

Stereospecific Deoxygenation of Aliphatic Epoxides to Alkenes under Rhenium Catalysis

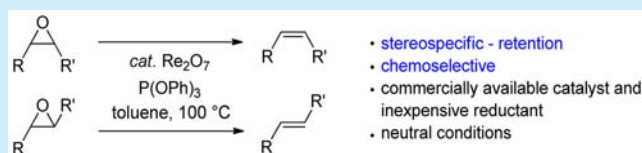
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S Supporting Information

ABSTRACT: The combination of a catalytic amount of Re_2O_7 and triphenyl phosphite as a reductant is effective for the deoxygenation of unactivated aliphatic epoxides to alkenes. The reaction proceeds stereospecifically with variously substituted epoxides under neutral conditions and is compatible with various functional groups. Protection and deprotection of a double bond functionality using an epoxide are shown as an example of the current rhenium-catalyzed deoxygenation protocol. The effect of reductants for the stereoselectivity has also been studied, indicating that the use of electron-deficient phosphines or phosphites is the key for the stereospecific deoxygenation.



Deoxygenation of epoxides into alkenes is a fundamental but important transformation in both organic¹ and biological chemistry.² Although the corresponding reverse oxygenation reactions, epoxidation of alkenes, have been well-investigated and widely applied in organic synthesis,³ catalytic deoxygenation of epoxides leading to alkenes has been much less developed. Stemming from the seminal work by Sharpless et al. in 1972 using a stoichiometric amount of WCl_6 and $^n\text{BuLi}$, a variety of promoters have been developed for the effective deoxygenation of epoxides.^{4,5} In recent years, catalytic deoxygenation has been realized with high valent oxorhenium complexes including MeReO_3 and $\text{ReIO}_2(\text{PPh}_3)_2$, and an oxoruthenium complex together with PPh_3 , H_2 , or Na_2SO_3 as reductants.⁶ While synthetically attractive, most of these protocols still suffer from relatively high catalyst loadings, harsh conditions, and limited scope of substrates (e.g., only effective for activated epoxides such as styrene oxides (aryl epoxides) or conformationally locked cyclohexene oxides (cyclic epoxides)). Far less attention has been focused on *stereospecific deoxygenation of unactivated aliphatic epoxides*. This is because the reported catalytic system generally requires high temperatures (usually 150 °C or higher) and longer reaction times (12–100 h), which tend to form side products from isomerization of intermediates. The reaction also occurs without control of product stereochemistry, leading to the formation of the thermodynamically favored (*E*)-alkene as the major product.⁶ Thus, the operationally simple and stereospecific deoxygenation of the more abundant unactivated epoxides with a combination of an inexpensive catalyst and reductant under mild conditions would be of significant interest.

Based on our recent studies on the use of rhenium complexes as valuable catalysts for organic reactions,⁷ we initiated a project

studying the chemo- and stereoselective deoxygenation of epoxides with readily available catalysts and practical reductants under mild reaction conditions. We now report the rhenium-catalyzed deoxygenation of epoxides to alkenes under relatively mild conditions using triphenyl phosphite as a reductant.⁸ In addition, we disclose here that the structure of the reductants affects the regioselectivity of the deoxygenation.

Deoxygenation of *cis*-1,6-diphenyl-3-hexene oxide **1a** was carried out as a model reaction in toluene at 100 °C in the presence of various rhenium catalysts (10 mol %–Re) with PPh_3 as a reductant. Although the reaction took place in the presence of MeReO_3 , $\text{ReOCl}_3(\text{PPh}_3)_2$, and $\text{ReIO}_2(\text{PPh}_3)_2$, which showed high catalytic performance against styrene oxides and cyclohexene oxide under the previously reported reaction conditions,⁶ moderate to low stereoselectivities were observed (Table 1, entries 1–3). Low-valent rhenium complexes including $\text{Re}_2(\text{CO})_{10}$ and $[\text{ReBr}(\text{CO})_3(\text{thf})_2]$ were ineffective, and **1a** was recovered intact. Among the catalysts screened, Re_2O_7 , which is less expensive and easy to handle, showed the highest catalytic efficiency to yield **2a** in >99% yield (*Z/E* = 60/40) and thus was chosen as the catalyst for further optimization (entry 4).^{9,10} Excellent stereoselectivity (*Z/E* = 92/8) was observed using P(OPh)_3 as a reductant in place of PPh_3 (entry 5). It should be noted that P(OPh)_3 is a valuable reductant due to its low cost, low toxicity, and good stability in the air.¹¹ Finally, **1a** was isolated in 94% yield (>99% GLC yield) with excellent stereocontrol even with a reduced catalyst loading (2.5 mol %) (entry 6). Control experiments demonstrated that no deoxygenation by P(OPh)_3 occurred in the absence of

