Facial Selectivities of Benzofluorenes Bearing a Carbonyl, an Olefin, or a Diene Group in Spiro Geometry.
π Spiro Substituent Effects.

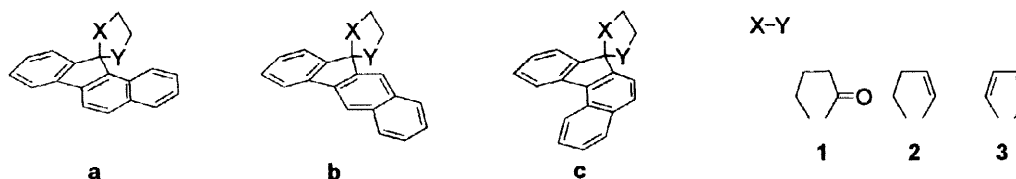Motonori Tsuji, Tomohiko Ohwada* and Koichi Shudo

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Abstract   Benzo[b]- and benzo[c]fluorenes bearing a ketone, an olefin, or a diene substituent in spiro geometry were synthesized to characterize the π facial selectivity, in comparison with that of the sterically biased benzo[a]fluorene system. We found that fully spiro-conjugated dienes show facially selective behaviors as Diels-Alder dienes, the favored direction depending on the aromatic system. This is in sharp contrast to the olefin analogues, which show essentially no preference.
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Benzo[a]- (**a**), benzo[b]- (**b**), and benzo[c]fluorenes (**c**) bearing a carbonyl (**1**), an olefin (**2**), or a diene (**3**) group in spiro geometry are three possible combinatorial isomers wherein the direction of fusion of the naphthalene is different (Scheme 1). The π reaction centers of the carbonyl, olefin, and diene groups are subject to spiro-conjugation with the planar aromatic π system. We have been investigating the effect of perturbation arising from spiro-conjugation on chemical reactivities, in particular facial selectivities.[1,2] With respect to the π faces of the relevant reaction centers (Scheme 1), the first aromatic system (**a**) is sterically biased (i. e., sterically unsymmetrical), while the latter two systems (**b** and **c**) are assumed to be free from steric bias. Here, we will focus on the *π spiro substituent effect* on the facial selectivities in terms of two factors, 1) the direction of fusion of the aromatic ring system (**a**, **b**, and **c**), and 2) the nature of the π reaction center (ketone, olefin or diene). We find that fully spiro-conjugated dienes (**3**, both X and Y are π centers (Scheme 1)) show facially selective behaviors, the favored direction depending on the aromatic system, although the half spiro-conjugated systems (one of X and Y is a π center (Scheme 1)), such as ketones (**1**) and olefins (**2**), show no selectivity except for the sterically biased systems (**1a** and **2a**) and the ketone **1c**.
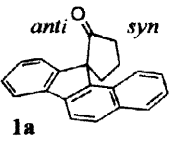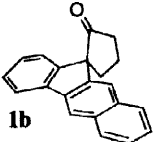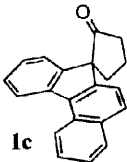
Scheme 1   Compounds Synthesized to Examine the π Spiro Substituent Effect.

Table 1 shows the π facial selectivity of reduction of the ketones[3] (**1a** - **c**) with sodium borohydride (NaBH$_4$), lithium aluminum hydride (LiAlH$_4$), and triethylsilane (Et$_3$SiH) in the presence of trifluoroacetic acid (TFA)[4,5]. While the sterically unbiased ketone (**1b**) does not show significant selectivity, the ketone **1c** show a *syn* preference (*syn* : *anti* = 60 : 40 for the addition) in the reduction with NaBH$_4$. As anticipated, the sterically biased ketone **1a** showed a large selectivity. An intriguing feature is the dependence of the preferred mode of attack upon the reducing reagents in the case of **1a**. With NaBH$_4$, the reaction from the side of the benzene ring was preferred (*anti* : *syn* = 91 : 9), whereas with LiAlH$_4$, the reaction occured mainly from the sterically

hindered side (*anti* : *syn* = 19 : 81). Furthermore, the reduction of **1a** with NaBH$_4$ was very slow as compared with the reductions of the ketones **1b** and **1c**. Ionic hydrogenation of **1a** was also slow. The results suggest the involvement of cation-π interaction between the lithium cation of LiAlH$_4$ and the terminal benzene ring of the naphthalene,[6] accelerating the reaction. In the cases of **1b** and **1c**, a similar complexation of LiAlH$_4$ might occur, but would not lead to facial selectivity because of the distance to the carbonyl group.
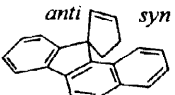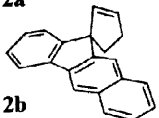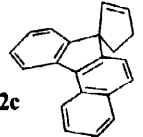
Table 1   Modes of Attack of Nucleophilic Reagents on 1a - c.

