Transition Metal-Catalyzed Enantioselective Ring-Opening Reactions of Oxabicyclic Alkenes

MARK LAUTENS,* KEITH FAGNOU, AND SHELDON HIEBERT

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

Received May 7, 2002

ABSTRACT

Over the past five years, several metal-catalyzed asymmetric ring-cleaving reactions have been developed that generate ring-opened products in high yield and enantiomeric excess. These reactions can be carried out with a range of nucleophiles including hydride, stabilized and nonstabilized carbanions, alcohols, amines, and carboxylates. To achieve these results, three different transition metals have been employed, namely nickel, palladium, and rhodium, leading not only to synthetically useful transformations but also to a greater understanding of the reaction manifolds possible with these metals. This Account covers the work by our group and by others toward the development of new metal-catalyzed asymmetric ring-opening reactions of oxabicyclic alkenes.

Introduction

There is a continuing need for the discovery of new reactions that control the relative and absolute stereochemistry in cyclic and acyclic compounds. One approach that has attracted attention is to utilize desymmetrization reactions of meso compounds since many stereocenters can be established rapidly and efficiently in one step.[1] Achieving an enantioselective symmetry-breaking reaction requires the presence two enantiotopic functional groups that can be efficiently differentiated, an area where chiral reagents or catalysts have been used with spectacular success.

Our attention was drawn to the synthetic potential associated with desymmetrizing the oxabicyclic core

Mark Lautens was born in Hamilton, Ontario, Canada, in 1959. He received his B.Sc.(Distinction) at the University of Guelph in 1981, and his Ph.D. from the University of Wisconsin–Madison in 1985 with Barry M. Trost. He was an NSERC Postdoctoral Fellow with David A. Evans at Harvard University from 1985 to 1987, prior to taking a position at the University of Toronto, where he now holds the AstraZeneca Chair in Organic Synthesis. In 2001, he was elected as a Fellow of the Royal Society of Canada.

Keith Fagnou was born in Saskatoon, Saskatchewan, Canada, in 1971. He received his bachelors degree in education with distinction (B.Ed.) from the University of Saskatchewan in 1995. In 2000, he received his M.Sc. under the supervision of Mark Lautens and completed a Ph.D. in 2002. He will join the faculty at the University of Ottawa in 2003.

Sheldon Hiebert was born in Steinbach, Manitoba, Canada, in 1974. He received his B.Sc. from the University of Manitoba in 1997, and in 1998 he joined the research group of Prof. Mark Lautens, conducting Ph.D. studies in the area of transition metal catalysis. He currently holds an NSERC postgraduate scholarship (M.Sc. and Ph.D.).

which can be readily prepared with a wide array of substitutents using [4 + 3] and [4 + 2] cycloadditions. By efficiently differentiating the two enantiotopic alkene carbon atoms or the two enantiotopic bridgehead alkoxy leaving groups, an enantioselective ring-opening desymmetrization process could be realized. We envisioned that a suitable enantioselective nucleophilic ring-opening reaction would not only reveal the latent stereochemistry of the oxabicyclic framework but also install new functionalities depending on the nature of the nucleophile. For example, S_N2' nucleophilic attack on [3.2.1] oxabicycles **1** would generate enantioenriched cycloheptenols **2** (Scheme 1). Importantly, the olefin functionality is retained after the ring-opening step, permitting oxidative cleavage to the linear compound **3**, possessing five contiguous stereocenters. When R is methyl, these fragments would constitute polypropionate subunits, which are important building blocks in many natural products. Similarly, [2.2.1] oxabicycles **4** would generate cyclohexenols **5**, which are useful in their own right and also as precursors to subunits such as **6**. This strategy could be applied to the readily available **7** to rapidly and efficiently generate functionalized dihydronaphthalenols **8**, which are important structural motifs in medicinal chemistry.
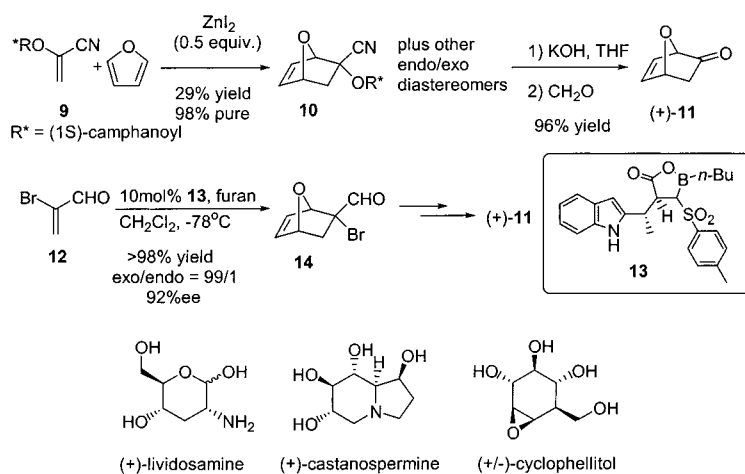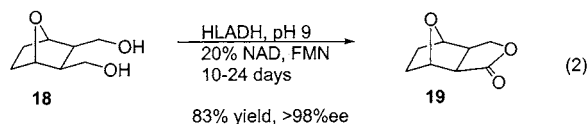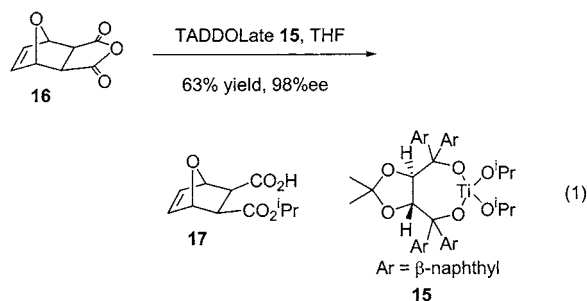
Scheme 1
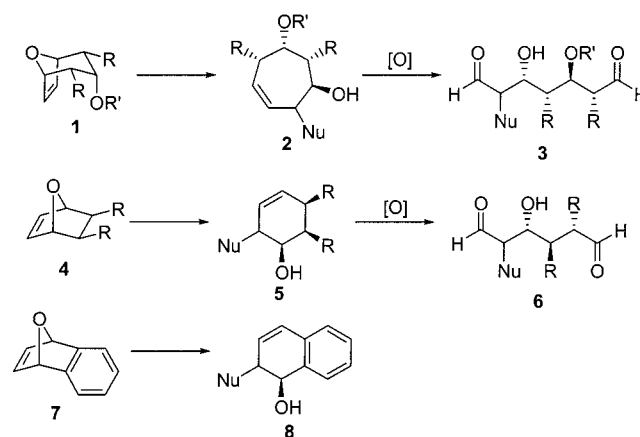
Background

The ring-opening chemistry of oxabicyclic compounds underwent significant growth in the late 1970s as a result of the development of new methods to assemble the [3.2.1] core and advances in Diels–Alder reactions with furans.[2] As a result, the oxabicyclic template has become increasingly common as a starting material in the preparation of both cyclic and acyclic compounds.[3] An examination of the literature reveals three main strategies that are employed to obtain enantiomerically pure products from oxabicyclic precursors. The first strategy establishes the absolute stereochemistry in the formation of the oxabicycle through the use of a diastereo- or enantioselective cycloaddition with furan. For example, Vogel found that the [4 + 2] reaction between furan and dienophile **9** can be used to generate **10** in isomerically pure

Scheme 2

form after purification.[4] Intermediate **10** can be easily converted into enantiomerically pure **11**, which has been coined a "naked sugar" due to its utility as a starting material in the preparation of rare D or L sugars, C-nucleosides, conduritols, and long-chain carbohydrates.[5] Thus, **11** served as the starting material in the synthesis of (+)-lividosamine, (+)-castanospermine, and cyclophellitol (Scheme 2). More recently, Corey has shown that the Diels–Alder reaction between furan and **12** can be catalyzed by Lewis acid **13** to give **14** in quantitative yield, 99:1 exo selectivity, and 92% ee.[6] Compound **14** can be converted into the "Vogel oxabicycle", thereby obviating the need for the use of a chiral auxiliary in its preparation.

