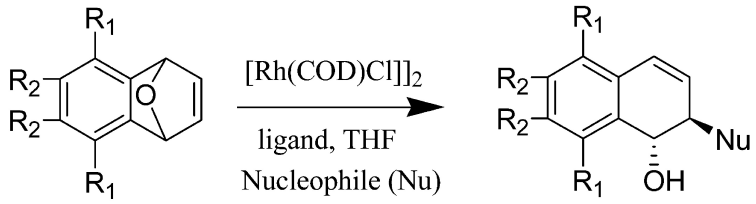
Article

Rhodium-Catalyzed Asymmetric Ring Opening Reactions of Oxabicyclic Alkenes: Application of Halide Effects in the Development of a General Process

Mark Lautens, Keith Fagnou, and Dingqiao Yang

J. Am. Chem. Soc., **2003**, 125 (48), 14884-14892• DOI: 10.1021/ja034845x • Publication Date (Web): 08 November 2003



R_1=R_2=H; R_1=OCH_3, R_2=H; R_1=H, R_2=OCH_3
Nu = ROH, ArOH, RCO_2H and RNH_2

Yield 44-99%
Ee 29-99%

More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 13 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
ARTICLES
Published on Web 11/08/2003

Rhodium-Catalyzed Asymmetric Ring Opening Reactions of Oxabicyclic Alkenes: Application of Halide Effects in the Development of a General Process

Mark Lautens,* Keith Fagnou,‡ and Dingqiao Yang†

Contribution from the Davenport Research Laboratories, Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, Ontario, Canada M5S 3H6

Received February 24, 2003; E-mail: mlautens@alchemy.chem.utoronto.ca

Abstract: We have demonstrated halide effects in the rhodium-catalyzed asymmetric ring opening reaction of oxabicyclic alkenes. By employing halide and protic additives, the catalyst poisoning effect of aliphatic amines is reversed allowing the amount nucleophile to react in high yield and ee. Second, by simply changing the halide ligand on the rhodium catalyst from chloride to iodide, the reactivity and enantioselectivity of reactions employing an aromatic amine, malonate or carboxylate nucleophile are dramatically improved. Third, through the application of halide effects and more forcing reaction conditions, less reactive oxabicycle [2.2.1] substrates react to generate synthetically useful enantioenriched cyclohexenol products. Application of these new conditions to the more reactive oxabenzonorbornadiene permits the reaction to be run with very low catalyst loadings (0.01 mol %).

Introduction

The utilization of metal catalyzed reactions in multifunctional substrates is often thwarted by catalyst poisoning or deactivation. Deactivation is especially problematic with substrates containing thiols and amines that are known to bind strongly to soft transition metals.[1] In order for more general and synthetically useful processes to be developed, means of overcoming catalyst poisoning must be discovered and exploited. An equally important challenge is to find ways of changing a poorly selective catalyst into a highly selective one. In asymmetric catalysis, the diversity of chiral ligands currently available makes it difficult to rapidly identify the "best" one.

The important role of spectator ligands in transition metal ligand-substitution reactions has long been recognized. In the development of new asymmetric transformations, however, attention is usually paid to the choice of metal and chiral ligand whereas halide ligands within the coordination sphere are often regarded as being of secondary importance. In fact, most discussions of halide ligands involve their removal from the coordination sphere and replacement with weakly coordinating anions such as triflate, hexafluorophosphate, and hexafluoroantimonate.[2] When more detailed studies are performed, interesting results have been obtained.[3]

In this full report, we describe the application of halide effects in the development of the rhodium-catalyzed asymmetric ring opening (ARO) reaction of oxabicyclic alkenes with a wide range of nucleophiles including alcohols, phenols, anilines, aliphatic amines, carboxylates, and malonates. Importantly, these halide studies provide a means of overcoming catalyst poisoning associated with amine nucleophiles and a means of improving poor enantioselectivities without needing to change the chiral ligand.[4] In some cases, an improvement in enantioselectivity of greater than 50% ee is obtained, simply by changing the halide ligand on the chiral catalyst. We also report conditions that will induce the ARO of less reactive substrates for the generation of cyclohexenols and the application of these conditions to achieve practical reactions that can be run in the absence of solvent and with catalyst loadings as low as 0.01 mol % [Rh].

Background

We previously reported that alcohols and phenols were excellent nucleophiles in the rhodium-catalyzed asymmetric ring opening (ARO) reaction of oxabenzonorbornadienes generating *trans*-1,2-disubstituted dihydronaphthalenols in high yield and excellent enantioselectivity.[5] Efforts to extend these first generation reaction conditions to other nucleophile classes gave mixed results (Scheme 1). For example, aliphatic amines failed to react, and aromatic amines gave products with low ee. Malonate

† Department of Chemistry, South China Normal University, Guangzhou, Guangdong, 436100, China.

‡ Present address: Department of Chemistry, University of Ottawa, 10 Marie Curie, Ottawa, Ontario, Canada K1N 6N5.

(1) For examples of catalyst deactiviation in olefin metathesis, see: (a) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856 (b) Bazan, G. C.; Oskam, J. H.; Cho, H.-N.; Park, L. Y.; Schrock, R. R. *J. Am. Chem. Soc.* **1991**, *113*, 6899. (c) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875.

(2) (a) Evans, D. A.; Murry, J. A.; von Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem.* **1995**, *107*, 864; *Angew. Chem., Int. Ed. Engl.* **1995**, *107*, 798. (b) O'Mahoney, D. J. R.; Belanger, D. B.; Livinghouse, T. *Synlett* **1998**, 443.

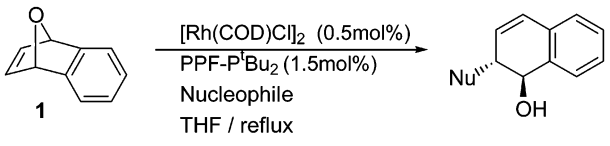
(3) For a review dealing with halide effects in transition metal catalysis, see: Fagnou, K.; Lautens, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 26.

(4) For a preliminary communication of these results, see: Lautens, M.; Fagnou, K. *J. Am. Chem. Soc.* **2001**, *123*, 7170.

(5) (a) Lautens, M.; Fagnou, K.; Rovis, T. *J. Am. Chem. Soc.* **2000**, *122*, 5650. (b) Lautens, M.; Fagnou, K.; Taylor, M. *Org. Lett.* **2000**, *2*, 1677. (c) Lautens, M.; Fagnou, K.; Taylor, M.; Rovis, T. *J. Organomet. Chem.* **2001**, *624*, 259.

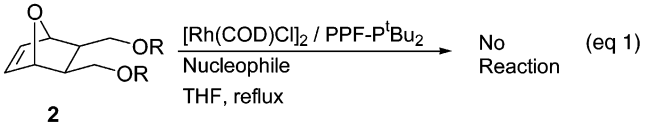
10.1021/ja034845x CCC: $25.00

Scheme 1

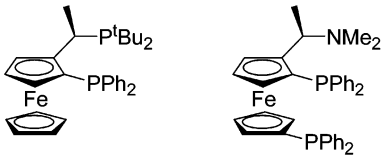


"First Generation Reaction Conditions"

Nucleophile	Outcome
Alcohols and Phenols	>90% yield, >90%ee
Aliphatic amines	no reaction
Aromatic Amines	>90% yield, 30-74%ee
Malonates	<50% yield, 50%ee
Carboxylates	>80% yield, 30-60%ee



(eq 1)



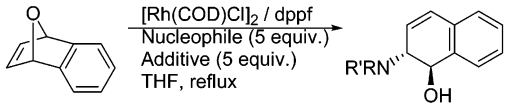
PPF-P^{t}Bu$_2$

BPPFA

nucleophiles also reacted poorly, generating both low yields and enantioselectivities. We discovered conditions where carboxylate nucleophiles reacted in high yield, but again ee's were poor. In addition, when the substrate was changed to less reactive oxabicyclo [2.2.1] adducts, no product formation was observed even after prolonged reaction time (eq 1).

