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High Regio-, Chemo-, and Stereoselectivity via Low-Temperature 4 + 3 Cycloadditions. Convergent Synthesis of Multifunctionalized Vinylmetals (M = Si, Sn) and *S*-Vinyl Benzenecarbothioates

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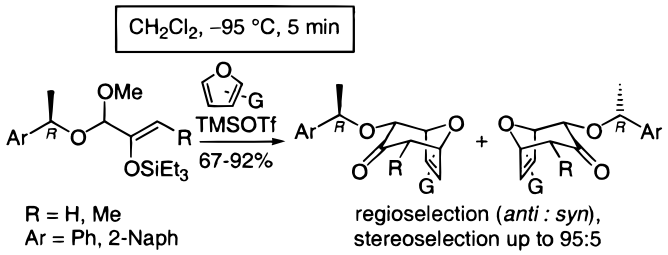
ABSTRACT



A series of enantiomerically pure 8-oxabicyclo[3.2.1]oct-6-en-3-ones functionalized in the unsaturated two-carbon bridge has been prepared by the title reaction. Carbocation reactivity has been fined-tuned at −95 °C and adjusted to diene nucleophilicity. Conventional electrophilic substitution of 3-silylated and 3-stannylated furan is suppressed in favor of the rapid 4 + 3 cycloaddition mode. In the case of cycloadduct 13A, stereoselectivity (17:1) is perfectly matched to regioselectivity (17:1). High stereoselection as well as unprecedented regioselection and chemoselection is attributed to the low-temperature cycloaddition protocol and the design of chiral auxiliary and tether.

8-Oxabicyclo[3.2.1]oct-6-en-3-ones are versatile templates in synthesis since they can be elaborated into substituted tetrahydropyrans and other useful derivatives that constitute important subunits in many bioactive natural products. We have presented applications of this concept targeting prominent polyoxygenated natural products such as lasonolide A,[1] phorboxazoles,[2] discodermolide,[2b] spongistatin,[3] dictyoxetanes,[4] mevinic acids,[5] and bryostatin.[6] Other recent efforts have been concerned with the synthesis of the phorbol skeleton,[7] polypropionate segments,[8] and highly functional-

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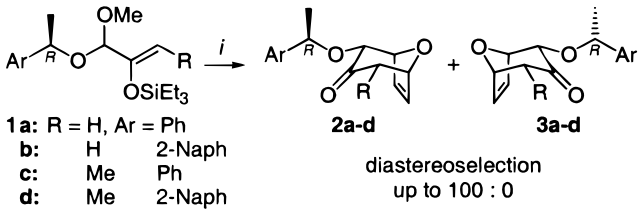
ized 5-8-5 ring systems.[9] A further chapter has been added by the synthesis of a wide variety of pseudo-C-glycosides.[10] Advances in asymmetric intermolecular 4 + 3 cycloaddition methodology have allowed us to prepare enantiopure oxabicycles.[11] In these and other cases, chiral auxiliaries function as asymmetric inductors.[12] Specifically, we have incorporated 1-phenylethyl and 1-(2-naphthyl)ethyl auxiliaries into acyclic mixed acetals **1a**−**d** (Scheme 1).

Scheme 1. Diastereoselective 4 + 3 Cycloaddition to Furan[a]

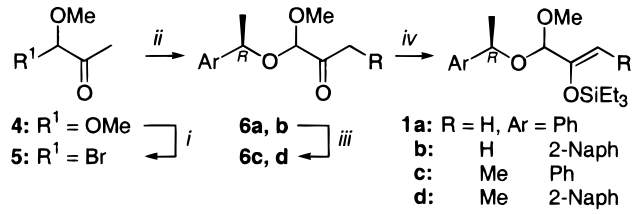


[a] (*i*) furan, DCM, TMSOTf, −95 °C, 5 min, 67−92%.

In contrast to stereoselection, control of regiochemistry for 3-substituted furans[13] and 2-substituted dienes, respectively, has not been possible.[14] Thus, rapid access to diverse chemodifferentiated oxabicyclic vinylic systems has been limited. Tolerance to various functionalities of the diene also needs to be extended.

