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Face Selectivity in the 1,3-Dipolar Cycloaddition Reactions of Benzonitrile Oxide with 5-Substituted Adamantane-2-thiones and 2-Methyleneadamantanes[†]

Wen-Sheng Chung,*[,‡] Tzong-Liang Tsai,[‡] Chia-Chin Ho,[‡] M. Y. N. Chiang,[§] and
W. J. le Noble[⊥]

Department of Applied Chemistry, National Chiao Tung University, Hsinchu, Taiwan 30050, Republic of China, Department of Chemistry, National Sun Yat-Sen University, Kaohsiung, Taiwan 804, Republic of China, and Department of Chemistry, State University of New York, Stony Brook, New York 11794

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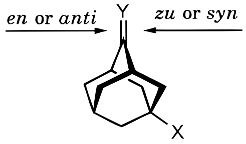
The 1,3-dipolar cycloaddition reactions of benzonitrile oxide with 5-substituted adamantane-2-thiones (**2**-**X**) and 2-methyleneadamantanes (**3**-**X**) produced two geometrically isomeric Δ^2-1,4,2−oxathiazolines (**5**-**X**s) and two Δ^2-isoxazolines (**6**-**X**s), respectively. The substituent was varied from fluoro, chloro, bromo, to phenyl. X-ray single-crystal analysis confirmed the configuration of (*Z*)-**5**-**F**. The product formation bias resulting from the favored attack of nitrile oxide on the *zu*-face is discussed in terms of transition-state hyperconjugation and frontier molecular orbital theory.

1,3-Dipolar cycloadditions offer a convenient one-step route for the construction of a variety of complex five-membered heterocycles that are synthetically useful compounds.[1] Nitrile oxide cycloadditions to terminal alkenes proceeded regioselectively to give 5-substituted Δ^2-isoxazolines as single products.[1b] The cycloaddition of nitrones and nitrile oxides to thiones leading to Δ^2-1,4,2-oxathiazolidines and Δ^2-1,4,2-oxathiazolines, respectively, have also drawn much attention recently.[2] Because of their extremely high reactivity toward 1,3-dipoles, thiones have been called *superdipolarophiles* by Huisgen.[2a,b]

5-Substituted adamantan-2-ones **1**-**X** and their derivatives have proven to be useful probes in research aimed at understanding the electronic factors in face selection.[3] Studies by le Noble *et al.*[3a] of a variety of reactions indicate that the reagent prefers to attack the face that is antiperiplanar to the more electron-rich vicinal bonds (*zu* and *en* face preference in **1** when **X** equals an electron-withdrawing and electron-donating group, respectively). Their results have been reconciled with Cieplak's transition-state hyperconjugation model.[4]



1–X, Y = O, X = F, Cl, Br and Ph
2–X, Y = S, X = F, Cl and Br
3–X, Y = CH$_2$, X = F, Cl, Br and Ph

The Diels−Alder reaction of 2,3-dimethylbuta-1,3-diene with 5-fluoroadamantane-2-thione (**2**-**F**) has been reported to follow Cieplak's prediction.[5] When frontier molecular orbital (FMO) theory is applied to this Diels−Alder reaction, the diene functions as the donor, and the reaction is controlled by the HOMO (diene)−LUMO (dienophile) interaction. In other words, this is a *normal* Diels−Alder-type reaction.[1a,2d,6] On the other hand, 1,3-dipolar cycloadditions of benzonitrile oxide with thiones **2**, or terminal alkenes **3**, are controlled mainly by the LUMO (dipole)−HOMO (dipolarophile) interaction (an *inverse* electron-demand type of reaction). Thus, 1,3-dipolar cycloaddition reactions to **2** and **3** provide an important test of the transition-state hyperconjugation model because Cieplak's model stresses that, regardless of the type of reaction (nucleophilic, electrophilic, radical addition, etc.), the newly developing σ^* orbital should attract electron density with the same directional preference provided the transition states are electron deficient.[3a,4c] We report here our study of the 1,3-dipolar cycloaddition reactions of benzonitrile oxide with 5-substituted adamantane-2-thiones (**2**-**X**) and 2-methyleneadamantanes (**3**-**X**). We find that the favored approach is indeed *syn* as predicted, in all instances.

