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Rhodium(I)-Catalyzed Cyclization Reaction of *o*-Alkynyl Phenols and Anilines. Domino Approach to 2,3-Disubstituted Benzofurans and Indoles

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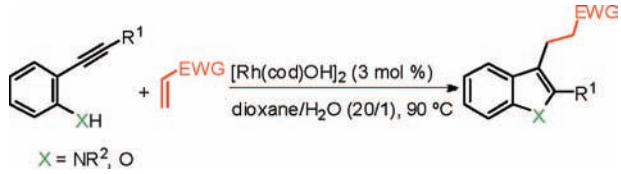
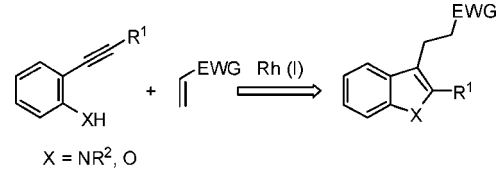
ABSTRACT



A rhodium-catalyzed cyclization of *o*-alkynylphenols and anilines followed by intermolecular conjugate addition that succeeds with alkyl and aryl alkynes is reported. In this reaction, 2,3-disubstituted benzofurans or indoles are obtained in one pot in good to excellent yields.

Substituted benzofuran and indole skeletons are widely found in bioactive compounds of medicinal interest.[1] Transition metal catalyzed annulation of *o*-alkynylphenols or anilines has been used to prepare these heterocycles, but limited methods exist to prepare the 2,3-disubstituted derivatives.[2,3] Benzofuran or indole annulation with rhodium catalysts have been reported[4] including a recent disclosure from Trost on the rhodium-catalyzed cycloisomerization to form indoles, benzofurans, and enol lactones.[5] Using $[Rh(cod)Cl]_2$/(4-$FC_6H_4)_3P$, he reported that terminal alkynes cyclize, but substrates bearing an internal alkyne fail to react. We report a general method to prepare both benzofurans and indoles including the 2,3-disubstituted derivatives via a cyclization/addition cascade using Rh(I), BINAP (Scheme 1).

Scheme 1. Synthesis of 2,3-Disubstituted Benzofuran and Indole



(1) Benzofuran: Keay, B. A.; Dibble, P. W. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, UK, 1996; Vol. 2, p 395. Indole: Gribble, G. W.; In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, UK, 1996; Vol. 2, p 207.

(2) For reviews, see: Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285, and references therein.

(3) Leading references: (a) Kondo, Y.; Shiga, F.; Murata, N.; Sakamoto, T.; Yamanaka, H. *Tetrahedron* **1994**, *50*, 11803. (b) Arcadi, A.; Cacchi, S.; Del Rosario, M.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280. (c) Nakamura, I.; Mizushima, Y.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15022. (d) Fürstner, A.; Davies, P. W. *J. Am. Chem. Soc.* **2005**, *127*, 15024. (e) Nakamura, M.; Ilies, L.; Otsubo, S.; Nakamura, E. *Org. Lett.* **2006**, *8*, 2803, and references therein.

(4) For a recent example of benzofuran synthesis via dealkylation−cyclization by a rhodium catalyst: (a) Oppenheimer, J.; Johnson, W. L.; Tracey, M. R.; Hsung, R. P.; Yao, P.-Y.; Liu, R.; Zhao, K. *Org. Lett.* **2007**, *9*, 2361. Intramolecular hydroamination: (b) Liu, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 1570. Amino-Claisen rearrangement of *N*-propargyl anilines: (c) Saito, A.; Kanno, A.; Hanzawa, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 3931.

(5) Trost, B. M.; McClory, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 2074.

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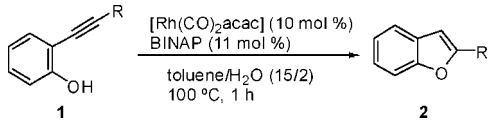
Table 1. Cyclization of 2-Alkynlphenol **1** into Benzofuran **2**[a]



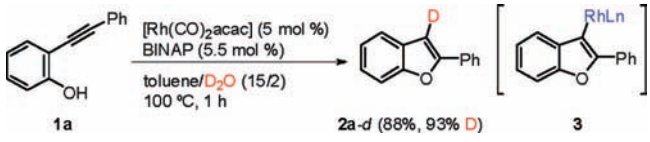
1 2

entry	R (**1**)	product	% yield[b]
1	C_6H_5- (**1a**)	**2a**	95
2[c]	C_6H_5- (**1a**)	**2a**	92
3[d]	n-C_4H_9- (**1b**)	**2b**	88
4[d]	4-MeO-C_6H_4- (**1c**)	**2c**	92
5[d]	3-F-C_6H_4- (**1d**)	**2d**	90
6[d]	$BzOCH_2CH_2$- (**1e**)	**2e**	97

