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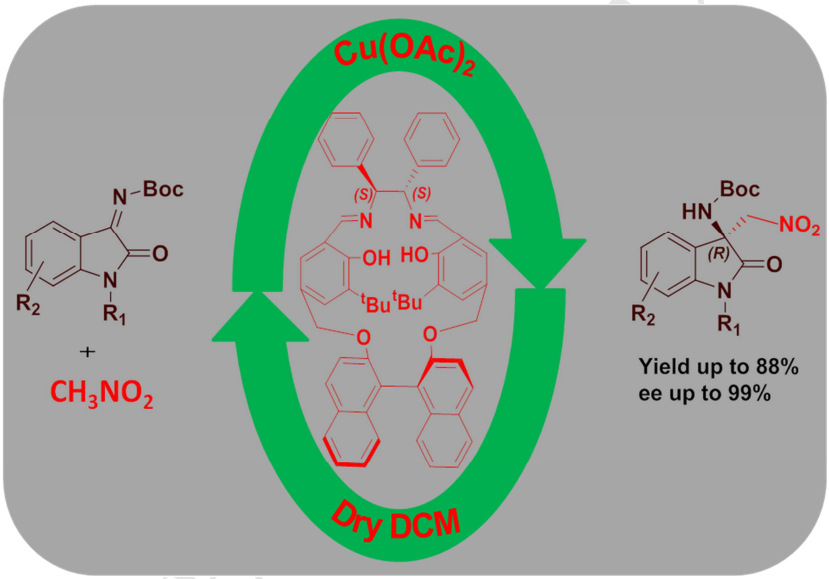

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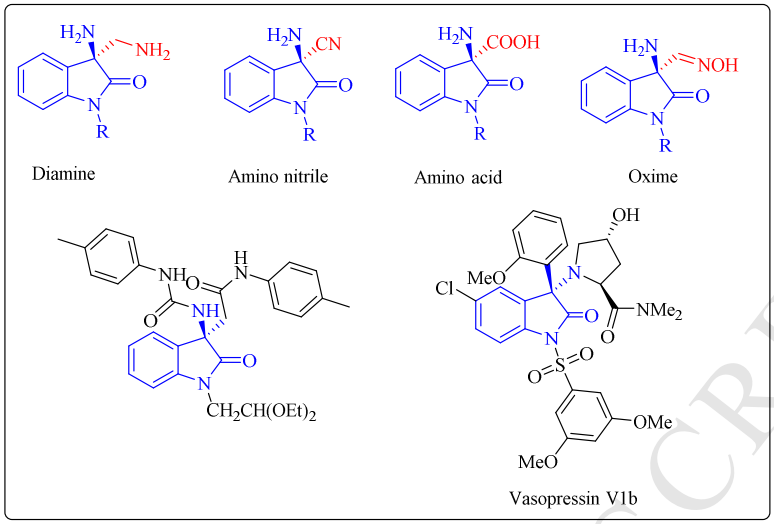
ABSTRACT: Chiral **Cu-1B** generated *in situ* was used as an efficient catalyst for the synthesis of *β*-nitroamines in high yield (88%) with excellent enantioselectivity (ee up to 99%) at RT in absence of co-catalyst via asymmetric aza-Henry reaction of various isatin derived *N*-Boc ketimines with nitromethane. This catalytic system did not work well with other nitroalkanes under the above optimized reaction conditions. To examine this catalytic behaviour, quantum chemical DFT calculations were performed with the nucleophiles ($CH_2NO_2^-$ and $CH_3CHNO_2^-$) for the conversion of **1a** to **2a** using macrocyclic **Cu-1B** complex. The DFT calculated results have shown that the reaction with $CH_2NO_2^-$ is more favourable than the corresponding $CH_3CHNO_2^-$. The calculated activation barriers suggest that the reaction with $CH_2NO_2^-$ is ~8.0 kcal/mol energetically favoured than $CH_3CHNO_2^-$. This catalytic protocol was further used to obtain chiral *β*-diamines (a building block for pharmaceuticals) at gram scale. In order to elucidate the reaction mechanism of asymmetric aza Henry reaction kinetic experiments were performed with different concentrations of the catalyst **Cu-1B**, nitromethane and **1g** as the representative substrate. The reaction of isatin *N-Boc* ketimine was first order with respect to the concentration of the catalyst and the nitromethane but did not depend on the initial concentration of the substrate. A possible mechanism for the aza Henry reaction was proposed.

Keywords: Asymmetric aza-Henry, Cu(II), Macrocyclic ligand, Recyclibility, (S)-diamine

Introduction

State-of-the-art in enantioselective catalysis involves the design and development of catalyst, capable of inducing the chirality in a wide range of substrates. Enantioselective aza-Henry reactions have become one of the important reaction, since the end products can easily be converted into many value added products viz., vicinal diamines[1-3] and *α*-amino carbonyl compounds[4-6]. The 3,3′-disubstituted oxindoles are observed in a broad range of naturally occurring indolizidine alkaloids[7]. Asymmetric aza-Henry reaction of isatin derived *N*-protected ketimines is the most straightforward and an atom economic approach for accessing chiral *β*-nitroamines from 3-substituted oxindol. Due to the presence of two vicinal nitrogen atoms in different oxidation states in *β*-nitroamines facilitated them to convert into vicinal diamines, *α*-aminoacids, *α*-aminonitriles, oximes and heterocyclic small molecules of pharmaceutical and industrial importance (Scheme 1)[8 -14]. Chronologically, Feng and coworkers for the first time reported chiral *N,N'*-dioxide-copper complex as a catalyst in enantioselective aza-Henry reaction of ketimines giving excellent enantioinduction in *β*-nitroamines with moderate yields[15]. Over the period both metal[16-19] and metal free[20-26] asymmetric aza Henry reaction protocols have been documented. Although most of these systems have shown good to high enantio-induction at low temperature in presence of co-catalysts with high catalyst loading. Therefore, to address these issues and non-recyclability of the catalysts which is also a major concerns considering the cost involved in the designing of these catalyst (typically multistep). In this line, with our continued efforts in developing the recyclable catalyst, recently our group has reported Cu(II) dimeric macrocyclic salen complexes with trigol and piperazine linkers for asymmetric aza- Henry reaction of isatin derived *N*-Boc ketimines with various nitroalkanes as nucleophile giving the desired *β*-nitroamines in high yields and enantioselectivity [27]. The present paper reports the Cu(II) monomeric macrocyclic salen complexes with (*S*)/(*R*) BINOL linker for the synthesis of *β*-nitroamines at RT via asymmetric aza-Henry reaction of isatin derived *N*-Boc ketimines with nitromethane. High yield of *β*-nitroamines with excellent enantio-induction was achieved under co-catalyst free condition. Chiral monomeric macrocyclic salen complex **Cu-1B** worked well up to five cycles with retention of its performance. Chiral *β*-diamine was synthesized using this protocol at gram scale. In order to understand the mechanism of aza-Henry reaction of isatin *N*-Boc ketimine with nitromethane, kinetic investigations were carried out. Based on kinetic, catalytic and experimental data, a probable mechanism for the aza-Henry reaction is also proposed.



