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ARTICLE TYPE

# Directed C-C Bond Cleavage of Cyclopropane Intermediate Generated from *N*-Tosylhydrazones and Stable Enaminones: Expedient Synthesis of Functionalized 1, 4–Ketoaldehydes †

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**An efficient method to construct functionalized 1, 4-ketoaldehydes bearing all-carbon *α*-quaternary centers *via* regioseletive C-C bond activation has been described. Through cyclopropanation of bench-stable enaminones with in situ generated diazo reagents from *N*-tosylhydrazones, followed by selective C-C bond cleavage of the cyclopropane ring affords the 1, 4-ketoaldehyde derivatives in good to excellent yields. This method works with broad substrate scope and high regioseletivity.**

Dioxygenated fragments are featured widely in many natural products and pharmaceuticals.[1] Therefore, there are important retrons in organic synthesis.[2] Although 1, 3- and 1, 5-dioxygenated compounds can be easily accessed in organic synthesis,[3] obtaining the 1, 4-dioxygenated compounds is more challenging which are common skeletons in bioactive molecules (**Fig 1**).[4] Accordingly, there have been much effort directed towards the development of new methods for the construction of 1, 4-ketoaldehyde compounds. Existing methods include the oxidation of hydroxyl aldehydes or hydroxyl ketones or 1, 4-diols[5], dearomatization of furan derivatives,[6] ozonolysis of *γ*-ketoalkenes[7], intramolecular isomerization[8] and intermolecular coupling of two different carbonyl species.[9] Other methods[10] include the use of noble-metals as catalysts for the acylation reaction, small ring opening and Tsuji-Wacker oxidation reactions. However, despite these advances, existing methods still have limitations such as using expensive catalysts, harsh reaction conditions and difficulty in preparing different carbonyl functionalities carrying an alpha-quartenary stereogenic center.

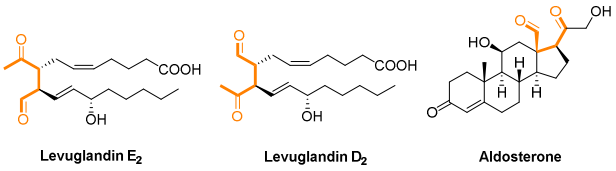
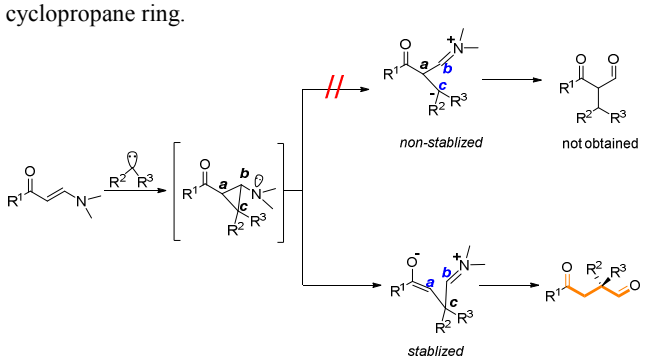



**Fig. 1** Bioactive molecules carrying 1, 4-ketoaldehydes.

In our continuing interest in this unique fragment[11] and enamine chemistry,[12] we envisage that the reaction of bench stable enaminones[13] with a carbene precursor in the presence of transition metal catalyst will lead to the formation of strain cyclopropanyl ring *via* C-C double bond activation (**Scheme 1**). The obtained strain cyclopropane ring intermediate which upon C-C bond cleavage with the assistance of the electron lone pair from the amine group will lead to the formation of 1, 4-ketoaldehydes. We believe that the carbonyl group at C-(***a***) will help to direct the selective cleavage of the C-C bond of the cyclopropane ring due to the stabilization of the anion intermediate. Herein, we report a new and efficient strategy for the synthesis of 1, 4-ketoaldehydes bearing all-carbon *α*-quaternary centers in the presence of cheap copper catalyst through regioselective C-C bond cleavage of the amino-cyclopropane ring.