[a] All reactions were run under the following conditions unless otherwise noted: **1** (0.2 mmol), $[Rh(CO)_2acac]$ (10 mol %), BINAP (11 mol %) in toluene (1.5 mL) and H_2O (0.2 mL). [b] Yields of isolated products. [c] Dioxane−H_2O (15:2) was used as a solvent. [d] $[Rh(CO)_2acac]$ (5 mol %) and BINAP (5.5 mol %) were used.

We found that *o*-alkynylphenol **1** afforded 2-alkyl- or arylbenzofuran **2** using Rh(I) and a bidentate ligand. The reaction tolerated a range of functional groups on the alkyne. The reaction of **1** in the presence of $[Rh(CO)_2acac]$ and BINAP afforded the corresponding benzofurans **2a**−**2e** in good yield (Table 1). When the reaction was conducted in the presence of D_2O, deuterium incorporation on the C-3 of benzofuran **2a** was observed supporting the generation of rhodium benzofuran **3** after the cyclization reaction (Scheme 2). Recognizing the possibility to construct a further carbon−carbon bond, we decided to search for a competent electrophile that could intercept **3**.[6,7]

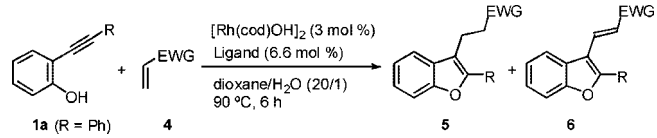
Scheme 2. Cyclization of **1a** to Rhodium Benzofuran and Trapping with D_2O



1a 2a-*d* (88%, 93% D) 3

When the reaction was carried out with **1a** (R = Ph) in the presence of acrylonitrile (**4a**), 2,3-disubstituted benzofurans **5a** and **6a** were obtained in high yield. In this reaction, a small amount of unsaturated product **6a** was produced. The selectivity was improved using BINAP as a ligand. As an initial attempt, $[Rh(CO)_2acac]$ was used in an addition reaction. However, **2a** was mainly obtained even though a trace amount of **5a** was observed on ^1H NMR. Other electron-deficient alkenes could be used (Table 2). The reaction of **1a** with ethyl acrylate afforded **5c** along with

Table 2. Synthesis of 2,3-Disubstituted Benzofuran[a]



1a (R = Ph) 4 5 6

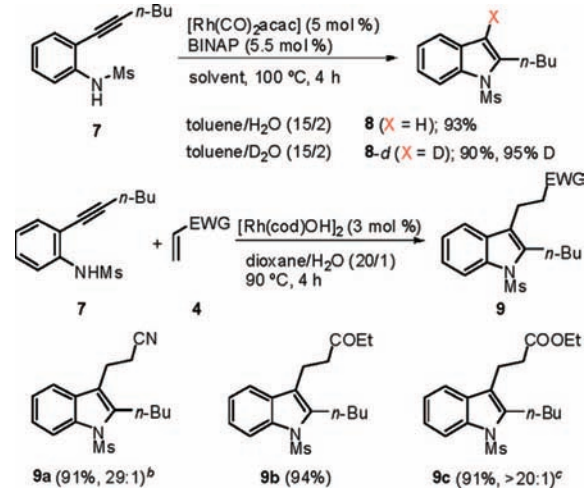
entry	EWG (**4**)	ligand	products	% yield[b]	**5**:**6**
1	CN (**4a**)	-	**5a** + **6a**	86	3.5:1
2	CN (**4a**)	BINAP	**5a** + **6a**	96	23:1
3	COEt (**4b**)	-	**5b** only	94	-
4	CO_2Et (**4c**)	-	**5c** + **6c**	92	2.4:1[c]
5[d]	CO_2Et (**4c**)	-	**5c** + **6c**	85	>20:1[c]

[a] All reactions were run under the following conditions unless otherwise noted: **1a** (0.2 mmol), **4** (2.0 mmol), $[Rh(cod)OH]_2$ (3 mol %) in dioxane (2 mL) and H_2O (0.1 mL). [b] Isolated yields. [c] Determined by ^1H NMR spectroscopy. [d] **1a** (0.2 mmol), **4c** (0.4 mmol), $[Rh(cod)OH]_2$ (3 mol %) in DME (2 mL) and H_2O (0.2 mL) at 85 °C.

unsaturated product **6c**.[8] By reducing the number of equivalents of **4c** to two, we observed that **5c** was now formed with much higher selectivity (>20:1 vs 2.4:1) and high yield.

