# Chemoselective Carbene insertion into the N−H Bond over O−H Bond Using a Well-Defined Single Site (P−P)Cu(I) Catalyst

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S *Supporting Information*

ABSTRACT: Phosphine-coordinated air-stable Cu(I) catalyst (**1**) has been synthesized and characterized. Catalyst **1** is found to be active toward highly chemoselective carbene insertion into the N−H bond over the O−H bond and also over the formation of olefins when numerous aminophenols were treated with a variety of α-aryl diazoesters under normal experimental conditions.
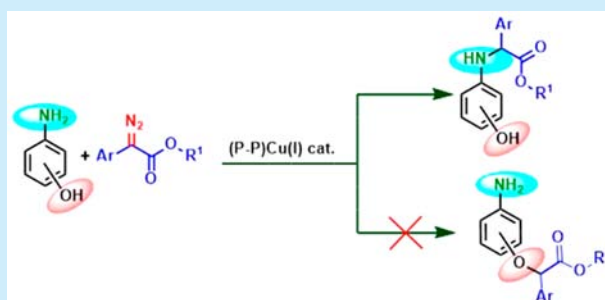
The transition-metal-mediated carbene insertion into the heteroatom−H bond has received significant interest in the synthetic community[1] because it leads to the formation of ubiquitous C−X (X = C, N, O, S, B, and Si) bonds.[2] In particular, carbene insertion into the N−H bond caters the α-amino acid derivatives and versatile building blocks.[3] Although the first catalytic N−H insertion was reported by Yates[4] using copper bronze as a catalyst and followed by Saegusa et al.[5] and Nicoud et al.[6] using CuCN as a catalyst, it has been neglected owing to the emergence of Rh as a powerful catalyst for carbene insertion into the N−H bond.[7] Cu received attention after Pérez et al.'s report on the Cu(I)−homoscorpionate system for N−H insertion.[8] Later, researchers developed new Cu(I)-based homogeneous,[9] heterogeneous,[10] biphasic,[11] and asymmetric versions of catalysts.[12] In recent years, chemists have started working with larger and structurally more complex molecules than ever before. To deal with the structurally complex molecules, chemoselective catalytic systems have to be developed that are able to catalyze selective carbene insertion into X−H bonds even in the presence of other functional groups without protection and deportation strategies. In this direction, few catalysts have been developed for selective X−H insertion in the presence of other functional groups like alkene and alkyne.[13] Apart from Rh and Cu catalysts, researchers have used Ru,[14] Fe,[15] Pd,[16] Ir,[17] Au,[18] and Ag[3] supported with N, O, and NHC based ligands. When we look at this chemistry microscopically, we see that chemists have neglected the phosphorus-based ligands in this area of research, though phosphorus ligands have shown excellent applications in C−H activation and many other significant organic reactions.[19] In practice, the phosphorus ligands are not useful for carbene insertion reactions.[9a,16a,] To the best of our knowledge, Jørgensen and co-workers have used an in situ generated phosphorus-based Cu(I) complex for N−H insertion reactions.[3] Recently, Pérez and co-workers have used tris(phosphino)borate ligand based Cu(I) complex[20] for N−H insertion reactions.

Nevertheless, these systems have suffered either by low yield or low selectivity.

In this regard, we herein report highly chemoselective carbene insertion into the N−H bond over the O−H bond and also over the formation of olefins from carbene dimerization using a well-defined novel (P−P)Cu(I) ((P−P = 2,8-dibromo-4,6-bis-(diphenylphosphanyl)-5-methyl-10,11-dihydro-5H-dibenzo-[b,f]azepine (**L1**)) catalyst.

The copper(I) catalyst was prepared from an equimolar mixture of ligand(**L1**)[21] and [Cu(CH₃CN)₄]ClO₄[22] in acetonitrile (Scheme 1). This novel complex was characterized and

Scheme 1. Preparation of Copper(I) Complex (Catalyst 1)
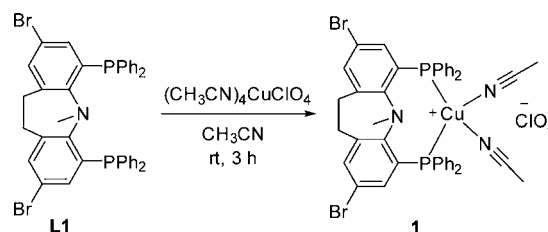
conformed using various standard spectroscopic techniques. A single peak was observed at 14.2 ppm in ^{31}P NMR for the coordinated phosphorus of ligand **L1** in complex **1**, whereas a peak at 18.3 ppm was observed for the free ligand **L1**.

