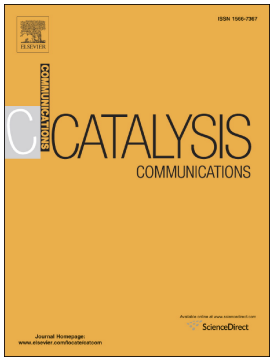

Enantioselective cross dehydrogenative coupling reaction catalyzed by Rose Bengal incorporated-Cu(I)-dimeric chiral complexes

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Enantioselective Cross Dehydrogenative Coupling reaction catalyzed by Rose Bengal incorporated-Cu(I)-Dimeric chiral complexes.

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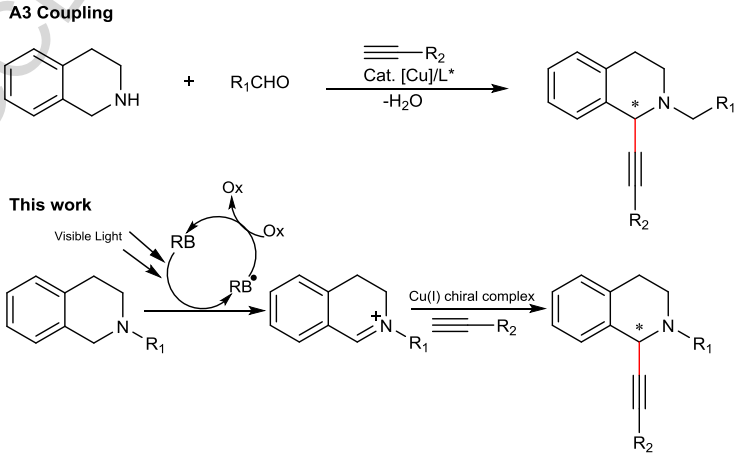
Abstract:

A novel dimeric chiral Cu(I) amino alcohol based *in-situ* generated catalyst in combination with Rose Bengal as a photo-redox catalyst were used for the first time for asymmetric cross dehydrogenative coupling of *N*-aryl tetrahydroisoquinoline with terminal alkynes enroute for propargylic amines synthesis using molecular oxygen as a terminal oxidant. This methodology provides an atom economical and green way to access diversified optically active alkynylation product selectively at C1-position of *N*-aryl tetrahydroisoquinoline under moderate conditions with high enantioselectivity (up to 99%) and excellent yield (up to 90%).

Keywords: Cross Dehydrogenative Coupling • Tetrahydroisoquinoline • Schiff bases • photo redox • Visible light • Alkynylation

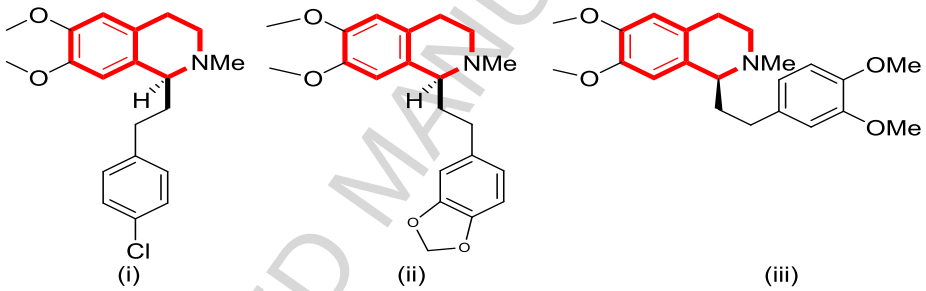
Introduction:

