Epoxide Hydrogenolysis Catalyzed by Ruthenium PNN and PNP Pincer Complexes

Fallyn L. Kirlin, Olivia J. Borden, Marianna C. Head, Sophie. E. Kelly, and Anthony R. Chianese*

Department of Chemistry, Colgate University, 13 Oak Drive, Hamilton, New York 13346, United States

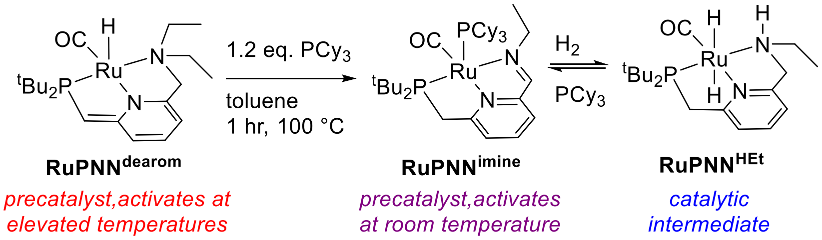
Abstract

The metal-catalyzed hydrogenolysis of epoxides to give alcohols has advanced rapidly in the past several years, with some catalysts selectively giving linear (anti-Markovnikov) products and other catalysts providing branched (Markovnikov) products. The currently known branched-selective catalyst systems require catalyst loadings of 1% or higher and typically require a strong base additive. We report herein that PNN- and PNP-ruthenium-pincer complexes containing N-H functional groups are highly active for branched-selective hydrogenolysis of epoxides. When isopropyl alcohol is used as the solvent, excellent yields of the branched alcohol products are obtained without strongly basic additives, using catalyst loadings as low as 0.03%. Epoxides with a directly attached secondary carbon give very high (>99:1) selectivity for the branched products. Aryl-substituted epoxides give branched:linear ratios ranging from 2.7 to 19.0. For aryl epoxides, a PNP-Ru catalyst showed a greater preference for the branched product than a PNN-Ru catalyst, and substrates with electron-rich aryl substituents showed a lower preference for the branched product.

Introduction

The selective hydrogenation and dehydrogenation of polar substrates has advanced steadily since the pioneering work of the Noyori[1] and Shvo[2] groups, demonstrating cooperation between a Lewis-acidic ruthenium center and a nearby basic site on the ligand. Although excellent reactivity was obtained for ketones and similarly electrophilic substrates, catalysts of this class did not promote the hydrogenation of less reactive carbonyl-containing substrates such as esters and amides. A major advance was achieved when Milstein and co-workers showed that the complex **RuPNN$^{\mathbf{dearom}}$** was active for the hydrogenation of esters[3] and the reverse reaction, the acceptorless dehydrogenative coupling of primary alcohols.[4] The same PNN-pincer complex was later demonstrated to catalyze the hydrogenation of carbonate esters[5] and carbon dioxide,[6] as well as an array of dehydrogenative coupling reactions.[7] Although the original catalyst **RuPNN$^{\mathbf{dearom}}$** lacked an acidic heteroatom site on the ligand (such as N-H or O-H), subsequent catalyst development by many research groups has converged on the beneficial effect of an N-H group in close proximity to the metal center for hydrogenation of polar substrates.[8] Computational studies have shown that this Noyori-type catalyst structure enables the metal-ligand-cooperative (MLC) heterolytic splitting of H_2 and its transfer to polar substrates with thermally accessible free-energy barriers.[8e, 8f, 8l, 8n, 8p, 9] Although these studies have typically located minimum-energy pathways involving deprotonation and reprotonation of the N-H group, Dub and Ikariya[9a] and Dub and Gordon[10] have recently shown that the N-H group can function as a hydrogen-bond donor without being deprotonated in some systems.

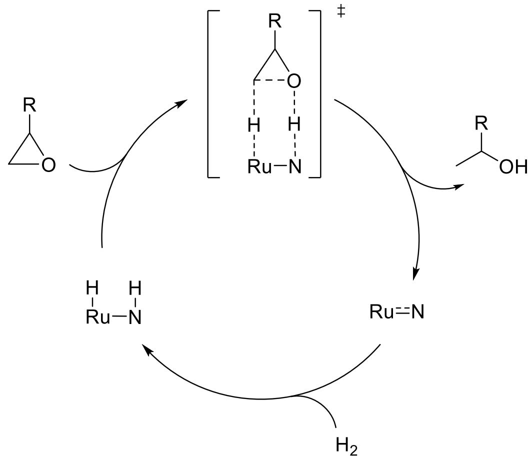
The originally proposed mechanism for ester hydrogenation catalyzed by **RuPNN$^{\mathbf{dearom}}$** involved heterolytic activation of hydrogen by the Lewis-acidic ruthenium center and a basic carbon site on the pincer ligand to give a dihydride intermediate, followed by transfer of these hydrogen atoms to the ester reactant and aldehyde intermediate.[3] Three computational studies supported the on-cycle intermediacy of this dihydride, albeit with variation in the overall pathway.[11] However, we recently demonstrated experimentally that **RuPNN**$^{\mathbf{dearom}}$ is not an active catalyst for ester hydrogenation in its own right.[12] On heating, **RuPNN**$^{\mathbf{dearom}}$ undergoes a ligand dehydroalkylation reaction to release ethane. In the presence of PCy_3, the five-coordinate ruthenium(0) species **RuPNN**$^{\mathbf{imine}}$ is formed, which converts in the presence of hydrogen to the Noyori-type complex **RuPNN**$^{\mathbf{HEt}}$ (Scheme 1). Although ruthenium(II) precursors are most commonly used in reactions of this type, several examples of ruthenium(0) precursors have been shown to be active catalysts for related hydrogenations and dehydrogenations.[13] **RuPNN**$^{\mathbf{imine}}$ is the most active one-component precatalyst for ester hydrogenation reported to date, giving thousands of turnovers for a range of substates at room temperature with no added base. In a comprehensive experimental and computational study, we demonstrated that **RuPNN**$^{\mathbf{HEt}}$ is a key on-cycle catalytic intermediate, and that the nascent N-H group is intimately involved in both hydrogen activation and the transfer of hydrogen to the substrate.[14]



