

Cuprous Oxide Catalyzed Oxidative C–C Bond Cleavage for C–N Bond Formation: Synthesis of Cyclic Imides from Ketones and Amines

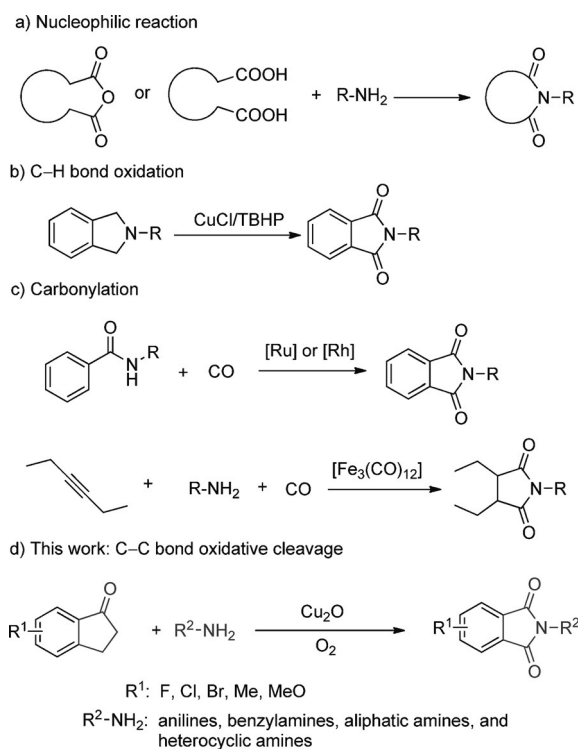
Min Wang, Jianmin Lu, Jiping Ma, Zhe Zhang, and Feng Wang*

Abstract: Selective oxidative cleavage of a C–C bond offers a straightforward method to functionalize organic skeletons. Reported herein is the oxidative C–C bond cleavage of ketone for C–N bond formation over a cuprous oxide catalyst with molecular oxygen as the oxidant. A wide range of ketones and amines are converted into cyclic imides with moderate to excellent yields. In-depth studies show that both α -C–H and β -C–H bonds adjacent to the carbonyl groups are indispensable for the C–C bond cleavage. DFT calculations indicate the reaction is initiated with the oxidation of the α -C–H bond. Amines lower the activation energy of the C–C bond cleavage, and thus promote the reaction. New insight into the C–C bond cleavage mechanism is presented.

The selective cleavage of C–C bonds offers a straightforward method for functionalizing the organic skeletons, and thus shows promising applications in organic synthesis and biomass conversion.^[1] But the nonpolar, thermodynamically stable, and kinetically inert character of C–C bonds makes it a challenge to increasing product selectivity.^[2] Nowadays chemical processes are being upgraded from traditional uncatalyzed reactions with stoichiometric oxidants, such as peroxides and metal salts,^[3] to catalyzed reactions using molecular oxygen.^[4]

Cyclic imides are widely used in biological, medicinal, and polymer chemistry.^[5] They have been synthesized by heating dicarboxylic acids or anhydrides with an amine (Scheme 1 a).^[6] In general, harsh thermal reaction conditions and activation reagents are mandatory. Recently studied oxidation of cyclic amines and carbonylation reactions have broadened the substrate scope using precious metal and carbonyl catalysts (Scheme 1 b and c).^[7]

Herein we report a new reaction for the synthesis of cyclic imides by oxidative coupling of a cyclic ketone with an amine (Scheme 1 d). To obtain good imide selectivity, each activation steps in the reaction, including C–H bond, C–C bond, and O=O bond (molecular oxygen) activation, should be kept selective over one catalyst.^[8] Very recently, we found that Cu₂O can activate oxygen and more interestingly, it enables the selective cleavage of strong C–C bonds over weak C–N bonds in tertiary amines.^[9] This ability indicates that the Cu₂O



