

Rhodium(III)-Amine Dual Catalysis for the Oxidative Coupling of Aldehydes by Directed C–H Activation: Synthesis of Phthalides

Peng Wen Tan, Nur Asyikin Binte Juwaini, and Jayasree Seayad*

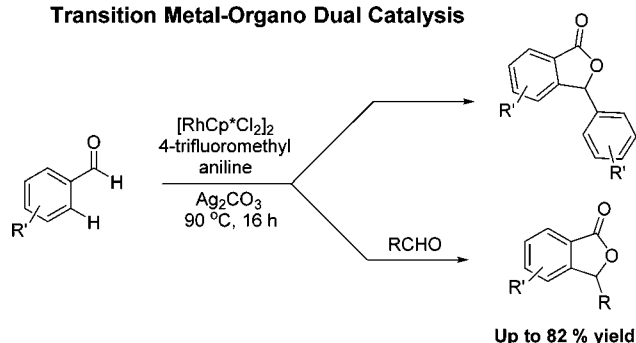
Organic Chemistry, Institute of Chemical and Engineering Sciences, 8 Biomedical Grove,
Neuros, #07-01, Singapore 138665

jayasree_seayad@ices.a-star.edu.sg

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ABSTRACT

Transition Metal–Organo Dual Catalysis



A novel oxidative coupling of aldehydes to form C3-substituted phthalides facilitated by co-operative dual catalysis of a Rh(III) complex and an aryl amine is reported. The reaction involves a cascade *ortho* C–H activation–insertion–annulation sequence. This methodology is efficient and applicable for the homo- and heterocoupling of various functionalized aldehydes generating the corresponding phthalides in moderate to high yields.

Phthalide scaffolds, particularly C3-substituted phthalides, are prevalent in many natural products as well as biologically active compounds and are also useful as synthetic intermediates for complex organic molecules.¹ They are traditionally synthesized by multistep synthetic pathways using stoichiometric organic and organometallic reagents.² Recently, alternative transition metal catalyzed methods for the synthesis of

phthalides were developed such as Rh-, Pd-, and Co-catalyzed cascade arylation–lactonization of phthalaldehyde³ or iodo benzoates⁴ using boron reagents and zinc respectively, Rh- and Ru-catalyzed intramolecular ketone hydroacylation,⁵ and Ru-catalyzed reductive cyclization of 2-arylacetylcarboxylates.⁶ Lately, further elegant methods based on C–H activation have been reported. Synthetic methods by means of direct C–H activation are attractive from a green chemistry perspective, as they minimize the necessity of prefunctionalization and thus improve the overall atom economy of the process in addition to reducing the use of environmentally hazardous reagents and generation of wastes.⁷ For instance, a Ru-catalyzed oxidative *ortho* C–H bond alkenylation of benzoic acid

(1) (a) Beck, J. J.; Chou, S.-C. *J. Nat. Prod.* **2007**, *70*, 891. (b) Yoganathan, K.; Rossant, C.; Ng, S.; Huang, Y.; Butler, M. S.; Buss, A. D. *J. Nat. Prod.* **2003**, *66*, 1116. (c) Zhou, J.; Gupta, K.; Yao, J.; Ye, K.; Panda, D.; Giannakakou, P.; Joshi, H. C. *J. Biol. Chem.* **2002**, *277*, 39777. (d) Witulski, B.; Zimmermann, A.; Gowans, N. D. *Chem. Commun.* **2002**, 2984. (e) Holler, U.; Gloer, J. B.; Wicklow, D. T. *J. Nat. Prod.* **2002**, *65*, 876. (f) Puder, C.; Zeck, A.; Beil, W. *J. Antibiot.* **2000**, *53*, 329. (g) Kobayashi, K.; Maeda, K.; Uneda, T.; Morikawa, O.; Konishi, H. *J. Chem. Soc., Perkin Trans. 1* **1997**, 443.

(2) (a) Hayat, S.; Rahman, A.; Choudhary, M. I.; Khan, K. M.; Bayer, E. *Tetrahedron Lett.* **2001**, *42*, 1647. (b) Hall, J. D.; Duncan-Gould, N. W.; Siddiqi, N. A.; Kelly, J. N.; Hoferlin, L. A.; Morrison, S. J.; Wyatt, J. K. *Bioorg. Med. Chem.* **2005**, *13*, 1409. (c) Pedrosa, R.; Sayalero, S.; Vicente, M. *Tetrahedron* **2006**, *62*, 10400.

