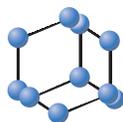


REVIEW ARTICLE

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SCIENCE

Recent Advances in Transition Metal-Catalyzed Reactions of Oxabenzonorbornadiene

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Abstract: Background: Oxabenzonorbornadiene (OBD) is a useful synthetic intermediate capable of undergoing multiple types of transformations due to three key structural features: a free alkene, a bridged oxygen atom, and a highly strained ring system. Most notably, ring-opening reactions of OBD using transition metal catalysts and nucleophiles produce multiple stereocenters in a single step. The resulting dihydronaphthalene framework is found in many natural products, which have been shown to be biologically active.

Objective: This review will provide an overview of transition metal-catalyzed reactions from the past couple of years including cobalt, copper, iridium, nickel, palladium and rhodium-catalyzed reactions. In addition, the recent derivatization of OBD to cyclopropanated oxabenzonorbornadiene and its reactivity will be discussed.

Conclusion: It can be seen from the review, that the work done on this topic has employed the use of many different transition metal catalysts, with many different nucleophiles, to perform various transformations on the OBD molecule. Additionally, depending on the catalyst and ligand used, the stereo and regioselectivity of the product can be controlled, with proposed mechanisms to support the understanding of such reactions. The use of palladium has also generated a cyclopropanated OBD, with reactivity similar to that of OBD. An additional reactive site exists at the distal cyclopropane carbon, giving rise to three types of ring-opened products.



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1. INTRODUCTION

Oxabenzonorbornadiene (OBD) **1** is a heterobicyclic [2.2.1] alkene [1]. Due to its fused bicyclic structure, OBD has two distinct faces: the *exo* face and the *endo* face. The *exo* face is composed of a five-membered ring, which includes the bridging oxygen, and the more sterically hindered *endo* face is composed of a six-membered ring, which excludes the bridging oxygen [1]. There are many structural features of OBD which contribute to its reactivity: i) a free alkene, ii) a bridging oxygen atom which allows for the coordination of electrophiles, Lewis acids and metals, and iii) ring strain imparted by the bicyclic structure [2]. OBD has ring strain energy of 36.1 kcal/mol and the alleviation of this strain is a driving force behind ring-opening reactions of OBD [3].

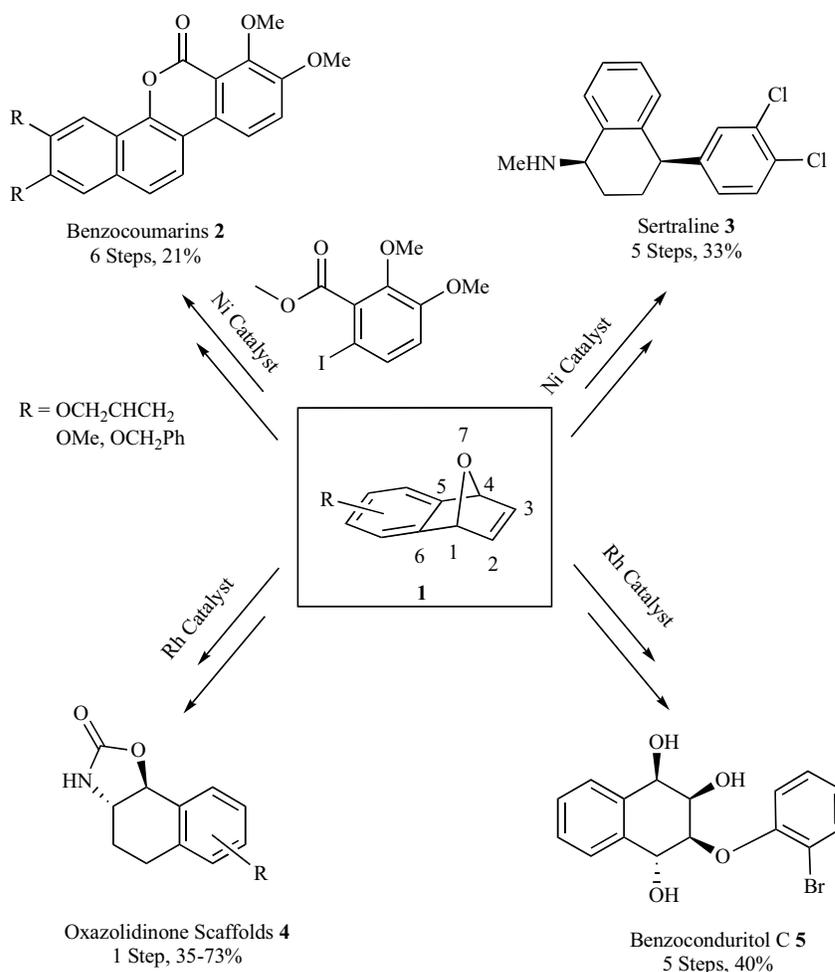
OBD is a very versatile compound and has been shown to undergo numerous different types of reactions including cycloadditions [4, 5], dimerization [6], and ring-opening reactions [7]. Ring-opening of OBD is of particular interest with respect to the synthesis of natural products, as it allows for the creation of multiple stereocenters in a single step with a high degree of regio- and stereoselectivity. Additionally, the 1,2-dihydronaphthalene sub-structures are found in a wide range of compounds possessing biological activity [1]. There are several natural products, which involve the ring-opening of OBD in their synthesis. Some examples of these include: i) benzocoumarin derivatives **2**, potential anti-inflammatory, anti-dyslipidemic and antioxidant agents [8], ii) serotonin

re-uptake inhibitor (anti-depressant) [9], iii) chiral oxazolidinone scaffolds **4**, chiral auxiliaries used in asymmetric transformations [10], and iv) benzoconduritol C **5**, a glycosidase inhibitor with antibiotic, antileukemic and growth regulation activity [11] (Scheme 1).

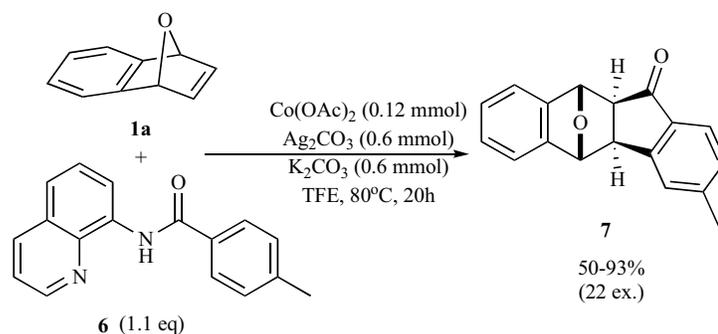
The Lautens group pioneered the study of asymmetric ring-opening (ARO) of oxabicyclic compounds [12], and since then, a lot of work has been done to study the reactivity of OBDs, namely using different transition metal-catalysts with various nucleophiles. Transition metal-catalysts, which have been used in ring-opening reactions of OBD, include Cu [13, 14], Fe [15], Ir [16], Ni [17, 18], Pd [19, 20], Pt [21-23], Rh [24, 25], Ru [26, 27], and Zr [28]. The goal of these ring opening reactions is to construct new carbon-heteroatom or carbon-carbon bonds within the dihydronaphthalene framework. To this end, alcohols [29], amines [30], phenols [31], and thiols [32] have been used as nucleophiles to construct new carbon-heteroatom bonds and Grignard [33], organoaluminum [34], organoboron [35], organocuprate [36], organolithium [37], and organozinc reagents [38] have been used as the source of carbon nucleophiles to construct new carbon-carbon bonds.

Another area of interest in the study of OBD reactivity is the reactivity of substituted OBDs. Substituents of varying electronic properties and steric bulk can be added to the aryl or bridgehead positions of OBD (C1, C4) to investigate how their presence influences the outcome of the reaction. This is of particular interest with bridgehead substituents. In its most basic form, OBD is a symmetrical molecule. However, the addition of a substituent at the bridgehead carbon renders the molecule asymmetrical and the modification could significantly alter the outcome of a ring-opening reaction. As OBD becomes asymmetrical, more unique sites of reactiv-

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Scheme 1. Natural products synthesized from ring-opening of oxabenzonorbornadiene.



Scheme 2. Co-catalyzed synthesis of dihydroepoxybenzo-fluorenone derivatives.

ity arise, and two potential products can be formed from the nucleophilic ring-opening depending on whether the nucleophile adds to the olefin carbon closest, or furthest, from the C1-substituent. The addition of this substituent also influences the steric and electronic properties of the compound, which could alter the way OBD interacts with incoming nucleophiles [39].

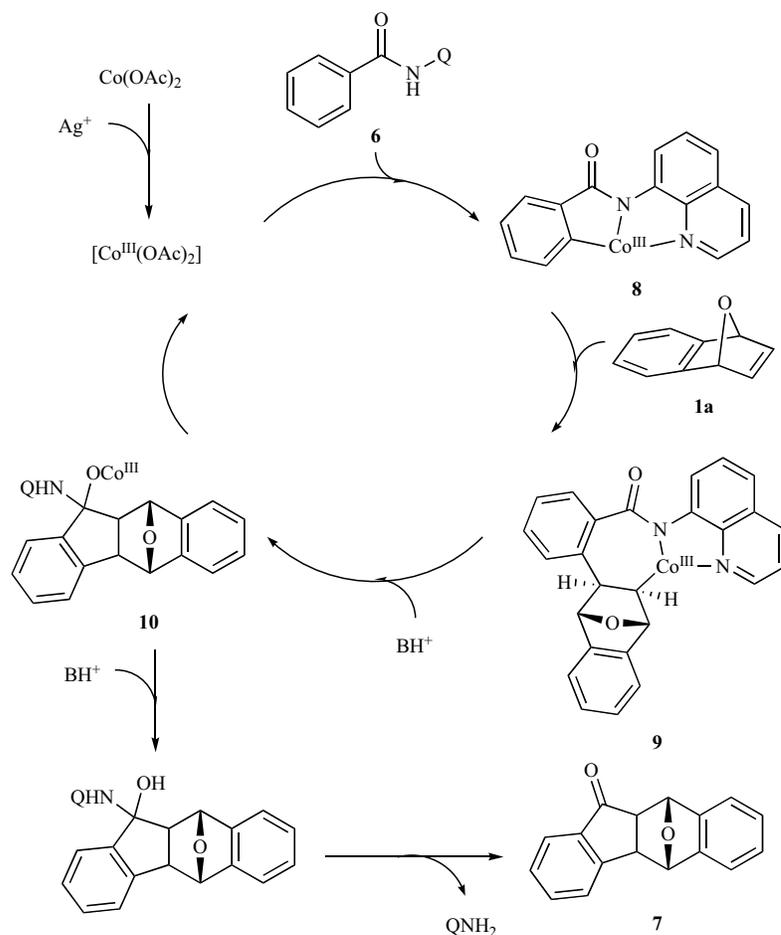
As can be seen from the aforementioned literature, there are several different products, which can be formed, based on the type of nucleophile, substituents, and reaction conditions used. Therefore, it is important to develop an understanding of OBDs reactivity, and how steric and electronic changes to OBD affect reaction outcomes. It is also highly important to obtain a full understanding of the conditions, which produce each product, as precise manipula-

tion of such conditions is required to obtain the maximum yield and selectivity. To this end, the goal of this review is to provide an overview of recent developments and advances in transition metal-catalyzed reactions of OBD from the past couple of years.

2. TRANSITION METAL CATALYZED REACTIONS OF OBD

2.1. Cobalt-Catalyzed Reactions

A number of noble metals such as Pd, Rh, Ru and Ir are capable of catalyzing C-H bond functionalization [40] and C-C bond formation. However, these second and third-row transition metal-catalysts are expensive [41]. Co, an earth-abundant first-row transition metal, has received attention in C-H bond activations [41] due to its lower



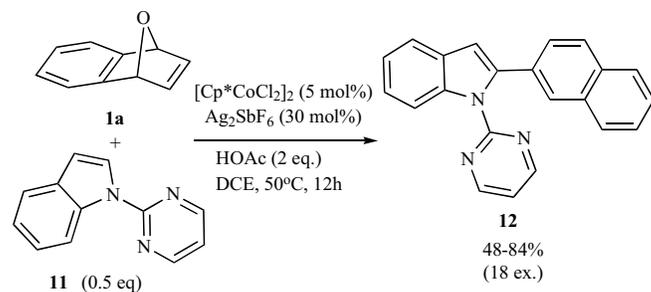
Scheme 3. Mechanism of Co-catalyzed synthesis of dihydroepoxybenzo-fluorenone derivatives.

cost and wide functional group tolerance. Air-stable and commercially available, Co (II) and Co (III) salts have been shown to be capable of functionalizing C (sp²)-H bonds with alkenes and alkynes [40]. They have also demonstrated high efficiency, due to the greater Lewis acidity of Co (III) and increased metal-substrate coordination [41].

Gandeepan *et al.* used Co-catalyzed C-H bond activation to synthesize dihydroepoxybenzofluorenone derivatives **7** from OBD **1a** and aromatic/vinylic amides **6** (Scheme 2). Normally, a [4+2] or [4+1] cycloaddition product is observed with transitional metal-catalyzed C-H activation reactions between secondary amides and alkenes. This was however, an unusual annulation reaction which produced a [3+2] cycloaddition product. Co(OAc)₂ was found to be the optimized catalyst, with Ag⁺ from Ag₂CO₃ being used to oxidize Co(II) to the catalytically active Co(III). During the reaction, 8-aminoquinine is released from the amide and can coordinate to the Co catalyst, thus reducing its activity. As a result, a high catalyst loading (40 mol%) is needed. Advantages to this reaction include its mild conditions, which tolerate a diverse range of functional groups and its high diastereoselectivity [40].

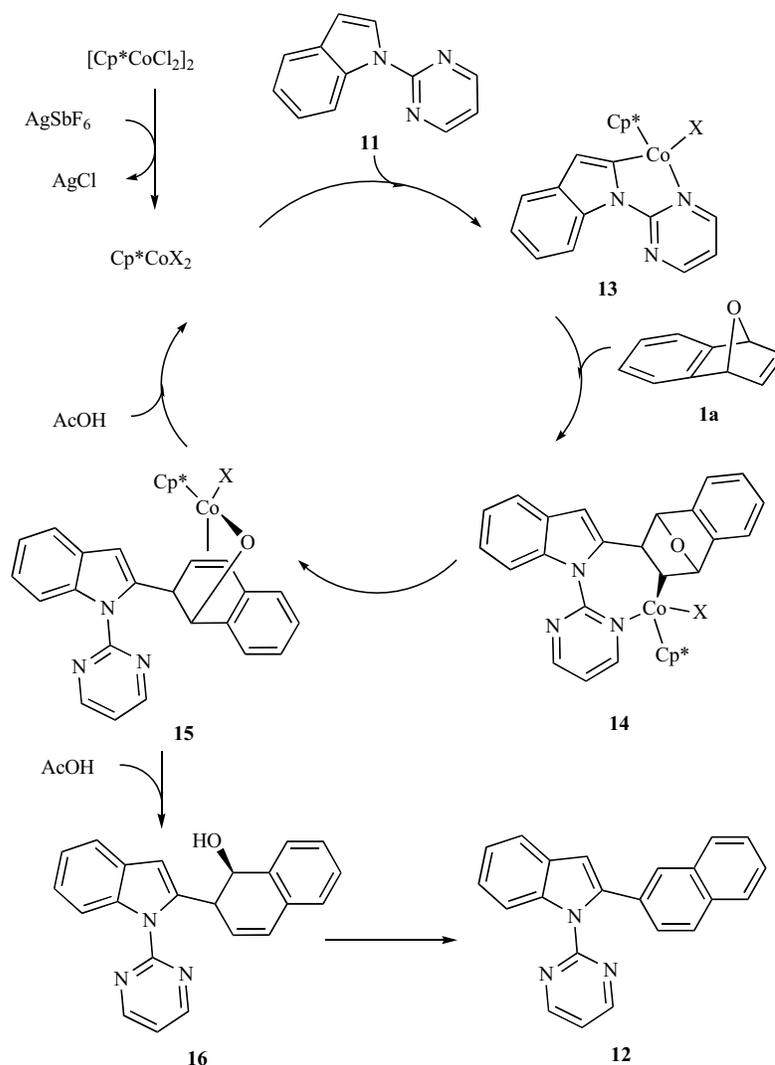
The mechanism is initiated by Ag⁺ oxidizing Co (II) to Co (III), which can coordinate to the amide. Cyclometalation is achieved through C-H bonds cleavage to form intermediate **8**. The more sterically hindered C-H bond is activated, and this selectivity arises due to coordination of Co with the neighbouring oxygen which functions as a directing group. Coordination of OBD to the Co center followed by migratory insertion generates a seven-membered ring intermediate **9**. The imposed stereochemistry of the observed product occurs at this step *via* addition to the OBD at the *exo* face. As

there are no suitable β-hydrogens, **9** cannot undergo β-hydride elimination. Steric hindrance from OBD and the quinolyl moiety prevent reductive elimination to a six-membered lactam. Therefore, intermediate **10** is formed through an intramolecular nucleophilic addition of the C-Co bond to the amide carbonyl; the [3+2] cycloaddition step. Protodemetalation and elimination of the quinolyl moiety produce the final product **7** and regenerate the Co (III) species, which is catalytically active (Scheme 3) [40].