**Scheme 1.** Our strategy to synthesis of 1, 4-ketoaldehydes.

*N*-Tosylhydrazones[14] are selected as the carbene sources since they can be easily prepared and the corresponding carbenes can be generated using copper catalyst. The initial exploration began

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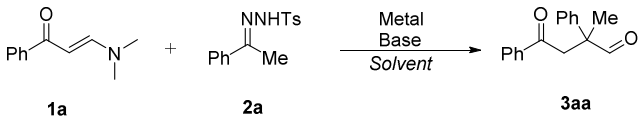
by reacting enaminone **1a** with *N*-tosylhydrazone **2a** in the presence of CuI and LiO$^t$Bu in DCE at 80 °C (**Table 1**, entry 1). To our delight, the desired 2-methyl-4-oxo-2, 4-diphenylbutanal **3aa** could be obtained albeit in low yield (11%). The structure was determined by NMR spectra and one of the products structure **3ba** was further confirmed by single crystal X-ray analysis (See **SI**). Continuing screening the reaction conditions revealed that the solvent and base had a significant influence on the reaction efficiency. For instance, using $K_2CO_3$ in toluene furnished the desired 1, 4-ketoaldehyde in 47% yield (**Table 1**, entry 3 and **SI**). Various common copper salts were examined as catalysts (See **SI**). Both Cu(I) and Cu(II) were found to promote the reactions in good efficiency (**Table 1**, entries 4-7). Among them, the more basic copper catalyst $Cu(OH)_2$ was found to afford the product in the highest yield (88% yield) (**Table 1**, entry 7). Further optimization of the reaction conditions revealed that when enaminone **1a** was reacted with *N*-tosylhydrazone **2a** using 10 mol% $Cu(OH)_2$ and 2.0 equiv. $K_2CO_3$ in toluene at 80 °C under Ar atmosphere, the desired product was obtained in 94% isolated yield (**Table 1**, entry 8).

**Table 1.** Optional reaction conditions.[a]



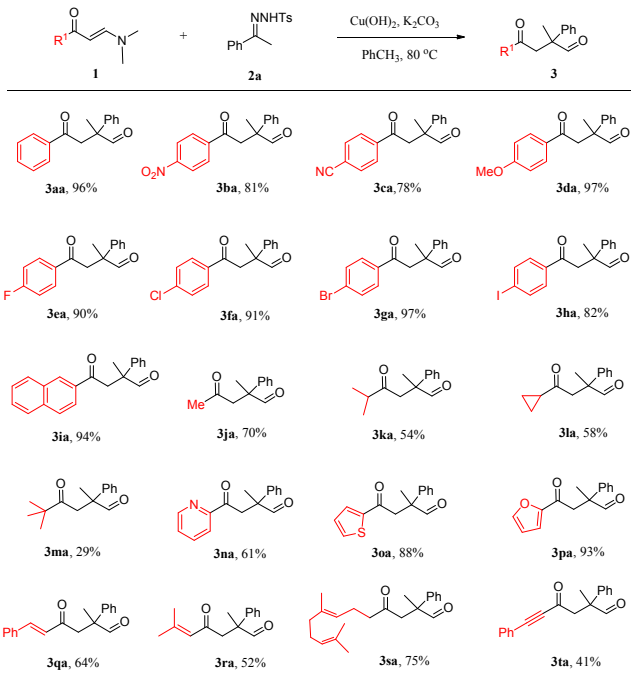

**1a** **2a** **3aa**

| entry | metal | base | solvent | Yield (%)[b] |
|---|---|---|---|---|
| 1 | CuI | LiO$^t$Bu | DCE | 11 |
| 2 | CuI | LiO$^t$Bu | $PhCH_3$ | 33 |
| 3 | CuI | $K_2CO_3$ | $PhCH_3$ | 47 |
| 4 | Cu(TC) | $K_2CO_3$ | $PhCH_3$ | 68 |
| 5 | CuOAc | $K_2CO_3$ | $PhCH_3$ | 71 |
| 6 | $Cu(OAc)_2$ | $K_2CO_3$ | $PhCH_3$ | 47 |
| 7 | $Cu(OH)_2$ | $K_2CO_3$ | $PhCH_3$ | 88 |
| 8 | $Cu(OH)_2$[c] | $K_2CO_3$ | $PhCH_3$ | 96/94[d] |