C-1 substituted tetrahydroisoquinoline derivatives have shown diverse biological activities and are pharmaceutically important motifs such as ligand receptors,[1] enzyme inhibitors,[2] anticancer,[3] antitubulin[4] and therapeutic agents.[5] Derivatisation of tetrahydroisoquinoline at the C-1 position has provided potential bioactive compounds[6] like methopoline, desoxyline and homolaudanosine[7] (Scheme 2). In this direction C-C bond formation via cross-dehydrogenative coupling (CDC) reaction is one of the most atom efficient processes to yield the desired products,[8-16] although other synthetic processes are known in the literature.[17] Enantioselective CDC reaction on tetrahydroisoquinoline is important but scantly reported.[18-24] These reports have utilized copper complexes of chiral ligands selected from Pybox, BINAP, QUINAP as catalysts to give the desired products. This pathway is alternative over A3 coupling for the synthesis of propargylic amines[25] (Scheme 1). In recent years several amino alcohol derived Schiff base complexes were efficiently used for various organic transformation by our group[26] and also by others.[27] In order to check the scope of chiral ligands, we utilized chiral amino alcohol-derived Schiff bases (**L_1-L_5**) in Cu(I) catalyzed CDC of *N*-aryl tetrahydroisoquinolines with terminal alkynes.



Scheme1: Approach for Optically active C-1 substituted THIQ.

On the other hand, the photo-redox pathway using visible light is well explored by the groups of Macmillan, Stephenson, Yoon[28-29] and others.[30-31] For the substitution of *N*-aryl-tetrahydroisoquinoline at C-1 position with a variety of nucleophiles, various metals (Ir, Ru) and organic dyes have been used as a catalyst. Li et al.[22] for the first time combined $[Ir(ppy)_2(dtbbpy)]PF_6$ complex with CuBr/QUINAP for enantioselective C-1 substitution of *N*-aryl tetrahydroisoquinoline. These metal-based photocatalysts are expensive and at the same time may leave toxic metal residue in the products. Various research groups have used organic dyes as a photoredox catalyst in the past. For example Rueping et al. reported organic dye catalysed C1 substitution of THIQ.[32] Konig et al. reported Eosin Y for various organic transformations.[33]



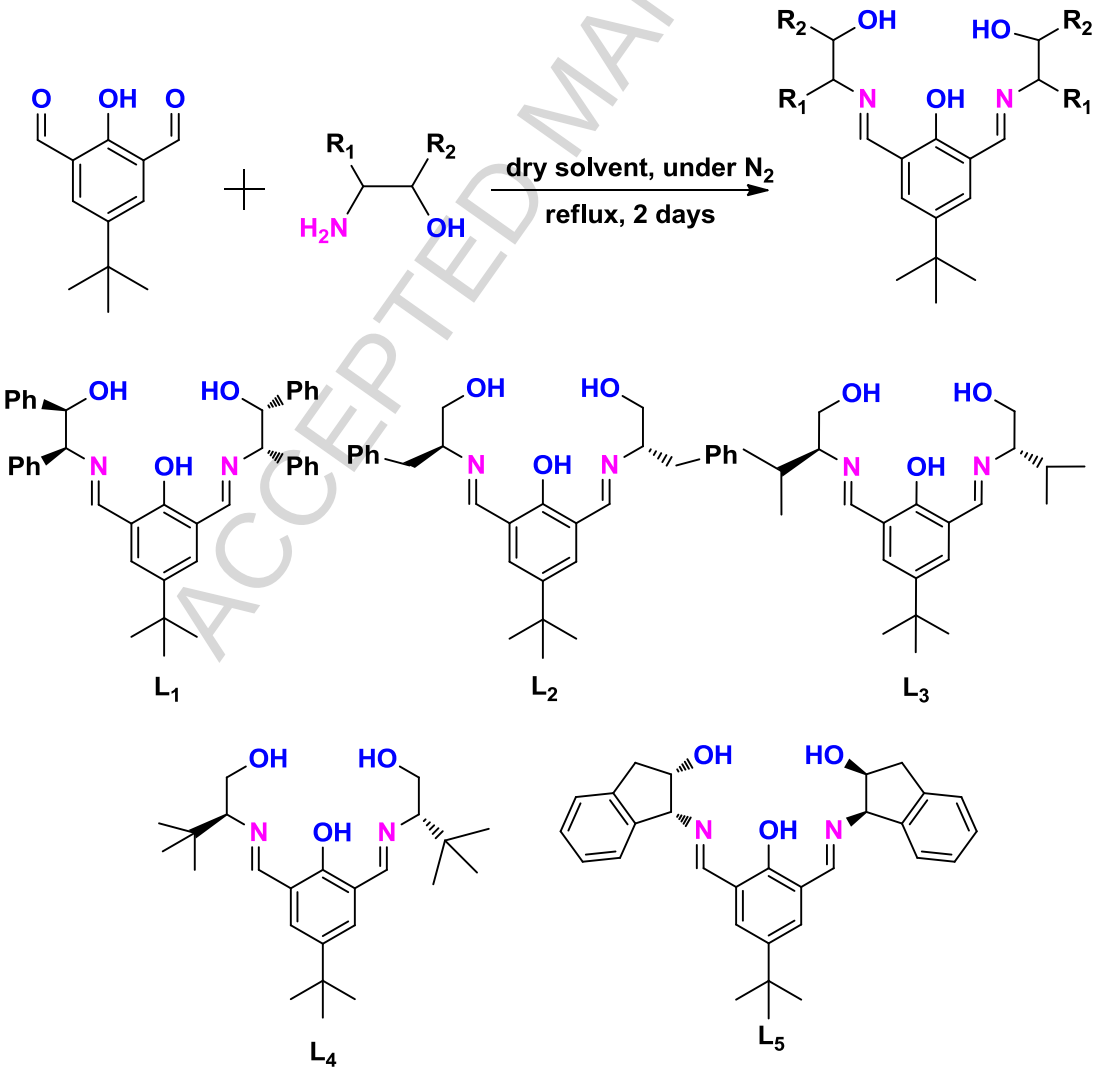
Scheme 2. Important molecules contain chiral tetrahydroisoquinoline.