Results and Discussion. The four chiral mixed acetals **1a**−**d** were synthesized according to Scheme 2. The aromatic

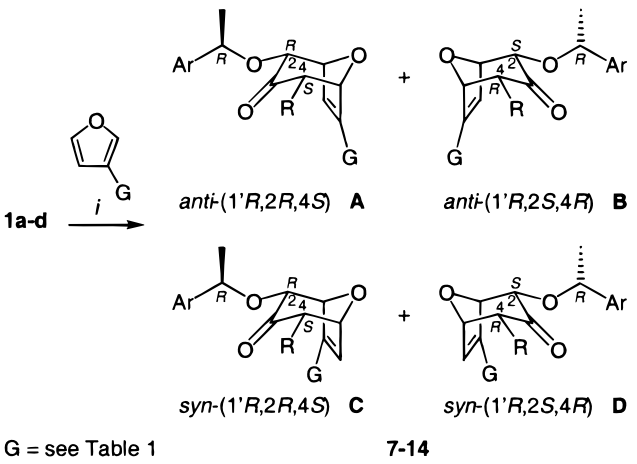
Scheme 2. Synthesis of Enol Ethers **1a**−**d**[a]



[a] (*i*) AcBr, neat, rt, 93%; (*ii*) *R*-ArCH(Me)OH, Et_2O, BuLi, −20 °C, then add **5** at −78 °C, 46% (80% borsm); (*iii*) 1. cyclohexylamine, Et_2O, $CaCl_2$, rt, 67−77%; 2. LDA, MeI, THF, −78 °C, 66%; (*iv*) LDA, TESCl, NEt_3, Et_2O, −78 °C, 76−88%.

moiety Ar was varied to evaluate its role in π-facial shielding during the cycloaddition.[11a]

Scheme 3. Four Possible Single Isomers **A**−**D** Expected from Cycloadditions to 3-Substituted Furans[a]



[a] (*i*) TMSOTf, DCM, −95 °C, 5 min.

Furans were synthesized according to literature procedures starting from 3-bromofuran and furan-3-carboxylic acid, respectively.[15] Functionalities were chosen so as to test compatibility with the cycloaddition procedure, to allow necessary postcycloaddition transformations, and on general grounds. Our focus was on heteroatoms such as silicon, tin, sulfur, and halogen (Scheme 3, Table 1).

Table 1

no.	R	Ar	G	cyclo-adducts (**A**−**D**)	diastereo-selectivity[a]	regio-selectivity[b] *anti*:*syn*	overall yield [%][c]
1	H	Ph	Br	**7**	7:1	10:1	50
2	Me	Ph	$SnBu_3$	**8**			>51[d]
3	H	Ph	$SiEt_3$	**9**	7:1	1.3:1	74
4	H	2-Naph	$SiEt_3$	**10**	6:1	1.3:1	73
5	H	Ph	SCOPh	**11**	1.2:1	6:1	79
6	H	2-Naph	SCOPh	**12**	1.5:1	6:1	74
7	**Me**	**Ph**	**SCOPh**	**13**	**17:1**	**17:1**	**75**
8	Me	2-Naph	SCOPh	**14**	13:1	14:1	75

[a] Diastereoselectivities refer to ratio (**A** + **C**):(**B** + **D**). [b] Regioselectivities refer to ratio (**A** + **B**):(**C** + **D**). [c] Overall yields refer to (**A** + **B** + **C** + **D**). [d] Isolated yield of cycloadduct **8A**. Other isomers could not be identified due to side products.

The cycloadditions were performed by simply dissolving both furan derivatives (1 equiv) and enol ethers **1a**−**d** (1

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(14) Rigby, J. H.; Pigge, F. C. *Org. React.* **1997**, *51*, 351.
(15) (a) 3-Silylfurans were synthesized according to Lukevics, E.; Gevorgyan, V. N.; Goldberg, Y. S.; Shymanska, M. V. *J. Organomet. Chem.* **1984**, *263*, 283. (b) 3-Stannylfurans were synthesized according to Bailey, T. R. *Synthesis* **1991**, 242. (c) 3-Thiofurans were synthesized according to Alvarez-Ibarra, C.; Quiroga, M. L.; Toledano, E. *Tetrahedron* **1996**, *52*, 4065.

equiv) in dry DCM. After cooling to −95 °C in a MeOH/liquid N_2 bath, catalytic trimethylsilyl triflate (less than 10 mol %) was added slowly and without interruption (method A). In some experiments it was found that the starting furan component had not entirely been consumed. In this case we added the enol ether (1.2 equiv) to a mixture of trimethylsilyl triflate (10 mol %) and furan component (1 equiv) in dry DCM at −95 °C (method B). Thus, better yields were obtained.