Scheme 1. Conversion of Milstein's Catalyst **RuPNN**$^{\mathbf{dearom}}$ to the form active for ester hydrogenation.

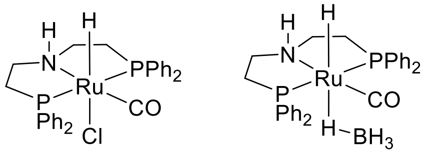
After demonstrating that **RuPNN**$^{\mathbf{imine}}$ is a highly active precatalyst for ester hydrogenation, we decided to examine its applicability for the reaction of hydrogen with related polar compounds. In this context, the hydrogenolysis of epoxides[15] has been explored less comprehensively. Several catalyst systems have been reported that give the linear (anti-Markovnikov) alcohol as the major product. Norton and coworkers reported a Ti-Co dual catalytic system that selectively gave linear products through a proposed radical mechanism.[16] Scheuermann and coworkers reported the linear-selective hydrogenolysis of epoxides using a combination of triflic acid and iridium-PCP-pincer complexes.[17] In this system, acid catalyzes epoxide hydrolysis to give the 1,2-diol, and iridium nanoparticles formed in situ catalyze diol hydrogenolysis, giving the terminal alcohol as the sole product.[18] Beller and coworkers described an Fe/tetraphos/trifluoroacetic acid system[19] and a Co/triphos/$Zn(OTf)_2$ system[20] that selectively gave anti-Markovnikov products. In this work, acid-catalyzed isomerization of the epoxide to the aldehyde was shown to precede transition-metal-catalyzed hydrogenation to give the terminal alcohol. Werner and coworkers reported an erbium-cobalt dual system using ammonia-borane as the hydrogen source, which also gives anti-Markovnikov alcohol products.[21] In this system, $Er(OTf)_3$ catalyzes initial isomerization to the aldehyde, and a cobalt-pincer complex catalyzes transfer hydrogenolysis to give the product alcohol. The cobalt systems reported by the Beller[20] and Werner[21] groups are also effective for the anti-Markovnikov-selective hydrogenolysis of 1-aryl-2-alkyl-substituted epoxides and even trisubstituted epoxides.

In contrast to the linear-selective examples described above, some catalysts have been reported to give the branched (Markovnikov) alcohols as major products. Heterogeneous Pd/C catalysts typically give a mixture of branched and linear products in the hydrogenolysis of aliphatic epoxides,[15a] although some modified catalysts have shown good selectivity for the branched isomer.[22] Ikariya and coworkers reported that a Ru/$Ph_2PCH_2CH_2NH_2$/KOH system gave excellent branched selectivity for alkyl-substituted epoxides, while the hydrogenolysis of styrene oxide gave an 89:11 ratio of branched to linear product.[23] The authors proposed a Noyori-type MLC mechanism for epoxide ring-opening, where Ru-H and N-H moieties participate in the cooperative transfer of hydrogen to the epoxide substrate (Scheme 2). Recently, Thiyagarajan and Gunanathan reported that the commercially available PNP-pincer complex **Ru-MACHO** in combination with KO^tBu catalyzes the selective hydrogenolysis of monosubstituted epoxides to the branched products, giving excellent selectivity for alkyl-substituted epoxides and very good selectivity for aryl epoxides.[24] Again, a Noyori-type MLC mechanism was proposed. Very recently, Jiao, de Vries, Pignataro, and coworkers reported an iron-cyclopentadienone catalyst system that selectively gives the branched or linear product depending on the choice of Lewis-acid cocatalyst. A computational study lent support to a Noyori-type MLC mechanism for both branched and linear products, as well as a competing pathway for linear products involving Lewis-acid-catalyzed isomerization to the aldehyde followed by iron-catalyzed aldehyde hydrogenation.[25]



Scheme 2. Proposed Noyori-type mechanism for cooperative epoxide hydrogenolysis.

