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Reactivity versus Stability of Oxiranes under Palladium-Catalyzed Reductive Conditions

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This review highlights the different selectivities and efficiencies of the Pd-catalyzed reductive procedures that have been applied to substrates containing an epoxide ring. The proposed mechanisms are also described with, in some cases, personal comments.

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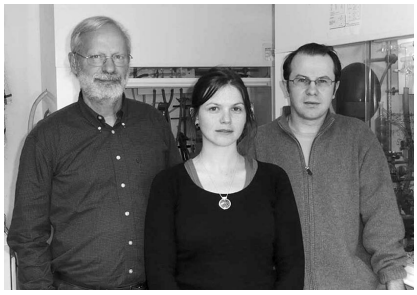


Emilie Thiery (middle) was born in Paris in 1982. She received her Master in Organic Chemistry at the University of Orsay (2005), where she worked on lanthanide catalysis under the supervision of J.-L. Namy. She is currently completing her PhD, studying Pd-catalyzed reactions and mechanisms assisted by ESI-MS analysis.

Jean Le Bras (right) was born in Brest in 1970 and obtained his Engineering Diploma from ENSCP – Paris and his MSc degree (DEA) from Université P. et M. Curie. In 1996, he joined the group of H. Amouri, where he studied Ir-mediated phenol functionalization and obtained his PhD in 1998. Then, he joined the group of J. A. Gladysz for two years in Salt Lake City (USA) and then in Erlangen (Germany), working on the synthesis of organometallic complexes with 17 valence electrons and polyynediyl chains. In 2000, he became a CNRS fellow at Université de Reims Champagne-Ardenne.

Jacques Muzart (left) was born in 1946, in Vienne la Ville, a small village in the Argonne area, 200 km east of Paris. He studied chemistry at the Université de Reims Champagne-Ardenne and received his degrees (Doctorat de 3ème cycle in 1972, Doctorat d'Etat in 1976) for his work with J.-P. Pète on photochemical rearrangements of α,β-epoxy ketones and β-diketones. He was appointed at the Centre National de la Recherche Scientifique (CNRS) in 1971 and spent 15 months (1977–1978) as a postdoctoral fellow of National Science Foundation working with E. J. Corey at Harvard University on natural product synthesis. In 1988, he was promoted to Directeur de Recherche CNRS. The research interests of the team are concentrated on transition metal catalysis with particular emphasis on oxidations, asymmetric reactions, C-H activation, valorization of agricultural byproducts, and the use of water and molten salts as solvents for organic synthesis.

1. Introduction

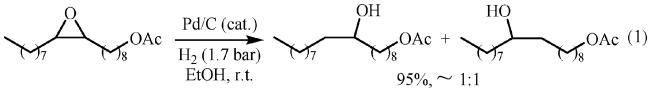
Owing to the effective epoxidation methods of olefins,[1] the reduction of epoxides into the corresponding alcohols constitutes a useful transformation in organic synthesis. Among the different reductive oxirane opening procedures,[2] catalytic hydrogenolysis ranks among the simplest and has been extensively utilized for the reduction of a variety of oxirane substrates, and one of the most powerful transition-metal catalysts is palladium.[3] Seeing the importance of this reaction, it seems of interest to provide an overview of the different Pd-catalyzed procedures in highlighting the corresponding selectivities and the possible mechanisms. This is the aim of the present review that is organized by type of substrate with, mainly, a chronological account of the reports. The reductive species are hydrogen and hydride transfer agents; their use will be successively examined in the text, but will be together gathered in some tables and schemes to facilitate the comparisons.

2. Unactivated Epoxides

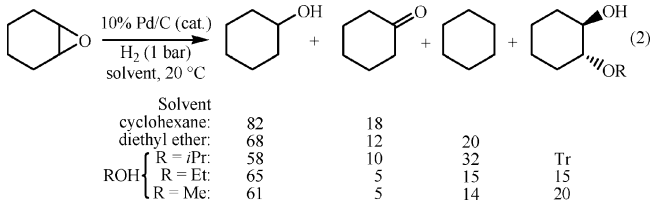
This section concerns the substrates bearing no unsaturation in the α-position of the oxirane.

2.1. Using Molecular Hydrogen

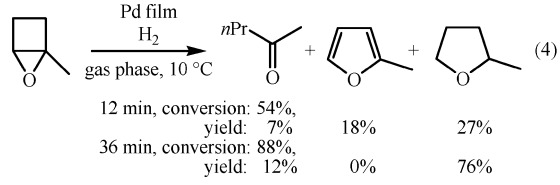
The hydrogenolysis of ethylene oxide[4] and alkyl epoxides by molecular hydrogen over Pd black or supported Pd is an old reaction that was patented as early as at least 1930[5] and has led to a number of papers. The reductive cleavage of the less-crowded C–O bond is usually the main reaction observed. When both extremities of aliphatic epoxides are similarly crowded, as for example, *cis*-9,10-epoxyoctadecan-1-ol, *cis*-9,10-epoxyoctadecyl acetate [Equation (1)],[6] *cis*-6,7-epoxyoctadecanoic acid,[7] and methyl *cis*-9,10-epoxystearate,[8] the two corresponding hydroxy compounds are formed in nearly equal amounts.[9] Nevertheless, the quality of the catalyst and the presence of additives can have an influence on the selectivity.[10]



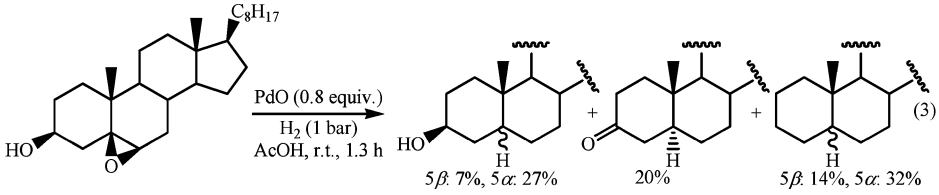
The selectivity can also be solvent dependent as depicted in Equation (2). Alcohols are often used but with possible solvolysis of the substrate.[11] The formation of a ketone and the cleavage of the C–OH bond have been observed[11–14] [Equation (2)].[11] This last side reaction can be particularly efficient in acetic acid [Equation (3)].[15,16] Furthermore, AcOH can react with the oxirane even in the absence of any catalyst.[16]



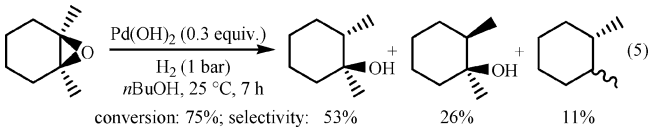
Hydrogenolyses have also been carried out in the gas phase. Sénéchal and Cornet observed that the hydrogenation of gaseous 1,2- and 2,3-epoxybutanes into butanols is accompanied by the formation of butanone, butanal, and butane; the reduction of the carbonyl compounds into butanols is a minor process under their experimental conditions.[17] Under similar conditions, the reaction of 1-methylepoxycyclopentane led mainly to the cleavage of the more crowded C–O bond and afforded *trans*-2-methylcyclopentanol,[18] whereas that of strained 1-methyl-1,2-epoxycyclobutane led to C–C bond cleavage yielding 2-pentanone and 2-methylfuran, and the latter compound evolved into 2-methyltetrahydrofuran [Equation (4)].[19]

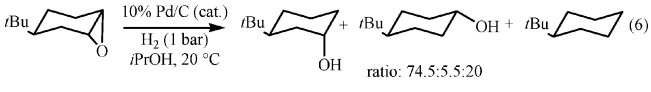


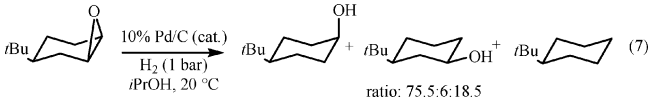
Sugi et al. disclosed that, in butanol, 1,2-epoxy-1,2-dimethylcyclohexane leads to both diastereoisomeric alcohols with predominance of the *trans* isomer [Equation (5)].[13] Subsequently, the stereoselectivity of the Pd/C-catalyzed ring opening of 4-*tert*-butyl-1-methylenecyclohexane oxide[12] and a range of substituted cyclohexene oxides was carefully studied by Geneste et al.[11,20] The hydrogenolysis of *cis*- and *trans*-1,2-epoxy-4-*tert*-butylcyclohexanes gives preferentially axial alcohols [Equations (6) and (7)] and the use of D_2 instead of H_2 has shown that deuterolysis proceeds essentially through *trans* addition.[11,21] This agrees with the deuterolysis of 2,5:3,4-dianhydro-D-altritol [Equation (8)].[22,23] The hydrogenolysis of *cis*- [Equation (9)] and *trans*-1,2-epoxy-1-methyl-4-*tert*-butylcyclohexanes [Equa-

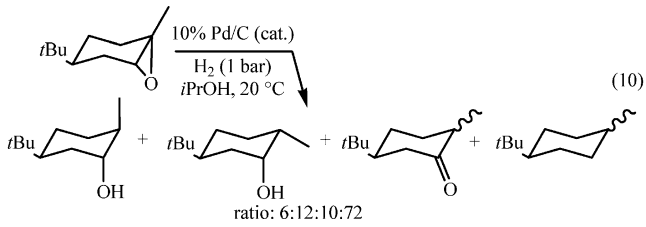


tion (10)][11] and carvomenthene oxides[20] is less selective and reveals a competition between *cis* and *trans* addition, in particular from the former substrate.

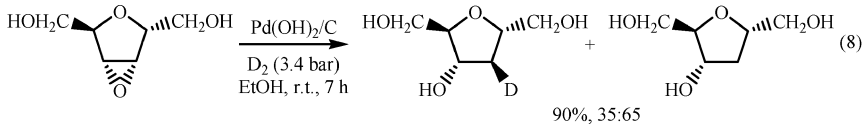








In 1998, Sajiki, Hirota et al. disclosed a new isolable hydrogenation catalyst, namely, Pd/C(en), obtained from Pd/C and ethylenediamine[24] that was used under pressure of hydrogen for the reduction, in MeOH, of epoxides, (Table 1, entries 3 and 6; Table 2, entries 1 and 7).[25,26] As shown in Tables 1 and 2, the reduction with Pd/C(en) is usually more selective than that with Pd/C. In contrast to MeOH, slight or no hydrogenolysis occurred in THF under Pd/C(en) ca-



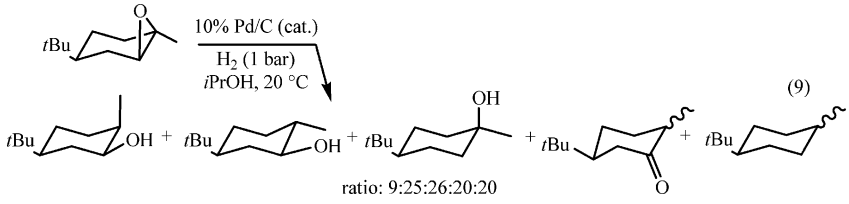
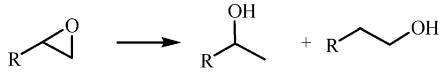
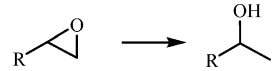


Table 1. Influence of the experimental conditions on the reactivity of 1,2-epoxydecane, 2-phenethyloxirane, and 3-phenyl-1,2-epoxypropane.

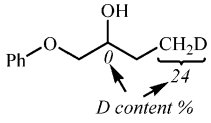


Entry	Catalyst (equiv. or wt.-%)	Reductive species	Solvent	Temp. [°C]	Time [h]	**2**-OH [%]	**1**-OH [%]
R = C_8H_{17}							
1[25]	10% Pd/C (10 wt.-%)	H_2 (1 bar)	MeOH	r.t.	6	57	13
2[25]	10% Pd/C (10 wt.-%)	H_2 (5 bar)	MeOH	r.t.	3	60	12
3[25]	10% Pd/C(en) (10 wt.-%)	H_2 (5 bar)	MeOH	r.t.	24	81	0
4[29]	10% Pd/C (0.04 equiv.)	H_2 (1 bar)	EtOH	23	2.5	73	12
5[29]	10% Pd/C (0.04 equiv.)	HCO_2NH_4 (3 equiv.)	EtOH	23	48	79	2
R = $PhCH_2CH_2$							
6[25]	10% Pd/C(en) (10 wt.-%)	H_2 (5 bar)	MeOH	r.t.	24	95	<5
7[29]	10% Pd/C (0.04 equiv.)	HCO_2NH_4 (3 equiv.)	EtOH	23	3.5	85	<5
8[30]	5% Pd/C (0.005 equiv.)	HCO_2NH_4 (2 equiv.)	MeOH	45	18	80	
R = $PhCH_2$							
9[31]	Pd^0EnCat (0.05 equiv.)	H_2 (40 bar)	MeOH	23	19	71	14
10[32]	MAGPd (0.02 equiv.)	H_2 (balloon)	EtOAc	23	4	85	15
11[33]	$Pd_{OAc,N}$ (0.01 equiv.) + nBu_4NBr (0.5 equiv.)	H_2 (balloon)	H_2O	80	48	13	75
12[31]	Pd^0EnCat (0.05 equiv.)	HCO_2H/NEt_3 (4 equiv.)	EtOAc	23	very slow reaction		

Table 2. Influence of the experimental conditions on the reactivity of phenoxymethyloxirane, hydroxymethyloxirane, and benzyloxymethyloxirane.