Remarkably, all reactions without exception were complete after the first sample for TLC was taken (less than 5 min). Further addition of either trimethylsilyl triflate or of one of the starting components gave no increase in yield. Workup and column chromatography provided enantiopure cycloadducts.[16] Side products resulting from electrophilic substitution, including *ipso* substitution, of the heteroatom-substituted furan were not detected or were formed only in neglible yield.

Dilution plays an important role: after initial experiments at a concentration of 0.1 M, all experiments were conducted at higher dilution (0.005 M). Selectivities remained unchanged, but yields increased by about 20% (Table 1).

Compatibility with functional groups such as stannyl (G = Bu_3Sn), silyl (G = Et_3Si), and bromine (G = Br) was high, and stable enantiopure oxabicyclic vinylic adducts were obtained. 3-(*tert*-Butyldimethylsilyl)furan (G = $SiBu^tMe_2$), however, gave only decomposed materials indicated early on by a yellow or light brown reaction solution. In all other experiments the mixture remained colorless. For silylated furan (G = $SiBu^tMe_2$), we assume that the steric bulk will obstruct approach of allyl cations in the preferred compact mode.

Given equatorial substituents in the three-carbon bridge and compact transition states, four possible single isomers, **A**, **B**, **C**, and **D**, can be envisaged in principle (Scheme 3 and Table 1). We were pleased to find that 3-thiobenzoylfuran (mp 49−50 °C)[15c] reacted cleanly. It was hoped that the cycloadducts were crystalline, and this proved to be the case. With simple acetal **1a** two major products were obtained. Rather than being regioisomers, they were *anti* adducts with *R* and *S* configuration at carbon C2 (**11A**:**11B** = 1.2:1). X-ray diffraction furnished the relative and also absolute configuration directly, without recourse to the chiral auxiliary (sulfur as heavy atom). Terminally methylated acetal **1c** and 3-thiobenzoylfuran reacted with high *anti*-selectivity (17:1) and perfectly matched stereoselectivity (17:1), giving **13A** (67% yield, X-ray crystal structure).[17] Three minor isomers **13B**−**D** were obtained in 8% yield altogether. The high regioselectivity observed for G = Br (10:1) and G = SCOPh (17:1) is unprecedented for intermolecular 4 + 3 cycloadditions to 3-substituted furans. The observed *anti*-orientation is in accord with a class B reaction[18] which passes through a short-lived cationic intermediate or transition state equivalent (Scheme 4).

Partial positive charge developing at carbon C3 is stabilized by bromonium resonance and especially thionium resonance. π-Facial discrimination[11a,c] is attributed to the W-configurated allyl cation intermediate which is rigidified by silicon−oxygen chelation and sandwiched by the aryl group of the chiral auxiliary and diene moiety (Scheme 5).[19]

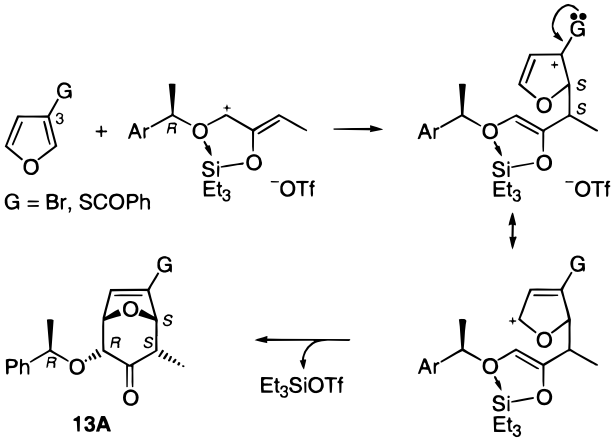
2,5- and 3,4-Disubstituted Furans. 3,4-Dibromofuran[20] showed a comparable, even slightly higher facial selectivity

(16) The chiral auxiliaries remain configurationally stable under the reaction conditions (ref 11c). Products are obtained as single isomers (ee > 98%). See also: X-ray crystal structure of cycloadducts **11A**, **11B**, and **13A** (Table 1).

