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An Efficient Waste-Free Oxidative Coupling via Regioselective C–H Bond Cleavage: Rh/Cu-Catalyzed Reaction of Benzoic Acids with Alkynes and Acrylates under Air

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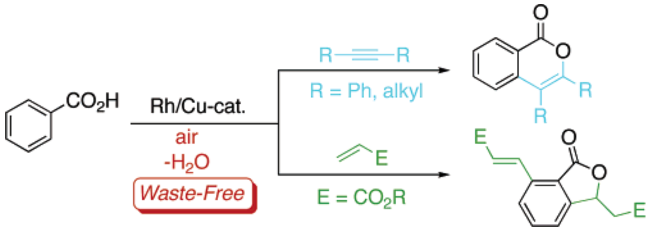
ABSTRACT



The direct oxidative coupling of benzoic acids with internal alkynes proceeds efficiently in the presence of a rhodium/copper catalyst system under air to afford the corresponding isocoumarin derivatives. The reaction forms no wastes except for water. Under similar conditions, the aerobic coupling with acrylates also takes place smoothly to produce 7-vinylphthalide derivatives via divinylation and subsequent cyclization.

The intermolecular coupling of aromatic substrates with alkenes or alkynes by transition-metal catalysis is now recognized to be a powerful tool to construct various π-conjugated vinylarene frameworks. The regioselective C−C coupling is usually carried out using halogenated or metalated aromatic reagents.[1] In such processes, however, there is a substantial problem of forming stoichiometric amounts of salt wastes as byproducts.

One of the most promising methods to avoid the salt formation is the aerobic oxidative coupling via C−H bond cleavage using unactivated aromatic substrates, in which no wastes are formed except for water.[2,3] On such a strategic ground, the chelation-assisted version employing an appropriate functional group that brings about regioselective C−H bond activation appears to be useful as an advanced tool for precision synthesis (Scheme 1), although to date this

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[1] For example, see: (a) Tsuji, J. *Palladium Reagents and Catalysts*, 2nd ed.; John Wiley & Sons: Chichester, UK, 2004. (b) de Meijere, A.; Diederich, F. *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2004. (c) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169. (d) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.

[2] Pd: (a) Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2528. (b) Stahl, S. S. *Science* **2005**, *309*, 1824. (c) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400 and references therein. (d) Yamada, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2005**, *70*, 5471. (e) Tani, M.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2004**, *69*, 1221. (f) Yokota, T.; Tani, M.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2003**, *125*, 1476. (g) Dams, M.; De Vos, D. E.; Celen, S.; Jacobs, P. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3512. (h) Shue, R. S. *J. Chem. Soc., Chem. Commun.* **1971**, 1510. (i) Fujiwara, Y.; Moritani, I.; Danno, S.; Teranishi, S. *J. Am. Chem. Soc.* **1969**, *91*, 7166. Rh: (j) Matsumoto, T.; Periana, R. A.; Taube, D. J.; Yoshida, H. *J. Catal.* **2002**, *206*, 272. (k) Matsumoto, T.; Yoshida, H. *Chem. Lett.* **2000**, 1064. Ru: (l) Weissman, H.; Song, X.; Milstein, D. *J. Am. Chem. Soc.* **2001**, *123*, 337.

[3] For recent reviews concerning C−H bond functionalization, see: (a) Miura, M.; Satoh, T. *Top. Organomet. Chem.* **2005**, *14*, 55. (b) Sigman, M. S.; Schults, M. *Org. Biomol. Chem.* **2004**, *2*, 2551. (c) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (d) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (e) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. (f) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698.

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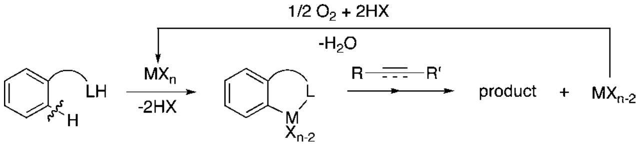
Scheme 1



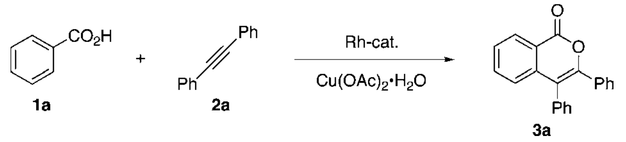
approach has not been extensively explored. In some rare examples, we demonstrated that 2-phenylphenols, *N*-(arylsulfonyl)-2-phenylanilines, and benzoic acids can directly and regioselectively couple with alkenes under air in the presence of a Pd/Cu catalyst.[4]

