DOI: 10.1002/adsc.201600840

Advanced Synthesis & Catalysis

Very Important Publication

Molybdenum-Catalyzed Stereospecific Deoxygenation of Epoxides to Alkenes

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Received: July 29, 2016; Revised: October 11, 2016; Published online: ■■ ■■, 0000

Supporting information for this article can be found under: http://dx.doi.org/10.1002/adsc.201600840.

Abstract: Mild and simple catalytic systems consisting of molybdenum(VI) dichloride dioxide [MoO_2Cl_2] as a catalyst and a phosphine as reductant have been developed for the stereospecific deoxygenation of epoxides to alkenes. The reactions using 1,2-bis(diphenylphosphino)ethane (dppe) and triphenylphosphine (PPh_3) proceed with retention and inversion of stereochemistry, respectively. The mild reaction tolerates the presence of various functional groups and affords stereodefined substituted olefins in good yields.

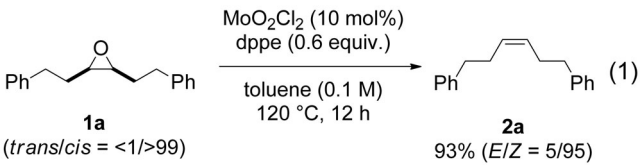
Keywords: molybdenum; deoxygenation; epoxides; alkenes; stereospecific process

While the epoxidation of olefins has been extensively studied and has found many applications in organic synthesis,[1] the reverse reaction, deoxygenation of epoxides, has not received much attention despite its potential utility for the stereoselective synthesis of multisubstituted olefins.[2] Preceded by the extensive development of a variety of stoichiometric reducing agents since the early 1950s,[3] significant advances have recently been made in the catalytic deoxygenation of epoxides, among which the reactions in the presence of a catalytic amount of oxorhenium complexes and various reductants are particularly noteworthy.[4,5,6] However, the reactions have several drawbacks such as limited substrate scope (e.g., only effective for styrene oxides and cycloalkene oxides) or poor chemo- and stereoselectivity. On the other hand, we recently reported a general and practical method for the stereoretentive deoxygenation of epoxides under rhenium catalysis.[7] Nevertheless, the low availability of rhenium still remains a major issue to be addressed with the growing demand for sustainability. Herein we report simple molybdenum-based catalytic systems for the stereospecific deoxygenation of epoxides, including unactivated aliphatic epoxides, that proceed under mild conditions to afford stereodefined substituted olefins. Attractive features include the use of an abundant and inexpensive molybdenum complex as a catalyst,[8] good functional group compatibility, and the control of stereochemistry by the appropriate choice of reaction conditions.

We commenced our investigation with the deoxygenation of *cis*-1,6-diphenyl-3-hexene oxide (**1a**) in the presence of MoO_2Cl_2 as a catalyst and various phosphine reductants, because similar catalytic systems were known to be effective for the deoxygenation of sulfoxides, *N*-oxides, and nitro compounds.[4a,9] After extensive experimentation, we established two complementary reaction conditions that stereospecifically afford (*Z*)- and (*E*)-1,6-diphenyl-3-hexene (**2**) with retention and inversion of stereochemistry, respectively. Thus, the deoxygenation of *cis*-epoxide **1a** proceeded with stereoretention to afford *Z*-olefin **2a** using 1,2-bis(diphenylphosphino)ethane (dppe) as a reductant [Eq. (1)], while **1a** was converted to *E*-olefin **2b** with stereoinversion using PPh_3 as a reductant [Eq. (2)].