[a] Conditions: A mixture of **1a** (0.1 mmol, 1 equiv), **2a** (0.2 mmol, 2 equiv), base (0.20 mmol, 2.0 equiv), catalyst (20 mol %) and solvent (2 mL) were sealed in Schlenk tube under Ar atmosphere at 80 °C and the mixture was stirred for 24h or until the **1a** was consumed completely. [b]Yields were determined by $^1$H NMR *vs* an internal standard, [c]10 mol % catalyst-loading, [d]Yields were isolated, Cu(TC) = Copper(I) thiophene-2-carboxylate, DCE = dichloroethane.

With the optimized reaction conditions in hand, we proceeded to survey the scope of the reactions with different enaminones **1** (**Table 2**). Generally, the reactions tolerated a broad range of substituted enaminones to afford the corresponding 1, 4-ketoaldehyes in good to excellent yields. Investigation the electronic influence of the phenyl group showed that although both electron-withdrawing (**3ba** and **3ca**) and electron-donating (**3da**) groups performed well and resulted in good yields, electron-rich enaminone seems to work better (97% yield). Halogen substituents (F, Cl, Br and I) at the *para*-position of phenyl group worked well under standard conditions affording the desired products in good to excellent yields (**3ea-3ha**). It is worth to note that the chloro, bromo and iodo functionalities are useful synthetic functional groups in coupling reactions[15], and this allows possible transformations to other functional 1, 4-ketoaldehydes. Naphthyl substrate also proceeded efficiently to give the corresponding product in 94% yield (**3ia**). Obvious steric effect was observed when different aliphatic enaminones were explored. Examination of different $R^1$ revealed the efficiency of the reaction in the order of primary, secondary, followed by tertiary alkyl groups: **3ja**, 70%; **3ka**, 54%; **3la**, 58%; **3ma**, 29%. Notably, the strained-ring cyclopropanyl substitution is well tolerated in this catalytic conditions. Hetero-aromatic ring substrates were examined to test the possible competition reaction of $sp^2$ C-H bonds of enamine with hetero-aromatic rings. Gratifyingly, this reaction did not affect the hetero-aromatic ring, affording the products in good to excellent yields. The results have been achieved for electron-rich five member-rings in 88% and 93% yields (**3oa-3pa**) while electron-deficient pyridinyl group gave the product in 61% yield (**3na**). When the enaminones bearing multiple double bonds were used in the reaction, the reaction proceeded in high regioselectivity, reacting only with the enamine moiety rather than the conjugated (**3qa-3ra**) or unconjugated double bonds (**3sa**). Alkynyl substitution also remained intact under the reaction condition albeit in lower yield (**3ta**).

**Table 2.** Substrate scope for reaction of enaminones[a,b]




[a]Conditions: 0.2 mmol **1** and 0.4 mmol **2a** with 10 mol% $Cu(OH)_2$ and 2.0 eq. $K_2CO_3$ were stirred in 4 mL dry toluene under Ar protection at 80 °C. [b]Isolated yields.

