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Copper(I)-Catalyzed N–H Olefination of Sulfonamides for *N*-sulfonyl Enaminones Synthesis

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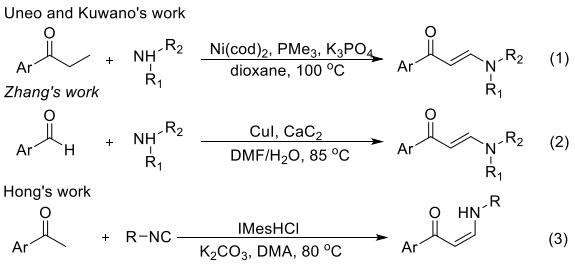
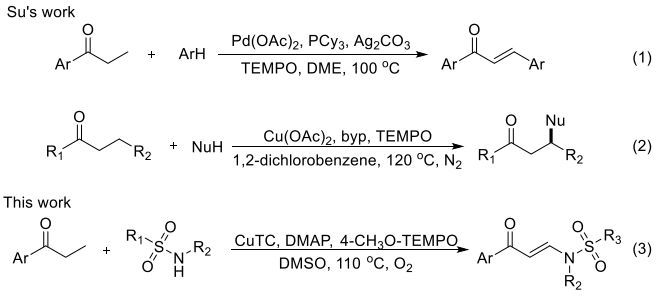
This paper reports copper-catalyzed N–H olefination of sulfonamides for enaminones synthesis using saturated ketones as olefin sources. With TEMPO derivatives and O_2 as oxidants, this method provided an efficient way to produce various enaminones in good yields. Mechanism studies helped figure out the stable intermediates and develop novel methodologies for the difunctionalization of saturated ketones.

Enaminones constitute a powerful class of significant intermediates which are versatile for various chemical transformations, especially for heterocyclic compounds synthesis.[1] Such enaminone structures exist in both drug molecules and natural products. Our group has a long-term interest in the application of such structures, in natural product synthesis,[2] ligand designing,[3] gas-phase reactions in mass spectrometry,[4] and so on. Traditionally, the 1, 4-conjugate addition of nucleophiles to a triple bond was the most predominating approach for enaminone synthesis. Over the past few years, increasing novel methodologies for constructing such structures have been reported.[5] In 2009, Uneo and Kuwano reported a method involving the nickel-catalyzed formation of a carbon–nitrogen bond at the β-position of propiophenone, highlighting α, β-unsaturated ketone as the key intermediate (Scheme 1, entry 1).[6] In 2017, Hong and co-workers developed Au-catalyzed chemoselective method for synthesizing *N*-sulfonyl enaminones, by employing Au(I) and Au(III) as catalysts to obtain two different isomers.[7] Recently, they reported another work, in which *N*-heterocyclic carbene was utilized as organocatalyst to activate isocyanides during transformation (Scheme 1, entry 3).[8] In 2013, Zhang et al. developed a step-economical protocol for the synthesis of enaminones via a three component reaction of calcium carbide, aryl aldehyde, and amine, demonstrating the versatility of the acetylide ion, which can bridge both electrophiles and nucleophiles (Scheme 1, entry 2).[9] In 2012, Li used diethyl azodicarboxylate to synthesize *cis*-β-enaminones via transformation of substituted propargylamines.[10] In 2014, Chang and co-workers later described the iridium-catalyzed direct intermolecular C–H amidation of ester and ketone derivatives[11]. However, most of these reported methods suffer from several limitations, such as inconvenient starting materials, narrow scope, and special requirement for expensive substrates.



Scheme 1 Representative examples to synthesize enaminones



Scheme 2 Strategies in β-functionalization of ketone

Unlike reported works, we chose propiophenone as the source of olefination, 4-CH_3O-TEMPO and O_2 as the oxidants to synthesize the target compounds via the radical-relay process in our research. This one-step strategy could modify β-carbon and

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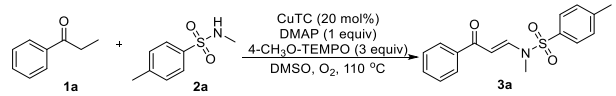
introduce the unsaturated structure to the compound. The existence of *α, β*-disubstituted compounds during the transformation also provided the potential to realize the multi-functionalization of ketones.

