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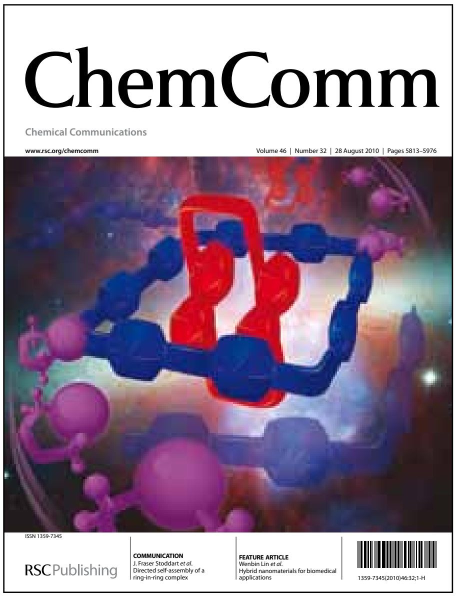

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ARTICLE TYPE

Copper-catalyzed oxidation of arene-fused cyclic amines to cyclic imides

Xiaoyu Yan[a], Kun Fang[a], Hailan Liu[a], Chanjuan Xi*[a,b]

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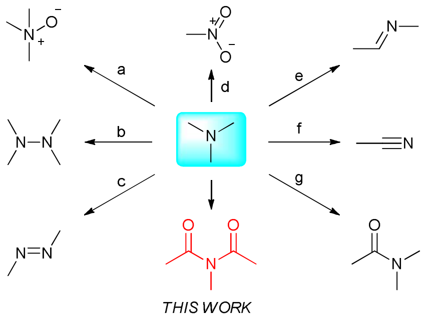
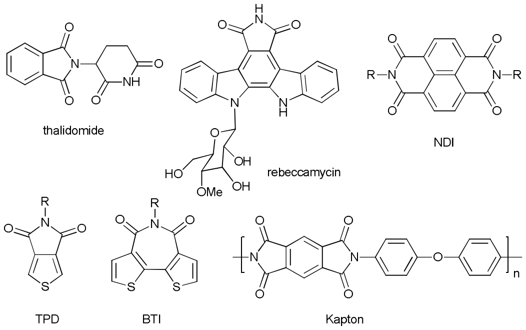
DOI: 10.1039/b000000x

A novel copper-catalyzed oxidation of arene-fused cyclic amines to the corresponding cyclic imides has been developed. The reaction can be used to synthesize 1,3-disubstituted TPD in high yields.

Oxidation reactions are one of the fundamental functional group transformation reactions in organic synthesis.[1] Catalytic oxidative transformation of ubiquitously present C–H bonds to polar functional groups (e.g., C–O, C–N bonds) and molecular skeletons is a straightforward and versatile approach to constructing complex molecules.[2,3] Amines are desirable starting materials to prepare other chemicals because they are abundant and inexpensive chemicals. Oxidation of amines can afford a large number of organic compounds.[4,5] For examples, oxidation can occur on nitrogen atom to afford amine oxides,[4c-4d] hydrazines,[4e-4g] azo compounds,[4f-4m] and nitro compounds (Scheme 1, a-d).[4n-4p] The oxidation can also occur on vicinal carbon atom to afford imines,[5a-5g] nitriles,[5h-5l] and amides (Scheme 1, e-g).[5m-5p] However, to the best of our knowledge, there is no efficient method for direct oxidation of amines to imides.[6]



Scheme 1 Amine oxidation reaction



Scheme 2 Examples of arene-fused cyclic imides

The imide functional group, which consists of two acyl groups bound to nitrogen, is a key component in various chemical reactions and plays a huge role in modern organic synthesis. Among them, arene-fused cyclic imides play vital role in pharmaceuticals,[7a] fungicides,[7b] polymers,[7c] organic semiconductors, and organic photovoltaics.[7d-7f] Some selections are shown in Scheme 2.

Owing to the widespread occurrence of this structural motif, efficient means for the chemical synthesis of imides is of continuing interest. Traditionally, the syntheses of imides have relied primarily on the heating dicarboxylic acids (or anhydrides) with an amine, and acylation of an amide.[8] Recently, a straightforward synthesis of imides is *via* the oxidation of amides.[9] However, in contrast to the plethora of methods available for the oxidation of amines,[4,5] procedures for the oxidation of amines to imides were, until recently, rather limited.[6] Herein, we describe a copper-catalyzed direct oxidation of arene-fused cyclic amines to afford arene-fused cyclic imides. To the best of our knowledge, this is the first example of metal-catalyzed oxidation of cyclic amines to imides under mild conditions.

