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Pd-Catalyzed Ring Opening of Oxa- and Azabicyclic Alkenes with Aryl and Vinyl Halides: Efficient Entry to 2-Substituted 1,2-Dihydro-1-naphthols and 2-Substituted 1-Naphthols

Chi-Li Chen and Stephen F. Martin*

Department of Chemistry and Biochemistry, The University of Texas, Austin, Texas 78712

sfmartin@mail.utexas.edu

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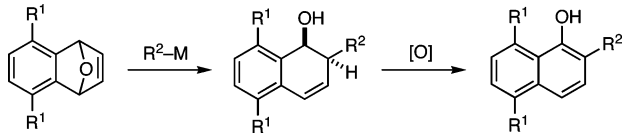


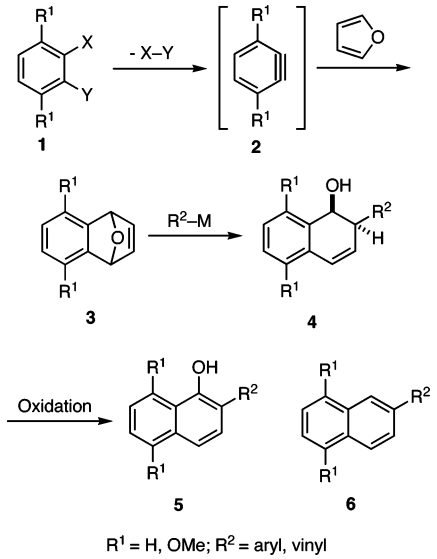
An efficient syntheses of 2-substituted 1,2-dihydro-1-naphthols and 2-substituted 1-naphthols has been developed that involves the sequential palladium-catalyzed ring opening of oxabicyclic alkenes with aryl and vinyl halides followed by oxidation of with IBX. In the first step of the sequence, a combination of $Pd(OAc)_2$, PPh_3, Zn, and PMP in dry DMF was employed to catalyze the ring opening of 7-oxabenzonorbornadienes with aryl and vinyl halides to afford the corresponding *cis*-2-substituted 1,2-dihydronaphthols in good to excellent yields. These reactions occurred under very mild conditions with a variety of aryl halides bearing electron-withdrawing or -donating groups. Similarly, a 7-azabenzonorbornadiene substituted with an electron-withdrawing group on the nitrogen atom underwent facile ring-opening reaction with aryl halides to provide *cis*-2-substitued (1,2-dihydro-1-naphthyl)carbamates in excellent yields. Oxidation of the intermediate1,2-dihydro-1-naphthols using IBX yielded the corresponding 2-substituted 1-naphthols in good to excellent yields.

Introduction

In the context of developing general synthetic approaches to *C*-aryl glycosides,[1] we discovered a facile and efficient entry to 1,2-dihydro-1-naphthols and 1-naphthols from benzenoid precursors according to the reactions outlined in Scheme 1.[2] The essential features comprise the well-known Diels−Alder reactions of benzynes **2**, which are generated in situ from suitable precursors **1**, with furan to give oxabenzonorbornadienes **3**. Subsequent ring opening of **3** with a variety of organometallic reagent then furnishes substituted dihydro-1-naphthols **4** that are transformed into the substituted 1-naphthols **5** by an oxidation.

Although numerous procedures and various tactics for inducing the ring opening of 7-oxabenzonorbornadienes **3** to give **4** are known,[3−15] most suffer from one or more limitations associated with their efficiency, generality, and/or ease of execution. Most relevant to the present work are the findings of Cheng, who described the ring opening of some oxabicyclic

SCHEME 1



(1) (a) Kaelin, D. E., Jr.; Lopez, O. D.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 6937−6938. (b) Apsel, B.; Bender, J. A.; Escobar, M.; Kaelin, D. E., Jr.; Lopez, O. D.; Martin, S. F. *Tetrahedron Lett.* **2003**, *44*, 1075−1077. (c) Kaelin, D. E., Jr.; Sparks, S. M.; Plake, H. R.; Martin, S. F. *J. Am. Chem. Soc.* **2003**, *125*, 12994−12995.

(2) For a preliminary report of some of these investigations, see: Chen, C.-L.; Martin, S. F. *Org. Lett.* **2004**, *6*, 3581−3584.

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alkenes with aryl and vinyl halides in the presence of nickel and palladium catalysts.[13] However, these reactions were not general as the Pd(0)-catalyzed reaction of electron-deficient aryl iodides with **3** gave primarily dehydration products **6** rather than the desired ring-opened products **4**.[13a,b] Transformations involving aryl and vinyl bromides as substrates typically proceeded in low yields,[13b,c] and there were no reports of reactions of aryl chlorides. In related work directed toward the synthesis of *C*-aryl glycosides, we had discovered that reactions of **3** with glycal iodides were sometimes inefficient, perhaps as a consequence of the instability of the glycal iodides under the reaction conditions.

Despite the ubiquity of oxidative transformations in organic synthesis, it is perhaps surprising that examples of the oxidation of dihydronaphthols are rare.[16] During the course of work directed toward the synthesis of *C*-aryl glycosides,[1a] we found that oxidations of substituted dihydronaphthols **4** (R^1 = OMe) to give the corresponding aromatic compounds **5** (R^1 = OMe) were often accompanied by extensive dehydration to give **6** as a deleterious side reaction. DDQ emerged as a useful oxidant in some cases, but we found that such conversions were sometimes difficult to optimize and reproduce.[1a] In the context of solving various problems associated with the generality of ring-opening reactions of oxabenzonorbornadienes **3** and the oxidation of the resultant 1,2-dihydronaphthols **4**, we developed a reliable and efficient protocol for preparing substituted compounds of the general form **4** and **5** from benzene derivatives according to Scheme 1. We now report the details of these investigations.[2]

(3) For reviews, see: (a) Chiu, P.; Lautens, M. *Top. Curr. Chem.* **1997**, *190*, 1−85. (b) Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48−58.

(4) DIBAL-H: (a) Lautens, M.; Chiu, P.; Colucci, J. T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 281−283. (b) Lautens, M.; Rovis, T. *J. Org. Chem.* **1997**, *62*, 5246−5247.