Since the last century, *β*-functionalization of saturated ketones has been a research hotspot, and various approaches to construct *β*-functionalized ketones have been reported.[12] In 2016, on the basis of previous works for synthesizing chalcones and heterocyclic analogues (Scheme 2, entry 1),[13] Su reported a copper-catalyzed direct *β*-functionalization of saturated ketones, in which the target compounds were obtained via conjugate addition to *α, β*-unsaturated ketones (Scheme 2, entry 2).[14] In 2017, our group reported the direct *α*-oxyacylation of ketones with carboxylic acids under air condition to form an *α*-carbon radical intermediate that can undergo further transformation to establish new C–O bond.[15] Inspired by the above-mentioned works, we surmised that the simultaneous functionalization of *α*-carbon and *β*-carbon might be possible. As the continuation of our previous works, we still focused on the research on copper-catalyzed functionalization of ketones. In this paper, we report a novel TEMPO-assisted Cu-catalyzed synthetic strategy to construct *N*-sulfonyl enaminones.

Table 1 Optimization of the reaction conditions[a]

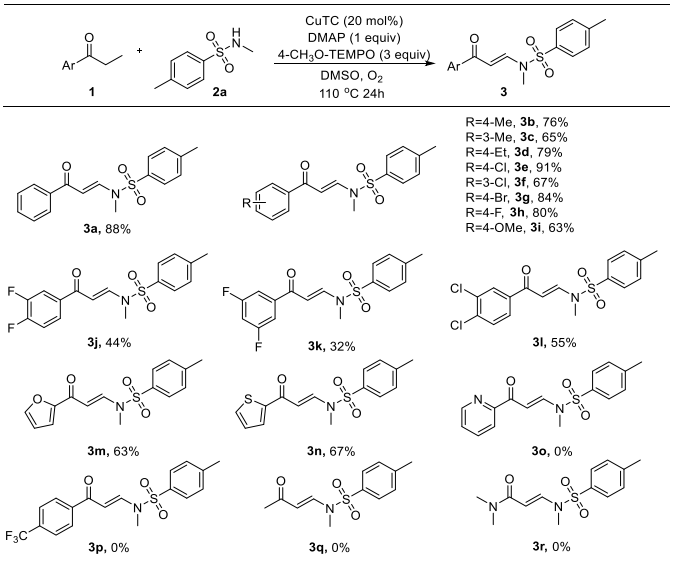


entry	variation from standard condition	isolated yield
1	none	88
2	1,10-phenanthroline instead of DMAP	65
3	byp instead of DMAP	42
4	Cs_2CO_3 instead of DMAP	trace
5	pyridine instead of DMAP	79
6	N_2 atmosphere	trace
7	TBHP instead of 4-CH_3O-TEMPO	trace
8	TEMPO instead of 4-CH_3O-TEMPO	77
9	4-Acetyl-TEMPO instead of 4-CH_3O-TEMPO	81
10	CuI instead of CuTC	78
11	$Cu(OAc)_2$ instead of CuTC	65
12	$NiCl_2$ instead of CuTC	trace
13	$Pd(OAc)_2$ instead of CuTC	trace

[a] Reaction conditions: **1a** (0.9 mmol), **2a** (0.3 mmol), catalysts (20 mol%), addtives and oxidants were stirred in DMSO (2 mL) at 110 °C under O_2 atmosphere (operating in Schlenk tube) for 24 h.

