Cascade Reaction of α, β-Unsaturated Ketones and 2-Aminoaryl Alcohols for the Synthesis of 3-Acylquinolines by a Copper Nanocatalyst

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Abstract: 3-Acylquinolines possess widespread applications in functional chemicals. However, the convenient and selective synthesis of such important substructures has to date remained a challenge. Herein, we report a method to access 3-acylquinolines from α , β -unsaturated ketones and 2-aminoaryl alcohols in one pot with a copper nanocatalyst supported on nitrogen-silica-doped carbon (Cu/N–SiO₂–C). Mechanistically, the construction of the product involves a cascade procedure including radical-type oxidation of 2-aminoaryl alcohols, aza-Michael addition and annulation. This developed protocol proceeds with merits of mild reaction conditions, good functional group tolerance, earth-abundant and reusable copper catalyst, easily available stocks and O₂ as the sole oxidant, which provides an alternative way for the sustainable synthesis of quinoline derivatives.

Keywords: heterogeneous catalysis; doped carbon materials; cascade reaction; 3-acylquinolines

Introduction

Functionalized quinolines are an important class of nitrogen-heterocycles with wide-ranging applications across pharmaceutical, agrochemical, materials and fine chemical research. The classic methods for the synthesis of quinolines such as Skraup, Combes, Doebner-von Miller and Friedländer reaction have been well established.^[1] As an outstanding member in the quinoline family, 3-acylquinoline derivatives exhibit excellent performance in pharmaceutical including antihypertension,^[2a] antitumor,^[2b] antiplasmodial,^[2c] etc.^[2d] In addition, due to the functional group of carbonyl, 3-acylquinolines could be easily derived into a variety of valuable and complex compounds.^[3] Therefore, the efficient construction of acyl-containing quinolines is of high importance in synthetic organic chemistry.

To date, considerable efforts have been devoted to the development of synthetic strategies for the formation of 3-acylquinolines through various intramolecular and intermolecular reactions. In the past decade, substituted enamines, $^{[4a]}$ enynes $^{[4b,c]}$ and imines $^{[4d]}$ were designed as ingenious scaffolds to access 3-acylquinolines by intramolecular C-C coupling. However, more synthetic methods focus on intermolecular reactions which has advantage in avoiding the complex preparation of substrates. For instance, Pd-catalyzed carbocyclizations of alkenylanilines and alkynes,^[5] Cu-catalyzed cascade reactions of 2-azidobenzaldehydes and ketones,^[6] enaminone-modified Povarov reaction^[7] and double C-H functionalization of electron-deficient acetylenes^[8] were well developed as the alternative paths to obtain 3-acylquinolines not long ago. Besides, Tiwari and Li group reported the efficient protocols to access 3-acylquinolines by copper-catalyzed ring-opening/reconstruction of anthranils with oxo-compounds using TEMPO as the oxidants.^[9]

Among the various available starting materials, 2aminobenzaldehyde serve as a versatile synthon, readily involving in the construction of C-C and C-N bond to get high value-added quinoline derivatives. So far, the reported methods for the preparation of 3acylquinolines from 2-aminobenzaldehyde include phosphine-catalyzed and transition-metal catalyzed condensation of ynones with o-aminobenzaldehyde (Scheme 1, a),^[10] Cu–MOFs consisting of polyhedral cages for 3-acylquinolines synthesis from β -dicarbonyl compounds and so on (Scheme 1, b),^[11] Zn-promoted Friedländer-type synthesis of 3-aroylquinolines from enaminones (Scheme 1, c),^[12] and Cu-catalyzed double $C(sp^3)$ -H bond functionalization of saturated ketones (Scheme 1, d).^[13] Despite all these advances, most of them suffer from the use of pre-functionalized reagents, harsh reaction conditions, less environmentally friendly additives, high load of non-recoverable catalysts. Hence, the search for facile synthesis of 3acylquinolines from simple and readily available starting materials with green and efficient catalyst is of great significance.

