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Synthesis of 3-Unsubstituted Phthalides from Aryl Amides and Paraformaldehyde via Ruthenium(II)-Catalyzed C-H Activation

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Abstract: A straightforward and convenient route has been developed for the synthesis of 3-unsubstituted phthalide derivatives from aryl amides and paraformaldehyde by ruthenium(II)-catalyzed C-H activation. The reaction proceeds through tandem *ortho*-hydroxymethylation of aryl amide and subsequent intramolecular lactonization.

Phthalide features a 3*H*-isobenzofuran-1-one skeleton, which widely exists in natural products such as Taiwanin C,[1] phomoarcherins[2] and djalonensin[3] (Figure 1). They are biologically active and found useful to treat diseases such as circulatory and heart diseases.[4] Moreover, they are versatile synthetic intermediates in organic synthesis.[4] According to their structural characteristics, phthalides can be divided into three classes: 3-unsubstituted, 3-substituted and dimeric ones.[4] Owing to their high importance, many synthetic methods have been developed.[4]

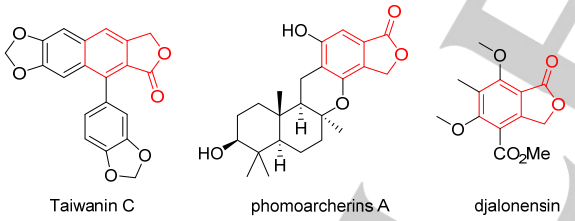
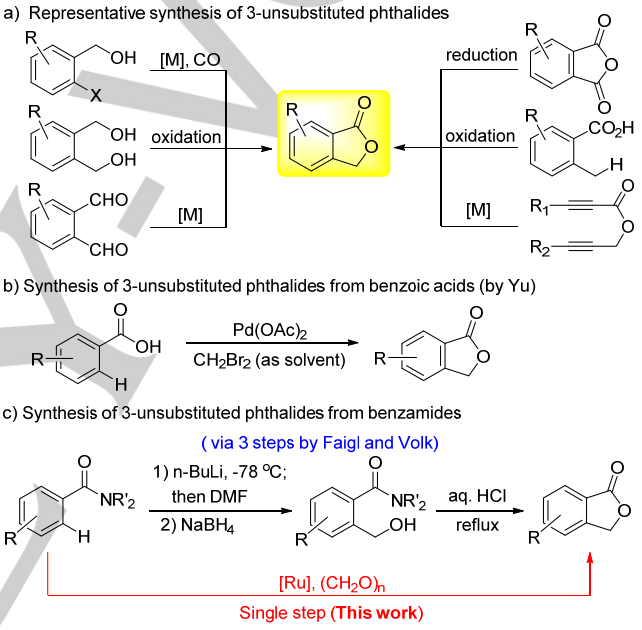


Figure 1. Representative Natural Products and Drug Candidates with an 3-Unsubstituted Phthalide Skeleton.

Specifically, as the synthesis of 3-unsubstituted phthalides is regarded, the representative synthetic methods include cyclocarbonylation of *ortho*-halobenzyl alcohol,[5] oxidation of phthalyl alcohol,[6] Cannizzaro-type lactonization of dialdehyde,[7] reduction of phthalic anhydride,[8] oxidative annulation of *ortho*-methyl benzoic acid,[9] [2+2+2] cycloaddition of 1,6-diyne,[10] and so on (Scheme 1a). Normally, in these reactions, advanced functionalized substrates are demanded. Remarkably, Yu and co-workers reported a facile route to synthesize 3-unsubstituted phthalides with readily available aromatic carboxylic acid by $Pd(OAc)_2$ catalyzed C-H activation, in which dibromomethane was used as both reagent and solvent (Scheme 1b).[11] Herein, we present a another facile way to synthesize 3-unsubstituted phthalides with aryl amides and paraformaldehyde via C-H activation promoted by a readily available ruthenium[12] catalyst.



