

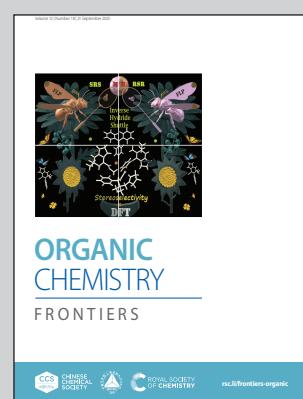
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## Oxidative copper-catalyzed synthesis of $\beta$ -amino ketones from allyl alcohols and anilines

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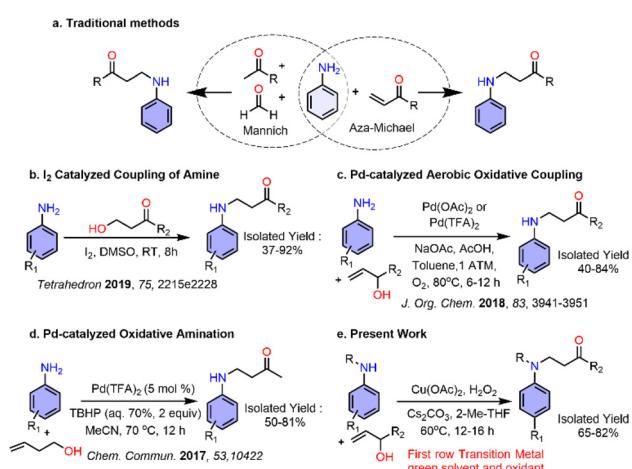
A copper-catalyzed method has been developed for synthesizing  $\beta$ -amino ketones using allyl alcohols and substituted anilines in 2-methyl-THF at 60 °C. This reaction employs hydrogen peroxide ( $\text{H}_2\text{O}_2$ ) as the oxidant and cesium carbonate as the base. Cost-effectiveness, and a very good yield (65–82%) make this process a helpful alternative to the Pd-catalyzed coupling reaction of allylic alcohols with substituted anilines or substituted *N*-alkyl anilines.

### Introduction

$\beta$ -Amino ketones are essential building blocks for synthesizing various heterocyclic compounds and are widely found in natural products.<sup>1,2</sup> Drugs containing the  $\beta$ -aminoketone moiety exhibit notable biological activities.<sup>3</sup> For example, tolperisone<sup>4</sup> improves blood circulation, oxyfedrine<sup>5</sup> treats coronary diseases, and sitagliptin<sup>6</sup> manages blood sugar levels as an antidiabetic agent. Recent research has focused on developing new methods to prepare  $\beta$ -aminoketones with enhanced yields, faster reaction rates, and cost-effectiveness.<sup>7</sup>

The Mannich reaction has been a well-established method for synthesizing  $\beta$ -aminoketones, although it often requires harsh conditions and long reaction times.<sup>8–11</sup> An alternative approach for synthesizing  $\beta$ -aminoketones is the aza-Michael reaction, in which amines undergo conjugate addition to  $\alpha,\beta$ -unsaturated carbonyl compounds.<sup>12–14</sup> This approach offers better economic benefits than Mannich-type reactions. However, it typically requires basic conditions, stoichiometric or catalytic amounts of Lewis acids, and organic solvents like protic fluorinated alcohols. Furthermore, the polymerization of unstable  $\alpha,\beta$ -unsaturated carbonyl compounds catalyzed by acidic or basic agents limits the broader applicability of the aza-Michael reaction.<sup>15,16</sup> To address this limitation, Miao *et al.* reported an iodine-catalysed coupling reaction between  $\beta$ -hydroxyketones and aniline to yield  $\beta$ -aminoketones and benzo[*h*]quinolones at room temperature (RT).<sup>17</sup> This selective reaction avoids the aza-Michael addition and is restricted to aniline. In this context, allyl alcohols are often considered an alternative to  $\alpha,\beta$ -unsaturated carbonyl compounds.<sup>18</sup> Ouyang *et al.* developed a novel Pd-catalyzed intermolecular cascade oxidative amination of homoallylic alcohols to yield