Scheme 1. The methods for the synthesis of the cyclic imide. TBHP = *tert*-butyl hydroperoxide.

catalyst is unique for C–C bond-cleavage reactions. Inspired by this result, we discovered that Cu₂O catalyzed the C–C bond cleavage of ketones to synthesize cyclic imides. The method can be used in synthesizing various cyclic imides from anilines, benzylamines, aliphatic, and heterocyclic amines. Moreover, the combination of experiments and DFT results has revealed that the presence of both α -C–H and β -C–H bonds are essential for C–C bond cleavage, a transient carbanion intermediate is involved, and that the α -C–H bond is initially oxidized. To the best of our knowledge, this is the first report on conversion of ketones into cyclic imides.

We commenced our study with 1-indanone and aniline in the presence of a Cu₂O catalyst, which can either be obtained from a commercial source or prepared according to the literature.^[10] The solvent polarity remarkably affects the catalytic performance. Reactions in DMSO show higher activity (Table 1, entries 1–7). The catalyst was reused and gave a comparably good result (entry 7), and no reaction occurred without either oxygen or the catalyst (entries 8 and 9).

The substrate scope of the amines was then tested (Table 2). Under the optimized reaction conditions, a wide

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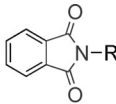
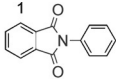
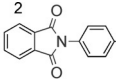
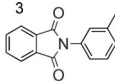
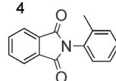
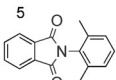
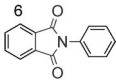
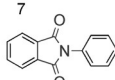
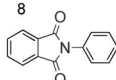
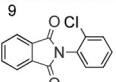
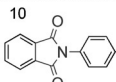
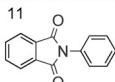
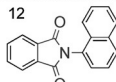
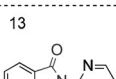
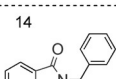
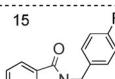
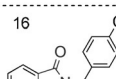
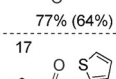
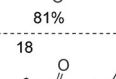
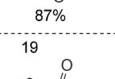
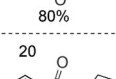
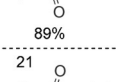
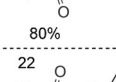
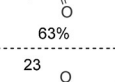
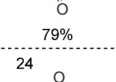
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201508071>.

Table 1: Screening of the reaction conditions.^[a]

Entry	Solvent	Imide [%]
1	octane	25
2	toluene	38
3	THF	40
4	MeCN	40
5	1,4-dioxane	48
6	methanol	57
7	DMSO	87 (89 in 2nd use)
8	DMSO, no catalyst	0
9	DMSO, in N ₂	0

[a] Reaction conditions: 0.5 mmol 1-indanone, 1 mmol aniline, 10 mg Cu₂O, 2 mL solvent, 0.6 MPa O₂, 110 °C, 6 h. The yield was determined by GC analysis using n-dodecane as the internal standard. The main byproduct is *o*-phthalic anhydride. DMSO = dimethylsulfoxide, THF = tetrahydrofuran.

Table 2: Substrate scope of amines.^[a]

 + R-NH₂ $\xrightarrow[0.6 \text{ MPa O}_2, 110 \text{ }^\circ\text{C}, 8 \text{ h, DMSO}]{\text{Cu}_2\text{O}}$ 			
1  89% (70%)	2  76% (60%)	3  79% (63%)	4  90% (64%)
5  76% (72%)	6  56%	7  89% (74%)	8  92% (74%)
9  89% (74%)	10  90% (64%)	11  84% (74%)	12  66% (36%)
13  77% (64%)	14  81%	15  87%	16  80%
17  89%	18  80%	19  63%	20  79%
21  91%	22  97%	23  81%	24  82%

