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Asymmetric Henry reaction of trifluoromethyl ketone and aldehyde using Cu(II)-complex: computational study offers the origin of enantioselectivity with varied size of catalysts

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ABSTRACT

Chiral ligand **3** was synthesised from inexpensive and readily available (1*R*,2*R*)-(+)-1,2-diphenyl-1,2-diaminoethane and *tert*-butylbromoacetate. In situ generated complex obtained by the reaction of ligand **3** with copper triflate was used as catalyst for asymmetric Henry reaction of trifluoromethyl ketone having different substituents in the aromatic ring with nitromethane at 0 °C in presence of *N*,*N*-DIPEA as additive to give nitroaldol products in excellent enantioselectivity (*ee* upto 99%) with good yield (upto 80%). Ligand **3** with in situ generated complex with copper acetate was also found to be good catalyst for asymmetric nitroaldol reaction of aldehydes (*ee* up to 80–92%, yield up to 85%) with nitromethane at −5 °C. The DFT calculations performed with B3LYP and M06-2X functionals revealed the role of non-covalent interactions (such as π−π interaction and hydrogen bonding) and the steric factors in the catalyst play important role towards the enhancement of enantioselectivity.

1. Introduction

Nitroaldol or Henry reaction is one among cent percent atom-economic method for the synthesis of α-hydroxynitroalkanes, thus providing straight access to valuable bi-functional compounds, such as 1,2-amino alcohols and α-hydroxy carboxylic acids.[1] Ever since the inventive work on asymmetric Henry reaction,[2] using BINOL-derived heterometallic complex disclosed by Shibasaki in 1992, this area of research got impetus and subsequently several catalytic systems containing chiral ligands with metal atoms like Zn,[3] Co,[4] Cu,[5] Mg,[6] and Cr[7] have been reported. Moreover, organocatalysts have also been reported[8] for this reaction. The high commercial value of enantiopure nitroaldol products particularly as building blocks for pharmaceuticals, agrochemicals[9] and interest in academia[10] has been constant source of inspiration to explore newer catalytic systems that accommodate variety of substrates to synthesize newer target molecules. In this direction it is worth mentioning that although, the asymmetric Henry reaction of aldehydes and aldimines (aza-Henry) with various nitroalkanes has been extensively studied, ketones,[11,12a–i] as Henry acceptors remained relatively less explored possibly due to their less reactive nature. As a result, couple of activated α-keto esters have been reported to react with nitromethane in the presence of chiral Lewis acids,[12] or organocatalysts.[13]

Further, in recent years the application of organo-fluorine compounds,[14] particularly in the field of pharmaceutical and agrochemical has gain impetus due to enhanced bioavailability. In particular, it has been observed that inclusion of trifluoromethyl group,[15] greatly enhance the targeted activity e.g., drugs like Efavirenz (anti-HIV),[16] where presence of α-trifluoromethyl tetrasubstituted carbon centre was reported to have an important role. To synthesize α-trifluoromethyl tetrasubstituted carbons, among the several methods till reported in the literature,[17] asymmetric Henry reaction is one of the most effective method by using a chiral catalyst.[18]

In this paper we wish to disclose new Cu(II) complexes as catalysts for asymmetric Henry reaction of trifluoromethyl substituted

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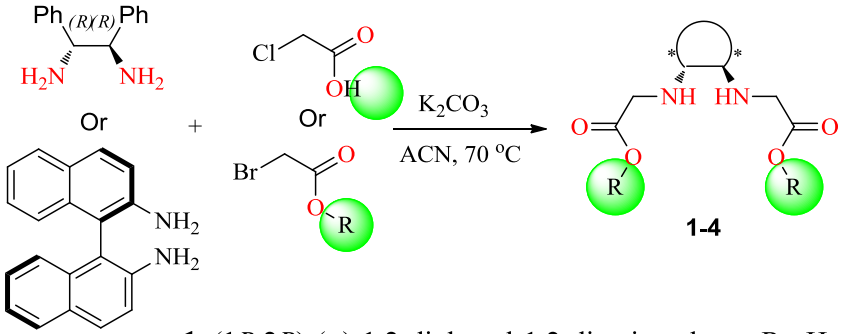
ketones and aldehydes as Henry acceptor with the nitromethane. We have also tried to rationalize the mechanism of trifluoromethyl ketone with nitromethane by which enantioselectivity is achieved with the use of most effective **3**-Cu(II) complex as catalyst with the help of density functional theory studies.

2. Results and discussion

Due to the commercial value of asymmetric Henry products of trifluoromethyl ketones we used these as substrates with nitromethane. To catalyse this reaction we have in situ generated copper complexes of ligands **1**–**4** derived from chiral diamine vis, (1*R*,2*R*)-(+)-1,2-diphenyl-1,2-diaminoethane or (*R*)-(+)-1,1′-binaphthyl-2,2′-diamine. Accordingly, ligands **1**–**4** were synthesized in a single step by the reaction of an appropriate diamine with chloroacetic acid (for ligand **1**) or alkylbromoacetate (for ligands **2**–**4**) (Scheme 1). The ligand **1** in combination with $Cu(OAc)_2 \cdot H_2O$, however, gave the product in 55% yield with 45% ee in the asymmetric Henry reaction of 2,2,2-trifluoro-1-phenylethanone and nitromethane as model reaction at room temperature in ethanol (Table 1, entry 1).

Next we attempted to improve the reaction performance by using organic and inorganic additives in the above optimized condition (Table 2, entry 2) and the data are given in Table 3. In case of inorganic additives like 4 Å MS, hydrotalcite, K_2CO_3, Cs_2CO_3, there was an improvement in the product yield but the enantioselectivity dropped significantly. However, with the addition of *N*,*N*-DIPEA as an organic base additive, the yield of the product was improved almost by 10% however, the ee of the product was almost similar (Table 3, entry 5). A more basic triethylamine caused severe drop in the product ee 36% (Table 3, entry 6).

