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# Remote Electronic Effects in the Rhodium-Catalyzed Nucleophilic Ring Opening of Oxabenzonorbornadienes

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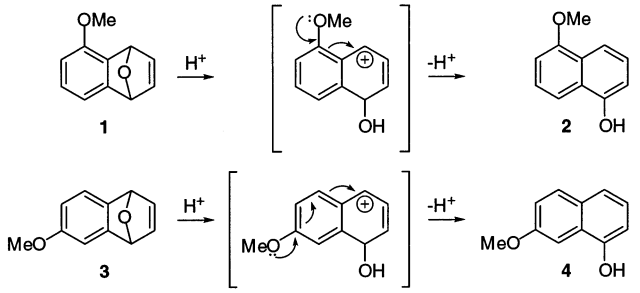
We report the application of our rhodium-catalyzed nucleophilic ring-opening methodology to unsymmetrically arene-substituted oxabenzonorbornadienes. The regioselectivity of the ring opening was investigated using a variety of nucleophiles that led to a broad selection of dihydronaphthalene products. It was found that good to excellent regioselectivities are obtained using strongly $\pi$-donating substituents, whereas $\sigma$-donating and electron-withdrawing functionalities have a minimal effect. Post ring-opening manipulations of functional groups in the dihydronaphthalene products were shown to give efficient access to mono- and diamine tetrahydronaphthalene building blocks.

## Introduction

Oxabicyclic compounds and particularly 7-oxabicyclo-[2.2.1]hept-2-ene derivatives are valuable intermediates for the synthesis of a variety of compounds of biological interest.[1] For instance, Vogel[2] has described the regioselective exo-addition of various electrophiles to the C=C double bond of 7-oxabicyclo[2.2.1]hept-5-en-2-one and closely related systems. The stereochemical outcome of these electrophilic additions is controlled by conjugative interactions of the carbonyl group across the bicyclic system or by neighboring group participation of a ketal substituent.

The regioselective cleavage of the oxygen bridge to give functionalized cyclohexanes is central to many synthetic strategies. A regioselective ring opening using organolithium reagents and 7-oxanorbornenes has been investigated by Arjona and Plumet[3] for cases where the olefinic moiety is directly substituted with appropriate Michael acceptor functionalities such as a vinyl sulfone. Similarly, methylthio substitution of the double bond of a 7-oxanorbornene enabled a regioselective ring opening promoted by a Lewis acid catalyst.[4]

**SCHEME 1**




Remote electronic effects mediated by an aromatic $\pi$-system have been thoroughly investigated for the transformation of substituted oxabenzonorbornadienes to the corresponding naphthols under protic conditions.[5] In two typical examples, treatment of oxabenzonorbornadienes **1** and **3** under acidic conditions gave one of two possible regioisomeric naphthol products (**2** and **4**) exclusively, since in both cases the depicted carbocationic intermediate is strongly favored by conjugative stabilization (Scheme 1).[6] However, the formation of the aromatic compounds from these chiral precursors entails a loss of all stereochemical information.

We therefore envisaged a regioselective ring opening of oxabenzonorbornadienes in which a remote substituent

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(3) For selected references, see: (a) Arjona, O.; Fernández de la Pradilla, R.; Garcia, E.; Martin-Domenech, A.; Plumet, J. *Tetrahedron Lett*. **1989**, *30*, 6437. (b) Arjona, O.; Fernández de la Pradilla, R.; Mallo, A.; Plumet, J.; Viso, A. *Tetrahedron Lett*. **1990**, *31*, 1475. (c) Arjona, O.; de Dios, A.; Fernández de la Pradilla, R.; Plumet, J.; Viso, A. *J. Org. Chem*. **1994**, *59*, 3906. (d) Arjona, O.; Borrallo, C.; Iradier, F.; Medel, R.; Plumet, J. *Tetrahedron Lett*. **1998**, *39*, 1977.

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(6) In an analogous experiment, even the weak $\sigma$-donating methyl group gave Batt a regioselectivity of 3:1, whereas the $\sigma$-withdrawing bromo group gave an inverted regioselectivity of 1:9 (ref 5b).

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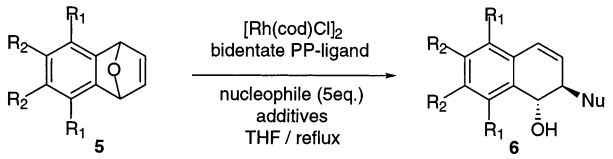
**SCHEME 2**[a]




[a] Bidentate PP−ligand = dppf, PPF−P$^t$Bu$_2$. Nucleophile = ROH, RR′NH, phthalimide, RCOOH, dimethylmalonate.

controls which C−O bond is broken while conserving the stereochemical information in the dihydronaphthalene products. It was necessary to replace the deprotonation step in an equivalent reactive intermediate by an addition of a nucleophile. The rhodium-catalyzed nucleophilic ring opening of oxabenzonorbornadienes developed in our group was potentially well suited to achieve this objective.[7]

Since we first reported the reductive and alkylative nucleophilic ring opening of oxabenzonorbornadienes using nickel and palladium catalysts,[8] we have successfully extended this methodology using rhodium catalysts and a variety of nucleophiles to include asymmetric additions of aliphatic alcohols,[9a] phenols,[9b,c] carboxylates,[9d] both aliphatic and aromatic amines,[9e] malonates,[9e] and most recently boronic acids.[10] The stereocontrolled addition of heteroatom nucleophiles to different oxabenzonorbornadienes of general structure **5** cleanly gives trans-substituted dihydronaphthalene products **6** (Scheme 2), whereas the addition of boronic acids was found to lead to the corresponding cis-products.[10]

The hydronaphthalene core can be found in a variety of natural and synthetic compounds, possessing a wide range of biological activities.[11] Given the medicinal interest, our goal was to prepare a diverse range of substitutional patterns on the hydronaphthalene pharmacophore in order to investigate the regioselectivity of opening unsymmetrically arene-substituted oxabenzonorbornadienes. If we could establish the necessary requirements for highly regioselective opening, subsequent modification of the dihydronaphthalene products promised to generate diverse structures within the hydronaphthalene scaffold.

## Results and Discussion

**Synthesis of Unsymmetrically Arene-Substituted Oxabenzonorbornadienes.**[12] We required versatile and efficient synthetic routes leading to multigram quantities of diversely substituted oxabenzonorbornadienes. There exists a multitude of methods for oxabenzonorbornadiene preparation[13] that differ in the way a highly reactive benzyne intermediate is formed. In all cases, the benzyne intermediate reacts with furan in a [4 + 2]-cycloaddition to form the strained oxabicyclic framework.[14] We selected three commonly used strategies of benzyne formation for the synthesis of five known and seven novel oxabenzonorbornadienes for reasons of their directness and reliability.[15]

Method I starts from suitable anthranilic acid derivatives.[16] These are treated with isoamyl nitrite in order to obtain the corresponding benzyne via an intermediate diazonium species. Substrates **8**[5a] and **11**[5a,b] (Table 1) were accessed accordingly using literature procedures.

Method II starts from substituted aryl bromides with an additional leaving group in the ortho-position, usually a second halogen or a tosylate substituent.[5c−e,17] Metal−halogen exchange using butyllithium and the subsequent expulsion of the second leaving group reliably gives the benzyne intermediate at different characteristic temperatures. We observed immediate elimination of lithium bromide at −78 °C, whereas lithium chloride is only eliminated at approximately −20 °C,[18] thus confirming once again the order of elimination found by Bunnett (I > Br > Cl > F).[19] In most cases, the yields of oxabenzonorbornadienes accessed by metal−halogen exchange are good and reproducible, making this the method of choice provided that the dihalide precursor is easily accessible and all other substituents are stable

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(12) For synthetic procedures of all oxabenzonorbornadienes used in this study, see Supporting Information.

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(14) The oxygen bridge causes a decrease in the bond angles between the benzene ring and the bridgehead carbons from the ideal 120° to typically 104.4 ± 0.5°, as determined by X-ray structure analysis of compounds **1**, **3**, and **13** (see Supporting Information).

(15) For selected references concerning alternative and more recent methods of benzyne generation, see: (a) Kitamura, T.; Meng, Z.; Fujiwara, Y. *Tetrahedron Lett.* **2000**, *41*, 6611. (b) Birkett, M. A.; Knight, D. W.; Little, P. B.; Mitchell, M. B. *Tetrahedron* **2000**, *56*, 1013. (c) Kitamura, T.; Yamane, M.; Inoue, K.; Todaka, M.; Fukatsu, N.; Meng, Z.; Fujiwara, Y. *J. Am. Chem. Soc.* **1999**, *121*, 11674. (d) Effenberger, F.; Daub, W. *Chem. Ber.* **1991**, *124*, 2113. (e) Furukawa, N.; Shibutani, T.; Fujihara, H. *Tetrahedron Lett.* **1987**, *28*, 2727. (f) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211.

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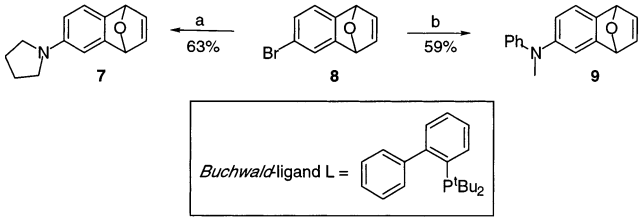
**TABLE 1. Regioselectivity of the Ring-Opening Reaction Using Methanol as a Nucleophile**

| entry[a] | substrate | $R_1$[b] | $R_2$[c] | $R_3$[c] | $R_4$[b] | products **17** + **18** | yield[d] of **17** + **18** (ratio[e]) |
|---|---|---|---|---|---|---|---|
| 1 | **10** | H | Ac | H | H | **a** | 83% (1.05:1) |
| 2 | **11**[5a−b,15c] | H | H | H | $CH_3$ | **b** | 86% (1.05:1) |
| 3 | **12** | H | H | $CF_3$ | H | **c** | 84% (1.05:1) |
| 4 | **13** | $OCH_3$ | H | H | Ac | **d** | 62% (1.1:1) |
| 5 | **8**[5a] | H | H | Br | H | **e** | 75% (1.8:1) |
| 6 | **1**[5d,20e] | $OCH_3$ | H | H | H | **f** | 81% (3.5:1) |
| 7 | **14** | $OCH_3$ | H | H | Cl | **g** | 82% (3.9:1) |
| 8 | **15** | $OCH_3$ | H | Cl | H | **h** | 82% (4.9:1) |
| 9 | **3**[5d] | H | H | $OCH_3$ | H | **i** | 89% (12:1) |
| 10 | **16**[5d,21] | $OCH_3$ | H | $OCH_3$ | H | **j** | 80%[f] (>25:1) |
| 11 | **9** | H | H | $N(CH_3)Ph$ | H | **k** | 58%[f] (>25:1) |

[a] In the order of increasing regioselectivity. [b] Proximal positions. [c] Distal positions. [d] Yield of purified material. Conditions: 2.5 mol % $[Rh(cod)Cl]_2$/5 mol % dppf, THF/MeOH 1:1, reflux, 0.2 M in substrate. [e] Determined by crude $^1H$ NMR and confirmed by isolated yields for all cases where regioisomers were separable by column chromatography. [f] Only one regioisomer was observed.

