Highly *Like*-Selective [4 + 2] Cycloadditions of Chiral Dienols: The Importance of 1,3-Allylic Strain in the Hydroxy-Directed Stereocontrol

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Received May 1, 1995[®]

Abstract: The chiral open-chain dienols **3a,b**, which possess 1,3-allylic strain due to the presence of a *cis* substituent, give with the dienophiles maleic anhydride (MA), *N*-phenyl maleimide (NPM), 4-phenyl- (PTAD), and 4-methyl-1,2,4-triazoline-3,5-dione (MTAD) the corresponding [4 + 2] cycloadducts in very good yields and with high *like* selectivity. In contrast to previous reports on dienols without 1,3-allylic strain, the sense of diastereoselectivity does not vary with the dienophile type. The *cis* substituent aligns preferred conformations in the ground and transition states for which the hydrogen atom is placed in the sterically most biased *inside* position. Sterically and electronically controlled dienophile attack on these rotamers leads to the observed *like* stereochemistry. The participation of electronic features, most prominently hydroxy-directed stereocontrol, is substantiated by solvent effects in the triazolinedione cycloadditions, i.e., lower π-facial selectivities are observed in polar solvents. The present results demonstrate the efficacy of 1,3-allylic strain in promoting conformational preferences in [4 + 2] cycloadditions with asymmetric dienols.

Introduction

The π-facial selectivity of electrophilic attack on olefins with an adjacent stereogenic center constitutes a fascinating stereochemical feature in organic chemistry.[1] The Diels–Alder reaction, which ranks as one of the most versatile synthetic methods for the construction of six-membered rings,[2] offers a unique opportunity to exercise π-facial stereocontrol because up to four stereogenic centers are generated in one single chemical act. It does not surprise, therefore, that many studies have been conducted to achieve diastereofacial control. In this context, of particular interest has been the π-facial selectivity exerted by allylic substituents in both the dienophile[3] or the diene. For the latter, high and predictable stereocontrol in the [4 + 2] cycloaddition of chiral acyclic dienes constitutes a challenging subject, both experimentally[4] and theoretically.[5] While for the rigid 5-substituted cyclopentadienes[6] and semicyclic dienes[7] the steric and electronic effects of directing heteroatom substituents are restricted to operate exclusively on one of the diastereotopic π faces, the conformational flexibility of open-chain dienes significantly enhances the complexity of mechanistic rationalizations.

Previous experimental studies[4] have clearly demonstrated that subtle steric and electronic features of both the diene and dienophile remarkably influence the π-facial selectivity of the Diels–Alder reaction (Scheme 1). Thus, while protection of the free hydroxy group enhances the preference of *like* attack[8] for the carbon dienophiles *N*-phenyl maleimide (NPM) and also maleic anhydride (MA),[4b,c,g] the opposite trend is observed for the heterodienophile 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD), although for the latter the stereochemistry of the products was not rigorously established.[4g] Furthermore, modest *unlike* se-

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[®] Abstract published in *Advance ACS Abstracts*, August 15, 1995.

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(2) See, for example, Desimoni, G.; Tacconi, G.; Bario, A.; Pollini, G. *Natural Product Synthesis Through Pericyclic Reactions*; ACS Monograph 180; American Chemical Society, Washington, DC, 1984; Chapter 5.