Overcoming Catalyst Poisoning with Aliphatic Amines. In every instance, when the first generation conditions were employed with simple amines such as pyrrolidine, no reaction was observed. Given the importance of the 2-aminotetralin motif in medicinal chemistry,[6] we chose to probe the poor reactivity of simple amines in detail. An important factor to determine was whether the lack of reactivity with aliphatic amines was a consequence of poorer nucleophilicity or if they were reacting with the rhodium catalyst and poisoning the reaction. A competition experiment was carried out involving a good nucleophile (*N*-methylaniline) and a poor nucleophile (pyrrolidine). When run independently, *N*-methylaniline results in complete consumption of **1** in less than 30 min (Table 1, Entry 1), while pyrrolidine fails to react after 8 h (Entry 2). When both nucleophiles are added to the reaction mixture, *neither* nucleophile adds after 6 h (Entry 3), indicating that the pyrrolidine is deactivating the catalyst and preventing the addition of the otherwise good nucleophile. If the poor reactivity of pyrrolidine resided solely with a problem of nucleophilicity, then the *N*-methylaniline should have still reacted.

Table 1.



entry	nucleophile	additive	time	product	yield (%)[a]
1	*N*-methylaniline	none	30 min	**2**	98
2	pyrrolidine	none	6 h	**3**	nr
3	*N*-methylaniline	pyrrolidine	8 h	**2**	nr

Conditions: Substrate, $Rh(COD)Cl]_2$ (2.5 mol %), dppf (5 mol %) dissolved in THF and heated to reflux. Nucleophile (5 equiv) and additive (5 equiv if employed) added and reacted for indicated duration. [a] Yield determined by ^{1}H NMR.

The change in reaction color when aliphatic amines are added to the catalyst mixture qualitatively supports the notion that the aliphatic amines are reacting at the rhodium center. With good nucleophiles such as alcohols, phenols, and aromatic amines, the reaction mixture is typically dark red in color. When an aliphatic amine such as pyrrolidine is added to the reaction mixture, an instantaneous color change to yellow is noted and no ring opening is observed. Because amines are known to be good ligands for rhodium,[7] it is likely that the catalyst poisoning may be due to binding/interaction of the basic amine to the metal center.

As any interaction of the amine with the rhodium catalyst should be affected by the presence of other species in solution capable of binding to the metal, the effect of additives was examined. Preliminary studies revealed that the use of a proton/halide additive, such as $Et_3N{\cdot}HCl$, promoted the reaction between **1** and pyrrolidine. For example, addition of an equimolar amount of pyrrolidine and $Et_3N{\cdot}HCl$ gives complete consumption of **1** after 6 h at 5 mol % catalyst loading providing **3** in 85% isolated yield (Scheme 2).

As $Et_3N{\cdot}HCl$ contains a proton and a halide, reactions were performed to determine which aspect of this additive was influencing the reaction outcome. For example, addition of 5 equiv of camphorsulfonic acid (CSA) and 10 equiv of pyrrolidine, resulting in the formation of a 1:1 mixture of free pyrrolidine and pyrrolidine hydrosulfinate salt, to a reaction of **1** with 5 mol % rhodium catalyst in refluxing THF gives 92% conversion obtained after 25 h as observed by crude ^{1}H NMR.[8]

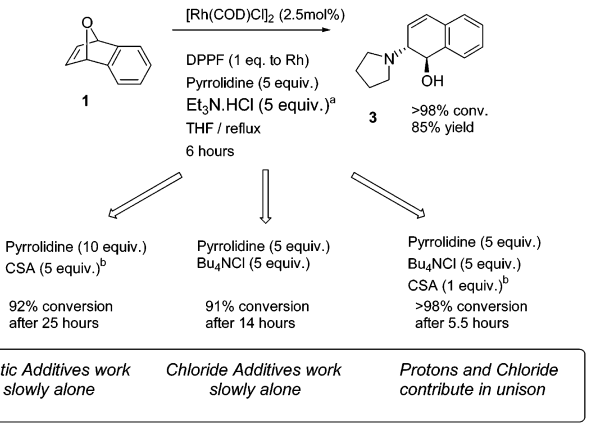
The influence of chloride additive in the absence of a proton source was also examined. In this case, reaction of **1** with 5 mol % catalyst, 5 equiv of pyrrolidine and 5 equiv of tetrabutylammonium chloride gives 91% conversion after 14 h. While this is less than the time required to obtain the same conversion with CSA, it is still longer than that required when

(6) Aminotetralins have received increased attention in recent years since to the discovery of potent anti-Parkinsonian activity of apomorphine. Cotzias, G. C.; Papavasiliou, P. S.; Fehling, C.; Kaufman, B.; Mena, I. *New Engl. J. Med.* **1970**, *282*, 42. Since this time, structurally simplified analogues have been shown to maintain high affinity to the dopamine and/or serotonin receptors. For example, Cannon prepared and tested several piperidine-fused analogues and found them to retain good binding to dopamine receptors. See: Cannon, J. G.; Amoo, V. E. D.; Long, J. P.; Bhatnagar, R. K.; Flynn, J. R. *J. Med. Chem.* **1986**, *29*, 2529; Cannon, J. G.; Lee, T.; Goldman, H. D.; Long, J. P.; Flynn, J. R.; Verimer, T.; Costall, B.; Naylor, R. J. *J. Med. Chem.* **1980**, *23*, 1; Cannon, J. G.; Suarez-Gutierrez, C.; Lee, T.; Long, J. P.; Costall, B.; Fortune, D. H.; Naylor, R. J. *J. Med. Chem.* **1979**, *22*, 341. Wikstrom later showed that certain piperidine-fused analoges were devoid of dopaminergic activity, but showed serotonin agonism. See: Wikstrom, H.; Andersson, B.; Elebring, T.; Svensson, K.; Carlsson, A.; Largent, B. *J. Med. Chem.* **1987**, *30*, 2169; Wilkstrom, H.; Andersson, B.; Elebring, T.; Jacyno, J.; Allinger, N. L.; Svensson, K.; Carlsson, A.; Sundell, S. *J. Med. Chem.* **1987**, *30*, 1567; Wilkstrom, H.; Sanchez, D.; Lindberg, P.; Arvidsson, Hacksell, L.-E.; U.; Johansson, A.; Nilsson, J. L. G.; Hjorth, S.; Carlsson, A. *J. Med. Chem.* **1982**, *25*, 925.

(7) *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon Press: Elmsford, NY, 1982; Vol. 5.

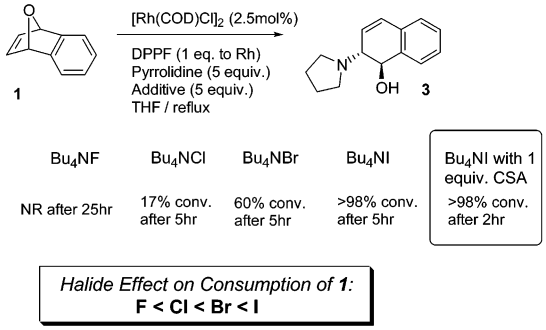
(8) Percent conversion in these reactions was determined by comparison of the bridgehead proton signals of the oxabenzonorbornadiene to a mesitylene internal standard in the ^{1}H NMR of the crude reaction mixture.

Scheme 2



[a] Conditions: Substrate, $[Rh(COD)Cl]_2$ (2.5 mol %) and dppf (5 mol %) were dissolved inTHF and stirred at room temperature for 3−5 min. The halide additive was then added and the mixture heated and at first sign of reflux, pyrrolidine (5 equiv.) was added. [b] In reactions using CSA, it was added immediately after the addition of the pyrrolidine nucleophile.

Scheme 3



Conditions: Substrate, $[Rh(COD)Cl]_2$ (2.5 mol %) and dppf (5 mol %) were dissolved in THF and stirred at room temperature for 3−5 min. The halide additive was then added and the mixture heated and at first sign of reflux, pyrrolidine (5 equiv) was added.

