JOC The Journal of Organic Chemistry

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b01094 • Publication Date (Web): 04 Jun 2019

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Palladium/Lewis Acid Co-Catalyzed Ring-Opening Reactions of Unsymmetrical Oxabenzonobornadienes with Oximes

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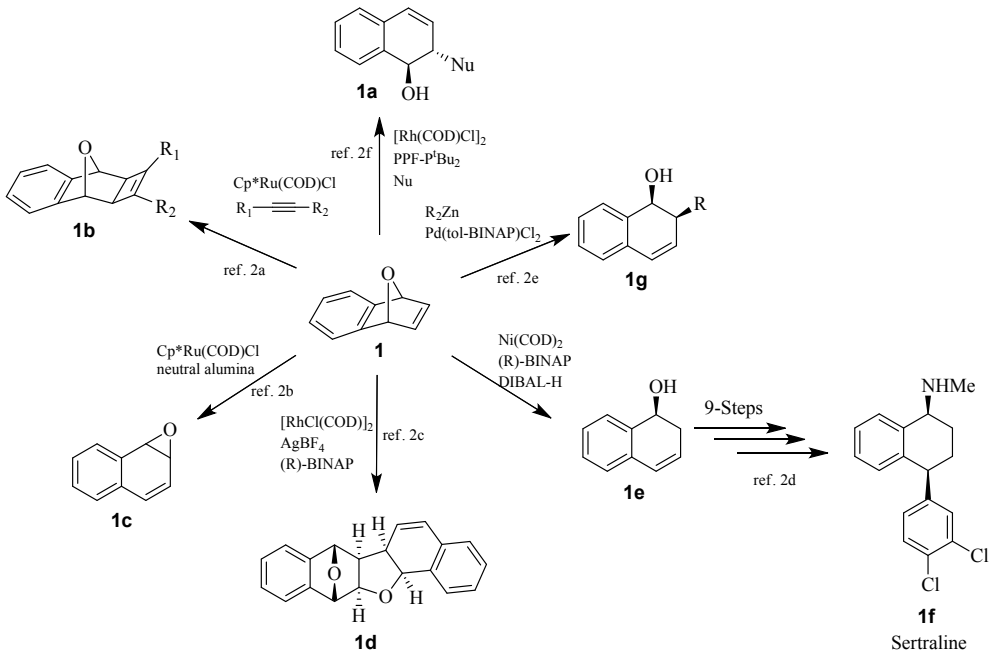
Received Date (will be automatically inserted after manuscript is accepted)

ABSTRACT: The palladium/Lewis acid co-catalyzed ring-opening reaction of various C_1-substituted unsymmetrical oxabenzonorbornadienes (OBD) with oxime nucleophiles was investigated. The effects of various C_1 substituents were explored. Moderate to excellent yields and excellent regioselectivities were obtained for electron-withdrawing groups. The presence of electron-donating alkyl groups lead to isomerization of the corresponding OBD to afford the

substituted naphthol derivatives. Additionally, a mechanism for the formation of C_2 regioisomeric ring-opened products has been proposed.

Oxabicyclic alkenes have proven to be valuable synthetic precursors for the preparation of complex polycyclic and acyclic systems.[1a-c] Transition metal-catalyzed ring-opening reactions of oxabicyclic alkenes have been extensively investigated by Lautens, Cheng and others as well as our group on account of their ability to generate multiple stereocenters in a single step (Scheme 1).[2] Of particular interest is the nucleophilic ring-opening reaction of oxabicyclic alkenes as many of these products are synthetic precursors to bioactive molecules (Scheme 1).[1a] The nucleophilic ring-opening reaction can provide either *trans*- or *cis*- stereochemistry of the nucleophile to the adjacent hydroxyl group depending on the metal catalyst and nucleophile employed.[2e-f] *Trans*- stereoisomeric ring opened products (**1a**) can be obtained utilizing rhodium catalysts which assist in nucleophilic addition (Scheme 1).[2f] Conversely, *cis*- sterioisomeric ring opened products (**1g**) can be obtained utilizing a palladium catalyst (Scheme 1).[2e]

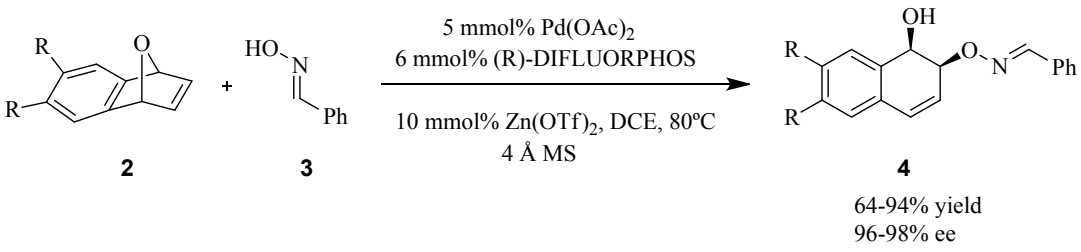
Notably, in 2003, Lautens *et al.* employed an enantioselective reductive ring opening reaction to obtain enantiopure 1,2-dihydronapth-1-ol, which was then used in the synthesis of sertraline, a potent antidepressant (Scheme 1).[1a, 2d]



Scheme 1. Previously reported ring-opening methodology on oxabicyclic alkenes.

