Domino Reactions

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Rhodium(I)-Catalyzed Domino Asymmetric Ring Opening/ Enantioselective Isomerization of Oxabicyclic Alkenes with Water**

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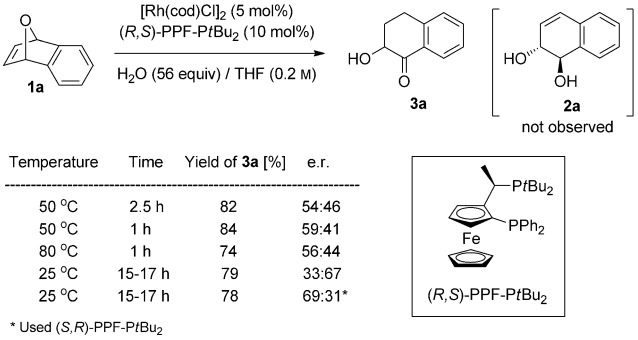
Rhodium(I)-catalyzed asymmetric ring-opening (ARO) reaction of strained bicyclic alkenes has been demonstrated as a highly efficient and enantioselective process for generating a functionalized dihydronaphthalene core.[1] Our group has previously reported that chiral Rh^I complexes catalyze ring opening of oxa- and azabicyclic alkenes with soft nucleophiles such as alcohols, phenols, thiols, amines, anilines, malonates and carboxylates in high yield and enantioselectivity.[2] The products are generated by an S_N2' nucleophilic displacement of the bridgehead leaving group with inversion to give the 1,2-*trans* product as a single regio- and diastereomer. This method has been recently demonstrated as a viable strategy for synthesizing bioactive aminotetralins rotigotine and (*S*)-8-OH-DPAT.[3]

Although various heteroatom nucleophiles have been employed in ARO, the use of water—the simplest nucleophile—has not been demonstrated. Based on previous studies,[2] water-induced ARO of oxabenzonorbornadiene **1a** should yield chiral *trans*-1,2-diol **2a**. Instead, we isolated the unexpected 2-hydroxy-1-tetralone product **3a** exclusively in the presence of catalytic $[Rh(cod)Cl]_2$/(*R*,*S*)-PPF-P*t*Bu_2 (cod = cyclooctadiene) in aqueous THF[4] (Scheme 1). Reaction at 25 °C afforded enantio-enriched **3a** (enantiomeric ratio, e.r. = 33:67), a higher reaction temperature (50 or 80 °C) caused a significant decrease in enantioselectivity. To the best of our knowledge, the formation of tetralone products such as **3a** is unprecedented in ARO reactions. We subsequently investigated the effects of ligand, catalyst loading, concentration, and reaction temperature (Table 1).

No reaction took place without added ligand (entry 1). Reaction at 25 °C (0.2 M concentration) with 5 mol% $[Rh(cod)Cl]_2$ and 10 mol% (*R*,*S*)-PPF-P*t*Bu_2 gave tetralone product **3a** in 79% yield (entry 2, cf. Scheme 1). As the catalyst loading was decreased to 2 mol%, we obtained a mixture of diol **2a** (major product) and tetralone **3a**

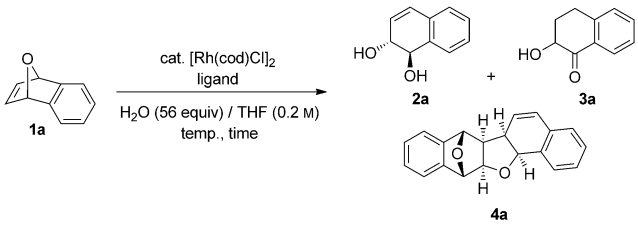


Temperature	Time	Yield of **3a** [%]	e.r.
50 °C	2.5 h	82	54:46
50 °C	1 h	84	59:41
80 °C	1 h	74	56:44
25 °C	15-17 h	79	33:67
25 °C	15-17 h	78	69:31*

* Used (*S*,*R*)-PPF-P*t*Bu_2

Scheme 1. Formation of 2-hydroxy-1-tetralone **3a** by Rh^I-catalyzed ARO of oxabenzonorbornadiene **1a** with water.

Table 1: Combined effects of ligand, catalyst loading, concentration, and reaction temperature.