We found that the yield and stereochemical outcome of the reaction depend strongly on the structure

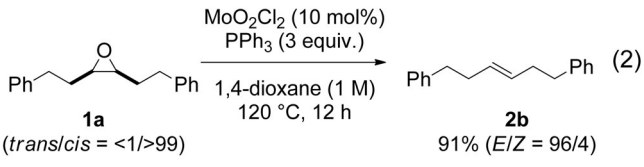
Conditions A: stereoretention



1a (*trans*/*cis* = <1/>99)

2a 93% (*E*/*Z* = 5/95) (1)

Conditions B: stereoinversion

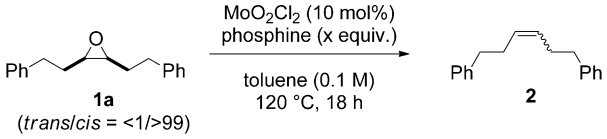


1a (*trans*/*cis* = <1/>99)

2b 91% (*E*/*Z* = 96/4) (2)

of the phosphines, but in a rather unpredictable fashion (Table 1). Thus, while dppe stereoretentively afforded the *Z*-olefin **2a** from the *cis*-epoxide **1a** (entry 2), the reactions using related bidentate phosphines with different backbones resulted in the formation of a mixture of the stereoisomers (entries 1, 3–5). The deoxygenation reactions with monodentate phosphines with various electronic and steric properties took place with low yield and stereoselectivity in most cases, but the reactions with PPh_3 and tri(2-furyl)phosphine were worth further investigation because they showed either good yield or high stereoinversion efficiency (entries 6 and 14). Although we could not improve the product yield with tris(2-furyl)-phosphine as a reductant, the inversion ratio with PPh_3 was improved by increasing the reaction concentration,[10] which was instead accompanied by a decrease in the product yield because of the formation of 1,6-diphenylhexan-3-one *via* Lewis acid-promoted ring-opening rearrangement (entries 7 and 8).[11] The side reaction could be suppressed by performing the reaction with 3 equiv. of PPh_3 in concentrated 1,4-dioxane, and thus we achieved the smooth deoxygenation with stereoinversion that affords *E*-olefin **2b** from *cis*-epoxide **1a** (entry 10).

Table 1. Molybdenum-catalyzed deoxygenation of epoxides with phosphine reductants.[a]



Entry	Phosphine[i]	x	Alkene Yield [%][b]	*E*/*Z*[c]
1	dppm	0.6	35	45/55
2[d]	dppe	0.6	98 (93)	5/95
3	dppp	0.6	66	34/66
4	dppb	0.6	90	41/59
5	dpppent	0.6	77	66/34
6	PPh_3	1.2	92	67/33
7[e]	PPh_3	1.2	91	83/17
8[f]	PPh_3	1.2	76	95/5
9[f,g]	PPh_3	1.2	76	97/3
10[h]	PPh_3	3.0	91 (91)	96/4
11	$P(4\text{-}MeOC_6H_4)_3$	1.2	78	82/18
12	$P(4\text{-}F_3CC_6H_4)_3$	1.2	34	77/23
13	$P(2\text{-}MeC_6H_4)_3$	1.2	8	65/35
14	$P(2\text{-furyl})_3$	1.2	55	93/7
15	$P(OPh)_3$	1.2	9	79/21
16	PMe_3	1.2	48	26/74
17	$P(n\text{-}Bu)_3$	1.2	83	44/56
18	PCy_3	1.2	22	58/42

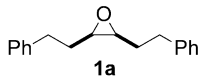
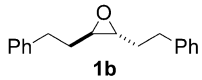
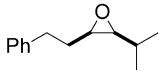
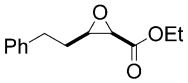
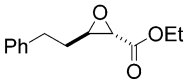
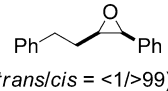
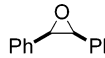
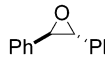
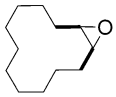
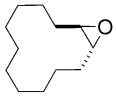
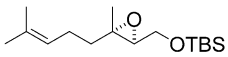
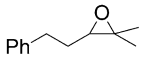
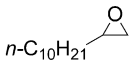
[a] Reactions were performed on a 0.3 mmol scale with MoO_2Cl_2 (10 mol%) and phosphine (1.2 equiv. P) in toluene (0.1 M) at 120 °C for 18 h.
[b] The yields were determined by ^1H NMR. Yields in parentheses refer to isolated yields.
[c] Determined by GLC.
[d] For 12 h [conditions in Eq. (1)].
[e] 0.3 M.
[f] 1 M.
[g] 1,4-Dioxane as a solvent.
[h] The reaction was performed with PPh_3 (3.0 equiv,) in 1,4-dioxane (1 M) for 12 h [conditions in Eq. (2)].
[i] dppm = $Ph_2PCH_2PPh_2$, dppe = $Ph_2P(CH_2)_2PPh_2$, dppp = $Ph_2P(CH_2)_3PPh_2$, dppb = $Ph_2P(CH_2)_4PPh_2$, dpppent = $Ph_2P(CH_2)_5PPh_2$.