(5) Arylboronic acids: (a) Murakami, M.; Igawa, H. *Chem. Commun.* **2002**, 390−391. (b) Lautens, M.; Dockendorff, C.; Fagnou, K.; Malicki, A. *Org. Lett.* **2002**, *4*, 1311−1314. (c) Lautens, M.; Dockendorff, C. *Org. Lett.* **2003**, *5*, 3695−3698.

(6) Organozinc halide reagents: (a) Rayabarapu, D. K.; Chiou, C.-F.; Cheng, C.-H. *Org. Lett.* **2002**, *4*, 1679−1682. (b) Li, M.; Yan, X.-X.; Hong, W.; Zhu, X.-Z.; Cao, B.-X.; Sun, J.; Hou, X.-L. *Org. Lett.* **2004**, *6*, 2833−2835.

(7) Dialkylzinc reagents: (a) Lautens, M.; Renaud, J.-L.; Hiebert, S. *J. Am. Chem. Soc.* **2000**, *122*, 1804−1805. (b) Lautens, M.; Hiebert, S.; Renaud, J.-L. *Org. Lett.* **2000**, *2*, 1971−1973. (c) Lautens, M.; Hiebert, S.; Renaud, J.-L. *J. Am. Chem. Soc.* **2001**, *123*, 6834−6839. (d) Bertozzi, F.; Pineschi, M.; Macchia, F.; Arnold, L. A.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2002**, *4*, 2703−2705. (e) Lautens, M.; Hiebert, S. *J. Am. Chem.* Soc. **2004**, *126*, 1437−1447.

(8) Alkenylzirconium reagents: Wu, M.-S.; Rayabarapu, D. K.; Cheng, C.-H. *J. Org. Chem.* **2004**, *69*, 8407−8412.

(9) Organolithium reagents: Caple, R.; Chen, G. M. S.; Nelson, J. D. *J. Org. Chem.* **1971**, *36*, 2874−2876.

(10) Organomagnesium reagents: (a) Arrayás, R. G.; Cabrera, S.; Carretero, J. C. *Org. Lett.* **2003**, *5*, 1333−1336. (b) Nakamura, M.; Matsuo, K.; Inoue, T.; Nakamura, E. *Org. Lett.* **2003**, *5*, 1373−1375.

(11) Phenylstannanes: Fugami, K.; Hagiwara, S.; Oda, H.; Kosugi, M. *Synlett* **1998**, 477−478.

(12) Aryl triflates: Moinet, C.; Fiaud, J.-C. *Tetrahedron Lett.* **1995**, *36*, 2051−2052.

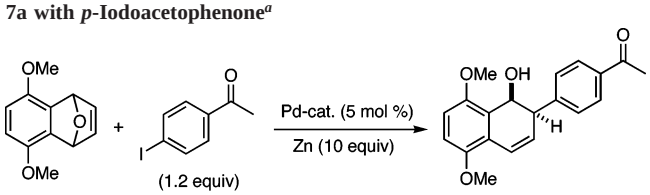
(13) Aryl halides: (a) Duan, J.-P.; Cheng, C.-H. *Tetrahedron Lett.* **1993**, *34*, 4019−4022. (b) Duan, J.-P.; Cheng, C.-H. *Organometallics* **1995**, *14*, 1608−1618. (c) Feng, C.-C.; Nandi, M.; Sambaiah, T.; Cheng, C.-H. *J. Org. Chem.* **1999**, *64*, 3538−3543.

(14) Thiols: Leong, P.; Lautens, M. *J. Org. Chem.* **2004**, *69*, 2194−2196.

(15) Alcohols and amines: Lautens, M.; Fagnou, K.; Rovis, T. *J. Am. Chem. Soc.* **2000**, *122*, 5650−5651.

(16) For the oxidative coupling of dihydronaphthols to give binaphthyl diols, see: Fillion, E.; Trépanier, V. E.; Mercier, L. G.; Remorova, A. A.; Carson, R. J. *Tetrahedron Lett.* **2005**, *46*, 1091−1094.

TABLE 1. Pd-Catalyzed Ring Opening of Oxabenzonorbornadiene 7a with *p*-Iodoacetophenone[a]



entry	catalyst, ligand (ratio)	solvent	time (h)	yield (%)[b]
1	$Pd(OAc)_2$, PPh_3 (1:2.2)	DMF	3	87
2	$(PPh_3)_2PdCl_2$	DMF	4.5	91
3	$Pd(PPh_3)_4$	DMF	12	85
4	$Pd(dppf)Cl_2$	DMF	16	32
5	$Pd_2(dba)_3$, dppe (1:2)	DMF	16	0
6	$(PPh_3)_2NiCl_2$	DMF	16	2
7	$NiCl_2$, dppf (1:1)	DMF	16	0
8	$NiCl_2$, dppe (1:1)	DMF	16	0
9	$Pd(OAc)_2$, PPh_3 (1:2.2)	THF	18	10
10	$Pd(OAc)_2$, PPh_3 (1:2.2)	Tol	18	3
11	$Pd(OAc)_2$, PPh_3 (1:2.2)	MeCN	8	44
12[c]	$Pd(OAc)_2$, PPh_3 (1:2.2)	DMF	3	95
13[d]	$Pd(OAc)_2$, PPh_3 (1:2.2)	DMF	3	60
14[c,e]	$Pd(OAc)_2$, PPh_3 (1:2.2)	DMF	3	90
15[c,f]	$Pd(OAc)_2$, PPh_3 (1:2.2)	DMF	2	64

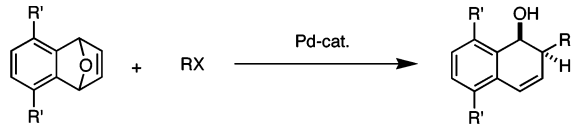
[a] Conditions: 0.05 M of **7a**, room temperature except as noted. [b] Isolated yield of product after chromatography. [c] PMP (0.5 equiv) used as additive. [d] Et_3N (8 equiv) used as additive. [e] Reaction performed at 45 °C. [f] Reaction performed at 60 °C.