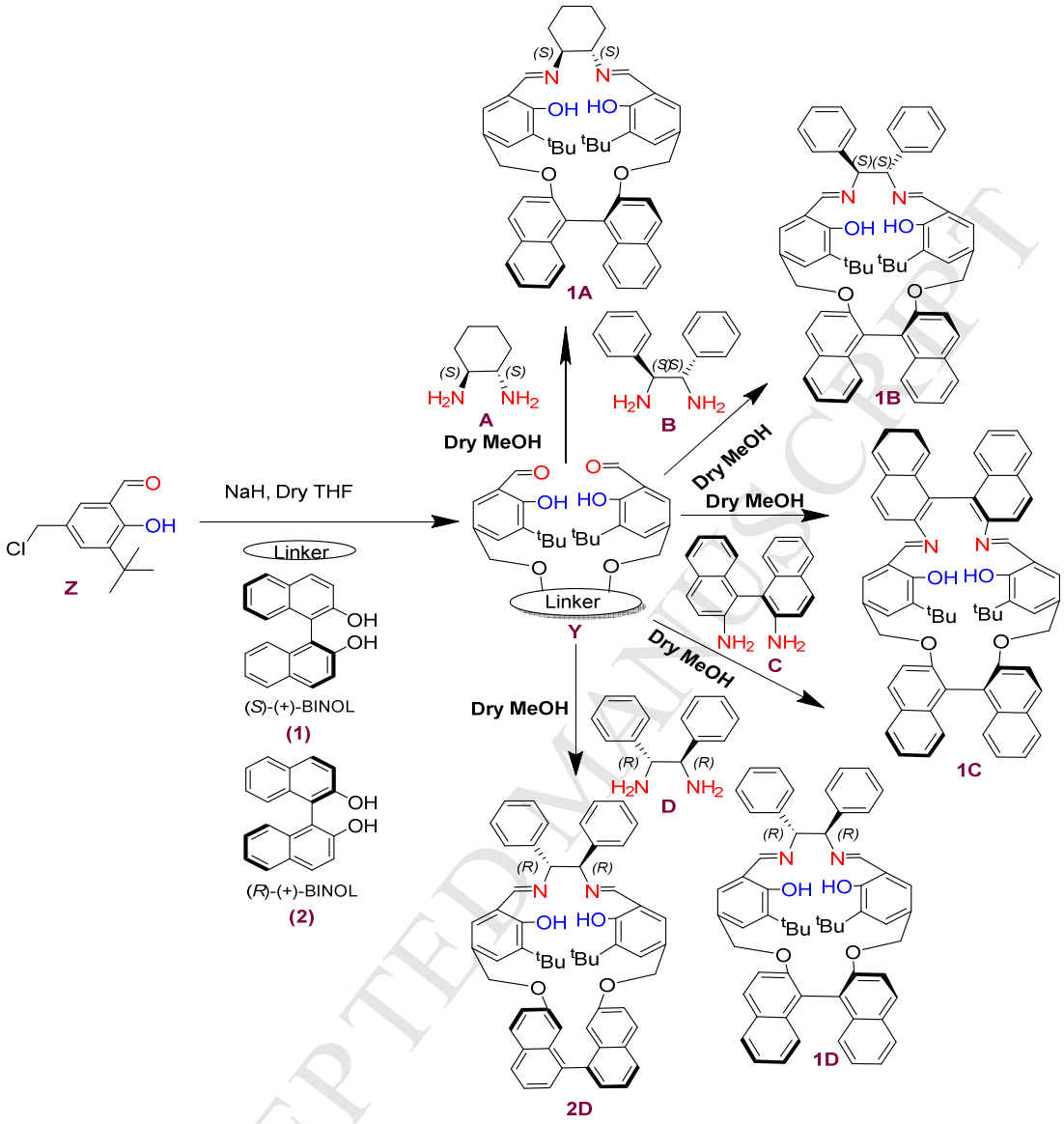
Scheme 1. Various molecules derived from *β*-nitroamine and pharmaceutically active molecules.

Result and Discussion

Mechanistically in aza-Henry reaction, it is well-known that designing of an efficient catalyst needs bi-functional reactive sites (acidic and basic sites) for achieving higher yield and enantioselectivity in the product[28]. Acidic site (metal center) helps to strengthen the electrophilic nature of the imine nitrogen atoms that get bind to the metal center in aza-Henry reaction while basic sites require for abstraction of proton from the nitromethane to generate nitronate ion, the active nucleophile. The monomeric macrocyclic complexes due to their higher molecular weight have less solubility in non-polar solvent like hexane, hence offer recyclable character of the catalyst as well as reduce the catalyst loading.