Several nucleophiles have been investigated in the ring opening reactions of oxabicylic alkenes including various alcohols[3], thiols[2f], organoboronic acids[4], amines[5], and carboxylates[6]. However, until recently there were no reported examples of ring-opening reactions utilizing an oxime nucleophile.[7] Oximes have

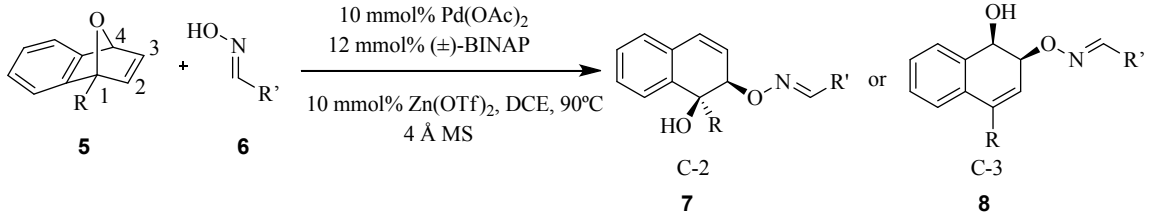
become a valuable tool in organic chemistry as a result of their role in the popular Beckmann reaction.[8] Furthermore, oximes have recently attracted attention as key structural motifs present in various antifungal agents.[9] In early 2019, Fan *et al.* reported the first ring opening reaction of aza/oxabicyclic alkenes (**2**) with oxime nucleophiles (**3**) utilizing an electron poor (R)-DIFLUORPHOS ligand and a palladium/Lewis acid co-catalyst (Scheme 2).[7] The group was able to obtain both excellent yields and enantioselectivity (**4**), however, only symmetrical oxabicyclic alkenes (**2**) were studied (Scheme 2).



Scheme 2. Previously reported ring-opening methodology with oxime nucleophiles.

Substituting the C_1 position of an oxabicyclic alkene renders the compound asymmetric and thus introduces several new steric and electronic factors in the

transition metal catalyzed ring-opening reactions. Interestingly, Lautens and Fagnou[10] obtained a single regioisomer in the rhodium catalyzed ring-opening reaction with alcohol nucleophiles (attack on C_3) (Scheme 5). Previous work by our group[11] has further demonstrated C_3 regioselectivity in the palladium-catalyzed ring opening reaction with aryl iodide nucleophiles (Scheme 5). Based upon these findings, we set out to determine the effect of C_1 substitution on controlling regioselectivity in the palladium/Lewis acid co-catalyzed ring-opening reaction with oxime nucleophiles (**6**) on unsymmetrical oxabenzonorbornadienes (**5**) (OBDs) (Scheme 3).



5 **6** **7** **8**

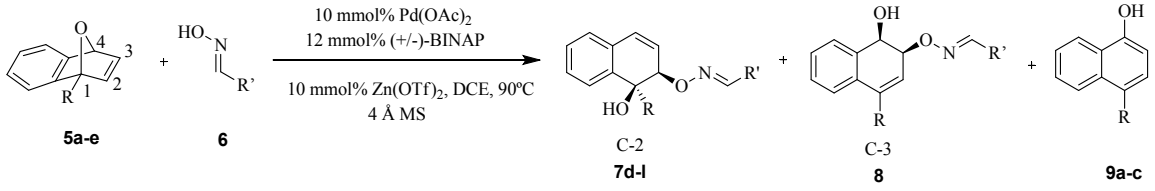
Scheme 3. Potential regioisomers formed through the ring-opening reaction of an unsymmetrical OBD.

The investigation began with methyl-substituted OBD, which afforded only isomerized naphthol product (**9**) in excellent yield (95%) (Table 1, entry 1). A

series of experiments were performed in hopes of preventing the isomerization, including removal of the Lewis acid. However, removal of the Lewis acid resulted only in isolation of starting material after prolonged reaction conditions. The isomerized naphthol product (**9**) was also obtained for ethyl and *t*-butyl substituted OBD in 90 and 91% yields, respectively (Table 1, entries 2-3). Our group[2b] and many others[12a-b] have reported similar OBD isomerizations utilizing similar transition metal or Lewis acid catalyzed systems. In these studies, the electronic nature of the C_1 substituent played a key role in whether or not ring-opened products were obtained. The ring-opened product (**7**) could be obtained only if the electronics of the R group at C_1 were reversed through substitution with an electron-withdrawing group rather than the electron donating alkyl group. Moderate to good yields (64-75%) of ring-opened product (**7**) were obtained for ketone, and ester substituted OBDs (Table 1, entries 4-6). Further, the product (**7**) obtained was exclusively the C_2 regioisomer, rather than the previously reported C_3 isomer investigated by Lautens and Fagnou[10] as well as our group[11] (Table 1, entries 4-6). The relative stereochemistry of the ring-opened product (**7**)

was confirmed by various NMR experiments. Following these results, we then chose the ketone substituted OBD (**5e**) to explore the scope with various oxime nucleophiles (Table 1, entries 7-12). Excellent yields were obtained for *o, m, p*-OMe-C_6H_4 substituted oxime derivatives, ranging from 85-91% yields (Table 1, entries 7-9), whereas, poor yields were obtained for *o, m, p*-NO_2-C_6H_4 ranging from 46-49%, (Table 1, entries 10-12). The regioselective C_2 addition was also retained in all cases when utilizing the various substituted oxime nucleophiles (Table 1, entries 7-12).

Table 1. Ring Opening Reactions of Oxabenzonorbornadienes.



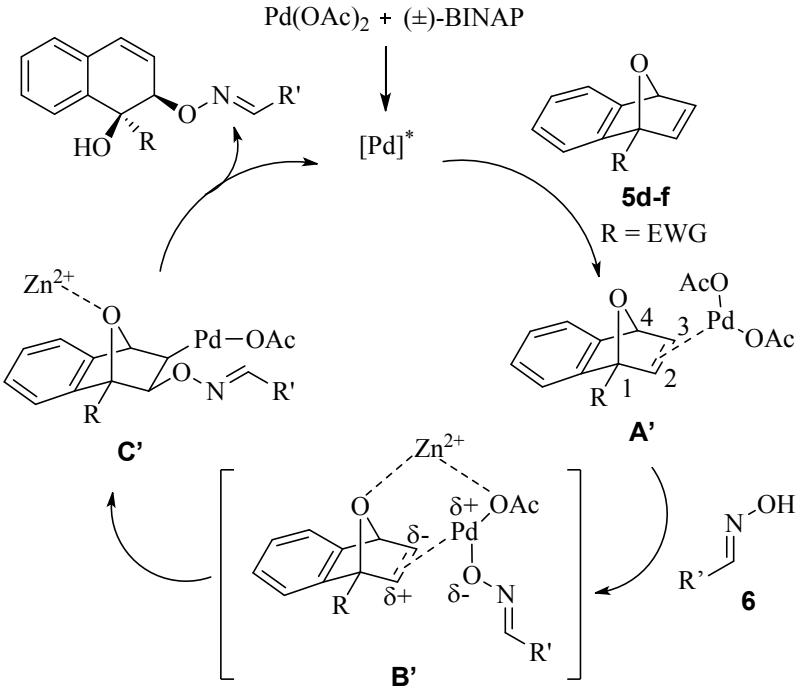
entry	OBD	R	R'	7 (%)[a]	8 (%)[a]	9 (%)[a]
1	**5a**	Me	Ph	0	0	95
2	**5b**	Et	Ph	0	0	90
3	**5c**	^{t}Bu	Ph	0	0	91
4	**5d**	COOMe	Ph	74	0	0
5	**5e**	C(O)Me	Ph	75	0	0