Scheme 4. Co-catalyzed synthesis of 2-functionalized indoles.

Kong *et al.* used a Co (III) catalyst to synthesize 2-functionalized indoles **12** from OBD **1a** and N-pyrimidinylindoles **11** *via* C-C coupling (Scheme 4). In these examples, [Cp*CoCl₂]₂ were found to be the optimized catalyst. The silver salt Ag₂SbF₆ plays a dual role in this reaction: Ag⁺ oxidizes the Co (II) catalyst to the catalytically active Co (III) species, and also functions as a Lewis acid to activate OBD. The mild conditions enable a wide range of functional groups to be incorporated into the final product with high selectivity and efficiency [41].

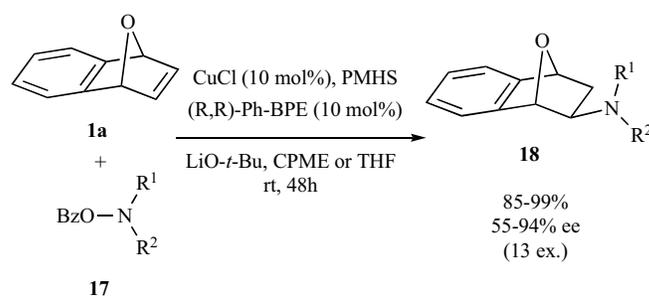


Scheme 5. Mechanism of Co-catalyzed synthesis of 2-functionalized indoles.

The mechanism for the 2-naphthylation of N-pyrimidinylindole begins with the oxidation of the Co (II) catalyst to Co (III) by Ag^+ . Ortho-selective C-H metalation of N-pyrimidinylindole yields the five-membered metallacycle **13**. OBD then coordinates to the Co followed by migratory insertion to give the seven-membered ring **14**. β -oxygen elimination produces the alkoxide intermediate **15**, which undergoes protonolysis to regenerate the active Co (III) catalyst, and a dihydronaphthol intermediate **16**. The final naphthalene product **12** is formed through dehydration (Scheme 5) [41].

2.2. Copper-Catalyzed Reactions

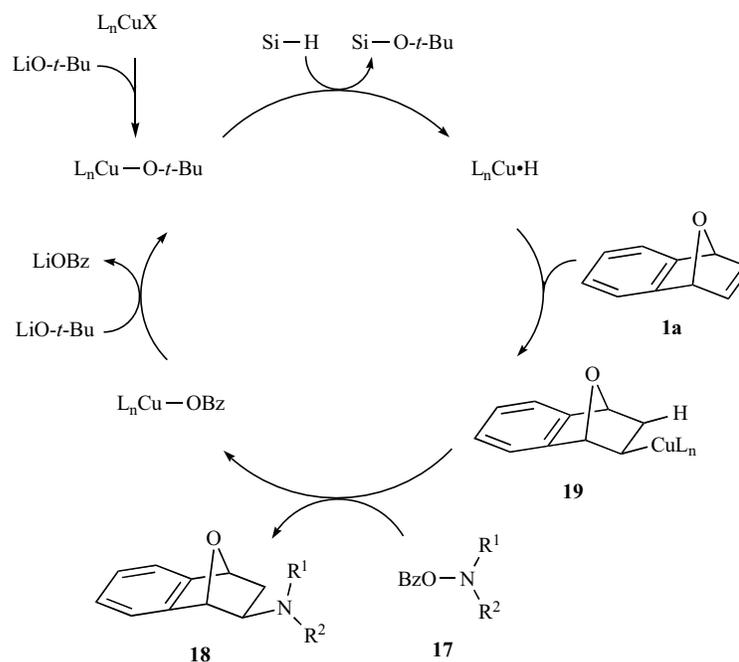
Miki *et al.* developed a copper-catalyzed hydroamination of OBD **1a** using polymethylhydrosiloxane (PMHS) and O-benzoyl-hydroxylamines **17** to improve upon the scope and selectivity for this asymmetric reaction (Scheme 6). The optimized catalyst, CuCl, used in conjunction with the chiral ligand 1,2-bis [(2R, 5R)-2,5-diphenylphospholano] ethane ((R,R)-Ph-BPE) yielded an enantioselective *exo*-hydroaminated OBD derivative **18** with no ring-opened by-products. The choice of solvent was dependent on the substituents on the hydroxylamine; overall CPME or THF gave better yields and enantiomeric ratio while THF worked better for hydroxylamines containing coordinating olefin substituents. The oxabenzonorbomenylamine product has displayed potential as an inhibitor for the neutral nicotinic acetylcholine receptor and as dopaminergic and adrenergic ligands [42].



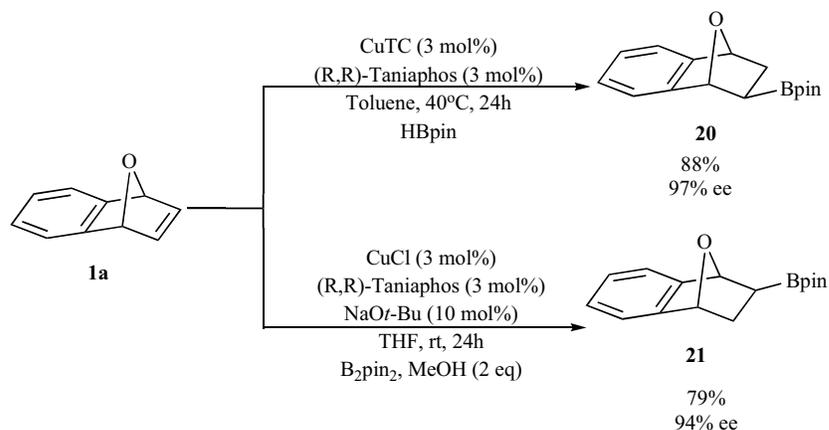
Scheme 6. Cu-catalyzed hydroamination of OBD.

The hydroamination reaction is carried out using an umpolung electrophilic amination strategy. In the first step of the mechanism, a $\text{L}_n\text{CuO-}t\text{Bu}$ complex is generated through ligand exchange of CuCl with lithium *tert*-butoxide, which is then further reacted with the hydrosilane PMHS to form $\text{L}_n\text{Cu-H}$. Intermediate **19** is formed through hydrometalation on the *exo* face of OBD; this is also the enantioselectivity-determining step. The final chiral amine is formed by stereoretentive electrophilic amination with the hydroxylamine, and the catalyst is regenerated by ligand exchange with lithium *tert*-butoxide (Scheme 7) [42].

Lee *et al.* have developed a method for enantiodivergent hydroboration of OBD **1a** using a CuI catalyst, which provides excel-



Scheme 7. Mechanism of Cu-catalyzed hydroamination of OBD.



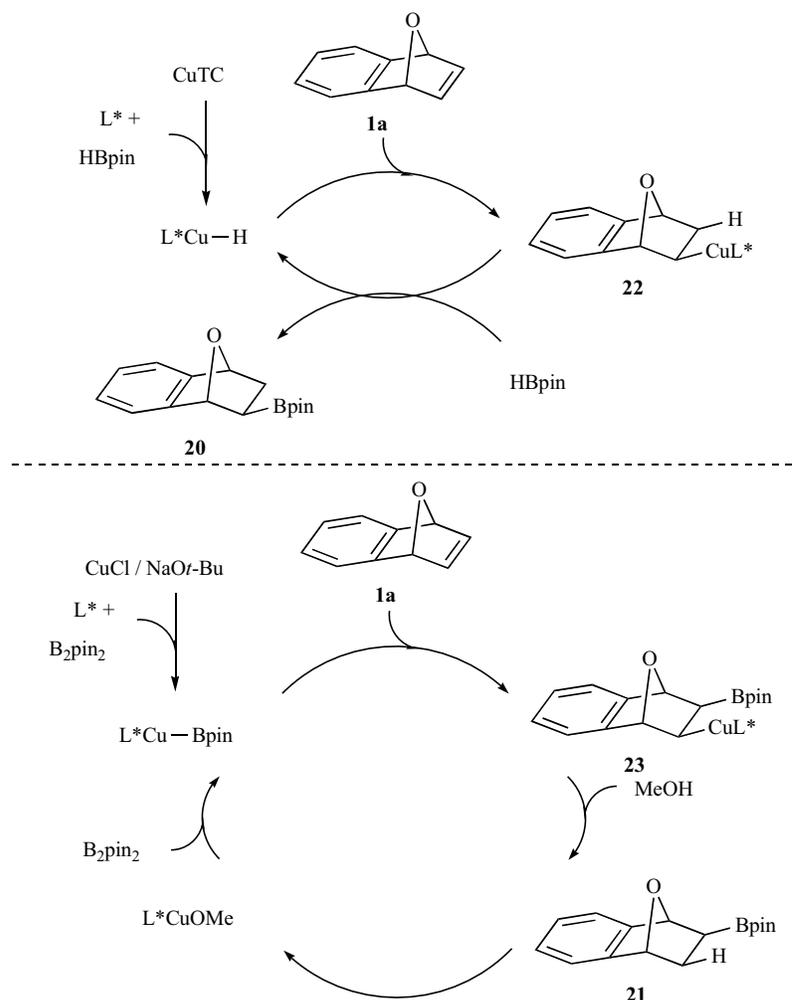
Scheme 8. Cu-catalyzed enantiodivergent hydroboration of OBD.

lent selectivities of the desired enantiomers (Scheme 8). For both pathways, a copper (I) catalyst with the same chiral (R,R)-Taniaphos ligand was used. As the same copper-Taniaphos complex is used, the resulting enantiomer formed is determined by the borylating reagent used. For the (R)-enantiomeric product **20**, pinacolborane (pinBH) was used as the hydroborating reagent with CuTC and (R,R)-Taniaphos as the optimized catalyst and ligand. For the (S)-enantiomeric product **21**, bis (pinacolato)diboron (B_2pin_2) with methanol was used as the hydroborating reagent, with CuCl and (R,R)-Taniaphos as the optimized catalyst and ligand. This is a very useful and unique hydroboration method as it enables the synthesis of both enantiomers from the same starting material and chiral ligand with high yields and enantioselectivities [43].

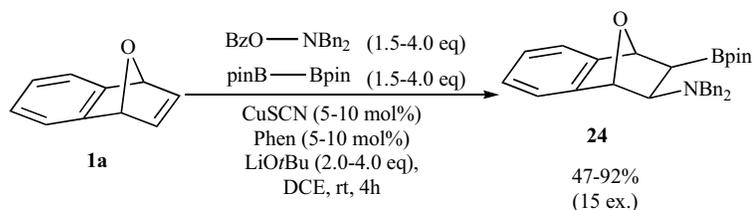
The two enantiomers are formed through alternate pathways based on the borylating reagents' ability to react with the catalyst and form two different organocopper intermediates. With HBpin, a catalytically active Cu-H species is formed from CuTC and HBpin, which form intermediate **22** through hydrocupration. The final product **20** is then formed from transmetalation with HBpin. With B_2pin_2 , a catalytically active Cu-C species is formed from CuCl, NaOt-Bu and B_2pin_2 which forms intermediate **23** through bory-

lucupration. The final product **21** is then generated by protonolysis with methanol (Scheme 9) [43].

Sakae *et al.* added amine and boron moieties across the alkene of OBD **1a** in a copper-catalyzed aminoboration reaction (Scheme 10). The products had exclusive *exo*-selectivity, and no ring-opened side products were observed. This reaction employed the nucleophilic diboron reagent bis (pinacolato) diboron (pinB-Bpin) and the electrophilic hydroxylamine O-benzoyl-N,N-dibenzyl-hydroxylamine to form the aminoborated products **24**. CuSCN, the optimized catalyst, was used with the ligand 1,10-phenanthroline (phen) and LiOt-Bu. The reaction was compatible with a wide range of O-benzoylhydroxylamines and acyclic amines. Further developed by using the chiral bisphosphine ligand (R,R)-Ph-BPE with CuCl, an asymmetric transformation was observed with excellent enantioselectivity (94% ee). Although a high degree of regiochemistry was already seen when using a C1-methyl OBD; the boryl moiety was preferentially added to the olefin carbon furthest from the C1-substituent. This reaction has further potential, as the boryl group can be transformed into other oxygen of nitrogen containing functional groups with good diastereoselectivity. For example, the boryl group could be hydroxylated using oxone/acetone or aminated using $MeONH_2/BuLi/Boc_2O$ [44].



Scheme 9. Mechanisms for Cu-catalyzed enantiodivergent hydroboration of OBD.



Scheme 10. Cu-catalyzed aminoboration of OBD.

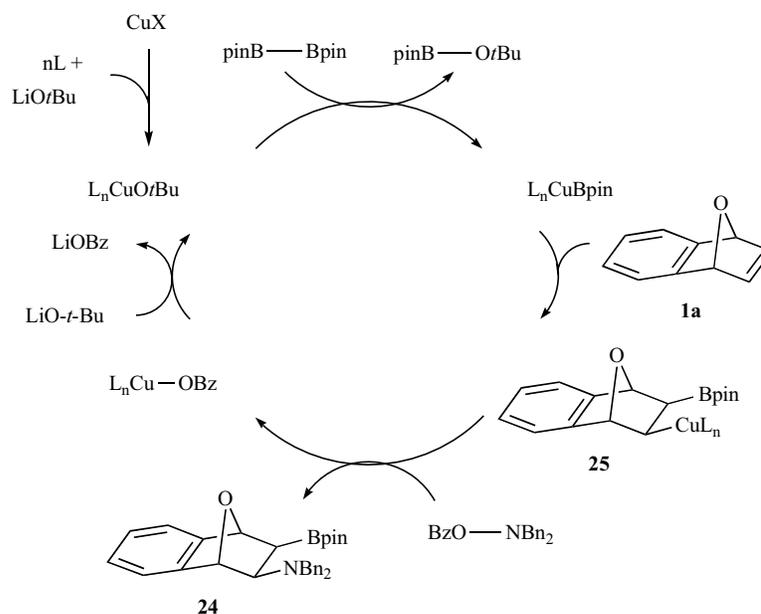
The mechanism begins with ligand exchange on the CuSCN catalyst using phen and LiOtBu to form $L_nCuOtBu$, which further reacts with pinB-Bpin to produce $L_nCuBpin$. Coordination of this complex to the alkene of OBD followed by borylcupration on the *exo* face yields intermediate **25**; this is also the enantioselective step when using the chiral ligand. The final product **24** is produced through an electrophilic amination using the hydroxylamine with retention of stereochemistry. The catalyst is regenerated by ligand exchange with LiOtBu (Scheme 11) [44].

