ChemComm

This article is part of the

New advances in catalytic C–C bond formation via late transition metals web themed issue

Guest editor: Professor Michael Krische

All articles in this issue will be gathered together online at
www.rsc.org/catalytic_CC.

COMMUNICATION

Rhodium(III)-catalyzed oxidative carbonylation of benzamides with carbon monoxide†‡
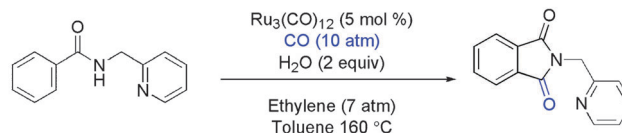
Ya Du, Todd K. Hyster and Tomislav Rovis*

An efficient strategy for the oxidative carbonylation of aromatic amides *via* C–H/N–H activation to form phthalimides using an 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.
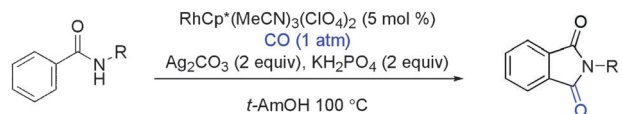
Previously, we[8] and others[9] have reported the coupling of benzamides and α,β-unsaturated amides with alkynes to access isoquinolones and pyridones utilizing Rh-(III) C–H activation. We imagined that if the alkyne was replaced with CO, we could access unique phthalimides *via* an analogous approach. This approach has been employed previously in the 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 catalysts 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

Department of Chemistry, Colorado State University, Fort Collins, CO 80523, USA. E-mail: rovis@lamar.colostate.edu;
Fax: +1 970 491-1801; Tel: +1 970 491-7208

† This article is part of ChemComm 'Advances in catalytic C–C bond formation *via* late transition metals' web issue.
‡ Electronic supplementary information (ESI) available: Experimental procedures for the preparation of catalyst and coupling products and characterization of catalyst and products; copies of ^{1}H and ^{13}C NMR spectra of all compounds. See DOI: 10.1039/c1cc15843k

Scheme 1

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 the product (Table 1, entries 2 and 3). However, when the catalyst is replaced with its cationic counterpart in the presence of Ag$_2$CO$_3$,[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, entries 7 and 8), with increased concentration resulting in a greater yield (Table 1, entry 9). ClO$_4$ was found to be a better anion partner for the catalyst because of increased solubility, and as a consequence higher

Table 1 Optimization

Entry	Catalyst[d]	Oxidant[e]	Solvent [M]	Yield (%)
1[a]	[RhCp*Cl$_2$]$_2$	Cu(OAc)$_2$	*t*-AmOH [0.3]	4
2[a]	[RhCp*Cl$_2$]$_2$	AgOAc	*t*-AmOH [0.3]	7
3[a]	[RhCp*Cl$_2$]$_2$	Ag$_2$CO$_3$	*t*-AmOH [0.3]	5
4	A	Cu(OAc)$_2$	*t*-AmOH [0.3]	2
5	A	AgOAc	*t*-AmOH [0.3]	18
6	A	Ag$_2$CO$_3$	*t*-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$_3$	*t*-AmOH [0.6]	56
10	B	Ag$_2$CO$_3$	*t*-AmOH [0.6]	80
11[b]	B	Ag$_2$CO$_3$	*t*-AmOH [0.6]	85
12[c]	B	Ag$_2$CO$_3$	*t*-AmOH [0.6]	94