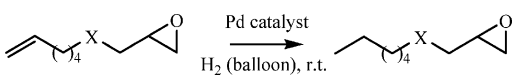
Entry	Catalyst (equiv. or wt.-%)	Reductive species	Solvent	Temp. [°C]	Time [h]	Product [%]
R = $PhOCH_2$						
1[25]	10% Pd/C(en) (10 wt.-%)	H_2 (1 bar)	MeOH	r.t.	24	95
2[34]	10% Pd/C (10 wt.-%)	H_2 (1 bar)	D_2O	r.t.	24	92[a]
3[29]	10% Pd/C (0.04 equiv.)	HCO_2NH_4 (3 equiv.)	EtOH	23	1	91
4[32]	MAGPd (0.02 equiv.)	H_2 (balloon)	EtOAc	23	0.5	97
5[30]	5% Pd/C (cat.)	HCO_2NH_4 (2 equiv.)	dioxane	reflux	3	70
R = $HOCH_2$						
6[35][b]	5% Pd/C (5 wt.-%) NaOH (0.05 equiv.)	H_2 (1.7 bar)	EtOH	r.t.	6	>80[c]
7[25]	10% Pd/C(en) (10 wt.-%)	H_2 (1 bar)	MeOH	r.t.	22	89
8[32]	MAGPd (0.02 equiv.)	H_2 (balloon)	EtOAc	23	5	99
R = $PhCH_2OCH_2$						
9[29][b]	10% Pd/C (0.04 equiv.)	HCO_2NH_4 (3 equiv.)	EtOH	23	0.75	80[c]

[a] Deuterated alcohol: 

[b] Optically active substrate. [c] No change in optical purity.

talysis.[26,27] This observation led Sajiki et al. to carry out the selective reduction, in THF, of C=C bonds (Table 3, entries 1 and 2) and nitro and azide functionalities in tolerating the presence of oxiranes.[27] According to these authors, THF oxygen atoms, instead of the oxirane oxygen atoms, occupy the surface of the catalyst, hence, blocking the hydrogenolysis of the epoxide.[28] The formation of low amounts of 1-decanol from 1,2-epoxy-9-decene (Table 3, entry 1) would be due to the isomerization of the olefin moiety leading finally to the cleavage of the heterocycle.[27] The influence of a remote C=C bond to the opening of the oxirane was previously observed from epoxides of limonene.[20]

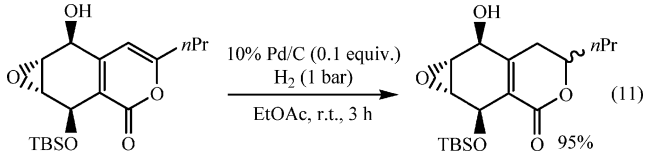
Table 3. Influence of the experimental conditions on the reactivity of unsaturated epoxides.

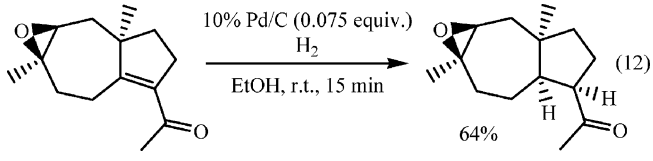


Entry	X	Catalyst (equiv. or wt.-%)	Solvent	Time [h]	Product [%]
1[27]	CH_2	5% Pd/C(en) (10 wt.-%)	THF	3	82[a]
2[27]	O	5% Pd/C(en) (10 wt.-%)	THF	3	92
3[36]	CH_2	$Pd_{OAc,N}$ (0.01 equiv.)	PhMe	4	94
4[36]	CH_2	$Pd_{OAc,N}$ (0.01 equiv.)	H_2O	4	92
5[36]	CH_2	$Pd_{OAc,N}$ (0.01 equiv.)	H_2O	24	91

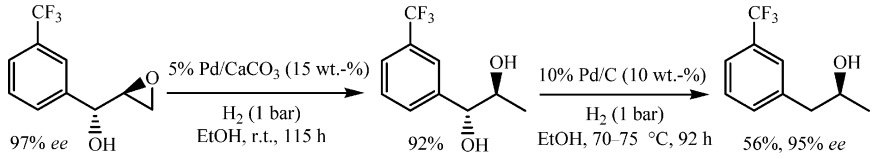
[a] Traces of 1-decanol were detected.

In 2004, we reported the hydrogenation of olefins over palladium nanoparticles, namely $Pd_{OAc,N}$, obtained from palladium salts and tri-*n*-butylamine in molten tetrabutylammonium bromide.[37] Recently, we observed that $Pd_{OAc,N}$ is able to selectively catalyze the hydrogenation of the C=C bond of 1,2-epoxy-9-decene in high yields, even with water as solvent (Table 3, entries 3–5).[36] Note, however, that some selective hydrogenation of a C=C bond in the presence of a remote oxirane over Pd/C in EtOAc,[38,39] PhMe,[40] and even EtOH[41] has been reported as illustrated in Equations (11) and (12).



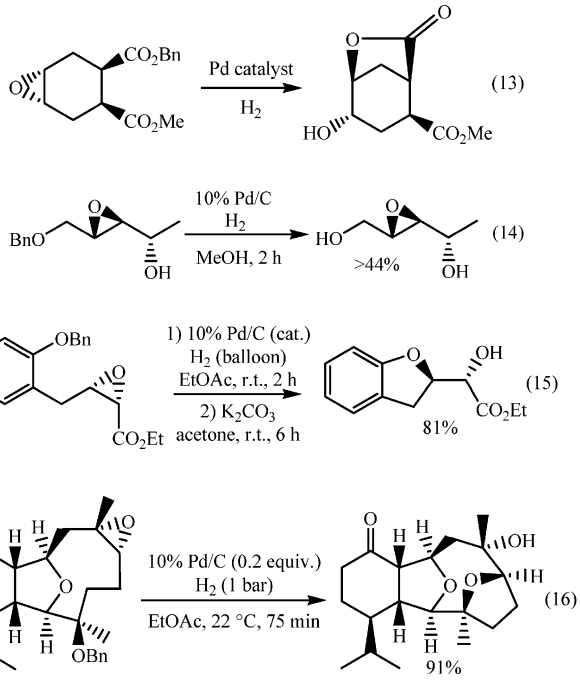


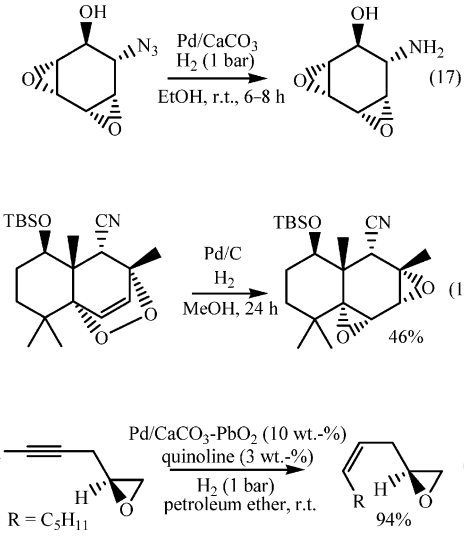
Duhamel et al. tried, without success, to carry out the one-pot hydrogenolysis of both the oxirane and the benzylic alcohol moieties of 1-(*m*-trifluoromethylphenyl)-2,3-epoxypropan-1-ol by using Pd/C as the catalyst.[42] Finally, the transformation was effectively realized in EtOH through a two-step procedure: the hydrogenolysis of the oxirane was obtained over $Pd/CaCO_3$ at room temperature, whereas that of the benzylic alcohol occurred over Pd/C at 70–75 °C (Scheme 1).



Scheme 1. Two-step reductive cleavage of oxirane and benzylic alcohol units.[42]

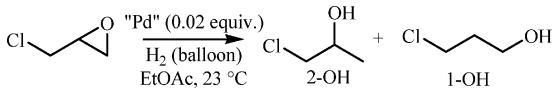
The one-pot cleavage of both the benzyl ester and oxirane moieties of 4,5-epoxy-1,2-*cis*-cyclohexanedicarboxylate leading to a lactone was carried out by using palladium and hydrogen [Equation (13)].[43] Nevertheless, the selective hydrogenolysis of the benzyl ether moiety of (*S*)-1-{3-[(benzyloxy)methyl]oxiran-2-yl}ethanol was observed [Equation (14)],[44] and Das and Panda added a base to carry out the cyclization step [Equation (15)].[45] The cleavage of benzyl ethers in the presence of remote epoxides has also been carried out with $Pd(OH)_2$ as the catalyst, H_2 (3.5 bar) in MeOH at room temperature, but in low yields.[46,47] In the framework of the synthesis of (+)-vigulariol, Hoppe et al. recently reported the reaction shown in Equation (16).[48] According to the authors, the debenzylation occurred first, which was followed by attack of the alcohol onto the oxirane. The possible stability of oxiranes towards hydrogenolysis by using supported Pd catalysts in alcoholic solvents is also illustrated in Equations (17)[49] and (18).[50] The semihydrogenation of a C≡C bond by using Lindlar's catalyst, eventually with quinoline as an additive, is also compatible with the presence of an oxirane [Equation (19)].[51] Consequently, this cascade reaction did not involve the hydrogenolysis of the epoxide. In contrast, Subbarao et al. found that the addition of silver nitrate to Pd/C allows, at room temperature in EtOH, the selective hydrogenolysis of oxiranes in the presence of alkenes (H_2 pressure: 2 bar); this could be due to the formation of a π complex between the double bond and silver.[52]





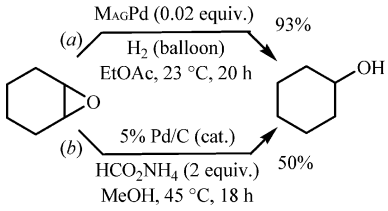
In 2003, Ley, Spencer, et al. described a recyclable polyurea-encapsulated palladium catalyst, namely, Pd^0EnCat, prepared by reduction of polyurea-coordinated $Pd(OAc)_2$ with formic acid.[53] This catalyst mediates the room-temperature hydrogenolysis of 3-phenylepoxypropane in methanol, but a pressure of hydrogen is required and a mixture of the corresponding primary and secondary alcohols is obtained (Table 1, entry 9).[31,54] This substrate was also reduced by using a balloon fitted with hydrogen, EtOAc as the solvent, and a magnetically separable palladium catalyst, MAGPd, as described by Park et al. in 2007 (Table 1, entry 10).[32] The above two catalysts led to the secondary alcohol as the main product. In contrast, $Pd_{OAc,N}$ associ-

Table 4. Catalytic activity of various Pd catalysts in the hydrogenolysis of epichlorhydrin.[32]

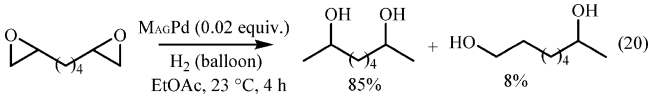


Catalyst	Time [h]	% Conversion	Yield of **2**-OH [%]	Yield of **1**-OH [%]
MAGPd	4	>99	99.8	0.2
5% Pd/C	4	89	83	6
5% Pd/C	20	>99	91	9
5% Pd/Al_2O_3	4	70.9	70	0.9
5% Pd/Al_2O_3	20	>99	98.3	1.7
5% $Pd/CaCO_3$	4	65.1	64.5	0.6
5% $Pd/CaCO_3$	20	91.3	89.1	2.2
5% $Pd/BaCO_3$	4	14.9	14.5	0.4
5% $Pd/BaCO_3$	20	70	68.7	1.3
4.3% Pd^0EnCat	20	0		

ated to nBu$_4$NBr favors, in water at 80 °C, the formation of the primary alcohol (Table 1, entry 11).[33] MAGPd is more active in the hydrogenolysis of epichlorhydrin than commercial Pd catalysts (Table 4). Moreover, MAGPd can be reused 25 times without activity loss, and it is effective for the hydrogenolysis of various terminal and internal epoxides [Table 1, entry 10; Table 2, entries 4 and 8; Equation (20); Scheme 2, path *a*].

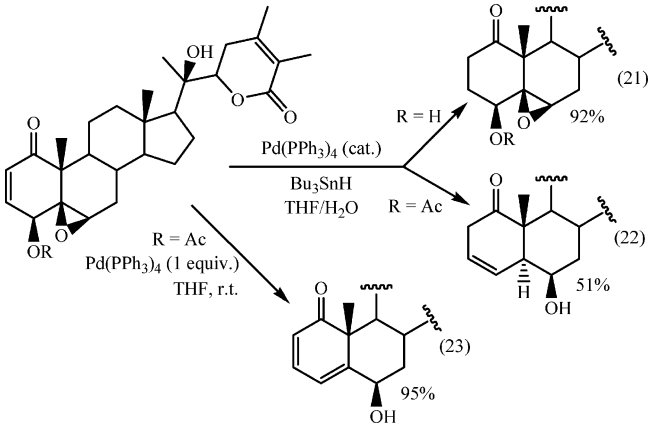


Scheme 2. Hydrogenolysis of cyclohexene oxide.[30,32]

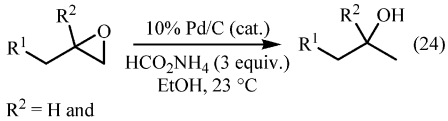


2.2. Using Hydride Transfer Agents

In 1982, Keinan et al. disclosed the Pd-catalyzed reduction of α,β-unsaturated carbonyl compounds[55] and the reductive cleavage of allylic acetates,[56] both with (nBu)$_3$SnH as the hydrogen source. Subjecting the multifunctionalized substrate shown in Equation (21) to these conditions led to the selective reduction of the C=C bond,[55] whereas concomitant reduction of the epoxide occurred from the corresponding acetylated substrate [Equation (22)].[56] In the absence of an hydrogen source, the reaction of the acetylated substrate, using mainly a stoichiometric amount of Pd(PPh$_3$)$_4$, also led to the cleavage of the oxirane but afforded a dienic compound [Equation (23)].[57]



In 1994, Iyer et al. described the Pd/C-catalyzed hydrogenolysis of epoxides by using ammonium formate as the hydrogen source in methanol or dioxane.[30] The reactions, carried out between 45 and 105 °C, led to yields lower than those obtained with molecular hydrogen (Table 1, entry 8; Table 2, entry 5; Scheme 2, path *b*). In 1995, Dragovich et al., who were not aware of Iyer's paper, reported that the Pd/C-catalyzed reduction of 1,2-epoxydecane, at room temperature in ethanol, with either ammonium formate or molecular hydrogen, led to similar yields but with different rates and regioselectivities: the reaction proceeded at a much faster rate with the latter but the 2-decanol/1-decanol ratio decreased from 97:3 to 86:14 (Table 1, entries 4 and 5).[29,58] These transfer hydrogenation conditions were used for the selective reduction of a panel of terminal alkyl epoxides [Table 1, entry 7; Equation (24)]. Interestingly, the reductive cleavage of an optically active oxirane occurs with little or no loss of optically activity and can be performed without hydrogenolysis of a benzyl ether (Table 2, entry 9).[29] Instead of a supported Pd catalyst, Ley et al. tested the use of Pd^{0}EnCat for the reduction of 3-phenylepoxypropane, but the reaction of this unactivated oxirane was very sluggish (Table 1, entry 12).[31]



R^2 = H and
R^1 = PhCH$_2$ (3.5 h: 85%), PhO (1 h: 91%), HO(CH$_2$)$_7$ (10 h: 95%), TBSO(CH$_2$)$_3$ (48 h: 92%), PhCH$_2$CO$_2$(CH$_2$)$_3$ (6 h: 97%)
R^2 = Me and
R^1 = PhCH$_2$ (5 h: 90%), PhO (3 h: 95%)

2.3. Mechanism

The nature of the catalyst, solvent, and hydrogen source can have a decisive role on the efficiency and regioselectivity, their relative importance depending on the substrate. To comment about these aspects is out of the scope of the present review.