Results and Discussion

The reaction of thione **2**-**F** with benzonitrile oxide generated *in situ* from benzohydroximoyl chloride (**4**) and

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[‡] National Chiao Tung University.

[§] National Sun Yat-Sen University.

[⊥] State University of New York.

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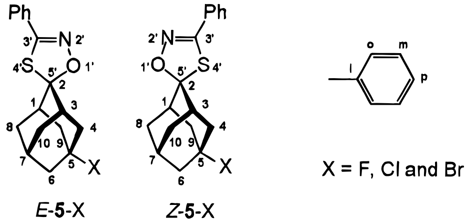
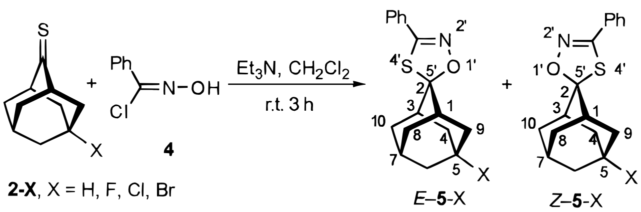
Table 1. Calculated[a] and Observed[b] ^{13}C Chemical Shifts of 5-Substituted 3′-Phenyladamantane-2-spiro-5′-(1′,4′,2′-oxathiazolines)



	5-H	(*E*)-5-F	(*Z*)-5-F	(*E*)-5-Cl	(*Z*)-5-Cl	(*E*)-5-Br	(*Z*)-5-Br
C_1, C_3	39.34	42.02 (42.44) $J = 9.2$	41.75 (42.44) $J = 9.2$	42.11 (42.44)	41.98 (42.44)	42.79 (43.34)	42.74 (43.34)
C_2	112.28	109.39 (110.48)	109.93 (110.48)	109.28 (109.98)	109.67 (109.98)	109.17 (109.98)	109.49 (109.98)
C_4, C_9	37.27	38.31 (38.58) $J = 20.2$	41.49 (42.27) $J = 20.2$	43.04 (43.28)	46.54 (46.97)	44.74 (45.08)	48.00 (47.77)
C_5	26.83	90.09 (89.90) $J = 186.8$	90.54 (90.63) $J = 185.0$	64.84 (65.90)	65.08 (66.63)	61.00 (64.10)	61.00 (64.83)
C_6	37.01	42.19 (42.01) $J = 16.5$	42.24 (42.01) $J = 16.5$	47.01 (46.71)	47.01 (46.71)	48.46 (48.51)	48.46 (48.51)
C_7	26.10	29.78 (29.93) $J = 9.2$	29.13 (29.20) $J = 9.2$	29.91 (29.93)	29.29 (29.20)	30.64 (30.83)	30.06 (30.10)
C_8, C_{10}	33.58	35.65 (35.47)	32.10 (31.78)	35.36 (34.97)	31.79 (31.28)	35.29 (34.97)	31.73 (31.28)
$C_{3'}$	156.40	156.21	156.01	156.24	156.48	156.19	156.42
C_i	128.89	128.46	128.46	128.44	128.44	128.39	128.39
C_o	128.58	128.70	128.72	128.70	128.70	128.69	128.69
C_m	127.58	127.63	127.68	127.65	127.65	127.63	127.63
C_p	130.62	130.91	130.96	130.93	130.93	130.93	130.93

[a] Calculated values are in parentheses. [b] Measured with a Varian Unity 300 NMR spectrometer operated at 75.4 MHz and reported in δ units, $CDCl_3$ (δ 77.00). *J* is in Hz. In the parent compound **5-H**, the sulfur is understood to be *syn* to C_8 and C_{10}.

Scheme 1



X = F 69:31 (82%)
X = Cl 65:35 (78%)
X = Br 61:39 (75%)

