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Regio- and Diastereo-Chemically Controlled Photocycloaddition of an Arene and an Alkene Linked by a Chiral Auxiliary

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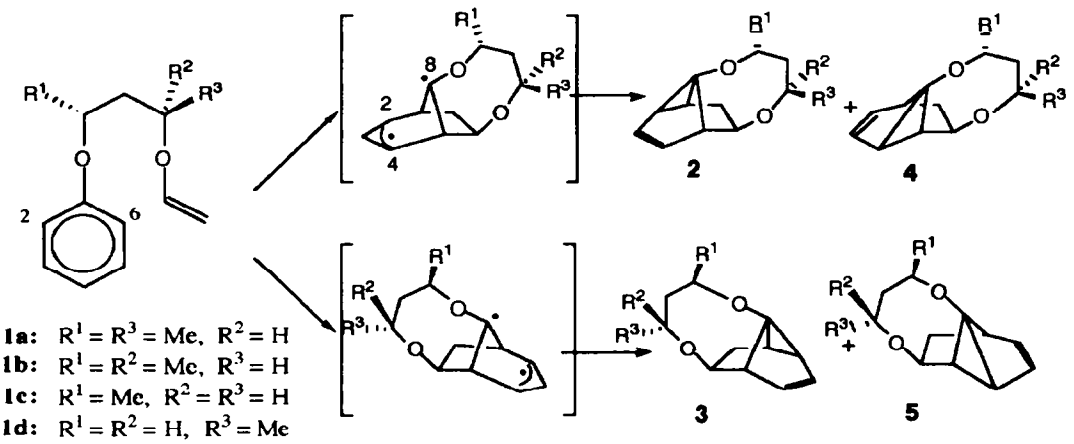
Abstract: Intramolecular *meta*-arene-alkene photocycloaddition of **1b**, the substrate having a chiral auxiliary as a linking bridge between the arene and the alkene, resulted in high diastereofacial differentiation of the alkene at the addition step and sufficient regiocontrol of the subsequent ring closure step to give a single diastereomer **4**.

Meta-arene-alkene photocycloaddition produces 3-tricyclo[3.2.1.$0^{2,8}$]octene derivatives, which are convenient and useful synthetic intermediates for polycyclic compounds.[1] Our idea to access optically active compounds by this reaction is that if the arene and the prochiral alkene are connected with an optically active linking bridge prior to the reaction and are subjected to intramolecular reaction by photo-irradiation, highly regio- and stereocontrolled cycloaddition could take place.[2] We report herein a novel *meta*-arene-alkene photocycloaddition to give an enantiomerically pure tricyclic compound. Optically active 2,4-pentanediol[3] and its analogs were employed as the chiral linking bridge, and phenyl and vinyl groups were connected with the bridge though ether bonds. Regio- and diastereo-chemical courses of this reaction are shown in Scheme 1. By analogy with the reaction between anisole and alkenes, the photoaddition site of the arene moiety was expected to be the 2,6-positions.[4] Thus, factors to be controlled by the linking bridge are the diastereoface of the prochiral alkene in the addition step and the position of the subsequent cyclopropane ring formation step. The expected cycloadducts are two pairs of diastereomers, **2** to **5**.

The substrates **1** (**a**-**e**) were easily prepared from the corresponding diols.[5] Photo-irradiation of **1** in pentane (ca. 1 mmol/l) with a low pressure mercury lamp (30 W) through Vycor filter at room temperature produced a mixture of cycloadducts from which each isomer was isolated by MPLC.[6] The isolated yields and calculated differentiation ratios are shown in Table 1.[7] Of the two stereogenic centers, the arene side and the alkene side, on the linking bridge, the stereogenic center of the arene side was found to play an essential role in the diastereofacial differentiation of the alkene moiety in the addition step (**1a**, **1b**). Even in the absence of the stereogenic center on the alkene side, complete diastereoface differentiation took place (**1c**). On the other hand,