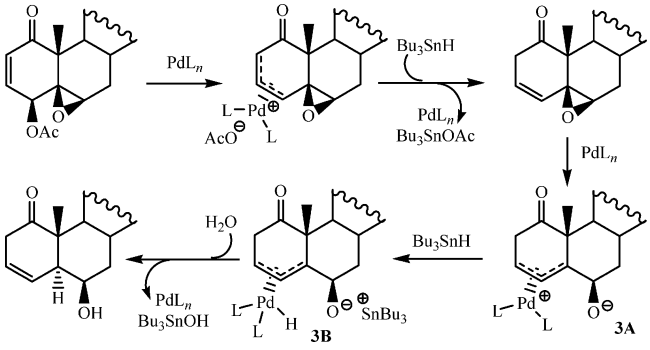
2.3.1. In the Presence of Molecular Hydrogen

The formation of PdH species from the activation of molecular hydrogen by palladium is usually admitted. The key step of epoxide cleavage would be, in most cases, the coordination of the oxygen atom to the catalyst,[11,13] but interaction with the C–C bond has also been suggested.[13,19,59] The Pd/C-catalyzed formation of mainly secondary alcohols from terminal epoxides [Scheme 1, Tables 1–4, Equations (20) and (24)] and axial alcohols from 1,2-epoxy-4-*tert*-butylcyclohexanes [Equations (6) and (7)] could be due to steric reasons and indicates that the oxirane unit of these substrates approaches the catalyst surface from the less-hindered side. According to Geneste et al., if the molecule is diadsorbed after C–O bond cleavage, hydrogen would add in a *cis* fashion. Because the addition from 1,2-epoxy-4-*tert*-butylcyclohexanes is *trans*, the authors suggest that a roll over without desorption of the molecule[60] on the catalytic surface precedes the hydrogen addition.[11] *trans*-Addition has also been exemplified from 2,5:3,4-di-

anhydro-D-altritol [Equation (8)].[22] The predominant *cis* addition from 1,2-epoxy-1,2-dimethylcyclohexane [Equation (5)],[13] *cis*-1,2-epoxy-1-methyl-4-*tert*-butylcyclohexane [Equation (9)],[11] and carvomenthene oxides[20] would be due to the steric effect of the methyl groups that prevents the roll over or makes it more difficult. Moreover, the approach of the oxirane to the catalyst surface is highly dependent on the substituents; indeed, the transformation of the two stereoisomers of 2,3-epoxybutane involves different approaches.[61] The formation of η^3-oxoallylpalladium intermediates, envisaged to explain the concurrent formation of ketones, has been supported by deuterolysis experiments.[17] Such intermediates may also lead to the alcohols.

2.3.2. In the Presence of Tributyltin Hydride

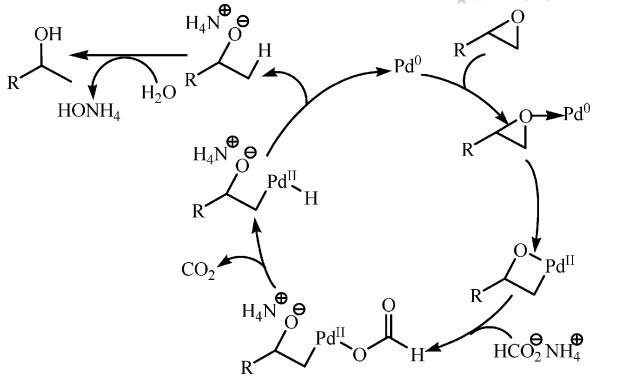
Concerning the reduction depicted in Equation (22), we suspect that the first step is the transformation of the γ-acetoxy-α,β-unsaturated carbonyl moiety into the corresponding β,γ-unsaturated ketone (Scheme 3). The vinylic epoxide thus obtained reacts with the Pd catalyst to afford η^3-allylpalladium intermediate **3A**, the reaction of which with tin hydride leads to the isolated product. The 5α-configuration of the introduced hydrogen agrees with the formation of transient hydridopalladium complex **3B**.[62] Note that this oxirane hydrogenolysis concerns, in fact, an α,β-unsaturated epoxide, a topic that is highlighted in Section 5.



Scheme 3. Suggested mechanism for the cascade reduction of an α′,β′-epoxy allylic acetate.

2.3.3. In the Presence of Ammonium Formate

To the best of our knowledge, no mechanism has been proposed for the Pd-catalyzed reduction of epoxides by ammonium formate. For the reduction of allylic acetates under similar conditions, the formation of hydridopalladium species has been suggested,[63] but an alternative mechanism without such species has been invoked.[64] Given these reports, we suspect, for epoxides, the mechanism depicted in Scheme 4. The insertion of palladium into a C–O bond of the oxirane leads to a palladacycle that reacts with ammonium formate to afford, after elimination of carbon dioxide, a hydridopalladium intermediate. Reductive elimination of palladium followed by hydrolysis of the released alkoxyammonium provides the alcohol.



Scheme 4. Suggested mechanism for the reduction of epoxides by ammonium formate.

3. Arylepoxides

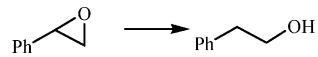
This section summarizes the Pd-catalyzed hydrogenolysis of oxiranes having an aryl substituent. The reactivity of the substrates for which the aryl epoxide unit is in the α-position of a carbonyl group or a C=C bond will be documented in Sections 4 and 5, respectively.

3.1. Using Molecular Hydrogen

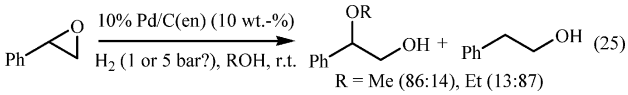
The Pd-catalyzed reductive cleavage of styrene oxide into 2-phenylethanol has been the subject of intensive research as illustrated by the number of patents[65,66] and reports. Various Pd catalysts have been used at room temperature to 125 °C under 1–100 bar of hydrogen in various solvents, or in the gas phase;[67–69] some of the results are gathered in Table 5. Deoxygenation is scarcely observed with Pd/C.[68,69] Interestingly, the use of low amounts of $Pd_{OAc,N}$ as the catalyst, in methanol and especially water, at room temperature and atmospheric hydrogen pressure provides high yields (Table 5, entries 4 and 8), whereas other solvents were less effective (Table 5, entries 5–7).[33] An unexpected reaction was encountered by Sajiki et al. by using Pd/C(en) in alcohols; indeed, the regioselective alcoholysis of the oxirane can be the main reactive pathway [Equation (25)].[25] This contrasts with the use of 5% Pd/C (Table 5, entry 1) [70–72] and aqueous Pd colloids[73] for reactions that were, however, carried out at higher hydrogen pressure. In fact, we recently reported the methanolysis of an aryl epoxide by using Pd/C and atmospheric pressure of hydrogen [Equation (26)].[74] Moreover, we observed that the $Pd_{OAc,N}$-catalyzed hydrogenolysis of epoxidized vinyl arenes in water can lead to the corresponding hydrolysis compounds as side products [Equation (27)].[33] In contrast to the $Pd_{OAc,N}$ catalyst that did not mediate the hydrogenolysis of the Ar–Cl bond of (*m*-chlorophenyl)oxirane [Equation (27)], Pd/C may induce such a reaction as reported by Sajiki et al. under deuteriolysis conditions [Equation (28)].[23,34]

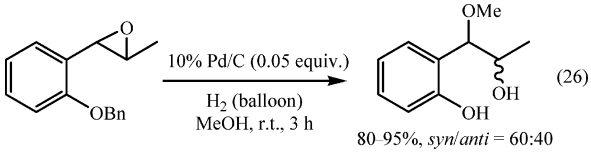
The hydrogenolysis of *trans*-stilbene oxide and 2,3-epoxy-3-arylpropan-1-ols has also been carried out under various experimental conditions. Whereas Pd/C (from Aldrich, ref. 205680) leads to deoxygenation of the former,

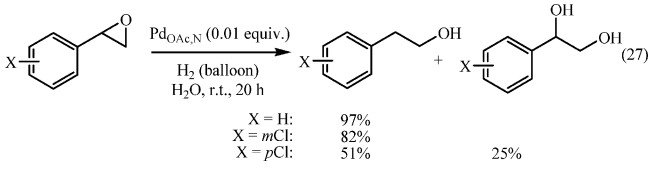
Table 5. Reactivity of styrene oxide under Pd-catalyzed hydrogenolysis conditions.

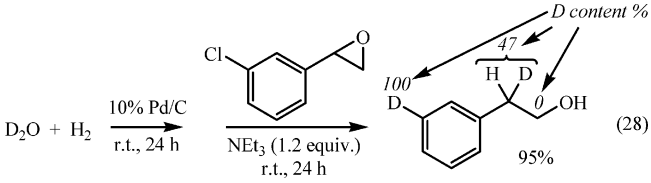


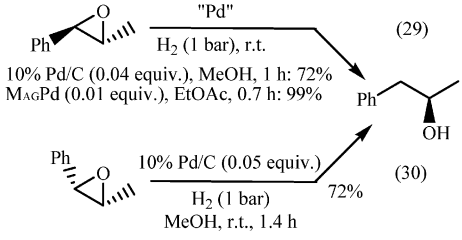
Entry	Catalyst (equiv. or wt.-%)	Reductive species	Solvent	Temp. [°C]	Time [h]	Conv. [%]	Yield [%]
1[71]	5% Pd/C (4 wt.-%)	H_2 (15 bar)	MeOH	28	0.5	96.8	95
2[75]	Pd^0EnCat (0.1 equiv.)	H_2 (balloon)	EtOH	r.t.	16	100	100
3[32]	MAGPd (0.01 equiv.)	H_2 (balloon)	EtOAc	23	1.5	100	96
4[33]	$Pd_{OAc,N}$ (0.01 equiv.)	H_2 (balloon)	MeOH	r.t.	20	100	88
5[33]	$Pd_{OAc,N}$ (0.01 equiv.)	H_2 (balloon)	EtOAc	r.t.	20	0	0
6[33]	$Pd_{OAc,N}$ (0.01 equiv.)	H_2 (balloon)	MeCN	r.t.	20	77	34
7[33]	$Pd_{OAc,N}$ (0.01 equiv.)	H_2 (balloon)	[bmim][PF_6]	r.t.	20	55	16
8[33]	$Pd_{OAc,N}$ (0.01 equiv.)	H_2 (balloon)	H_2O	r.t.	20	100	97
9[29]	10% Pd/C (0.04 equiv.)	HCO_2NH_4 (3 equiv.)	EtOH	23	1.5	100	58
10[30]	5% Pd/C (0.005 equiv.)	HCO_2NH_4 (2 equiv.)	MeOH	reflux	2	100	100
11[31]	Pd^0EnCat (0.05 equiv.)	HCO_2H + NEt_3 (4 equiv.)	EtOAc	23	4	100	84
12[76]	5% Pd/Urea-MCF (0.1 equiv.)	HCO_2NH_4 (5 equiv.)	EtOAc	25	12	100	91



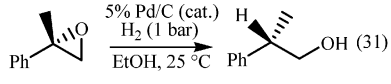






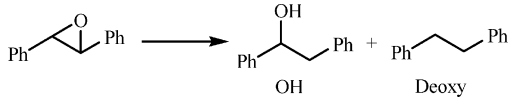


Pd^0EnCat, MAGPd, and $Pd_{OAc,N}$ afford selectively 1,2-diphenylethanol (Table 6, entries 1–5). As for 2,3-epoxy-3-arylpropan-1-ols, they selectively give the corresponding α-diols (Table 7, entries 1–3). As expected, (*R*,*R*)- and (*S*,*R*)-1,2-epoxy-1-phenylpropanes both led to (*R*)-1-phenyl-2-propanol [Equations (29) and (30)], and a quantitative yield was obtained by using MAGPd as the catalyst.[32,77]



Mitsui et al. reported that the Pd-catalyzed reductive cleavage of chiral α-methylstyrene oxide with hydrogen, at room temperature in EtOH, leads predominantly to

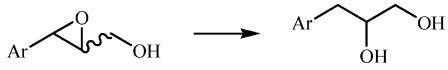
Table 6. Hydrogenolysis of *trans*-stilbene oxide.



Entry	Catalyst (equiv.)	Reductive species	Solvent	Temp. [°C]	Time [h]	OH Yield [%]	Deoxy Yield [%]
1[75]	5% Pd/C (0.1)	H_2 (balloon)	EtOH	r.t.	16	0	100
2[75]	Pd^0EnCat (0.1)	H_2 (balloon)	EtOH	r.t.	16	93	7
3[32]	MAGPd (0.01)	H_2 (balloon)	EtOAc	23	0.5	94	<1
4[33]	$Pd_{OAc,N}$ (0.01)	H_2 (balloon)	H_2O/MeCN (2:1)	r.t.	20	92	
5[33]	$Pd_{OAc,N}$ (0.01)	H_2 (balloon)	H_2O	80	15	98	
6[75]	Pd^0EnCat (0.1)	HCO_2NH_4	MeOH/H_2O	r.t.	16	98	2
7[31][a]	Pd^0EnCat (0.05)	HCO_2H + NEt_3 (4 equiv.)	EtOAc	23	5	99	
8[76][a]	5% Pd/Urea-MCF (0.1)	HCO_2NH_4 (5 equiv.)	EtOAc	25	24	99	

[a] The catalyst was recycled 10 times without any loss in reactivity and selectivity.