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(4) (a) Heilbron, I. M.; Jones, E. R. H.; McCombie, J. T.; Weedon, B. C. L. *J. Chem. Soc.* **1945**, 88–90. (b) Grée, R.; Kessabi, J.; Mosset, P.; Martelli, J.; Carrie, R. *Tetrahedron Lett.* **1984**, *25*, 3697–3700. (c) Franck, R. W.; Argade, S.; Subramaniam, C. S.; Frechet, D. M. *Tetrahedron Lett.* **1985**, *26*, 3187–3190. (d) McDougal, P. G.; Rico, J. G.; VanDerveer, D. *J. Org. Chem.* **1986**, *51*, 4492–4494. (e) Messager, J. C.; Toupet, L. *Acta Crystallogr., Sect. B: Struct. Sci.* **1986**, *B42*, 371–378. (f) Reitz, A. B.; Jordan, A. D., Jr.; Maryanoff, B. E. *J. Org. Chem.* **1987**, *52*, 4800–4802. (g) Tripathy, R.; Franck, R. W.; Onan, K. D. *J. Am. Chem. Soc.* **1988**, *110*, 3257–3262. (h) Fleming, I. *Pure Appl. Chem.* **1988**, *60*, 71–78. (i) Martelli, J.; Grée, D.; Kessabi, J.; Grée, R. *Tetrahedron*, **1989**, *45*, 4213–4226. Cases for which the stereogenic center is attached to C-2 of the diene are given: (j) Hatakeyama, S.; Sugawara, K.; Takano, S. *J. Chem. Soc., Chem. Commun.* **1992**, 953–955. (k) Bloch, R.; Chaptal-Gradoz, N. *Tetrahedron Lett.* **1992**, *33*, 6147–6150. (l) Bloch, R.; Chaptal-Gradoz, N. *J. Org. Chem.* **1994**, *59*, 6162–6169.

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(6) (a) Brown, F. K.; Houk, K. N.; Burnell, D. J.; Valenta, Z. *J. Org. Chem.* **1987**, *52*, 3050–3059. (b) Paquette, L. A.; Vanucci, C.; Rogers, R. D. *J. Am. Chem. Soc.* **1989**, *111*, 5792–5800. (c) Macaulay, J. B.; Fallis, A. G. *J. Am. Chem. Soc.* **1990**, *112*, 1136–1144. (d) Ishida, M.; Beniya, Y.; Inagaki, S.; Kato, S. *J. Am. Chem. Soc.* **1990**, *112*, 8980–8982. (e) Ishida, M.; Aoyama, T.; Beniya, Y.; Yamabe, S.; Kato, S.; Inagaki, S. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3430–3439. (f) Adam, W.; Jacob, U.; Prein, M. *J. Chem. Soc., Chem. Commun.* **1995**, 839–840.

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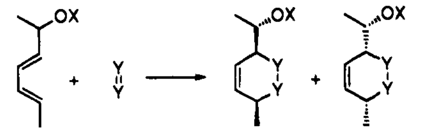
(8) Throughout this paper we use the term *like* to describe the dienophile approach on the *re* face of the double bond with an adjacent *R*-configurated allylic center (cf. also footnote 5 in ref 4g).

Scheme 1. π-Facial Selectivities in the Diels–Alder Reaction of Chiral Dienes

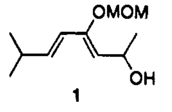


X	Y=Y	*like* : *unlike*
H	MA	71 : 29
H	NPM	63 : 27
H	PTAD	26 : 74
H	DMAD	27 : 73
Me	NPM	83 : 17
Me	TCNE	33 : 67
$SiMe_3$	NPM	88 : 12
$SiMe_3$	PTAD	15 : 85

lectivity has also been observed for these and similar substrates when tetracyanoethylene (TCNE)[4b,e] or dimethyl acetylenedicarboxylate (DMAD)[4g] were employed as dienophiles.

Several theoretical models[5,9] and empirical rules[4c,g] have been put forward over the years to account for the observed diastereoselectivities, neither of which gives a consistent rationalization of all the experimental data. Additionally, a computational study on model reactions by Dannenberg[5b] revealed that several transition states of similar energy are involved for both the *like* and the *unlike* cycloaddition pathways. This ineffective discrimination between the different transition state conformations is reflected in the moderate π-facial selectivities for simple dienes (Scheme 1).

