ORGANIC CHEMISTRY

Anti-Markovnikov alcohols via epoxide hydrogenation through cooperative catalysis

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The opening of epoxides typically requires electrophilic activation, and subsequent nucleophilic (S_N2) attack on the less substituted carbon leads to alcohols with Markovnikov regioselectivity. We describe a cooperative catalysis approach to anti-Markovnikov alcohols by combining titanocene-catalyzed epoxide opening with chromium-catalyzed hydrogen activation and radical reduction. The titanocene enforces the anti-Markovnikov regioselectivity by forming the more highly substituted radical. The chromium catalyst sequentially transfers a hydrogen atom, proton, and electron from molecular hydrogen, avoiding a hydride transfer to the undesired site and resulting in 100% atom economy. Each step of the interconnected catalytic cycles was confirmed separately.

Anti-Markovnikov alcohols, in which the hydroxyl group is bound to the less substituted of two adjacent carbons, can of course be obtained by hydroboration and oxidation, but these are stoichiometric reactions [(*1*), see also (*2*–*6*)]. There have been several reports of the catalytic generation of anti-Markovnikov products from the corresponding olefins. In 1986, it was reported that trans-PtHCl(PMe$_3$)$_2$ (Me, methyl) could catalyze the hydration of 1-hexene to 1-hexanol, but this work has proven difficult to reproduce (*7*–*9*). The Grubbs laboratory (*10*) has reported the formal anti-Markovnikov hydration of olefins, principally of monosubstituted styrenes, via a triple relay process that combines Pd-catalyzed oxidation, H$^+$-catalyzed hydrolysis, and Ru-catalyzed reduction. The Nicewicz laboratory (*11*, *12*) has reported the anti-Markovnikov hydrofunctionalization of olefins by nucleophilic attack on the cation radicals generated (with organic photoredox catalysts) by their single-electron oxidation. Lei and co-workers have demonstrated the visible-light–mediated anti-Markovnikov hydration of olefins (*13*). The enzyme-catalyzed formal anti-Markovnikov hydration of styrenes has been realized by the Arnold group (*14*).

The hydrogenation of epoxides is a highly attractive yet largely unexplored method of preparing alcohols. The combination of appropriately regioselective hydrogenation with the epoxidation of olefins will permit the two-step synthesis of anti-Markovnikov alcohols (Fig. 1).

Previous studies [recently reviewed by Huang and Doyle (*15*)] have reported catalysts for the hydrogenation of epoxides, but anti-Markovnikov regioselectivity has been rare. An early homogeneous catalyst, [HCo(CN)$_5$]$^{3-}$ (*16*), is said to have hydrogenated styrene oxide to β-phenylethanol, but no experimental details were provided (*17*). A later report indicated that 6 mol % RhCl$_3$py$_3$-NaBH$_4$ (py, pyridine) in dimethylformaldehyde (DMF) hydrogenated (1 atm) styrene oxide to β-phenylethanol in 3 hours (the absolute concentrations used were not stated) (*18*, *19*). Rh(NBD)(PR$_3$)$_2$$^+$ (NBD, norbornadiene) yielded a multiplicity of products from both styrene oxide and butadiene monoxide (*20*–*22*). The catalysis of transfer hydrogenation by Rh$_2$(acac)$_4$ (*23*) (acac, acetylacetonate) and the use of ^{i}PrOH/H$_2$ (^{i}PrOH, isopropanol) with Cp*Ru(Ph$_2$PCH$_2$CH$_2$NH$_2$)H (*24*) (Ph, phenyl) principally yielded the branched alcohol from styrene oxide and similar results from other unsymmetrical epoxides. Heterogeneous catalysts, principally Pd/C, produce the anti-Markovnikov alcohols for styrene oxide and the Markovnikov alcohols for monosubstituted alkyl epoxides, mostly with high selectivity; higher alkyl epoxides yield complex mixtures (*25*).

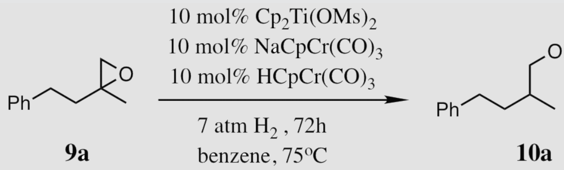
Epoxide opening typically requires electrophilic activation followed by nucleophilic (S_N2) attack on the less substituted carbon; H$^+$ and H$^-$ addition to epoxides in this vein typically leads to Markovnikov alcohols (*26*–*29*). A mechanism that does not involve electrophilic activation of an epoxide is mandatory for avoiding the formation of a Markovnikov product. In this study, we demonstrate that such a result can be accomplished by using radicals as intermediates in cooperative Ti/Cr catalysis (Fig. 2).