Here we are reporting low cost and eco-friendly organic dyes as a photo redox catalyst like Rose Bengal (RB), Rhodamine B (RhB) and Fluorescein (F) in combination with *in situ* formed Cu(I)-chiral complexes to produce optically active 1-alkynyl tetrahydroisoquinoline derivatives with excellent enantiomeric excess (ee up to 99 %) and moderate to good yield. Pharmaceutically important moieties can be synthesized by using this protocol.

Results and Discussion

In our quest to explore low cost and eco-friendly organic dye, chiral ligands (**L_1-L_5**) derived by the reaction of readily available aminoalcohols selected from (1*S*,2*R*)-(+)-2-Amino-1,2-

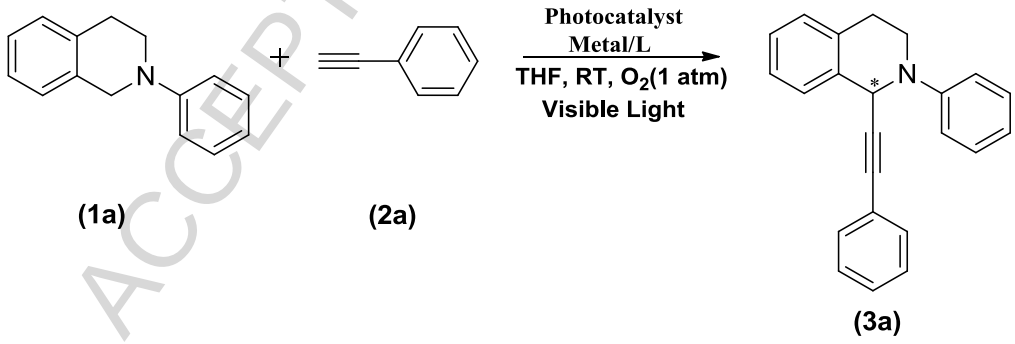
diphenylethanol **L_1**, (*S*)-(-)-phenylalaninol **L_2**, (*S*)-(+)-valinol **L_3**, (*S*)-(+)-tert-leucinol **L_4**, and (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol **L_5** with 4-*tert*-butyl-2,6-diformylphenol were synthesized. Initially we screened the *in situ* generated complexes derived from **L_1-L_5** (6 mol%) with CuBr (5 mol%) as catalyst in combination with Rose Bengal (5 mol%) as represntavive photoredox catalyst for cross-dehydrogenative coupling of (**1a**) with alkyne (**2a**) (Table 1, entry 1-5) by irradiation of visible fluorescent green light (10 W) with molecular oxygen as a mild oxidant. Data in Table 1 revealed that ligand **L_4** gave better results in terms of enantioselectivity (60%) with moderate yield (65%) (Table 1, entry 4). In order to improve the enantioselectivity and yield of the product attempts were made by varying the metal source viz., CuI, CuCl, Cu(OTf) and Cu(OTf)2 with ligand **L_4** (Table 1,