Entry	Ligand	Catalyst loading[c]	*T* [°C]	*t* [h]	**2a** [%]	**3a** [%]	**4a** [%]
1	–	5/–	25	15–17	< 5	< 5	< 5
2	(*R*,*S*)-PPF-P*t*Bu_2	5/10	25	15–17	< 5	79[a]	< 5
3	(*R*,*S*)-PPF-P*t*Bu_2	2/4.4	25	15–17	53[a]	29[a]	< 5
4[d]	(*R*,*S*)-PPF-P*t*Bu_2	2/4.4	25	15–17	74[a]	10[a]	< 5
5[e]	(*R*,*S*)-PPF-P*t*Bu_2	2/4.4	25	15–17	< 5	70[a]	< 5
6	(*R*,*S*)-PPF-P*t*Bu_2	2/4.4	25	40	7[b]	81[b]	< 5
7	(*R*,*S*)-PPF-P*t*Bu_2	2/4.4	50	2.5	< 5	80[b]	< 5
8	(*R*,*S*)-PPF-P*t*Bu_2	1/2.2	25	15–17	89[a,f]	< 5	< 5
9	(*R*,*S*)-PPF-P*t*Bu_2	0.5/1.2	25	72	35[a,g]	< 5	< 5
10	(*S*,*S*)-DIOP	5/10	25	15–17	59[a,h]	< 5	< 5
11	DPPF	5/10	75	17	26[a,i]	< 5	< 5
12	(*S*)-BINAP	5/10	25	15–17	< 5	< 5	91[a,j]
13	BIPHEP	5/10	25	15–17	< 5	< 5	70[b]
14[k]	TPPDS	5/15	80	13	< 5	< 5	< 5

[a] Yield of isolated product. [b] Determined by ^1H NMR spectroscopy of the crude material. [c] Mol% $[Rh(cod)Cl]_2$/mol% ligand. [d] Concentration = 0.1 M. [e] Concentration = 0.4 M. [f] e.r. > 99:1. [g] Recovered 39% of starting material. [h] e.r. = 87:13. [i] No product formation at 25 °C after 17 h. [j] e.r. > 99:1. [k] Reaction was run in neat water with and without sodium dodecyl sulfate.

(entry 3). Reaction concentration also had a significant effect on product distribution. Lower concentration (0.1 M) favored diol formation whereas higher concetration (0.4 M) favored tetralone formation (entries 4 and 5). It was found that

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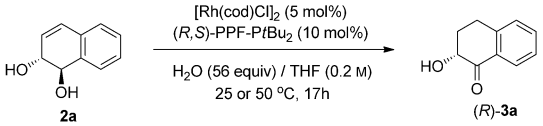
elevated reaction temperature and prolonged reaction time caused preferential formation of tetralone **3a** over diol **2a** (entries 6 and 7). At 1 mol% catalyst loading, diol **2a** was formed cleanly in good yield (89%) and excellent enantioselectivity (e.r. > 99:1) (entry 8).[5] Further decreases in catalyst loading led to incomplete conversion (entry 9). Other ligands that gave diol **2a** included (*S*,*S*)-DIOP (entry 10) and DPPF (entry 11), albeit in lower yields, the latter required heating at 75 °C. A lower e.r. of 87:13 was observed by using (*S*,*S*)-DIOP as the chiral ligand. When (*S*)-BINAP (entry 12) and BIPHEP (entry 13) were used, the dimeric product **4a** was obtained in good yields through a Rh^I-catalyzed cyclodimerization process that has been previously described.[6] However, our conditions employed a neutral Rh^I catalyst in the presence of water whereas the literature reports used cationic Rh^I sources under strictly anhydrous conditions. Both protocols gave the product in excellent enantioselectivity (e.r. > 99:1). Finally, reactions carried out in neat water using a water-soluble ligand TPPDS did not yield any product (entry 14).[7] We also screened other Rh^I sources such as $[Rh(cod)OH]_2$, $[Rh(CO)_2Cl]_2$, and $Rh(cod)_2OTf$, all of which showed no reactivity.[8]

We speculated that **2a** is an intermediate en route to **3a** through an isomerization process. To test this hypothesis, we subjected **2a** (various enantiomeric compositions) to the catalytic conditions (Scheme 2). In all cases, **2a** isomerized to **3a** in good yields.



