CONFORMATION AND FACIAL SELECTIVITIES OF CHIRAL SIX-MEMBERED 1,3-DIHETEROCYCLES INVOLVING AN ENONE FUNCTION[‡]

Masayuki Sato,* Satoshi Sunami, and Chikara Kaneko*

Pharmaceutical Institute, Tohoku University, Sendai 980-77, Japan

Abstract--Ground-state as well as excited-state reactions of chiral 1,3-dioxin-4-ones and related compounds which involve an enone function in their ring are reviewed with emphasis of the facial selectivity. Sofa conformation of the ring systems and pyramidalization of the enone portions in these heterocycles so far been proposed as the origins of the facial selectivity are summarized and the discrepancies between facial selectivities verified by experimental results and the predicted selectivities from either the conformation or the pyramidalization are pointed out. The reactions of chiral 1,3-dioxane-4,6-diones, 1,3-oxazine-4,6-diones and their 5-benzylidene derivatives are also surveyed. Finally, the present authors' opinion which accounts for all of the reported reactions having facial selectivities is proposed. This review also includes the present authors' opinion for the origin of these conformation and pyramidalization.

1. INTRODUCTION

An enone system is one of the most important functionality in organic synthesis. It undergoes a variety carbon-carbon bond forming reactions such as Diels-Alder reactions and Michael reactions. Therefore, enone syntems having readily removable chiral auxiliary provide general methods for asymmetric synthesis of a wide range of chiral compounds. Among various methodologies for asymmetric synthesis, the chiral enone method is most reliable, because the major diastereomer may be isolated by conventional method ultimately leading to pure enantiomer after removal of the chiral auxiliary.

[‡] Dedicated to the memory of Professor Yoshio Ban.

The first class of such enones is acyclic acid derivatives represented by acrylates having a chiral auxiliary in the acid residue. So far, a variety of chiral auxiliaries have been developed to differentiate the acryloyl enone face.[1] The potential of this class of enones in asymmetric synthesis has been well recognized. The second class of chiral enones is a series of heterocyclic compounds involving them in thier rings. Owing to their rigid conformation, they show high diastereofacial selectivity without chelation control which is frequently required for the first class of enones. In addition, some of them undergo photo[2+2]addition to which acyclic enones are not susceptible. Thus, five-membered compounds A,[2] B,[3] C,[4] D,[5,6] and E,[7] six-membered compounds F[8] and G, and a seven-membered compound H[9,10] have been successfully utilized in enantioselective as well as in diastereoselective syntheses of a variety of enantiomerically pure compounds (EPC).


A: X=O
B: X=NAr

C: X=O
D: X=NCOPh

E

F: X=CH$_2$
G: X=O

H
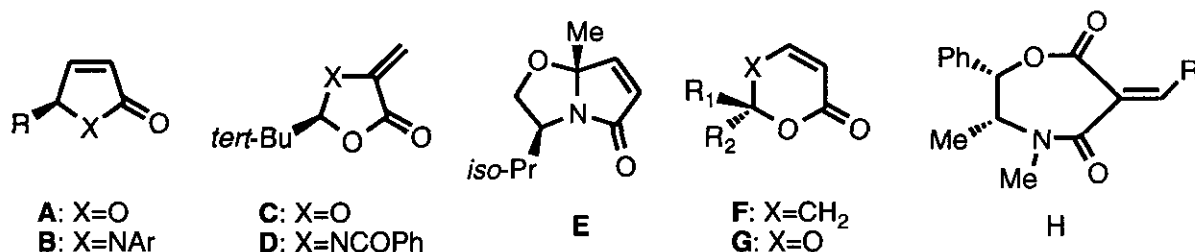
We have been studying asymmetric synthesis using chiral six-membered heterocyclic enone systems such as 1,3-dioxin-4-ones G, 5-methylene-1,3-dioxane-4,6-diones, and their nitrogen analogues. It is the purpose of this review to summerize the synthetic utility of such chiral heterocyclic enone systems and to account for the origin of diastereofacial selectivites of the chiral enones involved in 6-membered heterocycles.

2. SURVEY OF FACIAL SELECTIVITIES IN THE REACTIONS OF CHIRAL 1,3-DIOXIN-4-ONES

In 1986, Demuth *et al.* studied photo[2+2]addition of the spirocyclic dioxinone (**1a**) with alkenes and, as a result, photoaddition of a cyclobutene to **1a** was found to give selectiviely the *cis-anti-cis* adduct which was formed by reaction on the same face as the isopropyl group.[11] Shortly after, we examined photoaddition of **1b** to alkenes and found the same facial selectivity.[12] Both

groups have reasoned the observed facial selectivity by the sofa conformation of the hetero-ring. It should be noted that X-ray crystallographic analyses of these spirocyclic dioxinones so far examined have revealed that, irrespective of the substituents on the enone double bonds, they have a sofa conformation with five of the six atoms approximately in a plane and the acetal carbon out of the plane. Throughout this review, we refer to facial selectivity in terms of the top and bottom faces relative to the sofa conformation (cf. **1**). Thus, the above two reactions were explained by assuming that the reactions had occurred from the less hindered bottom face.


1a: R=Me
1b: R=H

2a: R'=*tert*-Bu, R=Me, Y=H
2b: R'=cyclohexyl, R=Y=H
2c: R'=*tert*-Bu, R=Me, Y=Br

I

3
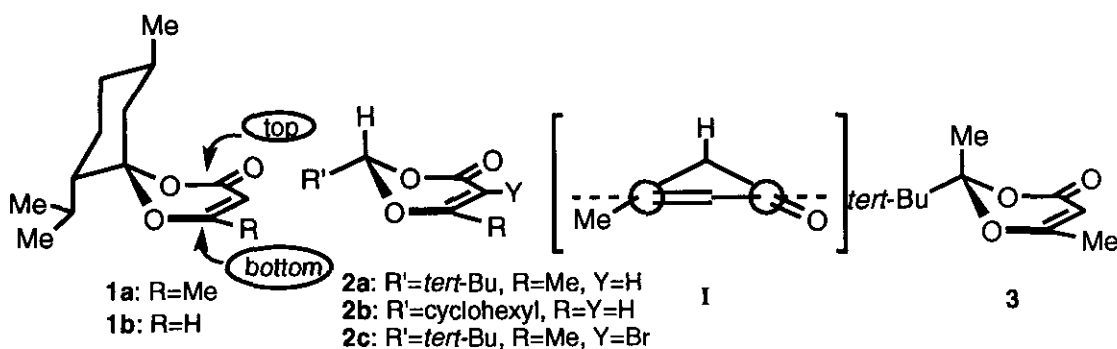
In 1988, Seebach *et al.* examined the reactions of 2-*tert*-butyl-6-methyl-1,3-dioxin-4-one   (**2a**) with dialkylcuprates and thiophenoxide and found that the nucleophiles were introduced on the top face.[13]   They also demonstrated that catalytic hydrogenation took place again on the top face. Seebach *et al.* reasoned the facial selectivity by pyramidalization [by X-ray analysis, they confirmed that, in addition to the sofa conformation of **2a** having C(2) pointed to the side of the C(2) hydrogen atom, C(6) is pyramidalized toward the C(2) hydrogen side (the top face), cf. I]. We also reported that cuprate addition to the spirodioxinone (**1b**) and catalytic hydrogenation of its 6-methyl derivative (**1a**) occurred preferentially on the top face.[12]

