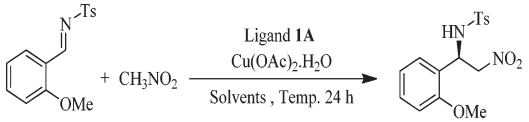


2b **3b**

Entry	Metal source	Time (h)	Yield[b] (%)	ee[c] (%)
1	$CuCl_2{\cdot}2H_2O$	10	30	35
2	$Cu(OAc)_2{\cdot}H_2O$	24	80	90
3	$(CuOTf)_2{\cdot}H_20$	20	60	50
4	CuI	5	—	—

[a] All the reactions were performed with **2b** (0.2 mmol), nitromethane (5.0 mmol), ligand **1A** (0.02 mmol), CuX_2/CuX (0.03 mmol) in toluene. [b] Isolated yields after flash column chromatography. [c] Determined by HPLC (Chiralcel OD-H).

Table 3 Screening of solvent, catalyst loading and reaction temperature for the asymmetric aza Henry reaction of **2b** using the ligand **1A–Cu(II)** with nitromethane[a]



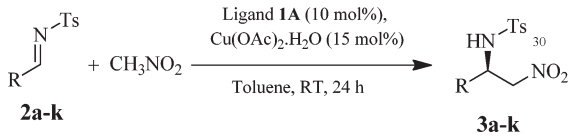
2b **3b**

Entry	Solvent	Cat. loading (mol%)	Temp (°C)	Yield[b] (%)	ee[c] (%)
1	CH_3NO_2	10	RT	40	45
2	CH_2Cl_2	10	RT	30	15
3	$CHCl_3$	10	RT	25	20
4	Benzene	10	RT	75	90
5	Toluene	10	RT	80	90
6	Xylene	10	RT	72	75
7	THF	10	RT	42	35
8	Toluene	2	RT	30	61
9	Toluene	5	RT	62	75
10	Toluene	8	RT	65	69
11	Toluene	12	RT	80	68
12	Toluene	10	40	85	67
13	Toluene	10	0	54	56
14	Toluene	10	−10	35	50

[a] All the reactions were performed with **2b** (0.2 mmol), nitromethane (5.0 mmol), with ligand **1A** and $Cu(OAc)_2{\cdot}H_2O$ in solvents. [b] Isolated yields after flash column chromatography. [c] Determined by HPLC (Chiralcel OD-H).

The temperature effect on this reaction was our next parameter for the optimization study after we fixed the solvent, as toluene and catalyst loading 10 mol%. In case of temperature optimization, our initial reaction temperature RT (entry 5) turned out to be the optimum as increasing or lowering the reaction temperature (Table 3, entries 12–14) had adverse effects on product yield and ee. To see the general applicability of the catalyst **1A–Cu(II)**, the above optimized reaction condition was applied to the enantioselective aza-Henry reaction for a variety of aromatic and aliphatic *N*-tosylimines **2a–k** as a substrate having electron donating (Table 4, entries 2–5) and withdrawing (Table 4, entries 6, 7) substituents on the aromatic ring and bulkier 1/2-naphthyl moieties (Table 4, entries 8, 9) with nitromethane. To our satisfaction, the catalytic system has demonstrated good to excellent enantio-induction (ee, 86–>99%) without much influence of substituents and their position on the aromatic ring of the substrate, however there is marginal effect on the product yield of their respective chiral β-nitroamines (yield up to 80%). The use of nitroalkanes other than nitromethane is less explored in the case of an asymmetric aza-Henry reaction; hence, the present protocol was tested for its efficacy in the aza-Henry reaction of various aromatic *N*-tosylimines with nitroethane. Fortunately, the catalytic system has demonstrated good to excellent enantio-induction (ee, 45–>99%) without much influence of substituents and their position on the aromatic ring of the substrate, however there is a marginal effect on the product yield of their respective chiral β-nitroamines (yield up to 80%). Among these, the substrates with electron donating groups

Table 4 Variation of substrates in the asymmetric aza-Henry reaction[a]



Entry	*R*	Yield[b] (%)	ee[c] (%)
1	C_6H_5 (**2a**)	78 (**3a**)	86
2	2-MeO C_6H_5 (**2b**)	80 (**3b**)	90
3	4-MeO C_6H_5 (**2c**)	70 (**3c**)	>99
4	2-Me C_6H_5 (**2d**)	78 (**3d**)	90
5	4-Me C_6H_5 (**2e**)	71 (**3e**)	89
6	2-F C_6H_5 (**2f**)	80 (**3f**)	>99
7	4-F C_6H_5 (**2g**)	77(**3g**)	>99
8	1-Naphthyl C_6H_5 (**2h**)	72 (**3h**)	89
9	2-Naphthyl C_6H_5 (**2i**)	79 (**3i**)	99
10	$C_6H_5CH_2$ (**2j**)	68 (**3j**)	99
11	$CH_3(CH_2)_6CH$ (**2k**)	75 (**3k**)	90

