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SYNTHESIS OF SPIRO-FUSED NITROGEN HETEROCYCLIC COMPOUNDS *VIA N*-METHOXY-*N*-ACYLNITRENIUM IONS USING PHENYLIODINE(III) BIS(TRIFLUOROACETATE) IN TRIFLUOROETHANOL

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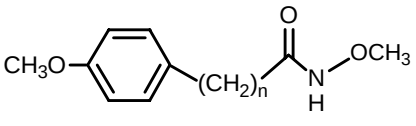
Abstract-Spirodienones and spirodienes bearing the nitrogen atom bound to the spiro carbon have been synthesized from *N*-methoxy-(4-methoxyphenyl)amides and *N*-methoxyphenylamides, respectively, by the intramolecular *ipso* attack of a nitrenium ion generated with phenyliodine(III) bis(trifluoroacetate) in trifluoroethanol.

Transformation of benzenoid compounds to nonbenzenoid compounds can provide valuable intermediates for the synthesis of a variety of organic compounds.[1] In previous work, we reported the synthesis of spirodienones bearing the nitrogen atom bound to the spiro carbon atom. The procedure involved intramolecular *ipso* attack of a nitrenium ion generated from an *N*-chloro-*N*-methoxyamide moiety appended to the *o*- or *p*-methoxybenzene substrate.[2] Very recently the same type of the *ipso* cyclization has been performed to afford spirodienone compounds using phenyliodine(III) bis(trifluoroacetate) (PIFA).[3] These spiro compounds have proved to be valuable intermediates for the synthesis of biologically important compounds.[4]

We now report the successful development of a useful new method for the selective conversion of benzenoid compounds, such as *N*-methoxy-(4-methoxyphenyl)amides (**1a-c**) and *N*-methoxyphenylamides (**3a-i**), to 2,5-cyclohexadienone (**2a-c**) and 2,5-cyclohexadiene derivatives (**5a-i** and **6**), respectively. This new procedure features intramolecular *ipso* attack of a nitrenium ion generated with PIFA under mild reaction conditions. We have initiated efforts to undertake the synthesis of spirodienones using PIFA instead of *t*-BuOCl, since the latter presents environmental problems related to disposal.

N-Methoxy-(4-methoxyphenyl)- propionamide (**1b**) was submitted to the same cyclization reaction reported previously.[5] Reaction of the starting *N*-methoxyamide (**1b**) with PIFA in chloroform at 65 ºC led to the corresponding spirodienone compound (**2b**) (34%) and an undesired methoxime derivative (**2d**) (31%) (Scheme 1).



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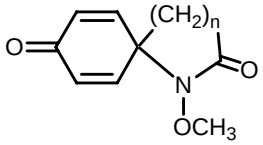

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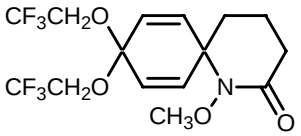
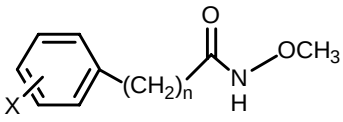


2e



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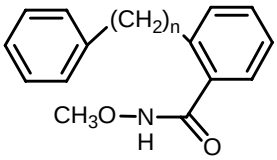
3e, n = 2, X = 4-CH_3



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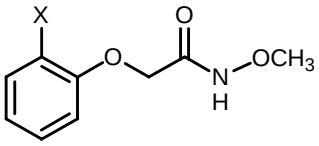

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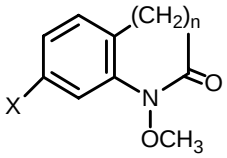

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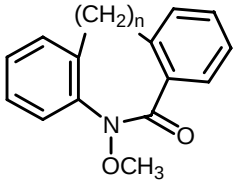
4b, n = 3, X = H
4c, n = 4, X = H
4e, n = 2, X = CH_3



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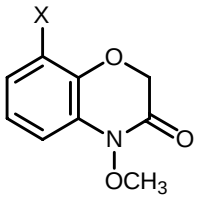
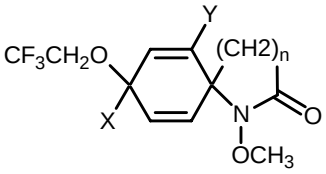
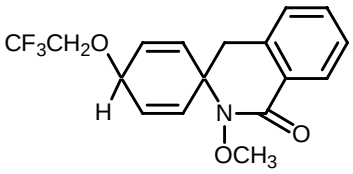


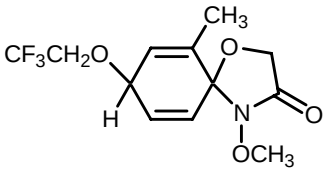
4h, X = H
4i, X = CH_3



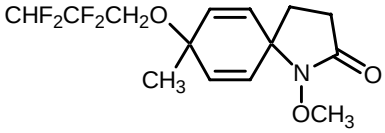
5a, n = 2, X = H, Y = H
5b, n = 3, X = H, Y = H
5d, n = 2, X = H, Y = CH_3
5e, n = 2, X = CH_3, Y = H