Scheme 3. Synthesis of Chiral Schiff bases.

entries 6-9). It was delighted to see that Cu(OTf) gave a good yield (80%) and moderate enantioselectivity (75%) of the product (Table1, entry 9). Encouraged by the preliminary results with the identified catalyst **Cu(I)OTf-L_4** and to ascertain an effective combination of photoredox catalyst other organic dyes namely, Rhodamine-B and Fluorescein (5 mol%) were used for cross-dehydrogenative coupling of (**1a**) with alkyne (**2a**) in THF (Table 1, entries 10,11). Among the three dyes used Rose Bengal gave better results (Table 1, entry 9) than other dyes where the conversion was low. This observation is inconsonance to the earlier reports.[30] Next attempts were made to vary the loading of Rose Bengal (RB) as photo redox catalyst in the range (2.5 & 10 mol%) (Table 1, entries 12,13) where best results in term of yield and enantioselectivity were obtained with 5 mol% loading (Table 1, entry 9). On conducting the blank reaction in absence of visible light no conversion was observed which infers that visible light is essential source for the reaction (Table 1, entry 14).

Table1. Optimization of the Ligand, Metal Source and Photocatalyst for Enantioselective CDC reaction[a].



(1a) (2a) (3a)

Entry	Ligand	Metal	Yield[b][%]	ee[c][%]
1[(d)]	L_1	CuBr	50	35
2[(d)]	L_2	CuBr	60	39
3[(d)]	L_3	CuBr	55	40
4[(d)]	L_4	CuBr	65	60
5[(d)]	L_5	CuBr	45	45
6[(d)]	L_4	$Cu(OTf)_2$	45	21
7[(d)]	L_4	CuI	35	50

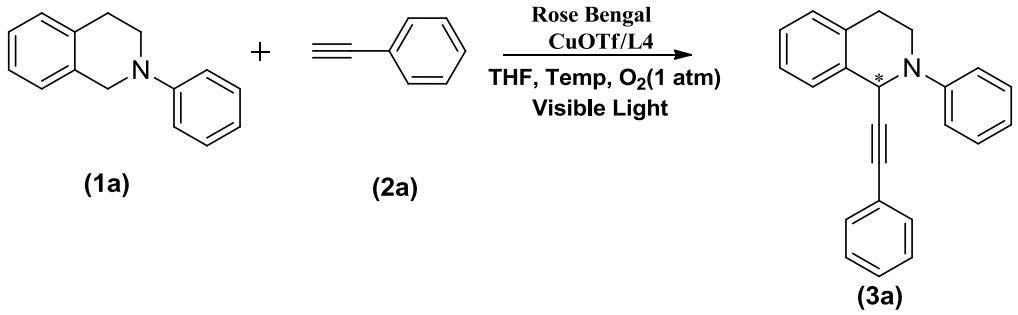
8[(d)]	**L_4**	CuCl	30	49
9[(d)]	**L_4**	Cu(OTf)	80	75
10[(e)]	**L_4**	Cu(OTf)	45	30
11[(f)]	**L_4**	Cu(OTf)	39	21
12[(d1)]	**L_4**	Cu(OTf)	65	60
13[(d2)]	**L_4**	Cu(OTf)	35	49
14[(g)]	**L_4**	Cu(OTf)	-	-

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol, 2.0 equiv), metal (0.005 mmol, 5 mol%) and **L** (0.006 mmol, 6 mol%), THF (1.0 ml), Visible light 10 W CFL green light, 36 h, [b] yield based on NMR using internal Standard, rt = room temperature (30 °C), Molecular Oxygen (O_2) (1atm), [c] determined by HPLC analysis on Daicel Chiralcel OD-H Column; [d] 5 mol % Rose Bengal [d1] & [d2] 10 mol % & 2.5 mol % Rose Bengal [e] & [f] Rhodamine-B & Fluorescein. [g] Without using Visible light source.