$\beta$ -aminoketones using TBHP as the terminal oxidant.<sup>19</sup> The formation of C–N and C=O bonds in this reaction is distinct from traditional Heck or redox-relay Heck reactions, as well as nucleopalladation. However, this methodology is limited to a single homoallylic alcohol with aniline. Recently, Kumar *et al.* introduced a palladium-mediated oxidative coupling of allyl alcohol derivatives with substituted anilines or substituted *N*-alkyl anilines to synthesize  $\beta$ -aminoketones in toluene at 80 °C, achieving moderate to good yields (Scheme 1).<sup>20</sup> Despite these advancements, the high cost and limited availability of Pd make it an unsustainable resource for large-scale catalytic processes. Therefore, Pd-based catalysts must be replaced with earth-abundant first-row transition metal (TM) based catalysts, which are more affordable and environmentally friendly. To the best of our knowledge, the synthesis of  $\beta$ -aminoketones from allyl alcohols and amines using first-row transition metal catalysts has not been explored. In this study, we present a



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Scheme 1 Synthesis of  $\beta$ -amino carbonyl compounds.



copper-catalyzed method for synthesizing  $\beta$ -aminoketones using allyl alcohols and substituted anilines in 2-Me-THF at 60 °C, employing environmentally friendly hydrogen peroxide ( $\text{H}_2\text{O}_2$ ) as an oxidant and cesium carbonate as a base (EHS:<sup>21</sup> 10; greenness:<sup>21</sup> 7.4) (Scheme 1). EHS and greenness parameters address issues like air and water quality, waste management, the reduction of harmful environmental impacts and how “green” a process is. 2-Me-THF is a promising green solvent<sup>22,23</sup> and its low miscibility with water allows for easier phase separation and extraction processes.

## Synthetic procedure

We initially started our optimization studies by using *N*-methyl aniline (1 equivalent (eq.)), but-3-en-2-ol (2 eq.), hydrogen peroxide ( $\text{H}_2\text{O}_2$ ; 10 eq.) as the oxidant, and cesium carbonate ( $\text{Cs}_2\text{CO}_3$ ; 3 eq.) as the base. Various catalytic systems were screened, in which 10 mol% of cupric iodide ( $\text{CuI}_2$ ) showed trace amounts of the desired product (Table 1, entry 1). Replacing  $\text{CuI}_2$  with Cupric chloride ( $\text{CuCl}_2$ ) did not result in any significant increment in the yield (Table 1, entry 2). The desired product was obtained in 30% yield when cupric acetate ( $\text{Cu(OAc)}_2$ ) was used as the catalyst (Table 1, entry 3) at RT. Raising the reaction temperature to 60 °C showed a significant increase in the product yield to ~82% (Table 1, entry 4).

We screened various solvents (HPLC grade) such as 2-methyl-tetra-hydrofuran (2-Me-THF), toluene, methanol (MeOH), ethanol (EtOH), acetonitrile (MeCN), tetrahydrofuran (THF), water, ethyl acetate (EtOAc), and dimethylformamide (DMF). Studies revealed that 2-Me-THF could promote the reaction more efficiently than any other solvent (Table 1, entries 4–13).

Of all the bases scanned,  $\text{Cs}_2\text{CO}_3$  (Table 1, entry 4) worked the best. We used potassium carbonate ( $\text{K}_2\text{CO}_3$ ), sodium carbonate ( $\text{Na}_2\text{CO}_3$ ), sodium acetate (NaOAc), and pyridine but observed lower product yield (Table 1, entries 14–17). Moreover, when *tert*-butyl hydroperoxide (TBHP) 10 eq. was used as the oxidant in the presence of  $\text{Cs}_2\text{CO}_3$  and  $\text{Cu(OAc)}_2$  (Table 1, entry 18), the isolated yield decreased to 60% as compared to the condition where  $\text{H}_2\text{O}_2$  was used as an oxidant (Table 1, entry 4). No desired product was obtained in the absence of base (Table 1, entry 19). However, when 1 or 2 eq.  $\text{Cs}_2\text{CO}_3$  was added to the reaction mixture, less amount of product was formed (entries 20 and 21). Similarly, less product was formed when fewer than 10 eq.  $\text{H}_2\text{O}_2$  was used in the reaction mixture (entries 22 and 23).