As proposed previously,[5d,f,9b,10] incorporation of 1,3-allylic strain[11] in the chiral diene substrate through a *cis* substituent should efficiently discriminate between the different conformations of the stereogenic unit in the transition state and, thus, enhance π-facial selectivities.[10] Indeed, high *like* selectivities have been observed in the [4 + 2] cycloaddition of NPM to the chiral dienes **1** and **2**,[4d,f] for which the alkoxy substituent at



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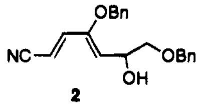
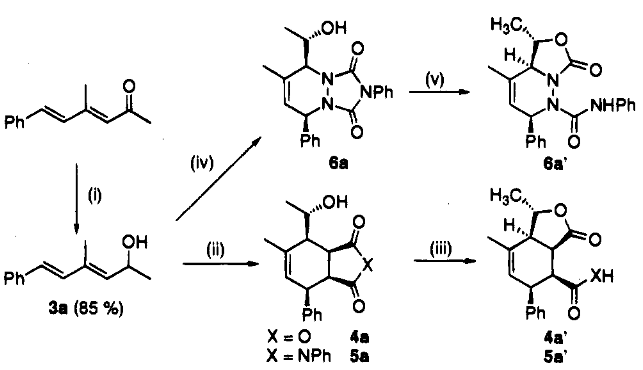


2

C-2 of the diene unit provides the essential 1,3-allylic strain. Nevertheless, from the mechanistic point of view, it is difficult to compare these results with those for simple dienic alcohol derivatives (Scheme 1) since the electron-donating alkoxy substituents and the presence of an additional oxygen-containing functional group at the stereogenic center in dienol **2** significantly alters the electronic properties of the diene.[12] Furthermore, so far it has not been tested whether opposite π-facial selectivity also applies for PTAD as dienophile to such highly selective substrates. Consequently, we have initiated the present study to assess the stereocontrolling factors in the [4 + 2] cycloaddition of NPM, MA, and PTAD to simple chiral diene systems, which possess 1,3-allylic strain either imposed by an additional alkyl substituent at the C-2 position or by the *Z,E* geometry of the diene system.

Scheme 2. Preparation of and Cycloadditions to the Dienol **3a**[a,b]



[a] Only the preferred *like* cycloadducts are shown.[b] (i) $NaBH_4$, MeOH, 85%; (ii) MA or NPM, benzene; (iii) $CDCl_3$, room temperature; (iv) PTAD; (v) NaH, THF.

Results

The chiral dienol **3a** was obtained in 85% yield by sodium borohydride reduction of (*E,E*)-4-methyl-6-phenyl-3,5-hexadiene-2-one[13] (Scheme 2). The [4 + 2] cycloaddition of this substrate with the standard dienophiles MA, NPM, and PTAD afforded the corresponding cycloadducts in good to excellent yields (Scheme 2). The diastereomeric ratios were determined directly on the crude product mixture by NMR analysis; the results are summarized in Table 1. In the reaction of dienol **3a** with MA in benzene at room temperature, the initial cycloadduct **4a** was not observed; instead, the lactones **4a′** were obtained directly as a mixture of two diastereomers (dr 94:6, entry 1). In contrast, for NPM as dienophile the lactonization was sufficiently slow, and cycloadduct **5a** was detected as a single diastereomer (dr ≥ 95:5, entry 2). On standing in solution or silica gel chromatography, the imide **5a** was converted to the anilide **5a′**, which was obtained as a single diastereomer in 82% yield. While the cycloaddition of dienol **3a** with PTAD in CH_2Cl_2 at −78 °C (entry 3) gave urazole **6a** as a single diastereomer, the diastereoselectivity dropped to 92:8 at 0 °C (entry 4). Furthermore, only a modest (dr 73:27) π-facial selectivity was observed for PTAD when the more polar acetone (entry 5) was used as solvent.

The *like* attack of the dienophiles was proven by NOE measurements on the respective rearranged cycloadducts **4a′**,**5a′**, and **6a′**. The **6′** product was obtained by treatment of urazole **6a** with sodium hydride in THF (Scheme 2). In each case, signal enhancements between the methyl group and the hydrogen atom in the five-membered ring and *vice versa* were observed, which clearly demonstrates their *cis* relationship and, thus, the *like* stereochemistry of the initial cycloadduct.

