

Asymmetric Dihydroxylations of 1-Substituted (*E*)- and (*Z*)-3-Methylpent-2-en-4-ynes: Full Compliance with the Sharpless Mnemonic Re-established and Embellished

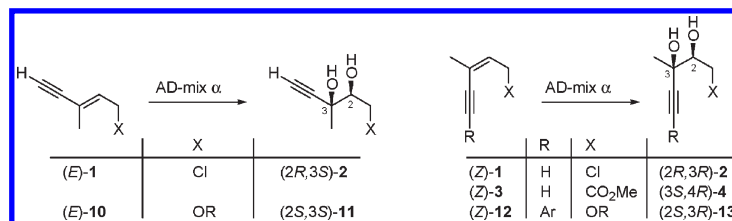
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ABSTRACT



Asymmetric dihydroxylations (“ADs”) of the pentenynyl chlorides (*E*)- and (*Z*)-1 or the pentenynyl-based ester (*Z*)-3 in the presence of (DHQ)₂-containing ligands delivered diol stereoisomers (2*R*,3*S*)-2, (2*R*,3*R*)-2, and (3*S*,4*R*)-4, respectively. The ADs of pentenynyl ethers (*E*)-10 and (*Z*)-12, respectively, have the same stereochemical preference under analogous conditions; these reattributions correct previous reports of the contrary. The Sharpless mnemonic rationalizes all these results implying that each substrate prefers a Sharpless/Norby instead of a Chapleur orientation in the transition state.

Recently¹ we have shown that in the presence of Sharpless’ ligands (DHQ)₂PHAL (which is responsible for stereocontrol effected by AD-mix α²) or (DHQ)₂AQN³ the 1-chlorinated 3-methylpent-2-en-4-ynes (*E*)- and (*Z*)-1 are dihydroxylated asymmetrically.⁴ This furnished chloro-

diols (2*R*,3*S*)- and (2*R*,3*R*)-2, respectively, in yields of up to 73% (Scheme 1). Enantioselectivities reached 85% *ee* with (*E*)-1 as the substrate and 91% *ee* starting from (*Z*)-1. The configurational proof in the (*E*)-series was based on an X-ray structural analysis and the proof in the (*Z*)-series on a correlation with a compound derived from the (*E*)-series.

Another 1-substituted 3-methylpent-2-en-4-yne, namely ester (*Z*)-3, reacted with the same facial selectivity with Sharpless’ AD-mix α as chloride (*Z*)-1, proceeding via dihydroxyester (3*S*,4*R*)-4 directly⁵ to the hydroxylactone (4*S*,5*R*)-5⁶ (Scheme 2). The correct configuration of the latter was not recognized correctly⁷ before we found that ester (*Z*)-6 and AD-mix α gave the *identically* configured lactone (4*S*,5*R*)-8 via dihydroxyester (3*S*,4*R*)-7.⁸ This was shown by an X-ray analysis of the derived bromobenzoate

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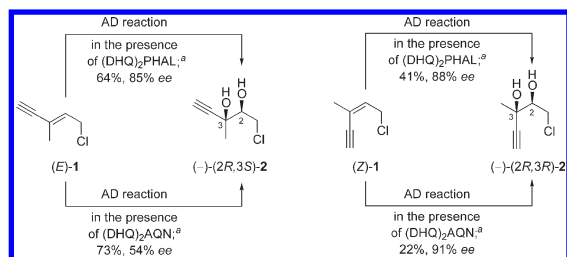
[‡] Gymnasium Goetheschule.

(1) Burghart-Stoll, H.; Kapferer, T.; Brückner, R. *Org. Lett.* (DOI: 10.1021/OL103061g).

(2) (a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768–2771 (in the presence of MeSO₂NH₂). (b) Footnote 6 in Jeong, K.-S.; Sjö, P.; Sharpless, K. B. *Tetrahedron Lett.* **1992**, *33*, 3833–3836 (in the absence of MeSO₂NH₂).

(3) (a) Becker, H.; Sharpless, K. B. *Angew. Chem.* **1996**, *108*, 447–449. (b) Becker, H.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 448–451.

