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Copper-Catalyzed Asymmetric Allylic C-H Amination of Alkenes using *N*-arylhydroxylamines

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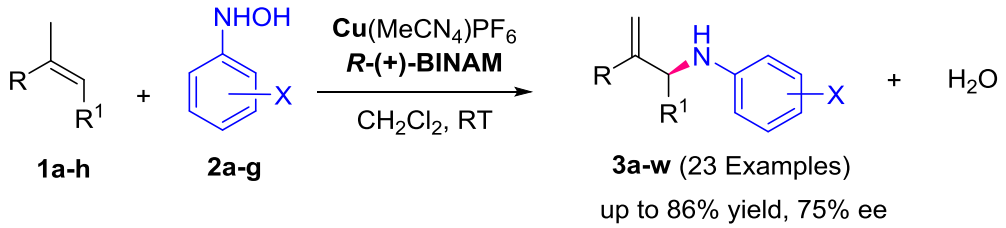
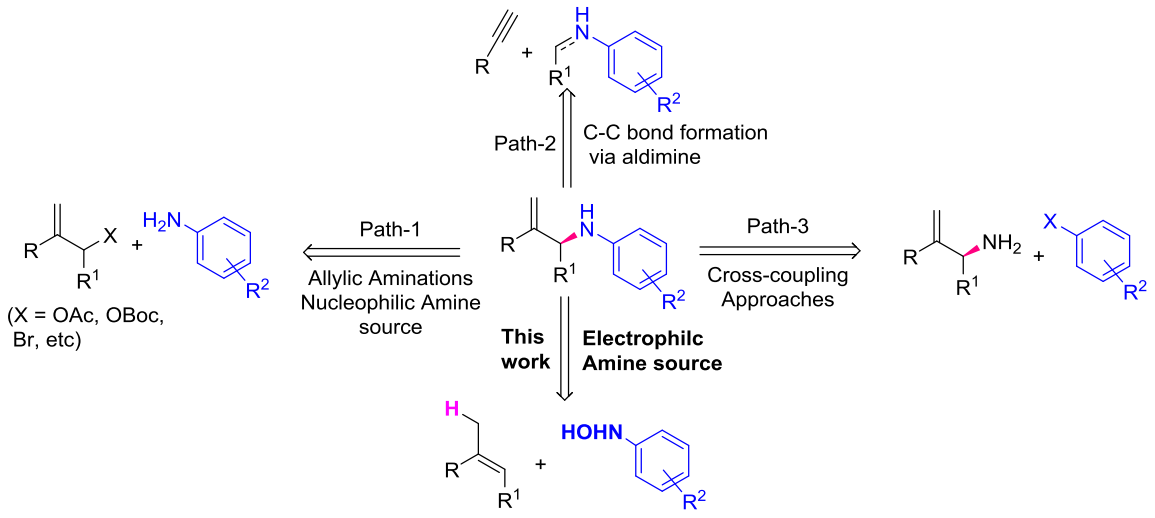
Abstract: The first copper-catalyzed asymmetric allylic C-H amination of alkenes using *N*-arylhydroxylamines as aminating agents is disclosed. Enantioselective C-N bond formation reactions are promoted in the presence of $Cu(MeCN)_4PF_6$ as a pre-catalyst and R(+)-BINAM as a chiral ligand. This protocol delivers chiral *N*-aryl allylamines in good yields and enantioselectivities. Data regarding the effect of ligand structure and solvents on the efficiency and enantioselectivity of amination reactions are presented. Furthermore, isolation of metal-ligand-nitroso complex, ESI-MS reaction monitoring analysis and the computational calculations provided additional insights on mechanistic pathway. DFT modeling of the reaction pathway suggests that the stereoselectivity is determined in the conversion of (BINAM)Cu(PhNO)(η^2-alkene)$^+$ to (BINAM)Cu(N-Ar hydroxylamine) via a concerted, asynchronous transition state for C-N bond formation. This catalytic approach features operational simplicity, high product yields with good enantioselectivity, and no byproducts except water.