(3) Kuriyama, M.; Ishiyama, N.; Shimazawa, R.; Shirai, R.; Onomura, O. *J. Org. Chem.* **2009**, *74*, 9210.

(4) Chang, H. T.; Jeganmohan, M.; Cheng, C. H. *Chem.—Eur. J.* **2007**, *13*, 4356.

(5) (a) Phan, D. H. T.; Kim, B.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 15608. (b) Willis, M. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 6026. (c) Omura, S.; Fukuyama, T.; Murakami, Y.; Okamoto, H.; Ryu, I. *Chem. Commun.* **2009**, 6741.

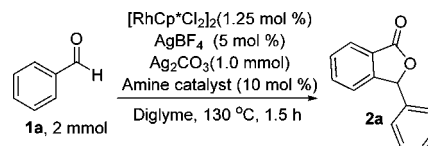
(6) Zhang, B.; Xu, M.-H.; Qiang, G. *Org. Lett.* **2009**, *11*, 4712.

derivatives followed by an oxa-Michael reaction to form 3-alkyl phthalides was reported by Ackermann and Pospech.⁸ In 2012, Shi and Li⁹ demonstrated a Rh-catalyzed *ortho* functionalization of essentially electron rich benzoic acids with aldehydes to form aryl and alkyl substituted phthalides albeit the reaction required harsh conditions (48 h at 150 °C). Similarly, with the use of a Rh(III) catalyst, Ellmann et al.¹⁰ developed a method that involves a cascade *ortho* C–H bond activation and addition of benzimidates to aldehydes to form various aryl and alkyl substituted phthalides at 110 °C (20 h). Although the reaction was efficient, presynthesis of the benzimidates was necessary and that involved multistep protocols using harmful reagents. We report herein the synthesis of C-3 substituted phthalides directly by the oxidative homo- and heterocoupling of readily available aldehydes *via* dual catalysis using a Rh(III) complex and an aryl amine under relatively mild conditions.

In our initial studies using benzaldehyde (**1a**) with catalytic [RhCp*Cl₂]₂¹¹ and AgBF₄ in the presence of Ag₂CO₃ as the oxidant at 130 °C, we observed the formation of traces of the phthalide, 3-phenyl-1,3-dihydro-2-benzofuran-1-one (**2a**). We envisaged that the presence of catalytic amounts of amines will be able to enhance the reactivity by forming imine, iminium, or amination intermediates *in situ* which could act as better directing groups for the Rh-catalyzed *ortho* C–H activation compared to the aldehyde functionality itself.¹²

Accordingly, after screening various primary and secondary amines (Table 1), we were delighted to discover that primary aryl amines particularly 4-trifluoromethylaniline

Table 1. Screening of Amine Catalysts for the Oxidative Homocoupling of Benzaldehyde to 3-Phenyl-1,3-dihydro-2-benzofuran-1-one



entry	amine catalyst	yield (%) ^a
1	—	trace
2	pyrrolidine	trace
3	cyclohexylamine	trace
4	<i>N</i> -methylaniline	10
5	aniline	28
6	<i>p</i> -anisidine	trace
7	4-trifluoromethylaniline	69

^aNMR yield determined by using CH₂Br₂ as the internal standard.

indeed catalyzed the reaction efficiently giving up to 69% NMR yield of the phthalide in 1.5 h at 130 °C. Traces of side products such as *N*-benzylidene-4-(trifluoromethyl)aniline (**4a**) and benzyl alcohol (**5a**) were also detected by GC-MS and ¹H NMR.

