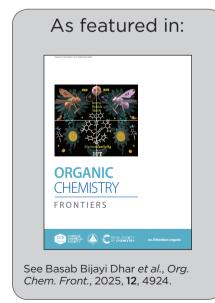


Showcasing research from Dr. Basab Bijayi Dhar's laboratory, Department of Chemistry, School of Natural Sciences, Shiv Nadar Institution of Eminence, Delhi NCR, Uttar Pradesh, Pin: 201314, India.

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Oxidative copper-catalyzed synthesis of β -amino ketones from allyl alcohols and anilines

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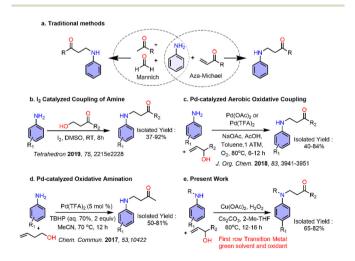
A copper-catalyzed method has been developed for synthesizing β -amino ketones using allyl alcohols and substituted anilines in 2-methyl-THF at 60 °C. This reaction employs hydrogen peroxide (H_2O_2) as the oxidant and cesium carbonate as the base. Cost-effectiveness, and a very good yield (65–82%) make this process a helpful alternative to the Pd-catalyzed coupling reaction of allylic alcohols with substituted anilines or substituted N-alkyl anilines.

Introduction

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

The Mannich reaction has been a well-established method for synthesizing β-aminoketones, although it often requires harsh conditions and long reaction times.8-11 An alternative approach for synthesizing β-aminoketones is the aza-Michael reaction, in which amines undergo conjugate addition to α,β-unsaturated carbonyl compounds. 12-14 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 α,β-unsaturated carbonyl compounds catalyzed by acidic or basic agents limits the broader applicability of the aza-Michael reaction. 15,16 To address this limitation, Miao et al. reported an iodine-catalysed coupling reaction between β-hydroxyketones and aniline to yield β-aminoketones and benzo[h]quinolones at room temperature (RT). This selective reaction avoids the aza-Michael addition and is restricted to aniline. In this context, allyl alcohols are often considered an alternative to α,β-unsaturated carbonyl compounds. 18 Ouyang et al. developed a novel Pd-catalyzed intermolecular cascade oxidative amination of homoallylic alcohols to yield

β-aminoketones using TBHP as the terminal oxidant. 19 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 β-aminoketones in toluene at 80 °C, achieving moderate to good yields (Scheme 1).20 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 β-aminoketones from allyl alcohols and amines using first-row transition metal catalysts has not been explored. In this study, we present a



Scheme 1 Synthesis of β -amino carbonyl compounds.

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copper-catalyzed method for synthesizing β-aminoketones using allyl alcohols and substituted anilines in 2-Me-THF at 60 °C, employing environmentally friendly hydrogen peroxide (H₂O₂) as an oxidant and cesium carbonate as a base (EHS:²¹ 10; greenness:²¹ 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^{22,23} 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 (H2O2; 10 eq.) as the oxidant, and cesium carbonate (Cs2CO3; 3 eq.) as the base. Various catalytic systems were screened, in which 10 mol% of cupric iodide (CuI₂) showed trace amounts of the desired product (Table 1, entry 1). Replacing CuI2 with Cupric chloride (CuCl2) 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 (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-methyltetra-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, Cs₂CO₃ (Table 1, entry 4) worked the best. We used potassium carbonate (K2CO3), sodium carbonate (Na₂CO₃), 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 Cs₂CO₃ and Cu(OAc)₂ (Table 1, entry 18), the isolated yield decreased to 60% as compared to the condition where H₂O₂ 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. Cs₂CO₃ 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. H₂O₂ 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^a

Entry	Catalyst	Oxidant	Base	Solvent	Temp. (°C)	Isolated yield (%)
1	CuI ₂	H_2O_2	Cs ₂ CO ₃	2-Me-THF	25	Trace
2	$CuCl_2$	H_2O_2	Cs_2CO_3	2-Me-THF	25	Trace
3	Cu(OAc) ₂	H_2O_2	Cs_2CO_3	2-Me-THF	25	30
4	Cu(OAc)2	H_2O_2	Cs_2CO_3	2-Me-THF	60	82
5	$Cu(OAc)_2$	H_2O_2	Cs_2CO_3	Toluene	60	70
6	Cu(OAc) ₂	H_2O_2	Cs_2CO_3	EtOAc	60	≤7
7	Cu(OAc) ₂	H_2O_2	Cs_2CO_3	DCM	60	≤5
8	Cu(OAc) ₂	H_2O_2	Cs_2CO_3	DMF	60	<u>≤</u> 7
9	Cu(OAc) ₂	H_2O_2	Cs_2CO_3	Water	60	55
10	Cu(OAc) ₂	H_2O_2	Cs_2CO_3	MeOH	60	30
11	$Cu(OAc)_2$	H_2O_2	Cs_2CO_3	EtOH	60	40
12	Cu(OAc) ₂	H_2O_2	Cs_2CO_3	MeCN	60	45
13	Cu(OAc) ₂	H_2O_2	Cs_2CO_3	THF	60	50
14	Cu(OAc) ₂	H_2O_2	K_2CO_3	2-Me-THF	60	60
15	Cu(OAc) ₂	H_2O_2	Na_2CO_3	2-Me-THF	60	35
16	Cu(OAc) ₂	H_2O_2	NaOAc	2-Me-THF	60	0
17	Cu(OAc) ₂	H_2O_2	Pyridine	2-Me-THF	60	0
18	Cu(OAc) ₂	TBHP	$\overset{\circ}{\mathrm{Cs}_2}\mathrm{CO}_3$	2-Me-THF	60	60
19	Cu(OAc) ₂	H_2O_2		2-Me-THF	60	0
20	Cu(OAc) ₂	H_2O_2	$Cs_2CO_3^b$	2-Me-THF	60	32
21	$Cu(OAc)_2$	H_2O_2	$Cs_2CO_3^c$	2-Me-THF	60	58
22	Cu(OAc) ₂	$2(eq.)H_2O_2$	Cs_2CO_3	2-Me-THF	60	54
23	$Cu(OAc)_2^2$	5(eq.)H ₂ O ₂	Cs_2CO_3	2-Me-THF	60	68