The *Z,E*-configurated dienol **3b**, which was prepared by sodium borohydride reduction of easily accessible (*Z,E*)-4-methyl-3,5-heptadiene-2-one[14] (Scheme 3), did not react with NPM in refluxing benzene. The much more reactive dienophile PTAD (entry 6) gave a single diastereomer of the urazole **6b** in CH_2Cl_2. Similar to dienol **3a** (entry 5), **3b** exhibited a reduced diastereoselectivity (ca. 75:25) when the reaction was run in acetone (entry 7). Small amounts of unidentified products were formed when the reaction with PTAD (entry 7) was run at 0 °C, which were present only in traces at −78 °C. Similar results were obtained for MTAD (entry 8). Furthermore, when the hydroxy group was converted to its methyl ether **3c**, cycloaddition with PTAD gave the two diastereomeric urazoles

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[9] (a) Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7162–7166. (b) Houk, K. N. *Pure Appl. Chem.* **1983**, *55*, 277–282. (c) Houk, K. N.; Moses, R. S.; Wu, Y.-D.; Rondan, N. G.; Jäger, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880–3882. (d) Fleming, I.; Lewis, J. L. *J. Chem. Soc., Chem. Commun.* **1985**, 149–151. (e) McGarvey, G. J.; Williams, J. M. *J. Am. Chem. Soc.* **1985**, *107*, 1435–1437.

[10] Broeker, J. L.; Hoffmann, R. W.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5006–5017.

[11] Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841–1860.

[12] For example: (a) Thiem, R.; Rotscheidt, K.; Breitmaier, E. *Synthesis* **1989**, 836–843. (b) Rieger, R.; Breitmaier, E. *Synthesis* **1990**, 697–701, π stacking has been argued.

[13] Kluge, A. F.; Lilliya, C. P. *J. Org. Chem.* **1971**, *36*, 1988–1995.

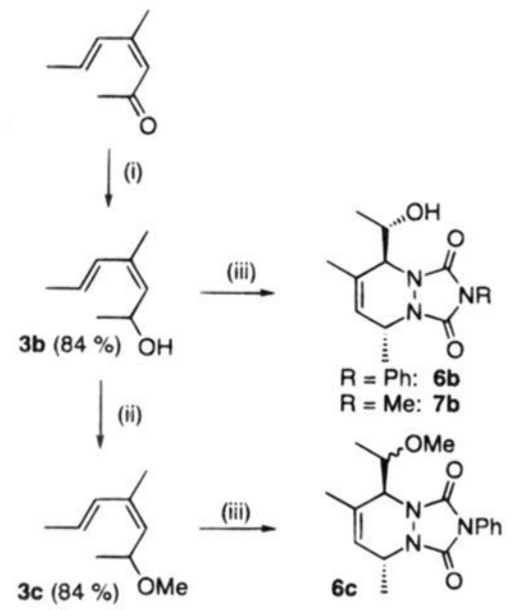
[14] Balaban, A. T.; Mihai, G.; Nenitzescu, C. D. *Tetrahedron* **1962**, *18*, 257–259.

Table 1. Reaction Conditions and Product Data in the [4 + 2] Cycloaddition[a] of Chiral Dienes **3**

entry	substrate	dienophile	solvent	*t*	*T* (°C)	yield[b] (%)	product	dr[b,c]
1	**3a**	MA	C_6H_6	8 days	25	79[d]	**4a′**	94:6
2	**3a**	NPM	C_6H_6	8 days	25	82[d]	**5a**	≥95:5
3	**3a**	PTAD	CH_2Cl_2	15 min	−78	≥95	**6a**	≥97:3
4	**3a**	PTAD	CH_2Cl_2	5 min	0	≥95	**6a**	92:8
5	**3a**	PTAD	$(CH_3)_2CO$	5 min	0	≥95	**6a**	73:27
6	**3b**	PTAD	CH_2Cl_2	15 min	−78	≥95	**6b**	≥95:5
7	**3b**	PTAD	$(CH_3)_2CO$	5 min	0	91[e]	**6b**	ca. 75:25
8	**3b**	MTAD	CH_2Cl_2	5 min	−78	≥95	**7b**	≥95:5
9	**3c**	PTAD	CH_2Cl_2	5 min	0	≥95	**6c**	71:29[f]

[a] All cycloadditions were run to complete conversion of the diene **3**. [b] Determined by NMR analysis of the crude reaction mixtures; error ca. 3% of the stated values. [c] Ratio of *like* and *unlike* cycloadducts. [d] Yield of isolated material after silica gel chromatography. [e] An unidentified more polar byproduct (8%) was present when the reaction was run at 0 °C. [f] The stereochemistry of the products was not established.