**SCHEME 3**[a]



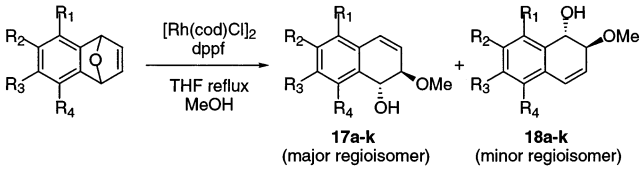

[a] Reaction conditions: (a) 1.2 equiv of pyrrolidine, 1.4 equiv of $NaO^tBu$, 7 mol % $Pd(OAc)_2$, 14 mol % L, toluene (1 M in aryl halide **8**), 60 °C, 15 h. (b) 1.2 equiv of *N*-methylaniline, 1.4 equiv of $NaO^tBu$, 5 mol % $Pd_2(dba)_3$, 10 mol % L, toluene (1 M in aryl halide **8**), 60 °C, 19 h.

toward butyllithium. Substrates **3**,[5d] **10**, and **12** (Table 1) were prepared using this methodology.

Method III starts from substituted anisoles containing a leaving group in the meta-position and takes advantage of the ortho-directing properties of the methoxy group.[20] Thus, treatment of suitably substituted anisoles with LDA efficiently generates the corresponding benzynes via ortho-lithiation and the subsequent elimination of the adjacent leaving groups. Substrates **1**[5d,20e] and **13**−**16**[5d,21] (Table 1) were reliably prepared in one-step procedures following this strategy, the yields ranging from 46 to 76%.

While significantly expanding the scope of methods II and III, we also showed that manipulation of the substituents on an oxabenzonorbornadiene was possible. Thus, the Buchwald−Hartwig amination methodology[22] was employed to access nitrogen-substituted oxabenzonorbornadienes **7** and **9** from bromo-substituted **8** (Scheme 3). None of the aforementioned direct methods had been successful in delivering nitrogen substitution. Also, deprotection of the ketal functionality in the synthetic precursors to substrates **10** and **13** proved to be possible using the mild procedure described by Sterzycki[23] (PPTS in wet acetone, 60 °C). It is noteworthy that the otherwise acid-sensitive oxabenzonorbornadienes are sufficiently stable to these reaction conditions.

**SCHEME 4**




**Regioselectivity of the Rhodium-Catalyzed Ring-Opening Reaction.** With a representative selection of unsymmetrically substituted oxabenzonorbornadiene substrates in hand, a standard set of ring-opening reaction conditions[9c] was employed (Scheme 4), enabling a direct comparison of the regioselectivities for almost all substrates (Table 1).[24] Methanol was chosen as the standard nucleophile, since it can easily be used in large excess while being small enough not to dominate the $R_f$ in the ring-opened products, thus generally facilitating chromatographic separation of regioisomers. Though the nature of the respective nucleophiles (e.g., nucleophilicity, ability to act as a ligand to rhodium, solubility, and necessity for additives) brings minor variations in reactivity for a given oxabenzonorbornadiene substrate, the regioselectivity has been found to be largely substrate-dominated. The catalyst system employed also strongly affects the outcome of these reactions, and we screened a variety of systems for regioselectivity by variation of the catalyst precursor,[25a] the phosphine ligand,[25b] and the remaining ligands[25c] on the rhodium(I) center. Though some catalyst systems such as $[Rh(CO)_2Cl]_2$ gave significantly higher regioselectivities than others, reactions with this catalyst were accompanied by a greater number of byproducts. In many cases (e.g., using monodentate ligands), intractable mixtures of unidentified products were obtained. Our studies demonstrated that the origi-

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(24) The ring opening of the pyrrolidinyl-substituted substrate **7** (scheme 3) with methanol gives a product that proved to be unstable under standard ring-opening reaction conditions. However, ring opening with *N*-methylaniline gives one regioisomer exclusively in 86% yield.

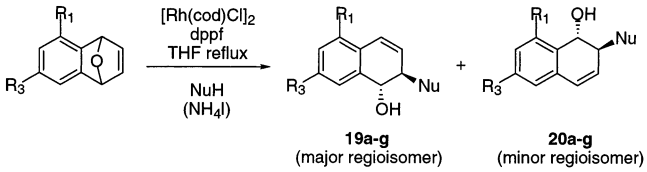
(25) (a) $[Rh(CO)_2Cl]_2$, $[Rh(cod)Cl]_2$. (b) Monodentate: $PPh_3$, $P(O^iPr)_3$, $P(2\text{-furyl})_3$, (*o*-biphenyl)$P(^tBu)_2$, 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)-biphenyl. Bidentate: dppm, dppe, dppp, dppb, dpppe, dppf. (c) $Cl^-$, $I^-$, CO, solvent molecule.

nal catalyst system[9a] (2.5 mol % $[Rh(cod)Cl]_2$/5 mol % dppf) proved to be the most reliable for the ring openings, generally giving reproducible yields and regioselectivities, although the catalyst formed with dppf proved to be far less active than the Rh−JOSIPHOS complexes used in asymmetric ring openings (ARO).[9]

Table 1 gives the results of the standard ring-opening experiments in the order of increasing regioselectivity, using methanol as a nucleophile. The structural assignment of the two regioisomers was accomplished by X-ray structure analysis[26] of the major regioisomers **17f** and **17i** containing both proximal and distal[27] methoxy substitution (entries 6 and 9). For all other entries, the comparison of the $^1H$ NMR data of the two respective regioisomers with the data recorded for entries 6 and 9 enabled an unambiguous assignment of substituent positioning. The $^1H$ NMR signals of the aromatic and olefinic protons revealed characteristic coupling patterns and relative chemical shifts for both proximal and distal substitution.

The results (Table 1) clearly show that substrates with strong $\pi$-donating substituents, containing either oxygen or nitrogen atoms, lead to high regioselectivity (entries 6−11), whereas $\pi$-withdrawing groups (e.g., acetyl group, entry 1), $\sigma$-withdrawing groups ($CF_3$ group, entry 3), and $\sigma$-donating groups (methyl group, entry 2) have practically no effect on regioselectivity. Even the weak $\sigma$-donating methyl group had shown significant regioselectivity for the conversion of substrate **11** to the corresponding naphthols.[5b,6] In our study, however, only the $\pi$-withdrawing acetyl group and the methyl group were able to reverse the regioselectivity observed in all other entries. Significantly, the $CF_3$ group minimally favors the same regioisomer as a methoxy group, indicating that its $\sigma$-withdrawing properties do not influence this process. Moreover, an acetyl group, placed in a para-position to a methoxy group, not only fails to enhance regioselectivity, as is characteristic for electrophilic aromatic substitution reactions, but almost completely counteracts the influence of the methoxy group (entry 4). Halogen substituents have a small but distinct influence on regioselectivity by virtue of their poor $\pi$-donating ability, as seen from entry 5 or by comparison of entries 6−8. Again, it is particularly noteworthy that bromo substitution (entry 5) favors the same regioisomer as the analogous methoxy substitution (entry 9), clearly indicating that $\pi$-donating abilities overwhelmingly dominate the rhodium-catalyzed reaction. In stark contrast to this result, the ionic reaction pathway of naphthol formation under protic conditions gave Batt the reversed regioselectivity for proximal bromo-substitution.[5b,6] Finally, the rhodium-catalyzed nucleophilic ring opening has proven to be sufficiently chemoselective to allow for bromo substitution on the aromatic ring.

**SCHEME 5**




**19a-g** (major regioisomer) **20a-g** (minor regioisomer)

In addition to the obvious electronic effects, there also exists a small steric component in the cases of proximal substitution that seems to inhibit the catalyst's approach to the C−O bond that will be broken en route to the electronically favored product. In this sense, the electronically "wrong" regioisomer is (minimally) favored by the overriding steric effect in the case of the weak $\sigma$-donating methyl group (entry 2), whereas the difference in regioselectivity shown in entries 6 and 9, where a single methoxy group is placed in the proximal and distal positions, respectively, may be at least partially attributed to the stronger steric hindrance exerted by the proximal substitution. Steric effects also cause a rise in regioselectivity going from entry 6 to entry 7, since we would expect a decrease due to the unfavorable 1,4-relationship of the two substituents. Entry 8, on the other hand, illustrates the increase in regioselectivity seen for the corresponding 1,3-substituents.

Chromatographic separation of the regioisomers is generally easy with substrates having proximal substitution, whereas distal substitution results in little difference in the $R_f$. In all but two cases (entries 1 and 2), where the regioselectivity is reversed, the major product has a higher $R_f$ and can be isolated in high purity, whereas the minor component can be accompanied by significant amounts of impurities.

An aliphatic amine substituent was found to be the most effective in obtaining high regioselectivity, activating the bicyclic system so strongly that most dihydronaphthalene products are no longer stable to the reaction conditions. To compare the ring opening of substrate **7** with that of the other substrates, it was therefore necessary to change to *N*-methylaniline as a nucleophile (Scheme 5), since the corresponding products generally are more stable.[28] Entries 1−3 of Table 2 give the regioselectivities for the ring opening of the three most selective systems. The results show that two methoxy groups placed in a reinforcing 1,3-relationship (entry 1) are approximately equal to one aromatic nitrogen substituent (entry 2). Aliphatic nitrogen substitution (entry 3) clearly gives the highest selectivity, though the dihydronaphthalene product **19c** is very acid-sensitive.[29] Strongly activated dihydronaphthalene products such as **19c** must be reduced to the corresponding tetrahydronaphthalene if they are to be stored over a longer period of time (see below). Finally, it must be noted that strong $\pi$-donating groups are a necessary condition in order to obtain synthetically useful regioselectivities (>10:1).

(26) Data were collected on a Nonius Kappa CCD diffractometer using a combination of $\phi$ and $\omega$ scans with $\kappa$ offsets. Data were integrated and scaled using the Denzo-SMN package [Otwinowski, Z.; Minor, W. *Methods in Enzymology*; Academic Press: London, 1997, 307.]. The structure was solved and refined using SHELXTL V6.12. The full-matrix least-squares refinement was based on $F^2$ [Sheldrick, G. M. SHELXTL/PC, version 6.12 for Windows NT. Bruker AXS, Inc.: Madison, WI; 2001.]. See Supporting Information.

(27) In this paper, the positions of $R_1$ and $R_4$ within the structures of Scheme 3 will be termed proximal in relation to the dihydrofuran moiety. The positions of $R_2$ and $R_3$ will be termed distal.

(28) *N*-Methylaniline is the most versatile nucleophile and reacts with all the substrates examined to date. The regioselectivity using *N*-methylaniline is always slightly below the regioselectivity observed with methanol.

(29) The silica used for column chromatography had to be thoroughly neutralized with triethylamine prior to purification. Otherwise, **19c** was cleanly converted to its corresponding naphthol in 89% overall yield.