^a 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), Cu(OAc)₂ (10 mol%), at 60 °C under air for 12 h-16 h. ^b (1 eq.). ^c (2 eq.).

hols, in the presence of 10 mol% Cu(OAc)₂, Cs₂CO₃ (3 eq.), and H₂O₂ (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 β -amino carbonyl compounds. Reaction conditions: unless specified otherwise, aniline/ substituted aniline (1 eq.), allyl alcohol (2 eq.), Cs_2CO_3 (3 eq.), H_2O_2 (10 eq.), solvent (5 mL), $Cu(OAc)_2$ (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 Cs_2CO_3 (3 eq.), H_2O_2 (10 eq.) (condition: 10 mol% $Cu(OAc)_2$, 60 °C, 16 h) and \sim 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 Cu(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 Cu(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

NH

HO

2a

Standard condition

without Cu(OAc)₂

3b, n.d.

Standard condition

NH

HO

2e

Standard condition

TEMPO

No effect

No effect

No effect

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

[C₁₂H₁₈CuNO][†] (*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, Cu(OAc)₂, H₂O₂, and Cs₂CO₃. This suggests that the reaction does not follow the aza-Michael addition pathway *via the in situ* generation of an α,β-unsaturated ketone. The reaction was not quenched by 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) or carbon tetrachloride (CCl₄), indicating that the reaction does not follow a radical pathway. Based on the above results, two possible reaction mechanisms are proposed in Fig. 1 (Cu^{II}/Cu⁰ redox pathway – Path A) and Fig. S4 (Cu^{III}/Cu^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 $\mathrm{Cu^{II}/Cu^{0}}$ redox pathway. The calculations showed that the process begins with the interaction between $\mathrm{Cu(OAc)_{2}}$ and aromatic amine, leading to the generation of intermediate INT I. In the next step, a π -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 $\mathrm{mol^{-1}}$), 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 – β -H-elimination followed by a reductive elimin-

Fig. 1 Proposed reaction mechanism of Cu-catalyzed synthesis of β -amino cbonyl compounds – path A, *via* base-assisted elimination.

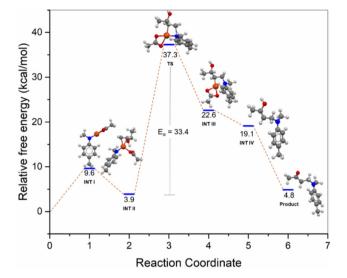


Fig. 2 Free energy diagram for reaction pathway A via base-assisted elimination. The free energies (in kcal mol^{-1}) were calculated at the M06L/LanL2DZ level.

ation and a base-assisted elimination. DFT studies suggest that abstraction of $\beta\text{-H}$ by a base (here acetate ion) is more energetically favourable (Fig. 2) as compared to the $\beta\text{-H-elimination}$ 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, Cu^0 and acetic acid. After that, the regeneration of Cu^{II} species took place by H_2O_2 to support the catalytic cycle.

Alternatively, in path B, a Cu^{III}/Cu^I redox pathway was investigated (Fig. S4), where the Cu(II) center in intermediate INT I' undergoes a disproportionation reaction²⁴ with another Cu^{II} species, yielding the Cu^{III} intermediate INT II' and a Cu^I species. Successively, allyl alcohol coordinates to the Cu^{III} of INT II' and the proposed cycle continues with Cu^{III} intermediates. Eventually, it leads to the formation of Cu^I species, which is then oxidised to Cu^{II} in the presence of H₂O₂. The DFT studies (Fig. S4) suggest that the disproportionation of INT I' Cu^{II} to **INT II**' Cu^{III} is a highly energy-demanding step needing 35 kcal mol⁻¹, which is higher than that of the TS step (33.4 kcal mol⁻¹) of Cu^{II}/Cu⁰ redox pathway. Similarly, for Cu^{III}/Cu^I redox pathway, the copper elimination is plausible via β-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 β -H-elimination (Fig. S5). Looking at the energy profile of both reaction proceeding by CuII as well as that of Cu^{III} intermediates, we propose that the Cu^{II} to Cu⁰ reaction pathway is more favourable for our system. Also, we performed the reaction using a Cu^I salt under the optimized conditions. In this case, no product formation was observed, indicating that Cu^I is not catalytically competent under our reaction conditions. This experimental observation further supports the likelihood of a Cu^{II}/Cu⁰ catalytic cycle (path A) for our system.

Conclusions

In summary, a copper-catalyzed method has been developed for the synthesis of β -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 β -amino ketones, HR-MS for $\left[C_{12}H_{18}CuNO\right]^+$, proposed mechanism - path A & path B, characterization data of β -amino ketones pages, spectroscopic characterization of β -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/d5q000961h.

CCDC 2450251 contains the supplementary crystallographic data for this paper. 25

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