Substance	Reductants	Time (h)	Temp. (°C)	S. M.[a] (%)	Yield (%)	Attack *anti / syn*
1a	NaBH$_4$ (4.1 eq.) / CH$_2$Cl$_2$ - MeOH	15	-45	86[b]	12[b]	91 : 9
	Et$_3$SiH (17.6 eq.) / TFA	22.3	60	18[b]	21[b]	72 : 28
	LiAlH$_4$ (1.1 eq.) / THF	1.5	3	-	100	19 : 81
1b	NaBH$_4$ (4.0 eq.) / MeOH	1.5	-45	-	100	48 : 52
	Et$_3$SiH (17.8 eq.) / TFA	4.2	60	-	39[b]	46 : 54
	LiAlH$_4$ (1.0 eq.) / THF	3	3	-	100	52 : 48
1c	NaBH$_4$ (4.1 eq.) / MeOH	2.7	-45	-	100	40 : 60
	Et$_3$SiH (17.6 eq.) / TFA	4.5	60	-	39[b]	55 : 45
	LiAlH$_4$ (1.2 eq.) / THF	1	3	-	99	48 : 52

a: Starting material.   b: Yields were estimated by ^{1}H NMR.

The sterically congested olefin **2a**[3], as would be expected, showed an *anti* preference in the electrophilic oxidations with *m*-chloroperbenzoic acid (mCPBA) and osmium tetroxide (OsO$_4$), the reagents attacking preferentially from the less hindered benzene ring side.[5] The "sterically unbiased" olefins[3] (**2b** and **2c**) showed negligible biases in epoxidation and dihydroxylation (Table 2).[5]

Table 2   Distributions of Diastereomers in Diols and Epoxides Formed by Oxidative Electrophilic Reagents.
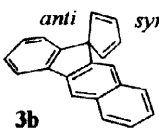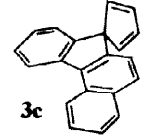
Substance	Reactants	Time (h)	Temp. (°C)	S. M.[a] (%)	Yield (%)	Attack *syn / anti*
2a	OsO$_4$ (1.2 eq.) / pyridine	7	-45	44>[b]	63	20 : 80
	mCPBA (2.0 eq.) / CHCl$_3$	192	-3	9	54	23 : 77
2b	OsO$_4$ (1.2 eq.) / pyridine	2	-45	-	100	52 : 48
	mCPBA (2.0 eq.) / CHCl$_3$	8	-3	1	99	46 : 54
2c	OsO$_4$ (1.2 eq.) / pyridine	2	-45	-	98	53 : 47
	mCPBA (2.0 eq.) / CHCl$_3$	8	-3	2	97	50 : 50

a: Starting material.   b: Including by-product.

From these experimental results, we can conclude that the spiro ketones and spiro olefins bearing a benzofluorene (except **1c** in the case of the NaBH$_4$ reduction) showed little or no π facial selectivity in the absence of a steric influence. We may account for the lack of interaction of the spiro π substituents (π fragments) in terms of the large energy gap of these fragments (Scheme 2): in the cases of the ketones, the
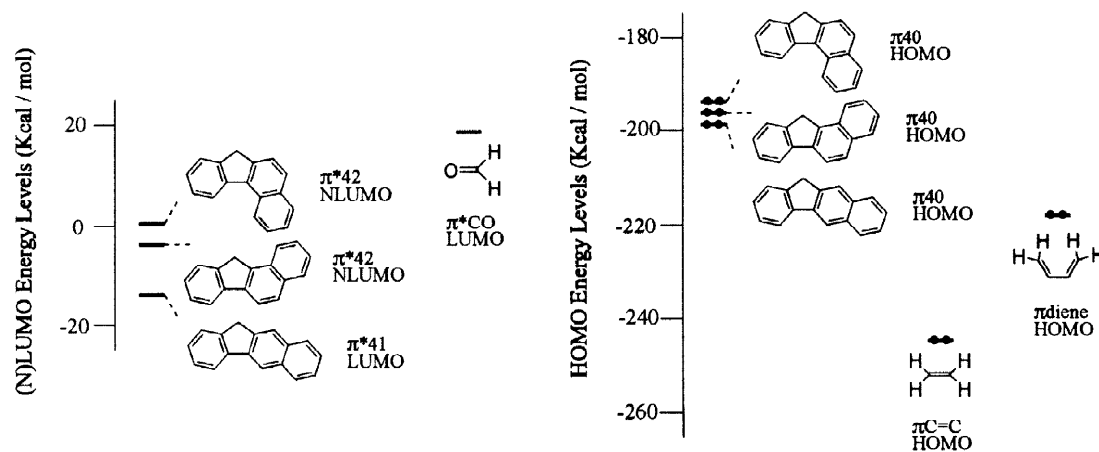
unoccupied carbonyl π^* orbital is perturbed by the lower-lying unoccupied aromatic π^* orbitals of the benzofluorenes, while in the cases of the olefins, the occupied olefin π orbital is perturbed by the high-lying occupied aromatic π orbitals of the benzofluorenes.[7] In the case of the ketone **1c**, the relevant energy gap is apparently smaller than that of **1b**, leading to effective interaction, which is consistent with the observed selectivity of **1c** (no selectivity in the case of **1b**) in the reaction with NaBH₄. In the cases of the sterically unbiased olefins (**2b** and **2c**), there are consistently large energy gaps.