Temperature is another important parameter that influences the enantioselectivity of the product more than the product yield. In view of this we screened our reaction over a temperature range from 40 °C to −10 °C keeping other reaction parameters as constant as given in Table 3 entry 5 (Fig. 1). At 0 °C, there was an increase in enantioselectivity (ee: 96%) while the product yield was nearly similar as obtained at room temperature (27 °C). However, a further decrease in the reaction temperature was detrimental to the reaction performance. Similarly, a temperature higher than RT, ee of the product dropped significantly.



1. (1*R*,2*R*)-(+)-1,2-diphenyl-1,2-diaminoethane, R= H
2. (1*R*,2*R*)-(+)-1,2-diphenyl-1,2-diaminoethane, R= Et
3. (1*R*,2*R*)-(+)-1,2-diphenyl-1,2-diaminoethane, R= *t*-Bu
4. (*R*)-(+)-1,1'-binaphthyl-2,2'-diamine, R = *t*-Bu

Scheme 1. Synthesis of ligands **1**–**4**.

On replacing acid group with ester group, e.g., ethyl group as in ligand **2**, the corresponding catalyst under the similar reaction conditions provided only marginally improved catalytic activity (yield 58%), but enantioselectivity improved significantly (ee, 65%) (Table 1, entry 2). This prompted us to increase the bulkiness of the alkyl group of the ester, and as a result when we used ligand **3** having tertiary butyl group and found that there was a further increase in the ee of the product (85%) but the yield (60%) was not drastically altered (Table 1, entry 3). On changing the chiral collar of ligand **3** to (*R*)-(+)-1,1′-binaphthyl-2,2′-diamine to get ligand **4**, we got relatively lower enantioselectivity (ee, 60%; Table 1, entry 4) in the product under similar condition. Therefore, we selected ligand **3** for this reaction for further optimization of other reaction parameters.

After zeroing down on ligand **3**, we next experimented with copper sources, as we know that different anions have different dissociation ability and particularly with copper the generated complexes may have different geometry, which in turn may greatly influence the catalytic activity and enantioselectivity.[5k,l] Further, our previous experience with Henry reaction suggests that the counter ions have a role in generating the active nucleophile from the nitroalkanes by abstracting the proton.[5l,m] As a consequence we have varied different copper salts having various counter ions with different basicity (Table 2). Among the various copper salt (Table 2), $Cu(OTf)_2$ along with the ligand **3** proved to the best combination of catalytic system to give better yield and enantioselectivity (Table 2, entry 2).

With the above optimized parameters in hand, solvents were screened for further improvement. As summarized in Table 4, among the alcohols used MeOH gave slightly higher yields (Table 4, entry 1) but comparable enantioselectivity was obtained with ethanol (Table 4, entry 2), however, with ^{i}PrOH the performance was not so promising (Table 4, entry 3). In the case of ether-type solvents such as Et_2O and THF, lower enantioselectivities were observed (Table 4, entries 4, 7). The enantioselectivity in chlorinated hydrocarbons viz, chloroform and dichloromethane (entries 5 & 6) was as good as we obtained with methanol, but product yield was relatively low. Further, it is appropriate to change ligand versus metal ratio knowing that copper is known to form bimetallic complexes; hence by keeping metal loading and other reaction parameters constant as per the entry 1, we optimized the ligand loading. On reducing the ligand loading to 2 mol % and 3 mol %, lower enantioselectivities and yields were obtained (entries 8 & 9). Also, by increasing the ligand loading to 10 mol %, there was no improvement in the yield as well as enantioselectivity. Hence it can be concluded that any free ligand or metal adversely affect the enantioselectivity. On the basis of the data generated the optimized condition constitutes, 5 mol % $Cu(OTf)_2$ with 5 mol % the ligand **3** as catalysts and 5 mol % *N*,*N*-DIPEA as an additive in MeOH at 0 °C for

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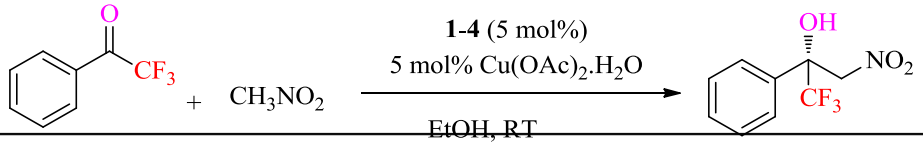
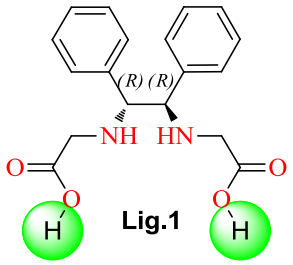
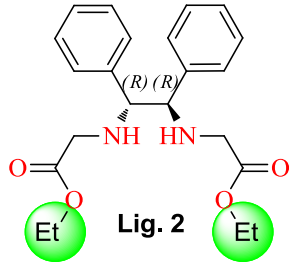
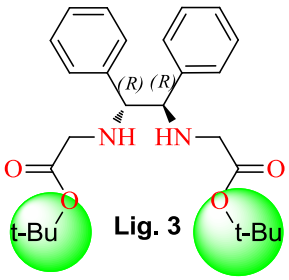
Table 1
Screening of ligands **1**–**4** for the asymmetric Henry reaction of 2,2,2-trifluoro-1-phenylethanone with nitromethane[a]

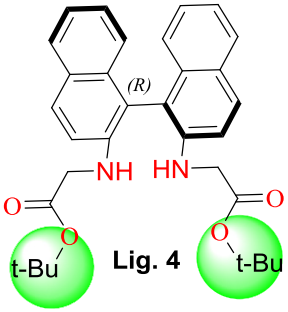






Entry	%Yield[b]	% Ee[c]	Entry	%Yield[b]	% Ee[c]
1	55	45	2	58	65

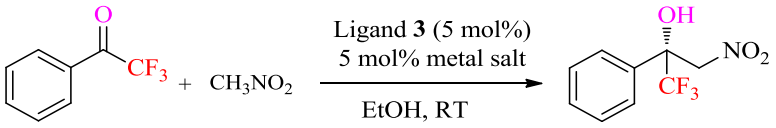




Entry	%Yield[b]	% Ee[c]	Entry	%Yield[b]	% Ee[c]
3	60	85	4	45	60

[a] All the reactions were carried out with 0.5 mmol of substrate and 5 mmol of nitromethane.
[b] Isolated yield after flash column chromatography.
[c] Determined by HPLC (Chiralcel OD column).