Results and Discussion

Palladium-Catalyzed Ring-Opening Reaction. In our studies directed toward developing useful methods for the synthesis of *C*-aryl glycosides, we discovered that oxabenzonorbornadienes underwent ring opening with glycal iodides in the presence of $PdCl_2(PPh_3)_2$, Zn, $ZnCl_2$, and Et_3N, although the reactions required some experimentation to optimize.[1a,b] These basic conditions, which were originally reported by Cheng,[13a,b] seemed to constitute a useful point of embarkation for the present investigations. In the context of preparing 2-aryl naphthol derivatives, the challenge lay in discovering milder conditions that would be applicable to aryl halides bearing a wide variety of substituents. In this context, those aryl halides with electron-withdrawing substituents posed the greatest difficulty as premature dehydration of the intermediate dihydronaphthols was known to be a significant problem.[13a,b] We thus selected the reaction of dimethoxy oxabenzonorbornadiene **7a** with *p*-iodoacetophenone as the test system in which to optimize conditions for forming the ring-opened product **8a** (Table 1).

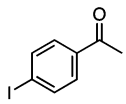
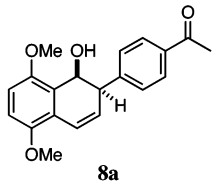
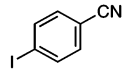
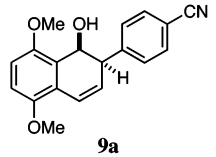
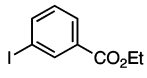
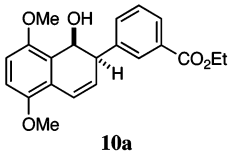
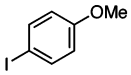
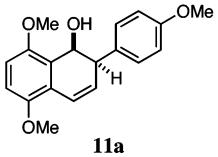
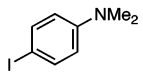
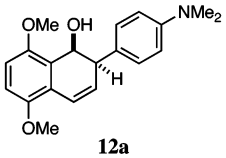
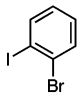
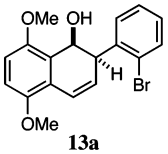
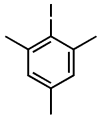
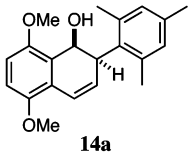
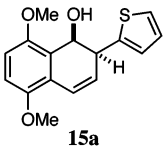
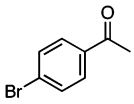
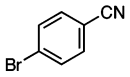
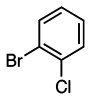
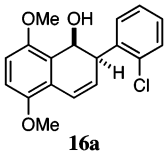
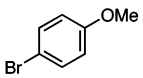
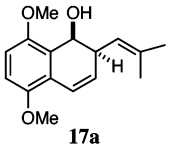
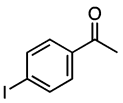
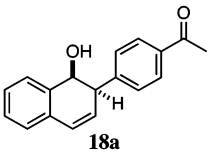
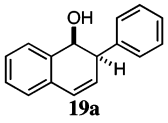
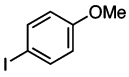
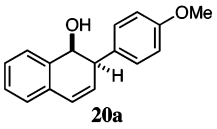
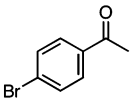
A variety of palladium and nickel precatalysts were screened for their ability to convert **7a** into **8a** in the presence of activated zinc powder (Table 1, entries 1−8). However, only $Pd(OAc)_2$/PPh_3, $(PPh_3)_2PdCl_2$, and $Pd(PPh_3)_4$ gave **8a** in reasonable yields, with $Pd(OAc)_2/PPh_3$ providing the fastest rates of reaction. The nature of the solvent proved important, with the reactions being slower in THF, toluene, and MeCN (entries 9−11) than in DMF. Moreover, significant amounts of the naphthalene byproduct arising from the dehydration of **8a** were observed when MeCN was used as solvent. Two tertiary amines 1,2,2,6,6,-pentamethylpiperidine (PMP, entry 12) and Et_3N (entry 13) were examined as additives. Use of PMP, which has been employed to advantage in Heck reations,[17] resulted in improved yields of **8a** to 95%, whereas the yield using Et_3N was lower, in part owing to formation of naphthalene products via dehydration of

TABLE 2. Pd-Catalyzed Ring Opening of 7a and 7b with Aryl and Vinyl Halides[a]



7a R^1 = OMe
7b R^1 = H

8a-20a

Oxabicycle	RX	Temp (°C)[b]	Time (h)	Product	Yield (%)[c]
7a		rt	3	 **8a**	95
		rt	4	 **9a**	90
		rt	2.5	 **10a**	92
		35	1.5	 **11a**	95
		35	2.5	 **12a**	83
		35	25	 **13a**	94
		60	20	 **14a**	71
		70	1.5	 **15a**	73[e]
		55	15	**8a**	71[d]
7a		45	12	**9a**	73[d]
		60	26	 **16a**	90[d]
		65	14	**11a**	73[d]
		75	3.5	 **17a**	62[e]
7b		rt	2	 **18a**	97
		35	2	 **19a**	95
		35	2.5	 **20a**	97
		50	6	**18a**	70

[a] Conditions: 0.05 M of **7a** or **7b** in DMF, RX (1.2 equiv), $Pd(OAc)_2$ (5 mol %), PPh_3 (11 mol %), PMP (0.5 equiv), Zn (10 equiv). [b] Oil bath temperature. [c] Isolated yield of product after chromatography. [d] $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %). [e] $Pd(OAc)_2$ (15 mol %), PPh_3 (30 mol %).

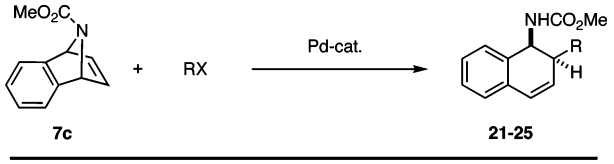
the intermediate 1,2-dihydro-1-naphthols. Increasing the temperature also tended to reduce the yields by increasing the amount of dehydration as a side reaction (entries 14 and 15). After extensive screening of various combinations of palladium and nickel precatalysts, solvents, amine bases, and temperatures, we eventually discovered that the combination of $Pd(OAc)_2$, PPh_3, PMP, and Zn in DMF was highly effective for promoting the ring opening of **7a**.