the alkene side stereogenic center did not participate sufficiently in the stereocontrol, despite its close proximity to the prochiral reaction site. As for the regiocontrol, substrate **1b** brought about perfect results. Although the substituents and relative configuration of linking bridge were evidently responsible for the ratio of the regioisomers, no systematic rules for elucidating individual cases were observed. Regioisomers, **2** and **4**, were interconvertible under photo-irradiation. When either **2** or **4** was photolyzed under the same conditions as in the cycloaddition, the ratio obtained for **2** and **4** was as same as that in the cycloaddition. In this respect, the ratio of the regioisomers was determined to be the composition of the photo-stationary state (photo equilibrated mixture) of each reaction system.[8]



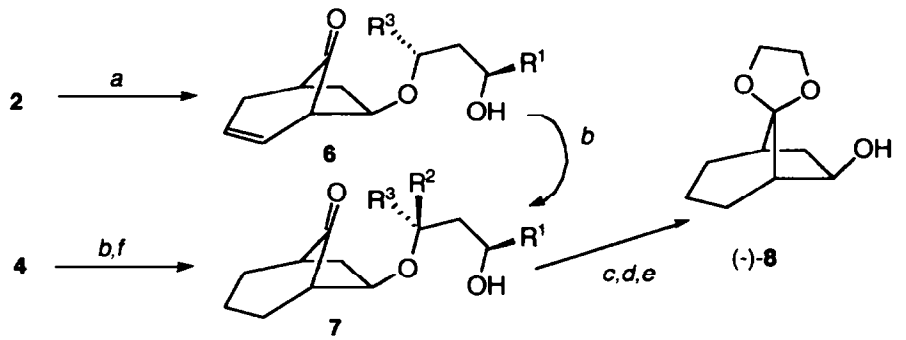
Scheme 1

Table 1. Isolated Product Yields and Differentiation Ratios of the Photolysis of 1

1	Reaction time	Isolated Product yield 2	3	4	5	Olefin addition[a] *si* attack : *re* attack	Ring closure[b] 2,8-position : 4,8-position
1a	9 h	40%	——	15%	——	100 : 0	73 : 27
1b	4 h	——	——	70%	——	100 : 0	0 : 100
1c	10 h	16%	——	27%	——	100 : 0	38 : 62
1d	9 h	9%	34%	< 1%[c]	< 1%[c]	20 : 80	> 98 : < 2
1e	44 h	19% (racemic mixture)		——	——		100 : 0

a. Diastereoface differentiation of alkene was calculated with the isolated product yields as *si*-attack = (2+4) and *re*-attack = (3+5).
b. Regio control of ring closure was calculated with the isolated product yields as 2,8-position = (2+3) and 4,8-position = (4+5).
c. Trace amounts of two cycloadducts were detected in the reaction mixture, but were not isolated enough to determine their yields.

The structures of the cycloadducts were determined by their H-H spin couplings on ^{1}H-NMR spectra. The stereochemistry was chemically correlated with the stereochemically established compound **8**[9] as shown in scheme 2. From **2** (**2a**, **2b** and **2c**), (-)-(1*R*,5*S*,6*R*)-**8** was obtained in an enantiomerically pure state[10] through acid catalyzed opening of the cyclopropane ring, hydrogenation of the olefin, acetalization with ethylene glycol, and elimination of the chiral auxiliary. From **3d**, (+)-(1*S*,5*R*,6*S*)-**8** was produced in the same way. On the other hand, acid treatment of **4** resulted in a complex mixture, so that the olefin in **4** (**4a** and **4b**) was hydrogenated and then cyclopropyl ring was opened by oxymercuration/reduction procedure to give **7**. By the elimination of chiral diol from this, enantiomerically pure (-)-**8** was obtained.



a: 4N HCl/acetone, b: H_2/Pd-C, c: ethylene glycol/TsOH, d: PCC
e: K_2CO_3/MeOH-H_2O, f: $Hg(OAc)_2$ then $NaBH_4$

Scheme 2

In conclusion, the chiral linkage bridge of **1b** fully controlled the overall reaction resulting in the single cycloadduct, which could be converted to enantiomerically pure bicyclic compounds. The flexible nature of the chiral auxiliary in our present and reported[3] substrates gave us further tasks about the diastereoface differentiation control mechanism, either by equilibrium constants between conformational isomers of the substrates (thermodynamic control) or by activation energy difference (kinetic control).[11] Conformational analysis of the substrates and application of the present reaction to various substituted substrates is now on progress.