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Table 1. Rhenium-Catalyzed Deoxygenation of Epoxide **1a**

entry	epoxide	catalyst	reductant	yield ^b /%	Z/E ^a
1	1a	MeReO ₃	PPh ₃	97	88/12
2	1a	ReOCl ₃ (PPh ₃) ₂	PPh ₃	59	24/76
3	1a	ReIO ₂ (PPh ₃) ₂	PPh ₃	87	65/35
4	1a	Re ₂ O ₇	PPh ₃	>99	60/40
5	1a	Re ₂ O ₇	P(OPh) ₃	>99	92/8
6 ^c	1a	Re ₂ O ₇	P(OPh) ₃	>99 (94)	97/3
7 ^d	1a	Re ₂ O ₇	P(OPh) ₃	>99	98/2
8 ^e	1a	Re ₂ O ₇	P(OPh) ₃	>99	99/1
9 ^c	1a'	Re ₂ O ₇	P(OPh) ₃	>99 (96)	1/99
10 ^{e,f}	1a	Re ₂ O ₇	P(OPh) ₃	>99 (92)	98/2

^aDetermined by GLC. ^bDetermined by ¹H NMR. Values in parentheses are isolated yields. ^c2.5 mol % of Re₂O₇ and 1.2 equiv of P(OPh)₃ for 6 h. ^d2.5 mol % of Re₂O₇ and 1.2 equiv of P(OPh)₃ at 80 °C for 36 h. ^e0.25 mol % of Re₂O₇ and 1.2 equiv of P(OPh)₃ for 48 h. ^f5 mmol scale.

Re₂O₇ even at 150 °C for 24 h. Importantly, almost complete retention of stereochemistry (Z/E = 98/2) was observed when the reaction was examined at 80 °C, although a prolonged reaction time (36 h) was required for achieving complete conversion of **1a** (entry 7). Moreover, deoxygenation occurred with complete retention of stereochemistry to furnish **2a** quantitatively, when the amount of catalyst loading was decreased to 0.25 mol % (entry 8). Under the same reaction conditions described in entry 6, *trans*-1,6-diphenyl-3-hexene oxide **1a'** furnished exclusively the *E*-olefin in 96% yield with complete retention of configuration (Z/E = 1/99) (entry 9). A similar reaction time was required for complete conversion of these *cis*- and *trans*-epoxides. The results in entries 6 and 9 clearly showed that the current deoxygenation proceeded stereospecifically. The reaction proceeded even on a gram scale. Treatment of a mixture of 1.26 g (5.0 mmol, *cis/trans* = >99/<1) of **1a** with a Re₂O₇ catalyst (1.0 mol %) in toluene in a 50 mL Schlenk flask at 100 °C for 18 h gave 1.09 g of **2a** with retention of stereochemistry (entry 10).