We next investigated the scope of the reaction with respect to the alkynyl phenols and electrophiles (Table 3). 2-Hexynylphenol **1b** gave the product in high yield. The reaction tolerated a range of functional groups on the aromatic ring (entries 2, 3, and 5−7).

Scheme 3. Synthesis of 2,3-Disubstituted Indole[a]



7 4 9

9a (91%, 29:1)[b] 9b (94%) 9c (91%, >20:1)[c]

[a] All reactions were run under the following conditions unless otherwise noted: **7** (0.2 mmol), **4** (2.0 mmol), $[Rh(cod)OH]_2$ (3 mol %) in dioxane (2 mL) and H_2O (0.1 mL). [b] $[Rh(cod)OH]_2$ (3 mol %) and BINAP (7 mol %) were used. [c] An amount of 2 equiv of ethyl acrylate was used. The ratio was determined by ^1H NMR spectroscopy.

This reaction can also be adapted to the synthesis of indoles. 2-Substituted indole **8** was obtained from *o*-alkynyl aniline derivative **7**. In a labeling experiment, deuterium was incorpo-

(6) For reviews on rhodium-catalyzed 1,4-addition, see: (a) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169. (b) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (c) Miura, T.; Murakami, M. *Chem. Commun.* **2007**, 217.

(7) For a recent example of a rhodium-catalyzed cascade reaction consisting of ring expansion/1,4-addition: Matsuda, T.; Shigeno, M.; Murakami, M. *J. Am. Chem. Soc.* **2007**, *129*, 12086.

(8) Lu reported that LiBr inhibited β-hydride elimination in a palladium-catalyzed aminopalladation, addition reaction (ref 9a). In our case, there was not an obvious effect with LiBr in the reaction.

Table 3. Synthesis of 2,3-Disubstituted Benzofuran: Scope of *o*-Alkynylphenol[a]

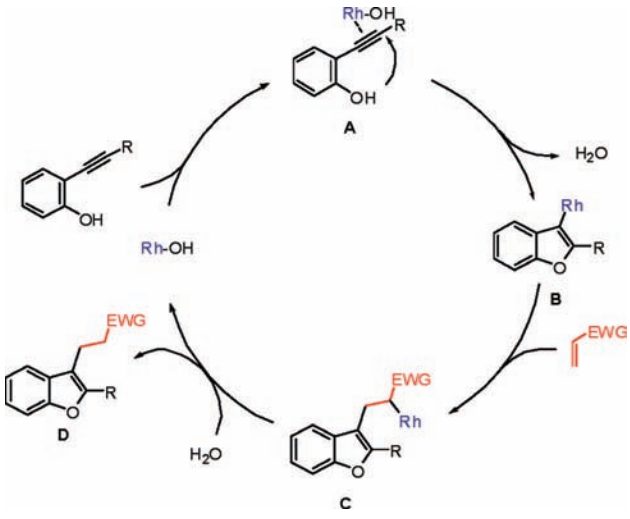
entry	R (**1**)	EWG (**4**)	products	% yield[b]	**5**:**6**
1[c]	*n*-Bu (**1b**)	CN (**4a**)	**5ba** + **6ba**	83	15:1
2[c]	4-MeO-C_6H_4 (**1c**)	CN (**4a**)	**5ca** + **6ca**	96	18:1
3[c]	3-F-C_6H_4 (**1d**)	CN (**4a**)	**5da** + **6da**	92	65:1
4	*n*-Bu (**1b**)	COEt (**4b**)	**5bb**	70	-
5	4-MeO-C_6H_4 (**1c**)	COEt (**4b**)	**5cb**	91	-
6	3-F-C_6H_4 (**1d**)	COEt (**4b**)	**5db**	86	-
7	$CH{=}CH_2$ (**1f**)	COEt (**4b**)	**5fb**	75	-

