Iridium-promoted conversion of terminal epoxides to primary alcohols under acidic conditions using hydrogen

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Iridium-promoted conversion of terminal epoxides to primary alcohols under acidic conditions using hydrogen†

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Alena N. Rainsberry, [a] Jarrod G. Sage, [a] and Margaret L. Scheuermann [a]*

A strategy for the conversion of terminal epoxides to primary alcohols is presented. The reaction uses hydrogen as the only stoichiometric reagent and is promoted by an iridium precatalyst under acidic conditions. Selectivity for the formation of a terminal alcohol over an internal alcohol is observed for both alkyl- and aryl-substituted terminal epoxides in isolated yields of up to 50 % and 72 % respectively.

Recent progress in green oxidation reactions has enabled the selective and large-scale epoxidation of alkenes.[1,2] As a result epoxides are an increasingly attractive precursor for chemical synthesis.[3] For example, an epoxidation reaction followed by hydrogenation with H_2 as the hydrogen source would be an atom-economical, two-step route for the conversion of alkenes to alcohols (Figure 1a). The selective formation of primary alcohols would be especially valuable as current routes for the conversion of alkenes to primary alcohols suffer from poor selectivity for the primary alcohol (Figure 1b) or quantitative byproduct formation (Figure 1c).[4]

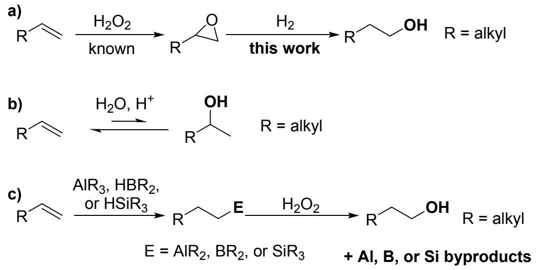

Figure 1. a) Atom-economical conversion of terminal alkene to a primary alcohol through an epoxide intermediate. **(b)** Direct hydration of alkenes typically favors formation of the secondary alcohol. **(c)** Current routes that offer high selectivity for the primary alcohol result in the formation of stoichiometric byproducts.

In most cases, the regioselectivity of epoxide hydrogenation and transfer hydrogenation reactions is substrate-controlled.[5] For terminal aliphatic epoxides, the formation of secondary alcohols is favored over the formation of primary alcohols using a range of heterogeneous[6–12] and putative homogeneous catalysts.[13,14]

There are only two examples of homogeneous precatalysts that exhibit any selectivity for the formation of primary alcohols over secondary alcohols in reactions involving aliphatic epoxides. In one case, treatment of hexene oxide with hydrogen gas and a ruthenium catalyst (10 mol %) resulted in production of 1-hexanol (40 %, by GC) and hexanal (18 %); the fate of the remaining material was not identified.[15] In the other example, a mixture containing 1-dodecanol and 2-dodecanol in a 88:12 ratio was isolated in 41 % yield from the hydrogenation of dodecene oxide with Rh (5 mol %) and Ti (10 mol %) co-catalysts, again with the fate of the remaining material not identified.[16] Further, this system requires a stoichiometric reductant such as Mn or Zn and an excess of collidine hydrochloride in addition to hydrogen gas.

Here we report the conversion of terminal epoxides to alcohols with high selectivity for formation of the primary alcohol over the secondary alcohol. The transformation of both aryl- and alkyl-substituted epoxides is promoted by a (POCOP)IrCO precatalyst[17] under aqueous acidic conditions using hydrogen gas as the only stoichiometric reagent.

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[a] Department of Chemistry; Western Washington University; 516 High Street - MS-9150; Bellingham WA, 98225. Email: margaret.scheuermann@wwu.edu

† Footnotes relating to the title and/or authors should appear here.

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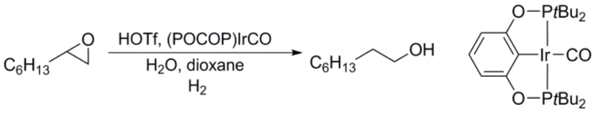
Table 1. Variation of the reaction conditions using epoxyoctane as a model substrate.