6	**5f**	$CH_2OC(O)$-*p*-NO_2-C_6H_4	Ph	64	0	0
7	**5e**	C(O)Me	*p*-OMe-C_6H_4	91	0	0
8	**5e**	C(O)Me	*m*-OMe-C_6H_4	87	0	0
9	**5e**	C(O)Me	*o*-OMe-C_6H_4	85	0	0
10	**5e**	C(O)Me	*p*-NO_2-C_6H_4	49	0	0
11	**5e**	C(O)Me	*m*-NO_2-C_6H_4	46	0	0
12	**5e**	C(O)Me	*o*-NO_2-C_6H_4	47	0	0

[a] Isolated yields after column chromatography.

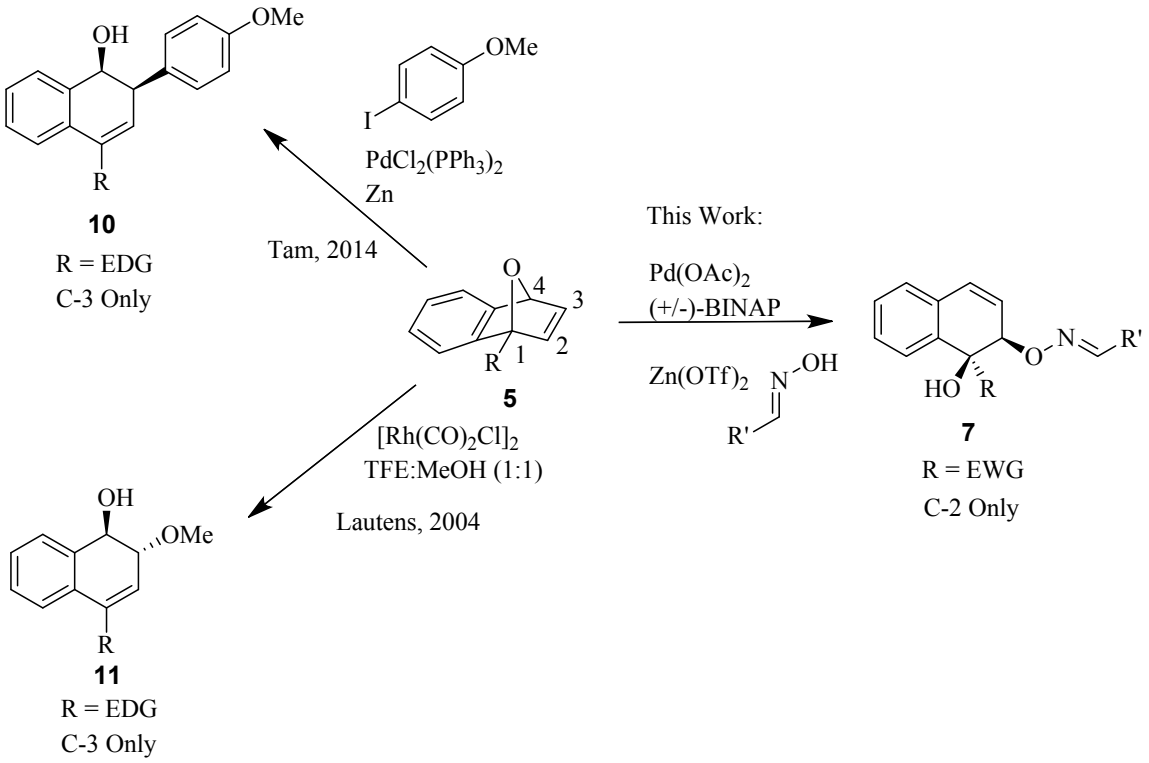
A potential mechanism for the reaction can be proposed based on the relative stereochemistry of the observed products (Scheme 4). Following the formation of the active palladium (II) species, the palladium coordinates to the *exo*- face (**A'**), after which, nucleophilic displacement of the acetate by the oxime nucleophile and proton transfer leads to intermediate **B'**. *Cis*-[1,2]-migration across the *exo*-face of the alkene affords the oxime derivative on the C_2 position and the palladium on C_3 (**C'**). It is likely that substituting C_1 with an electron-withdrawing group imposes enhanced electrophilicity on the C_2 site, resulting in delivery of the

oxime nucleophile to the more electron deficient carbon (Scheme 4). Finally, β-oxygen elimination affords the ring-opened product and regenerates the active palladium after protonation of the oxygen bridgehead (Scheme 4). Through a series of experiments the presence of the $Zn(OTf)_2$ was found to be paramount for the reactions progression. Thus, we postulate that the Lewis acid plays a dual role, wherein it aids in the addition of the palladium across the alkene and activates the bridgehead oxygen for the final β-oxygen elimination step.



Scheme 4. Potential mechanism for ring opened products.