With the above results, in the following scope and limitation studies, the reactions were conducted either with dppe as a reductant in toluene (0.1 M) for the stereoretentive deoxygenation (conditions A), or with PPh_3 in 1,4-dioxane (1 M) for the deoxygenation with stereoinversion (conditions B), respectively. Careful monitoring of the reaction revealed that the *E*/*Z* ratio remained constant throughout the reaction. Moreover, when **2a** and **2b** were subjected to the reaction conditions described in Eqs. (1) and (2), no olefin isomerization was observed. These results indicate that the stereochemical outcome is due not to stereoconvergent isomerization of olefin product but to the stereospecific deoxygenation itself.

The scope of the stereoretentive deoxygenation reaction under conditions A is summarized in Table 2. The reactions with *cis*-epoxides bearing a linear alkyl, a branched alkyl, an ethoxycarbonyl, and a phenyl group and *cis*-cyclododecene oxide proceeded smoothly with retention of stereochemistry to afford the corresponding *Z*-olefins (entries 1, 3, 4, 6, and 9), while *cis*-stilbene oxide showed moderate stereoselectivity (entry 7). *trans*-Epoxides also took part in the reaction and were converted to *E*-olefins with good yield and selectivity (entries 2, 5, 8, and 10). While trisubstituted epoxides including the one derived from geraniol were also deoxygenated to the corresponding olefins (entries 11 and 12), the monosubstituted epoxide gave the olefin product in low yield (entry 13). Under conditions A, we did not find any carbonyl products formed *via* the Lewis acid-promoted rearrangement.

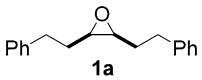
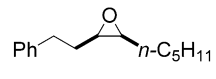
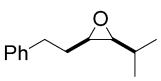
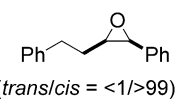
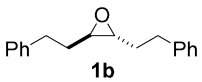
The scope of the deoxygenation reaction under conditions B is illustrated in Table 3. The reactions with *cis*-epoxides bearing a linear alkyl and a phenyl group took place with inversion of stereochemistry to afford the corresponding *E*-olefins (entries 1, 2, and 4), while a *cis*-epoxide bearing a bulky alkyl group showed low inversion efficiency (entry 3). *trans*-Epoxides were also poor substrates under standard conditions B (entry 5). However, we could improve the inversion efficiency by performing the reaction with tris(2-furyl)phosphine in MeCN solvent, albeit in moderate yield (entry 7).[12] The last reaction, which transforms a *trans*-epoxide to a thermodynamically

Table 2. Molybdenum-catalyzed deoxygenation of epoxides with stereoretention.[a]

Entry	Epoxide	Alkene Yield [%][b]	Alkene *E*/*Z*[c]
1[d]	 **1a** (*trans*/*cis* = <1/>99)	93	5/95
2	 **1b** (*trans*/*cis* = >99/<1)	94	98/2
3	 (*trans*/*cis* = 6/94)	90	9/91
4	 (*trans*/*cis* = 3/97)	92	6/94
5	 (*trans*/*cis* = >99/<1)	94	>99/<1
6[e]	 (*trans*/*cis* = <1/>99)	96	15/85
7[f]	 (*trans*/*cis* = <1/>99)	92	26/74
8[f]	 (*trans*/*cis* = >99/<1)	94	>99/<1
9	 (*trans*/*cis* = <1/>99)	98	<1/>99
10	 (*trans*/*cis* = >99/<1)	83	98/2
11[g]	 (*trans*/*cis* = >99/<1)	84	>99/<1
12		71	–
13[f,g]		41	–

