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Rhodium(III)-Catalyzed Oxidative Carbonylation of Benzamides with Carbon Monoxide

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Abstract

An efficient strategy for the oxidative carbonylation of aromatic amides via C-H/N-H activation to form phthalimides under Rh(III) catalyst has been developed. The reaction shows a preference for C-H bonds of electron-rich aromatic amides and tolerates a variety of functional groups.

The carbonylation of organic compounds has become one of the most important metal catalyzed C-C bond-forming processes.¹ Carbon monoxide as a C1 feed stock has been employed in a variety of palladium catalyzed transformations,^{2,3} including the formation of esters from aryl halides,⁴ aryl tosylates,⁵ alkyl and aryl indium reagents among many others.⁶ Furthermore, cyclopentanones have been formed via the Pauson-Khand reaction between an alkene, alkyne and CO.⁷ In these cases the organometallic intermediate inserts CO as a π -component to access molecules with increased complexity.

Previously, we⁸ and others⁹ have reported the coupling of benzamides and α,β -unsaturated amides with alkynes to access isoquinolones and pyridones utilizing Rh-(III) C-H activation. We imagined that if the alkyne was replaced with CO, we could access unique phthalimides via an analogous approach. This approach has been employed previously in work by Chatani and coworkers,¹⁰ who found that benzamides are able to direct C-H insertion in the presence of CO at high pressure utilizing ruthenium catalyst and pyridyl substituted amides (Scheme 1). Yu and coworkers have also demonstrated that palladium can facilitate the formation of succinamides via Pd (II) C-H activation from highly electron deficient amides under 1 atm of CO.¹¹ We speculated that Rh(III) might allow for a more general approach to access phthalimides from a broad variety of amides with 1 atm of CO. Herein, we provide a complete description of our development of the methodology, mechanistic insights, and product derivatization.

Our studies began with conditions which were used with success in the formation of isoquinolones from benzamides and alkynes. When the alkyne is replaced with CO the desired product is obtained in 4% yield (Table 1, entry 1). A brief survey of oxidants did not result in appreciable increase in product (Table 1, entry 2 and 3). However, when the catalyst is replaced with its cationic counterpart in the presence of Ag₂CO₃,¹² the desired phthalimide is obtained in 45% yield (Table 1, entry 6). A screen of solvents confirmed *t*-AmOH to be an ideal solvent (Table 1, entry 7 and 8), with increased concentration resulting in a greater yield (Table 1, entry 9). ClO₄ was found to be a better anion partner for the

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[‡]Electronic Supplementary Information (ESI) available: Experiment procedures for the preparation of catalyst and coupling products and characterization of catalyst and products; copies of ¹H and ¹³CNMR spectra of all compounds. See DOI: 10.1039/b000000x/

catalyst because of increased solubility, and as a consequence higher yield is obtained (Table 1, entry 10). Different acid or base additives were examined to tune the pH, with KH_2PO_4 being ideal for the reaction and the desired product then is obtained in 94% yield (Table 1, entry 12).

This reaction was examined with various amides under our optimized conditions (Chart 1). It is found that the reaction of amides (**1b–1f**) bearing alkyl groups at the nitrogen atom proceeds smoothly to deliver phthalimides in excellent yields. *N*-Isopropyl benzamide **1g** is also tolerated but with slower reaction rate. On the other hand, *N*-cyclohexyl benzamide provides less than 10% desired product.

A variety of substitution patterns on the aromatic ring are permitted. Substrates bearing *p*-methoxy and *p*-phenyl substituents (**1h–1k**) are efficient. Amide bearing mildly electron-withdrawing group (**1l**) provides phthalimide in lower yield. Stronger electron-withdrawing substituents are not tolerated.¹³ Substitution at the *meta* position leads to 3-substituted phthalimides as single regioisomers (**2m** and **2n**). Amides bearing *ortho* substituents such as methoxy, methyl, phenyl and fluoro afford phthalimides in minimal yields. *Ortho* Cl, Br, I amides mainly provide dehalogenated phthalimides (Scheme 2).

With respect to the aryl substituents on nitrogen, *N*-phenyl benzamide provides no phthalimide under our conditions. Amide derived from alanine methyl ester results in the desired product in moderate yield (**2o**). A thiophene derived amide is tolerated under our reaction conditions providing the derived imide in modest yield (**2p**).