Table 3   Diels-Alder Reactions of Dienes with Dienophiles.

Substance	Dienophiles	Time (h)	Temp. (°C)	S.M.[a] (%)	Yield (%)	Attack	
						syn-endo	anti-endo
3b	MA (9.9 eq.)	48	60	-	92	62	38
	NPMI (6.3 eq.)	48	60	trace [b]	86 [b]	60	40
	NPTAD (4.9 eq.)	2	3	-	100	57	43
3c	MA (9.7 eq.)	24	60	16	75	28	72
	NPMI (6.4 eq.)	48	60	22 [b]	54 [b]	27	73
	NPTAD (4.9 eq.)	2	3	-	100	37	63

a: Starting material.   b: Yields were estimated by ¹H NMR.

In order to reduce the energy gap further and allow effective interaction, we designed and synthesized the corresponding dienes[3] (**3b** and **3c**). These diene systems involve complete spiro-conjugation,[2, 8] leading to an effective overlap of the diene π orbital and the aromatic π orbital. Furthermore, the HOMO of the diene is close to that of the aromatic benzofluorenes (Scheme 2). The highest occupied orbital (HOMO) of the diene π orbitals is therefore subject to effective perturbation by the aromatic π fragment.
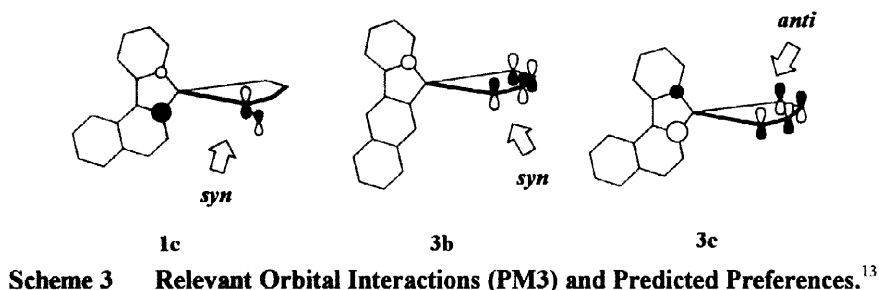

Scheme 2   Energy Gaps of the π Fragment Orbitals (PM3 (kcal / mol)).[13]

We detected facial selectivities of the sterically unbiased dienes (**3b** and **3c**) in Diels-Alder reactions with several dienophiles (maleic anhydride (MA), N-phenylmaleimide (NPMI), and N-phenyl-1,3,5-triazoline-2,4-dione (NPTAD)) (Table 3).[9, 10] Endo isomers of the adducts were predominantly formed. The direction of fusion of the aromatic ring changed the facial preference. The diene **3b** favored syn addition of the dienophiles with respect to the naphthalene ring, whereas the diene **3c** showed a reverse anti preference for the additions.[5, 11]

Nonequivalent orbital interactions of the π reaction center with the aromatic π orbitals at the ipso positions are thought to be crucial for facial preference of aromatic spiro systems (Scheme 3).[1, 13] In the case of the occupied

π reaction center, reactions on the opposite side of the out-of-phase motif may be favored, while in the case of the unoccupied π* reaction center, those on the side of the additional in-phase motif may be favored.[1, 13] The observed preferences of the dienes (*syn* (**3b**) and *anti* (**3c**)), in addition to the ketone **1c** (*syn*), seem to be consistent with this idea (see Scheme 3). A detailed scrutiny based on theoretical calculations is in progress.[12]

In summary, we have found divergent facial selective behavior of benzofluorenes with a π spiro substituent depending on the nature of the π reaction center. Aromatic ring systems also modified the facial selectivity.