Therefore, the chiral macrocyclic salen ligands **1A-1D, 2D** were synthesized according to our reported procedure[29], in a stepwise manner by the interaction of 3-(*tert*-butyl)-5-(chloromethyl)-2-hydroxybenzaldehyde **Z** with (*S*)- (+)-(BINOL) **1**/(*R*)- (-)-(BINOL) **2** as linker to prepare the corresponding dialdehyde **Y**[30]. The condensation of dialdehyde **Y** with (1*S*,2*S*)-(+) 1,2 diamino cyclohexane **A**/(1*S*,2*S*)-(-) 1,2-diphenylethylene diamine **B**/ *R*-(+)1,1'binaphyhyl-2,2'-diamine **C**/(1*R*,2*R*)-(+)-1,2-diphenylethylene diamine **D** gave macrocyclic chiral salen ligands **1A-1D, 2D** (Scheme 2).

At the very beginning, chiral monomeric macrocyclic salen ligands **1A-1D**, **2D** (10 mol%) with $Cu(OTf)_2.H_2O$ (10 mol%) were screened in aza-Henry reaction of **1a** as a representative substrate (0.5 mmol) with nitromethane (10 equivalent) in THF. Data in the Figure 1 concede that the *in-situ* generated complexes **Cu-1B** and **Cu-1D** with monomeric macrocyclic ligands with diphenyldiamine collar **B** and **D** with (*S*)-(+) BINOL linker worked better in term of reactivity and enantioselectivity of *β*-nitroamine with opposite configuration. Therefore, **Cu-1B** was subjected to change in the reaction parameters and variation with other copper sources.



Scheme 2. Synthetic route for chiral monomeric macrocyclic ligands 1A-D, 2D.

After achieving the encouraged preliminary results with the catalyst **Cu-1B** and to further improve the reactivity and enantioselectivity of the product *β*-nitroamine, we explored the screening of several copper salts with the ligand **1B** using **1a** as model substrate based on the concept that use of copper salts with different counter ions effect the catalytic performance[31]. Besides, the counter anions in the metal source also assist the abstraction of proton from nitroalkane to generate nitronate ion which acts as nucleophile in aza-Henry reaction[19,31,32]. Among the copper salts used, $Cu(OAc)_2 \cdot H_2O$ with macrocyclic ligand **1B** gave good yield and enantioselectivity of the product *β*-nitroamine (Table 1, entry 2) in the absence of any base additive, hence, this catalyst was subjected to other reaction parameters optimization such as catalyst loading, choice of solvents and temperature as these parameters are known to influence the yield and enantioselectivity of the products.

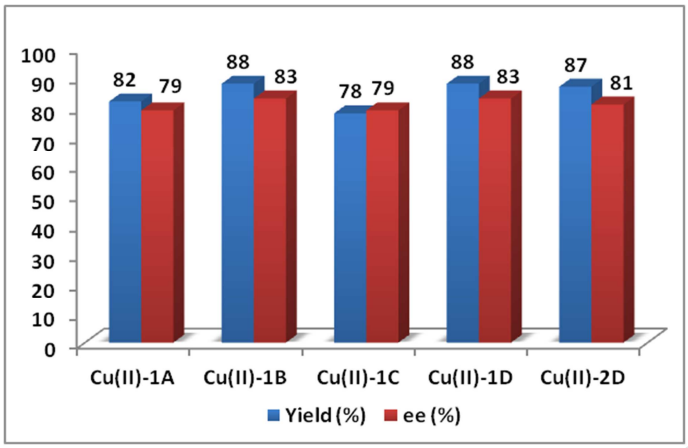
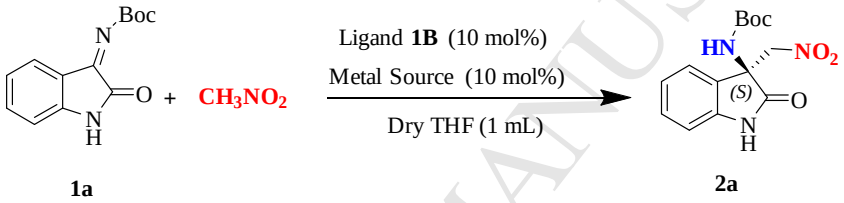


Figure 1. Screening of the catalysts in aza Henry reaction of **1a** with nitromethane

Table 1 Screening of various counter ions of copper salts for enantioselective aza-Henry reaction of **1a** using the macrocyclic ligand **1B** [a]



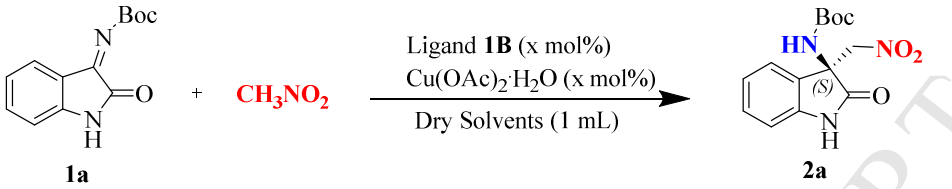
1a **2a**

Entry	Metal source	Yield (%)[b]	Ee (%)[c]
1	$Cu(OTf)_2 \cdot H_2O$	88	83
2	$Cu(OAc)_2 \cdot H_2O$	88	89
3	$CuCl_2 \cdot 2H_2O$	61	45
4	$Cu(NO_3)_2 \cdot 6H_2O$	78	73
5	CuBr	11	-

[a]All the reactions were performed with **1a** (0.2 mmol), nitromethane (1.0 mmol), ligand **1B** (0.02 mmol), Metal source (0.02 mmol) in THF. [b]Isolated yields after flash column chromatography. [c]Determined by HPLC (Chiralcel IA).