5f



5i



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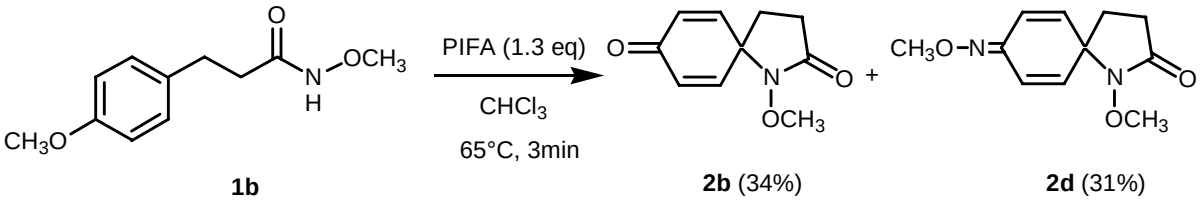
Scheme 1



1b **2b** (34%) **2d** (31%)

The effects of solvent on the reaction of several *N*-methoxyamides (**1a-c**) with PIFA were studied. The results are presented in Table 1. These results show that the yields of the spirodienone compounds are

greatly improved trifluoroethanol (TFEA) as solvent.

Table 1. Synthesis of spirodienones from *N*-methoxy-(4-methoxyphenyl)amides with PIFA in solvents

entry	starting compound	solvent	reaction time (min)	product (yield, %)
1	**1a**	$CHCl_3$	10	**2a** (51)
2	**1a**	TFEA	10	**2a** (63)
3	**1b**	$CHCl_3$	15	**2b** (57)
4	**1b**	HFIP[a]	10	**2b** (64)
5	**1b**	TFEA	15	**2b** (80)
6	**1c**	TFEA	10	**2c** (50), **2e** (20)

[a] HFIP : hexafluoroisopropanol.

Since a *para*-methoxy group will promote *ipso* cyclization through its strong electron-donationg effect in the electrophilic reaction, the method we report should be particularly effective with *para*-methoxyphenyl compounds. Next, we investigated the reactions of unactivated monobenzenoid compounds using TFEA and HFIP as solvent, in the expectation that the yields of benzannulated compounds would be increased at the expense of spirocyclization. In HFIP this was the case and the 7- and 8- membered benzannulated compounds were produced in high yields (Table 2).

Table 2. Synthesis of 7- and 8-membered benzannulated compounds from *N*-methoxyphenylamides with PIFA in HFIP

entry	starting compound	reaction time (min)	product (yield, %)
1	**3c**	30	**4c** (72)
2	**3f**	1	**4f** (84)
3	**3g**	1	**4g** (84)

However, in TFEA we obtained an unexpected result. Thus, treatment of **3a** with PIFA in TFEA for 1 min under ice cooling afforded the benzannulated compound (**4a**) (55%) and the spirodiene compound (**5a**) (34%). From *o*-tolyl derivative (**3d**) the spirodiene compound (**5d**) (84%) was exclusively obtained. Most reactions of unactivated monobenzenoid aromatics lead to substitution rather than addition. Thus, the synthesis of spirodiene compounds from the corresponding benzenoid compounds is energetically disfavored because it is necessary to disrupt the benzenoid aromaticity.[6] *ipso*-Cyclization in the absence of other activating groups on the phenyl group to form the spirodiene derivatives is a very unusual result, since this requires the loss of aromaticity. Several unactivated benzenoid compounds reacted similarly and the

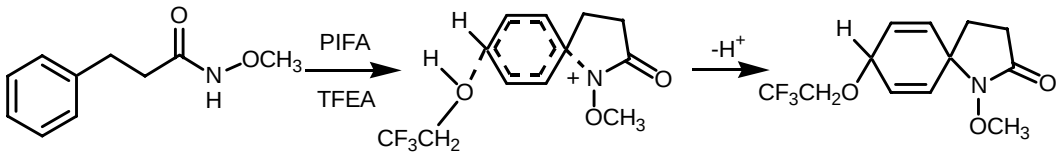
results are presented in Table 3.

Table 3. Cyclization of *N*-methoxyphenylamides with PIFA in TFEA

entry	starting compound	reaction time (min)	product (yield, %)
1	**3a**	1	**4a** (55), **5a** (34)
2	**3b**	15	**4b** (50), **5b** (48)
3	**3d**	5	**5d** (84)
4	**3e**	1	**4e** (20), **5e** (62)
5	**3f**	3	**4f** (44), **5f** (46)
6	**3h**	5	**4h** (79)
7	**3i**	3	**4i** (38), **5i** (31)

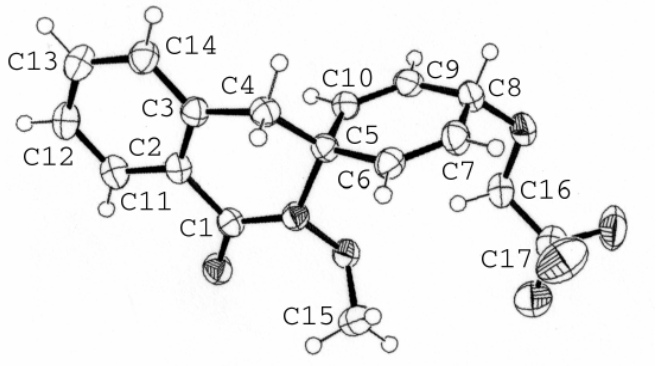
HFIP is known to have high ionizing power, low nucleophilicity and can stabilize a nitrenium ion.[7] However, no spirodiene compounds were obtained in HFIP. However, in 2,2,3,3-tetrafluoro-1-propanol the spiro compound (**6**) (60%) was obtained along with **4e** (18%). The critical part of the process described herein consists of coupled attack on the benzenoid ring by external nucleophile (trifluoroethanol) and internal electrophile (acylnitrenium ion), the over-all results being 1,4-addition that can proceed in the absence of a *para*-methoxy substituent.

