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A Direct Approach to 5-Hydroxybenzofurans via a Platinum-Catalyzed Domino Rearrangement/5-*endo-dig* Cyclization Reaction of Quinols

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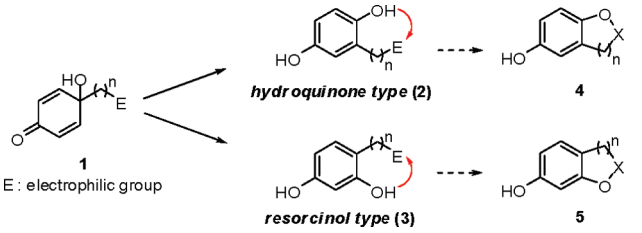
A highly efficient and atom-economical construction of 2-substituted 5-hydroxybenzofurans was accomplished by employing a platinum-catalyzed domino dienone−phenol rearrangement/5-*endo-dig* cyclization reaction of quinols bearing alkynes.

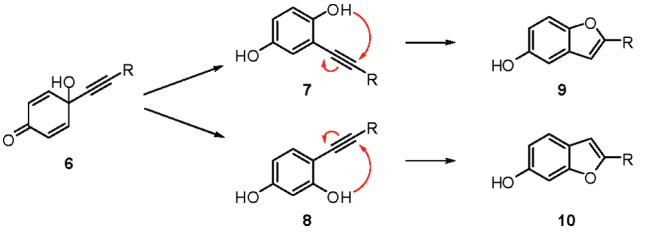
Transformation of 4,4-disubstituted cyclohexadienones to 3,4-disubstituted phenol derivatives via bond migration, known as the dienone−phenol rearrangement, has been a useful strategy for the synthesis of highly substituted phenols.[1] In particular, depending on the reaction conditions, this rearrangement of quinol **1** results in either hydroquinone **2** or resorcinol **3** (Scheme 1).[2] As part of our continued interest on the facile construction of heterocycles under mild conditions,[3] we envisioned that subsequent cyclization after the rearrangement would occur to form a bicyclic product, **4** or **5** if the starting quinol **1** has an appropriate electrophilic group.

SCHEME 1. General Plan for the Synthesis of Bicycles via a Tandem Rearrangement/Cyclization Sequence



Along this line, we anticipated that quinols bearing an alkyne unit **6** would rearrange to either **7** or **8**, setting the stage for the subsequent intramolecular cyclization to provide 5- or 6-hydroxybenzofuran (Scheme 2). Since both types of substitution patterns are frequently found in a number of natural products and pharmaceuticals, we decided to explore the feasibility of this strategy. To the best of our knowledge, no examples on the dienone−phenol rearrangement of the quinols containing an alkyne moiety have been disclosed yet. Here we wish to communicate our preliminary result on the atom-economical synthesis of benzofurans[4] featuring a domino rearrangement/intramolecular 5-*endo-dig* ring closure reaction[5] of quinols **6**.

SCHEME 2. Domino Dienone−Phenol Rearrangement/ 5-*endo-dig* Cyclization



2-Arylbenzofurans constitute a class of natural products displaying a variety of interesting biological activities including anticancer, antimicrobial, and

(1) (a) Metlesics, W.; Wesseley, F.; Budzikiewicz, H. *Tetrahedron* **1959**, *6*, 345. (b) Miller, B. *Acc. Chem. Res.* **1975**, *8*, 245. (c) Whiting, D. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 3, p 803. (d) In *Strategic Applications of Named Reactions in Organic Synthesis*; Kürti, L., Czarkó, B., Eds.; Academic Press: Oxford, UK, 2005; p 142 (e) In *Name Reactions*; Li, J.-J., Ed.; Springer: New York, 2006; p 202.

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antioxidant activities.[6] For example, as shown in Figure 1, 3-(γ,γ-dimethylpropenyl)moracin M was known to exhibit modest cyclooxygenase inhibitory activity whereas moracin O was recently reported to strongly inhibit hypoxia-induced HIF-1α accumulation in human hepatocellular carcinoma cell line Hep3B cells.