Until 1993, no work has been reported on the preparation and reactions of dioxiones such as **2**, which possess a dialkylated chiral center at C(2). In 1993, Lange *et al.* reported the preparation and reactions (both ground-state and excited-state reactions) of the dioxinone (**3**).[14] Just like as in the case of **2a**, photo[2+2]addition occurred primarily from the bottom face while the conjugate addition proceeded exclusively from the top face. Their explanation for the observed facial selectivity for the conjugate addition is pyramidalization (again verified by X-ray

analysis) and hence the same with that proposed by Seebach *et al*.[13]

Though Lange *et al*. did not mention the origin of the bottom face preference for the photoaddition reactions, he found very important experimental data for the photoaddition reactions (room temperature) of **2a** and **3**. These are: 1) photocycloaddition of **3** to cyclohexene or the related ketal yielded the adducts formed by exclusive attack on the bottom face, while the same reaction to cyclopentene (smaller than the former two alkenes) proceeded in *ca*. 9 (the bottom face attack):1 (the top face attack). On the contrary, the same reactions[15] of **2a** to these larger alkenes (cyclohexene and the related ketal) did afford 50:50 mixtures, respectively. Surely, steric effects are responsible for the photoaddition reactions. Lange's result is in good accordance with the previously reported photoaddition reactions reported by Demuth,[11] Seebach,[15] and ours.[12,16] Thus, for the spirodioxinones, the bottom face attack is preferred (note that **1a** and **1b** have an axial alkyl chain at C(2) position). We also examined the photoaddition of cyclopentene to 2-cyclohexyl-1,3-dioxin-4-one (**2b**) at various temperature and observed a slight bottom face preference when the reaction was carried out at -78 °C.[16]

If the ground state reactions are restricted only to the above mentioned three reactions (cuprate addition, thiophenoxide addition, and catalytic hydrogenation), one could then conclude that the photoadditions generally take place from the face (the bottom face) opposite to that (the top face) for the ground-state reactions. However, that is not the case. There are ground-state reactions of the spirodioxinones (**1**) which proceed in the same facial selectivity (the bottom face preference) with that of photoaddition reactions. For example, the spirodioxinones having an electron-withdrawing group at the 5- or 6-position (i.e. **1c**) accept cyclopentadiene from the bottom face with an excellent selectivity.[17,18] The bottom face preference of the dioxinones in Diels-Alder

1c   **2d**   **1d**
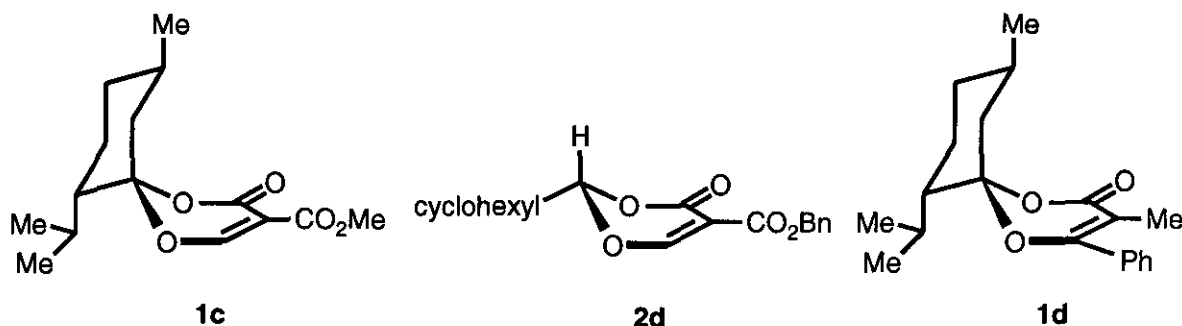
reaction is not restricted to the spirodioxinones (1) and the nonspirodioxinones (i.e. 2d) accept preferentially the diene from the bottom face.[16] The same bottom face preference was also observed when the spirodioxinone (1d) was reacted with molecular fluorine.[19]

In closing this section, it seems worthy to comment on the conformation and some ground-state reactions of novel chiral dioxinones (4a and 4b) synthesized recently in our laboratory.[20]

4a: R=*l*-menthyl, R'=H
4b: R=Me, R'=H
4c: R=R'=Me

J
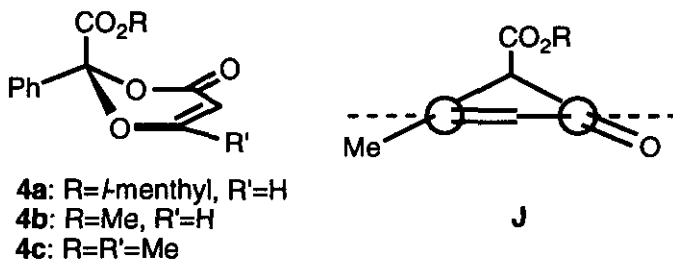
X-Ray crystallographic analysis of **4a** indicated that its 2-phenyl group took the quasi-equatorial orientation in the sofa conformation of the dioxinone ring and [1]H-nmr analysis has verified that its conformation is retained in solution. As will be mentioned in Section 4.2, the significant pyramidalization towards the axial alkoxycarbonyl group comparable to that (I) of **2a** was recently verified (cf. **J**) in compound (**4c**). When **4a** was subjected to the conjugate addition with methyl- or phenylmagnesium bromide/cuprous iodide, a single product was obtained in each reaction. Remarkable fact is that the products are the ones that the reagents have attacked from the bottom face (the opposite side of pyramidalization!!). The fact that the corresponding methyl ester (**4b**) showed the same facial selectivity indicates that preference of the bottom face attack in the conjugate addition is a common phenomenon in **4**, irrespectively of the kinds of R in the 2-alkoxycarbonyl group. To summarize the experimental data mentioned in this section, the preferred faces (top or bottom faces of the sofa conformation) of the ground-state and photo[2+2]cycloaddition reactions of four kinds of chiral dioxinones (1~4) are shown in Table 1.

The degrees of selectivity for the respective reactions are shown by ± (nearly 0% de), + (*ca.* 50% de), ++ (*ca.* 90% de), and +++ (100% de) in parentheses.

The complete theory should account for the reasons 1) why each type of ground-state reaction exhibits the different facial selectivity, 2) why the selectivity is differed (the face selectivity as

well as the degree of facial selectivity [de]) either by the kinds of substituents at the 2-position
of the dioxinone ring and/or by the types of dioxinones. The answer will be provided in Section
4.