**TABLE 2. Regioselectivity of the Ring-Opening Reaction Using the Most Selective Substrates with Different Nucleophiles**

| entry[a] | substrate | $R_1$ | $R_3$ | nucleophile (NuH) | products **19** + **20** | yield[b] of **19** (ratio[c]) |
|---|---|---|---|---|---|---|
| 1 | **16** | $OCH_3$ | $OCH_3$ | *N*-methylaniline | **a** | 84% (11:1) |
| 2 | **9** | H | $N(CH_3)Ph$ | *N*-methylaniline | **b** | 80% (11:1) |
| 3 | **7** | H | $N(C_4H_8)$ | *N*-methylaniline | **c** | 86%[d] (>25:1) |
| 4 | **16** | $OCH_3$ | $OCH_3$ | dibenzylamine | **d** | 77% (11:1) |
| 5 | **16** | $OCH_3$ | $OCH_3$ | phenol | **e** | 74%[d] (>25:1) |
| 6 | **16** | $OCH_3$ | $OCH_3$ | dimethylmalonate | **f** | 55%[d] (>25:1) |
| 7 | **16** | $OCH_3$ | $OCH_3$ | 4-hydroxyacetophenone | **g** | 50% (18:1) |

[a] In the order of increasing regioselectivity (entries 1−3) or decreasing yield (entries 4−7). [b] Yield of purified material. Conditions: 2.5 mol % $[Rh(cod)Cl]_2$/5 mol % dppf, THF reflux, 0.4 M in substrate, 5 equiv of nucleophile, 2.5 equiv of ammonium iodide (entries 4 and 6). [c] Determined by crude $^1$H NMR and confirmed by isolated yields for all cases where regioisomers were separable by column chromatography. [d] Only one regioisomer was observed.

There are no spectroscopic parameters with which to predict the regioselectivity of a given substrate with certainty, though selective systems often give distinctly different chemical shifts for the $^1$H-signals corresponding to the bridgehead positions (typically 5.60−6.00 ppm). Even the two C−O bond lengths[30] within the bicyclic moiety have been shown to be equal within experimental error.

**Using Other Nucleophiles on Highly Activated Systems.** The dimethoxy-substituted oxabenzonorbornadiene **16**[5d,21] was chosen for a study on the use of other nucleophiles (Scheme 5) because it is easily prepared from 5-chloro-1,3-dimethoxybenzene on a multigram scale while giving synthetically useful regioselectivities. At the same time, substrate **16** leads to regioisomers that are easily separated thanks to proximal substitution.

Entries 4−7 in Table 2 are listed in order of decreasing yield.[31] The nature of the nucleophile has a very limited influence on regioselectivity, whereas the yield of the ring-opened product strongly depends on the nucleophilicity and the tendency of NuH to be eliminated from the dihydronaphthalene products, giving the substituted naphthol derivatives. Thus, the adduct from the more easily eliminated 4-hydroxyacetophenone is isolated in lower yield than the corresponding phenol-derived dihydronaphthalene (entries 5 and 7). The benzoic acid-derived product could only be isolated with great care.[31] Dimethylmalonate (entry 6) and pyrrolidine[31] are best used as nucleophiles with ammonium iodide as an additive.[9e] In the case of strongly activated systems, the reduced stability of the substrate and products becomes the limiting factor. Fortunately, dibenzylamine efficiently gives the desired product **19d** in good yield and excellent purity. Ammonium iodide (2.5 equiv) was added to facilitate the dissociation of the amine from the rhodium center.

In conclusion, a representative member of each class of nucleophiles[32] used in previous publications[9] was tried on the highly activated system of substrate **16**. Moderate to good yields were obtained in each case with the exception of the carboxylate family, which has been shown to give products that are prone to decomposition under the reaction conditions.

**Introducing Amino Functionalities to Ring-Opened Dihydronaphthalenes.** Our next goal became the development of post ring-opening strategies suitable for the preparation of nitrogen-substituted tetrahydronaphthalenes including **22**, **24**, **27**, and **28** (Scheme 6). Finding suitable conditions for the selective reduction of the olefin in the substituted dihydronaphthalenes proved to be challenging in some cases. For instance, catalytic hydrogenation using either Pd/C or Pt/C led to over-reduction at benzylic positions. In addition, an azide was considered as a likely intermediate in our routes so that selective olefin reductions were of interest.

1-Amino-tetrahydronaphthalene **22** was obtained by standard $H_2$/Pt/C reduction[33] of ring-opened intermediate **17j**, followed by Mitsunobu-type inversion of the hydroxy group in **21** using DPPA as an azide source[34] and $H_2$/Pd/C reduction[35] of the corresponding (*cis*)-azide intermediate.[36] Since the benzylic position in **21** is highly activated, the Mitsunobu-reaction was conducted in toluene at −20 °C in order to minimize the competing elimination process while at the same time completely inhibiting epimerization observed at 0 °C, which led to the formation of the corresponding (*trans*)-azide.[36] The 2-amino-tetrahydronaphthalene **24** was prepared by a very efficient diimide reduction[37] of **19d**, followed by double deprotection of **23** using ammonium formate to act as a catalytic hydrogen transfer agent.[38] Deprotection of **23** was completed in 15 min, and compound **24** was best isolated as its hydrochloride by simple extraction of the product with 2 M HCl and concentration of the resulting aqueous solution. Hydrogenation of **23** using

(30) As determined by X-ray structure analysis of compounds **1**, **3**, and **13** (cf. ref 26).

(31) Ring opening with triethylammonium benzoate gave the corresponding (very unstable) dihydronaphthalene product in only 25% yield (9:1 ratio). It was not fully characterized. Ring opening with pyrrolidine/ammonium iodide gave complete decomposition under standard reaction conditions.

(32) Alcohols, phenols, aliphatic and aromatic amines, carboxylates, and malonates.

(33) For a review on olefin reductions, see: Siegel, S. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1991, p 417 and references therein.

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(36) $^1$H NMR presents a valuable tool for the determination of the relative configuration of 1,2-disubstituted tetrahydronaphthalenes, since the cis-configuration invariably gives a smaller vicinal coupling constant than the corresponding trans-configuration. Thus, the (*cis*)-azide intermediate gave a $^1$H NMR signal of H(1) = 4.61 (d, $J$ = 3.6 Hz), whereas the corresponding (*trans*)-azide showed a $^1$H NMR signal of H(1) = 4.44 (d, $J$ = 6.3 Hz). Analogously, (*trans*)-azide **25** gave a $^1$H NMR signal of H(1) = 4.53 (d, $J$ = 9.7 Hz) with an even larger vicinal coupling constant.

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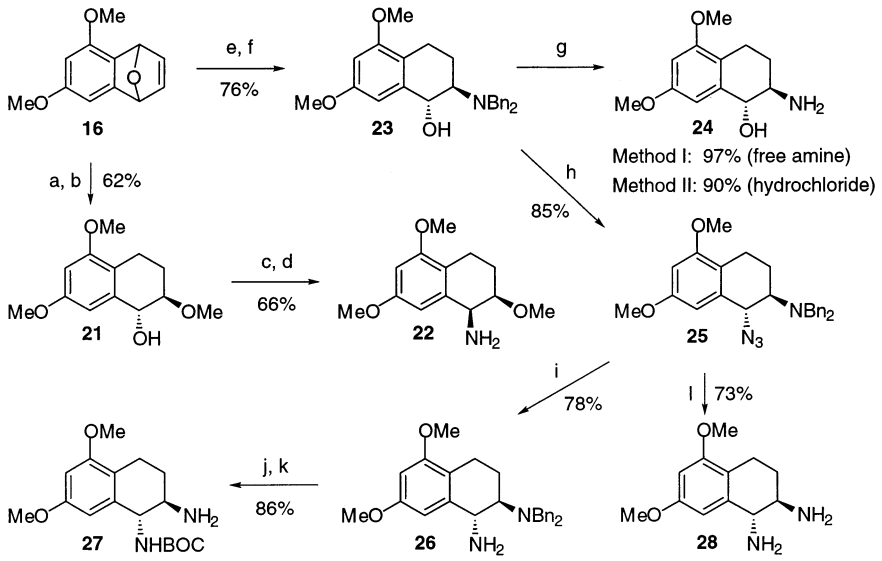
**SCHEME 6**[a]



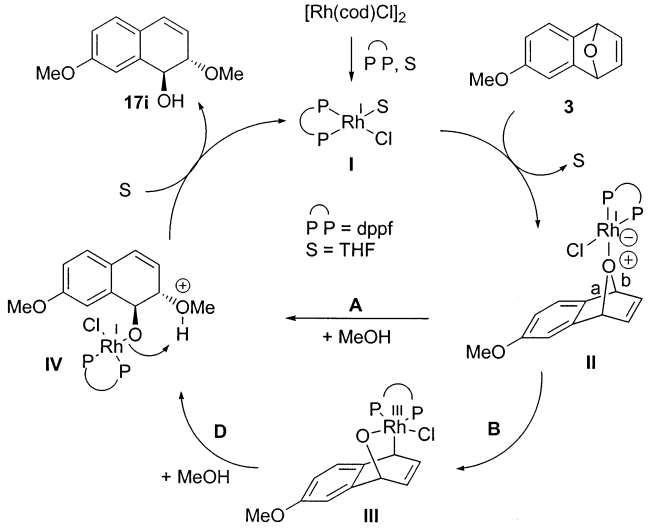

[a] Reaction conditions: (a) $[Rh(cod)Cl]_2$, dppf, THF/MeOH reflux. (b) $H_2$, Pt/C. (c) $PPh_3$, DEAD, DPPA, toluene, −20 °C. (d) $H_2$, Pd/C. (e) $[Rh(cod)Cl]_2$, dppf, $HNBn_2$, THF reflux. (f) HN=NH. (g) Method I: EtOAc/MeOH, 1500psi $H_2$, 5d. Method II: $HCO_2NH_4$, Pd/C, MeOH/EtOAc, 15 min reflux. (h) MsCl/TEA, $NaN_3$ in DMF. (i) $H_2$, Pd/C. (j) $BOC_2O$, TEA. (k) $HCO_2NH_4$, Pd/C, MeOH. (l) $HCO_2NH_4$, Pd/C, MeOH.

$H_2$/Pd/C[39] was very clean but sluggish, and the addition of acetic or formic acid also led to partial epimerization at the benzylic position.