## Substrate scope

With the optimal conditions in hand, reaction scope was explored by using various substituted anilines and allyl alco-

**Table 1** Optimization of reaction conditions<sup>a</sup>

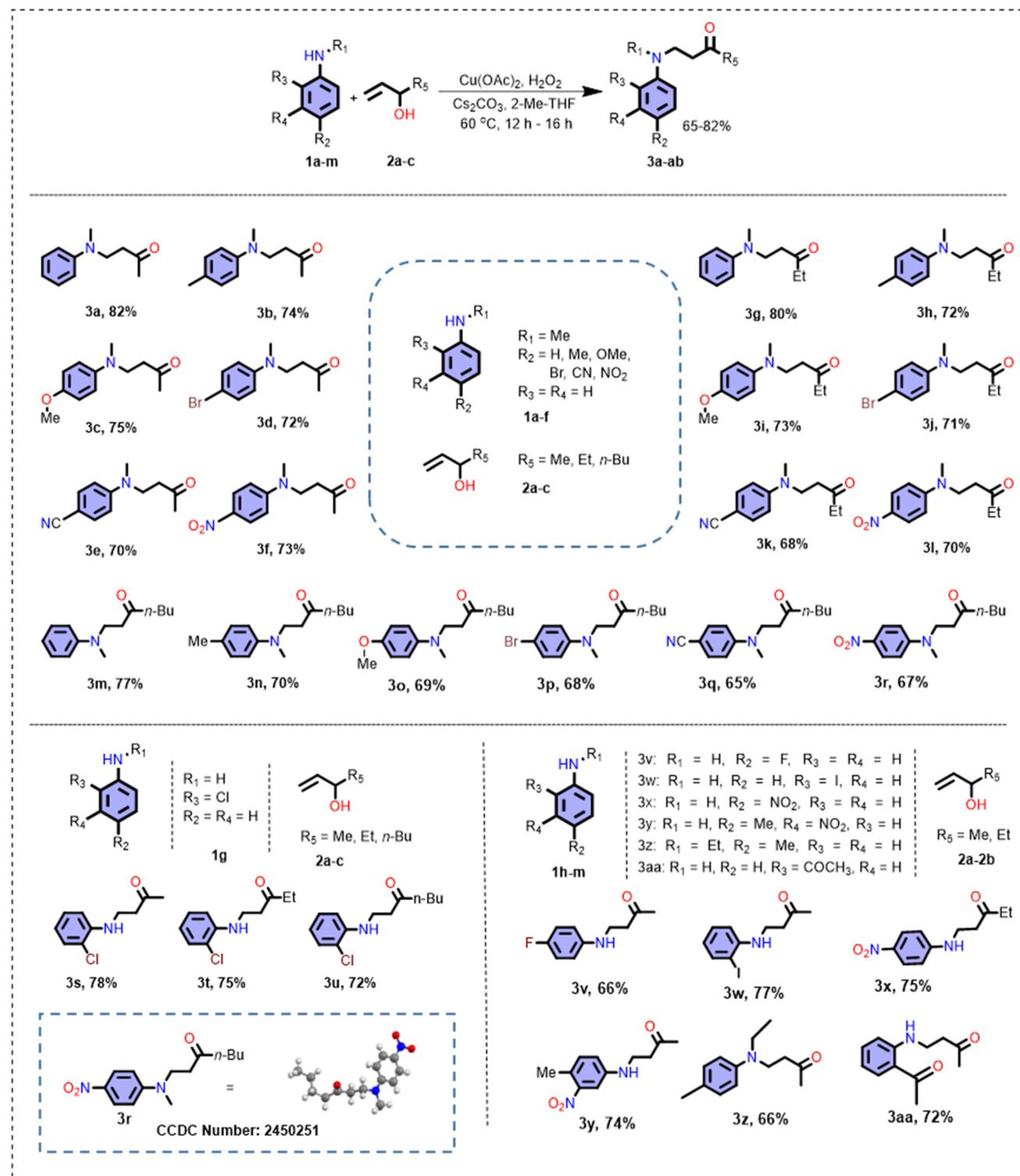
Entry	Catalyst	Oxidant	Base	Solvent	Temp. (°C)	Isolated yield (%)
1	$\text{CuI}_2$	$\text{H}_2\text{O}_2$	$\text{Cs}_2\text{CO}_3$	2-Me-THF	25	Trace
2	$\text{CuCl}_2$	$\text{H}_2\text{O}_2$	$\text{Cs}_2\text{CO}_3$	2-Me-THF	25	Trace
3	$\text{Cu(OAc)}_2$	$\text{H}_2\text{O}_2$	$\text{Cs}_2\text{CO}_3$	2-Me-THF	25	30
4	$\text{Cu(OAc)}_2$	$\text{H}_2\text{O}_2$	$\text{Cs}_2\text{CO}_3$	<b>2-Me-THF</b>	<b>60</b>	<b>82</b>
5	$\text{Cu(OAc)}_2$	$\text{H}_2\text{O}_2$	$\text{Cs}_2\text{CO}_3$	Toluene	60	70
6	$\text{Cu(OAc)}_2$	$\text{H}_2\text{O}_2$	$\text{Cs}_2\text{CO}_3$	EtOAc	60	$\leq 7$
7	$\text{Cu(OAc)}_2$	$\text{H}_2\text{O}_2$	$\text{Cs}_2\text{CO}_3$	DCM	60	$\leq 5$
8	$\text{Cu(OAc)}_2$	$\text{H}_2\text{O}_2$	$\text{Cs}_2\text{CO}_3$	DMF	60	$\leq 7$
9	$\text{Cu(OAc)}_2$	$\text{H}_2\text{O}_2$	$\text{Cs}_2\text{CO}_3$	Water	60	55