Scheme 2



Generally the spirodiene products are obtained as a mixture of *cis* and *trans* isomers, the presence of which was detected by the measurement of the NMR spectra. To determine the structure accurately, *cis* and *trans* isomers of compound (**5f**) were separated by careful column chromatography to give a solid and an oil.

Figure 1. ORTEP drawing of the X-Ray crystallographic structure of ***cis*-5f**



The solid product was submitted to single-crystal X-Ray crystallography. The X-Ray diffraction data (Figure 1) unambiguously revealed its structure to be *cis*.

In conclusion, we have developed a potentially useful new method for the selective conversion of *N*-methoxy-(4-methoxyphenyl)amides and *N*-methoxyphenylamides to 2,5-cyclohexadienone and 2,5-cyclohexadiene derivatives, respectively, under mild conditions using PIFA in TFEA. Complementing this procedure, if HFIP is used as solvent, the 7- and 8- membered benzannulated nitrogen heterocyclic compounds are produced in high yields from *N*-methoxyphenylamides and no spirodiene derivatives are formed.

EXPERIMENTAL

All the melting points were determined with a Yanagimoto hot-stage melting point apparatus and are uncorrected. ^{1}H NMR (270 MHz) spectra and ^{13}C NMR spectra (68 MHz) were measured on a JEOL JNM-EX270 spectrometer with tetramethylsilane ($MeSi_4$) as an internal reference. ^{1}H NMR and ^{13}C NMR spectral data are reported in parts per million (δ) relative to $MeSi_4$. IR spectra were recorded on a JASCO IR 810 spectrophotometer. MS spectra were obtained with a JEOL JMX-DX 300 spectrometer with a direct inlet system at 70 eV. Elemental analyses were performed in the Microanalytical Laboratory of this University.

The following compounds were synthesized by the literature method.[2] Spectral data of *N*-methoxy-3-phenylpropionamide (**3a**) and *N*-methoxy-2-phenoxyacetamide (**3h**) were identical with those of authentic samples. [2]

***N*-Methoxy-2-(4-methoxypheny)acetamide (1a).** mp 87.5-88 ˚C (AcOEt) (lit., [2] mp 87-88.5 ˚C).

***N*-Methoxy-3-(4-methoxypheny)propionamide (1b).** mp 75-75.5 ˚C (AcOEt/hexane) (lit., [3] mp 72-73 ˚C).

***N*-Methoxy-4-(4-methoxypheny)butyramide (1c).** mp 59-60 ˚C (AcOEt/hexane) (lit., [2] mp 53-54 ˚C).

***N*-Methoxy-4-phenylbutyramide (3b).** mp 59-60.5 ˚C (AcOEt/hexane) (lit., [2] mp 57.5-58 ˚C).

***N*-Methoxy-5-phenylpentanamide (3c).** IR (neat) 3200, 1660, 1515, 1465, 1100 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.42-1.63 (m, 4H), 1.96 (t, J = 7.0 Hz, 2H), 2.56 (t, J = 7.0 Hz, 2H), 3.56 (s, 3H), 7.12-7.32 (m, 5H), 10.95 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 24.90, 30.88, 32.93, 35.52, 64.26, 125.72, 128.25, 128.30, 142.02, 170.89; EI-MS *m/z* 207 (M^+, 1.0), 161 (100), 117 (46.1), 91 (94.7). HR-MS *m/z* for $C_{12}H_{17}NO_2$ calcd 207.1259, found 207.1256.

***N*-Methoxy-3-(2-methylphenyl)propionamide (3d).** mp 56-57 ˚C (ether/pet. ether); IR (KBr) 3150, 1650, 1510, 1440, 1070 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 2.20-2.45 (m, 5H), 2.96 (t, J = 8.2 Hz, 2H), 3.67 (s, 3H), 7.04-7.20 (m, 4H), 9.04 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 19.28, 28.65, 33.67, 64.23, 125.99, 126.33, 128.57, 130.18, 135.78, 138.37, 170.05; EI-MS *m/z* 193 (M^+, 2.5), 147 (44.2), 119 (32.7), 105 (100). Anal. Calcd

for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.53; H, 7.54; N, 7.15.

***N*-Methoxy-3-(4-methylphenyl)propionamide (3e).** mp 62.5-64 ˚C (ether/ pet. ether); IR (KBr) 3170, 1650, 1540, 1440, 1075 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.02 (t, J = 7.7 Hz, 2H), 2.25 (s, 3H), 2.76 (t, J = 7.7 Hz, 2H), 3.53 (s, 3H), 7.07 (s, 4H), 10.95 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 30.46, 35.30, 55.19, 64.27, 113.88, 129.28, 132.37, 158.05, 170.14. Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.24; H, 7.72; N, 7.25.

2-Benzyl-*N*-methoxybenzamide (3f). mp 99-100 ˚C (AcOEt/hexane); IR (KBr) 3140, 1640, 1540, 1330, 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.69 (s, 3H), 4.20 (s, 2H), 7.11-7.45 (m, 9H), 8.15 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 38.66, 64.30, 126.13, 126.26, 127.60, 128.40, 128.98, 130.70, 131.07, 132.64, 139.80, 140.43, 167.53; EI-MS *m/z* 241 (M^+, 5.5), 210 (11.0), 195 (100), 165 (26.4). Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.80. Found: C, 74.57; H, 6.36; N, 5.79.

