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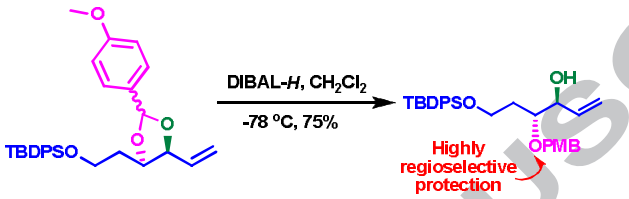

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Highly regioselective homoallyl alcohol protection through ring opening of *p*-methoxybenzylidene acetal

Yada Bharath[a,b], Spandana Maduri[a] and Debendra K. Mohapatra[a,b,*]

[a]*Natural Products Chemistry Division, CSIR-Indian Institute of Chemical Technology, Hyderabad-500 007, India*
[b]*Academy of Scientific and Innovative Research (AcSIR), Mathura Road, New Delhi-110 025, India*

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ABSTRACT

A highly regioselective homoallylic alcohol protection was achieved in the reductive cleavage of anisylidene acetal with DIBAL-*H* during the selective protection of hydroxyl group in terminal unsaturated diols which was unlikely compare to the diols present adjacent to internal and cyclic double bond. Reductive cleavage of terminal olefenic diols protected as its acetals gave exclusively allyl alcohol product in good to excellent yield. Though the actual reason of such observation is not quite clear, the current reductive protocol can be applied as an efficient solution for indirect protection of less reactive hydroxy group in preference to that of more reactive allylic one as PMB-mono ether.

Protection and deprotection of hydroxyl functional groups plays a pivotal role in organic synthesis containing more than one hydroxy group.[1] In this aspect, the readily installed and manipulated benzylidene or *p*-methoxybenzylidene acetals gained immense importance and widespread applications in organic synthesis particularly in carbohydrate chemistry for the immediate protection of the 1,2- and 1,3-diol derivatives.[2] The most advantageous factor in the use of these benzylidene or *p*-methoxybenzylidene acetals is that they can be reductively opened in a regioselective manner exposing a free hydroxyl group and a benzyl or *p*-methoxybenzyl ether enabling the opportunity for further transformation. The regioselective opening of cyclic acetals was first performed by Doukas and Fontaine in 1951 to open the acetal diosgenin by the reagent combination of $LiAlH_4$ and HCl.[3] The HCl was later replaced by active Lewis acid $AlCl_3$ and was extensively used by Brown et al. for the regioselective opening of the cyclic acetals.[4] Today, a plethora of reagent combinations are available for regioselective opening of cyclic acetals.[5] For the synthesis of 4-*O*-benzyl ethers the reagents include: $LiAlH_4$–$AlCl_3$,[6] DIBAL-*H*,[6c,7] $BH_3.NMe_3$–$AlCl_3$,[8] $BH_3.HNMe_2$–BF_3OEt_2,[9] $BH_3.NMe_3$–Me_2BBr,[10] Et_3SiH–$PhBCl_2$,[11] PS-DESTM–$PhBCl_2$,[11a] polymethyl hydrosiloxane (PMHS)–$AlCl_3$,[12] and BH_3.THF alone[6c] or in combination with Ph_2BBr,[13a] Bu2BOTf,[13b,c] lanthanide triflates,[13d] $Cu(OTf)_2$,[13e] or $CoCl_2$.[13f] Alternatively, for the synthesis of 6-*O*-benzyl ethers, the reagents used include: $NaCNBH_3$–HCl,[14] $NaCNBH_3$-MsOH,[15] BH_3NMe_3–$AlCl_3$,[8a] $BH_3.HNMe_2$–BF_3OEt_2,[9a] or silanes, such as Et_3SiH[16] in combination with TFA,[16a] TfOH,[11a] or BF_3OEt_2,[9b,16b] and Me_2EtSiH–$Cu(OTf)_2$.[13e] However, the regioselective reductive opening of benzylidene or *p*-methoxybenzylidene acetals of unsymmetrical 1,2-diols is less explored.[12]

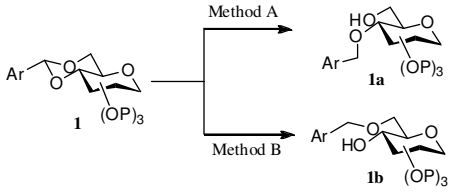
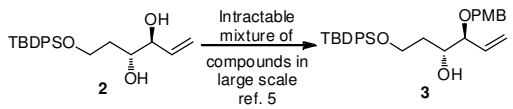


Figure 1: Regioselective reductive ring opening of acetals.