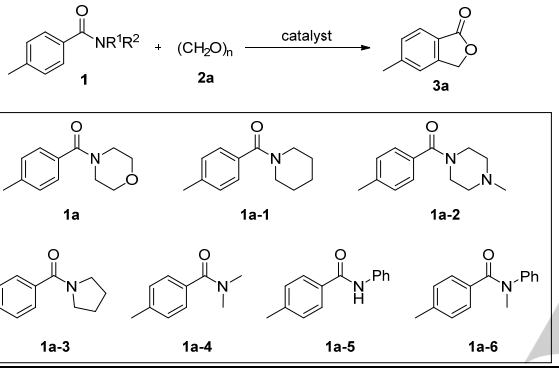
Scheme 1. Synthesis of 3-Unsubstituted Phthalides

Our study was intrigued by a previously reported procedure for the synthesis of 3-unsubstituted phthalides from benzamides by Faigl, Volk and coworkers,[13] involving *ortho*-lithiation, formylation, reduction and lactonization processes (Scheme 1c). Encouraged by the advances in the *ortho*-hydroxymethylation with paraformaldehyde via transition metal catalyzed C-H activation (e.g., ruthenium catalysis by Zhou,[14] Ding,[15] Wu,[16] and Kim[17] with pyridyl or pyrimidinyl as the directing group, rhodium catalysis by Kim[18] with azobenzene as substrate, manganese catalysis by Glorius[19] with pyridyl or pyrimidinyl as the directing group, cobalt-catalyzed hydroxymethylarylation of terpenes with formaldehyde and arenes by Chen[20]) and recent progress in the synthesis of 3-substituted phthalides from benzamides and aldehydes by rhenium-[21] and rhodium-catalysis[22], we proposed that it might be possible to prepare 3-unsubstituted phthalides in a single step by a sequential transition-metal-catalyzed *ortho*-hydroxymethylation and intramolecular lactonization strategy.

Initial studies indicated that (*p*-cymene)Ru^{II} could catalyzed the C-H activation reaction of N-morpholinyl benzamide **1a** and

paraformaldehyde to give the phthalide **3a** (Table 1, entry 1). In contrast, $Pd(OAc)_2$, $[Cp^*IrCl_2]_2$ and $[Cp^*RhCl_2]_2$ proved catalytically inactive (entries 2-4). Other ruthenium catalysts such as $RuCl_3•H_2O$ and $Ru_3(CO)_{12}$ were also tested. But no reactions were observed (entries 5-6). Besides N-morpholinyl benzamide **1a**, some other amide substrates were studied. However, none of them gave better outcomes (entries 7-12). Interestingly, when the structurally similar N-piperidinyl amide **1a-1** was used as the substrate, no product was obtained. As the oxygen atom of the morpholinyl ring has a negligible effect on amidic resonance,[23] the high reactivity may be attributed to the enhanced electrophilicity of the C=O bond, which should be beneficial to the lactonization step. Moreover, compared with other amine anions, morpholine anion is a better leaving group owing to the negative inductive effect of oxygen.

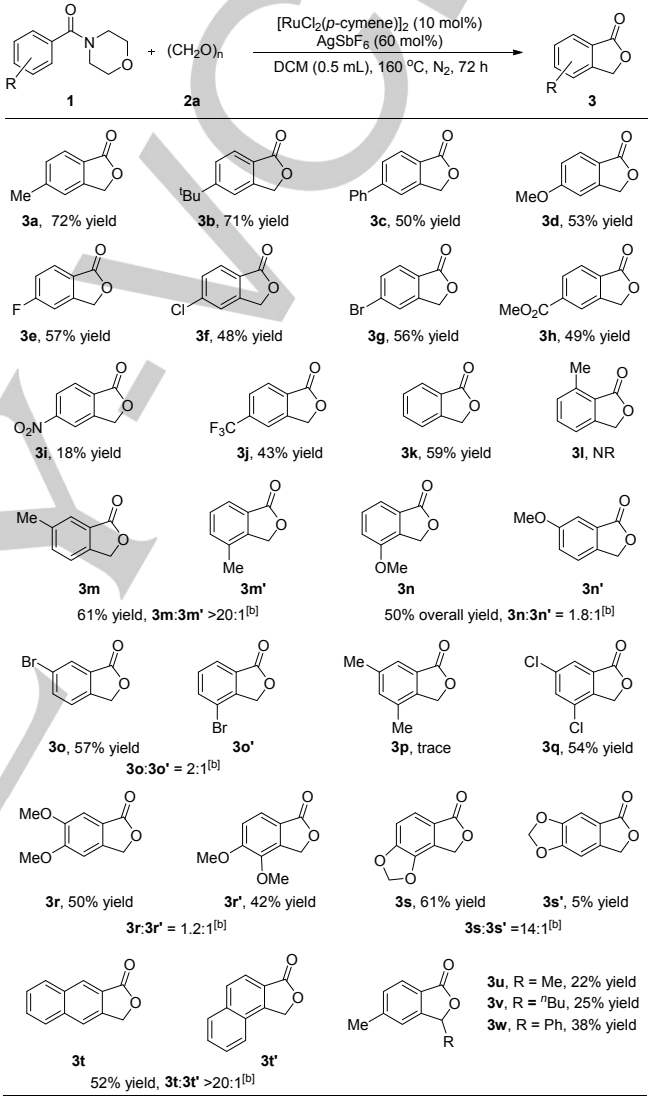
Table 1. Optimization of Reaction Conditions