We have examined the substituent effects at the C_1 position of various OBD derivatives in the palladium catalyzed ring opening reaction. Throughout these examples, it is shown that the ring-opened product obtained is exclusively the C_2 regioisomer (Table 1, entries 4-12). In addition to this, we were able to show that the ring-opened product could only be obtained if the C_1 position was substituted with an electron-withdrawing group (Table 1, entries 4-6). Interestingly, the single regioisomer we obtained is the opposite regioisomer (**7**) obtained in previous work by Lautens and Fagnou[10] as well as our group[11] (Scheme 5). Thus, we have demonstrated a highly efficient method in generating the previously elusive C_2 regioisomer with an oxime nucleophile utilizing palladium catalysis.



Scheme 5. Previous studies on the regioselectivity of ring opening reactions with oxabenzonobornadiene.

In conclusion, we have reported the first regioselective study into the palladium/Lewis acid co-catalyzed ring opening reactions with oxime nucleophiles on unsymmetrical OBDs. It was demonstrated that the reaction is highly regioselective for the C_2 position on unsymmetrical OBDs, with no C_3 regioisomers formed in all cases (Table 1, entries 4-12). Further, we have also demonstrated the requirement of electron-withdrawing groups in the

palladium/Lewis acid co-catalyzed system, whereby substitution of the C_1 position for slightly electron donating alkyl groups leads entirely to the isomerized naphthol derivatives (Table 1, entries 1-3).

Experimental Section

General Information: All reactions carried out in an atmosphere of dry argon. ^{1}H NMR spectra were recorded on 600 or 400 MHz in $CDCl_3$, ^{13}C{H}- NMR spectra were recorded on 150 or 100 MHz in $CDCl_3$. Chemical shifts for ^{1}H NMR spectra are reported in parts per million (ppm) with the solvent resonance as the internal standard (chloroform: δ 7.26). Chemical shifts for ^{13}C NMR spectra are reported in parts per million with the solvent as the internal standard (chloroform: δ 77.16). ^{1}H NMR spectra were recorded on 600 or 400 MHz in $CDCl_3$, ^{13}C{^{1}H} proton-decoupled carbon NMR spectra were recorded on 150 or 100 MHz in $CDCl_3$. Multiplicities are given as s (singlet), d (doublet), t (triplet), dd (doublet of doublets), td (triplet of doublets), or m (multiplet). IR spectra were obtained on

thin films on NaCl disks using a Bomem MB-100 FTIR or Nicolet-380 FTIR spectrophotometer. Analytical thin-layer chromatography was performed on Merck precoated silica gel 60 F254 plates. HRMS samples were ionized by chemical ionization (CI), electron impact (EI) or electrospray ionization (ESI) as specified, and detection of the ions was performed by time of flight (TOF). C_1-Substituted oxabenzonorbornadienes **5a-e** were prepared according to known literature procedures.[3,13,14]

General Procedure for the Pd-Lewis Acid Co-Catalyzed Ring Opening Reaction (Table 1, Entry 1): $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 10 mol %) was weighed into an oven dried screw-cap vial. The vial was purged with nitrogen and was taken into inert atmosphere Drybox where (±)-BINAP (14.9 mg, 0.024 mmol) dissolved in 1 mL of DCE was added. The mixture was stirred for 30 min, after which, $Zn(OTf)_2$ (7.3 mg, 0.02 mmol) was added in 0.4 mL of DCE. This solution was then stirred for an additional 10 min, then 4 Å MS (0.5 mmol) were added along with the oxabenzonorbornadiene (**5a**) (37 mg, 0.2 mmol) dissolved in 0.3 mL of DCE. This solution was stirred for another 10 min and the oxime (99 mg, 0.6 mmol)

was then added in another 0.3 mL of DCE. The entire reaction mixture was then exported from the Drybox and stirred at 90°C (heating mantle) for 36 h. The crude product was purified by flash chromatography to yield the corresponding ring opened product (Ethyl acetate: hexanes mixture).

Oxabenzonorbornadiene 5f: C_1-Substituted hydroxymethyloxabenzonorbornadiene[3] (200 mg, 1.148 mmol) was added into a N_2 purged RBF. *p*-NO_2-Benzoylchloride (312 mg, 1.722 mmol) was then added dilute in 1 mL of $CHCl_3$. To this solution was then added pyridine (0.3 mL, 3.444 mmol) and the mixture was stirred for 1.5 h under ambient temperature. The crude product was then co-concentrated with toluene (5 mL, 3×) and purified by column chromatography to give oxabenzonorbornadiene **1a** (152.7 mg, 0.5175 mmol, 45%) as a white solid (m.p 119-120°C). R_f 0.6 (EtOAc:pentanes 2:1); ^{1}H NMR ($CDCl_3$, 400 MHZ) δ 8.24 (m, 4H), 7.28 (m, 1H), 7.23 (m, 1H), 7.13 (dd, 1H, *J*= 1.8 , 5.5 Hz), 7.01 (m, 2H), 6.92 (d, 1H, *J*= 5.5 Hz), 5.77 (d, 1H, *J*= 1.8 Hz), 5.30 (d, 1H, *J*= 12.6 Hz), 5.15 (d, 1H, *J*= 12.6 Hz); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 164.7, 150.8, 150.1, 147.6, 145.3, 141.9, 135.1, 131.1 (2C), 125.6, 125.3,

126.7 (2C), 120.6, 119.4, 91.1, 82.5, 62.7; IR (CH_2Cl_2, NaCl) 3499 (m), 3060 (w), 2951 (w), 1734 (s), 1255 (s), 937 (m), 758 (m) cm^{-1}; HRMS (HRESI) calcd for $C_{18}H_{13}NO_5Na$ $[M+Na]^+$ *m/z* 346.0691, found 346.0689.

