

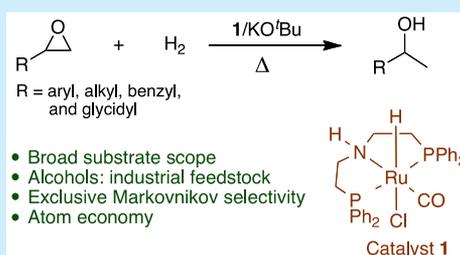
Ruthenium-Catalyzed Selective Hydrogenation of Epoxides to Secondary Alcohols

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S Supporting Information

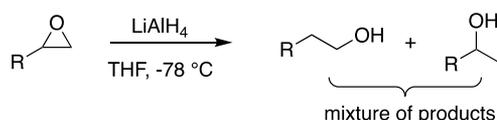
ABSTRACT: A ruthenium(II)-catalyzed highly selective Markovnikov hydrogenation of terminal epoxides to secondary alcohols is reported. Diverse substitutions on the aryl ring of styrene oxides are tolerated. Benzylic, glycidyl, and aliphatic epoxides as well as diepoxides also underwent facile hydrogenation to provide secondary alcohols with exclusive selectivity. Metal–ligand cooperation-mediated ruthenium *trans*-dihydride formation and its reaction involving oxygen and the less substituted terminal carbon of the epoxide is envisaged for the origin of the observed selectivity.



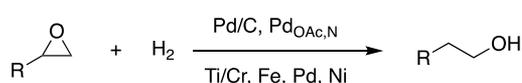
The regioselective ring opening of epoxides to selectively provide one of the two isomeric products is an important transformation in medicinal chemistry and is a highly promising industrial process for the synthesis of alcohols.¹ Conventional methods for the epoxide hydrogenation reactions are mainly based on the use of stoichiometric amounts of strong reducing reagents such as LiAlH₄, which provide a mixture of both primary and secondary alcohols (Scheme 1a).² The classical methods often failed to provide satisfactory results and suffer from (i) requirement and safety issues with the use of cryogenic conditions, (ii) difficulties associated with a more reactive lithium base, leading to a mixture of alcohol products, and (iii)

Scheme 1. Traditional and Catalytic Approaches to the Hydrogenation of Epoxides

a) Traditional approach: Hydrogenation of epoxides to alcohols



b) Previous work: anti-Markovnikov selectivity to primary alcohols



c) This work: Markovnikov selectivity to secondary alcohols

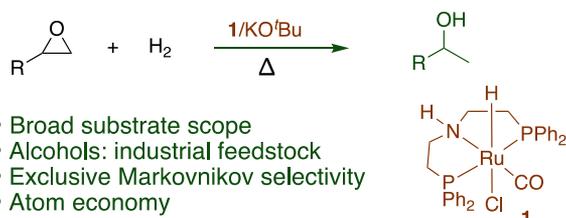


Table 1. Optimization for Regioselective Hydrogenation of Styrene Oxide Catalyzed by 1^a

entry	H ₂ (bar)	temp (°C)	conv (%) ^b	yield (%) ^c	ratio A/B ^d
1	10	75	40	38	80:20
2	30	75	78	76	92:8
3	50	75	>99	99	94:6
4	50	100	>99	98	90:10
5	50	50	30	28	>99:<1
6 ^e	50	75	60	54	>99:<1
7 ^f	50	75			
8 ^g	50	75			
9 ^h	50	75	>99	97	94:6

^aReaction conditions: styrene oxide (0.5 mmol), catalyst 1 (1 mol %), and KO^tBu (2 mol %) and toluene (1.5 mL), heated to the indicated temperature under H₂ pressure. ^bConversion of styrene oxide was determined by GC analysis using benzene as an internal standard. ^cYields were calculated for the isolated mixture of products A and B after column chromatography. ^dAlcohol ratio was determined from the ¹H NMR analysis of the reaction mixture. ^e0.5 mol % catalyst 1 was used. ^fOnly 5 mol % of KO^tBu was used. ^gReaction was performed without catalyst and base. ^hReaction was performed on a 1 mmol scale.

the generation of copious reactive waste in the environment. Moreover, the presence of sensitive functionalities limits the substrate scope. However, the preparation of secondary alcohols directly from alkenes via acid-catalyzed hydration reactions³ and the two-step Wacker oxidation of alkenes to ketones, followed by reduction are also extensively studied in the literature.^{4,5} Modern

