# Copper(II)-Catalyzed [2+2+2] Annulation of Enaminones with Maleimides by a Traceless Directing Group Strategy

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## Abstract

An efficient copper-catalyzed annulation of enaminones with maleimides has been developed. This reaction provides a practical approach towards the synthesis of various pyrrolo[3,4-e]isoindoles in moderate to good yields. Notable features of the method include the use of a 2-aminopyridine group as a traceless directing group, wide scope of substrates with good functional group compatibility and applicability to gram scale.

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**Keywords**
Copper | Enaminone | Maleimide | C-H bond activation | Annulation | Traceless directing group | Pyrrolo[3,4-e]isoindoles | S

**Comprehensive Summary**

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Background and Originality Content

Due to the general presence of the benzene core in a large majority of natural products, industrial chemicals, medicines and functional materials[1], so the establishment of benzene ring is an important research orientation that attracted a significant amount of attention in modern organic synthesis. The traditional and well-explored methods include Diels-Alder reaction, Reppe trimerization of Alkynes, Danheiser annulation, and Dötz [3+2+1] Reaction.[2] In recent decades, many efficient synthetic strategies toward the functionalized benzenes are emerged, such as C-H functionalization of preexisting arenes, the oxidative cyclization of alkenes, transition-metal catalyzed cascade cyclization of alkenes et al.[3] Enaminones can be considered as donor-acceptor alkene molecules, that the 1, 2-positions of C=C bond are replaced respectively by electron-withdrawing groups (EWG) and electron-donating groups (EDG). It could undergo various functionalization reactions and tandem reactions.[4] As a extremely efficient synthon, enaminone has a wide range of applications to build a heterocyclic skeleton [5] or benzene ring[6-9] in organic synthetic chemistry. Wan's group[6] and Dong's group [7]reported the acid-promoted [2+2+2] trimerization of*N,N* -disubstituted enaminone via C-N bond cleavage to build benzene ring. Wan and co-workers[8] realized the acid-promoted formal [4+2] cycloaddition for the synthesis of benzaldehyde by means of *N,N* -disubstituted enaminone and dienals. In 2019, Sosnovskikh et al.[9] developed a method for the construction of the benzene core through self-condensation of available enaminodiones.

In addition, transition-metal-catalyzed annulation reaction of enaminone provided an efficient strategy for the synthesis of benzene derivatives. Such as, Rh(III)-catalyzed *N,N* -disubstituted alkenyl-enaminones or *N,N* -disubstituted aryl-enaminones C-H coupling with alkynes,[10] Rh(III)-catalyzed*N,N* -disubstituted aryl-enaminones C-H functionalization with vinylene carbonate, vinyl esters, sulfoxonium ylides, or α-diazo-β-ketoesters,[10a,11]Indium(III)-catalyzed *N,N* -disubstituted enaminones with 3-formylchromones.[12] For the*N* -substituted *NH* -enaminones, it was a common way to generate polysubstituted NH-enaminones and heterocyclic substances via C-H bond functionalization and tandem cyclization.[13] Moreover, by using transition-metal catalyst, *NH* -enaminones usually underwent C-H/N-H activation and annulation with nucleophile to construct nitrogen-containing heterocyclic compounds[14] or fused ring compounds[15] (Scheme 1A). Our group has been extensively involved in the transition-metal-catalyzed C-H bond transformation of enaminones.[16] Most recently, we established a methord of Rh-catalyzed [4+2] annulation via C-H bond activation and subsequent tautomeric O-H bond cleavage by employing alkynes and N-heterocycles enaminones (Scheme 1B).[16d] The mechanistic investigation showed that *N* -heterocycles such as *N* -pyridinyl,*N* -pyrimidinyl and *N* -isoquinolinyl enaminones are operative and plays the role of directing group (DG) by coordinating the metal to enable C-H activation. Herein, to continue our interest in the C-H bond functionalization of enaminones and inspired by oriented strategy, we described a copper-catalyzed [2+2+2] annulation for the synthesize of pyrrolo[3,4-e]isoindoles[17] via the C-H activation and C-N bond cleavage of *N* -pyridinyl enaminones with maleimides (Scheme 1C). The traceless directing group was essential in this reaction for olefination of maleimides, which is quite challenging compared to the alkylation of maleimides because maleimide was identified as a suitable Michael acceptor.[18]Notably, contrast to previous reports that relied on the use of expensive Au, Rh and Pd catalysts[19], cheap and commercially available copper(II) was used as an efficient catalyst .