Having identified optimal conditions for effecting the palladium-catalyzed ring opening of **7a** with **8a**, it remained to vary the nature of the aryl halide and the oxabenzonorbornadiene to explore the scope of this process. Toward this end, a series of electron-rich and electron-deficient aryl iodides were screened and found to serve as excellent partners in ring-opening reactions with **7a** and **7b** to give the corresponding products **8a**−**15a** and **18a**−**20a** with high stereoselectivity and in good to excellent yields (Table 2). Under the mild conditions employed, only small amounts of dehydration products were observed, and the corresponding *trans*-1,2-dihydro-1-naphthols were not detected in the ^{1}H NMR spectra of the crude reaction mixtures. Aryl bromides bearing electron-withdrawing and electron-donating groups underwent facile reaction with **7a** or **7b**, albeit at higher temperatures than the corresponding aryl iodides, to provide the expected ring-opened products **8a**, **9a**, **11a**, and **16a**−**18a** (Table 2). The difference in reactivity of aryl iodides and bromides is sufficient that it may be exploited as exemplified by selective formation of **13a** from *o*-bromoiodobenzene. As is typical of most palladium-catalyzed cross-coupling processes, reactions involving electron-rich halides required higher temperatures than the corresponding electron-deficient halides.[18] Furthermore, mesityliodide and 2-iodothiophene required higher temperatures in order to obtain good yields of products, suggesting that these couplings may sensitive to steric and coordination effects.[19]

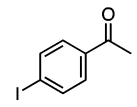
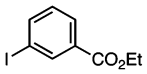
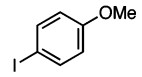
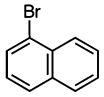
We also briefly explored the ring-opening reactions of the 7-azabenzonorbornadiene **7c** and discovered that the same conditions that had been developed for **7a** and **7b** were effective. Aryl iodides bearing electron-donating and -withdrawing groups as well as simple aryl bromides could be used in these cross-couplings to give the expected *cis*-2-substitued (1,2-dihydro-1-naphthyl)carbamates in excellent yields (Table 3). No dehydroamination to give naphthalene byproducts was observed under the conditions employed.

Oxidation of 1,2-Dihydronaphthols. Having established the generality of the cross-couplings of the 7-oxabenzonorbornadienes **7a** and **7b**, we turned our attention to developing conditions for effecting the oxidation of the intermediate dihydronaphthols to give naphthols. Oxidation of alcohols to give ketones is one of the most frequently used reactions in organic synthesis, but other than our previous work,[1a,b] there are few examples of oxidations leading to substituted 1-naphthols.[16] For example, we recently reported that glycal-substituted *cis*-1,2-dihydronaphthols could be oxidized to the corresponding *C*-aryl glycosides under carefully defined conditions using recrystallized DDQ.[1a,b] However, oxidation of **11a** under these

TABLE 3. Pd-Catalyzed Ring Opening of 7c with Aryl Halides[a]

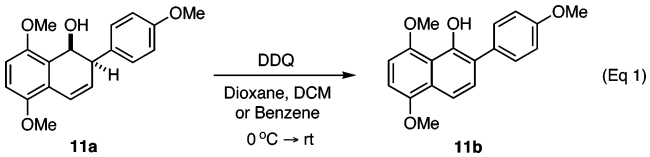


7c **21-25**

RX	Temp (°C)[b]	Time (h)	Product	Yield (%)[c]
	rt	12	**21**	91
	rt	6	**22**	96
	40	7	**23**	92
	40	7	**24**	96
	65	12	**25**	92[d]

[a] Conditions: 0.05 M of **7c** in DMF, RX (1.2 equiv), $Pd(OAc)_2$ (5 mol %), PPh_3 (11 mol %), PMP (0.5 equiv), Zn (10 equiv). [b] Oil bath temperature. [c] Isolated yield of product after chromatography. [d] $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %).

conditions yielded only trace amounts of the desired 2-aryl-1-naphthol **11b**, and little starting **11a** was recovered (Eq 1). We



11a **11b** (Eq 1)

then examined numerous oxidants to effect this transformation, but the naphthol **11b** was invariably isolated in poor yield together with the dehydration product and/or recovered starting material as well as several unidentified products. For example, oxidation of **11a** with Dess−Martin periodinane, PCC, Swern reagent, $Pd(OAc)_2$/pyridine/O_2/toluene,[20] $Pd(OAc)_2$/$NaHCO_3$/O_2/DMSO,[21] $Pd(PPh_3)_4$/PhBr/DMF/K_2CO_3 or NaH,[22] or IBX/H_2O/acetone/β-cyclodextrin[23] did not furnish the naphthol **11b** in more than about 30% yield, and simple dehydration was the major reaction in all of these experiments. Other oxidants including TPAP, DMSO/NEt_3/py-SO_3, MnO_2, *p*-chloranil, $Pd(nbd)Cl_2$/sparteine/O_2,[24] NCS/DMS/Et_3N, and DMDO[25] were similarly ineffective, giving only trace amounts of **11b** together

(17) For a discussion of use of different bases for Heck reactions, see: Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945−2964.

(18) For example, see: (a) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028. (b) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989−7000.

(19) For example, see: (a) Duan, J.-P.; Cheng, C.-H. *J. Chin. Chem. Soc.* **1994**, *41*, 749−754. (b) Schuman, M.; Lopez, X.; Karplus, M.; Gouverneur, V. *Tetrahedron* **2001**, *57*, 10299−10307.

(20) Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 6750−6755.

(21) Peterson, K. P.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 3185−3189.

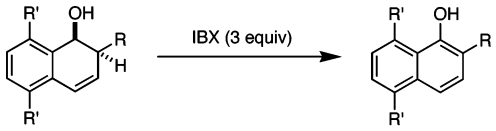
(22) Tamaru, Y.; Yamada, Y.; Inoue, K.; Yamamoto, Y.; Yoshida, Z.-I. *J. Org. Chem.* **1983**, *48*, 1286−1292.