triethylamine in methylene chloride occurs smoothly at room temperature to give a 69:31 (GC ratio) mixture of *E*- and *Z*- adducts **5-F** in 82% yield after chromatography (Scheme 1). Both adducts are stable to the reaction conditions, and they are characterized as 5-fluoro-3′-phenyladamantane-2-spiro-5′-(Δ^2-1′,4′,2′-oxathiazolines) on the basis of their mass and NMR spectroscopy.[7] In all instances examined (X = F, Cl, Br), the major isomer was (*E*)-**5-X**, which results from *syn* attack of the nitrile oxide on **2-X** (see Scheme 1). The configurational assignment of the epimers **5-X** was based on the relative shielding power of oxygen *vs* sulfur directly "above" the flanking methylene groups. The *shielding effect* of an oxygen atom on these CH bonds in a series of spirocyanooxetanes[8] was found to be 1.59 ± 0.17 ppm when the **1-X** substituent was fluoro, chloro, bromo, or phenyl. On the other hand, a sulfur atom was found to have a *deshielding effect* of 0.6 ppm in 5-fluorospiro[adamantane-2,2′-thiocyclohex-4′-ene]. Thus, C-4 and C-9 (identified by their ^{19}F coupling), which are syn to the oxygen in the parent compound **5-H**, are determined to be shielded *vs* C-8 and C-10 by a margin of ≥2.2 ppm. Moreover, application of the ^{13}C NMR additivity scheme[9] to the oxathiazolines furthermore led to carbon resonances correctly predicted to be within ±0.4 ppm if the major product is assumed to have the *E*-configuration, whereas deviations of several ppm are found when the opposite assumption is used (Table 1). Finally, the configuration of (*Z*)-**5-F** was established independently by means of an X-ray structural determination (see Figure 1).[7]

The reaction of benzonitrile oxide with 5-substituted methyleneadamantanes **3-X** was sluggish at room temperature but was accelerated by refluxing in THF for 24 h to give two isoxazolines **6-X**s in 72−88% isolated yield (see Scheme 2). Again, these products were proven to be stable under the reaction conditions; *i.e.*, both products are formed in kinetically controlled processes. In all instances examined (where X = F, Cl, Br, and Ph), the major isomer (~60:40 ratio as determined by both GC and ^{1}H NMR integration) has the *Z* configuration. It should be noted that the major product (*Z*)-**6-X** is still derived from *syn* attack of the nitrile oxide on **3-X**. Strong NOE of the 4'-methylene hydrogens and the flanking pair at C-8 and C-10, but not at C-4 and C-9, confirmed the configuration of the major isomer to be (*Z*)-**6-X**. No traces of the regioisomers **7-X** or **8-X** were detected in the reactions of **2-X** or **3-X** with benzonitrile oxide, which is consistent with a previous observation of thione **2-H**.[2d] Thus, the 1,3-dipolar cycloaddition reactions of adamantanethiones **2-X** and methyleneadaman-

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(7) All compounds mentioned in this paper have been completely characterized; see the Experimental Section. The final structural assignment of oxathiazolines was not straightforward. We were initially misled by the X-ray crystal structure of (*Z*)-**5-Br**, which crystallized from a 95:5 mixture of (*E*)-:(*Z*)-**5-Br** (due to poor separation). Fortunately, (*Z*)-**5-F** can be separated in pure form by means of column chromatography, and this finally revealed the fact that only the *Z*-form of oxathiazoline produced single crystals.

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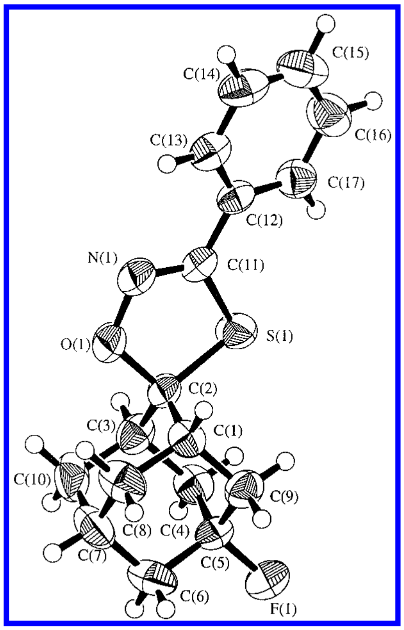
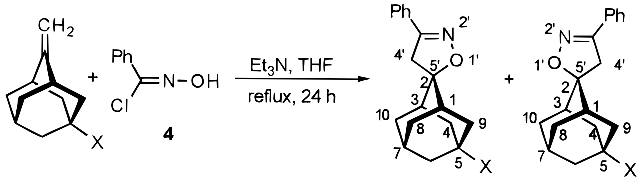


Figure 1. ORTEP drawing of oxathiazoline *Z*-**5**-**F**.