10	$\text{Cu(OAc)}_2$	$\text{H}_2\text{O}_2$	$\text{Cs}_2\text{CO}_3$	MeOH	60	30
11	$\text{Cu(OAc)}_2$	$\text{H}_2\text{O}_2$	$\text{Cs}_2\text{CO}_3$	EtOH	60	40
12	$\text{Cu(OAc)}_2$	$\text{H}_2\text{O}_2$	$\text{Cs}_2\text{CO}_3$	MeCN	60	45
13	$\text{Cu(OAc)}_2$	$\text{H}_2\text{O}_2$	$\text{Cs}_2\text{CO}_3$	THF	60	50
14	$\text{Cu(OAc)}_2$	$\text{H}_2\text{O}_2$	$\text{K}_2\text{CO}_3$	2-Me-THF	60	60
15	$\text{Cu(OAc)}_2$	$\text{H}_2\text{O}_2$	$\text{Na}_2\text{CO}_3$	2-Me-THF	60	35
16	$\text{Cu(OAc)}_2$	$\text{H}_2\text{O}_2$	NaOAc	2-Me-THF	60	0
17	$\text{Cu(OAc)}_2$	$\text{H}_2\text{O}_2$	Pyridine	2-Me-THF	60	0
18	$\text{Cu(OAc)}_2$	TBHP	$\text{Cs}_2\text{CO}_3$	2-Me-THF	60	60
19	$\text{Cu(OAc)}_2$	$\text{H}_2\text{O}_2$	–	2-Me-THF	60	0
20	$\text{Cu(OAc)}_2$	$\text{H}_2\text{O}_2$	$\text{Cs}_2\text{CO}_3$ <sup>b</sup>	2-Me-THF	60	32
21	$\text{Cu(OAc)}_2$	$\text{H}_2\text{O}_2$	$\text{Cs}_2\text{CO}_3$ <sup>c</sup>	2-Me-THF	60	58
22	$\text{Cu(OAc)}_2$	2(eq.) $\text{H}_2\text{O}_2$	$\text{Cs}_2\text{CO}_3$	2-Me-THF	60	54
23	$\text{Cu(OAc)}_2$	5(eq.) $\text{H}_2\text{O}_2$	$\text{Cs}_2\text{CO}_3$	2-Me-THF	60	68