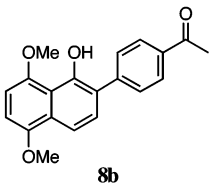
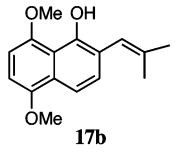
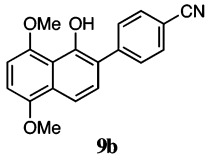
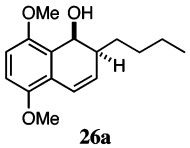
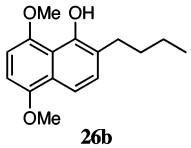
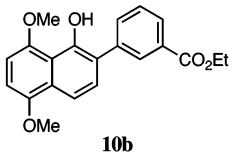
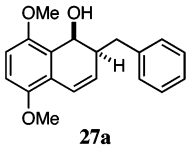
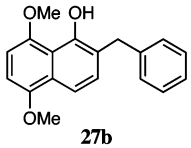
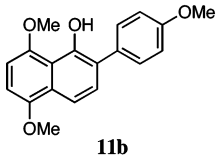
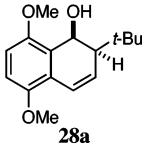
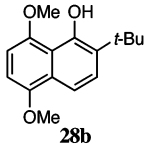
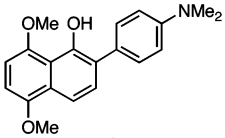
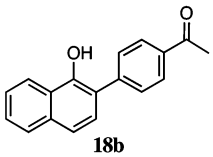
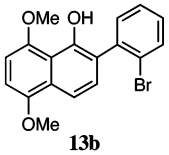
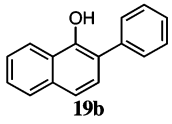
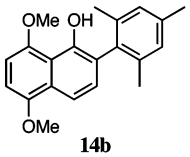
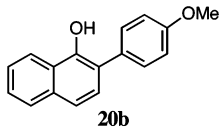
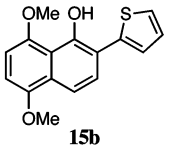
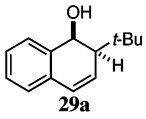
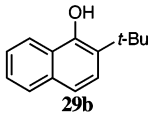
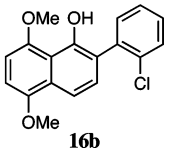
(23) Surendra, K.; Krishnaveni, N. S.; Reddy, M. A.; Nageswar, Y. V. D.; Rao, K. R. *J. Org. Chem.* **2003**, *68*, 2058−2059.

(24) Bagdanoff, J. T.; Ferreira, E. M.; Stoltz, B. M. *Org. Lett.* **2003**, *5*, 835−837.

(25) (a) Murray, R. W.; Singh, M.; Rath, N. *J. Org. Chem.* **1997**, *62*, 8794−8799. (b) Lee, J. S.; Fuchs, P. L. *Org.* Lett. **2003**, *5*, 2247−2250.

TABLE 4. Oxidation of 2-Substituted 1,2-Dihydro-1-naphthols with IBX

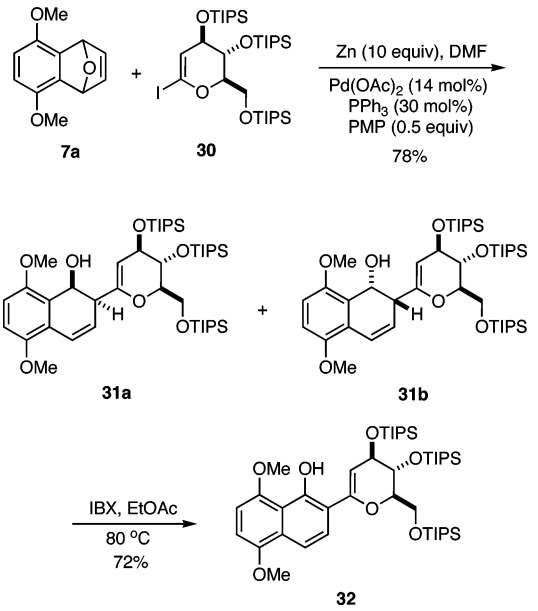


Alcohol	Solvent	Temp (°C)[a] /Time (h)	Product	Yield (%)[b]	Alcohol	Solvent	Temp (°C)[a] /Time (h)	Product	Yield (%)[b]
8a	EtOAc	60/14	 **8b**	88	**17a**	EtOAc	80/1.5	 **17b**	67
9a	acetone	40/20	 **9b**	76	 **26a**	EtOAc	80/3.5	 **26b**	85
10a	acetone	40/20	 **10b**	81	 **27a**	EtOAc	80/3	 **27b**	91
11a	EtOAc	60/14	 **11b**	94	 **28a**	EtOAc	80/3	 **28b**	91
12a	EtOAc	60/5	 **12b**	80	**18a**	THF	40/3	 **18b**	46[d]
13a	EtOAc	60/16	 **13b**	92	**19a**	THF	40/3	 **19b**	63[d]
14a	EtOAc	80/3	 **14b**	95	**20a**	THF	40/3.5	 **20b**	52[d]
15a	EtOAc	80/3	 **15b**	81[c]	 **29a**	THF	50/2.5	 **29b**	80[d]
16a	EtOAc	60/24	 **16b**	84					

[a] Oil bath temperature. [b] Isolated yield of product after chromatography. [c] IBX (1.5 equiv). [d] IBX (2 equiv).

with several unidentified products and/or recovered starting material. Gratifyingly, we eventually discovered that oxidation of **11a** with IBX[26] (3 equiv) in EtOAc at 60 °C for 14 h afforded naphthol **11b** in 94% yield. This reaction also proceeded at 80

SCHEME 2



°C in 3 h to provide **11b** in similar yield. Although acetone and THF were also found to be suitable solvents, DMSO, which is frequently used as solvent in IBX oxidations,[27] was not satisfactory because the naphthol products underwent more rapid decomposition, presumably by oxidation, in DMSO than in the other solvents. For example, when a homogeneous solution of **11b** in DMSO containing IBX was stirred at room temperature for 2 h, less than 10% of **11b** was recovered.

Having discovered that IBX was an effective oxidant for converting **11a** into **11b**, we then surveyed its utility as an oxidant of other substituted dihydronaphthols to give the corresponding 1-naphthols, and these results are summarized in Table 4. Yields were generally good to excellent with only small amounts of the corresponding naphthalenes being observed in the crude reaction mixtures. Because the product 1-naphthols were found to be somewhat unstable toward excess IBX, the yields in these oxidations were found to depend critically upon temperatures, reaction times, solvents, and the number of equivalents of IBX. Some experimentation was thus necessary to optimize the yield for oxidizing a given dihydronaphthol. For example, the oxidations of **8a** and **12a** in EtOAc to give **8b** and **12b** proceeded in 51% and 60% yields, respectively, at 80 °C, whereas the corresponding yields were 88% and 80% when the reactions were performed at 60 °C. Although ethyl acetate was frequently the solvent of choice, oxidations of **9a** and **10a** proceeded in higher yields in acetone because **9b** and **10b** appeared to be less stable toward IBX in EtOAc. It is noteworthy that this oxidation is not limited to the production of 2-aryl-1-naphthols, as IBX may also be used to oxidize 2-alkyl-1,2-dihydronaphthols to give 2-alkyl-1-naphthols as exemplified by the oxidations of **26a**−**29a**. However, in preliminary experiments, the *cis*-2-substitued (1,2-dihydro-1-naphthyl)carbamates **21**−**25** did not undergo clean oxidation to the corresponding protected naphthylamines using IBX.