The single-crystal X-ray studies of complex **1**[23] revealed that the geometry around the copper(I) ion is slightly deviated from tetrahedral environment (Figure 1), which is commonly observed for copper(I) complexes. More interestingly, the complex **1** is air stable unlike most of the Cu(I) complexes.
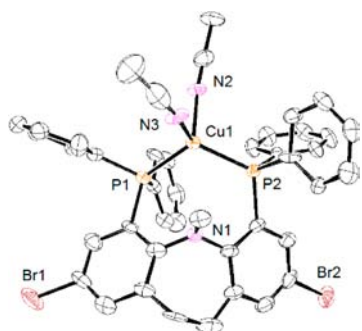
Figure 1. Molecular structure of copper(I) complex; thermal ellipsoids are set at 50% probability. Perchlorate anion and hydrogen atoms are omitted for clarity. Important bond lengths (Å) and bond angles (deg): Cu1−P1 2.247(3), Cu1−P2 2.249(2), Cu1−N2 2.059(8), Cu1−N3 2.022(9), P1−Cu1−P2 115.90(10), P1−Cu1−N2 111.0(2), P1−Cu1−N3 110.2(3), P2−Cu1−N2 106.7(2), P2−Cu1−N3 118.3(3), N2−Cu1−N3 92.0(4).

We started our investigation on catalytic carbene insertion into the N−H bond with 2-aminophenol and α-phenyl diazoacetate in DCM at rt with 2 mol % of complex **1** as a catalyst (Scheme 2). The reaction was completed in 5 h and given N−H-inserted product in 67% isolated yield along with carbene-dimerized product.

Scheme 2. Copper-Catalyzed Chemoselective N−H Insertion of α-Phenyl Diazoacetate into 2-Aminophenol
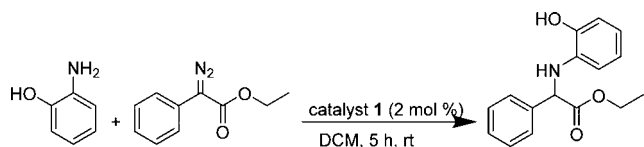
Evidence for the selective carbene insertion into the N−H bond was confirmed by ^{1}H NMR with the appearance of a new singlet at 5.07 ppm for *N*-acetyl methine hydrogens, and in the ^{13}C NMR, a peak was observed at 61.6 ppm for N-acetyl tertiary carbon. In the IR spectrum, bands were observed at 3323 and 3394 cm^{-1}, which can be attributed to the stretching modes of N−H and O−H bonds, respectively. Surprisingly, we have not observed any O−H inserted product. This result clearly revealed that the ligand plays the crucial role for selective carbene insertion only into N−H bond. Nevertheless, relatively more nucleophilicity of amine nitrogen over −OH cannot be ignored. This result prompted us to optimize the reaction conditions that would minimize dimerization of diazo and maximize the selective N−H insertion. In order to identify the best solvent for this reaction, we have screened some of the commonly used organic solvents. We observed a best yield of 83% in methanol (Table S1, entry 5 (Supporting Information)) at rt with 2 mol % of copper catalyst **1**. We have not observed any competitive products of carbene inserted into the methanol −OH bond or aminophenol −OH bond.

In order to understand the role of catalyst **1**, we have examined various Cu(I) sources as catalysts for carbene insertion into the N−H bond, and the results are given in Table 1. With a simple [(CH$_3$CN)$_4$Cu]ClO$_4$ salt, we observed 56% of N−H-inserted product and 8% O−H-inserted product of 2-aminophenol (Table 1, entry 1), and when we used phosphine ligands we observed a longer reaction time. With triphenylphosphine we observed 18% of N−H-inserted product in 8 h (Table 1, entry 2),

Table 1. Screening of Various Catalysts for Chemoselective N−H Insertion

entry[a]	catalyst	time (h)	yield (%) (N−H/OH)	dimer
1[b]	(CH$_3$CN)$_4$CuClO$_4$	5	56/8	36
2	(CH$_3$CN)$_4$CuClO$_4$ + 2PPh$_3$	8	18/−	52
3[b,c]	(CH$_3$CN)$_4$CuClO$_4$ + 1,10-phenanthroline	4	48/11	25
4	(CH$_3$CN)$_4$CuClO$_4$ + dppe	12	53/6	27
5	catalyst **1**	6	83/−	13