During the selective protection of allyl alcohol over homoalyl alcohol in diol **2** to obtain **3** (Scheme 1) by selective protection using PMB-Br towards the total synthesis of amphidinolactone A,[17] the reaction was efficient in milligram scale, but during gram scale synthesis, it ended up with intractable mixture of products.



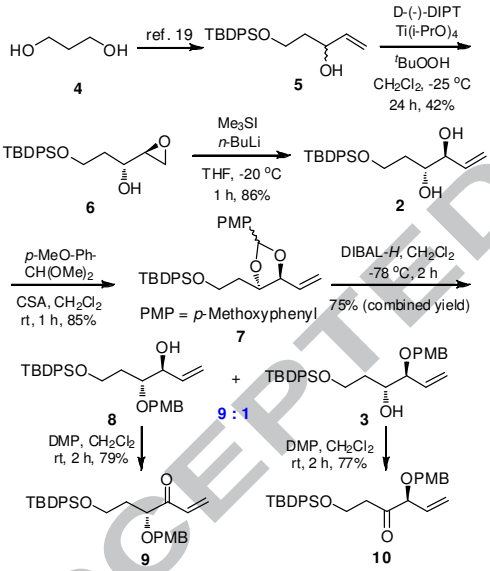
Scheme 1: Selective protection of allylic alohol in presence of homoallylic alcohol.

To circumvent the problem, we thought of improving the yield as well as selectivity in the protection of hydroxyl group in diol as its PMB-acetal followed by reductive cleavage using diisobutylaluminium hydride (DIBAL-*H*) as reported in the litertature. As per the earlier literature precedence,[18] reductive

* Corresponding author. Tel.: +91-40-27193128; fax: +91-40-27160512; e-mail: mohapatra@iict.res.in

cleavage of *p*-methoxyphenyl (PMP)-acetal moiety using DIBAL-*H* afforded regioisomers depending on the selective co-ordination of the DIBAL-*H* to the neighbouring groups present in the system leading to major product as homoallyl alcohol in case of diols adjacent to cyclic or internal double bonds. Notably, to the best of our knowledge this indirect sequence via reductive cleavage of PMP-acetal for substrate bearing terminal olefinic bond have not been studied in general. In this communication, we describe an indirect sequence for the highly regioselective protection of terminal olefinic diol, based on two easily manipulating steps, namely an acid catalyzed PMP-acetal protection and its reductive cleavage.

To prepare diol **2**, propane-1,3-diol (**4**) was monosilylated followed by Swern oxidation gave aldehyde which upon vinyl Grignard addition furnished **5** in 68% yield over three steps.[19] Sharpless enantioselective epoxidation[20] using D-(–)-diisopropyl tartarate as the chiral source and in the presence of *t*-BuOOH and Ti(*i*-PrO)$_4$, at –25 °C furnished (*R*)-3-(*tert*-butyldiphenylsilyloxy) -1-((*S*)-oxiran-2-yl)propan-1-ol (**6**) {$[\alpha]_D^{25}$ –6.8 (*c* 1.6, $CHCl_3$)} in 42% yield. Epoxide **6** was treated with dimethyl sulfonium methylide at –20 °C in THF to obtain diol **2** in 86% yield. With good quantities of diol **2** in hand, the *p*-methoxyphenyl acetal **7** was prepared using *p*-methoxybenzylidenedimethylacetal[21] in presence of catalytic amount of CSA in CH_2Cl_2 as a mixture (4:1) of separable diastereomers in 85% yield. Reductive cleavage of acetal **7** was achieved in a regioselective manner using DIBAL-*H*[22] at –78 °C in CH_2Cl_2 to give a mixture (9:1) of silica gel



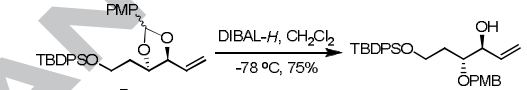
Scheme 2: Regioselective ring opening of *p*-methoxybenzylidene acetal **7**.