We then employed these new protocols for converting oxabenzonorbornadienes into 1-naphthols in developing an improved route to *C*-aryl glycosides such as **32**.[1a,b] Thus, reaction of **7a** with glycal iodide **30** provided a mixture (4:1) of diastereomeric *cis*-dihydronaphthols **31a** and **31b** (Scheme 2). Subsequent oxidation of this mixture with IBX cleanly provided the *C*-aryl glycoside **32** in with no dehydration of the intermediate dihydronaphthols **31a** and **31b** being observed.

(26) More, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001−3003.

(27) (a) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019−8022. (b) Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272−7276. (c) Wirth, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 2812−2814.

Summary

We have developed a general and efficient method for the synthesis of 2-substituted 1,2-dihydro-1-naphthols and 2-substituted 1-naphthols from oxabenzonorbornadienes, which are readily accessed by the Diels−Alder reactions of benzynes with furan. The procedure involves sequential palladium-catalyzed ring opening of these oxabenzonorbornadienes with aryl or vinyl halides followed by oxidation of the intermediate dihydronaphthols with IBX. The palladium-catalyzed reaction is conducted under mild conditions and is applicable to aryl iodides and bromides with both electron-withdrawing and -donating groups, as well as to glycal iodides. The formation of naphthalene byproducts, which are otherwise commonly observed, is suppressed under the conditions of these reactions.

Experimental Section

General Procedure for Palladium-Catalyzed Ring Opening of Bicyclic Alkenes. 1,2,2,6,6-Pentamethylpiperidine (PMP) (67 μL, 0.37 mmol) was added to a mixture of bicyclic alkene (0.74 mmol), aryl or vinyl halide (0.88 mmol), $Pd(OAc)_2$ (9 mg, 5 mol %), PPh_3 (21 mg, 11 mol %), and activated Zn (480 mg, 7.4 mmol) in DMF (14.7 mL) under argon. The resulting mixture was heated at the indicated bath temperature (see Tables 2 and 3) with stirring until the starting bicyclic alkene was fully consumed as indicated by TLC. The reaction was allowed to cool to room temperature, 50% EtOAc/hexanes (60 mL) was added, and the mixture was filtered through a pad of Celite. The filtrate was washed with saturated aqueous NaCl (4 × 10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified by flash chromatography, eluting with EtOAc/hexanes in the ratio given to provide the 2-substituted 1,2-dihydro-1-naphthol derivatives (**8a**−**20a**, **21**−**25**).

***cis*-1,2-Dihydro-5,8-dimethoxy-2-mesityl-1-naphthol (14a).** 15% EtOAc/hexanes; white solid; mp 117−118 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.95 (dd, J = 9.8, 3.4 Hz, 1 H), 6.89 (s, 2 H), 6.82 (d, J = 8.9 Hz, 2 H), 6.76 (d, J = 8.9 Hz, 1 H), 6.21 (ddd, J = 9.8, 3.4, 1.2 Hz, 1 H), 5.16 (ddd, J = 5.5, 4.2, 1.2 Hz, 2 H), 4.13−4.02 (m, 1 H), 3.82 (s, 3 H), 3.80 (s, 3 H), 2.48 (s, 3 H), 2.34 (s, 3 H), 2.26 (s, 3 H), 1.65 (d, J = 4.2 Hz, 1 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 150.9, 149.4, 139.2, 136.7, 135.9, 133.2, 131.9, 130.7, 129.0, 124.4, 122.7, 117.5, 111.1, 109.9, 62.7, 56.1, 55.9, 42.3, 21.4, 20.9, 20.6; IR ($CDCl_3$) 3597, 2939, 1598, 1482, 1262, 1086 cm^{-1}; mass spectrum (CI) m/z 325.1802 [$C_{21}H_{25}O_3$ (M + H) requires 325.1804], 307 (base), 205.

***cis*-1,2-Dihydro-5,8-dimethoxy-2-(2-thienyl)-1-naphthol (15a).** 25% EtOAc/hexanes; orange liquid; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.27−7.24 (m, 1 H), 7.12−7.09 (m, 1 H), 7.07−7.00 (comp, 2 H), 6.82 (d, J = 9.1 Hz, 1 H), 6.78 (d, J = 9.1 Hz, 1 H), 6.07 (ddd, J = 9.8, 2.4, 1.4 Hz, 1 H), 5.17−5.10 (m, 1 H), 4.12−4.05 (m, 1 H), 3.82 (s, 3 H), 3.81 (s, 3 H), 1.83 (d, J = 5.4 Hz, 1 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 150.7, 149.6, 143.1, 128.5, 126.8, 125.6, 124.3, 124.2, 122.2, 122.0, 111.5, 111.1, 64.5, 56.1, 56.0, 42.7; IR ($CDCl_3$) 3594, 2938, 1602, 1486, 1259, 1087 cm^{-1}; mass spectrum (CI) m/z 288.0831 [$C_{16}H_{16}O_3S$ requires 288.0820], 271 (base).

***cis*-1,2-Dihydro-5,8-dimethoxy-2-(2-methyl-propenyl)-1-naphthol (17a).** 20% EtOAc/hexanes; orange liquid; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.91 (dd, J = 9.8, 3.1 Hz, 1 H), 6.79 (d, J = 9.0 Hz, 1

H), 6.74 (d, $J = 9.0$ Hz, 1 H), 5.80−5.71 (m, 1 H), 5.62−5.53 (m, 1 H), 4.93 (ddd, $J = 6.4$, 4.7, 1.2 Hz, 1 H), 3.81 (s, 3 H), 3.79 (s, 3 H), 3.34−3.24 (m, 1 H), 1.80 (d, $J = 1.1$ Hz, 3 H), 1.77 (d, $J = 6.4$ Hz, 1 H), 1.69 (d, $J = 1.3$ Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 150.5, 149.5, 134.4, 130.6, 125.2, 122.4, 122.3, 120.8, 111.1, 110.6, 63.6, 56.1, 56.0, 39.6, 25.9, 18.2; IR ($CDCl_3$) 3586, 2937, 1597, 1483, 1259, 1088 cm^{-1}; mass spectrum (CI) *m*/*z* 260.1400 [$C_{16}H_{20}O_3$ requires 260.1412], 243 (base).