[a]All the reactions are carried out with 0.5 mmol (with respect to 2-aminophenol) in 5 mL of methanol with 2 mol % of catalyst in a 25 mL Schlenk flask under argon atmosphere. Diazo compound added at 0 °C followed by warming to rt. Isolated product yield. [b]We observed trace amount of methanol O−H inserted product. [c]We observed 10% of unidentified product.

with 1,2-bis(diphenylphosphino)ethane(dppe) we observed 53% of N−H-inserted product and 6% of O−H-inserted product in 12 h (Table 1, entry 4), and in the case of 1,10-phenanthroline with Cu(I) salt we observed 48% of N−H-inserted product, 11% of O−H-inserted product, and 10% of unidentified products (Table 1, entry 3). In the case of simple [(CH$_3$CN)$_4$Cu]ClO$_4$ salt and complex of 1,10-phenanthroline we observed a trace amount of methanol O−H inserted product. This results clearly revealed that the chemoselective N−H insertion over O−H insertion occurs mainly because of catalyst **1**.

These results further motivated us to explore the substrate scope for this reaction. In order to understand the substrate scope of our reaction and catalyst **1**, first a wide range of α-aryl diazoacetate compounds was explored with 2-aminophenols (Table 2). All of the α-aryl diazoacetate compounds smoothly underwent a selective N−H insertion reaction to afford the

Table 2. Copper(I) Complex Catalyzed Chemoselective N−H Insertion of α-Aryl Diazoacetate into 2-Aminophenol

entry[a]	Ar	R^1	time (h)	3	yield[b] (%)
1	Ph	Et	6	**a**	83
2	Ph	^{i}Pr	5	**b**	81
3	Ph	Bn	6	**c**	90
4	o-ClC$_6$H$_4$	Et	5	**d**	76
5	m-ClC$_6$H$_4$	Et	5	**e**	78
6	p-ClC$_6$H$_4$	Et	5	**f**	82
7	p-BrC$_6$H$_4$	Et	4	**g**	76
8	o-OMeC$_6$H$_4$	Et	5	**h**	78
9	p-OMeC$_6$H$_4$	Et	4	**i**	80
10	o-OMe, p-OMeC$_6$H$_3$	Et	5	**j**	71

[a]All the reactions are carried out with 0.5 mmol (with respect to 2-aminophenol) in 5 mL methanol with 2 mol % of catalyst in a 25 mL Schlenk flask under argon atmosphere. [b]Isolated product yield.

corresponding hydroxy-functionalized α-amino esters, more interestingly all the reactions given good to excellent yield (71−90%). The electronic effects on the aryl ring of α-aryl diazoacetate were also examined (Table 2, entries 6, 7, and 9), and the electronic effects of diazo compounds marginally reflected on the yield and reaction times. Among the α-aryl diazoacetates, benzyl 2-diazo-2-phenylacetate (Table 2, entry 3) gave the highest yield 90% and ethyl 2-diazo-2-(3,4-dimethoxyphenyl)acetate (Table 2, entry 10) gave the lowest yield 71% with 2-aminophenol.

The results of the selective carbene insertion into the N−H bond of 2-aminophenol turned our interest toward conducting similar reactions with 3- and 4-aminophenols with different α-aryl diazoacetates. Both 3- and 4-aminophenols smoothly underwent selective carbene insertion into the N−H bond with a wide range of α-aryl diazoacetate compounds to afford the corresponding hydroxy-functionalized α-amino esters (Tables S3 and S4).

Unlike 2-aminophenol, 3- and 4-aminophenols have significant electronic effects on the reaction of α-aryl diazoacetate. In the case of 3-aminophenol, increasing the electron density on the aryl ring causes a decrease in the yield and decreasing the electron density on the aryl ring produced more yield (Table S3, entries 6, 7, and 9); the rate of reaction is relatively faster with electron-donating groups on the aryl part of α-aryl diazoacetates. We observed the highest yield with *o*- and *p*-Cl-substituted α-aryl diazoacetates (Table S3, entries 4 and 6) and the lowest yield with *o*-OMe-substituted α-aryl diazoacetates (Table S3, entry 8). On the other hand, in case of 4-aminophenol, increasing electron density on aryl ring decreased the yield, and decreasing electron density on aryl ring offered relatively more yield (Table S4, entry 6, 7 and 9). We observed more yield (85% and 86%) with *o*-OMe and *m,p*-OMe substituents on aryl part of α-aryldiazoacetates (Table S4, entry 8 and 10) and lowest yield was observed with α-phenyldiazoacetates (Table S4, entry 1).