$Et_3N{\cdot}HCl$ is employed. By combining the protic (CSA) and chloride (Bu_4NCl) additives, complete consumption of **1** occurs in 5.5 h which is comparable to that obtained with $Et_3N{\cdot}HCl$. These results demonstrate that both a proton and chloride ion can act independently to induce a slow reaction, and act together to promote a faster consumption of **1**.[9]

The success of chloride ions in promoting ring opening in the presence of aliphatic amines prompted us to investigate the effect of varying the halide (Scheme 3). To isolate any changes in reactivity to the nature of the halide, these reactions were run in the absence of an added proton source. In a typical reaction, **1** was treated with 5 mol % catalyst, 5 equiv of pyrrolidine and 5 equiv of R_4NX in refluxing THF. An examination of the results reveals a distinct trend within the halide group with respect to the time required to obtain high conversion. For example, use of Bu_4NF did not promote reaction after 25 h. With 5 mol % catalyst, Bu_4NCl gives 17% conversion after 5 h by ^1H NMR, while Bu_4NBr gives 60% conversion. The best results were obtained with Bu_4NI, which gives complete consumption of **1** in less than 5 h. As was observed with Bu_4NCl, the addition of CSA in conjunction with Bu_4NI leads to a more rapid consumption of starting material, so that 100% conversion occurs after only 2 h.

Experimental evidence supports the hypothesis that the halide additives are acting at the rhodium metal. A visual indication is a change in color of the reaction solution depending on the halide. As previously described, addition of an aliphatic amine to a rhodium catalyst solution changes the color of the solution from dark red to yellow which is associated with catalyst poisoning. No ring opening is observed when this is the case. When Bu_4NI and CSA are added to this solution, a color change back to dark red is observed over approximately 5 min and reaction of **1** with the aliphatic amine occurs. We also verified that no reaction occurs with Bu_4NI, CSA, and rhodium catalyst in the absence of nucleophile, indicating that the product is not being formed by ring opening with the iodide followed by S_N2 displacement of the halide by the amine.

The effect of halide/proton additives was found to be generally applicable for the addition of a variety of aliphatic amines (Table 2). Although the use of amine hydrochlorides could be employed for secondary amines, only the combination of Bu_4NI and CSA gave complete consumption of **1** when primary amines were used (Entries 7 and 9 vs 8 and 10). The combined use of halides and acid represents a technically simple method for the effective reversal of catalyst poisoning by aliphatic amines.

The use of halide additives also has pronounced effects on the enantioselectivity of the ARO reaction with aliphatic amines, the nature of which is highly dependent on the chiral ligand employed in the transformation (Table 3). Initial experiments employed PPF−P^{t}Bu$_2$ as the chiral ligand with *p*-methoxybenzylamine as the nucleophile along with 5 equiv of R_4NX and 1 equiv of CSA. Again, no reaction was observed when Bu_4NF was employed as the halide additive. With the other halides a distinct trend in enantioselectivity was observed that parallels reactivity. For example, Bu_4NCl gives **9** in 52% yield and 29% ee after 5 h, which increases to 67% and 42% respectively when Bu_4NBr is used. The best results were obtained with Bu_4NI, which gives **9** in 72% yield and 72% ee after similar reaction time.

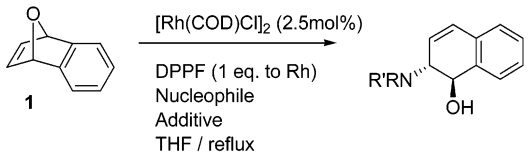
Removing the chloride ligand from the coordination sphere of the rhodium and replacing it with iodide prior to the addition of reagents and additives further improves the enantioselectivity. The halide exchange is performed by dissolving $[Rh(COD)Cl]_2$ and PPF−P^{t}Bu$_2$ in THF followed by transfer of this solution via cannula to another flask containing 1.5 equiv of silver triflate (per chloride atom). After stirring for approximately 5 min, this heterogeneous mixture is transferred to a flask containing 2 equiv of Bu_4NI (relative to the rhodium monomer). After a few minutes, the solution becomes dark red/brown and is ready to be used. Application of this [RhI(PPF−P^{t}Bu$_2$)] catalyst to the reaction conditions using Bu_4NI and CSA as additives gives **9** in 71% yield and 81% ee.[10] Analogous results were observed with dibenzylamine as the nucleophile. In this case, slightly higher yields and enantioselectivities are obtained in the formation of **6** (Entries 5−7).

In contrast to the parallel trends in reactivity and enantioselectivity obtained with PPF−P^{t}Bu$_2$ as the chiral ligand, use of BPPFA gives an inverse relationship between reactivity and

(9) HCl is known to react stoichiometrically with rhodium-amine complexes to generate anionic dihalorhodium species, see: Vallarino, L. M.; Sheargold, S. W. *Inorg. Chim. Acta* **1979**, *36*, 243.

(10) The establishment of the absolute stereochemistry of these dihydronaphthalene compounds has previously been reported. See: refs 4 and 5.

Table 2. Scope of Ring Opening Reactions with Aliphatic Amines



entry	nucleophile	additive	time	product	% yield[a] (conv.)[b]
1	piperidine	Et_3N·HCl (5 equiv)	16 h	**4**	84
2	diethylamine	Et_3N·HCl (5 equiv)	16 h	**5**	82
3	diethylamine	TBAI (5 equiv)/CSA (1 equiv)	2.5 h	**5**	85
4	dibenzylamine	Et_3N·HCl (5 equiv)	6 h	**6**	84
5	dibenzylamine	TBAI (5 equiv)/CSA (1 equiv)	0.5 h	**6**	91
6	tetrahydroisoquinoline	Et_3N·HCl (5 equiv)	24 h	**7**	81
7	benzylamine	Et_3N·HCl (5 equiv)	72 h	**8**	31 (45)
8	benzylamine	TBAI (5 equiv)/CSA (1 equiv)	6 h	**8**	81 (>98)
9	*p*-methoxybenzylamine	Et_3N·HCl (5 equiv)	72 h	**9**	44 (52)
10	*p*-methoxybenzylamine	TBAI (5 equiv)/CSA (1 equiv)	7 h	**9**	82 (>98)

Conditions: Substrate, $[Rh(COD)Cl]_2$ (2.5 mol %) and dppf (5 mol %) were dissolved in THF andstirred for 3−5 min. The halide additive was then added and the reaction mixture heated to relux. On first sign of reflux, the amine (followed by CSA if used) were added. [a] Isolated yield. [b] Percent conversion determined by crude ^{1}H NMR by comparison to a mesitylene internal standard.

Table 3. Effect of Halide Ligand on Enantioselectivity[a]

				yield (ee[c])	
entry	nucleophile	product	I	PPF−P^{t}Bu$_2$	BPPFA
1	*p*-methoxybenzylamine	**9**	Cl	52 (29)	57 (78)
2	*p*-methoxybenzylamine	**9**	Br	67 (42)	67 (39)
3	*p*-methoxybenzylamine	**9**	I	72 (72)	79 (33)
4	*p*-methoxybenzylamine	**9**	I[b]	71 (81)	
5	dibenzylamine	**6**	Cl	89 (31)	86 (76)
6	dibenzylamine	**6**	I	86 (74)	
7	dibenzylamine	**6**	I[b]	91 (88)	

[a] 2 mol % $[Rh(COD)Cl]_2$, 5 mol % ligand, 5 equiv nucleophile, 5 equiv halide additive, 1 equiv CSA, 0.1 M in THF. [b] Prior to the addition of the reagents, a halide exchange was performed, see Experimental Section. [c] ee determined by CSP HPLC with a Chiralcel OD column.

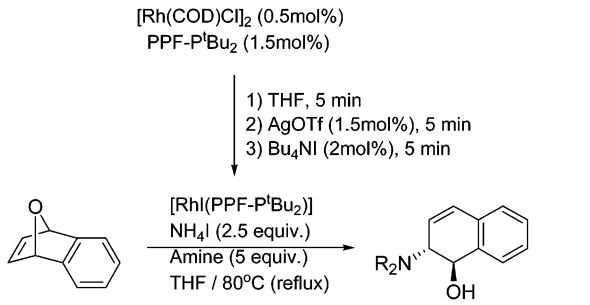
ee. As observed with PPF−P^{t}Bu$_2$, the best reactivity with BPPFA and *p*-methoxybenzylamine as the nucleophile is obtained with Bu_4NI as the additive. In contrast, BPPFA gives the product in higher enantioselectivity with Bu_4NCl. These results underline the complex nature of halide effects in enantioselective catalysis and reinforce the notion that the halide and chiral ligand act together to influence the selectivity in these transformations.