entry[a]	1	2a (mmol)	catalyst (mol%)	$AgSbF_6$ (mol%)	T (°C)	yield (%)[b]
1	**1a**	0.6	$[RuCl_2(p\text{-cymene})]_2$ (5)	20	100	12
2	**1a**	0.6	$Pd(OAc)_2$ (5)	0	100	nr
3	**1a**	0.6	$[Cp^*IrCl_2]_2$ (5)	20	100	nr
4	**1a**	0.6	$[Cp^*RhCl_2]_2$ (5)	20	100	nr
5	**1a**	0.6	$RuCl_3•H_2O$ (5)	20	100	nr
6	**1a**	0.6	$Ru_3(CO)_{12}$ (5)	20	100	nr
7	**1a-1**	0.6	$[RuCl_2(p\text{-cymene})]_2$ (5)	20	100	nr
8	**1a-2**	0.6	$[RuCl_2(p\text{-cymene})]_2$ (5)	20	100	trace
9	**1a-3**	0.6	$[RuCl_2(p\text{-cymene})]_2$ (5)	20	100	6
10	**1a-4**	0.6	$[RuCl_2(p\text{-cymene})]_2$ (5)	20	100	5
11	**1a-5**	0.6	$[RuCl_2(p\text{-cymene})]_2$ (5)	20	100	nr
12	**1a-6**	0.6	$[RuCl_2(p\text{-cymene})]_2$ (5)	20	100	nr
13[c]	**1a**	1.0	$[RuCl_2(p\text{-cymene})]_2$ (5)	60	140	38
14[c,d]	**1a**	1.0	$[RuCl_2(p\text{-cymene})]_2$ (5)	60	140	51
15[c,d]	**1a**	1.0	$[RuCl_2(p\text{-cymene})]_2$ (10)	60	140	56
16[c,d]	**1a**	1.0	$[RuCl_2(p\text{-cymene})]_2$ (10)	60	160	59
17[c,d]	**1a**	2.0	$[RuCl_2(p\text{-cymene})]_2$ (10)	60	160	72

[a] Reaction conditions: Under N_2, **1** (0.2 mmol), **2a**, catalyst (5 mol%), $AgSbF_6$, DCM (1 mL), for 24 h. [b] For entries 1-12, yields were measured by ^1H NMR spectra; For entries 13-17, isolated yields were reported. [c] DCM (0.5 mL). [d] For 72 h.

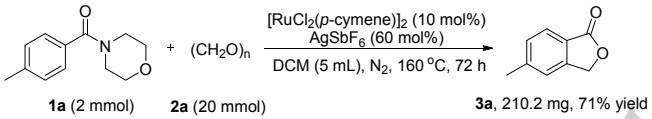
Preliminary optimization of reaction conditions indicated that the product **3a** could be obtained in 38% yield when the reaction was conducted with 1.0 mmol paraformaldehyde in 0.5 mL DCM at 140 °C (entry 13). When the reaction time was extended to 72 h, the yield increased to 51% (entry 14). Increasing the catalyst loading to 10 mol% and elevating the reaction temperature to 160 °C led to a better yield of 59% (entries 15-16). It was observed that paraformaldehyde underwent sublimation severely at 160 °C. Therefore, 2 mmol of paraformaldehyde was used. Gladly, the product could be obtained in 72% yield (entry 17). Detailed optimizations of reaction conditions were given in the Supporting Information.