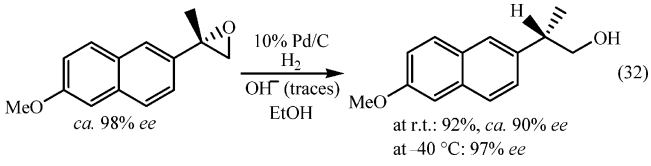
Table 7. Hydrogenolysis of 2,3-epoxy-3-phenylpropan-1-ol and 2,3-epoxy-3-(*m*-trifluorophenyl)-1-propanol.



Entry	Catalyst (equiv. or wt.-%)	Reductive species	Solvent	Temp. [°C]	Time [h]	Yield [%]
1[75][a]	Pd^0EnCat (0.1 equiv.)	H_2 (balloon)	EtOH	r.t.	16	100
2[32][a]	MAGPd (0.01 equiv.)	H_2 (balloon)	EtOAc	23	2	94
3[42][b]	5% Pd/C (10 wt.-%)	H_2 (1 bar)	EtOH	20	19	100
4[31][a]	Pd^0EnCat (0.05 equiv.)	HCO_2H (4 equiv.) + NEt_3 (4 equiv.)	EtOAc	23	5	95
5[76][a]	5% Pd/Urea-MCF (0.1 equiv.)	HCO_2NH_4 (5 equiv.)	EtOAc	25	24	98

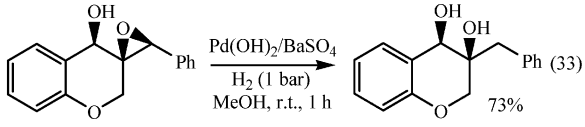
[a] Ar = Ph. [b] Ar = $mCF_3C_6H_4$; optically active substrate (96%*ee*); preservation of the enantioselectivity in the course of the hydrogenolysis.

stereochemically inverted 2-phenylpropan-1-ol [Equation (31)];[69,78,79] the inversion/retention ratio is dependent on the quality of the catalyst and additives.[80] A decrease in the reaction temperature can be required to preserve the optical activity, as shown by Hamon et al. [Equation (32)], who used such a transformation, as a key step, for the synthesis of (*S*)-naproxen and (*S*)-flurbiprofen.[81]



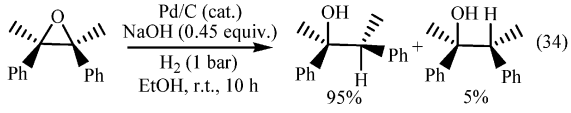
(32)

In alcohols, α,β-epoxyalcohols such as 3-benzylidene-3,4-dihydro-2*H*-chromen-4-ol oxide [Equation (33)][82] and 1,3-diphenylprop-2-en-1-ol oxide[83] lead cleanly to the corresponding α-diols.

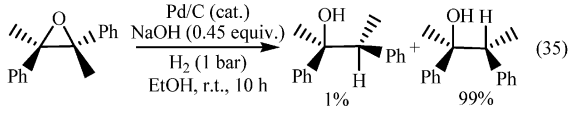


(33)

The hydrogenolysis of tetrasubstituted aryl epoxides was studied by Mitsui and Nagahisa.[78,84] In the presence of homemade Pd/C and sodium hydroxide, the hydrogenation in EtOH leads mainly to the *anti* compound from *cis*-2,3-dimethyl-2,3-diphenyloxirane [Equation (34)],[84] whereas the *trans* epoxide affords essentially the *syn* alcohol [Equation (35)].[78,84] A lower selectivity and trace amounts of 2,3-diphenylbutane were obtained in the absence of NaOH.[84] It seems of interest to point out that Pd/C-catalyzed procedures with base as additive come across in various reports.[65,70,78,84,85] This could be to neutralize the trace amounts of acid contained in some Pd/C catalysts.[78] In fact, the literature contains information on the possible acidity of homemade[78] and commercial Pd/C catalysts[86] and misinterpretations of results.[87,88]

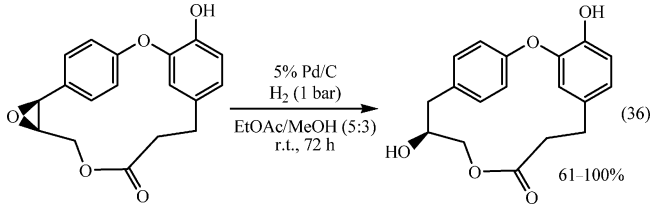


(34)

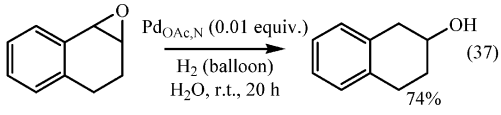


(35)

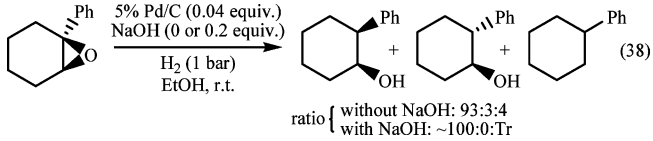
Selective C_α–O bond cleavage is also obtained from alicyclic aryl epoxides as shown in Equations (36)[89] and (37).[33] 1,2-Epoxy-1-phenylcyclohexane leads mainly to *cis*-2-phenylcyclohexanol; the quantity of *trans*-2-phenylcyclohexanol and phenylcyclohexane that are simultaneously produced is considerably reduced by the addition of NaOH [Equation (38)].[85]



(36)



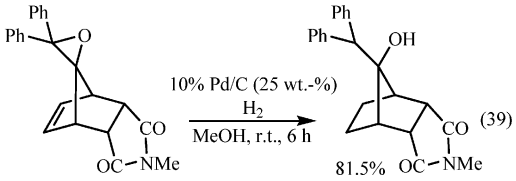
(37)

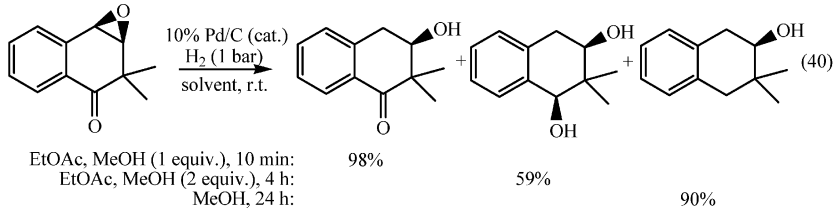


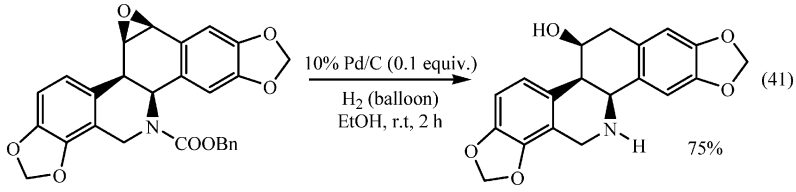
(38)

By using Paar shaker, Poos and Rosenau observed the reduction, over Pd/C in MeOH, of both the C=C bond and the oxirane of the imide depicted in Equation (39); unfortunately, the hydrogen pressure was not indicated.[90] In other respects, Tomkinson et al. showed that the selectivity of the

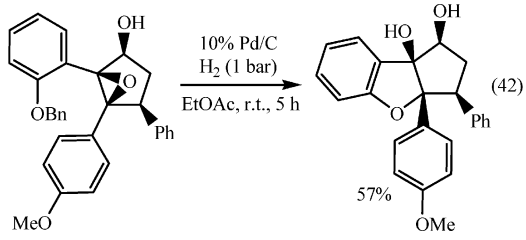
hydrogenolysis of an aryl epoxide in the presence of an aryl carbonyl depends on the experimental conditions [Equation (40)].[91] Both ring opening and removal of the Cbz protecting group occurred under Pd/C catalysis and a hydrogen atmosphere [Equation (41)].[92]







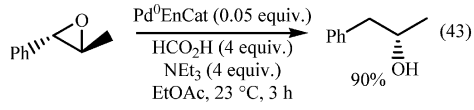
To synthesize rocaglaol analogues, Ragot et al. carried out the cyclization step shown in Equation (42).[93] Whereas EtOH as the solvent led to degradation products, the cascade reaction proceeded effectively in EtOAc. According to the authors, the first step of the reaction is the hydrogenolysis of the benzyl ether. Consequently, the oxirane opening occurs through intramolecular nucleophilic attack of the phenol unit (or of the corresponding palladium phenolate) rather than from hydrogenolysis.

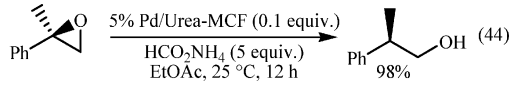


The opening of an oxirane induced by the cleavage of a benzyl ether was described by Schkeryantz and Danishefsky (Scheme 5).[94]

3.2. Using Hydride Transfer Agents

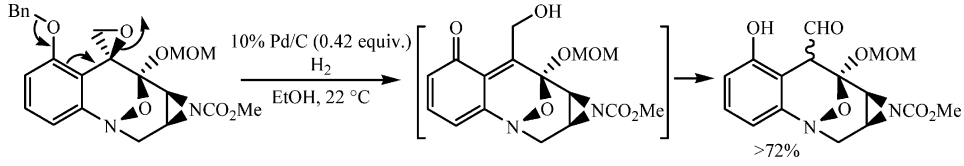
Ammonium formate or mixtures of formic acid and triethylamine have been used as hydride sources for the Pd-catalyzed reductive cleavage of aryl epoxides (Tables 5–7); the results are similar to those obtained by using molecular hydrogen.[29–31,75] With Pd^0EnCat as the catalyst, Yu et al. reported up to ten successive recycle runs without a decrease in the yields and retention of the stereochemistry from enantiomerically pure *trans*-β-methyl styrene oxide [Equation (43)].[31] Recently, Ying et al. used palladium nanoparticles supported on siliceous mesocellular foam, namely, Pd/Urea-MCF, for the hydrogenolysis of aryl epoxides by ammonium formate (Tables 5–7); the catalyst is recyclable (Table 6, entry 8) and led to (*R*)-2-phenylpropan-1-ol from (*R*)-2-methyl-2-phenyloxirane [Equation (44)].[76,95]





3.3. Regio- and Stereoselectivity, Mechanism

The regioselectivity of the hydrogenolysis of terminal aryl epoxides contrasts that of terminal alkyl epoxides, as primary instead of secondary alcohols are mainly produced.

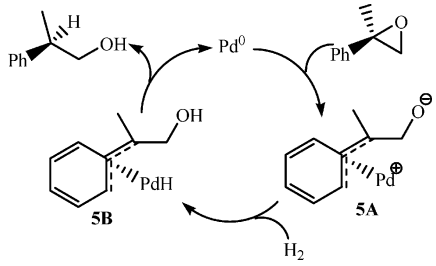


Scheme 5. Cascade reaction induced by the cleavage of a benzyl oxygen bond.[94]

3.3.1. In the Presence of Molecular Hydrogen

It is not surprising that the hydrogenolysis of aryl epoxides occurs essentially at the level of the benzylic C–O bond, as cleavage of the PhC–O bond of benzylic alcohols and benzylic ethers mediated by hydrogen in the presence of supported palladium is a common reaction.[96]

The inverted stereochemistry of the α-carbon center observed from the chiral substrates depicted in Equations (31) and (32), the stereoselectivity of the hydrogenolysis of 2,3-dimethyl-2,3-diphenyloxiranes [Equations (34) and (35)] and 1-phenylcyclohexene oxide [Equation (38)] suggests a (η^3-benzyl)palladium intermediate. The formation of such species from the reaction of soluble Pd^0 complexes with naphthylmethyl acetates,[97] or benzyl acetate,[98] trifluoroacetate,[99] or carbonate,[100] is documented. It is also known that (i) the Pd^0-mediated formation of η^3-allylpalladium species from allylic acetates and carbonates proceeds with inversion of configuration,[101] and (ii) the reaction of these complexes with hydrides occurs through the coordination of H^- to the palladium atom followed by reductive elimination of palladium.[102] Given this literature information, the (η^3-benzyl)palladium intermediate formed from (*R*)-2-methyl-2-phenyloxirane must have the configuration shown in Scheme 6. The reaction of this complex, **5A**, with hydrogen affords hydrido palladium complex **5B**. The intermolecular delivery of the hydride to the exocyclic extremity of the η^3-benzyl unit of **5B** leads to (*R*)-2-phenylpropan-1-ol. Moreover, the formation of a (η^3-benzyl)palladium intermediate followed by the nucleophilic addition of alcohol or water would also explain the results shown in Equations (25)–(27);[103] note, however, that alcoholysis of alkyl epoxides has also been observed [Equation (2)].[11]

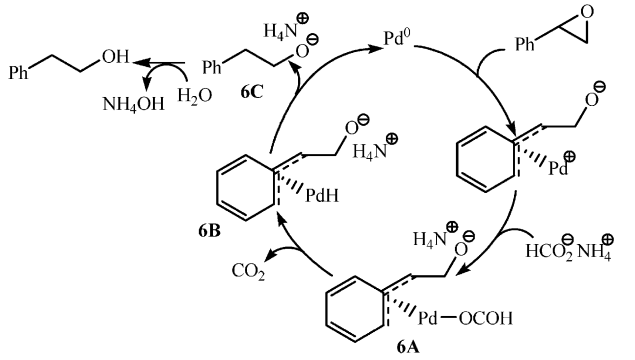


Scheme 6. Proposed mechanism for the Pd-catalyzed hydrogenolysis of aryl epoxides by hydrogen.