Table 2
Variation of metal salt for the asymmetric Henry reaction of 2,2,2-trifluoro-1-phenylethanone with nitromethane[a]



Entry	Metal salts	Yield[b](%)	Ee[c](%)
1	$Cu(OAc)_2 \cdot H_2O$	60	85
2	$Cu(OTf)_2$	62	90
3	CuBr	42	34
4	CuI	46	52
5	$C_6H_5(CuOTf)_2$	54	48

[a] All the reactions were carried out with 0.5 mmol of substrate and 5 mmol of nitromethane.
[b] Isolated yield after flash column chromatography.
[c] Determined by HPLC (Chiralcel OD column).

model substrate 2,2,2-trifluoro-1-phenylethanone with nitromethane.

To find out the substrate generality, the scope of this catalytic system in case of the asymmetric Henry reaction of various trifluoromethyl aryl ketone were tested under the optimized reaction conditions (Table 5, entries 1–6). As compared to the trifluoromethyl phenyl ketone, the substrate with 4-fluoro phenyl gave the highest ee upto >99% in the product (Table 5, entry 2). However, other substituents at the same position, irrespective of their electronic features gave more or less similar but slightly lower ee in the product.

Though, we have successfully utilized the ligand **3** with copper triflat as an efficient catalyst for the asymmetric Henry reaction of trifluoromethyl ketone with nitromethane there was an earnest quest about the scope of the ligand **3** on varying the substrate like aldehydes with nitromethane.

In order to get the optimal reaction condition for asymmetric Henry reaction of benzaldehyde with nitromethane using the

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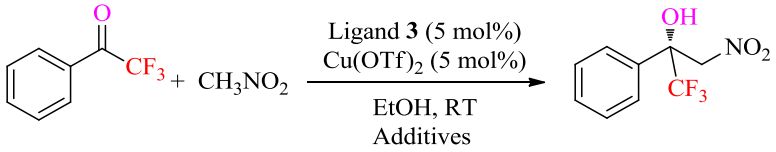
Table 3
Screening of the additives for the asymmetric Henry reaction of 2,2,2-trifluoro-1-phenylethanone with nitromethane[a]



Entry	Additive	Yield[b] (%)	Ee[c](%)
1	4 Å MS	75	72
2	Hydrotalcite	82	45
3	K_2CO_3	86	46
4	Cs_2CO_3	90	38
5	*N,N*-DIPEA	71	89
6	Et_3N	86	36

[a] All the reactions were carried out with 0.5 mmol of substrate and 5 mmol of nitromethane.
[b] Isolated yield after flash column chromatography.
[c] Determined by HPLC (Chiralcel OD column).

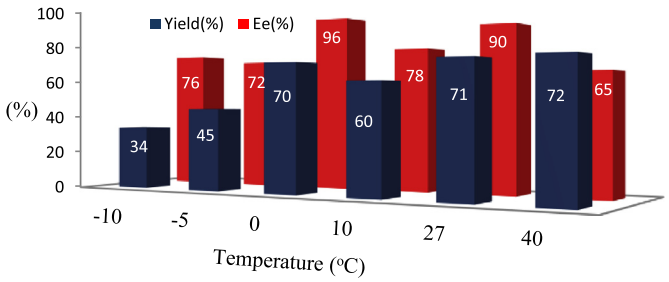
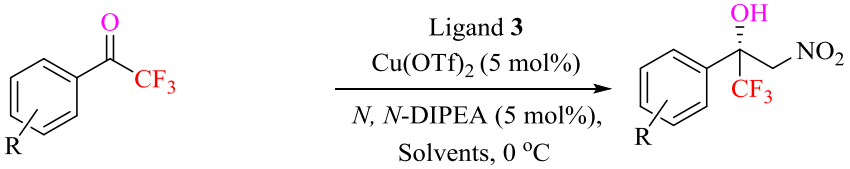


Fig. 1. Screening of the temperature.

loading at −5 °C in THF is optimum to catalyse the asymmetric Henry reaction of benzaldehyde with nitromethane (Fig. 2).

Further exploration of the scope of the ligand **3** was focused on varying the substrate like aldehydes viz, benzaldehyde, 2-MeO-benzaldehyde, 3-MeO-benzaldehyde, 4-MeO-benzaldehyde, 2-Me-benzaldehyde, 4-Me-benzaldehyde, 4-fluorobenzaldehyde, 1-naphthaldehyde, cyclohexanal and thiophene-2-carboxaldehyde (entries 1–10) with nitromethane at optimized parameters. To our delight, the reaction tolerated variety of aldehydes as substrate bearing electron withdrawing or electron donating group at different substitution position of aromatic ring, giving the corresponding

Table 4
Variation of amount of ligand and solvent for the asymmetric Henry reaction of 2,2,2-trifluoro-1-phenylethanone with nitromethane[a]



Entry	Ligand (mol %)	Solvent	Yield[b] (%)	Ee[c] (%)
1	5	MeOH	74	97
2	5	EtOH	70	96
3	5	^{i}PrOH	65	92
4	5	THF	65	82
5	5	CH_2Cl_2	56	95
6	5	$CHCl_3$	54	98
7	5	Et_2O	68	78
8	2	MeOH	54	57
9	3	MeOH	59	62
10	7	MeOH	76	88
11	10	MeOH	78	85

[a] All the reactions were carried out with 0.5 mmol of substrate and 5 mmol of nitromethane.
[b] Isolated yield after flash column chromatography.
[c] Determined by HPLC (Chiralcel OD column).

ligand **3** we again varied copper source by using different copper salts viz, copper acetate, copper triflat, CuBr, CuI and $CuCl_2$, (Table 6, entries 1–5). Among these copper salts, $Cu(OAc)_2$ with ligand **3** gave good result in term of enantioselectivity and yields compared to other salts while for the substrate trifluoromethyl aryl ketone copper triflat performed better.