2.3. Iridium-Catalyzed Reactions

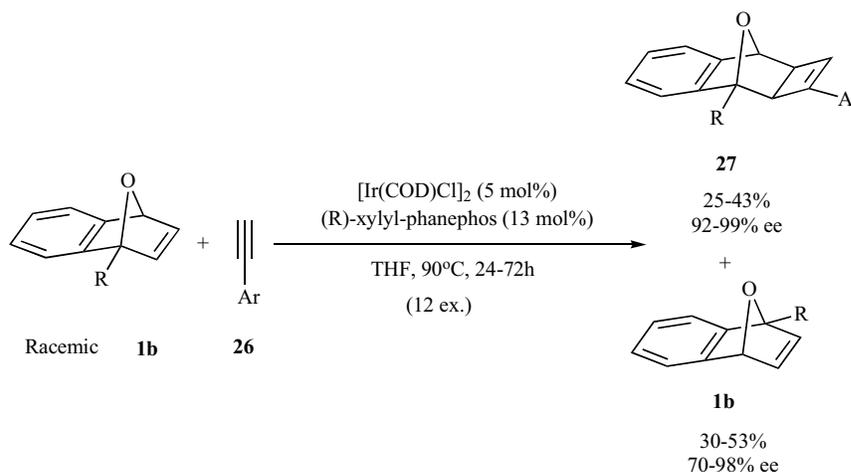
Yang *et al.* used an iridium catalyst with the chiral phosphine ligand (R)-xylyl-phanephos, to perform kinetic resolution of racemic C1-substituted OBDs **1b** via a [2+2] cycloaddition reaction with aryl acetylenes **26** (Scheme 12). Two resultant products, the *exo* cyclobutene derivative **27** and unreacted OBD **1b**, were obtained in high enantiomeric purities. Previous examples have been

focused on symmetrical derivatives, whereas this reaction successfully separated asymmetrical derivatives, indicating strong progress in the kinetic resolution of OBDs [45].

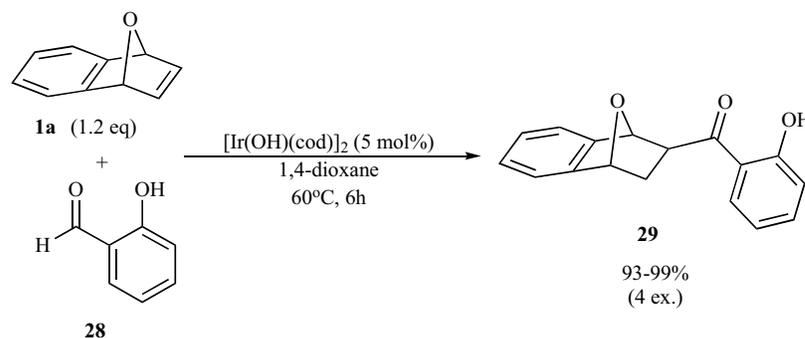
The reaction conditions consisting of aryl acetylene, [Ir(COD)Cl]₂ and (R)-xylyl-phanephos in THF had previously been used for asymmetric hydroalkynylation of unsubstituted OBDs with high enantioselectivities. However, no reaction was observed with C1, C4-disubstituted OBD. Therefore, the authors wanted to extend their study to include C1-monosubstituted OBDs. To study the scope of the reaction, several aryl acetylenes and C1-substituted OBDs were tested. Excellent selectivities of the cyclobutene products were obtained (92–99.9% ee) with moderate yields (25–43%). Although recovered OBD starting material generally had higher yields (29–50%), lower enantiomeric purity was observed (83–97% ee), and indicating small amounts of the other enantiomer remained unreacted. In all cases for the [2+2] cycloaddition, the acetylene



Scheme 11. Mechanism of Cu-catalyzed aminoboration of OBD.



Scheme 12. Ir-catalyzed kinetic resolution of OBD using aryl acetylenes.

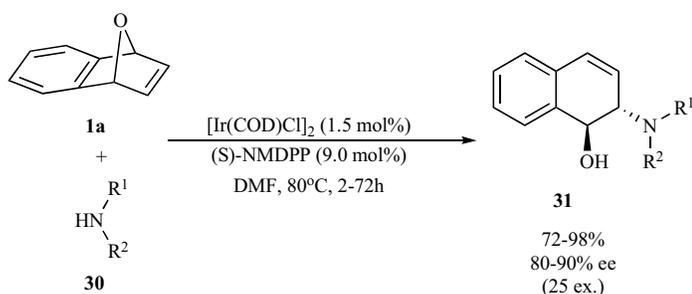


Scheme 13. Ir-catalyzed hydroacylation OBD.

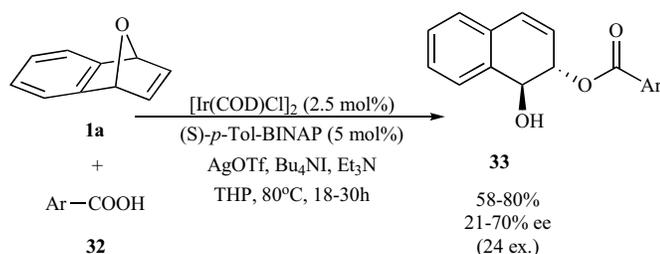
was added to the *exo* face of the OBD with the aryl substituent aligned on the same side as the C1-substituent [45].

Nagamoto *et al.* stereoselectively hydroacylated OBD **1a** using salicylaldehyde **28** and a hydroxoiridium catalyst (Scheme 13). There are many transition metal-catalyzed intramolecular hydroacylation reactions with aldehydes, primarily using rhodium catalysts, but few intermolecular examples. The primary problem with inter-

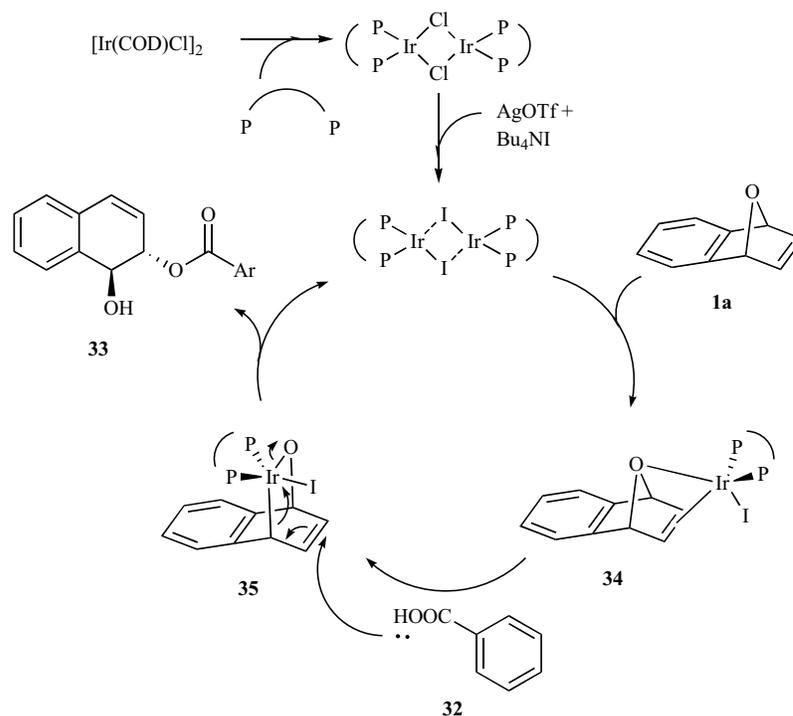
molecular hydroacylation is the competing decarbonylation reaction. However, it was found that a hydroxoiridium complex coordinated to 1,5-cyclooctadiene could catalyze the hydroacylation of OBD with salicylaldehyde and its derivatives with high yields and stereoselectivity. The *exo*-acetylated product **29** was exclusively obtained, and with the addition of the chiral ligand (*S,S*)-Me-tfb*, the hydroacylated product could be formed with high enantioselectivity [46].



Scheme 14. Ir-catalyzed ARO of OBD with amines.



Scheme 15. Ir-catalyzed ARO of OBD with aryl carboxylic acids.



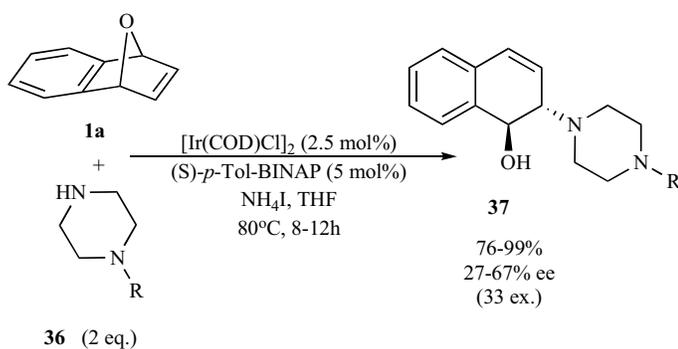
Scheme 16. Mechanism of Ir-catalyzed ARO of OBD with aryl carboxylic acids.

Yu *et al.* performed asymmetric ring-openings of OBD **1a** using amine nucleophiles **30** (Scheme 14). The catalyst $[\text{Ir}(\text{COD})\text{Cl}]_2$, when used with the chiral monophosphine ligand (S)-(+)-neomenthyl-diphenylphosphine ((S)-NMDPP), had previously been used to asymmetrically ring-open OBDs with phenols and naphthols. A series of primary and secondary amines including N-methylaniline were investigated, providing good yields (72-98%) and enantioselectivities (80-90% ee). In all cases the product formed was in the S, S configuration **31**. The use of amine nucleophiles was therefore able to expand the scope of these reaction conditions [47].

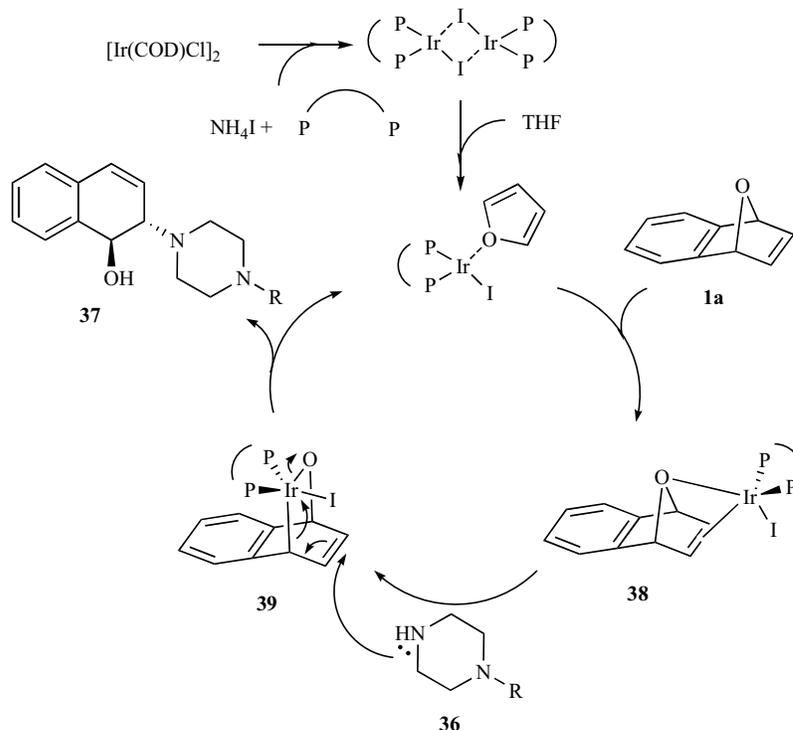
Long *et al.* performed iridium-catalyzed ARO of OBD **1a** with aryl carboxylic acids **32** (Scheme 15). The optimized conditions were found to be the iridium (I) catalyst $[\text{Ir}(\text{COD})\text{Cl}]_2$ and the chiral bisphosphine ligand (S)-*p*-Tol-BINAP, with the Ag(I) salt

(AgOTf), ammonium halide (Bu_4NI) and base (Et_3N) additives. The trans carboxylic acid products, 1-hydroxy-1, 2-dihydro-naphthalen-2-yl esters **33**, were obtained in good yields and moderate enantioselectivities, with the hydroxyl group and carboxylic acid nucleophile in a trans configuration. An interesting trend was observed with substituted benzoic acids: substituents in the meta position gave higher yields, while substituents in the para position gave higher enantioselectivities. Overall, electron-withdrawing substituents gave higher yields and enantioselectivities than electron-donating groups [48].

In the following mechanism, the $[\text{Ir}(\text{COD})\text{Cl}]_2$ catalyst reacts with AgOTf to remove a chloride, followed by ligand exchange with the chiral bisphosphine ligand, (S)-*p*-Tol-BINAP, replacing 1,5-cyclooctadiene (COD). With the addition of Bu_4NI , the active



Scheme 17. Ir-catalyzed ARO of OBD with N-substituted piperazines.



Scheme 18. Mechanism of Ir-catalyzed ARO of OBD with N-substituted piperazines.

catalyst $[\text{Ir}((\text{S})\text{-}p\text{-Tol-BINAP})\text{I}]_2$ is formed and coordinates to the oxygen and olefin in OBD **34**. Oxidative insertion of the iridium catalyst into the C-O bond forms **35**. The final product **33** is formed by the nucleophilic attack of the carboxylic acid from the *endo* face of OBD in an $\text{S}_{\text{N}}2'$ reaction, resulting in the observed *trans* configuration of the product. In the same step, the active iridium catalyst is regenerated (Scheme **16**) [48].

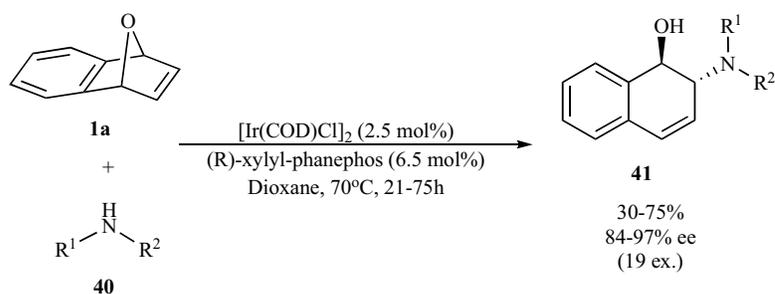
Yang *et al.* studied ARO of OBD **1a** with N-substituted piperazine nucleophiles **36** (Scheme **17**). The optimized conditions were found to be the iridium catalyst, $[\text{Ir}(\text{COD})\text{Cl}]_2$, with the chiral bidentate phosphine ligand, (*S*)-*p*-Tol-BINAP, and additive NH_4I . High yields of the ring-opened products, *trans*-2-N-substituted piperazine 1,2-dihydronaphthalenols **37**, were obtained with moderate enantioselectivities. The hydroxyl group and piperazine nucleophile were exclusively obtained in the *trans* configuration [49].

The active catalytic complex, $[\text{Ir}((\text{S})\text{-}p\text{-Tol-BINAP})\text{I}]_2$, is formed through ligand exchange of $[\text{Ir}(\text{COD})\text{Cl}]_2$ and (*S*)-*p*-Tol-BINAP with NH_4I , which is subsequently cleaved by the solvent THF to form a monomeric complex. This complex coordinates to the oxygen and olefin on the *exo* face of OBD **38**, then inserts into the C-O bond *via* oxidative insertion yielding a π -allyl iridium

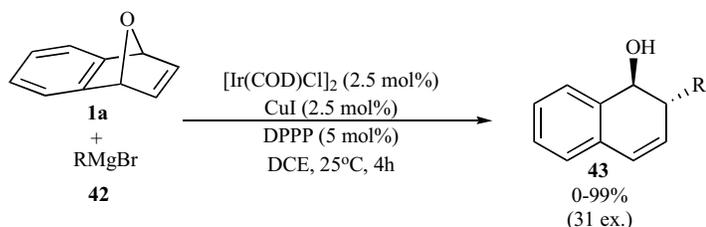
alkoxide complex **39**. Nucleophilic attack of the piperidine from the *endo* face of OBD yields the final product in a *trans* configuration **37** *via* an $\text{S}_{\text{N}}2'$ reaction and regenerates the catalyst (Scheme **18**) [49].