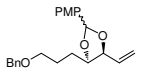
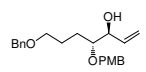
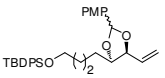
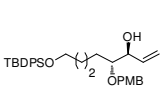
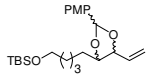
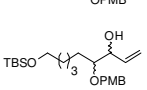
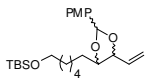
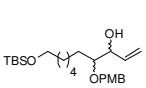
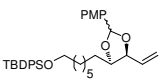
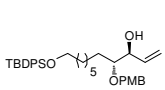
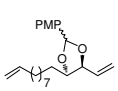
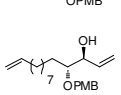
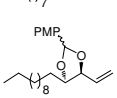
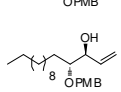
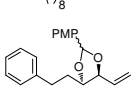
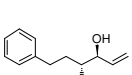
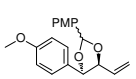
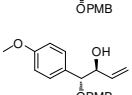
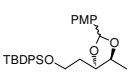
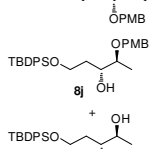
column separable *p*-methoxybenzyl (PMB) mono-ethers **8** and **3**, respectively in 75% combined yield (Scheme 2). The existence of two positional isomers **8** and **3** was further confirmed by chemical conversion via oxidation approach. Accordingly, compounds **8** and **3** were converted to their corresponding ketones **9** and **10**, respectively, using Dess-Martin periodonane[23] at 0 °C in CH_2Cl_2. From the ^{1}H NMR spectra, it was observed that the chemical shift values of olefinic protons in α,β-unsaturated ketone **9** was deshielded to a higher δ value (6.80 ppm) compared to β,γ-unsaturated ketone **10**.

From the above experimental observation, it was quite clear that the major regioisomer formed on the reductive cleavage of acetal with DIBAL-*H* was unmarked allylic alcohol substrate **7**. On the basis of this result, we thought to further improve the regioselectivity using an external hydride source in presence of acid. We have observed that, use of a combination of $NaCNBH_3$ and TFA (trifluoro acetic acid)[24a] as a reducing agent in CH_2Cl_2 cleaved acetal **7** with a lesser regioselectivity than DIBAL-*H* giving a mixture of PMB mono-ethers **8** and **3** in a ratio of 7:3, respectively. Similarly, the regioselective ring opening of acetal **7** employing Wei's reductive cleavage conditions (BH_3/Bu_2OTf in THF)[25] resulted in the formation of both the alcohols **8** and **3** in a 3:2 ratio. The significantly decreased selectivity of this reductive cleavage either through chelation or via direct hydride transfer could not support us to give an exact reason for such regioselectivity under DIBAL-*H* reduction conditions.

With the optimized reductive cleavage protocol in hand, next the study of broad substrate scope in tolerating functionalities and protecting groups and for the same a number of different acetals (**7a-h**) were treated with DIBAL-*H* to produce the corresponding allylic alcohols (**8a-h**, Table 1) in 70-80% yield. We found this reductive method to be compatible with acetals carrying a variety of protecting groups such as benzyl (**7a**), TBDPS (**7b**, **7e**), and TBS (**7c**, **7d**), providing the required regioisomeric allylic alcohols (**8a-e**) in good yield. The efficiency of substrates bearing a straight aliphatic chain (**7f**, **7g**) or a aromatic group (**7h**, **7i**) either at the proximal or distant end of anisylidene acetal, further proved the independent role of the protecting groups as well as steric bulk of the neighboring groups. To verify the role of terminal double bond, methyl group