Treating the dibenzylamino-alcohol **23** under various Mitsunobu-type reaction conditions was not as successful as in the case of its methoxy counterpart **21**, possibly because of the steric bulk of the dibenzylamine functionality. A combination of in situ mesylation[40] and subsequent double-$S_N2$ reaction using a DMF solution of sodium azide as a source of nucleophile[41] to open the cationic aziridium intermediate finally gave the anticipated (*trans*)-azide **25** with clean retention of configuration.[36] The neighboring group participation of the dibenzylamino group in this transformation was confirmed by X-ray structure analysis[26] of compound **25**. Complete reduction of azide **25** under the aforementioned catalytic hydrogen transfer conditions[38] directly gives (*trans*)-diamine **28**. However, the reduction can also be interrupted at the $N^2$,$N^2$-dibenzyl-protected diamine **26** by using standard $H_2$/Pd/C reduction,[35] allowing for an exchange of protecting groups,[38,42] to give the $N^1$-BOC-protected diamine **27**, now leaving the 2-amino-group free for further derivatization. With the two monoprotected diamines **26** and **27** in hand, virtually any further derivatization of the amino groups can be envisaged, thus making these compounds potentially valuable building blocks for tetrahydronaphthalene-based biologically active agents.[11]

**Proposed Catalytic Cycle.** While we were able to obtain detailed information on the mechanism of the palladium-catalyzed ring opening using organozinc nucleophiles,[8c] we do not have any direct evidence for the ring-opening reaction using Rh catalysts and heteroatom-containing nucleophiles. However, the results obtained with unsymmetrical substrates are in agreement with a pathway that is triggered by coordination to the bridging oxygen (and perhaps the alkene) followed by regioselective insertion into the bridging C−O bond to give **III**, Scheme 7. Bond *b* in intermediate **II** should be more prone to cleavage as a result of the stabilization of positive charge that results following ionization. We cannot rule out a direct displacement (pathway **A**) or stepwise ionization in analogy with the reactions described in Scheme 1, but the observation of a steric effect (in cases of proximal substitution) suggests that pathway **B** is the dominant process. Nucleophilic attack on the $\sigma$-enyl or $\pi$-allyl form of **III** would yield **IV** and ultimately the observed product and the regenerated catalyst.

**SCHEME 7**

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## Conclusions

A representative selection of unsymmetrically arene-substituted oxabenzonorbornadienes was synthesized. The regioselectivity of their rhodium-catalyzed nucleophilic ring opening was investigated using a variety of nucleophiles. It was found that good to excellent regioselectivities are obtained using strongly $\pi$-donating substituents containing either oxygen or nitrogen donor atoms, whereas $\sigma$-donating and electron-withdrawing functionalities only have a minimal effect. The dominance of $\pi$-donating abilities in controlling regioselectivity is in stark contrast to other reactions such as electrophilic aromatic substitution reactions and the conversion of oxabenzonorbornadienes to their corresponding naphthols. Distal arene substitution generally gives higher regioselectivity when compared to an equivalent proximal substitution (steric effect). Whereas the regioselectivity is largely substrate-controlled, the yield in ring-opened dihydronaphthalenes depends on the leaving-group properties of NuH.

Subsequent modifications of the ring-opened dihydronaphthalenes were shown to quickly lead to interesting tetrahydronaphthalene building blocks. In particular, vicinal (*trans*)-diamines are readily accessible from the corresponding oxabenzonorbornadienes.

## Experimental Section

All flasks were flame-dried under a stream of nitrogen before use. Solvents were freshly distilled prior to their use. Reactions were conducted using standard inert atmosphere techniques. Yields are given for purified products only unless otherwise stated. Regioisomer ratios were determined by crude $^1$H NMR and confirmed by isolated yields for all cases where regioisomers were separable by column chromatography.

**General Procedure for the Rh-Catalyzed Ring-Opening Reaction.** A round-bottom flask was equipped with a reflux condenser, flame-dried under a stream of nitrogen, and charged with an oxabenzonorbornadiene substrate (1 mmol) that was dissolved in anhydrous THF (2.5 mL). $[Rh(cod)Cl]_2$ (2.5 mol %) and dppf (5 mol %) were added simultaneously before immediately heating the resulting dark orange solution to reflux. As soon as boiling was observed, the nucleophile methanol (2.5 mL) was added and the reaction mixture was stirred under nitrogen at reflux temperature until the starting oxabenzonorbornadiene was consumed, as determined by TLC (typically 1−3 h). Nonvolatile nucleophiles were used in smaller excess (5 equiv). If the additive ammonium iodide was used (2.5 equiv), it was added together with the catalyst. After completion, the reaction mixture was concentrated and the crude product was purified by flash chromatography. When carboxylic acids or phenols were employed as nucleophiles, chromatography was preceded by an extractive workup using dichloromethane and 2 M aqueous NaOH.

**6-(Pyrrolidin-1-yl)-1,4-dihydro-1,4-epoxidonaphthalene (7).** A Schlenk flask was flame-dried under a stream of nitrogen. The flask was charged with aryl bromide **8** (513 mg, 2.30 mmol), anhydrous toluene (2.3 mL), $Pd(OAc)_2$ (36 mg, 7 mol %), (*o*-biphenyl)P($^t$Bu)$_2$ (96 mg, 14 mol %), sodium *t*-butoxide (0.31 g, 1.4 equiv), and pyrrolidine (0.23 mL, 1.2 equiv). The resulting dark reaction mixture was heated to 60 °C for 15 h, diluted with diethyl ether (50 mL), filtered through Celite, and concentrated. The resulting crude product was purified by flash chromatography (10% ethyl acetate/hexane), yielding adduct **7** (309 mg, 63%) as a brown oil that solidified upon refrigeration: mp 79−83 °C; IR ($CHCl_3$, cm$^{-1}$) 2973 (w), 1622 (m), 1605 (w), 1582 (w), 1494 (m), 1479 (s), 1461 (s), 1372 (s); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.08 (d, $J$ = 8.0 Hz, 1H), 7.00 (dd, $J$ = 5.5, 1.7 Hz, 1H), 6.95 (dd, $J$ = 5.5, 1.7 Hz, 1H), 6.67 (d, $J$ = 1.9 Hz, 1H), 6.04 (dd, $J$ = 8.0, 2.2 Hz, 1H), 5.67−5.65 (m, 1H), 5.63−5.61 (m, 1H), 3.28−3.22 (m, 4H), 2.01−1.93 (m, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 150.8, 146.1, 143.9, 141.8, 134.5, 120.8, 106.7, 105.9, 82.8, 82.4, 48.1, 25.6. HRMS calcd for $C_{14}H_{15}NO$ ($M^+$): 213.1154. Found: 213.1155.

**6-(Methylphenylamino)-1,4-dihydro-1,4-epoxidonaphthalene (9).** A Schlenk flask was flame-dried under a stream of nitrogen. The flask was charged with aryl bromide **8** (1.08 g, 4.84 mmol), anhydrous toluene (5 mL), $Pd_2(dba)_3$ (221 mg, 5 mol %), (*o*-biphenyl)P($^t$Bu)$_2$ (159 mg, 11 mol %), sodium *t*-butoxide (0.65 g, 1.4 equiv), and *N*-methylaniline (0.63 mL, 1.2 equiv). The resulting dark reaction mixture was heated to 60 °C for 19 h, diluted with diethyl ether (100 mL), filtered through Celite, and concentrated. The resulting crude product was purified by flash chromatography (10% ethyl acetate/hexane), yielding adduct **9** (712 mg, 59%) as a brown oil that solidified upon refrigeration: mp 83−84 °C; IR ($CHCl_3$, cm$^{-1}$) 1592 (m), 1495 (s), 1470 (m); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.25 (t, $J$ = 7.7 Hz, 2H), 7.15 (d, $J$ = 7.7 Hz, 1H), 7.04−6.89 (m, 6H), 6.60 (dd, $J$ = 7.6, 1.7 Hz, 1H), 5.68 (s, 1H), 5.61 (s, 1H), 3.27 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 150.4, 149.1, 146.5, 143.2, 142.3, 141.8, 129.2, 120.8, 120.7, 119.7, 116.6, 115.4, 82.5, 82.2, 40.8. HRMS calcd for $C_{17}H_{15}NO$ ($M^+$): 249.1154. Found: 249.1165.

**(*trans*)-6-Acetyl-2-methoxy-1,2-dihydronaphthalen-1-ol (17a).** Following the general procedure, starting from oxabenzonorbornadiene **10** and using the nucleophile methanol, a 1.05:1 mixture of regioisomers **17a** and **18a** was obtained that was inseparable by flash chromatography (20% ethyl acetate/hexane; 83% combined yield). A small sample of the pure major regioisomer was isolated, giving adduct **17a** as a colorless solid: mp 103−104 °C; IR ($CHCl_3$, cm$^{-1}$) 3587 (w), 1683 (s), 1427 (w), 1279 (m), 1267 (m), 1200 (m), 1112 (m); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.85 (dd, $J$ = 8.0, 1.6 Hz, 1H), 7.70 (d, $J$ = 8.0 Hz, 1H), 7.66 (d, $J$ = 1.6 Hz, 1H), 6.51 (dd, $J$ = 10.0, 1.9 Hz, 1H), 6.13 (dd, $J$ = 9.9, 1.9 Hz, 1H), 4.94 (dd, $J$ = 11.0, 2.7 Hz, 1H), 4.14 (ddd, $J$ = 11.0, 2.1, 2.1 Hz, 1H), 3.53 (s, 3H), 2.95 (d, $J$ = 3.3 Hz, 1H), 2.60 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 198.0, 141.4, 136.8, 132.6, 128.4, 128.3, 127.7, 125.8, 125.2, 82.4, 72.8, 57.1, 26.9. HRMS calcd for $C_{13}H_{14}O_3$ ($M^+$): 218.0943. Found: 218.0950.

**(*trans*)-2-Methoxy-8-methyl-1,2-dihydronaphthalen-1-ol (17b).** Following the general procedure, starting from oxabenzonorbornadiene **11** and using the nucleophile methanol, a 1.05:1 mixture of regioisomers **17b** and **18b** was obtained. Separation by flash chromatography (25% ethyl acetate/hexane) yielded adducts **17b** and **18b** as colorless oils (86%). **17b**: IR ($CHCl_3$, cm$^{-1}$) 3592 (w), 2930 (w), 1586 (w), 1467 (w), 1100 (m), 1085 (s); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.19 (dd, $J$ = 7.5, 7.4 Hz, 1H), 7.11 (d, $J$ = 7.3 Hz, 1H), 7.01 (d, $J$ = 7.4 Hz, 1H), 6.69 (d, $J$ = 9.6 Hz, 1H), 6.12 (dd, $J$ = 9.6, 5.2 Hz, 1H), 4.97−4.92 (m, 1H), 4.01 (ddm, $J$ = 5.2, 1.9 Hz, 1H), 3.39 (s, 3H), 2.46 (s, 3H), 1.59 (br s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 137.7, 132.9, 131.5, 131.3, 131.0, 128.9, 126.0, 123.8, 76.7, 65.9, 56.6, 18.4. HRMS calcd for $C_{12}H_{14}O_2$ ($M^+$): 190.0994. Found: 190.0994.