For the Pd/C-catalyzed hydrogenolysis of styrene oxide in MeOH in the presence of NaOH, Rode et al. propose S_N2 attack of OH^- onto the oxirane leading to the cleavage of the less-hindered C–O bond. The secondary alkoxide thus formed evolves towards 1-phenylethane-1,2-diol, the hydrogenolysis of which gives 2-phenylethanol.[70]

3.3.2. In the Presence of Ammonium Formate

As above, a (η^3-benzyl)palladium intermediate is conceivable. Its reaction with ammonium formate would afford ammonium alcoholate **6A**, which suffers elimination of carbon dioxide to yield **6B**. Reductive elimination from **6B** regenerates the catalyst and delivers **6C**, the hydrolysis of which gives the product (Scheme 7).



Scheme 7. Proposed mechanism for the Pd-catalyzed hydrogenolysis of aryl epoxides by ammonium formate.

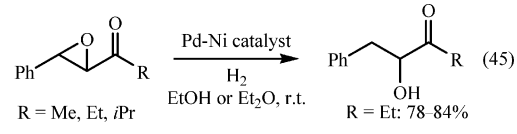
4. α,β-Epoxy Carbonyls

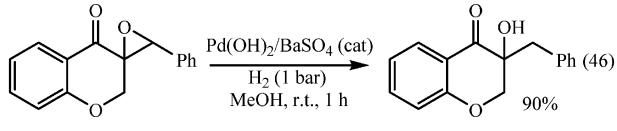
As illustrated below, the regioselectivity of oxirane opening of α,β-epoxy ketones and α,β-epoxyesters depends greatly on the nature of the β-substituent(s). Consequently, this topic is divided into two sections.

4.1. β-Aryl-α,β-epoxy Carbonyls

4.1.1. Using Molecular Hydrogen

Between the years of 1949–1951, Temnikova and Kropachev reported that the hydrogenation of epoxides of styryl ketones over a Pd-Ni catalyst leads to the cleavage of the benzylic C–O bond to afford the corresponding α-ketols [Equation (45)].[104] Such a regioselectivity was subsequently confirmed by different teams as illustrated in Table 8 (entries 1 and 2)[78,105] and Equation (46).[82] When the carbonyl group belongs to an aryl ketone unit, slight quantities of the product resulting from the cleavage of the C_α–O bond have been, sometimes, observed, and the reductive cleavage of the epoxide can be followed by the hy-





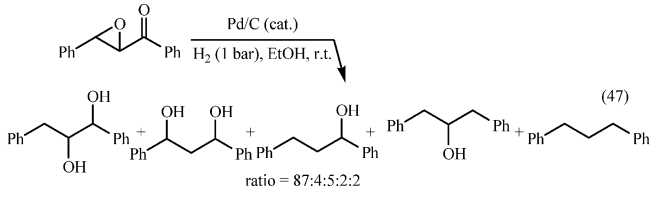
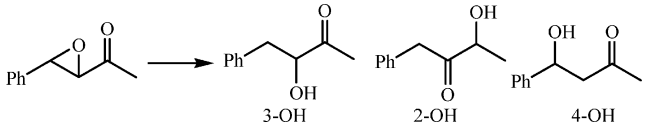


Table 8. Hydrogenolysis of *trans*-4-phenylbut-3-enone oxide under various conditions.



Entry	Catalyst (equiv.)	Reductive species	Solvent	Temp. [°C]	Time h	Product, yield [%]
1[78]	Pd/C (cat.)	H_2 (1 bar)	EtOH	r.t.	?	3-OH, 88
2[105]	5% Pd/C (0.08)	H_2 (1 bar)	THF	r.t.	?	3-OH, 81
3[30]	5% Pd/C (cat.)	HCO_2NH_4 (2 equiv.)	MeOH	65	20	u.d.[a]
4[105]	5% Pd/C (0.05)	HCO_2H + NEt_3 (2 equiv.)	THF	66	?	3-OH, 66
5[105]	$Pd(OAc)_2$ (0.05)	HCO_2H + NEt_3 (2 equiv.)	THF	66	?	3-OH, 81
6[105]	$Pd(OAc)_2$ (0.05)[b]	HCO_2H + NEt_3 (2 equiv.)	THF	66	?	4-OH, 96
7[31]	Pd^0EnCat (0.05)	HCO_2H + NEt_3 (4 equiv.)	EtOAc	23	6	3-OH, 75 + 2-OH, 12

[a] u.d.: Mixture of unidentified products. [b] With dppe (0.1 equiv.).

drogenation of the ketone and the hydrogenolysis of the hydroxy substituents [Equation (47)];[83] such an over reduction occurs in various solvents.[78,106,107]

In 1987, Ferreira et al. reported the synthesis of optically active α-hydroxydihydrochalcones from (–)-*trans*-epoxychalcones with a slight decrease in optical activity by using $Pd/BaSO_4$ as the catalyst in EtOH [Equation (48)].[108] A similar reaction but with almost complete preservation of the chirality was depicted by Corey and Zhang from (2*S*,3*R*)-phenyl *trans*-2,3-epoxy-3-phenyl propionate by using Pd/C in THF (Table 9, entry 1).[109] As shown in Table 9 (entries 2 and 3), the hydrogenolysis of β-phenyl-α,β-epoxy esters occurs effectively by using MAGPd or $Pd_{OAc,N}$ as the catalyst; the use of the latter in water leads to the selective reduction of the heterocycle of benzyl 3-phenyloxirane-2-carboxylate (entry 4).

Recently, Florio et al. described the hydrogenolysis of 4,5-epoxy-1,2-oxazin-6-ones in MeOH.[110] As depicted in Table 10, the reactivity depends highly on the nature of the R substituent. When R was an alkyl group, the main reaction observed over Pd/C or Pearlman's catalyst,[111] even under 20 bar of hydrogen, was the cleavage of the O–N bond (Table 10, entries 1–4). When R was an aromatic substituent, the Pearlman/H_2 pressure method led to hydrogenolysis of both the O–N and the PhC–O bonds (Table 10, entries 5–7).

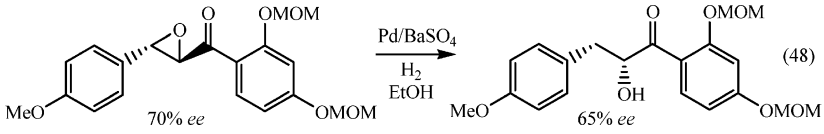
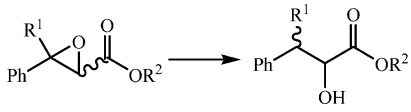


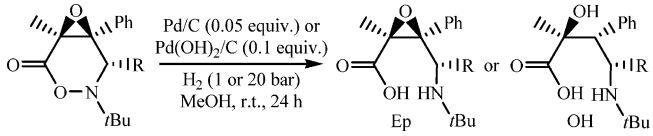
Table 9. Hydrogenolysis of α,β-epoxyesters.



Entry	R^2	Catalyst (equiv.)	Reductive species	Solvent	Temp. [°C]	Time [h]	Yield [%]
R^1 = H							
1[109]	Ph[a]	5% Pd/C (cat.)	H_2 (1 bar)	THF	r.t.	1	95[b]
2[32]	Et	MAGPd (0.01)	H_2 (balloon)	EtOAc	23	1	95
3[33]	Et	$Pd_{OAc,N}$ (0.01)	H_2 (balloon)	H_2O	r.t.	20	80
4[33]	Bn	$Pd_{OAc,N}$ (0.01)	H_2 (balloon)	H_2O	r.t.	21	84
5[30]	Me	5% Pd/C (cat.)	HCO_2NH_4 (2 equiv.)	MeOH	65	3	95
6[31]	Et	Pd^0EnCat (0.05)	HCO_2H + NEt_3 (4 equiv.)	EtOAc	23	13	92
7[76]	Me	5% Pd/Urea-MCF (0.1)	HCO_2NH_4 (5 equiv.)	EtOAc	25	24	94
R^1 = Me							
8[30]	Me	5% Pd/C (cat.)	HCO_2NH_4 (2 equiv.)	MeOH	65	3	95
9[31]	Et	Pd^0EnCat (0.05)	HCO_2H + NEt_3 (4 equiv.)	EtOAc	23	24	94

[a] Optically active substrate (93%*ee*). [b] Optically active product (92%*ee*).

Table 10. Hydrogenolysis of 4,5-epoxy-1,2-oxazin-6-ones.[110]



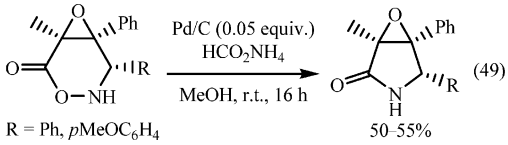
Entry	R	Catalyst	Pressure	Product, yield [%]
1	C_6H_{11}	Pd/C	1 bar	Ep, 64
2	C_7H_{15}	Pd/C	1 bar	Ep, 78
3	C_6H_{11}	$Pd(OH)_2/C$	20 bar	Ep[a]
4	C_7H_{15}	$Pd(OH)_2/C$	20 bar	Ep[a]
5	Ph	$Pd(OH)_2/C$	20 bar	OH, 60
6	$pMeOC_6H_4$	$Pd(OH)_2/C$	20 bar	OH, 48
7	$pCF_3C_6H_4$	$Pd(OH)_2/C$	20 bar	OH, 44

[a] Main product.

4.1.2. Using Hydride Transfer Agents

The Pd/C-catalyzed reduction of *trans*-4-phenylbut-3-en-one oxide by HCO_2NH_4 in refluxing MeOH gives a mixture of compounds (Table 8, entry 3).[30] With a mixture of HCO_2H/NEt_3 (1:1), the course of the reaction depends highly on the nature of the catalyst: in refluxing THF, Pd/C and $Pd(OAc)_2$ afford 3-hydroxy-4-phenylbutan-2-one (Table 8, entries 4 and 5), whereas the $Pd(OAc)_2$/dppe system provides selectively 4-hydroxy-4-phenylbutan-2-one (Table 8, entry 6).[105] Moreover, Pd^0EnCat at room temperature in EtOAc leads to a 6:1 mixture of 3-hydroxy-4-phenylbutan-2-one/2-hydroxy-4-phenylbutan-3-one (Table 8, entry 7).[31] In contrast, high yields of α-hydroxy esters have been isolated from β-phenyl-α,β-epoxy esters by using Pd/C in MeOH and Pd^0EnCat or Pd/Urea-MCF in EtOAc (Table 9, entries 5–9).[30,31,76]

The Pd/C-catalyzed reduction with HCO_2NH_4 of 4,5-epoxy-1,2-oxazin-6-ones having a secondary nitrogen atom led to α,β-epoxy-γ-butyrolactams [Equation (49)] through the cleavage of the O–N bond and subsequent cyclization.[110] Despite the aromaticity of the R substituent, the reduction of the epoxide did not occur; this seems to contrast with the reaction in which molecular hydrogen was employed (Table 10).

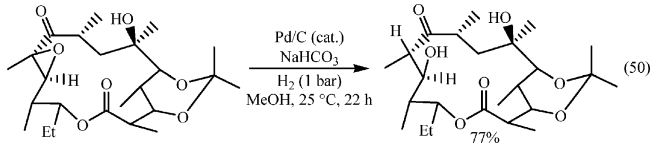


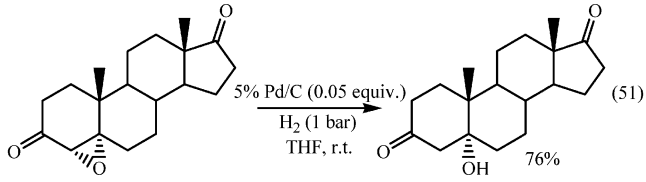
4.2. Other α,β-Epoxy Carbonyls

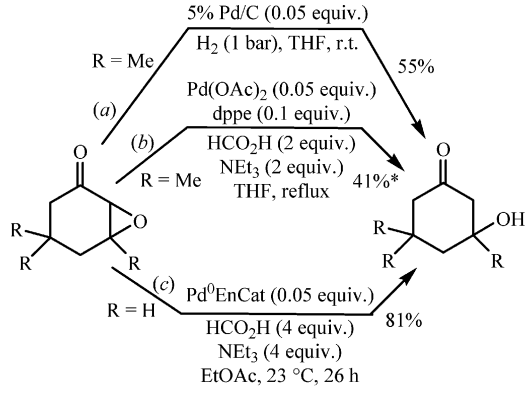
This section will contain examples of α,β-epoxy carbonyl compounds with no aryl group in the β-position.

4.2.1. Using Molecular Hydrogen

In 1975, Corey et al. disclosed that the Pd/C-catalyzed reduction of the α,β-epoxy ketone unit of the macrolactone shown in Equation (50) produced the selective cleavage of the $C_α$–O bond; they, furthermore, observed that the incorporated hydrogen atom was *syn* to the resulting hydroxy substituent.[112] Twelve years later, Torii et al. reported the selective $C_α$–O bond hydrogenolysis of various epoxy ketones [Equation (51) and Scheme 8, path *a*].[105] The concomitant hydrogenation of the C=O bond can, however, occur when the carbonyl group bears an aromatic substituent (Scheme 9, path *a*).[105]

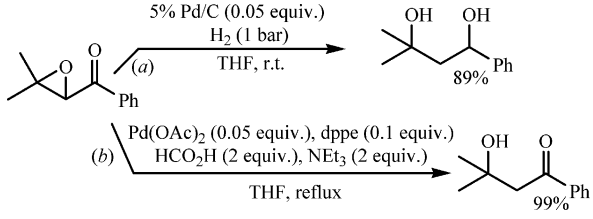






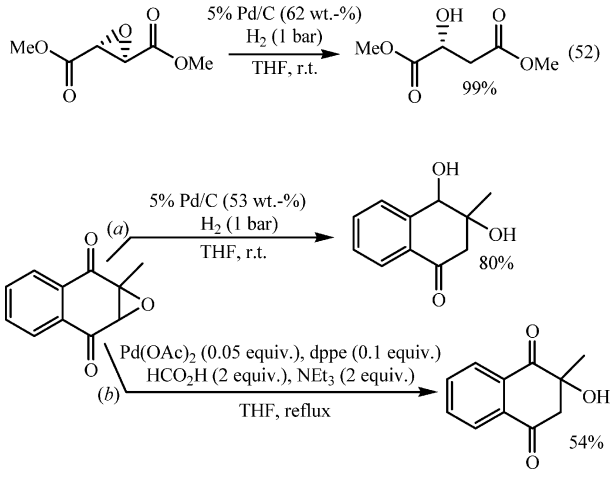
* Isophorone was also produced (48% yield).