Scheme 3. Preparation of and Cycloadditions to the Chiral Dienes **3b,c**[a]



[a] (i) NaBH$_4$, MeOH, 84%; (ii) 1. NaH, Et$_2$O, 2. MeI, 84%; (iii) MTAD or PTAD, CH$_2$Cl$_2$.

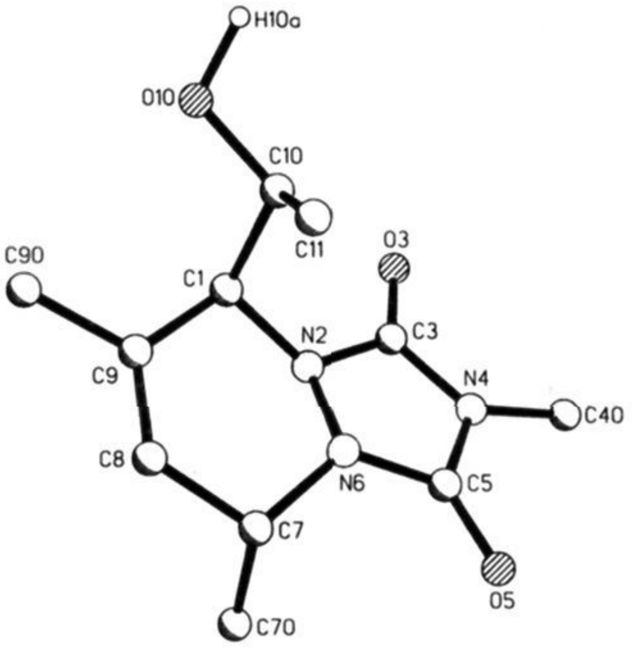


Figure 1. X-ray structure of urazole **7b**.

6c in only modest (71:29) diastereoselectivity (entry 9). An X-ray structure determination of urazole **7b** (Figure 1) unequivocally established the stereochemistry and, thus, the preference for *like* attack in the reaction of dienol **3b** with triazolinediones.

Discussion

The very high π-facial selectivities that have been achieved with both conventional carbon dienophiles MA and NPM and the highly reactive triazolinediones MTAD and PTAD clearly demonstrate the remarkably high *like*-directing ability of allylic hydroxy groups. The *cis* substituents are essential to provide 1,3-allylic strain. These stereochemical results are rationalized mechanistically in terms of the six representative conformations of the allylic stereogenic center, displayed in Figure 2 by the Newman projections.[15] These conformations have been previously invoked[4g] as model rotamers in the discussion of diastereoselectivities of the Diels−Alder reaction.

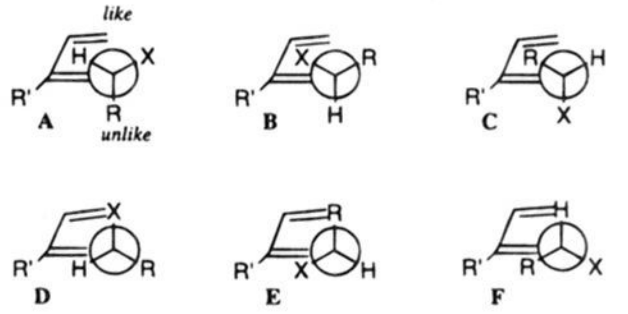


Figure 2. Model transition state conformations for the diene (cf. ref 15).