The readers who are interested in applications of chiral dioxinones to the synthesis of enantio-
merically pure compounds (e.g. (-)-grandisol, Corey lactone, carbocyclic C-nucleosides, iridoids,
etc.) should refer to the reviews.[21-25]

Table 1. Diastereoselectivity of a Variety of Reactions of 1,3-Dioxin-4-ones
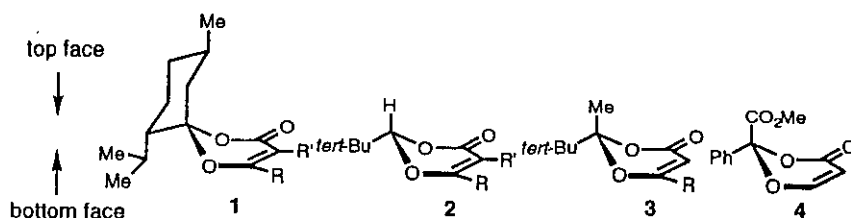
| Ground-state reaction	R	R'	Diastereofacial selectivity (efficiency)			
			1	2	3	4
conjugate addition (R$_2$CuLi)	H, Me	H	top (+++)	top (+++)	top (+++)	bottom (+++)
Michael addition (PhS)	Me	H	−	top (+++)	−	−
catalytic hydrogenation	Me	H	top (+++)	top (+++)	−	−
[4+2] cycloaddition	H	CO$_2$Me	bottom (++)	bottom (++)	−	−
fluorine addition (F$_2$)	Ph	Me	bottom (+++)	−	−	−
Excited-state reaction						
photo[2+2]cycloaddition	H, Me	H	bottom (++)	bottom (r. t. ±) " (-78 °C +)	bottom (+++)	−

3. SURVEY OF FACIAL SELECTIVITIES OF THE REACTIONS OF CHIRAL SIX-MEMBERED 4,6-DIOXO-1,3-DIHETEROCYCLES AND THEIR 5-BENZYLIDENE DERIVATIVES

Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) and its derivatives are remarkable com-
pounds exhibiting versatile reactivities.[26] Successful results obtained by use of chiral 1,3-
dioxin-4-ones in asymmetric synthesis mentioned in the foregoing section prompted us to

prepare chiral Meldrum's acid and its benzylidene derivatives as versatile intermediates for asymmetric synthesis.

3.1. Spirodioxanediones and their 5-benzylidene derivatives

Since two hetero atoms incorporated at the 1- and 3-positions in a six-membered 5-en-4-one ring is enough to fix the conformation, we have been interested in synthesizing chiral methylene Meldrum's acids (**6**). It is because, if the ring conformation is again fixed, the exo-methylene functions in them could be utilized as the chiral units for EPC synthesis. One of the inherent uncertainty in this plan lies in controlling the stereochemical (geometrical) disposition of the substituents (Ar) at the terminal (prochiral) carbon of the exo-methylene group. However, this problem has been solved by crystallization-induced asymmetric transformations (second-order asymmetric transformation). Thus, Knoevenagel condensation of the chiral Meldrum's acid (**5**) obtained by reaction of *l*-menthone with malonic acid with an appropriate arylaldehyde afforded the corresponding benzylidene compounds (**6**) as a mixture of *E*- and *Z*-isomers (*ca.* 1:1).
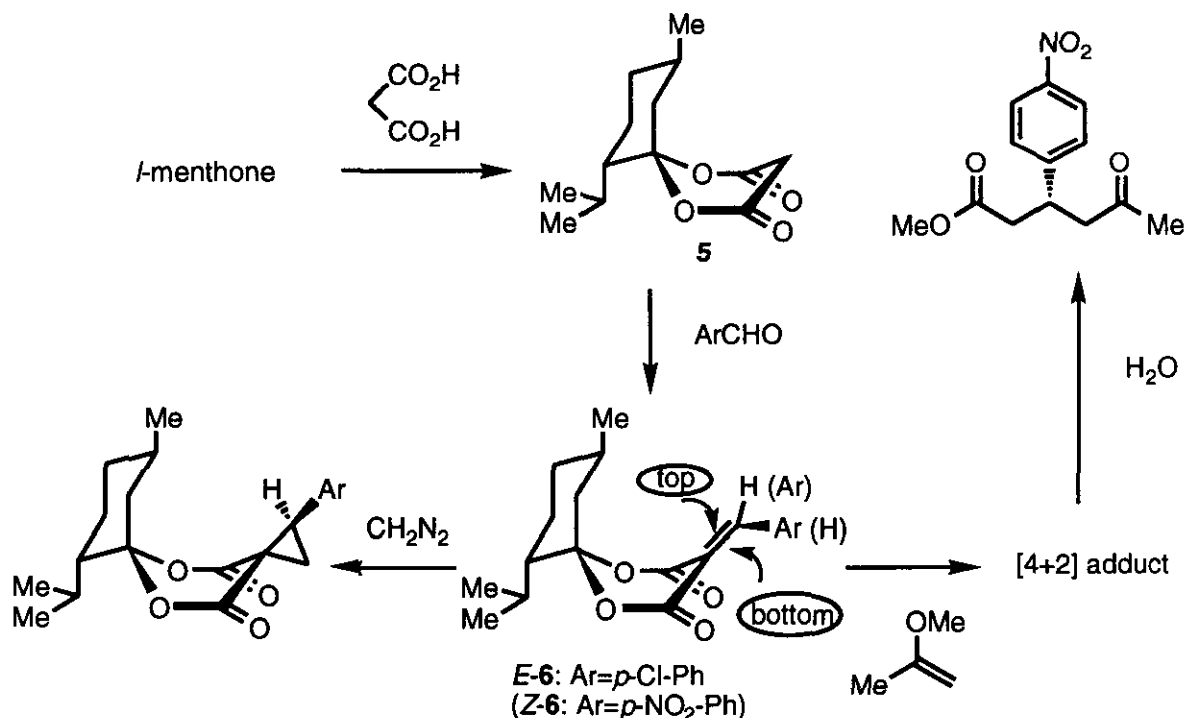
Slow recrystallization from ether afforded a single isomer. The E- and Z-configurations of the final products depended upon the kind of the aldehydes used. For example, p-nitrobenzaldehyde afforded the Z-isomer $(Z$-$6)$, and p-chlorobenzaldehyde gave the E-isomer $(E$-$6)$. X-Ray crystallographic analysis demonstrated that 6 has a boat conformation as depicted.

When E-6 was treated with diazomethane at -78 °C, only the single diastereomer (X-ray analysis not only revealed its structure, but also showed the boat conformation of its hetero-ring system) was obtained which corresponded to the attack of the reagent from the bottom face.[27] The same bottom face preference was also observed when Z-6 was subjected to the Diels-Alder reaction with 2-methoxypropene. Again, high degree of diastereofacial selection was observed.[28] Since 6 has a boat conformation as depicted in the formula, it is reasonable to explain that the high selectivity at the bottom face is due to this face being far more exposed than the other face (the top face).