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Table 2. Scope of Regioselective Hydrogenation of Terminal Epoxides Catalyzed by **1**^a

entry	epoxide	product	conv (%) ^b	yield (%) ^c	entry	epoxide	product	conv (%) ^b	yield (%) ^c		
1 ^d			2a	>99	99	11			2k	73	67
2 ^e			2b	90	72	12			2l	>99	97
3 ^{fg}			2c	75	42	13			2m	67	65
4 ^g			2d	>99	96	14			2n	>99	98
5 ^g			2e	41	40	15 ^h			2o	>99	98
6 ^g			2f	41	37	16 ^h			2p	>99	99
7 ^g			2g	>99	95	17 ^h			2p	>99	99
8			2h	>99	98	18 ^h			2q	>99	98
9			2i	>99	98	19 ^h			2r	67	62
10			2j	>99	97	20 ^{hi}			2s	>99	46

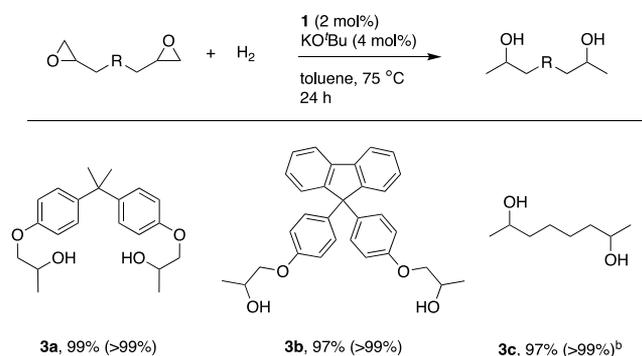
^aReaction conditions: epoxide (0.5 mmol), catalyst **1** (1 mol %), and KO^tBu (2 mol %) and toluene (1.5 mL) were heated to 75 °C under 50 bar H₂ pressure for 24 h. ^bConversion of epoxides determined by GC analysis using benzene as an internal standard. ^cReported yields correspond to isolated pure compounds. ^dIsolated as a mixture of A and B (94:6). ^e10% of primary alcohol is isolated. ^f26% of primary alcohol isolated. ^gReaction was performed using 3 mol % of catalyst and 6 mol % of base at 100 °C. ^hReaction was performed using 5 mol % of catalyst **1** and 10 mol % of base at 100 °C. ⁱ42% of primary alcohol was isolated.

transition-metal catalysis is an attractive and alternative method for the selective ring opening of epoxides.

During the last two decades, heterogeneous and homogeneous catalyst systems have been developed for the selective hydrogenation of epoxides to provide alcohols. Palladium heterogeneous catalyst (Pd/C) was extensively studied for the hydrogenolysis of epoxides to alcohols.⁶ However, controlling the regioselectivity of ring opening and the substrate scope has been less documented in heterogeneous catalysis. Thus, homogeneous catalyzed reactions were developed for the selective ring opening of epoxides, exploring the specific reactivity of transition-metal complexes.^{7,8} Hydroelementation (hydroboration and hydrosilylation) reactions are an alternative protocol for the selective ring opening of epoxides, which delivered the protected alcohols.^{9,10}

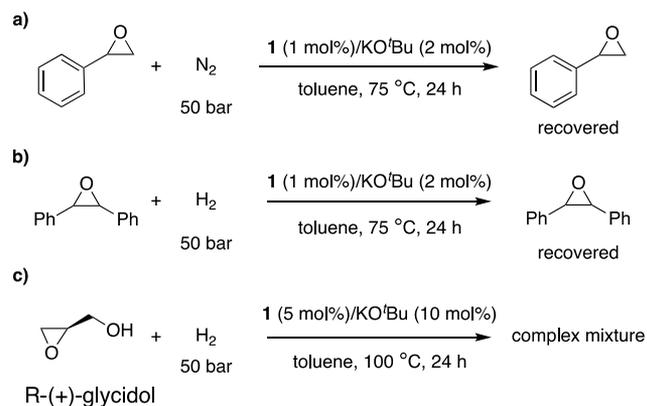
Very recently, the groups of Gansäuer, Norton, and Beller have reported the anti-Markovnikov selective hydrogenation epoxides to primary alcohols.¹¹ Despite these enticing developments to attain anti-Markovnikov selective reactions, studies toward Markovnikov selective products remain limited in the literature.^{6,7} Ikariya and coworkers have reported the pioneering ruthenium-catalyzed Markovnikov hydrogenation of terminal epoxides.⁸ However, the reported methods explored a narrow substrate scope and predominantly pertain to styrene oxides. Thus, developing a new protocol for the selective Markovnikov ring opening of epoxides is highly desirable. Recently, we have reported the pincer Ru-MACHO (**1**)-catalyzed cross-coupling of secondary alcohols,¹² the synthesis of ketazines,¹³ and the α -alkylation¹⁴ and α -olefination¹⁵ of nitriles using alcohols. Herein we present the highly selective Markovnikov hydrogenation of epoxides to secondary alcohols catalyzed by **1**.