First, we varied the catalyst loading from 1 mol% to 10 mol% (Table 2, entries 1-5) in aza Henry reaction of **1a** with nitromethane and found that 5 mol % of the catalyst is sufficient to give 85% yield with 93% enantioselectivity in chiral *β*-nitroamine (Table 2, entry 3). To further promote the reactivity and enantioselectivity of *β*-nitroamine, different solvents viz., dichloromethane, toluene, tetrahydrofuran, acetonitrile, methanol and chloroform [Table 2, entries 3, 6-10] were explored in aza Henry reaction of **1a** with nitromethane. However, DCM gave the best performance (yield 88% and ee 99%) (Table 2, entry 8). Next with the above optimized reaction conditions a range of temperature was varied from RT to 0 ^{o}C (Table 2; entries 8, 11, 12). However, reducing the reaction temperature (10 ^{o}C & 0 ^{o}C) caused a reduction in both yield and ee (entries 11, 12) which may be due to the solubility issue of the substrate at lower temperatures.

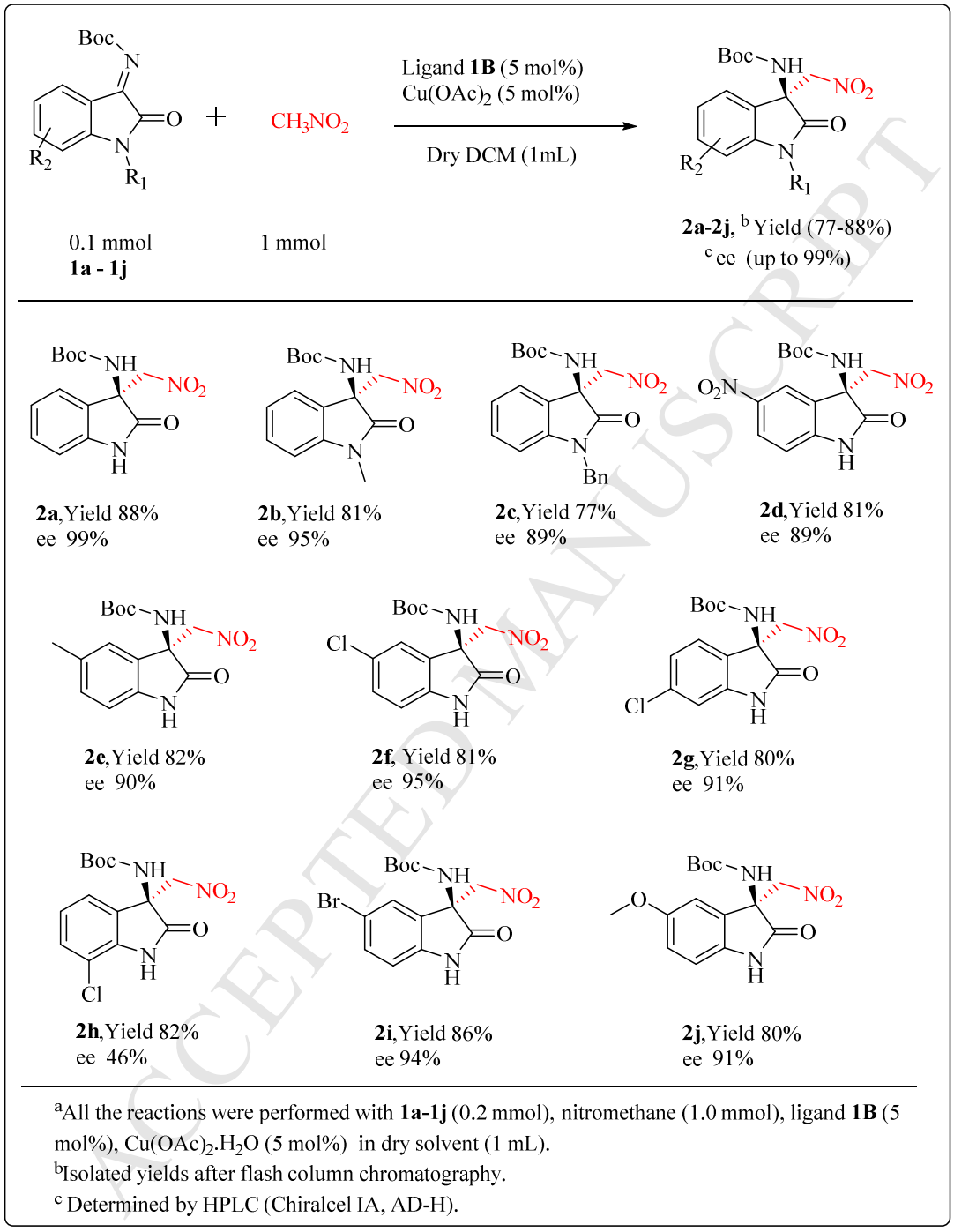
Table 2. Optimization of the reaction conditions [a]



Entry	Catalyst (mol%)	Solvent	Temp	Yield (%)[b]	ee (%)[c]
1	1	THF	RT	15	-
2	2.5	THF	RT	63	78
3	5	THF	RT	85	93
4	7.5	THF	RT	86	90
5	10	THF	RT	88	89
6	5	Toluene	RT	63	74
7	5	ACN	RT	78	80
8	5	DCM	RT	88	99
9	5	MeOH	RT	79	83
10	5	$CHCl_3$	RT	80	91
11	5	DCM	10˚C	66	92
12	5	DCM	0˚C	63	92

[a] All the reactions were performed with **1a** (0.2 mmol), nitromethane (1.0 mmol), ligand **1B** (x mol%), $Cu(OAc)_2.H_2O$ (y mol%) in dry solvent (1 mL). [b]Isolated yields after flash column chromatography. [c]Determined by HPLC (Chiralcel IA).