[a] 0.5 mmol 1-indanone, 1 mmol amines, 10 mg Cu₂O, 0.6 MPa O₂, 2 mL DMSO, 110 °C, 8 h. The yield was determined by GC analysis using n-dodecane as the internal standard. The data within parentheses shows the yield of the isolated product.

range of amines were coupled with a ketone to form N-substituted cyclic imides with moderate to excellent yields. Electron-donating or electron-withdrawing substituents show

little effect on the reaction (entries 1–11). 1-Naphthylamine and *tert*-butylamine give moderate yield because of the steric hindrance for C–N bond formation (entries 12 and 19). Amines bearing halo, Me, OH, or MeO groups afford the corresponding imides in yields ranging from 76 to 92% (entries 2–11, 15, 16, 24). The S- and N-containing heterocyclic amines, which usually poison noble-metal centers, can also be converted into imides with yields ranging from 77 to 89% (entries 13 and 17).

The scope of the reaction with respect to ketone was then investigated (Table 3). Substituted 1-indanones, including halo, Me, and MeO substituents were all converted into the corresponding imides with yields in the 86–90% range. Apparent substituent effects are observed. Different to the oxidation reaction, such as alcohol and amine oxidation,^[11] ketones with electron-withdrawing substituents are more easily oxidized. A higher reaction temperature and longer reaction time is needed for the conversion of methoxy-substituted 1-indanones.

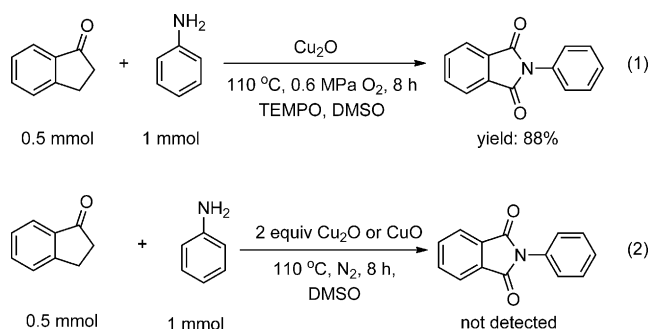
Table 3: Substrate scope of ketones.^[a]

1 86% (120 °C, 12 h)	2 84% (120 °C, 12 h)	3 86% (64%)
4 82% (54%)	5 92% (73%)	6 90% (78%)

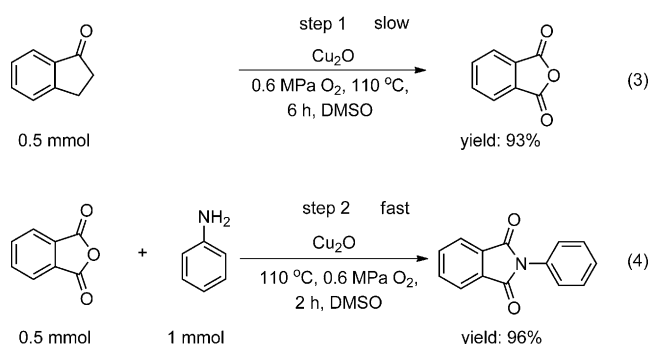
[a] 0.5 mmol 1-indanone, 1 mmol aniline, 10 mg Cu₂O, 0.6 MPa O₂, 2 mL DMSO, 110 °C, 8 h. The yield was determined by GC analysis using n-dodecane as the internal standard. The data within parentheses shows the yield of the isolated product.

We then studied the reaction mechanism. It is a nonradical process given the fact that addition of a radical inhibitor, (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO), did not hinder the reaction [Eq. (1)]. A reaction of 1-indanone and aniline with 2.0 equivalents of either Cu₂O or CuO under N₂ gives no product, thus excluding the possibility of the redox cycle of copper oxides, and therefore showing that it is also not a Mars–van-Krevelen reaction [Eq. (2)].^[12] Based on the above results and the previous study in selective oxidation,^[13] we conclude that oxygen is activated on the Cu₂O surface to form an adsorbed active species. The actual reaction may be very complex since it includes multimolecular adsorption and activation steps.

