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Rhenium-Catalyzed Phthalide Synthesis from Benzamides and Aldehydes via C−H Bond Activation

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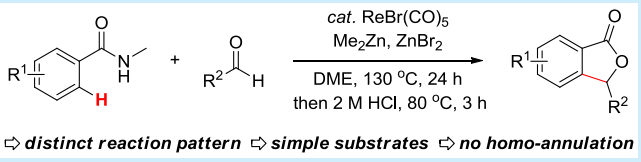
Supporting Information

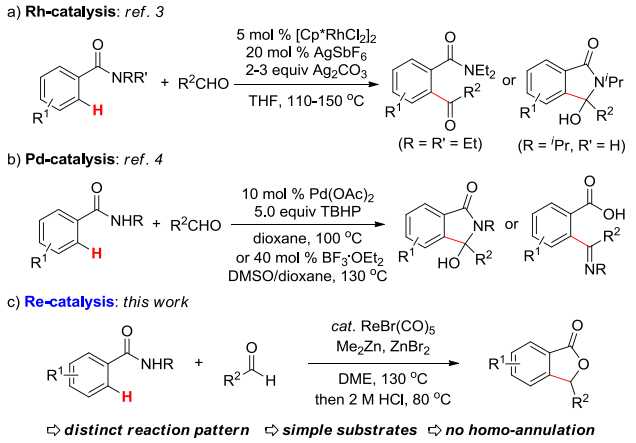
ABSTRACT: The [4 + 1] annulation of benzamides and aldehydes for phthalide synthesis was achieved via rhenium-catalyzed C−H activation, which demonstrates an unprecedented reaction pattern distinct from those of other transition-metal catalyses. The reaction also features readily available starting materials, a wide scope for both electro-rich and electro-deficient substrates, and the elimination of homo-annulation byproducts.



In the past few decades, the strategic use of C−H bond activation for new chemical bond formation and the expedient buildup of molecular complexity from hydrocarbon feedstock has attracted tremendous attention.[1] In comparison with the widely studied C−H activation reactions with alkynes and alkenes, the direct C−H addition to polar unsaturated C−X (X = heteroatom) bonds, such as the C═O bond of aldehydes, has met limited success until recently.[2] Although benzamides are easily available and commonly used substrates for *ortho*-C−H bond transformations, only a few C−H activation reactions between benzamides and aldehydes have been reported so far.[3,4] Kim et al. described a Rh-catalyzed oxidative *ortho*-C−H acylation of tertiary benzamides with aldehydes (Scheme 1a).[3a] Shortly afterward, the same group developed a tandem Rh-catalyzed *ortho*-C−H acylation/intramolecular cyclization reaction of secondary benzamides and aldehydes to access 3-hydroxyisoindolin-1-ones under slightly modified conditions.[3b] Later on, Huang and Zhao et al. provided an alternative approach to 3-hydroxyisoindolin-1-ones from benzamides and aldehydes by using a Pd-based catalytic system (Scheme 1b).[4a] With the aid of a Lewis acid and modified conditions, they further demonstrated the efficient synthesis of biaryl imino-carboxylic acids through the ring-opening process of 3-hydroxyisoindolin-1-one intermediates.[4b]

Recently, we have reported a Re/Mg-cocatalyzed [4 + 2] annulation of benzamides and alkynes to furnish varied 3,4-dihydroisoquinolinones.[5a] With our continuous interest in Re-catalysis,[5,6] we herein disclose a Re-catalyzed [4 + 1] annulation of benzamides and aldehydes to afford phthalide derivatives (Scheme 1c), which showcases a distinct reaction pattern of benzamides and aldehydes from those previously achieved by using Rh and Pd catalysis.[3,4] This Re-catalyzed reaction is compatible with a wide range of electronically and sterically varied benzamides and aldehydes, thus providing a complementary protocol to previous methods.[7,8]

Scheme 1. Transition-Metal-Catalyzed C−H Bond Activation Reactions of Benzamides with Aldehydes



At the outset, we selected benzamide **1a** and *p*-methylbenzaldehyde **2b** as model substrates to optimize the reaction conditions.[9] After an extensive survey of various