***N*-Methoxy-2-phenethylbenzamide (3g).** mp 71-72 ˚C (AcOEt/hexane); IR (KBr) 3200, 1650, 1510, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.95 (t, J = 7.7 Hz, 2H), 3.07 (t, J = 7.7 Hz, 2H), 3.81 (s, 3H), 7.05-7.45 (m, 9H), 7.75 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 35.11, 38.02, 64.31, 125.92, 127.27, 128.30, 128.64, 130.33, 130.53, 132.80, 140.36, 141.38, 167.95; EI-MS *m/z* 255 (M^+, 0.04), 209 (100), 131 (41.6), 91 (28.7); FAB-MS (3-nitrobenzyl alcohol) *m/z* 256 (M^++1, 100). Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.25; H, 6.74; N, 5.50.

***N*-Methoxy-(2-methylphenoxy)acetamide (3i).** mp 79.5-80 ˚C (ether); IR (KBr) 3220, 1670, 1500, 1440, 1075 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.27 (s, 3H), 3.84 (s, 3H), 4.55 (s, 2H), 6.76 (d, J = 8.1 Hz, 1H), .6.94 (t, J = 7.7 Hz, 1H), 7.10-7.23 (m, 2H), 9.12 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 16.35, 64.70, 67.16, 111.26, 121.96, 126.37, 127.04, 130.98, 154.99, 165.54; EI-MS *m/z* 195 (M^+, 69.9), 164 (12.5), 148 (59.8), 121 (52.7), 108 (88.4), 91 (100). Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.17. Found: C, 61.56; H, 6.72; N, 7.10.

Reaction of *N*-Methoxy-3-(4-methoxyphenyl)propionamide (1b) with PIFA in $CHCl_3$

To PIFA (267 mg, 6.21 mmol) in $CHCl_3$ (4 mL) was added **1b** (100 mg, 4.78 mmol) in $CHCl_3$ (2 mL) at 65 ˚C in an argon atmosphere. After stirring the reaction mixture for 3 min, 10% Na_2CO_3 (20 mL) was added under cooling. The aqueous layer was extracted with AcOEt (30 mL × 2), and the combined organic layer was washed with brine (30 mL), dried over Na_2SO_4 and concentrated. The residue was chromatographed on a column of silica gel with AcOEt as an eluent to give **2b** (31 mg, 34 %) and **2d** (33 mg, 31 %).

1-Methyoxy-1-azaspiro[4.5]deca-6,9-diene-2,8-dione (2b). mp 130-132 ˚C (AcOEt) (lit., [3] mp 127-128 ˚C).

1-Methyoxy-1-azaspiro[4.5]deca-6,9-diene-2,8-dione-8-(*O*-methyloxime) (2d). mp 118-121 ˚C (AcOEt); IR (KBr) 1730, 1460, 1335 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.05 (t, J = 7.9 Hz, 2H), 2.46 (t, J = 7.9 Hz, 2H), 3.77 (s, 3H), 3.97 (s, 3H), 6.03 (dd, J = 10.1, 2.5 Hz, 1H), 6.14 (dd, J = 10.2, 2.5 Hz, 1H), 6.44 (dd, J

= 10.1, 2.0 Hz, 1H), 7.04 (dd, *J* = 10.2, 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 25.97, 29.79, 62.40, 62.88, 64.91, 118.14, 126.26, 133.16, 136.96, 146.33, 170.89; EI-MS *m/z* 222 (M^+, 100), 191 (32.1), 148 (57.7), 135 (31.9), 104 (26.5), 90 (24.5). Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.38; H, 6.26; N, 12.50.

Reaction of *N*-Methoxy-3-(4-methoxyphenyl)propionamide (1b) with PIFA in TFEA. Typical Procedure

To **1b** (100 mg, 4.78 mmol) in TFEA (5 mL) was added PIFA (226 mg, 5.26 mmol) under cooling in an argon atmosphere. After stirring the reaction mixture for 15 min, 10% Na_2CO_3 (20 mL) was added under cooling. The aqueous layer was extracted with AcOEt (30 mL × 2), and the combined organic layer was washed with brine (30 mL), dried over Na_2SO_4 and concentrated. The residue was chromatographed on a column of silica gel with AcOEt as an eluent to give **2b** (74 mg, 80 %).

1-Methoxy-1-azaspiro[3.5]nona-5,8-diene-2,7-dione (2a). mp 106-108 ˚C (AcOEt/hexane) (lit., [2] mp 105-106 ˚C).

1-Methoxy-1-azaspiro[5.5]undeca-7,10-diene-2,9-dione (2c). mp 110-111 ˚C (AcOEt/hexane) (lit., [2] mp 110-111 ˚C).