The reaction of the third substrates, benzoic acids, seems to be of particular interest because of their wide availability as aryl sources, comparable to that of aryl halides.[5] The reactions of benzoic acid with styrene and an acrylate afford isocoumarin and phthalide derivatives, respectively, via ortho vinylation and subsequent oxidative or nonoxidative cyclization.[4a]

Isocoumarin and phthalide nuclei are found in various natural products that exhibit a broad range of interesting biological properties.[6] Although these reactions have high potential to provide clean synthetic routes to such heterocycles,[7] their efficiency is moderate to low: decomposition of the homogeneous palladium-based catalyst into inactive bulk metal seems to be involved. During palladium-catalyzed oxidation, in general, the regeneration of Pd(II) from Pd(0) is considered to be the crucial step to determine catalyst efficiency.[2c] Moreover, the coupling partners are so far limited to some alkenes, and the reactions with other unsaturates including alkynes are unexplored. In the context of our study of catalytic coupling of benzoic acid derivatives,[8] we have succeeded in finding that the environmentally benign, direct cyclizative coupling of benzoic acids with internal alkynes can be realized by using Rh[2j,k,9] in place of Pd as the principal catalyst component to afford isocoumarin derivatives in good to excellent yields.

When benzoic acid (**1a**, 0.5 mmol) was treated with diphenylacetylene (**2a**, 0.6 mmol) in the presence of $[Cp^*RhCl_2]_2$ (1 mol %) and $Cu(OAc)_2\cdot H_2O$ (5 mol %) under air in DMF at 120 °C for 2 h, 3,4-diphenylisocoumarin (**3a**) was formed in 96% yield (entry 1 in Table 1, Cp* = η^5-pentamethylcyclopentadienyl). None or trace amounts of **3a** were obtained in the case using $RhCl_3$, $Rh(acac)_3$, $[RhCl(cod)]_2$, or $[RhCl(C_2H_4)_2]_2$ in place of $[Cp^*RhCl_2]_2$ (entries 2−5, acac = acetylacetonate, cod = cyclooctadiene). The addition of $Cu(OAc)_2\cdot H_2O$ was crucial for the reaction. Thus, the reaction did not proceed without the cocatalyst (entry 6). DMF was found to be the solvent of choice. In other solvents such as DMSO, diglyme, and *n*-nonane, the reaction did not proceed catalytically (entries 7−9).

Table 1. Reaction of Benzoic Acid (**1a**) with Diphenylacetylene (**2a**)^a



entry	Rh catalyst	solvent	time (h)	yield of **3a**^{b}
1	$[Cp^*RhCl_2]_2$	DMF	2	96(93)
2^c	$RhCl_3\cdot H_2O$	DMF	5	0
3^c	$Rh(acac)_3$	DMF	5	0
4	$[RhCl(cod)]_2$	DMF	5	<1
5	$[RhCl(C_2H_4)_2]_2$	DMF	5	<1
6^d	$[Cp^*RhCl_2]_2$	DMF	5	0
7	$[Cp^*RhCl_2]_2$	DMSO	5	2
8	$[Cp^*RhCl_2]_2$	diglyme	5	0
9	$[Cp^*RhCl_2]_2$	*n*-nonane	5	0
10^e	$[Cp^*RhCl_2]_2$	DMF	5	41

^{a} Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), Rh catalyst (0.005 mmol), $Cu(OAc)_2\cdot H_2O$ (0.025 mmol), solvent (2.5 mL) at 120 °C under air. ^{b} GC yield based on the amount of **1a** used. Value in parentheses indicates yield after purification. ^{c} Rh catalyst (0.01 mmol) was used. ^{d} Without $Cu(OAc)_2\cdot H_2O$. ^{e} At 100 °C.