The second strategy employs an asymmetric transformation on a meso oxabicycle that does not induce ring opening, but rather sets the absolute stereochemistry and allows for a subsequent ring-opening step. For example, chemical and enzymatic esterification processes have been used effectively toward this goal. Seebach has shown that the tartrate-derived TADDOLate **15** will react with the oxabicyclic anhydride **16** to generate the isopropyl hemiester **17** in 63% yield and 98% ee (eq 1).[7] Similar

alcohol dehydrogenase (HLADH) in the presence of nicotine adenine dinucleotide (NAD) and flavin mononucleotide (FMN) to give lactone **19** in 83% yield and >98% ee (eq 2).[9]

Another method to desymmetrize the oxabicyclic core without inducing ring opening is to employ chiral bases such as **20** in enantioselective deprotonation reactions.[10] For example, a key step in a synthesis of a fragment of lasonolide A was the enantioselective deprotonation of oxabicyclic **21** with (S)-**20**. Anion trapping generates **22** in 71% yield and 97% ee as a mixture of epimers (eq 3).[11] Similarly, (R)-**20** was used to enantioselectively deprotonate **23**, which was trapped as the silyl enol ether **24** in 97% yield and 75% ee. Enol ether **24** is a key intermediate in the preparation of two fragments of scytophycin C.[12]


$$(3)$$

$$(4)$$
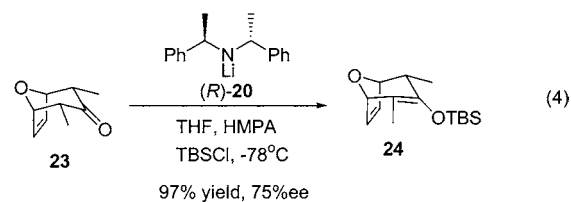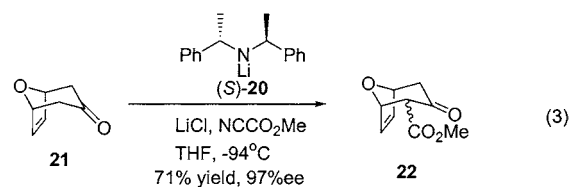
The third strategy, which until recently has received far less attention, employs a desymmetrization reaction as the ring-opening event. In this way, new stereocenters are established simultaneously as the meso symmetry is broken. Examples of high-yielding, highly enantioselective ring-opening desymmetrization reactions of oxabicyclic alkenes are fairly rare. The first report of such a transformation appeared in 1995 by Moinet and Fiaud,[13] where the treatment of **7** with a palladium(0) BINAP complex, phenyl triflate, and sodium formate in dimethylformamide (DMF) at 55 °C for 166 h led to the formation of two products (eq 5). The minor product **25**, arising from a

reactions have also been carried out using enzymes such as pig liver esterase (PLE).[8] Enzymes have also been used in oxidative and reductive processes. Jones showed that oxabicyclic diol **18** was selectively oxidized by horse liver

$$(1)$$

$$(2)$$

carbopalladation and subsequent β-oxygen elimination, was obtained in 13% yield and 96% ee. The major product **26**, arising from carbopalladation without ring-opening, was isolated in 71% yield and 64% ee. The authors noted that changing the aryl component from phenyl triflate to phenyl iodide reversed the product distribution, giving **25** preferentially. When phenyl iodide is used, however, the products are obtained in racemic form.


$$(5)$$

25
13% (96%ee)

26
71% (64%ee)
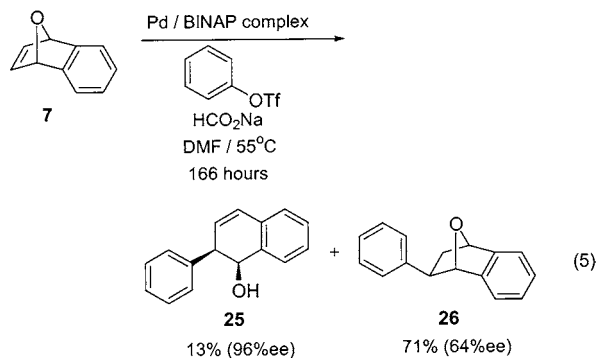
More recently, Waymouth has desribed the asymmetric ring opening of several oxabicyclic alkenes using group IV metal catalysts.[14] In the best case, chiral zirconium catalyst **27** was used to deliver an ethyl nucleophile (Et$_3$-Al) to oxabicycle **28**, generating ring-opened **29** in 64% yield and 96% ee (eq 6). The authors also report the application of these catalysts for hydridic ring openings and in the ring openings of other oxabicyclic substrates, but the yields and/or enantioselectivities are lower.

$$(6)$$

29

(nimind)$_2$ZrCl$_2$ **27**
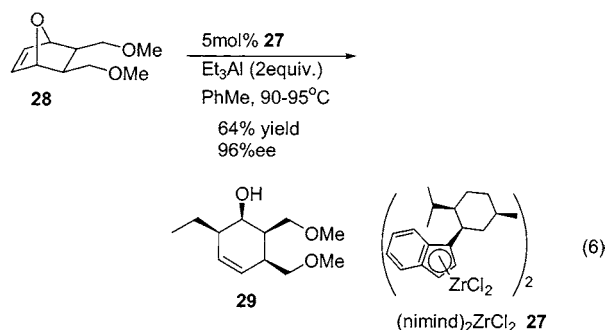
Nickel-Catalyzed Asymmetric Ring Opening with a Hydride Nucleophile

Early efforts in the development of a reductive ring-opening reaction in our group employed *t*-Bu$_2$CuCNLi$_2$ or *t*-BuLi/MgBr$_2$ as a source of hydride. While these reactions did produce the desired products, they were generally inefficient and unselective.[15] Much better results were obtained when DIBAL-H was used as a Lewis acidic source of hydride.[16] In fact, when **30** was treated with DIBAL-H in refluxing hexane, **31** was obtained in 83% yield (eq 7).[17] The addition of a catalytic amount of nickel led to a cleaner and more efficient reaction. In the presence of 3−10 mol % Ni(COD)$_2$, the reaction was rapid, even at −78 °C, and under these conditions **28** could be converted to **32** in >90% yield in both toluene and THF.[18]

The nickel-catalyzed reductive ring opening gave access to an asymmetric variant of this reaction by the addition

$$(7)$$

30   **31**

$$(8)$$

28   **32**
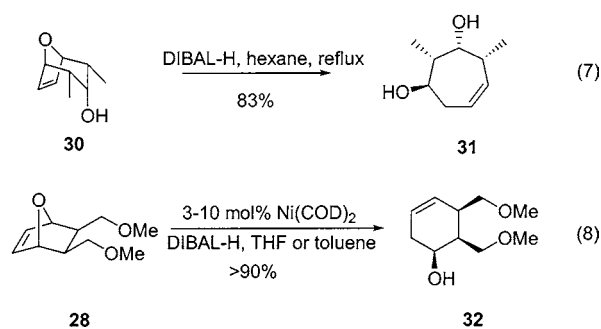
of chiral ligands. The use of Ni(COD)$_2$ with BINAP[19] (1.5 equiv relative to nickel) was found to give the best results for the ring opening.[20] Interestingly, the rate of addition of DIBAL-H to the reaction was found to be important for obtaining products in good enantiomeric excess. When DIBAL-H was added rapidly to **28** in the presence of the catalyst, **32** was obtained in 56% ee (Scheme 3). When the rate of addition was slowed to 7 min, **32** was obtained in 82% ee. The best results were obtained when DIBAL-H was added by syringe pump over 1 h, generating **32** in 97% yield and 97% ee. A variety of cycloheptenols could be obtained in good yield and enantiomeric excess using this protocol. Lower catalyst loadings could be used, but a delicate balance needs to be found between the amount of catalyst and the rate of addition of DIBAL-H. For example, when 4 mol % catalyst is used, the DIBAL-H must be added over 8 h to maintain 92% ee in the product.

Scheme 3

28   **32**

96% yield, 97%ee

81% yield, 84%ee

88% yield, 91%ee
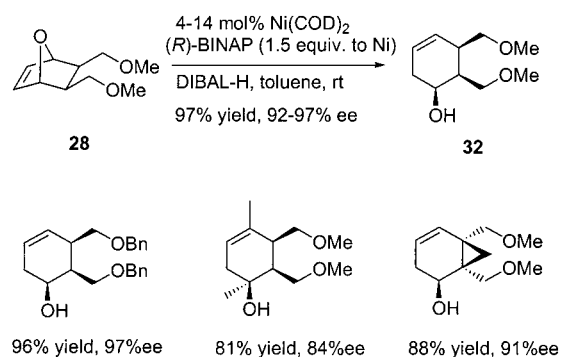
The methodology was extended to oxabenzonorbornadiene substrates.[21] Due to the increased sensitivity of these substrates toward Lewis acids such as DIBAL-H, a change in solvent from toluene to THF was necessary to reduce the amount of side products formed. A range of substrates reacted efficiently under these conditions with moderate sensitivity to steric effects but little sensitivity to electronic effects, with both electron-rich and electron-deficient substrates giving good results (Scheme 4).

We have applied the enantioselective reductive ring opening to the total synthesis of the clinically important antidepressant agent sertraline.[22] The product from ring opening of oxabenzonorbornadiene was converted in nine steps to sertraline in 33% overall yield (Scheme 5).