Finally, adopting the *in situ* generated complex from the ligand **1B** (5 mol%) with $Cu(OAc)_2$ (5 mol%) in DCM with nitromethane (5 mmol) at RT as the optimum reaction condition, we applied this catalytic protocol for aza-Henry reaction of various isatin *N*-protected ketimines **1a-1j** with different substituents on the aromatic ring and *N* protecting groups (Scheme 3)**.** *β*-nitroamines **2a-2g, 2i-2j** were achieved in good to high yield (77-88%) with excellent enantio-induction (ee up to, 99%) except **2h** at room temperature by using **Cu(II)-1B** as a catalyst in dichloromethane. There was no clear trend seen in the electronic effect of the substituents on the yield as well as enantioselectivity of the product. Thus, **Cu(II)-1B** complex performed efficiently at low catalyst loading (5 mol%) by producing the desired *β*-nitroamines in higher enantioselectivity than the previously reported copper(II) nitrogen containing ligand systems[12,14].



Scheme 3. Substrate scope in aza Henry reaction of isatin *N*-protected ketimines [a]

To further expand the scope of this reaction protocol, less explored nitroethane, 1-nitropropane were also used as nucleophile under the optimized reaction conditions. However, low product yield (24%) was obtained without diastereoselectivity and enantioselectivity.

To understand the reason behind the behaviour of these nitroalkanes to react with **1a**, we have performed the quantum chemical DFT calculations. The effect of nucleophiles ($CH_2NO_2^-$ and $CH_3CHNO_2^-$) for the conversion of **1a** to **2a** using macrocyclic **Cu(II)–1B** complex has been investigated. For computational simplicity, we have modelled the -CH_3 of –Boc protected isatin derived ketimine **1a** with hydrogen atom in all cases. Initially, the **1a** coordinates with **Cu(II)-1B** complex (Figures 2 & 3). The nucleophiles ($CH_2NO_2^-$ and $CH_3CHNO_2^-$) approaches the **1a** complex with **Cu(II)-1B** to coordinate with the copper atom using the two oxygen atoms of the nitro group. The copper coordinated nucleophile simultaneously attacks the carbon center of **1a** to form the product. The transition state geometry shows the coordination and attack of the nucleophile to the reactant a (**TS-1**). We have observed that the nitro oxygen of nucleophile $CH_2NO_2^-$ interacts with copper atom very strongly i.e., the O…Cu distances are 2.07 Å and 2.11 Å, whereas, corresponding O…Cu distances in $CH_3CHNO_2^-$ are 2.11 Å and 2.13 Å, respectively. The imaginary frequencies for two nucleophiles ($CH_2NO_2^-$ and $CH_3CHNO_2^-$) are 504.8 and 767.7 cm^{-1} respectively. The computed activation barriers seem to be a downhill process with M06-2X/6-31+G(d) level of theory. The energy barrier calculated for the attack of the nucleophile $CH_2NO_2^-$ is 8.3 kcal/mol is favoured compared to the nucleophile $CH_3CHNO_2^-$ at same level of theory. The mulliken charge analysis performed for $CH_2NO_2^-$ and $CH_3CHNO_2^-$ suggests that the negatively charged carbon of the former anion is -0.93, whereas the later anion has -0.51. This result clearly suggests that the nucleophilicity of $CH_2NO_2^-$ is more compared to $CH_3CHNO_2^-$ and hence the rate of reactions would be different in these case. The PES corroborates the above observation.

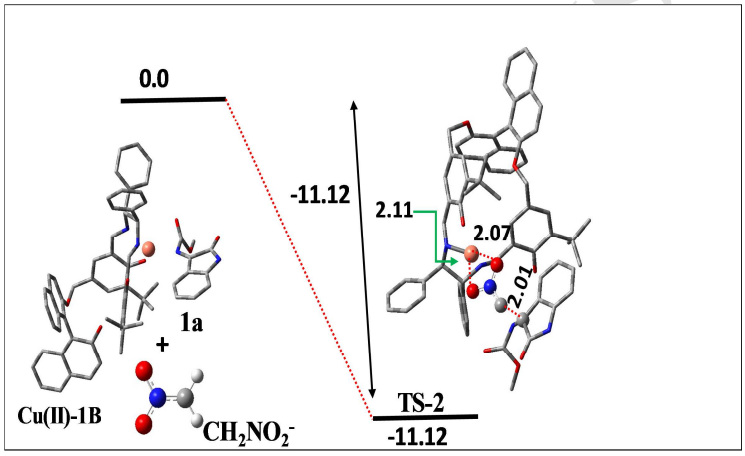


Figure 2. The potential energy profile for production of **2a** from **1a** nitro methane using Cu catalyst (**Cu(II)-1B**) at the M06-2X/6-31+G(d)//PM6 level of theory. The relative energy differences are given in kcal/mol.

The calculated results corroborate the formation of product **2a** much more feasible with nitromethane compared to nitroethane.

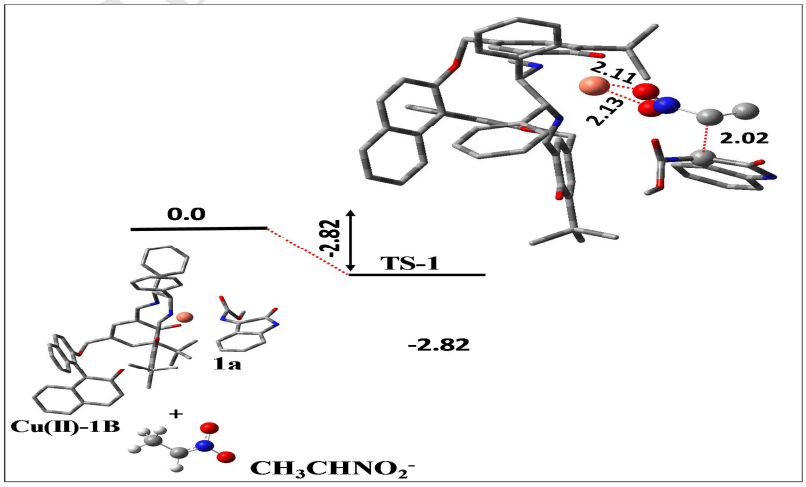


Figure 3. The potential energy profile for production of **2a** from **1a** nitroethane using Cu catalyst (**Cu(II)-1B**) at the M06-2X/6-31+G(d)//PM6 level of theory. The relative energy difference is given in kcal/mol.