1-Methoxy-9,9-bis(2,2,2-trifluoroethoxy)-1-azaspiro[5.5]undeca-7,10-diene-2-one (2e). IR (neat) 1680, 1420, 1285 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.81-1.99 (m, 4H), 2.56 (t, *J* = 6.1 Hz, 2H), 3.71(s, 3H), 3.86 (q, $J_{H\text{-}F}$ = 8.5 Hz, 2H), 4.00 (q, $J_{H\text{-}F}$ = 8.5 Hz, 2H), 5.98 (d, *J* = 10.3 Hz, 2H), 6.25 (d, *J* = 10.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.96, 31.77, 33.34, 60.27 (q, $J_{C\text{-}F}$ = 35.4 Hz), 61.14 (q, $J_{C\text{-}F}$ = 35.4 Hz), 62.31, 63.94, 94.33, 123.44 (q, $J_{C\text{-}F}$ = 276.4 Hz), 123.46 (q, $J_{C\text{-}F}$ = 276.4 Hz), 126.02, 136.58, 168.47; EI-MS *m/z* 389 (M^+, 2.0), 343 (22.4), 290 (100), 260 (55.7), 258 (52.3), 230 (46.3), 189 (69.2). HR-MS *m/z* for $C_{15}H_{17}NO_4F_6$ calcd 389.1062, found 389.1085.

Reaction of *N*-Methoxy-5-phenypentanamide (3c) with PIFA in HFIP. Typical Procedure

To **3c** (100 mg, 4.83 mmol) in HFIP (5 mL) was added PIFA (228 mg, 5.31 mmol) under cooling in an argon atmosphere. After stirring the reaction mixture for 30 min, 10% Na_2CO_3 (20 mL) was added under cooling. The aqueous layer was extracted with AcOEt (30 mL × 2), and the combined organic layer was washed with brine (30 mL), dried over Na_2SO_4 and concentrated. The residue was chromatographed on a column of silica gel with AcOEt-hexane (1:1) as an eluent to give **4c** (71 mg, 72 %).

1-Methoxy-3,4,5,6-tetrahydro-1-benzoazocin-2(1*H*)-one (4c). IR (neat) 1680, 1460, 1380 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.24-1.50 (m, 1H), 1.74-2.10 (m, 3H), 2.22-2.25 (m, 1H), 2.41 (dd, *J* = 12.2, 8.1 Hz, 1H), 2.54 (t, *J* = 13.5 Hz, 1H), 2.87 (dd, *J* = 13.5, 8.1 Hz, 1H), 3.77 (s, 3H), 7.25-7.46 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 25.13, 29.19, 31.07, 33.30, 60.84, 125.68, 127.27, 129.25, 130.10, 136.88, 140.29, 170.26;

EI-MS *m/z* 205 (M^+, 100), 174 (19.8), 146 (57.2), 130 (66.1), 118 (50.7), 106 (91.8). HR-MS *m/z* for $C_{12}H_{15}NO_2$ calcd 205.1103, found 205.1118.

5,6-Dihydro-5-methoxy-11*H*-dibenzo[*b*,*e*]azepin-6-one (4f). mp 132-133 ˚C (AcOEt/hexane); IR (KBr) 1665, 1460, 1335 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.67 (br s, 1H), 3.92 (s, 3H), 4.11 (br s, 1H), 7.10-7.35 (m, 5H), 7.40 (td, *J* = 7.5, 1.5 Hz, 1H), 7.57 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.95 (dd, *J* = 7.7, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 38.94, 62.66, 120.57, 126.55, 126.62, 126.98, 127.25, 127.46, 130.94, 131.10, 132.19, 134.72, 137.88, 141.46, 164.81; EI-MS *m/z* 239 (M^+, 76.6), 208 (53.3), 194 (21.4), 180 (100). Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.21; H, 5.39; N, 5.84.

5-Methoxy-5,6,11,12-tetrahydrodibenzo[*b*,*f*]azocin-6-one (4g). mp 122-123 ˚C (AcOEt/hexane); IR (KBr) 1660, 1460, 1360 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.28-3.08 (m, 2H), 3.34-3.62 (m, 2H), 3.94 (s, 3H), 6.95-7.37 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 31.49, 33.01, 62.03, 126.39, 126.94, 127.36, 127.41, 129.03, 129.20, 130.07, 130.09, 135.03, 136.06, 136.96, 139.37, 169.47; EI-MS *m/z* 253 (M^+, 37.9), 222 (93.2), 204 (100), 194 (33.2). Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.81; H, 5.97; N, 5.50.

Reaction of *N*-Methoxy-3-phenylpropionamide (3a) with PIFA in TFEA. Typical Procedure

To **3a** (100 mg, 5.58 mmol) in TFEA (5 mL) was added PIFA (264 mg, 6.14 mmol) under cooling in an argon atmosphere. After stirring the reaction mixture for 1 min, 10% Na_2CO_3 (20 mL) was added under cooling. The aqueous layer was extracted with AcOEt (30 mL × 2), and the combined organic layer was washed with brine (30 mL), dried over Na_2SO_4 and concentrated. The residue was chromatographed on a column of silica gel with AcOEt-hexane (2:1) as an eluent to give **4a** (54 mg, 55 %) and **5a** (53 mg, 34 %). 1-Methoxy-3,4-dihydro-2(1*H*)-quinolinone (**4a**) was determined by comparison of the spectral data with those of the authentic sample. [2]

1-Methoxy-1,3,4,5-tetrahydro-2*H*-1-benzoazepin-2-one (4b). mp 46-47 ˚C (hexane) (lit., [2] mp 45-46 ˚C).