The [3.2.1] oxabicycles proved to be more difficult to open than either of the [2.2.1] systems. When the reaction was carried out at room temperature, a significant amount

Scheme 4

80% yield, 97% ee 94% yield, 97% ee

93% yield, 96% ee 73% yield, 88% ee

Scheme 5

sertraline
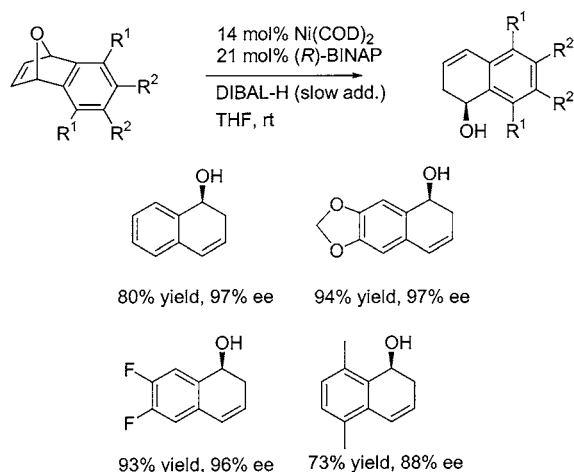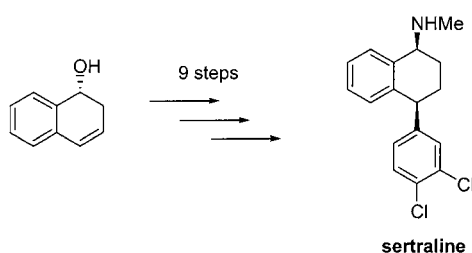
of product from reduction of the double bond without ring opening was obtained, and the enantiomeric excess of the trace amounts of ring-opened product was poor. The yield of the ring-opened products could be improved, however, if the reaction was heated to 60 °C.[23] In addition, increasing the temperature also had a beneficial effect on the enantioselectivity. For example, when **33** was reacted at room temperature, **34** was obtained in 20% yield and 56% ee (along with 70% of the reduced product). Heating **33** to 60 °C provided **34** in 83–95% yield and 97% ee (Scheme 6). In fact, a variety of substrates worked well using this protocol, giving yields typically >80% and enantiomeric excesses from 91 to 99%.

Scheme 6

87% yield, 95%ee 67% yield, 95%ee

89% yield, 99%ee 88% yield, 95%ee
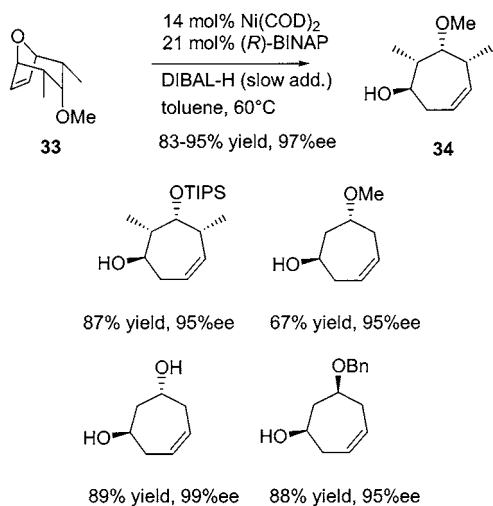
## Palladium-Catalyzed Asymmetric Ring Opening with Alkyl Nucleophiles

Alkyl nucleophiles were the first class of nucleophiles shown to induce ring opening of oxabicyclic systems. In 1971, Caple and co-workers reacted BuLi with oxabenzanorbornadiene and obtained a ring-opened product.[24] Using cuprates, we were able to achieve the first example of alkylative ring opening of a [3.2.1] oxabicycle, **35**, to give the product **36** in good yield (eq 9).[25] Plumet and co-workers found that alkyllithium reagents also worked when reactions were carried out in pentane.[26] We were able to use this finding in the development of the first example of an asymmetric ring opening of a [3.2.1] oxabicycle. When substoichiometric amounts of sparteine were added to the reaction of BuLi with **37**, the product **38** was obtained in 52% ee (eq 10).[27]
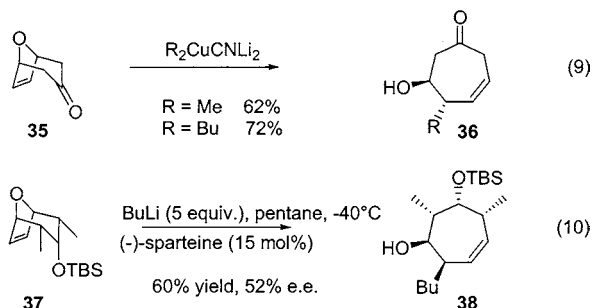
Further studies were carried out using organomagnesium and organolithium reagents with a variety of catalysts. Nickel and rhodium bearing chiral phosphine ligands gave mixtures of products with low or no enantioselectivity. Organozinc reagents showed more promise and have the advantage of being broadly tolerant of various functional groups. They also transmetalate well to other transition metals, making them ideal for use with a variety of catalyst systems.[28]

A survey of various catalyst systems revealed that palladium coupled with the use of the otherwise unreactive dialkylzinc was ideal. For example, using a catalyst prepared from $PdCl_2(CH_3CN)_2$ and bis(diphenylphosphino)ferrocene (dppf) in dichloromethane at room temperature, a variety of diorganozincs induce ring opening to give **39** as exclusively the syn diastereomer in good yield (Scheme 7).[29]

Scheme 7

R = Me, Et, *t*-Bu, vinyl, TMSCH$_2$
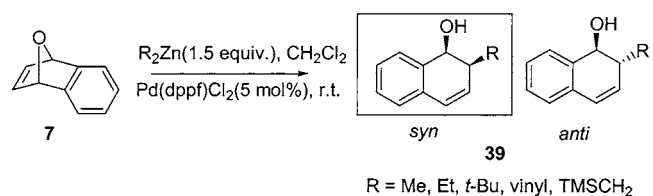
Very recently, Feringa published a report on a highly enantioselective addition of dialkylzinc reagents to oxabenzonorbornadienes catalyzed by a copper phosphoramidite catalyst.[30] The addition is complementary to the palladium-catalyzed reaction, giving *anti*-**39** arising from endo attack of the alkyl nucleophile.

An examination of chiral phosphines for the palladium-catalyzed reaction found that 2-(2-(diphenylphosphino)-phenyl)-4-*tert*-butyl-1,3-oxazoline (*t*-Bu-POX)[31] gave the best results for addition of dimethylzinc, and that 2,2′-bis(di-4-tolylphosphino)-1,1′-binaphthyl (Tol-BINAP) gave the best results for larger nucleophiles such as diethylzinc and bis(trimethylsilylmethyl)zinc. Using these systems, yields greater than 80% and enantioselectivities in excess of 90% could be achieved. Substrates with a variety of substituents on the aromatic ring, including both electron-rich and electron-deficient substrates, gave good results (Scheme 8).

