2,3-Disubstituted Benzofurans and Indoles Naohiro Isono and Mark Lautens* Davenport Research Laboratories, Department of Chemistry, University of Toronto, Toronto, Ontario, Canada M5S 3H6 mlautens@chem.utoronto.ca

Rhodium(I)-Catalyzed Cyclization

Anilines. Domino Approach to

Reaction of o-Alkynyl Phenols and

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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 reported⁴ 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-FC₆H₄)₃P, he reported that terminal alkynes cyclize, but

(1) Benzofuran: Keay, B. A.; Dibble, P. W. In *Comprehensive Hetero-cyclic 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.

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



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).

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⁽⁴⁾ For a recent example of benzofuran synthesis via dealkylationcyclization 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.

Table 1. Cyclization of 2-Alkynlphenol 1 into Benzofuran 2^a



^{*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 H₂O (0.2 mL). ^{*b*} Yields of isolated products. ^{*c*} Dioxane-H₂O (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 D₂O, 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



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

	+ ∫ ^{EWG} -	[Rh(cod)OH] ₂ (3 mol Ligand (6.6 mol %) dioxane/H ₂ O (20/1) 90 °C, 6 h		FWG	
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	$\rm CO_2 Et~(4c$.) -	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 H₂O (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 H₂O (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-Hexy-nylphenol **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).





^{*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 H₂O (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 palladiumcatalyzed 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 <i>o</i> -Alkynylph	enol
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entry	R (1)	EWG (4)	products	% yield ^b	5:6
1^c	<i>n</i> -Bu (1b)	CN (4a)	$\mathbf{5ba} + \mathbf{6ba}$	83	15:1
2^c	$4-MeO-C_6H_4$ (1c)	CN (4a)	5ca + 6ca	96	18:1
3^c	$3-F-C_{6}H_{4}(1d)$	CN (4a)	$\mathbf{5da} + \mathbf{6da}$	92	65:1
4	<i>n</i> -Bu (1b)	COEt (4b)	5bb	70	-
5	$4-MeO-C_6H_4$ (1c)	COEt (4b)	5cb	91	-
6	$3-F-C_{6}H_{4}(1d)$	COEt (4b)	5db	86	-
7	$CH=CH_2$ (1f)	COEt (4b)	5fb	75	-
a			1 4 (0 0 1) 4 (0 0		1 22 2 22 22

^{*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 H₂O (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 Rhintermediate 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



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

(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%).



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



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 atomeconomical. Further exploration of the reaction scope and other types of cyclizations is currently under investigation.

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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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(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 $^\circ$ 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.

⁽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.