3.2. 1,3-Oxazine-4,6-diones and their 5-benzylidene derivatives

By knowing that the 5-benzylidene-1,3-dioxane-4,6-diones (6) exhibit remarkable selectivity as mentioned in section 3.1, we then have been interested in synthesizing $7b$ whose methylene carbon acts by itself as the stereogenic center due to nonequivalent carbonyl groups attached to

Ar=C$_6$H$_4$OMe(p) S-7 R-7

	R
a	H
b	Me

S-$7b$ →   Y=C$_6$H$_5$CH$_2$, F

R-$7b$ →   Y=C$_6$H$_5$CH$_2$, F
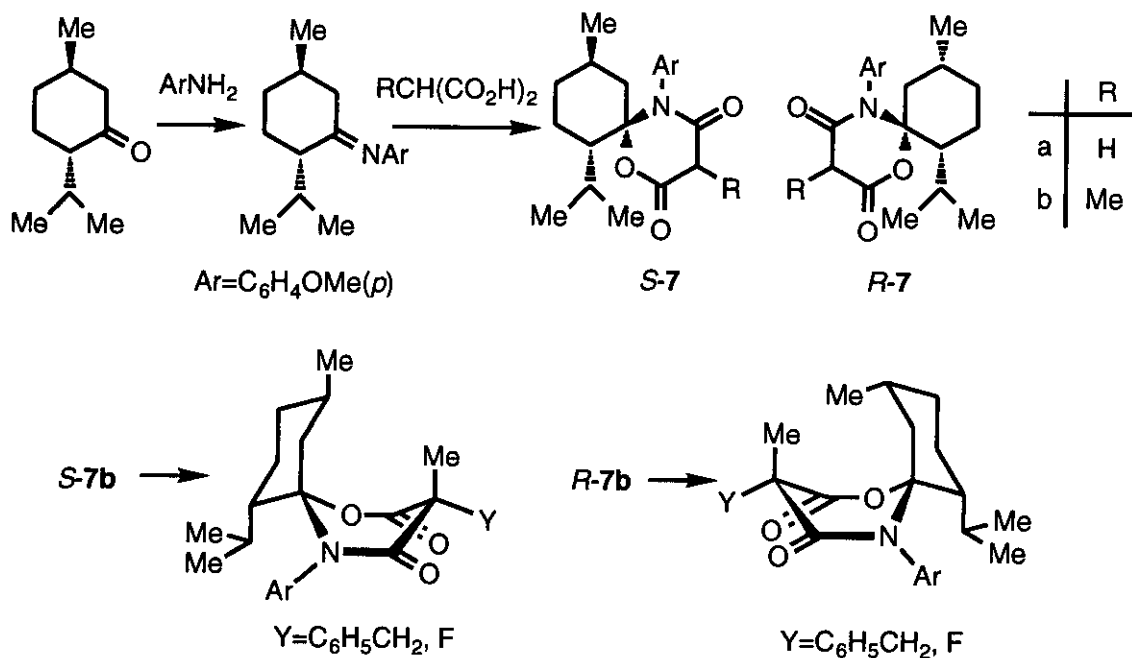
it. [29] As expected, the base-catalyzed alkylation of **7b** occurred from the bottom face (81% de at -15 °C and 89% de at -50 °C).

Base-catalyzed fluorination of **7b** by 1-fluoro-2,4,6-trimethylpyridinium triflate also gave the product which had accepted the reagent from the bottom face (90% de at -78 °C).[30]

Knoevenagel condensation of **7a** with an appropriate arylaldehyde followed by recrystallization afforded only *Z*-isomer (*Z*-**8**) of the corresponding benzylidene derivative as the sole product, irrespectively of the kind of the aldehydes. Again, the boat conformation of the six-membered ring was confirmed by X-ray crystallographic analysis.[31] It should be noted however that X-ray crystallographic analysis of *Z*-**8** has revealed that two boat-conformations (*Z*-**8**-**A**) and (*Z*-**8**-**B**) exist in 1:1 ratio (Figure 1).[31]
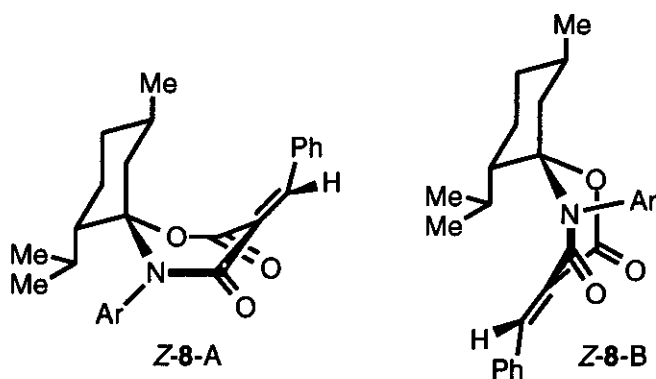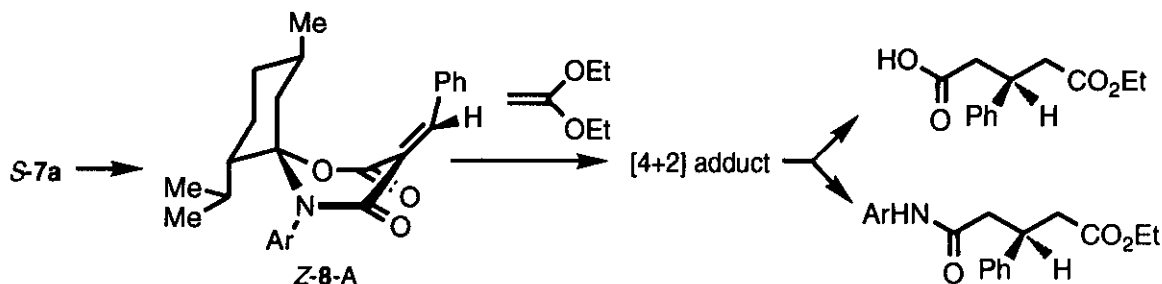

Figure 1. Stereostructures of *Z*-**8**-**A** and *Z*-**8**-**B**

The reaction of the benzylidene derivative (*Z*-**8**) with ketene diethylacetal gave preferentially the products corresponded to the bottom face attack of the ketene to *Z*-**8**. Thus, it is reasonable to assume that *Z*-**8** took, in solution, the conformation depicted by *Z*-**8**-**A**.

In an attempt to create chiral nonspirooxazinediones, we then synthesized **9a** and its benzylidene derivative (**10**), both of which again took the boat conformation with phenyl group in an axial orientation.[32] Base-catalyzed alkylation of the mono-methyl derivative (**9b**) and hetero Diels-Alder reaction of **10** with ketene diethylacetal proceeded preferentially from the bottom face.[33] Though the facial selectivity in each reaction was relatively low (e.g. *ca.* 75% de for the alkylation of **9b** and *ca.* 80% de for the hetero Diels-Alder reaction of **10**), the reactions of **10** has suggested that, if one can find out some chiral functional group capable to take an axial orientation which not only acts as the alternative for the phenyl group but alsofacilitates the optical resolution of the oxazinediones, the more efficient building blocks will be elaborated.