Scheme 8
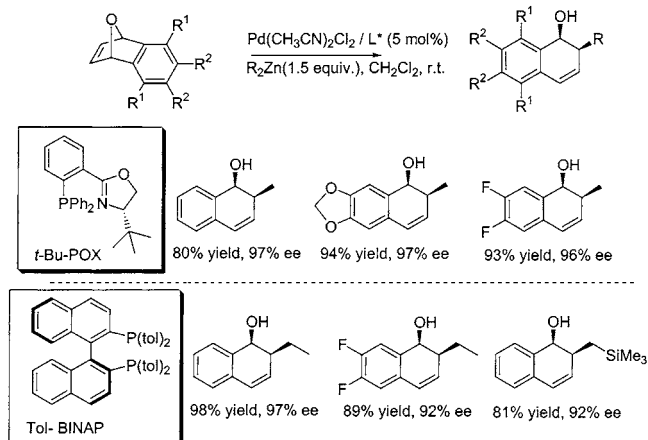
Applying the same conditions we developed for the oxabenzonorbonadienes gave no reaction with [2.2.1] and [3.2.1] oxabicyclic alkenes and azabenzonorbornadienes. However, changing the solvent to dichloroethane and increasing the temperature to reflux led to better reactivity.[32] To obtain high enantioselection, the chiral ligand also needed to be modified. By changing the backbone of the ligand from one based on a substituted benzene to one based on ferrocene, products could be obtained in typically >90% ee. The use of 2-(diphenylphosphino)-1-(4-*tert*-butyl-1,3-oxazolin-2-yl)ferrocene (*t*-Bu-DIPOF)[33] gave the best results for the ring opening of [2.2.1] oxabicyclic substrates. For example, substrate **40** gave product **41** in 87% yield and 91% ee (Scheme 9).
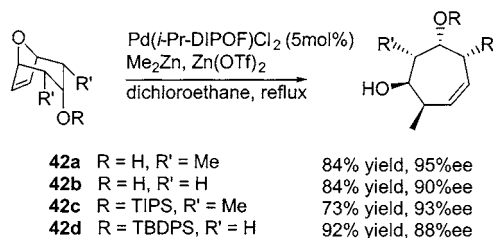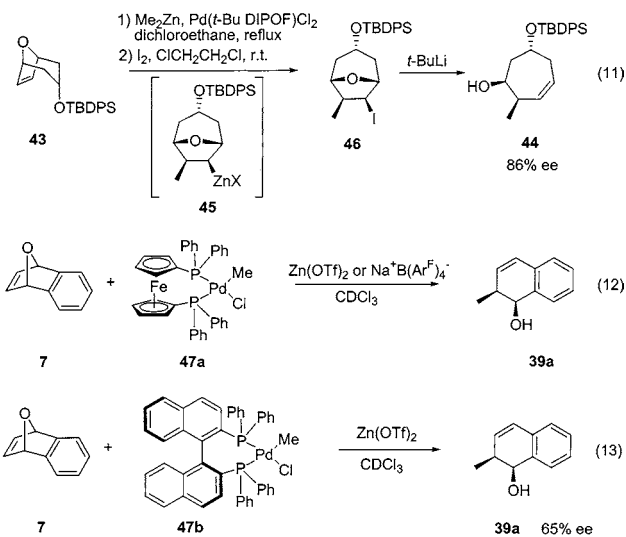
Scheme 9
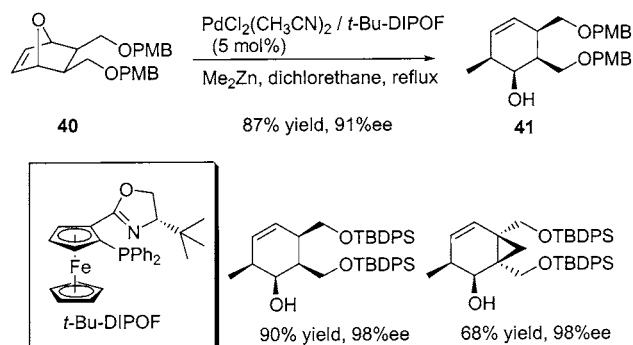
An important observation was made when studying these reactions with [3.2.1] oxabicycles. Using the same

conditions as described above, good results were obtained only with alcohols **42a,b**. Protection of the alcohol as a silyl ether rendered the reaction very slow and low yielding (typically less than 50%). To increase the reactivity of the catalyst or substrate, the effects of various additives were examined. $Zn(OTf)_2$ was highly effective in increasing the yields with protected substrates (Scheme 10).

Scheme 10

|		
42a	R = H, R' = Me	84% yield, 95%ee
42b	R = H, R' = H	84% yield, 90%ee
42c	R = TIPS, R' = Me	73% yield, 93%ee
42d	R = TBDPS, R' = H	92% yield, 88%ee

Two mechanistic possibilities were initially considered for these reactions. The first involves coordination of palladium to the alkene, followed by cleavage of the bridging carbon−oxygen bond to form a π-allylpalladium species. The second mechanism involves a carbopalladation of the alkene by a palladium alkyl species, followed by β-oxygen elimination to give the ring-opened product.[34] Two key experiments provided good evidence for the carbopalladation mechanism. The first experiment involved trapping of the carbometalated intermediates. When **43** was treated with Me_2Zn and a chiral catalyst in refluxing dichloroethane, a small amount of **44** was obtained in 81% ee. The major product, however, arose from methyl addition to the alkene without ring opening. When the proposed intermediate **45** was quenched with iodine, **46** was obtained (eq 11). Treatment of **46** with *t*-BuLi gave **44** in 86% ee. The similarity of the enantiomeric excesses of the products obtained by both routes provided good evidence that an enantioselective carbometalation was taking place.

The second set of key experiments involved the synthesis and reaction of methylpalladium species **47**. When **7** was treated with a stoichiometric amount of **47a**, no

Scheme 11
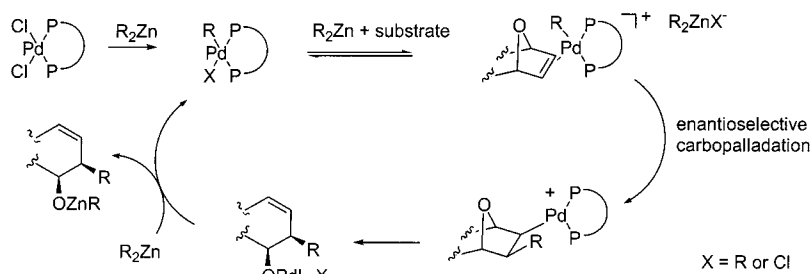
reaction took place in the absence of any additive. However, addition of $Zn(OTf)_2$, a Lewis acid, or $NaB(Ar^F)_4$, which is known to form cationic palladium by chloride abstraction,[35] rapidly produced **39a**. Furthermore, reaction of **7** with **47b** and $Zn(OTf)_2$ gave **39a** in 65% ee, which is very similar to the 67% ee obtained with $Pd[(S)\text{-BINAP}]\text{-}Cl_2$ (5 mol %) and Me_2Zn.
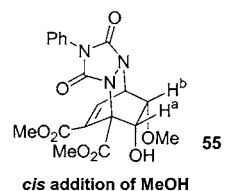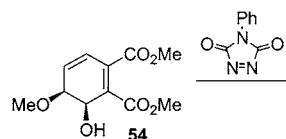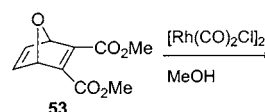
We propose the generation of a cationic alkylpalladium(II) species, which undergoes an enantioselective carbopalladation on the substrate alkene followed by β-oxygen elimination (Scheme 11). Transmetalation with dialkylzinc would then regenerate the catalyst and give the zinc alkoxide product.

We have used the palladium-catalyzed alkylative ring-opening together with the nickel-catalyzed reductive ring-opening methodologies to complete a total synthesis of the polyether antibiotic ionomycin.[36] Two of the four fragments in our synthesis were derived from oxabicycle **48** (Scheme 12). The $C_{17}-C_{23}$ fragment **49** can be synthesized from **50**, which comes from an asymmetric addition of a hydride to **48**. Likewise, fragment **51** can be obtained from **52**, which comes from an asymmetric addition of a methyl nucleophile to **48**.

Rhodium-Catalyzed Asymmetric Ring Opening with Heteroatom Nucleophiles

Our initial efforts in the development of an asymmetric ring opening with heteroatom nucleophiles were inspired

by a report by Hogeveen and Middelkoop, where treatment of **53** with catalytic $[Rh(CO)_2Cl]_2$ in methanol resulted in a diastereoselective ring opening to generate *syn*-**54** in good yield (eq 14).[37] The syn relative stereo-

(14)

cis addition of MeOH

(15)
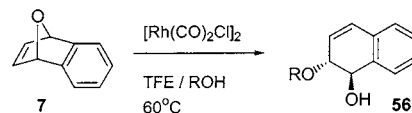
ROH = MeOH, EtOH, iPrOH, TMS Ethanol

chemistry was proven by Ashworth and Berchtold through the formation of cycloadduct **55** and analyzing the coupling constants of H^a and H^b in the ^1H NMR.[38] For our

Scheme 12

ionomycin

Scheme 13

initial studies, we chose **7** as our model substrate due to its high reactivity in our earlier studies.

Treatment of **7** under the Hogeveen and Middelkoop conditions failed to induce ring opening, but changing the solvent to a 1:1 mixture of methanol and trifluoroethanol (TFE) and heating the reaction to 60 °C gave **56** in >70% yield. The relative stereochemistry between the two oxygens was determined to be trans, arising from endo nucleophilic attack.