Zhou *et al.* developed a method for ARO of OBD **1a** with amine nucleophiles **40**, producing highly enantioselective ring-opened products **41** (Scheme **19**). Their optimized catalyst and chiral ligand system, $[\text{Ir}(\text{COD})\text{Cl}]_2$ and (*R*)-xylyl-phanephos, was discovered by chance when studying [2+2] cycloaddition reactions with OBD. A wide scope of primary and secondary amine nucleophiles was studied, giving moderate to good yields of the products accompanied by high enantioselectivity. It was noted that the steric properties of alkyl groups on N-alkyl substituted anilines greatly decreased the yield, but there was little impact on the enantioselectivity. Electron-donating substituents were observed to lead to longer reaction times, but otherwise, electronic properties of the substituents on N-methyl aryl amines had no significant impact on reaction outcome [50].

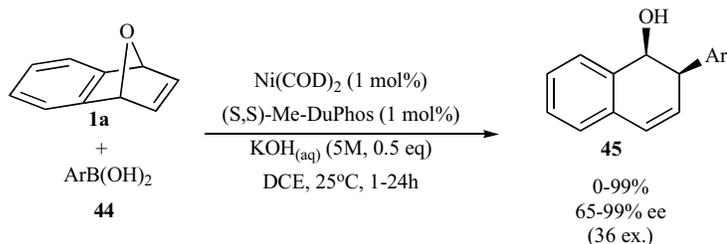
Cheng *et al.* developed an iridium/copper co-catalytic system to ring-open OBD **1a** with Grignard reagents **42**, yielding 1,2-dihydronaphthalenols **43** (Scheme **20**). In many previous examples of nucleophilic ring-openings of OBD with Grignard reagents, the



Scheme 19. Ir-catalyzed ARO of OBD with amines.



Scheme 20. Ir-catalyzed ring-opening of OBD with Grignard reagents.



Scheme 21. Ni-catalyzed ARO of OBD with arylboronic acids.

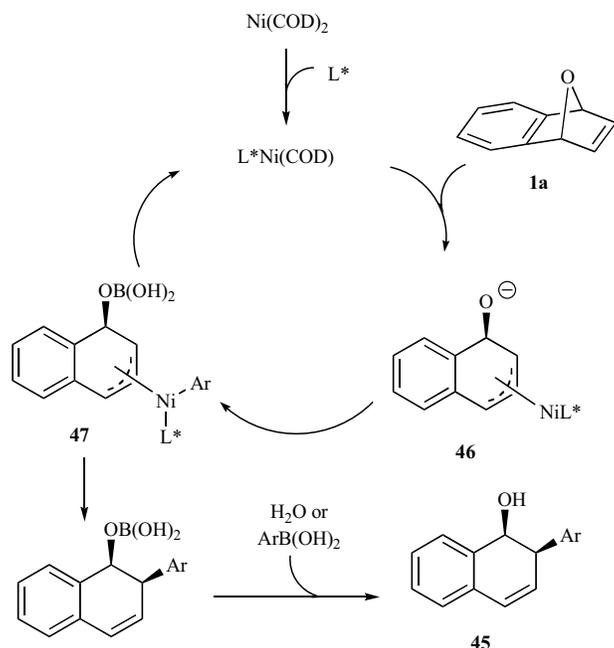
hydroxyl group and nucleophile end up in the *cis* configuration. However, with the synergistic catalysis between $[\text{Ir}(\text{COD})\text{Cl}]_2$ and CuI , which functions as a Lewis acid, the products formed by this reaction were exclusively obtained in the *trans* configuration. A broad range of Grignard reagent were investigated with moderate to high yields obtained. It was also seen that aryl Grignard reagents resulted in greater yields than their alkyl counterparts due to the greater carbanion nucleophilicity of the aryl group [51].

2.4. Nickel-Catalyzed Reactions

Zeng *et al.* used a nickel catalyst to asymmetrically ring open OBDs **1a**, with arylboronic acids **44**, to produce *cis*-2-aryl-1,2-dihydronaphthalenols **45** with a (1*S*, 2*R*) configuration (Scheme 21). The optimized conditions were found to be $\text{Ni}(\text{COD})_2$ with the chiral bidentate ligand (S,S)-Me-DuPhos. Arylboronic acids are used as carbon nucleophiles and have the advantages of being stable, with low toxicity and large structural diversity. The scope of the reaction was examined using a series of mono- and disubstituted arylboronic acids. It was found that the electronic nature of the substituents had little impact on the reactions outcome. However, sterics played a significant role, with *ortho* substituents giving lower yields than substituents in the *meta* or *para* positions. When substituents existed on OBD, electronic properties were more important, with electron-withdrawing groups being more reactive. With few exceptions, these reactions gave very high yields and enantioselectivities [52].

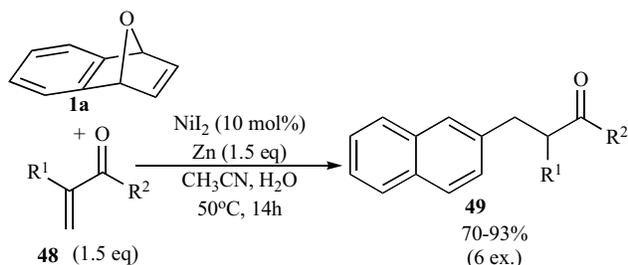
The mechanism begins through ligand exchange with $\text{Ni}(\text{COD})_2$ and (S,S)-Me-DuPhos to form the active chiral $\text{Ni}(0)$ catalyst, which adds to OBD. This complex chelates to the olefin and oxygen of OBD, then inserts *via* oxidative addition to form the (π -allyl)-nickel I(II) intermediate **46**. The chelation step is responsible

for providing the *exo* selectivity of the reaction. **46** Transmetalates with the arylboronic acid, previously activated by a base, to form the (alkenyl)-(π -allyl)-nickel (II) intermediate **47**. The final product **45** is formed by reductive elimination and protonolysis, and the active $\text{Ni}(0)$ catalyst is regenerated (Scheme 22) [52].



Scheme 22. Mechanism of Ni-catalyzed ARO of OBD with arylboronic acids.

Mannathan *et al.* investigated nickel-catalyzed reductive couplings of OBD **1a** with activated alkenes **48** to synthesize 2-alkylnaphthalenes **49** (Scheme 23).



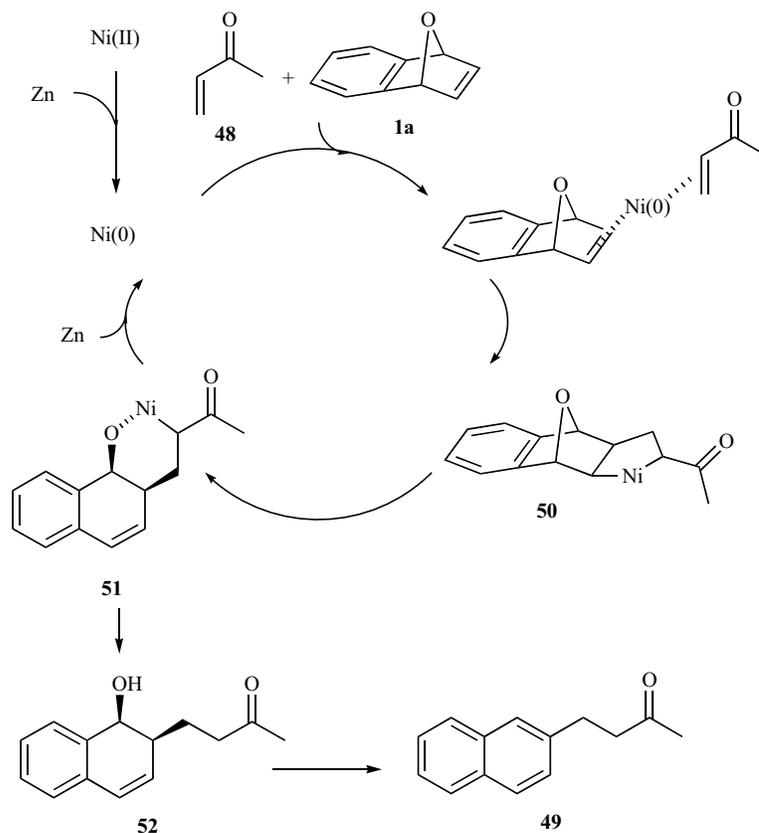
Scheme 23. Ni-catalyzed coupling of OBD to alkenes.

The optimized reaction conditions consisted of the nickel catalyst, NiI_2 , Zn as a mild reducing agent, and water as a hydrogen source. The addition of any monodentate or bidentate phosphine was seen to shut down the reaction. Various vinyl ketones were investigated, including enones with substituents in the α and β positions. The unsubstituted and α -substituted vinyl ketones gave good conversions, however, β -substituents and cyclic enones failed to

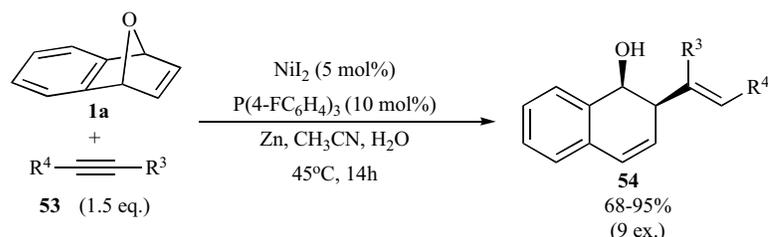
yield the desired products. During the reaction, the alkene was added *cis* to the hydroxyl group and bond formation occurred exclusively at the methylene carbon of the vinyl ketone, giving the reaction of a high degree of stereo- and regioselectivity. The final 2-alkylnaphthalene was formed through a dehydration reaction of the corresponding *cis*-2-alkyl-1, 2-dihydronaphthols, which resulted in a more stabilized aromatization product [53].

To begin the reaction, Ni (II) is reduced to Ni (0) by zinc. This Ni (0) species are able to coordinate to the olefins of OBD and the vinyl ketone followed by oxidative cyclometallation to form the nickelacyclopentane intermediate **50**. Intermediate **51** is produced through β -oxygen elimination and is then protonated by water to form the *cis*-2-alkyl-1, 2-dihydronaphthol **52**. The final 2-alkylnaphthalene **49** is formed through a dehydration reaction. The active Ni (0) species is regenerated through reduction with zinc (Scheme 24) [53].

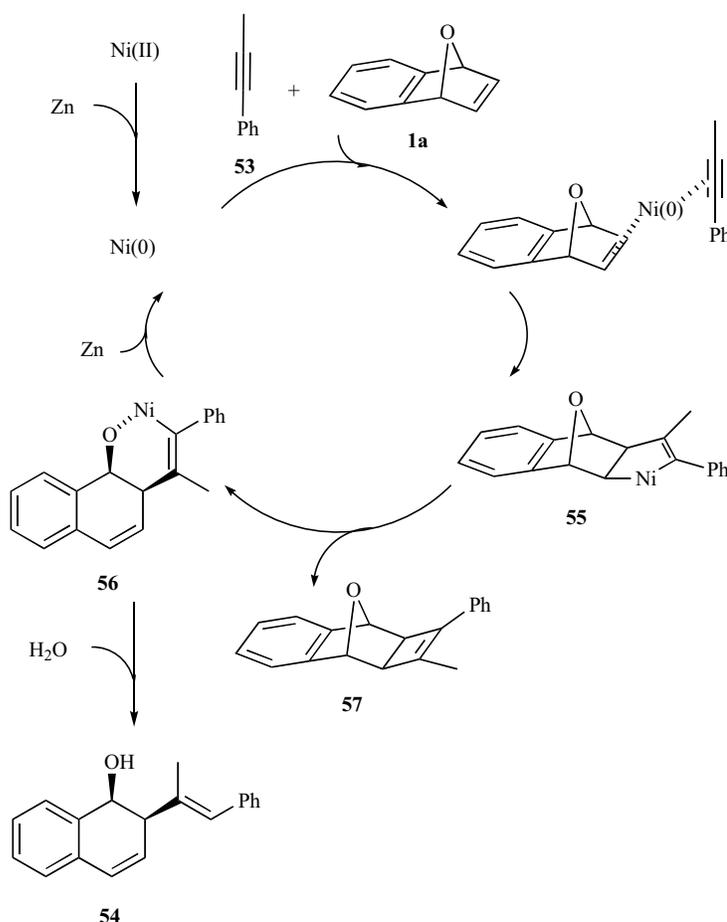
When Mannathan *et al.* extended the scope of this reaction to include reductive couplings of OBD **1a** with electron-rich alkynes **53**, the desired product, a *cis*-2-alkenyl-1, 2-dihydronaphthalene derivative **54**, was obtained with a 25% yield using 1-phenyl-1-propyne (Scheme 25). Through further optimization, improved yields for the coupling with alkynes was found to occur using NiI_2 ,



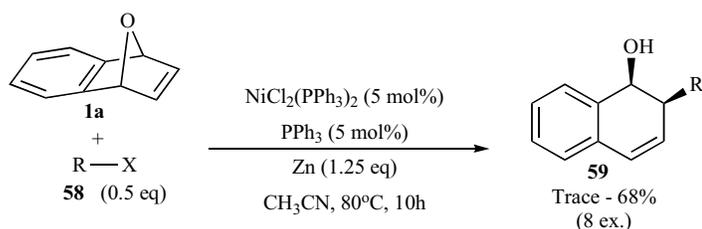
Scheme 24. Mechanism of Ni-catalyzed coupling of OBD to alkenes.



Scheme 25. Ni-catalyzed coupling of OBD to alkynes.



Scheme 26. Mechanism of Ni-catalyzed coupling of OBD to alkynes.



Scheme 27. Ni-catalyzed coupling of OBD to alkyl halides.

tris(4-fluorophenyl)-phosphine, and zinc. It was noted that electron-deficient ligands provided better yields. Various alkynes were explored, and phenylacetylenes, terminal alkynes and aliphatic alkynes were all found to be compatible. During the reaction, the alkyne was added *cis* to the hydroxyl group and only one regioisomer was obtained for each given alkyne [53].

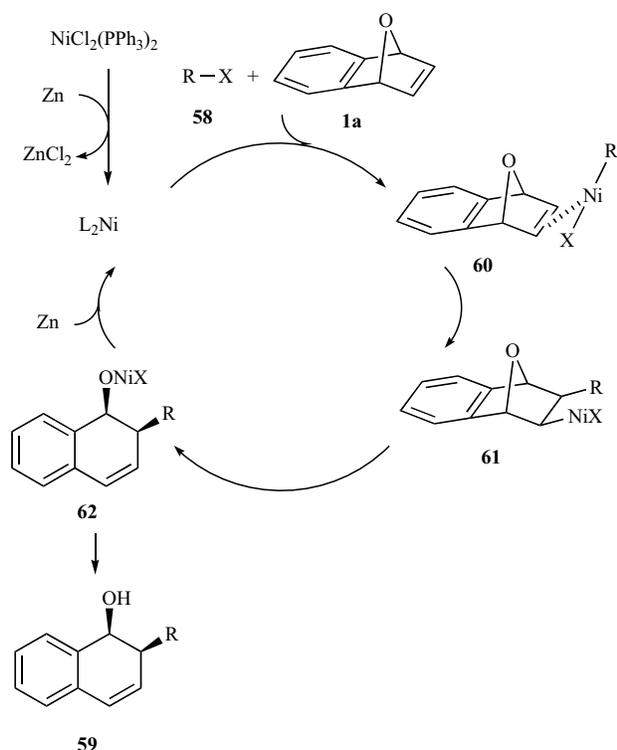
This mechanism for en-yne coupling begins the same as the coupling reaction with enones. The Ni (II) precatalyst is reduced to Ni(0) using zinc. This active Ni(0) catalyst can coordinate with the alkyne and olefin of OBD, followed by oxidative coupling of the alkene and alkyne to form the nickelacyclopentene intermediate **55**. The final product **54** is formed through β -oxygen elimination (intermediate **56**) and protonation by water. The Ni(0) catalyst is reformed by reduction with zinc. Without water present in the reaction medium, there is an alternative pathway which produces **57** in a 66% yield *via* a [2+2] cycloaddition with the alkyne (Scheme 26) [53].