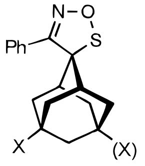
Scheme 2



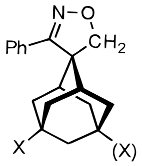
3-**X**, X = F, Cl, Br and Ph **4** *Z*-**6**-**X** *E*-**6**-**X**

X = F	60:40	(72%)
X = Cl	61:39	(81%)
X = Br	56:44	(76%)
X = Ph	56:44	(88%)

tanes **3**-**X** with benzonitrile oxide are regiospecific. This is probably due to the steric interaction between the phenyl group and the bulky adamantyl group of **2** or **3** in the transition state.



7-**X**



8-**X**

An attempt to react nitrile oxide with adamantanone **1**-**H** was unsuccessful even at high temperature and with a long reaction time. Kinetic studies[2a,b] of 1,3-dipolar additions of nitrones to thiones revealed that the weakness of the C=S π bond was not responsible for the high reaction rates; instead, the low HOMO–LUMO energy gap of the C=S π bond was suggested to be the decisive factor. AM1 calculations[10] of the HOMO–LUMO energy of **1**–**3** reveal that all of the 1,3-dipolar reactions described here are LUMO (dipole)–HOMO (dipolarophile) controlled reactions, and the rates diminish in the order $k(C{=}S) > k(C{=}CH_2) >> k(C{=}O)$. The 1,3-dipolar cycloaddition reaction of thione **2**-**F** with benzonitrile oxide was also carried out in solvents with increasing polarity; they were varied from *n*-hexane ($E_T = 30.9$) to methanol ($E_T = 55.5$) to water ($E_T = 63$). In all (14) solvents studied ($E_T = 30.9$–63), the face selectivity was hardly affected; *i.e.*, they all fall in the range of 64 ± 4% in favor of (*E*)-**5**-**F**. The results argue against the involvement of zwitterionic intermediates in the reaction pathways and favor a concerted mechanism for the 1,3-dipolar cycloaddition reaction.

The present study provides strong support for the Cieplak transition-state hyperconjugation model: while the dipolarophiles **1**–**3** behave as electron donors in an inverse electron-demand-type 1,3-dipolar addition, the dienophiles **2** and **3** behave as electron acceptors in a normal Diels–Alder reaction. Nevertheless, *both* the diene (in a Diels–Alder reaction) and the dipole (in a 1,3-dipolar cycloaddition) approach the trigonal carbon from the same direction antiparallel to the most electron-rich bonds. Although the involvement of electrostatic effects in face-selectivity is not excluded, claims to that effect have relied mainly on calculations.[3b,c] *Ab initio* and semiempirical calculations of the transition states for 1,3-dipolar cycloaddition reactions of 5-substituted adamantane-2-thiones and 2-methyleneadamantanes are now in progress and will be reported in due course.[10] We are presently studying the electronic effect of *para*-substituted phenylnitrile oxides in 1,3-dipolar cycloaddition reactions.

Experimental Section

General Procedure for the Synthesis of 5-Substituted 3′-Phenyladamantane-2-spiro-5′-(1′,4′,2′-oxathiazolines) 5-X. All 5-substituted 3′-phenyladamantane-2-spiro-5′-(1′,4′,2′-oxathiazolines) were prepared from the corresponding adamantane-2-thiones **2**-**X** with a standard procedure[2d] described below for the fluoro derivative (**X** = F). Triethylamine 0.124g (1.22 mmol) was added gradually at 0 °C to a stirred solution of **2**-**F** (0.15g, 0.82 mmol) and benzohydroximoyl chloride (0.19g, 1.22 mmol) in 10 mL of dry dichloromethane. After being stirred for 3 h at rt, the mixture was poured into 15 mL of water. Following removal of the organic solvent, the solid residue was purified on a silica gel column by elution with *n*-hexane/dichloromethane gradient to give two isomeric adducts (*E*)- and (*Z*)-**5**-**F**. The isolated yields based on converted starting materials are as follows: **5**-**F** 82%, **5**-**Cl** 78%, and **5**-**Br** 75%. For all ^{13}C NMR spectra data, see Table 1; all ^{1}H NMR spectra were measured at 300 MHz in $CDCl_3$.