(17) **Selected Spectroscopic Data. 4 + 3 Cycloaddition, Method A**. To a solution of furan component (1.0 equiv) and silyl enol ether (1.0 equiv) in DCM (0.005 M solution) was added TMSOTf (0.1 equiv) at −95 °C. After 5 min a saturated aqueous $NaHCO_3$ solution was added and the mixture was allowed to reach room temperature. The aqueous layer was extracted with DCM (3×), and the combined organic phase was dried ($MgSO_4$) and concentrated. The crude product was purified by column chromatography (silica gel, PE/MTBE). **Method B**. To a solution of furan component (1.0 equiv) in DCM (0.005 M solution) was added TMSOTf (0.1 equiv) at −95 °C. A solution of acetal component (1.2 equiv) in DCM (25 mL/mmol) was then added slowly. Workup after 5 min as described for method A. **Benzenecarbothioic Acid, *S*-[(1*S*,2*R*,5*S*)-3-Oxo-2-{(1*R*)-phenylethoxy}-8-oxabicyclo[3.2.1]oct-6-en-6-yl] Ester (11A) and Benzenecarbothioic Acid, *S*-[(1*R*,2*S*,5*R*)-3-Oxo-2-{(1*R*)-phenylethoxy}-8-oxabicyclo[3.2.1]oct-6-en-6-yl] Ester (11B).** Benzenecarbothioic acid *S*-(3-furanyl) ester (63 mg, 0.311 mmol) and silyl enol ether **1a** were allowed to react according to the general procedure (method B) to afford **11A** (43 mg, 37%) and **11B** (35 mg, 30%). Data for **11A**: crystalline solid, mp 105 °C, $[\alpha]^{25}_D = +31.2°$ (c = 1, $CHCl_3$); IR ($CHCl_3$) ν 3064, 3000, 2980, 2928, 2864, 1724, 1680, 1448, 1176, 1104, 896 cm^{-1}; ^1H NMR δ 8.00−7.25 (m, 10 H, Ar), 6.68 (d, J = 1.8 Hz, 1 H, H7), 5.35 (d, J = 5.0 Hz, 1 H, H5), 4.85 (q, J = 6.4 Hz, 1 H, H8), 4.81 (dd, J = 5.1, 1.8 Hz, 1 H, H1), 3.95 (d, J = 5.1 Hz, 1 H, H2), 2.68 (dd, J = 16, 5.0 Hz, 1 H, $H4_{ax}$), 2.55 (d, J = 16 Hz, 1 H, $H4_{eq}$), 1.51 (d, J = 6.4 Hz, 3 H, H9); ^{13}C NMR δ 205.22 (4°, C3), 188.42 (4°, C10), 143.05 (4°, C6), 136.29 (3°, C7), 136.08, 135.60 (4°, Ar), 134.17, 128.90, 128.72, 128.09, 127.76, 126.44 (3°, Ar), 81.36, 80.83, 79.66, 79.51 (3°, C1, C2, C5, C8), 44.91 (2°, C4), 24.11 (1°, C9); MS (120 °C) m/z 276 (5), 195 (1), 153 (5), 138 (9), 123 (1), 105 (100), 77 (14); HRMS calcd for $C_{14}H_{12}O_4S$ 276.0456, found 276.0455. Crystal structure analysis: $C_{22}H_{20}O_4S$, M = 380.46, monoclinic, space group $P2_1$ (No. 4), a = 6.342(1), b = 7.256(1), and c = 20.630(2) Å, α = 90°, β = 91.48(1)°, γ = 90°, V = 949.0(2) $Å^3$, Z = 2, ρ_{calcd} = 1.332 g cm^{-3}, F(000) = 400, crystal size 0.54 × 0.66 × 0.20 mm, T = 300 K, μ(Mo Kα) = 2.0 cm^{-1}. Data for **11B**: crystalline solid, mp 105−110 °C, $[\alpha]^{25}_D = +90.1°$ (c = 1, $CHCl_3$); IR ($CHCl_3$) ν 3064, 3000, 2980, 2928, 2872, 1728, 1680, 1448, 1176, 1100, 900 cm^{-1}; ^1H NMR δ 8.0−7.25 (m, 10 H, Ar), 6.71 (d, J = 1.9 Hz, 1 H, H7), 5.43 (dd, J = 4.4, 1.4 Hz, 1 H, H5), 5.19 (dd, J = 4.9, 1.9 Hz, 1 H, H1), 4.78 (q, J = 6.4 Hz, 1 H, H8), 4.10 (d, J = 4.9 Hz, 1 H, H2), 2.65 (dd, J = 16, 4.5 Hz, 1 H, $H4_{ax}$), 2.53 (dd, J = 16, 1.4 Hz, 1 H, $H4_{eq}$), 1.52 (d, J = 6.4 Hz, 3 H, H9); ^{13}C NMR δ 202.38 (4°, C3), 188.34 (4°, C10), 142.31 (4°, C6), 136.08 (3°, C7), 136.01, 135.86 (4°, Ar), 134.19, 128.91, 128.57, 127.92, 127.59, 126.40 (3°, Ar), 81.25, 79.58, 79.40, 77.40 (3°, C1, C2, C5, C8), 44.75 (2°, C4), 23.69 (1°, C9); MS (140 °C) m/z 279 (1), 276 (2), 219 (1), 167 (2), 149 (6), 138 (3), 105 (100), 77 (9); HRMS calcd for $C_{14}H_{12}O_4S$ 276.0456, found 276.0445. Crystal structure analysis: $C_{22}H_{20}O_4S$, M = 380.46, monoclinic, space group $P2_1$ (No. 4), a = 10.547(1), b = 8.792(1), and c = 11.535(2) Å, α = 90°, β = 115.88(1)°, γ = 90°, V = 962.4(2) $Å^3$, Z = 2, ρ_{calcd} = 1.313 g cm^{-3}, F(000) = 400, crystal size 0.44 × 0.74 × 1.2 mm, T = 300 K, μ(Mo Kα) = 1.9 cm^{-1}. **(1*S*,2*R*,5*S*)-Benzenecarbothioic Acid, *S*-[4-Methyl-3-oxo-2-{(1*R*)-phenylethoxy}-8-oxabicyclo[3.2.1]oct-6-en-6-yl] Ester (13 A)**. Benzenecarbothioic acid *S*-(3-furanyl) ester (60 mg, 0.29 mmol) and silyl enol ether **1a** were allowed to react according to the general procedure (method B) to afford **13A** (78 mg, 67%), colorless solid, mp 70 °C, $[\alpha]^{25}_D = +104.7°$ (c = 1, $CHCl_3$); IR ($CHCl_3$) ν 3064, 2980, 2932, 2876, 1724, 1676, 1448, 1228, 1176, 1132, 1084, 904, 880 cm^{-1}; ^1H NMR δ 8.00−7.20 (m, 10 H, Ar), 6.75 (d, J = 2.0 Hz, 1 H, H7), 5.24 (d, J = 4.5 Hz, 1 H, H5), 4.82 (dd, J = 5.1, 2.0 Hz, 1 H, H1), 4.81 (q, J = 6.5 Hz, 1 H, H9), 4.02 (dd, J = 5.1, 0.6 Hz, 1 H, H2), 2.86 (ddq, J = 7.2, 4.5, 0.6 Hz, 1 H, H4), 1.51 (d, J = 6.5 Hz, 3 H, H10), 1.10 (d, J = 7.2 Hz, 3 H, H8); ^{13}C NMR δ 206.73 (4°, C3), 188.24 (4°, C11), 143.13 (4°, C6), 137.75 (3°, C7), 136.21, 134.51 (4°, Ar), 134.08, 128.89, 128.70, 128.02, 127.50, 126.40 (3°, Ar), 83.64, 81.59, 81.45, 79.22 (3°, C1, C2, C5, C9), 50.55 (2°, C4), 24.12 (1°, C10), 9.15 (1°, C8); MS (120 °C) m/z 290 (3), 271 (1), 232 (1), 204 (2), 167 (7), 152 (13), 139 (2), 105 (100), 91 (2), 77 (16); HRMS calcd for $C_{15}H_{14}O_4S$ 290.0613, found 290.0615. Crystal structure analysis: $C_{23}H_{22}O_4S$, M = 394.49, monoclinic, space group $P2_1$ (No. 4), a = 7.397(2), b = 6.217(2), and c = 22.032(5) Å, α = 90°, β = 96.68(2)°, γ = 90°, V = 1006.3(5) $Å^3$, Z = 2, ρ_{calcd} = 1.302 g cm^{-3}, F(000) = 416, crystal size 0.37 × 0.28 × 0.04 mm, T = 300 K, μ(Mo Kα) = 1.9 cm^{-1}.