For mechanistic rationalizations, it is helpful to classify the six rotamers in terms of the steric and electronic interactions which an incoming dienophile experiences on approaching the *like* and *unlike* faces. We recognize the three rotamer pairs **A/E**, **B/F**, and **C,D**, for which within each pair both rotamers should give approximately the same extent of π-facial selectivity but of opposite sense. For example, in case of the **A,E** rotamer pair an approaching electrophile will encounter a perpendicular alkyl group on one π face and the hydrogen atom and the substituent X on the other. This implies a low overall π-facial selectivity as long as the respective rotamers are not discriminated effectively through steric strain in the ground and/or transition state. In this context, quantum mechanical calculations are revealing, in which the modest experimental preferences for either *like*[5b] or *unlike*[9b,c] attack in related systems (X = OMe) were rationalized in terms of the preference of the methoxy group either for the *outside* **A** or the *inside* **E** conformations (Figure 2). Clearly, for substrates without 1,3-allylic strain (Figure 2, R′ = H), subtle stereoelectronic effects such as preference for a certain alignment of the C−X bond with respect to the π system dictate the preferred conformation of the stereogenic unit in the transition state, and, therefore, low selectivities are expected. Furthermore, π-facial selectivities vary strongly with the dienophile[4c−e,g] since the reaction partner will also alter the weak stereoelectronic effects.

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[15] The conformations are arranged in the order of increasing 1,3-allylic interaction from the left to the right, in which the steric demand is assumed as H < X < R. With the present choice of conformations, for which the dihedral angle C−C−C−X is changed in 60° steps, all the essential features with respect to π-facial selectivities can be rationalized; however, these rotamers do not necessarily represent transition state geometries. For a discussion of preferred ground state rotamers cf. ref 10 and the following: (a) Gung, B. W.; Wolf, M. A.; Zhu, Z. *J. Org. Chem.* **1993**, *58*, 3350−3354. (b) Gung, B. W.; Wolf, M. A. *J. Org. Chem.* **1993**, *58*, 7038−7044. (c) Gung, B. W.; Gerdeman, M. S.; Fouch, R. A.; Wolf, M. A. *J. Org. Chem.* **1994**, *59*, 4255−4261.

In contrast, for olefins with a *cis* substituent (Figure 2, $R' \neq H$), 1,3-allylic strain will impose strong conformational preferences. For example, rotamers **A** and **D** in Figure 2 are intrinsically favored[10] since the smallest substituent, namely the hydrogen atom, occupies the sterically most biased *inside* position. This preference of ca. 3–4 kcal/mol should apply both for the ground and transition state[10] and should lead to high π-facial selectivities, provided the substituent X possesses the propensity to direct through steric and electronic features. Thereby highly selective attack of the electrophile on the preferred conformations would be dictated by the X substituent. This renders substrates with 1,3-allylic strain most suitable to study substituent effects on π-facial selectivities. For these systems, the preferred conformation in the transition state is mainly determined by steric strain and not by stereoelectronic effects. Therefore, the steric and electronic features of different functional groups can be studied under nearly identical geometrical conditions.

The above mechanistic rationalization shall now be applied to the present study, in which the unprotected hydroxy group showed a high *like*-directing ability in the Diels–Alder reaction with the various employed dienophiles. Two factors work synergistically for this functional group: sterically controlled attack should occur from the less biased *like* face in conformers **A** and **D** (Figure 2), and attractive electronic interactions between the OH group and the incoming dienophile should enhance the preference for *like* attack since in both decisive conformations the OH functionality resides on the *like* face.[16] In fact, the observed solvent effect, i.e., a lower diastereoselectivity in the polar solvent acetone (Table 1), strongly favors the involvement of electronic interactions. In the case of the hydroxy group, besides hydrogen bonding,[17] also electrostatic interactions may operate. Thus, Hehre[5a] rationalized experimental π-facial selectivities by assuming that the hydroxy functionality enhances the nucleophilicity of that particular face of the π system on which it resides. However, a key feature is for the *cis* substituent to assure that the electronic effects operate only on the *like* face. Thus, the conformations **C**, **E**, and **F** (Figure 2), for which the hydroxy group is located on the *unlike* face, are disfavored due to considerable 1,3-allylic strain.