[a] Catalyst loading is 2.5 mol%. [b] 1 equiv. KH$_2$PO$_4$. [c] 2 equiv. KH$_2$PO$_4$.
[d] A = RhCp*(MeCN)$_3$(SbF$_6$)$_2$, B = RhCp*(MeCN)$_3$(ClO$_4$)$_2$. [e] 2 equiv.
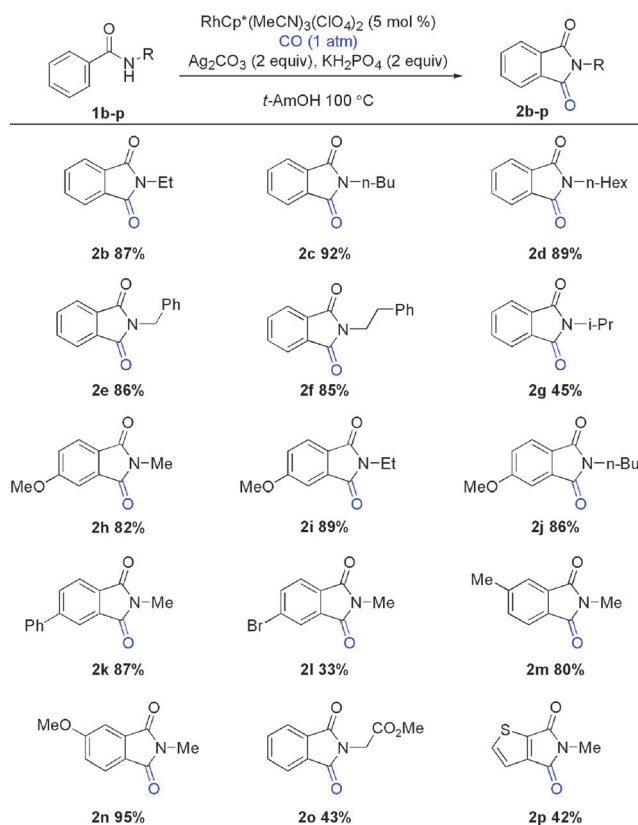
Chart 1 Reaction scope.

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 a 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 a mild 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).
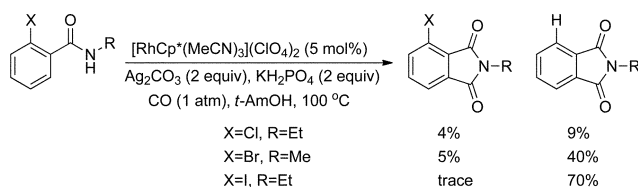
Scheme 2
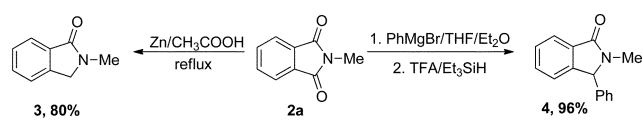
Scheme 3

With respect to the aryl substituents on nitrogen, *N*-phenyl benzamide provides no phthalimide under our conditions. Amide derived from glycine 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 Zn/CH_3COOH under reflux[14] provides reduction product **3** in 80% yield. Grignard reaction of **2a** and subsequently TFA/triethylsilane reduction[15] 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** (Fig. 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 $RhCp*(MeCN)_3(ClO_4)_2$-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 the C–H activation event to
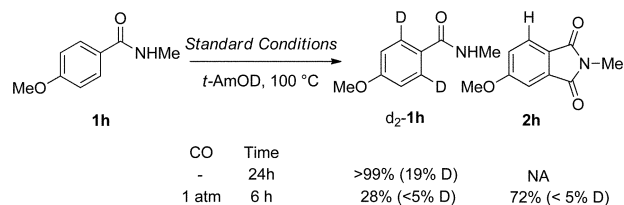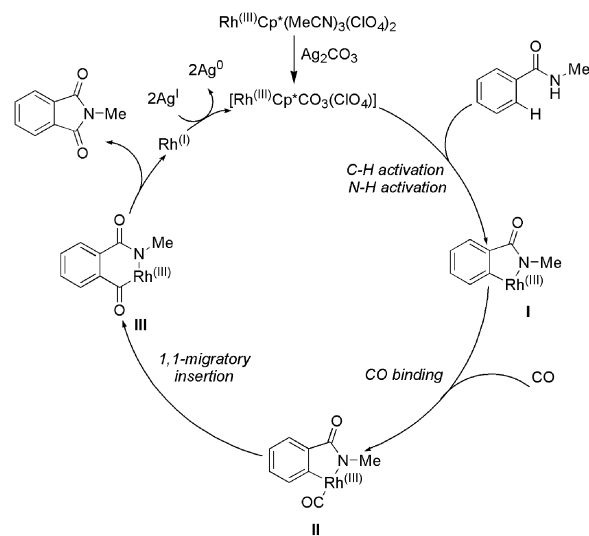
CO	Time		
-	24h	>99% (19% D)	NA
1 atm	6 h	28% (<5% D)	72% (< 5% D)

Fig. 1 Reversible C–H activation.

Scheme 4

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$_2$CO$_3$ 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 an Rh(III) catalyst in the presence of an 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.