A study of the effects of added ligands revealed that [Rh(COD)Cl]$_2$ performed better than [Rh(CO)$_2$Cl]$_2$, since insoluble precipitates frequent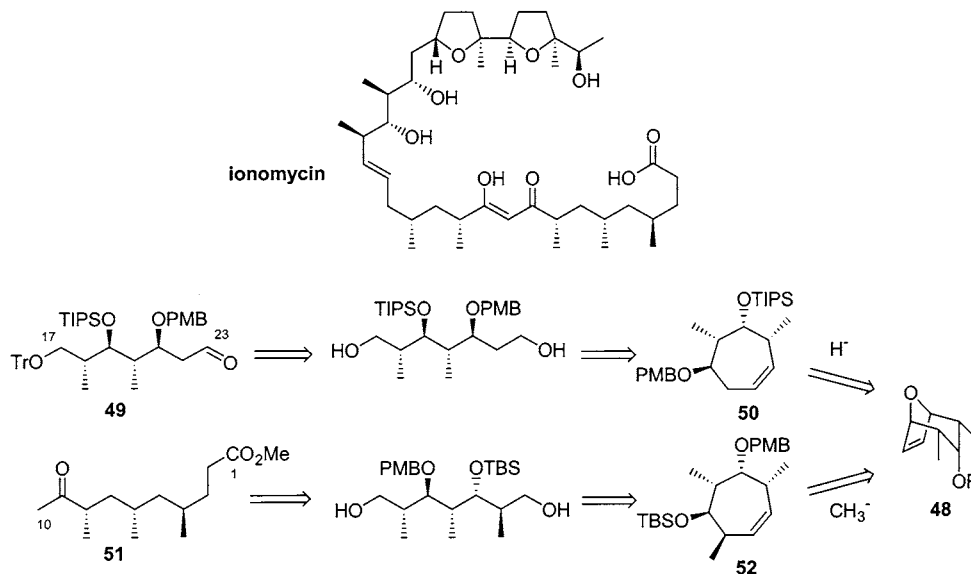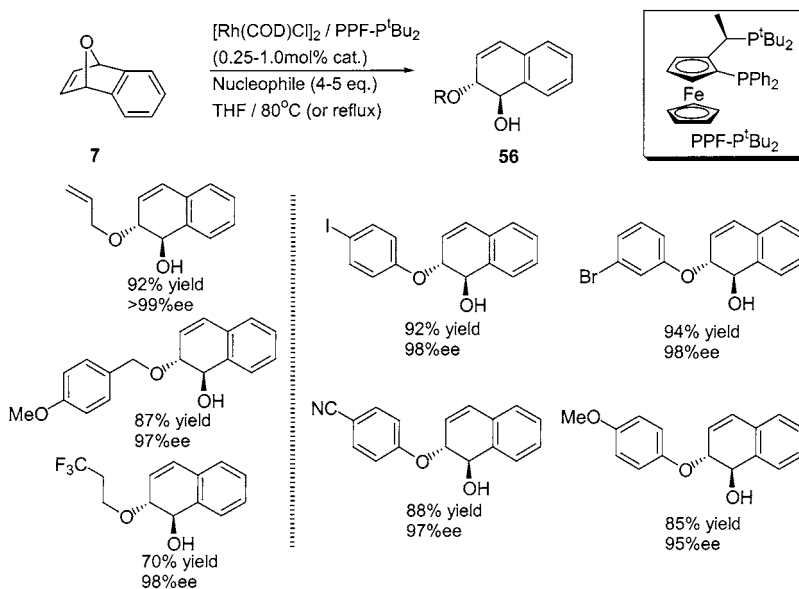ly occurred on mixing [Rh-(CO)$_2$Cl]$_2$ with many bidentate ligands. An initial screen of a variety of achiral ligands revealed that bis(diphenylphosphino)ferrocene (dppf) was a good ligand for this reaction. An examination of chiral ligands led to the finding that PPF−P^{t}Bu$_2$[39] was optimal, generating **56** in up to 96% ee when the reactions were run at 80 °C (Scheme 13). Using these new phosphine rhodium catalysts, THF could be used in place of TFE. Thus, treatment of **7** with as little as 0.25 mol % rhodium and chiral ligand in a 1:1 mixture of refluxing alcohol and THF provides a variety of dihydronaphthalene products in high yield and excellent enantioselectivity.[40] Phenols are also good nucleophiles for this transformation, adding in typically >80% yield and >95% ee.[41,42]

Our early efforts at extending this system to other nucleophile classes revealed several problems. For example, anilines were found to efficiently induce ring opening, but the enantioselectivity was poor. Furthermore, aliphatic amines and carboxylic acids failed to react. That the aliphatic amine was acting as a poison was demonstrated when the addition of an otherwise good nucleophile failed when pyrrolidine was present.[43]

The 2-aminotetralin core is an important structural motif in medicinal chemistry, and as a consequence, we were particularly interested in the use of aliphatic amines in these transformations. To overcome the catalyst poi-
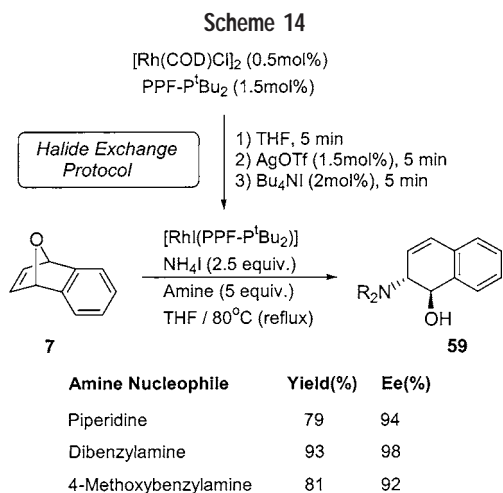
soning associated with basic amines, we investigated the application of various additives and found that the addition of triethylamine hydrochloride resulted in complete consumption of **7**, to give **58** in 85% yield (eq 16). Since Et$_3$N·HCl is both a protic and a halide source, we carried out studies to explore each characteristic and found that they are both important contributors to the reactivity. For example, use of either camphorsulfonic acid (CSA) or tetrabutylammonium chloride alone resulted in a slower reaction than with Et$_3$N·HCl or with CSA and Bu$_4$NCl combined.
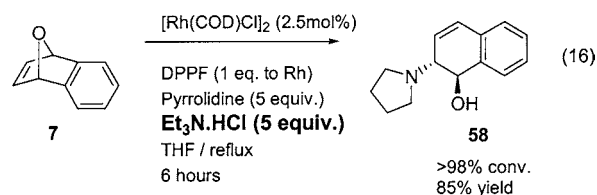
We found that the nature of the halide had a pronounced effect on both the reactivity and the enantioselectivity of these reactions. For example, addition of Bu$_4$-NF failed to induce reaction after 25 h. On the other hand, Bu$_4$NI resulted in complete conversion after 5 h. Bu$_4$NCl and Bu$_4$NBr were less effective. The trend of increasing reactivity (F ≪ Cl < Br < I) was found for several aliphatic amines. In a similar manner, the dependence of enantioselectivity on the halide additive using PPF−P^{t}Bu$_2$ as the chiral ligand was found to increase down the halide group, being maximal with iodide additive.[44]

While Bu$_4$NI acts as an effective additive for this reaction, the ammonium salt greatly impedes the isolation of pure product. To ameliorate this problem, other protic halide additives were studied, and it was found that ammonium iodide is superior in terms of both reactivity and enantioselectivity. In addition, the purification process is much simpler due to the ease of removing ammonium salts at the end of these reactions.[45]

To maximize the enantioselectivity, the chloride ligand originating from the rhodium source, [Rh(COD)Cl]$_2$, was removed and replaced with iodide in situ using a halide exchange protocol. Addition of a silver salt and subsequent addition of a slight excess of iodide effectively results in the formation of a new bisphosphine iodide complex, as evidenced by ^{31}P NMR. Use of this catalyst in the reaction with a variety of aliphatic amines and NH$_4$I as the additive results in high yields of **59**, with enantioselectivities typically greater than 90% ee (Scheme 14).

Scheme 14

Amine Nucleophile	Yield(%)	Ee(%)
Piperidine	79	94
Dibenzylamine	93	98
4-Methoxybenzylamine	81	92

The application of halide effects with aniline nucleophiles also led to improved reactivity and enantioselectivity. Greater than 90% ee was obtained for a wide range of aromatic amines as well as with phthalimide under the modified conditions (Scheme 15). In some cases, improve-
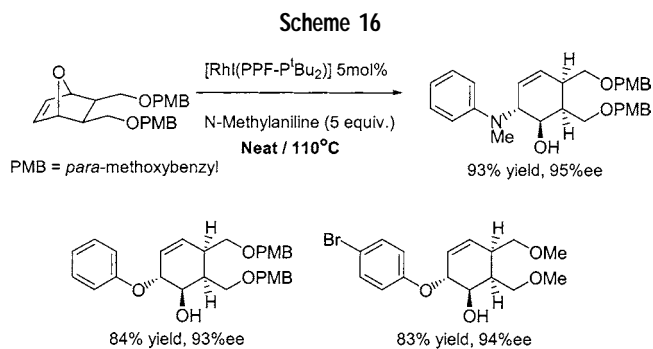
Scheme 15

Activated Nitrogen Nucleophiles

[Rh-I] cat: 97% yield, 92%ee
[Rh-Cl] cat: 92% yield, 74%ee

[Rh-I] cat: 90% yield, 98%ee
[Rh-Cl] cat: 55% yield, 45%ee

Malonate Nucleophiles

[Rh-I] cat: 97% yield, 98%ee
[Rh-Cl] cat: 56% yield, 51%ee

[Rh-I] cat: 95% yield, 97%ee

Ammonium Carboxylate Nucleophiles

[Rh-I]: 95% (92%ee)
[Rh-Cl]: 81% (61%ee)