(*E*)-**5**-**F**: colorless solid; mp 91.5–92.5 °C; δ_H 1.72–2.0 (m, 8 H), 2.0–2.3 (m, 1 H), 2.4–2.6 (bs, 2 H), 2.7 (bs, 2 H), 7.3–7.5 (m, 3 H), 7.6–7.7 (m, 2 H); MS (EI, *m/z*) 303 (M^+, 81), 184 (59), 168 (11), 135 (100), 91 (18), 79 (16); HRMS calcd for $C_{17}H_{18}ONSF$ 303.1094, found 303.1095.

(*Z*)-**5**-**F**: colorless solid; mp 82.5–83 °C; δ_H 1.5–1.7 (m, 2 H), 1.9–2.2 (m, 6 H), 2.2–2.4 (m, 3 H), 2.65 (bs, 2 H), 7.3–7.5 (m, 3 H), 7.6–7.7 (m, 2 H); MS (EI, *m/z*) 303 (M^+, 56), 184 (29), 168 (9), 135 (100), 91 (8), 79 (8); HRMS calcd for $C_{17}H_{18}ONSF$ 303.1094, found 303.1089.

(*E*)-**5**-**Cl**: colorless solid; mp 147–148 °C; δ_H 1.75–2.2 (m, 9 H), 2.62 (bs, 2 H), 2.65–2.80 (m, 2 H), 2.65 (bs, 2 H), 7.3–7.5 (m, 3 H), 7.60–7.75 (m, 2 H); MS (EI, *m/z*) 321 ($M^+ + 2$, 13), 319 (M^+, 33), 200 (26), 184 (8), 135 (100), 91 (14), 79 (17); HRMS calcd for $C_{17}H_{18}ONSCl$ 319.0799, found 319.0789. Anal. Calcd for $C_{17}H_{18}ONSCl$: C, 63.84; H, 5.67; N, 4.38; S, 10.03. Found: C, 64.02; H, 5.6; N, 4.43; S, 10.12.

(*Z*)-**5**-**Cl** could not be isolated; however, the ^{13}C and GC–MS spectra can be obtained from the (*E*) and (*Z*)-**5**-**Cl** mixture: MS (EI, *m/z*) 321 ($M^+ + 2$, 5), 319 (M^+, 14), 200 (19), 184 (13), 135 (100), 91 (29), 79 (40).

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[10] The HOMO energies for the dipolarophiles are as follows: **2** = −8.49 eV; **3** = −9.60 eV; **1** = −10.02 eV. Details of the energy and coefficient for frontier orbitals obtained by means of AM1 calculations will be published in a later paper. We thank Prof. J.-H. Yu of NTHU for the calculations.

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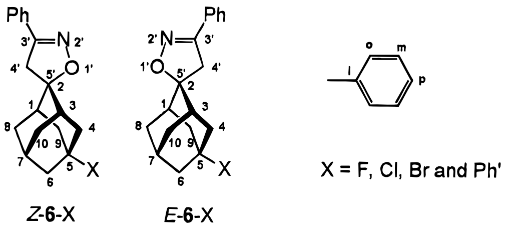
Table 2. Calculated[a] and Observed[b] ^{13}C Chemical Shifts of 5-Substituted 3′-Phenyl-4′-hydrospiro(adamantane-2:5′-Δ^2-isoxazolines)