Temperature	e.r. of **2a**	e.r. of **3a** (yield)
50 °C	>99:1	50:50 (78%)
25 °C	>99:1	15:85 or 82:18* (74%)
25 °C	75:25	20:80 (80%)
25 °C	50:50	21:79 (83%)

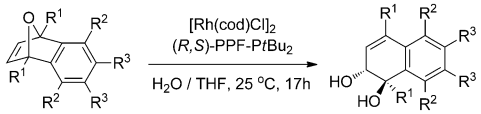
*Used (*S*,*R*)-PPF-P*t*Bu_2

Scheme 2. Rh^I-catalyzed enantioselective isomerization of diol **2a** to tetralone **3a**.

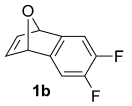
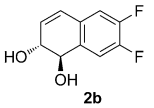
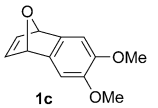
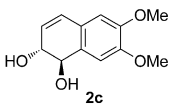
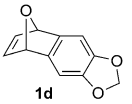
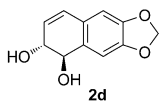
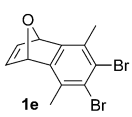
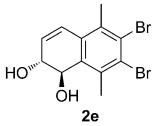
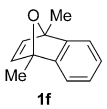
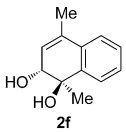
An interesting feature of this isomerization is that a much higher e.r. was observed than in the one-pot process using oxabicycle **1a** (cf. Scheme 1). At 25 °C, the enantio-enriched (*R*)-**3a** was obtained in 15:85 e.r. whereas the one-pot process only gave 33:67 e.r.[9] When repeating this reaction with different concentrations, we found a significant impact on conversion. At 0.1 M concentration, only 12% product was isolated (e.r. = 24:76) with 88% unreacted starting material. At 0.4 M concentration, the product was obtained in a high yield of 89% (e.r. = 22:78). However, changing the concentration did not lead to any improvement in enantioselectivity. Preliminary studies showed that the conversion increased linearly with catalyst loading and suggested that the reaction is first order in the Rh catalyst (see Supporting Information). The enantioselectivities (no significant differences) were not dependent on the enantiopurity of the starting material, which suggested the formation of a common achiral intermediate during isomerization. Furthermore, the process was catalyst-controlled since the (*S*,*R*)-ligand gave the opposite enantiomer of **3a**. These results supported the notion that a Rh^I-catalyzed domino reaction[10] took place to generate **3a** from **1a** (cf. Scheme 1): diol **2a** was first formed from oxabicycle **1a** by Rh^I-catalyzed ARO with water as the nucleophile, at a higher catalyst loading **2a** was subsequently converted to tetralone **3a** by Rh^I-catalyzed enantioselective isomerization. The presence of the allylic alcohol is crucial for the isomerization since the analogous allylic methyl ether (obtained from MeOH-induced ARO) did not isomerize after 17 h at 50 °C.

To investigate the generality of Rh^I-catalyzed ARO with water, we next studied the scope of oxabicyclic alkenes (Table 2). The effects of the remote substituents on the oxabicyclic alkenes were studied by using difluoro-substituted **1b**, dimethoxy-substituted **1c**, and methylenedioxy-substituted **1d**. Chiral *trans*-1,2-diol products **2b**–**d** were obtained with excellent enantioselectivities (e.r. > 99:1) (entries 1–3).

Table 2: Scope of oxabicyclic alkenes in Rh^I-catalyzed ARO with water: diol formation.[a]



R^1 = H, Me
R^2 = H, Me
R^3 = H, F, OMe, Br,

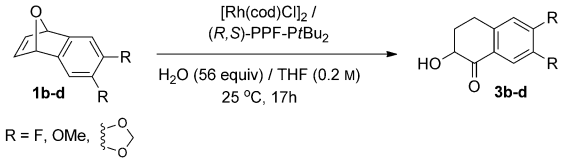
Entry	Substrate	Product	Catalyst loading[b]	Yield[c] (e.r.)
1[d]	 **1b**	 **2b**	2/4.4	83 (>99:1)
2	 **1c**	 **2c**	1/2.2	82 (>99:1)
3	 **1d**	 **2d**	0.5/1.1	64 (>99:1)
4[e]	 **1e**	 **2e**	5/10	68 (>99:1)
5[e]	 **1f**	 **2f**	5/10	79 (>99:1)

