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Reaction of 2,2-Difluorovinyl Ketones with Heteroatom Nucleophiles: A General One-Pot Synthesis of α-Oxoketene Acetals[1]

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Abstract: 2,2-Difluorovinyl ketones readily react with heteroatom nucleophiles such as thiols, alcohols, and amines to undergo stepwise replacement of the two fluorine atoms *via* addition–elimination process. The reaction affords α-oxoketene acetals including *S,S*-, *N,S*-, *N,N*-, *O,S*-, and *O,O*-acetals in good to excellent yields.

INTRODUCTION

α-Oxoketene acetals, including variants of acetal groups such as *S,S*-, *N,S*-, *N,N*-, *O,S*-, and *O,O*-acetals, have received considerable attention in organic synthesis.[2-4] These acetals possess synthetic potential for a variety of transformations *via* 1,2-nucleophilic addition to the carbonyl group and/or 1,4-addition to the enone moiety. These reactivities are widely utilized in the construction of i) carbocyclic,[2,5] ii) heterocyclic,[2,6] iii) polyene,[7] and iv) aldol systems.[2,4]

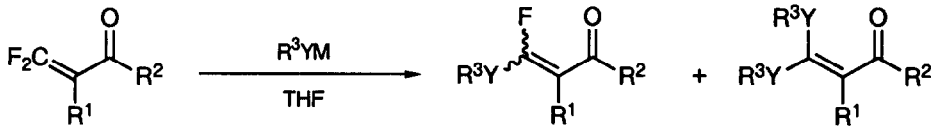
Because of their versatility as 1,3-electrophilic 3-carbon synthons, a number of strategies and reaction conditions have been reported for the preparation of the family of α-oxoketene acetals. There are, however, few general procedures which can be adopted in preparing the acetals regardless of their kinds. In addition, most of the methods in the literature are prone to restriction of substituents, especially those of the acetal moiety due to the requirement for alkylation on sulfur or oxygen. α-Oxoketene *O,O*-acetals are synthesized by the alkylation on the ester carbonyl oxygen of β-ketoesters.[4c] Similarly, the alkylation on the sulfur of β-ketodithioesters, β-ketothioamides, and β-ketothioesters are preferably adopted to prepare the *S,S*-, *N,S*-, and *O,S*-acetals, respectively.[2,3] These procedures, however, suffer from difficulty in the preparation of the *S*- and *O*-aryl acetals. On the other hand, introduction of heteroatoms by substitution at the β-vinylic carbon of enones might provide a general entry to a wide variety of α-oxoketene mixed acetals,[2,8] which are particularly useful in the synthesis of functionalized cyclic compounds. Herein we wish to report a general one-pot synthesis of α-oxoketene acetals with various heteroatom substituents starting from 2,2-difluorovinyl ketones **1** *via* substitution for the fluorines.

RESULTS AND DISCUSSION

Having developed a facile method for the preparation of 2,2-difluorovinyl ketones **1** from 2,2,2-trifluoroethyl *p*-toluenesulfonate,[9] we recently revealed the remarkable reactivity of their fluorines toward nucleophilic substitution *via* addition–elimination process, and successfully applied it to the synthesis of fully substituted α,β-unsaturated ketones in the reaction with carbon nucleophiles.[10] These results prompted us to investigate the reaction of **1** with heteroatom nucleophiles, which effects the formation of α-oxoketene acetals by successive replacement of the two fluorines.

Initially we attempted the reaction of difluorovinyl ketones with oxygen nucleophiles. Treatment of 2-butyl-3,3-difluoro-1-phenyl-2-propen-1-one (**1a**; R^1=^{n}Bu, R^2=Ph) with 1.0 equiv of lithium phenolate in tetrahydrofuran (THF) at 0 °C induced replacement of the fluorine to give the monosubstituted product **2a** (R^1=^{n}Bu, R^2=Ph, R^3Y=PhO) as a *E*/*Z* mixture (13/87)[11] in 84% yield (Table 1, Entry 1). On the other hand, the disubstituted product, *O*,*O*-acetal **3a** (R^1=^{n}Bu, R^2=Ph, R^3Y=PhO) was obtained in 82% yield when 2.2 equiv of phenolate was employed (Table 1, Entry 3). The dialcoholate of catechol (1.0 equiv) was found to undergo intramolecular double substitution to afford cyclic acetal **3b** in 63% yield (Table 1, Entry 4). In the case of aliphatic alcoholates as nucleophiles, the monosubstituted products were unstable to be easily hydrolyzed leading to the corresponding β-ketoesters (*vide infra*).

Thiols brought about a similar substitution even at a lower temperature (–78 °C) or under less basic conditions (K_2CO_3 or Et_3N) as shown in Table 1 (Entries 5–7). The *E*/*Z* ratios of the monosubstituted product **2c** (R^1=^{n}Bu, R^2=Ph, R^3Y=PhS) did not depend on the used bases. The results (Table 1, Entries 1 *vs.* 3, 5 *vs.* 8, and 9 *vs.* 10) disclosed that the substitution for the two fluorine atoms in **1** was readily effected in turn by heteroatom nucleophiles and accordingly controlled by the stoichiometry of the added nucleophiles (1.0 or 2.2–2.5 equiv), which might permit stepwise introduction of two different heteroatom groups.