To the best of the present authors' knowledge, the benzylideneoxazepanediones (**13**)[34] are the only heterocyclic compounds so far prepared. Our efforts along the above line of work have then led to novel oxazinediones (**12**)[35] which could serve as the better alternatives of **13**.[36]

9a: R=H
9b: R=Me

10

12a: R=*l*-menthyl
12b: R=Me

13
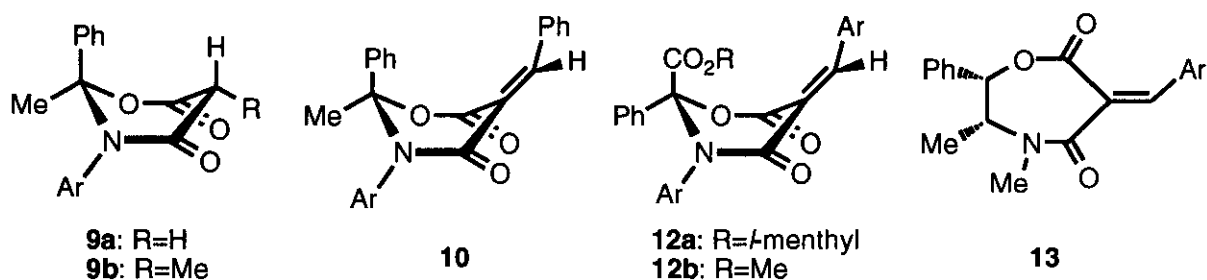
The oxazinediones (2*R*- and 2*S*-**11**) not only were prepared readily by the route shown in Scheme 4, but also could be separated into each diastereomer merely by fractional recrystallization. The corresponding benzylidene derivative (e.g. 2*R*-**12**) showed almost complete bottom face preference (≥98%) when used as the heterodienes in Diels-Alder reaction and as the Michael acceptors in conjugate addition reactions.[35]

Inspection of X-ray data of **12** has revealed that a downward flexion of the lactone C=O to the plane of Ph-C=C is much larger than that of the amide C=O. It is obvious that the selective formation of *Z*-isomer in the oxazienedione series (**8**, **10** and **12**) is due to this steric requirement.[37]

M=*l*-menthyl
Ar=C$_6$H$_4$OMe(*p*)
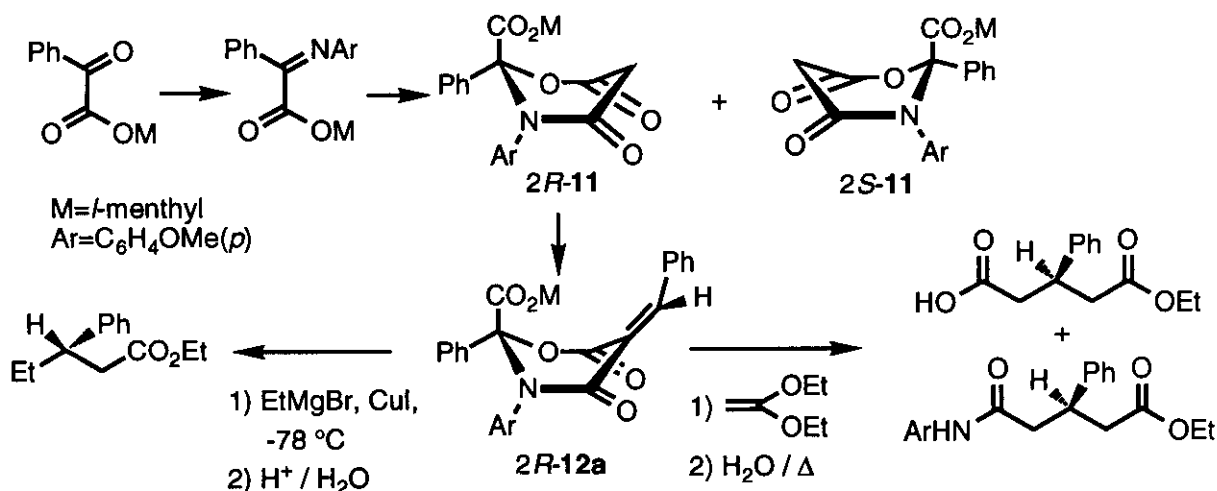
4. 1,3-DIHETERO-4(AND 4,6-DI)-OXO SIX-MEMBERED RINGS: ORIGINS OF CONFORMATION AND FACIAL SELECTIVITY

As mentioned in foregoing sections, using dioxinones (1~4), dioxanediones (6), and oxazinediones (7, 8, 9b, 10 and 12), a series of methodologies for providing highly diastereoselective transformations has been elaborated in this and other laboratories. The common structural feature of these six-membered heterocyclic compounds which not only was verified from crystallographic analysis but also accounted for the diastereofacial selectivity is the sofa (1~4) or boat conformation (5~12) of the hetero rings with acetal carbon out of the plane including at least four other atoms except the one at the 5-position. The bottom face preference in some reactions of the dioxinones (1 and 2) was explained by the sofa conformation by Demuth's and our groups. The pyramidalization at sp^2 carbon in the dioxinones (1 and 2) (cf. I) was proposed as the origin of the top face preference by Seebach's and Lange's groups.

In this section, discussions are made to clarify to what extent the pyramidalization (origin of the top face attack) of the trigonal carbon atoms in the sofa conformation (origin of the bottom face attack) can be used as a guide to predict the diastereofacial selectivity (cf. Table 1 for the reactions of the dioxinone series). The discussions are made in the following order: 1) ring con-

formation as well as the orientation of the substituents on the acetal carbon, 2) pyramidalization, and 3) correlation of these conformatinal features to the observed diastereofacial selectivity.

4.1. Origin of ring conformation

In order to gain valuable informations for the origins of 1) the boat conformation of the 1,3-dihetero-4,6-dioxo six-membered ring compounds (5~12) and 2) the conformation of their substituents attached to the acetal carbon, we synthesized compound (14) and carried out its X-ray crystallographic analysis.[38]
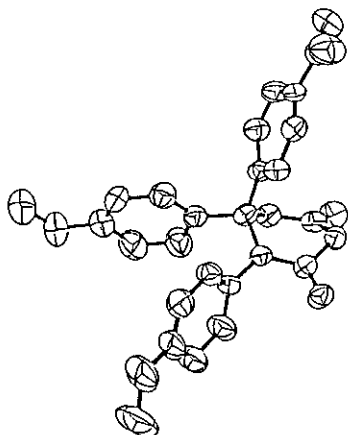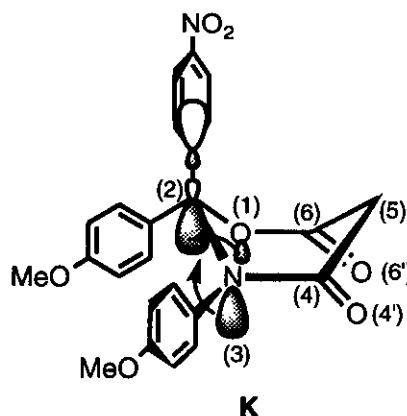