1-Methoxy-7-methyl-3,4-dihydro-2(1*H*)-quinolinone (4e). IR (neat) 1700, 1430, 1330, 1200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.37 (s, 3H), 2.68 (t, *J* = 7.3 Hz, 2H), 2.87 (t, *J* = 7.3 Hz, 2H), 3.92 (s, 3H), 6.85 (d, *J* = 7.8 Hz, 1H), 7.02-7.09 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.42, 24.45, 31.69, 62.45, 112.72, 121.15, 123.96, 127.39, 137.38, 137.50, 165.55; EI-MS *m/z* 191 (M^+, 100), 160 (29.0), 142 (38.8), 132 (50.1), 117 (31.5), 106 (14.9). HR-MS *m/z* for $C_{11}H_{13}NO_2$ calcd 191.0946, found 191.0955.

4-Methoxy-2*H*-1,4-benzoxazin-3(4*H*)-one (4h). mp 50-51 ˚C (MeOH) (lit., [8] mp 58-59 ˚C).

4-Methoxy-8-methyl-2*H*-1,4-benzoxazin-3(4*H*)-one (4i). IR (neat) 1710, 1480, 1375 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.24 (s, 3H), 3.96 (s, 3H), 4.68 (s, 2H), 6.90 (d, *J* = 7.5 Hz, 1H), .6.96 (t, *J* = 7.5 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 15.38, 62.97, 68.14, 110.31, 122.22, 126.23, 126.50, 126.73, 141.96,

160.21; EI-MS *m/z* 193 (M^+, 100), 162 (19.3), 134 (94.7). HR-MS *m/z* for $C_{10}H_{11}NO_3F_3$ calcd 193.0739, found 193.0738.

***cis*- and *trans*-1-Methoxy-8-(2,2,2,-trifluoroethoxy)-1-azaspiro[4.5]deca-6,9-dien-2-one (5a).** IR (neat) 1725, 1410, 1285 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.93-2.10 (m, 2H), 2.45 (t, J = 8.3 Hz, 2H), 3.66-3.87 (m, 5H), 4.67-4.77 (m, 1H), 5.94-6.19 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 25.74, 26.01, 29.33, 29.96, 59.98, 60.17, 61.50 (q, J_{C-F} = 34.5 Hz), 63.38 (q, J_{C-F} = 34.5 Hz), 64.61, 64.82, 67.37, 67.98, 123.77 (q, J_{C-F} = 227.2 Hz), 123.96 (q, J_{C-F} = 227.2 Hz), 128.28, 129.16, 132.75, 132.95, 170.82, 171.20; EI-MS *m/z* 277 (M^+, 1.0), 246 (14.9), 189 (100). HR-MS *m/z* for $C_{12}H_{14}NO_3F_3$ calcd 277.0926, found 277.0934.

***cis*- or *trans*-1-Methoxy-9-(2,2,2,-trifluoroethoxy)-1-azaspiro[5.5]undeca-7,10-dien-2-one (5b).** IR (neat) 1680, 1415, 1295 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.79-1.94 (m, 4H), 2.47-2.60 (m, 2H), 3.73 (s, 3H), 3.79 (q, J_{H-F} = 8.9 Hz, 2H), 4.64-4.72 (m, 1H), 5.99 (dd, J = 10.4, 3.1 Hz, 2H), 6.10 (dd, J = 10.4, 1.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 17.06, 33.31, 37.50, 61.43 (q, J_{C-F} = 34.5 Hz), 61.89, 63.65, 67.78, 123.98 (q, J_{C-F} = 277.2 Hz), 127.03, 133.85, 168.40; EI-MS *m/z* 291 (M^+, 0.7), 245 (97.1), 202 (38.9), 189 (100), 89 (99.9); FAB-MS (3-nitrobenzyl alcohol) *m/z* 292 (M^++1, 100). FAB-HRMS (3-nitrobenzyl alcohol) *m/z* for $C_{13}H_{17}NO_3F_3$ calcd 292.1161, found 292.1163.

***trans*- or *cis*-1-Methoxy-9-(2,2,2,-trifluoroethoxy)-1-azaspiro[5.5]undeca-7,10-dien-2-one (5b).** IR (neat) 1675, 1420, 1285 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.80-2.00 (m, 4H), 2.53 (t, J = 6.2 Hz, 2H), 3.69 (s, 3H), 3.74 (q, J_{H-F} = 8.6 Hz, 2H), 4.65-4.75 (m, 1H), 6.02-6.13 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 17.70, 33.34, 36.81, 61.29, 63.46 (q, J_{C-F} = 34.7 Hz), 63.95, 70.03, 123.73 (q, J_{C-F} = 278.0 Hz) 128.00, 133.69, 167.79; EI-MS *m/z* 291 (M^+, 0.7), 245 (73.6), 202 (32.3), 189 (100), 89 (96.2); FAB-MS (3-nitrobenzyl alcohol) *m/z* 292 (M^++1, 100). FAB-HRMS (3-nitrobenzyl alcohol) *m/z* for $C_{13}H_{17}NO_3F_3$ calcd 292.1161, found 292.1166.