1 YM=OLi, SLi, SH, NH_2 **2** **3**

Thus, the synthesis of α-oxoketene mixed acetals was examined next. When **1a** was treated with lithium phenolate (1.0 equiv) followed by lithium benzenethiolate (1.5 equiv), the desired *O*-phenyl,*S*-phenyl acetal **4a** (R^3Y=PhO, R^4Z=PhS) was obtained in 85% yield along with only a small amount of other homoacetals (Table 2, Entry 1). The reverse addition of nucleophiles, benzenethiolate and then phenolate, under similar conditions gave almost no *O*,*S*-acetal but the monosubstituted product **2c**. This result showed apparently that the stronger nucleophile of two should be added afterward to proceed the reaction smoothly. The monosubstituted product of an aliphatic alcohol, 3-phenylpropanol, was generated *in situ* and also utilized for the second replacement by thiolates in spite of its instability mentioned above, leading to the *O*-alkyl,*S*-aryl and *O*-alkyl,*S*-alkyl acetals, **4b** (R^3Y=Ph$(CH_2)_3$O, R^4Z=PhS) and **4c** (R^3Y=Ph$(CH_2)_3$O, R^4Z=EtS) (Table 2, Entries 2 and 3). Consequently, this procedure opened a new way to α-oxoketene *O*,*S*-acetals, of which synthetic methods were quite limited.[3,8] In a similar manner, the *S*-phenyl,*S*-ethyl mixed acetal **4d** was also effectively obtained by successive treatment

with lithium ethanethiolate and lithium benzenethiolate (Table 2, Entry 4). Concerning the *E*/*Z* isomers of *O*,*S*- and *S*,*S*-acetals, they were obtained in 2:1 to 1:1 mixture.

Table 1. The Reaction of 2,2-Difluorovinyl Ketones with *O*- and *S*-Nucleophiles (R^1=^{n}Bu)

Entry		R^2	R^3YM (eq)	Conditions	Yd./% of 2(*E*/*Z*) [a)b)]	Yd./% of 3 [a)]
1	**1a**	Ph	PhOLi (1.0)	0 °C, 0.5 h	**2a** 84 (13/87)	trace
2	**1b**	^{c}Hex	PhOLi (1.0)	0 °C, 1 h	**2b** 71 (11/89)	trace
3	**1a**	Ph	PhOLi (2.2)	r.t., 2 h	**2a** 5 [c)]	**3a** 82
4	**1a**	Ph	dilithium catecholate (1.0)	–78 °C–r.t., 2 h	—[d)]	**3b** 63
5	**1a**	Ph	PhSLi (1.0)	–78–0 °C, 1 h	**2c** 85 (40/60)	**3c** 7
6	**1a**	Ph	PhSH (1.0) [e)]	0 °C, 1 h	**2c** 80 (42/58)	trace
7	**1a**	Ph	PhSH (1.0) [f)]	r.t., 2 h	**2c** 85 (40/60)	trace
8	**1a**	Ph	PhSLi (2.2)	0 °C, 0.5 h	trace [c)]	**3c** 87
9	**1a**	Ph	EtSLi (1.0)	–78 °C, 1 h	**2d** 74 (66/34)	trace
10	**1a**	Ph	EtSLi (2.5)	0 °C, 0.5 h	trace [c)]	**3d** 83
11	**1a**	Ph	$PhNH_2$(4.1)	r.t.–reflux, 2.5 h	—[d)]	**3e** 88

a) Isolated yield. b) Numbers in parentheses show the ratios determined by GLC analysis. Configuration was assigned by ^{13}C and ^{19}F NMR measurement. See Ref.11. c) Ratio was not determined. d) Not isolated. e) K_2CO_3 (3.5 equiv) was employed as a base. f) Et_3N (1.0 equiv) was employed as a base.

Furthermore, we tried to apply this method for the preparation of the *N*,*N*- and *N*,*S*-acetals, which are valuable synthons with additional reactivity patterns because of their nucleophilicity as enamines besides the electrophilicity as enones.[2a] Screening of the conditions for replacement by nitrogen nucleophiles revealed that employing 2.0 equiv of amines provided better results than 1.0 equiv of amines with bases such as ^{n}BuLi and Et_3N. When aniline (4.1 equiv) was added to **1a**, the expected *N*,*N*-acetal **3e** (R^1=^{n}Bu, R^2=Ph, R^3Y=PhNH), which existed in β-ketoamidine form, was obtained in 88% yield (Table 1, Entry 11). Successive treatment of **1a** with 2.0 equiv of amines and then 1.0–1.5 equiv of lithium thiolates or the other amines (2.2 equiv) eventually afforded the corresponding *N*,*S*- or *N*,*N*-acetals **4e-h** in high yields (Table 2, Entries 5-8). In the case of secondary amines, unstable monoamino compounds were generated *in situ* as the intermediates, which in turn reacted with the second nucleophiles, while the reaction of **1** with primary amines proceeded presumably *via* reactive α-oxoketene imines.[12]

In summary, 2,2-difluorovinyl ketones (**1**) serve as a versatile precursor yielding variants of α-oxoketene acetals by the successive addition of two different heteroatom nucleophiles, such as those of oxygen, sulfur, and

nitrogen *via* replacement of the fluorine atoms. Combined with the synthetic reaction of 1 which includes the introduction of R^1 and R^2CO groups with BR^1_3 and R^2COCl,[9] this sequence of reactions provides a general and facile entry to the class of α-oxoketene acetals, where the substituents can be selected independently. Moreover, it is proved here that fluorine acts as a powerful functional group for further synthetic elaborations, and we continue to study along this line.