Generally, 2-aminobenzyl alcohols as synthetic materials are more stable and cheaper than the relevant aldehydes, and a great diversity of α , β -unsaturated ketones are easily available. In our previous work, we realized the synthesis of quinolines from α , β -unsaturated ketones and 2-aminobenzyl alcohols using an iridium-catalyzed transfer hydrogenation strategy.^[14] With our continuous interest in the design of non-noble metal catalysts as well as the construction of quinolones,^[15] we were therefore motivated to develop a new method to synthesize 3-acylquinolines by employing heterogeneous catalysts. In consideration of the natural abundance of copper and its capability in the activation of inert substrates via oxidation, and the

potential of silica-doped carbon materials to favor mass transfer as well as the adjustment of electronic properties of supporting materials by N-element.^[16] We herein report the preparation and characterization of a new copper nanocatalyst supported on N–SiO₂-doped carbon, and describe, for the first time, its application to catalyze the one pot cascade reactions to afford 3acylquinolines from α , β -unsaturated ketones and 2aminoaryl alcohols (Scheme 2).

Advanced

Catalysis

Synthesis &

Results and Discussion

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Typically, the catalyst was prepared as follows: The mixture of $Cu(OAc)_2$ and 1,10-phenanthroline in ethanol was stirred at 80 °C for 1 hour. Silica was then introduced into the above solution by in situ hydrolysis of the added $Si(OC_2H_5)_4$ (TEOS) with aqueous ammonia. After that, the commercially available powder Vulcan XC-72R as the support was added and refluxed for 3 h at 80 °C. Finally, the catalyst was afforded by successive removal of the suspension, dried overnight, pyrolyzed at 800 °C, which is named as Cu/N-SiO₂-C (the Cu content is 3.69 wt%, which is determined by ICP-OES measurements). Similarly, the materials prepared in absence of TEOS, 1,10phenanthroline and metal source are donated as Cu/ N-C, Cu/SiO₂-C and N-SiO₂-C, respectively. And the catalysts prepared with different metal sources are denoted as Metal/N-SiO₂-C, respectively.

To examine our tentative idea, we chose the reaction of 2-aminobenzyl alcohol **1a** with chalcone **2a** as a model system. By performing the reaction in DMF at 50 °C in the presence of *t*-BuOK under air condition, we tested the effect of four different nanocatalysts, respectively (Table 1, entries 1–4). Gratifyingly, Cu/N–SiO₂–C exhibited good catalytic activity to give title product **3aa** in 86% yield (entry 2). Subsequently, several different solvents were examined



Scheme 1. Synthesis of 3-acylquinolines from 2-amino-benzal-dehyde.

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Scheme 2. 1 a with various α , β -unsaturated ketones.

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Table 1. Optimization of reaction conditions.^[a]

	OH O HH ₂ Ph 2a	<u>catalyst,</u> ^p h base, te	solvent , (N Ph 3aa
Entry	Catalyst	Solvent	Additive	Yield (%) ^[b]
1 2 3 4 5 6 7 8 9 10 11	Co/N-SiO ₂ C Cu/N-SiO ₂ C Mn/N-SiO ₂ C Fe/N-SiO ₂ C Cu/N-SiO ₂ C Cu/N-SiO ₂ C Cu/N-SiO ₂ C N-SiO ₂ C Cu/NC Cu/NC Cu/SiO ₂ C	DMF DMF DMF DMF Toluene EtOH CH ₃ CN DMSO DMF DMF DMF	t-BuOK t-BuOK t-BuOK t-BuOK t-BuOK t-BuOK t-BuOK t-BuOK t-BuOK t-BuOK	29 86 37 trace 18 12 trace 80 0 67 54
$12 \\ 13 \\ 14 \\ 15^{[c]} \\ 16^{[d]} \\ 17^{[e]} \\ 18^{[f]}$	Cu(OAc) ₂ Cu/N–SiO ₂ –C Cu/N–SiO ₂ –C Cu/N–SiO ₂ –C Cu/N–SiO ₂ –C Cu/N–SiO ₂ –C Cu/N–SiO ₂ –C	DMF DMF DMF DMF DMF DMF DMF	t-BuOK t-BuONa K ₂ CO ₃ t-BuOK t-BuOK t-BuOK t-BuOK	58 61 0 (8, 86, 86) (2, 79, 86) 52 0

^[a] Unless otherwise stated, the mixture of 2-aminobenzyl alcohol 1a (0.3 mmol), catalyst (15 mg, Cu: 2.88 mol%), additive (0.3 mmol) and 1.0 mL of solvent was stirred at 50 °C for 1 hour, chalcone 2a (0.3 mmol) was then added successively under air atmosphere, the resulting mixture was stirred at 50 °C for 1 hour.