The reports by Ikariya[23] and Gunanathan[24] show that Noyori-type bifunctional ruthenium catalysts have promise in the selective hydrogenolysis of epoxides, preferentially promoting hydride attack on the less sterically hindered carbon. However, there is room for improvement in catalyst performance. Both reported systems employ catalytic amounts of a strong base – either KOH or KO^tBu – and both require at least 1 mol % of ruthenium catalyst to achieve good yields. Both systems are also limited to monosubstituted epoxides. Although the system reported by Jiao, de Vries, Pignataro, and coworkers[25] employs the abundant metal iron, it requires a high 5% catalyst loading and operates at 150 °C. Because **RuPNN^{imine}** is a highly active precatalyst for ester hydrogenolysis and is known to form the Noyori-type catalyst **RuPNN^{HEt}** in the presence of hydrogen, we decided to examine its activity for the hydrogenolysis of epoxides. Additionally, we were curious whether **Ru-MACHO-BH**, a commercially available borohydride derivative of **Ru-MACHO**, might catalyze epoxide hydrogenolysis without the need for added base (Figure 1).[26] We found that both **RuPNN^{imine}** and **Ru-MACHO-BH** are highly active one-component catalysts for branched-selective epoxide hydrogenolysis, and that the use of isopropyl alcohol as solvent enables high yields to be obtained at catalyst loadings as low as 0.03%.



Ru-MACHO
activated by strong base

Ru-MACHO-BH
does not require base for activation

Figure 1. Hydridochloride and hydridoborohydride forms of the Ru-MACHO catalyst.

Catalyst Comparison and Optimization

At the outset of our study, we sought to address three challenges in epoxide hydrogenolysis: 1) to achieve high yields for a range of substrates with low catalyst loading; 2) to eliminate the need to add strong base as a cocatalyst; and 3) to determine whether product racemization can be avoided, potentially enabling the synthesis of chiral secondary alcohols from enantiomerically pure epoxides. Although the previous reports on branched-selective epoxide hydrogenolysis did not describe studies of the enantiospecificity of the reaction,[23-25] Ikariya stated in a 2007 review that product racemization prevented the development of an enantiospecific version of this reaction.[27] We chose to compare **RuPNN^{imine}**, discovered in our laboratory, with **Ru-MACHO-BH**.[26] We began by studying the hydrogenolysis of (*R)*-styrene oxide, monitoring the overall yield, branched:linear (b:l) ratio, and enantiomeric excess (ee) of the branched alcohol product over time. In all cases where an enantioenriched product was formed, the major enantiomer was (*S*)-1-phenylethanol, resulting from retention of configuration at the secondary carbon.

We first compared reactions catalyzed by 1 mol % **RuPNN^{imine}** or **Ru-MACHO-BH** at 60 °C in toluene, with or without 10 mol % NaO^{t}Bu added (Figure 2). Under these conditions, both ruthenium complexes showed a benefit from added base in terms of the rate of reaction. Reactions catalyzed by **Ru-MACHO-BH** were sluggish, reaching less than 20% yield after 3 hours even with added base. Interestingly, the b:l ratio increased substantially over time when no base was present, but was nearly constant over time when NaO^{t}Bu was added to the reaction. Early on, reactions catalyzed by **Ru-MACHO-BH** showed a low but measurable ee, which quickly fell to zero after about two hours of reaction, indicating that the branched alcohol product is racemized under the reaction conditions. Reactions catalyzed by **RuPNN^{imine}** showed somewhat faster conversion to product, especially with added base, where an overall yield of 58% was obtained after 3.5 hours. The addition of base also gave a higher selectivity for the branched product. Completely racemic product was observed at all time points for both experiments with **RuPNN^{imine}**, indicating that product racemization is much faster than epoxide hydrogenolysis under these conditions.

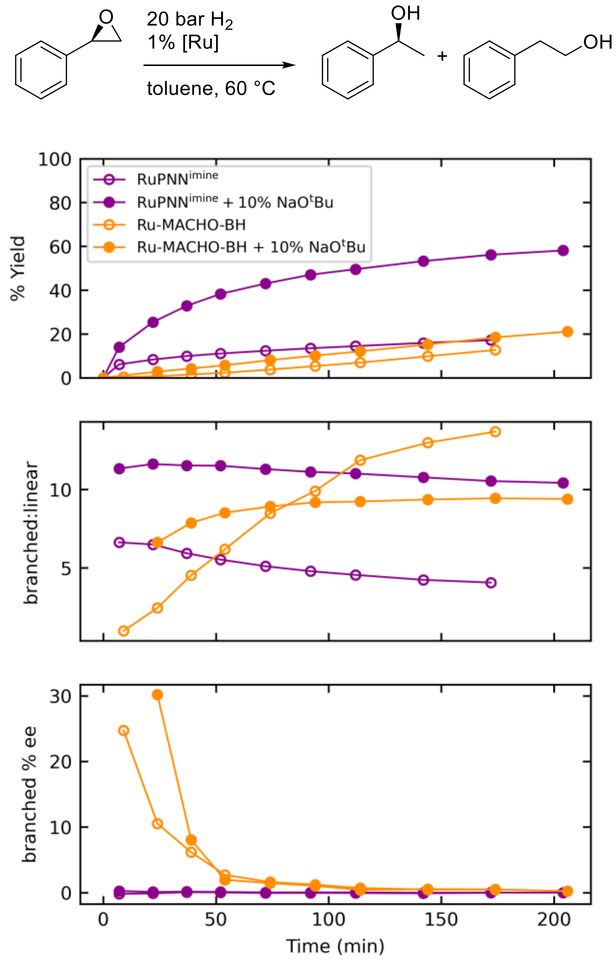


Figure 2. Time-course study of (*R*)-styrene oxide hydrogenolysis in toluene.