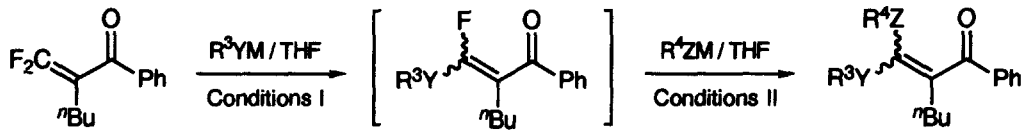


Table 2. One-Pot Synthesis of α-Oxoketene Mixed Acetals from **1a**

Entry	R^3YM (eq)	Conditions I	R^4ZM (eq)	Conditions II	Yield /% (*E*/*Z*) [a]
1	PhOLi (1.0)	0 °C, 0.5 h	PhSLi (1.5)	0 °C, 0.5 h	**4a** 85 (2:1)
2	$Ph(CH_2)_3OLi$ (1.1)	0 °C, 1 h	PhSLi (1.5)	r.t., 3 h	**4b** 68 (3:2)
3	$Ph(CH_2)_3OLi$ (1.1)	0 °C~r.t., 2.5 h	EtSLi (1.5)	r.t., 1 h	**4c** 57 (3:2)
4	EtSLi (1.0)	–78 °C~r.t., 2 h	PhSLi (1.5)	0 °C, 1 h	**4d** 78 (3:2)
5	Et_2NH (2.0)	0 °C, 0.5 h	PhSLi (1.2)	0 °C, 0.5 h	**4e** 90 [b]
6	Et_2NH (2.0)	0 °C, 0.5 h	EtSLi (1.5)	0 °C~r.t., overnight	**4f** 86 [b]
7	$PhCH_2NH_2$ (2.0)	0 °C, 3 h	PhSLi (1.0)	0 °C, 0.5 h	**4g** 85 [c]
8	Et_2NH (2.0)	0 °C, 1 h	$PhNH_2$(2.2)	r.t., 2 h	**4h** 85 [c]

a) Isolated yield. Numbers in parentheses show the ratios determined by ^{13}C and/or ^1H NMR measurement. Configuration was not assigned. b) Obtained as a single isomer, judging from ^{13}C and ^1H NMR spectra. c) Exists in β-ketoimine form.

EXPERIMENTAL SECTION

General. Melting points were measured in open capillary tubes and are uncorrected. IR spectra were recorded on a Shimazu IR-408 spectrometer. NMR spectra were obtained on a JEOL JNM-FX-60, a JEOL JNM-FX-100, a JEOL JNM-EX-270, or a JEOL JNM-A-500 spectrometer. Chemical shift value were given in ppm relative to internal Me_4Si (for ^1H and ^{13}C NMR: δ-value) or internal C_6F_6 (for ^{19}F NMR). Mass spectra were taken with a JEOL JMS-DX-300 spectrometer. Elemental analyses were performed with a YANAKO MT-3 CHN Corder apparatus. THF was distilled from sodium benzophenone ketyl prior to use.

2-Butyl-3,3-difluoro-1-phenyl-2-propen-1-one (1a)[9] Butyllithium (50 ml, 1.66 M in hexane, 83 mmol) was added to a solution of 2,2,2-trifluoroethyl *p*-toluenesulfonate (10 g, 39 mmol) in THF (200ml) at

–78 °C over 20 min under a nitrogen atmosphere. The reaction mixture was stirred for 20 min at –78 °C and then tributylborane (43 ml, 1 M in THF, 43 mmol) was added at –78 °C over 10 min. After being stirred for 1 h, the reaction mixture was warmed up to room temperature and stirred for an additional 3 h. The solution was treated with hexamethylphosphoric triamide (HMPA, 40 ml) and cuprous iodide (15.0 g, 79 mmol) at 0 °C and stirred for 30 min at the same temperature. To the resulting solution was added benzoyl chloride (6.1 g, 43 mmol) and the mixture was stirred at room temperature for 1 h. The reaction was quenched with phosphate buffer (pH 7), followed by addition of a large quantity of ice-cold water (about 200ml). To the resulting mixture was added aqueous hydrogen peroxide (50 ml, 30%) dropwise at 0 °C. After being stirred for 1 h at room temperature, the mixture was filtered. Organic materials were extracted with AcOEt three times. The combined extracts were washed with aqueous $Na_2S_2O_3$ and brine, and then dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (hexane–Et_2O 50:1) followed by bulb-to-bulb distillation to give **1a** (6.1 g, 69%). bp 50 °C/0.5 mmHg (bath temp.). IR (neat) 2970, 1710, 1660, 1450, 1330, 1220, 1140, 940, 700 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.90 (3H, m), 1.04–1.63 (4H, m), 2.24–2.52 (2H, m), 7.24–7.56 (3H, m), 7.56–7.80 (2H, m). ^{19}F NMR ($CDCl_3/C_6F_6$) 80.1 ppm (1F, dt, J_{FF}=19 Hz, J_{FH}=2 Hz), 89.2 ppm (1F, d, J_{FF}=19 Hz). ^{13}C NMR ($CDCl_3$) δ=13.7, 22.3, 25.2, 30.5, 94.8 (dd, J_{CF}=17 Hz, 11 Hz), 128.5, 128.7 (d, J_{CF}=2 Hz), 133.1, 138.2, 157.8 (t, J_{CF}=298 Hz), 193.2 (dd, J_{CF}=8 Hz, 3 Hz). MS (75 eV) *m/z* (rel intensity) 224 (M^+; 42), 181 (19), 105 (100), 77 (54). HRMS Found: *m/z* 224.1011. Calcd for $C_{13}H_{14}OF_2$: M, 224.1013. Anal. Found: C, 69.46; H, 6.28. Calcd for $C_{13}H_{14}OF_2$: C, 69.63; H, 6.29.