[a] Reactions were performed on a 0.2–0.3 mmol scale with MoO_2Cl_2 (10 mol%) and dppe (0.6 equiv.) in toluene (0.1 M) at 120 °C for 18 h (conditions A).
[b] Isolated yield.
[c] Determined by GLC.
[d] For 12 h.
[e] At 100 °C.
[f] For 2 h.
[g] At 150 °C.

Table 3. Molybdenum-catalyzed deoxygenation of epoxides with stereoinversion.[a]

Entry	Epoxide	Phosphine	Alkene Yield [%][b]	Alkene *E*/*Z*[c]
1	 **1a** (*trans*/*cis* = <1/>99)	PPh_3	91	96/4
2	 (*trans*/*cis* = 5/95)	PPh_3	68	96/4
3	 (*trans*/*cis* = 6/94)	PPh_3	76	62/38
4	 (*trans*/*cis* = <1/>99)	PPh_3	71	87/13
5		PPh_3	77[d]	41/59
6[e]	 **1b**	PPh_3	71[d]	21/79
7[e]	(*trans*/*cis* = >99/<1)	$P(2\text{-furyl})_3$	50	8/92

[a] Reactions were performed on a 0.2 mmol scale with MoO_2Cl_2 (10 mol%) and PPh_3 (3.0 equiv.) in 1,4-dioxane (1 M) at 120 °C for 12 h (conditions B).
[b] Isolated yield.
[c] Determined by GLC.
[d] Yield determined by ^1H NMR.
[e] The reaction was performed with a phosphine (1.2 equiv.) in MeCN (1 M) for 18 h.

less stable *Z*-olefin, is the most challenging and will be our next research project, as it requires further optimization.[13]

The mild and neutral reaction conditions allowed us to explore the functional group compatibility of the deoxygenation reaction further (Supporting Information, Table S6). Thus, the stereoretentive deoxygenation reactions of **1a** were performed in the presence of compounds bearing various functional groups.[14] The reactions proceeded smoothly in the presence of ester, ketone, nitrile, alcohol, aryl bromide, aryl methyl ether, internal alkyne, and terminal alkyne without much affecting the yield and stereoselectivity of the reaction, while carboxylic acid, aldehyde, and phenol negatively affected the product/recovery yields and/or stereoselectivity. It should be noted that alcohol, internal alkyne, and terminal alkyne remained intact and did not significantly affect the deoxygenation reaction in the present molybdenum-based system, whereas these functional groups decomposed or shut down the deoxygenation reaction under the rhenium catalysis, that we developed previously.[7]