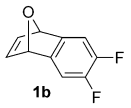
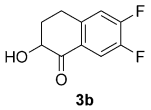
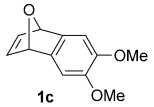
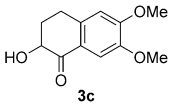
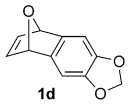
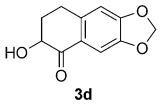
[a] Reaction conditions: substrate **1b–f** (0.2–1.2 mmol scale), $[Rh(cod)Cl]_2$ (0.5–5 mol%), (*R*,*S*)-PPF-P*t*Bu_2 (1.1–10 mol%), H_2O (56 equiv), THF (0.2 M). [b] Mol% $[Rh(cod)Cl]_2$/mol% (*R*,*S*)-PPF-P*t*Bu_2. [c] Yield [%] of isolated product. [d] Reaction was run for 48 h. [e] No formation of tetralone product at 25 °C or 50 °C.

The *trans* stereochemistry was unambiguously confirmed for **2d** by X-ray crystallography.[5] Substrate **1b** required 2 mol% catalyst and longer reaction time (entry 1), whereas **1d** required only 0.5 mol% catalyst to furnish the product (entry 3). We have also previously observed a similar activating effect by the electron-donating group on the aromatic ring of oxabicyclic alkenes in MeOH-induced ring opening.[1a] More sterically hindered dimethyldibromo substrate **1e** and the bridgehead dimethyl-substituted substrate **1f** required higher catalyst loadings (entries 4 and 5). Both diol products **2e** and **2f** were obtained with excellent e.r. (> 99:1).

Under the same reaction conditions but higher catalyst loadings, tetralone products **3b–d** were formed by the domino process from oxabicycles **1b–d** (Table 3). No tetralone

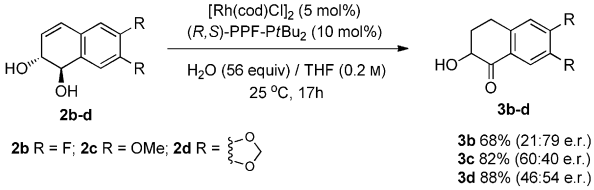
Table 3: Rh^I-catalyzed domino ARO/isomerization of oxabicyclic alkenes with water.[a]



Entry	Substrate	Product	Catalyst loading[b]	Yield[c] (e.r.)
1	 **1b**	 **3b**	5/10	65 (37:63)
2	 **1c**	 **3c**	2/4.4	64 (42:58)
3	 **1d**	 **3d**	2/4.4	83 (47:53)

[a] Reaction conditions: substrate **1b–d** (0.2–1.2 mmol scale), [Rh(cod)Cl]$_2$ (2–5 mol%), (*R*,*S*)-PPF-P*t*Bu$_2$ (4.4–10 mol%), H_2O (56 equiv), THF (0.2 M). [b] Mol% [Rh(cod)Cl]$_2$/mol% (*R*,*S*)-PPF-P*t*Bu$_2$. [c] Yield [%] of isolated product.

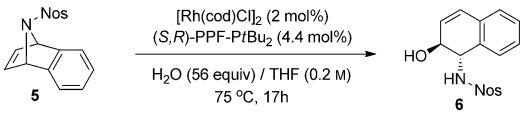
formation was observed with substrate **1e** and **1f** even at higher reaction temperature (50 °C) (cf. Table 2, entries 4 and 5). Although products **3b–d** were formed in moderate to good yields, only low enantioselectivities were obtained (Table 3). However, it is noteworthy that the e.r. obtained in the isomerization of **2b** to **3b** gave a significant improvement compared to the domino process (21:79 vs. 37:63) [Eq. (1)]. Nos-protected azabicyclic alkene **5** underwent Rh^I-catalyzed



(1)

3b 68% (21:79 e.r.)
3c 82% (60:40 e.r.)
3d 88% (46:54 e.r.)