Scheme 8. Reduction of epoxides of 2-cyclohexenones.[31,105]



Scheme 9. Reduction of 3-methyl-1-phenylbut-2-en-1-one oxide.[105]

The reduction of oxiranes having both extremities substituted by a carbonyl group has also been studied. Whereas $Pd/BaSO_4$ is an inefficient catalyst for the hydrogenolysis of 1,2-bis(2,4,6-trimethylbenzoyl)ethene oxide,[113] the use of Pd/C is effective for the reduction of dimethyl fumarate oxide, with preservation of chirality [Equation (52)],[105] and 2-methylnaphthalene-1,4-dione oxide (Scheme 10, path *a*).[105]

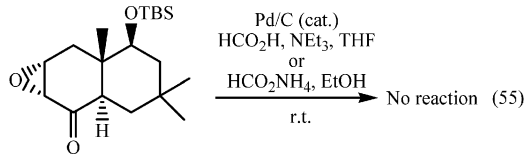


Scheme 10. Reduction of 2-methylnaphthalene-1,4-dione oxide.[105]

Gawron et al. obtained a mixture of malic, succinic, and diglycolic acids from the hydrogenolysis, over Pd/C at room temperature, of aqueous solutions of *cis*- and *trans*-epoxysuccinic acids. The authors showed that malic acid is stable under their experimental conditions. Consequently, succinic acid is produced from the hydrogenolysis of both C–O bonds of the oxirane rather than from the hydrogenation of fumaric or maleic acid that would be issued from the dehydration of malic acid. Moreover, experiments with the use of deuterium led to the conclusion that the hydrogenolysis of the substrates into malic acids proceeds in a *trans* fashion [Equations (53) and (54)].[114] Subsequently, *trans*-epoxysuccinic acid was hydrogenated at 100 °C by using various supported palladium catalysts in either MeOH or under solvent-free conditions; the same three compounds were isolated, but it was proposed that fumaric or maleic acid is the source of succinic acid.[115]

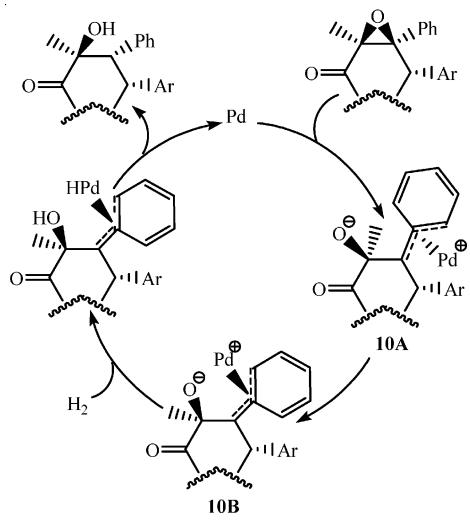
4.2.2. Using Hydride Transfer Agents

In contrast to hydrogen, HCO_2H/NR_3 and HCO_2NH_4, under Pd catalysis, are in most cases unreactive towards ketone.[116,117] Consequently, β-ketols were obtained in high yields by using the $Pd(OAc)_2$/dppe association (Schemes 8–10, paths *b*)[105] or Pd^0EnCat (Scheme 8, path *c*)[31] as the catalyst. Surprisingly, no reaction at all was observed from the treatment of the epoxy ketone shown in Equation (55) under Torii's[105] or Dragovich's[29] experimental conditions.[118]



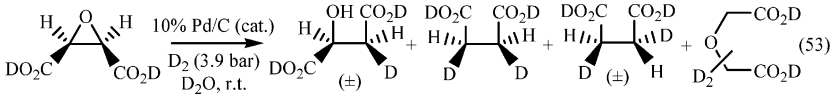
4.3. Regio- and Stereoselectivity, Mechanisms

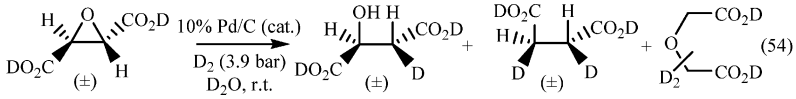
Given the above results, the regioselectivity of the hydrogenolysis of β-aryl-α,β-epoxy carbonyl compounds is similar to that of aryl epoxides; consequently, the mechanisms proposed in Schemes 6 and 7 can be envisaged for these substrates. Nevertheless, the hydrogenolysis of 4,5-epoxy-1,2-oxazin-6-ones (Table 10, entries 5–7) that results in *cis* addition would imply an enantioface exchange at the level of the (η^3-benzyl)palladium intermediate. For these 4,5-epoxy-1,2-oxazin-6-ones, this exchange could be promoted by the steric hindrance exercised by the substituents in the α- and γ-positions and/or by stabilizing anion–cation interactions, as illustrated in Scheme 11 with intermediates **10A** and **10B**, respectively (the mechanism of enantioface exchange will be discussed in Section 5.3).



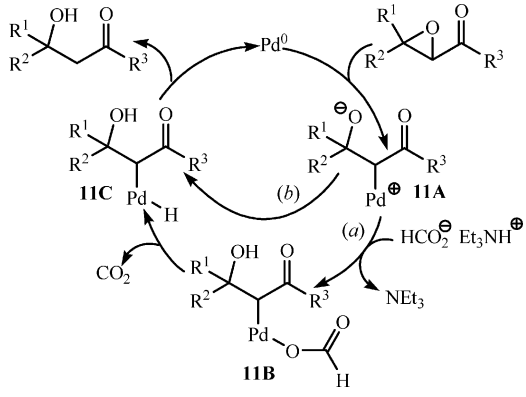
Scheme 11. Possible mechanism for the hydrogenolysis of the oxirane of 4,5-epoxy-1,2-oxazin-6-ones.

As for the cleavage of the C_α–O bond, Torii et al., who used the reductive HCO_2H/NEt_3 mixture, in 1989 proposed

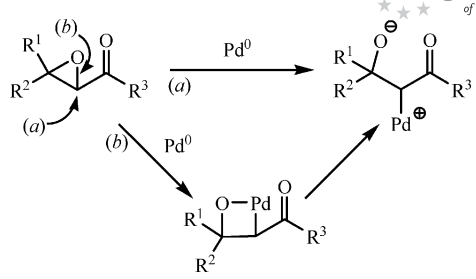




the mechanism depicted in Scheme 12, path *a*.[105] The interaction of the epoxy ketone with the catalyst leads to zwitterionic intermediate **11A**, which affords **11B** from its reaction with the ammonium salt, subsequent elimination of carbon dioxide to yield **11C**. This latter complex could be also obtained when molecular hydrogen is the reductive source (Scheme 12, path *b*). Noyori et al. previously envisaged an intermediate similar to **11A** for the rearrangement, catalyzed by soluble Pd^0 complexes, of α,β-epoxy ketones into β-diketones; these authors suggested that such an intermediate is formed by back-side displacement of the oxirane (Scheme 13, path *a*) (either in a classical nucleophilic manner or by an electron-transfer process) or from front-side oxidative addition leading to a palladaoxetane, followed by heterolytic rupture of the O–Pd bond (Scheme 13, path *b*).[119] As **11A** could be in equilibrium with the corresponding O–palladium enolate and η^3-oxoallyl palladium complexes,[120] the distinction between these two possible pathways is not straightforward, even from substrates with a quaternary C_α or optical activity.



Scheme 12. Torii's mechanism of reduction of α,β-epoxy ketones.[105]

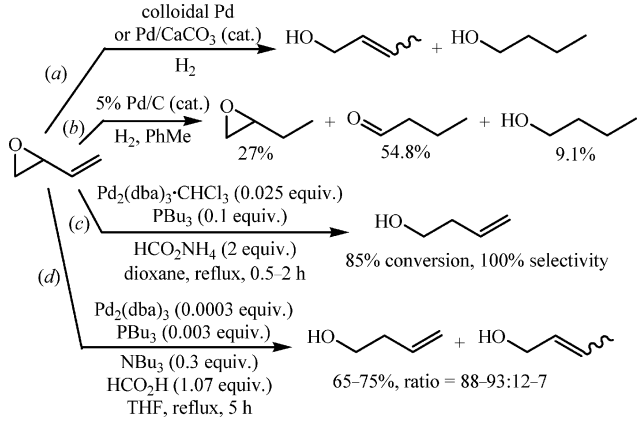


Scheme 13. Back-side displacement of the oxirane or front-side oxidative addition.

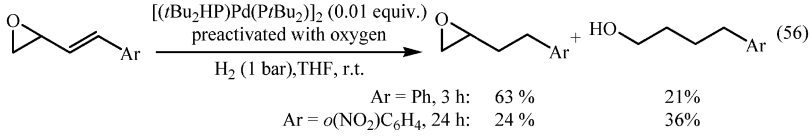
5. 1-Alkenylepoxides

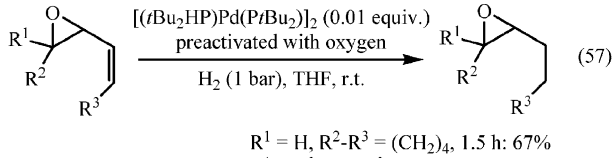
5.1. Using Molecular Hydrogen

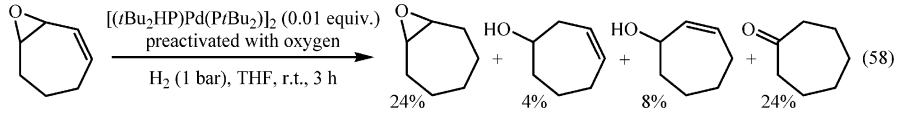
In 1958, Petrov et al. disclosed the hydrogenation, over colloidal Pd or $Pd/CaCO_3$, of butadiene oxide[121] and chloroprene oxide,[122] into *n*-butanol. The authors showed that



Scheme 14. Hydrogenolysis of 3,4-epoxy-1-butene.[40,121,123,124]







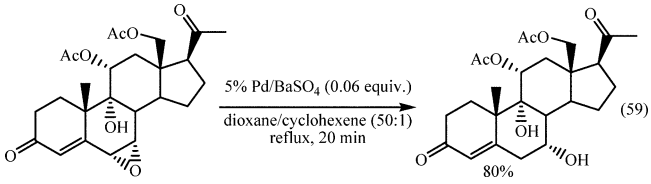
crotyl alcohol was an intermediate leading to *n*-butanol from the former substrate (Scheme 14, path *a*).[121] According to a 1991 patent from Eastman Kodak Company, the hydrogenation of the same substrate provides, over 5% Pd/C in toluene, a mixture of 1,2-epoxybutane, butyraldehyde, and *n*-butanol (Scheme 14, path *b*).[40]

With the soluble dinuclear palladium complex [(tBu$_2$HP)-Pd(PtBu$_2$)]$_2$ preactivated with oxygen, Alper et al. reported that the selectivity depends on the substitution of the 1,3-diene monoxide unit [Equations (56)–(58)].[125]

5.2. Using Hydride Transfer Agents

5.2.1. Using Cyclohexene

In 1971, Wehrli et al. disclosed the transformation of the 1,3-diene monoxide units of multifunctionalized steroids into homoallylic alcohols by using cyclohexene as the hydrogen source [Equation (59)].[126–128]

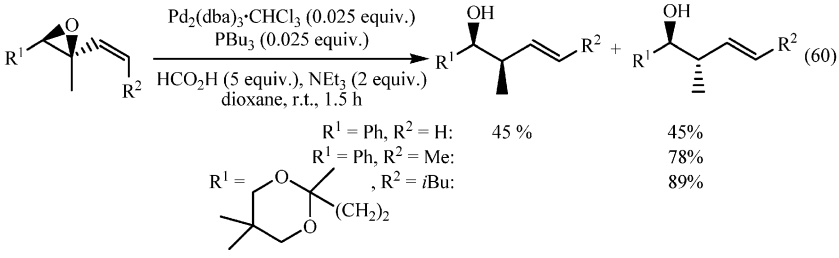


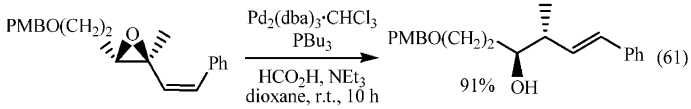
5.2.2. Using Formate Salts

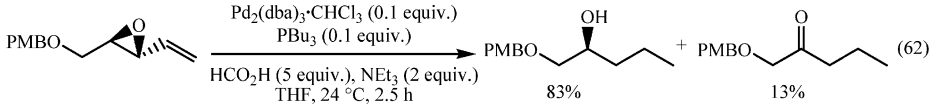
In 1984, Tsuji et al. reported the Pd-catalyzed reduction of 1,3-butadiene monoepoxide into 3-buten-1-ol by using a mixture of Pd$_2$(dba)$_3$·CHCl$_3$/P(nBu)$_3$ as the catalyst and ammonium formate as the reducing species (Scheme 14, path *c*),[123] but it is noteworthy that such a reaction was previously orally presented by T. Tsuda.[129] McCombs tested various modifications of this method for the preparation of 3-buten-1-ol on an industrial scale (Scheme 14, path *d*); this was patented in 1993 by Eastman Chemical Company.[124] Substituted alkenyl epoxides with a (*Z*)-alkenyl bond lead to (*E*)-homoallylic alcohols with a *syn*/*anti* ratio depending on the substituents [Equations (60)[130] and (61)].[131] The hydrogenolysis of the epoxide can be followed by the over-reduction of the C=C bond yielding the saturated alcohol and/or its migration leading to the ketone [Equation (62)].[132]