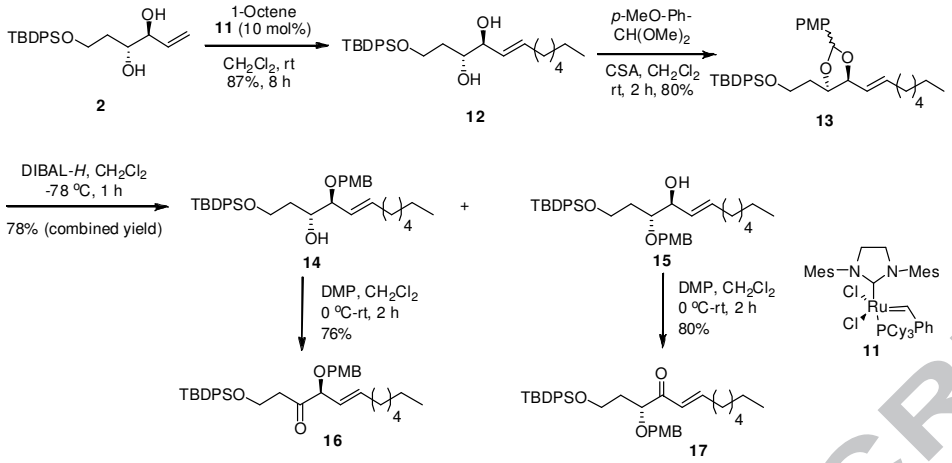
Table 1. Regioselective ring opening of *p*-methoxybenzylidene acetals[a,b]



Entry	acetals[c] (**7**)	allyl alcohols (**8**)	*t* [h]	Yield[d] [%]
a			2.0	75
b			2.0	73
c			1.5	72
d			2.0	80
e			2.5	70
f			2.0	75
g			3.0	78
h			2.5	75
i			2.0	72
j			1.5	28 48

8j:8j' = 35:65

[a]Reaction conditions: Acetal (1 mmol), DIBAL-*H* (1.4 M in Hexane, 8 mmol), CH_2Cl_2, –78 °C. [b]Selected acronyms: Bn = benzyl; PMB = *p*-methoxybenzyl; TBS = *tert*-butyldimethylsilyl; TBDPS = *tert*-butyldiphenylsilyl. [c]All acetals were identified by satisfactory NMR and Mass spectra analyses. [d]Isolated yields.



Scheme 3. Regioselective ring opening of *p*-methoxybenzylidene acetal in case of internal double bond.

was introduced adjacent to 1,2-diol instead of vinyl group. *p*-Methoxybezylidene acetal **7j** was prepared following standard protocol and subjected to regioselective reductive opening of the cyclic acetal group following DIBAL-*H* conditions. As expected, the reaction ended up with a mixture of two regioisomers **8j** and **8j'** in a ratio of 35:65 by HPLC.

Further to support for this end result drawn based on the previous approaches,[24] we thought about the protection of internal allylic diol as acetal with anisaldehyde dimethyl acetal followed by its reductive cleavage with DIBAL-*H*. To check the selectivity in internal alkene system, we have prepared compound **13** starting from diol **2**. Compound **2** was subjected to cross metathesis with 1-octene using Grubbs' catalyst II[26] to afford compound **12** in 87% yield with exclusively *E*-isomer. PMB-acetal protection of compound **12** with *p*-methoxybenzylidene acetal furnished acetal **13** as a diastereomeric mixture in 80% yield. Reductive cleavage of acetal compound **13** with DIBAL-*H* gave alcohols **14** and **15** as a separable mixture of regioisomers (31:69 by HPLC analysis) in 78% combined yield (under similar reaction conditions as described in Table 1). To confirm the regioselectivity, the alcohols **14** and **15** were subjected to Dess-Martin periodinane oxidation in CH_2Cl_2 to obtain ketones **16** and **17** in 76% and 80% yield, respectively as shown in Scheme 3.

In conclusion, we report an unusual result which was observed in the reductive cleavage of anisylidene acetal with DIBAL-*H* during the selective protection of hydroxyl group in terminal unsaturated diols. Reductive cleavage of terminal olefenic diols protected as its acetals gave exclusively allyl alcohol product in good to excellent yield, where as in case of internal olefinic acetal, the reductive cleavage proceeds with less selectivity giving both allyl and homo allyl alcohol. Though the actual reason of such observation is not quite clear, the current reductive protocol can be applied as an efficient solution for indirect protection of less reactive hydroxyl group in preference to that of more reactive one as PMB-mono ether.

Acknowledgments

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Supporting Information

Supplementary data associated with this article can be found, in the online version, at http://dx.doi/xxxxxx.