[Rh-I]: 81% (90%ee)
[Rh-Cl]: 72% (31%ee)
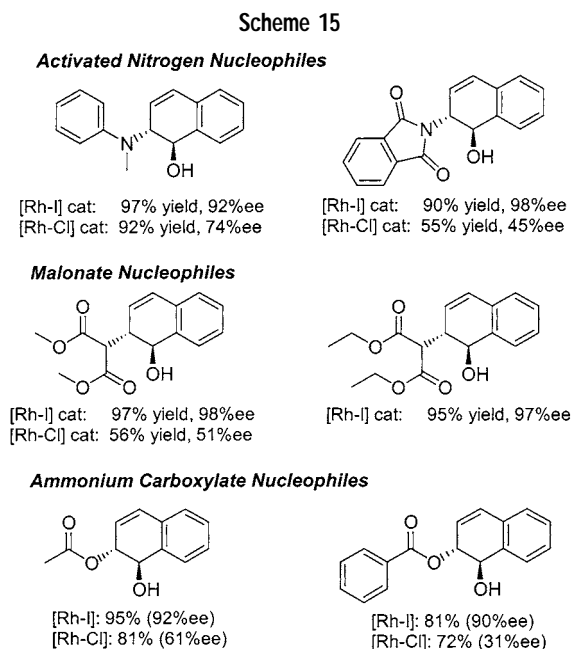
ments in enantioselectivity of up to 50% were obtained on changing the halide ligand from chloride to iodide.

The in situ-generated Rh—I catalyst can also be used with malonate nucleophiles to generate a new carbon—carbon bond. Importantly, the relative stereochemistry
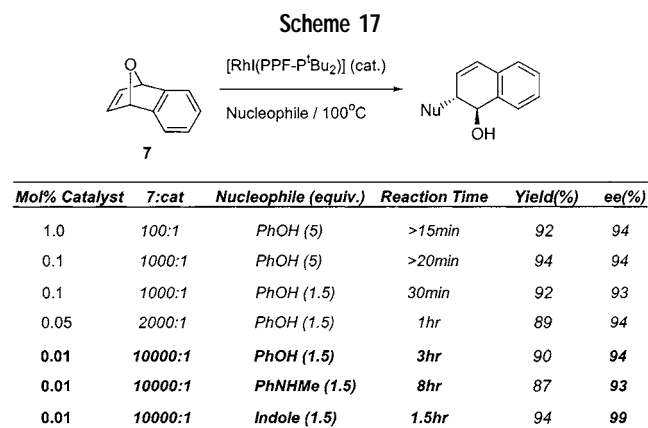
was again determined to be trans relative to the alcohol functionalaity and so is complementary to the selectivity observed in the palladium-catalyzed addition of dialkylzinc nucleophiles.

To overcome the lack of reactivity observed with carboxylic acid nucleophiles, we examined carboxylate salts but determined that a proton source was required. Ammonium carboxylates served as good nucleophiles, retaining the enhanced nucleophility of a carboxylate as well as providing a proton source. With ammonium acetate, for example, the desired product can be obtained in >80% yield. As with the aniline and malonate nucleophiles, the use of the Rh—I catalyst was required to obtain high enantioselectivity.[46]

Less reactive oxabicyclo[2.2.1]heptenes failed to react under any of the conditions described above, even after prolonged reaction times. To overcome this barrier, higher reaction temperatures and more concentrated reaction conditions were examined. At 110 °C, with 5 equiv of nucleophile *in the absence of solvent*, the Rh—I PPF—P^{t}Bu$_2$ catalyst promoted clean conversion to the desired products as single diastereomers in >90% ee (Scheme 16).

Scheme 16

Applying these new reaction conditions with **7** revealed that the reactions can be run with as little as 1.5 equiv of the nucleophile, in the absence of solvent and with only 0.01 mol % catalyst (Scheme 17). Furthermore, the reaction products are frequently crystalline solids and can be easily isolated in pure form by simple recrystalization of the crude product.

Scheme 17

Mol% Catalyst	7:cat	Nucleophile (equiv.)	Reaction Time	Yield(%)	ee(%)
1.0	100:1	PhOH (5)	>15min	92	94
0.1	1000:1	PhOH (5)	>20min	94	94
0.1	1000:1	PhOH (1.5)	30min	92	93
0.05	2000:1	PhOH (1.5)	1hr	89	94
0.01	**10000:1**	**PhOH (1.5)**	**3hr**	**90**	**94**
0.01	**10000:1**	**PhNHMe (1.5)**	**8hr**	**87**	**93**
0.01	**10000:1**	**Indole (1.5)**	**1.5hr**	**94**	**99**

Scheme 18

28

[Rh(COD)Cl]₂ / PPF-PᵗBu₂

—B(OH)₂ 1.2eq.

THF, aq. Cs₂CO₃
Room Temperature

60
91% yield
95%ee

71% yield
94%ee

87% yield
96%ee

91% yield
95%ee

95% yield
95%ee

85% yield
95%ee

95% yield
92%ee

Rhodium-Catalyzed Asymmetric Ring Opening with Aryl- and Alkenylboronic Acids

Tremendous success has been recently achieved in the rhodium-catalyzed asymmetric 1,4-conjugate addition of organoboronic acids to electron-deficient olefins. A variety of substrates, including α,β-unsaturates ketones, esters, and amides as well as alkenylphophonates and nitroalkenes, undergo addition in synthetically useful yields and enantioselectivities.[47] Inspired by this work, we investigated whether rhodium could be used to catalyze the addition of an organoboron reagent to one of the two enantiotopic olefinic carbon atoms of an oxabicyclic substrate.

Excellent results were obtained for the addition of arylboronic acids to the [2.2.1] oxabicyclic substrates in the presence of catalytic [Rh(COD)Cl]₂ and PPF−PᵗBu₂. The addition took place to give ring-opened products arising from exo attack of the aryl nucleophiles. For example, treatment of **28** with 2.5 mol % [Rh(COD)Cl]₂, 5 mol % PPF−PᵗBu₂, 1.2 equiv of 4-methylphenylboronic acid, and 0.5 equiv of Cs₂CO₃ (5.0 M in H₂O) in THF at room temperature provides **60** in 91% yield and 95% ee. A wide range of electronically diverse arylboronic acids and a vinylboronic acid react in an analogous fashion (Scheme 18).[48]

Application of these reaction conditions to the asymmetric ring opening of **7** leads to a complex mixture of products. Fortunately, better results are obtained by simply changing the arylboronic acid to the corresponding ethylene glycol ester. For example, treatment of **7** with 1.2 equiv of **61** provides **62** in 78% yield and 92% ee (eq
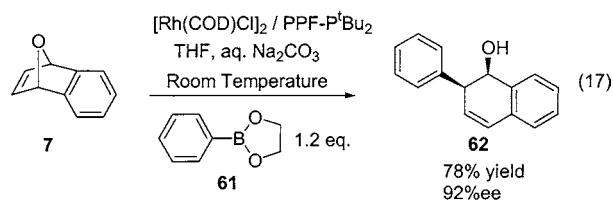
17). It is important to note that the bridgehead carbon−oxygen bond cleaved in these reactions is *opposite* to that of reactions with heteroatom nucleophiles despite the use of the same catalyst, i.e., [Rh(COD)Cl]₂/PPF−PᵗBu₂. This supports the notion that the mechanisms of the two reaction types are different.

A plausible catalytic cycle for this transformation involves reaction of the rhodium catalyst with the organoboronic acid to generate arylrhodium complex **63**, which then coordinates to the oxabicycle on the exo face and delivers the nucleophile to one of the enantiotopic carbons, to generate an organorhodium intermediate, **64**. Since no β-hydrogens are present, β-hydride elimination is not possible. As a result, β-oxygen elimination occurs to generate rhodium alkoxide **65**, which will liberate the product and regenerate the catalyst upon hydrolysis (Scheme 19).

Scheme 19

65

RhL₂X
(X = Cl or OH)

H₂O

P
Rh−Ar
P
63

O
Rh
Ar P P
64
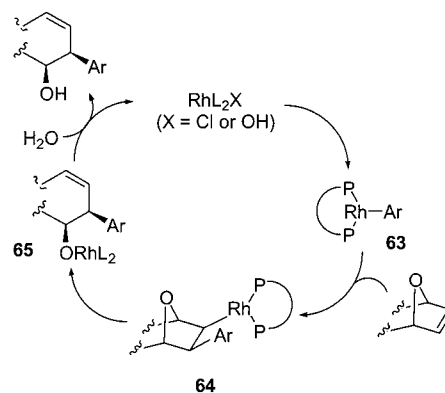
Conclusion

We have demonstrated that enantioselective metal-catalyzed asymmetric ring-opening reactions of meso oxabicyclic alkenes occur in high yield and typically >90% ee. These reactions can be carried out with a range of nucleophiles including hydride, alkylzincs, alcohols, amines,

7

[Rh(COD)Cl]₂ / PPF-PᵗBu₂
THF, aq. Na₂CO₃
Room Temperature

61 1.2 eq.