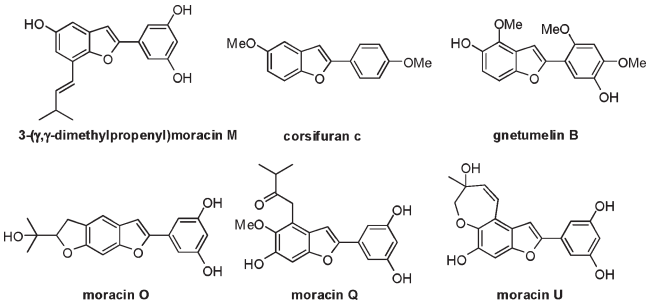
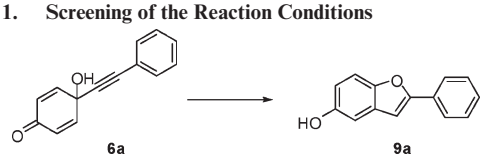


FIGURE 1. Some representative 2-arylbenzofuran natural products.

The requisite quinols for this study were easily prepared from the nucleophilic addition of lithium acetylides to 1,4-benzoquinones. Optimal reaction conditions were screened with **6a**. Initial screening of the catalysts revealed that $PtCl_2$ is capable of promoting this domino sequence, furnishing the desired benzofuran product in 60% yield (Table 1, entries 1−7). Comparison of the NMR data of the product with the literature values[7] indicates that the product isolated from the reaction mixture is 5-hydroxy-2-phenylbenzofuran **9a**. Later, its structure was unambiguously established on the basis of X-ray crystallographic analysis of O-methylated analogue, **9a′**.[8,9] No isomeric 6-hydroxy-2-phenylbenzofuran[10] was observed from the crude NMR analysis.

It turned out that solvent also plays a crucial role in this process. While the reaction in either MeOH or EtOH at 80 °C gave a complex mixture, use of *i*-PrOH led to 60% of **9a** (Table 1, entries 1, 8, and 9). A rather low yield of **9a**, however, was obtained in *t*-BuOH (Table 1, entry 10). Interestingly, no product was isolated in dioxane whereas the mixed solvent system (dioxane:H_2O, 1:1) afforded the desired product albeit in low yield (Table 1, entries 11 and 12). No desired product was obtained in toluene at 50 °C

TABLE 1. Screening of the Reaction Conditions



entry	catalyst[a]	solvent	temp (°C)	time (h)	yield (%)[b]
1	$PtCl_2$	*i*-PrOH	80	5	60
2	CuI	*i*-PrOH	80	24	NR[c]
3	$CuCl_2$	*i*-PrOH	80	24	CM[d]
4	$ZnCl_2$	*i*-PrOH	80	24	NR
5	$InCl_3$	*i*-PrOH	80	24	NR
6	$BiCl_3$	*i*-PrOH	80	24	NR
7	$AuCl_3$	*t*-PrOH	80	24	NR
8	$PtCl_2$	MeOH	80	24	CM
9	$PtCl_2$	EtOH	80	24	CM
10	$PtCl_2$	*t*-PrOH	80	34	30
11	$PtCl_2$	dioxane	50	24	CM
12	$PtCl_2$	dioxane:H_2O (1:1)	80	24	23
13	$PtCl_2$	toluene	50	24	CM
14	$PtCl_2$	DME	80	34	25
15	$PtCl_2$	DME:MeOH (20:1)	40	48	86
16	$PtBr_2$	DME:MeOH (20:1)	40	96	70
17	PtI_2	DME:MeOH (20:1)	40	48	NR
18	$PtCl_4$	DME:MeOH (20:1)	rt	3	60
19	$PtCl_4$	DME	rt	3	75
20	$PtCl_4$[e]	DME	rt	6	78
21	$PtCl_4$[f]	DME	rt	24	76
22	$PtCl_4$[e]	THF	rt	24	62
23	$PtCl_4$[e]	EA	rt	24	60

[a]10 mol % catalyst loading unless otherwise noted. [b]Isolated yield. [c]No reaction. [d]Complex mixture. [e]5 mol %. [f]1 mol %.