Next, we have varied the solvents, loading of catalyst (0.5–7.5 mol %), temperature (−5 to 35 °C) and found that the results obtained by using reaction condition of 0.5 mol % of catalyst products in good yield (up to >85%) and enantioselectivities (ee up to >92%) with very low catalyst loading (0.5 mol %) so far reported in literature using THF as solvent at low temperature (−5 °C). Among all the substrates, benzaldehyde with nitromethane gave good yield and highest enantioselectivity (Table 7, entry 1).

A possible mechanism of asymmetric Henry reaction of trifluoromethyl ketones with nitromethane catalysed by **Catalyst-3** is shown in Scheme 2. In order to rationalize the observed enantioselectivity in Henry product, we have performed density functional

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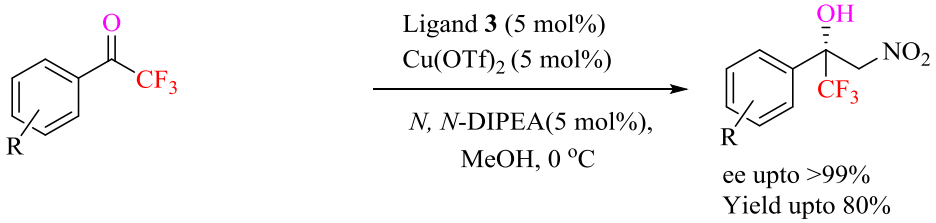
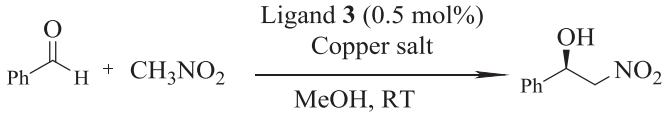
Table 5
Variation of substrates for the asymmetric Henry reaction of trifluoromethyl aryl ketones with nitromethane[a]



Entry	Substrate	Yield[b] (%)	Ee[c] (%)
1	2,2,2-trifluoro-1-phenylethanone	74	97
2	2,2,2-trifluoro-1-(4-fluorophenyl)ethanone	80	>99
3	2,2,2-trifluoro-1-(4-bromophenyl)ethanone	70	92
4	2,2,2-trifluoro-1-(4-chlorophenyl)ethanone	80	88
5	2,2,2-trifluoro-1-(4-methylphenyl)ethanone	62	90
6	2,2,2-trifluoro-1-(2,4-dimethoxyphenyl)ethanone	85	80

[a] All the reactions were performed with trifluoromethyl aryl ketones (0.5 mmol), nitromethane (5.0 mmol), ligand **3** (5 mol %), $Cu(OTf)_2$ (5 mol %) in 1 mL of MeOH at 0 °C for 24 h.
[b] Isolated yields after flash column chromatography.
[c] Determined by HPLC (Chiralcel OD, OD-H etc.).

Table 6
Variation of metal salts for the asymmetric Henry reaction[a]



Entry	Metal salts	Yield[b](%)	Ee[c](%)
1	$Cu(OAc)_2 \cdot H_2O$	72	80
2	$Cu(OTf)_2$	62	68
3	CuBr	42	51
4	CuI	35	28
5	$CuCl_2$	54	60

[a] All the reactions were carried out with 0.5 mmol of substrate and 5 mmol of nitromethane.
[b] Isolated yield after flash column chromatography.
[c] Determined by HPLC.

calculations with the **Catalyst-1** and **Catalyst-3** as per the details given below.

3. Computational study

The Experimental results have shown that the enantioselectivity of Henry reactions is increasing with size of the **Catalyst-1** to **Catalyst-3** (Table 1). To rationalize the observed enantioselectivity, we have performed density functional calculations using B3LYP DFT functional with the **Catalyst-1** and **Catalyst-3** (see Scheme 1). B3LYP DFT functional has been employed to examine the Henry reactions and results were in good agreement with the experimental results.[19,20] We have located the transition state structures for both the *Re* and *Si* face of the trifluoromethyl ketone with nitromethane in the presence of catalysts. To investigate the role of steric effect on the enantioselectivity **Catalyst-1** and **Catalyst-3** has been considered. **Catalyst-1** furnished the lowest enantioselectivity in the series, whereas, **Catalyst-3** gave the highest enantioselectivity (Table 1).

Catalyst-1 has adopted distorted trigonal bipyramidal geometry, with Cu(II) ion coordinated to ligand, (1*R*,2*R*)-(+)-1,2-diphenyl-

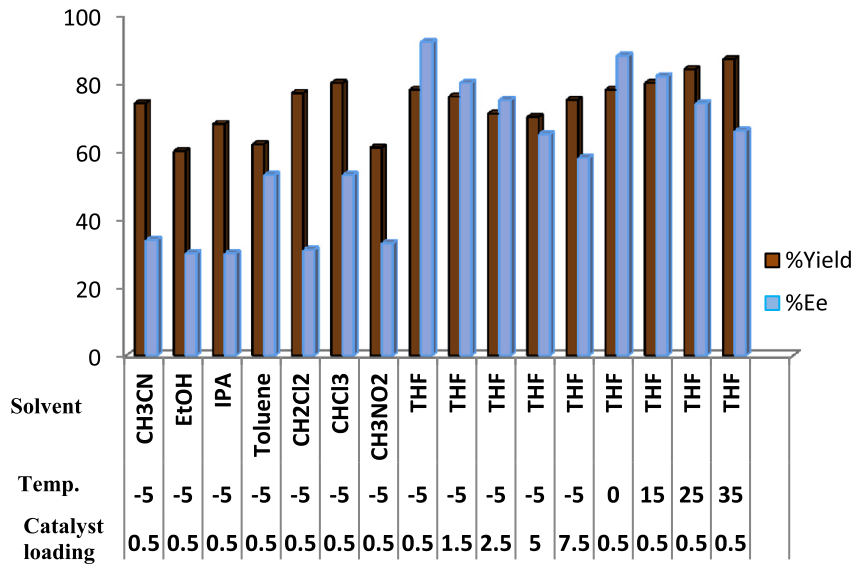
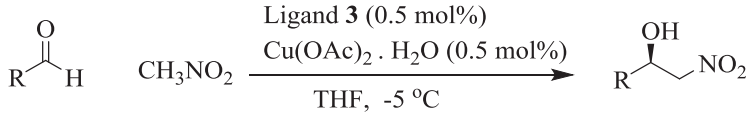