To demonstrate the synthetic utility of this reaction (Scheme 3), phthalimide **2a** was subjected to Clemmensen reduction conditions. Treatment of **2a** with $\text{Zn}/\text{CH}_3\text{COOH}$ under reflux¹⁴ provides reduction product **3** in 80% yield. Grignard Reaction of **2a** and subsequently TFA/triethylsilane reduction¹⁵ affords lactam **4** in 96% yield.

A series of experiments were designed to probe the mechanism of the reaction. When the reaction is conducted in *t*-AmOD in the absence of CO, 19% deuterium incorporation is observed at the *ortho* positions of amide **1h** (Figure 1). If the same reaction is conducted in the presence of CO, no deuterium incorporation is observed in the unreacted starting material or in the product. These experiments suggest that, under the reaction conditions, the C–H insertion step is largely irreversible.

On the basis of the experiment results, a plausible mechanism for the $\text{RhCp}^*(\text{MeCN})_3(\text{ClO}_4)_2$ -catalyzed oxidative carbonylation of benzamides with CO is proposed (Scheme 4). The pre-catalyst decomposes to incorporate a carbonate ligand.¹⁶ Coordination of an equivalent of amide directs C–H activation event to generate the 5-membered rhodacycle **I**. A molecule of CO can coordinate to the putative rhodacycle to form species **II**. Migratory insertion of CO into the Rh–C bond then takes place to forge the new C–C bond, generating 6-membered rhodacycle **III**. At this point reductive elimination can occur to afford the desired phthalimide and a Rhodium (I) species. This species can undergo two single electron oxidations via Ag_2CO_3 to render the catalytically active rhodium complex.

In conclusion, we have developed a Rh(III) catalyzed oxidative carbonylation phthalimide synthesis via C–H/N–H activation. The reaction utilizes Rh(III) catalyst in the presence of Ag(I) oxidant, and is proposed to proceed by N–H metalation of the amide followed by *ortho* C–H activation. The resultant rhodacycle undergoes CO insertion to form phthalimides in good to excellent yields. Importantly, in this reaction, the amide substrates and the coupling partner CO are both fully incorporated into the desired products.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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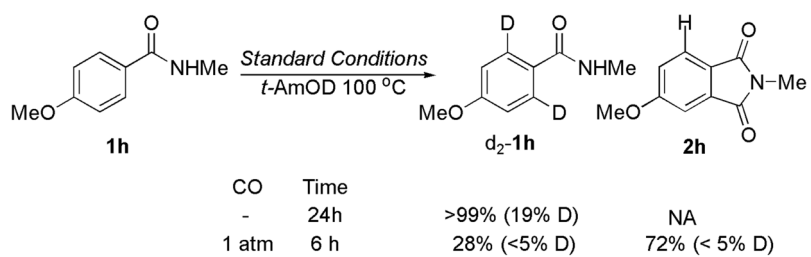
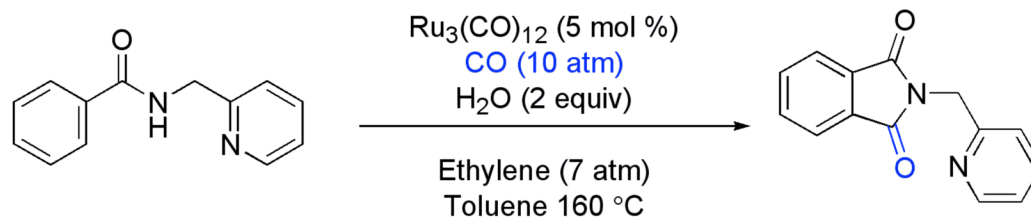
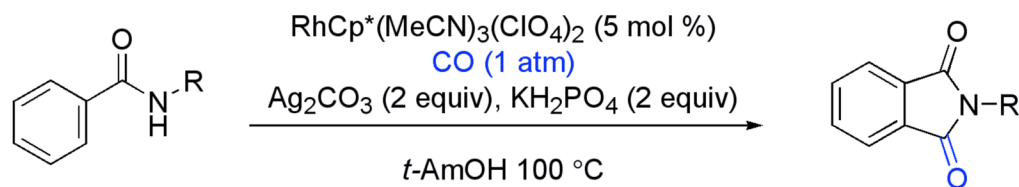
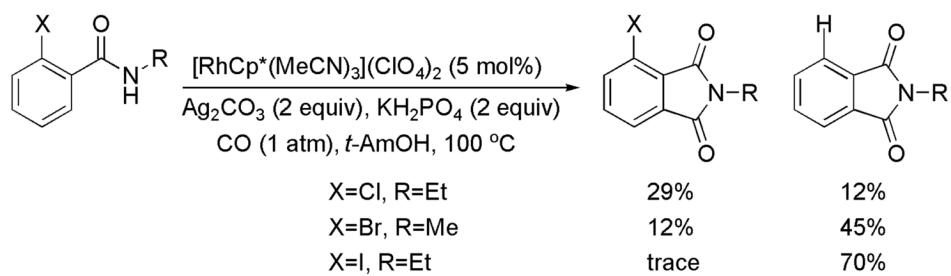