Relatively more nucleophilic amines such as *p*-anisidine, pyrrolidine, and cyclohexyl amine gave only traces of the product. Consequently, further screening and optimization of reaction parameters were carried out using 4-trifluoromethylaniline as the amine catalyst (Table 2). The presence of the Rh catalyst particularly [RhCp*Cl₂]₂ was necessary for the reaction to occur. Reactions without any rhodium catalyst or by using other Rh(I) and Rh(III) precursors such as [Rh(cod)Cl]₂, Rh(acac)₃, and RhCl₃ (entries 1–3, Table 2) did not generate any products. Silver additives with weakly co-ordinating counterions were also essential, among which AgOTf and AgSbF₆ were found to work reasonably well, but AgBF₄ was the best (entries 4–6, Table 2). The addition of an oxidant was necessary, as in the absence of any oxidant only traces of the product were generated. Among the oxidants studied (entries 8–10, Table 2), Ag₂CO₃ was the most suitable. When molecular oxygen was used as the oxidant only 15% yield of the phthalide was obtained while a significant amount of benzaldehyde was found to be converted to benzoic acid. The use of simple bases such as KOAc and Cs₂CO₃ (entries 11 and 12, Table 2), instead of the oxidant, resulted only in the formation of the corresponding imine, *N*-benzylidene-4-(trifluoromethyl) aniline (**4a**). Diglyme was the best solvent for this reaction followed by ethyl lactate while the reaction was also effective under neat conditions. The yield increased to 78% by lowering the temperature to 90 °C and prolonging the reaction time to 16 h. The reaction was also found to occur at 70 °C under these conditions, albeit with a slight drop in the yield (76%).

After attaining the optimized conditions, we explored the scope of this methodology for the homocoupling of different functionalized aryl aldehydes to form C3-substituted

- (7) For selected reviews on C–H activation: (a) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960. (b) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 2. (c) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (d) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (e) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740T. (f) Lyons, W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (g) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.—Eur. J.* **2010**, *16*, 2654. (h) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (i) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (j) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (k) Stuart, D. R.; Fagnou, K. *Science* **2007**, *317*, 1172. (l) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (m) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826. (n) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. (o) Arndtsen, B. A.; Bergman, R. G.; Mobley, T. A.; Peterson, T. H. *Acc. Chem. Res.* **1995**, *28*, 154.

- (8) Ackermann, L.; Pospech, J. *Org. Lett.* **2011**, *13*, 4153.

- (9) Shi, X.; Li, C.-J. *Adv. Synth. Catal.* **2012**, *16*, 2933.

- (10) Lian, Y.; Bergman, R. G.; Ellman, J. A. *Chem. Sci.* **2012**, *3*, 3088.

- (11) For selected reports on Rh-catalyzed C–H activation: (a) Brasse, M.; Cámpora, J.; Ellman, J. A.; Bergman, R. G. *J. Am. Chem. Soc.* **2013**, *135*, 6427. (b) Shi, Z.; Grohmann, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 1. (c) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651. (d) Sharma, S.; Park, E.; Park, J.; Kim, I. S. *Org. Lett.* **2012**, *14*, 906. (e) Satoh, T.; Miura, M. *Chem.—Eur. J.* **2010**, *16*, 11212. (f) Muralirajan, K.; Parthasarathy, K.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2011**, *50*, 4169. (g) Patureau, F. W.; Besset, T.; Kuhl, N.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 2154. (h) Besset, T.; Kuhl, N.; Patureau, F. W.; Glorius, F. *Chem.—Eur. J.* **2011**, *17*, 7167. (i) Park, J.; Park, E.; Kim, A.; Lee, Y.; Chi, K.-W.; Kwak, J. H.; Jung, Y. H.; Kim, I. S. *Org. Lett.* **2011**, *13*, 4390. (j) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624.

- (12) (a) Lian, Y.; Hummel, J. R.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2013**, *135*, 12548. (b) Park, S. H.; Kim, J. Y.; Chang, S. *Org. Lett.* **2011**, *13*, 2372. (c) Kuninobu, Y.; Matsuki, T.; Takai, K. *Org. Lett.* **2010**, *12*, 2948. (d) Fukutani, T.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Commun.* **2009**, 5141.