Scheme 2. Scope of the Regioselective Hydrogenation of Terminal Diepoxides Catalyzed by **1**^a



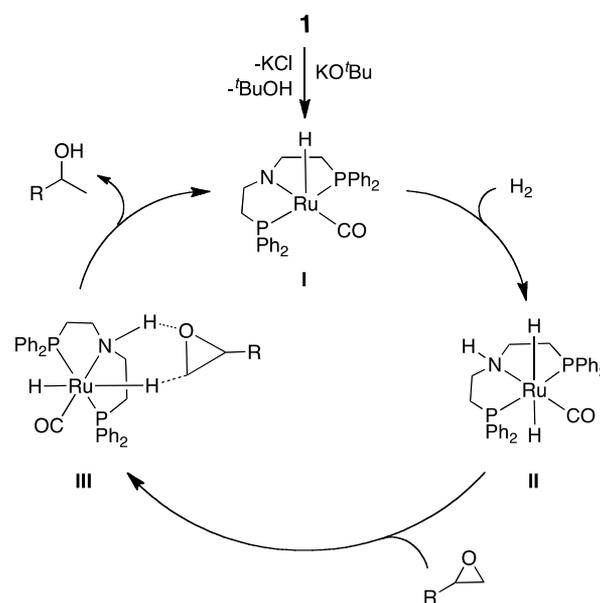
^aReaction conditions: diepoxide (0.5 mmol), catalyst **1** (2 mol %), and KO^tBu (4 mol %) and toluene (1.5 mL) were heated to 75 °C under 50 bar H₂ pressure for 24 h. The conversion of diepoxides determined by GC analysis using benzene as an internal standard is given within parentheses. Reported yields correspond to the isolated pure compound. ^bReaction was performed using 10 mol % of catalyst and 20 mol % of base at 100 °C.

Scheme 3. Mechanistic Studies for the Hydrogenation of Terminal Epoxides Catalyzed by **1**



At the outset, styrene oxide (0.5 mmol), catalyst **1** (1 mol %), and base (2 mol %) in toluene solution were heated to 75 °C under hydrogen pressure (10 bar). Upon completion, gas chromatography (GC) and ¹H NMR analyses of the reaction mixture indicated 40% conversion of styrene oxide and the formation of both isomers of alcohols 80:20 (branched: linear, entry 1, Table 1). This result implies the predominant formation of secondary alcohol under our catalytic conditions. Increasing hydrogen pressure to 30 bar resulted in higher conversion and yield (78 and 76%, respectively) and provided increased selectivity for the secondary alcohol (92:8, entry 2, Table 1). Increasing hydrogen pressure to 50 bar under similar catalytic conditions resulted in the quantitative conversion of styrene oxide, and alcohols were isolated in 99% yield with very good selectivity for the secondary alcohol (94:6, entry 3, Table 1). Furthermore, varying the temperature and reducing the catalyst load were found to be less effective on the catalysis (entries 4–6, Table 1). No product formation was observed by employing only the base and without the catalyst and the base (entries 7 and 8, Table 1). These results clearly indicated that catalyst **1** and the base are playing a crucial role in promoting the selective ring opening of epoxides.

Scheme 4. Plausible Mechanism for the Selective Hydrogenation of Epoxides Catalyzed by **1**



As the optimal reaction condition was attained, the substrate scope of epoxides was investigated (Table 2). Remarkably, except for four substrates (see later), all other terminal epoxides subjected to catalysis exhibited complete regioselectivity for Markovnikov hydrogenation and delivered only secondary alcohols. The presence of electron-donating and halogen substitutions on the aromatic ring of epoxide was very well tolerated. 4-Methylstyrene oxide afforded 90% conversion with 72% yield of **2b**, whereas 10% of the corresponding primary alcohol was also isolated (entry 2, Table 2). 4-*tert*-Butylstyrene oxide provided only 28% conversion, however, with exclusive regioselectivity for the secondary alcohol under the optimized conditions. With increased catalyst load and temperature (3 mol % and 100 °C), 75% conversion was observed in which 42 and 26% of secondary and primary alcohols were isolated, respectively (entry 3, Table 2). Gratifyingly, the electron-withdrawing group containing styrene oxides provided excellent selectivity in moderate to excellent yield (entries 4–6, Table 2). 2-Benzyloxirane provided a high yield and exclusive selectivity for the secondary alcohol (entry 7, Table 2). Notably, the palladium-catalyzed hydrogenation of 2-benzyloxirane under heterogeneous conditions provided a mixture of both primary and secondary alcohols.^{6b} Furthermore, a variety of aromatic and aliphatic glycidyl terminal epoxides was tested, which resulted in very good yields of secondary alcohols with exclusive selectivity (entries 8–14, Table 2). Unactivated aliphatic epoxides were subjected to an increased catalyst load (5 mol %) and base (10 mol %), in which most of the substrates provided quantitative conversion, and the products were isolated in good to excellent yield (entries 15–19, Table 2). However, under similar conditions, when 1,1-disubstituted epoxide 2-methyl-2-phenyloxirane was subjected to hydrogenation, the formation of a mixture of both isomers of alcohols was observed in the reaction mixture (branched: linear, 50:49, entry 20, Table 2).