With the optimized reaction conditions in hand, a variety of epoxides were subjected to the deoxygenation reaction in the presence of Re₂O₇. The series of epoxides having linear, branched, and cyclic alkyl chains shown in Table 2 were deoxygenated to the corresponding alkenes with complete retention of stereochemistry in all cases (all the reactions were examined on 0.50 mmol scale). For example, isopropyl group substituted epoxide **1b** and cyclic *cis*-cyclododecene oxide **1c** were deoxygenated efficiently to give the corresponding olefins **2b** and **2c** with complete retention of stereochemistry (entries 1 and 2). The deoxygenation of arylene oxide **1d** proceeded with high selectivity (entry 3). To determine the influence of the number of substituents on the epoxide rings, deoxygenations of mono- and trisubstituted aliphatic epoxides **1e** and **1f** were carried out next. The epoxides gave the corresponding mono- and trisubstituted olefins **2e** and **2f** in excellent yields even with a reduced amount of catalyst (entries 4 and 5). The current protocol was also extended to catalytic deoxygenation of α,β -epoxyesters. Both (*E*)- and (*Z*)- α,β -unsaturated esters **2g** and **2h** were obtained selectively in 93% and 90% yields from

Table 2. Rhenium-Catalyzed Deoxygenation of Epoxides **1a'**

entry	epoxide	time / h	alkene
1	1b (<i>cis/trans</i> = >99/<1)	6	2b 91% (Z/E = 98/2)
2	1c (<i>cis/trans</i> = 98/2)	8	2c 74% (Z/E = 98/2)
3 ^b	1d (<i>cis/trans</i> = 95/5)	2	2d 91% (Z/E = 93/7)
4	1e	8	2e 90%
5 ^b	1f	48	2f 88%
6	1g (<i>cis/trans</i> = <1/>99)	6	2g 93% (Z/E = <1/>99)
7	1h (<i>cis/trans</i> = 97/3)	6	2h 90% (Z/E = 94/6)
8 ^b	3	48	4 81% (Z/E = <1/>99)

^a0.50 mmol scale. Ratio of stereoisomers was determined by GLC. ^b1.0 mol % of Re₂O₇ was used.

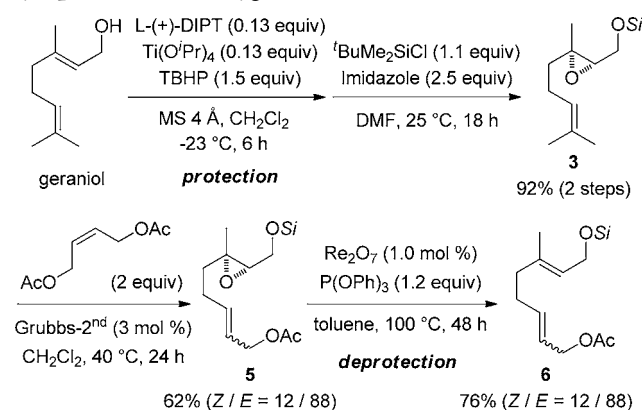
trans- and *cis*- α,β -epoxyesters **1g** and **1h** with excellent stereocontrol (entries 6 and 7).

Since the reaction proceeded under neutral and relatively mild conditions, chemoselective deoxygenation was achieved in the presence of other chemicals including ketone, ester, ether, halide, and nitrile (Table S1 in Supporting Information).¹² The reaction proceeded without affecting these functional groups to furnish the corresponding olefin **2a** in >93% yields with almost complete retention of stereochemistry, and additives were recovered quantitatively. When aldehyde, 3-phenylpropanal, was added to the reaction mixture, the recovery yields of the additive was decreased to 48%.

The excellent tolerance of functional groups demonstrated above makes the current reaction quite useful especially for the total synthesis of natural products. This is further demonstrated by the stereospecific deoxygenation of the monoterpene oxide, geraniol oxide (Table 2, entry 8). Deoxygenation of the hydroxy group protected geraniol oxide **3** proceeded without isomerization of the double bond to afford **4** in 81% yield. This result illustrates good chemoselectivity against the silyl group as

well as the wide substrate scope of the current stereospecific deoxygenation even with the sterically crowded trisubstituted epoxide. Furthermore, it is possible to *protect* the double bond functionality by applying the current rhenium-catalyzed deoxygenation.¹ For example, olefin cross-metathesis¹³ following the deoxygenation (deprotection) of **3**, which was prepared by the epoxidation (protection) of geraniol, resulted in the selective functionalization of one of the double bonds with the allylic double bonds intact (Scheme 1). In contrast, the direct olefin metathesis of **4** or geraniol without the current *protection/deprotection* protocol gave a complex mixture of products.