Initial trials still focused on the Cu-O_2 catalytic system. With investigations in screening a variety of metal catalysts, oxidants and additives, optimized reaction conditions were determined as follows: *N*-methyl-*p*-toluene sulfonamide (**2a**, 0.3mmol), propiophenone (**1a**, 3 equiv), CuTC (copper (I) thiophene-2-carboxylate, 20 mol%), DMAP (*N*,*N*-dimethyl-4-aminopyridine, 1 equiv), 4-CH_3O-TEMPO (4-methoxy-2,2,6,6-tetramethylpiperidine 1-oxyl, 3 equiv), DMSO was used as solvent, and the reaction proceeded under O_2 atmosphere at 110 °C for 24 h (entry 1). Compared with other additives, DMAP showed prior promotion to the reaction, which might work as a base and the ligand (entries 2–5). Given that the reaction involved the dehydrogenation process, attempting to enhance the oxidative ability of the catalytic system by introducing some co-oxidants and operating the reaction under O_2 atmosphere produced better results, and 4-CH_3O-TEMPO was the most effective oxidant (entries 6–9). Furthermore, both Cu(I) and Cu(II) salts could function as catalysts, and CuTC produced the best result (entries 10 and 11). Other catalysts such as Ni and Pd were also tested, but found to be unsuitable for the condition (entries 12 and 13).

Table 2 Substrate Scope of Ketones[a]



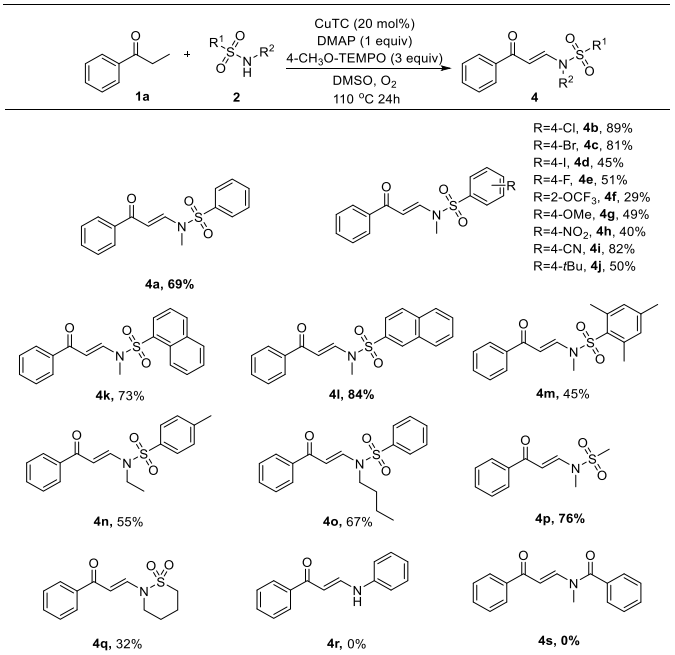
[a] Reaction conditions: **1** (0.9 mmol), **2a** (0.3 mmol), CuTC (20 mol%), DMAP(100 mol%), 4-CH_3O-TEMPO (3 equiv), DMSO (2 mL), 110 °C, O_2, 24 h.

Under optimized reaction conditions, various aromatic ketones were investigated to broaden the substrate scope of the model reaction (Table 2). In general, the yields for most of the tested aromatic ketones were good, and sometimes even excellent. Ketones with either electron-donating or electron-withdrawing substituents on the aromatic ring reacted moderately under the standard condition. In particular, ketones with weak electron-donating or weak electron-withdrawing substituents, such as the aliphatic group and halogen group (**3a, 3e, 3g,** and **3h**), performed much better in the reaction. Disubstituted substrates were also examined, and different dichloro- and difluoro- compounds could be obtained at moderate yield (**3j, 3k,** and **3l**). Notably, electron-donating heterocyclic ketones (**3m** and **3n**) proceeded well in the reaction, whereas electron-withdrawing heterocyclic ketones (**3o**) did not work. Strong electron-donating substituents (**3i**) contributed less to the reaction, leading to a decrease in yield. Furthermore, the steric effect had a huge influence on the transformation, as isobutyrophenone, *n*-butyrophenone, and valerophenone did not work under the reaction conditions. Aliphatic ketones (**3q**), carboxylic acids, and amides (**3r**) failed to afford corresponding products.