It is well known in literature that metal ligand ratio play an important role in cases where the active catalyst is generated *in situ*. Therefore we conducted the catalytic reaction with metal to ligand ratio 1:0.6, 1:1.2 and 1:1.8 using RB (5 mol%) for cross-dehydrogenative coupling of (**1a**) with alkyne (**2a**) in THF (Table 2, entries 1-3). It is evident from data that better results in term of product yield and ee is achieved in M:L (1:1.2) and found to be optimum.

Having established the M:L ratio, we next studied other reaction parameters (i.e., catalyst loading, effect of solvent and temperature) to maximize the yield and ee of the product using (**1a**) as a representative substrate with alkyne (**2a**) in the presence of **Cu(I)OTf-L_4** as catalyst and RB as photoredox catalyst. At first we altered the catalyst loading by keeping other reaction parameters constant. On decreasing the catalyst loading to 2.5 mol% caused decrease in both activity and enantioselectivity (Table 2, entry 4) however, on increasing the catalyst loading from 5 mol% to 7.5 mol% and 10 mol% (Table 2, entries 5, 6) there was no observable change in the product yield but there is loss in enantioselectivity. Hence 5 mol% catalyst loading is found to be optimum.

Table 2. Optimization of the reaction parameters[a]



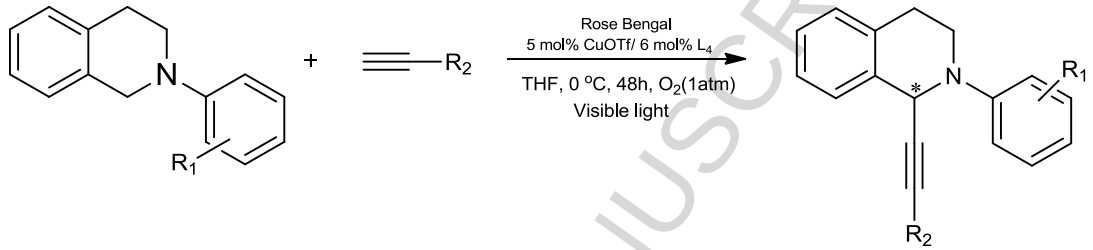
Entry	Solvent	Catalyst Loading	Temp[°C]	Metal/ L_4	Yield[b][%]	Ee[c][%]
1	THF	5	RT	1:0.6	78	50
2	THF	5	RT	1:1.2	80	75
3	THF	5	RT	1:1.8	80	65
4	THF	2.5	RT	1:1.2	45	40
5	THF	7.5	RT	1:1.2	80	65
6	THF	10	RT	1:1.2	82	70
7	$CHCl_3$	5	RT	1:1.2	20	18
8	CH_2Cl_2	5	RT	1:1.2	45	65
9	CH_3CN	5	RT	1:1.2	54	21
10	C_6H_6	5	RT	1:1.2	40	32
11[(d)]	THF	5	0	1:1.2	81	99
12[(d)]	THF	5	-10	1:1.2	80	92

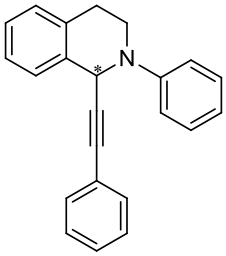
[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol, 2.0 equiv), $(CuOTf)_2$tol.complex (0.005 mmol, 5 mol%) and L_4 (0.006 mmol, 6 mol%), THF (1.0 ml), 5 mol% Rose Bengal, Visible light 10W CFL light, 36 h, [b] yield based on NMR using Internal Standard; [c] determined by HPLC analysis on Daicel Chiralcel OD-H Column, (d) reaction time 48 h.