	6-H	(*Z*)-**6-F**	(*E*)-**6-F**	(*Z*)-**6-Cl**	(*E*)-**6-Cl**	(*Z*)-**6-Br**	(*E*)-**6-Br**	(*Z*)-**6-Ph**	(*E*)-**6-Ph**
C_1, C_3	36.90	39.86 (40.00) $J = 10.5$	39.30 (40.00) $J = 10.1$	39.96 (39.00)	39.71 (39.00)	40.72 (40.90)	40.56 (40.90)	37.56 (37.50)	37.41 (37.50)
C_2	91.39	89.19 (89.59)	89.53 (89.59)	88.94 (89.09)	89.24 (89.09)	88.86 (89.09)	89.10 (89.09)	90.42 (90.49)	90.75 (90.49)
C_4, C_9	33.25	38.24 (38.25) $J = 19.0$	40.04 (40.57) $J = 18.9$	43.01 (42.95)	45.21 (45.27)	44.49 (44.75)	46.73 (47.07)	38.90 (38.64)	40.91 (40.97)
C_5	26.49	90.96 (90.29) $J = 184.3$	91.06 (90.68) $J = 184.4$	66.10 (66.29)	66.11 (66.68)	62.78 (64.49)	62.64 (64.88)	34.94 (34.19)	35.37 (34.58)
C_6	37.25	42.34 (42.25) $J = 17.9$	42.41 (42.25) $J = 16.7$	47.23 (46.95)	47.30 (46.95)	48.74 (48.75)	48.80 (48.75)	42.38 (42.75)	43.21 (42.75)
C_7	26.88	29.78 (29.98) $J = 9.9$	29.39 (29.59) $J = 9.7$	29.97 (28.98)	29.70 (28.59)	30.75 (30.88)	30.54 (30.48)	27.50 (27.48)	27.12 (27.09)
C_8, C_{10}	35.57	33.92 (33.77) $J = 1.7$	31.70 (31.45) $J = 1.8$	33.66 (33.27)	31.41 (30.95)	33.63 (33.27)	31.38 (30.95)	34.75 (34.69)	32.41 (32.35)
$C_{3'}$	156.07	156.01	156.16	156.03	156.14	156.02	156.12	156.13	156.13
$C_{4'}$	43.84	43.04	44.11	43.12	44.06	43.22	44.04	43.45	43.93
C_i	130.41	129.92	129.91	129.94	129.91	129.92	129.88	130.30	130.27
C_o	128.58	128.67	128.68	128.68	128.70	126.68	128.70	128.64	128.64
C_m	126.31	126.35	126.36	126.36	126.38	126.36	126.38	126.36	126.34
C_p	129.64	129.92	129.95	129.94	129.97	129.98	129.98	129.76	129.76
$C_{i'}$								149.97	149.48
$C_{o'}$								124.94	124.79
$C_{m'}$								128.16	128.28
$C_{p'}$								125.74	125.95

[a] Calculated values are in parentheses. [b] Measured by means of a Bruker DRX-300 NMR spectrometer operating at 75.4 MHz and reported in δ units, $CDCl_3$ (δ 77.00). *J* is in Hz. In the parent compound **6-H**, the oxygen is understood to be *syn* to C_4 and C_9.

(*E*)-**5-Br**: colorless solid; mp 181−182 °C; δ_H 1.8−2.0 (m, 4 H), 2.12 (bs, 1 H), 2.15−2.30 (m, 2 H), 2.38 (bs, 2 H), 2.58 (bs, 2 H), 2.85−3.00 (m, 2 H), 7.3−7.5 (m, 3 H), 7.60−7.75 (m, 2 H); MS (EI, *m/z*) 365 ($M^+ + 2$, 53), 363 (M^+, 51), 246 ($M^+ + 2 - PhCNO$, 22), 244 ($M^+ - PhCNO$, 21), 165 (40), 135 (100), 91 (28), 79 (36); HRMS calcd for $C_{17}H_{18}ONS^{79}Br$ 363.0293, found 363.0291. Anal. Calcd for $C_{17}H_{18}ONSBr$: C, 56.05; H, 4.98; N, 3.85. Found: C, 56.02; H, 4.85; N, 3.87.

(*Z*)-**5-Br**: colorless solid; mp 158−158.5 °C; δ_H 1.65−1.75 (m, 2 H), 2.10 (bs, 1 H), 2.3−2.6 (m, 10 H), 7.35−7.50 (m, 3 H), 7.65−7.70 (m, 2 H); MS (EI, *m/z*) 365 ($M^+ + 2$, 27), 363 (M^+, 26), 246 ($M^+ + 2 - PhCNO$, 9), 244 ($M^+ - PhCNO$, 9), 165 (17), 135 (100), 91 (13), 79 (18); HRMS calcd for $C_{17}H_{18}ONS^{79}Br$ 363.0293, found 363.0297.

General Procedure for the Synthesis of 5-Substituted 3′-Phenyl-4′-hydrospiro[adamantane-2:5′-Δ^2-isoxazolines] 6-X. (*E*)- and (*Z*)-**6-X** were synthesized by the use of a procedure similar to that of Zwanenburg *et al.*[12] An excess of triethylamine (1.5 mol equiv) was added to a well-stirred solution of the methyleneadamantanes **3-X** (100 mg) and benzohydroximoyl chloride (1.5 mol equiv) in anhydrous THF (10 mL). The mixture was stirred at reflux for 24 h, diluted with dichloromethane, washed with water, and dried with $MgSO_4$. After filtration and solvent evaporation, the residue was purified on a silica gel column with *n*-hexane/dichloromethane to give two isomeric adducts (*E*)- and (*Z*)-**6-X**. The isolated yields based on converted starting materials are as follows: **6-F** 72%, **6-Cl** 81%, **6-Br** 76%, and **6-Ph** 88%. For all ^{13}C NMR spectra data see Table 2.