More sulfonamide derivatives were investigated to expand the utility of this catalytic system. As shown in Table 3, weak electron-donating and electron-withdrawing groups on the benzene ring (**4b** and **4c**) showed good performance, whereas stronger electron-donating and electron-withdrawing substituents demonstrated lower reactivity (**4g** and **4h**), almost similar to the ketone substrates mentioned above. Steric hindrance did not make considerably

influence to the result, and even the trisubstituted (**4m**) and disubstituted (**4k** and **4l**) substrates could afford corresponding enaminones. Besides, the lengthening of the carbon chain slightly influenced the yield to some extent (**4o**). In addition, alkyl sulfonyl amide (**4p**) and cyclic sulfonyl amide (**4q**) could proceed smoothly. Unfortunately, the primary sulfonamide, formamide (**4s**), alkyl amine, and aromatic amine (**4r**) did not work in the reaction.

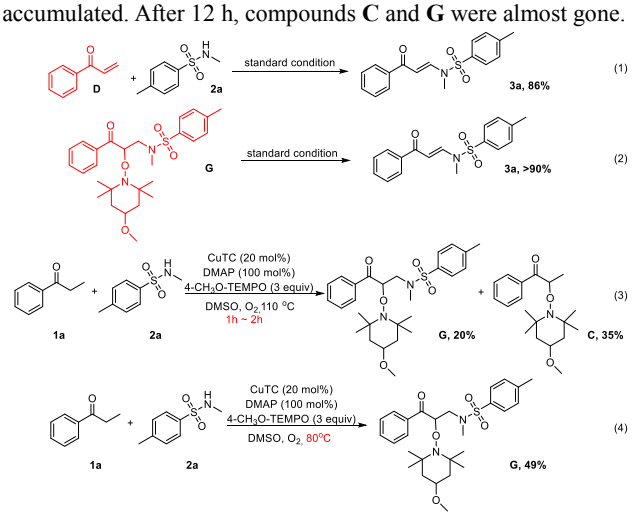
Table 3 Substrate Scope of Sulfonamides[a]



[a] Reaction conditions: **1a** (0.9 mmol), **2** (0.3 mmol), CuTC (20 mol%), DMAP (100 mol%), 4-CH_3O-TEMPO (3 equiv), DMSO (2 mL), 110 °C, O_2, 24 h.

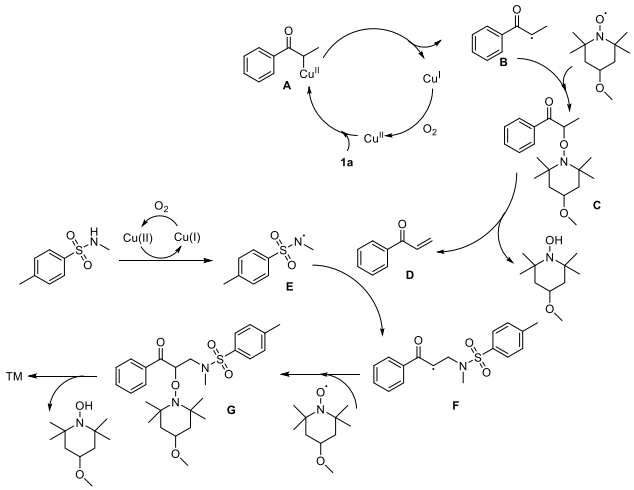
To obtain further insight into the mechanism of the reaction, several control experiments were conducted (Scheme 3). When the reaction was conducted under N_2 atmosphere, only trace yield was obtained (Table 1, entry 6). The reaction of *α*, *β*-unsaturated ketone with *N*-methyl-*p*-toluene sulfonamide was investigated under standard conditions, giving the corresponding enaminone an excellent yield of 86 % (Scheme 3, entry 1). Therefore, *α*, *β*-unsaturated ketone might be an important intermediate. By utilizing *α*, *β*-disubstituted compound **G** into the system, the target molecule was obtained with a yield of more than 90 % yield indicating that compound **G** might play a crucial role in the transformation (Scheme 3, entry 2). When the reaction time was controlled between 1 and 2 h, compounds **G** and **C** could be produced and separated with the yield at 20 % and 35 %, respectively (Scheme 3, entry 3). Surprisingly, when the reaction temperature was set at 80 °C, only *α*, *β*-disubstituted compound was got instead of the downstream enaminone products (Scheme 3, entry 4). These results suggested that enaminone products could be synthesized by further elimination of compound **G**, which might be a thermodynamic-controlled step.