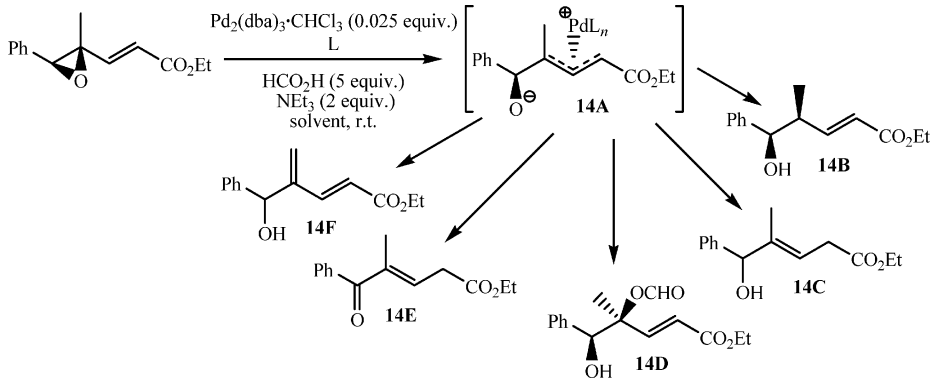
Through the various 4,5-epoxy-2-alkenoates reduced by Shimizu, Tsuji, and coworkers,[130,133–136] the influence of the experimental conditions on the selectivity was particularly studied by using (*E*)-ethyl *trans*-4,5-epoxy-4-methyl-5-phenyl-2-pentenoate as the substrate.[130] The catalyst induces the formation of cationic η^3-allylpalladium complex **14A**, which leads to various compounds (Scheme 15) with a selectivity depending on the nature of the ligand, Pd/L ratio (Table 11), and solvent. Subsequently, Kobayashi et al. have also exemplified the influence of the nature of the ligand and solvent on both reactivity and selectivity using (*Z*)-methyl *trans*-4,5-epoxy-4-butyl-2-heptenoate as the substrate (Table 12).[137]

The Shimizu/Tsuji procedure was applied to a panel of other γ,δ-epoxy-α,β-unsaturated esters to effectively afford the corresponding δ-hydroxy-α,β-unsaturated esters (Tables 13 and 14). *trans*-Epoxides with an (*E*)-double bond lead to *syn*-isomers (Table 13), whereas those with a (*Z*)-double bond afford mainly *anti*-isomers with, however, a selectivity depending strongly on both the ligand and the solvent (Table 12). *anti*-Isomers are also the main









Scheme 15. Pd-catalyzed reaction of (*E*)-ethyl 4,5-epoxy-4-methyl-5-phenyl-2-pentenoate with the HCO_2H/NEt_3 mixture.[130]

Table 11. Reaction of (*E*)-ethyl 4,5-epoxy-4-methyl-5-phenyl-2-pentenoate in dioxane under conditions shown in Scheme 15.[130]

L	L/Pd	Time [h]	Products, yield [%]				
			14B	**14C**	**14D**	**14E**	**14F**
None		48	58	27	0	0	0
$P(nBu)_3$	0.5	6.5	99	0	0	0	0
$P(nBu)_3$	1.5	2	63	0	0	34	0
$P(nBu)_3$	2.5	2	Tr	0	0	92	0
PPh_3	0.5	5	98	0	0	0	0
PPh_3	2	1	13	0	7	16	61
PCy_3	2	8.5	96	0	0	0	0
$P(OMe)_3$	1	4	98	0	0	0	0
$P(OMe)_3$	2	0.5	11	0	6	27	55

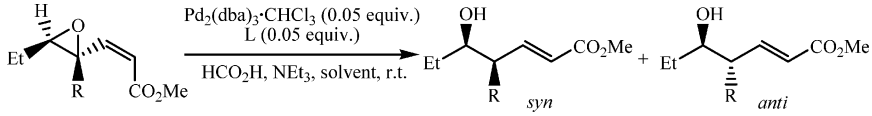
products from *cis*-γ,δ-epoxy-(*E*)-α,β-unsaturated esters (Table 14).

Working towards the total synthesis of kalmanol, Borrelly and Paquette, in 1996, confirmed the pronounced selectivity dependency on the phosphane ligand by using the Shimizu/Tsuji procedure to reduce the multifunctionalized β-alkenyl-α,β-epoxy ester shown in Equation (63).[144]

Alicyclic γ,δ-epoxy-α,β-unsaturated ketones are rather reluctant to react. The complete conversion is attained with difficulty,[134,145] and a mixture of homoallylic and allylic alcohols is obtained.[134,145,146] Shimizu et al. reported that the ratio between these two unsaturated alcohols depends highly on the catalytic system [Equation (64)] and the quality of formic acid.[134]

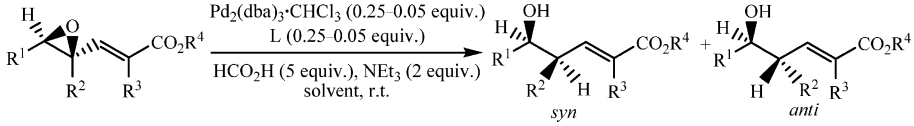
Roussi et al. disclosed that the hydrolysis of 6α,7α-epoxyandrost-4-ene-3,17-dione can lead to dienic ketone **15A**, δ-hydroxy-α,β-unsaturated ketone **15B**, and δ-hydroxy-saturated ketone **15C**; the selectivity depends on the solvent and its quality (Scheme 16). Under optimized conditions in dioxane, **15B** was obtained in 52% yield at room temperature, and **15C** in 49% yield at 80 °C.[147] Note that the reduction of the C=C bond of α,β-unsaturated ketones by HCO_2H/NEt_3 was already known with the use of Pd/C as the catalyst at 100 °C.[116a]

Table 12. Hydrogenolysis of *trans*-γ,δ-epoxy-(*Z*)-α,β-unsaturated esters.[137,138]

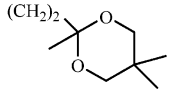


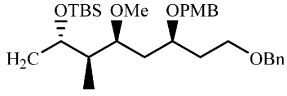
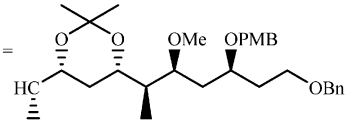
L	Solvent	Time [h]	Yield [%]	*syn*/*anti*
R = Bu[137]				
$P(nBu)_3$	dioxane	24	60	17:83
PCy_3	dioxane	48	70	49:51
$P(o\text{tolyl})_3$	dioxane	48	40	55:45
(–)-dppe	dioxane	24	76	18:82
PPh_3	dioxane	5	83	12:88
PPh_3	THF	24	95	16:84
PPh_3	DMF	1	84	5:95
PPh_3	DMAc	6	60	6:94
PPh_3	DMPU	3	58	7:93
R = CH_2iBu[138]				
PPh_3	DMF	3	73	4:96

Table 13. Hydrogenolysis of *trans*-γ,δ-epoxy-(*E*)-α,β-unsaturated esters.



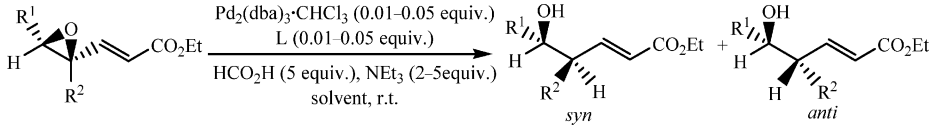
Entry	L	Solvent	R^1	R^2	R^3	R^4	Yield [%]	*syn*/*anti*
1[130]	P(*n*Bu)$_3$	dioxane	Ph	Me	H	Et	97	100:0
2[130]	P(*n*Bu)$_3$	dioxane	[a]	Me	H	Et	91	100:0
3[139]	P(*n*Bu)$_3$	dioxane	Ph	Me	H	Bn	28–30	100:0
4[130]	P(*n*Bu)$_3$	dioxane	Et	Me	H	Et	91	100:0
5[137]	P(*n*Bu)$_3$	dioxane	Et	Bu	H	Et	84	>99:1
6[134]	PPh$_3$	dioxane	Et	Me	Me	Et	75–90	100:0
7[134]	PPh$_3$	dioxane	[b]	Me	H	Et	90–93	100:0
8[140]	P(*n*Bu)$_3$	dioxane	[c]	Me	H	Et	96	100:0
9[140]	P(*n*Bu)$_3$	dioxane	[d]	Me	Me	Et	72	100:0
10[140]	P(*n*Bu)$_3$	dioxane	[e]	Me	H	Et	78	100:0
11[141]	P(*n*Bu)$_3$	dioxane	[f]	Me	Me	Et	71–75	100:0
12[135]	PPh$_3$	dioxane	Me	H	H	Et	84	
13[140]	P(*n*Bu)$_3$	dioxane	[g]	H	Me	Et	99	
14[142]	P(*n*Bu)$_3$	THF[h]	C_5H_{11}	H	H	Et	87	

[a] R^1 =  [b] R^1 = $(CH_2)_2CMe_2OSiMe_2tBu$. [c] R^2 = $CH_2CH(OPMB)(CH_2)_2OBn$

[d] R^1 =  [e] R^1 = 

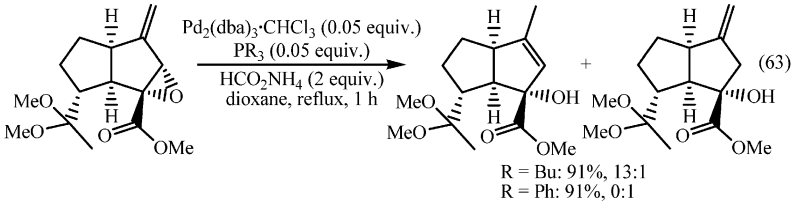
[f] R^1 = $(CH_2)_2CHMeEt$. [g] R^1 = $CHMeCH(OMe)CH_2CH(OPMB)(CH_2)_2OBn$. [h] Reaction was carried out at reflux.

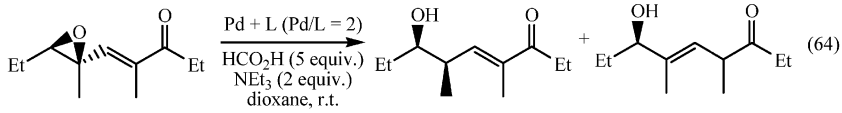
Table 14. Hydrogenolysis of *cis*-γ,δ-epoxy-(*E*)-α,β-unsaturated esters.



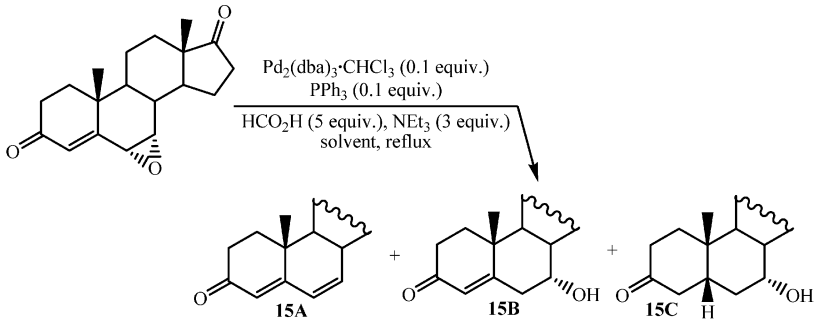
Entry	L	Solvent	R^1	R^2	Yield [%]	*syn*/*anti*
1[130]	P(*n*Bu)$_3$	dioxane	Et	Me	82	0:100
2[137]	P(*n*Bu)$_3$	dioxane	Et	Bu	44	21:79
3[143]	PPh$_3$	THF[a]	Me	Me	98	5:95

[a] Reaction was carried out under reflux.





with $Pd_2(dba)_3$·$CHCl_3$
L = PPh_3 (2:1), PBu_3 (60 °C, 3:2), $P(OEt)_3$ (4:1), $P(OMe)_3$ (8:1–16:1)
with $Pd(OAc)_2$
L = PBu_3 (1:4)



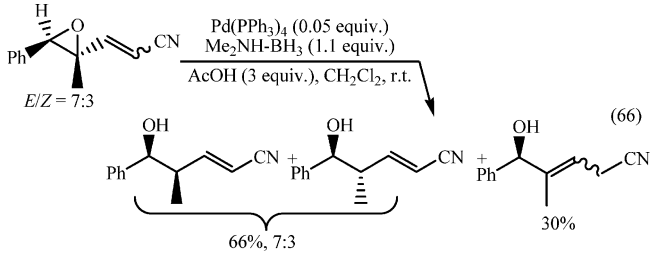
Solvent	CH_2Cl_2	Distilled CH_2Cl_2	Dioxane	Distilled dioxane	THF	Distilled THF
Selectivity **15A/15B/15C**	68:32:0	Tr:35:64	9:91:0	Tr:Tr:>95	17:83:0	5:6:89

Scheme 16.