Scheme 1. AD Reactions of the Methylpentenyne-Based Chlorides (*E*)- and (*Z*)-1

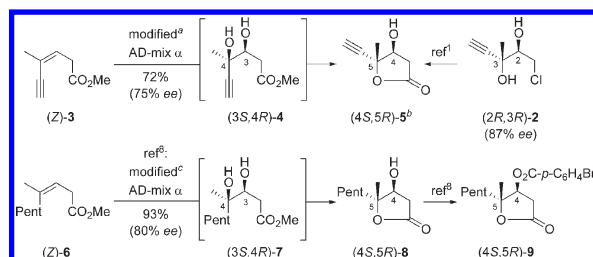


^a $\text{K}_3\text{Fe}(\text{CN})_6$ (3.0 equiv), $\text{K}_2\text{OsO}_2(\text{OH})_4$ (1.0 mol %), dihydroquinidine-based ligand (2.0 mol %), buffer (3.0 equiv each of NaHCO_3 and K_2CO_3), and MeSO_2NH_2 (1.0 equiv).

(4*S*,5*R*)-9. A proof of the steric course of the AD reaction of ester (*Z*)-3 was obtained by an independent synthesis¹ of the same lactone (4*S*,5*R*)-5 from the chlorodiols (2*R*,3*R*)-2.

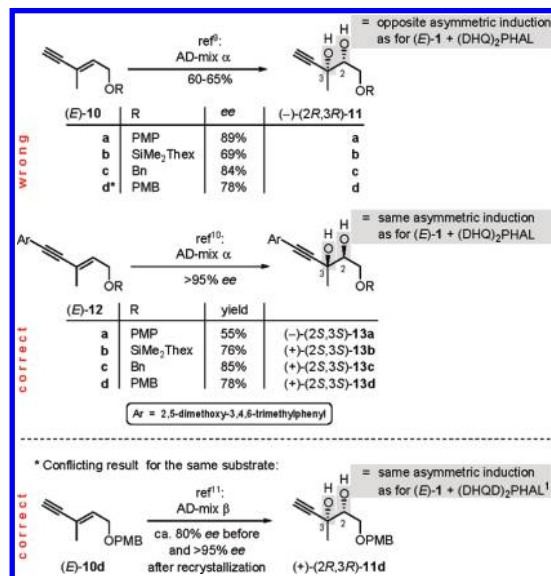
Disconcertingly, the stereoselectivity of our AD (*E*)-1 + AD-mix $\alpha \rightarrow$ (2*R*,3*S*)-2 differed from the selectivities reported for ADs of certain ethers, which share an (*E*)-configured methylpentenyne with our substrate: AD-mix α was claimed to convert ethers (*E*)-10a–d into diols (2*R*,3*R*)-11a–d (Scheme 3, top).⁹ Similarly, our ADs (*Z*)-1 + AD-mix $\alpha \rightarrow$ (2*R*,3*R*)-2 and (*Z*)-3 + AD-mix $\alpha \rightarrow$ (3*S*,4*R*)-4/(4*S*,5*R*)-5 had opposite stereoselectivities as the ADs of several ethers, which share a (*Z*)-configured methylpentenyne with our substrates: AD-mix α allegedly transforms ethers (*Z*)-12a and b into dihydroxyethers (2*R*,3*S*)-13a and b, respectively (Scheme 4, bottom).¹⁰ Incidentally Nakatani et al. (Scheme 3, bottom) contradicted this (without recognizing it) when they dihydroxylated the PMB ether (*E*)-10d in the presence of AD-mix β and isolated diol

Scheme 2. AD Reactions of the Methylpentenyne-Based Ester (*Z*)-3 and the Related Ester (*Z*)-6⁸



^a $\text{K}_3\text{Fe}(\text{CN})_6$ (3.0 equiv), $\text{K}_2\text{OsO}_2(\text{OH})_4$ (2.0 mol %), (DHQ)₂PHAL (10 mol %), K_2CO_3 (3.0 equiv), and MeSO_2NH_2 (1.0 equiv). ^b Prepared from (*Z*)-3: $[\alpha]_D^{20} = -4.9$ ($c = 0.83$ in CHCl_3); prepared from (2*R*,3*R*)-2: $[\alpha]_D^{20} = -5.6$ ($c = 0.5$ in CHCl_3). ^c $\text{K}_3\text{Fe}(\text{CN})_6$ (3.0 equiv), $\text{K}_2\text{OsO}_2(\text{OH})_4$ (0.8 mol %), (DHQ)₂PHAL (1.6 mol %), K_2CO_3 (3.0 equiv), and MeSO_2NH_2 (1.0 equiv).