Furthermore, monitoring the reaction course through ^{1}H-NMR was difficult due to the excess amounts of TEMPO. Therefore, *in situ* TLC detection was conducted to observe the reaction course. We collected reaction samples at various reaction time points (0.5, 1, 2, 3, 5, 7, 12, and 18 h) for TLC measurement. The TLC results indicated that some stable key intermediates could appear during the reaction and the exact structure of these intermediates could be determined (See ESI†). At the beginning of the reaction, compound **C** was rapidly generated, which may be the precursor of *α*, *β*-unsaturated ketone. Almost simultaneously, *α*, *β*-disubstituted compound **G** was formed. When the reaction time reached 4 h, the product emerged and gradually accumulated. After 12 h, compounds **C** and **G** were almost gone.



Scheme 3 Control experiments

On the basis of the observations, a possible mechanism was proposed in Scheme 4**.** Initially, the copper–ketone complex **A** was rapidly formed through the deprotonation process. The homolysis of Cu(II)–C bond in complex **A** produced Cu(I) species and key radical

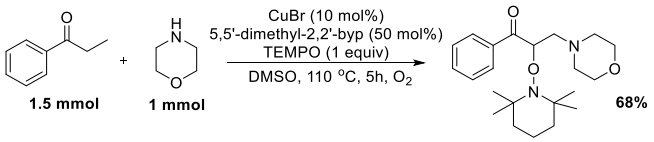


Scheme 4 Proposed mechanism

intermediate **B**, which was immediately captured by 4-CH_3O-TEMPO to form compound **C**.[16] The elimination of 4-CH_3O-TEMPOH from **C** gave rise to the formation of *α*, *β*-unsaturated ketone **D**.[17] The sulfonamide was transformed to corresponding radical species **E** through the SET process. The radical addition between **E** and **D** produced the radical intermediate **F**, which subsequently reacted with another 4-CH_3O-TEMPO molecule to construct the *α*, *β*-disubstituted compound **G**. Finally, the elimination of 4-CH_3O-TEMPOH from **G**

resulted in the formation of the product.

On the basis of our mechanistic studies, the reaction was also applied to synthesize α, β-disubstituted products. According to the preliminary screening results for the optimization of the reaction condition, using morpholine as the *N*-source, TEMPO as the oxidant,



Scheme 5 Application in synthesizing α, β-disubstituted product

and byp as the additive, the corresponding α, β-disubstituted products could be obtained with good yield. Its structure was determined via X-ray crystallographic analysis and NMR (Scheme 5).

In conclusion, we developed a versatile approach for the synthesis of *N*-sulfonyl enaminones with a wide range of ketones and sulfonamides in good to excellent yields. *In situ* TLC detection helped in studying the underlying mechanism, in which possibly involved some radical intermediates. Our findings may provide an entry into accessing functionalization at the α- and β-position of the carbonyl group, and disclose the potential to realize multi-modification of the saturated ketones. Further studies aimed at broadening the reaction scope for more amines and inactivated ketones are underway in our laboratory. Investigations involving the synthesis of α, β-disubstituted ketone derivatives are currently under exploration.

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Conflicts of interest

There are no conflicts to declare.

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