Introduction: Chiral allylamines are currently the convenient and vital compounds in organic chemistry and their synthesis is an important industrial and synthetic goal.[1] Often these

allylamines are transformed into a range of useful products by oxygenation, amination, reduction, oxidation or metathesis reactions of the double bond. Thus, chiral allylamines have been used as starting materials for the synthesis of numerous compounds such as chiral amine drugs, chiral amino acids, different alkaloids, and carbohydrate derivatives.[2] Remarkably, the chiral amine frameworks are present in an estimated 45% of pharmaceutical drug candidates. [3] Therefore, considerable effort has been directed toward the asymmetric synthesis of chiral allylamines. In this regard, catalytic enantioselective allylic substitution has emerged as a useful synthetic tool to access chiral amines.[4] However, these traditional approaches rely on nucleophilic substitution of allylic esters or halides, which require a pre-functionalization at the respective allylic-carbon atom. Recently, catalytic enantioselective allylic C–H amination methods[5] have attracted significant attention from the synthetic community due to the unique atom and step economies of such processes.[6] Most of these methods are associated with the use of complex olefin substrates, catalysts of expensive metals such as Pd, Ir, Rh and toxic chiral phosphine ligands. Additionally, these reported methods use either carbamates or chiral sulfonimidamides[7] as nitrogen reagents and are not useful for obtaining *N*-aryl allylamines in enantioselective fashion. Aromatic amines with a stereocenter α to the nitrogen atom are important structural motifs in a number of biologically active compounds.[8] Thus, a procedure to prepare optically active aromatic amines, in particular, an enantioselective route to *N*- aryl allylamines would be useful because of the dual amine and alkene functionality.

Despite the progress in catalytic asymmetric allylic amination, the synthesis of chiral *N*-aryl allylamines through allylic amination has proven to be very challenging and remains largely unexplored. Aromatic amines have not been used commonly in allylic amination,[9] presumably because of their lower nucleophilicity than the more commonly used benzylamine or stabilized anionic nitrogen nucleophiles.[10] A few allylic amination reactions use anilines as a nucleophilic substrate to react with either allylic halides, alcohols or esters as electrophilic substrates. (Scheme 1, path 1)[11] Alternatively, reaction of metal coordinated aryl aldimines with alkynes produce chiral allylamines.[12] (path 2) Additionally, cross-coupling of chiral allylamines and haloarenes have also been reported.[13] (path 3) However, a direct enantioselective allylic *N*-aryl amination reaction using simple alkene has not been reported.



Scheme 1. Alternate approaches for making chiral N-aryl allylamines

Results and Discussion:

Following the seminal work by Sharpless on stoichiometric amination,[14] several catalytic allylic amination reactions have been developed using ArNHOH, ArNO and $ArNO_2$ as aminating agents by us and others.[15] We have studied mechanistic aspects of this reaction including, isolation of catalytic intermediates, kinetic experiments and computational studies.[16] We have isolated an iron azodioxide and Cu(I)-nitrosoarene complexes, implicated as reactive intermediates in metal catalyzed allylic *N*-aryl amination reactions.[17] Although the non-asymmetric version of this allylic *N*-aryl amination has been known for two decades, surprisingly, no asymmetric variant has been reported till date. Based on our experience on allylic C-H amination chemistry, we hypothesized that the kinetically controlled C-N bond formation would be feasible, in presence of a suitable metal pre-catalyst and a chiral ligand, if at least one of the substrates binds to metal center and is activated. The asymmetric environment or the chiral pocket around the metal center would then favor the selective formation of one of the allylic amine enantiomers. Our hypothesis was examined systematically and we developed the first catalytic enantioselective synthesis of chiral *N*-aryl allylamines using *N*-arylhydroxylamines and simple alkenes as reaction partners. (Scheme 1) In parallel to this study, we have developed an approach for catalytic asymmetric α-amination of carbonyl compounds.[18]

For initial experimentation, the reaction of 2-methyl-2-pentene (**1b**) and *N*-phenylhydroxylamine (**2a**) was selected as a model amination reaction (Table 1) and screened a