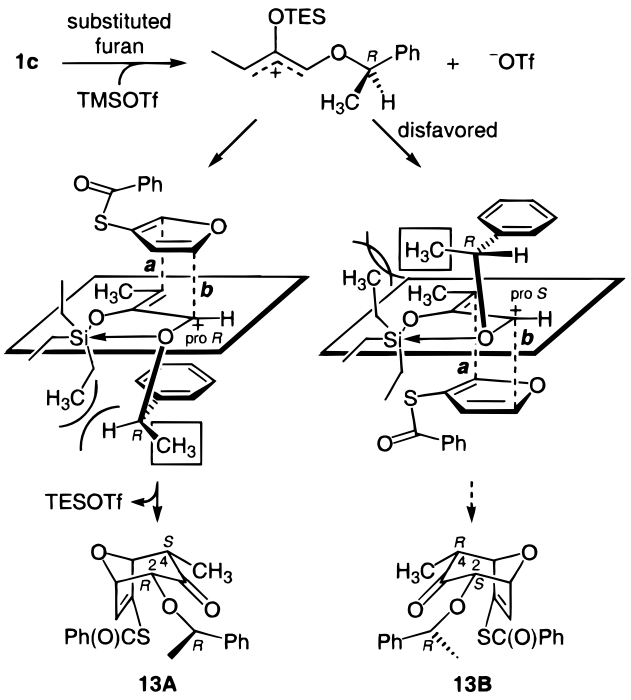
(18) Hoffmann, H. M. R. *Angew. Chem.* **1984**, *96*, 29; *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1.