The Gansäuer group has established that Ti(III) (**1**) can generate radicals (**2**) by the one-electron reduction of epoxides (*30*, *31*). The more-substituted radicals **2** are generally formed and have been quenched to **5** by H• transfer from 1,4-cyclohexadiene (*30*), Bu$_3$SnH (*32*), thiols (*33*), silanes (*34*), or precious-metal hydrides (*35*). Cleavage of the alkoxide ligand from Ti(IV) by H$^+$ transfer from collidinium, and reduction of the resulting Ti(IV) complex back to **1** with Mn powder, have made the reaction catalytic in Ti.

The Norton group has shown that CpCr(CO)$_3$H **3**, which has a bond dissociation energy of only 62 kcal mol^{-1}, can transfer H• to organic radicals (*36*–*40*). Compound **3** should thus react to form Ti(IV) alkoxides **5** by H• transfer to **2**. The regeneration of **3**, by the hydrogenation of CpCr(CO)$_3$• **4** and its dimer (*41*), should make this reaction catalytic in Cr.

In addition, it seemed possible that the Cr hydride **3** could regenerate **1** and render epoxide opening catalytic in Ti. Compound **3** is acidic, with a pK_a (where K_a is the acid dissociation constant) of 13.3 in acetonitrile (*42*), close to that of collidinium commonly used by the Gansäuer group; it should thus be capable of cleaving the

Table 1. Control experiments. Experiments were performed on either a 1- or 0.5-mmol scale.



Entry	Deviation from "standard condition"	Yield*
1	Time dependence	12 hours (34%), 24 hours (58%), 48 hours (85%), 72 hours (95%)
2	No Ti catalyst	24 hours (7%), 72 hours (29%)
3	No Cr catalysts	0%
4	5 mol % instead of 10 mol % for all catalysts	81%

*Yield determined by ^{1}H NMR using hexamethylbenzene as an internal standard.

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alcohol **6** from the Ti(IV) alkoxide **5** by protonolysis. The conjugate base of compound **3**, the $[CpCr(CO)_3]^-$ anion, is a good one-electron reducing agent, with a potential of −0.67 V [versus Fc/Fc$^+$ (Fc, ferrocene; Fc$^+$, ferrocenium)] (*43*) in acetonitrile, very close to that of Cp_2TiCl_2 (*44*). In preliminary experiments both the protonolysis and the one-electron reduction were observed experimentally. The addition of $CpCr(CO)_3H$ to a solution of $Cp_2TiCl(OEt)$ (Et, ethyl) in CD_3CN released free ethanol [confirmed by the ^1H nuclear magnetic resonance (NMR) spectrum of the reaction mixture (figs. S1 and S2)]. Addition of $Na[CpCr(CO)_3]$ to Cp_2TiCl_2 in CD_3CN or THF-d_8 (THF, tetrahydrofuran) generated Cp_2TiCl along with a mixture of **4** $[CpCr(CO)_3\bullet]$ and its dimer. The addition of hydrogen gas generated $CpCr(CO)_3H$ [its hydride peak was observed by ^1H NMR (fig. S3)].

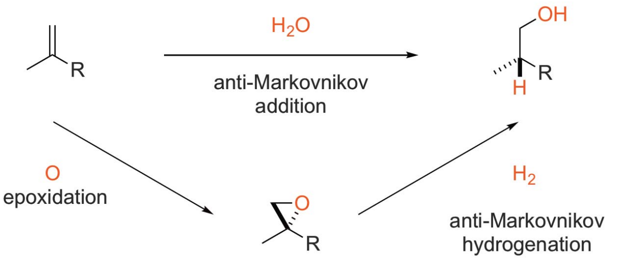


Fig. 1. Two-step approach to anti-Markovnikov addition of H_2O to olefins. R, alkyl.