set of privileged chiral ligands[19] with 1:2 metal-ligand ratio using our previously established reaction conditions.[16] (Scheme 1) Preliminary investigations suggested that the tested privileged chiral ligands are not effective in terms of both the enantioselectivity and the product formation. However, surprisingly, simple amino alcohols such as R(+)-2-phenyl glycinol (**L1**, 4.9% ee) and R(+)-2'-amino-1'-binapthalen-2-ol (**L2**, 9.3% ee) induced some enantioselectivity at room temperature. Consequently, we have varied the reaction temperatures and solvents while keeping pre-catalyst and ligand the same. Replacing the 1,4-dioxane with dichloromethane, substantially improved the enantioselectivity (**L2**, 28.2% ee) without compromising % yield. When we lowered the reaction temperature to 0° C, the % yield of desired allylamine product dropped considerably while the formation of azo and azoxybenzene byproducts significantly increased (entry 9, Table 1). Lowering catalyst loading to 5% led to decrease in yield while maintaining similar % ee. Considering these conditions and the structural features of **L1** and **L2** ligands, we tested some commercially available ligands with diol, amino alcohol, and diamine functionalities including axially chiral compounds. Except (R)-(+)-1,1′-Binaphthyl-2,2′-diamine (BINAM, **L3**, 69% ee, entry 6), none of them improved enantioselectivity. Based on these observations, we anticipated that the structurally modified R(+)-BINAM ligand may improve the electronic and steric effects of the catalytic system thereby enhancing enantioselectivity.[20] Accordingly, ligands **L6**, **L7** and **L9** were acquired commercially and other substituted BINAM ligands (**L5**, **L8** and **L10**) were prepared using catalytic reduction, halogenation and cross-coupling methods.[21] We have introduced aryl substitutions on ortho-position to the amine group on BINAM. Even though they are equally effective in terms of enantioselectivity, none of them outperformed R(+)-BINAM ligand. With the systematic optimization of ligands, pre-catalysts, metal-ligand ratios and solvents at room temperature, we found that 1:2 ratio of $Cu(MeCN)_4PF_6$ and R(+)-BINAM using dichloromethane as a solvent worked well in terms of product yields and enantioselectivity. The initial results of this work have been patented.[22]

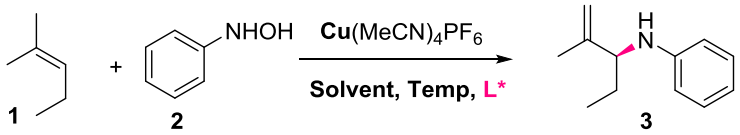
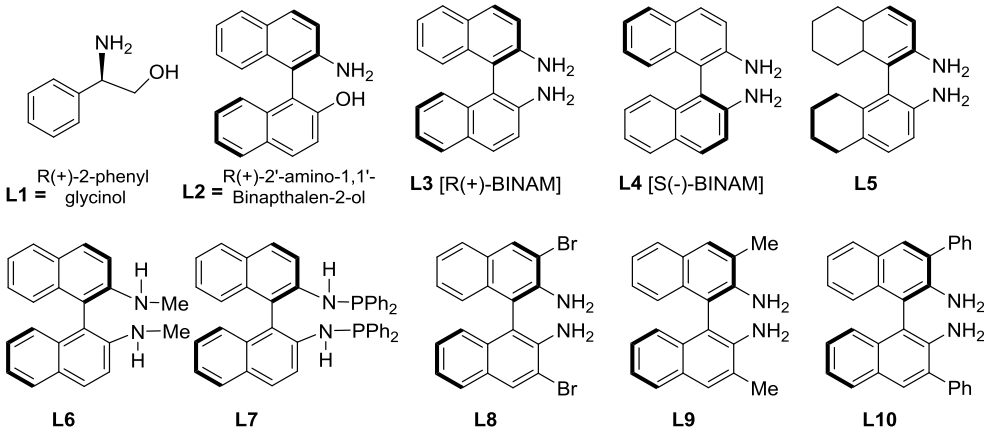


Table 1. Selected screening data toward the catalytic synthesis of chiral *N*-aryl allylamines



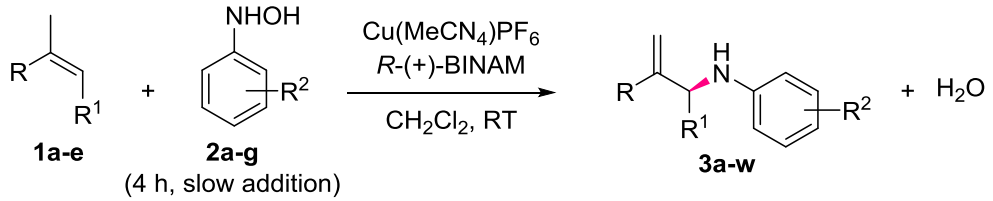
Entry	Ligand	Temp (^{o} C)	Solvent	% Yield[a]	% ee[b]
1	L1	RT	Dioxane	46	5
2	L2	RT	Dioxane	62	9
3	L2	RT	CH_2Cl_2	58	28
4	L3	RT	CH_2Cl_2	62	70
5	L3[c]	RT	CH_2Cl_2	65	62
6	**L3[d]**	**RT**	**CH_2Cl_2**	**67**	**69**
7	L3	RT	$CHCl_3$	54	46
8	L3	50	CH_2Cl_2	68	23
9	L3	0	CH_2Cl_2	6	ND
10	L4	RT	CH_2Cl_2	64	73
11	L5	RT	CH_2Cl_2	62	56
12	L6	RT	CH_2Cl_2	53	14
13	L7	RT	CH_2Cl_2	13	<5
14	L8	RT	CH_2Cl_2	64	43
15	L9	RT	CH_2Cl_2	58	46
16	L10	RT	CH_2Cl_2	60	39