Scheme 4. 4 + 3 Cycloaddition via a Short-Lived Cationic Intermediate or Transition State Equivalent (Class B).[18] Simplified Model for Regioselection

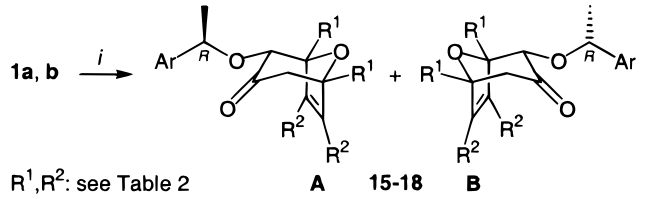


than that of the parent furan, albeit in diminished yield. 2,5-Dimethylfuran reacted with a drastic drop in stereoselection. It is assumed that the two methyl groups on the emerging bridgeheads prevent optimum π-stacking of allyl and diene components in the transition state. The nature of the aromatic moiety of the chiral auxiliary seems to play a minor role in this case (Scheme 6 and Table 2).

Scheme 5. Proposed Models of Diastereomeric Transition States (***a***, Short Bond; ***b***, Long Bond)[19]



Scheme 6. . 4 + 3 Cycloadditions to Symmetrically Substituted Furans[a]



[a] (*i*) 2,5- or 3,4-substituted furan, TMSOTf, DCM, −95 °C, 5 min.

Table 2

no.	R^1	R^2	Ar	cycloadducts **A**, **B**	diastereo-selectivity	overall yield [%]
1	H	Br	Ph	**15**	17:1	50
2	H	Br	2-Naph	**16**	16:1	49
3[a]	Me	H	Ph	**17**	1.2:1	49
4	Me	H	2-Naph	**18**	1.5:1	47

[a] Pierau, S. Ph.D. Thesis, Hannover, 1998.

In conclusion, the design, generation, and intermolecular capture of chiral allyl cations at −95 °C in solvent dichloromethane on a practical scale[11] represents a breakthrough of preparative carbocation chemistry. Experimental conditions are unusually mild, and the diverse selectivities now established, especially regioselectivity and chemoselectivity, are unprecedented.

Acknowledgment. We thank Sabine Pierau for experimental contributions and helpful discussion, the Land of Lower Saxony GradföG for a Ph.D. fellowship (H.B.), U. Eggert for her help, and Dr. Wartchow for X-ray crystal work.

Supporting Information Available: Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) In our model the tether of allyl cation and aryl group facilitates π-stacking and thus *enhances selectivity*. Replacement of the methyl group (box) by a simple hydrogen generates a more floppy ensemble of reactants and causes not only loss of stereoselection as expected (racemic mixture of cycloadducts) but also collapse of regioselectivity (*anti:syn* = 1.1:1)!

(20) 3,4-Dibromofuran was synthesized according to: Gorzynski, M.; Rewicki, D. *Liebigs Ann. Chem.* **1986**, 625.