^[b] GC yield.

- [c] Yields are with respect to the use of 50 mol%, 150 mol% and 200 mol% *t*-BuOK, respectively.
- ^[d] Yields are with respect to the temperature at 30 °C, 40 °C and 60 °C, respectively.
- ^[e] All the substrates were mixed in one time.
- ^[f] Argon atmosphere.

with the effective catalyst Cu/N-SiO₂-C under the same employed reaction conditions (entries 5-8). So, the results indicated the use of DMF as a solvent was more effective for the formation of **3 aa**. In order to investigate the structure-function relationship of the copper-catalyst, we employed N-SiO₂-C, Cu/N-C, Cu/SiO_2 -C, $Cu(OAc)_2$ to evaluate the reaction, respectively (entries 9–12). Interestingly, N–SiO₂–C was unable to afford the compound **3 aa**, implying that the Cu species is the catalytic active ingredient. In comparison, Cu/N-SiO₂-C (entry 2) showed higher catalytic activity than Cu/SiO₂-C (entry 11), suggesting that the introduction of nitrogen improved the catalytic activity. Next, we focused our attention on the effects of different bases (entries 13-15). Obviously, the weak inorganic base K₂CO₃ was difficult to afford the desired compound, and an equivalent of t-BuOK was found to be the most appropriate choice. Then, the

screening of temperature reveals that DMF heated to $50 \,^{\circ}$ C is favorable, and a further increase of temperature did not improve the yield any more (entry 16). In addition, mixing all the substrates in one time decreased the yield of **3 aa**, and no product was found under argon atmosphere (entries 17, 18), suggesting that the oxidation of 2-aminobenzyl alcohol is very important to the reaction. Therefore, the optimal conditions are as described in entry 2 of Table 1.

Characterization of Cu/N-SiO₂-C was performed by TEM, SEM, XPS, EDS and ICP-OES, respectively. The micrograph in Figure 1 (a, b, c) and Figure S1 illustrate the morphology of Cu/N-SiO₂-C. The scanning electron microscope (SEM, Figure S1) showed that Cu/N-SiO₂-C displays relatively uniform irregular sphere-like morphology. And the transmission electron microscopy (TEM, Figure 1) showed the existence of Cu nanoparticles, which are not completely uniformly distributed in the catalyst. Some of the copper particles are clustered together, and portion of the copper particles and nitrogen and silicon are uniformly distributed in the catalyst, which indicates that some of the copper exists on the surface of the catalyst in other forms, and the specific form of existence will be explained from the following characterization. The element mapping images reveal the distribution of Cu, N, Si and C (Figure 1), which is in accordance with the result of EDS (Figure S2, SI). Further, copper content of the Cu/N-SiO₂-C was detected as 3.69 wt% by means of ICP-OES analysis.



Figure 1. (a, b, c) TEM images of $Cu/N-SiO_2-C$ and (d, e, f, g, h) the corresponding elemental mapping images of C, N, Si and Cu, respectively.