[a]Measured by GC-MS [b]Measured by chiral GC [c]1:1 and [d]**1:1.2** metal-Ligand ratio

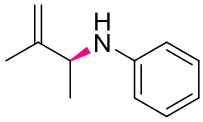
With these optimized conditions, the scope of the substrate structure was investigated. The initial focus was set on variations of the alkenes (**1a-1h**) using *N*-phenyl hydroxylamine (**2a**) as an amine source. (Table 2) Along with the 2-methyl-2-pentene (**1b**), we have considered a set of homologous alkenes to check the effect of chain length and substitutions (**1a, 1c, 1d, 1e**). Even though the product yields are comparable, enantioselectivities slightly increased as the

chain length increased. Keeping the alkene partners same, we chose a set of substituted *N*-aryl hydroxylamines (**2b**-**2g**) having methyl and halo-substituents at different positions on ring. Both electron-deficient and electron-rich aryl hydroxylamine partners reliably delivered desired chiral allylamine products (**3f**-**3t**) (Table 2). Compared to phenylhydroxylamine (**2a**) and *p*-tolyl hydroxylamine (**2b**), haloaryl hydroxylamines (**2c**-**2f**) produced relatively higher yields and enantioselectivities of desired *N*-aryl allylamines (**3j**-**3q, 3s, 3t**). However, when compared to the *N*-aryl allylamines **2c** (*p*-iodo) and **2e** (*m*-iodo), presence of large 'iodo' group at ortho-position (**2f**) negatively impacted the enantioselectivity as well as isolated yield. Moreover, the *N*-aryl hydroxylamine with para-withdrawing group (*p*-CN, **2g**) led to low conversion as well as poor enantioselectivity. It should be noted here, the chiral allylamine products with halo substituent can undergo further coupling reactions for the elaboration of more complex chiral amine compounds.[23]

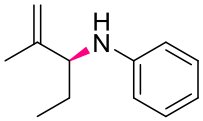
Table 2. Asymmetric Allylic Amination of Olefins by *N*-Hydroxylamines[a, b, c]



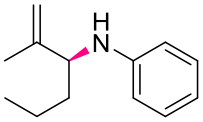
1a-e + **2a-g** (4 h, slow addition) → **3a-w**