Next, we sought to assess the effect of polar solvents on the hydrogenolysis of (*R*)-styrene oxide. Although Thiyagarajan and Gunanathan found that a Ru-MACHO/KO^{t}Bu system was effective in toluene,[24] Ikariya and coworkers reported that isopropyl alcohol was most effective in their Ru/$Ph_2PCH_2CH_2NH_2$/KOH system.[23] We previously found that isopropyl alcohol was a uniquely effective solvent for ester hydrogenation catalyzed by **RuPNN^{imine}**.[12] Figure 3 shows the time course of the hydrogenolysis of (*R*)-styrene oxide catalyzed by 1 mol % **RuPNN^{imine}** at 60 °C in five polar solvents, with no added base. Very slow conversion was observed in methanol, ethanol, and 1,1,1-trifluoroethanol (TFE). Interestingly, although only 4% yield was obtained after 3.5 hours in TFE, almost exclusively linear product was formed: the b:l ratio was 1:103 at the end of the reaction. We speculate that this may arise from a combination of catalyst transformation to a less active form and acid-catalyzed isomerization of the epoxide to phenylacetaldehyde in this solvent. Only 23% yield was reached in THF, although the b:l ratio was very high throughout the reaction, consistently between 17:1 and 19:1. Isopropyl alcohol gave by far the fastest reaction, with the overall yield reaching 90% after three hours, albeit with lower b:l selectivity of 6:1. Complete product racemization was observed for all solvents except ethanol, although only 7% yield was obtained in ethanol.

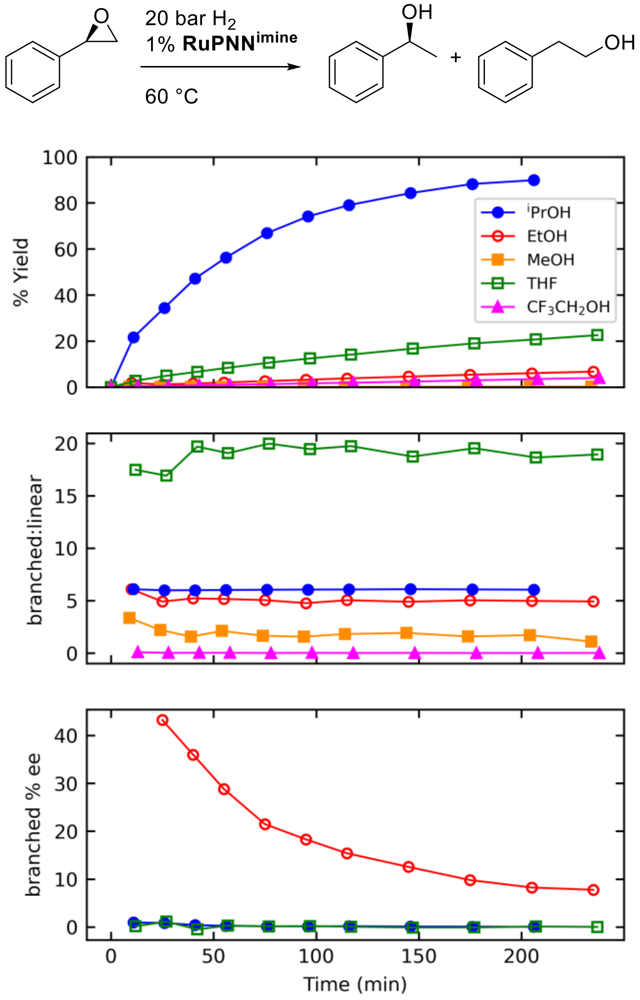


Figure 3. Solvent comparison for (*R*)-styrene oxide hydrogenolysis catalyzed by **RuPNN^{imine}**.

We then conducted the same solvent screen using **Ru-MACHO-BH** as the catalyst, again with no added base (Figure 4). Sluggish conversion was observed in TFE, and again the linear product was predominant: after 3.5 hours, a 5% overall yield was obtained with a b:l ratio of 1:30. The reaction was slow in THF (2% yield) and proceeded at a moderate pace in methanol (26% yield). The imprecision in the measurement of the the b:l over time ratio in THF arises from the very small amount of product formed in this reaction. Encouragingly, a nearly complete reaction was observed in both ethanol (94% yield) and isopropyl alcohol (95% yield). Of the reactions that gave significant conversion to products, the highest b:l ratio of 10:1 was seen in isopropyl alcohol. Product racemization was slower with **Ru-MACHO-BH** than with **RuPNN^{imine}**, although all solvents other than methanol gave nearly racemic product by the end of the reaction.