(*Z*)-**6-F**: colorless solid; mp 91−93 °C; δ_H 1.62−1.85 (m, 6 H), 1.94 (bs, 2 H), 2.17 (bs, 3 H), 2.45−2.60 (m, 2 H), 3.17 (s, 2 H), 7.35−7.55 (m, 3 H), 7.55−7.72 (m, 2 H); MS (EI, *m/z*) 285 (M^+, 100), 268 (65), 117 ($M^+ - C_{10}H_{13}OF$, 31), 91 (20), 77 (40); HRMS calcd for $C_{18}H_{20}ONF$ 285.1530, found 285.1529. Anal. Calcd for $C_{18}H_{20}ONF$: C, 75.76; H, 7.06; N, 4.91. Found: C, 75.52; H, 6.93; N, 5.03.

(*E*)-**6-F**: colorless solid; mp 142−143 °C; δ_H 1.52 (bs, 1 H), 1.56 (bs, 1 H), 1.88−2.10 (m, 6 H), 2.15−2.35 (m, 5 H), 3.21 (s, 2 H), 7.32−7.50 (m, 3 H), 7.60−7.75 (m, 2 H); MS (EI, *m/z*) 285 (M^+, 100), 268 (38), 117 ($M^+ - C_{10}H_{13}OF$, 33), 91 (12), 77 (28); HRMS calcd for $C_{18}H_{20}ONF$ 285.1530, found 285.1523. Anal. Calcd for $C_{18}H_{20}ONF$: C, 75.76; H, 7.06; N, 4.91. Found: C, 75.55; H, 7.03; N, 5.09.

(*Z*)-**6-Cl**: colorless solid; mp 146−147 °C; δ_H 1.65−1.90 (m, 4 H), 1.99 (bs, 1 H), 2.03 (bs, 1 H), 2.05−2.25 (m, 5 H), 2.71 (bs, 1 H), 2.75 (bs, 1 H), 3.16 (s, 2 H), 7.35−7.45 (m, 3 H), 7.60−7.75 (m, 2 H); MS (EI, *m/z*) 303 ($M^+ + 2$, 32), 301 (M^+, 100), 286 (15), 284 (44), 266 ($M^+ - {}^{35}Cl$, 7), 117 (40), 91 (58), 77 (92); HRMS calcd for $C_{18}H_{20}ON^{35}Cl$ 301.1235, found 301.1237. Anal. Calcd for $C_{18}H_{20}ONCl$: C, 71.63; H, 6.68; N, 4.64. Found: C, 71.54; H, 6.64; N, 4.69.

(*E*)-**6-Cl**: colorless solid; mp 122−123 °C; δ_H 1.62 (bs, 1 H), 2.10−2.35 (m, 12 H), 3.22 (s, 2 H), 7.35−7.45 (m, 3 H), 7.60−7.70 (m, 2 H); MS (EI, *m/z*) 303 ($M^+ + 2$, 8), 301 (M^+, 24), 286 (4), 284 (12), 117 (32), 91 (47), 77 (100); HRMS calcd for $C_{18}H_{20}ON^{35}Cl$ 301.1235, found 301.1230. Anal. Calcd for $C_{18}H_{20}ONCl$: C, 71.63; H, 6.68; N, 4.64. Found: C, 71.54; H, 6.66; N, 4.69.

(*Z*)-**6-Br**: colorless solid; mp 152−154 °C; δ_H 1.60−1.95 (m, 4 H), 2.17 (bs, 3 H), 2.24 (bs, 1 H), 2.38 (bs, 1 H), 2.91 (bs, 1 H), 2.95 (bs, 1 H), 3.14 (s, 2 H), 7.35−7.50 (m, 3 H), 7.65−7.72 (m, 2 H); MS (EI, *m/z*) 347 ($M^+ + 2$, 68), 345 (M^+, 69), 330 (8), 328 (8), 266 ($M^+ - {}^{79}Br$, 100), 117 ($M^+ - C_{10}H_{13}OBr$, 31), 91 (43), 77 (48); HRMS calcd for $C_{18}H_{20}ON^{79}Br$ 345.0729, found 345.0731. Anal. Calcd for $C_{18}H_{20}ONBr$: C, 62.44; H, 5.82; N, 4.04. Found: C, 62.39; H, 5.87; N, 4.04.