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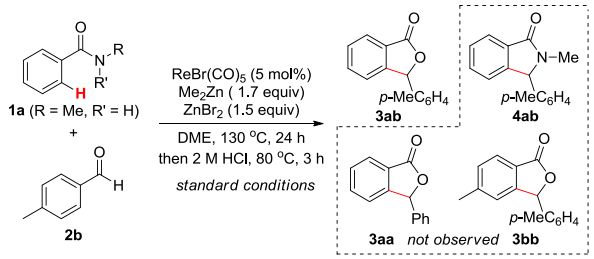
reaction parameters, phthalide **3ab** was obtained in 79% ^{1}H NMR yield and 71% isolated yield under the catalysis of $ReBr(CO)_5$ with the aid of Me_2Zn and $ZnBr_2$ (Table 1, entry

Table 1. Screening of Reaction Parameters[a]



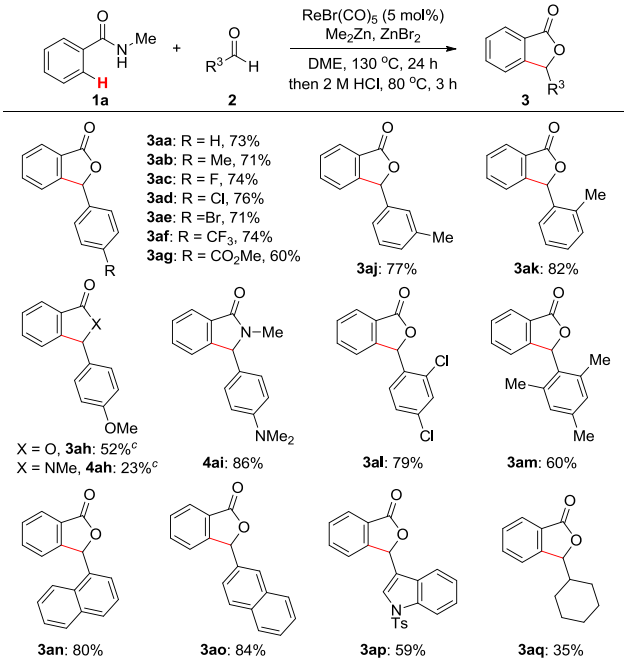
entry	variations of standard conditions	yield of **3ab** (%)[b]
1	none	79 (71)[c]
2	THF instead of DME	60
3	1,4-dioxane instead of DME	32
4	MeCN, *t*-BuOMe, PhOMe, $(i\text{-Pr})_2O$, DMSO, *c*-hexane, DCE instead of DME	0
5	without $ReBr(CO)_5$	0
6	$Re_2(CO)_{10}$ instead of $ReBr(CO)_5$	37
7	$ReCl(CO)_5$ instead of $ReBr(CO)_5$	61
8	$MnBr(CO)_5$ instead of $ReBr(CO)_5$	15
9	without Me_2Zn and $ZnBr_2$	trace
10	without Me_2Zn or without $ZnBr_2$	trace
11	Et_2Zn, $AlMe_3$, or PhMgBr instead of Me_2Zn	0
12	$FeBr_2$ instead of $ZnBr_2$	32
13	$FeCl_3$ instead of $ZnBr_2$	24
14	$MgBr_2$ instead of $ZnBr_2$	15
15	$CuBr_2$ instead of $ZnBr_2$	39
16	R = OMe, R′ = H	0
17	R = NMe_2, R′ = H	16
18	R = Et, R′ = H	66
19	R = R′ = Me	0

[a]Reaction conditions: **1a** (0.3 mmol), **2b** (0.2 mmol), cat. (5 mol %), Me_2Zn (0.34 mmol), $ZnBr_2$ (0.3 mmol), DME (1.5 mL), 130 °C, 24 h, then quenched with 2 M HCl (2 mL), 80 °C, 3 h. [b]Determined by ^{1}H NMR. [c]Isolated yield on 0.5 mmol scale.