***cis*- and *trans*-1-Methoxy-6-methyl-8-(2,2,2,-trifluoroethoxy)-1-azaspiro[4.5]deca-6,9-dien-2-one (5d).** IR (neat) 1720, 1460, 1280 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.81 (t, J = 1.5 Hz, 1.7H), 1.82 (t, J = 1.3 Hz, 1.3H), 1.86-2.19 (m, 2H), 2.31-2.59 (m, 2H), 3.65-3.83 (m, 5H), 4.60-4.76 (m, 1H), 5.73-5.79 (m, 0.6H), 5.82-5.88 (m, 0.4H), 5.95-6.04 (m, 1.6H), 6.07 (ddd, J = 9.9, 3.2, 1.8 Hz, 0.4H); ^{13}C NMR ($CDCl_3$) δ 17.90, 17.94, 26.40, 26.46, 27.84, 28.35, 61.46 (q, J_{C-F} = 34.8 Hz), 61.97, 62.06, 63.15 (q, J_{C-F} = 34.8 Hz), 63.92, 64.16, 69.12, 70.34, 123.97 (q, J_{C-F} = 271.2 Hz), 124.15 (q, J_{C-F} = 271.2 Hz), 125.14, 125.61, 127.46, 127.56, 134.71, 135.24, 139.47, 139.89, 170.92, 171.22; EI-MS *m/z* 291 (M^+, 1.0), 260 (4.4), 244 (10.3), 203 (100). HR-MS *m/z* for $C_{13}H_{16}NO_3F_3$ calcd 291.1082, found 291.1076.

***cis*- and *trans*-1-Methoxy-8-methyl-8-(2,2,2,-trifluoroethoxy)-1-azaspiro[4.5]deca-6,9-dien-2-one (5e).** IR (neat) 1725, 1415, 1295 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (s, 2.1H), 1.44 (s, 0.9H), 1.90-2.11 (m, 2H), 2.45 (t, J = 7.8 Hz, 2H), 3.54 (q, J_{H-F} = 8.8 Hz, 0.6H), 3.64-3.86 (m, 4.4H), 5.83-5.97 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 25.81, 25.98, 27.59, 27.93, 29.24, 29.69, 60.20, 61.98 (q, J_{C-F} = 34.5 Hz), 62.16 (q, J_{C-F} = 34.5 Hz), 64.07, 64.58, 123.83 (q, J_{C-F} = 277.0 Hz), 124.00 (q, J_{C-F} = 277.0 Hz), 131.31, 131.41, 133.22, 134.32, 170.86,

171.28; EI-MS *m/z* 291 (M^+, 1.4), 260 (10.9), 203 (100). HR-MS *m/z* for $C_{13}H_{16}NO_3F_3$ calcd 291.1082, found 291.1084**.**

***cis*-1-Oxo-2-methoxy-3,4-dihydro-2*H*-isoquinoline-3-spiro-1'-[4'-(2,2,2-trifluoroethoxy)cyclohexa-2',5'-diene] (5f).** mp 123-125 ˚C (AcOEt/hexane); IR (KBr) 1680, 1465, 1295 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.16 (s, 2H), 3.81 (q, J_{H-F} = 8.9 Hz, 2H), 3.89 (s, 3H), 4.67-4.77 (m, 1H), 6.02 (dd, *J* = 10.4, 3.3 Hz, 2H), 6.13 (dd, *J* = 10.4, 1.5 Hz, 2H), 7.14 (d, *J* = 7.4 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.50 (td, *J* = 7.4, 1.5 Hz, 1H), 8.17 (dd, *J* = 7.6, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 41.96, 61.51 (q, J_{C-F} = 34.0 Hz), 62.11, 64.50, 67.87, 124.08 (q, J_{C-F} = 277.2 Hz), 127.39, 127.49, 127.51, 127.95, 128.25, 132.41, 132.92, 134.12, 165.05; EI-MS *m/z* 339 (M^+, 1.7), 308 (55.7), 293 (100), 240 (23.9), 210 (22.2), 194 (22.2), 132 (21.6), 118 (52.8), 90 (17.7). Anal. Calcd for $C_{17}H_{16}NO_3F_3$: C, 60.18; H, 4.75; N, 4.13. Found: C, 60.20; H, 4.77; N, 4.13.

***trans*-1-Oxo-2-methoxy-3,4-dihydro-2*H*-isoquinoline-3-spiro-1'-[4'-(2,2,2-trifluoroethoxy)cyclohexa-2',5'-diene] (5f).** IR (neat) 1680, 1465, 1285 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.22 (s, 2H), 3.76 (q, J_{H-F} = 8.6 Hz, 2H), 3.84 (s, 3H), 4.66-4.75 (m, 1H), 6.03-6.16 (m, 4H), 7.17 (d, *J* = 7.4 Hz, 1H), 7.40 (t, *J* = 7.7 Hz, 1H), 7.49 (td, *J* = 7.4, 1.5 Hz, 1H), 8.16 (dd, *J* = 7.7, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 41.37, 61.77, 63.98 (q, J_{C-F} = 34.5 Hz), 64.66, 70.40, 123.93 (q, J_{C-F} = 278.3 Hz), 127.54, 127.65, 127.84, 128.45, 129.35, 131.78, 132.91, 134.74, 164.81; EI-MS *m/z* 339 (M^+, 1.6), 308 (54.3), 293 (100), 240 (16.9), 210 (19.2), 194 (24.3), 132 (24.1), 118 (59.0), 90 (19.4). HR-MS *m/z* for $C_{17}H_{16}NO_3F_3$ calcd 339.1082, found 339.1081.