Methyl *N*-[*cis*-1,2-Dihydro-2-(4-acetylphenyl)-1-naphthyl]carbamate (21). 30% EtOAc/hexanes; yellow solid; mp 112−113 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.85−7.77 (m, 2 H), 7.32−7.13 (comp, 6 H), 6.71 (dd, $J = 9.6$, 1.5 Hz, 1 H), 6.11 (d, $J = 9.6$, 4.8 Hz, 1 H), 5.35 (dd, $J = 10.3$, 7.0 Hz, 1 H), 4.66 (d, $J = 10.3$ Hz, 1 H), 3.96−3.85 (m, 1 H), 3.60 (s, 3 H), 2.54 (s, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 197.4, 156.3, 143.1, 136.0, 134.4, 134.0, 132.7, 129.0, 128.8, 128.3, 128.2, 127.9, 126.4, 125.4, 52.6, 52.1, 44.6, 26.3; IR ($CDCl_3$) 3320, 2952, 1721, 1681, 1519, 1269 cm^{-1}; mass spectrum (CI) *m*/*z* 322.1445 [$C_{20}H_{20}NO_3$ (M + H) requires 322.1443] (base), 247.

Methyl *N*-[*cis*-1,2-Dihydro-2-(3-ethoxycarbonylphenyl)-1-naphthyl]carbamate (22). 25% EtOAc/hexanes; pale yellow solid; mp 126−127 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.93−7.86 (m, 1 H), 7.80 (s, 1 H), 7.33−7.13 (comp, 6 H), 6.71 (dd, $J = 9.6$, 1.6 Hz, 1 H), 6.12 (dd, $J = 9.6$, 4.7 Hz, 1 H), 5.31 (dd, $J = 10.0$, 7.1 Hz, 1 H), 4.69 (d, $J = 10.0$ Hz, 1 H), 4.32 (q, $J = 7.1$ Hz, 2 H), 3.96−3.87 (m, 1 H), 3.59 (s, 3 H), 1.34 (t, $J = 7.1$ Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 166.3, 156.5, 138.1, 134.2, 133.2, 132.9, 130.6, 130.2, 129.5, 128.8, 128.5, 128.4, 128.3, 128.0, 126.5, 125.6, 60.9, 52.8, 52.2, 44.7, 14.2; IR ($CDCl_3$) 3337, 2981, 1717, 1522, 1283 cm^{-1}; mass spectrum (CI) *m*/*z* 352.1541 [$C_{21}H_{22}NO_4$ (M + H) requires 352.1549] (base), 277.

General Procedure for IBX Oxidation of 2-Substituted 1,2-Dihydro-1-naphthol. IBX (0.66 mmol) was added to a solution of 2-substituted 1,2-dihydro-1-naphthol (**8a**−**20a**, **26a**−**29a**) (0.22 mmol) in EtOAc (3.3 mL). The resulting suspension was then heated with vigorous stirring in an oil bath at the indicated temperature (see Table 4) until the starting material was fully consumed (TLC). The reaction was then allowed to cool to room temperature and diluted with 30% EtOAc/hexanes (15 mL). The mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash chromatography, eluting with EtOAc/hexanes in the ratio given to provide the 2-substituted 1-naphthols (**8b**−**20b**, **26b**−**29b**).

5,8-Dimethoxy-2-mesityl-1-naphthol (14b). 10% EtOAc/hexanes; white solid; mp 134−135 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.60 (s, 1 H), 7.76 (d, $J = 8.5$ Hz, 1 H), 7.17 (d, $J = 8.5$ Hz, 1 H), 6.95 (s, 2 H), 6.70 (d, $J = 8.4$ Hz, 1 H), 6.65 (d, $J = 8.4$ Hz, 1 H), 3.98 (s, 3 H), 3.96 (s, 3 H), 2.31 (s, 3 H), 2.02 (s, 6 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 150.5, 150.3, 150.2, 136.6, 135.1, 129.6, 128.0, 127.6, 123.2, 115.7, 112.8, 103.5, 102.7, 56.3, 55.7, 21.1, 20.3; IR ($CDCl_3$) 3381, 2918, 1612, 1511, 1391, 1252 cm^{-1}; mass spectrum (CI) *m*/*z* 323.1648 [$C_{21}H_{23}O_3$ (M + H) requires 323.1647] (base).

5,8-Dimethoxy-2-(2-thienyl)-1-naphthol (15b). 10% EtOAc/hexanes; pale reddish solid; mp 106−107 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 10.42 (s, 1 H), 7.77 (d, $J = 8.9$ Hz, 1 H), 7.71 (d, $J = 8.9$ Hz, 1 H), 7.63 (dd, $J = 3.7$, 1.1 Hz, 1 H), 7.34 (dd, $J = 5.0$, 1.1 Hz, 1 H), 7.12 (dd, $J = 5.0$, 3.7 Hz, 1 H), 6.72 (d, $J = 8.5$ Hz, 1 H), 6.64 (d, $J = 8.5$ Hz, 1 H), 4.04 (s, 3 H), 3.94 (s, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 150.3, 150.2, 150.1, 140.0, 127.3, 126.8, 126.7, 125.1, 125.0, 116.7, 116.1, 113.2, 104.4, 103.3, 55.6, 55.7; IR ($CDCl_3$) 3318, 2917, 1611, 1506, 1395, 1251 cm^{-1}; mass spectrum (CI) *m*/*z* 287.0734 [$C_{16}H_{15}O_3S$ (M + H) requires 287.0742] (base).