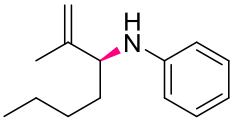
3a (58%), 53% *ee*



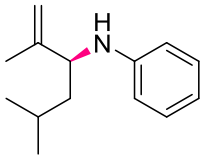
3b (67%), 69% *ee*



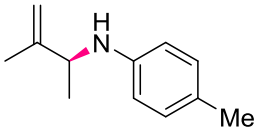
3c (61%), 63% *ee*



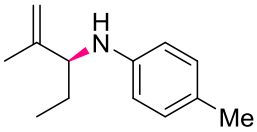
3d (59%), 61% *ee*



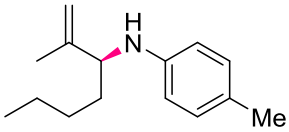
3e (65%), 67% *ee*



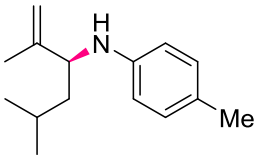
3f (55%), 53% *ee*



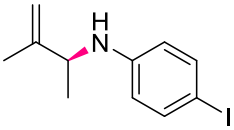
3g (58%), 72% *ee*



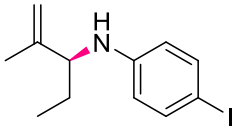
3h (62%), 66% *ee*



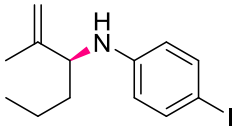
3i (65%), 46% *ee*



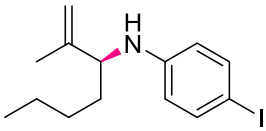
3j (76%), 70% *ee*



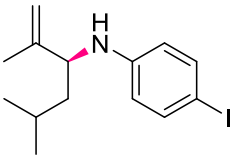
3k (86%), 79% *ee*



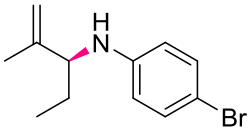
3l (78%), 60% *ee*



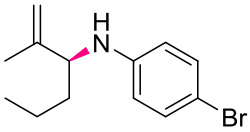
3m (81%), 73% *ee*



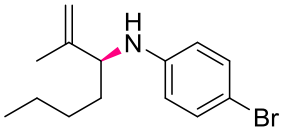
3n (73%), 61% *ee*



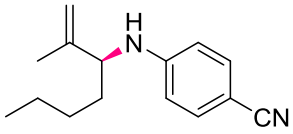
3o (79%), 48% *ee*



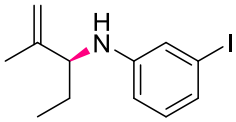
3p (71%), 63% *ee*



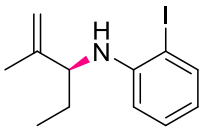
3q (62%), 60% *ee*



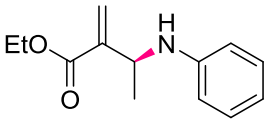
3r (35%), 26% *ee*



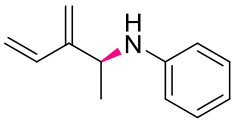
3s (82%), 75% *ee*



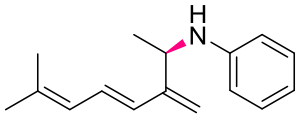
3t (68%), 29% *ee*



3u (54%), 23% *ee*
(57%), 51% *ee*[d]



3v (48%), 40% *ee*



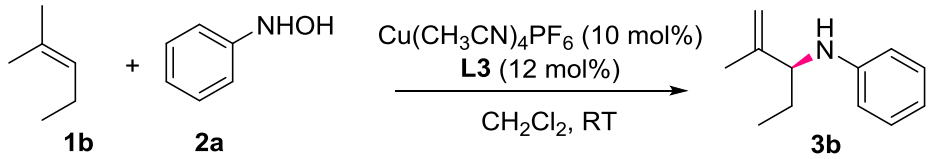
3w (58%), 39% *ee*

[a] Reaction conditions: PhNHOH (0.5 mmol), olefin (1.5 mmol), $Cu(MeCN)_4PF_6$ (10 mol %), *R*-(+)-BINAM (12 mol %), dichloromethane (6 mL), T = 25 °C, 5-8 h. [b] Yields were reported after isolation from silica column. [c] Enantiomeric excess (*ee*) was measured by chiral HPLC. [d] Used L10 as a chiral ligand.

We have previously reported non-asymmetric amination approaches for making highly functionalized *N*-aryl aza Baylis-Hillman adducts[15k] and aminomethyl dienes/trienes.[17b] With that knowledge, we extended the current asymmetric catalytic approach to new substrates such as ethyl tiglate (**1f**), 3-methylpent-1,3-diene (**1g**), 2,6-dimethyloct-2,4,6-triene (**1h**). The α,β-unsaturated ester **1f** produced the corresponding chiral amine (**3u**) in good yield but with low enantioselectivity. However, enantioselectivity was increased from 23% to 51% when the same reaction performed in presence of ligand **L10**. Additionally, the diene **1g** and triene **1h** also produced the corresponding allylamines (**3v**, **3w**) with moderate enantioselectivities. (Table 2) Overall, this catalytic allylic C-H amination method works well with simple alkenes and *N*-aryl hydroxylamines.

Having developed the optimized catalytic method, we turned our attention on studying mechanistic aspects of the reaction. Over the past decade, various methodologies have been developed to enhance the ability of ESI- MS to continuously monitor catalytic reactions as they proceed which helped in determining the mechanistic pathways of several homogenous catalytic mechanisms.[24] We adopted the ESI-MS online reaction monitoring analysis approach to identify intermediate complexes and determine their catalytic behavior. We pursued online monitoring ESI-MS analysis in a sequential manner by injecting sample after adding each reagent. A solution of $Cu(CH_3CN)_4PF_6$ and R(+)-BINAM (**L3**) in dichloromethane was stirred for 10 min, and then monitored by ESI(+)-MS. As shown in table 3, four clusters identified and are attributed to $[Cu(BINAM)]^+$, $[Cu(H_2O)(BINAM)]^+$, $[Cu(CH_3CN)(BINAM)]^+$, and $[Cu(BINAM)_2]^+$ respectively. The ESI(+)-MS/MS of first three complexes have a 1:1 metal-ligand ratio, whereas the last one has 1:2 metal-ligand ratio. After 10 minutes of mixing $Cu(CH_3CN)_4PF_6$ and R(+)-BINAM, alkene (1) was added followed by slow addition of phenyl hydroxylamine (2) over an hour and the sample collected for ESI(+)-MS analysis. (Table 3)

Table 3. Reaction for ESI(+)-MS (5 eV) analysis and the identified clusters.