Next, we turn our attention to investigate the scope of *N*-tosylhydrazones under the same reaction conditions. (Table 2). With regard to the substituent effect on the phenyl ring, various functional groups containing hydrazones were examined in this transformation. The halogen substituents on the *para*-site of phenyl ring were well tolerated and gave the desired products up to 92% yield (**3ab-3ae**). The electronic effect to this protocol was

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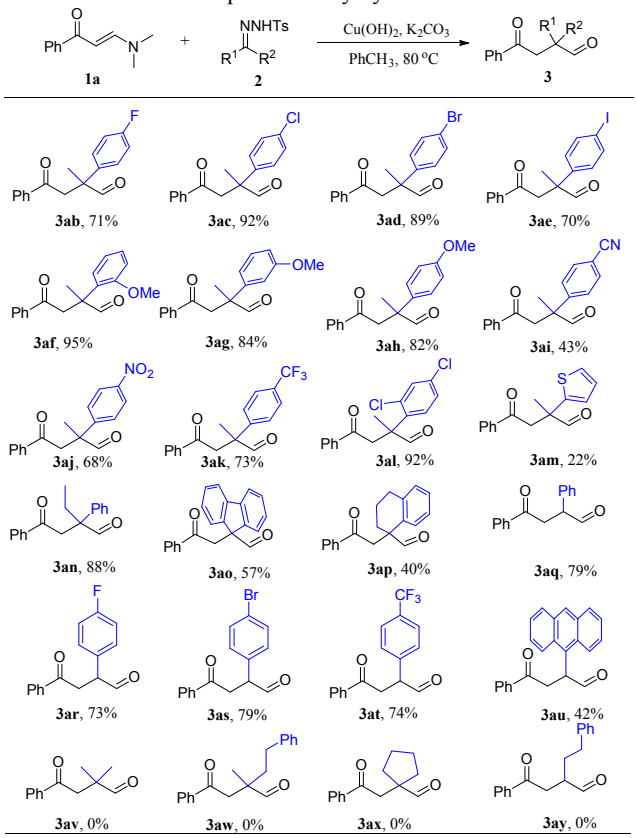
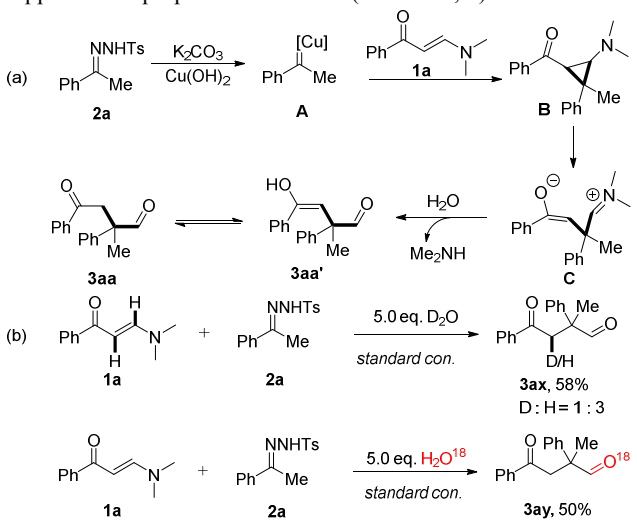
observed as the *ortho*-, *meta*- and *para*-MeO substitutions (**3ag-3ah**) gave better results to electron-withdrawing groups (**3ai-3ak**). Multiple substitutions on the phenyl ring had less influence on the reaction and gave the 2-(2, 4-dichlorophenyl)-2-methyl-4-oxo-4-phenylbutanal in 92% yield (**3al**). Heterocycles could also survived under this standard reaction condition albeit in lower yield (**3am**). In addition to simple phenyl acetone derived *N*-tosylhydrazones, other substituents such as ethyl group also proceeded well and gave the desired 1, 4-ketoaldehydes in 88% yield (**3an**). It is worth to note that cyclic ketone derived *N*-tosylhydrazones (**3ao-3ap**) could also afford the desired products in good yields, thus offering an efficient approach for the construction of natural products containing *spiro*-ring structure. Finally, aldehyde derived *N*-tosylhydrazones were also examined in the reaction condition, the results revealed that various 2-mono-substituted 1, 4-ketoaldehydes could be obtained in moderate to good yields (**3aq-3at**). Unfortunately, no desired product was obtained when aliphatic *N*-tosylhydrazones were used as the substrates (**3av-3ay**).