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Subsequently, X-ray photoelectron spectroscopy (XPS) analysis was employed to identify the surface chemistry of the developed Cu/N-SiO₂-C, the Cu2p spectra shows three peaks. The peak at 935.3 eV can be attributed to copper phyllosilicate species.^[17] And the peak at 932.2 eV can be assigned to copper (II) 2p3/2, due to the relaxation effects the peak at 933.6 eV can be ascribed to C-N-Cu.^[18] The content of copper phyllosilicate species, copper (II) and C–N–Cu in Cu/N-SiO₂–C is 52%, 34.5% and 13.5%, respectively (Table S1, SI). In the N region of Cu/ N-SiO₂-C, there are three distinct peaks (Figure 2) with electron binding energies of 398.4 (pyridine-type),^[19] 400.6 (graphitic-type)^[20] and 402.0 eV (N-Cu), and the peak at 402.0 eV in this case can be assigned to N-Cu as the Cu associate with 1,10phenanthroline frequently arise in the higher BE, while the graphitic-type N originates from the calcination of the 1,10-phenanthroline. Deconvolution shows that around 15% of the N atoms are bound to the copper metal (see Table S2, N-Cu, SI), which derives from the graphitization of the Cu–Phen complex. In order to figure out the single factor influence for the surface chemistry of the catalysts, the XPS analysis data of Cu/N-C, Cu/SiO₂-C and N-SiO₂-C were shown in Figure S3. Table S1 and S2. Compared with Cu/ N-SiO₂-C, the contents of pyridine-type N and graphitic-type N in the N region of the catalysts are similar, and they exhibit no catalytic activity (see Table 1, entry 9). However, the only difference is the content of N–Cu, indicating that N–Cu plays an important role in the catalytical process (Table S2). This may be due to the introduction of nitrogen could change the electron structure of the catalytic material, and enhance the binding effect between the metal and the supporting material, thus improving the catalytic performance of the catalytic material.^[21] In addition, compared with Cu/N-C (Table 1, entry 10), Cu/N-SiO₂-C (Table 1, entry 2) exhibits better catalytic activity due to the addition of silica to the catalyst. This may be due to the potential of silica in modifying the micropore size of carbon material to favor the mass transfer and increasing the dispersion of active species, thus improving the catalytic performance of the catalytic



Figure 2. Cu 2p (left) and N 1s (right) XPS spectra of Cu/ N–SiO₂–C.

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material.^[16] Combined with the above characterization and experimental results, it can be inferred that the Cu–O serves as the catalytic active ingredient, and the presence of N and silica could affect the catalytic activity of the catalyst.

Having established the optimal reaction conditions, we set out to explore the generality of this synthetic protocol. First, the reactions of **1a** in combination with a wide range of α , β -unsaturated ketones (see the Scheme S2, substrates 2 a-2 n, SI) were examined. As shown in Scheme 3, all the reactions proceeded smoothly with a good tolerance of various functional groups. Different substituted aryl groups connect with olefinic bond in α , β -unsaturated ketones had good performance in the construction of desired products (Scheme 2, **3aa–3ah**). In addition, the aryl group link to carbonyl in α , β -unsaturated ketones also delivered 3-acylquinolines in good isolated yields (3 ai-3 ak). To some extent, the above results certify that electron withdrawing groups and electron donating groups in substrates 2 have no obvious influence on the reaction. Furthermore, heterocyclic substituents such as thienyl and pyridine were successfully introduced to the quinoline skeleton in excellent yields (3 al, 3 am). Interestingly, due to the special structure of 2-(pyridin-2-yl)quinoline, the product **3 am** could be utilized as a practical bidentate ligand. For the aliphatic substituents, 1-phenylbut-2-en-1-one 2n and 4,4-dimethvlpent-1-en-3-one 20 resulted in a deficient conversion to the product **3an** and **3ao**, respectively, which is possibly owing to the unstable property of aliphatic α , β -unsaturated ketones **2 n** and **2 o**.

Subsequently, we turned our attention to the reactions of various α -aminoaryl alcohols 1 with different substitution patterns. Similar to the results described in Scheme 2, all the reactions furnished the



Scheme 3. Variation of 1 and 2.

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3-benzoylated products in moderate to excellent isolated yields (Scheme 3, 3ba-3ep). 2-amino-3-methylphenyl methanol **1 b** reacted with three different α , β unsaturated ketones to afford desired compounds in high yields (3ba, 3bb, 3bg), indicating that the cascade annulations have good tolerance of the steric influence of ortho-methyl substituent. Compared with 2-aminophenyl methanol 1a, halogen-substituted α aminobenzyl alcohol was well tolerated, as exemplified by the presence of chlorine atom para to amino group in the phenyl ring (3 ca, 3 cc, 3 ce). In addition, furan could be well installed on the skeleton of 3-acylquinoline by the elegant synthetic strategy (3 cp). Moreover, the strong electron donating group, 5-methoxy of the aromatic alcohol also had great compatibility with transformation to deliver the target molecules in good yields (3da, 3dd, 3dg). For the secondary alcohol 1-(2-aminophenyl)ethanol 1e, large amounts of undesired product 2-(4-methylquinolin-2-yl)aniline was formed by the bimolecular condensation of intermediate ketone from the oxidation of 1e, so that the yield of target compound 3ea is poor. As expected, 2aminopyridin-3-yl methanol 1 f could react with α , β unsaturated ketones to afford product 3 fi and 3 fk in excellent yields. Gratifyingly, ester-containing reactant 2 q was also suitable for this method to supply the corresponding product 3 eq which could be easily used for further chemical synthesis.