2-Butyl-1-cyclohexyl-3,3-difluoro-2-propen-1-one (1b)[9] Compound **1b** was prepared by the method described for **1a** using 2,2,2-trifluoroethyl *p*-toluenesulfonate (111 mg, 0.44 mmol), butyllithium (0.56 ml, 1.63 M in hexane, 0.92 mmol), tributylborane (0.48 ml, 1 M in THF, 0.48 mmol), HMPA (0.6 ml), cuprous iodide (167 mg, 0.88 mmol), and cyclohexanecarbonyl chloride (71 μl, 0.53 mmol). Purification by thin layer chromatography on silica gel (hexane–Et_2O 3:1) gave **1b** (76 mg, 76%). IR (neat) 2940, 1700, 1670, 1450, 1320, 1285, 1140, 965 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.89 (3H, m), 1.04–1.96 (14H, m), 2.00–2.32 (2H, m), 2.56–2.92 (1H, m). ^{19}F NMR ($CDCl_3/C_6F_6$) 85.4 ppm (1F, d, J_{FF}=15 Hz), 90.3 ppm (1F, d, J_{FF}=15 Hz). ^{13}C NMR ($CDCl_3$) δ=13.8, 22.3, 23.8, 25.9, 26.0, 29.1, 30.8 (d, J_{CF}=2 Hz), 49.2 (d, J_{CF}=6 Hz), 96.3 (dd, J_{CF}=14 Hz, 8 Hz), 160.3 (dd, J_{CF}=304 Hz, 299 Hz), 201.4 (t, J_{CF}=8 Hz). MS (75 eV) *m/z* (rel intensity) 230 (M^+; 49), 187 (48), 147 (100), 105 (38), 83 (42), 55 (60). HRMS Found: *m/z* 230.1483. Calcd for $C_{13}H_{20}OF_2$: M, 230.1482.

2-Butyl-3-fluoro-3-phenoxy-1-phenyl-2-propen-1-one (2a) To the THF (1.5 mL) solution of phenol (41 mg, 0.43 mmol) was added butyllithium (0.27 mL, 1.57 M in hexane, 0.43 mmol) at 0 °C, and the mixture was stirred for 10 min to generate lithium phenolate under a nitrogen atmosphere. The resulting solution was added to the THF (1.5 mL) solution of **1a** (97 mg, 0.43 mmol) and stirred for 30 min at 0 °C. Phosphate buffer (pH 7) was then added to quench the reaction. Organic materials were extracted with AcOEt three times. The combined extracts were washed with brine, and then dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by thin layer chromatography on silica gel (hexane–AcOEt 20:1) to give **2a** (108 mg, 84%). IR (neat) 2960, 1640, 1595, 1495, 1330, 1210, 940, 890, 755, 690 cm^{-1}. ^1H NMR ($CDCl_3$–CCl_4 1:1, for 13/87 *E/Z* mixture) δ=0.66–1.14 (3H, m), 1.14–1.84 (4H, m), 2.18–2.76 (2H, m), 6.52–7.94 (10H, m). ^{19}F NMR (C_6D_6/C_6F_6) (*Z*)-form (major): 89.5 (1F, s); (*E*)-form (minor): 81.2 (1F, s). ^{13}C NMR ($CDCl_3$) (*Z*)-form (major): δ=13.8, 22.5, 26.5, 30.7 (d, J_{CF}=2 Hz), 103.1 (d, J_{CF}=17 Hz) 117.1, 124.8, 128.4, 128.6, 129.9, 132.6, 139.0, 153.5, 155.7 (d, J_{CF}=241 Hz), 194.7 (d, J_{CF}=3 Hz); (*E*)-form (minor): δ=13.8, 22.5, 26.0, 30.9, 104.0 (d, J_{CF}=24 Hz), 116.5, 124.3, 128.1, 128.5, 129.6, 132.3, 138.7 (d, J_{CF}=3 Hz), 153.1, 156.3 (d, J_{CF}=295 Hz), 195.3 (d, J_{CF}=9 Hz). MS (70 eV) *m/z* 298 (M^+), 235, 135, 105, 77. HRMS Found: *m/z* 298.1371. Calcd for $C_{19}H_{19}O_2F$: M, 298.1369.