To carry out multigram scale ring opening reactions, alternatives to the use of tetraalkylammonium salts was required to facilitate product isolation which was greatly impeded by the formation of emulsions during extraction.[11] To overcome these technical difficulties, NH_4I was employed, resulting in higher yields and enantioselectivities as well as easier product isolation. For example, application of the halide exchange protocol to the reaction of **1** with a variety of amines using 1.5−2 equiv NH_4I provides the corresponding products in good yield and 92 to 98% ee (Table 4).

Improving Enantioselectivity with Activated Amines. The enhanced enantioselectivities obtained with aliphatic amines using the [Rh−I] catalyst prompted us to investigate the influence of the halide ligand on ee with activated amine nucleophiles. It is important to note that aromatic amines induce ring opening without the use of halide/protic additives, but because the halide was found to influence both the reactivity and the enantioselectivity, we questioned whether the poor enantioselectivity associated with aromatic amines could be improved by simply changing the halide ligand on the rhodium catalyst.

(11) See Lautens, M.; Fagnou, K.; Zunic, V. *Org. Lett.* **2002**, *4*, 3465.

Table 4.



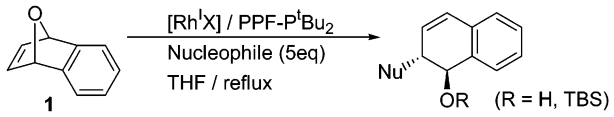
entry	nucleophile	product	yield (%)[a]	ee (%)[b]
1	dibenzylamine	**6**	86	99
2	tetrahydroisoquinoline	**7**	85	97
3	4-methoxybenzylamine	**9**	81	92
4	*n*-methylpiperazine	**10**	96	99

Conditions (X Ligand = I): $[Rh(COD)Cl]_2$ (0.5 mol %), ligand (1.5 mol %) added to flask followed by addition of AgOTf (2 mol %) then Bu_4NI (4 mol %). To this was added **1** followed by heating to relux. At first sign of reflux, NH_4I (1.5−2 equiv) was added followed by the nucleophile (3−4 equiv). The reaction was heated at reflux until complete as judged by TLC analysis. [a] Isolated yield. [b] ee determined by CSP HPLC with a Chiralcel OD or AD column.

Initial reactions employed *N*-methylaniline as the nucleophile. Rhodium catalysts with F, Cl, Br, and I ligands were examined, as well as the cationic triflate complex. The results are described in Scheme 4. A prominent halide/counterion effect was noted in these reactions. With *N*-methylaniline, the best results are obtained with the triflate, F and I catalysts.

The effect of the catalyst counterion was investigated with other activated nucleophiles. Good yields and excellent enantioselectivities can be obtained with a variety of activated amines including tetrahydroquinoline, phthalimide, 4-nitroaniline, and 1-aminonaphthalene (Table 5). Our preferred catalyst is the rhodium-iodide complex, due to its ease of preparation and the high yields and enantioselectivity associated with its use. Although the cationic triflate catalyst can be used in some cases to generate the product in high ee, the reaction outcome is

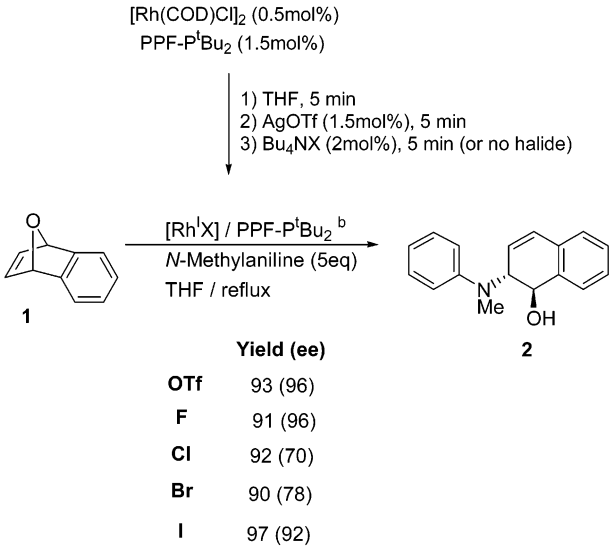
Table 5. Effect of Counterion on Enantioselectivity[a]



			yield (ee[b])				
entry	nucleophile	product	OTf	F	Cl	Br	I
1	tetrahydroquinoline	**11**	94 (96)	92 (96)	89 (65)	86 (74)	95 (91)
2	phthalimide	**12**	0[e]	74 (94)	55 (45)[c]	78 (79)	90 (98)
3	4-nitroaniline	**13**			89 (58)[c,d]		86 (92)[d]
4	1-aminonaphthalene	**14**			79 (48)[c,d]		84 (91)[d]

[a] Conditions: Prior to the addition of the reagents, a halide exchange was performed by dissolution of $[Rh(COD)Cl]_2$ (0.5 mol %), PPF−P^{t}Bu$_2$ (1.5 mol %) in THF and then sequential treatment with AgOTf (1.5 mol %) and R_4NX (2 mol %). To this solution was added the substrate and 5 equiv nucleophile, 0.2 M in refluxing THF. [b] ee was determined by CSP HPLC with a Chiralcel OD or AD column. [c] Halide exchange was not performed; $[Rh(COD)Cl]_2$ (1 mol %) and PPF−P^{t}Bu$_2$ (2.5 mol %) were disolved in THF and used directly. [d] Product was isolated as the *tert*-butyldimethylsilyl ether for ease of separation from unreacted nucleophile. [e] Only decomposition to naphthol was observed.

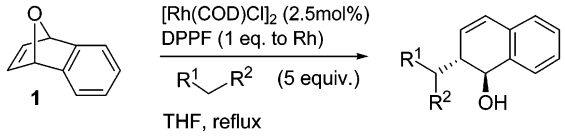
Scheme 4



dependent on the amine used. For example, although excellent results are obtained with the rhodium-triflate catalyst with *N*-methylaniline, only decomposition to naphthol is observed when phthalimide is employed (Entry 2). High yields and ee's are also obtained with the rhodium-fluoride catalyst; however, the hygroscopic nature of the fluoride salts makes this method technically difficult compared to the use of iodide salts in the preparation of the Rh−I catalyst. The fact that both fluoride and iodide generate the product in high ee with *N*-methylaniline is difficult to explain, because they lie at opposite ends of the halide group and exhibit different properties. We are continuing to investigate halide/ ligand combinations and the change in ee to develop a deeper understanding of these effects. Regardless, the ability to improve the enantioselectivity of a chiral catalyst by changing the halide ligand represents a useful tool in the development of new asymmetric transformations.

We established that the trends are due to the nature of the halide and do not arise from other factors produced by the halide exchange protocol. The reactions with *N*-methylaniline and tetrahydroquinoline were performed with a catalyst prepared by simply combining $[Rh(COD)Cl]_2$ and PPF−P^{t}Bu$_2$ *and* with a catalyst where the chloride was first removed with AgOTf then added back in the form of Bu_4NCl. With both nucleophiles, similar yields and enantioselectivities were obtained with both procedures.