Notes and references

1 *Modern Carbonylation Methods*, ed. L. Kollár, Wiley-VCH, Weinheim, 2008.
2 (*a*) A. Schoenberg, I. Bartoleti and R. F. Heck, *J. Org. Chem.*, 1974, **39**, 3318; (*b*) A. Schoenberg and R. F. Heck, *J. Org. Chem.*, 1974, **39**, 3327; (*c*) R. Giri and J.-Q. Yu, *J. Am. Chem. Soc.*, 2008, **130**, 14082; (*d*) R. Giri, J. K. Lam and J.-Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 686; (*e*) B. Haffemayer and M. J. Gaunt, *Chem. Sci.*, 2011, **2**, 312; (*f*) Y. Lu, D. Leow, X. Wang, K. M. Engle and J.-Q. Yu, *Chem. Sci.*, 2011, **2**, 967.
3 During the preparation of this manuscript, a related Pd(II) catalyzed carbonylation of *N*-alkoxybenzamides was reported. See: J. W. Wrigglesworth, B. Cox, G. C. Lloyd-Jones and K. I. Booker-Milburn, *Org. Lett*, 2011, **13**, 5326.
4 W. Mägerlein, A. F. Indolese and M. Beller, *Angew. Chem., Int. Ed.*, 2001, **40**, 2856 and references cited therein.
5 R. H. Munday, J. R. Martinelli and S. L. Buchwald, *J. Am. Chem. Soc.*, 2008, **130**, 2754 and references cited therein.
6 Y. Zhao, L. Jin, P. Li and A. Lei, *J. Am. Chem. Soc.*, 2008, **130**, 9429.
7 (*a*) P. L. Pauson, *Tetrahedron*, 1985, **41**, 5855; (*b*) N. E. Schore, *Org. React.*, 1991, **40**, 1; (*c*) S. T. Ingate and J. Marco-Contelles, *Org. Prep. Proced. Int.*, 1998, **30**, 121; (*d*) O. Geis and H.-G. Schmalz, *Angew. Chem., Int. Ed.*, 1998, **37**, 911; (*e*) Y. K. Chung, *Coord. Chem. Rev.*, 1999, **188**, 297; (*f*) K. M. Brummond and J. L. Kent, *Tetrahedron*, 2000, **56**, 3263; (*g*) P. A. Wender, N. M. Deschamps and G. G. Gamber, *Angew. Chem., Int. Ed.*, 2003, **42**, 1853; (*h*) P. A. Wender, M. P. Croatt and N. M. Deschamps, *J. Am. Chem. Soc.*, 2004, **126**, 5948; (*i*) Y. Ni and J. Montgomery, *J. Am. Chem. Soc.*, 2006, **128**, 2609 and references therein.
8 (*a*) T. K. Hyster and T. Rovis, *J. Am. Chem. Soc.*, 2010, **132**, 10565; (*b*) T. K. Hyster and T. Rovis, *Chem. Sci.*, 2011, **2**, 1606.
9 (*a*) N. Guimond, C. Gouliaras and K. Fagnou, *J. Am. Chem. Soc.*, 2010, **132**, 6908; (*b*) S. Mochida, N. Umeda, K. Hirano, T. Satoh and M. Miura, *Chem. Lett.*, 2010, **39**, 744; (*c*) G. Song, D. Chen, C.-L. Pan, R. H. Crabtree and X. Li, *J. Org. Chem.*, 2010, **75**, 7487; (*d*) N. Guimond, S. L. Gorelsky and K. Fagnou, *J. Am. Chem. Soc.*, 2011, **133**, 6449.
10 (*a*) S. Inoue, H. Shiota, Y. Fukumoto and N. Chatani, *J. Am. Chem. Soc.*, 2009, **131**, 6898; (*b*) N. Hasegawa, V. Charra, S. Inoue, Y. Fukumoto and N. Chatani, *J. Am. Chem. Soc.*, 2011, **133**, 8070.
11 E. J. Yoo, M. Wasa and J.-Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 17378.
12 C. White, S. J. Thompson and P. M. Maitlis, *J. Chem. Soc., Dalton Trans*, 1977, 1654.
13 For example, *p*-CHO benzamide affords 11% desired product.
14 J. H. Brewster and A. M. Fusco, *J. Org. Chem.*, 1963, **28**, 501.
15 T. Bousquet, J.-F. Fleury, A. Daïch and P. Netchitaïlo, *Tetrahedron*, 2006, **62**, 706.
16 The use of AgOTf as an oxidant affords no desired product. In the presence of AgOTf and Li$_2$CO$_3$, the desired product is obtained in 23% yield.