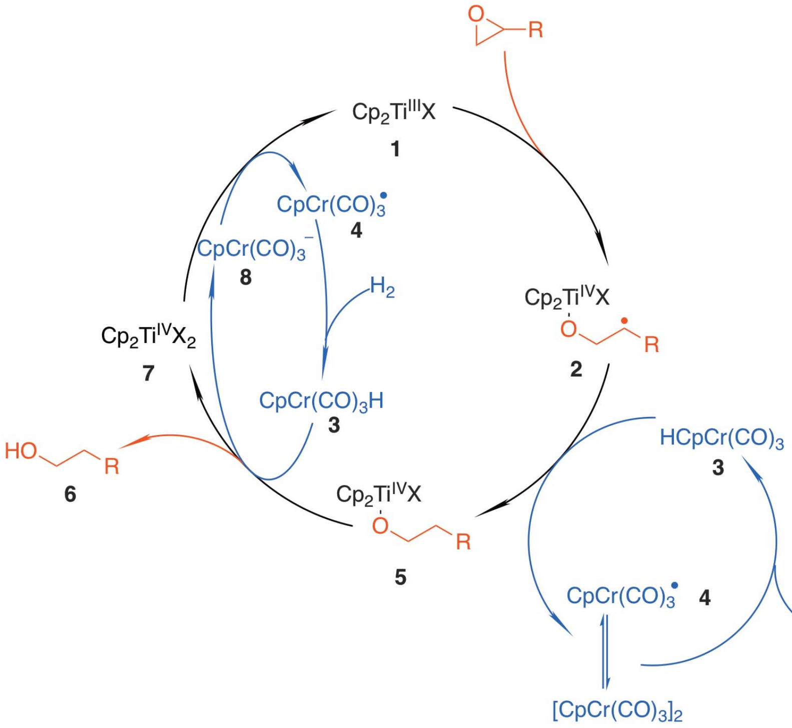


Fig. 2. A plausible but hypothetical catalytic cycle for the anti-Markovnikov hydrogenation of epoxide by activation and sequential delivery of H_2 as H•, H^+, and e^-. Cp, cyclopentadienyl; X, mesylate or triflate.

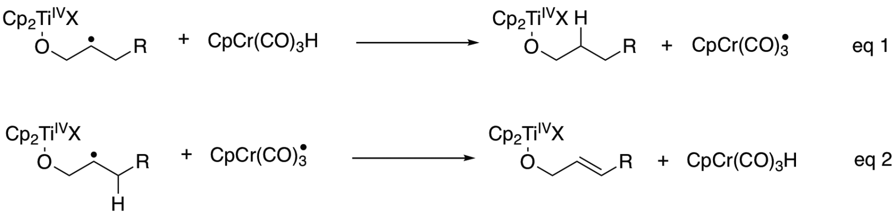


Fig. 3. Competition reactions between hydrogen atom transfer (top) and hydrogen atom abstraction (bottom).

We hoped that the Ti-catalyzed epoxide opening and the Cr-catalyzed delivery of H_2 as H•, H^+, and e^- would jointly transform epoxides into anti-Markovnikov alcohols (*45*–*47*). Treatment of **9a** in THF with 7 atm H_2 in the presence of 10 mol % Cp_2TiCl_2 and 10 mol % $NaCpCr(CO)_3$ generated the anticipated product **10a**, albeit in modest yield. Extensive optimization (table S1) identified 10 mol % $Cp_2Ti(OMs)_2$ (OMs, mesylate), 10 mol % $NaCpCr(CO)_3$, and 10 mol % $HCpCr(CO)_3$ in benzene as the most efficient system. With **9a** we obtained 34% conversion after 12 hours, 58% after 24 hours, and 85% after 48 hours.

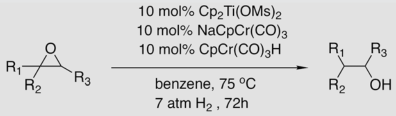
The data in Table 1 show that both Ti and Cr (entry 1) are required for the efficient operation of the catalyst. By itself the Ti has no activity (entry 3), whereas the Cr [as $HCpCr(CO)_3$] has very little (10 mol % gives only 7% conversion to **10a** in 24 hours). (The Cr system presumably has some e^- transfer activity.) Furthermore, the catalyst loading can be reduced (entry 4) to 5 mol% without substantially diminishing the yield.

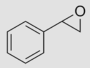
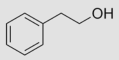
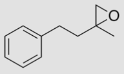
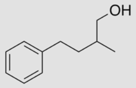
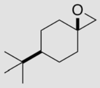
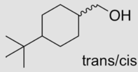
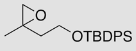
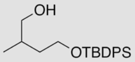
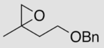
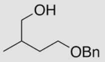
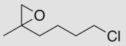
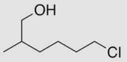
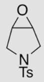
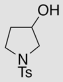
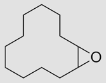
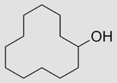
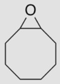
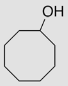
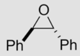
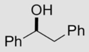
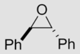
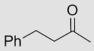
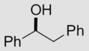
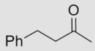
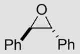
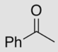
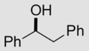
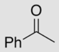
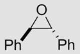
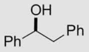
In the experiments described in Table 2, we explored the scope of our reaction. Monosubstituted (entry 1), 1,2-disubstituted (entries 7 to 10), and 1,1-disubstituted (entries 2 to 6) epoxides, either linear or cyclic, are suitable substrates. The tosyl substituent on the nitrogen in entry 7 and the chloride substituent in entry 6, easily reduced with samarium diiodide (*48*), remain unperturbed after our reaction. (The major by-product in entry 7 is 1-tosylpyrrole and 1-tosyl-3-pyrroline; the tosyl substituent on the nitrogen remains intact.) Functional groups that are susceptible to nucleophilic attack, such as the ketones in entries 11 and 12 and the nitrile in entry 13, remain intact after our reaction. Reasonable yields are obtained with silyl (entry 4) and benzyl (entry 5) ethers. Gram-scale reactions can be conducted without a significant decline in yield (entries 5 and 10).