Table 6. Ring Opening with Stabilized Carbon Nucleophiles



entry	nucleophile	R^1	R^2	rxn time	product	yield (%)[a]
1	**15**	CO_2Me	CO_2Me	48 h	**19**	51
2	**15** − Na salt	CO_2Me	CO_2Me	24 h	**19**	NR
3	**15**/Et_3N	CO_2Me	CO_2Me	24 h	**19**	19
4	**16**	CO_2Me	NO_2	30 min	**20**	92
5	**17**	SO_2Ph	-CN	30 min	**21**	94
6	**18**	CO_2Me	-NC	8 h		nr

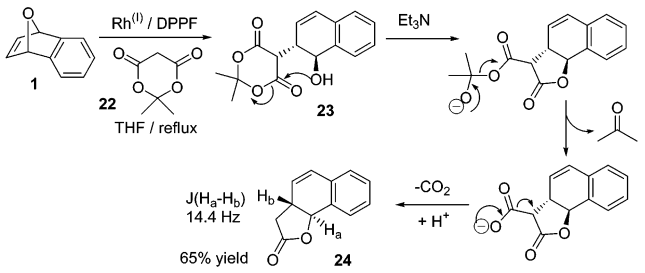
Conditions: $[Rh(COD)Cl]_2$ (2.5 mol %), dppf (5 mol %), nucleophile (5 equiv), and **1** reacted in THF (0.1 M) at reflux. [a] Isolated yield.

Carbon-Based Nucleophiles and the Formation of Carbon−Carbon Bonds. The observation that heteroatom nucleophiles that performed best in the absence of additives have pK_a values between 9 and 16 led us to examine analogous reactions with malonate nucleophiles. Initial experiments revealed that treatment of **1** with 5 equiv of dimethylmalonate **15** under rhodium catalysis produced **19** in only moderate yield, giving incomplete conversion after prolonged reaction times (Table 6, Entry 1). Reaction with the sodium salt of **15** resulted in no reaction after 24 h, and the use of **15** and an equimolar amount of triethylamine resulted in an erosion of reactivity compared to when no base was added (Entries 2, 3). In contrast to the poor reactivity of dimethylmalonate, other activated carbon nucleophiles reacted in high yield. For example, reaction of **1** with 5 equiv of (phenylsulfonyl)acetonitrile **16** or (phenylsulfonyl)-nitromethane **17** and 5 mol % catalyst efficiently induces ring opening and generates **20** and **21** in 94% and 96% yields respectively (Entries 4 and 5). The regiochemistry and relative stereochemistry of **21** was proven by X-ray crystallography.[12]

We rationalize the difference in reactivity between dimethylmalonate and **16** or **17** by invoking the ability of 1,3-dicarbonyl compounds to bind in a bidentate fashion to transition metal complexes. If coordination occurs, then poisoning of the rhodium catalyst may result, providing an explanation for the poor reactivity. In contrast to the efficient reactions with **16** and **17**, isocyanide **18** did not induce ring opening. On addition of the nucleophile to the catalyst solution, a color change from

(12) Lough, A. J.; Fagnou, K.; Lautens, M. *Acta Crystallogr.* **2002**, *E58*, 664−665.

Scheme 5



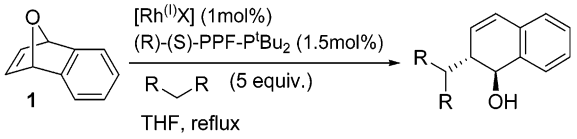
red to green was noted, suggesting that the nucleophile was interacting at the rhodium center.

In another example, **1** was reacted with 5 equiv of Meldrum's acid **22**, whose 1,3-dicarbonyl groups are tied back in a ring preventing bidentate coordination. Complete reaction was observed within 4 h as determined by TLC analysis. Isolation of **23** at this point was not possible by flash chromatography, but treatment of the crude mixture with 3−4 equiv of triethylamine led to the isolation of **24** in 65% yield. Lactone **24** would be produced by nucleophilic attack of the hydroxyl group on one of the two carbonyl groups of **23**. Loss of acetone and subsequent decarboxylation generates **24** upon protonation (Scheme 5). The trans stereochemistry of **24** is supported by analysis of the ^{1}H NMR coupling constant between H_a and H_b. The dihedral angle between H_a and H_b predicted by molecular modeling (MM2) for the cis product is estimated at 36°, whereas that of the trans product is 172°. The expected ^{1}H coupling constant for the cis compound should be small (4−8 Hz) whereas that of the trans species should be large (10−14 Hz). The experimentally observed *J* value of 14.4 Hz provides strong evidence for the assigned *trans*-relative stereochemistry.[13]

We have also found that proper choice of the halide ligand on the rhodium catalyst improves the low reactivities and enantioselectivities associated with some malonate nucleophiles so that the reactions become nearly quantitative (^{1}H NMR analysis) with greater than 90% isolated yields and greater than 96% ee. Initial experiments revealed that a catalyst generated in situ by a combination of $[Rh(COD)Cl]_2$ and PPF−P^{t}Bu$_2$ failed to give complete conversion (54% yield **19** in 57% after 24 h) with dimethylmalonate as the nucleophile (Table 7, Entry 1). Use of Meldrum's acid with the [RhCl(PPF−P^{t}Bu$_2$)] catalyst also gave low conversion, providing **24** in 24% yield and 87% ee (Entry 5). We were pleased to find that much better results could be obtained by employing the rhodium-iodide or fluoride catalyst, although the former was preferred due to its ease of preparation. By simply changing the halide counterion from chloride to iodide, complete reactions were obtained in typically less than 20 min. For example, reaction with 1 mol % [RhI(PPF−P^{t}Bu$_2$)] and 5 equiv of dimethylmalonate gives **19** in 93% yield and 98% ee (Entry 2). Diethylmalonate reacts analogously, providing **26** in 95% yield and 97% ee (Entry 4). Meldrum's acid can also be used with the Rh−I catalyst, giving **24** in 71% yield and 96% ee (Entry 6). In contrast, use of the cationic rhodium triflate catalyst results only in decomposition to naphthol (Entry 3). The improved reactivity of the rhodium-iodide catalyst may be, in part, due to the robust nature of the Rh−I species that disfavors displacement of the halide ligand by the 1,3-dicarbonyl anion.

(13) Pavia, D. L.; Lampman, G. M.; Kriz, G. S In *Introduction to Spectroscopy: A Guide for Students of Organic Chemistry*, 2nd ed.; Saunders College Publishing: 1996; p 193.

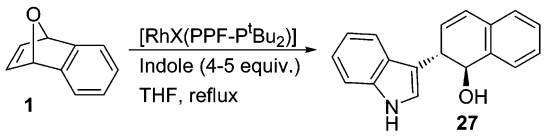
Table 7. ARO with Various Stabilized Carbon Nucleophiles



entry	X ligand[a]	nucleophile	R group	product	yield (%)[b]	ee (%)[c]
1	Cl	**15**	CO_2Me	**19**	54	51
2	I	**15**	CO_2Me	**19**	93	98
3	F	**15**	CO_2Me	**19**	88	97
4	OTf	**15**	CO_2Me	**19**	0	
5	I	**25**	CO_2Et	**26**	95	97
6	Cl	**22**[d]	$-CO_2C(Me)_2CO_2C$	**24**	24	87
7	I	**22**[d]	$-CO_2C(Me)_2CO_2C$	**24**	71	96

[a] Conditions: (X Ligand = Cl): $[Rh(COD)Cl]_2$ (0.5 mol %), ligand (1.5 mol %), nucleophile (5 equiv), additive (5 equiv), and **1** reacted in THF (0.1 M) at reflux. Conditions: (X Ligand = I): $[Rh(COD)Cl]_2$ (0.5 mol %), ligand (1.5 mol %) dissolved in THF followed by sequential treatment with AgOTf (2 mol %) then Bu_4NI (4 mol %). To this, **1** was added then the nucleophile (5 equiv) followed by refluxing in THF (0.1 M) at reflux. [b] Isolated yield. [c] ee determined by CSP HPLC with a Chiralcel OD or AD column. [d] Upon consumption of **1** by TLC analysis, the crude mixture was treated with 10 equiv Et_3N at reflux for 3 h.