Table 2 summarizes the results for the coupling employing a series of benzoic acids and alkynes under the optimized conditions. The reaction of **1a** with dialkylacetylenes **2b** and **2c** proceeded efficiently, as did that with diphenylacetylene, to produce 3,4-dialkylisocoumarins **3b** and **3c** in good yields (entries 1 and 2). From unsymmetrical alkylphenylacetylenes, **2d** and **2e**, 4-alkyl-3-phenylisocoumarins **3d** and **3e** were predominantly formed in 84 and 88% yields, along with minor amounts (5 and 10%, respectively) of their regioisomers, 3-alkyl-4-phenylisocoumarins (entries 3 and 4). In contrast, 1-phenyl-2-(trimethylsilyl)acetylene did not couple with **1a** at all: only a desilylative homocoupling product was detected by GC-MS. Electron-rich (entries 5, 7 and 8),

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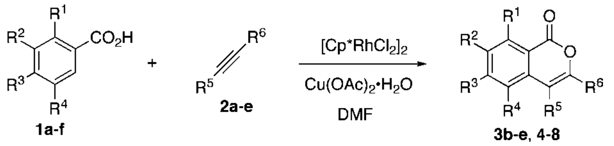
(6) For example, see: (a) Subramanian, V.; Rao Batchu, V.; Barange, D.; Pal, M. *J. Org. Chem.* **2005**, *70*, 4778. (b) Mali, R. S.; Babu, K. N. *J. Org. Chem.* **1998**, *63*, 2488 and references therein.

(7) Pt-catalyzed oxidative cyclization of amino acids: Dangel, B. D.; Johnson, J. A.; Sames, D. *J. Am. Chem. Soc.* **2001**, *123*, 8149.

(8) (a) Sugihara, T.; Satoh, T.; Miura, M. *Tetrahedron Lett.* **2005**, *46*, 8269. (b) Sugihara, T.; Satoh, T.; Miura, M.; Nomura, M. *Adv. Synth. Catal.* **2004**, *346*, 1765. (c) Sugihara, T.; Satoh, T.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4672. (d) Yasukawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 12680. (e) Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 5286. (f) Oguma, K.; Miura, M.; Satoh, T.; Nomura, M. *J. Organomet. Chem.* **2002**, *648*, 297. (g) Kametani, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **2000**, *41*, 2655. (h) Kokubo, K.; Matsumasa, K.; Miura, M.; Nomura, M. *J. Org. Chem.* **1996**, *61*, 6941. (i) Kokubo, K.; Miura, M.; Nomura, M. *Organometallics* **1995**, *14*, 4521.

(9) For examples of rhodium-catalyzed aerobic oxidation, see: (a) Fazlur-Rahman, A. K.; Tsai, J.-C.; Nicholas, K. M. *J. Chem. Soc., Chem. Commun.* **1992**, 1334. (b) Bressan, M.; Morvillo, A. *Inorg. Chim. Acta* **1989**, *166*, 177. (c) Mimoun, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 734. (d) Mimoun, H.; Perez-Machirant, M. M.; Sérée de Roch, I. *J. Am. Chem. Soc.* **1978**, *100*, 5437.

Table 2. Reaction of Benzoic Acids **1a**−**f** with Alkynes **2a**−**e**[a]



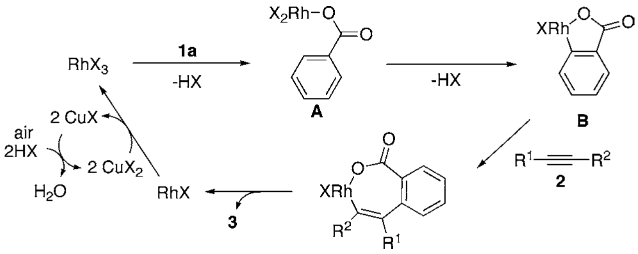
entry	1	R¹	R²	R³	R⁴	2	R⁵	R⁶	product, % yield[b]
1	**1a**	H	H	H	H	**2b**	*n*-Pr	*n*-Pr	**3b**, 83(77)
2	**1a**	H	H	H	H	**2c**	*n*-C_7H_{15}	*n*-C_7H_{15}	**3c**, 97(94)
3	**1a**	H	H	H	H	**2d**	Me	Ph	**3d**, 84(79)[c]
4	**1a**	H	H	H	H	**2e**	*n*-Bu	Ph	**3e**, 88(84)[c]
5	**1b**	H	H	Me	H	**2a**	Ph	Ph	**4**, 94(84)
6[d]	**1c**	H	H	Cl	H	**2a**	Ph	Ph	**5**, 84(76)
7[d]	**1d**	H	Me	H	H	**2a**	Ph	Ph	**6**, 81(75)
8[d]	**1e**	H	OMe	H	OMe	**2a**	Ph	Ph	**7**, 97(92)
9[d]	**1f**	Me	H	H	H	**2a**	Ph	Ph	**8**, 91(83)