**(*trans*)-2-Methoxy-7-trifluoromethyl-1,2-dihydronaphthalen-1-ol (17c).** Following the general procedure, starting from oxabenzonorbornadiene **12** and using the nucleophile methanol, a 1.05:1 mixture of regioisomers **17c** and **18c** was obtained. Separation by flash chromatography (20% ethyl acetate/hexane) yielded adducts **17c** and **18c**, which each crystallized from dichloromethane as colorless needles (84%). **17c**: mp 115−116 °C; IR ($CHCl_3$, cm$^{-1}$) 3595 (w), 1619 (w), 1437 (w), 1327 (s), 1266 (m), 1192 (m), 1167 (s), 1129 (s), 1093 (m), 1074 (s); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.87 (s, 1H), 7.49 (dm, $J$ = 8.0 Hz, 1H), 7.16 (d, $J$ = 8.0 Hz, 1H), 6.48 (dd, $J$ = 9.9, 2.2 Hz, 1H), 6.18 (dd, $J$ = 10.0, 2.1 Hz, 1H), 4.93 (d, $J$ = 11.0 Hz, 1H), 4.14 (ddd, $J$ = 11.0, 2.2, 2.1 Hz, 1H), 3.53 (s, 3H), 2.98 (br s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 137.0, 135.4 (q, $J$ = 1.4 Hz), 129.9 (q, $J$ = 33 Hz), 129.8, 127.3, 126.4, 125.0

(q, $J$ = 3.7 Hz), 124.3 (q, $J$ = 272 Hz), 122.2 (q, $J$ = 3.7 Hz), 82.5, 72.4, 57.1; $^{19}$F NMR (282 MHz, $CDCl_3$) $\delta$ −62.92. HRMS calcd for $C_{12}H_{11}F_3O_2$ ($M^+$): 244.0711. Found: 244.0717.

**(*trans*)-8-Acetyl-2,5-dimethoxy-1,2-dihydronaphthalen-1-ol (17d).** Following the general procedure, starting from oxabenzonorbornadiene **13** and using the nucleophile methanol (12 h reflux), a 1.1:1 mixture of the regioisomers **17d** and **18d** was obtained. Separation by flash chromatography (40% ethyl acetate/hexane) yielded both adducts **17d** and **18d** (62%). **17d** (white solid): mp 88−89 °C ($CHCl_3$); IR ($CHCl_3$, cm$^{-1}$) 3502 (w, br), 1663 (m), 1573 (s), 1485 (w), 1464 (w), 1437 (w), 1264 (s); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.70 (d, $J$ = 8.8 Hz, 1H), 7.14 (d, $J$ = 9.9 Hz, 1H), 6.84 (d, $J$ = 8.8 Hz, 1H), 6.27 (ddd, $J$ = 9.9, 5.5, 1.1 Hz, 1H), 4.86−4.82 (m, 1H), 4.26 (d, $J$ = 3.8 Hz, 1H), 4.07 (dd, $J$ = 5.5, 1.6 Hz, 1H), 3.89 (s, 3H), 3.39 (s, 3H), 2.62 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 202.2, 158.7, 137.4, 131.32, 131.30, 124.7, 123.2, 121.6, 109.5, 75.3, 65.6, 56.6, 55.9, 28.6. HRMS calcd for $C_{14}H_{16}O_4$ ($M^+$): 248.1049. Found: 248.1049.

**(*trans*)-2-Methoxy-7-bromo-1,2-dihydronaphthalen-1-ol (17e).** Following the general procedure, starting from oxabenzonorbornadiene **8** and using the nucleophile methanol, a 1.8:1 mixture of regioisomers **17e** and **18e** was obtained. Separation by flash chromatography (10% ethyl acetate/hexane) yielded both adducts **17e** and **18e** as white solids (75%). Adduct **17e** crystallized from chloroform as white needles: mp 119−120 °C; IR ($CHCl_3$, cm$^{-1}$) 3593 (w), 1590 (w), 1478 (m), 1192 (s), 1110 (s), 1092 (s); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.74 (s, 1H), 7.35 (dd, $J$ = 8.0, 1.8 Hz, 1H), 6.93 (d, $J$ = 8.1 Hz, 1H), 6.40 (dd, $J$ = 10.0, 2.0 Hz, 1H), 6.07 (dd, $J$ = 10.0, 2.1 Hz, 1H), 4.87 (br d, $J$ = 10.6 Hz, 1H), 4.08 (ddd, $J$ = 10.6, 2.2, 2.2 Hz, 1H), 3.51 (s, 3H), 2.78 (d, $J$ = 2.9 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 138.2, 131.1, 131.0, 128.5, 127.8, 127.7, 127.5, 122.0, 82.4, 72.3, 57.1. HRMS calcd for $C_{11}H_{11}BrO_2$ ($M^+$): 253.9942. Found: 253.9939.

**(*trans*)-2,5-Dimethoxy-1,2-dihydronaphthalen-1-ol (17f).** Following the general procedure, starting from oxabenzonorbornadiene **1** and using the nucleophile methanol, a 3.5:1 mixture of regioisomers **17f** and **18f** was obtained. Separation by flash chromatography (25% ethyl acetate/hexane) yielded both adducts **17f** and **18f** as colorless oils (81%). Only the major regioisomer **17f** crystallized from cyclohexane as colorless crystals, which were used for X-ray structure analysis: mp 73−74 °C; IR ($CHCl_3$, cm$^{-1}$) 3588 (w), 1626 (w), 1598 (w), 1577 (w), 1474 (s), 1460 (m), 1267 (s), 1109 (s); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.26−7.18 (m, 2H), 6.86 (dd, $J$ = 10.2, 1.9 Hz, 1H), 6.82−6.78 (m, 1H), 6.03 (dd, $J$ = 10.2, 2.2 Hz, 1H), 4.84 (dd, $J$ = 10.4, 3.6 Hz, 1H), 4.08 (ddd, $J$ = 10.4, 2.2, 2.2 Hz, 1H), 3.85 (s, 3H), 3.53 (s, 3H), 2.76 (br s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 155.0, 137.5, 129.0, 125.7, 122.5, 120.7, 117.6, 110.3, 82.0, 72.7, 56.9, 55.8. HRMS calcd for $C_{12}H_{14}O_3$ ($M^+$): 206.0943. Found: 206.0937.

**(*trans*)-8-Chloro-2,5-dimethoxy-1,2-dihydronaphthalen-1-ol (17g).** Following the general procedure, starting from oxabenzonorbornadiene **14** and using the nucleophile methanol, a 3.9:1 mixture of regioisomers **17g** and **18g** was obtained. Separation by flash chromatography (25% ethyl acetate/hexane) yielded both adducts **17g** and **18g** as colorless oils (82%). **17g**: IR ($CHCl_3$, cm$^{-1}$) 3593 (w), 1635 (w), 1586 (w), 1576 (w), 1471 (s), 1463 (s), 1440 (m), 1284 (s), 1263 (s), 1193 (m), 1105 (m), 1083 (s); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.24 (d, $J$ = 8.8 Hz, 1H), 7.11 (d, $J$ = 9.9 Hz, 1H), 6.79 (d, $J$ = 8.9 Hz, 1H), 6.16 (dd, $J$ = 9.8, 5.4 Hz, 1H), 5.14 (s, 1H), 4.01 (ddd, $J$ = 5.5, 1.9, 0.5 Hz, 1H), 3.82 (s, 3H), 3.40 (s, 3H), 2.04 (br s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 154.5, 133.2, 129.6, 126.5, 123.99, 123.98, 122.3, 112.5, 75.6, 65.8, 56.7, 56.1. HRMS calcd for $C_{12}H_{13}ClO_3$ ($M^+$): 240.0553. Found: 240.0555.

**(*trans*)-7-Chloro-2,5-dimethoxy-1,2-dihydronaphthalen-1-ol (17h).** Following the general procedure, starting from oxabenzonorbornadiene **15** and using the nucleophile methanol, a 4.9:1 mixture of regioisomers **17h** and **18h** was obtained. Separation by flash chromatography (20% ethyl acetate/hexane) yielded both adducts **17h** and **18h** as colorless oils (82%). Only the major regioisomer **17h** crystallized from dichloromethane as white needles: mp 140−142 °C; IR ($CHCl_3$, cm$^{-1}$) 3589 (w), 1626 (w), 1589 (w), 1570 (m), 1462 (s), 1423 (m), 1276 (s), 1111 (s), 1101 (s), 1049 (s); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.23−7.21 (m, 1H), 6.79−6.77 (m, 1H), 6.76 (dd, $J$ = 10.3, 2.1 Hz, 1H), 6.03 (dd, $J$ = 10.2, 2.2 Hz, 1H), 4.80 (br d, $J$ = 11.0 Hz, 1H), 4.06 (ddd, $J$ = 11.0, 2.2, 2.2 Hz, 1H), 3.82 (s, 3H), 3.50 (s, 3H), 2.72 (br s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 155.5, 138.9, 134.4, 126.1, 121.8, 119.4, 117.9, 111.0, 82.1, 72.6, 57.0, 56.0. HRMS calcd for $C_{12}H_{13}ClO_3$ ($M^+$): 240.0553. Found: 240.0555.

**(*trans*)-2,7-Dimethoxy-1,2-dihydronaphthalen-1-ol (17i).** Following the general procedure, starting from oxabenzonorbornadiene **3** and using the nucleophile methanol, a 12:1 mixture of the regioisomers **17i** and **18i** was obtained. Purification by flash chromatography (33% ethyl acetate/hexane) yielded adduct **17i** (89%) as a white solid which crystallized from cyclohexane/dichloromethane as colorless needles, which were used for X-ray structure analysis: mp 94−95 °C; IR ($CHCl_3$, cm$^{-1}$) 3590 (w), 1632 (w), 1606 (s), 1516 (w), 1496 (s), 1480 (m), 1464 (m), 1448 (m), 1432 (m), 1275 (s), 1155 (s), 1110 (s), 1032 (s); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.17 (d, $J$ = 2.6 Hz, 1H), 7.01 (d, $J$ = 8.2 Hz, 1H), 6.75 (ddm, $J$ = 8.2, 2.6 Hz, 1H), 6.41 (dd, $J$ = 9.9, 2.1 Hz, 1H), 5.92 (dd, $J$ = 10.0, 2.2 Hz, 1H), 4.86 (br dd, $J$ = 10.3, 3.5 Hz, 1H), 4.09 (ddd, $J$ = 10.4, 2.2, 2.2 Hz, 1H), 3.83 (s, 3H), 3.50 (s, 3H), 2.70 (d, $J$ = 3.7 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 159.8, 137.9, 127.9, 127.8, 125.2, 124.3, 113.1, 111.1, 82.5, 72.8, 56.9, 55.6. HRMS calcd for $C_{12}H_{14}O_3$ ($M^+$): 206.0943. Found: 206.0938.

**(*trans*)-2,5,7-Trimethoxy-1,2-dihydronaphthalen-1-ol (17j).** Following the general procedure, starting from oxabenzonorbornadiene **16** and using the nucleophile methanol, adduct **17j** was obtained as a single regioisomer. Purification by flash chromatography (25% ethyl acetate/hexane) yielded adduct **17j** (80%) as a white solid: mp 71−73 °C ($CHCl_3$); IR ($CHCl_3$, cm$^{-1}$) 3586 (w), 1623 (w), 1605 (s), 1576 (w), 1487 (w), 1464 (m), 1149 (s), 1047 (s); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.79 (d, $J$ = 2.2 Hz, 1H), 6.75 (dd, $J$ = 10.0, 2.0 Hz, 1H), 6.35 (d, $J$ = 2.2 Hz, 1H), 5.89 (dd, $J$ = 10.2, 2.2 Hz, 1H), 4.79 (d, $J$ = 10.4 Hz, 1H), 4.06 (ddd, $J$ = 10.4, 2.2, 2.2 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.49 (s, 3H), 2.89 (br s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 160.7, 156.2, 138.8, 122.9, 122.3, 114.2, 101.8, 97.9, 82.3, 72.9, 56.8, 55.7, 55.6. HRMS calcd for $C_{13}H_{16}O_4$ ($M^+$): 236.1049. Found: 236.1053.