In unsymmetrical cases, the product is the anti-Markovnikov alcohol, as expected from the formation of the more-substituted radical **2** in the epoxide opening. The major by-product is an allylic alcohol, presumably resulting from an H• abstraction similar to that depicted in Fig. 3, eq. 2. This side reaction is well documented for both $CpCr(CO)_3\bullet$ and $Cp_2TiCl\bullet$ and has, under different conditions, been used to beneficial effect. The phenyl substituents make entries 1 and 10 interesting cases, as the reduction of benzylic radicals is known to be difficult in titanocene-mediated methodology (*33*).

The addition of extra $CpCr(CO)_3H$ (in entry 8) gives an elevated rate of H• transfer (Fig. 3, eq. 1) to the β-metalloxy radical **2** and competes effectively for **2** with H• abstraction by $CpCr(CO)_3\bullet$

Table 2. Substrate scope of the anti-Markovnikov hydrogenation of epoxides. All reactions, unless otherwise noted, were conducted on a 1- or 0.5-mmol scale. TBDPS, tert-butyldiphenylsilyl; Bn, benzyl; Ts, tosyl.



entry	epoxide	product	yield [%]†
1			51
2			70
3		 trans/cis: 54/46	48(10)
4			60(12)
5			81, 74‡
6			55
7			49
8			65(26)
9			52(33) 65(19)*
10			96, 82‡
11	 and  1.0 eq.	 and 	88 99% recovery
12	 and  1.0 eq.	 and 	94 85% recovery
13	 and Ph—≡N 1.0 eq.	 and Ph—≡N	91 81% recovery

*30 mol % HCpCr(CO)$_3$. †Yield of allylic alcohol is shown in parentheses. ‡Gram-scale reaction with 8 mmol of substrate.

(Fig. 3, eq. 2). As a result, the allyl alcohol byproduct is suppressed and the saturated alcohol is formed in greater quantity.

The Cr and Ti catalysts in Fig. 2 appear to interact several times during their operations: first by H• transfer from the Cr to the β-titanoxy radical **2**, then by the transfer from the Cr of a proton (to the alkoxy ligand of **5**) and an electron [to the Ti(IV) in **7**]. The reaction between the titanium alkoxide **5** and the chromium hydride **3** is formally a PCET (proton-coupled electron transfer), but we have not established the exact sequence of events (*49*, *50*). A dual mechanism in which there is no direct interaction between the two catalysts was defined in 2005 by Baker, Bazan, and co-workers as "concurrent tandem catalysis" (*51*). However, the interactions between our catalysts make this reaction an example of a new classification—"cooperative catalysis"—proposed in 2012 by Patil and co-workers (*52*). Recent examples of "cooperative [tandem] catalysis" have been offered by the Hartwig (*53*) and Blum (*54*) groups. The major challenge is catalyst compatibility: All reagents and intermediates of both catalysts must be compatible (*55*). Moreover, the rates of the two catalytic cycles must be well matched so that the intermediates of one cycle do not accumulate (*56*).

Our Ti/Cr cooperative catalyst system produces anti-Markovnikov alcohols exclusively from a broad range of epoxide substrates. The Ti system avoids nucleophilic attack on the epoxide, and the Cr system activates H_2 in a highly unusual manner: via H^+, H•, and e^-. By using H_2 as the only stoichiometric reagent, our process results in excellent atom economy.

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17. When we placed an aqueous solution of 0.3 mmol Co(II), 1.53 mmol KCN, and 0.6 mmol styrene oxide under 1 atm H_2 and stirred it for 16 hours, we observed 20% conversion to hydroxy nitrile. Our standard substrate **9a**

produced the hydroxy nitrile in 40% yield under similar conditions in 72 hours.

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SUPPLEMENTARY MATERIALS

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Anti-Markovnikov alcohols via epoxide hydrogenation through cooperative catalysis

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Markovnikov falls to chromium and titanium
Ring opening of strained triangular epoxides is a versatile method for making alcohols. However, these reactions are limited by their tendency to leave the oxygen on the more heavily substituted carbon, in accord with the Markovnikov rule. Yao *et al.* now show that a pair of catalysts working cooperatively can invert this selectivity pattern. A titanium catalyst pries the ring open while a chromium catalyst activates and delivers hydrogen. In an unusual mechanistic twist, the chromium complex appears to deliver a hydrogen atom, a proton, and an electron at different stages of the cycle.
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