For reusability experiments, aza-Henry reaction of **1a** with **Cu(II)-1B** was conducted under the optimized reaction condition using nitromethane as nucleophile. After the first catalytic run (entry 8, Table 2), the macrocyclic complex was precipitated from the reaction mixture by the addition of hexane. The monomeric **Cu(II)-1B** was recycled five times without any noticeable loss in their activity and enantioselectivity (Figure 4).

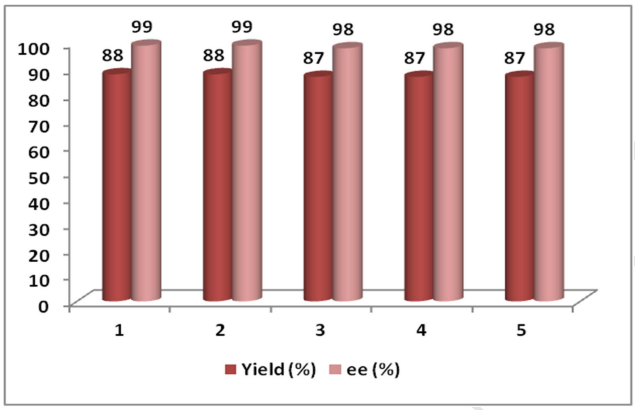
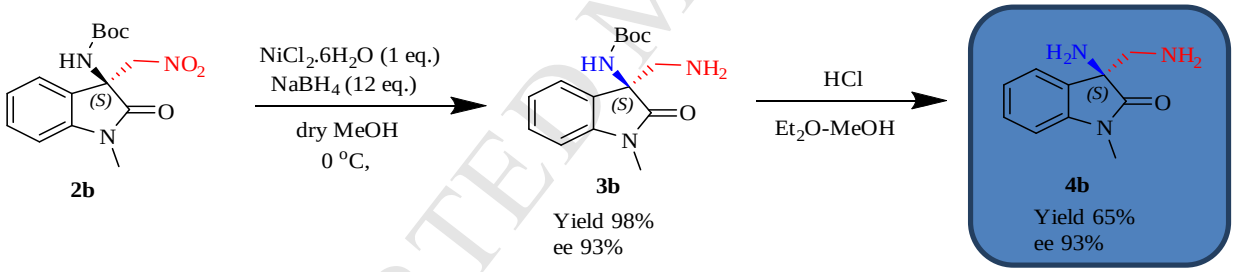


Figure 4. Recyclability study of **Cu(II)-1B** complex

Using this reaction protocol, enantio-enriched *β*-diamine was prepared in gram scale with good yield and enantioselectivity (**Scheme 4**).



Scheme 4. Synthesis of *β*-diamine from aza-Henry product

The CD spectra recorded for **Cu(II)-1B** and **Cu(II)-1D** in THF (0.001 M) were illustrated in Figure 5. It shows three opposites peaks at 582 nm (d-d transition, indicate the formation of complex) 344 nm and 296 nm indicating that the metal complexes gain geometrically opposite chirality from the respective chiral ligands originating from **1B** and **1D**[33] and upon complexation brings enantiopure geometrical chirality.

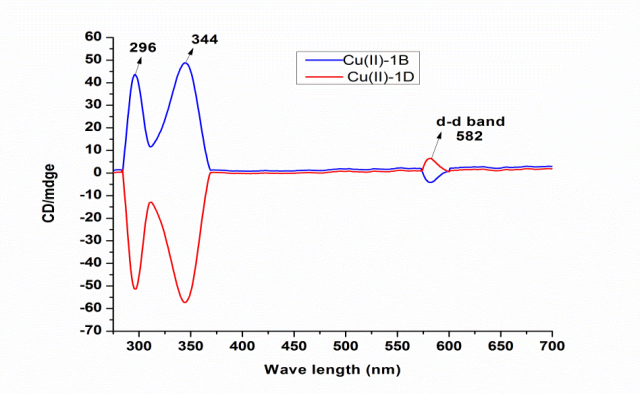


Figure 5. CD spectra of complexes **Cu(II)-1B** and **Cu(II)-1D** in THF (1×10^{-3} M).

Kinetic study

In order to understand the mechanism of aza Henry reaction of isatin *N*-Boc ketimine, kinetic experiments were performed with **1g** as a model substrate as a function of the concentration of catalyst **Cu(II)-1B**, substrate and nitromethane as nucleophile. In all the kinetic runs the plots of formation of *β*-nitroamine with time was found to be linear in beginning of the reaction and exhibit saturation close to completion (Figure 6a). Based on this observation, the initial rate constants k_{obs} was determined by directly estimating the amount of the product *β*-nitroamine formed up to completion of the reaction.

Effect of catalyst concentration on reaction rate

Aza-Henry reaction of **1g** was studied by conducting the kinetic experiments at different concentration of the catalyst **Cu(II)-1B** [0.0025-0.01 M] at constant concentration of **1g** [0.1 M] and nitromethane [0.5 M]. From the kinetic data a linear plot of k_{obs} of the *β*-nitroamine formation versus log[catalyst] with unit slopes (d log k_{obs}/d log[catalyst] ~1) was obtained which passes through the origin, indicating that the aza Henry reaction is of first order with respect to the concentration of the catalyst (Figure 6b).

Effect of substrate concentration on reaction rate

Kinetic experiments were carried out at different initial concentration of isatin *N* protected ketimine **1g** ranging from (0. 067-0.169 M) by keeping the concentration of other reactants and physical conditions constant from which the rate was calculated. The plot of k_{obs} against [substrate] showed the zero order dependence of the reaction on the substrate concentration (dlog k_{obs}/dlog[substrate] ~ 1) (Figure 6c).