**(*trans*)-2-Methoxy-7-(methylphenylamino)-1,2-dihydronaphthalen-1-ol (17k).** Following the general procedure, starting from the oxabenzonorbornadiene **9** and using the nucleophile methanol, adduct **17k** was obtained as a single regioisomer. Purification by flash chromatography (15% ethyl acetate/hexane, containing 2% triethylamine; silica was thoroughly neutralized with triethylamine/hexane before application of crude product) yielded adduct **17k** (58%) as a brown oil; IR ($CHCl_3$, cm$^{-1}$) 3590 (w), 1612 (m), 1593 (s), 1557 (w), 1495 (s), 1111 (s); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.33−7.20 (m, 3H), 7.11−6.93 (m, 4H), 6.79 (dd, $J$ = 8.2, 2.5 Hz, 1H), 6.41 (dd, $J$ = 9.8, 1.5 Hz, 1H), 5.90 (dd, $J$ = 9.9, 2.5 Hz, 1H), 4.82 (d, $J$ = 10.2 Hz, 1H), 4.08 (ddd, $J$ = 10.0, 2.4, 1.9 Hz, 1H), 3.49 (s, 3H), 3.33 (s, 3H), 2.67 (br s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 149.0, 148.7, 137.3, 129.5, 128.2, 127.4, 124.5, 123.7, 122.6, 122.3, 117.6, 115.7, 82.3, 72.7, 56.9, 40.5. HRMS calcd for $C_{18}H_{19}NO_2$ ($M^+$): 281.1416. Found: 281.1423.

**(*trans*)-5,7-Dimethoxy-2-(methylphenylamino)-1,2-dihydronaphthalen-1-ol (19a).** Following the general procedure, starting from oxabenzonorbornadiene **16** and using the nucleophile *N*-methylaniline, a 11:1 mixture of the regioisomers **19a** and **20a** was obtained. Separation by flash chromatography (20% ethyl acetate/hexane) yielded adducts **19a** and **20a** as colorless, viscous oils (92%). **19a**: IR ($CHCl_3$, cm$^{-1}$) 3584 (w), 1730 (w), 1599 (s), 1576 (m), 1503 (s), 1464 (m), 1149 (s); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.26−7.19 (m, 2H), 6.95−6.90 (m, 2H), 6.86 (dd, $J$ = 10.0, 2.5 Hz, 1H), 6.79−6.73 (m, 1H),

6.74 (d, $J$ = 2.2 Hz, 1H), 6.36 (d, $J$ = 2.3 Hz, 1H), 5.74 (dd, $J$ = 10.0, 2.9 Hz, 1H), 4.97 (d, $J$ = 10.3 Hz, 1H), 4.67 (ddd, $J$ = 10.3, 2.7, 2.6 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 2.82 (s, 3H), 2.49 (br s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 160.7, 156.3, 150.5, 139.5, 129.4, 123.8, 123.6, 118.1, 114.8, 114.2, 102.2, 97.9, 70.6, 63.4, 55.7, 55.6, 33.4. HRMS calcd for $C_{19}H_{21}NO_3$ ($M^+$): 311.1521. Found: 311.1513.

**(*trans*)-2,7-Bis-(methylphenylamino)-1,2-dihydronaphthalen-1-ol (19b).** Following the general procedure, starting from oxabenzonorbornadiene **9** and using the nucleophile *N*-methylaniline, a 11:1 mixture of regioisomers **19b** and **20b** was obtained. Purification by flash chromatography (10% ethyl acetate/hexane, containing 2% triethylamine; silica was thoroughly neutralized with triethylamine/hexane before application of crude product) yielded adduct **19b** as a brown oil (80%); IR ($CHCl_3$, cm$^{-1}$) 3582 (w), 1611 (m), 1594 (s), 1556 (w), 1495 (s); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.32−6.92 (m, 11H), 6.82−6.74 (m, 2H), 6.51 (dd, $J$ = 9.7, 2.4 Hz, 1H), 5.75 (dd, $J$ = 9.6, 3.0 Hz, 1H), 5.00 (d, $J$ = 9.9 Hz, 1H), 4.69 (ddd, $J$ = 9.9, 2.7, 2.7 Hz, 1H), 3.33 (s, 3H), 2.83 (s, 3H), 2.36 (br s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 150.5, 149.1, 148.7, 138.0, 129.54, 129.46, 129.42, 127.5, 124.7, 124.5, 122.7, 122.5, 118.1, 117.6, 115.8, 114.8, 70.5, 63.7, 40.5, 33.5. HRMS calcd for $C_{24}H_{24}N_2O$ ($M^+$): 356.1889. Found: 356.1896.

**(*trans*)-2-(Methylphenylamino)-7-(pyrrolidin-1-yl)-1,2-dihydronaphthalen-1-ol (19c).** Following the general procedure, starting from oxabenzonorbornadiene **7** and using the nucleophile *N*-methylaniline, adduct **19c** was obtained as a single regioisomer. Purification by flash chromatography (10% ethyl acetate/hexane, containing 2% triethylamine; silica was thoroughly neutralized with triethylamine/hexane before application of crude product) yielded adduct **19c** as a light brown oil (89%): IR ($CHCl_3$, cm$^{-1}$) 3586 (w), 1611 (s), 1599 (s), 1551 (w), 1503 (s), 1487 (m), 1448 (m), 1377 (s); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.28−7.21 (m, 2H), 7.00−6.92 (m, 3H), 6.80−6.73 (m, 2H), 6.51 (dd, $J$ = 9.8, 2.5 Hz, 1H), 6.41 (dd, $J$ = 8.2, 2.5 Hz, 1H), 5.62 (dd, $J$ = 9.6, 3.3 Hz, 1H), 4.97 (d, $J$ = 9.3 Hz, 1H), 4.67 (ddd, $J$ = 9.1, 2.8, 2.7 Hz, 1H), 3.37−3.25 (m, 4H), 2.81 (s, 3H), 2.32 (br s, 1H), 2.06−1.93 (m, 4H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 150.6, 148.0, 138.0, 129.9, 129.4, 128.0, 121.6, 120.1, 117.9, 114.6, 110.3, 109.5, 70.7, 63.3, 47.8, 33.3, 25.6. HRMS calcd for $C_{21}H_{24}N_2O$ ($M^+$): 320.1889. Found: 320.1883.

**(*trans*)-2-Dibenzylamino-5,7-dimethoxy-1,2-dihydronaphthalen-1-ol (19d).** Following the general procedure, starting from the oxabenzonorbornadiene **16** and using both the nucleophile dibenzylamine and the additive ammonium iodide, a 11:1 mixture of regioisomers was obtained from which the major adduct **19d** was isolated (77%) by means of flash chromatography (5% ethyl acetate/hexane, containing 2% triethylamine; silica was neutralized with the eluent before application of crude product). Compound **19d** crystallized from dichloromethane as colorless crystals: mp 105−106 °C; IR ($CHCl_3$, cm$^{-1}$) 3488 (w, br), 1603 (s), 1574 (w), 1494 (w), 1485 (m), 1463 (s), 1453 (s), 1429 (m), 1148 (s), 1044 (s); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.32−7.27 (m, 8H), 7.26−7.20 (m, 2H), 6.83 (dd, $J$ = 10.2, 2.9 Hz, 1H), 6.72 (d, $J$ = 2.0 Hz, 1H), 6.30 (d, $J$ = 2.4 Hz, 1H), 5.99 (dd, $J$ = 10.1, 2.3 Hz, 1H), 4.89 (d, $J$ = 12.3 Hz, 1H), 3.97 (d, $J$ = 13.6 Hz, 2H), 3.78 (s, 3H), 3.76 (s, 3H), 3.62 (ddd, $J$ = 12.5, 2.7, 2.4 Hz, 1H), 3.58 (d, $J$ = 13.7 Hz, 2H), 3.23 (br s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 160.7, 156.1, 139.8, 139.3, 129.1, 128.7, 127.4, 123.6, 121.4, 114.0, 101.4, 97.7, 69.5, 62.5, 55.7, 55.6, 54.9. HRMS calcd for $C_{26}H_{27}NO_3$ ($M^+$): 401.1991. Found: 401.2006.

**(*trans*)-5,7-Dimethoxy-2-(phenoxy)-1,2-dihydronaphthalen-1-ol (19e).** Following the general procedure, starting from oxabenzonorbornadiene **16** and using the nucleophile phenol, a >25:1 mixture of regioisomers was obtained from which the major adduct **19e** was isolated (74%) by means of flash chromatography (5% ethyl acetate/hexane, containing 2% triethylamine; silica was neutralized with triethylamine/hexane before application of crude product). **19e** (white solid): mp 123−124 °C ($CHCl_3$); IR ($CHCl_3$, cm$^{-1}$) 3595 (w), 1604 (s), 1587 (m), 1579 (m), 1495 (s), 1464 (m), 1456 (m), 1429 (m), 1149 (s); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.32−7.24 (m, 2H), 7.00−6.92 (m, 3H), 6.85 (d, $J$ = 2.3 Hz, 1H), 6.79 (d, $J$ = 10.4 Hz, 1H), 6.37 (d, $J$ = 2.2 Hz, 1H), 5.85 (dm, $J$ = 10.2 Hz, 1H), 5.10−5.03 (m, 2H), 3.84 (s, 3H), 3.80 (s, 3H), 2.72 (br s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 160.9, 157.6, 156.4, 138.5, 129.9, 123.0, 122.4, 121.5, 116.0, 114.1, 102.0, 98.0, 79.2, 72.9, 55.8, 55.7. HRMS calcd for $C_{18}H_{18}O_4$ ($M^+$): 298.1205. Found: 298.1210.

**(*trans*)-5,7-Dimethoxy-2-(dimethoxycarbonylmethyl)-1,2-dihydronaphthalen-1-ol (19f).** Following the general procedure, starting from oxabenzonorbornadiene **16** and using both the nucleophile dimethylmalonate and the additive ammonium iodide, a >25:1 mixture of regioisomers was obtained from which the major adduct **19f** was isolated (55%) as a colorless oil by means of flash chromatography (33% ethyl acetate/hexane): IR ($CHCl_3$, cm$^{-1}$) 1751 (m), 1732 (s), 1606 (m), 1577 (w), 1492 (w), 1150 (s); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.82 (dd, $J$ = 9.9, 1.3 Hz, 1H), 6.57 (d, $J$ = 2.0 Hz, 1H), 6.37 (d, $J$ = 2.2 Hz, 1H), 5.76 (dd, $J$ = 9.9, 4.0 Hz, 1H), 4.57 (br dd, $J$ = 6.1, 6.0 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.72 (s, 3H), 3.70 (s, 3H), 3.49 (d, $J$ = 8.1 Hz, 1H), 2.43 (br d, $J$ = 6.6 Hz, 1H), 3.31−3.25 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 169.0, 168.7, 160.7, 156.4, 138.2, 122.5, 122.3, 114.2, 103.6, 98.2, 70.9, 55.7, 55.6, 52.8, 52.7, 52.6, 42.1. HRMS calcd for $C_{17}H_{20}O_7$ ($M^+$): 336.1209. Found: 336.1212.