62
78% yield
92%ee

(17)

carboxylates, malonates, and aryl-/alkenylboron compounds. The methodologies have found use in the total syntheses of several biologically interesting molecules, such as sertraline and ionomycin. Mechanistic studies have contributed to a greater understanding of the catalytic behavior of the three different transition metals involved.

Our current studies are focused on expanding the scope the reactions, utilizing the ring-opened products as scaffolds in medicinal chemistry, and developing a better understanding of the reaction mechanisms and source of the diastereo- and enantioselectivity.

References

(1) For reviews on this subject, see: (a) Ward, R. S. Non-Enzymatic Asymmetric Transformations Involving Symmetrical Bifunctional Compounds. *Chem. Soc. Rev.* **1990**, *19*, 1−19. (b) Magnuson, S. R. Two Directional Synthesis and its Use in Natural Product Synthesis. *Tetrahedron* **1995**, *51*, 2167−2213. (c) Willis, M. C. Enantioselective Desymmetrization. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1765−1784.

(2) For reviews on [4 + 3] cycloadditions, see: (a) Hosomi, A.; Tominaga, Y. [4 + 3] Cycloadditions. In *Comprehensive Organic Synthesis*; Trost, B., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 5, Chapter 5.1, p 593. (b) Hoffmann, H. M. R. The Cycloaddition of Allyl Cations to 1,3-Dienes: General Method for the Synthesis of Seven-Membered Carbocycles. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1−88. (c) Noyori, R.; Hayakawa, Y. Reductive Dehalogenation of Polyhalo Ketones with Low-Valent Metals and Related Reducing Agents. *Org. React.* **1983**, *29*, 163−344.

(3) For reviews, see: (a) Lautens, M. Ring Opening of Oxabicyclic Compounds as a Route to Cyclic and Acyclic Compounds with Multiple Stereocenters. *Synlett* **1993**, 177−185. (b) Woo, S.; Keay, B. A. S$_N$2′ and "S$_N$2′ Like" Ring Openings of Oxa-n-Cyclo Systems. *Synthesis* **1996**, 669−686. (c) Chiu, P.; Lautens, M. Using Ring-Opening Strategies of Oxabicyclic Compounds as a Strategy in Organic Synthesis. *Top. Curr. Chem.* **1997**, *190*, 1−85.

(4) Vieira, E.; Vogel, P. The Preparation of Optically Pure 7-Oxabicyclo-[2.2.1]hept-5-ene Derivatives. The CD Spectrum of (+)-(1*R*)-7-Oxabicyclo[2.2.1]hept-5-en-2-one. *Helv. Chim. Acta* **1983**, *66*, 1865−1871. Vogel has also reported a method for the resolution of these oxabicyclic intermediates: Black, K. A.; Vogel, P. Optical Resolution of 7-Oxabicyclo[2.2.1]hept-2-ene Derivatives. Diastereoselectivity in the Formation of Cyanohydrine-Brucine Complexes. *Helv. Chim. Acta* **1984**, *67*, 1612−1615.

(5) For example, see: (a) Vogel, P. Synthesis of Rare Carbohydrates and Biomolecules from Furan. *Bull. Soc. Chim. Belg.* **1990**, *99*, 395−439. (b) Vogel, P.; Fattori, D.; Gasparini, F.; Le Drian, C. Optically Pure 7-Oxabicyclo[2.2.1]Hept-5-en-2-yl Derivatives (Naked Sugars) as New Chirons. *Synlett* **1990**, 173−185.

(6) Corey, E. J.; Loh, T.-P. Catalytic Enantioselective Diels−Alder Addition to Furan Provides a Direct Route to Many Chiral Natural Products. *Tetrahedron Lett.* **1993**, *34*, 3979−3982.

(7) Seebach, D.; Jaeschke, G.; Wang, Y. M. Highly Enantioselective Opening of Cyclic *meso*-Anhydrides to Isopropoyl Hemiesters with Diisopropoxytitanium TADDOLates. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2395−2396.

(8) Bloch, R.; Guibe-Jampel, E.; Girard, C. Stereoselective Pig Liver Esterase-Catalyzed Hydrolysis of Rigid Bicyclic *meso*-Diesters: Preparation of Optically Pure 4,7-Epoxytetra- and Hexa-Hydrophthalides. *Tetrahedron Lett.* **1985**, *26*, 4087−4090.

(9) Jones, J. B.; Francis, C. J. Enzymes in Organic Synthesis. 32. Stereospecific horse liver alcohol dehydrogenase-catalyzed oxidations of *exo*- and *endo*-oxabicyclic *meso* diols. *Can. J. Chem.* **1984**, *62*, 2578−2582.

(10) Bunn, B. J.; Cox, P. J.; Simpkins, N. S. Enantioselective Deprotonation of 8-Oxabicyclo[3.2.1]ocatan-3-one Systems Using Homochiral Lithium Amide Bases. *Tetrahedron* **1993**, *49*, 207−218.

(11) Nowakowski, M.; Hoffmann, H. M. R. Asymmetric Synthesis of the C(18)−C(24) Unit of Lasonolide A. *Tetrahedron Lett.* **1997**, *38*, 1001−1004.

(12) Hunt, K. W.; Grieco, P. A. Oxabicyclo[3.2.1]octenes in Organic Synthesis: Direct Ring Opening of Oxabicyclo[3.2.1] Ring Systems with Diisobutylaluminum Hydride and a Silyl Ketene Acetal−Synthesis of the Chiral C(19)−C(26) and C(27)−C(32) Fragments of Scytophycin C. *Org. Lett.* **2002**, *4*, 245−248.

(13) Moinet, C.; Fiaud, J.-C. Palladium-catalysed Asymmetric Hydrophenylation of 1,4-Dihydro-1,4-Epoxynaphthalene. *Tetrahedron Lett.* **1995**, *36*, 2051−2052.

(14) Millward, D. B.; Sammis, G.; Waymouth, R. M. Ring-Opening Reactions of Oxabicyclic Alkene Compounds: Enantioselective Hydride and Ethyl Additions Catalyzed by Group 4 Metals. *J. Org. Chem.* **2000**, *65*, 3902−3909.

(15) Lautens, M.; Chiu, P. The Reductive Ring-Opening of Oxabicyclic Compounds. *Tetrahedron Lett.* **1991**, *32*, 4827−4830.

(16) Lenox, R. S.; Katzenellenbogen, J. A. A Stereoselective Method for the Synthesis of Both Olefinic Isomers from a Single Precursor. The Conjugate Reduction of α,β-Unsaturated Epoxides. *J. Am. Chem. Soc.* **1973**, *95*, 957−959.

(17) Lautens, M.; Chiu, P.; Colucci, J. T. Reductive Ring-Opening of Oxabicyclic Compounds with Diisobutylaluminum Hydride. Application to the Synthesis of the C$_{17}$−C$_{23}$ Subunit of Ionomycin. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 281−283

(18) (a) Lautens, M.; Chiu, P.; Ma, S.; Rovis, T. Nickel-Catalyzed Hydroalumination of Oxabicyclic Alkenes. Ligand Effects on the Regio- and Enantioselectivity. *J. Am. Chem. Soc.* **1995**, *117*, 532−533. (b) Lautens, M.; Ma, S.; Chiu, P. Synthesis of Cyclohexenols and Cycloheptenols via the Regioselective Reductive Ring Opening of Oxabicyclic Compounds. *J. Am. Chem. Soc.* **1997**, *119*, 6478−6487.

(19) Takaya, H.; Akutagawa, S.; Noyori, R. (*R*)-(+)- and (*S*)-(−)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl (BINAP). *Org. Synth. 67*, 20−32.

(20) Lautens, M.; Rovis, T. Scope of the Nickel Catalyzed Asymmetric Reductive Ring Opening Reaction. Synthesis of Enantiomerically Enriched Cyclohexenols. *Tetrahedron* **1998**, *54*, 1107−1116.

(21) Lautens, M.; Rovis, T. General Strategy toward the Tetrahydrophthalene Skeleton. An Expedient Total Synthesis of Sertraline. *J. Org. Chem.* **1997**, *62*, 5246−5247.

(22) Lautens, M.; Rovis, T.; Smith, N. D.; Ostrovsky, D. Metal Catalyzed Hydrometalations and Their Applications in Synthesis. *Pure Appl. Chem.* **1998**, *70*, 1059−1064.