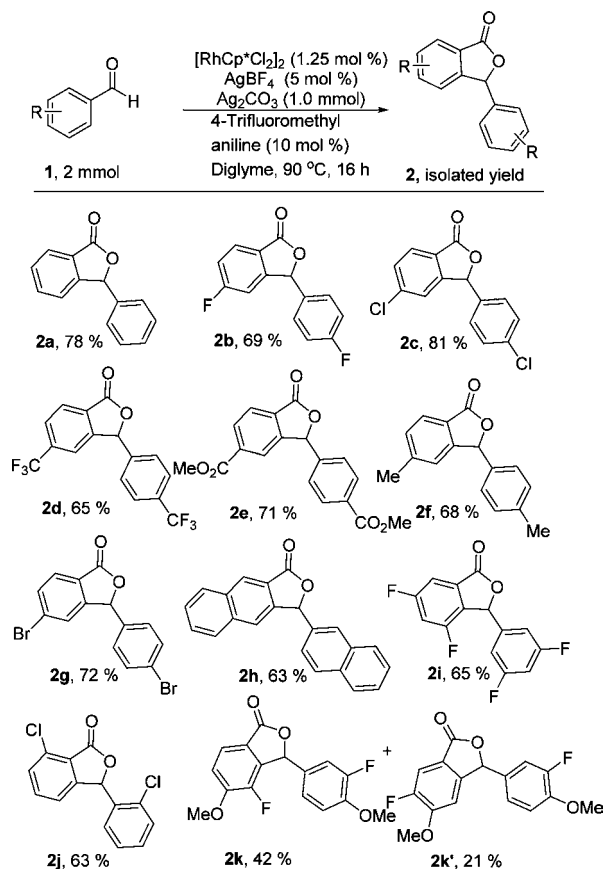
Table 2. Optimization Studies on the Homocoupling of Benzaldehyde to 3-Phenyl 1,3-dihydro-2-benzofuran-1-one

entry	rhodium catalyst	silver additive	oxidant	solvent	temp (°C)	time (h)	yield ^{a,b} (%)
1	Rh(cod) ₂ Cl ₂	AgBF ₄	Ag ₂ CO ₃	diglyme	130	1.5	—
2	Rh(acac) ₃	AgBF ₄	Ag ₂ CO ₃	diglyme	130	1.5	—
3	RhCl ₃	AgBF ₄	Ag ₂ CO ₃	diglyme	130	1.5	—
4	(RhCp*Cl ₂) ₂	—	Ag ₂ CO ₃	diglyme	130	1.5	—
5	(RhCp*Cl ₂) ₂	AgBF ₄	Ag ₂ CO ₃	diglyme	130	1.5	69
6	(RhCp*Cl ₂) ₂	AgSbF ₆	Ag ₂ CO ₃	diglyme	130	1.5	52
7	(RhCp*Cl ₂) ₂	AgOTf	Ag ₂ CO ₃	diglyme	130	1.5	62
8	(RhCp*Cl ₂) ₂	AgBF ₄	AgOAc	diglyme	130	1.5	41
9	(RhCp*Cl ₂) ₂	AgBF ₄	benzoquinone	diglyme	130	1.5	—
10	(RhCp*Cl ₂) ₂	AgBF ₄	O ₂ (1 atm)	diglyme	130	1.5	15
11	(RhCp*Cl ₂) ₂	AgBF ₄	— ^c	diglyme	130	1.5	—
12	(RhCp*Cl ₂) ₂	AgBF ₄	— ^d	diglyme	130	1.5	—
13	(RhCp*Cl ₂) ₂	AgBF ₄	Ag ₂ CO ₃	<i>p</i> -xylene	130	1.5	41
14	(RhCp*Cl ₂) ₂	AgBF ₄	Ag ₂ CO ₃	ethyl lactate	130	1.5	57
15	(RhCp*Cl ₂) ₂	AgBF ₄	Ag ₂ CO ₃	DMF	130	1.5	18
16	(RhCp*Cl ₂) ₂	AgBF ₄	Ag ₂ CO ₃	—	130	16	44 ^e
17	(RhCp*Cl ₂) ₂	AgBF ₄	Ag ₂ CO ₃	diglyme	90	16	78
18	(RhCp*Cl ₂) ₂	AgBF ₄	Ag ₂ CO ₃	diglyme	70	16	76
19	(RhCp*Cl ₂) ₂	AgBF ₄	Ag ₂ CO ₃	diglyme	50	16	14