Then, to further shed light on the reaction mechanism, we monitored the reaction products. The gas products contain CO₂, which was confirmed by limewater (see Figure S1 in the Supporting Information) and also detected by mass spec-



trometry (MS; see Figure S2). *o*-Phthalic anhydride was detected (see Figure S3). We then found that the reaction of *o*-phthalic anhydride with aniline quickly generated *N*-phenylphthalimide [Eqs. (3) and (4)]. This result infers that *o*-phthalic anhydride is an intermediate en route to the imide. Now it becomes clear that there are two steps: the oxidation of 1-indanone to *o*-phthalic anhydride [Eq. (3)] and the imidization reaction of *o*-phthalic anhydride with amines [Eq. (4)]. In first step, 1-indanone is oxidized to *o*-phthalic anhydride with 93 % GC yield within 6 hours. The second step is much faster and 96 % GC yield of the imide is obtained after 2 hours. Step 2 could also occur without catalyst and oxygen. Cu₂O and oxygen show little effect on the step 2.



No reaction takes place if the ketone is lacking both two α -C-H bonds and two β -C-H bonds (Table 4, entries 2–4). By employing 1,2-indandione and 1,2,3-indantrione as reactants, phthalic anhydrides are obtained with 99 % conversion after 2 hours, which is much faster than that with 1-indanone (entries 5 and 6). Therefore, 1,2-indandione and 1,2,3-indantrione are two intermediates formed by the C-H bond oxidation of 1-indanone.

Correlating $-\ln(1-C)$ (C is the conversion of substituted 1-indanones) against reaction time (ks) indicates a linear relationship and a pseudo-first-order reaction with respect to the substituted 1-indanones. The apparent activation energy, E_a , is determined to be 78 kJ mol⁻¹ (Figure 1 a). The addition of aniline lowers activation energy ($E_a = 70$ kJ mol⁻¹) and increases the reaction rate (see Figure S4). This change may result from the fact that aniline either as basic molecule helps deprotonate the C-H bond, or as a ligand coordinates to the surface copper sites to increase reactivity.^[14] A linear relationship between $\log(k_X/k_H)$ and substituent constant σ was established for substituted 1-indanone ($X = p\text{-OCH}_3, p\text{-H}, p\text{-$

Table 4: Oxidation of the derivatives of 1-indanone.^[a]

1	2	3
conv. 93% (6 h)	no reaction	no reaction
4	5	6
no reaction	conv. 99% (2 h)	conv. 99% (2 h)

[a] 0.5 mmol substrate, 10 mg Cu₂O, 2 mL DMSO, 110 °C, 0.6 MPa O₂, 8 h. Conversions were determined by GC analysis using *n*-dodecane as the internal standard.

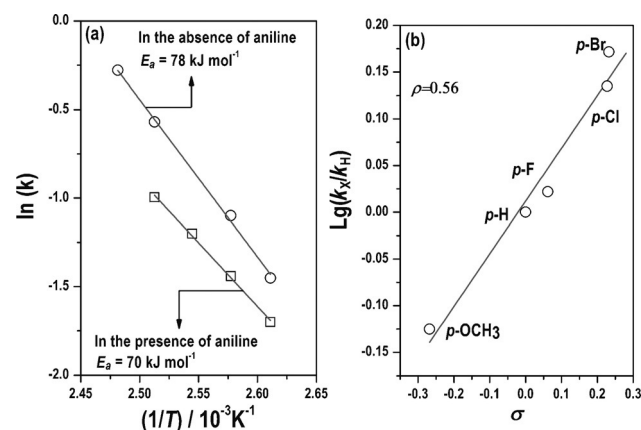


Figure 1. a) Arrhenius plot with or without the addition of aniline. b) Hammett plot of the oxidation of substituted 1-indanones.