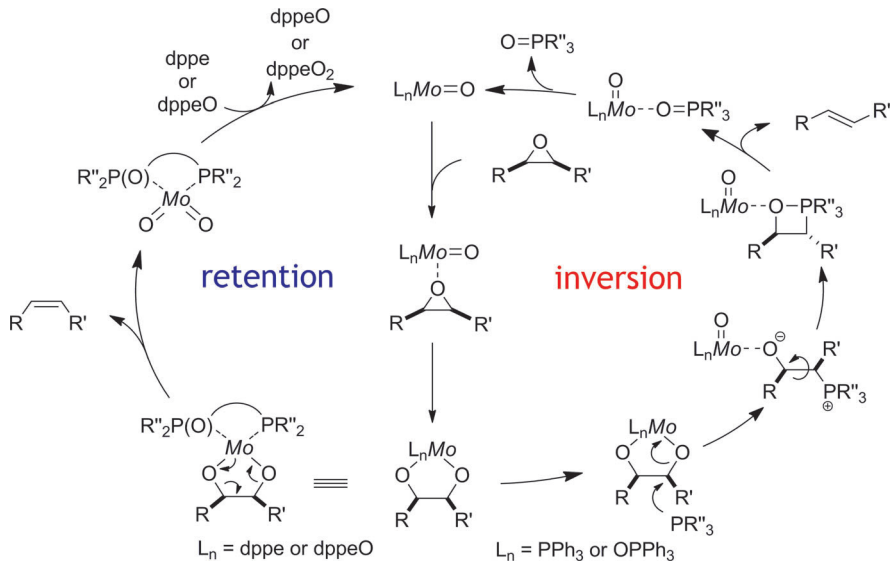


Figure 1. A possible mechanism.

While the origin of the stereoselectivity is not fully understood at this stage, we propose that the stereospecific reactions proceed through the mechanisms shown in Figure 1. First, the well-known reduction of $Mo(VI)O_2Cl_2$ by a phosphine generates the $Mo(IV)OCl_2$ active species,[5,9,15,16] which reacts with an epoxide to form a molybdena-2,5-dioxolane intermediate.[17] Similar intermediates have been proposed in the related molybdenum-catalyzed deoxydehydration of vicinal diols.[18] Under conditions A, stereoretentive olefin extrusion takes place to form a dioxomolybdenum(VI) complex, which is subsequently reduced by a phosphine to regenerate the active species.[19] Considering that the reaction reaches completion with 0.6 equiv. of dppe, the dppe monoxide that is formed after the initial deoxygenation also functions as an oxygen atom acceptor.[20] Under conditions B, the intermolecular nucleophilic attack of PPh_3 takes place from the backside of one of the C–O bonds with inversion of stereochemistry and forms the oxaphosphetane intermediate, which subsequently gives an *E*-olefin and regenerates the active species. The effect of the concentration may be explained by the general trend that intramolecular processes are preferred over intermolecular processes under dilute conditions.

In conclusion, we have developed a simple and efficient molybdenum-catalyzed deoxygenation reaction of epoxides that proceeds stereospecifically to afford stereodefined olefins. An unprecedented switch of the stereoselectivity controlled by phosphine reductants was achieved, in which the reactions with dppe and PPh_3 took place with retention and inversion of stereochemistry, respectively. Further studies on the development of molybdenum-based sustainable catalytic systems to replace rhenium catalysis are ongoing in our laboratory.

Experimental Section

Typical Procedure

cis-1,6-Diphenyl-3-hexene oxide (75.8 mg, 0.30 mmol) was added to a stirred mixture of MoO_2Cl_2 (6.0 mg, 30 μmol) and dppe (71.7 mg, 0.18 mmol) in toluene (2.7 mL) in an oven-dried test tube under argon, and the resulting mixture was stirred at 120 °C for 12 h. The reaction mixture was then filtered through a pad of silica gel with Et_2O and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/AcOEt = 50/1) to afford 1,6-diphenyl-3-hexene as a colorless oil; yield: 66.0 mg (93%). The *E*/*Z* ratio was determined to be 5/95 by GLC analysis. The spectral data were in accord with those reported in the literature.[7]

Acknowledgements

We thank MEXT for financial support, and KAKENHI Grant-in-Aid for Scientific Research (A) No. 26248030.

References

[1] a) J. E. Bäckvall, *Modern Oxidation Methods*, Wiley-VCH, Weinheim, **2010**; b) B. S. Lane, K. Burgess, *Chem. Rev.* **2003**, *103*, 2457; c) Q. H. Xia, H. Q. Ge, C. P. Ye, Z. M. Liu, K. X. Su, *Chem. Rev.* **2005**, *105*, 1603.

[2] a) A. B. Flynn, W. W. Ogilvie, *Chem. Rev.* **2007**, *107*, 4698; b) E.-i. Negishi, Z. Huang, G. Wang, S. Mohan, C. Wang, H. Hattori, *Acc. Chem. Res.* **2008**, *41*, 1474.