<sup>a</sup> Reaction conditions: unless specified otherwise, all reactions were performed with *N*-methyl aniline (1 eq.), but-3-en-2-ol (2 eq.), base (3 eq.), oxidant (10 eq.), solvent (5 mL),  $\text{Cu(OAc)}_2$  (10 mol%), at 60 °C under air for 12 h–16 h. <sup>b</sup> (1 eq.). <sup>c</sup> (2 eq.).



hols, in the presence of 10 mol%  $\text{Cu}(\text{OAc})_2$ ,  $\text{Cs}_2\text{CO}_3$  (3 eq.), and  $\text{H}_2\text{O}_2$  (10 eq.) in 2-Me-THF at 60 °C and the substrate scope is shown in Scheme 2. The reaction with unsubstituted

and *N*-monosubstituted anilines yielded mono-alkylated products. *N*-Monosubstituted amines showed slightly better reactivity compared to unsubstituted amines. Amines with both



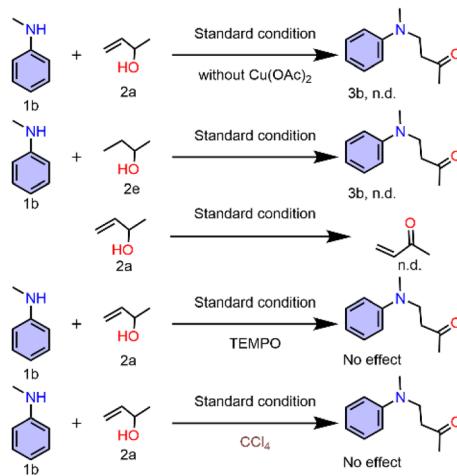
**Scheme 2** Substrate scope for Cu-catalyzed synthesis of  $\beta$ -amino carbonyl compounds. Reaction conditions: unless specified otherwise, aniline/ substituted aniline (1 eq.), allyl alcohol (2 eq.),  $\text{Cs}_2\text{CO}_3$  (3 eq.),  $\text{H}_2\text{O}_2$  (10 eq.), solvent (5 mL),  $\text{Cu}(\text{OAc})_2$  (10 mol%), at 60 °C under air for 12 h–16 h. All yields are isolated yield.

electron-donating groups (EDG) and electron-withdrawing groups (EWG) were tolerated well. Anilines with EDG in the *para* position exhibited faster reaction rates based on substrate consumption than anilines with EWG in the *para* position. Nevertheless, for electron-donating groups, the dimer of substituted anilines was identified as the byproduct (Fig. S2). Importantly, a wide range of halogen substituents (*ortho* and *para*) were well tolerated in this system and gave desired products in good yields. In the case of C3-substituted allyl alcohols, such as cinnamyl alcohol, the expected product was not obtained, while substitution at the C1 position of allyl alcohol resulted in the desired products.

To highlight the utility of the method, the reaction was also carried out on a relatively large scale (1 mmol scale) with *N*-methyl aniline (1 eq.) and but-3-en-2-ol (2 eq.) in 10 mL of 2-Me-THF with  $\text{Cs}_2\text{CO}_3$  (3 eq.),  $\text{H}_2\text{O}_2$  (10 eq.) (condition: 10 mol%  $\text{Cu}(\text{OAc})_2$ , 60 °C, 16 h) and ~75% yield (isolated) was observed.

## Mechanism

To gain further insights into the reaction mechanism, several control experiments were performed (Scheme 3). When *N*-methyl aniline and but-3-en-2-ol were used as the reagents under standard conditions, no reaction occurred without  $\text{Cu}(\text{OAc})_2$ , highlighting the essential role of the catalyst. Additionally, the absence of the oxidant prevented the formation of the desired product, indicating the necessity of the oxidant in the reaction. However, in the presence of a stoichiometric amount of  $\text{Cu}(\text{OAc})_2$  at 60 °C, ~23% product was isolated after 24 h. Furthermore, replacing allyl alcohol (**2a**) with butan-2-ol resulted in no reaction, suggesting that the double bond in allyl alcohol may interact with the copper center to facilitate the process. In the high-resolution mass spectrometry (HR-MS) analysis (positive mode) of the reaction mixture, we identified an intermediate species with the chemical formula