**Scheme 1** Different activation and annulation modes of*NH* -enaminone

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Results and Discussion

**Table 1** Optimization of the reaction conditions[a]

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| Entry | $\text{Cu(OAc)}_2$ (x) | Solvent | Additive | Yield[b](%) |
|---|---|---|---|---|
| 1 | $\text{Cu(OAc)}_2$ (20) | Toluene | – | 25 |
| 2 | – | Toluene | – | 0 |
| 3 | $\text{Cu(OAc)}_2$ (50) | Toluene | – | 39 |

| | | | | |
|---|---|---|---|---|
| 4 | $Cu(OAc)_2$(100) | Toluene | – | 37 |
| 5 | $Cu(OAc)_2$ (50) | THF | – | 37 |
| 6 | $Cu(OAc)_2$ (50) | DCE | – | 31 |
| 7 | $Cu(OAc)_2$(50) | MeCN | – | 53 |
| 8 | $Cu(OAc)_2$ (50) | 1,4-Dioxane | – | 38 |
| 9 | $Cu(OAc)_2$ (50) | EtOH | – | 0 |
| 10 | $Cu(OAc)_2$ (50) | MeCN | BPO | 18 |
| 11 | $Cu(OAc)_2$ (50) | MeCN | $K_2S_2O_8$ | 34 |
| 12 | $Cu(OAc)_2$ (50) | MeCN | DTBP | 72 |
| 13 | $Cu(OAc)_2$ (50) | MeCN | TBHP | 61 |

[a] Reaction coditions: enaminone **1a**(0.15 mmol), *N* -methylmaleimide **2a** (0.2 mmol), 20-100 mol% catalyst, 1.0 equiv additive and 2.0 mL solvent, reacted under air at 80 °C for 16 h; [b] Yield of isolated product based on **2a** .

We commenced our investigation with the model reaction of*N* -pyridinyl enaminone **1a** and *N* -methylmaleimide**2a** . Systematical screening on the catalyst, solvent, additive, temperature, etc. was executed (see full data in the Supporting Information Table S1). The typical data proved that $Cu(OAc)_2$ was essential and 0.5 equiv $Cu(OAc)_2$ was the best loading to catalyze the formation of pyrrolo[3,4-e]isoindole **3a** in 39% yield (entries 1-4, Table 1). The reaction took place in the media of Toluene, THF, DCE, MeCN and 1,4-Dioxane (entries 5-8, Table 1), while it hardly proceeded in EtOH (entry 9, Table 1). We also studied several additives and the results indicated that the use of 1 equiv of Dibutylperoxide (DTBP) was beneficial to the reaction, with a 72% yield being obtained (entries 10-13, Table 1). At last, the reaction temperature of 80°C was favorable to give better results (see the Supporting Information Table S1).

With the established optimal reaction conditions, we subsequently investigated the substrate scope of *N* -pyridinyl enaminones**1** . As showed in Table 2, the present method was highly tolerable to enaminones (**3a-3l** , Table 2). The*N* -pyridinyl enaminones bearing electron-donating groups (methyl) on the aromatic ring at the para-, meta-, ortho-site or the disubstituted position, could afford the target products in satisfactory yields. *N* -pyridinyl enaminones with various electron-withdrawing groups, such as halide, cyan and trifluoromethyl attached on the aromatic ring, were also to be proven compatible, providing the corresponding products in good yields. To our delight, the reaction using a simple alkyl-based enaminone of type **1** (methyl instead of Ph in **1a** ) was also occurred smoothly (**3m** , Table 2). In addition, fused aromatic enaminone (**3n** , Table 2) and heteroaryl-derived enaminones (**3o** and **3p** , Table 2) could also converted into the corresponding products. Additionally, the reaction could also be applied to conjugated group of styryl enaminone and the desired product **3q** was acquired in 62% yield. Moreover, the enaminone in which the carbonyl β-position is

**Table 2** Substrate scope of enaminones.

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Reaction conditions: enaminone **1** (0.15 mmol),*N* -methylmaleimide **2a** (0.2 mmol), 50 mol% $Cu(OAc)_2$, 1.0 equiv DTBP and 2.0 mL MeCN, reacted under air at 80 °C for 16 h. Yields given are isolated yields. [a]The yield from the 1 mmol scale synthesis of**3a** is shown in parentheses.

replaced by a methyl group was also compatible in this transformation (**3r** , Table 2). Notably, the enaminones derived from the natural product progesterone were successfully transformed into the fused phthalimideds (**3s** and **3t** , Table 2), demonstrating the vital application of this method for the late stage diversification of natural products. For instance, 1 mmol scale synthesis of **3a**was shown to explore the potential application of this transformation protocol.