2-Butyl-1-cyclohexyl-3-fluoro-3-phenoxy-2-propen-1-one (2b) Compound **2b** was prepared by the method described for **2a** using **1b** and lithium phenolate. Purification by thin layer chromatography on silica gel (hexane–AcOEt 20:1) gave **2b**. IR (neat): 2940, 1765, 1715, 1595, 1495, 1455, 1195, 1165, 1110, 750, 690 cm^{-1}. ^1H NMR ($CDCl_3$–CCl_4 1:1, for 11/89 *E/Z* mixture) δ=0.60–2.06 (17H, m), 2.06–2.56 (2H, m), 2.56–3.16 (1H, m), 6.80–7.60 (5H, m). ^{19}F NMR (C_6D_6/C_6F_6) (*Z*)-form (major): 89.4 (1F, s); (*E*)-form (minor): δ=86.9 (1F, s). ^{13}C NMR (C_6D_6) (*Z*)-form (major): δ=14.1, 22.8, 25.7, 26.3, 26.4, 29.7, 31.5 (d, J_{CF}=2 Hz), 50.0 (d, J_{CF}=8 Hz), 104.7 (d, J_{CF}=16Hz), 117.4, 125.0, 130.2, 153.9, 157.9 (d, J_{CF}=297 Hz), 201.5 (d, J_{CF}=7 Hz); (*E*)-form (minor): δ=14.1, 22.8, 25.1, 26.3, 26.4, 29.7, 31.7 (d, J_{CF}=2 Hz), 49.2 (d, J_{CF}=2 Hz), 106.3 (d, J_{CF}=21 Hz), 116.7, 124.9, 130.3, 154.0, 158.4 (d, J_{CF}=295 Hz), 201.9 (d, J_{CF}=9 Hz). MS (70 eV) *m/z* 304(M^+), 222, 221, 211, 191, 83, 77, 55. HRMS Found: *m/z* 304.1823. Calcd for $C_{19}H_{25}O_2F$: M, 304.1838. Anal. Found: C, 75.02; H, 8.41. Calcd for $C_{19}H_{25}O_2F$: C, 74.97; H, 8.28.

2-Butyl-3-fluoro-1-phenyl-3-phenylthio-2-propen-1-one (2c) Compound **2c** was prepared by the method described for **2a** using **1a** and lithium benzenethiolate. Purification by thin layer chromatography on silica gel (hexane–AcOEt 15:1) gave **2c** along with **3c**. IR (neat) 2970, 1665, 1595, 1480, 1450, 1315, 1275, 1215, 1170, 1105, 1070, 935, 740, 690 cm^{-1}. ^1H NMR ($CDCl_3$, for 40/60 *E/Z* mixture) δ=0.77–0.98 (3H, m), 1.22–1.53 (4H, m), 2.48–2.71 (2H, m), 7.18–7.60 (8H, m), 7.83–7.97 (2H, m). ^{19}F NMR ($CDCl_3$–CCl_4 1:1/C_6F_6) (*E*)-form (major): 75.8 (1F, t, J_{FH}=3 Hz); (*Z*)-form (minor): 84.8 (1F, s). ^{13}C-NMR ($CDCl_3$) (*E*)-form (major): δ=13.7, 22.5, 30.0 (d, J_{CF}=2 Hz), 30.7 (d, J_{CF}=2 Hz), 127.2 (d, J_{CF}=15 Hz), 128.2, 128.6, 129.0, 129.4, 130.8, 131.2, 133.3, 137.2, 153.4 (d, J_{CF}=302 Hz), 194.5 (d, J_{CF}=2 Hz); (*Z*)-form (minor): δ=13.7, 22.5, 28.8, 31.1, 128.0, 128.6, 129.2, 129.3, 129.8 (d, J_{CF}=18 Hz), 130.7, 130.8, 133.4, 137.1 (d, J_{CF}=4 Hz), 152.0 (d, J_{CF}=309 Hz), 194.7 (d, J_{CF}=7 Hz). MS (70 eV) *m/z* 314, 237, 205, 105, 77. HRMS Found: *m/z* 314.1095. Calcd for $C_{19}H_{19}FOS$: M, 314.1141. Anal. Found: C, 72.79; H, 6.15. Calcd for $C_{19}H_{19}FOS$: C, 72.58; H, 6.09.