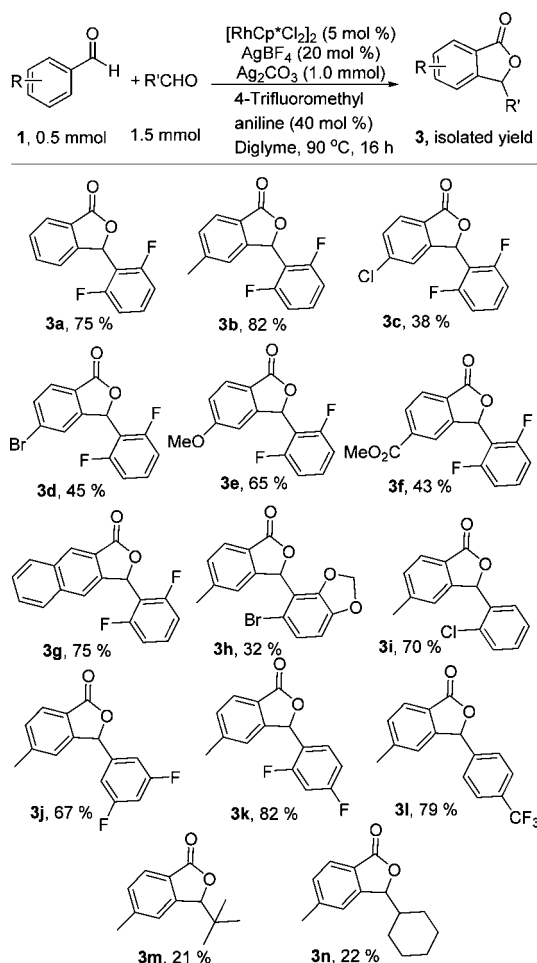
^a Reaction conditions: benzaldehyde (2 mmol), [Rh] (2.5 mol %), silver additive (5 mol %), 4-trifluoromethyl aniline (10 mol %), oxidant (1 mmol), solvent (0.2 mL). ^b NMR yield, determined by using CH₂Br₂ as the internal standard. ^c In the presence of 1 mmol of KOAc (formation of imine was detected by GC-MS). ^d In the presence of 1 mmol of Cs₂CO₃ (formation of imine was detected by GC-MS). ^e Neat reaction (benzaldehyde, 0.5 mmol).

phthalides (Scheme 1). In general, fairly electron-rich and -poor aldehydes were effective and functional groups such as chloro, bromo, fluoro, ester, alkoxy, and trifluoromethyl were well tolerated. Substitutions at *para*-, *meta*-, and *ortho*- positions were suitable. Thus, the monosubstituted aryl aldehydes **1a–1k** gave the corresponding C-3 aryl substituted phthalide derivatives **2a–2j** in 63–81% isolated yields. In the case of the disubstituted benzaldehyde derivative 3-fluoro-4-methoxybenzaldehyde, the corresponding regioisomeric phthalides **2k** and **2k'** were formed in a ratio of 2:1 with an overall yield of 63%.

The scope of heterocoupling of aldehydes using this protocol was then examined (Scheme 2). Initially, we performed the reaction of two different aryl aldehydes, one of them having substituted *ortho* positions. As such, the reaction of benzaldehyde (**1a**) with 2,6-difluorobenzaldehyde (**1l**) in a molar ratio of 1:3 resulted in the corresponding heterocoupled phthalide product 3-(2,6-difluorophenyl)-1,3-dihydro-2-benzofuran-1-one (**3a**) selectively in high isolated yield (75%). Only a trace amount of 3-phenyl 1,3-dihydro-2-benzofuran-1-one (**2a**) (the homocoupled product of benzaldehyde) was observed under these conditions. Under similar conditions, other aldehydes such as 4-methyl, 4-chloro, 4-bromo, 4-methoxy, and 4-carbomethoxy benzaldehydes as well as 2-naphthaldehyde reacted with 2,6-difluorobenzaldehyde forming the corresponding heterocoupled phthalide derivatives (**3b–3g**) in moderate to high yields (38–82%). Similarly, 4-methyl benzaldehyde (**1f**) reacted with 5-bromo-2*H*-1,3-benzodioxole-4-carbaldehyde (**1m**) to form 3-(5-bromo-2*H*-1,3-benzodioxol-4-yl)-5-methyl-1,3-dihydro-2-benzofuran-1-one in 32% yield.