4-Methylnapthalenol 9a (Table 1, entry 1): The crude product was purified by column chromatography to give the isomerized product **9a** (30.1 mg, 0.190 mmol, 95%) as a pale yellow oil: R_f 0.6 (EtOAc:hexanes 2.5:7.5); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.26 (dd, 1H, *J*= 1.4, 7.4 Hz), 7.98 (dd, 1H, *J*= 1.6, 7.9 Hz), 7.61-7.52 (m, 2H), 7.16 (dd, 1H, *J*= 0.8, 7.6 Hz), 6.72 (d, 1H, *J*= 7.6 Hz), 5.25 (s, 1H), 2.65 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 149.9, 133.6, 126.8, 126.4, 126.2, 125.1, 124.6, 124.3, 122.1, 108.3, 18.9. Spectral data are in accord with those reported in the literature.[15]

4-Ethylnapthalenol 9b (Table 1, entry 2): The crude product was purified by column chromatography to give the isomerized product **9b** (31.0 mg, 0.179 mmol, 90%) as an orange oil: R_f 0.6 (EtOAc:hexanes 2.5:7.5); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.23 (m, 1H), 8.02 (dd, 1H, *J*= 1.2, 7.6 Hz), 7.56-7.48 (m, 2H), 7.16 (d, 1H, *J*= 7.6 Hz), 6.75 (d, 1H, *J*= 7.6 Hz), 5.13 (s, 1H), 3.04 (q, 2H, *J*= 7.2 Hz),

1.36 (t, 3H, *J*= 7.5 Hz); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 149.8, 132.9, 132.7, 126.2, 124.8, 124.7, 124.5, 123.8, 122.2, 108.2, 25.4, 15.2; IR (CH_2Cl_2, NaCl) 3335 (w), 2966 (m), 2929 (m), 2874 (w), 1658 (m), 1624 (w), 1598 (m), 1456 (m), 1380 (m), 1300 (m), 1274 (m), 1148 (w), 1054 (w), 763 (s); HRMS (HREI) calcd for $C_{12}H_{12}O$ [M^+] *m/z* 172.0888, found 172.0880.

4-Tertbutylnapthalenol 9c (Table 1, entry 3): The crude product was purified by column chromatography to give isomerized product **9c** (36.1 mg, 0.180 mmol, 91%) as a purple oil: R_f 0.6 (EtOAc:hexanes 2.5:7.5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.44 (dd, 1H, *J*= 1.2, 7.9 Hz), 8.30 (dd, 1H, *J*= 1.4, 8.1 Hz), 7.53-7.46 (m, 2H), 7.32 (d, 1H, *J*= 8.0 Hz), 6.73 (d, 1H, *J*= 8.0 Hz), 5.27 (s, 1H), 1.60 (s, 9H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 150.0, 138.7, 132.6, 126.8, 125.7, 126.1, 124.1, 123.0, 122.7, 107.5, 35.5, 31.9 (3C); IR (CH_2Cl_2, NaCl) 3378 (m), 2958 (m), 1598 (m), 823 (m), 763 (s) cm^{-1}; HRMS (HREI) calcd for $C_{14}H_{16}O$ [M^+] *m/z* 200.1201, found 200.1201.

(E)-BenzaldehydeO-((1R,2S)-1-hydroxy-1-methoxycarbonyl-1,2-dihydronapthalen-2-yl)oxime 7d (Table 1, entry 4): The crude product was

purified by column chromatography to give the ring opened product **7d** (47.8 mg, 0.148 mmol, 74%) as a clear oil: R_f 0.3 (EtOAc:hexanes 2.5:7.5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.21 (s, 1H), 7.55 (m, 2H), 7.39 (m, 3H), 7.33 (td, 1H, *J*= 1.3, 7.5 Hz), 7.25 (td, 1H, *J*= 1.4, 7.5 Hz), 7.19 (d, 1H, *J*= 7.4 Hz), 7.12 (d, 1H, *J*= 7.6 Hz), 6.59 (dd, 1H, *J*= 2.6, 9.9 Hz), 6.03 (dd, 1H, *J*= 2.4, 9.9 Hz), 5.64 (t, 1H, *J*= 2.5 Hz), 3.90 (s, 3H), 3.71 (s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 175.2, 150.6, 133.9, 132.5, 131.7, 130.4, 129.6, 128.9 (2C), 128.5, 128.1, 127.5, 127.4 (2C), 126.9, 126.1, 82.3, 77.8, 53.3; IR (CH_2Cl_2, NaCl) 3504 (w), 3059 (w), 2951 (w), 1736 (s), 1255 (s), 937 (m), 758 (m) cm^{-1}. HRMS (HRESI) calcd for $C_{19}H_{18}NO_4$ $[M+H]^+$ *m/z* 324.1236, found 324.1234.

(E)-BenzaldehydeO-((1R,2S)-1-hydroxy-1-methylcarbonyl-1,2-dihydronapthalen-2-yl)oxime 7e (Table 1, entry 5): The crude product was purified by column chromatography to give the ring opened product **7e** (45.9 mg, 0.149 mmol, 75%) as an orange oil. This experiment was repeated in a larger scale and similar yield of **7e** was obtained (554.3 mg, 1.799 mmol, 72%): R_f 0.4 (EtOAc:hexanes 2.5:7.5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14 (s, 1H), 7.49 (m, 2H), 7.38 (m, 3H),

7.33 (t, 1H, *J*= 4.9 Hz), 7.24 (m, 1H), 7.20 (d, 1H, *J*= 4.9 Hz), 7.04 (d, 1H, *J*= 5.0 Hz), 6.62 (dd, 1H, *J*= 1.5, 6.5 Hz), 6.09 (dd, 1H, *J*= 1.8, 6.5 Hz), 5.54 (t, 1H, *J*= 1.7 Hz), 4.27 (s, 1H), 2.49 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 209.3, 150.3, 133.9, 132.9, 131.7, 130.4, 129.5, 128.9 (2C), 128.7, 128.5, 127.9, 127.4 (2C), 126.7, 126.2, 81.7, 80.7, 26.1; IR (CH_2Cl_2, NaCl) 3438 (w), 3026 (w), 2925 (w), 1712 (s), 1533 (m), 942 (m), 757 (s), 693 (m) cm^{-1}; HRMS (HRESI) calcd for $C_{19}H_{18}NO_3$ $[M+H]^+$ *m/z* 308.1287, found 308.1287.