2-Butyl-3-ethylthio-3-fluoro-1-phenyl-2-propen-1-one (2d) Compound **2d** was prepared by the method described for **2a** using **1a** and lithium ethanethiolate. Purification by thin layer chromatography on silica gel (hexane–AcOEt 10:1) gave **2d**. IR (neat) 2950, 1655, 1600, 1450, 1320, 1280, 1215, 1075, 935, 800, 765, 720, 690 cm^{-1}. ^1H NMR ($CDCl_3$, for 66/34 *E/Z* mixture) δ=0.87 (0.9H, t, *J*=7.3 Hz), 0.89 (2.1H, t, *J*=7.3 Hz), 1.19 (0.9H, t, *J*=7.3 Hz), 1.03–1.46 (4H, m), 1.33 (2.1H, t, *J*=7.3 Hz), 2.47–2.55 (2H, m), 2.69 (0.6H, qd, *J*=7.3, 0.9 Hz), 2.82 (1.4H, q, *J*=7.3 Hz), 7.42–7.49 (2H, m), 7.52–7.58 (1H, m), 7.81–7.89 (2H, m). ^{19}F NMR ($CDCl_3/C_6F_6$) (*E*)-form (major): 82.3 (1F, s); (*Z*)-form (minor): 75.0 (1F, s). ^{13}C NMR ($CDCl_3$) (*E*)-form (major): δ=13.8, 15.4, 22.5, 25.7 (d, J_{CF}=3 Hz), 30.6, 30.7 (d, J_{CF}=3 Hz), 124.2 (d, J_{CF}=13 Hz), 128.5, 128.9, 133.0, 138.1, 156.3 (d, J_{CF}=303), 194.7 (d, J_{CF}=2 Hz); (*Z*)-form (minor): δ=13.7, 14.8, 22.5, 26.7, 28.5 (d, J_{CF}=2 Hz), 30.3 (d, J_{CF}=2 Hz), 127.6 (d, J_{CF}=19 Hz), 128.6, 129.2, 133.1, 137.5 (d, J_{CF}=4 Hz), 155.2 (d, J_{CF}=307 Hz), 195.4 (d, J_{CF}=8 Hz). MS (70 eV) *m/z* 266 (M^+), 237, 105 (base peak), 77. HRMS Found: *m/z* 266.1146. Calcd for $C_{15}H_{19}OFS$: M, 266.1141. Anal. Found: C, 67.80; H, 7.31. Calcd for $C_{15}H_{19}OFS$: C, 67.64; H, 7.19.

2-Butyl-3,3-diphenoxy-1-phenyl-2-propen-1-on (3a) Compound **3a** was prepared by the method described for **2a** using **1a** and lithium phenolate. Purification by thin layer chromatography on silica gel (hexane–AcOEt 20:1) gave **3a** along with **2a**. IR (neat) 2950, 1660, 1595, 1495, 1330, 1210, 1120, 940, 890, 760, 690 cm^{-1}. ^1H NMR ($CDCl_3$–CCl_4 1:1) δ=0.89 (3H, m), 1.12–1.84 (4H, m), 2.32–2.86 (2H, m), 6.40–8.12 (15H, m). ^{13}C NMR ($CDCl_3$) δ=13.8, 22.6, 27.3, 31.2, 111.7, 116.9, 117.3, 123.2, 123.7, 128.0, 128.3, 128.9, 129.4, 131.9, 139.3, 152.5, 153.9, 196.7. MS (70 eV) *m/z* 279 (M^+–PhO, base peak), 105, 77. Anal. Found C, 80.85; H, 6.71. Calcd for $C_{25}H_{24}O_3$: C, 80.62; H, 6.49.

2-(1-Butyl-2-oxo-2-phenylethyliden)-1,3-benzodioxole (3b) To the THF (1.5 mL) solution of catechol (49 mg, 0.45 mmol) was added butyllithium (0.58 mL, 1.62 M in hexane, 0.94 mmol) at 0 °C, and the mixture was stirred for 10 min to generate dilithium catecholate under a nitrogen atmosphere. The resulting solution was added to the THF (25 mL) solution of **1a** (100 mg, 0.45 mmol) at –78 °C and warmed to room temperature with stirring for 2 h. After removal of the solvent under reduced pressure without quenching, the residue was distilled by a bulb-to-bulb distillation apparatus to give **3b** (82 mg, 63%). mp 102–4 °C (hexane). IR (KBr disk) 2940, 1675, 1590, 1570, 1480, 1350, 1230, 1120, 895, 740, 695 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.94 (3H, m), 1.10–1.88 (4H, m), 2.36–2.80 (2H, m), 6.68–7.82 (9H, m). ^{13}C NMR ($CDCl_3$) δ=14.0, 22.5, 26.1, 31.4, 92.7, 109.6, 109.6, 124.1, 127.9, 128.1, 130.9, 141.3, 144.3, 144.9, 165.1, 194.6. MS (70 eV) *m/z* 294 (M^+), 251 (base peak), 105, 77. HRMS Found: *m/z* 294.1259. Calcd for $C_{19}H_{18}O_3$: M, 294.1256. Anal. Found: C, 77.18; H, 6.16. Calcd for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16.