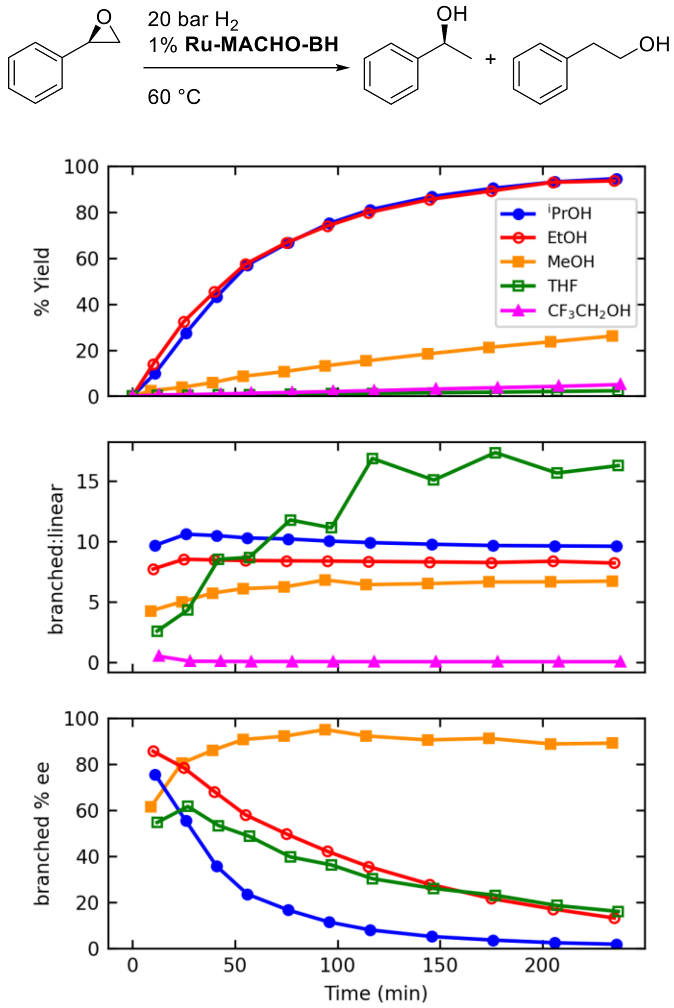


Figure 4. Solvent comparison for (*R*)-styrene oxide hydrogenolysis catalyzed by **Ru-MACHO-BH**.

Although the choice of catalyst and solvent significantly affect the rate of reaction, the b:l ratio, and the product ee, no set of conditions was found that optimizes all three together. For example, very high selectivity for the branched isomer was seen for **RuPNN$^{\text{imine}}$** in THF, but a slow overall reaction was observed and the product was completely racemized. On the other hand, minimal product racemization was observed for **Ru-MACHO-BH** in methanol, but again these conditions gave a slow reaction. Because isopropyl alcohol gave high reaction rates and good b:l ratios with both ruthenium catalysts, we chose this solvent for further study. Plots of the natural logarithm of epoxide concentration vs. time were nearly linear for both experiments conducted in isopropyl alcohol (Figure 5), indicating that the reaction likely displays first-order kinetics with respect to epoxide concentration with both catalysts.

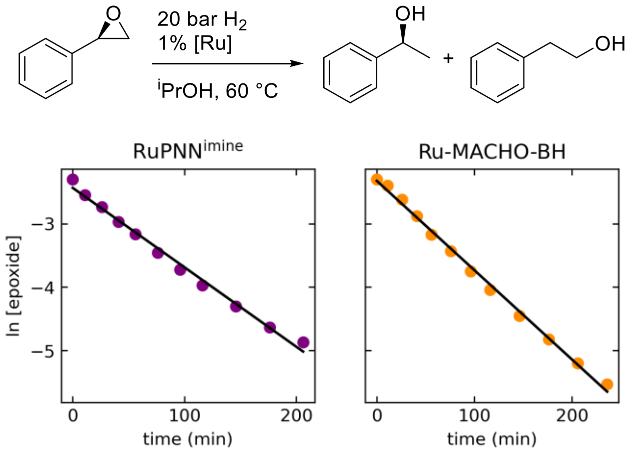
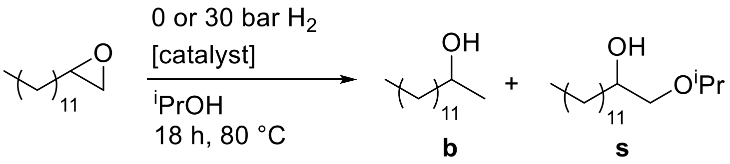


Figure 5. Plots of ln[epoxide] vs. time for the hydrogenolysis of (*R*)-styrene oxide catalyzed by **RuPNN$^{\mathbf{imine}}$** and **Ru-MACHO-BH**. For **RuPNN$^{\mathbf{imine}}$**, the regression equation is ln[epoxide] = –0.0125t – 2.44, with R^2 = 0.992. For **Ru-MACHO-BH**, the regression equation is ln[epoxide] = –0.0141t – 2.33, with R^2 = 0.996.