Scheme 6



Halide Ligand	Yield (%)	Ee (%)
Cl	87	78
I	93	97

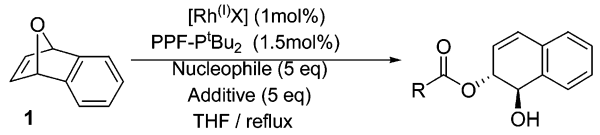
Indole is also a good nucleophile in these transformations for the formation of new carbon−carbon bonds. Although good reactivity is observed with the rhodium-chloride catalyst, only the rhodium-iodide catalyst provides **27** in high enantioselectivity (Scheme 6). In our initial report, we tentatively assigned the product as the *N*-alkylated species, but ^{1}H-^{13}C coupled NMR and H/D exchange revealed that alkylation occurs exclusively at C^3.

Carboxylate Nucleophiles and the Preparation of Allylic Acetates. We previously reported that the poor reactivity of carboxylic acids can be improved by the use of ammonium carboxylate salts.[14] As observed with other nucleophiles, low enantioselectivities were obtained in the formation of **28** and **29** with the first generation catalyst (Table 8, Entries 1 and 3). Better results were obtained by using PPF−P^{t}Bu$_2$ with a rhodium iodide or fluoride complex prepared in situ from the rhodium chloride. Using the halide exchange protocol, products **28** and **29** were obtained in >90% yield and 94% ee (Entries 2 and 5). The difference in the enantioselectivities between the chloro and the iodo complexes is particularly striking with benzoate as the nucleophile. With the Rh−Cl catalyst, **29** is formed in only 31% ee. Changing to the Rh−I complex gives **29** in 91% yield and 92% ee. Methacrylic acid and propionic acid react in similar yields and ee's (Entries 5 and 6).

Ortho-Substituted Phenol Nucleophiles. We previously reported that 2-bromophenol was a poor nucleophile with the first generation catalyst generated from $[Rh(COD)Cl]_2$ and PPF−P^{t}Bu$_2$. When the rhodium source was changed from to

(14) Lautens, M.; Fagnou, K. *Tetrahedron* **2001**, *57*, 5067.

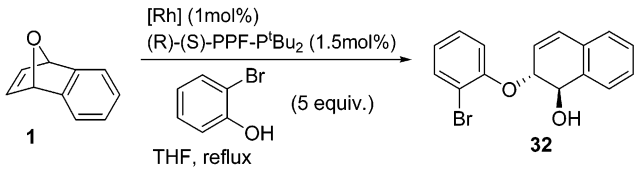
Table 8. ARO with Carboxylate Nucleophiles



entry	X ligand[a]	nucleophile/additive	product	yield (%)[b]	ee (%)[c]
1	Cl	ammonium acetate	**28**	81	61
2	I	ammonium acetate	**28**	93[d]	92
3	F	ammonium acetate	**28**	87	94
4	Cl	ammonium benzoate	**29**	72	31
5	I	ammonium benzoate	**29**	91[d]	92
6	I	propionic acid/Et_3N	**30**	75	91
7	I	methacrylic acid/Et_3N	**31**	71	91

[a] Conditions (X Ligand = Cl): $[Rh(COD)Cl]_2$ (0.5 mol %), ligand (1.5 mol %), nucleophile (5 equiv), additive (5 equiv), and **1** reacted in THF (0.1 M) at reflux. Conditions (X Ligand = I): $[Rh(COD)Cl]_2$ (0.5 mol %), ligand (1.5 mol %) added to flask followed by addition of AgOTf (2 mol %) then Bu_4NI (4 mol %). To this was added **1**. The nucleophile (5 equiv) and additive (5 equiv) were added to this solution in THF (0.1 M) at reflux. [b] Isolated Yield. [c] ee determined by CSP HPLC with a Chiralcel OD collumn. [d] These reactions were run on a 1 gram scale.

Table 9. Effect of Rhodium Catalyst on Deactivation by *ortho*-Bromophenol



entry	Rh source	X ligand[a]	time	yield (%)[b]	ee (%)[c]
1	$[Rh(COD)Cl]_2$	Cl	24 h	17	97
2	$[Rh(CO)_2Cl]_2$	Cl	24 h	92	97
3	$[Rh(COD)Cl]_2$	I	1.5 h	94	95

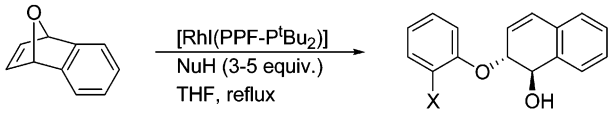
[a] Conditions (X Ligand = Cl): $[Rh(COD)Cl]_2$ or $[Rh(CO)_2Cl]_2$ (0.5 mol %), ligand (1.5 mol %), nucleophile (5 equiv), additive (5 equiv), and **1** reacted in THF (0.1 M) at reflux. Conditions (X Ligand = I): $[Rh(COD)Cl]_2$ (0.5 mol %), ligand (1.5 mol %) added to flask followed by addition of AgOTf (2 mol %) then Bu_4NI (4 mol %). To this was added **1**. The nucleophile (5 equiv) was added to this solution in THF (0.1 M) at reflux. [b] Isolated yield. [c] ee determined by CSP HPLC with a Chiralcel OD or AD column.

$[Rh(CO)_2Cl]_2$ better reactivity was observed but >24 h was required to consume the starting material. The improved reactivity of the carbonyl-catalyst was attributed to blocking bidentate the binding of the *ortho*-halophenol through the halide and oxygen groups.[5b] We were pleased to find that the rhodium iodide catalyst generated in situ by halide ligand exchange does not suffer from the catalyst poisoning observed with the chloride analogue in the presence of 2-bromophenol. When the [RhI-(PPF−P^{t}Bu$_2$)] complex is used, **32** is obtained in 93% yield and 94% ee in less than 1.5 h with 1 mol % catalyst.

The rhodium iodide catalyst was found to efficiently induce ring opening with a wide range of *ortho*-substituted phenols in good yield and excellent enantioselectivities (Table 10). These include halide substituents (Entries 1 to 3) as well as 2-methoxy and cyano substituents (Entries 4 and 5) all of which could have deactivated the catalyst through bidentate binding.

Substrate and Nucleophile Scope Investigation. We investigated the generality of the rhodium-catalyzed ring opening reaction with other oxabicyclic substrates and found that both **40** and **41** react in high yield with a wide range of nucleophiles (Table 11). Alcohols (Entries 1 and 2), phenols (Entries 3 to 6), carboxylates (Entries 7 and 8), aromatic amines (Entries 9 and 10) and aliphatic amines (Entries 11 to 16) can all be used to induce ring opening through the proper choice of additives to form a wide range of highly functionalized dihydronaphthalenes in an efficient manner.

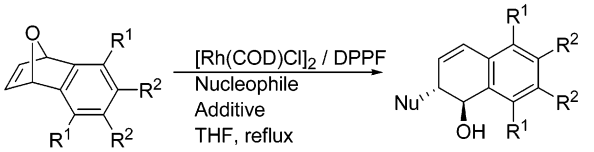
Table 10. Addition of Various *ortho*-Substituted Phenol Nucleophiles



entry	*ortho*-substituent	product	yield (%)[a]	ee (%)[b]
1	F	**33**	86	99
2	Cl	**34**	85	97
3	I	**35**	60	96
4	-CN	**36**	65	99
5	OMe	**37**	58	99
6	CF_3	**38**	80	97
7	-COMe	**39**	41	97

Conditions (X Ligand = I): $[Rh(COD)Cl]_2$ (0.5 mol %), ligand (1.5 mol %) added to flask followed by addition of AgOTf (2 mol %) then Bu_4NI (4 mol %). To this was added **1**. The *ortho*-substituted phenol nucleophile (5 equiv) was added to this solution in THF (0.1 M) at reflux. [a] Isolated yield. [b] ee determined by CSP HPLC with a Chiralcel OD or AD column.