Proposed structures	Formula	Calculated	Found
$[Cu(BINAM)]^+$	$C_{20}H_{16}CuN_2$	347.0609	347.0612

$[Cu(H_2O)(BINAM)]^+$	$C_{20}H_{18}CuN_2O$	365.0715	365.0706
$[Cu(CH_3CN)(BINAM)]^+$	$C_{22}H_{19}CuN_3$	388.0875	388.0863
$[Cu(BINAM)_2]^+$	$C_{40}H_{32}CuN_4$	631.1923	631.1934
[Cu(**3**)(BINAM)]$^+$	$C_{32}H_{32}N_3Cu$	522.1970	522.1981
[Cu(BINAM)(**1b**-H)(PhN=O)]$^+$	$C_{32}H_{32}N_3OCu$	537.1841	537.1844

After 1 hour, the ESI(+)-MS showed two new clusters at *m/z* 522 and 537, and they could be attributed to [Cu(**3**)(BINAM)]$^+$ and [Cu(BINAM)(**1b**+PhNO)-H]$^+$ respectively. As shown in table 3, the HRMS confirmed the formula of predicted structures (**Figure 1**). Based on these observations, we can conclude that there are two types of complexes formed in the reaction with different metal-ligand ratios i.e. 1:1 and 1:2. However, 1:1 metal-ligand complex seems to be responsible for asymmetric induction in C-N bond formation.

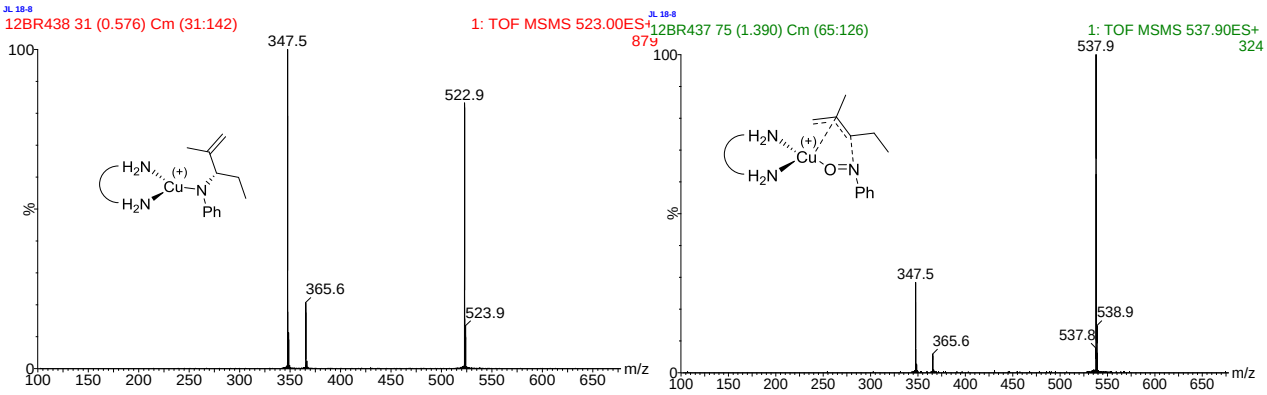
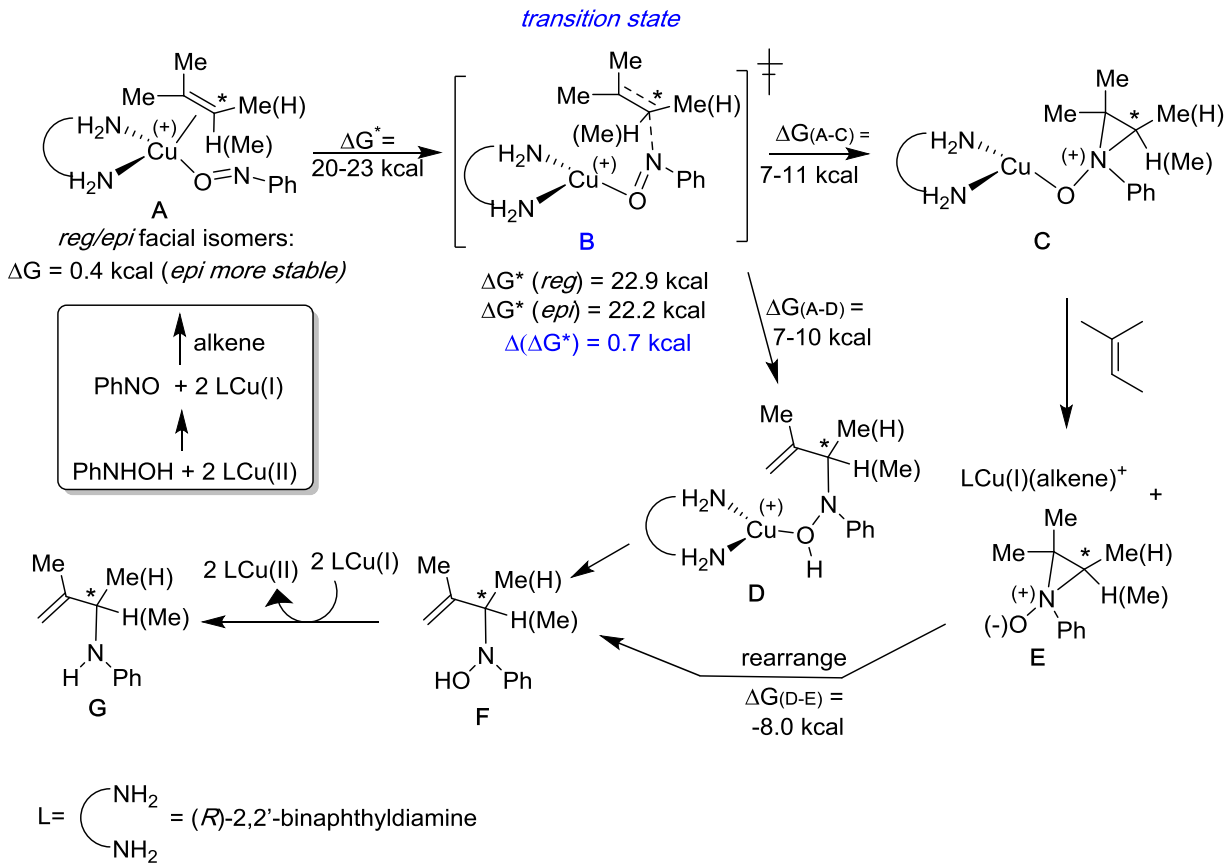