[a] Reaction conditions: **1** (0.5 mmol), **2a** (0.6 mmol), $[Cp^*RhCl_2]_2$ (0.005 mmol), $Cu(OAc)_2{\cdot}H_2O$ (0.025 mmol) in DMF (2.5 mL) at 120 °C for 2 h under air. [b] GC yield based on the amount of **1** used. Value in parentheses indicates yield after purification. [c] A minor amount of 3-alkyl-4-phenyl isomer was formed (see text). [d] At 140 °C.

electron-deficient (entry 6), and sterically hindered (entry 9) benzoic acids were found to react with **2a** smoothly to give the corresponding substituted isocoumarins **4**−**8** in 81−97% yields. It is noted that the reaction of 3-toluic acid (**1d**) exclusively gave a single regioisomer, 7-methyl-3,4-diphenylisocoumarin (**6**) (entry 7).

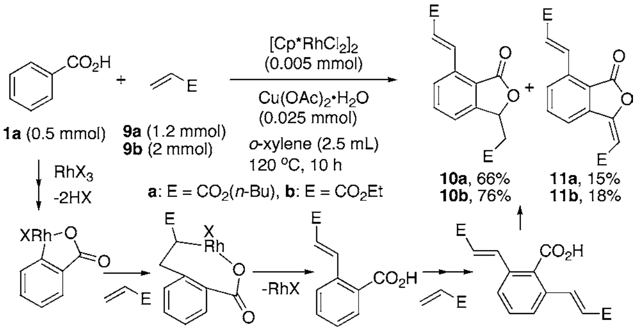
A plausible mechanism for the reaction of benzoic acid (**1a**) with alkyne **2** is illustrated in Scheme 2, in which neutral ligands are omitted. Coordination of the carboxylate oxygen to Rh(III)X_3 gives a rhodium(III) benzoate **A**. Subsequent ortho rhodation to form a rhodacycle intermediate **B**,[10] alkyne insertion, and reductive elimination occur to produce isocoumarin **3**. The resulting Rh(I)X species may be oxidized in the presence of the copper cocatalyst under air to regenerate Rh(III)X_3. It should be noted that no deposition of deactivated bulk metal is observed during the reaction, and this often occurs in Pd/Cu-catalyzed reactions.[2c]

Scheme 2



It is worth noting that benzoic acid (**1a**) also reacted with *n*-butyl acrylate (**9a**) smoothly under similar conditions using a less polar solvent such as *o*-xylene (Scheme 3). Interestingly, disubstitution at both the ortho positions occurred to afford 7-vinylphthalide **10a** as a 1:2 coupling product in 66% isolated yield along with a minor amount of its dehydrogenated, separable derivative **11a**. In DMF, which is the solvent of choice for the isocoumarin synthesis (Table 1), the reaction was sluggish to give **10a** in poor yield (ca. 10%). The reaction of **1a** with ethyl acrylate (**9b**) also proceeded efficiently in *o*-xylene to give the corresponding phthalide **10b** in 76% yield.

Scheme 3



In this reaction, a rhodacycle intermediate, generated in a manner similar to that in the reaction with alkynes (**B** in Scheme 2), may undergo alkene insertion and successive β-hydride elimination to form the ortho monovinylated benzoic acid. Prior to the nucleophilic cyclization, the second vinylation takes place to lead to the divinylated product **10** along with **11**. This is in marked contrast to the palladium-catalyzed reaction, in which the cyclization selectively occurs after the first vinylation.[4a]

In summary, an efficient, waste-free coupling of benzoic acids with unsaturated compounds via regioselective C−H bond cleavage has been accomplished by using a Rh/Cu catalyst under air. In comparison with the combination of Pd/Cu, Rh/Cu catalyst systems for oxidative C−C coupling reactions have been less common. The present catalyst system and related ones are expected to be applicable to other coupling reactions. Work is underway toward a better understanding of the catalysis.

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Supporting Information Available: Standard experimental procedure and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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