Phosphine-Catalyzed Solvolysis Side Reaction

Having identified isopropyl alcohol as an optimal solvent for base-free epoxide hydrogenolysis catalyzed by **RuPNN$^{\mathbf{imine}}$** and **Ru-MACHO-BH**, we turned our attention to attempting to achieve high yields with low catalyst loadings. The solvent screening experiments described above were conducted with an initial substrate concentration of 0.1 M, but the apparent first-order kinetics in epoxide concentration hinted that faster rates could be achieved at higher concentrations. We therefore conducted a series of experiments at a range of catalyst loadings, with 0.5 M 1-tetradecene oxide (racemic) in isopropyl alcohol, at a slightly elevated temperature of 80 °C and an increased hydrogen pressure of 30 bar. The results are collected in Table 1. Under these conditions, **Ru-MACHO-BH** (Entries 1-4) gave nearly full conversion and an excellent yield of the branched alcohol product **b** with a catalyst loading as low as 0.03 mol %. Surprisingly, the yield of alcohol **b** was lower than the conversion with **RuPNN$^{\mathbf{imine}}$** as catalyst, and we identified the solvolysis side product **s**, formed in 5% yield (Entry 5). To investigate the origin of this solvolysis reaction, we performed a series of control experiments. Repeating the reaction with **RuPNN$^{\mathbf{imine}}$** as catalyst but without hydrogen gave no hydrogenolysis product **b**, but the solvolysis product **s** was still formed (Entry 6). Interestingly, when 0.5% **RuPNN$^{\mathbf{HEt}}$** was used as catalyst instead, no reaction occurred in the absence of hydrogen and the epoxide substrate was completely recovered (Entry 7). When 0.5% PCy_3 was used as catalyst, again without hydrogen, **s** was formed as the only observed product in 92% yield (Entry 8). Based on these observations, we concluded that the solvolysis reaction is catalyzed not by the ruthenium complexes in solution, but by the PCy_3 released when **RuPNN$^{\mathbf{imine}}$** is used as catalyst. Interestingly, the control experiments shown in Entries 6 and 7 also demonstrate that transfer hydrogenation from isopropyl alcohol does not occur in the absence of hydrogen. To avoid this side reaction, we used **RuPNN$^{\mathbf{HEt}}$** directly as the hydrogenolysis catalyst (Entries 9 and 10). Gratifyingly, the branched alcohol **b** was formed with excellent yield and selectivity, albeit at a higher loading than with **Ru-MACHO-BH** (compare Entries 3 and 9).

Table 1. Solvolysis side reaction catalyzed by PCy_3.

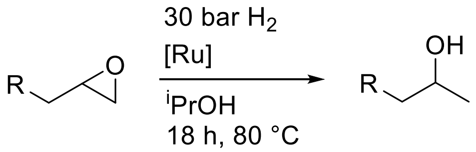


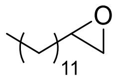
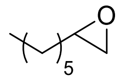
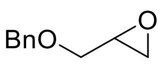
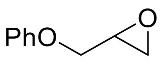
Entry	catalyst	mol %	P_{H2} (bar)	% Conv.	% Yield **b**	% Yield **s**
1	RuMACHO-BH	0.25	30	100	99	0
2	RuMACHO-BH	0.13	30	100	99	0
3	RuMACHO-BH	0.063	30	99	98	0
4	RuMACHO-BH	0.031	30	95	94	0
5	$\text{RuPNN}^{\text{imine}}$	0.13	30	100	95	5
6	$\text{RuPNN}^{\text{imine}}$	0.50	0	13	0	10
7	$\text{RuPNN}^{\text{HEt}}$	0.50	0	0	0	0
8	PCy_3	0.50	0	100	0	92
9	$\text{RuPNN}^{\text{HEt}}$	0.13	30	99	98	0
10	$\text{RuPNN}^{\text{HEt}}$	0.063	30	77	75	0

Substrate Scope

After identifying conditions for selective epoxide hydrogenolysis with low catalyst loading, we decided to examine the reactivity of a series of epoxide substrates to compare the activity and selectivity of **Ru-MACHO-BH** vs. **RuPNN^{HEt}**. For each substrate, we tested a range of catalyst loadings to determine the lowest loading that gave nearly full conversion under the reaction conditions. Table 2 shows the results for monosubstituted epoxides with a directly attached secondary sp^3-hybridized carbon. For both aliphatic epoxides (Entries 1-4) and glycidyl ethers (Entries 5-8), regioselectivity for the branched alcohol was essentially complete, with less than 1% of the linear product detected. For each substrate, **Ru-MACHO-BH** gave full conversion with a lower loading than **RuPNN^{HEt}**. As the two aliphatic epoxides tested (Entries 1-4) would be expected to react very similarly, the higher loadings required for full conversion of 1-octene oxide (Entries 3,4) most likely result from catalyst deactivation by a minor impurity in this substrate. Substrates in this class also showed high regioselectivity for the branched product in prior work by Ikariya[23] and Gunanathan,[24] although a higher catalyst loading of 1% or 5%, respectively, was employed in those reports and the addition of catalytic amounts of a strong base was necessary. For the hydrogenolysis of phenyl glycidyl ether catalyzed by **Ru-MACHO-BH** (Entry 7), we isolated the alcohol product in 97% yield at gram scale.