1). 1,2-Dimethoxyethane (DME) proved to be the best solvent, with others resulting only in a decreased yield of **3ab**, if any at all (entries 2−4). No reaction occurred in the absence of $ReBr(CO)_5$, and other rhenium and manganese carbonyl catalysts gave inferior results (entries 5−8). The presence of Me_2Zn and $ZnBr_2$ was shown to be essential for achieving the catalytic turnovers (entries 9 and 10). Surrogates of Me_2Zn such as Et_2Zn, $AlMe_3$, and PhMgBr demonstrated no reactivity at all (entry 11). Variations of other Lewis acid additives instead of $ZnBr_2$ gave much lower yields of **3ab** under otherwise identical conditions (entries 12−15). Of particular note, no formation of lactam **4ab** or homoannulation phthalide **3aa** or **3bb** was detected during the screening process, which underlined the high chemoselectivity of this reaction. In addition, *N*-methoxybenzamide displayed no reactivity at all in the reaction, and *N*′,*N*′-dimethylbenzohydrazide gave **3ab** in very low yield (entries 16 and 17). *N*-Ethylbenzamide was shown to be less reactive than **1a**, whereas no reaction occurred with *N*,*N*-dimethylbenzamide (entries 18 and 19).

With the optimized conditions in hand, the scope of aldehydes was first explored (Scheme 2). It turned out that a

Scheme 2. Scope of Aldehydes[a,b]



[a]Reaction conditions: **1a** (0.75 mmol), **2** (0.5 mmol), $ReBr(CO)_5$ (5 mol %), Me_2Zn (0.85 mmol), $ZnBr_2$ (0.75 mmol), DME (3.75 mL), 130 °C, 24 h, then quenched with 2 M HCl (5 mL), 80 °C, 3 h. [b]Isolated yields of product **3** are shown. [c]*p*-Toluenesulfonic acid (2 M, 5 mL) instead of HCl, 80 °C, 4 h.

series of electronically varied aromatic aldehydes were amenable to this reaction, giving the corresponding phthalides **3aa−g** in good yield. When electron-rich *p*-methoxylbenzaldehyde **2h** was employed as the substrate, phthalide **3ah** was obtained as the major product with the contaminant formation of lactam **4ah**. Interestingly, lactam **4ai** became the sole product from the reaction of *p*-(*N*,*N*-dimethyl)benzaldehyde **2i** and benzamide **1a**. The benzylic cation intermediates stabilized by electron-donating groups might account for the formation of lactam products (vide infra). Meta- and ortho-substituted aromatic aldehydes were also compatible with the reaction conditions, leading to phthalides **3aj−m** in moderate to good yield. Also, 1- and 2-naphthaldehydes and indolyl aldehyde gave the expected products **3an−p** with ease. Unfortunately, the use of aliphatic aldehydes such as cyclohexanecarbaldehyde **2q** resulted in the formation of phthalide **3aq** in relatively low yield.

Next, the scope of benzamides was examined (Scheme 3). Benzamides bearing both electron-donating and electron-withdrawing substituents were compatible in the reaction, and a wide range of functional groups including OMe, OCF_3, CF_3, CO_2Me, F, Cl, Br, and I remained intact after the reaction (**3bk−kk**), which allowed for further synthetic transformations of the reaction products. Ortho-substituted benzamide showed a slightly lower reactivity, giving phthalide **3lk** in a synthetically useful yield. When two C−H bonds were available in the starting material, the sterically less congested one was preferably functionalized (**3mk** and **3mk′**). Naphthamides were also suitable substrates for this reaction, with 2-naphthamide affording two regioisomeric products (**3nk**, **3ok**, and **3ok′**).