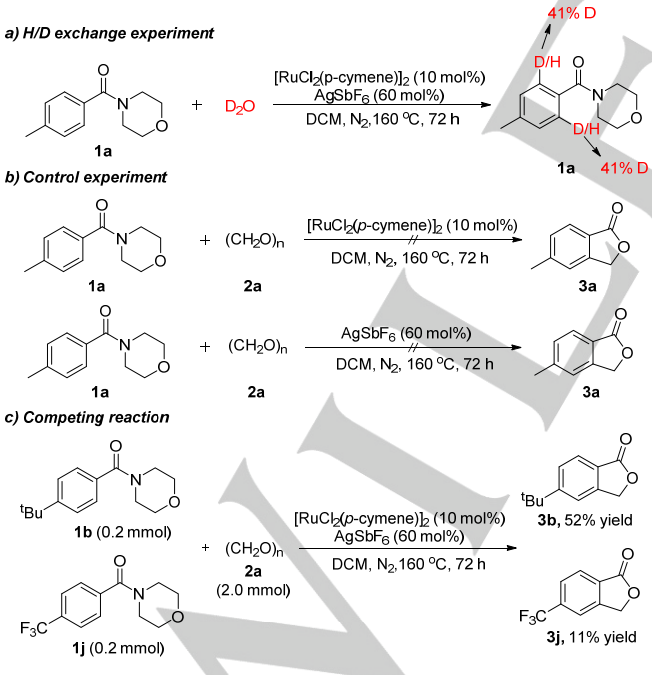
Scheme 2. Substrate Scope. [a] Amide **1** (0.2 mmol), **2a** (2.0 mmol, 60 mg), $[RuCl_2(p\text{-cymene})]_2$ (10 mol%), $AgSbF_6$ (60 mol%), DCM (0.5 mL), 160 °C, 72 h. Isolated yields were reported. [b] Determined by ^1H NMR analysis of the crude reaction mixture.

With the optimized reaction conditions in hand, the substrate scope of aryl amides were investigated (Scheme 2). As demonstrated by various *para*-substituted amides, substituents with differed electronic properties are well tolerated (**3a**-**k**), affording various phthalides in moderate to good yields. The *ortho*-substituted amide was found to be unreactive, which might be due to the steric effect. Then some *meta*-substituted amides were examined. Notably, high regioselectivity (>20:1) was

observed for 3-methylbenzamide. In contrast, inferior regioselectivities were obtained when the less sterically bulkier substrates were employed such as 3-methoxy and 3-bromo benzamides. Then some disubstituted benzamides were investigated. While 3,5-dimethyl benzamide could hardly react probably due to the steric reasons, the 3,5-dichloro benzamide could be transformed to the desired product in 54% yield. 3,4-Dimethoxy benzamide could be used as substrate, but the regioselectivity was poor (**3r**:**3r' =** 1.2:1). In contrast, the piperonylic acid derived amide showed a high regioselectivity (**3s**:**3s' =** 14:1), which might be attributed to electronic reasons. Finally, 2-naphthamide was also applicable, affording the product in moderate yield and high regioselectivity (**3t**:**3t'** > 20:1). Interestingly, when acetaldehyde and pentanal were subjected to the reaction conditions, the desired products could also be obtained, albeit in low yields (**3u** and **3v**). We also tested a representative aromatic aldehyde, namely benzaldehyde, affording the product **3w** in 38% yield. Aromatic heterocyclic aldehydes such as furan-2-carbaldehyde and picolinaldehyde had been investigated as well, but no reactions were detected. To prove the practical utility of this methodology, the reaction of **1a** with paraformaldehyde was performed on a large scale (2 mmol). The product **3a** was isolated in 71% yield (Scheme 3).