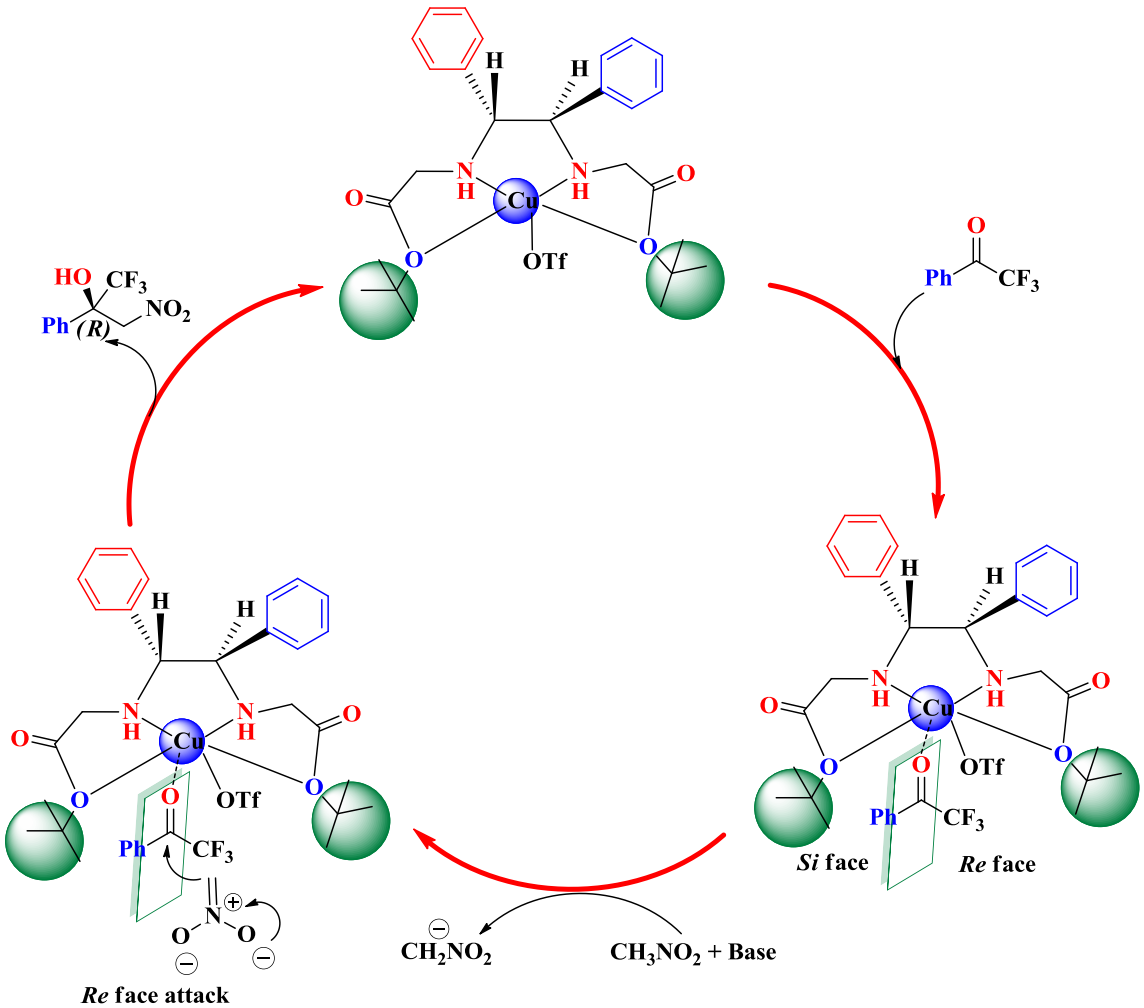
Fig. 2. Variation of catalyst loading, temperature and solvents for the asymmetric Henry reaction.

Table 7
Variation of substrates for the asymmetric Henry reaction of aldehydes with nitromethane[a]



Entry	R	Yield[b](%)	Ee[c](%)
1	C_6H_5–	78	92[e]
2	2-MeO–C_6H_5–	85	88
3	3-MeO–C_6H_5–	76	80
4	4-MeO–C_6H_5–	79	81
5	2-Me–C_6H_5–	80	80
6	4-Me–C_6H_5–	78	80
7	4-F–C_6H_5–	75	82[f]
8	1-naphthyl-	81	85
9	Thiophene-2-carboxyl	78	82
10	Cyclohexyl-	82	80

[e,f]2,6-lutidine (10 mo%) Used as additive.
[a] All the reactions were performed with aldehydes (0.5 mmol), nitromethane (5.0 mmol), ligand **3** (0.5 mol %), $Cu(OAc)_2 \cdot H_2O$ (0.5 mol %) in 1 mL of THF at −5 °C for 24 h.
[b] Isolated yields after flash column chromatography.
[c] Determined by HPLC (Chiralcel OD-H etc.).



Scheme 2. A probable mechanism of the asymmetric Henry reaction of trifluoromethyl ketone with nitromethane.