Figure 2a. Perspective view of 14

Figure 2b. Perspective schematic drawing of 14 with the atomic numbering

The molecular structure of 14 thus determined has revealed two interesting characteristics: 1) the molecule is in a boat conformation with C(2) and C(5) pointing upward and 2) the p-nitrophenyl group takes a quasi-axial orientation. We explained the conformation at the 2-position of 14 in terms of a stabilizing interaction between the lone pairs on N(3) and/or O(1) and the $\sigma*$ orbital on the axial C(2)-aryl bond. It is clear on energetic grounds that the stabilizing interaction between the lone-pair electrons on the heteroatoms and $\sigma*_{p^-}$ nitrophenyl(axial)-C(2) should be more important than that between the lone-pair electrons and the p-methoxyphenyl(axial)-C(2) bond in the hypothetical conformation whose two C(2)-aryl groups are reversed from 14. Hence, the stabilizing interaction depicted in **K** (Figure 2b) leads to an upward shift of the C(2) atom with the p-nitrophenyl group in an axial orientation.[39]

Connection of the Newman projections along the C(6)-O(1) and C(4)-N(3) bonds of the observed

boat conformation results in **14-a**. The nitrogen and/or oxygen lone-pair (p_z-orbitals: dotted

lines) are perpendicular to the plane of C(2)-O(1)-C(6) and/or C(2)-N(3)-C(4) and the p_z-orbitals

(solid lines) of C(4) and C(6) are perpendicular to the O(1)-C(6)-C(5) and N(3)-C(4)-C(5) planes,

respectively. From this figure, it is clear that the angles (θ) between the p_z-orbitals (O and N)

and the p_z-orbitals of C(4 and 6) are much smaller than the corresponding angles (θ') of the
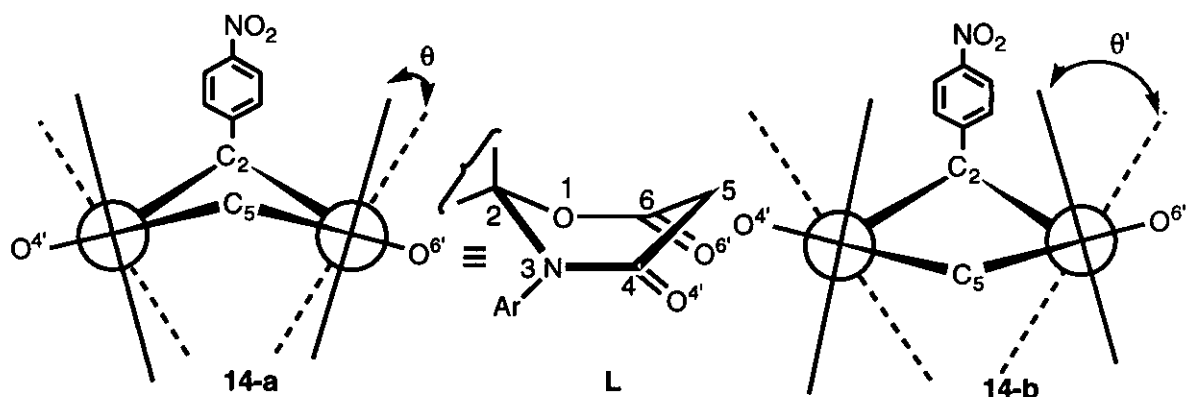

Figure 3. **14-a** and **14-b**: Newman projections of **14** along the O(1)-C(6) and the N(3)-C(4)
bonds. Solid lines: p_z-orbitals of C(6 and 4) in the C=O π-bonds and dotted lines: p_z-orbitals of O(1) and N(3). L: the side view of **14-a** with $\theta = 0°$.

hypothetical chair conformation (cf. **14-b**). Thus, the boat conformation (**14-a**) is more likely

to enjoy a stabilizing π-interaction between the heteroatoms and the C-O π-bonds.[40] In other

words, if one considers only the above π-overlap, the ideal conformation is the one having θ

equals to zero and hence corresponds to **L** in which the C(2)-O(1) and C(6)=O bonds and C(2)-N(3)

and C(4)=O bonds are parallel, respectively. In **L**, both C=O bonds are twisted towards the bottom

side.

In good accordance with the above considerations, X-ray crystallographic analysis of the

dioxinone (**4a**) revealed a sofa conformation with the *l*-menthyloxycarbonyl group (an

electron-withdrawing group) in a quasi-axial orientation.[41] This should be because the n_O-σ^*_{C-COOR}

interaction is more important than the corresponding n_O-σ^*_{C-Ph} interaction (note that

σ^*_{C-COOR} is lower in energy and hence a better electron acceptor than σ^*_{C-Ph}).

The observed conformation of the oxazinediones (**9** and **10**) both having an axial phenyl group
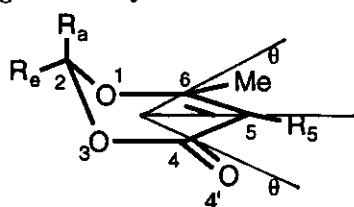
at the 2-position indicates that the above mentioned electronic effects predominate over the
steric requirements (*A* values of Me and Ph are 1.70 and 2.87, respectively[42,43]). On the
contrary, when the two substituents on the acetal carbon are alkyl or hydrogen (cf. **1~3**), the
more bulky substituent takes an equatorial orientation.[6]

Taking the dioxinones as example, we can conclude from the above mechanistic consideration
that 2-monoalkylated or 2,2-dialkylated dioxinones should have the sofa conformation with the
bulkier 2-substituent in an equatorial orientation, while those with two substituents on the 2-
position differing markedly in their electronic character should take a conformation with the
more electronagative substituent in an axial orientation. This conclusion is in good accordance
with the experimental results mentioned in Section 2.

4.2. Pyramidalization in the enone portion of the dioxinones (1~4)

As pointed out for the first time by Seebach *et al.* and then later by Lange *et al.*, the dioxinones
(**1a**, **2a** and **3**) are pyramidalized and all of which accepts the reagents in cuprate addition and
catalytic hydrogenation from the direction into which the center is pyramidalized. The trigonal

Table 2.   Comparison of the Degree of Pyramidalization in 1,3-Dioxinones[a]

Compd.	Re	Ra	R_5	C_4-$O_{4'}$ (°)	C_6-Me (°)
1a[b]	*l*-menthyl		H	9.24	7.41
2c[b]	*tert*-Bu	H	Br	12.57	11.85
3[b]	*tert*-Bu	Me	H	6.86	5.89
4c[c,d]	Ph	CO$_2$Me	H	12.40	6.82
				15.30	13.78

a)   The positions of C(6)-Me and C(4)-O(4') are shown and the degrees of pyramidalization at
     C(4) and C(6) are defined as the angle θ between the line C(4)-O(4') and/or C(6)-Me and the
     plane C(4)-C(5)-C(6).
b)   Deta reported in Lange's paper (ref. 14).   Original X-ray data of **1a**, **2c**, and **3** are given in
     refs. a: 11,   b: 13, and c: 14, respectively.
c)   Calculated from the data given in our recent paper (ref. 44).
d)   Crystallized with two independent molecules (1:1) in the unit cell.

carbon atoms of novel dioxinones (**4a** and **4b**) which accept the conjugate addition from the bottom face was found to be pyramidalized again towards the top face just like in the other dioxinones. Table 2 summarizes pyramidalization (found by X-ray crystallographic analyses) of four dioxinones (**1a, 2c, 3,** and **4c**).[44] As seen from Table 2, it is clear that the sp^2 carbons on the 4- and 6-positions in all dioxinones are pyramidalized in the same direction (the top side) with comparable magnitude.