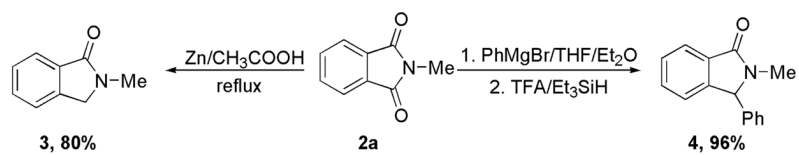
Figure 1.
Reversible C–H activation

• Chatani 2009:**• This Work**

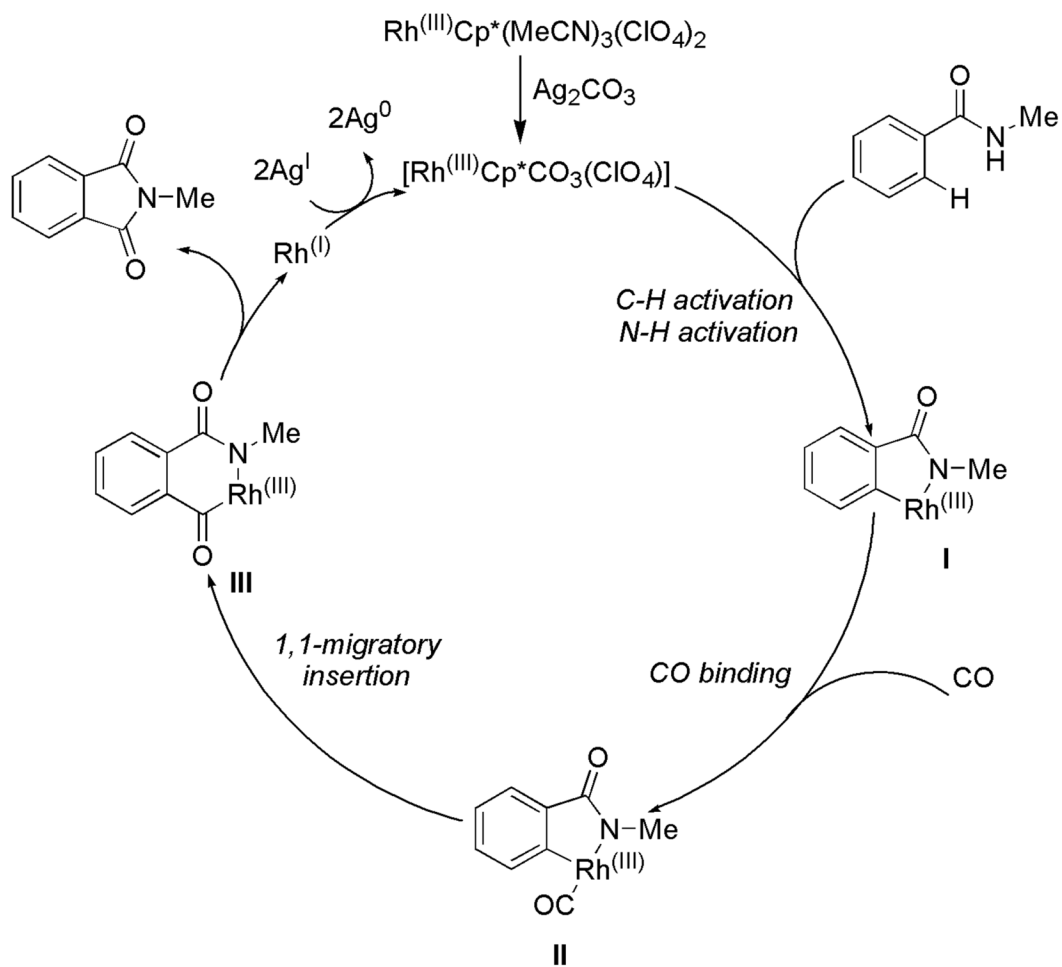
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