Shukla *et al.* have used a nickel-catalyzed coupling to synthesize *cis*-2-alkyl-1,2-dihydronaphthol derivatives **59** from OBD **1a**

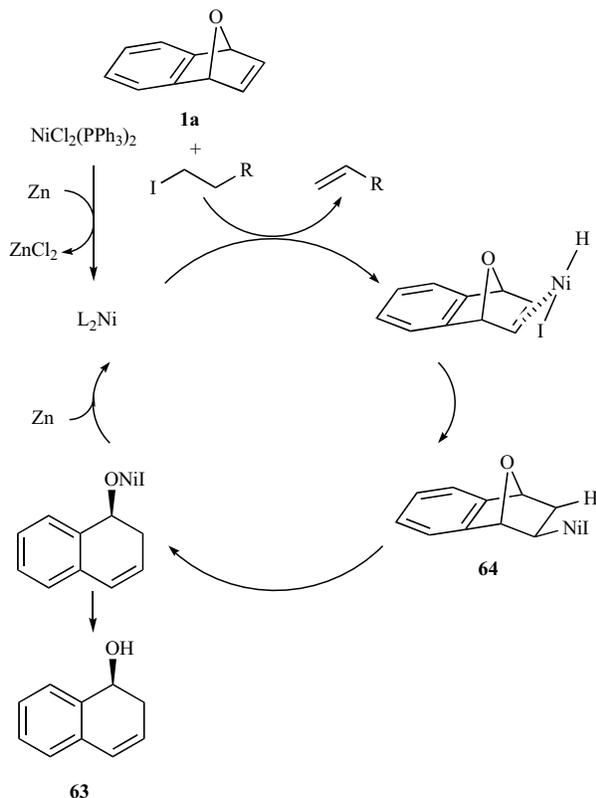
and saturated alkyl halides **58** in a Heck-type reaction (Scheme 27). They began their study using acrylates as the alkene-coupling partner and then expanded the reaction scope to include oxabicyclic alkenes. The optimized conditions were found to include

$\text{Ni}(\text{PPh}_3)_2\text{Cl}_2$, PPh_3 , Zn powder, and water. The addition of exogenous PPh_3 was important for the outcome of the reaction, and substituting it for other phosphine ligands adversely impacted the reaction. They studied the scope of this reaction by studying the reaction of OBD with a wide range of saturated alkyl iodides; primary, secondary, and sterically bulky (*e.g.* neopentyl iodide) all formed the desired products in moderate yields. The moderate yields were the result of the formation of dihydronaphthol as a side product (30-40%), which was produced *via* a competing β -hydride elimination pathway before coupling can occur. Therefore, this paper represents some of the first examples of coupling with sp^3 alkyl halides as substrates, which contain β -hydrogens, as they have generally been avoided in the past [54].

The reaction begins with the reduction of $\text{NiCl}_2(\text{PPh}_3)_2$ by zinc to the active Ni(0) catalyst. This Ni(0) catalyst undergoes oxidative



Scheme 28. Mechanism of Ni-catalyzed coupling of OBD to alkyl halides to form 1,2-dihydronaphthol derivatives.



Scheme 29. Mechanism of formation for the 1,2-dihydronaphthol side product.

addition with the alkyl halide, forming a Ni(II) species which can coordinate to the olefin on the *exo* face of OBD forming intermediate **60**. Carbonickelation leads to the formation of intermediate **61**

followed by β -oxygen elimination to give **62**. The final product **59** is formed through protonation using water and the active Ni(0) catalyst is regenerated by zinc (Scheme **28**) [54].

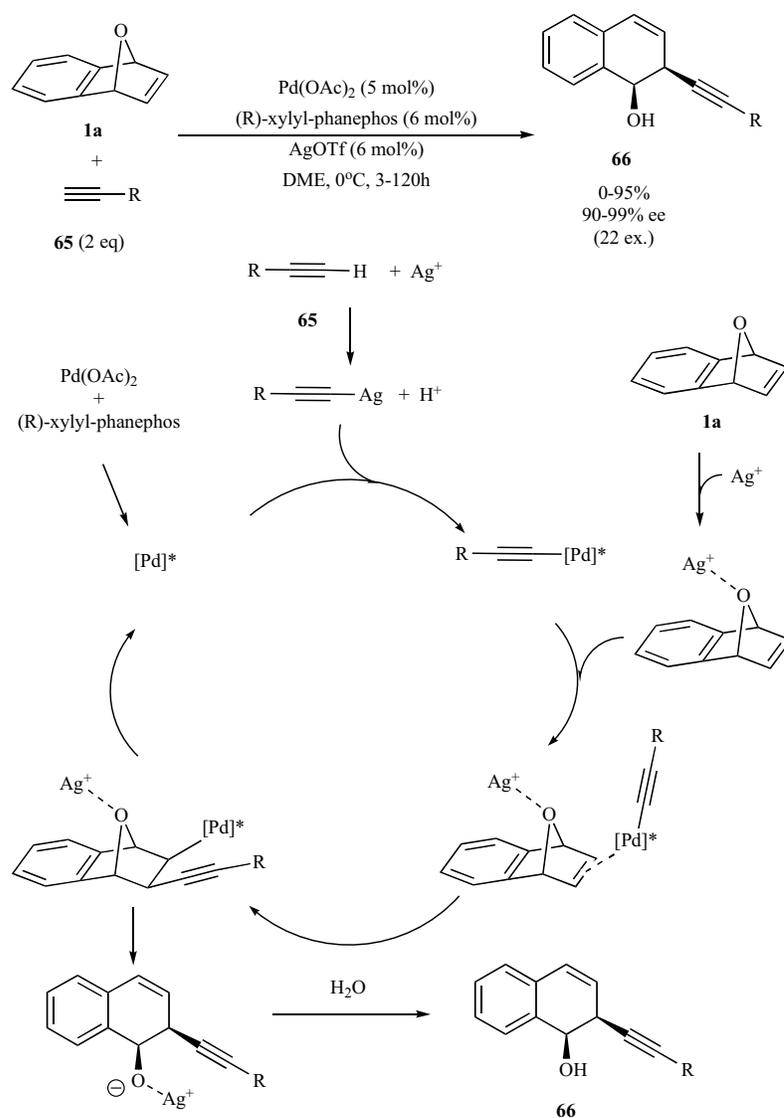
In the case where dihydronaphthol **63** is formed as a side product, the mechanism begins the same way with the formation of RNiX *via* oxidative addition. However, before it has the chance to react with OBD, β -hydride elimination occurs forming a nickel hydride species, which can hydronickelate with OBD **64**. The rest of the mechanism proceeds the same way with β -oxygen elimination and protonation, yielding the dihydronaphthol (Scheme **29**) [54].

2.5. Palladium-Catalyzed Reactions

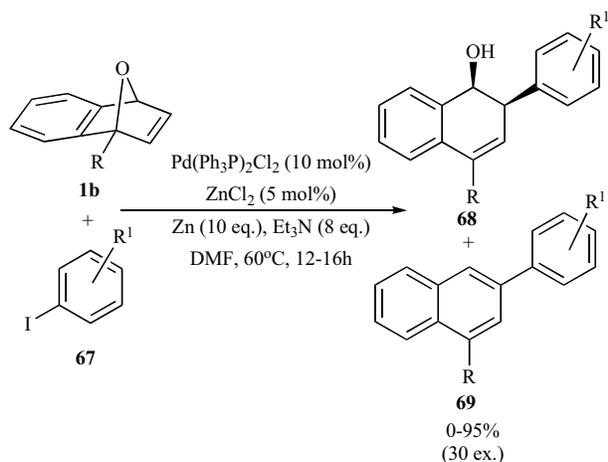
Liu *et al.* developed a co-catalytic system capable of enantioselective nucleophilic ring-opening of OBD **1a** with terminal alkynes **65** (Scheme **30**). Although there have been previous reports of alkynylative ring-opening of OBD, these reactions were not asymmetric, and attempts to swap out the achiral ligand with a chiral one were not successful. Thus, co-catalytic systems were explored. The optimized conditions were found to be Pd(OAc)₂, with the chiral phosphine ligand (R)-xylyl-phanephos, and silver co-catalyst Ag-OTf, which functions as a Lewis acid activator. The choice of Lewis acid is important, as it must be capable of activating both the OBD and alkyne. To explore the scope of this reaction, a series of terminal alkynes were studied. Aryl acetylenes worked well under these reaction conditions giving moderate to high yields and excellent enantioselectivities. Sterically bulky substituents required longer reaction times and electron-donating groups in the ortho or para position decreased the enantioselectivity slightly. Unlike the aryl acetylenes, alkyl acetylenes did not yield the desired product. Substituents on the OBD were also studied, with electron-withdrawing and bulky groups on the benzene requiring longer reaction times. The products **66** were obtained in good to high yields with excellent enantioselectivities in all cases. The *cis* product was obtained unlike the previous *trans* examples due to an internal nucleophilic attack of the OBD-Pd-alkyne complex [55].

Our group wanted to study the impact of C1-substitution on Pd-catalyzed nucleophilic ring-opening of OBD **1b** with aryl iodides **67** (Scheme **31**). Two model C1-substituted substrates were chosen for study: an electron-donating ethyl group and an electron-withdrawing methyl ester group. The electronic nature of the C1-substituted group was found to affect the outcome of the reaction. The electron-donating group produced a 1,2-dihydronaphthalenol **68** derivative, whereas the electron-withdrawing group led to aromatization of the product through a dehydration reaction, yielding a 2-arylated naphthalene derivative **69** in a lower yield. Despite these differences, only a single regioisomer was obtained in all cases: a result of the aryl iodide being added to the carbon in the olefin furthest from the C1-substituent. When the OBD substrate scope was expanded, the same trend was observed, with electron-donating C1-substituents leading to 1,2-dihydronaphthalenol derivatives in higher yields, whereas electron-withdrawing substituents produced the corresponding 2-arylated naphthalene derivatives. Sterics also played a role in the outcome of the reaction as bulky groups such as *t*Bu or biphenyl greatly decreased the yield [39].

The next step examined the effect of electron-donating and withdrawing substituents on the aryl iodide as compared to the unsubstituted aryl iodide standard. As seen before, the electronic nature of the substituents controlled which ring-opened product was formed. The electron-donating methoxy or methyl groups gave good conversion to the 1,2-dihydronaphthalenol regardless of the position of the substituent relative to the iodide group, and in all cases the yields were higher than the unsubstituted aryl iodide (75%). Reaction with iodonitrobenzenes, however, produced 2-arylated naphthalene derivatives in lower yields. The presence of an electron-withdrawing group on either the OBD or aryl iodide led to



Scheme 30. General reaction and mechanism of Pd-catalyzed ARO of OBD with terminal alkynes.

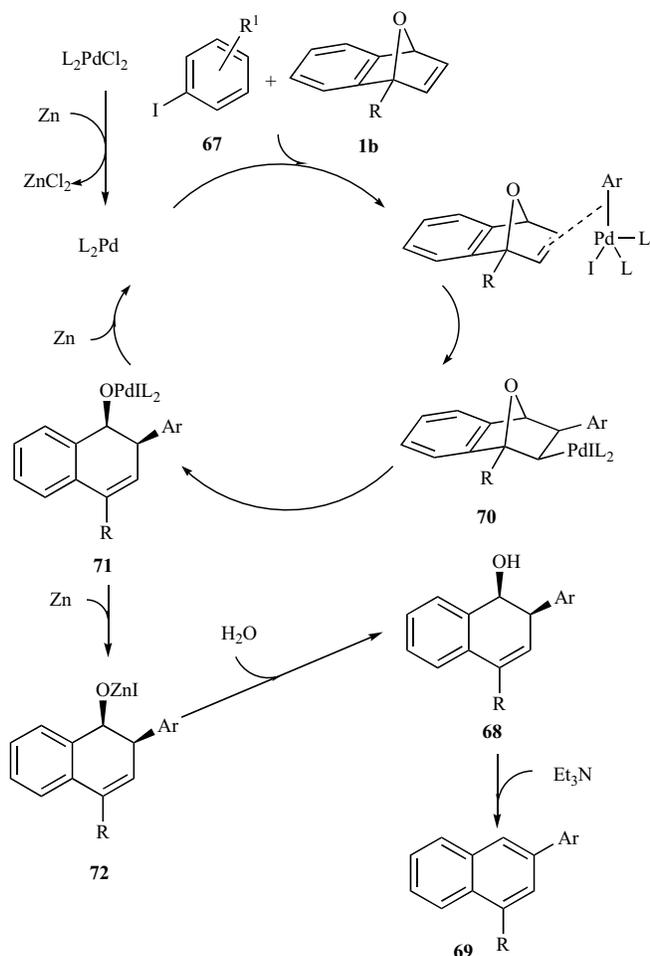


Scheme 31. Pd-catalyzed ring-opening of C1-substituted OBD with aryl iodides.

the formation of the dehydrated product. Like before, only a single regioisomer was formed by the addition of the aryl iodide to the olefin carbon furthest from the C1-substituent [39].

In the following mechanism, the Pd(II) precatalyst is reduced by Zn to the active catalyst Pd (0), which can undergo oxidative addition with the aryl iodide. This aryl palladium complex can coordinate with the oxygen and olefin of OBD from the *exo* face, followed by carbopalladation to give intermediate **70**. β -oxygen elimination gives the ring-opened intermediate **71**. The palladium is removed by reduction with zinc to form **72** while simultaneously regenerating the catalyst. Protonation forms the 1,2-dihydronaphthalenol product **68**, which can undergo base-catalyzed dehydration to form the 2-arylated naphthalene **69** if there are any electron-withdrawing groups on the OBD or aryl nucleophile (Scheme 32) [39].

Chen *et al.* used a palladium/silver co-catalytic system to synthesize 1,2-diarylethanones **74** from OBD **1a** and aryl acetylenes **73** (Scheme 33). This is an extension of previous work done by the Chen group where it was discovered that 1,2-diarylethanones were forming as byproducts during Pd/Cu co-catalyzed reactions of OBD with terminal alkynes. After optimizing for the formation of this by-product, it was discovered that the best conditions included the palladium (II) catalyst Pd (OAc)₂, with the racemic phosphine ligand BINAP and the silver catalyst AgOTf. This reaction was studied with a series of terminal aromatic alkynes which all reacted well to produce the expected product in high yields (>90%). A little



Scheme 32. Mechanism of Pd-catalyzed ring-opening of OBD with aryl iodides.

more variability in the yield was seen when the scope of the reaction was expanded to include different substituted OBDs [56].

One notable difference in the outcome of the reaction was seen when OBD **1c**, with alkoxy substituents on the benzene ring, was reacted with phenylacetylene **73** (Scheme 34). Instead of the usual 1,2-diarylethanones **74**, 1,2-diarylacetylenes **75** were formed in moderate to high yields, demonstrating that the electronic nature of

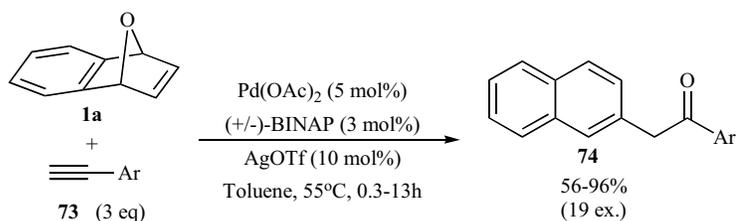
the substituents on the benzene ring of OBD affect the outcome of this reaction [56].