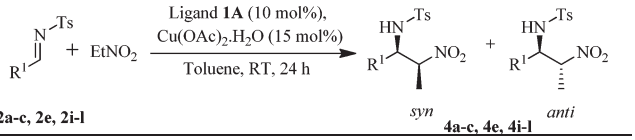
[a] All the reactions were performed with **2a–k** (0.2 mmol), nitromethane (5.0 mmol), ligand **1A** (0.02 mmol), $Cu(OAc)_2{\cdot}H_2O$ (0.03 mmol) in 0.6 ml of toluene at RT for 24 h. [b] Isolated yields after flash column chromatography. [c] Determined by HPLC (Chiralcel OD-H, AD-H, IA, IC).

(Table 5, entries 2–4) gave the best results in terms of both enantioselectivity and diastereoselectivity with *syn* as the major diastereomer.

In order to understand the probable mechanism of the catalytic asymmetric aza-Henry reaction, a stepwise overlay of the UV-vis spectra were recorded in THF (Fig. 2). In case of *in situ* generated Cu(II) complex **1A–Cu(II)** two new bands appeared at 622 nm (for d–d transition) and at 389 nm (LMCT) confirming the complexation.

On addition of *N*-tosylimine to this complex, there was a slight blue shifting (6 nm) in the LMCT band, possibly due to the formation of an intermediate with little higher energy than

Table 5 Variation of substrates with nitroethane in asymmetric aza-Henry reaction[a]



Entry	R^1	Yield[b] (%)	*Syn*/*ant*[c]	Ee[d] (%) *syn*	Ee[d] (%) *anti*
1	C_6H_5 (**2a**)	82 (**4a**)	90/10	81	85
2	2-MeO C_6H_5 (**2b**)	78 (**4b**)	97/03	99	69
3	4-MeO C_6H_5 (**2c**)	72 (**4c**)	48/52	93	99
4	4-Me C_6H_5 (**2e**)	68(**4e**)	98/02	99	45
5	2-Naphthyl C_6H_5 (**2i**)	70 (**4i**)	93/07	89	65
6	2-Cl C_6H_5 (**2l**)	65 (**4l**)	70/30	69	46

[a] All the reactions were performed with [c], **2e**, **2i–l** (0.2 mmol), nitroethane (5.0 mmol), ligand **1A** (0.02 mmol), $Cu(OAc)_2{\cdot}H_2O$ (0.03 mmol) in 0.6 ML toluene for 24 h at RT. [b] Isolated yields after flash column chromatography. [c] Determined from NMR data. [d] Determined by HPLC (Chiralcel AD-H, OD-H, IA, IC).

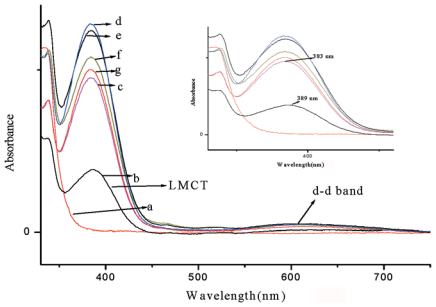


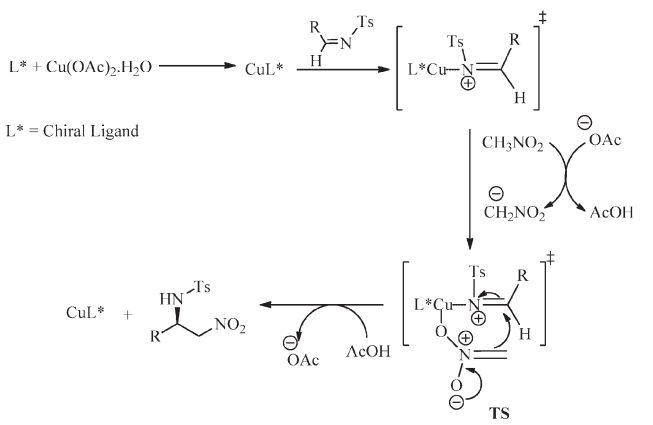
Fig. 2 A stepwise overlay of UV-vis spectra in THF solvent (a) ligand (b) complex (c) complex, imine (d) complex, imine and nitromethane after 1 h (e) complex, imine and nitromethane after 5 h (f) complex, imine and nitromethane after 10 h (g) complex, imine and nitromethane after 15 h.

the complex itself. When nitromethane was added to this solution, a transition state (TS) with hyperchromic shift was observed which was decreased gradually with time due to the release of the catalyst with product formation[37] (Scheme 2).