To gain insight into the product forming information, 2-aminophenyl methanol 1a was treated by standard conditions without α , β -unsaturated ketones in 1 hour (Scheme 4, eq 1). Oxidation product 2-aminobenzaldehyde 1a' was detected in 97% GC yield, implying that the oxidative process was highly efficient. Subsequently, 1a' was used directly as the substrate to react with 2 a under the same conditions to afford desired product 3 aa in an excellent yield and a



Scheme 4. Control experiments.

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tiny amount of by-product 2-phenylquinoline (eq 2). Besides, without the catalyst, the same reaction generated 3 aa in 36% yield and a plenty of intermediate dihydrogen quinoline 3 aa' had not been oxidized in a prolonged time (eq 3). Furthermore, the second step of the model reaction was interrupted after 0.5 hour. By the GC-MS analysis, product 3aa and 3 aa' were detected in 43% and 28% yields, respectively. So, the above results indicate that the coppernanocatalyst is very important to the selective oxidation of alcohols and dehydroaromatization of large steric hindrance dihydrogen quinoline (eq 4). However, the excess BHT significantly suppressed the oxidation of 1a, showing that, the reaction may involve a radical-type oxidation (eq 5). Meanwhile, the generation of quinone is consistent with the Karlin's reports, $^{\left[22\right] }$ suggesting that the oxidative system of Cu/ $N-SiO_2-C$ with O_2 possibly generate a superoxo copper(II) species.

Based on the above-observed findings and the reported mechanisms,^[22,23] the plausible reaction pathway is proposed in Scheme 5. In order to facilitate the exhibition of mechanism, the catalyst Cu/N-SiO2-C was written as O=Cu^{II}Nx in Scheme 5. Here, O=Cu^{II} denotes that a divalent copper species is formed between copper and oxygen after calcination of the precursor $Cu(OAc)_2$ which was confirmed by XPS analysis. The Nx means that the copper species contains an unknown amount of Cu-N coordination bonds which was also confirmed by XPS analysis. Initially, 2-aminophenyl methanol 1a proceeds depro-



Scheme 5. Possible reaction pathway.

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tonation by t-BuOK to generate alkoxide 1 aa which associate with nano-Cu (II) to give compound 1bb. Then, (hydroxo)copper species 1 cc is formed by alcoholysis and followed by oxidation to produce copper(II)-hydroperoxide 1 dd. Next, the radical hydrogen abstraction from the C_{α} carbon of **1bb** by the homolytic cleavage of peroxy bond, resulting in water and a radical species 1ee. Further, the 1ee can be transformed into the 2-aminobenzaldehyde 1a' and original nano-Cu (II) catalyst by elimination, thereby completing the catalytic oxidation cycle. Finally, the intermediate 1a' proceeds aza-Michael addition, dehydration and dehydroaromatization to afford the product **3 aa**. However, the retro-aldol reaction of **2 a** produces acetophenone, which can participate in the Friedlander reaction with 1a' to produce 2-phenylquinoline as a by-product.

To check the stability of the developed catalyst material (Cu/N–SiO₂–C), it was recycled and reused for six consecutive runs with the model reaction. As illustrated in Figure 3, the catalytic activity maintains very well. After six recycles, the Cu content dropped from 3.69 wt% to 3.28 wt% (determined by ICP-OES analysis). In comparison with the fresh catalyst (Cu/N–SiO₂–C), TEM and SEM images showed no obvious change of the morphology of the used catalyst (Figure S1 and Figure S4). In addition, according to



Figure 3. Recyclability of the Cu/N–SiO₂–C catalyst.