Scheme 3. AD Reactions of the Methylpentenyne-Based Ethers (*E*)-10⁹ and (*E*)-12¹⁰ from the Literature^{11,12}



(2*R*,3*R*)-11d, which was dextrorotatory.¹¹ According to Tietze and Görlitzer the same diol (2*R*,3*R*)-11d stemmed from (*E*)-10d and AD-mix α but was levorotatory.⁹

Ancillary findings by Tietze and Görlitzer increased our worries. Ethers (*E*)-12a–d and AD-mix α reportedly gave the diols (2*S*,3*S*)-13a–d (Scheme 3, center);¹⁰ this amounts to a reversal of the asymmetric induction in the ADs (*E*)-10a–d + AD-mix $\alpha \rightarrow$ (2*R*,3*R*)-11a–d (Scheme 3, top). Why an *sp*-bonded arene moiety in (*E*)-12a–d instead of an *sp*-bonded H-atom in (*E*)-10a–d should have such an

(12) The AD reaction of the *para*-methoxybenzoate of the alcohol, which underlies the ethers (*E*)-10a–d, in the presence of AD-mix α gave a levorotatory triol with 86% ee; the “configuration of the major enantiomer was assigned tentatively by application of the Sharpless mnemonic” as (2*S*,3*S*), i.e. differently than Tietze’s (2*R*,3*R*)-10a–d: Alvarez, S.; Alvarez, R.; de Lera, A. R. *Tetrahedron Asymmetry* **2004**, *15*, 839–846. Our results are analogous and therefore corroborate de Lera’s conclusion.

- (4) (a) Lohray, B. B. *Tetrahedron: Asymmetry* **1992**, *3*, 1317–1349. (b) Johnson, R. A.; Sharpless, K. B. In *Asymmetric Catalysis in Organic Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; pp 227–272; (c) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547. (d) Poli, G.; Scolastico, C. *Methoden Org. Chem. (Houben-Weyl)*, 4th ed. —, Vol. E21e; Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E., Eds.; Thieme: Stuttgart, 1995; pp 4547–4598. (e) Salvadori, P.; Pini, D.; Petri, A. *Synlett* **1999**, 1181–1190. (f) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 357–389. (g) Bolm, C.; Hildebrand, J. P.; Muñoz, K. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: Weinheim, 2000; pp 399–428. (h) Krief, A.; Colaux-Castillo, C. *Pure Appl. Chem.* **2002**, *74*, 107–113. (i) Kolb, H. C.; Sharpless, K. B. In *Transition Metals for Organic Synthesis*; Beller, M.; Bolm, C., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 2, pp 275–298. (j) Noe, M. C.; Letavic, M. A.; Snow, S. L.; McCombie, S. *Org. React.* **2005**, *66*, 109–625. (k) Zaitsev, A. B.; Adolfsson, H. *Synthesis* **2006**, 1725–1756.

- (5) Method: (a) Harcken, C.; Brückner, R. *Angew. Chem.* **1997**, *109*, 2866–2868. Harcken, C.; Brückner, R. *Angew. Chem., Int. Ed.* **1997**, *36*, 2750–2752. (b) Kapferer, T.; Brückner, R. *Eur. J. Org. Chem.* **2006**, 2119–2133.

- (6) The enantiopurity of this specimen was determined by chiral HPLC after *tert*-butyldiphenylsilylation (see Supporting Informations).

- (7) Böhnke, O. *Dissertation*, Universität Freiburg, 2002, pp 63, 124, 151.

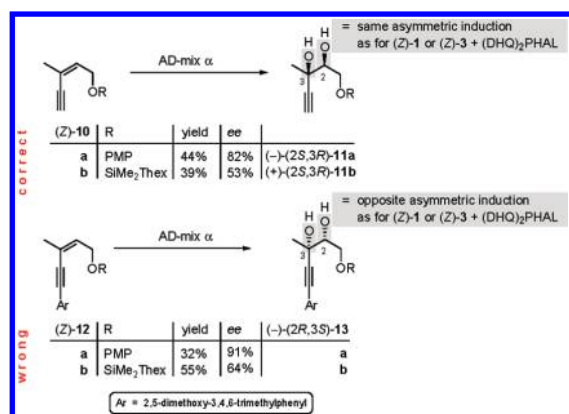
- (8) Kapferer, T.; Brückner, R.; Herzig, A.; König, W. A. *Chem.—Eur. J.* **2005**, *11*, 2154–2162.