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3. This compound of C_2 symmetry has been proved to be an excellent bidentate chiral auxiliary for diastereoface differentiating cycloaddition. In this case, the mono-enol ether of the diol can coordinate with the reagent through the hydroxy group in making a substrate-reagent complex *in situ*, so that the reaction was proposed to take place by a quasi-intramolecular mechanism resulting in a high diastereofacial control. Sugimura, T.; Nishiyama, N.; Tai, A. *Tetrahedron: Asymmetry* **1993**, *4*, 43-44. Sugimura, T.; Katagiri, T.; Tai, A. *Tetrahedron Lett.* **1992**, *33*, 367-368. Sugimura, T.; Futagawa, T.; Tai, A. *Chem. Lett.* **1990**, 2291. Sugimura, T.; Yoshikawa, M.; Futagawa, T.; Tai, A. *Tetrahedron* **1990**, *46*, 5955. Sugimura, T.; Futagawa, T.; Yoshikawa, M.; Tai, A. *Tetrahedron Lett.* **1989**, *30*, 3807. Sugimura, T.; Futagawa, T.; Tai, A. *Tetrahedron Lett.* **1988**, *29*, 5775.
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5. The substrate **1a** was prepared from (2*R*,4*R*)-pentanediol and cyclohexanone in four steps as follows; 1) formation of the ketal by dehydration catalyzed by acid (96 % yield), 2) dibromination at the 2,6-position of the cyclohexane ring by treatment with pyridinium bromide perbromide (79 %), 3) elimination of bromine and aromatization with sodium methoxide in DMSO at room temperature (93 %), 4) ether exchange reaction with ethyl vinyl ether and mercuric acetate under reflux (79 %). The substrate **1b** was obtained from the product of the above step-3 by epimerization at the 2-position by the Mitsunobu reaction (66 %) followed by vinyl ether formation (74.3 %). The substrate, **1c** and **1d**, were prepared from the cyclohexanone ketal of (3*R*)-1,3-butanediol (22.4 % and 14.4 % yield, respectively), and **1e** was prepared from cyclohexanone acetal of 1,3-propanediol (55.9 % yield) by the same procedure employed for the synthesis of **1a**.
6. All photocycloadducts were over 99 % d.e. as determined by capillary GLC analysis (OV-1, 25 m, 150 °C) of their hydrogenation product (H_2/ Pd-C).
7. The solution was photolyzed until no substrate was detected in all cases. Major side reaction was elimination of vinyl group from the substrate.
8. The cycloadducts, **2** to **5**, showed similar UV spectra, and their absorbances at 254 nm were almost same (ε of **2b** at 254nm = 240 in pentane). Thus, the ratios of the regioisomers depended on the quantum yields of their photo-isomerizations.
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10. Enantiomeric purity of **8** was confirmed by ^{19}F-NMR of its Mosher's ester in $CDCl_3$ with Eu(fod)$_3$. For detail, see ref. 9.
11. *Meta*-arene-alkene photocycloaddition was expected to proceed through exciplex. Thus, the conformational equilibration should be considered both in ground state and in locally excited state including equilibrium between locally excited state and exciplex. The activation energy to go to the adduct is revealed as quantum yield from the exciplex. De Vaal, P.; Lodder, G.; Cornelisse, J., *J. Phys. Org. Chem.* **1992**, *5*, 581. Cornelisse, J. *Chem. Rev.* **1993**, *93*, 615 and references therein.

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