(E)-BenzaldehydeO-((1R,2S)-1-hydroxy-1-methanol-1-(4-nitrobenzoate)-1,2-dihydronapthalen-2-yl)oxime 7f (Table 1, entry 6): The crude product was purified by column chromatography to give the ring opened product **7f** (56.8 mg, 0.128 mmol, 64%) as a yellow oil: R_f 0.4 (EtOAc:hexanes 2.5:7.5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.34-8.25 (m, 4H), 8.09 (s, 1H), 7.81 (dd, 1H, *J*= 1.2, 7.4 Hz), 7.48 (m, 2H), 7.41-7.33 (m, 5H), 7.21 (dd, 1H, *J*= 1.2, 7.2 Hz), 6.75 (d, 1H, *J*= 9.6 Hz), 6.29 (m, 1H), 5.00 (d, 1H, *J*= 5.8 Hz), 4.56 (d, 1H, *J*= 11.6 Hz), 4.38 (dd, 1H, *J*= 1.4, 11.6 Hz), 3.61 (d, 1H, *J*= 1.2 Hz); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 164.5, 150.8, 150.7, 136.9, 135.5, 132.2, 131.9, 131.4, 131.0 (2C), 130.6, 129.1, 128.9

(2C), 128.6, 127.5, 127.3 (2C), 126.1, 123.7 (2C), 123.6, 76.9, 75.1, 69.1; IR (CH_2Cl_2, NaCl) 3552 (w), 3055 (w), 2952 (w), 1726 (s), 1527 (s), 1271 (s), 948 (m), 718 (m) cm^{-1}; HRMS (HRESI) calcd for $C_{25}H_{21}N_2O_6$ $[M+H]^+$ *m/z* 445.1400, found 445.1400.

(E)-4-MethoxybenzaldehydeO-((1R,2S)-1-hydroxy-1-methylcarbonyl-1,2-dihydronapthalen-2-yl)oxime 7g (Table 1, entry 7): The crude product was purified by column chromatography to give the ring opened product **7g** (61.6 mg, 0.183 mmol, 91%) as a yellow oil: R_f 0.3 (EtOAc:hexanes 2.5:7.5); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.09 (s, 1H), 7.43 (d, 2H, *J*= 8.8 Hz), 7.33 (td, 1H, *J*= 1.2, 7.5 Hz), 7.24-7.18 (m, 2H), 7.04 (d, 1H, *J*= 7.6 Hz), 6.90 (d, 2H, *J*= 8.8 Hz), 6.61 (dd, 1H, *J*= 2.3, 9.8), 6.08 (dd, 1H, *J*= 2.7, 9.8 Hz), 5.51 (t, 1H, *J*= 2.5 Hz), 4.29 (s, 1H), 3.81 (s, 3H), 2.48 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 209.1, 161.4, 149.9, 134.0, 133.0, 129.5, 128.9 (2C), 128.7, 128.4, 127.8, 126.7, 126.3, 124.3, 114.4 (2C), 81.8, 80.6, 55.5, 26.2; IR (CH_2Cl_2, NaCl) 3457 (w), 3002 (w), 2934 (w), 1712 (s), 1606 (s), 1513 (s), 1252 (s), 938 (m) cm^{-1}; HRMS (HRESI) calcd for $C_{20}H_{20}NO_4$ $[M+H]^+$ *m/z* 338.1392, found 338.1388.

(E)-3-MethoxybenzaldehydeO-((1R,2S)-1-hydroxy-1-methylcarbonyl-1,2-dihydronapthalen-2-yl)oxime 7h (Table 1, entry 8): The crude product was purified by column chromatography to give the ring opened product **7g** (58.6 mg, 0.174 mmol, 87%) as an orange oil: R_f 0.4 (EtOAc:hexanes 2.5:7.5) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.11 (s, 1H), 7.34-7.19 (m, 4H), 7.04 (m , 3H), 6.94 (ddd, 1H, *J*= 0.8, 2.6, 8.2 Hz), 6.62 (dd, 1H, *J*= 2.3, 9.84 Hz), 6.09 (dd, 1H, *J*= 2.76, 9.84 Hz), 5.53 (t, 1H, *J*= 2.5 Hz), 4.26 (s, 1H), 3.83 (s, 3H), 2.48 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 208.9, 160.0, 150.1, 133.9, 132.9, 129.9, 129.5, 128.7, 128.6, 127.8, 126.7, 126.1, 120.5, 116.8, 111.4, 81.7, 80.7, 55.5, 26.1; IR (CH_2Cl_2, NaCl) 3454 (m), 2933 (w), 1712 (s), 1578 (m), 1261 (m), 944 (m) cm^{-1}; HRMS (HRESI) calcd for $C_{20}H_{20}NO_4$ $[M+H]^+$ *m/z* 338.1392, found 338.1390.

(E)-2-MethoxybenzaldehydeO-((1R,2S)-1-hydroxy-1-methylcarbonyl-1,2-dihydronapthalen-2-yl)oxime 7i (Table 1, entry 9): The crude product was purified by column chromatography to give the ring opened product **7h** (57.3 mg, 0.169 mmol, 85%) as a yellow oil: R_f 0.4 (EtOAc:hexanes 2.5:7.5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.54 (s, 1H), 7.59 (dd, 1H, *J*= 1.7, 7.7 Hz), 7.38-7.30 (m, 2H), 7.24-7.18

(m, 2H), 7.04 (d, 1H, *J*= 7.6 Hz), 6.95 (t, 1H, *J*= 7.6 Hz), 6.89 (d, 1H, *J*= 8.4 Hz), 6.60 (dd, 1H, *J*= 2.3, 9.8 Hz), 6.09 (dd, 1H, *J*= 2.7, 9.8 Hz), 5.53 (t, 1H, *J*= 2.5 Hz), 4.32 (s, 1H), 3.83 (s, 3H), 2.47 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 209.2, 157.9, 146.6, 134.0, 133.0, 131.7, 129.5, 128.6, 128.4, 127.8, 126.7 (2C), 126.4, 120.9, 120.3, 111.3, 81.9, 80.7, 55.7, 26.2; IR (CH_2Cl_2, NaCl) 3462 (w), 2918 (w), 2361 (w), 1711 (s), 1599 (m), 1252 (s), 938 (m), 755 (s) cm^{-1}; HRMS (HRESI) calcd for $C_{20}H_{20}NO_4$ $[M+H]^+$ *m/z* 338.1392, found 338.1394.