Subsequently, the scope of maleimides were also investigated to further examine the universality of this reaction. As shown in Table 3, a series of maleimides reacted with enaminone **1a** smoothly. Different*N* -alkyl maleimides, such as ethyl, *n* -propyl,*t* -butyl and cyclohexyl were found to be highly compatible with**1a** , resulting in the target products **3u** -**3x** in good yields. We were pleased to find that when *N* -benzyl maleimide was employed, product **3y** was obtained in 65% yield. Moreover,*N* -aryl maleimides were also well tolerated in this reaction and gave the corresponding products in acceptable yields (**3z** and**3aa** , Table 3).

**Table 3** Substrate scope of maleimides.

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`image7.emf` available at https://authorea.com/users/792552/articles/1083871-copper-ii-catalyzed-2-2-2-annulation-of-enaminones-with-maleimides-by-a-traceless-directing-group-strategy

Reaction conditions: enaminone **1a** (0.15 mmol), **2** (0.2 mmol), 50 mol% $Cu(OAc)_2$, 1.0 equiv DTBP and 2.0 mL MeCN, reacted under air at 80 °C for 16 h. Yields given are isolated yields.

To understand the mechanism of this reaction, a series of experiments was carried out (Scheme 2). Initially, using *N,N* -disubstituted enaminone **4a** or *N* -phenyl enaminone **5a** instead of *N* -pyridinyl enaminone **1a** to react with **2a**failed to generate the target product **3a** , implying that the presence of the pyridine ring was critical (eq a and eq b, Scheme 2). We supposed the pyridine heterocyclerole may act as the role of directing group in the reactions. Furthermore, *N* -pyridinyl enaminone**1a** was treated with $D_2O$ (3.0 equiv) under the standard conditions, and 60% deuterium incorporation at the carbonyl α-C-H bond was observed (eq c, Scheme 2). The deuterium exchange studies indicated that C-H activation step was reversible.

According to the above studies and existing literatures, a plausible reaction pathway accounting for the formation of **3a** was proposed (Scheme 3). Initially, C-H bond activation[15b, 16b-c] of **1a** occurred to provide a six-membered metallocycle **A** , and further 1,2-migratory insertion of maleimide **2a** into complex **A**lead to the formation of eight-membered coppercycle intermediate**B** .[18e, 20] Subsequently, another molecule of maleimide**2a** inserted into the carbon-copper bond of intermediate**B** , leading to the formation of the complex **C** . This was followed by the β-hydride elimination of the complex **C** to generate the intermediate **D** and Cu(0) species, which was further oxidized by DTBP under air to regenerate the active Cu(II) catalyst.[21] Then, an oxidative dehydrogenation occured with intermediate **D** to furnish intermediate**E** .[17, 22] Next, the intermediate**E** underwent a 6π electrocylization[23] to afford intermediate **F** . Finally, the intermediate **F**eliminated one molecule of 2-aminopyridine[24] to yield the desired product **3a** .

**Scheme 2** Mechanistic studies

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**Scheme 3** A proposed mechanism

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## Conclusions

In summary, we have successfully demonstrated the [2+2+2] annulation of *N* -pyridinyl enaminones with maleimides by using Cu(II) catalyst. This strategy utilized a pyridine heterocyclerole group as the Traceless Directing Group (TDG) and demonstrated excellent functional group tolerance and mild conditions, which allowed access to synthesize pyrrolo[3,4-e]isoindoles in good yields. Meanwhile, based on the control experiments and deuterium exchange studies, a plausible reaction mechanism was also proposed. This TDG strategy would promote wide applications of enaminones in organic chemistry and further studies on the application of this strategy were in progress in our laboratory.

## Experimental

**Procedure for the synthesis of 3.** Enaminone **1** (0.15 mmol) and Maleimides **2** (0.2 mmol) were dissolved in MeCN (2.0 mL) in a 10 mL tube. Subsequently, $Cu(OAc)_2$ (0.05 mmol) and DTBP (0.1 mmol) were successively added. The tube was stirred at 80°C for 16 hours with oil bath heating under air. After cooling down to room temperature, the mixture was directly employed to reduced pressure to remove the solvent, and the resulting residue was purified by flash column chromatography to give pure product **3**by using mixed petroleum ether, ethyl acetate and triethylamine (v/v = 5:1 to 2:1) as eluent.

## Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.202400xxx.

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**Copper(II)-Catalyzed [2+2+2] Annulation of Enaminones with Maleimides by a Traceless Directing Group**

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