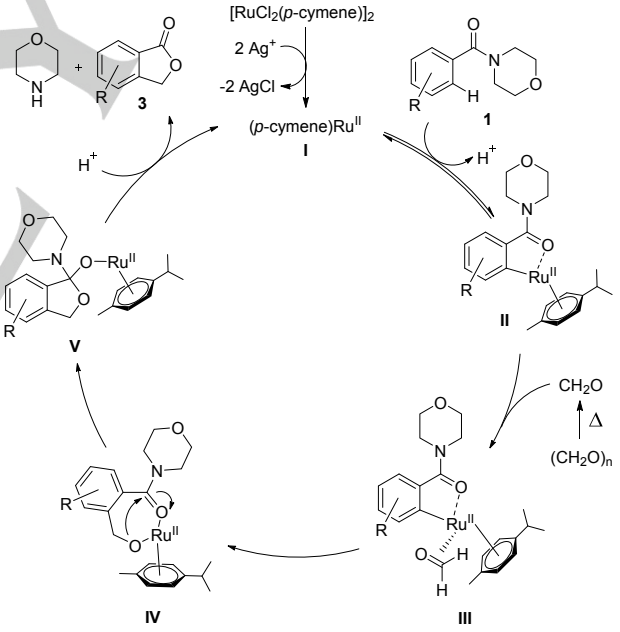
Scheme 3. A 2 mmol Scale Reaction



Scheme 4. Mechanistic Studies

To shed some light on the reaction mechanism, several control experiments were performed. First, a H/D exchange experiment was carried out (Scheme 4a). As expected, 41% deuterium incorporation at the *ortho*-position was observed, implying that the C−H activation step is reversible. Second, it was confirmed that no phthalide product was detected in the absence of either $AgSbF_6$ or $[RuCl_2(p\text{-cymene})]_2$ (Scheme 4b), indicating dechlorination of $[RuCl_2(p\text{-cymene})]_2$ is essential to give the catalytically active species. Third, a competing experiment was conducted with two amide substrates bearing an electron-donating and an electron-withdrawing group, respectively (Scheme 4c). It was found that the yield of phthalide **3b** was much higher than that of phthalide **3j**, suggesting the electronically enriched aromatic ring possesses higher reactivity towards this reaction.

According to above observations and previous reported studies,[14-19] a plausible catalytic cycle is proposed (Scheme 5). First, $[RuCl_2(p\text{-cymene})]_2$ is converted by $AgSbF_6$ to the catalytically active ruthenium species **I**, which reacts with the amide **1** to generate a five-membered ruthenium intermediate **II** through chelate directed C-H activation. Second, coordination with the formaldehyde forms the intermediate **III,** which further transforms to the intermediate **IV** through migratory insertion of carbonyl group into the Ru-C bond. Finally, intramolecular nucleophilic attack of the amide by the alkoxide gives the intermediate **V**, which collapses to give the desired product **3** together with morpholine as the only side product. Meanwhile, the catalyst is regenerated. During this course, the excess of $AgSbF_6$ may assist the morpholine leaving by coordination to its oxygen atom.



Scheme 5. Proposed Mechanism

In summary, we describe a straightforward and convenient synthesis of 3-unsubstituted phthalide derivatives by a ruthenium(II)-catalyzed C-H activation. The reactants involve aryl amides and paraformaldehyde which are cheap and easily available. The reaction proceeds via *ortho*-hydroxymethylation of aryl amide and subsequent intramolecular lactonization.

Acknowledgements

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Keywords: Ruthenium(II)-Catalyzed • C-H Activation • Aryl Amides • Paraformaldehyde

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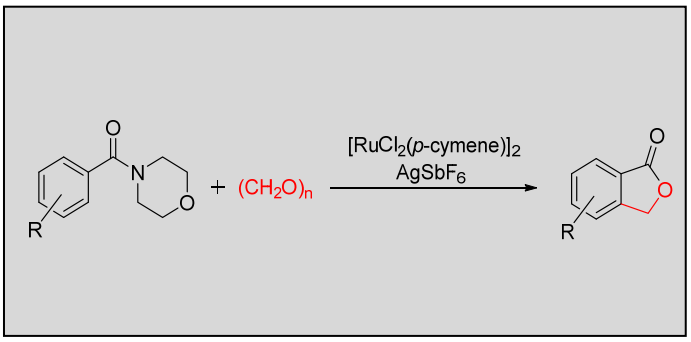

C-H Activation

A straightforward and convenient route has been developed for the synthesis of 3-unsubstituted phthalide derivatives from aryl amides and paraformaldehyde by ruthenium(II)-catalyzed C-H activation. The reaction proceeds through tandem *ortho*-hydroxymethylation of aryl amide and subsequent intramolecular lactonization.