**(*trans*)-2-(4-Acetylphenoxy)-5,7-dimethoxy-1,2-dihydronaphthalen-1-ol (19g).** Following the general procedure, starting from the oxabenzonorbornadiene **16** and using the nucleophile 4-hydroxyacetophenone, a >25:1 mixture of regioisomers was obtained from which the major adduct **19g** was isolated (50%) by means of flash chromatography (33% ethyl acetate/hexane; silica was neutralized with triethylamine/hexane before application of crude product). **19g** (white solid): mp 123−124 °C ($CH_2Cl_2$); IR ($CHCl_3$, cm$^{-1}$) 3601 (w), 1731 (w), 1674 (m), 1599 (s), 1576 (m), 1507 (m), 1487 (w), 1250 (s); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.92 (d, $J$ = 8.6 Hz, 2H), 6.96 (d, $J$ = 8.8 Hz, 2H), 6.85 (d, $J$ = 2.0 Hz, 1H), 6.84 (dd, $J$ = 10.2, 1.6 Hz, 1H), 6.39 (d, $J$ = 1.8 Hz, 1H), 5.80 (dd, $J$ = 10.1, 1.8 Hz, 1H), 5.14 (dm, $J$ = 10.4 Hz, 1H), 5.09 (dd, $J$ = 10.4, 3.3 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 2.86 (d, $J$ = 3.8 Hz, 1H), 2.55 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 197.0, 161.7, 161.1, 156.6, 138.3, 130.92, 130.86, 123.7, 121.2, 115.4, 114.0, 102.3, 98.1, 79.4, 72.7, 55.8, 55.7, 26.5. HRMS calcd for $C_{20}H_{20}O_5$ ($M^+$): 340.1312. Found: 340.1319.

**(*trans*)-2,5,7-Trimethoxy-1,2,3,4-tetrahydronaphthalen-1-ol (21).** 5% Pt/C (416 mg, 10 mol %) was added to a solution of dihydronaphthalene **17j** (252 mg, 1.07 mmol) in ethyl acetate (4 mL). The flask was purged with nitrogen, fitted with a double balloon of hydrogen, and stirred at room temperature for 14 h. The black suspension was filtered through Celite, and the resulting crude was purified by flash chromatography (33% ethyl acetate/hexane), yielding the adduct **21** (198 mg, 78%) as a white solid: mp 80−82 °C ($CHCl_3$); IR ($CHCl_3$, cm$^{-1}$) 3587 (w), 1610 (m), 1597 (m), 1489 (m), 1464 (m), 1456 (m), 1200 (s), 1147 (s), 1052 (s); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.71 (d, $J$ = 2.2 Hz, 1H), 6.35 (d, $J$ = 2.5 Hz, 1H), 4.60 (dd, $J$ = 7.6, 2.9 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.49 (s, 3H), 3.39 (ddd, $J$ = 10.4, 7.7, 3.3 Hz, 1H), 2.83 (ddd, $J$ = 17.6, 6.0, 4.1 Hz, 1H), 2.68 (d, $J$ = 3.6 Hz, 1H), 2.53 (dddm, $J$ = 17.6, 10.4, 6.0 Hz, 1H), 2.24 (dddd, $J$ = 13.2, 5.8, 3.6, 3.3 Hz, 1H), 1.64 (dddd, $J$ = 13.0, 10.6, 10.6, 6.0 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 159.5, 157.8, 138.6, 117.1, 102.1, 97.9, 82.1, 72.9, 56.8, 55.6, 55.5, 23.8, 21.3. HRMS calcd for $C_{13}H_{18}O_4$ ($M^+$): 238.1205. Found: 238.1215.

**(*cis*)-2,5,7-Trimethoxy-1,2,3,4-tetrahydronaphthalen-1-ylamine (22).** Diethyl azodicarboxylate (DEAD, 0.89 mL, 2.1 equiv) and diphenylphosphoryl azide (DPPA, 1.23 mL, 2.1 equiv) were added dropwise to a cooled solution of tetrahydronaphthalene **21** (640 mg, 2.69 mmol) and triphenylphosphine (1.57 g, 2.2 equiv) in toluene (10 mL, −20 °C). The colorless solution was kept at −20 °C for 30 min and then left

to warm to room temperature over a period of 30 min, at which time the reaction was quenched with excess 2-propanol/triethylamine. After an additional 15 min at room temperature, the solution was diluted with diethyl ether and washed with brine. The crude product was then purified by flash chromatography (5% ethyl acetate/hexane), giving the corresponding intermediate (*cis*)-azide (559 mg, 79%) as a colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.42−6.40 (m, 2H), 4.61 (d, $J$ = 3.6 Hz, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 3.66 (ddd, $J$ = 9.2, 4.4, 3.6 Hz, 1H), 3.49 (s, 3H), 2.86 (ddd, $J$ = 17.6, 5.5, 4.7 Hz, 1H), 2.50 (ddd, $J$ = 17.3, 9.1, 7.3 Hz, 1H), 2.09−1.93 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 159.2, 158.3, 133.9, 117.9, 104.6, 98.7, 78.7, 61.7, 56.6, 55.6, 55.5, 22.8, 21.3. 10% Pd/C (225 mg, 10 mol %) was added to a solution of the previously obtained (*cis*)-azide (559 mg, 2.12 mmol) in ethyl acetate (30 mL). The flask was purged with nitrogen, fitted with a double-balloon of hydrogen, and stirred at room temperature for 18 h. The black suspension was filtered through Celite, and the filter was washed with dichloromethane. The amine product was then extracted with 0.5 M aqueous HCl. The aqueous phase was washed four times with dichloromethane, basified with 2 M aqueous NaOH, and reextracted with dichloromethane, yielding adduct **22** (423 mg, 84%) as a colorless oil: IR ($CHCl_3$, $cm^{-1}$) 2938 (m), 1610 (s), 1595 (s), 1490 (m), 1464 (s), 1454 (m), 1199 (s), 1148 (s), 1093 (s); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.57 (d, $J$ = 2.2 Hz, 1H), 6.33 (d, $J$ = 2.0 Hz, 1H), 4.03 (d, $J$ = 3.7 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.49 (ddd, $J$ = 9.9, 3.4, 3.2 Hz, 1H), 3.45 (s, 3H), 2.80 (ddd, $J$ = 17.6, 5.3, 5.3 Hz, 1H), 2.49 (ddd, $J$ = 17.5, 9.3, 6.6 Hz, 1H), 2.02−1.93 (m, 1H), 1.92−1.84 (m, 1H), 1.65 (br s, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 159.1, 158.0, 140.2, 117.4, 104.5, 97.6, 79.5, 56.3, 55.6, 55.5, 51.7, 21.9, 21.2. HRMS calcd for $C_{13}H_{19}NO_3$ ($M^+$): 237.1365. Found: 237.1369.

**(*trans*)-2-Dibenzylamino-5,7-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-ol (23).** Sodium periodate (9.9 g, 10 equiv) was added in portions at 0 °C to a solution of dihydronaphthalene **19d** (1.88 g, 4.67 mmol) and hydrazine monohydrate (8.9 mL, 40 equiv) in ethanol (50 mL)/THF (15 mL)/water (15 mL). The resulting suspension was slowly heated to 75 °C (open reflux condenser, nitrogen formation!) and kept at this temperature until a light yellow solution was obtained (3 h). The reaction mixture was diluted with dichloromethane and washed three times with 2 M aqueous NaOH and once with brine. Concentration yielded adduct **23** (1.89 g, 100%) as a pale brown solid: mp 132−134 °C; IR ($CHCl_3$, $cm^{-1}$) 3464 (w, br), 1609 (s), 1596 (m), 1489 (m), 1465 (s), 1455 (m), 1431 (m), 1197 (s), 1148 (s); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.33−7.28 (m, 8H), 7.26−7.21 (m, 2H), 6.72 (d, $J$ = 2.4 Hz, 1H), 6.30 (d, $J$ = 2.4 Hz, 1H), 4.71 (d, $J$ = 9.9 Hz, 1H), 3.93 (d, $J$ = 13.4 Hz, 2H), 3.78 (s, 3H), 3.75 (s, 3H), 3.68 (s, 1H), 3.47 (d, $J$ = 13.4 Hz, 2H), 2.92 (ddd, $J$ = 17.3, 5.8, 1.5 Hz, 1H), 2.80 (ddd, $J$ = 12.5, 10.1, 2.6 Hz, 1H), 2.43 (dddm, $J$ = 17.3, 12.3, 6.0 Hz, 1H), 2.19 (dm, $J$ = 12.6 Hz, 1H), 1.63 (dddd, $J$ = 12.6, 12.4, 12.4, 5.9 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 159.2, 157.7, 140.1, 139.4, 129.1, 128.7, 127.4, 116.4, 101.4, 97.5, 68.5, 61.4, 55.5, 55.4, 53.7, 23.2, 19.0. HRMS calcd for $C_{26}H_{29}NO_3$ ($M^+$): 403.2147. Found: 403.2144.

**(*trans*)-2-Amino-5,7-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-ol (24): Method I.** 10% Pd/C (128 mg, 10 mol %) was added to a solution of tetrahydronaphthalene **23** (488 mg, 1.21 mmol) in ethyl acetate (6 mL)/methanol (6 mL). The black suspension was placed in a hydrogenation bomb equipped with a manometer, purged three times with 1000 psi of hydrogen, and then stirred at room temperature under 1500 psi hydrogen for 5 days. The black suspension was filtered through Celite, and the filter was washed with methanol, giving adduct **24** (262 mg, 97%) as a white solid (free amine): mp 152−156 °C (dec.); IR ($CHCl_3$, $cm^{-1}$) 1608 (m), 1594 (m), 1489 (m), 1463 (m), 1456 (m), 1145 (s); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.73 (d, $J$ = 2.4 Hz, 1H), 6.35 (d, $J$ = 2.4 Hz, 1H), 4.30 (br d, $J$ = 8.5 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 2.91−2.83 (m, 1H), 2.79 (ddd, $J$ = 17.4, 6.0, 2.9 Hz, 1H), 2.55 (dddm, $J$ = 17.4, 11.2, 6.0 Hz, 1H), 2.04 (dddd, $J$ = 13.0, 6.2, 3.1, 3.1 Hz, 1H), 1.79 (br s, 3H), 1.62 (dddd, $J$ = 13.0, 11.4, 11.2, 6.0 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 159.3, 157.9, 139.9, 117.4, 101.7, 97.6, 75.8, 55.6, 55.5, 54.5, 30.2, 22.1. HRMS calcd for $C_{12}H_{17}NO_3$ ($M^+$): 223.1208. Found: 223.1208. **Method II.** 10% Pd/C (321 mg, 30 mol %) and ammonium formate (318 mg, 5 equiv) were added to a solution of tetrahydronaphthalene **23** (408 mg, 1.01 mmol) in ethyl acetate (3.5 mL)/methanol (7 mL). The black suspension was refluxed for 15 min, treated with triethylamine (3.5 mL), and filtered through Celite. The filter was washed thoroughly with 10% triethylamine/methanol, and the resulting crude was dried under high vacuum, dissolved in 2 M aqueous HCl, and washed three times with dichloromethane. Concentration of the aqueous solution gave adduct **24** (236 mg, 90%) as a white solid (hydrochloride salt): mp 223−225 °C (dec.); $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 6.73 (d, $J$ = 2.2 Hz, 1H), 6.42 (d, $J$ = 2.2 Hz, 1H), 4.91 (s, 4H), 4.61 (br d, $J$ = 9.3 Hz, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.23 (ddd, $J$ = 12.1, 9.3, 3.0 Hz, 1H), 2.87 (ddd, $J$ = 17.6, 6.0, 2.5 Hz, 1H), 2.59 (dddm, $J$ = 17.6, 11.6, 6.1 Hz, 1H), 2.25 (dddd, $J$ = 12.9, 6.3, 3.0, 2.8 Hz, 1H), 1.86 (dddd, $J$ = 12.4, 12.2, 12.2, 6.2 Hz, 1H); $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta$ 161.1, 159.2, 140.1, 117.1, 103.2, 98.5, 71.8, 56.0, 55.9, 55.7, 26.3, 22.5.