$p\text{-Cl}, p\text{-Br}$ (Figure 1 b). The resulting Hammett parameter, ρ , is 0.56, thus suggesting the reaction is substituent-sensitive and carbanions are involved. The α -C-H and β -C-H bond are cleaved by a proton transfer on the catalyst surface. Electron-withdrawing substituents can decrease the negative charge on the carbanions and thus stabilize the intermediates. DFT calculations find that 1-indanone adsorbs on the Cu₂O-(111) surface in a horizontal manner (Figure 2), where three aryl carbon atoms bind to three adjacent copper atoms on the top sites. The oxygen atom in the carbonyl group binds to the surface on the bridge site. The adsorption is exothermic with -1.86 eV. Two possible pathways for the oxidation of 1-indanone are calculated (Figure 3; the detailed adsorption and transition state are provided in the Supporting Information). One is the oxidation of the α -C-H bond (Path A), and the other is the oxidation of the β -C-H bond (Path B). The overall the E_a value of the α -C-H oxidation is 2.91 eV, which is much lower than that of the β -C-H bond oxidation (3.56 eV). In the initial step for the C-H bond oxidation, the activation energy for deprotonating one α -H at the Cu₂O surface is only 0.44 eV, which is much lower than that of removing a β -H (1.67 eV). Furthermore, Path A is thermodynamically favored as evidenced by a more-negative reaction enthalpy (-0.75 eV vs 0.01 eV). These results indicate that the α -C-H bond oxidation is preferred and Path A is the

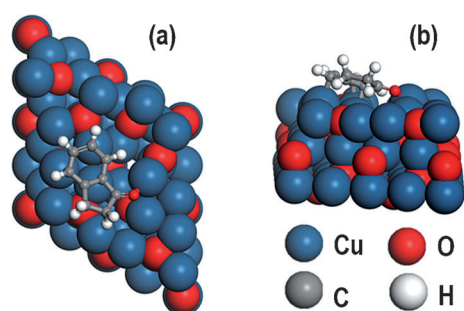
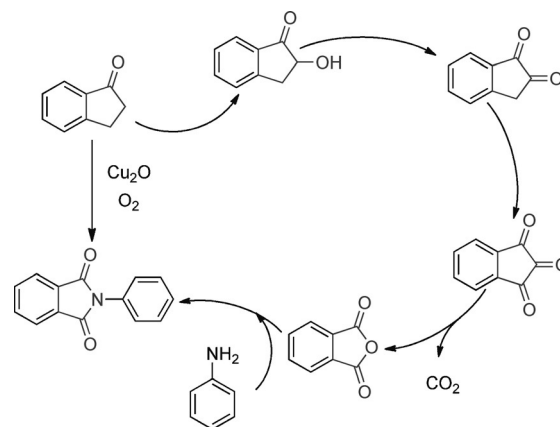


Figure 2. The adsorption of 1-indanone on $\text{Cu}_2\text{O}(111)$. a) Top view. b) Side view.

main reaction route. In addition, α -hydroxy-1-indanone is unstable and is further oxidized to 1,2-indandione with merely 0.14 eV activation energy.

Based on the above-mentioned results and the following experiments, we may come to a tentative reaction mechanism (Scheme 2). In the initial step, one of the α -C-H bonds in 1-indanone is oxidized by the activated oxygen to give α -hydroxy-1-indanone, which is further oxidized to 1,2-indandione by the oxidation of the other α -C-H bond.^[15] Then, the oxidation of the α -C-H bond adjacent to carbonyl group is repeated for 1,2-indandione with the formation of the 1,2,3-indantrione intermediate. This step shows why the β -C-H bond is indispensable. The 1,2,3-indantrione intermediate is further converted into *o*-phthalic anhydride, thus releasing CO_2 . We detected 1,2,3-indantrione by in situ IR. It first appears and then disappears as the reaction proceeds (see Figure S5). Finally, the fast reaction of *o*-phthalic anhydride with an amine forms the imide. The acceleration of the reaction by the amine may be due either to the base activation of the α -C-H bond or to adjusting the catalytic properties



Scheme 2. Possible reaction mechanism for the Cu_2O -catalyzed oxidation of ketones with amines to generate imides.

by coordination on the Cu_2O surface.^[14] It is under investigation.