References and notes

1. (a) Greene, T. W.; Wuts, P. G. M. *Protecting Groups in Organic Synthesis*; John Wiley & Sons: New York, **1999**; (b) Hanessian, S. *Preparative Carbohydrate Chemistry*; Marcel Dekker: New York, **1997**; (c) Kocienski, P. J. *Protecting Groups*; George Thieme: Stuttgart, **1994**.
2. (a) Liptak, A.; Borbas, A.; Bajza, I. in *Comprehensive Glycoscience: From Chemistry to Systems Biology*, ed. Kamerling, J. P. Elsevier, Amsterdam, **2007**, *vol. 1*, pp. 203–259; (b) Wang, C.-C.; Lee, J.-C.; Luo, S.-Y.; Kulkarni, S. S.; Huang, Y.-W.; Lin, C.-C.; Chang, K.-L.; Hung, S.-C.; *Nature*, **2007**, *446*, 896; (c) Wang, C.-C.; Kulkarni, S. S.; Lee, J.-C.; Luo, S.-Y.; Hung, S.-C.; *Nat. Protoc.*, **2008**, *3*, 97; (d) Zhu, X.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 1900; (e) Chang, K.-L.; Zulueta, M. M. L.; Lu, X.-A.; Zhong, Y.-Q.; Hung, S.-C.; *J. Org. Chem.* **2010**, *75*, 7424.
3. Doukas, H. M.; Fontaine, T. D. *J. Am. Chem. Soc.* **1951**, *73*, 5917.
4. (a) Legetter, B. E.; Brown, R. K. *Can. J. Chem.* **1964**, *42*, 990; (b) Legetter, B. E.; Diner, U. E.; Brown, R. K. *Can. J. Chem.* **1964**, *42*, 2113; (c) Lipt ak, A.; Jodal, I.; Nanasi, P. *Carbohydr. Res.* **1975**, *44*, 1; (d) Liptak, A.; Imre, J.; Harangi, J.; Nanasi, P.; Neszmelyi, A. *Tetrahedron* **1982**, *38*, 3721.
5. (a) Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organci Chemistry*, 4th ed.; Wiley-Interscience: Hoboken, NJ, **2007**; pp 323-327. (b) Stick, R. V.; Williams, S. J. *Carbohydrates: The Essential Molecules of Life*; Elsevier, London, UK, **2009**; pp 51-52.
6. Fügedi, P.; Lipták, A.; Nánási, P.; Szejtli, J. *Carbohydr. Res.* **1982**, *104*, 55.
7. (a) Mikami, T.; Asano, H.; Mitsunobu, O. *Chem. Lett.* **1987**, 2033; (b) Tanaka, N.; Ogawa, I.; Yoshigase, S.; Nokami, J. *Carbohydr. Res.* **2008**, *343*, 2675.
8. (a) Ek, M.; Garegg, P. J.; Hultberg, H.; Oscarson, S. J. *Carbohydr. Chem.* **1983**, 2, 305; (b) Fügedi, P.; Birberg, W.; Garegg, P. J.; Pilotti, Å. *Carbohydr. Res.* **1987**, *164*, 297.
9. (a) Oikawa, M.; Liu, W.-C.; Nakai, Y.; Koshida, S.; Fukase, K.; Kusumoto, S. *Synlett* **1996**, 1179; (b) Tanaka, K.; Fukase, K. *Synlett* **2007**, 164.
10. Ghosh, M.; Dulina, R. G.; Kakarla, R.; Sofia, M. J. *J. Org. Chem.* **2000**, *65*, 8387.
11. (a) Sakagami, M.; Hamana, H. *Tetrahedron Lett.* **2000**, *41*, 5547; (b) Dilhas, A.; Bonnaffé, D. *Tetrahedron Lett.* **2004**, *45*, 3643.
12. Chandrasekhar, S.; Reddy, Y. R.; Reddy, C. R. *Chem. Lett.* **1998**, 1273.
13. (a) Guindon, Y.; Girard, Y.; Berthiaume, S.; Gorys, V.; Lemieux, R.; Yoakim, C. *Can. J. Chem.* **1990**, *68*, 897; (b) Jiang, L.; Chan, T.-H. *Tetrahedron Lett.* **1998**, *39*, 355; (c) Hernandez-Torres, J. M.; Achkar, J.; Wei, A. *J. Org. Chem.* **2004**, *69*, 7206; (d) Wang, C.-C.; Luo, S.-Y.; Shie, C.-R.; Hung, S.-C. *Org. Lett.* **2002**, *4*, 847; (e) Shie, C.-R.; Tzeng, Z.-H.; Kulkarni, S. S.; Uang, B.-J.; Hsu, C.-Y.; Hung, S.-C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1665;