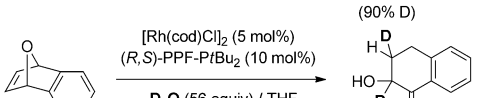
ARO with water to give the amino alcohol product **6** [Eq. (2)]. The e.r. was significantly lower than that from the



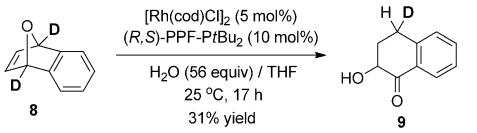
(2)

oxabicyclic alkenes and the reaction required a higher temperature. No isomerization was observed with **6** and the Boc-protected azabicycle was unreactive.

The mechanism of water-induced ARO to form chiral *trans*-1,2-diol products **2a–f** is presumably analogous to the previously proposed mechanistic working model using alcohols as the nucleophile.[1a] But the pathway for the formation of 2-hydroxy-1-tetralone products **3a–d** is of particular interest since it is unprecedented in ARO reactions. Reaction conducted in D_2O showed deuterium-incorporation at the α- and β-positions of the tetralone product **7** [Eq. (3)]. The deuterium-labeled oxabicyclic alkene **8** afforded the tetralone product **9** with retention of one deuterium at the benzylic position [Eq. (4)].



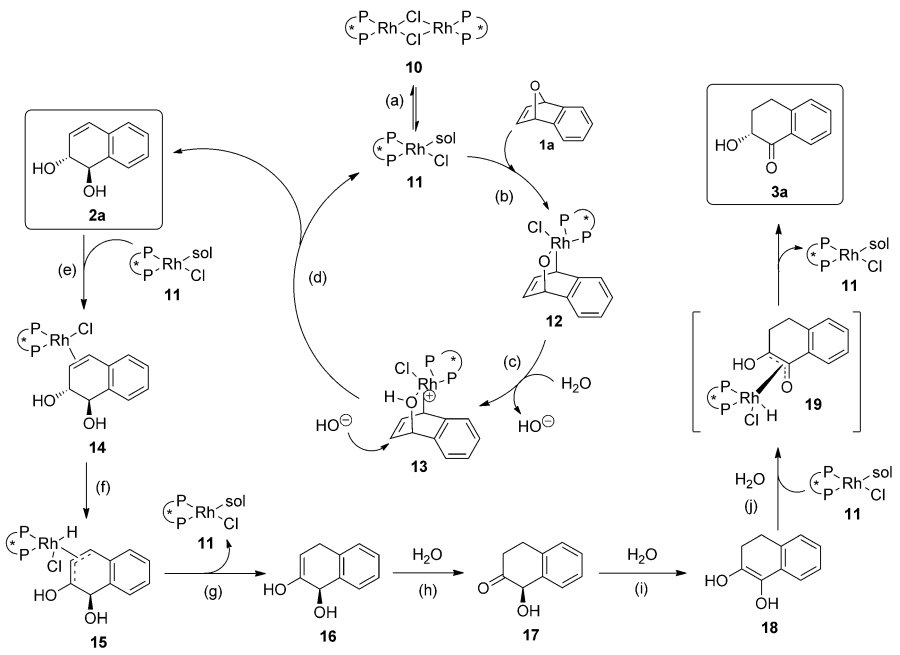
(3)



(4)

Based on the these results and the isomerization studies, we proposed the following mechanism for Rh^I-catalyzed domino ARO/enantioselective isomerization of oxabicyclic alkene **1a** with water to generate diol **2a** and tetralone **3a** (Scheme 3).