It is therefore obvious that even the facial selectivity observed in the conjugate addition reactions cannot be explained by pyramidalization.

While there are other possible explanations for the origin and direction of the pyramidalization in all of the dioxinones (**1~4**), the simplest one is the following. As we have already pointed out for the boat conformation of the oxazinedione (**14**) shifting of the acetal carbon to the top side (by stereoelectronic effect mentioned already) results in the same (top) side shift of the C(5) atom in order to maximize the π-overlap in the O-C=O and N-C=O moieties. The same boat conformation was verified in the X-ray crystallographic analyses of the corresponding benzylidene derivatives (**6**,[27] **8**,[13] and **12**[35]) and even 6-methyl-3-benzylidene-5,6-dihydropyran-2,4-dione (**15**).[45]
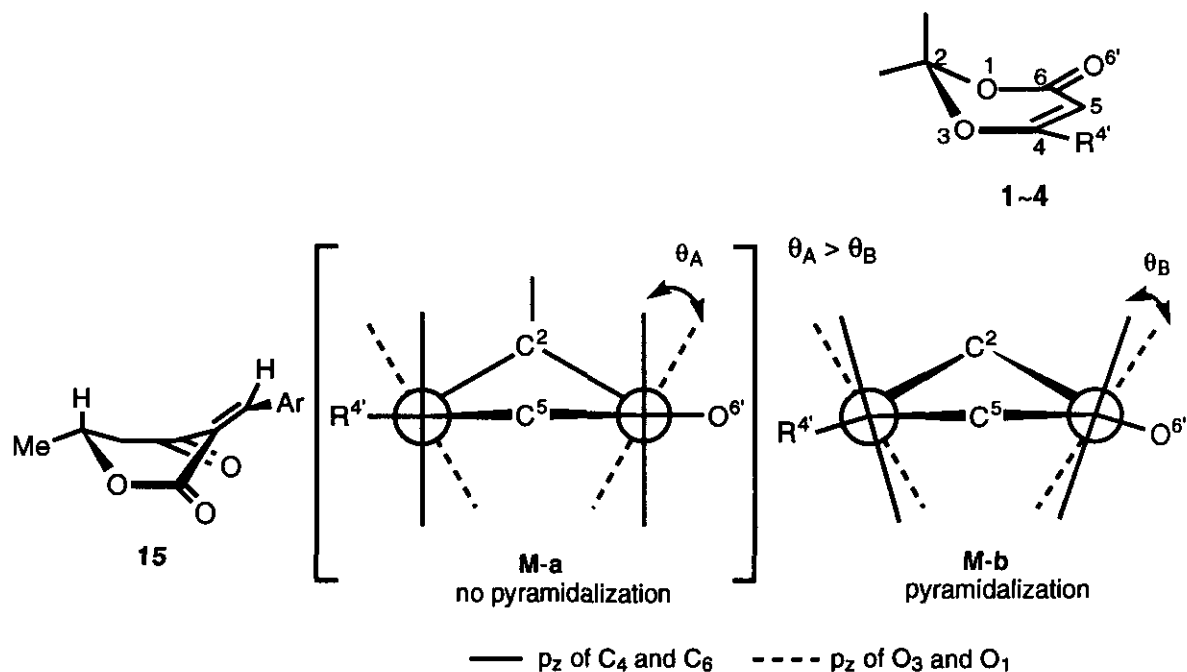

Figure 4. Newman projections of **1~4**

Though their methylene malonate moieties [C=C-(CO)$_2$] are formally π-conjugated, the C=C and two C=O bonds are distorted appreciably from planarity due to significant steric hindrance in the planar structure.[4][6]

If this argument is applied to the O-C=O and O-C=C bonds in the dioxinones (1~4) whose C(2) has already shifted to the top side, the C(6)=O and C(4)-R bonds are expected to twist towards the bottom side (cf. the arrow symbols in M-a). However, in contrast to the CO-CH$_2$-CO moiety in the oxazinedione (14), the two unsaturated bonds in the dioxinones are conjugated (C=C-C=O) and hence should be coplanar. In order to satisfy the above two requirements {1: maximizing the π-conju-gation of the 5 atoms [O(3)-C(4)=C(5)-C(6){=O}-O(1)] and 2: minimizing the corresponding angle θ, (for the definition of θ, see 14-a and its explanation)} at the same time, O(6') and R(4') in the dioxinones (1~4) should shift to the bottom side. In other words, the sp^2 carbons at the 4- and 6-positions should be pyramizalized toward the top side [the same side as C(2)] (cf. M-b). Hence, we can conclude that the sofa conformation of the ring and pyramidalization of the enone portion [C(4) to C(6)] of the dioxinone have the same origin and pyramidalization of C(6) is always in the same direction as that in which C(2) is shifted.

4.3. Origin of the facial selectivities of the dioxinones (1~3) and related compound (4~7)

As summarized in Table 1, the conjugate additions for 1, 2 and 3 occur from the top face. It is obvious that the sofa conformation of these dioxinones suggests that the top face attack is sterically more difficult than the bottom face due to unfavorable 1,3-diaxial relationship betweenthe incoming reagent (R) and the C(2)-axial substituent (R$_a$). As mentioned already, Seebach *et al.* explained for the first time the top face preference observed in some thermal reactions by pyramidalization. Thus, taking the conjugated addition as an example, Seebach has suggested that pyramidalization of the enone portion [(C(4) to C(6)] of the dioxinone (2a) is not causing stereoselectivity, but that both phenomena have the same origin. Later, this proposal was accepted as a reasonable one by Lange *et al.* for the same reaction of 3. In other words, they considered that the reactions occur preferentially from the direction into which the center is pyramizalized. Their explanation, however, is applicable neither to Diels-Alder reaction of 1c and 2d and fluorine addition to 1d nor even to the corresponding reaction (the conjugate

addition reaction) of **4**,[41] for which the preferred face is the bottom face. We consider that facial selectivity in the conjugate addition reactions for **1~3** is best explained by the so-called Cieplak theory.[47,48] Thus, for the dioxinones (**1~3**), the n_O lone-pair electrons interact with the antibonding orbital ($\sigma_{\ddagger}^*$) of the incipient bond (C-R) (cf. **N**) and this hyperconjugation would cause the top face attack of the reagent (R). In **4**, the electron-withdrawing substituent (CO_2R) takes an axial orientation. Therefore, such interaction would become less effective. It is because, the lone-pair electrons in question interact strongly with the antibonding orbital of $\sigma_{C(2)\text{-}COOR}$ (cf. **O**), and hence the hyperconjugation facilitating the top face attack (cf. **N**) would become less effective.