- (9) Tietze, L. F.; Görlitzer, J. *Liebigs Ann. Recl.* **1997**, 2221–2225.

- (10) Tietze, L. F.; Görlitzer, J. *Synthesis* **1997**, 877–885.

- (11) (a) Nakatani, K.; Okamoto, A.; Saito, I. *Angew. Chem.* **1997**, *109*, 2881–2884. Nakatani, K.; Okamoto, A.; Saito, I. *Angew. Chem., Int. Ed.* **1997**, *36*, 2794–2797. (b) Nakatani, K.; Okamoto, A.; Matsuno, T.; Saito, I. *J. Am. Chem. Soc.* **1998**, *120*, 11219–11225.

Scheme 4. AD Reactions of the Methylpentenyne-Based Ethers (Z)-10⁹ and (Z)-12¹⁰ from the Literature¹⁴



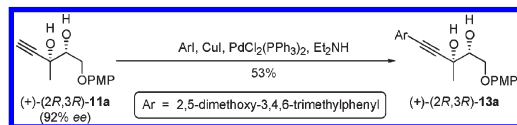
effect was not clear.¹³ The same structural change seemed to swap the asymmetric inductions in the AD-mix α-mediated dihydroxylations of the C_{sp}-arylated ethers (Z)-12a,b [$\rightarrow$ (2R,3S)-13a and b, respectively,¹⁰ Scheme 4, bottom] compared to the C_{sp}-unsubstituted ethers (Z)-10a,b [$\rightarrow$ (2R,3S)-11a and b, respectively,⁹ Scheme 4, top].

The pivotal role of Sharpless ADs in organic synthesis⁴ compelled us to check these matters by correlating selected Tietze/Görlitzer diols with ours. We showed both for ether (E)-10a and ether (Z)-12a,b—i.e., for representative

(13) There are AD reactions, however, where remote anisyl groups modify the extent of enantiocontrol, albeit not its direction: (a) Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *Tetrahedron Lett.* **1995**, 36, 3481–3484. (b) Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *J. Am. Chem. Soc.* **1995**, 117, 10805–10816. (c) Corey, E. J.; Noe, M. C.; Guzman-Perez, A. *J. Am. Chem. Soc.* **1995**, 117, 10817–10824. (d) Corey, E. J.; Noe, M. C.; Ting, A. Y. *Tetrahedron Lett.* **1996**, 37, 1735–1738. (e) Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1996**, 118, 11038–11053.

(14) The AD reaction of the *para*-methoxybenzoate of the alcohol, which underlies the ethers (Z)-10a,b, with AD-mix α gave a levorotatory triol with 56% ee; the “absolute configuration of the major enantiomer was assigned tentatively by application of the Sharpless mnemonic” as (2S,3R), i.e. differently than Tietze’s (2R,3S)-12a,b; Alvarez, S.; Alvarez, R.; de Lera, A. R. *Tetrahedron Asymmetry* **2004**, 15, 839–846. Our results are analogous and therefore corroborate de Lera’s conclusion.

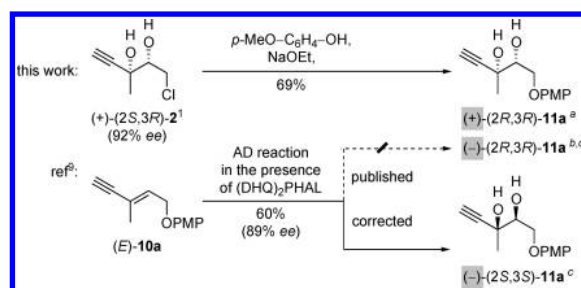
(15) We proved the steric course of Tietze’s and Görlitzer’s transformation⁹ (E)-12a + AD-mix α $\rightarrow$ (-)-(2S,3S)-13a (Scheme 3, center) by gaining the enantiomeric product (+)-(2R,3R)-13a by a Sonogashira coupling between diol (+)-(2R,3R)-11a (proof of the 3D structure of the latter: Scheme 5, top) and 1-iodo-2,5-dimethoxy-3,4,6-trimethylbenzene.¹⁸ (2S,3S)-13a (>95% ee) exhibited $[\alpha]_D^{20} = -13.5$ ($c = 1$ in CHCl₃) whereas (2R,3R)-13a (92% ee) exhibited $[\alpha]_D^{20} = +11.4$ ($c = 0.3$ in CHCl₃); i.e., these compounds had inverse rotational powers.