(POCOP)IrCO

Entry[a]	Temp. °C	Ir mol %	HOTf mol %	1-Octanol (%)[b]	1,2-Octanediol (%)	Dioctyl ether (%)[c]
1	195	0.6	0.50	63	7	2
2	195	1.2	0.50	63	7	2
3	195	0.6	0.25	31	52	<1
4	180	0.6	0.50	40	42	<1
5[d]	195	0.6	0.50	41	47	<1
6	195	0	0.50	4	<1	<1
7	195	0	10	2	<1	<1

[a] Reactions were carried out in a stainless steel reactor with a PTFE liner. Reaction conditions: substrate (1.4 mmol), dioxane (0.7 mL), HOTf (added as 0.68 M aq stock solution), (POCOP)IrCO (quantity varies by entry), decane (25 µL), H_2 (charged to 600 psi at 25 °C), held at 35 °C for 90 min then heated at the indicated temperature for 15 h. [b] Yields measured by GC-FID using decane as an internal standard. [c] Percent represents the fraction of the substrate incorporated into dioctyl ether. [d] Heated for 3 hours at 195 °C.

The conversion of terminal epoxides to primary alcohols requires that a more sterically hindered C–O bond be selectively cleaved in the presence of a less sterically hindered C–O bond. Thus the problem of selective epoxide hydrogenation has similarities to the challenge of selective biomass deoxygenation.[18,19] Taking inspiration from the glycerol deoxygenation literature,[20-27] we found that a (POCOP)IrCO precatalyst[20–22] (Table 1) in the presence of triflic acid (HOTf), water, dioxane, and hydrogen gas at 195 °C was able promote the conversion of our 1,2-epoxyoctane model substrate to 1-octanol in 63 % yield. Notably, no 2-octanol was detected by GC-MS. The side products identified by GC-MS and quantified by GC-FID were 1,2-octanediol (7 %) and dioctyl ether (2 %) (Table 1, Entry 1). Small quantities of various side products, including alkenes, alkanes, and higher mass species were also observed, an occurrence consistent with previous reports of polyol deoxygenation.[20–27] These unquantified side products likely account for the remaining mass. In the absence of hydrogen the quantity of 1-octanol detected was less than 1 %.

The observed 1,2-octanediol is likely an intermediate in the reaction. A sample of epoxyoctane in dioxane exposed to triflic acid (10 mol %) for 90 min at 35 °C gave a 39 % yield of 1,2-octanediol confirming that 1,2-octanediol can form readily under the reaction conditions. When an authentic sample of 1,2-octanediol was exposed to the standard reaction conditions, the resulting product mixture contained 1-octanol (70 %), 1,2-octanediol (8 %), and dioctyl ether (<1 %). In the absence of hydrogen, a complex mixture of products was observed.

Decreasing the acid concentration (Table 1, Entry 3) resulted in a lower yield of 1-octanol and more 1,2-octanediol suggesting a rate-determining diol dehydration. Lowering the temperature or reaction time (Table 1, Entries 4 and 5) also resulted in the observation of more 1,2-octanediol. Control experiments in the absence of iridium (Table 1, Entries 6 and 7) yielded limited quantities of alcohols suggesting that with the PTFE liner in place the contribution of the stainless steel reactor to the observed 1-octanol formation was minimal.[27]

We propose a mechanism in which the acid and iridium species participate in a tandem catalytic process involving an initial acid-catalyzed ring opening of the epoxide to the 1,2-octanediol followed by an acid-catalyzed dehydration to an enol (Figure 2). The enol rearranges to an aldehyde that can undergo an Ir-catalyzed hydrogenation to form the alcohol. Increasing the loading of the iridium had little effect on either the reaction yield or selectivity (Table 1, Entry 2) suggesting that the hydrogenation step is not rate determining under the standard reaction conditions. A rapid hydrogenation step is important because an aldehyde intermediate would be expected to have limited stability under the reaction