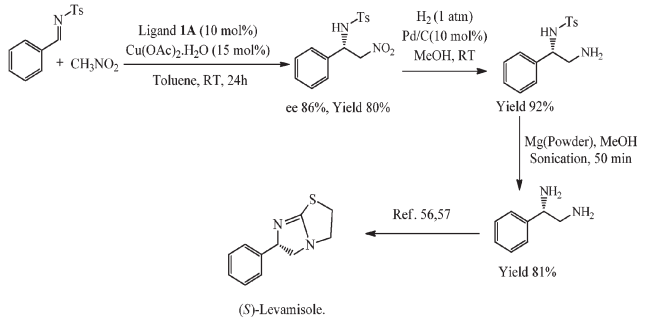
Having established the aza-Henry parameters with catalyst **1A–Cu(II)** the present protocol was extended to the synthesis of chiral drug (*S*)-levamisole (an anthelminthic agent used to treat parasitic worm infections in humans) at 1 g scale with good yield and retention of enantioselectivity in three steps (Scheme 3).

In addition to high reactivity and enantioselectivity in the aza-Henry reaction, the catalyst **1A–Cu(II)** is recyclable as evidenced by the recycling experiments (Fig. 3). The recyclability experiments were carried out by using **2b** (2.0 mmol) as a model substrate with nitromethane (5.0 mmol) as nucleophile in toluene at room temperature using the complex **1A–Cu(II)** (10 mol%) as a catalyst. After the completion of the catalytic reaction, the catalyst was recovered quantitatively and successfully recycled five times without any apparent loss in activity and enantioselectivity (Fig. 3).

In order to investigate the stability of the recycled catalyst, IR spectra of the recycled catalyst were recorded and compared with the IR of the fresh catalyst (Fig. 4). From the



Scheme 2 A probable mechanism for the catalytic asymmetric aza-Henry reaction.



Scheme 3 Synthetic route to produce (*S*)-levamisole.

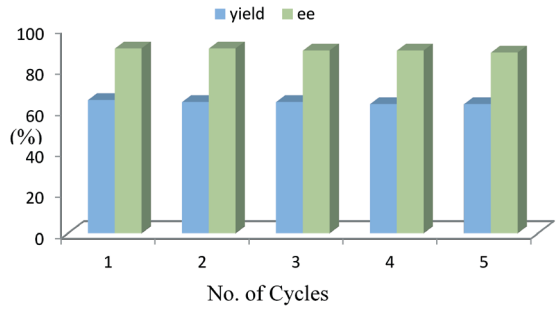


Fig. 3 Recyclability study of the catalytic system for the asymmetric aza-Henry reaction.

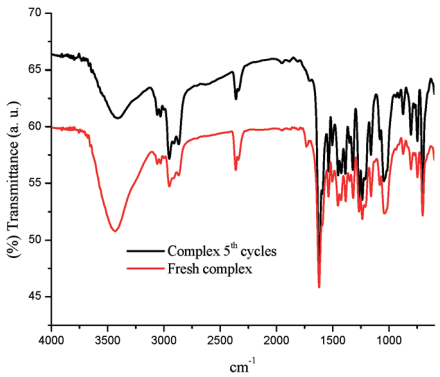


Fig. 4 IR spectra of fresh catalyst and recycled catalyst after 5 cycles.

spectra it was clear that there is no change in the structure of the complex after the recycling study.

Conclusion

In conclusion, we have designed a series of chiral dimeric ligands derived from (*S*)/(*R*) 1,1′-bi(2-naphthol)-bis-aldehyde and piperazine-bis-aldehyde as linkers with various amino-alcohol functionalities for the asymmetric aza-Henry reaction of different *N*-tosylimines having both electron donating and withdrawing substituents on the aromatic ring with nitro-alkanes giving both very good to excellent enantioselectivity and yield. To find out the scalable property of catalytic system, a gram level catalytic run demonstrated the synthesis of (*S*)-levamisole (an anthelminthic agent for human) in three steps.