***cis*- or *trans*-4-Methoxy-6-methyl-8-(2,2,2-trifluoroethoxy)-1-oxa-4-azaspiro[4.5]deca-6,9-dien-3-one (5i).** IR (neat) 1720, 1405, 1285 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.86 (t, *J* = 1.6 Hz, 3H), 3.73 (dq, J_{H-F} = 8.7, *J* = 1.7 Hz, 2H), 3.84 (s, 3H), 4.35 (d, *J* = 5.6 Hz, 2H), 4.63-4.73 (m, 1H), 5.75-6.73 (m, 2H), 6.26 (ddd, *J* = 10.1, 3.4, 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 16,72, 62.17 (q, J_{C-F} = 34.7 Hz), 64.47, 64.93, 69.34, 87.30, 123.38 (q, J_{C-F} = 277.5 Hz), 129.40, 130.77, 132.30, 137.84, 167.11; EI-MS *m/z* 293 (M^+, 7.7), 262 (13.5), 205 (100). HR-MS *m/z* for $C_{12}H_{14}NO_4F_3$ calcd 293.0875, found 293.0873.

***trans*- or *cis* -4-Methoxy-6-methyl-8-(2,2,2-trifluoroethoxy)-1-oxa-4-azaspiro[4.5]deca-6,9-dien-3-one (5i).** IR (neat) 1720, 1405, 1285 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.87 (t, *J* = 1.6 Hz, 3H), 3.71 (dq, J_{H-F} = 8.6, *J* = 0.8 Hz, 2H), 3.80 (s, 3H), 4.36 (d, *J* = 1.1 Hz, 2H), 4.60-4.72 (m, 1H), 5.95-6.08 (m, 2H), 6.27 (dt, *J* = 9.9, 2.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 16,57, 62.87 (q, J_{C-F} = 34.6 Hz), 64.68, 64.89, 69.51, 87.21, 123.77 (q, J_{C-F} = 277.2 Hz), 129.47, 129.88, 132.35, 136.92, 166.80; EI-MS *m/z* 293 (M^+, 7.5), 262 (4.7), 205 (100). HR-MS *m/z* for $C_{12}H_{14}NO_4F_3$ calcd 293.0875, found 293.0865.

Reaction of *N*-Methoxy-3-(4-methylphenyl)propionamide (3e) with PIFA in 2,2,3,3-Tetrafluoro-1-propanol.

To **3e** (100 mg, 5.18 mmol) in 2,2,3,3-tetrafluoro-1-propanol (5 mL) was added PIFA (245 mg, 5.69 mmol) under cooling in an argon atmosphere. After stirring the reaction mixture for 5 min, 10% Na_2CO_3 (20 mL)

was added under cooling. The aqueous layer was extracted with AcOEt (30 mL × 2), and the combined organic layer was washed with brine (30 mL), dried over Na_2SO_4 and concentrated. The residue was chromatographed on a column of silica gel with AcOEt-hexane (1:1) as an eluent to give **4e** (18 mg, 18 %) and **6** (100 mg, 60 %).

***cis*- and *trans*-1-Methoxy-8-(2,2,3,3-tetrafluoropropoxy)-1-azaspiro[4.5]deca-6,9-dien-2-one (6).** IR (neat) 1720, 1415, 1210 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (s, 1.9H), 1.37 (s, 1.1H), 1.88-2.16 (m, 2H), 2.35-2.48 (m, 2H), 3.50 (tt, J_{H-F} = 12.5, J = 1.7 Hz, 0.7H), 3.68 (tt, J_{H-F} = 13.0, J = 1.7 Hz, 1.3H), 3.73 (s, 1.1H), 3.75 (s, 1.9H), 5.65-5.75 (m, 0.25H), 5.59-5.90 (m, 4.5H), 6.04-6.14 (m, 0.25H); ^{13}C NMR ($CDCl_3$) δ 25.81, 25.96, 27.63, 28.00, 29.17, 29.68, 60.19, 61.39 (q, J_{C-F} = 28.5 Hz), 61.72 (q, J_{C-F} = 29.0 Hz), 64.55, 64.67, 71.01, 71.05, 108.91 (tt, J_{C-F} = 248.5, 34.0 Hz), 109.05 (tt, J_{C-F} = 248.3, 34.4 Hz), 114.95 (tt, J_{C-F} = 248.2, 26.2 Hz), 115.04, (tt, J_{C-F} = 247.7, 26.2 Hz), 131.50, 131.56, 133.09, 133.11, 171.25, 170.87; EI-MS *m/z* 323 (M^+, 2.0), 292 (12.6), 235 (100). HR-MS *m/z* for $C_{14}H_{17}NO_3F_4$ calcd 323.1145, found 323.1144.

X-Ray Crystallography of *cis*-5f

Crystal data. Crystal dimensions 0.45 x 0.50 x 0.50 mm, $C_{17}H_{16}NO_3F_3$, M = 339.31, triclinic, P-1 (No.2), a = 7.189(2), b = 10.567(3), c = 11.976(3) Å, α = 66.206(6)°, β = 78.796(9)°, γ = 71.444(6)°, V = 786.9(4) $Å^3$, Z = 8, D_c = 1.432 g/cm^3, μ = 1.21 cm^{-1}, T = 173(1) K, 3249 reflections measured, refinement based on 2566 reflections. F (000) = 352.00, *GOF* on F = 1.20, No. of parameters = 233, R = 0.077 [$I > 2.00\,\sigma(I)$], R_w = 0.132, largest positive and negative difference peaks +0.32 and –0.44 $e^-/Å^3$. Data collection and refinement data were collected on a Rigaku RAXIS imaging plate area detector with graphite monochromated Mo-Kα radiation. (λ = 0.71069 Å). The structure was solved by direct method (MULTAN88) and expanded using Fourier techniques. All non-hydrogen atoms were refined anisotropically. All calculations were performed using the CrystalStructure[9,10] software package.

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