Initially, we used *N*-butylisoindoline[10] **1a** as the starting material to study the oxidation reaction. In the preliminary experiment, the oxidation reaction of *N*-butylisoindoline was examined in acetonitrile at 50 °C in the presence of 10 mol % CuCl and 10 equivlants of TBHP (*tert*-butyl hydroperoxide). Phthalimide **2a** was formed in 54% yield (Table 1, entry 1). We then examined the effect of different solvents, such as dimethylformamide (DMF), dioxane, toluene, 1,2-dichloroethane (DCE), and dichloromethane (entries 2-6), and we found the yield increased to 82% in dichloromethane (entry 6). Temperature screening experiments (entries 6-8) revealed that the best reaction temperature is at 50 °C (entry 6). When 5 equivalents of TBHP were used, the yield of **2a** decreased to 54% (entry 9). Furthermore, the effect of other copper salts was also examined. Cu(OAc)$_2$, CuCl$_2$, CuBr, and CuI as catalyst gave product **2a** in 77%, 74%, 66%, and 25% yields, respectively (entries 10-13). We also checked FeCl$_3$ as catalyst and **2a** was obtained in 48% yield (entry 14).

On the basis of these results, the optimal condition involved the following parameters: CuCl as catalyst, TBHP (10 eq) as oxidant, dichloromethane as solvent, and reaction temperature at 50 °C. Under the optimized condition, a study on the substrate scope was carried out, and the results are summarized in Table 2. A series of *N*-substituted isoindolines were oxidized to phthalimides in morderate to high yields (Table 2, entries 1-10).

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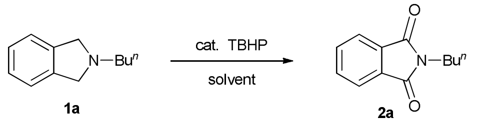
N-Alkyl isoindolines **1a-1c** were converted to phthalimide **2a-2c** in 68-73% isolated yield (entries 1-3). *N*-Allyl-, *N*-benzyl- and *N*-methyloxycarbonylmethylisoindolines **1d-1f** were converted to phthalimide **2d-2f** in 40-48% isolated yield (entries 4-6). It is noteworthy that oxidation of *N*-benzylisoindoline **1e**, which has two different types of benzyl, afforded cyclic imide **2e**. No formation of *N*-benzoylisoindolin-1-one was observed. *N*-Aryl isoindolines **1g-1j** were converted to phthalimide **2g-2j** in 30-47% isolated yield (entries 7-10). 5-Chloroisoindoline **1k** afforded the corresponding phthalimide **2k** in 48% yield (entry 11). Besides isoindolines, naphthalene-fused piperidine **1l** can also proceeded, and the corresponding imide **2l** was isolated in 75% yield (entry 12). In the case of *N*-allyl-, benzyl- , aryl, and methyloxycarbonylmethyl substituted isoindolines, ring-open and degradative byproducts were detected by GC-MS.

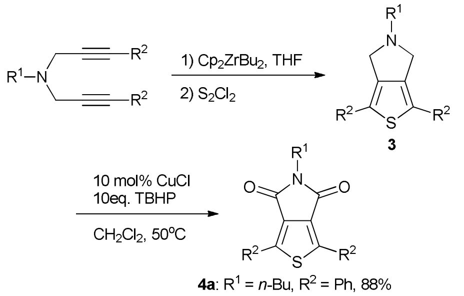
Table 1 Optimization of reaction[a]



1a **2a**

entry	catalyst	solvent	temperature	yield[b]
1	CuCl	CH_3CN	50	54
2	CuCl	DMF	50	39
3	CuCl	dioxane	50	74
4	CuCl	toluene	50	46
5	CuCl	DCE	50	64
6	CuCl	CH_2Cl_2	50	82(68)
7	CuCl	CH_2Cl_2	30	78
8	CuCl	CH_2Cl_2	70	66
9[c]	CuCl	CH_2Cl_2	50	54
10	$Cu(OAc)_2$	CH_2Cl_2	50	77
11	$CuCl_2$	CH_2Cl_2	50	74
12	CuBr	CH_2Cl_2	50	66
13	CuI	CH_2Cl_2	50	25
14	$FeCl_3$	CH_2Cl_2	50	48

[a] *Reaction condition*: isoindoline 0.4 mmol, catalyst 10 mol%, solvent 1 mL, TBHP (70% in water) 4 mmol, sealed tube, 24 h. [b] GC yield, isolated yield are given in parentheses. [c] 2 mmol TBHP was used.