Table 2. Hydrogenolysis of monosubstituted epoxides with an attached secondary carbon.[a]

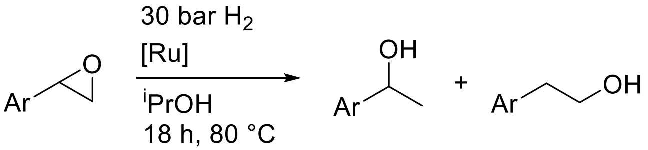


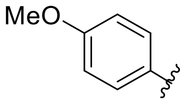
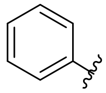
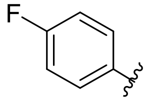
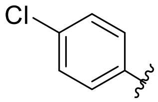
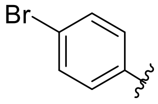
Epoxide	Entry	Ru	mol %	% Conv.	% Yield	b:l
	1	RuMACHO-BH	0.063	99	98	> 99:1
	2	RuPNN^{HEt}	0.13	99	98	> 99:1
	3	RuMACHO-BH	0.25	100	97	> 99:1
	4	RuPNN^{HEt}	0.50	100	97	> 99:1
	5	RuMACHO-BH	0.063	100	100	> 99:1
	6	RuPNN^{HEt}	0.50	100	96	> 99:1
	7	RuMACHO-BH	0.063	99	99 (97)	> 99:1
	8	RuPNN^{HEt}	0.13	97	97	> 99:1

[a] Unless otherwise stated, yields are calculated analytically by analysis of the reaction mixture using the calibrated GC-FID response factors for the reactant vs. a tetradecane internal standard. The yield in parentheses (Entry 7) is based on isolation of the product at gram scale.

We next examined the reactivity of aryl-substituted epoxides (Table 3), which have shown more variable regioselectivity in previous reports.[23-25] The parent styrene oxide was converted cleanly to a mixture of the linear and branched phenyl ethanol products with both **Ru-MACHO-BH** and **RuPNN^{HEt}**, and **Ru-MACHO-BH** showed a markedly higher selectivity for the branched product. Substrates with a range of para-substituents were also hydrogenated in high yields. Neither catalyst was effective for substrates with a strongly withdrawing trifluoromethyl or nitro substituent. As was observed for the substrates above in Table 2, **Ru-MACHO-BH** generally delivered full conversion at a lower loading than **RuPNN^{HEt}**.

Table 3. Hydrogenolysis of aryl-substituted epoxides.



Ar	σ_p	Ru	mol %	% Conv.	% Yield	b:l
	-0.27	RuMACHO-BH	0.13	99	99	5.6
		RuPNN^{HEt}	0.50	100	99	2.7
	0	RuMACHO-BH	0.031	98	95	12.2
		RuPNN^{HEt}	0.063	100	99	5.8
	0.06	RuMACHO-BH	0.063	96	93	16.2
		RuPNN^{HEt}	0.50	100	97	7.9
	0.23	RuMACHO-BH	1.0	98	97	18.9
		RuPNN^{HEt}	1.0	100	99	7.5
	0.23	RuMACHO-BH	1.0	94	90	19.0
		RuPNN^{HEt}	4.0	99	93	7.1

We observed that the branched-to-linear selectivity for aryl epoxides was quite consistent in experiments with different catalyst loadings, and was also consistent over time in individual reactions in isopropyl alcohol (see Figures 3 and 4 above). Therefore, this selectivity is likely kinetic in origin and might be expected to show a linear free-energy relationship with the electronic nature of the para-substituent. Figure 6 shows Hammett plots[28] for the five aromatic epoxides that were successfully hydrogenated. For both catalysts, there is a good correlation between the logarithm of the branched:linear ratio and the Hammett constant σ_p. The positive slope indicates that withdrawing substituents favor the branched product for both **RuPNN^{HEt}** and **Ru-MACHO-BH**. The similar slopes (0.84 for **RuPNN^{HEt}** and 1.03 for **Ru-MACHO-BH**) indicate that the catalysts are similarly sensitive to the para-substituent, and the greater offset for **Ru-MACHO-BH** shows that it has a greater intrinsic selectivity for the branched isomer than **RuPNN^{imine}** under the reaction conditions employed. A computational and experimental mechanistic study on these reactions is currently in progress, and we hesitate to speculate on the mechanistic origin of the substituent effect at this time.

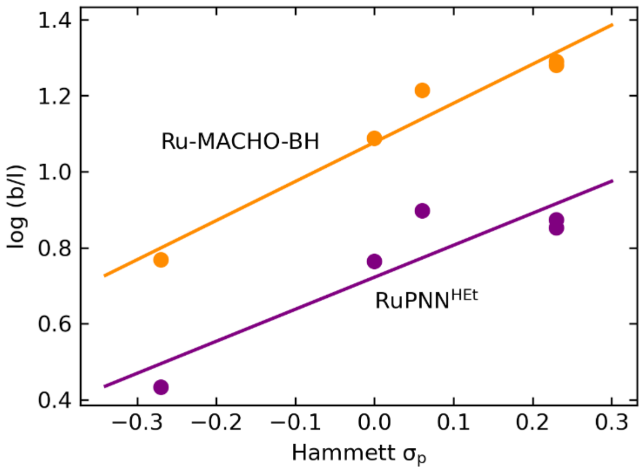
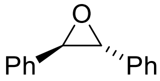
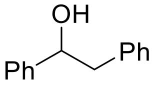
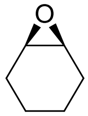
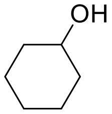
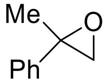
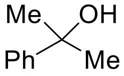


Figure 6. Hammett plots for the b:l selectivity in the hydrogenolysis of aryl epoxides. For **Ru-MACHO-BH**, the linear regression equation is $y = 1.03x + 1.08$, with $R^2 = 0.96$. For **RuPNN^{HEt}**, the equation is $y = 0.84x + 0.72$, with $R^2 = 0.82$.