5,8-Dimethoxy-2-(2-methyl-propenyl)-1-naphthol (17b). 10% EtOAc/hexanes; orange solid; mp 75−77 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.77 (s, 1 H), 7.64 (d, $J = 8.6$ Hz, 1 H), 7.32 (d, $J = 8.6$ Hz, 1 H), 6.66 (d, $J = 8.4$ Hz, 1 H), 6.59 (d, $J = 8.4$ Hz, 1 H), 6.43 (s, 1H), 3.99 (s, 3 H), 3.92 (s, 3 H), 1.95 (s, 3 H), 1.82 (s, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 151.0, 150.3, 150.1, 135.5, 129.2, 126.9, 121.3, 120.6, 115.5, 112.0, 103.7, 102.5, 56.5, 55.7, 26.5, 19.7; IR ($CDCl_3$) 3586, 2937, 1597, 1483, 1259, 1088 cm^{-1}; mass spectrum (CI) *m*/*z* 259.1329 [$C_{16}H_{19}O_3$ (M + H) requires 259.1334] (base).

5,8-Dimethoxy-2-(*tert*-butyl)-1-naphthol (28b). 10% EtOAc/hexanes; yellow solid; mp 109−110 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 10.06 (s, 1 H), 7.61 (d, $J = 8.9$ Hz, 1 H), 7.45 (d, $J = 8.9$ Hz, 1 H), 6.63 (d, $J = 8.4$ Hz, 1 H), 6.55 (d, $J = 8.4$ Hz, 1 H), 4.00 (s, 3 H), 3.91 (s, 3 H), 1.47 (s, 9 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 152.7, 150.2, 150.1, 131.2, 127.0, 126.0, 116.0, 111.9, 103.2, 101.9, 56.4, 55.7, 34.8, 29.5; IR ($CDCl_3$) 3364, 2958, 1607, 1515, 1399, 1252 cm^{-1}; mass spectrum (CI) *m*/*z* 261.1491 [$C_{16}H_{21}O_3$ (M + H) requires 261.1491] (base).

***cis*-1,2-Dihydro-5,8-dimethoxy-2-(*n*-butyl)-1-naphthol (26a).** *n*-BuLi (1.67 mL, 2.20 M solution in pentane, 3.68 mmol) was added to a solution of oxabenzonorbornadiene **7a** (150 mg, 0.74 mmol) and TMEDA (222 μL, 1.47 mmol) in THF (7.4 mL) under argon at −78 °C over 5 min. After 40 min of stirring at −78 °C, EtOH (1 mL) was added. The resulting mixture was allowed to warm to room temperature, and then water (10 mL) and hexane (80 mL) were added. The organic layer was separated, and the aqueous layer was extracted with hexane (2 × 15 mL). The combined organic layers were washed with saturated aqueous NaCl (2 × 20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified by flash chromatography, eluting with Et_3N/EtOAc/hexanes (0.1:1:5) to give **26a** (190 mg, 98%) as a colorless oil whose ^{1}H and ^{13}C NMR spectral data were consistent with those reported.[2]

***cis*-1,2-Dihydro-5,8-dimethoxy-2-benzyl-1-naphthol (27a).** A solution of benzyllithium, which had been generated from *n*-BuLi (0.89 mL, 2.10 M solution in pentane, 1.88 mmol) and toluene (6 mL) containing TMEDA (226 μL) at 0 °C, was added to a solution of oxabenzonorbornadiene **7a** (153 mg, 0.75 mmol) in toluene (10 mL) under argon at 0 °C over 1 min. After 3 min of stirring at 0 °C, H_2O (1 mL) was added. The resulting mixture was allowed to warm to room temperature, and water (10 mL) and Et_2O (80 mL) were added. The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 15 mL). The combined organic layers were washed with saturated aqueous NaCl (2 × 20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified by flash chromatography, eluting with Et_3N/EtOAc/hexanes (0.1:1:5) to give **27a** (194 mg, 87%) as a white solid (mp 89−90 °C; lit.[2] mp 89−90 °C) whose ^{1}H and ^{13}C NMR spectral data were consistent with those reported.[2]

***cis*-1,2-Dihydro-5,8-dimethoxy-2-(*tert*-butyl)-1-naphthol (28a).** *t*-BuLi (1.08 mL, 1.70 M solution in pentane, 1.84 mmol) was added to a solution of oxabenzonorbornadiene **7a** (150 mg, 0.74 mmol) in THF (7.4 mL) under argon at −78 °C over 5 min. After 30 min of stirring at −78 °C, EtOH (1 mL) was added. The resulting mixture was allowed to warm to room temperature, and water (10 mL) and hexane (80 mL) were added. The organic layer was separated, and the aqueous layer was extracted with hexane (2 × 15 mL). The combined organic layers were washed with saturated aqueous NaCl (2 × 20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified by flash chromatography, eluting with Et_3N/EtOAc/hexanes (0.1:1:5) to give **28a** (184 mg, 95%) as a white solid; mp 112−113 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.96 (dd, $J = 10.0$, 3.2 Hz, 1 H), 6.74 (s, 2 H), 6.09−6.01 (m, 1 H), 5.25 (ddd, $J = 8.5$, 4.2, 1.4 Hz, 1 H), 3.82 (s, 3 H), 3.78 (s, 3 H), 2.10−2.04 (m, 1 H), 1.42 (d, $J = 8.5$ Hz, 1 H), 1.17 (s, 9 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 149.9, 149.4, 128.4, 126.1, 122.4, 121.4, 110.8, 110.3, 62.3, 56.1, 55.9, 49.6, 32.3, 28.6; IR ($CDCl_3$) 3590, 2959, 1598, 1482, 1261, 1086 cm^{-1}; mass spectrum (CI) *m*/*z* 262.1570 [$C_{16}H_{22}O_3$ requires 262.1569], 245, 189 (base).

***cis*-1,2-Dihydro-2-(*tert*-butyl)-1-naphthol (29a).** *t*-BuLi (1.22 mL, 1.70 M solution in pentane, 2.08 mmol) was added to a solution of oxabenzonorbornadiene **7b** (120 mg, 0.83 mmol) in THF (8.3

mL) under argon at −78 °C over 5 min. After 30 min of stirring at −78 °C, EtOH (1 mL) was added. The resulting mixture was allowed to warm to room temperature, and water (10 mL) and Et_2O (80 mL) were added. The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 15 mL). The combined organic layers were washed with saturated aqueous NaCl (2 × 20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified by flash chromatography, eluting with Et_3N/EtOAc/hexanes (0.1:1:7) to give **29a** (157 mg, 93%) as a white solid (mp 75−76 °C; lit.[9] mp 75−76 °C) whose ^1H and ^{13}C NMR spectral data were consistent with those reported.[9]

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Supporting Information Available: Summary of general experimental practices and copies of ^1H NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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