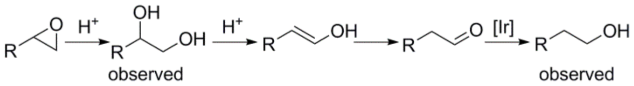
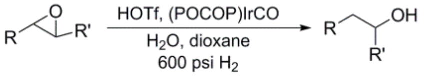


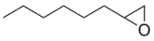
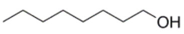
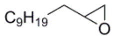
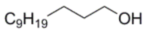
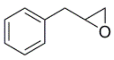
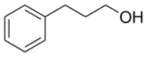
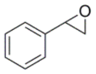
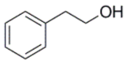
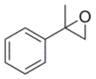
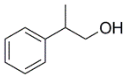
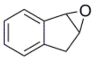
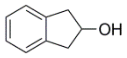
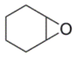
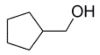
Figure 2. Proposed mechanism for the conversion of a terminal epoxide to a primary alcohol catalyzed by acid in the first two steps and iridium in the final step.

conditions. An octanal peak was detected in some chromatograms however its abundance never exceeded 1 %.

Primary alcohols were obtained as the major product for several minimally-functionalized alkyl-epoxides (Table 2, Entries 1-3). With aryl-substituted epoxides, the primary alcohols (Entries 4 and 5) were obtained. 2,2-Disubstituted epoxides (Entry 5) also formed primary alcohols preferentially.

Table 2. Substrate scope.



Entry[a]	Substrate	Major product	Yield (%)
1			63[b] 48[c]
2			58[b] 50[c]
3			39[b] 38[c]
4			88[b] 72[c]
5			55[b] 53[c]
6			46[b] 35[c]
7			39[b] 26[c]

[a] Reactions were carried out in stainless steel reactor with a PTFE liner. Reaction conditions: substrate (1.4 mmol, 130–250 mg), (POCOP)IrCO (0.65 mol %, 5.0 mg, 0.0088 mmol), dioxane (0.7 mL), HOTf (0.5 mol %, added as 0.68 M aq stock solution, 10 μL), decane (25 μL), H_2 (charged to 600 psi at 25 °C), heated at 35 °C for 90 min then 195 °C for 15 hours. [b] Yields measured by GC-FID using decane as an internal standard. [c] Isolated yield.

We briefly examined the reactivity of non-terminal epoxides (Entries 6 and 7). Our mechanistic proposal involves a dehydration step, and with the dehydration step comes the possibility of rearrangement reactions. Consistent with this proposal, the major product from the reaction of cyclohexene oxide was cyclopentanemethanol. Indene oxide with a smaller five-membered ring did not undergo a rearrangement and the major product was 2-indanol.

In summary, we have reported that a (POCOP)IrCO precatalyst in the presence of HOTf and hydrogen can convert both aryl- and alkyl-substituted epoxides into primary alcohols. Compared with the two previously reported homogeneous precatalysts for the conversion of terminal aliphatic epoxides to primary alcohols, our system demonstrates improved selectivity for the desired primary alcohol and decreases the loading of the metal precatalyst by more than an order of magnitude. Mechanistic studies are consistent with a rate-determining diol dehydration, an observation that offers useful guidance on future directions. Work toward bypassing the diol intermediate and developing a method to accomplish this transformation under milder and more functional group-tolerant conditions is in progress.

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Conflicts of interest

There are no conflicts to declare.

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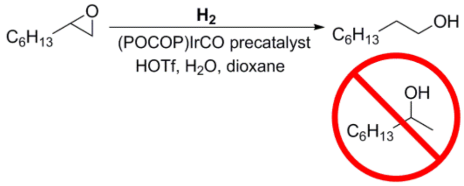

Terminal aliphatic epoxides can be converted to primary alcohols rather than the more commonly formed secondary alcohols.