(16) The steric course of the transformation (E)-12b + AD-mix α $\rightarrow$ (2S,3S)-13b (Scheme 3, center) was established unambiguously by acetone formation, desilylation, condensation with (-)-camphanoyl chloride, and an X-ray structural analysis of the resulting ester.¹⁰

(17) Differently than stated¹⁰ no proof was provided for the stereoselectivity of the transformation (E)-12c + AD-mix α $\rightarrow$ (2S,3S)-13c (Scheme 3, center): (2S,3S)-13c had been converted into what was drawn as the S-enantiomer of 6-(benzyloxy)-2,5,7,8-tetramethylchromane-2-carbaldehyde in seven steps,¹⁰ but this assignment was not corroborated experimentally.¹⁸

Scheme 5. AD Reactions Reassigned I: Proof That (E)-10a and AD-Mix α React Differently than Published



^a $[\alpha]_D^{20} = +23.6$ ($c = 1.1$ in CHCl₃). ^b Compatibility of this sense of the specific rotation with the depicted configuration is excluded by our work. ^c $[\alpha]_D^{20} = -22.0$ ($c = 1.0$ in CHCl₃).

substrates—that the stereodescriptors of the resulting diols must be reversed (Schemes 5 and 6, respectively). Moreover we proved the correctness of the stereodescriptors of diol (2S,3S)-13a^{15–18} obtained from ether (E)-12a and of diol (2S,3R)-11a^{19,20} obtained from ether (Z)-10a.

Chlorodiols (2S,3R)-2¹ and sodium 4-methoxyphenoxide in ethanol²¹ at reflux gave the PMP-containing diol (2R,3R)-11a (Scheme 5). It was dextrorotatory. Diol 11a prepared from the PMP ether (E)-10a and AD-mix α was levorotatory⁹ and therefore (2S,3S)-11a.²² By analogy, diols (-)-11b—c of Scheme 3 should be (2S,3S)-configured, too.

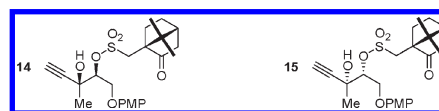
(18) (S)-6-(Benzyloxy)-2,5,7,8-tetramethylchromane-2-carbaldehyde is dextrorotatory (589 nm, $c = 5.2$ in CHCl₃) according to Cohen, N.; Lopresti, R. J.; Saucy, G. *J. Am. Chem. Soc.* **1979**, 101, 6710–6716.

(19) We proved the steric course of Tietze’s and Görlitzer’s transformation¹⁰ (Z)-10a + AD-mix α $\rightarrow$ (-)-(2S,3R)-11a (Scheme 4, top) by establishing that the enantiomeric product (2R,3S)-11a (preparation: Scheme 6, top) was dextrorotatory: (-)-(2S,3R)-11a (82% ee) showed $[\alpha]_D^{20} = -20.0$ ($c = 1$ in CHCl₃) while (2R,3S)-11a (92% ee) showed $[\alpha]_D^{20} = +22.3$ ($c = 0.37$ in CHCl₃).

(20) The facial selectivity of the functionalizations of (Z)-10a,b with AD-mix α (Scheme 4, top⁹) lacked experimental support. The resulting diols were Sonogashira-coupled to provide diols⁹ 13a,b with the same relative configurations as the ones obtained from (Z)-12a,b and AD-mix α in one step (Scheme 4, bottom¹⁰). However, differently than the authors believed (ref 10 and footnote 2 therein) no specific rotations were measured on the Sonogashira route (ref 22b). This left the absolute configuration of these specimens of (-)-ul-11a and (-)-ul-b unproved.