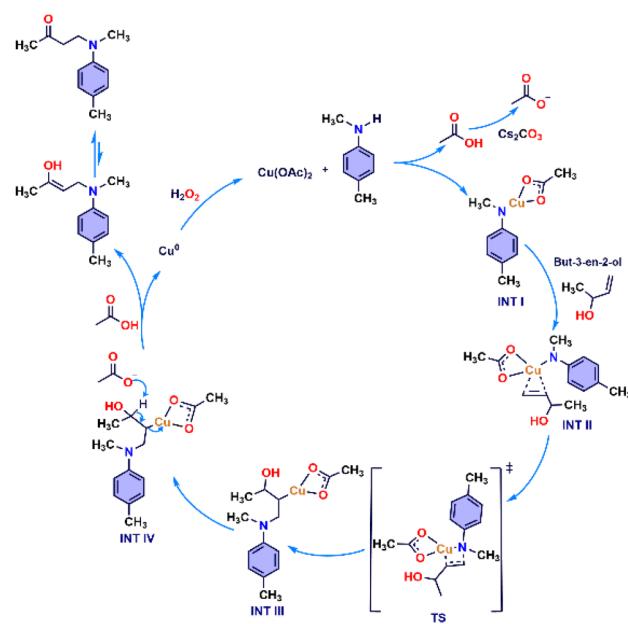


**Scheme 3** Control experiments (n.d. stands for not detected).

$[\text{C}_{12}\text{H}_{18}\text{CuNO}]^+$  (*m/z*: 255.0679) (Fig. S1), which could correspond to intermediate **II** (**INT II**) or **INT III** or **INT IV** of the proposed reaction mechanism (Fig. 1). Furthermore, but-3-en-2-one was not detected in the control experiment, where the reaction was carried out with but-3-en-2-ol,  $\text{Cu}(\text{OAc})_2$ ,  $\text{H}_2\text{O}_2$ , and  $\text{Cs}_2\text{CO}_3$ . This suggests that the reaction does not follow the aza-Michael addition pathway *via the in situ* generation of an  $\alpha,\beta$ -unsaturated ketone. The reaction was not quenched by 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) or carbon tetrachloride ( $\text{CCl}_4$ ), indicating that the reaction does not follow a radical pathway. Based on the above results, two possible reaction mechanisms are proposed in Fig. 1 ( $\text{Cu}^{\text{II}}/\text{Cu}^{\text{0}}$  redox pathway – Path A) and Fig. S4 ( $\text{Cu}^{\text{III}}/\text{Cu}^{\text{I}}$  redox pathway – Path B). For a better understanding of the proposed mechanisms, a density functional theory (DFT) study was performed.

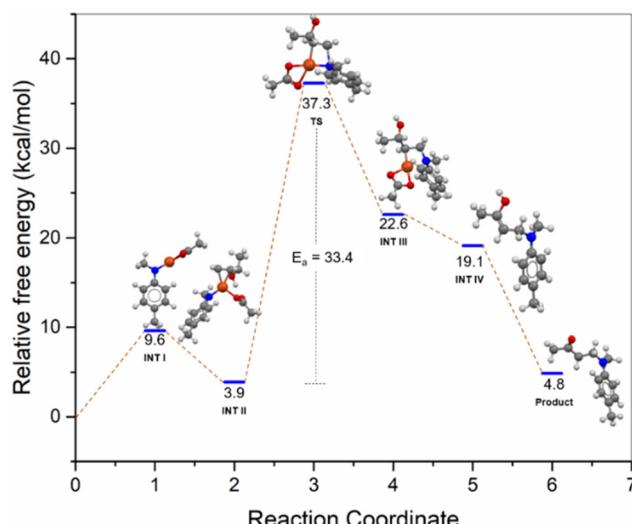
Density functional theory calculations were performed at the M06L/LanL2DZ level. Fig. 2 shows the free energy diagram for the  $\text{Cu}^{\text{II}}/\text{Cu}^{\text{0}}$  redox pathway. The calculations showed that the process begins with the interaction between  $\text{Cu}(\text{OAc})_2$  and aromatic amine, leading to the generation of intermediate **INT I**. In the next step, a  $\pi$ -copper intermediate (**INT II**) forms due to interaction between **INT I** and but-3-en-2-ol; the process is exothermic. **INT II** undergoes a rearrangement through a four-member transition state (TS) that promotes electron delocalization and the formation of intermediate **INT III**. The transition state barrier for this step is moderately high (33.4 kcal  $\text{mol}^{-1}$ ), which supports the fact that the reaction was not facile under room temperature conditions. Although the energy barrier can be traversed under conditions above room temperature.

Further, copper elimination is plausible *via* two pathways from here –  $\beta$ -H-elimination followed by a reductive elimin-



**Fig. 1** Proposed reaction mechanism of Cu-catalyzed synthesis of  $\beta$ -amino carbonyl compounds – path A, *via* base-assisted elimination.