Dimeric Rh complex **10** is cleaved by solvolysis or other processes to give monomeric complex **11** (a). The oxidative insertion with retention into a bridgehead C–O bond is the enantio-discriminating step which gives the enyl Rh alkoxide complex **12** (b). Protonation by water generates cationic Rh complex **13** and a hydroxide (c). Previous kinetic studies in alcohol-induced ARO reactions supported the formation of the cationic Rh species **13** and anionic nucleophile.[1a] Nucleophilic attack with inversion occurs in an S_N2' fashion to afford the *trans*-1,2-diol product **2a** as well as regenerates the catalyst **11** (d). Since an allylic alcohol is present in **2a**, at a higher catalyst loading, it undergoes a Rh^I-catalyzed isomerization process which leads to enol **16** (e)–(g).[11] We also recently reported a Rh^I-catalyzed domino process where ARO is followed by allylic alcohol isomerization then



Scheme 3. Proposed catalytic cycle of Rh^{I}-catalyzed domino ARO/enantioselective isomerization of oxabicyclic alkene **1a** with water.

oxidation to form bicyclo[2.2.2]lactones enantioselectively.[12] Tautomerization of enol **16** leads to 1-hydroxy-2-tetralone **17** (h), which explains deuteration at the β-position [cf. Eq. (3)]. Intermediate **17** undergoes further tautomerization via the ene-diol **18** to furnish the more thermodynamically favored 2-hydroxy-1-tetralone product **3a** (i)–(j), where protonation/deuteration takes place at the α-position [cf. Eq. (3)]. Tautomerization of this type is known in the literature, especially at elevated temperature and prolonged reaction times.[13] One of the deuterium atoms is lost in **9** [cf. Eq. (4)] during the tautomerization step (i), in the presence of much larger excess of H_2O, protonation rather than deuteration takes place (i)–(j). Control experiments showed that water is needed for the isomerization process and step (j) is irreversible.[14] If **3a** is formed via an achiral intermediate **18**, then the origin of the enantioselectivity is of particular interest. Bosnich and co-worker proposed an oxy-π-allyl mechanism for Rh-catalyzed isomerization of enols to carbonyl compounds.[15] In the same report, they obtained a chiral aldehyde with low enantioselectivity from a prochiral enol substrate by using a chiral Rh catalyst. It is therefore possible that **18** was converted to **3a** via an oxy-π-allyl Rh intermediate **19**. However, the possibility of an enantioselective protonation pathway of **18** through coordination of the chiral Rh catalyst to the two OH groups to generate **3a** cannot be completely ruled out.[16]

In conclusion, we have made the following new discoveries from the studies of Rh^{I}-catalyzed ARO of oxabicyclic alkenes with water. 1) Water is an effective nucleophile in the asymmetric ring-opening reactions of oxabicyclic alkenes. Chiral *trans*-1,2-diol products can be synthesized in one step with good yields and excellent enantioselectivities under mild conditions and with low catalyst loadings. 2) A domino reaction takes place at higher catalyst loadings to form 2-hydroxy-1-tetralone products by a Rh^{I}-catalyzed ARO/isomerization process where the Rh^{I} catalyst plays distinctive roles in each step. 3) The isomerization of diol intermediates is enantioselective at room temperature to give enantio-enriched tetralone products, presumably through an oxy-π-allyl mechanism or an enantioselective protonation step. An additional benefit of our method is the use of water to generate valuable products.[17] Chiral *trans*-1,2-diol frameworks such as **2a**–**f** are usually synthesized by multi-step organic transformations or enzymatic resolution and are useful building blocks for chiral 1,2-diphosphane and 1,2-diamine ligands in asymmetric catalysis.[18] Synthetic applications of the chiral diol products as well as further studies to improve the enantioselectivity for the formation of tetralone products and to understand the mechanism of the enantioselective isomerization step are on-going in our laboratory and will be reported in due course.

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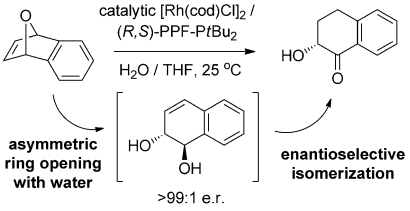
Communications

Domino Reactions

G. C. Tsui, M. Lautens* ____ ▮▮▮▮–▮▮▮▮

Rhodium(I)-Catalyzed Domino Asymmetric Ring Opening/ Enantioselective Isomerization of Oxabicyclic Alkenes with Water



Water-induced asymmetric ring opening: Enantio-enriched 2-hydroxy-1-tetralones are formed from oxabicyclic alkenes through a novel Rh^{I}-catalyzed domino reaction. The proposed mechanism involves water-induced asymmetric ring opening to generate chiral *trans*-1,2-diol intermediates and subsequent enantioselective isomerization (see scheme).