Next, we screened solvents like $CHCl_3$, DCM, CH_3CN, toluene and polar aprotic THF (Table 2, entries 7-10). Among these solvents screened, THF was found to be suitable for this study in terms of enantioselectivity and yield of the desired product (ee 75%, yield 80%) (Table 2, entry 3). Temperature also play crucial role for enantioselective CDC reaction so we varied temperature from RT to 0 °C. It was delighted to us that there was an improvement in the ee 99% of the CDC product with slight increase in the yield however, the reaction took little longer time 48 h (Table 2, entry 11). Further decrease in temperature to -10 °C has no effect on yield but there was a drop in ee of the product and reaction became very slow (Table 2, entry 12). The above optimized reaction condition (Table 2, entry 11) was further used to carry out enantioselective Cross-dehydrogenative coupling for rest of the tetrahydroisoquinolines viz., 2-phenyl-1,2,3,4-tetrahydroisoquinoline, 2-(4-Chlorophenyl)-

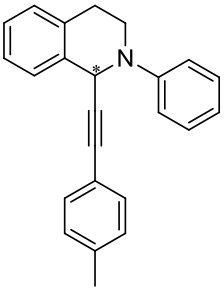
1,2,3,4-tetrahydroisoquinoline, 2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline, 2-(2-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline, 2-p-tolyl-1,2,3,4-tetrahydroisoquinoline, with aliphatic and aromatic alkynes viz., phenyl acetylene, 4-Ethynyltoluene, 1-ethynyl-4-fluorobenzene, 1-ethynyl-4-bromobenzene, 3-chloro-1-ethynylbenzene, ethynyltrimethylsilane, 1-decyne, cyclopropylacetylene (Table 3).

Table 3. Cu(I)-Schiff base photocatalysed enantioselective CDC reaction of N-phenyl-tetrahydroisoquinoline with terminal alkynes