Finally, we were interested to assess the activity of **RuPNN^{HEt}** and **Ru-MACHO-BH** for the hydrogenolysis of disubstituted epoxides. Although the linear-selective catalyst systems described in the introduction are generally effective for the hydrogenolysis of disubstituted epoxides,[16-17, 19-21] the Noyori-type ruthenium catalysts reported previously are not. Ikariya's catalyst system employing $PPh_2CH_2CH_2NH_2$ as ligand was ineffective for epoxides with more than one substituent,[23] and Gunanathan's **Ru-MACHO**/KO^{t}Bu system showed no conversion of stilbene oxide and gave approximately a 1:1 ratio of branched and linear alcohols from 2-phenylpropylene oxide with 5% catalyst loading.[24] Table 4 shows the results for three disubstituted epoxides using **RuPNN^{HEt}** or **Ru-MACHO-BH** in isopropyl alcohol with no added base. *Trans*-stilbene oxide (racemic) is hydrogenated fully by both catalysts, although a higher 2% catalyst loading is required. Interestingly, this substrate was reported to be completely unreactive under the conditions reported by Gunanathan (**Ru-MACHO**/KO^{t}Bu in toluene at 75 °C).[24] Cyclohexene oxide is also hydrogenated by both catalysts, although full conversion was not obtained with either catalyst even at a very high 4% catalyst loading. The 1,1-disubstituted substrate 2-phenylpropylene oxide was not hydrogenated effectively with **Ru-MACHO-BH** under the standard conditions, but **RuPNN^{HEt}** gave full conversion and 99% yield when a 4% catalyst loading was used. We speculated that the lack of reactivity of **Ru-MACHO-BH** might be partially due to the catalyst's low solubility in isopropyl alcohol. Gratifyingly, a 95% yield was obtained when a 1:1 mixture of toluene and isopropyl alcohol was used as the solvent. With both catalysts, only the branched product was detected for this substrate. To our knowledge, this is the first report of Markovnikov-selective hydrogenolysis of this commercially available epoxide.

Table 4. Hydrogenolysis of disubstituted epoxides.

$$\text{epoxide} \xrightarrow[\substack{{}^{i}\text{PrOH} \\ \text{18 h, 80 °C}}]{\substack{\text{30 bar H}_2 \\ \text{[Ru]}}} \text{alcohol}$$

Epoxide reactant	Alcohol product	Ru	mol %	% Conv.	% Yield	b:l
		RuMACHO-BH	2.0	96	96	n/a
		RuPNN^{HEt}	2.0	97	95	n/a
		RuMACHO-BH	4.0	72	68	n/a
		RuPNN^{HEt}	4.0	89	71	n/a
		RuMACHO-BH	4.0	4	4	> 10:1
		RuMACHO-BH[a]	4.0	97	95	>99:1
		RuPNN^{HEt}	4.0	100	99	> 99:1

[a] A 1:1 mixture of toluene and isopropyl alcohol was used as solvent.

Summary and Conclusion

We have shown that **RuPNN^{HEt}** and **Ru-MACHO-BH** are highly effective catalysts for the branched-selective hydrogenolysis of epoxides without the requirement of strongly basic additives. The use of isopropyl alcohol as solvent enables the complete conversion of epoxides to alcohols in high yield with low catalyst loadings. From a practical standpoint, the use of **Ru-MACHO-BH** is recommended for most applications due to its commercial availability and moderate cost ($95/g from Strem). In contrast, **RuPNN^{HEt}** is synthesized in two steps[14] from the commercially available Milstein Catalyst Precursor ($788/g from Strem). In our experiments, **Ru-MACHO-BH** also typically gave full substrate conversion at lower loadings compared to **RuPNN^{HEt}**. An experimental and computational mechanistic study of these reactions is currently in progress.

Author Information

Corresponding Author

*achianese@colgate.edu

ORCID

Fallyn L. Kirlin: 0000-0003-1180-471X
Olivia J. Borden: 0000-0002-5567-3566
Marianna C. Head: 0000-0002-7158-6630
Sophie. E. Kelly: 0000-0001-8350-3671
Anthony R. Chianese: 0000-0002-9140-6115

Supporting Information

Experimental procedures for epoxide hydrogenolysis and numerical data presented in Figures 2-4.

Conflicts of interest

The authors declare no competing financial interest.

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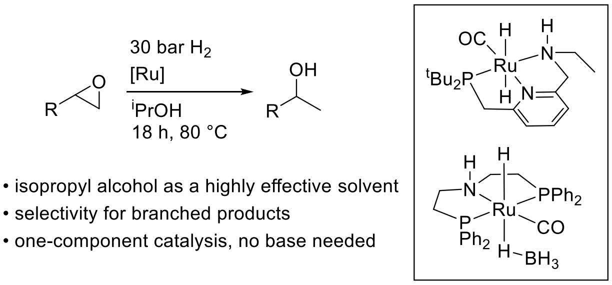
TOC Graphic:



- isopropyl alcohol as a highly effective solvent
- selectivity for branched products
- one-component catalysis, no base needed