Experimental section

General

Copper acetate monohydrate, copper triflate, copper chloride, copper iodide, nitromethane, nitroethane, (1*R*,2*S*)-1-amino-2,3-dihydro-1*H*-inden-2-ol, (*R*)-valinol, (*R*)-BINOL, (*S*)-BINOL, (1*R*,2*S* and 1*S*,2*R*)-2-amino-1,2-diphenyoethanol and piperazine anhydrous were purchased from Aldrich Chemicals and used as received. (*S*)-5,5′-(1,1′-binaphthyl-2,2′-diylbis(oxy)) bis(methylene)bis(3-*tert*-butyl-2-hydroxybenzaldehyde)/(*R*)-5,5′-(1,1′-binaphthyl-2,2′-diylbis(oxy))bis(methylene)bis(3-*tert*-butyl-2-hydroxybenzaldehyde) and 5,5′-(piperazine-1,4-diylbis(methylene)) bis(3-*tert*-butyl-2-hydroxybenzaldehyde) were synthesized by our reported procedure.[58,60] *N*-Tosylimines were synthesized by the reported method.[61,62] All the solvents were dried by standard procedures, distilled and stored under nitrogen. ^{1}H NMR spectra were obtained with a Bruker F113V spectrometer (200 MHz) and are referenced internally with TMS FT-IR spectra which were recorded on a Perkin Elmer Spectrum GX spectrophotometer in a KBr window. High-resolution mass spectra were obtained with a LC–MS (Q-TOFF) LC (Waters), MS (Micromass) instrument. For the product purification, column chromatography was performed using silica gel 60–200 mesh purchased from s.d. Fine-Chem Limited Mumbai (India). Enantiomeric excess (ee) of the products were determined by HPLC (Shimadzu SCL-10AVP) using Daicel Chiralpak AD, OD, AD-H, OD-H column with 2-propanol–hexane as eluent. Optical rotations were measured with a Digipol 781 Automatic Polarimeter Rudolph Instruments. UV-visible spectra were recorded on a Shimadzu UV 3101 PC NIR spectrophotometer (Japan). Circular Dichroism (CD) spectra were obtained by using a JASCO J-815 CD spectrophotometer (Japan).

Synthesis of ligands (1A–C, 2A–B, 3A–B, 4A)

Bis aldehydes, namely, (*S*)-5,5′-(1,1′-binaphthyl-2,2′-diylbis(oxy)) bis(methylene)bis(3-*tert*-butyl-2-hydroxybenzaldehyde)/(*R*)-5,5′-(1,1′-binaphthyl-2,2′-diylbis(oxy))bis(methylene)bis(3-*tert*-butyl-2-hydroxybenzaldehyde) and 5,5′-(piperazine-1,4-diylbis(methylene)) bis(3-*tert*-butyl-2-hydroxybenzaldehyde) (2 mmol) were dissolved in dry THF (50 ml) to which two equivalent of (1*R*,2*S* or 1*S*,2*R*)-2-amino-1,2-diphenylethanol/(1*R*,2*S*)-*cis*-1-amino-2-indanol/(*R*)-valinol (4 mmol) was added slowly under a nitrogen atmosphere. The resulting solution was stirred for 4 h at room temperature and the reaction was monitored by TLC. After completion of the reaction, the solvent was partially removed from the reaction mixture on a rotary evaporator that gave a yellow precipitate. The solid obtained after filtration was washed with hexane : DCM (50 : 1) to get the yellow colored desired ligands **1A–C**, **2A–B**, **3A–B** and **4A**. The characterization data of all the ligands are given in the ESI.†

Typical experimental procedure for the asymmetric aza-Henry reaction

Chiral dimeric ligands **1A–C**, **2A–B**, **3A–B** and **4A** (10 mol%) and $Cu(OAc)_2 \cdot H_2O$ (15 mol%) were added to a screw-capped vial containing a stirring magnetic bar. Anhydrous toluene (0.6 mL) was then added, and a clear green solution formed which was stirred for 4 h at RT. To the resulting solution, nitromethane or nitroethane (5.0 mmol, 10 equiv.) and desired *N*-tosylimines (0.2 mmol, 1 equiv.) were added. After running the reaction for the specified time as given in Tables 1, 4 and 5, the volatile components were removed under reduced pressure, and the crude product was purified by flash column chromatography.

Recycling of the catalyst 1A–Cu(II)

At the end of the catalytic reaction (checked by TLC), the solvent was completely removed from the reaction medium under reduced pressure and the resulting mass was extracted with hexane to remove the reactants and product. The remaining solid was further washed with hexane : EtOAc (85 : 15) six times, dried under reduced pressure for 2–3 h, and used as a recovered catalyst for recycling experiments of an asymmetric aza-Henry reaction of **2b** as a representative substrate with nitromethane.

Acknowledgements

Manoj K. Choudhary, Anjan Das and RIK are thankful to the DST project on catalysis and CSIR-Indus Magic Project CSC0123 for financial assistance. Manoj K. Choudhary is thankful to CSIR for awarding JRF and AcSIR for Ph.D. registration. The authors are also thankful to the Analytical Science and Centralized Instrumentation Facility Discipline for providing instrumental facilities.

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