Figure 1. ESI(+)-MS/MS of clusters at *m/z* 522 and *m/z* 537.

To foster further understanding of catalytic activity and reaction pathway, we made attempts to isolate and characterize the Cu-BINAM complex(**4a**). Although we were not successful in obtaining a single crystal of $Cu^I(MeCN)_4PF_6$/R(+)BINAM, our attempt with $Cu^{II}OTf_2$-R(+)BINAM complex (**4b**) was successful and it was characterized by X-ray crystallography. As can be seen from the crystal structure provided in supplementary information (Figure **S1**), the metal-ligand ratio of the isolated complex is 1:2. We treated this complex **4b** with nitrosobenzene and p-*N,N'*-dimethyl nitrosobenzene in two separate reactions. However, we were only able to isolate the metal-ligand-nitrosoarene complex (**4c**) with p-*N,N'*-dimethyl nitrosobenzene but not with nitrosobenzene. The X-ray crystallographic analysis of **4c** clearly indicates that two molecules of p-*N,N'*-dimethyl nitrosobenzene coordinated to the metal with

the trans-octahedral geometry. (Figure **S2**, SI) Later we tested the catalytic activity of complex **4b** for the reaction of *N*-phenylhydroxylamine (**2a**) and 2-methyl-2-pentene (**1b**). Although expected allylamine was produced, the very low enantioselectivity (<5% ee) of the product indicates the complex **4b** is probably not responsible for the asymmetric induction. We also treated the isolated intermediate complex **4c** with 2-methyl-2-pentene, but no allylamine product was observed. We have previously established that the p-*N,N'*-dimethylnitrosobenzene is less reactive towards alkenes to produce allylamine.[16,17] Nevertheless, the crystal structure of metal-ligand-nitrosoarene complex (**4c**) provides some important aspects of binding modes of ligand and nitrosoarene, and the nitroso-activation for the amination reactions.