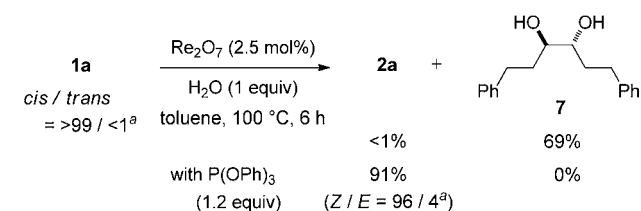
Scheme 1. Chemoselective Transformation of Double Bond by Epoxidation/Deoxygenation Protocol (Si = SiMe₂^tBu)



As shown in Table 1, the choice of reductants is crucial for the current stereospecific deoxygenation of epoxides. Preliminary studies to elucidate the origin of the selectivity and the reaction mechanism were carried out. First, the deoxygenation of **1a** in the presence of several phosphines and phosphites was carried out.¹⁴ Among the results obtained, we focused on the following two observations. (1) The deoxygenation occurred efficiently when triarylphosphines or phosphites were used as reductants. Alkylphosphines including tributylphosphine, tricyclohexylphosphine, and 1,2-bis(diphenylphosphino)ethane did not promote the reaction. (2) Good to excellent stereoselectivities were observed with the sterically hindered or electron-deficient phosphines and phosphites. Control experiments, in which (*Z*)-**2a** was subjected independently to the reaction conditions, demonstrated that none of the stereoisomer (*E*)-**2a** was produced in the presence of Re₂O₇ and phosphines and phosphites. This result clearly indicates that the isomerization from the (*Z*)- to (*E*)-isomer occurred during the deoxygenation process.

To obtain insight into the effect of phosphite, the reaction of Re₂O₇ with an equimolar amount of P(OPh)₃ in C₆D₆ was monitored by ³¹P NMR spectroscopy. The formation of O=P(OPh)₃ was observed even at 25 °C for 5 min, indicating that the current catalytic reaction is initiated by the rapid deoxygenation of Re₂O₇ by P(OPh)₃ to generate the active catalytic species. Furthermore, P(OPh)₃ was found to dramatically change the reactivity of Re₂O₇ by the reduction of a rhenium center. In the presence of 1.2 equiv of P(OPh)₃, the expected **2a** was obtained in 91% yield with high stereoselectivity (Z/E = 96/4) even in the presence of water (Scheme 2). This result also proved the robustness of the present stereoselective deoxygenation reaction against water. In

Scheme 2. Reactivity Switch of Re₂O₇ in the Presence of P(OPh)₃



^aDetermined by GLC.

sharp contrast, the yield of olefin **2a** decreased less than 1% and the formation of 1,2-diol **7** was observed in 69% yield, when the same reaction was examined in the absence of P(OPh)₃.¹⁵ We further confirmed that treatment of 0.50 equiv of P(OPh)₃ with 2.5 mol % of Re₂O₇ and **1a** for 6 h furnished a 50% yield of **2a** with high stereoselectivity (Z/E = 96/4). These results imply that phosphite plays a role in (1) the reduction of the high valent Re₂O₇ to form the rhenium active species suitable for the achievement of stereospecific deoxygenation of epoxides and (2) the regeneration of the rhenium species by deoxygenation after one catalytic cycle.

Based on the above observations, a plausible reaction mechanism is shown in Figure 1.¹⁶ The reaction initiates with

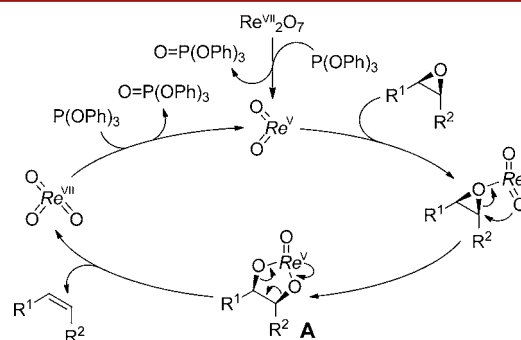


Figure 1. Proposed reaction mechanism.