**(*trans*)-(1-Azido-5,7-dimethoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-dibenzylamine (25).** Triethylamine (3.41 mL, 2.4 equiv) and methanesulfonyl chloride (1.59 mL, 2.0 equiv) were added consecutively to a cooled solution of tetrahydronaphthalene **23** (4.15 g, 10.3 mmol) in dichloromethane (190 mL). The resulting reaction mixture was kept at 0 °C for 30 min, at which time a saturated solution of sodium azide in anhydrous DMF (190 mL), freshly prepared at room temperature using 3.3 g (5 equiv) of sodium azide, was added. The reaction mixture was left to warm to room temperature and was stirred for an additional 3 h, after which it was diluted with diethyl ether and washed three times with water and once with brine. Flash chromatography (2% ethyl acetate/hexane) yielded the (*trans*)-azide **25** (3.75 g, 85%). Adduct **25** crystallized from dichloromethane to give colorless crystals, which were used for X-ray structure analysis: mp 108−109 °C; IR ($CHCl_3$, $cm^{-1}$) 2100 (s), 1610 (m), 1599 (m), 1493 (m), 1464 (m), 1455 (m), 1149 (s); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.45 (d, $J$ = 7.5 Hz, 4H), 7.31 (dd, $J$ = 7.5, 7.5 Hz, 4H), 7.22 (t, $J$ = 7.2 Hz, 2H), 6.57 (d, $J$ = 2.2 Hz, 1H), 6.30 (d, $J$ = 2.2 Hz, 1H), 4.53 (d, $J$ = 9.7 Hz, 1H), 3.92 (d, $J$ = 13.5 Hz, 2H), 3.77 (s, 3H), 3.73 (s, 3H), 3.54 (d, $J$ = 13.7 Hz, 2H), 3.02 (ddd, $J$ = 11.9, 10.1, 2.5 Hz, 1H), 2.89 (ddd, $J$ = 17.0, 4.8, 2.2 Hz, 1H), 2.30 (ddd, $J$ = 17.0, 12.3, 4.9 Hz, 1H), 2.22 (dm, $J$ = 12.8 Hz, 1H), 1.61 (dddd, $J$ = 12.4, 12.3, 12.3, 5.0 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 159.2, 157.8, 139.6, 137.0, 129.0, 128.5, 127.2, 118.8, 103.5, 97.8, 62.7, 60.1, 55.6, 55.5, 54.2, 22.8, 21.2. HRMS calcd for $C_{26}H_{29}N_4O_2$ ($M^+$ + 1): 429.2291. Found: 429.2274.

**(*trans*)-$N^2$,$N^2$-Dibenzyl-5,7-dimethoxy-1,2,3,4-tetrahydronaphthalene-1,2-diamine (26).** 10% Pd/C (156 mg, 10 mol %) was added to a solution of the previously obtained (*trans*)-azide **25** (626 mg, 1.46 mmol) in ethyl acetate (30 mL). The flask was purged with nitrogen, fitted with a double-balloon of hydrogen, and stirred at room temperature for 17 h. The black suspension was filtered through Celite, and the filter was thoroughly washed with 10% triethylamine/methanol. The resulting crude product was purified by flash chromatography (20% ethyl acetate/hexane, containing 2% triethylamine), yielding adduct **26** (458 mg, 78%), which crystallized from dichloromethane to give colorless crystals: mp 149−150 °C; IR ($CHCl_3$, $cm^{-1}$) 2937 (m), 1606 (s), 1594 (s), 1494 (m), 1488 (m), 1463 (s), 1454 (s), 1200 (s), 1146 (s); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.35−7.26 (m, 8H), 7.23−7.18 (m, 2H), 6.84 (d, $J$ = 2.2 Hz, 1H), 6.28 (d, $J$ = 2.4 Hz, 1H), 3.89 (d, $J$ = 9.6 Hz, 1H), 3.88 (d, $J$ = 13.2 Hz, 2H), 3.76 (s, 3H), 3.73 (s, 3H), 3.41 (d, $J$ = 13.2 Hz, 2H), 2.94 (ddd, $J$ = 17.0, 5.2, 2.0 Hz, 1H), 2.49 (ddd, $J$ = 12.1, 10.2, 2.5 Hz, 1H), 2.36 (dddm, $J$ = 17.0, 12.6, 5.6 Hz, 1H), 2.21 (dm, $J$ = 12.5 Hz, 1H), 1.79 (br s,

2H), 1.54 (dddd, $J$ = 12.4, 12.4, 12.4, 5.5 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 158.9, 157.5, 141.7, 139.9, 129.1, 128.4, 127.1, 117.4, 102.4, 97.0, 63.0, 55.6, 55.5, 54.0, 52.3, 23.6, 19.8. HRMS calcd for $C_{26}H_{31}N_2O_2$ ($M^+$ + 1): 403.2386. Found: 403.2389.

**(*trans*)-*N*$^1$-BOC-5,7-Dimethoxy-1,2,3,4-tetrahydronaphthalen-1,2-diamine (27).** Triethylamine (4.7 mL, 5.0 equiv) and di-*tert*-butyl dicarbonate (2.96 g, 2.0 equiv) were added consecutively to a solution of diamine **26** (2.73 g, 6.78 mmol) in ethyl acetate/methanol/dichloromethane (25 mL each), and the resulting solution was stirred for 30 min at room temperature. After the addition of diethylamine (2 mL) and further stirring for 30 min at room temperature, the solution was concentrated. The resulting crude intermediate was dried under high vacuum and dissolved in methanol (50 mL)/ethyl acetate (25 mL). After the addition of 10% Pd/C (2.2 g, 30 mol %) and ammonium formate (4.3 g, 10 equiv), the resulting black suspension was refluxed for 15 min and filtered through Celite. The filter was thoroughly washed with 10% triethylamine/methanol, and the resulting crude product was triturated in refluxing ethyl acetate (50 mL) for 1 h. Half of the solvent was then evaporated; ice-cold hexane was added (100 mL), and the solid was filtered off and washed with cold hexane, giving adduct **27** (1.88 g, 86% overall yield) as a fine white powder: mp 173−174 °C; IR ($CHCl_3$, $cm^{-1}$) 3435 (w), 3369 (w), 1708 (s), 1610 (m), 1596 (m), 1499 (s), 1490 (s), 1464 (m), 1455 (m); $^1$H NMR (300 MHz, $CD_3OD$) $\delta$ 6.38−6.36 (m, 2H), 4.84 (s, 3H), 4.38 (d, $J$ = 8.7 Hz, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 2.87 (ddd, $J$ = 10.7, 8.9, 3.1 Hz, 1H), 2.77 (ddd, $J$ = 17.5, 5.5, 4.1 Hz, 1H), 2.50 (dddm, $J$ = 17.7, 10.5, 6.3 Hz, 1H), 2.07 (dddd, $J$ = 13.1, 5.9, 3.9, 3.1 Hz, 1H), 1.64 (dddd, $J$ = 13.0, 10.7, 10.5, 5.7 Hz, 1H), 1.51 (s, 9H); $^{13}$C NMR (75 MHz, $CD_3OD$) $\delta$ 160.6, 159.4, 159.3, 139.5, 118.8, 104.1, 97.9, 80.5, 58.7, 55.9, 55.7, 52.9, 30.1, 29.0, 22.4. HRMS calcd for $C_{17}H_{26}N_2O_4$ ($M^+$): 322.1893. Found: 322.1890.

**(*trans*)-5,7-Dimethoxy-1,2,3,4-tetrahydronaphthalen-1,2-diamine (28).** 10% Pd/C (396 mg, 30 mol %) and ammonium formate (0.96 g, 10 equiv) were added to a solution of (*trans*)-azide **25** (534 mg, 1.25 mmol) in ethyl acetate (4.5 mL)/methanol (9 mL). The black suspension was refluxed for 25 min and filtered through Celite. The filter was thoroughly washed with 10% triethylamine/methanol, and the resulting crude was purified by flash chromatography (50% ethyl acetate/hexane, containing 2% triethylamine; 5% triethylamine/methanol). Removal of silica by dissolving the product in dichloromethane and filtering through cotton gave adduct **28** (202 mg, 73%) as a colorless oil: IR ($CHCl_3$, $cm^{-1}$) 2938 (m), 1607 (s), 1592 (s), 1488 (m), 1464 (s), 1456 (m), 1199 (s), 1146 (s); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.68 (d, $J$ = 2.5 Hz, 1H), 6.33 (d, $J$ = 2.2 Hz, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.48 (d, $J$ = 8.0 Hz, 1H), 2.82−2.70 (m, 2H), 2.54 (dddm, $J$ = 17.0, 10.3, 6.0 Hz, 1H), 2.05 (dddd, $J$ = 13.1, 6.3, 3.7, 3.5 Hz, 1H), 1.82 (br s, 4H), 1.62 (dddd, $J$ = 13.1, 10.4, 10.2, 5.9 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 159.1, 157.9, 141.7, 117.6, 102.8, 96.8, 58.4, 55.6, 55.5, 55.0, 30.0, 21.5. HRMS calcd for $C_{12}H_{18}N_2O_2$ ($M^+$): 222.1368. Found: 222.1363.

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**Supporting Information Available:** Preparation of the oxabenzonorbornadiene substrates **1**, **3**, **10**, **12**, **13** and **14**−**16**; spectral data for all oxabenzonorbornadiene substrates and all minor isomers **18** and **20**, which were obtained in ≥7% yield; $^1$H NMR spectra for all new compounds described in the Experimental Section, including all novel oxabenzonorbornadiene substrates; and X-ray crystallographic data for compounds **1**, **3**, **13**, **17f**, **17i**, and **25** (CIF and ORTEP). This material is available free of charge via the Internet at http://pubs.acs.org.

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