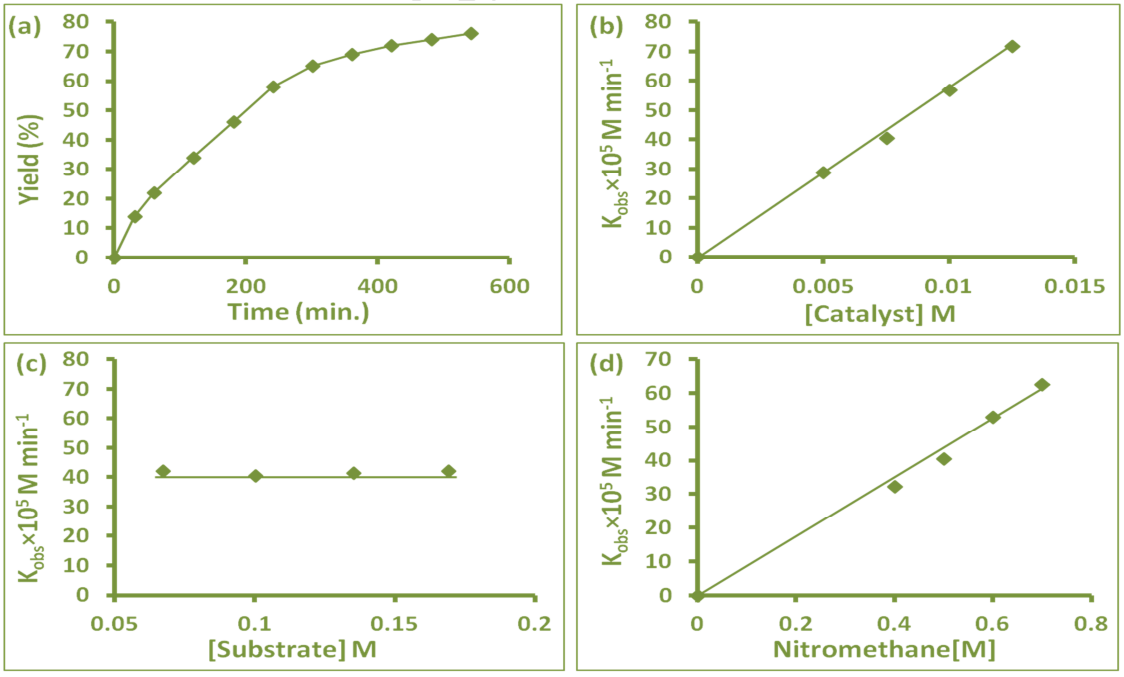
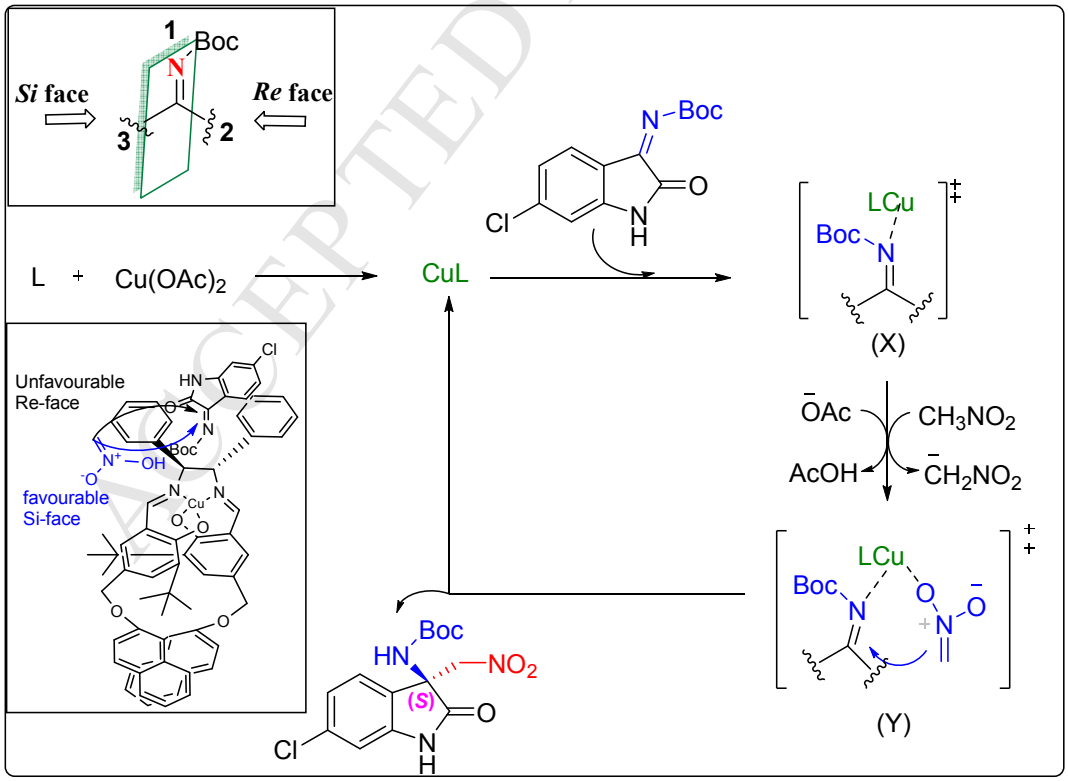


Figure 6. (a) Time-dependent plot for the formation of *β*-nitroamine at RT, [catalyst] = 0.005 M, [imine]= 0.1 M, and [nitromethane] = 0.5 M. **(b)** Plots of catalyst **Cu(II)-1B** concentration (0.0025-0.01 M) versus $k_{obs\times}10^5$, [imine]=0.1 M, [nitrometahne]=0.5 M; **(c)** substrate (**1g**) concentration (0.067-0.169 M) versus $k_{obs}\times10^5$, [catalyst]= 0.005 M, [nitromethane] =0.5M; **(d)** nitromethane concentration (0.4-0.7 M) versus $k_{obs}\times10^5$, [catalyst]=0.005 M, [imine]=0.1 M.