(E)-4-NitrobenzaldehydeO-((1R,2S)-1-hydroxy-1-methylcarbonyl-1,2-dihydronapthalen-2-yl)oxime 7j (Table 1, entry 10): The crude product was purified by column chromatography to give the ring opened product **7j** (34.4 mg, 0.098 mmol, 49%) as an orange liquid: R_f 0.2 (EtOAc:hexanes 2.5:7.5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.23 (m, 3H), 7.64 (d, 2H, *J*= 8.8 Hz), 7.35 (m, 1H), 7.27 (m, 1H), 7.23 (t, 1H, *J*= 7.5 Hz), 7.06 (d, 1H, *J*= 7.5 Hz), 6.65 (dd, 1H, *J*= 2.1, 9.8 Hz), 6.09 (dd, 1H, *J*= 2.8, 9.8 Hz), 5.53 (t, 1H, *J*= 2.5 Hz), 4.19 (s, 1H), 2.46 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 208.7, 148.7, 148.0, 137.8, 133.7, 132.8, 129.7, 129.1, 128.9, 128.0, 127.9 (2C), 126.6, 125.4, 124.2 (2C), 81.6, 81.2,

26.0; IR (CH_2Cl_2, NaCl) 3442 (w), 2922 (w), 2852 (w), 1712 (s), 1597 (s), 1344 (s), 951 (m) cm^{-1}; HRMS (HRESI) calcd for $C_{19}H_{16}N_2O_5Na$ $[M+Na]^+$ *m/z* 375.0957, found 375.0956.

(E)-3-NitrobenzaldehydeO-((1R,2S)-1-hydroxy-1-methylcarbonyl-1,2-dihydronapthalen-2-yl)oxime 7k (Table 1, entry 11): The crude product was purified by column chromatography to give the ring opened product **7k** (32.7 mg, 0.093 mmol, 46%) as an opaque oil: R_f 0.2 (EtOAc:hexanes 2.5:7.5); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.34 (s, 1H), δ 8.23 (d, 1H, *J=* 8.2 Hz), 8.20 (s, 1H), 7.79 (d, 1H, *J=* 7.7 Hz), 7.57 (t, 1H, *J=* 8.0 Hz), 7.35 (t, 1H, *J=* 6.7 hz), 7.25 (m, 2H), 7.05 (d, 1H, *J=* 7.5 Hz), 6.65 (dd, 1H, *J=* 1.9, 9.8 Hz), 6.10 (dd, 1H, *J=* 2.8, 9.8 Hz), 5.53 (t, 1H, *J=* 2.4 Hz), 4.21 (s, 1H), 2.48 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 208.7, 148.7, 147.8, 133.7, 133.6, 132.8 (2C), 130.0, 129.7, 129.0, 128.9, 127.9, 126.6, 125.5, 124.7, 121.9, 81.7, 81.1, 26.0; IR (CH_2Cl_2, NaCl) 3453 (w), 3071 (w), 2924 (w), 1711 (s), 1530 (s), 1353 (s), 953 (m) cm^{-1}; HRMS (HRESI) calcd for $C_{19}H_{16}N_2O_5Na$ $[M+Na]^+$ *m/z* 375.0957, found 375.0958.

(E)-2-NitrobenzaldehydeO-((1R,2S)-1-hydroxy-1-methylcarbonyl-1,2-dihydronapthalen-2-yl)oxime 7l (Table 1, entry 12): The crude product was purified by column chromatography to give the ring opened product **7l** (32.7 mg, 0.093 mmol, 47 %) as a yellow oil: R_f 0.3 (EtOAc:hexanes 2.5:7.5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.69 (s, 1H), 8.06 (dd, 1H, *J*= 1.1, 8.2 Hz), 7.74 (dd, 1H, *J*= 1.4, 7.8 Hz), 7.65 (td, 1H, *J*= 0.8, 7.4 Hz), 7.55 (td, 1H, *J*= 1.6, 8.3 Hz), 7.34 (td, 1H, *J*= 1.3, 7.5 Hz), 7.27-7.20 (m, 2H), 7.05 (d, 1H, *J*= 7.5 Hz), 6.64 (dd, 1H, *J*= 2.3, 9.9 Hz), 6.10 (dd, 1H, *J*= 2.8, 9.8 Hz), 5.53 (t, 1H, *J*= 2.6 Hz), 4.19 (s, 1H), 2.45 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 209.1, 147.9, 146.7, 133.8, 133.7, 132.9, 130.7, 129.6, 129.0, 128.9, 128.8, 127.9, 126.9, 126.7, 125.6, 125.0, 81.7, 81.2, 26.1; IR (CH_2Cl_2, NaCl) 3450 (w), 3068 (w), 2922 (w), 1711 (s), 1524 (s), 1347 (s), 950 (m) cm^{-1}; HRMS (HRESI) calcd for $C_{19}H_{16}N_2O_5Na$ $[M+Na]^+$ *m/z* 375.0957, found 375.0956.

Acknowledgements This work was supported by the Natural Sciences and Engineering Research Council of Canada (NSERC).

Supporting Information Available ^{1}H and ^{13}C NMR spectra all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References:

1) For reviews, see (a) Lautens, M.; Fagnou, K.; Hiebert, S. Transition Metal-Catalyzed Enantioselective Ring-Opening Reactions of Oxabicyclic Alkenes. *Acc. Chem. Res.* **2003**, *36*, 48. b) Cheng, C. H.; Rayabarapu, D. K. New Catalytic Reactions of Oxa-Azabicyclic Alkenes. *Acc. Chem. Res.* **2007**, *40*, 971. c) Lautens, M. Ring-Opening Reactions of Oxabicyclic Compounds as a Route to Cylic and Acyclic Compounds with Multiple Stereocenters. *Synlett* **1993**, *177*.