Scheme 1. Rh(III)-Amine Catalyzed Homocoupling of Aryl Aldehydes to Phthalides

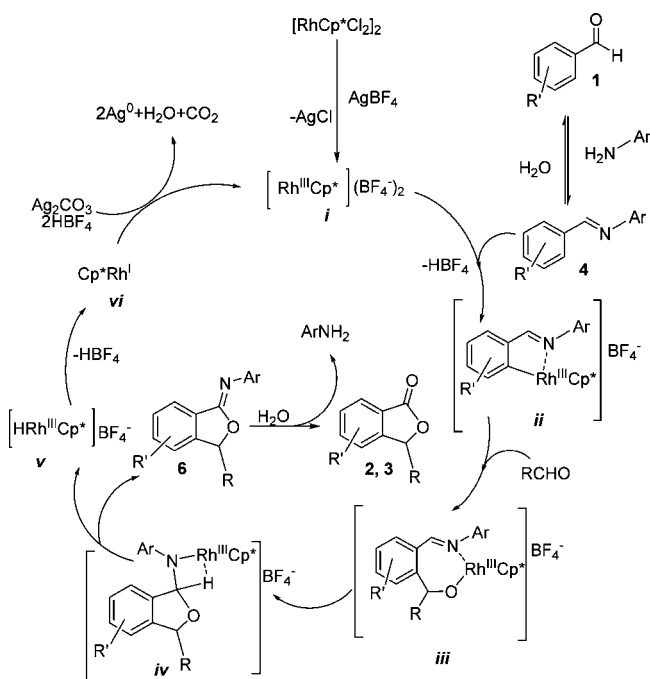
Scheme 2. Rh(III)-Amine Catalyzed Heterocoupling of Aldehydes to Phthalides



Next, the heterocoupling of two different aryl aldehydes having free *ortho* C–H bonds was studied. Remarkably, the reaction between 4-methyl benzaldehyde with 2-chloro, 2,5-difluoro, 3,5-difluoro, and 4-trifluoromethyl benzaldehydes in a molar ratio of 1:3 gave the corresponding phthalide derivatives (**3i–3l**) in high yields (67–82%). However, moderate amounts of homocoupled products of the excess aldehyde ($\text{R}'\text{CHO}$) were also found to form in these cases (NMR yields of 5–26% with respect to the excess aldehyde). More interestingly, aliphatic aldehydes, e.g. trimethyl acetaldehyde and cyclohexaldehyde, also reacted with 4-methyl benzaldehyde to form the corresponding phthalide derivatives **3m** and **3n** respectively though the yields were modest under these conditions.

The reaction is proposed to proceed through a Rh(III)–Rh(I) catalytic cycle (Scheme 3) initiated by the cationic Rh(III) complex **i** generated *in situ* from $[\text{RhCp}^*\text{Cl}_2]_2$ and AgBF_4 . The rhodium species **i** then activates the *ortho* C–H bond of the *in situ* formed imine derivative **4** forming the intermediate **ii**. Insertion of the second aldehyde molecule in the Rh–C bond in **ii** forms the rhodium species **iii** followed by the nucleophilic attack of the alkoxy oxygen on the electrophilic imine carbon leading to **iv**.

Scheme 3. Proposed Catalytic Cycle



Upon β -hydride elimination, the Rh(III) intermediate **iv** forms the Rh(III) hydride **v** and the imine intermediate **6** which then hydrolyzes to form the phthalide product. The $\text{Rh}^{\text{III}}\text{–H}$ species upon reductive elimination of HBF_4 results in **vi** which after oxidation by Ag_2CO_3 regenerates the active catalyst back for further turnovers.

In conclusion, we have developed a novel coupling reaction of aldehydes toward a single step method for the synthesis of C3-substituted phthalides by Rh(III)-amine dual catalysis. The reaction occurs under oxidative conditions by the *ortho* C–H activation of the aryl aldehyde. This methodology was applied for the homo- and heterocoupling of aldehydes forming various functionalized aryl and alkyl phthalide derivatives in moderate to high yields. We are currently studying the scope of this co-operative dual catalytic strategy toward the enantioselective synthesis of C3-substituted phthalides and other heterocyclic motifs by the *ortho* C–H activation of aryl aldehydes.

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Supporting Information Available. Experimental procedures and compound characterization data; ^1H , ^{13}C , and ^{19}F NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.