2-Butyl-1-phenyl-3,3-bis(phenylthio)-2-propen-1-one (3c) Compound **3c** was prepared by the method described for **2a** using **1a** and lithium benzenethiolate. Purification by thin layer chromatography on silica gel (hexane–AcOEt 10:1) gave **3c**. IR (neat) 2950, 1730, 1655, 1580, 1475, 1440, 1265, 1065, 1025, 740, 685 cm^{-1}. ^1H NMR ($CDCl_3$–CCl_4 1:1) δ=0.90 (3H, m), 1.08–1.80 (4H, m), 2.52–3.00 (2H, m), 6.80–7.28 (10H, m), 7.28–7.58 (3H, m), 7.72–8.08 (2H, m). ^{13}C NMR ($CDCl_3$) δ=13.8, 22.7, 30.5, 34.6, 127.3, 127.4, 128.4, 128.7, 129.1, 129.6, 131.2, 131.9, 133.0, 133.4, 133.4, 136.3, 152.6, 196.7. MS (70 eV) *m/z* 404 (M^+), 295, 105 (base peak), 77. HRMS Found: *m/z* 404.1267. Calcd for $C_{25}H_{24}OS_2$: M, 404.1268. Anal. Found: C, 74.33; H, 6.25. Calcd for $C_{25}H_{24}OS_2$: C, 74.22; H, 5.98.

2-Butyl-3,3-bis(ethylthio)-1-phenyl-2-propen-1-one (3d) Compound **3d** was prepared by the method described for **2a** using **1a** and lithium ethanethiolate. Purification by thin layer chromatography on silica gel (hexane–AcOEt 10:1) gave **3d**. IR (neat) 2925, 1665, 1595, 1450, 1315, 1260, 1210, 965, 900, 710, 690 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.64–1.70 (13H, m), 2.36–3.04 (6H, m), 7.20–7,56 (3H, m), 7.70–8.00 (2H, m). ^{13}C NMR ($CDCl_3$) δ=13.8, 14.2, 15.3, 22.7, 27.0, 28.0, 30.5, 34.1, 128.4, 129.0, 130.6, 132.9, 136.8, 150.7, 197.2. MS (70 eV) *m/z* 308 (M^+), 279 (base peak), 105, 77. HRMS Found: *m/z* 308.1287. Calcd for $C_{17}H_{24}OS_2$: M, 308.1268.

2-Butyl-3-oxo-3,N^1,N^2-triphenylpropanamidine (3e) Aniline (302 mg, 3.24 mmol) was added to the THF (2.5 mL) solution of **1a** (177 mg, 0.79 mmol) at room temperature under a nitrogen atmosphere. The mixture was stirred for 30 min and then heated under reflux for 2 h. After removal of the solvent under reduced pressure without quenching, the residue was purified by flash column chromatography on silica gel (hexane–AcOEt 15:1) to give **3e** (257 mg, 88%). mp 112–113 °C (hexane). IR (KBr) 3365, 2940, 1675, 1645, 1595, 1535, 1445, 1200, 1170, 905, 750, 695 cm^{-1}. ^1H NMR (C_6D_6) δ=0.65 (3H, t, *J*=6.9 Hz), 0.92–1.25 (4H, m), 1.76–1.98 (1H, m), 1.98–2.21 (1H, m), 4.93 (1H, dd, *J*=8.7, 5.8 Hz), 6.74–7.33 (11H, m), 7.70–8.01 (4H, m). ^{13}C NMR (C_6D_6) δ=13.8, 22.6, 30.0, 34.1, 47.3, 119.6, 122.3, 122.7, 128.9, 128.9, 129.3, 134.1, 136.6, 140.8, 150.4, 150.5, 200.8. MS (70 eV) *m/z* 370 (M^+), 314, 278, 222, 105, 77. HRMS Found: *m/z* 370.2084. Calcd for $C_{25}H_{26}N_2O$: M, 370.2045. Anal. Found: C, 81.06; H, 7.05; N, 7.49. Calcd for $C_{25}H_{26}N_2O$: C,81.05; H, 7.07; N, 7.56.

2-Butyl-1-phenyl-3-phenoxy-3-phenylthio-2-propen-1-one (4a) To the THF (1.5 mL) solution of phenol (70 mg, 0.75 mmol) was added butyllithium (0.47 mL, 1.60 M in hexane, 0.75 mmol) at 0 °C, and the mixture was stirred for 10 min to generate lithium phenolate under a nitrogen atmosphere. The resulting solution was added to the THF (1.5 mL) solution of **1a** (168 mg, 0.75 mmol) at 0 °C and stirred for 30 min at the same temperature. The reaction mixture was then treated at 0 °C with lithium benzenethiolate generated as above from benzenethiol (124.0 mg, 1.13 mmol) and butyllithium (0.71 mL, 1.60 M in hexane, 1.13 mmol) in THF (1.5 mL). After 30 min at 0 °C, phosphate buffer (pH 7) was added to quench the reaction.