[3] Selected early examples: a) W. Cole, P. L. Julian, *J. Org. Chem.* **1954**, *19*, 131; b) J. K. Kochi, D. M. Singleton, *J. Am. Chem. Soc.* **1968**, *90*, 1582; c) K. B. Sharpless, M. A. Umbreit, M. T. Nieh, T. C. Flood, *J. Am.*

Chem. Soc. **1972**, *94*, 6538; d) R. C. Larock, *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, Wiley-VCH, New York, **1993**, p 155.

[4] Catalytic deoxygenation of epoxides: a) S. C. A. Sousa, A. C. Fernandes, *Coord. Chem. Rev.* **2015**, *284*, 67; b) Z. Zhu, J. H. Espenson, *J. Mol. Catal.* **1995**, *103*, 87; c) K. P. Gable, F. A. Zhuravlev, F. T. Yokochi, *Chem. Commun.* **1998**, 799; d) K. P. Gable, E. C. Brown, *Organometallics* **2000**, *19*, 944; e) J. B. Arterburn, M. Liu, M. C. Perry, *Helv. Chim. Acta* **2002**, *85*, 3225; f) K. P. Gable, E. C. Brown, *Synlett* **2003**, 2243; g) J. E. Ziegler, M. J. Zdilla, A. J. Evans, M. M. Abu-Omar, *Inorg. Chem.* **2009**, *48*, 9998; h) S. Vkuturi, G. Chapman, I. Ahmad, K. M. Nicholas, *Inorg. Chem.* **2010**, *49*, 4744; i) S. Stanowski, K. M. Nicholas, R. S. Srivastava, *Organometallics* **2012**, *31*, 515.

[5] Mo-catalyzed deoxygenation of activated epoxides: L. Hills, R. Moyano, F. Montilla, A. Pastor, A. Galindo, E. Álvarez, F. Marchetti, C. Pettinari, *Eur. J. Inorg. Chem.* **2013**, 3352.

[6] Electrochemical deoxygenation of epoxides: a) J.-M. H, Z.-Q. Lin, D.-S. Chen, *Org. Lett.* **2012**, *14*, 22; b) B. R. Buckley, A. P. Patel, K. G. U. Wijayantha, *Synlett* **2014**, *25*, 197.

[7] T. Nakagiri, M. Murai, T. Takai, *Org. Lett.* **2015**, *17*, 3346.

[8] a) R. M. Bullock, *Catalysis without Precious Metals*, Wiley-VCH, Weinheim, **2010**; b) P. C. K. Vesborg, T. F. Jaramillo, *RSC Adv.* **2012**, *2*, 7933.

[9] a) R. Sanz, J. Escribano, R. Aguado, M. R. Pedrosa, F. J. Arnáiz, *Synthesis* **2004**, 1629; b) R. Sanz, J. Escribano, Y. Fernández, R. Aguado, M. R. Pedrosa, F. J. Arnáiz, *Synlett* **2005**, 1389; c) R. Sanz, J. Escribano, M. R.; Pedrosa, R. Aguado, F. J. Arnáiz, *Adv. Synth. Catal.* **2007**, *349*, 713; d) K. J. Akumar, D. K. Chand, *J. Chem. Sci.* **2009**, *121*, 111; e) C. C. Malakar, E. Merisor, J. Conrad, U. Beifuss, *Synlett* **2010**, 1766.

[10] The effect of the concentration on the *E*/*Z* ratio was not limited to this case but was more general. Thus, regardless of the phosphines used, the reactions under concentrated conditions preferred stereoinversion and increased the ratio of the *E*-olefin **2b**.

[11] a) B. Rickborn, in: *Comprehensive Organic Synthesis*, Vol. 3, (Ed.: B. M. Trost), Pergamon, Oxford, **1991**, p 733, and references cited therein; b) H. Alper, D. D. Roches, T. Durst, R. Legault, *J. Org. Chem.* **1976**, *41*, 3611; c) P. Wipf, W. Xu, *J. Org. Chem.* **1993**, *58*, 825; d) K. Suda, T. Kikkawa, S. Nakajima, T. Takanami, *J. Am. Chem. Soc.* **2004**, *126*, 9554, and references cited therein.