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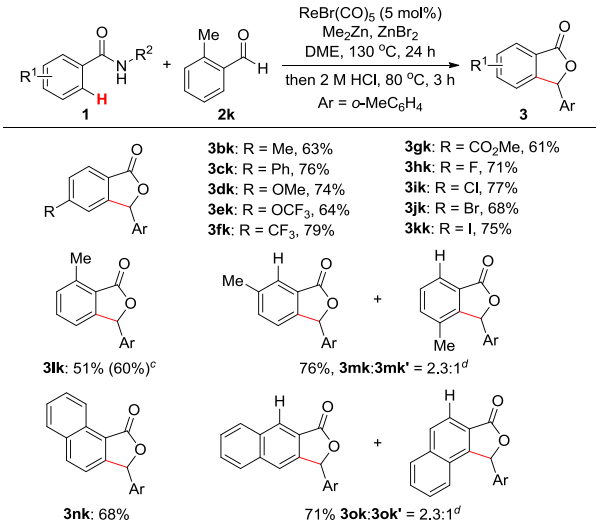
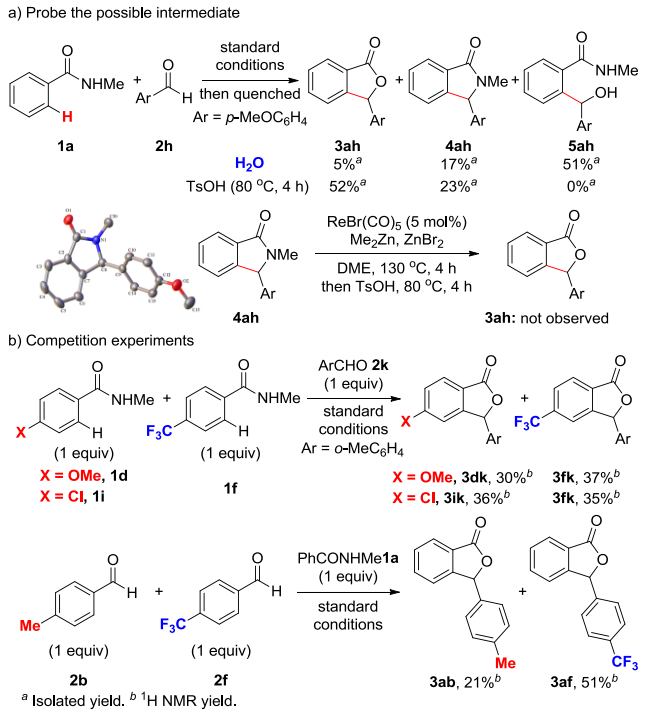
Scheme 3. Scope of Benzamides[a,b]



[a]Reaction conditions: **1** (0.75 mmol), **2k** (0.5 mmol), $ReBr(CO)_5$ (5 mol %), Me_2Zn (0.85 mmol), $ZnBr_2$ (0.75 mmol), DME (3.75 mL), 130 °C, 24 h, then quenched with 2 M HCl (5 mL), 80 °C, 3 h. [b]Isolated yields of product **3** are shown. [c]150 °C. [d]Determined by ^1H NMR.

To probe the possible reaction intermediates, the reaction of benzamide **1a** and *p*-methoxylbenzaldehyde **2h** was selected as a model reaction (Scheme 4a). Gratifyingly, alcohol **5ah** was obtained in 51% isolated yield, with the formation of phthalide **3ah** and lactam **4ah** in low yield when the reaction was directly quenched with water. In contrast, the treatment of the reaction with tosyl acid at 80 °C for 4 h resulted in the clearly increased yield of **3ah** and **4ah** with no detection of **5ah**. Furthermore, no formation of phthalide **3ah** was observed when pure lactam

Scheme 4. Mechanistic Experiments

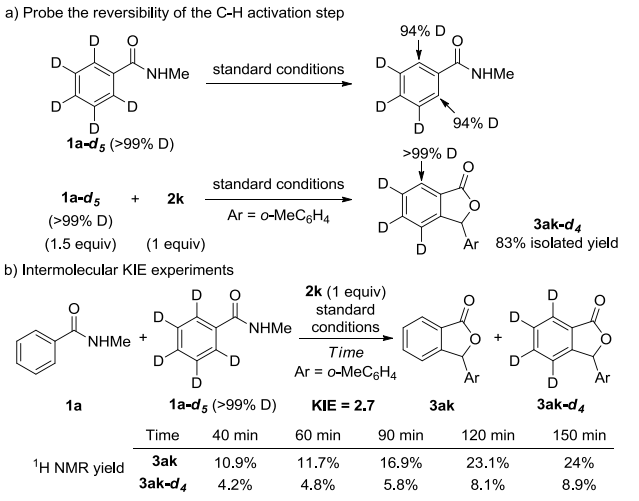


[a] Isolated yield. [b] ^1H NMR yield.

4ah was subjected to the standard reaction conditions. These results supported the intermediacy of alcohol **5ah** for the phthalide formation under the acidic conditions.[10] In addition, the competition experiments with benzamides bearing electronically varied substituents were conducted (Scheme 4b). The formation of product **3fk** derived from electron-deficient benzamide **1f** was slightly more favored than that of electron-rich benzamide **1d**. Not surprisingly, almost no difference was detected in the competition reaction between **1i** and **1f**. In contrast, the reaction had an obvious preference for the formation of product **3af** originating from electron-deficient aldehyde **2f** in comparison with phthalide **3ab** derived from aldehyde **2b** (Scheme 4b), which might be ascribed to the higher affinity of **2f** to nucleophilic attack.