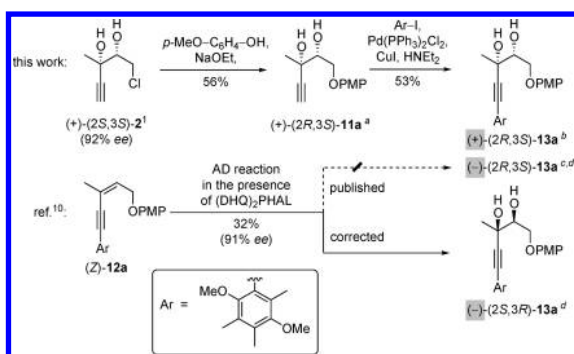
(21) Procedure: Gandolfi, C. A.; Di Domenico, R.; Spinelli, S.; Gallico, L.; Fiochi, L.; Lotto, A.; Menta, E.; Borghi, A.; Rosa, C. D.; Tognella, S. *J. Med. Chem.* **1995**, 38, 508–525.

(22) (a) The 3D structure of the dihydroxylation product (-)-“(2R,3R”)-11a should have emerged from the X-ray analysis of crystals of the monosulfonate derived with (+)-camphorsulfonyl chloride.⁹ The ORTEP plot depicted the compound as 14 (ref 22b, p 72), but the corresponding valence formula was flawed as 15 (ref 22b; p 70) and published as such.⁹ (b) Görlitzer, J. *Dissertation*, Universität Göttingen, 1997.



(23) (a) Jacobsen, E. N.; Markó, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, 110, 1968–1970. (b) Sharpless, K. B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, J.; Kawanami, Y.; Lübken, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* **1991**, 56, 4585–4588. (c) Reference 2b. (d) Kolb, H. C.; Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, 116, 1278–1291. (e) Vanhessche, K. P. M.; Sharpless, K. B. *J. Org. Chem.* **1996**, 61, 7978–7979. (f) Fristrup, P.; Tanner, D.; Norrby, P.-O. *Chirality* **2003**, 15, 360–368.

Scheme 6. AD Reactions Reassigned II: Proof That (Z)-12a and AD-Mix α React Differently than Published



^a $[\alpha]_D^{20} = +22.3$ ($c = 0.37$ in CHCl_3). ^b $[\alpha]_D^{20} = +13.6$ ($c = 0.33$ in CHCl_3).
^c Compatibility of this sense of the specific rotation with the depicted configuration is excluded by our work. ^d $[\alpha]_D^{20} = -12.6$ ($c = 1.0$ in CHCl_3).

According to Scheme 6 chlorodiol (2*S*,3*S*)-**2**¹ was converted via its PMP-ether (2*R*,3*S*)-**11a**²¹ and a Sonogashira coupling with 1-iodo-2,5-dimethoxy-3,4,6-trimethylbenzene into the dextrorotatory diol (2*R*,3*S*)-**13a**. Diol **13a** prepared from the arylated PMP-ether (Z)-**12a** and AD-mix α was levorotatory¹⁰ and hence (2*S*,3*R*)-configured.

In summary it has been shown that *all* heterosubstituted (*E*)- and (*Z*)-methylpentenyne, which have been *vic*-dihydroxylated to date under the influence of DHQ-containing ligands are attacked as if preferring a “Sharpless/Norrby orientation” in any of the Sharpless-mnemonic transition states²³ **16**–**19** (Figure 1) such that steric hindrance in zone 1, which is (the most) repulsive, is minimized.

With respect to alkenes containing a trisubstituted C=C bond we reduced the number of “Chapleur oriented”²⁴ AD substrates by (*E*)-**10a–d** and (Z)-**12a,b**. When/if one does

(24) A “Chapleur orientation” in the transition state of an AD represents the optimum of maximized bonding in zone 2 and minimized strain in zone 1.²⁵

(25) Moïtessier, N.; Henry, C.; Len, C.; Chapleur, Y. *J. Org. Chem.* **2002**, *67*, 7275–7282.

(26) Shao, H.; Rueter, J. K.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 5240–5244.

(27) (a) Menthyl angelates undergo ADs with stereoselectivities matching “Sharpless/Norrby orientations” in the transition state: Torres-Valencia, J. M.; Cerda-García-Rojas, C. M.; Joseph-Natan, P. *Tetrahedron: Asymmetry* **1998**, *9*, 757–764. (b) The same is true for disubstituted angelates: Nicolaou, K. C.; Yue, E. W.; La Greca, S.; Nadin, A.; Yang, Z.; Leresche, J. E.; Tsuri, T.; Naniwa, Y.; De Riccardis, F. *Chem.—Eur. J.* **1995**, *1*, 467–494.