2) a) Villeneuve, K.; Tam, W. Ruthenium-Catalyzed Processes: Dual [2+2] Cycloaddition versus Cyclopropanation of Bicyclic Alkenes with Propargylic Alcohols. *Organometallics* **2006**, *25*, 843. b) Villeneuve, K.; Tam, W. Ruthenium-Catalyzed Isomerization of Oxa/Azabicyclic alkenes: an Expedient Route for the Synthesis of 1,2-Napthalene Oxides and

Imines. *J. Am. Chem. Soc.* **2006**, *128*, 3514. c) Allen, A.; Le-Marquand, P.; Burton, R.; Villeneuve, K.; Tam, W. Ruthenium-Catalyzed [2+2] Cycloadditions of Alkynyl Suflides and Alkynyl Sulfones. *J. Org. Chem.* **2007**, *72*, 7849. d) Lautens, M.; Rovis, T.; Smith, N. D.; Ostrovsky, D. Metal Catalyzed hydrometlations and their applications in synthesis. *Pure & Appl. Chem.* **1998**, *70*, 1059. e) Lautens, M.; Hiebert, S. Scope of Palladium-Catalyzed Alkylative Ring Opening. *J. Am. Chem. Soc.* **2004**, *126*, 1437. f) Leong, P.; Lautens, M. Rhodium-Catalyzed Asymmetric Ring Opening of Oxabicyclic Alkenes with Sulfur Nucleophiles. *J. Org. Chem.* **2004**, *69*, 2194. g) Cheng, G.; Yang, W.; Li, Y.; Yang, D. Iridium/Copper Co-catalyzed *Anti*-Stereoselective Ring Opening of Oxabenzonorbornadienes with Grignard Reagents. *J. Org. Chem.* **2016**, *81*, 7817.

3) Webster, R.; Böing, C.; Lautens, M. Reagent-Controlled Regiodiverget Resolution of Unsymmetrical Oxabicyclic Alkenes Using a Cationic Rhodium Catalyst. *J. Am. Chem. Soc.* **2009**, *131*, 444.

4) Zhang, T.; Mo, D.; Dai, L.; Hou, X. Asymmetric Ring-Opening Reaction of Oxabicyclic Alkenes with Aryl Boronic Acids Catalyzed by P-Containing Palladacycles. *Org. Lett.* **2008**, *10*, 3689.

5) Cho, Y. H.; Zunic, V.; Senboku, H.; Olsen, M.; Lautens, M. Rhodium-Catalyzed Ring-Opening Reactions of *N*-Boc-Azabenzonorbornadienes with Amine Nucleophiles. *J. Am. Chem. Soc.* **2006**, *128*, 6837.

6) Lautens, M.; Fagnou, K. Rhodium-Catalyzed Asymmetric Ring Opening Reactionf with Carboxylate Nucleophiles. *Tetrahedron* **2001**, *57*, 5067.

7) Shen, G.; Khan, R.; Yang, F.; Yang, Y.; Pu, G.; Gao, Y.; Zhan, Y.; Luo, Y.; Fan, B. Pd/Zn Co-catalyzed Asymmetric Ring-Opening Reactions of Aza/Oxabicyclic Alkenes with Oximes. *Asian J. Org. Chem.* **2019**, *8*, 97.

8) Blatt, A. H. The Beckmann Rearrangement. *Chem. Rev.* **1933**, *12*, 215.

9) Xie, Q. -Y.; Huang, Z. -L.; Yan, H. –D.; Li, J.; Ye, L.-Y.; Che, L.-M.; Tu, S. Design, Synthesis, and Biological Activity of Oxime Ether Strobilurin Derivatives Containing Indole Moeity as Novel Fungicide. *Chem. Biol. Drug. Des.* **2014**, *85*, 743.

10) Lautens, M.; Fagnou, K. Rhodium-catalyzed asymmetric ring opening reactions of oxabicyclic alkenes: Catalyst and substrate studies leading to a mechanistic working model. *Proc. Nat. Acad. Sci. USA* **2004**, *101*, 5455.

11) Raheem, M. A.; Edmunds, M.; Tam, W. Regioselective palladium-catalyzed ring-opening reaction of C 1-substituted oxabenzonorbornadienes. *Can. J. Chem.* **2014**, *92*, 888.

12) a) Peng, F.; Fan, B.; Shao, Z.; Pu, X.; Li, P.; Zhang, H. $Cu(OTf)_2$-Catalyzed Isomerization of 7-Oxabicyclic Alkenes: A Practical Route to the Synthesis of 1-Naphthol Derivatives. *Synthesis* **2008**, *19*, 3043. b) Sawama, Y.; Ogata, Y.; Kawamoto, K.; Satake, H.; Shibata, K.; Monguchi, Y.; Saijki, H.; Kita, Y. Lewis Acid-Catalyzed Ring-Opening Functionalizations of 1,4-Epoxy-1,4-dihydronapthalenes. *Adv. Synth. Catal.* **2013**, *335,* 517.

13) Carlson, E.; Boutin, R.; Tam, W. Type 3 ring opening reaction of cyclopropanated oxabenzonorbornadienes with alcohol nucleophiles. *Tetrahedron* **2018**, *74*, 5510.

14) Carlson, E.; Haner, J.; Mckee, M.; Tam, W. Type 1 ring-opening reactions of cyclopropanated 7-oxabenzonorbornadienes with organocuprates. *Org. Lett.* **2014**, *16*, 1776.

15) Ballantine, M.; Menard, M. L.; Tam, W. Isomerization of 7-oxabenzonorbornadienes into naphthols catalyzed by $[RuCl_2(CO)_3]_2$. *J. Org. Chem.* **2009**, *74*, 7570.