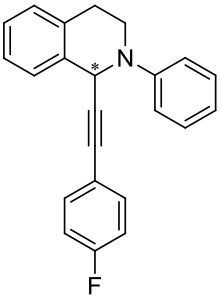




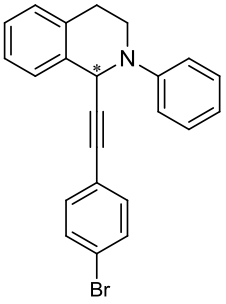
3a, 48h, yield 81%, ee 99%



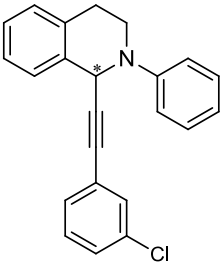
3b, 48h, yield 70%, ee 92%



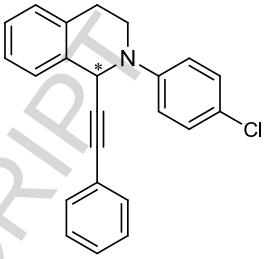
3c, 46h, yield 80%, ee 85%



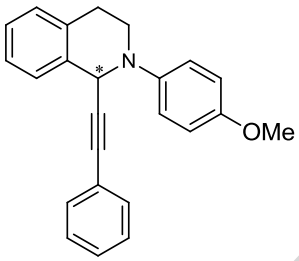
3d, 48h, yield 78%, ee 99%



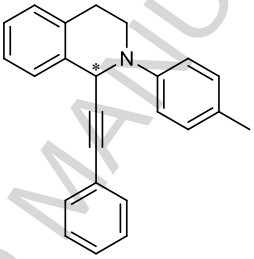
3e, 48h, yield 66%, ee 30%



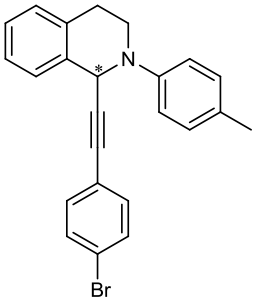
3f, 48h, yield 70%, ee 95%



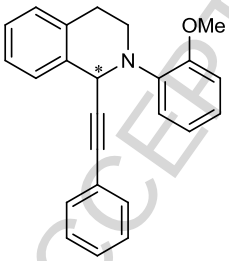
3g, 48h, yield 90%, ee 83%



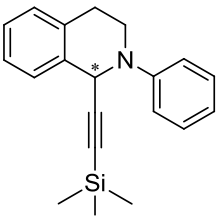
3h, 48h, yield 60, ee 99%



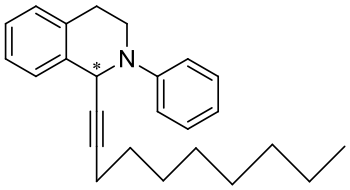
3i, 48h, yield 67%, 87%



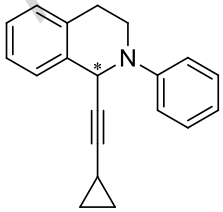
3j, 48h, yield 90%, ee 94%



3k, 48h, yield 50%, ee 99%

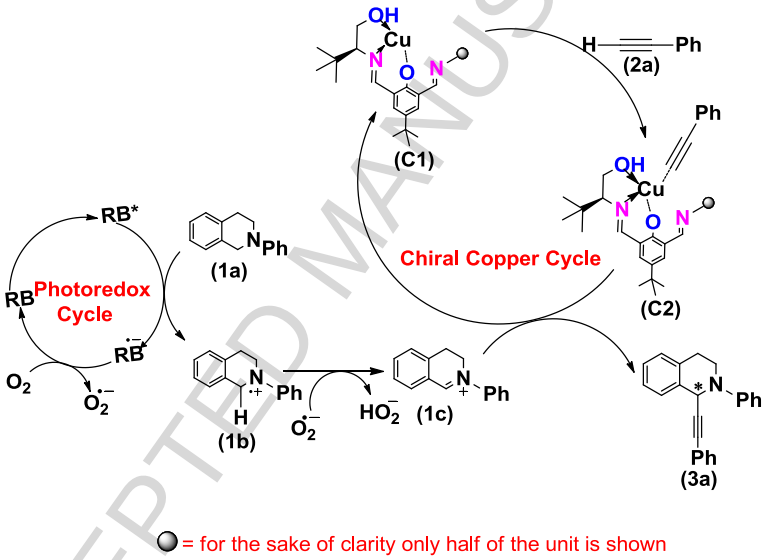


3l, 50h, yield 68, ee 99%



3m, 55h, yield 70%, ee 96%

The data in Table 3 showed that non-substituted aromatic alkynes gave 99% ee with 81% yield (Table 3, entry 3a), while para substituted electron donating as well as a withdrawing group has a marginal effect on yield and ee of the product (Table 3, entry 3b-3d). Substitution at meta-position played a negative role in ee and yield of the product which may be due to steric effect at meta position (Table 3, entry 3e). Corresponding changing the substitution on isoquinoline moiety has not shown any trend but good yield and high enantioinduction in the desired products was obtained (Table 3, entry 3f-3j). While varying the alkynes from aromatic to aliphatic with different groups such as trimethylsilyl, 1-decyne and cyclo propyl (Table 3, entry 3j, 3k, 3l) afforded satisfactory yields and excellent ee.



Scheme 4. Plausible Reaction Mechanism of Enantioselective CDC reaction of *N*-Phenyl-1,2,3,4-tetrahydroisoquinoline with terminal alkynes.

Based on experimental results a plausible mechanism is proposed (Scheme 3). The asymmetric induction mechanism is proposed on the similar lines as reported by Tan et al.[30] In the catalytic cycle the Rose Bengal (RB) goes to the excited state RB*[(34)] under the visible light irradiation and abstract one electron from THIQ (**1a**). Molecular oxygen completes the photo-redox cycle by oxidizing the RB radical anion to its ground state RB. Oxygen radical eventually abstracts the hydrogen from a C1 position of THIQ (**1a**) to form

prochiral iminium ion (**1c**). The *in situ* generated **Cu(I)OTf -L_4** activates terminal alkyne to form chiral acetylide species[35] which helps in the formation of optically active product (**3a**).

Conclusions

In conclusion, we have developed an atom economical and green way to access diversified optically active alkynylation product selectively at C1-position of *N*-aryl tetrahydroisoquinoline under moderate conditions with high enantioselectivity (up to 99%) and excellent yield (up to 90%) using dimeric Cu(I) amino alcohol Schiff base complex in combination with Rose Bengal dye as a photoredox catalyst.