To further expand the scope of the protocol, we turned our attention to diepoxides. Interestingly, aromatic and aliphatic diepoxides provided quantitative conversion and yield with the complete formation of the corresponding secondary diols (Scheme 2). The products were isolated as mesomers due to

the presence of C_2 symmetry. In contrast with previous reports, the exclusive regioselectivity to secondary alcohols makes this process a new green alternative for the synthesis of diols.⁶

Toward understanding the reaction mechanism, the reaction with N_2 gas (50 bar) was performed (devoid of hydrogen), in which no epoxide ring opening occurred (Scheme 3a). The absence of the isomerization of the epoxide to ketone confirms that the reaction does not proceed via Meinwald rearrangement.¹⁶ This result indicates the importance of H_2 gas in the initial formation of ruthenium dihydride intermediate II and its role in the selective epoxide ring-opening reactions. Notably, internal epoxides did not undergo ring opening under the optimized reaction conditions (Scheme 3b). An enantiopure chiral epoxide *R*-(+)-glycidol was subjected to our catalysis, which provided a complex mixture (Scheme 3c).

On the basis of these experimental observations and our previous reports^{12–15,17} involving catalyst I, a catalytic cycle for the regioselective ring opening of epoxides to secondary alcohols is proposed (Scheme 4). Catalyst I in the presence of base is converted to reactive unsaturated intermediate I.^{17b,18} The heterolytic activation of H_2 by I involving amine–amide metal–ligand cooperation leads to the formation of saturated ruthenium dihydride intermediate II.¹⁹ Perhaps the formation of intermediate III upon the reaction of II with epoxide preferably involves less substituted carbon and oxygen centers of the terminal epoxide. Hydrogen pressure also plays an important role in the conversion of epoxide as well as the product selectivity. At 10 bar hydrogen pressure, only 40% conversion of epoxide occurred, in which a considerable amount of anti-Markovnikov primary alcohol was formed, 20% (Table 1, entry 1), indicating the involvement of other mechanistic pathways at low pressure. However, the use of 50 bar hydrogen pressure provided the complete conversion and a very high selectivity for the Markovnikov secondary alcohols (Table 1, entries 3 and 9; Table 2), indicating that a high hydrogen pressure is essential for the effective formation of ruthenium dihydride intermediate II and its further selective reaction with epoxide. Notably, the internal epoxide failed to undergo ring opening when subjected to catalysis (Scheme 3b). Thus, the preferential approach of metal hydride to the less substituted terminal carbon of epoxide, precluding the internal tertiary carbon and the interaction of the acidic amine proton with the epoxide oxygen, leads to the selective formation of intermediate III. On III, the metal hydride and amine proton are concomitantly transferred to the epoxide through a six-membered cyclic transition state, resulting in the selective formation of the secondary alcohol and the regeneration of the active intermediate I to complete a catalytic cycle.

In conclusion, a ruthenium-catalyzed highly Markovnikov selective hydrogenation of epoxides is demonstrated. The catalyst exhibits superior reactivity to control regioselectivity with a wide substrate scope. Diverse aromatic, benzylic, glycidyl, and aliphatic terminal epoxides and also diepoxides were well tolerated to provide secondary alcohol products in good to excellent yield. Interestingly, this transformation contrasts the recently reported catalytic anti-Markovnikov selective hydrogenation of epoxides and compliments the efficient and selective synthesis of secondary alcohols from epoxides.¹¹ Metal–ligand cooperation-mediated dihydrogen activation to ruthenium trans-dihydride formation and its preferential reaction with oxygen and the less substituted terminal carbon of the epoxide is suggested to be the origin of observed Markovnikov selectivity. The concomitant transfer of amine proton and metal hydride to

the epoxide through a six-membered cyclic transition state is proposed to provide the selective formation of secondary alcohols. The synthetic utilities of such mechanistic pathway are currently under investigation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.9b03995>.

Experimental procedures, spectral data, and copies of 1H and ^{13}C NMR spectra of the products (PDF)

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Notes

The authors declare no competing financial interest.

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