In summary, we report a novel strategy for the Cu_2O -catalyzed oxidative C-C bond cleavage of a ketone for the C-N bond formation with molecular oxygen as the oxidant. A wide range of cyclic imides are synthesized from 1-indanone and amines with moderate to excellent yields. The presence of both the α -C-H and β -C-H bond is essential for C-C bond cleavage. Carbanion intermediates are involved, and the α -C-H is initially oxidized.

Acknowledgments

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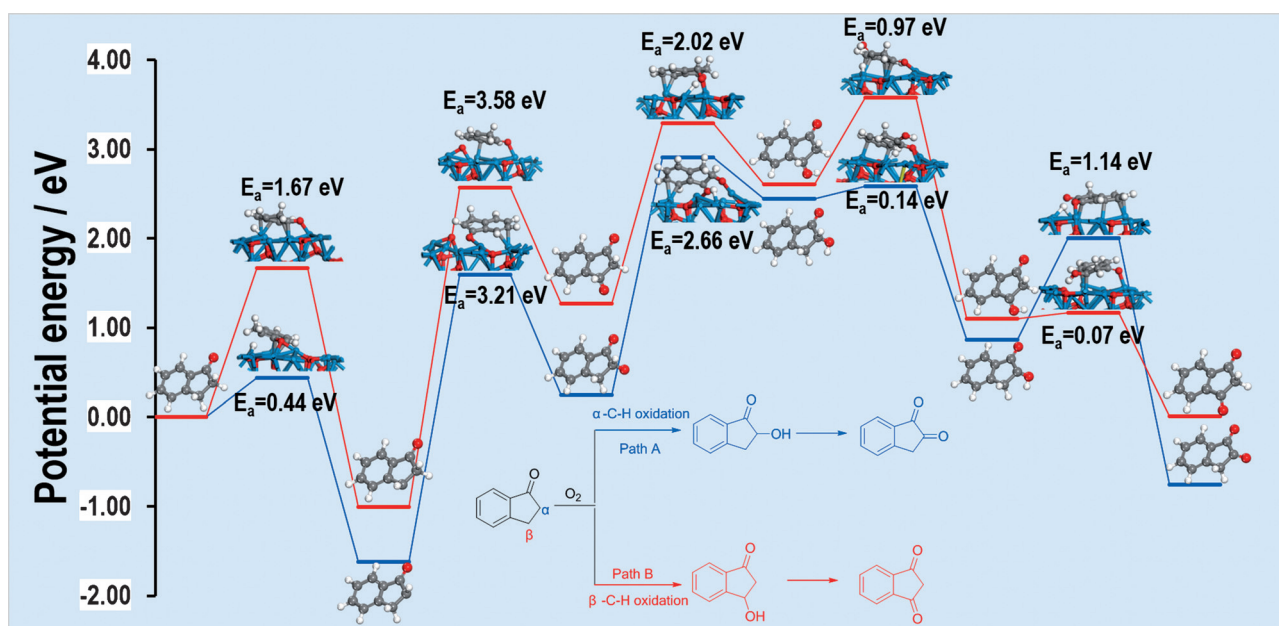


Figure 3. DFT calculation of the oxidation of the α -C-H and β -C-H bond of 1-indanone to 1,2-indandione and 1,3-indandione, respectively. Red O, blue Cu, grey C, white H.

Keywords: copper · density functional calculations · heterocycles · heterogeneous catalysis · oxidation

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