Given these features of the hydroxy group, one should expect that not only the Diels–Alder reaction of chiral dienols but also other electrophilic additions to allylic alcohols should occur with high *like* selectivities, as long as 1,3-allylic strain is operating. Specific examples are the [2 + 1] cycloaddition of carbenoids,[1] the epoxidation of olefins by peracids[1,18] or with metal catalysts,[1,19] and the oxyfunctionalization of olefins by singlet oxygen either in the ene reaction[20] or in the [4 + 2] cycloaddition,[21] which all exhibit high *like* preference for alcohols with *cis* substituents. The previous and present results suggest broad applicability of the concept of 1,3-allylic strain in aligning favored conformations of the chiral, acyclic substrates for electrophilic or dienophilic attack.[22] Which π face will be actually preferentially approached by the electrophile depends on steric and electronic interactions between the reagent and functionalities at the chirality center. When both factors go hand in hand, as in the case for the chiral allylic dienols **3a**,**b** of this study, for which the the conformations **A** and **D** (Figure 2) are favored through 1,3-allylic strain, high *like* π-facial selectivities are observed for all dienophiles (MA, NPM, MTAD, and PTAD) examined. From a practical point of view, it also important to note that it is irrelevant whether the 1,3-allylic strain is caused by an additional substituent at the C-2 position of the dienic system as in dienol **3a** or by the *Z,E* geometry of the π system as in substrate **3b**. Clearly, this happenstance enhances the utility of the present synthetic methodology.

Acknowledgment. We thank the *Deutsche Forschungsgemeinschaft* (SFB 347 "Selektive Reaktionen Metall-aktivierter Moleküle") and the *Fonds der Chemischen Industrie* for financial support.

Supporting Information Available: Detailed experimental procedures and spectral data of compounds **3**–**7** and graphical representations, crystallographic data, and tables of atomic coordinates and interatomic distances of the X-ray studies of urazole **7b** (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

JA9514048

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(16) In contrast, the methoxy substituent possesses a low directing propensity in systems with 1,3-allylic strain, as seen in the addition of PTAD to diene **3c**. Good agreement with the stereochemical results in other electrophilic additions to chiral allylic ethers are reported in refs 1, 20, and 21. The enhanced steric hindrance toward the incoming dienophile on the *like* face in the preferred conformations **A** and **D** is evident but also the poor hydrogen bonding ability of the methoxy substituent should decrease stereocontrol.

(17) (a) Tripathy, R.; Carroll, P. J.; Thornton, E. R. *J. Am. Chem. Soc.* **1990**, *112*, 6743–6744. (b) Tripathy, R.; Carroll, P. J.; Thornton, E. R. *J. Am. Chem. Soc.* **1991**, *113*, 7630–7640.

(18) In *m*-CPBA epoxidations there is overwhelming evidence for hydrogen bonding with the hydroxy group in the transition state (Chamberlain, P.; Roberts, M. L.; Whitham, G. H. *J. Chem. Soc. Sect. B* **1970**, 1374–1381.).

(19) Note, however, that coordination between the metal center [especially for VO(acac)$_2$] and the oxygen atom may force the hydroxy group to the *inside* position (ref 1; conformations **B** and **E** in Figure 2). An additional *geminal* substituent alters in these cases the stereochemical preferences and *unlike* attack is observed due to considerable 1,2-allylic strain in the transition state for the *like* attack.

(20) (a) Adam, W.; Nestler, B. *J. Am. Chem. Soc.* **1993**, *115*, 5041–5049. (b) Brünker, H.-G.; Adam, W. *J. Am. Chem. Soc.* **1995**, *117*, 3976–3982. (c) For a review on diastereoselective singlet oxygen ene reactions, cf. Prein, M.; Adam, W. *Angew. Chem.*, in press.

(21) (a) Adam, W.; Prein, M. *J. Am. Chem. Soc.* **1993**, *115*, 3766–3767. (b) Adam, W.; Prein, M. *Tetrahedron Lett.* **1994**, *35*, 4331–4334. (c) Adam, W.; Peters, E. M.; Peters, K.; Prein, M.; von Schnering, H. G. *J. Am. Chem. Soc.* **1995**, *116*, 6686–6690.

(22) For the dienophiles employed in the present study, different reaction mechanisms may operate, e.g., a nonconcerted, stepwise [4 + 2] cycloaddition has been reported for triazolinediones: Jensen, F.; Foote, C. S. *J. Am. Chem. Soc.* **1987**, *109*, 6376–6385.