Scheme 6. Utility of the 3-acylquinolines.

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the XPS results of used Cu/N–SiO₂–C (Figure S3, Table S1), a relatively high loss of copper phyllosilicate species was found, which maybe due to the weakened interaction between the carrier and the metal. And a slight decrease of relative Cu (II) content was found, counting for the slight deactivation of the catalyst.

Finally, we were interested in applying our synthetic protocol for rapid synthesis of some complex compounds. As shown in Scheme 6, 11-phenyl-11*H*indeno[1,2-*b*]quinoline **4a** could be efficiently prepared in 52% yield from **3aa** by reduction and Friedel-Crafts alkylation. Noteworthy, many azafluorene derivatives are endowed with significant biological and medicinal activities.^[24] Moreover, **3aa** had a good performance in Schmidt reaction^[25] by using azidotrimethylsilane as a nucleophilic reagent to afford *N*,2-diphenylquinoline-3-carboxamide **5a** in 64% yield.

Conclusion

In summary, we have developed a method for the one pot synthesis of functionalized 3-acylquinolines from 2-aminobenzyl alcohols and α , β -unsaturated ketones by a copper nanocatalyst supported on N–SiO₂-doped carbon. The catalyst was easily prepared from low-cost earth-abundant metal, which exhibited good catalytic performance towards the cascade reactions. A wide array of 3-acylquinolines were successfully obtained in reasonable to good yields upon isolation. The presented synthetic protocol proceeds with the merits of good functional tolerance, stable and reusable of copper catalyst, simple operation, mild conditions and molecular O₂ as the sole oxidant, which offers an alternative way for sustainable synthesis of functionalized quinolines.

Experimental Section

Procedure for the preparation of catalyst: The mixture of Cu(OAc)₂ (748 mg, 3.75 mmol) and 1,10-phenanthroline (2025 mg, 11.25 mmol) (Cu:phenanthroline=1:3 molar ratio) was added to ethanol (100 mL) and stirred at 80 °C for 1 hour. Silica was then introduced into the above solution by in situ hydrolysis of the added $Si(OC_2H_5)_4$ (TEOS) with aqueous ammonia. After that, the commercially available powder Vulcan XC-72R (5000 mg) as the support was added to the solution and refluxed for 3 h at 80 °C, then the solvent of the suspension was removed and the remained solid was dried overnight at 60 °C under vacuum. Then, the sample was grounded to a fine powder and then pyrolyzed at 800 °C under a constant argon flow for 2 hours, which is named as Cu/N-SiO₂-C (the Cu content is 3.69 wt%, which is determined by ICP-OES measurements). Similarly, the materials prepared in absence of TEOS, 1,10-phenanthroline and metal source are donated as Cu/N-C, Cu/SiO₂-C and N-SiO₂-C, respectively. And the catalysts



prepared with different metal sources are denoted as Metal/ $N{-}SiO_2{-}C,$ respectively.

Typical procedure for the synthesis of compound 3aa: 2aminobenzyl alcohol 1a (36.6 mg, 0.3 mmol), catalyst (15 mg, Cu: 2.88 mol%), t-BuOK (39.2 mg, 100 mol%) and DMF (1.0 mL) were introduced in a tube (25 mL), which was heated to 50 °C for 1 h under air atmosphere. Then, chalcone 2a (62.4 mg, 0.3 mmol) was added successively and the resulting reaction mixture was stirred at 50 °C for 1 h. After cooling down to room temperature, the reaction mixture was diluted by water and was extracted with ethyl acetate (5 mL×3). The combined organic layer was dried over by Na₂SO₄, followed by removing the solvent under vacuum. The residue was purified by preparative TLC on silica, eluting with petroleum ether (60– 90 °C)/ethyl acetate (25/1) to give quinoline **3 aa** as yellow solid.

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RESEARCH ARTICLE

Cascade Reaction of α , β -Unsaturated Ketones and 2-Aminoaryl Alcohols for the Synthesis of 3-Acylquinolines by a Copper Nanocatalyst

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