The mechanism for this reaction begins with ligand exchange between Pd(OAc)₂ and (±)-BINAP, yielding a palladium species which forms the palladium acetylide species **76** by reacting with the aryl acetylene. **76** coordinates to a silver-activated OBD **77** followed by carbopalladation of the olefin to give **78**. β-hydride elimination gives **79**, which is the point at which the mechanism diverges based on the substituents on the phenyl ring of OBD. If there are alkoxy substituents, the cation **80** is formed by the hydroxyl group leaving and then the 1,2-diarylacetylene **75** formed by proton elimination. Without the alkoxy substituents, the silver and hydroxyl group is transferred to the alkyne by intramolecular nucleophilic addition giving **81**. The 1,2-diarylethanone **74** is formed through proton elimination and keto-enol tautomerism (Scheme 35) [56].

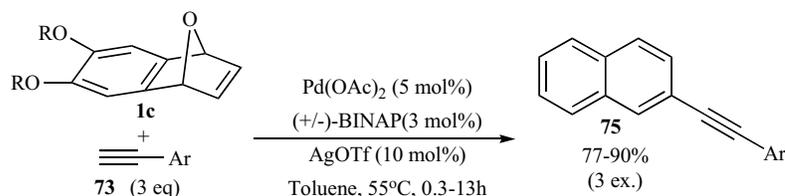
Li *et al.* performed ARO of OBD **1a** with phenols and naphthols **82** using a palladium and zinc co-catalytic system to produce *cis*-2-aryloxy-1,2-dihydronaphthalenols **83** (Scheme 36). The optimized conditions were found to use the transition metal-catalyst Pd(OAc)₂, with the chiral phosphine ligand (R)-Difluorophos and Lewis acid co-catalyst Zn(OTf)₂. To study the scope of the reaction, a wide range of phenols and naphthols were examined, with the corresponding product obtained in good yields and enantioselectivities. The main exception was with the sterically hindered 1-naphthol which had a significantly lower yield (50%). The next step examined substituted OBDs reacting with phenol. Although the ring-opened products were obtained with slightly lower yields, they had very high enantioselectivities. In all cases, the added phenol/naphthol was in the *cis* configuration with respect to the hydroxyl group [57].

The precatalyst Pd(OAc)₂ undergoes ligand exchange with (R)-Pd(OAc)₂. The resulting active chiral catalyst coordinates to the olefin of OBD and the oxygen of the phenol to form intermediate **84**, with the assistance of Zn²⁺ acting as a Lewis acid. Pd inserts into the O-H bond of the phenol followed by oxypalladation to form **85**. Intermediate **86** is formed through β-oxygen elimination followed by hydrolysis to give the final product **83** regenerating the chiral palladium complex in the process (Scheme 37) [57].

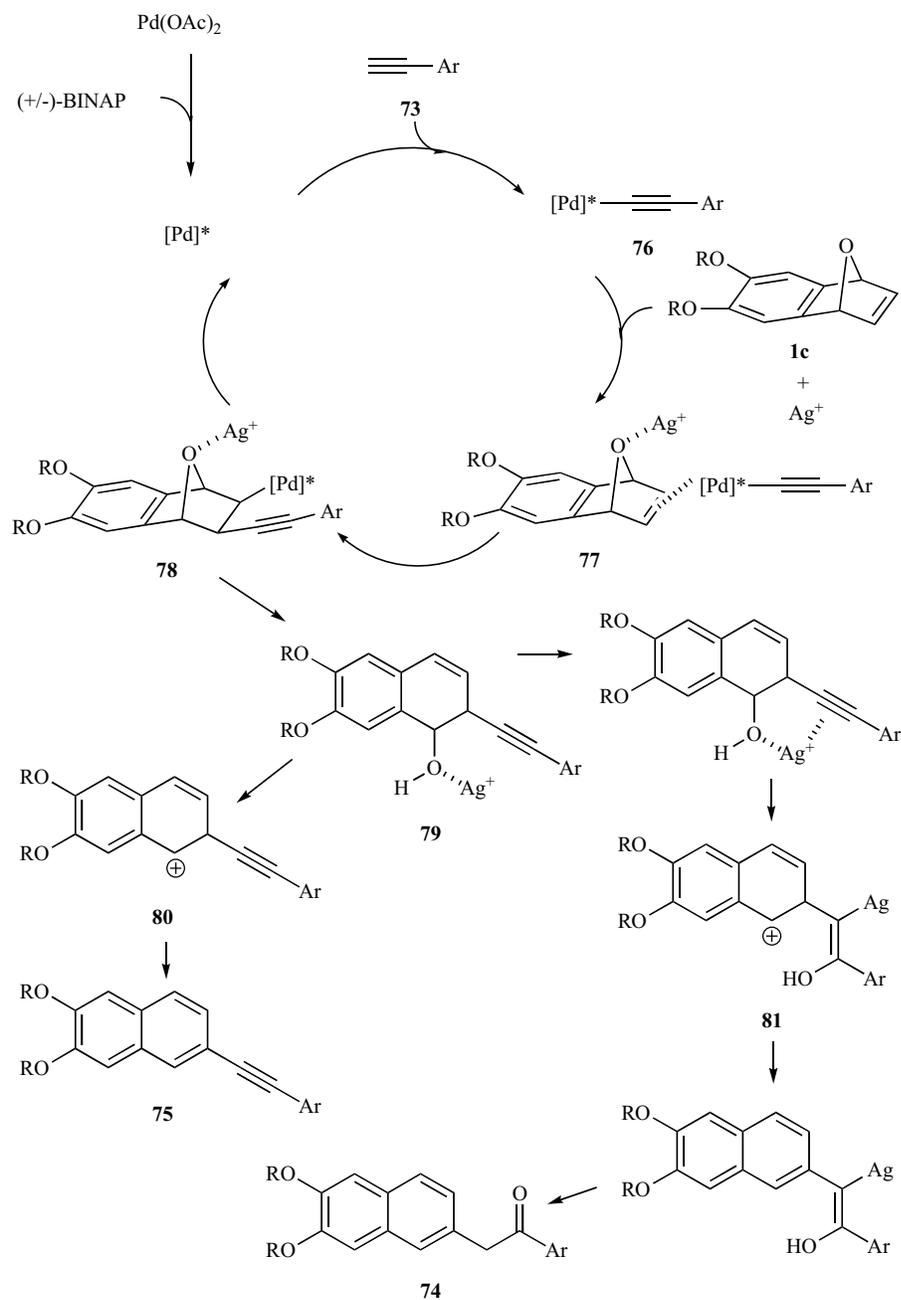
Zhou *et al.* studied ring-opening arylation of OBD **1a** using triarylyphosphine **87** as both the source of the aryl nucleophile and ligand for the palladium catalyst (Scheme 38). This is an unusual aryl donor as it presents some problems due to the thermodynamically stable C-P bond and strong interaction to metal centers. Typical donors include aryl halides and organoboron, organosilane and organometallic reagents. This paper explored C-P bond activation



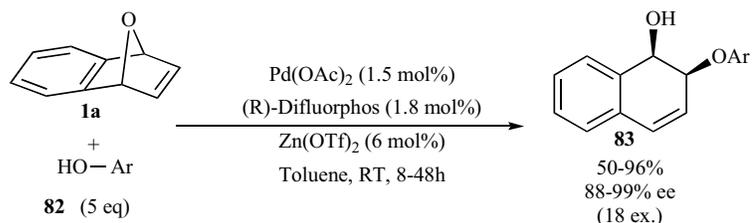
Scheme 33. Pd-catalyzed ring-opening of OBD with aryl acetylenes.



Scheme 34. Modified Pd-catalyzed ring-opening of OBD with aryl acetylenes.



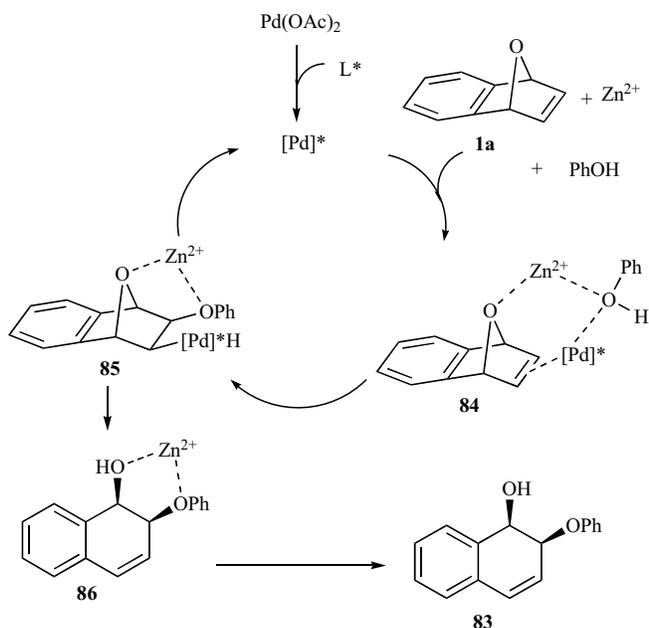
Scheme 35. Mechanism of Pd-catalyzed ring-opening of OBD with aryl acetylenes.



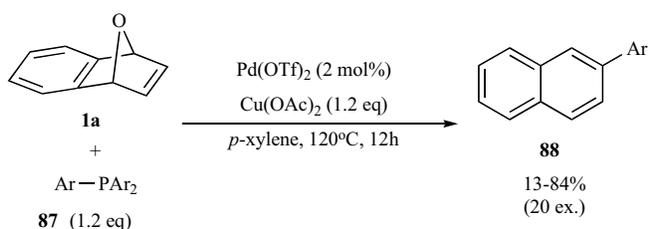
Scheme 36. Pd-catalyzed ARO of OBD with phenols.

of tertiary phosphines for use in aromatic coupling reactions. The optimized conditions consisted of the catalyst $\text{Pd}(\text{OTf})_2$, and $\text{Cu}(\text{OAc})_2$ as an oxidant. The scope of the reaction was examined using several tri (homo) arylphosphines with different substituents. The electronic properties of these substituents did not significantly impact the reaction, but sterics did, with 2-substituted phosphines

giving very low yields. The next step used unsymmetrical tri (hetero) triarylphosphines to examine the migratory abilities of substituted aryl groups. This was mainly dependent on the electronic nature of the substituents with electron-donating groups having greater migratory aptitudes than their electron-withdrawing counterparts. When different substituted OBDs were reacted with tris(4-



Scheme 37. Mechanism of Pd-catalyzed ARO of OBD with phenols.



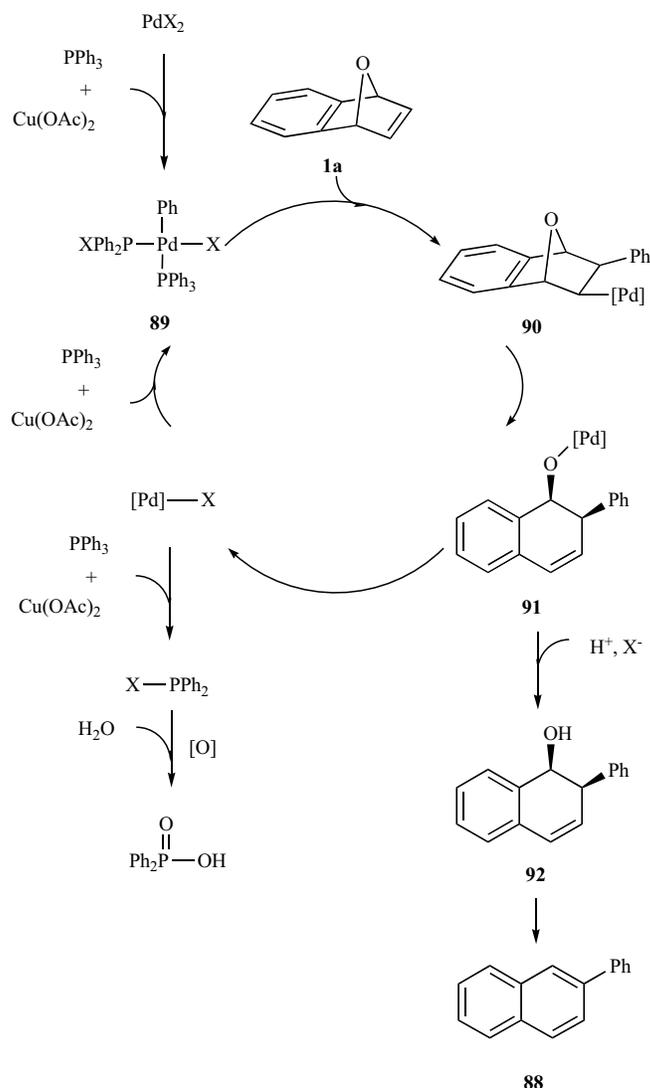
Scheme 38. Pd-catalyzed arylation of OBD with triarylphosphine.

methoxyphenyl)phosphine, the corresponding products **88** were obtained in moderate to good yields. With Cl-1-methyl substituents, the product showed a high degree of regioselectivity with the aryl group added to the olefin carbon furthest from the substituent [58].

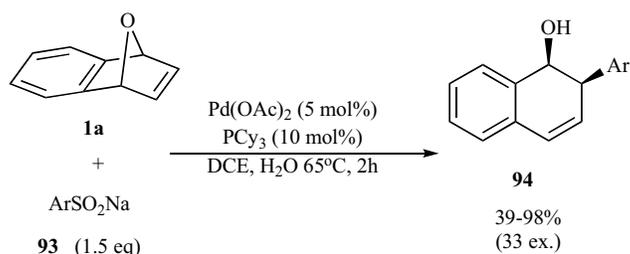
The mechanism begins with the catalytic Pd species **89** being generated by reacting the Pd (II) precatalyst with PPh₃ and the oxidant Cu(OAc)₂: a process which involves C-P bond cleavage and exchange between the phenyl and anion. This Pd species can coordinate and carbopalladate with the olefin in OBD to give **90**. β-oxygen elimination yields **91** and then **92** through acidolysis. The final naphthalene product **88** is formed through dehydration. The catalyst is regenerated by reaction of [Pd]-X with PPh₃ and Cu(OAc)₂, liberating PPh₂X, which reacts further to form diphenylphosphinic acid (Scheme 39) [58].

Li *et al.* investigated nucleophilic ring-opening of OBD **1a** with aryl sulfonates **93** to produce *cis*-2-aryl-1,2-dihydronaphthalenols **94** (Scheme 40). The optimized conditions were found to be Pd(OAc)₂, with the phosphine ligand PCy₃ which produced the ring-opened product with the hydroxyl group and aryl nucleophile exclusively in the *cis* configuration. The scope of potential sodium aryl sulfonates was examined and a clear trend with respect to the electronic properties of the substituents was noted. Electron-donating substituents resulted in approximately 20-30% higher yield, and sterics did not play a role in the outcome of the reaction. The effect of substituents on OBD was also examined with different electron donating and withdrawing groups, both providing good conversion to the ring-opened product [59].

The active palladium catalyst is generated through ligand exchange between the precatalyst, Pd(OAc)₂ and PCy₃. The (π-allyl)-Pd(II) intermediate **95** is formed through oxidative addition of OBD



Scheme 39. Mechanism of Pd-catalyzed arylation of OBD with triarylphosphines.