1,2-diaminoethane, (R=H) and OTf group (Fig. 3 and Scheme 1). We have located the transition state (TS) structures for the attack of nitromethane to *Re* and *Si* face of the coordinating ketone to the Cu(II) ion of **Catalyst-1** (Fig. 3). The calculated energy difference obtained for **Catalyst-1** using B3LYP level suggests that the attack of nitromethane from the *Si* face of ketone is energetically favoured than the *Re* face (ΔE=2.8 kcal/mol, Table 8). The calculated free energy of activation difference also showed similar preference

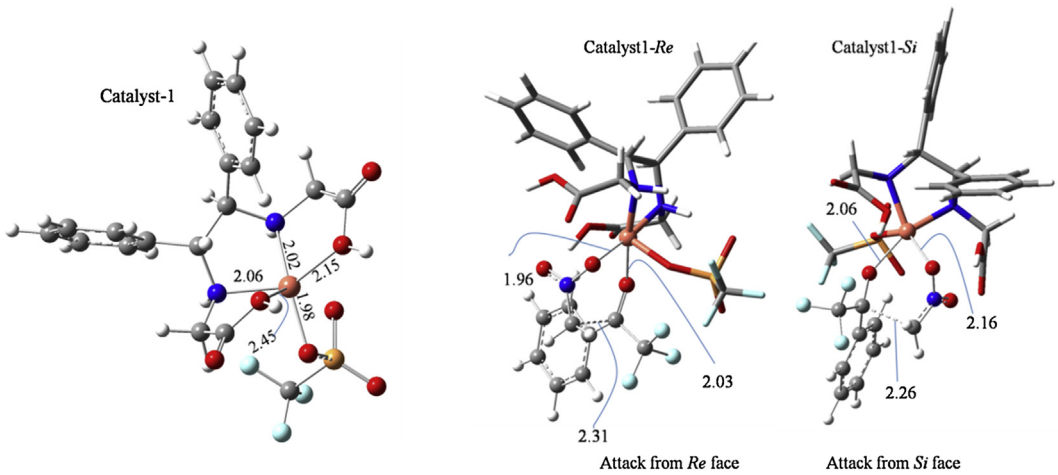


Fig. 3. All the optimized structures of the catalyst and catalyst, and reactant. **1) Catalyst-1** (see Scheme 1). (**Catalyst-1-*Re***) Transition state structure; trifluoromethyl ketone bound to **Catalyst-1** and the attack of the nitromethane occur from *Re* face of the ketone. (**Catalyst-1-*Si***) Transition state structure nitromethane approaches on the *Si* face of the ketone in presence of the **Catalyst-1**. (C; gray, H; white, S; yellowish orange, O; red, F; cyan, N; blue, Cu; reddish brown). Distances in angstrom (Å).

Table 8
The transition state energy difference calculated with B3LYP for the *Si* and *Re* face attack of nitromethane on the ketone with **Catalyst-1** and **Catalyst-3**. The corresponding Free energy differences are given in parenthesis. The single point energy difference calculated with M06-2X/6-31+G** level of theory using B3LYP optimized geometries. All the energy values are given in kcal/mol

Name	$\Delta E_{B3LYP/6-31G^*}$	$\Delta E_{M06-2X/6-31+G^{**}//B3LYP/6-31G^*}$
Catalyst-**1**	2.8(1.0)	4.7
Catalyst-**3**	−7.3(−7.3)	−8.0

(Table 8). Further, the calculated single point energy calculations with M06-2X level also supported the previous results (Table 8). The TS geometry analysis showed that the two −COOH groups of the ligand weakens the binding to the Cu(II) ion, however, the reactants nitromethane and ketone coordinates strongly to the Cu(II) ion of **Catalyst-1**. The stabilization of the *Si* face attack of nitromethane to the ketone arises due to the hydrogen bonding[21] interactions between the -OTf and −COOH groups and the less steric crowding than that of *Re* face (Figure S1, Supplementary data).

We have also examined the TS geometries for the Henry reaction with the **Catalyst-3** (Fig. 4). The calculated energy difference reveals that the attack of nitromethane to the ketone is preferred from the *Re*-face with the **Catalyst-3** (Table 8). The energetic preference for the attack of nitromethane to the ketone is much larger in the case of **Catalyst-3** than that of **Catalyst-1**. The single point energy calculations using M06-2X DFT functional also showed the larger preference for **Catalyst-3** (Table 8). These calculated results corroborate the experimental enantioselectivity observed with such catalysts (Table 1). The *Re* face attack is more energetically preferred due to the better π−π interaction[22] between two the phenyl rings of the ligand in the transition state geometry of the *Re* face than *Si* face attack of nitromethane to the ketone unit (Figure S2, Supplementary data). Further the attack from the *Re* face is also sterically favoured as the distance between the *tert*-butyl hydrogen and the nitromethane is larger in this case compared to the *Si* face attack (Figure S2, Supplementary data). To examine the role of solvent on the enantioselectivity, we have performed additional calculations with Polarizable continuum