(28) (a) AD stereoselectivities of monocarbamoylated alkyl angelates in line with “Sharpless/Norrby orientations” in the transition state but without proofs: Claudel, S.; Olszewski, T. K.; Mutzenardt, P.; Aroulanda, C.; Coutrot, P.; Grison, C. *Tetrahedron* **2006**, *62*, 1787–1798. (b) *dto.* regarding ADs of a mono- and a dimethylated ethyl angelate: Stritzke, K.; Schulz, S.; Nishida, R. *Eur. J. Org. Chem.* **2002**, 3884–3892.

(29) The diols from AD-mix α and 2-(trimethylsilyl)ethyl angelate (Liu, H.; Jensen, K. G.; Tran, L. M.; Chen, M.; Zhai, L.; Olsen, C. E.; Søhoel, H.; Denmeade, S. R.; Isaacs, J. T.; Christensen, S. B. *Phytochemistry* **2006**, *67*, 2651–2658) or a monosubstituted angelate [Xie, W.; Ding, D.; Zi, W.; Li, G.; Ma, D. *Angew. Chem.* **2008**, *120*, 2886–2890; Xie, W.; Ding, D.; Zi, W.; Li, G.; Ma, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 2844–2848 (Supporting Information)] were drawn—without proofs—as if emerging from “Chapleur orientated” substrates.

(30) Curran, D. P.; Ko, S.-B. *J. Org. Chem.* **1994**, *59*, 6139–6141.

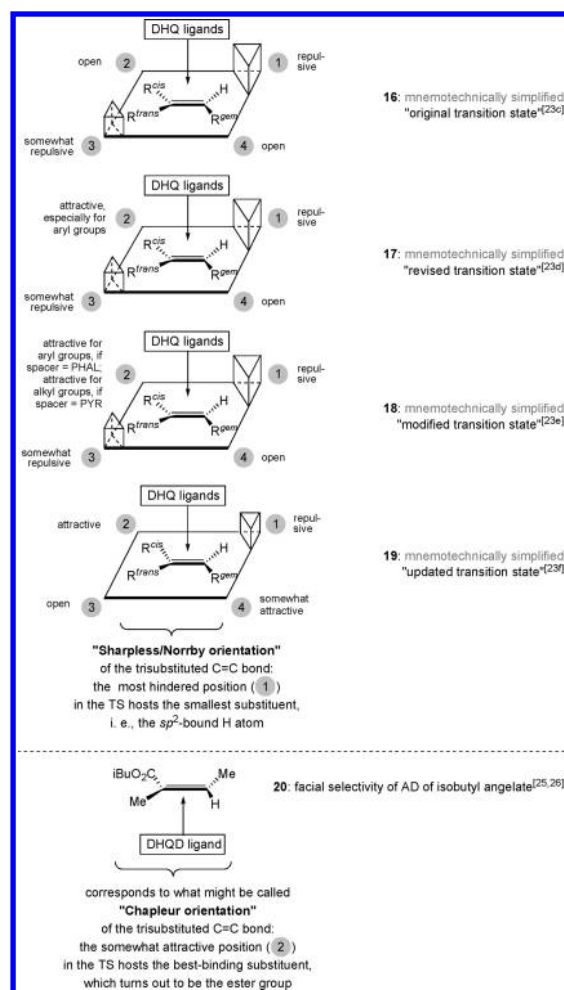


Figure 1. Stereoselectivities of ADs of standard substrates with a trisubstituted C=C bond in the presence of DHQ-containing ligands (top; DHQD-containing ligands attack from downside) and of isobutyl angelate in the presence of (DHQD)₂PHAL (bottom).

not accept the revised configuration²⁵ of the diol produced from isobutyl angelate and AD-mix β ,²⁶ this implies a “Chapleur orientation” **20**²⁵ (Figure 1) in the transition state,^{27–29} the only AD reaction affecting a “Chapleur oriented” trisubstituted C=C bond, of which we are aware may concern an α -alkyldenelactone.³⁰ It seems reasonable, accordingly, to base synthetic planning entailing an AD of a trisubstituted C=C bond on “Sharpless/Norrby orientations” **16**–**19** of the substrate and to specify that the *sp*²-bonded H-atom shall be in the (most) hindered position (1).

Acknowledgment. The authors thank Dr. Thomas Netscher (DSM, Basel) for donations of (*E*)- and (*Z*)-3-methylpent-2-en-4-yn-1-ol.

Supporting Information Available. Experimental procedures, characterization data, and copies of NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.