(23) Lautens, M.; Rovis, T. A New Route to the Enantioselective Synthesis of Cycloheptenols. Temperature Effects in the Asymmetric Reductive Ring Opening of [3.2.1] Oxabicycloalkenes. *J. Am. Chem. Soc.* **1997**, *119*, 11090−11091.

(24) Caple, R.; Chen, G. M.-S.; Nelson, J. D. The Addition of Butyllithiums to Benzonorbornadiene and 1,4-Dihydronaphthalene-1,4-*endo*-Oxide. *J. Org. Chem.* **1971**, *36*, 2874−2876.

(25) Lautens, M.; Di Felice, C.; Huboux, A. Ring Opening Reactions of an Oxabicyclic Compound with Cuprates. *Tetrahedron Lett.* **1989**, *30*, 6817−6820.

(26) Arjona, O.; de la Pradilla, R. F.; Garcia, E.; Martin-Domenech, A.; Plumet, J. Regio- and Stereospecific Synthesis of Substituted Cyclohexendiols from 7-Oxabicyclo[2.2.1]hept-5-en-2-ols and Organolithium Reagents. *Tetrahedron Lett.* **1989**, *30*, 6437−6440.

(27) Lautens, M.; Gajda, C.; Chiu, P. Studies in the Asymmetric Ring Opening of an Oxabicyclic Compound. Catalytic Asymmetric Induction using (−)-Sparteine. *J. Chem. Soc., Chem. Commun.* **1993**, 1193−1194.

(28) For a review on organozinc chemistry, see: Knochel, P.; Almena Perea, J. J.; Jones, P. Organozinc Mediated Reactions. *Tetrahedron* **1998**, *54*, 8275−8319.

(29) Lautens, M.; Renaud, J.-L.; Hiebert, S. Palladium-Catalyzed Enantioselective Alkylative Ring Opening. *J. Am. Chem. Soc.* **2000**, *122*, 1804−1805.

(30) Bertozzi, F.; Pineschi, M.; Macchia, F.; Arnold, L. A.; Minnaard, A. J.; Feringa, B. L. Copper Phosphoramidite Catalyzed Enantioselective Ring-Opening of Oxabicyclic Alkenes: Remarkable Reversal of Stereocontrol. *Org. Lett.* **2002**, *4*, 2703−2705.

(31) For the preparation and use of these POX ligands, see: (a) Williams, J. M. J. The Ups and Downs of Allylpalladium Complexes in Catalysis. *Synlett* **1996**, 705−710. (b) Sprinz, J.; Helmchen, G. Phosphinoaryl- and Phosphinoalkyloxazolines as New Chiral Ligands for Enantioselective Catalysis: Very High Enantioselectivity in Palladium Catalyzed Allylic Substitutions. *Tetrahedron Lett.* **1993**, *34*, 1769−1772. (c) von Matt, P.; Pfalz, A. Chiral

Phosphinoaryldihydrooxazoles as Ligands in Asymmetric Catalysis: Pd-Catalyzed Allylic Substitution. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 566−568. (d) Pfaltz, A. From Corrin Chemistry to Asymmetric Catalysis—A Personal Account. *Synlett* **1999**, 835−842.

(32) Lautens, M.; Hiebert, S.; Renaud, J.-L. Enantioselective Ring Opening of Aza and Oxabicyclic Alkenes with Dimethylzinc. *Org. Lett.* **2000**, *2*, 1971−1973.

(33) For the synthesis of the DIPOF ligands, see: (a) Richards, C. J.; Locke, A. J. Recent Advances in the Generation of Non-racemic Ferrocene Derivatives and Their Application to Asymmetric Synthesis. *Tetrahedron: Asymmetry* **1998**, *9*, 2377−2407. (b) Nishibayashi, Y.; Uemura, S. Asymmetric Synthesis and Highly Diastereoselective *ortho*-Lithiation of Oxazolinylferrocenes. *Synlett* **1995**, 79−81. (c) Sammakia, T.; Latham, H. A.; Schaad, D. R. Highly Diastereoselective OrthoLithiations of Chiral Oxazoline-Substituted Ferrocenes. *J. Org. Chem.* **1995**, *62*, 10−11.

(34) Lautens, M.; Hiebert, S.; Renaud, J.-L. Mechanistic Studies of the Palladium-Catalyzed Ring Opening of Oxabicyclic Alkenes with Dialkylzinc. *J. Am. Chem. Soc.* **2001**, *123*, 6834−6839.

(35) Brookhart, M.; Wagner, M. Polymers with Main-Chain Chirality. Synthesis of Highly Isotactic, Optically Active Poly(4-*tert*-butyl-styrene-*alt*-CO) Using Pd(II) Catalysts Based on C_2-Symmetric Bisoxazoline Ligands. *J. Am. Chem. Soc.* **1994**, *116*, 3641−3642.

(36) Lautens, M.; Colucci, J. T.; Hiebert, S.; Smith, N. D.; Bouchain, G. Total Synthesis of Ionomycin Using Ring-Opening Strategies. *Org. Lett.* **2002**, *4*, 1879−1882.

(37) Hogeveen, H.; Middelkoop, T. B. Rhodium and Proton Catalyzed Reactions of 7-Oxanorbornadienes with Methanol—Synthetic Route to Methoxycyclohexadienols. *Tetrahedron Lett.* **1973**, 3671−3674.

(38) Ashworth, R. W.; Berchtold, G. A. Stereochemistry of [Rh(CO)$_2$Cl]$_2$ Catalyzed Reaction of Oxabicyclo[2.2.1]Hepta-2,5-dienes with Methanol. *Tetrahedron Lett.* **1977**, 339−342. We also verified the stereochemistry by X-ray crystal analysis.

(39) For synthesis and use of PPF−P^{t}Bu$_2$, see: (a) Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A. A Novel Easily Accessible Chiral Ferrocenyldiphosphine for Highly Enantio-selective Hydrogenation, Allylic Alkylation, and Hydroboration Reactions. *J. Am. Chem. Soc.* **1994**, *116*, 4062−4066. (b) Hayashi, T.; Mise, T.; Fukushima, M.; Kagotani, M.; Nagashima, N.; Hamada, Y.; Matsumoto, A.; Kawakami, S.; Konishi, M.; Yamamoto, K.; Kumada, M. Asymmetric Synthesis Catalyzed by Chiral Ferrocenylphosphine-Transition Metal Complexes. I. Preparation of Chiral Ferrocenylphosphines. *Chem. Bull. Soc. Jpn.* **1980**, *53*, 1138−1151.

(40) Lautens, M.; Fagnou, K.; Rovis, T. Rhodium-Catalyzed Asymmetric Ring Opening of Oxabenzonorbornadiene: A New Enantioselective Carbon−Oxygen and Carbon−Nitrogen Bond Forming Process. *J. Am. Chem. Soc.* **2000**, *122*, 5650−5651.

(41) Lautens, M.; Fagnou, K.; Taylor, M. Rhodium-Catalyzed Asymmetric Ring Opening of Oxabicyclic Alkenes with Phenols. *Org. Lett.* **2000**, *2*, 1677−1679.

(42) Lautens, M.; Fagnou, K.; Taylor, M.; Rovis, T. Rhodium-Catalyzed Asymmetric Ring Opening of Oxabicyclic Alkenes with Oxygen Nucleophiles. *J. Organomet. Chem.* **2001**, *624*, 259.

(43) We also observed this trend in our rhodium-catalyzed ring-opening reactions of vinyl epoxides: Fagnou, K.; Lautens, M. Rhodium-Catalyzed Ring Opening of Vinyl Epoxides. *Org. Lett.* **2000**, *2*, 2319−2321.

(44) Lautens, M.; Fagnou, K. Effect of Halide Ligands and Protic Additives on the Reactivity and Enantioselectivity of Rhodium-Catalyzed Asymmetric Ring Opening Reactions. *J. Am. Chem. Soc.* **2001**, *123*, 7170−7171.

(45) Lautens, M.; Fagnou, K. Unpublished results.

(46) Lautens, M.; Fagnou, K. Rhodium-Catalyzed Asymmetric Ring Opening Reactions with Carboxylate Nucleophiles. *Tetrahedron* **2001**, *57*, 5067−5072.

(47) For a recent review, see: Hayashi, T. Rhodium-Catalyzed Asymmetric 1,4-Addition of Organoboronic Acids and Their Derivatives to Electron Deficient Alkenes. *Synlett* **2001**, 879−887.

(48) Lautens, M.; Dockendorff, C.; Fagnou, K.; Malicki, A. Rhodium-Catalyzed Asymmetric Ring Opening of Oxabicyclic Alkenes with Organoboronic Acids. *Org. Lett.* **2002**, *4*, 1311−1314.

AR010112A