Scheme 3   Relevant Orbital Interactions (PM3) and Predicted Preferences.[13]

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3) Benzo[b]fluorenes bearing the spiro substituents (**1b** and **2b**) were prepared as described in Thiele, J.; Schneider, J. *Liebigs Ann. Chem.*, **1909**, *350*, 287 - 299. Both benzo[a]- (**1a** and **2a**) and benzo[c]fluorenes (**1c** and **2c**) were prepared as described in Hopkinson, A. C.; Lee-Ruff, E.; Maleki, M., *Synthesis*, **1986**, 366 - 371. Both **3b** and **3c** were prepared from the corresponding olefins (**2b** and **2c**) as described in Müller, H.; Herberich, G. E. *Chem. Ber.*, **1971**, *104*, 2772 - 2780. **2d** was prepared by McMurry reaction of the corresponding dimethyl ketone as described in McMurry, J. E.; Lectka, T.; Rico, J. G. *J. Org. Chem.*, **1989**, *54*, 3748 - 3749. See also reference 1. All new compounds gave satisfactory NMR data and either combustion analysis or HRMS data.

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5) The configurations of the diastereomers were elucidated mainly on the basis of the characteristic anisotropy effects of the alcohol (the diol, the epoxide, or the olefin) described in reference 1. The structure of the major product obtained from the reaction of **3c** with MA was confirmed by X-ray crystal analysis. The structures of the major products obtained from the reactions of **3b** with MA and of **1a** with LiAlH₄ were confirmed by means of NOE enhancement experiments.

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8) The ¹³C NMR chemical shifts of the spiro carbon atoms of the diene (**3b**, 70.3 ppm; **3c**, 71.2 ppm) were at lower fields than those of the corresponding olefins (**2b**, 63.3 ppm; **2d**, 67.0 ppm; **2c**, 63.8 ppm) and ketones (**1b**, 64.2 ppm; **1c**, 64.9 ppm), or the corresponding cyclopentane derivatives (benzo[b]-, 57.2 ppm; benzo[c]-, 57.3 ppm). Semmelhack, M. F.; Foos, J. S.; Katz, S., *J. Am. Chem. Soc.*, **1973**, *95*, 7325 - 7336. See also reference 2.

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10) In an attempt to increase the facial selectivity of the olefin derivatives, we prepared a dimethyl olefin analogue of **2b** (ref. 3), because the dimethyl substitution raises the occupied olefin π orbital, leading to a reduction of the relevant energy gap. However no significant facial selectivity (*syn* : *anti* =48 : 52) of the dimethyl analogue was observed in the epoxidation reaction, although enhanced reactivity (0.5 hr at -45 °C), probably due to the raised olefin π orbital energy, was observed (ref. 5). This also indicates the effective orbital overlap of the diene systems due to the full spiro conjugation.

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12) Other possible orbital mechanisms are discussed in the following references. Halterman, R. L.; McEvoy, M. A., *J. Am. Chem. Soc.*, **1992**, *114*, 980 - 985. Halterman, R. L.; McCarthy, B. A.; McEvoy, M. A., *J. Org. Chem.*, **1992**, *57*, 5585 - 5589. Ishida, M.; Beniya, Y.; Inagaki, S.; Kato, S., *J. Am. Chem. Soc.*, **1990**, *112*, 8980 - 8982. Ishida, M.; Aoyama, T.; Beniya, Y.; Yamabe, S.; Inagaki, S., *Bull. Chem. Soc. Jpn.*, **1993**, *66*, 3430 - 3439. Frenking, G.; Köler, K. F.; Reetz, M. T., *Angew. Chem. Int. Ed. Engl.*, **1991**, *30*, 1146 - 1149.

13) These orbitals of the aromatic systems were selected according to the symmetry rule. In the case of ketone, the orbitals of the aromatic system were in an in-phase combination with a carbonyl π* orbital, and in the case of olefin or diene, the orbitals of the aromatic system were in an out-of-phase combination with an olefin or a diene π orbital. See reference 1.