[12] The use of 3.0 equiv. of a phosphine had adverse effects in MeCN.

[13] Deoxygenations of *trans*-epoxides to *Z*-olefins have been reported. However, they require stoichiometric amounts of strong bases. a) E. Vedejs, P. L. Fuchs, *J. Am. Chem. Soc.* **1973**, *95*, 822; b) P. B. Dervan, M. A. Shippey, *J. Am. Chem. Soc.* **1976**, *98*, 1265; c) B. Xiao, Z. Niu, Y.-G. Wang, W. Jia, J. Shang, L. Zhang, D. Wang, Y. Fu, J. Zeng, W. He, K. Wu, J. Li, J. Yang, L. Liu, Y. Li, *J. Am. Chem. Soc.* **2015**, *137*, 3791.

[14] a) K. D. Collins, F. Glorius, *Nat. Chem.* **2013**, *5*, 597; b) K. D. Collins, A. Rühling, F. Glorius, *Nat. Protoc.* **2014**, *9*, 1348; c) K. D. Collins, F. Glorius, *Acc. Chem. Res.* **2015**, *48*, 619.

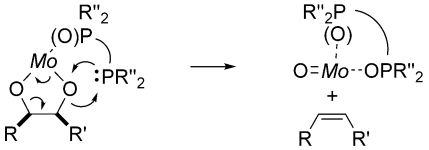
[15] a) K. Unoura, A. Yamazaki, A. Nagasawa, Y. Kato, H. Itoh, H. Kudo, Y. Fukuda, *Inorg. Chim. Acta* **1998**, *269*, 260, and references cited therein; b) T. Robin, F. Montilla, A. Galindo, C. Ruiz, J. Hartmann, *Polyhedron* **1999**, *18*, 1485.

[16] $Mo(IV)OCl_2$ is known to react rapidly with $Mo(VI)O_2Cl_2$ to form a dimeric $Mo_2(V)O_3Cl_4$; its involvement cannot be excluded. See ref. [8] and also a) R. H. Holm, *Chem. Rev.* **1987**, *87*, 1401; b) R. H. Holm, *Coord. Chem. Rev.* **1990**, *100*, 183; c) R. Aguado, J. Escribano, M. R. Pedrosa, A. De Cian, R. Sanz, F. J. Arnáiz, *Polyhedron* **2007**, *26*, 3842; d) P. M. Reis, B. Royo, *Tetrahedron Lett.* **2009**, *50*, 949; e) N. García, P. García-García, M. A. Fernández-Rodríguez, R. Rubio, M. R. Pedrosa, F. J. Arnáiz, R. Sanz, *Adv. Synth. Catal.* **2012**, *354*, 321.

[17] Alternatively, a molybdenaoxetane intermediate may be involved: a) Y. Hayasi, J. Schwartz, *Inorg. Chem.* **1981**, *20*, 3473; b) K. G. Moloy, *Inorg. Chem.* **1988**, *27*, 677.

[18] a) J. R. Dethlefsen, D. Lupp, B.-C. Oh, P. Fristrup, *ChemSusChem* **2014**, *7*, 425; b) D. Lupp, N. J. Christensen, J. R. Dethlefsen, P. Fristrup, *Chem. Eur. J.* **2015**, *21*, 3435; c) J. R. Dethlefsen, D. Lupp, A. Teshome, L. B. Nielsen, P. Fristrup, *ACS Catal.* **2015**, *5*, 3638.

[19] Alternatively, dppe (or dppeO) may intramolecularly attack the oxygen atom and thereby facilitate stereoretentive olefin extrusion in a single step without the intermediacy of a Mo(VI) complex.



[20] The reaction with dppe monoxide (1.2 equiv.) under conditions A afforded the product in 64% yield as a mixture of stereoisomers (*E*/*Z* = 51/49). The unexpectedly low selectivity may suggest that the active species should be formed in the presence of dppe.