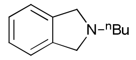
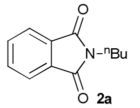
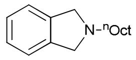
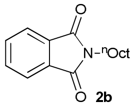
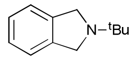
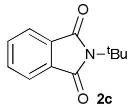
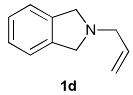
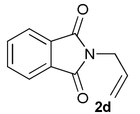
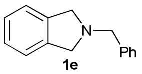
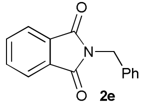
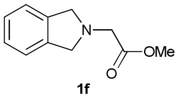
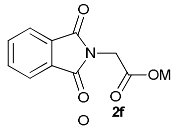
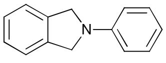
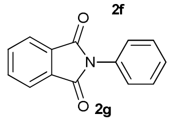
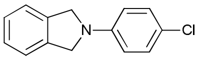
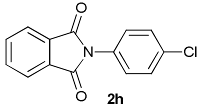
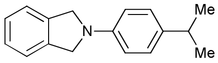
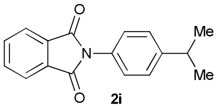
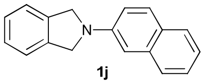
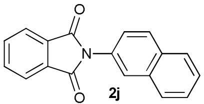
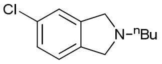
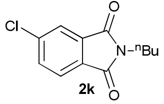
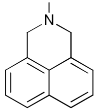
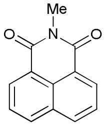
3

4a: R^1 = *n*-Bu, R^2 = Ph, 88%
4b: R^1 = *n*-Oct, R^2 = 2-Thienyl, 55%

Scheme 3 Copper catalyzed amine oxidation to afford TPD

Thieno[3,4-*c*]pyrrole-4,6-dione (TPD) unit, which has an imide group fused with thiophene ring, has become an important building block in organic solar cells and organic field-effect transistors.[11] The most common pathway toward TPD unit involves condensation of an amine with thiophene anhydride,[7f] which possesses two drawbacks: (i) 3,4-thiophenedicarboxylic acid is a relatively expensive starting material, (ii) the reaction needs more steps especially for preparation of 1,3-disubstituted TPD. In our reaction, 5,6-dihydrothieno[3,4-*c*]pyrroles **3**, which are easily prepared by zirconocene-mediated cyclization of bispropargylamines,[12] were conveniently converted into 1,3-disubstituted TPD (Scheme 3). The yields are moderate to high depending on the substituent of TPD. The structure of **4a** was also confirmed by XRD analysis.[‡]

Table 2 Scope of copper-catalyzed amine oxidation[a]

entry	amine	product	yield (%)[b]
1	 **1a**	 **2a**	68 (58)[c]
2	 **1b**	 **2b**	73
3	 **1c**	 **2c**	71
4	 **1d**	 **2d**	45
5	 **1e**	 **2e**	48 (42)[d]
6	 **1f**	 **2f**	40
7	 **1g**	 **2g**	42 (37)[d]
8	 **1h**	 **2h**	47
9	 **1i**	 **2i**	30
10	 **1j**	 **2j**	57
11	 **1k**	 **2k**	48
12	 **1l**	 **2l**	75

[a] *Reaction condition*: amine 0.4 mmol, catalyst 10 mol%, solvent 1 mL, TBHP (70% in water) 4 mmol, sealed tube, 24 h. [b] isolated yield. [c] 5 mmol scale. [d] 10 mmol scale.

We also investigated the oxidation reaction of acyclic amine under the standard condition. When amine **5** was used as substrate, only amide **6** was obtained in 74% isolated yield without observation of the desire imide (Scheme 4).[13] Although we must await for further investigations to elucidate the reaction

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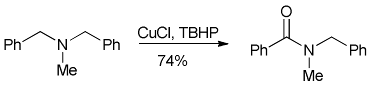
mechanism, one possible reaction was proposed (see supporting information).



5 **6**

Scheme 4 Copper-catalyzed oxidation of acyclic amine

In conclusion, we have developed an efficient methodology for the synthesis of arene-fused cyclic imides *via* copper-catalyzed oxidation of cyclic amine. The reaction proceeded with high selectivity. This reaction can be used to synthesize 1,3-disubstituted TPD in high yields. Further investigations are still in progress in this area.

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Notes and references

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[b] *State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China*

†Electronic Supplementary Information (ESI) available: Experimental procedures, full characterization including ^{1}H NMR and ^{13}C NMR data and spectra for all compounds. X-ray structure of **4a**. See DOI: 10.1039/b000000x/

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