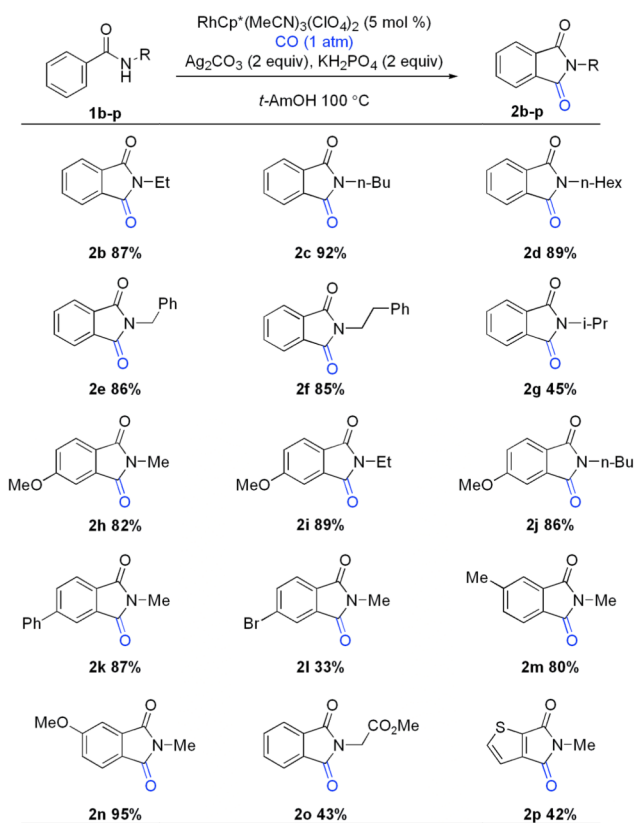
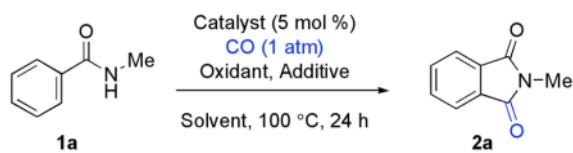


Chart 1.
Reaction Scope

Table 1

Optimization



Entry	Catalyst ^d	Oxidant ^e	Solvent [M]	Yield(%)
1 ^a	[RhCp*Cl ₂] ₂	Cu(OAc) ₂	<i>t</i> -AmOH [0.3]	4
2 ^a	[RhCp*Cl ₂] ₂	AgOAc	<i>t</i> -AmOH [0.3]	7
3 ^a	[RhCp*Cl ₂] ₂	Ag ₂ CO ₃	<i>t</i> -AmOH [0.3]	5
4	A	Cu(OAc) ₂	<i>t</i> -AmOH [0.3]	2
5	A	AgOAc	<i>t</i> -AmOH [0.3]	18
6	A	Ag ₂ CO ₃	<i>t</i> -AmOH [0.3]	45
7	A	Ag ₂ CO ₃	Dioxane [0.3]	40
8	A	Ag ₂ CO ₃	DCE [0.3]	12
9	A	Ag ₂ CO ₃	<i>t</i> -AmOH [0.6]	56
10	B	Ag ₂ CO ₃	<i>t</i> -AmOH [0.6]	80
11 ^b	B	Ag ₂ CO ₃	<i>t</i> -AmOH [0.6]	85
12 ^c	B	Ag ₂ CO ₃	<i>t</i> -AmOH [0.6]	94

^aCatalyst Loading is 2.5 mol %.

^b1 equiv KH₂PO₄.

^c2 equiv KH₂PO₄.

^dA = RhCp*(MeCN)₃(SbF₆)₂ B = RhCp*(MeCN)₃(ClO₄)₂.

^e2 equiv.