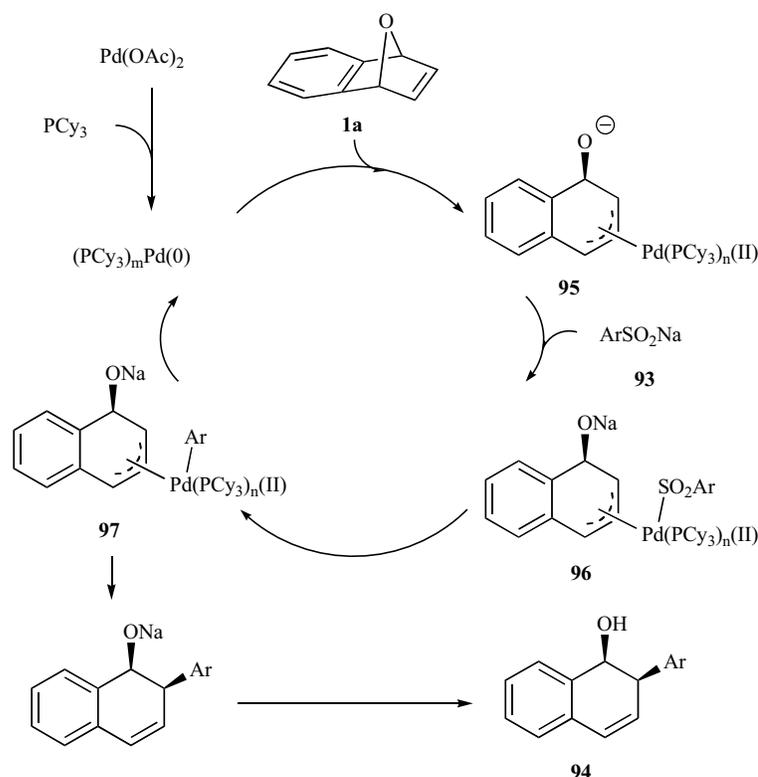


Scheme 40. Pd-catalyzed ring-opening of OBD with aryl sulfonates.

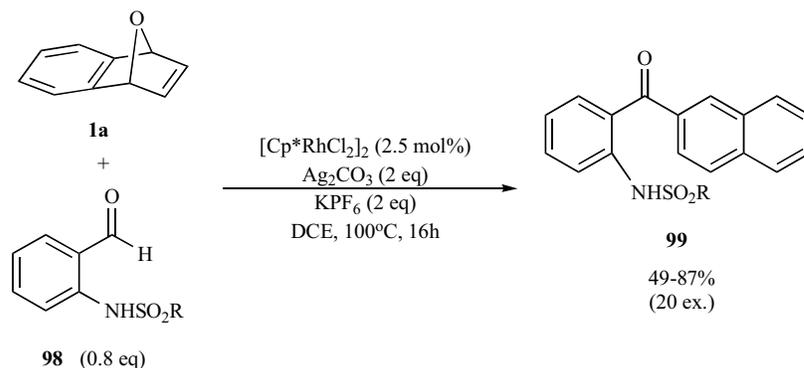
to the Pd complex. An exchange reaction between Pd and sodium aryl sulfonate gives **96**, which desulfonates to give the (aryl)(π-allyl)-Pd (II) intermediate **97**. The final product **94** is formed through reductive elimination and protonolysis and the Pd(0) catalyst is regenerated (Scheme 41) [59].

2.6. Rhodium-Catalyzed Reactions

Yang *et al.* investigated coupling of N-sulfonyl 2-amino-benzaldehydes **98** with OBD **1a** through Rh (III)-catalyzed C-H bond activation to produce diarylketones **99** (Scheme 42). The overall transformation is 2-naphthylation of the C-H bond in the N-



Scheme 41. Mechanism of Pd-catalyzed ring-opening of OBD with aryl sulfonates.



Scheme 42. Rh-catalyzed coupling of OBD to aminobenzaldehydes.

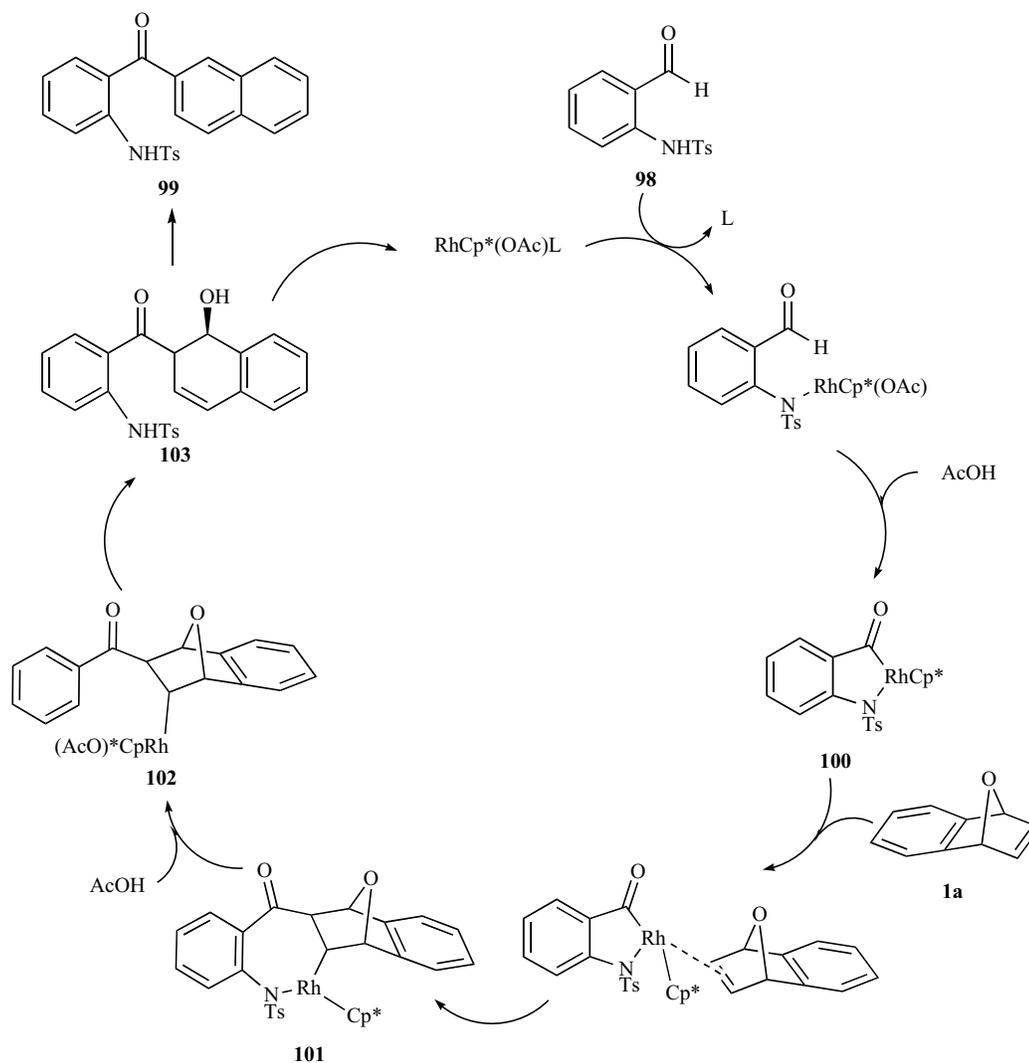
sulfonyl 2-aminobenzaldehyde. The optimized conditions included the catalyst $[\text{Cp}^*\text{RhCl}_2]_2$ with Ag_2CO_3 acting as a base and KPF_6 . The scope of the reaction was studied using a wide range of N-Ts 2-aminobenzaldehydes. Substituents on the benzene ring and different sulfonyl groups all produced the desired product with a good yield. The only exception was the sterically bulky biphenyl substituted sulfonyl group, which gave a poor conversion (49%). Different substituents on the OBD were also well tolerated [60].

In this mechanism, the rhodium catalyst coordinates to the sulfonamide followed by cyclometallation to produce the five-membered rhodacycle intermediate **100**. This rhodium complex coordinates to the olefin of OBD followed by migratory insertion to produce the seven-membered rhodacycle intermediate **101**. With the addition of AcOH , intermediate **102** is generated followed by elimination to produce the ring-opened intermediate **103**, which can dehydrate to form the final product (Scheme 43) [60].

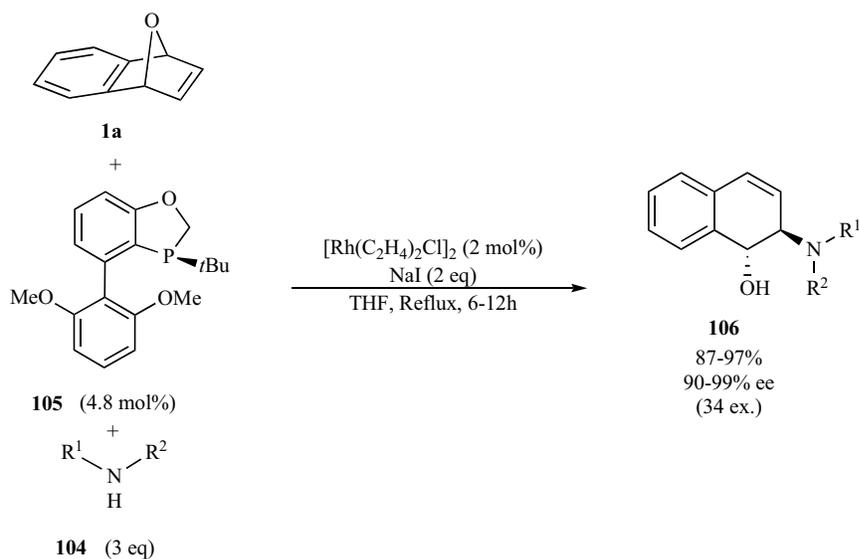
Luo *et al.* synthesized their own chiral monophosphine ligands **105** to use in enantioselective ring-openings of OBD **1a** with amines **104** (Scheme 44). After synthesizing a series of five chiral

phosphine ligands, it was found that the monophosphine ligand in Scheme 44 with the additive NaI gave the dihydronaphthalene ring-opened products **106** with the best yield and selectivity. Further studies focused on the scope of amines for which this catalyst could be used, including several piperazines, aliphatic amines, primary amines, and secondary aromatic amines. Most of the amines had good conversion to the desired product with excellent enantioselectivity. The only exceptions were seen with 2-chloro-N-methylaniline and pyrrole, both which gave very poor conversions [61].

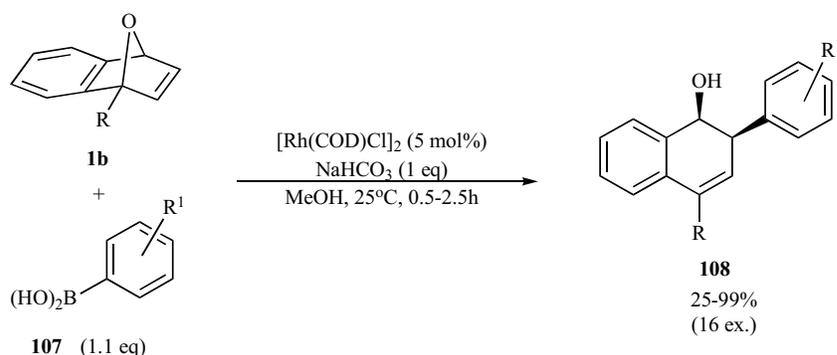
Our group wanted to investigate the effect of C1-substitution on OBD **1b** in a Rh-catalyzed nucleophilic ring-opening reaction with arylboronic acids **107** (Scheme 45). C1-ethyl OBD was chosen as the model substrate to study the effect of different electron-donating and electron-withdrawing substituents on the arylboronic acid relative to the unsubstituted arylboronic acid. The substituents did not greatly impact the outcome, with most reactions leading to excellent conversion to the desired product **108**. There was a slight decrease in yield with the ortho position due to unfavorable steric interactions, and an even sharper drop with a chloro group in the



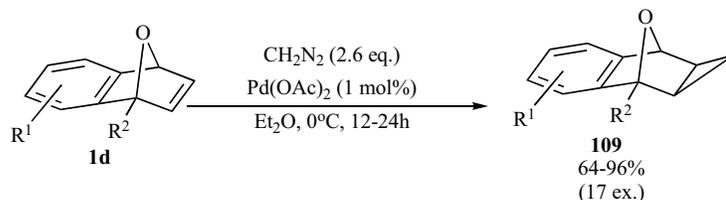
Scheme 43. Mechanism of Rh-catalyzed coupling of OBD to aminobenzaldehydes.



Scheme 44. Rh-catalyzed ARO of OBD with amines.



Scheme 45. Rh-catalyzed ring-opening of C1-substituted OBD with arylboronic acids.



Scheme 46. Pd-catalyzed cyclopropanation of OBD.

para position. The next phase of this study examined the impact of different substituents in the C1-position of OBD and there was a more significant impact on the yield observed. Sterically bulky substituents resulted in much lower yields while electron-withdrawing groups only provided moderate conversions to the dihydronaphthols. In all cases, only a single regioisomer was observed from the addition of the aryl group to the olefin carbon furthest from the C1-substituent. Additionally, the added nucleophile was in *cis* configuration with respect to the hydroxyl group, indicating that this reaction possesses a high degree of regio- and stereochemistry [62].

3. CYCLOPROPANATION OF OBD

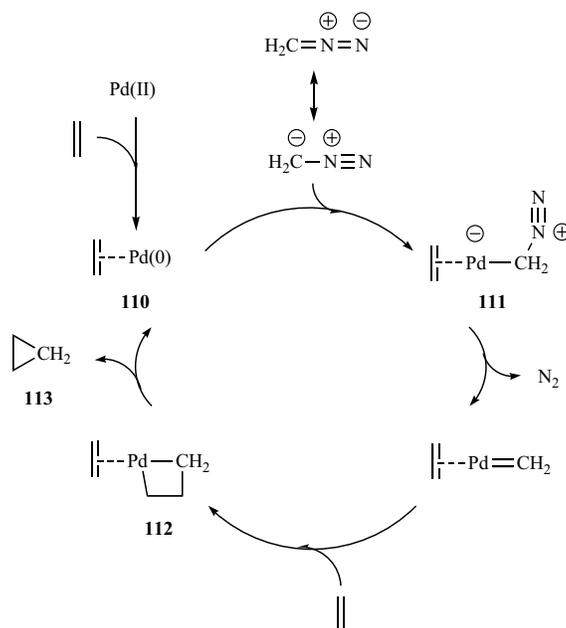
3.1. Cyclopropanated Oxabenzonorbornadiene Synthesis

Our group wanted to further derivatize OBD by adding a cyclopropane in place of the alkene, creating a cyclopropanated oxabenzonorbornadiene (CPOBD). Cyclopropanes are very strained and have been reported to have comparable reactivity to alkenes, so we wanted to explore how this derivatization would introduce new reactivity to the compound. To add this methylene equivalent across the alkene, several known cyclopropanation methods for cyclic and bicyclic alkenes were attempted but with no success. It was noted that all of the attempted methods were performed exclusively on carbocyclic systems. Therefore, a new method was applied which used diazomethane and a Pd (II) catalyst (Scheme 46). This method had been successful in cyclopropanating other heterocyclic systems and when applied to OBD **1d**, the cyclopropanated product **109** was obtained in a 90% yield. As diazomethane is a hazardous compound to work with, it was generated *in situ* using a commercially available precursor, Diazald[®] along with sodium hydroxide to produce the gas, which was then directed into the reaction vessel under an inert atmosphere. To test the applicability of this method, the substrate scope was expanded to include aryl and C1-substituted OBDs. These substituents were well tolerated with the corresponding CPOBDs obtained in moderate to high yields, with the lower yields obtained for bulkier substituents. In all cases the *exo*-cyclopropane derivative was obtained as the only stereoisomer [63].