Effect of nitromethane concentration on reaction rate

To check out the effect of concentration of nitromethane on reaction rate, we have performed the aza-Henry reaction with a variable concentration of nitromethane (0.4-0.7 M) by keeping constant concentration of the catalyst (0.005 M) and ketimine **1g**, 0.1 M). The plot of k_{obs} against [nitromethane] gave straight line (dlog k_{obs}/d log[nitromethane] ~ 1) which indicate the 1st order dependence of the reaction in term of the concentration of nitromethane (Figure 6d).

Overall the kinetic data revealed a first order dependence of rate on catalyst and nitromethane concentration and independent on substrate concentration. Based on kinetics data, a probable mechanism for the aza Henry reaction of **1g** as representative substrate, nitromethane as nucleophile using the catalyst **Cu(II)-1B** is proposed in Scheme 5. Since, the kinetics of the reaction is not effected by concentration of substrate display that the very fast interaction between catalyst and substrate **(X)** and the overall rate of the reaction does not depend on the substrate concentration. Since the reaction rate is first order dependent on catalyst and nitromethane concentrations, a possible intermediate **(Y)** can be proposed as rate determining step where the metal centre activated the substrate **1g** and also the nitronate ion followed by the nucleophilic attack to the activated substrate via Si face to produce the product (*S*)-*β*-nitroamine (Scheme 5). Such observation is inconsonance to those reported earlier by us and others[34-35]. Further on the basis of the observed absolute configuration of the product, a possible transition state with hexacoordinated copper metal center was generated by energy minimization where the Si face attack of the nucleophile to the imine **1g** was more favorable energetically than the Re face attack due to steric crowding.



Scheme 5. Probable mechanism for aza Henry reaction of **1g** with nitromethane in presence of **Cu(II)-1B** as catalyst.

Further, in order to understand the structure of the efficient *in situ* formed catalyst, **Cu(II)-1B** incorporating the ligand **1B** and $Cu(OAc)_2.H_2O$ was prepared and characterized by ESI-MS (given in supporting information).

Conclusions

In summary we have designed a series of chiral monomeric macrocyclic salen ligands for asymmetric aza Henry reaction of isatin *N* protected ketimines with $Cu(OAc)_2.H_2O$. It was found that chiral macrocyclic salen complex **Cu(II)-1B** at room temperature afforded chiral *β*-nitroamines with excellent yields (88%) and high enantioselectivity (ee>99%) under co-catalyst free condition. Incidentally, the *in-situ* formed macrocyclic salen complex **Cu-1B** retained its activity and enantioselectivity at multigram scale and was successfully recycled several times. To understand the reasons behind the inability of other nitroalkane (nitroethane) to react with **1a**, the quantum chemical DFT calculations were performed to examine the effect nucleophiles ($CH_2NO_2^-$ and $CH_3CHNO_2^-$) for the conversion of **1a** to **2a** using macrocyclic **Cu(II)–1B** complex. The calculated results corroborate the formation of product **2a** much more feasible with nitromethane compared to nitroethane. We further converted our reaction product chiral *β*-nitroamine to chiral *β*-diamines in two steps at gram scale. The kinetic investigations of a representative substrate **1g** show first-order dependence on the concentrations of the catalyst **Cu(II)-1B**, nitromethane, but no dependence on the initial concentration of the substrate, **1g**. A possible mechanism for the aza Henry reaction was proposed.

Experimental Section

Synthesis of ligands

Ligands **1A**, **1B**, **1D** and **2D** were synthesized by the reported procedure [30]. For the synthesis of ligand **1C** a solution of dialdehyde **Y** (250 mg, 0.37 mmol) in dry DCM (0.7 mL) was added to a solution of (*R)*-(+)1,1'binaphyhyl-2,2'-diamine **C** (127.8 mg, 0.0.45 mmol) in dry MeOH (0.4 mL) at room temperature. The stirring of the solution was continued at room temperature for 5 h, and the progress of the reaction was checked on TLC. After completion of the reaction the solvent was removed under reduced pressure. The bright yellow solid product thus obtained was taken in dichloromethane (20 mL) and the organic layer was washed with water (2 x 20 mL), brine (20 mL) and was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give the yellow ligand **1C** (Yield 83%).

Typical experimental procedure for asymmetric aza-Henry reaction

Chiral ligand **1B** (5 mol%, 0.01 mmol) and $Cu(OAc)_2$ (5 mol%, 0.01 mmol) were added to a screw-capped vial containing Dry DCM (1 mL) and a stirring magnetic bar. A blue color solution was formed after 30 minutes. *N* protected ketimines **1a-1g** (0.2 mmol, 1 equiv) were added to the resulting solution followed by nitromethane (1.0 mmol, 5 equiv). After running the reaction for 16 h, the volatile components were removed under reduced pressure and the crude product was purified by flash column chromatography (n-hexane:ethylacetate 2:8).

Recycling of the catalyst Cu(II)-1B

Recyclability experiments were carried out with 0.5 mmol of **1a**. After completion of catalytic run (checked on TLC), the solvent was completely removed from the reaction medium under reduced pressure. Precipitation of **Cu(II)-1B** was

carried out by adding excess of (n-hexane:ethylacetate 98:02) and further wash the precipitate with hexane, dried in vacuum and reused for the subsequent catalytic run without further purification.

Computational Methods

The optimization of ground state and transition state geometries was done using PM6 level of theory in aqueous phase [36]. We have characterized the stationary point by frequency calculations in order to verify that the transition structures which possess only one, imaginary frequency. There are no imaginary frequencies in the ground state geometries in frequency calculation. Further, we have calculated the single point calculation at M06-2X level of theory using the basis set 6-31+G(d) for carbon, hydrogen, oxygen and nitrogen and LANL2DZ basis set for copper atom in aqueous phase[37-40]. The SMD solvent model has been used for our calculations[41]. All calculations were performed with the Gaussian 09 suite of program[42].

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Supplementary Material

All the Characterization data of aza Henry products like ^{1}H NMR, ^{13}C NMR, optical rotation, HPLC profile and ESI-MS were provided in this section.