(f) Tani, S.; Sawadi, S.; Kojima, M.; Akai, S.; Sato, K. *Tetrahedron Lett.* **2007**, *48*, 3103.

14. (a) Garegg, P. J.; Hultberg, H. *Carbohydr. Res.* **1981**, *93*, C10; (b) Garegg, P. J.; Hultberg, H.; Wallin, S. *Carbohydr. Res.* **1982**, *108*, 97.
15. Zinin, A. I.; Malysheva, N. N.; Shpirt, A. M.; Torgov, V. I.; Kononov, L. O. *Carbohydr. Res*. **2007**, *342*, 627.
16. (a) DeNinno, M. P.; Etienne, J. B.; Duplantier, K. C. *Tetrahedron Lett.* **1995**, *36*, 669; (b) Debenham, S. D.; Toone, E. J. *Tetrahedron: Asymmetry* **2000**, *11*, 385.
17. (a) Mohapatra, D. K.; Das, P. P.; Pattanayak, M. R.; Yadav, J. S. *Eur. J. Org. Chem.* **2010**, 4775; (b) Mohapatra, D. K.; Pattanayak, M. R.; Das, P. P.; Pradhan, T. P.; Yadav, J. S. *Org. Biomol. Chem.* **2011***, 9, 5630*; (c) Tapas, R. P.; Mohapatra, D. K. *Tetrahedron Asymmetry* **2012**, *23*, 709.
18. (a) Banwell, M. G.; Kokas, O. J.; Willis, A. C. *Org. Lett.* **2007**, *9*, 3503; (b) Matweenko, M.; Banwell, M. G.; Willis, A. C. *Tetrahedron* **2008**, *64*, 4817; (c) Trost, B. M.; Amans, D.; Seganish. W. M.; Chung, C. K. *J. Am. Chem. Soc.* **2009**, *131*, 17087; (d) Trost, B. M.; Amans, D.; Seganish. W. M.; Chung, C. K. *Chem. Eur. J.* **2012**, *18*, 2961.
19. Holmes, A. B.; Hughes, A. B.; Smith, A. L. *J. Chem. Soc., Perkin Trans 1* **1993**, 633.
20. Matin, V. S.; Woodward, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc*. **1981**, *103*, 6237.
21. Banwell, M. G.; Mc Rae, K. J.; Willis, A. C. *J. Chem. Soc., Perkin Trans 1* **2001**, 2194.
22. (a) Da Silva, C. B.; Pale, P. *Tetrahedron Assymetry* **1998**, *9*, 3951; (b) Takano, S.; Akiyama, S.; Ogaswara, K. *Chem. Lett*. **1983**, 1593.
23. (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155; (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
24. (a) Davoren, J. E.; Harcken, C.; Martin, S. F. *J. Org. Chem.* **2008**, *73*, 391; (b) Ghosh, A. K.; Wang, Y.; Kim. J. T. *J. Org. Chem.* **2001**, *66*, 8973.
25. Herna´ndez-Torres J. M.; Achkar. J.; Wei, A. *J. Org. Chem.* **2004**, *69*, 7206.
26. (a) Chatterjee, A. K.; Sanders, D. P.; Grubbs, R. H. *Org. Lett.* **2002**, *4*, 1939; (b) Chatterjee, A. K.; Choi, T-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360; (c) Wulff, J. E.; Herzon, S. B.; Siegrist, R.; Myers, A. G. *J. Am. Chem. Soc.* **2007**, *129*, 4898.

HIGHLIGHTS

1. A highly regioselective homoallylic alcohol synthesis.
2. Protection of less reactive hydroxy group.
3. Exclusively monoprotection.