N: R_a, R_e=alkyl or H   **O**
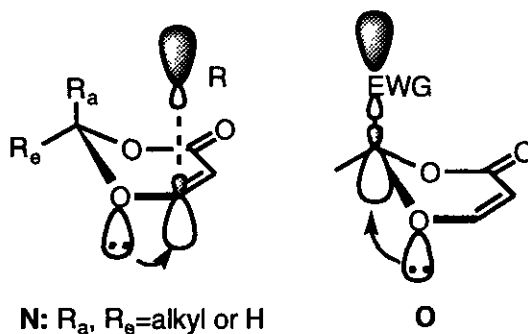
How, then, can one explain why the pericyclic reactions (Diels-Alder reactions) and the addition reactions of molecular fluorine to all kinds of the dioxinones (**1~4**) occur from the bottom face ? In other words, why in these reactions, does simple steric consideration (the bottom face preference) but not the above mentioned Cieplak effect (the top face preference) give the correct prediction ? The answer for this question would be provided by consideration of different steric requirements in each reaction as summarized below.

It is well known that the steric demands of conjugate addition (in a more general sense, nucleophilic addition[49]), pericyclic addition (e.g. Diels-Alder) and molecular fluorine addition reactions (in a more general sense, electrophilic addition) are significantly different from each other and the difference can be explained by the concept of "non-perpendicular attack". That is, the stabilizing HOMO-LUMO interaction in the transition state for an ionic attack on unsaturated bonds is maximized at a particular angle. Thus, nucleophilic attack occurs at an obtuse angle and electrophilic attack at an acute angle. This is, due to the unfavorable out-of-

phase interaction between the attacking nucleophile and the carbonyl-oxygen (a in **P'**), the nucleophile attacks at an angle of 109° (the "Burgi-Dunitz" angle, cf. **P**).[50] Due to the increase
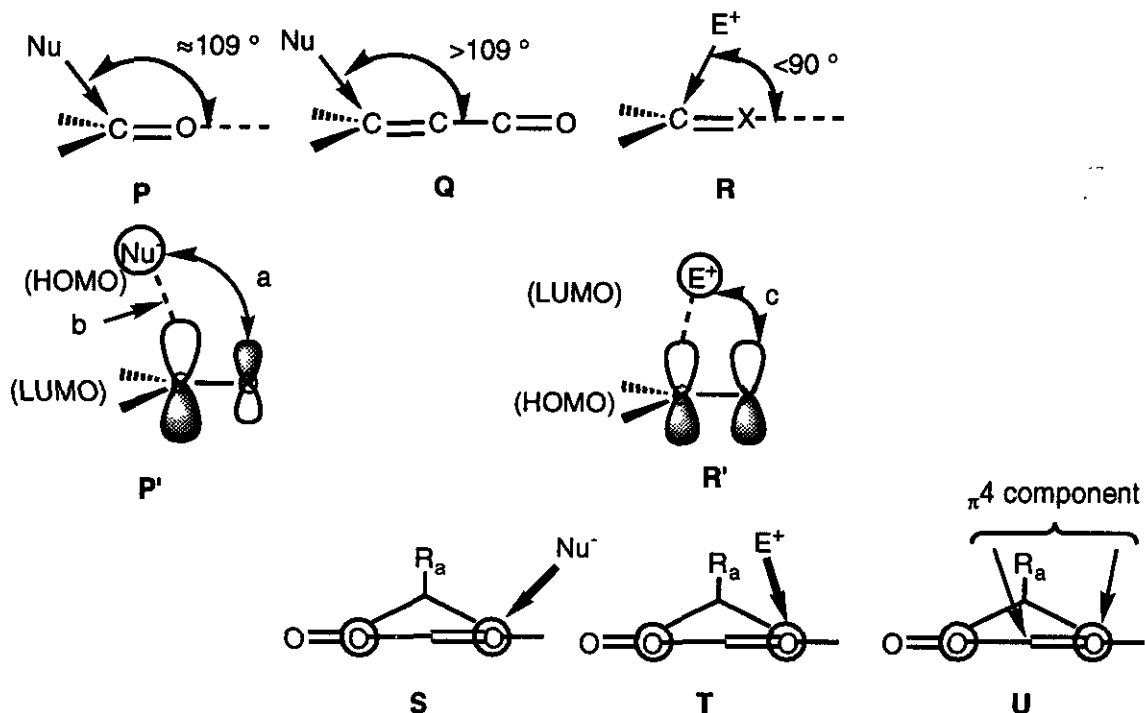
of out-of-phase interaction (a) relative to in-phase overlap (b), the angle increases further with conjugated enone systems **Q**.[51,52]   On the contrary, due to favorable in-phase interaction (c in **R'**), the angle becomes less than 90° for an electrophilic attack.[53]   On this basis, the trajectories of the attacking reagents (Nu⁻ and E⁺) to C(6) in dioxinones can be depicted as shown in formulae **S** and **T**. If the above argument is correct, it is clear that the unfavorable 1,3-diaxial interaction between the attacking reagent and the axial substituent on C(2) in the substrate is much larger in **T** (the transition state for an electrophilic attack) than in **S** (the transition state for a nucleophilic attack). This conclusion is in good accordance with the bottom face attack of molecular fluorine on 1-type dioxinones.[19,54] The bottom face preference for Diels-Alder reactions so far reported for all kinds of dioxinones is also explained by **U**, in which the steric hindrance is again significant for the top face attack.

5.   CONCLUSIONS

Ground-state reactions and excited-state reactions of chiral 1,3-dioxin-4-ones and related compounds all having an enone function in their ring are reviewed by focusing the *facial* selectivity in the C-C double bond in the enone functions.

Sofa conformation of the ring systems and pyramidalization of the enone portions in these heterocycles so far proposed as the origins of the facial selectivity are summarized and the discrepancies between the facial selectivities verified by experimental results and the predicted selectivities from either the conformation or the pyramidalization are pointed out. Finally, the present authors' opinion which accounts for all of the reported ground-state addition reactions to chiral dioxinones is proposed. The proposal can be summarized as in the following three factors: 1) the top face preference by Cieplak theory (stereoelectronic effects), 2) the bottom face preference by sofa conformation (steric effects), and 3) the trajectory of the attacking reagents. Among these factors, the third factor plays the balancing role between the former two factors.

The reasons previously proposed to account for the bottom face preference in the photo[2+2]-cycloaddition reactions are only briefly mentioned. Reverse pyramidalization in the excited dioxinones is obviously incorrect. The bottom face   preference in the photo[2+2]cycloaddition reactions would be mostly due to the steric factor as suggested originally by Demuth *et al.*[11] and then by us,[12]   since steric demands in the corresponding transition states (cf. **U** in which $_\pi 4$ component is replaced with $_\pi 2$ component) would be very similar to that (**U**) of [4+2] cycloaddition. The verification of the present proposal, which satisfies all of the experimental data so far reported, however, should await further researches.

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