Table 11. Substrate and Nucleophile Scope



R^1 = H, R^2 = OMe; **40**
R^1 = OMe, R^2 = H; **41**

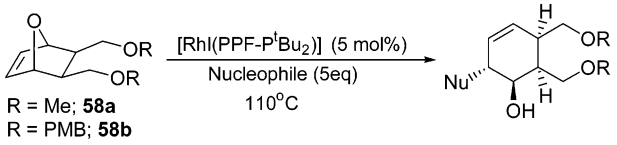
entry	R^1	R^2	nucleophile	additive	product	yield (%)[a]
1	H	OMe	methanol	none	**42**	93
2	OMe	H	methanol	none	**43**	78
3	H	OMe	phenol	none	**44**	65
4	OMe	H	phenol	none	**45**	81
5	H	OMe	4-hydroxyacetophenone	none	**46**	72
6	OMe	H	4-hydroxyacetophenone	none	**47**	89
7	H	OMe	benzoic acid	Et_3N	**48**	87
8	OMe	H	benzoic acid	Et_3N	**49**	98
9	H	OMe	*n*-methylaniline	none	**50**	83
10	OMe	H	*n*-methylaniline	none	**51**	77
11	H	OMe	pyrrolidine	NH_4I	**52**	80
12	OMe	H	pyrrolidine	NH_4I	**53**	80
13	H	OMe	dibenzylamine	NH_4I	**54**	97
14	OMe	H	dibenzylamine	NH_4I	**55**	76
15	H	OMe	morpholine	NH_4I	**56**	87
16	OMe	H	morpholine	NH_4I	**57**	53

Conditions: The substrate, $[Rh(COD)Cl]_2$ (2 mol %) and dppf (4 mol %) dissolved in THF followed by heating to reflux. The nucleophile (4−5 equiv) and additive, if required, were then added and reacted until complete as judged by TLC analysis. [a] Isolated yield.

Reactions of Activated [2.2.1]Oxabicyclic Alkenes and the Establishment of Solventless Reaction Conditions. Despite the successful realization of asymmetric ring opening reactions with a variety of oxabenzonorbornadienes, extension of this methodology to the less reactive members of this class with the first generation catalyst was not fruitful. With every nucleophile class, no reaction was observed with substrates such as **58** even after prolonged reaction times. Overcoming the lower reactivity of these [2.2.1] oxabicyclic alkenes required three modifications. First, the catalyst was changed to the rhodium-iodide catalyst as prepared by in situ halide ligand exchange. Second, the reaction temperature was increased to 110 °C and

third, the reactions were run in the absence of solvent.[15] For example, treatment of **58** with catalytic [RhI(PPF−P^{t}Bu$_2$)] and various nucleophiles at 110 °C produces cyclohexenol products in good yield and >90% ee (Table 4).[16] The analogous [RhCl] complex fails to catalyze the reaction with this substrate. As with **1**, only *trans*-1,2-cyclohexenols are formed. The fact that the reaction of **58** gives the *trans*-1,2-regioisomer as the exclusive product has mechanistic significance. Because the regio- and stereochemical outcome is the same when both **1** and **58** are reacted, it can be concluded that the outcome is not governed by the conjugation between the newly formed alkene and aromatic moiety present in the 1,2-dihydronaphthalene products. This finding lends support to our working model, where it is the presence of the newly formed alkoxide or alcohol that dictates the site of nucleophilic attack.

Table 12. Effect of Halide Ligand on Reactivity[a]



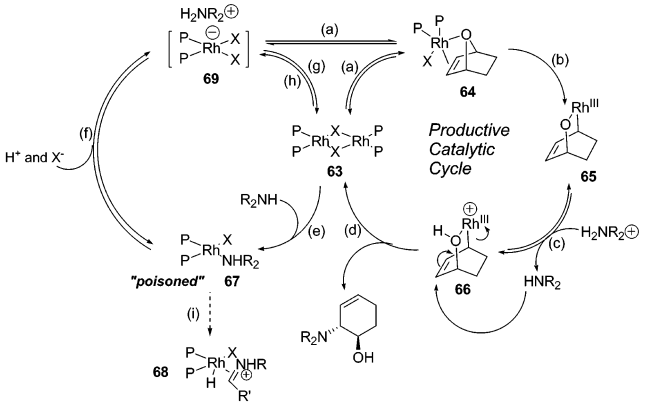
entry	R group[d]	nucleophile	product	yield[b] (% ee[c])
1	Me	*p*-bromophenol	**59**	83 (94)
2	PMB	phenol	**60**	84 (93)
3	PMB	*N*-methylaniline	**61**	93 (95)

[a] Conditions: Halide exchange was performed with [Rh(COD)Cl]$_2$ (2.5 mol %), PPF−P^{t}Bu$_2$ (7.5 mol %), AgOTf (7.5 mol %) and TBAI (10 mol %). To this was added **58** and nucleophile (5 equiv) followed by heating at 110 °C. [b] Isolated yield. [c] ee determined by CSP HPLC with a Chiralcel OD or AD column. [d] Me = methyl, PMB = *p*-methoxybenzyl.

Effect of Solvent-Free Reaction Conditions on Catalyst Loading in the Rhodium-Catalyzed ARO Reaction. Having identified the benefits of using more forcing conditions for the ring opening of less reactive [2.2.1] oxabicyclic alkenes, we returned to the more reactive oxabenzonorbornadiene substrate to determine what effect these new conditions would have on the catalyst loading required for efficient reaction to occur. In a typical experiment, the substrate **1** and the nucleophile (1.5 to 5 equiv) were added to a screw top vial that was then heated in an oil bath at 100 °C. To this melt was added an aliquot of a THF stock solution of [RhI(PPF−P^{t}Bu$_2$)] already in the presence of two to 3 equiv of **1** via gastight syringe (typically 10 to 20 μL). Following this procedure, we were gratified to learn that catalyst loadings as low as 0.01 mol % [Rh] can be used with only a slight excess of nucleophile to give products **62**, **2**, and **27** in quantitative yield and excellent enantioselectivity. Even at these catalyst loadings, the reactions are still complete in a reasonable amount of time (1.5 to 8 h). The combination of very low catalyst loadings, solventless conditions, technical ease, high yields, and easy handling of the reagents makes these reactions synthetically useful for the preparation of a variety of hydronaphthalene compounds.

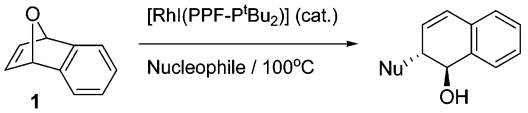
Although adding the catalyst solution to the reaction mixture premixed with two to 3 equiv of **1** relative to [Rh] is not required, we found that adding a catalyst substrate combination gave more reproducible reaction outcomes. This difference may be a result of catalyst interaction with the nucleophile prior to commencement of the catalytic cycle.

Scheme 7



(a) Substrate binding on the *exo*-face (displacement of a halide ligand or dimer bridge cleavage); (b) oxidative insertion; (c) protonation of the rhodium alkoxide; (d) nucleophilic attack and product liberation; (e) amine binding; (f) amine ligand protonation and nucleophilic displacement by a halide nucleophile; (g) dimer formation with loss of a halide ligand; (h) dimer cleavage by nucleophilic displacement with a halide; (i) α-oxidation of the amine ligand.

Table 13. Catalyst Loading Studies



entry	mol % catalyst	s:c	nucleophile (equiv)	time	product	yield (%)[a]	ee (%)[b]
1	1.0	100:1	PhOH (5)	>15 min	**62**	92	94
2	0.1	1000:1	PhOH (5)	>20 min	**62**	94	94
3	0.1	1000:1	PhOH (1.5)	30 min	**62**	92	93
4	0.05	2000:1	PhOH (1.5)	1 h	**62**	89	94
5	0.01	10000:1	PhOH (1.5)	3 h	**62**	90	94
6	0.01	10000:1	PhNHMe (1.5)	8 h	**2**	87	93
7	0.01	10000:1	indole (1.5)	1.5 h	**27**	94	99

Conditions: To a stock solution of the [RhI(PPF−P^{t}Bu$_2$] catalyst prepared in THF according to the standard halide exchange protocol was added 2 equiv of the oxabicyclic alkene substrate. In a screw cap vial was added the substrate and the nucleophile which were then melted together under a nitrogen atmosphere at 100 °C. To this melt at 100 °C, an aliquot of the catalyst stock solution was added via gastight syringe. The reaction progress was monitored periodically by the removal of aliquots and TLC analysis. [a] Isolated yield. [b] ee determined by CSP HPLC with a Chiralcel OD or AD column.