[a] All reactions were run under the following conditions unless otherwise noted: **1** (0.2 mmol), **4** (2.0 mmol), $[Rh(cod)OH]_2$ (3 mol %) in dioxane (2 mL) and H_2O (0.1 mL). [b] Isolated yields. [c] $[Rh(cod)OH]_2$ (3 mol %), BINAP (6.6 mol %) were used.

rated in the indole product using D_2O. Using the same strategy as for benzofurans, in situ trapping of the cyclized Rh-intermediate could be carried out with electrophiles such as acrylonitrile, ethyl vinyl ketone, and ethyl acrylate (Scheme 3).[9]

A plausible reaction mechanism is shown in Scheme 4. Alkyne-coordinated rhodium **A** is generated from the substrate and Rh(I). Then 3-rhodium benzofuran **B** is formed

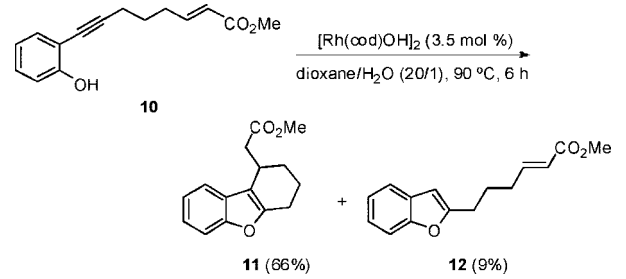
Scheme 4. Plausible Reaction Mechanism



via 5-*endo* cyclization. The key intermediate aryl rhodium **B** then reacts with an electrophilic alkene, and after protonation, the desired compound is obtained and Rh-hydroxide is regenerated.[10,11] Trost proposed vinylidene intermediates in the cycloisomerization of terminal alkynes.[5] Such intermediates are precluded in our substrates since the alkyne bears a substituent.

Domino double intramolecular cyclization was also possible (Scheme 5). In this reaction, after construction of the benzofuran ring, the arylrhodium reacted with the tethered α,β-unsaturated ester. The reaction of phenol **10** produced tricyclic benzofuran **11** in 66% yield, along with protonated product **12** in 9%.[12]

Scheme 5. Cascade Cyclization Reaction from *o*-Alkynylphenol **10**



In summary, we report a rhodium-catalyzed cyclization of *o*-alkynylphenols and anilines followed by intermolecular conjugate addition that succeeds with alkyl and aryl alkynes.[13] In this reaction, 2,3-disubstituted benzofurans or indoles are obtained in one pot in good to excellent yields. The rhodium-catalyzed reactions are convenient and atom-economical. Further exploration of the reaction scope and other types of cyclizations is currently under investigation.

Acknowledgment. We gratefully acknowledge NSERC (Canada), Merck-Frosst, Otsuka Pharmaceutical Co., Ltd. (Tokyo), and the University of Toronto for financial support.

Supporting Information Available: Experimental procedures 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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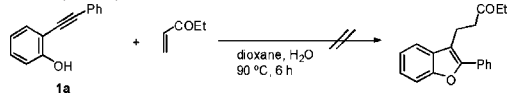
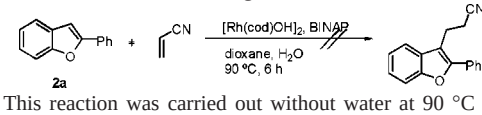
(9) For a recent example of tandem intramolecular cyclization of alkynylanilines and conjugate addition, see: (a) Pd: Shen, Z.; Lu, X *Tetrahedron* **2006**, *62*, 10896. (b) Au: Alfonsi, M.; Arcadi, A.; Aschi, M.; Bianchi, G.; Marinelli, F. *J. Org. Chem.* **2005**, *70*, 2265.

(10) Heating a dioxane solution of **1a** and ethyl vinyl ketone at 90 °C in the absence of the rhodium catalyst gave no 1,4-adduct product and recovered **1a** (100%).



(11) A control experiment was conducted using the rhodium catalyst in the presence of preformed benzofuran **2a** and acrylonitrile. No addition product was obtained, and the starting material was recovered in high yield.



(12) This reaction was carried out without water at 90 °C in 6 h. **11** was obtained in 11%, and **10** was recovered (49%).

(13) Following acceptance of this manuscript a recent paper appeared on related reactions using Pd(II) catalysts: Martínez, C.; Álverez, R. Aurrecoechea, J. M. *Org. Lett.* **2009**, *11*, 1083−1086.