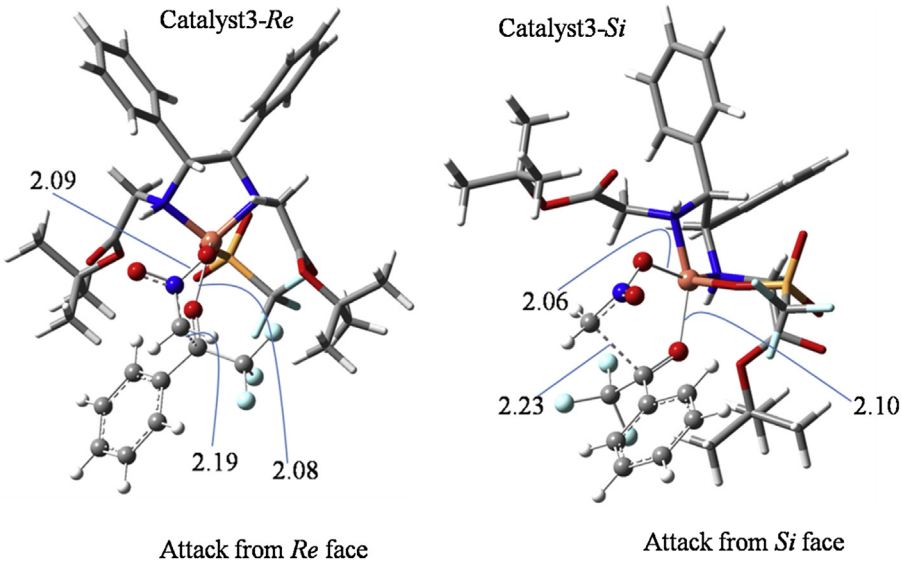


Fig. 4. (**Catalyst-3-*Re***) TS structure of nitromethane attack from *Re* face of the ketone bound to **Catalyst-3**. (**Catalyst-3-*Si***) Transition state structure of **Catalyst-3** bound ketone where nitromethane attacking from *Si* face of the ketone. All the distances are given in Å. (C; gray, H; white, S; yellowish orange, O; red, F; cyan, N; blue, Cu; reddish brown). Distances in angstrom (Å).

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model (PCM).[23] The single point calculations in methanol using the gas phase optimized geometries with the M06-2X level of theory show that the *Si* face attack for the **Catalyst-1** is more favourable by 1.2 kcal/mol compared to the *Re* face attack. Further, the *Re* face attack is favourable by 4.9 kcal/mol for **Catalyst-3** is in good agreement with the gas phase results.

4. Conclusions

This paper has disclosed the synthesis of new chiral ligands **1**–**4** and used them in copper catalysed asymmetric nitroaldol (Henry) reaction of trifluoromethyl aryl ketones and aldehydes with nitromethane. The DFT calculations revealed the role of non-covalent interactions and the steric effect towards the origin of enantioselectivity with the variation in the size of the catalysts used in this study. Optimization of the reaction parameters were carried out and ligand **3** with highest bulkiness along with diphenyldiamine collar proved to be the best one in combination with $Cu(OTf)_2$ in case of trifluoromethyl aryl ketones while $Cu(OAc)_2$ as metal source gave moderate to good yield along with excellent ee of the corresponding nitroaldol products of aldehydes.

5. Experimental section

5.1. Typical experimental procedure for the asymmetric Henry reaction of trifluoromethyl aryl ketones

Chiral ligand **3** (5 mol %) and $Cu(OTf)_2$ (5 mol %) were added to a screw-capped vial containing a stirring magnetic bar. A clear green solution formed after adding MeOH (1 mL) as solvent, which was stirred for 24 h at 0 °C. To the resulting solution of desired substrates trifluoromethyl aryl ketones (0.5 mmol, 1 equiv) were added and nitromethane (5.0 mmol, 10 equiv) also added into the solution using *N*,*N*-DIPEA (5 mol %) as additive. After running the reaction for the specified time as given in Table 5 the volatile components were removed under reduced pressure and the crude product was purified by flash column chromatography (EtOAc: Hexane 1:9).

5.1.1. Typical experimental procedure for the asymmetric Henry reaction of aldehydes. Chiral ligand **3** (0.5 mol %) and $Cu(OAc)_2 \cdot H_2O$ (0.5 mol %) were added to a screw-capped vial containing a stirring magnetic bar. A clear green solution formed after adding THF (1 mL) as solvent, which was stirred at −5 °C for 24 h. To the resulting solution of desired substrates aldehydes (0.5 mmol, 1equiv) were added and nitromethane (5.0 mmol, 10 equiv) also added into the solution. After running the reaction for the specified time as given in Table 8 the volatile components were removed under reduced pressure and the crude product was purified by flash column chromatography (EtOAc: Hexane 1:9).

5.2. Synthesis of ligands 1–4

*5.2.1. General procedure for synthesis of ligand **1**.* In a flame dried single necked round bottom flask, (1*R*,2*R*)-(+)-1,2-diphenyl-1,2-diaminoethane (424 mg, 2 mmol), freshly dried K_2CO_3 (~100 mg) in dry acetonitrile (30 mL) were taken under nitrogen atmosphere, to which bromoacetate (0.6 mL, 4.5 mmol) was added at RT with stirring. The mixture was stirred for 24 h at 70 °C. The reaction was monitored by TLC and cooled to RT, filtered and the solvent was removed from the filtrate under reduced pressure. The pure ligand **1** was obtained by column chromatography (15:85, EtOAc/Hexane); (313.7 mg, Yield 74%); Yellow colour oil; [Found: C, 65.82; H, 6.12; N, 8.15. $C_{18}H_{20}N_2O_4$ requires C, 65.84; H, 6.14; N, 8.53]; $[\alpha]_D^{25}$ +36.12 (*c* 0.5 in $CHCl_3$); ν_{max} (KBr) 3642, 3438, 2926, 2364, 1732, 1422, 1350, 1135, 700 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.13–6.98 (m, 10H), 3.71 (s, 2H), 3.15 (s, 4H), 2.11 (s, 2H); δ_C (200 MHz, $CDCl_3$) 171.6, 140.1, 128.1, 127.9, 127.8, 127.0, 68.3, 53.1; HRMS (ESI, *m*/*z*) [M^+−H] found 328.1422 $C_{18}H_{20}N_2O_4$ requires 328.1425.