Working Model: Influence of Halide/Protic Additives on Catalyst Poisoning. Although no direct evidence has been obtained on which to base a mechanism of action for the halide additives, knowledge drawn from the literature can guide an informed discussion regarding the role of the halide and protic additives in reversing the poisoning caused by the presence of aliphatic amines.

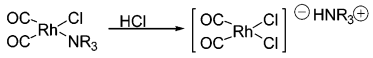
Our current working model is outlined in Scheme 7. The rhodium dihalide dimer **63** could enter two different cycles. In the productive catalytic cycle, the dimer will be cleaved by solvation or binding to the substrate to give **64**. Oxidative insertion followed by protonation of the rhodium alkoxide **65** by an ammonium salt will give the cationic complex **66**. Intermediate **66** will react with the nucleophile to give the ring opened product and regenerate the catalyst.

(15) The identification of these conditions came from the observation that reactions run for very prolonged periods in an oil bath at 100 °C were capricious and occasionally gave small amounts of product. After some experimentation, it was determined that in these cases, the THF solvent had actually evaporated, resulting in solventless reaction conditions.

(16) The absolute stereochemistry was established by X-ray crystallography for the *p*-bromobenzoate of **61**. Lautens, M.; Lough, A. J.; Fagnou, K. *Acta Crystallogr.* **2002**, *E58*, 542−543.

Alternatively, the rhodium dimer **63** may be cleaved by an amine nucleophile to give **67**. Because amine rhodium complexes are known to be stable, this interaction may be irreversible thereby sequestering the catalyst from the productive catalytic cycle. Rhodium amine complexes are also known to undergo α-oxidation to give rhodium hydride imine complexes **68**, which may also be a source of catalyst poisoning. In the presence of protic and halide additives, however, rhodium amine complex **67** could react to give the dihalorhodate complex **69**. This process would occur by nucleophilic displacement of the amine by a halide anion in an associative process common to square planar d^8 metal complexes. Dihalorhodate **69** could then reform the dimeric complex **63** by reaction with another rhodium monomer or go on to react directly with another substrate molecule with loss of one of the halide ligands. It is important to note that a new resting state for the catalyst may be established under these conditions in addition to, or in place of the dimeric complex, namely the dihalorhodate **69**.

Literature precedent exists for the proposed regeneration of an active catalyst from the putative poisoned complex **67**. It has been demonstrated that rhodium-amine complexes **70** will react with HCl to generate anionic dihalorhodium complexes **71** (eq 2).[9] In these transformations, both the halide and proton



70 **71** (eq 2)

act together to displace the amine from the metal center. The intermediacy of anionic transition metal complexes (analogous to the dihalorhodates in Scheme 7) has also been established in palladium-catalyzed cross coupling reactions by Amatore and Jutand.[17] and have been proposed in allylic substitution reactions.[18] Our proposal that the formation of rhodate complexes **69** prevents or reverses catalyst poisoning is similar in principle to the application of halide effects in diverting a reaction pathway by coordination site occupation.[3]

In this reaction, dimeric catalyst precursors **63** are implicated along the reaction pathway and may act as a catalyst reservoir or resting state. Because it is hypothesized that amine-induced cleavage of the dimeric complex **63** leads to catalyst poisoning, the stability and kinetic lability of **63** will play an important role in establishing a viable catalytic cycle. Experimental evidence has shown that the reactivity of halide bridged dimers changes dramatically with the nature of the halide,[3] being the least reactive toward cleavage when bridged by iodide ligands. For example, Buchwald found that cleavage of iodide bridged palladium dimers was slower than the corresponding chloride bridges species[19] and others have noted similar trends with other palladium complexes.[20,21]

Because of the speculative nature of the proposed reaction mechanism, a lack of precise knowledge of reaction intermediates and the complicated nature of halide-metal interactions, a detailed discussion of the influence of the halide ligand on the enantioselectivity is not possible at this point. One experimental observation deserves comment, however, since it is of mechanistic significance. In the working model,[22] we proposed that the enantiodiscriminating step is the oxidative insertion of the rhodium (I) catalyst into the bridgehead carbon−oxygen bond of the substrate. As this step occurs prior to nucleophilic attack, the nature of the nucleophile should not influence the enantioselectivity. Despite this prediction, reactions with nucleophiles other than alcohols and phenols give lower enantioselectivity with the same catalyst generated from $[Rh(COD)Cl]_2$ and PPF−P^tBu_2. To resolve this disparity between model and experimental outcome, it is reasonable to invoke nucleophile-catalyst interactions. If, in some cases, the nucleophile is bound to the catalyst during the enantiodiscriminating step, the resulting perturbation of the coordination sphere could negatively impact the chiral pocket created by the chiral ligand. By changing the chloride ligand to iodide or fluoride, this catalyst-nucleophile interaction may be prevented or minimized thereby maintaining the integrity of the highly enantioselective rhodium catalyst complex.

Conclusion

We have revealed the presence of several important halide effects in the rhodium-catalyzed asymmetric ring opening reaction of oxabicyclic alkenes and established a second generation rhodium catalyst that exhibits enhanced selectivity and reactivity. By employing halide additives in the presence of a protic additive, the poisoning effect of aliphatic amines is reversed allowing this class of nucleophile to be used in high yield and ee. Simply changing the halide ligand on the rhodium catalyst from chloride to iodide or fluoride leads to improvements in reactivity and enantioselectivity of reactions employing aromatic amine, malonate and carboxylate nucleophiles (Table 12). Finally, through the application of these halide effects and the identification of more forcing reaction conditions, less reactive oxabicyclic substrates can be used to generate synthetically useful enantioenriched cyclohexenol products. Application of these new conditions to the more reactive oxabenzonorbornadiene permits the reaction to be run with extremely low catalyst loadings (0.01 mol %) (Table 13).

Acknowledgment. We thank NSERC, the ORDCF, AstraZeneca and the University of Toronto for financial support of our research. We thank Solvias AG for generously providing us with the PPF-P^tBu_2 ligand used in these studies. K.F. thanks NSERC for a doctoral scholarship; Dingqiao Yang thanks the University of Toronto and China Scholarship Council for financial support.

Supporting Information Available: Experimental procedures for the preparation of starting materials and rhodium-catalyzed ring opening reactions, characterization data for all new compounds including ^1H NMR and ^{13}C NMR spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA034845X

(17) The coordination of halides to Pd(0) after the reduction of PdX_2L_2 complexes to generate anionic complexes was first proposed by Negishi. See: (a) Negishi, E.; Takahashi, T.; Akiyoshi, K. *J. Chem. Soc., Chem. Commun.* **1986**, 1338. For mechanistic work, see: (b) Amatore, C.; Azzabi, M.; Jutand, A. *J. Organomet. Chem.* **1989**, *363*, C41; (c) Amatore, C.; Azzabi, M.; Jutand, A. *J. Am. Chem. Soc.* **1991**, *113*, 8375; (d) Amatore, C.; Jutand, A.; Suarez, A. *J. Am. Chem. Soc.* **1993**, *115*, 9531; (e) Amatore, C.; Carre, E.; Jutand, A.; M'Barki, M. A.; Meyer, G. *Organometallics* **1995**, *14*, 5605. For recent reviews, see: (f) Amatore, C.; Jutand, A. *J. Organomet. Chem.* **1999**, *576*, 254; (g) Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, *33*, 314.

(18) Lloyd-Jones, G. C.; Stephen, S. C. *Chem. Commun.* **1998**, *21*, 2321.

(19) Widenhoefer, R. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 2755.

(20) (a) Widenhoefer, R. A.; Zhong, A. H.; Buchwald, S. L. *Organometallics* **1996**, *15*, 2745; (b) Bennett, M. A.; Longstaff, P. A. *J. Am. Chem. Soc.* **1969**, *91*, 6266.

(21) Chatt, J.; Venanzi, L. M. *J. Chem. Soc.* **1957**, 2445.

(22) Lautens, M.; Fagnou, K., submitted for publication.