(Table 1, entry 13). Although longer reaction time is required, we found that lowering the reaction temperature is beneficial.[11] In particular, we were able to obtain **9a** in 86% yield by using a mixed solvent (DME:MeOH, 20:1) after 48 h at 40 °C (Table 1, entries 14 and 15). Other Pt(II) salts ($PtBr_2$ and PtI_2) were examined under these conditions, displaying lower reactivities than $PtCl_2$ (Table 1, entries 16 and 17). Surprisingly, $PtCl_4$ was found to induce this domino sequence at room temperature, furnishing **9a** in 60−75% yields (Table 1, entries 18 and 19). Even 5 or 1 mol % catalyst loading of $PtCl_4$ was effective without compromising the yield (Table 1, entries 20 and 21). It seemed that superior reactivity of $PtCl_4$ to $PtCl_2$ might be, in part, ascribed to the solubility issues as $PtCl_4$ is completely soluble in DME whereas $PtCl_2$ is not. Solvents such as THF or EA can be used although the yield was a little lower than that in DME (Table 1, entries 22 and 23).

Mechanistically, an alkyne moiety in **6a** migrates to the adjacent carbon to generate alkynone **A**,[12] which undergoes cyclization with the aid of Pt salt[13] to give benzofuran **9a**

(6) (a) Demizu, S.; Kajiyama, K.; Takahashi, K.; Hiraga, Y.; Yamamoto, S.; Tamura, Y.; Okada, K.; Kinoshita, T. *Chem. Pharm. Bull.* **1988**, *36*, 3474. (b) Basnet, P.; Kadota, S.; Terashima, S.; Shimizu, M.; Namba, T. *Chem. Pharm. Bull.* **1993**, *41*, 1238. (c) Su, B.-N.; Cuendet, M.; Hawthorne, M. E.; Kardono, L. B. S.; Riswan, S.; Fong, H. H. S.; Mehta, R. G.; Pezzuto, J. M.; Kinghorn, A. D. *J. Nat. Prod.* **2002**, *65*, 163. (d) Dat, N. T.; Jin, X.; Lee, K.; Hong, Y.-S.; Kim, Y. H.; Lee, J. J. *J. Nat. Prod.* **2009**, *72*, 39. (e) Kapche, G. D. W. F.; Fozing, C. D.; Donfack, J. H.; Fosto, G. W.; Amadou, D.; Tchana, A. N.; Bezabih, M.; Moundipa, P. F.; Ngadjui, B. T.; Abegaz, B. *Phytochemistry* **2009**, *70*, 216. (f) Ni, G.; Zhang, Q.-J.; Zheng, Z.-F.; Chen, R.-Y.; Yu, D.-Q. *J. Nat. Prod.* **2009**, *72*, 966.

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(8) **9a′** was prepared in a quantitative yield upon exposure of **9a** to MeI and Cs_2CO_3 in acetone at rt. See the Supporting Information for spectral data of 5-methoxy-2-phenylbenzofuran (**9a′**). See also: Duan, X.-F.; Zeng, J.; Zhang, Z.-B.; Zi, G.-F. *J. Org. Chem.* **2007**, *72*, 10283.

(9) CCDC 739254 contains the supplementary crystallographic data for compound **9a′**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(10) McAllister, G. D.; Hartley, R. C.; Dawson, M. J.; Knaggs, A. R. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3453.

(11) Benzofuran product seemed unstable to high temperature.

(12) For the cyclization of alkynones, see: (a) Fukuda, Y.; Shiragami, H.; Utimoto, K.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5816. (b) Sromek, A. W.; Kel'in, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 2280. (c) Yao, T.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 11164. (d) Patil, N. T.; Wu, H.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 4531. (e) Kirsch, S. F.; Binder, J. T.; Liébert, C.; Menz, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 5878. (f) Zhang, J.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2006**, *45*, 6704. (g) Zhang, G.; Huang, X.; Li, G.; Zhang, L. *J. Am. Chem. Soc.* **2008**, *130*, 1814. (h) Xiao, Y.; Zhang, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1903. (i) Sniady, A.; Morreale, M. S.; Wheeler, K. A.; Dembinski, R. *Eur. J. Org. Chem.* **2008**, 3449.