**Table 3.** Substrates scope for *N*-tosylhydrazones [a, b]

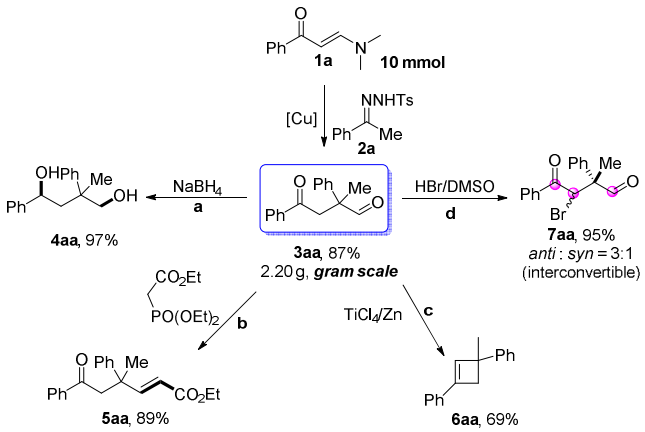



On the basis of the above results, a tentative mechanism is proposed for the reaction of enaminone with *N*-tosyl hydrazones under $Cu(OH)_2/K_2CO_3$ conditions (Scheme 2, **a**). Initially, copper carbenoid-**A** is formed from the *in situ* generated diazo precursor *N*-tosyl hydrazine **2a**. The resulting carbenoid-**A** underwent cyclopropanation reaction with enaminone **1a** to afford intermediate **B**. Due to ring strain and with the assistance of the nitrogen lone pairs, the C-C bond was regioselectively cleavaged at the ***α***-position of the carbonyl group to give ylide **C**, which subsequently underwent hydrolysis to afford the desired 1, 4-ketoaldehyde **3aa** and its enol form **3aa'**. The isotopic labeling experiments were then performed to probe the proposed mechanism. $D_2O$ exchange experiment was explored and found that the D-labeling product was detected in methylene C-H bond. Additionally, $O^{18}$ was also found in the 1, 4-keoaldehydes product when $H_2O^{18}$ was used in the catalytic system. These results supported our proposed mechanism (Scheme 2, **b**).




**Scheme 2.** Proposed reaction mechanism and isotopic labeling study.

To further demonstrate the synthetic utility of our developed protocol, the reaction was performed on 10 mmol scale of emaninone (Scheme 3). To our delight, the reaction proceeded smoothly and generated the corresponding product in 2.20 gram (87%) under the standard catalytic conditions. The 1, 4-ketoaldehydes obtained are versatile intermediates in organic synthesis. For example, the carbonyl groups could be easily reduced to 1, 4-diol **4aa** in 97% isolated yield (Scheme 3, **a**). Selectively reaction of the formyl group using ethyl 2-(diethoxyphosphoryl)acetate afforded the ethyl (*E*)-4-methyl-6-oxo-4,6-diphenylhex-2-enoate **5aa** in 89% yield (Scheme 3, **b**). An interesting cyclobutylene derivatives **6aa** could be obtained through intramolecular McMurry coupling reactions (Scheme 3, **c**).[16] Finally, it can also easily be halogenated with HBr in DMSO to afford 3-bromo-2-methyl-4-oxo-2, 4-diphenylbutanal **7aa** (Scheme 3, **d**).[17]




**Scheme 3.** Diverse transformations of 1, 4-ketoaldehydes.

In summary, a new and efficient method has been developed for the synthesis of 1, 4-ketoaldehydes bearing all-carbon *α*-quaternary centers. The special features of this method are (1) it

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works with a wide substrate scope tolerating diverse functionalities. (2) the reaction is performed using cheap copper catalyst under mild reaction conditions (3) the products are versatile and can be easily converted to a wide variety of useful synthetic building blocks. Isotopic labeling experiments supported our proposed reaction mechanism. Further studies on the catalytic and asymmetric protocol of this reaction as well as the application of this unique cascade transformations will be reported in due course.

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