To examine the reversibility of the C−H activation step, pentadeuterated benzamide **1a**-d_5 was first tested under the standard reaction conditions, and only a slight deuterium loss was found at the ortho positions of **1a**-d_5 (Scheme 5a). When

Scheme 5. Deuterium Labeling Experiments



	Time	40 min	60 min	90 min	120 min	150 min
^1H NMR yield	**3ak**	10.9%	11.7%	16.9%	23.1%	24%
	3ak-d_4	4.2%	4.8%	5.8%	8.1%	8.9%

aldehyde **2k** was subjected to the reaction of **1a**-d_5 under the same conditions, tetradeuterated phthalide **3ak**-d_4 was obtained in 83% isolated yield. Importantly, no D/H scrambling was detected at the remaining ortho position of **3ak**-d_4, which indicated that the C−H activation step was irreversible in the reaction. Furthermore, kinetic isotope effect (KIE) competition experiments were conducted with varied reaction times, and the KIE value was determined to be 2.7 (Scheme 5b).

On the basis of the above results, a tentative reaction mechanism is depicted in Scheme 6. Deprotonative coordination of benzamide **1a** with the rhenium catalyst gives intermediate **A**, which undergoes C−H bond cleavage with the aid of Me_2Zn, affording a five-membered rhenacycle **B**. The insertion of benzaldehyde **2** into the C−Re bond of **B** leads to the formation of a seven-membered rhenacycle **D** through the aldehyde-coordinated intermediate **C**. Ligand exchange of **D** with **1a** forms zinc species **E** and regenerates **A**, thus closing the catalytic cycle. Quenching of **E** with acid gives alcohol **5**, which undergoes intramolecular N- or O-attacked cyclization, affording lactam **4** or iminoether **F**, respectively.[10] The O-attacked cyclization is preferred in the reactions of electron-deficient and electron-neutral aldehydes, possibly through a S_N2 pathway. When electron-rich aldehydes are used, the *N*-

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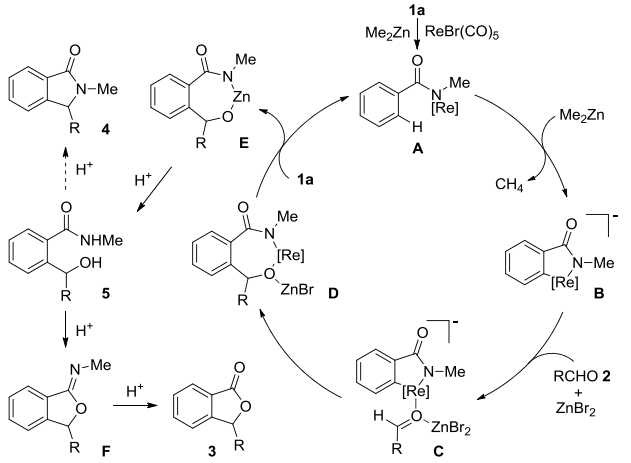
Scheme 6. Plausible Reaction Mechanism



attacked cyclization might occur via a S_N1 mechanism due to the enhanced stability of the benzylic cation intermediate derived from alcohol **5**. Of note, the direct cyclization of species **D** or **E** before quenching to afford **4** or **F**, respectively, cannot be ruled out as a minor reaction pathway for certain substrates. In the end, the acid-promoted hydrolysis of **F** gives rise to the formation of the final product **3**.

In summary, a rhenium-catalyzed [4 + 1] annulation of benzamides and aldehydes is developed, which provides an expedient approach to phthalide derivatives. This protocol is complementary to known methods for phthalide synthesis from benzimidates, benzoic acids, and benzaldehydes in terms of the simplicity of starting materials, the reaction scope of electronically varied substrates, and the elimination of homoannulation byproducts.[7,8] Also, this rhenium-catalyzed procedure shows a distinct reaction pattern of benzamides with aldehydes from those of previously reported Rh and Pd systems.[3,4] Further investigations of rhenium-catalyzed heterocycle synthesis via C−H activation is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02142.

Experimental details, characterization data, and NMR spectra for all new compounds (PDF)

Accession Codes

CCDC 1935437 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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