Experimental Section

General:

All the tertiary amines were synthesized according to the reported procedure[see ESI] and terminal alkynes were used as received. 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. Enantiomeric excesses (ee) of the products were determined by UHPLC by (Shimadzu CBM-20A) using Daicel Chiralpak OD-H, OD chiral columns with 2-IPA/hexane as eluent. Optical rotations were measured with a Digipol 781 Automatic Polarimeter Rudolph Instruments. Synthesis of chiral dimeric salen ligands **L_1-L_5** was carried out by our reported procedure.[r]

Typical experimental procedure for the enantioselective CDC of *N*-aryl-tetrahydroisoquinoline with terminal alkynes by using *in situ* Cu(I)OTf-L_4 catalyst:

In a reaction vial, Cu(I)OTf (5 mol%), with ligand (**L_4**) (6 mol%) were dissolved in THF and the reaction was stirred for 1 h at RT under inert conditions (Argon Atmosphere). It was then cooled to 0 ^{o}C and 2-phenyl-tetrahydroisoquinoline (0.1 mmol) was added followed by subsequently addition of RB (5 mol%) and phenylacetylene (0.2 mmol) under the irradiation of visible light with molecular oxygen (1 atm). The reaction was checked on TLC, eluting with hexane/dichloromethane/diethyl ether (100:60:1). When the reaction was completed, the excess solvent was evaporated by using rotary evaporator and the product was purified by

chromatography on silica gel (eluting with hexane/dichloromethane/diethyl ether, 100:60:1). ^{1}H NMR spectroscopy was used for characterization of the final product.

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Appendix A. Supplementary data

All the Characterization data of cross dehydrogenative coupling products like ^{1}H NMR, ^{13}C NMR, HPLC profile were provided in this section.

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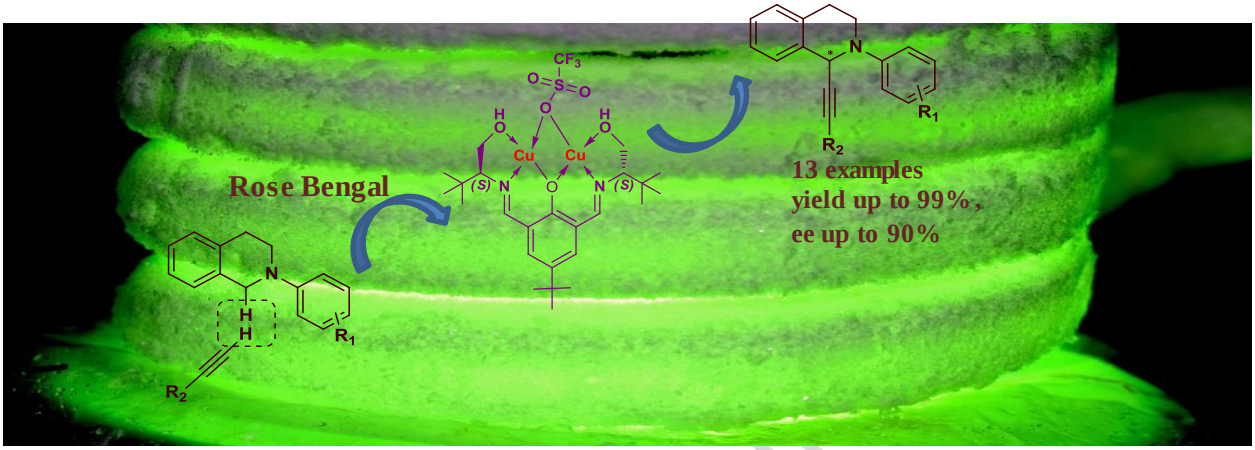
Graphical abstract



Research Highlights

- First asymmetric CDC reaction using Rose Bengal with Cu(I) chiral complexes.
- This protocol used for the synthesis of optically active propargylic amines.
- Excellent catalytic activity in terms of enantioselectivity and product yields.
- Synthesis of chiral Schiff base ligands using different amino alcohols.