**Fig. 2** Free energy diagram for reaction pathway A via base-assisted elimination. The free energies (in  $\text{kcal mol}^{-1}$ ) were calculated at the M06L/LanL2DZ level.

ation and a base-assisted elimination. DFT studies suggest that abstraction of  $\beta$ -H by a base (here acetate ion) is more energetically favourable (Fig. 2) as compared to the  $\beta$ -H-elimination process (Fig. S3). Both pathways release amino-but-2-en-2-ol, after which an exothermic step of Keto-enol tautomerism gives the desired product,  $\text{Cu}^0$  and acetic acid. After that, the regeneration of  $\text{Cu}^{\text{II}}$  species took place by  $\text{H}_2\text{O}_2$  to support the catalytic cycle.

Alternatively, in path B, a  $\text{Cu}^{\text{III}}/\text{Cu}^{\text{I}}$  redox pathway was investigated (Fig. S4), where the  $\text{Cu}^{\text{II}}$  center in intermediate **INT I'** undergoes a disproportionation reaction<sup>24</sup> with another  $\text{Cu}^{\text{II}}$  species, yielding the  $\text{Cu}^{\text{III}}$  intermediate **INT II'** and a  $\text{Cu}^{\text{I}}$  species. Successively, allyl alcohol coordinates to the  $\text{Cu}^{\text{III}}$  of **INT II'** and the proposed cycle continues with  $\text{Cu}^{\text{III}}$  intermediates. Eventually, it leads to the formation of  $\text{Cu}^{\text{I}}$  species, which is then oxidised to  $\text{Cu}^{\text{II}}$  in the presence of  $\text{H}_2\text{O}_2$ . The DFT studies (Fig. S4) suggest that the disproportionation of **INT I'**  $\text{Cu}^{\text{II}}$  to **INT II'**  $\text{Cu}^{\text{III}}$  is a highly energy-demanding step needing 35  $\text{kcal mol}^{-1}$ , which is higher than that of the TS step (33.4  $\text{kcal mol}^{-1}$ ) of  $\text{Cu}^{\text{II}}/\text{Cu}^0$  redox pathway. Similarly, for  $\text{Cu}^{\text{III}}/\text{Cu}^{\text{I}}$  redox pathway, the copper elimination is plausible via  $\beta$ -H-elimination followed by a reductive elimination or a base-assisted elimination. In this case, we also observed that base-assisted elimination (Fig. S4) is more energetically favourable as compared to  $\beta$ -H-elimination (Fig. S5). Looking at the energy profile of both reaction proceeding by  $\text{Cu}^{\text{II}}$  as well as that of  $\text{Cu}^{\text{III}}$  intermediates, we propose that the  $\text{Cu}^{\text{II}}$  to  $\text{Cu}^0$  reaction pathway is more favourable for our system. Also, we performed the reaction using a  $\text{Cu}^{\text{I}}$  salt under the optimized conditions. In this case, no product formation was observed, indicating that  $\text{Cu}^{\text{I}}$  is not catalytically competent under our reaction conditions. This experimental observation further supports the likelihood of a  $\text{Cu}^{\text{II}}/\text{Cu}^0$  catalytic cycle (path A) for our system.

## Conclusions

In summary, a copper-catalyzed method has been developed for the synthesis of  $\beta$ -amino ketones using allyl alcohols and substituted anilines in 2-methyl-THF at 60 °C. This approach offers a cost-effective and high-yielding alternative to traditional Pd-catalyzed coupling reactions, while also utilizing green solvents, first row transition metal catalysts, a mild base, and an environmentally friendly oxidant. To gain deeper insight into the proposed reaction mechanism, a DFT study was conducted.

## Author contributions

BBD conceptualized the work. All the synthesis and characterisation has been done by AK. Theoretical calculation has been done by KD. BBD wrote the manuscript with the help of all the co-authors.

## Conflicts of interest

There are no conflicts to declare.

## Data availability

The data supporting this article have been included as part of the SI.

The SI contains: general information and materials, general procedure for the preparation of  $\beta$ -amino ketones, HR-MS for  $[\text{C}_{12}\text{H}_{18}\text{CuNO}]^+$ , proposed mechanism - path A & path B, characterization data of  $\beta$ -amino ketones pages, spectroscopic characterization of  $\beta$ -amino ketones, X-ray crystallographic data, crystal data and structure refinements for 3r and Cartesian coordinates (Å) for DFT. See DOI: <https://doi.org/10.1039/d5qo00961h>.

CCDC 2450251 contains the supplementary crystallographic data for this paper.<sup>25</sup>

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