the rapid reduction of Re₂O₇ by P(OPh)₃.¹⁷ Subsequent coordination of the epoxide to the resulting oxorhenium species followed by the ring-opening of the epoxide gives five-membered-ring rhenoxolane intermediate **A** with retention of configuration. Finally, olefin extrusion via the cleavage of **A** and regeneration of the oxorhenium species by reduction with P(OPh)₃ complete the catalytic cycle.¹⁸

In summary, the present study describes the operationally simple deoxygenation of unactivated aliphatic epoxides to the corresponding alkenes using the reductant, P(OPh)₃, with Re₂O₇ catalyst. The reductant and catalyst are both inexpensive. The reaction proceeded with complete regioselectivity with broad functional group tolerance. This catalytic system promises to be useful, especially in natural products and pharmaceutical syntheses, which require mild conditions, selectivity, and functional group tolerance.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data for all new compounds, and copies of ¹H and ¹³C NMR spectra. The

Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01583.

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Notes

The authors declare no competing financial interest.

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(9) Investigation of other catalysts with 2 equiv of PPh₃: ReCl₃(PPh₃)₂ (MeCN) 57% (Z/E = 72/28), ReOCl₃(PPh₃)₂ 81% (86/14), MoO₂Cl₂ 43% (94/6), MoO₂Cl₂(dmf) 80% (96/4), Mo(CO)₆ 10% (85/15), MoO₂(acac)₂ 59% (47/53). Deoxygenation of **1a** was not observed with the following transition metal catalysts: Re₂(CO)₁₀, [ReBr(CO)₃(thf)]₂, MoO₃, W(CO)₆, and MnO₂.

(10) Investigation of solvents with 2.5 mol% of Re₂O₇ and 1.2 equiv of P(OPh)₃ for 6 h: ClC₆H₄ >99% (Z/E = 97/3), decane >99% (97/3), ClCH₂CH₂Cl >99% (97/3), dioxane >99% (97/3), MeCN 22% (95/5), DMF 18% (82/18).

(11) The price per 500 g of P(OPh)₃ is \$26, and that for PPh₃ is \$82 (TCI America Fine Chemicals).

(12) For intermolecular additive screens, see: (a) Collins, K. D.; Glorius, F. *Nat. Chem.* **2013**, *5*, 597. (b) Collins, K. D.; Glorius, F. *Acc. Chem. Res.* **2015**, *48*, 619.

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(14) Effect of phosphines and phosphites (1.2 equiv) on the regioselectivity in the deoxygenation of **1a** with 2.5 mol% of Re₂O₇ for 6 h: PPh₃ >99% (Z/E = 60/40), P(furyl)₃ 76% (68/32), P(*o*-tol) 7% (98/2), P(C₆F₅)₃ 55% (95/5), P(O(4-FC₆H₄))₃ >99% (97/3), PⁿBu₃ 2%, PCy₃ 0%, dppe 7%.

(15) Diol **7** was not converted to olefin **2a** in the presence of a Re₂O₇ catalyst with P(OPh)₃. Therefore, the active catalytic species generated from the reduction of Re₂O₇ with P(OPh)₃ should directly convert **1a** to **2a** without producing **7**, thus having different reactivity compared with the original high valent Re₂O₇ species.

(16) For a mechanism study of rhenium-catalyzed deoxygenation of epoxides, see: Bi, S.; Wang, J.; Liu, L.; Li, P.; Lin, Z. *Organometallics* **2012**, *31*, 6139.

(17) Because the regioselectivity of the reaction depends on the choice of reductants as noted in ref 14, coordination of phosphite to oxorhenium species cannot be ruled out.

(18) The decrease of the selectivity in the reaction using PPh₃ as a reductant (Table 1, entry 4) might be explained by considering the intermolecular nucleophilic attack of PPh₃ on the carbon atom of rhena-2,5-dioxolane intermediate **B** followed by PPh₃-facilitated reductive deoxygenation via the oxaphosphetane intermediate **C**.