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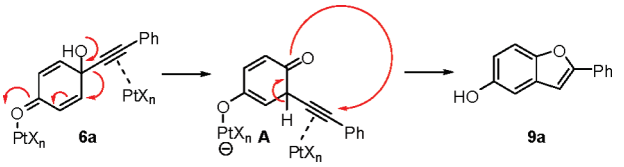
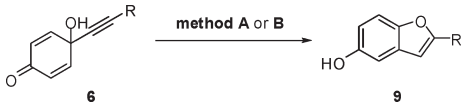
(Scheme 3). The exact role of Pt salt in the dienone−phenol rearrangement is not clear at this point but it presumably induces the migration by its action as a Lewis acid to coordinate to the dienone carbonyl oxygen as well as to the alkyne group. Notably, this cascade event occurs predominantly despite the presence of a sensitive functional group such as hydroxyl in **6a**, which is both propargylic and allylic.

SCHEME 3. Proposed Mechanism



Having found the optimal conditions, the reaction scope was examined with several quinols. As shown in Table 2, a number of aryl groups at the R position of **6** were tolerated under the reaction conditions (Table 2, entries 1−6). It should be mentioned that 5-methoxybenzofuran was also obtained as a minor product under condition A.[14,15] Heterocycle-containing benzofuran **9h** was produced from the corresponding quinol **6h** (Table 2, entry 7). 5-Hydroxybenzofurans containing alkyl groups at the C2 position were constructed in good yields as well (Table 2, entries 8−12). Exposure of **6n** and **6o** to these conditions also led to the corresponding benzofurans **9n** and **9o**, respectively (Scheme 4).

TABLE 2. Synthesis of Various 5-Hydroxybenzofurans

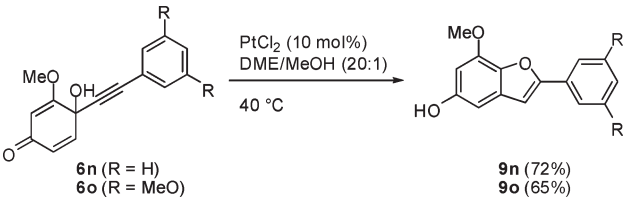


entry	substrate (R)		product	yield (%)[a,b]
1	4-MeOPh	**6b**	**9b**	75 (A)
2	3,5-$(MeO)_2$Ph	**6c**	**9c**	81 (A) 85 (B)[c]
3	4-MePh	**6d**	**9d**	80 (A)
4	4-FPh	**6e**	**9e**	81 (B)
5	3-FPh	**6f**	**9f**	83 (B)
6	6-methoxynaphthalen-2-yl	**6g**	**9g**	92 (A)
7	thiophen-3-yl	**6h**	**9h**	86 (A)
8	phenethyl	**6i**	**9i**	73 (A)[d]
9	*n*-butyl	**6j**	**9j**	77 (A)[d]
10	*tert*-butyl	**6k**	**9k**	78 (A)[d]
11	cyclohexenyl	**6l**	**9l**	79 (A)
12	cyclopentyl	**6m**	**9m**	69 (A)

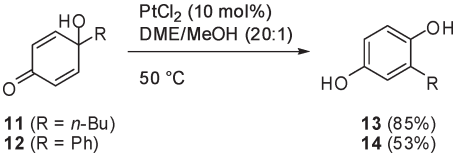
[a]Method A: $PtCl_2$ (10 mol %), DME/MeOH (20:1), 40 °C. Method B: $PtCl_4$ (5 mol %), DME, rt. [b]Isolated yield. [c]1 mmol scale. [d]50 °C.

To see if either simple alkyl or aryl group rearrangement could occur under these conditions, two quinols not having an alkyne unit, **11** and **12**,[16] were submitted to these conditions to provide **13** and **14**, implying this procedure should be useful for the synthesis of substituted 1,4-hydroquinones or benzoquinones (Scheme 5).