(*E*)-**6-Br**: colorless solid; mp 106−108 °C; δ_H 1.63 (bs, 1 H), 1.67 (bs, 1 H), 2.02−2.16 (m, 3 H), 2.20−2.50 (m, 8 H), 3.22 (s, 2 H), 7.30−7.45 (m, 3 H), 7.60−7.70 (m, 2 H); MS (EI, *m/z*) 347 ($M^+ + 2$, 90), 345 (M^+, 91), 330 (14), 328 (12), 266 ($M^+ - {}^{79}Br$, 90), 117 ($M^+ - C_{10}H_{13}OBr$, 42), 91 (73), 77 (100); HRMS

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(12) Bonini, B. F.; MacCagnani, G.; Mazzanti, G.; Thijs, L.; Ambrosius, H. P. M. M.; Zwanenburg, B. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1468.

calcd for $C_{18}H_{20}ON^{79}Br$ 345.0729, found 345.0724. Anal. Calcd for $C_{18}H_{20}ONBr$: C, 62.44; H, 5.82; N, 4.04. Found: C, 62.35; H, 5.89; N, 4.01.

(*Z*)-**6-Ph**: colorless solid; mp 130−132 °C; δ_H 1.75−2.05 (m, 8 H), 1.96 (bs, 2 H), 2.18−2.28 (m, 3 H), 3.21 (s, 1 H), 7.39−7.42 (m, 3 H), 7.65−7.69 (m, 2 H); MS (EI, *m*/*z*) 343 (M^+, 100), 326 (44), 155 (25), 117 (32), 91 (39), 77 (33); HRMS calcd for $C_{24}H_{25}ON$ 343.1938, found 343.1928. Anal. Calcd for $C_{24}H_{25}ON$: C, 83.93; H, 7.34; N, 4.08. Found: C, 83.96; H, 7.34; N, 4.07.

(*Z*)-**6-Ph**: colorless solid; mp 125.5−127 °C; δ_H 1.52−1.56 (m, 6 H), 1.96 (bs, 2 H), 2.18−2.28 (m, 3 H), 3.21 (s, 1 H), 7.39−7.42 (m, 3 H), 7.65−7.69 (m, 2 H); MS (EI, *m*/*z*) 343 (M^+, 100), 326 (40), 155 (18), 117 (18), 91 (28), 77 (27); HRMS calcd for $C_{24}H_{25}ON$ 343.1938, found 343.1938. Anal. Calcd for $C_{24}H_{25}ON$: C, 83.93; H, 7.34; N, 4.08. Found: C, 83.84; H, 7.31; N, 4.08.

X-ray Structure Analysis of (*Z*)-5-F. A colorless prism crystal of $C_{17}H_{18}ONSF$ was crystallized from 30% methylene chloride in hexanes. Its structure was determined by means of single-crystal X-ray analysis on a Rigaku AFC6S diffractometer with graphite-monochromated MoKα ($\lambda = 0.710\ 69$ Å) radiation at 296 ± 1 K, with an ω-2θ type scan at 16°/min (in ω). The crystals are C-centered monoclinic, with space group *C*2/*c* (15) and unit cell dimensions $a = 19.454(4)$ Å, $b = 6.635(5)$ Å, $c = 24.956(4)$ Å, $\beta = 111.30(2)°$, $V = 3001(1)$ Å^3, $Z = 8$, $\rho_{calcd} = 1.343$ g cm^{-3}, crystal size (mm) 0.33 × 0.41 × 0.46, μ(MoKα) = 2.24 cm^{-1}, $F(000) = 1280.00$, 2554 reflections, 2467 unique reflections, 1403 with $I > 3.00\sigma(I)$ and with 190 variable parameters. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The model was finally refined by the full-matrix least-squares methods with weight $\omega = 1/[\sigma^2(F_o)]$ to final *R* values of 0.048 and Rw = 0.037 (for details, see the Supporting Information).[13]

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[13] The author has deposited atomic coordinates for (*Z*)-**5**-**F** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.