In order to understand the substrate scope of our catalyst **1** for the chemoselective carbene insertion into the N−H bond, we investigated variety of aminophenols having various functional groups. All the aminophenols smoothly underwent selective carbene insertion (Scheme 3) and offered corresponding hydroxy functionalized α-amino esters in good yield.

In order to gain more evidence for chemoselective carbene insertion into the N−H bond, one of the products (**6f**) was subjected to the single-crystal XRD studies, and the molecular solid-state structure clearly revealed that the carbene from α-aryl diazoacetates inserted into the N−H bond of aminophenol and not into the −OH bond (Figure 2).

In summary, a novel air-stable well-defined copper(I) complex was synthesized and characterized using standard spectroscopic methods. Complex **1** promotes highly chemoselective insertion of carbenes generated from α-aryl diazoesters into the N−H bond over the O−H bond of various aminophenols under mild reaction conditions. In order to demonstrate the scope of the reaction, we screened a large number of aminophenols and α-aryl diazoesters and found good to excellent yields for 42 examples. We have examined similar reactions with different Cu(I) sources to understand the role of catalyst **1**. For other Cu(I) sources, the selectivity for the formation of N−H-inserted product decreased when compared to the selectivity observed with catalyst **1**. Further investigations in this line are in progress in our laboratory.

Scheme 3. Copper-Catalyzed Chemoselective N−H Insertion of α-Aryl Diazoacetate into Different Aminophenols
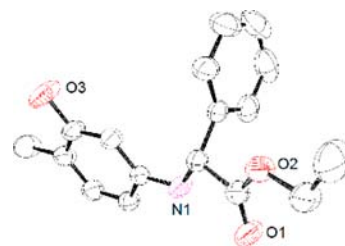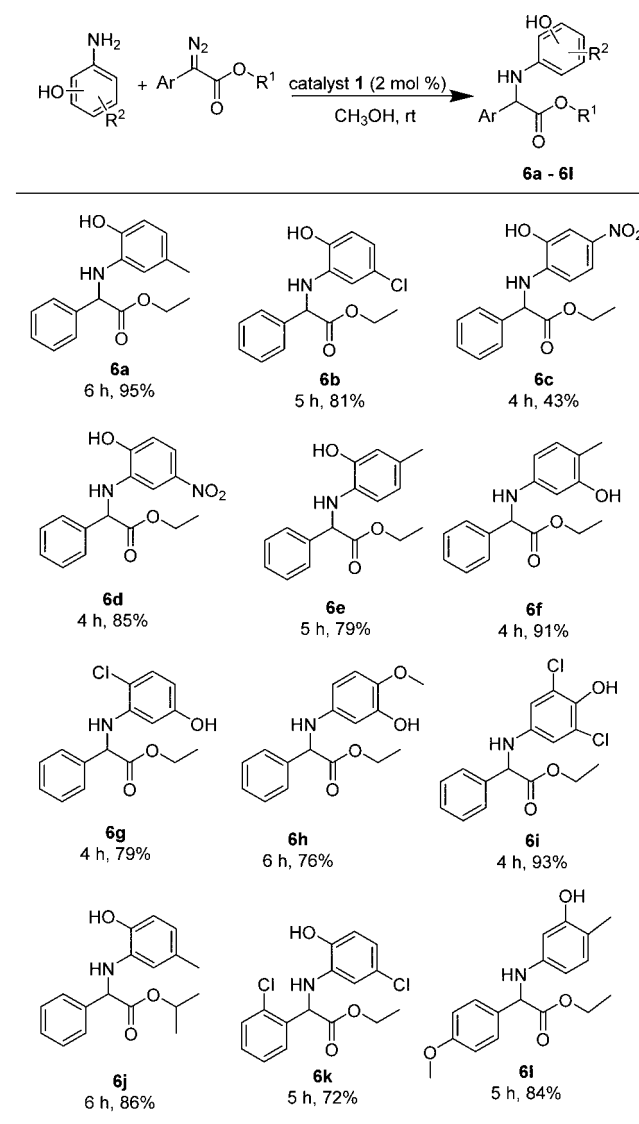

Figure 2. Molecular structure of ethyl 2-((3-hydroxy-4-methylphenyl)-amino)-2-phenylacetate (**6f**); thermal ellipsoids are set at 50% probability. Hydrogen atoms are omitted for clarity.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01776.

   X-ray cyrstallographic data (CIF)
   Optimization, procedures, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(23) CCDC 1018329 (complex **1**) and CCDC 1063462 (**6f**) contain the crystallographic information for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.