*5.2.2. General procedure for synthesis of ligand **2**.* In a flame dried single necked round bottom flask, (1*R*,2*R*)-(+)-1,2-diphenyl-1,2-diaminoethane (424 mg, 2 mmol), freshly dried K_2CO_3 (~100 mg) in dry acetonitrile (30 mL) were taken under nitrogen atmosphere, to which ethylbromoacetate (0.74 mL, 4.5 mmol) was added at RT with stirring. The mixture was stirred for 24 h at 70 °C. The reaction was monitored by TLC and afterward the reaction mixture was cooled to RT, filtered and the solvent was removed from the filtrate under reduced pressure. The pure ligand **2** was obtained by column chromatography (15:85, EtOAc/Hexane); (360.4 mg, Yield 85%); Yellow colour oil; [Found: C, 68.17; H, 7.22; N, 7.20. $C_{22}H_{28}N_2O_4$ requires C, 68.73; H, 7.34; N, 7.29]; $[\alpha]_D^{25}$ +18.25 (*c* 0.5 in $CHCl_3$); ν_{max} (KBr): 3372, 2925, 2362, 1729, 1458, 1378, 1125, 914, 845, 699 cm^{-1}; δ_H (200 MHz, $CDCl_3$, TMS) 7.23–6.97 (m, 10H), 4.69–4.65 (d, *J*=8 Hz, 2H), 3.77–3.73 (q, 4H), 3.30–3.26 (m, 2H), 1.16–1.12 (m, 6H); δ_C (200 MHz, $CDCl_3$) 171.0, 135.5, 129.1, 125.3, 114.9, 83.0, 69.3, 28.3; HRMS (ESI, *m*/*z*) [M^+−H] found 385.1242 $C_{22}H_{28}N_2O_4$ requires 385.1246.

*5.2.3. General procedure for synthesis of ligand **3**.* In a flame dried single necked round bottom flask, (1*R*,2*R*)-(+)-1,2-diphenyl-1,2-diaminoethane (424 mg, 2 mmol), freshly dried K_2CO_3 (~100 mg) in dry acetonitrile (30 mL) were taken under nitrogen atmosphere, to which *tert*-butylbromoacetate (0.88 mL, 4.5 mmol) was added at RT with stirring. The mixture was stirred for 24 h at 70 °C. The reaction was monitored by TLC and afterward the reaction mixture was cooled to RT, filtered and the solvent was removed from the filtrate under reduced pressure. The pure ligand **3** was obtained by column chromatography (15:85, EtOAc/Hexane); (373.2 mg, Yield 88%); Yellow colour oil; [Found: C, 70.86; H, 8.22; N, 6.13. $C_{26}H_{36}N_2O_4$ requires C, 70.88; H, 8.24; N, 6.36]; $[\alpha]_D^{25}$ +32.12 (*c* 0.5 in $CHCl_3$); ν_{max} (KBr): 3325, 2978, 2355, 1732, 1453, 1368, 1156, 941, 847, 701 cm^{-1}; δ_H (200 MHz, $CDCl_3$, 25 °C, TMS) 6.99–6.95 (m, 10H), 3.96–3.88 (d, *J*=16 Hz, 2H), 3.13–3.06 (d, *J*=14 MHz, 4H), 1.45–1.30 (m, 18H); δ_C (200 MHz, $CDCl_3$) 170.8, 137.9, 129.2, 127.8, 126.9, 80.0, 65.7, 52.6, 28.2; HRMS (ESI, *m*/*z*) [M^+−H] found 440.2729 $C_{26}H_{36}N_2O_4$ requires 440.2735.

*5.2.4. General procedure for synthesis of ligand **4**.* In a flame dried single necked round bottom flask, (*R*)-(+)-1,1′-binaphthyl-2,2′-diamine (426 mg, 1.5 mmol), freshly dried K_2CO_3 (~100 mg) in dry acetonitrile (30 mL) were taken under nitrogen atmosphere, to which *tert*-butylbromoacetate (0.58 mL, 3 mmol) was added at RT with stirring. The mixture was stirred for 24 h at 70 °C. The reaction was monitored by TLC and afterward the reaction mixture was cooled to RT, filtered and the solvent was removed from the filtrate under reduced pressure. The pure ligand **4** was obtained by column chromatography (15:85, EtOAc/Hexane) (289.2 mg, Yield 68%); Yellow solid; [Found: C, 74.92; H, 7.02; N, 5.24. $C_{32}H_{36}N_2O_4$ requires C, 74.97; H, 7.08; N, 5.46]; $[\alpha]_D^{25}$ +25.24 (*c* 0.5 in $CHCl_3$); ν_{max} (KBr) 3415, 3344, 2924, 2362, 1740, 16,199, 1431, 1365, 1248, 1156, 810, 619 cm^{-1}; δ_H (200 MHz, $CDCl_3$, TMS) 7.88–7.10 (m, 12H), 4.06 (s, 4H), 3.30 (s, 2H), 1.47 (s, 18H); δ_C (200 MHz, $CDCl_3$) 171.0, 145.1, 135.5, 129.1, 125.3, 123.1, 114.9, 83.0, 69.3, 28.3; HRMS (ESI, *m*/*z*) [M^+−H] found 512.6409 $C_{32}H_{36}N_2O_4$ requires 512.6415.

5.3. Computational methods

We have performed the geometry optimization and frequency calculations of **Catalyst-1** and **Catalyst-3** with 2,2,2-trifluoro-1-phenylethanone and nitromethane with density functional theory method using B3LYP,[24,25] functional and 6-31G(d),[26,27] basis set for

the H, N, O, C, S, F and the transition metal copper ion was treated with LANL2DZ,[28,29] basis set. The transition state structures of all the geometries were confirmed by only one imaginary frequency. We have performed single point energy calculations with higher basis set 6-31+G** for H, N, O, C, S, F and LANL2DZ basis set for copper ion with M06-2X,[30] DFT functional in gas phase. We have also performed the single point energy calculation in methanol solvent (ε=32.61) using the M06-2X DFT functional with the conjunction of 6-31+G** for H, N, O, C, S, F and LANL2DZ basis set for copper ion with Polarizable continuum model (PCM).[23] The energy differences were calculated using $\Delta E = E_{Re\ face} - E_{Si\ face}$ formulae. Free energy differences were also calculated using similar equation. All calculations were performed with Gaussian 09 program, Revision D.01.[31]

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2015.06.033.

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