5.2.3. Using Metal Hydrides

By using the Keinan procedure for the reduction of α,β-unsaturated carbonyl compounds, that is, cat. $Pd(PPh_3)_4$/nBu$_3$SnH,[55] Paterson and Craw selectively reduced the C=C bond of the β,γ-epoxy-α,β-unsaturated ketone shown in Equation (65).[148]

Guibé et al. examined the $Pd(PPh_3)_4$-catalyzed reduction of (*E*)-benzyl 4,5-epoxy-4-methyl-5-phenyl-2-pentenoate by using various hydride donors: the Me_2NH–BH_3/AcOH association led to the best chemical yield and selectivity (Table 15), and this procedure provided better results than those using the Tsuji/Shimizu method (Table 13, entry 3).[139] The $Pd(PPh_3)_4$/Me_2NH–BH_3/AcOH procedure was effective for the synthesis of homoallylic alcohols in high yields from various γ,δ-epoxy-α,β-unsaturated esters, whereas a large amount of the allylic alcohol is produced from the hydrogenolysis of the oxiranylacrylonitrile depicted in Equation (66).[139]



In the course of the synthesis of a segment of ciguatoxin CTX1B, Fujiwara et al. tested various reduction methods for the synthesis of homoallylic alcohols by using the vinyl

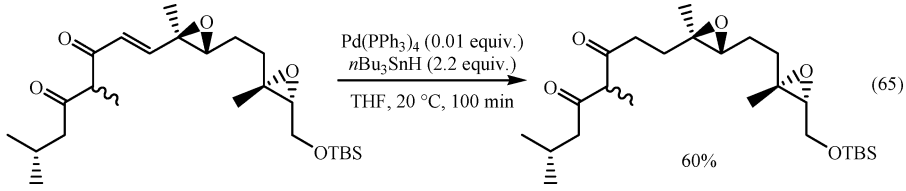
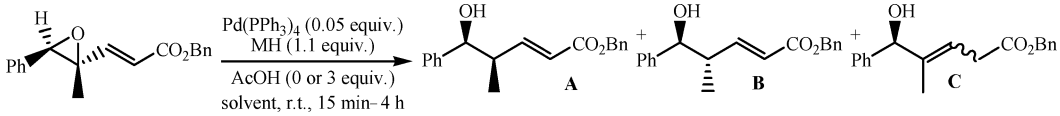
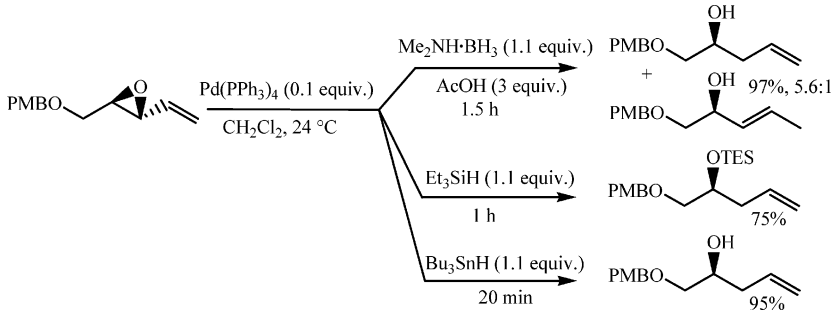


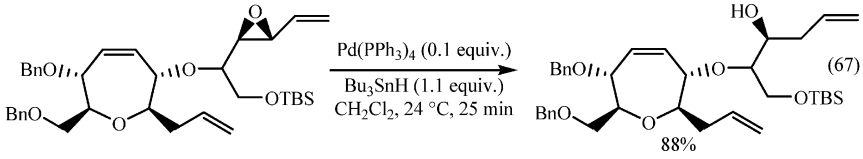
Table 15. Use of various hydride donors.[139]



MH	Solvent	AcOH	Time	(**A** + **B**) [%]	**A**/**B**	**C** [%]
$PhSiH_3$	CH_2Cl_2	none	4 h	53	80:20	37
H_3N–BH_3	CH_2Cl_2	none	15 min	72	70:30	15
Me_2NH–BH_3	CH_2Cl_2	none	15 min	78	87:13	Tr
$PhSiH_3$	THF	none	4 h	41	70:30	28
$NaBH_4$	THF	none	15 min	60	66:34	0
$PhSiH_3$	CH_2Cl_2	3 equiv.	1 h	74	>95:5	4
H_3N–BH_3	CH_2Cl_2	3 equiv.	15 min	85	92:8	0
Me_2NH–BH_3	CH_2Cl_2	3 equiv.	15 min	96	>95:5	0



Scheme 17. Influence of the nature of hydride species on the reduction of (*E*)-2,3-epoxy-1-(4-methoxybenzyloxy)-4-pentene.[132]



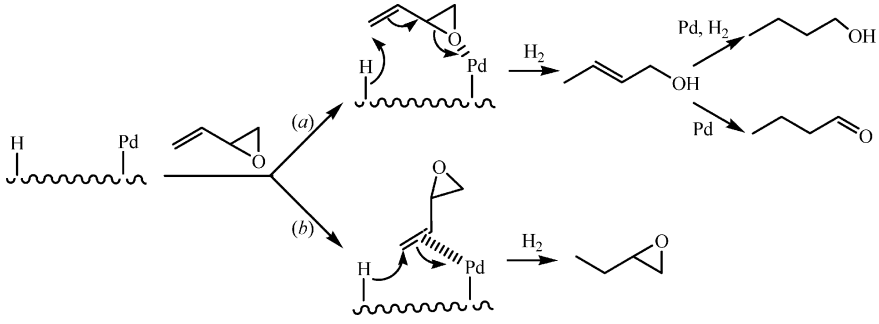
epoxide shown in Scheme 17 as a model compound.[132] As illustrated in Equation (62), the Tsuji/Shimizu procedure afforded a mixture of the saturated alcohol and the ketone. The method of Guibé led to a mixture of the homoallylic and allylic alcohols. With Et_3SiH as the hydrogen source, the silylation of the resulting homoallylic alcohol occurred.[149] Eventually, the best result was obtained with Bu_3SnH. Then, the $Pd(PPh_3)_4/Bu_3SnH$ procedure was successfully applied to the desired transformation [Equation (67)].

5.3. Mechanism

Apparently, the mechanism of the hydrogenolysis of the heterocycle of vinylic epoxides by hydrogen differs from that with formate salts and metal hydrides. In contrast, the use of cyclohexene as the reductive source leads, probably, to palladium hydride species that are involved in a manner rather similar to that by using molecular hydrogen (see Section 2.3.1). To the best of our knowledge, the only reports concerning the Pd-catalyzed reduction of alkenylepoxides in the presence of cyclohexene are from Wherli et al. (see Section 5.2.1), and without results allowing a specifically discussion of the mechanism. Besides, the regio- and stereoselectivities induced by formate salts and metal hydrides being almost identical, similar reactive pathways are suspected. Consequently, we will comment only on the possible mechanisms involved with molecular hydrogen and formate salts because they are the most used.

5.3.1. Using Molecular Hydrogen

The course of the hydrogenolysis by hydrogen seems to depend on the nature of the catalyst. Indeed, Petrov et al., having observed crotyl alcohol as an intermediate of the transformation over colloidal Pd and $Pd/CaCO_3$ of butadiene oxide into *n*-butanol, suggest that the reaction proceeds by initial 1,4-addition of hydrogen.[121] This contrasts with the results of Falling, who isolated a mixture of 1,2-epoxybutane, butyraldehyde, and 1-butanol from the hydrogenation of the same substrate over 5% Pd/C (Scheme 14, path *b*).[40] The formation of the primary alcohol by using these catalysts indicates participation of the C=C bond in the process, as terminal alkyl epoxides afford mainly secondary alcohols (see Section 2). Scheme 18 shows possible pathways leading to the compounds isolated by both research teams. The opening of the oxirane could be facilitated by the C=C bond (Scheme 18, path *a*); this has been proposed by Sajiki et al. under homogeneous conditions and from a



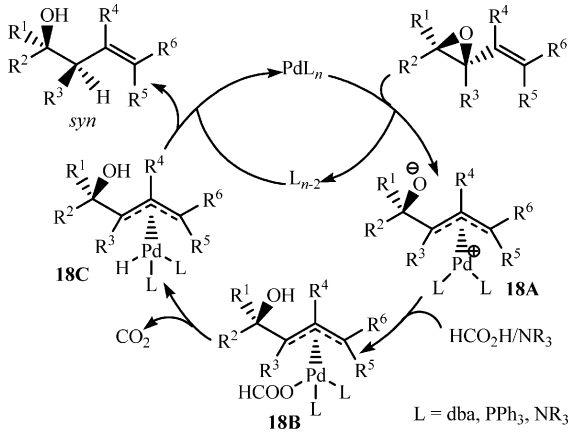
Scheme 18. Possible reaction pathways of butadiene monoxide.

different substrate.[27] A mechanism similar to that depicted in Scheme 18, path *b* can explain the results obtained by Alper et al. [Equations (56)–(58)] with their soluble catalyst.

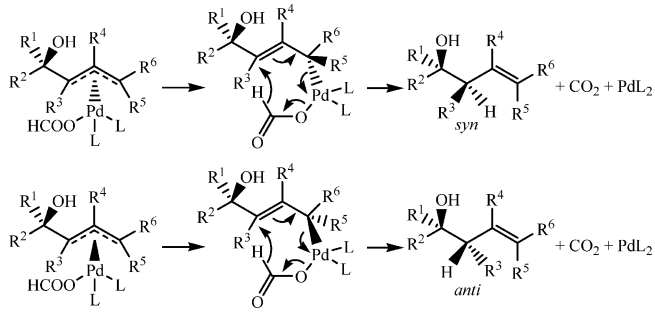
5.3.2. Using Formate Salts

The usual reaction of α,β-unsaturated epoxides in the presence of soluble Pd^0 catalysts is the cleavage of the $C_α$–O bond to afford the corresponding cationic $η^3$-allylpalladium complexes that are susceptible to nucleophilic additions, a reaction pathway that has been considerably exploited in organic synthesis[150] and that is also involved in the reductive cleavage mediated by hydride species. Herein, the discussion will be limited to the formation of the homoallylic alcohols (see Scheme 15 for the other compounds).

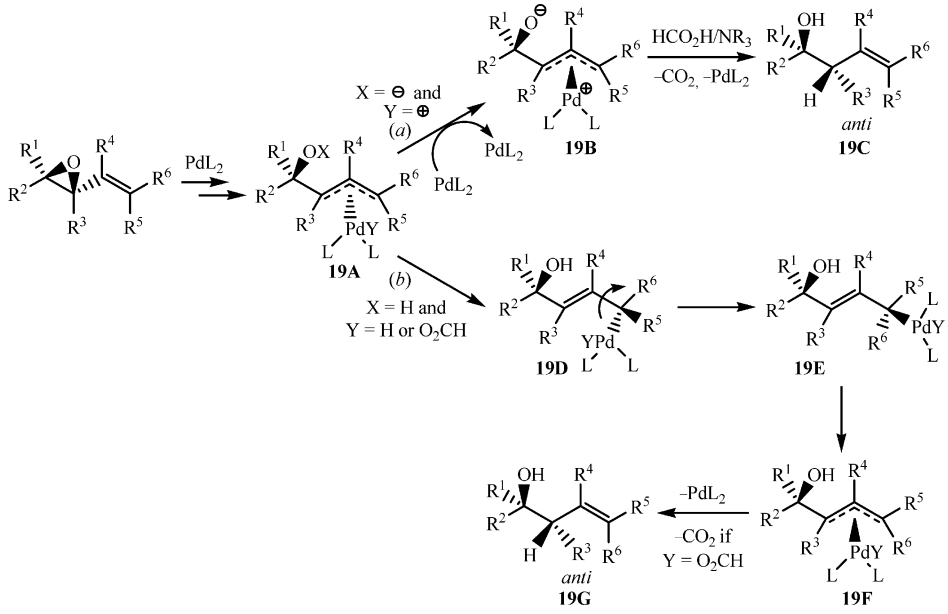
A possible reaction pathway leading to *syn* homoallylic alcohols is depicted in Scheme 19. The coordination of the catalyst to the C=C bond leads to $C_α$–O bond cleavage through *trans* attack to afford cationic complex **18A**, which reacts with HCO_2H/NR_3 to produce **18B**. The expulsion of carbon dioxide provides hydridopalladium intermediate **18C**, the reductive cleavage of which delivers the *syn* homoallylic alcohol and the catalyst. The formation of the *anti* homoallylic alcohol requires isomerization that can occur following the two pathways shown in Scheme 20. Enantioface exchange by redox transmetalation[137,151–154] of **19A** by the catalyst leads to **19B**, which provides *anti* homoallylic alcohol **19C** from its reaction with the hydride donor (path *a*). As for path *b*, it involves the π → σ → π rearrangement[155] that gives successively **19D**, **19E**, and **19F**. Reductive elimination from **19F** yields *anti* homoallylic alcohol **19G** that differs from **19C** by the stereochemistry of the C=C bond. Given the literature,[152,154] path *a* would be favored in the presence of high amounts of catalyst. Instead of the reductive elimination from $η^3$-allyl-hydridopalladium complexes, the hydride delivery can occur from a $η^1$-allylpalladium complex through the concerted cyclic reaction shown in Scheme 21 that brings about the same stereoselectivity.[134] Reductive elimination from a $η^1$-allyl-hydridopalladium complex stabilized by intramolecular coordination with the hydroxy group was also proposed (Scheme 22).[137] As both (*E*)- and (*Z*)-alkenyl epoxides lead



Scheme 19. Possible formation of *syn* homoallylic alcohols.

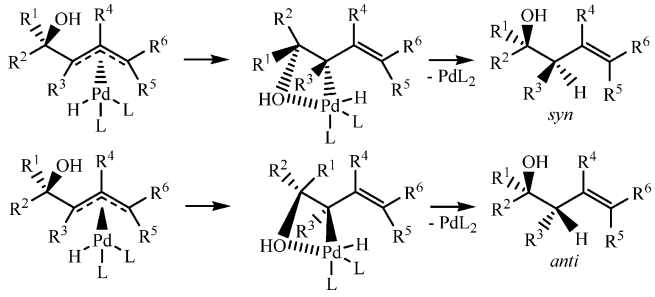


Scheme 21. Formation of the homoallylic alcohols through a concerted cyclic mechanism.



Scheme 20. Formation of *anti* homoallylic alcohols.

to (*E*)-homoallylic alcohols [Tables 12–14, Equations (60) and (61)], it seems that, at least for (*Z*)-alkenyl epoxides, path *b* of Scheme 20 is really involved.



Scheme 22. Formation of the homoallylic alcohols from stabilized η^1-allyl-hydridopalladium complexes.

6. Conclusions

Efficient hydrogenolysis of epoxides can be carried out by using various hydrogen sources with good prediction of the regioselectivity. In the case of multifunctionalized substrates, the course of the reaction can be catalyst dependent, and some of these catalysts, such as, Pd/C(en)[156] and $Pd_{OAc,N}$, in specific solvents lead to the chemoselective hydrogenation of functions that are tolerant with oxiranes. Some of the procedures have, however, been studied using a limited panel of substrates, and it would be of interest to analyze their effectiveness and selectivity from multifunctionalized substrates.

Abbreviations: Cy, cyclohexyl; dba, dibenzylidene acetone; DMAc, dimethylacetamide; DMPU, *N*,*N*′-dimethylpropylenurea; dppe, 1,4-bis(diphenylphosphanyl)ethane; MOM, methoxymethyl; nd, not determined; PMB, *p*-methoxybenzyl; TBS, *tert*-butyldimethylsilyl; Tr, trace.

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