The results of ESI-MS reaction monitoring analysis and isolation of copper-complexes prompted us to consider a theoretical (computational) investigation to predict possible intermediates and the reaction pathway for the asymmetric allylic amination. A potential reaction pathway that accounts for the enantioselectivity was addressed with the DFT-B3LYP method (SMD solvent model for CH_2Cl_2). Various $(diamine)_xCu(I,II)(alkene)(PhNO)^+$ species were evaluated for the reaction of *N*-phenyl hydroxylamine (**2a**) with 2-methyl-2-butene (**1b**) using R(+)-BINAM (**L3**) as the chiral ligand. An energetically viable pathway for the asymmetric amination that affords the corresponding chiral allylamine (ΔG_{calc}= -23.7 kcal) was found starting with $(R\text{-}BINAM)Cu(I)(alkene)(PhNO)^+$ **A** as a key intermediate (Scheme 2). Two alkene facial isomers of **A** were optimized (*pro-R* and *pro-S*) with the *pro-S* isomer being more stable by 0.4 kcal/mol. Two isomeric C-N bond-forming transition states (TS) **B**, generated from the facial isomers of **A**, could be located with activation energies of 22.2 and 22.9 kcal/mol, a difference ($\Delta\Delta G^*$) of 0.7 kcal. The lower activation energy from the *pro-S* isomer predicts the stereoselective formation of the (*S*)-allylamine with approximately 54% ee with the R(+)-BINAM ligand, in good agreement with our experimental results showing the (*S*)-allylamine (**3a**) being the major enantiomer with 53% ee.



Scheme 2. Plausible mechanistic pathway of Cu-catalyzed asymmetric allylic amination

The transition state **B** shows that C-N bond formation is initiated asynchronously before C-H bond-breaking (Figure 2). The preferred regioselectivity for attack at the less-substituted alkene is previewed by the differing C-N distances (1.84 vs. 2.6 Å) in the TS. The stepwise nature of the **A** to allyl hydroxylamine **F** conversion is comparable to that proposed for the corresponding uncatalyzed ArNO/alkene ene-reaction.[25] As C-N bond formation completes from TS **B**, two intermediates of comparable energy **C** or **D** may form; **C** is a Cu-coordinated aziridine *N*-oxide and **D** is a Cu-complexed *N*-allyl hydroxylamine. In the next step, the free aziridine *N*-oxide **E** detaches from complex **C** while the latter involves in association of alkene to generate (BINAM)Cu(alkene)$^+$. Rapid rearrangement of the aziridine N-oxide **E** via H-transfer and ring opening, a known process that occurs stereospecifically,[25] would produce the allyl hydroxylamine **F**. Alternatively, the hydroxylamine **F** could form via dissociation from complex **D**. Subsequent Cu(I) reduction of the hydroxylamine would give the allylamine **G** and (diamine)Cu(II) that can re-enter the catalytic cycle after one-electron reduction.

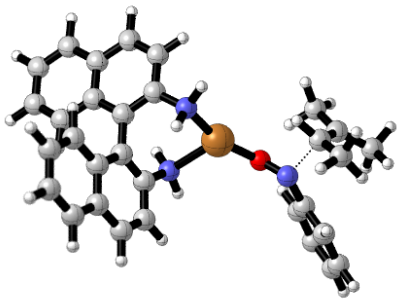


Figure 2. Favored *pro*-S transition state for the reaction of (*R*-BINAM)Cu(PhNO)(η^2-2-methyl-2-butene)$^+$ leading to the (*S*)-hydroxylamine **F**; N-C3 = 1.84 Å, N-C2 = 2.46 Å; C=grey, H=white, N=blue, O=red, Cu=bronze.

Conclusions:

We have developed a novel catalytic asymmetric allylic C-H amination approach for the amination of simple alkenes with *N*-arylhydroxylamines. This procedure can be operated without any special precautions as it works at room temperature utilizing an *in situ* generated copper catalytic system i.e. the combination of $Cu(CH_3CN)_4PF_6$ and R(+)-BINAM. We have extended this approach to access other useful chiral amine compounds employing α,β-unsaturated carbonyl compound, diene and triene as alkene partners. We have also established the configuration of major enantiomers obtained in this reaction. In order to gain additional insights on the reaction mechanism, we have monitored the reaction with ESI-MS analysis, isolated metal complexes and predicted the possible intermediates based on computational studies. Overall, this simple and straight forward methodology marks a significant step forward in the synthesis of the chiral *N*-aryl allylamine scaffolds. DFT modeling of the reaction pathway suggests that the stereoselectivity is determined in the conversion of (BINAM)Cu(PhNO)(η^2-alkene)$^+$ to (BINAM)Cu(N-Ar hydroxylamine) via a concerted, asynchronous transition state for C-N bond formation.

Conflicts of Interest:

There are no conflicts of interest

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