SCHEME 4

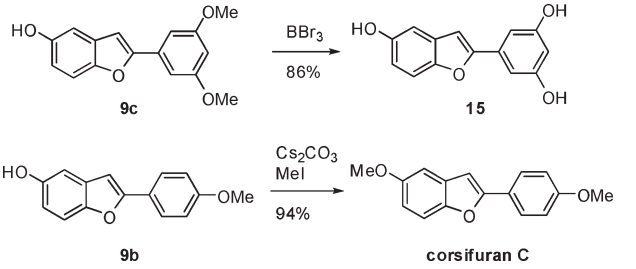


SCHEME 5



The basic benzofuran skeleton constructed by these methods can be further elaborated toward the synthesis of benzofuran-based natural products, which is briefly demonstrated in Scheme 6. For example, demethylation of **9c** with BBr_3 gave a 5-hydroxy regioisomer of moracin M in 86% yield. In addition, methylation of **9b** furnished corsifuran C in excellent yield.[17]

SCHEME 6. Further functionalization



In conclusion, we have developed the direct synthesis of 2-substituted 5-hydroxybenzofurans from alkyne-containing quinols using a Pt-catalyzed domino dienone−phenol rearrangement/intramolecular 5-*endo-dig* cyclization reaction sequence. This is the first example of the dienone−phenol rearrangement of quinols bearing alkynes. Also noteworthy is that this event was successfully coupled with the subsequent 5-*endo-dig* ring formation to allow for a ready access to a number of 5-hydroxybenzofurans having alkyl groups as well as aryl groups at the C2 position in good to excellent yields, which is unprecedented in the literature. Efforts to search for other catalytic systems to induce hydroxyl migration and to employ quinols for the construction of other carbo- and heterocycles are currently in progress, and will be reported soon.

Experimental Section

General Procedure for the Synthesis of 2-Substituted 5-Hydroxybenzofurans: Method A:. To a stirred solution of the quinols

(14) To directly obtain 5-methoxybenzofuran as the major product, use of MeOH as the sole solvent resulted in a complex mixture.

(15) For example, 2(3-fluorophenyl)-5-methoxybenzofuran (**9f′**) was isolated as a minor product by treatment of **6f** with $PtCl_2$. The structure of **9f′** was confirmed by X-ray crystallographic analysis. CCDC 739253 contains the supplementary crystallographic data for compound **9f′**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(16) For the preparation of **11** and **12**, see: Felpin, F.-X. *Tetrahedron Lett.* **2007**, *48*, 409.

(17) Spectral data of synthetic sample are in good agreement with those of natural corsifuran C. See: von Reuss, S. H.; König, W. A. *Phytochemistry* **2004**, *65*, 3113.

bearing an alkyne unit **6** (0.2 mmol) in DME/MeOH (20:1, 2 mL) was added $PtCl_2$ (10 mL). After being stirred at 40 °C for 48 h, the mixture was concentrated in vacuo and purified by flash column chromatography (hexanes:ethyl acetate:methylene chloride = 10:1:2) to afford 2-substituted 5-hydroxybenzofuran **9**. **Method B:** To a stirred solution of the quinols bearing an alkyne unit **6** (0.2 mmol) in DME (2 mL) was added $PtCl_4$ (5 mol %). After being stirred at rt for 6 h, the mixture was concentrated in vacuo, and purified by flash column chromatography (hexanes:ethyl acetate:methylene chloride = 10:1:2) to afford 2-substituted 5-hydroxybenzofuran **9**.

5-Hydroxy-2-phenylbenzofuran (9a):. ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 8.18 (br s, 1H), 7.91 (d, J = 8.3 Hz, 2H), 7.49 (t, J = 7.2 Hz, 2H), 7.40 (d, J = 7.7 Hz, 2H), 7.17 (d, J = 0.8 Hz, 1H), 7.06 (d, J = 2.5 Hz, 1H), 6.87 (dd, J = 2.5, 8.8 Hz, 1H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 157.2, 154.6, 150.3, 131.5, 131.0, 129.8, 129.4, 125.5, 114.2, 112.1, 106.4, 102.4; MS (EI) m/z 210 (M^+, 100), 181 (98), 165 (29), 152 (99), 127 (40), 105 (57), 76 (46); HRMS (EI) calcd for $[C_{14}H_{10}O_2]^+$ m/z 210.0681, found 210.0683.

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Supporting Information Available: Spectral data and copies of ^{1}H and ^{13}C NMR spectra of compounds **9**, **13**−**15**, and synthetic corsifuran C, and CIF files of **9a′** and **9f′**. This material is available free of charge via the Internet at http://pubs.acs.org.