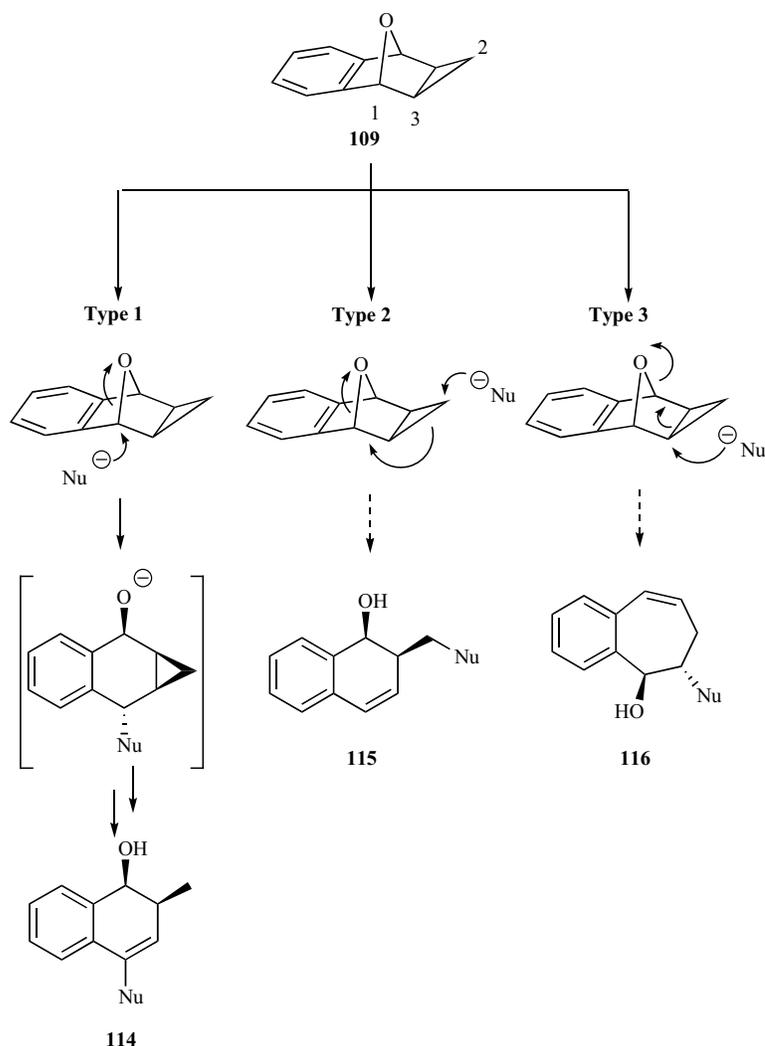
Our group published a follow-up procedure for the cyclopropanation of OBDs, which included modifications to the procedure,

making it safer and more efficient. These modifications included changing the solvent from Et_2O to THF and diluting the concentration of NaOH solution from 50% w/v to 25% w/v, which is used to generate the diazomethane *in situ*. Using this method, yields of previously reported CPOBDs were increased and the synthesis of seven new substrates was introduced [64].

The mechanism for cyclopropanation begins with the Pd (II) precatalyst being reduced to its active Pd(0) form. It coordinates to the alkene in a bridged η^2 manner **110** and then adds to diazomethane giving intermediate **111**. Nitrogen gas is released to give a carbene complex, which carbopalladates with a second alkene, generating the palladacyclobutane **112**. The cyclopropanated product **113** is formed through reductive elimination (Scheme 47) [64].



Scheme 47. Mechanism Pd-catalyzed cyclopropanation of alkenes with diazomethane.



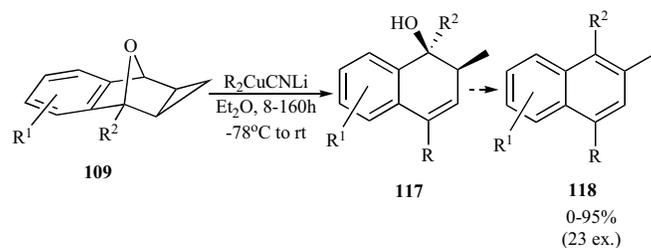
Scheme 48. Proposed nucleophilic ring-opening pathways of CPOBD.

Three nucleophilic ring-opening pathways for CPOBD **109** have been proposed based on the location where the nucleophile attacks (Scheme 48). If the nucleophile attacks the bridgehead carbon (C1), the carbon-oxygen bond is cleaved, followed by ring-opening of the cyclopropane which produces a substituted dihydronaphthol: a Type 1 ring-opening **114**. If the nucleophile attacks the external cyclopropane carbon, a carbon-carbon bond of the cyclopropane is cleaved, followed by cleavage of the carbon-oxygen bond producing 2-substituted dihydronaphthol: a Type 2 ring-opening **115**. If the nucleophile attacks the cyclopropane bridgehead carbon (C3), cleavage of the internal carbon-carbon cyclopropane bond occurs followed by cleavage of the bridging carbon-oxygen bond, producing a cycloheptenol derivative *via* ring-expansion: a Type 3 ring-opening **116** [65].

3.2. Type 1 Ring-Opening

Type 1 ring-opening reactions of CPOBD **109** were found to occur using organocuprates in diethyl ether (Scheme 49). 2-Methyl-1, 2-dihydronaphthalenols **117** were the primary product (up to 95%), with aromatization of the products occurring over time to produce naphthalene derivatives **118**. The scope of organocuprate reagents worked well with primary, secondary, tertiary, and aromatic nucleophiles. For aryl substituted CPOBD, para substituents were only moderately reactive, while no ring-opened product was obtained with ortho substituents. Alkyl bridgehead substituents

gave good yields and had high regioselectivity, but as was seen with the unsubstituted CPOBD, aromatization occurred over time [65].

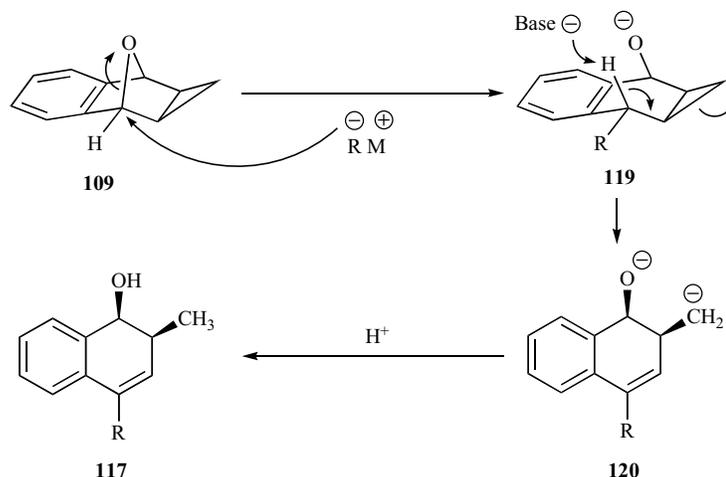


Scheme 49. Type 1 ring-opening of CPOBD with organocuprates.

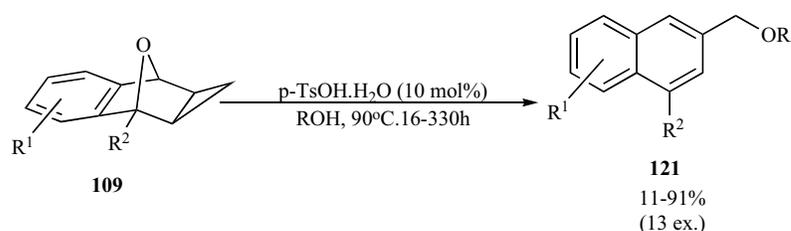
In this mechanism, the organocuprate nucleophile attacks the bridgehead of CPOBD **109** causing cleavage of the bridging C-O bond **119**. Removal of the original bridgehead proton results in the formation of the alkene in **120** and ring-opening of the cyclopropane. The final product **117** is generated by quenching the reaction with a proton source (Scheme 50) [65].

3.3. Type 2 Ring-opening

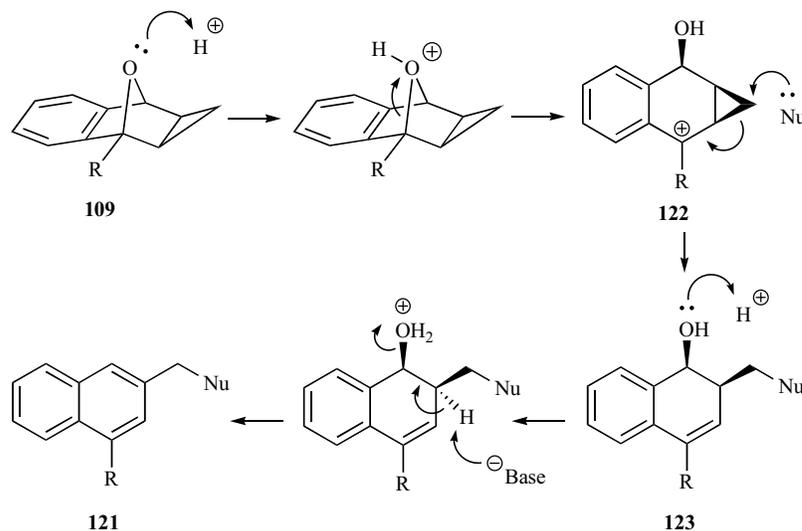
The Type 2 ring-opened products for CPOBD **109** were obtained using alcohol nucleophiles under acid-catalyzed conditions



Scheme 50. Mechanism of Type 1 ring-opening of CPOBD with organocuprates.



Scheme 51. Acid-catalyzed Type 2 ring-opening of CPOBD with alcohols.



Scheme 52. Mechanism of the acid-catalyzed Type 2 ring-opening of CPOBD with alcohols.

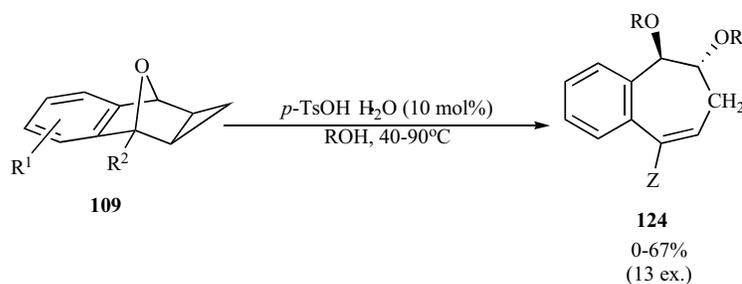
(Scheme 51). However, under these conditions, the expected 2-substituted dihydronaphthol product was aromatized to the corresponding 2-substituted naphthalene **121**. Using *p*-TsOH.H₂O in MeOH, 91% of the 2-(alkoxymethyl) naphthalene product was obtained. Select examples of substituted CPOBD were also investigated under these conditions. Para-dimethoxy substituents gave a moderate yield, while ortho-dibromo resulted in a poor yield. The best result was obtained with a C1-methyl substituent [66].

In the proposed mechanism for the acid-catalyzed Type 2 ring-opening of CPOBD **109**, the oxygen in position 7 coordinates with the acid catalyst, resulting in the cleavage of the carbon-oxygen bond and opening of the bridge to produce a cation intermediate **122**. For C1-substituted OBD, the opening of the carbon-

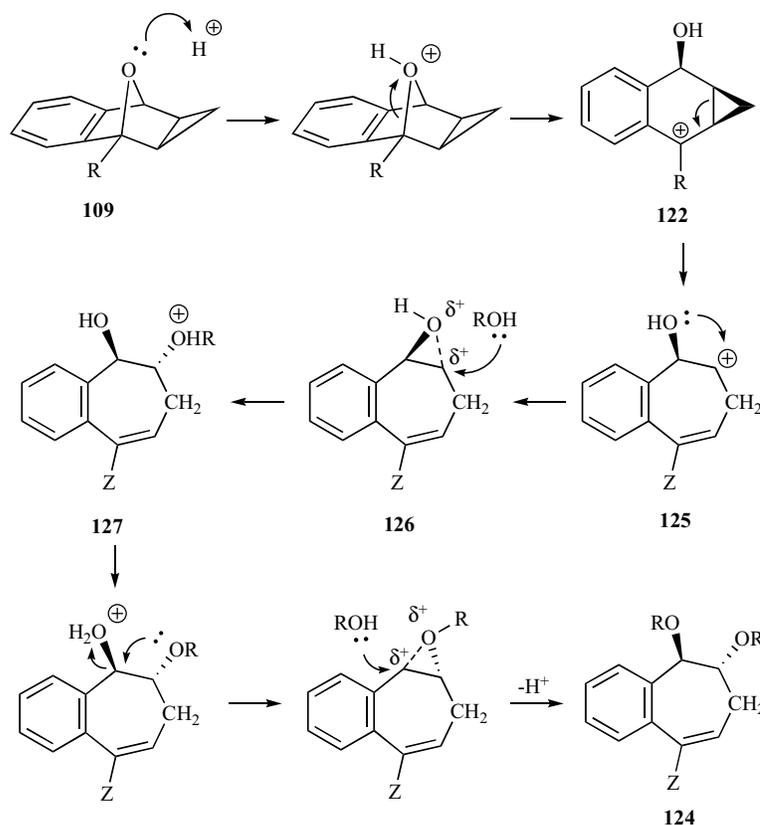
oxygen bond produces a single regioisomer, as formation of the tertiary carbocation is more stable than the secondary carbocation. The nucleophile attacks the external carbon in cyclopropane causing the carbon-carbon bond of the cyclopropane to be cleaved resulting in the formation of the 2-substituted dihydronaphthalenol **123**. The aromatized product naphthalene **121** is formed through an elimination reaction involving the removal of the hydrogen in position 2, causing the protonated hydroxide in position 1 to leave (Scheme 52) [66].

3.4. Type 3 Ring-Opening

The first examples of Type 3 ring-openings were discovered recently by the Tam group, using alcohol nucleophiles under acid-



Scheme 53. Acid-catalyzed Type 3 ring-opening of CPOBD with alcohols.



Scheme 54. Mechanism of the acid-catalyzed Type 3 ring-opening of CPOBD with alcohols.

catalyzed conditions, forming products **124** (Scheme 53). Originally found as a side product of the Type 2 ring-opening reaction, the conditions were reoptimized to favor the Type 3 pathway. With the acid catalyst *p*-TsOH·H₂O and a nucleophilic MeOH solvent, up to 67% yields of the ring-expanded products **124** were obtained. Lowering the temperature from 90°C to 40°C resulted in a greater ratio of Type 3:Type 2 ring-opened products, suggesting that the Type 2 product is the thermodynamic product, while the Type 3 product is the kinetic product. Steric bulk of the nucleophile was observed to significantly affect the reaction, with less sterically hindered alcohols (MeOH, EtOH) generating the highest yields, and sterically hindered alcohols (*t*BuOH) only producing trace amounts of product. The opposite trend was observed for C1-substituents, with less hindered substituents generating lower yields, and more hindered substituents generating higher yields. A possible explanation for this might be due to the C1-substituent blocking the Type 2 attack site, thus allowing the Type 3 pathway to arise [67].

The proposed mechanism for the Type 3 ring-opening, like the Type 2 ring-opening, begins with protonation of the bridging oxygen by the acid catalyst, followed by cleavage of the C–O bond to form the carbocation **122**. From here the mechanism diverges, with

a carbocation rearrangement occurring to give the ring-expanded cycloheptene **125**. Coordination of the cyclic alcohol to the carbocation forms a pseudo-oxirane **126**, and upon attack of the nucleophilic alcohol, the trans diol **127** is formed. The proton is transferred from the nucleophilic alcohol to the endogenous alcohol, followed by an intramolecular S_N2 to eliminate water. The nucleophilic solvent once again attacks, forming the final product **124** (Scheme 54) [67].

CONCLUSION

In the past couple of years, a lot of research has been conducted into understanding the reactivity of OBD under transition metal-catalyzed conditions. Numerous catalysts have been used including cobalt, copper, iridium, nickel, palladium and rhodium to construct new carbon-carbon or carbon-heteroatom bonds. The majority of reactions have resulted in the ring-opening of OBD, but there have been selected examples of adding functional groups across the alkene of OBD without inducing ring-opening. Much of the focus has also been given to controlling the regio- and stereoselectivity of the product. Through the use of chiral ligands, asymmetric ring-opening of OBD is possible, producing products with very high

enantioselectivity. The addition of a bridgehead substituent on OBD has enabled studies on regioselectivity with the nucleophile either adding to the carbon in the olefin closest or furthest from the substituent. Finally, further derivatization of OBD through cyclopropanation has led to new studies on the reactivity of this compound and the formation of new derivatized products.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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