Usual workup and following purification by thin layer chromatography on silica gel (hexane–AcOEt 20:1) gave **4a** (247 mg, 85%). IR (neat) 3060, 2950, 1665, 1590, 1490, 1320, 1280, 1165, 1110, 1070, 1025, 940, 745, 690 cm^{-1}. ^1H NMR (C_6D_6, for 2:1 *E/Z* mixture) δ=0.70 (2.1H, t, *J*=7.3 Hz), 0.85 (0.9H, t, *J*=7.3 Hz), 1.19 (1.4H, tq, *J*=7.3, 7.3 Hz), 1.37 (0.6H, tq, *J*=7.3, 7.3 Hz), 1.45–1.70 (2H, m), 2.66 (1.4H, t, *J*=7.9 Hz), 2.87 (0.6H, t, *J*=7.9 Hz), 6.64–7.38 (13H, m), 7.96–8.07 (0.6H, m), 8.12–8.24 (1.4H, m). ^{13}C NMR ($CDCl_3$) major isomer: δ=13.7, 22.7, 30.0, 30.3, 117.8, 123.1, 127.5, 128.6, 128.7, 129.3, 129.3, 131.0, 131.7, 133.2, 136.3, 137.4, 144.2, 155.0, 196.2; minor isomer: δ=13.9, 22.6, 31.0, 31.5, 117.9, 122.9, 127.5, 128.3, 128.7, 128.9, 128.9, 131.2, 131.4, 132.9, 133.9, 137.1, 146.2, 155.1, 196.6. MS (70 eV) *m/z* 389 (M^+), 295, 280, 279, 223. HRMS Found: *m/z* 388.1484. Calcd for $C_{25}H_{24}O_2S$: M, 388.1497. Anal. Found: C, 76.88; H, 6.35. Calcd for $C_{25}H_{24}O_2S$: C, 77.29; H, 6.23.

2-Butyl-1-phenyl-3-(3-phenylpropoxy)-3-phenylthio-2-propen-1-one (4b) Compound **4b** was prepared by the method described for **4a** using **1a**, lithium 3-phenylpropanolate, and lithium benzenethiolate. Purification by thin layer chromatography on silica gel (hexane–AcOEt 20:1) gave **4b**. IR (neat) 2950, 1660, 1600, 1585, 1455, 1320, 1280, 1140, 1025, 745, 700 cm^{-1}. ^1H NMR ($CDCl_3$, for 3:2 *E/Z* mixture) δ=0.89 (1.8H, t, *J*=7.3 Hz), 0.90 (1.2H, t, *J*=7.3 Hz), 1.05–1.13 (1.2H, m), 1.32–1.52 (4H, m), 1.85–1.91 (0.8H, m), 1.98 (1.2H, t, *J*=7.8 Hz), 2.60 (0.8H, t, *J*=8.1 Hz), 2.61 (0.8H, t, *J*=7.8 Hz), 2.69 (1.2H, t, *J*=7.6 Hz), 3.52 (1.2H, t, *J*=6.3 Hz), 3.91 (0.8H, t, *J*=6.3 Hz), 6.77 (1.2H, d, *J*=7.0 Hz), 7.06–7.54 (11.8H, m), 7.83–7.93 (2H, m). ^{13}C NMR ($CDCl_3$) major isomer: δ=13.9, 22.7, 30.2, 31.5, 31.5, 31.5, 69.5, 125.6, 126.9, 128.1, 128.2, 128.4, 128.5, 129.2, 129.3, 130.2, 132.5, 132.7, 139.2, 141.5, 147.0, 198.1; minor isomer: δ=13.8, 22.8, 29.8, 30.7, 31.1, 32.2, 69.1, 125.9, 126.6, 128.3, 128.4, 128.4, 128.6, 128.9, 129.1, 132.4, 132.7, 133.6, 138.1, 141.4, 151.1, 196.9. MS (70 eV) *m/z* 430 (M^+), 203, 105, 91, 77. HRMS Found: *m/z* 430.1926. Calcd for $C_{28}H_{30}O_2S$: M, 430.1966. Anal. Found: C, 77.77; H, 6.96. Calcd for $C_{28}H_{30}O_2S$: C, 78.10; H, 7.02.

2-Butyl-1-phenyl-3-(3-phenylpropoxy)-3-ethylthio-2-propen-1-one (4c) Compound **4c** was prepared by the method described for **4a** using **1a**, lithium 3-phenylpropanolate, and lithium ethanethiolate. Purification by thin layer chromatography on silica gel (hexane–AcOEt 10:1) gave **4c**. IR (neat) 2900, 1660, 1600, 1455, 1320, 1280, 1130, 940, 700 cm^{-1}. ^1H NMR ($CDCl_3$, for 3:2 *E/Z* mixture) δ=0.87 (1.2H, t, *J*=7.3 Hz), 0.89 (1.8H, t, *J*=7.3 Hz), 1.03 (1.2H, t, *J*=7.3 Hz), 1.28–1.44 (5.2H, m), 1.30 (1.8H, t, *J*=7.3 Hz), 2.00–2.08 (0.8H, m), 2.23 (1.2H, t, *J*=7.8 Hz), 2.47 (0.8H, q, *J*=7.3 Hz), 2.50 (0.8H, t, *J*=7.6 Hz), 2.57 (1.2H, t, *J*=7.6 Hz), 2.62 (1.2H, q, *J*=7.3 Hz), 2.80 (0.8H, t, *J*=7.8 Hz), 3.62 (1.2H, t, *J*=6.4 Hz), 3.98 (0.8H, t, *J*=6.4 Hz), 6.96 (1.2H, d, *J*=7.0 Hz), 7.11–7.33 (3.8H, m), 7.42 (2H, q, *J*=8.1 Hz), 7.47–7.55 (1H, m), 7.79–7.84 (1.2H, m), 7.87–7.92 (0.8H, m). ^{13}C NMR ($CDCl_3$) major isomer: δ=13.8, 15.2, 22.6, 25.8, 30.4, 31.3, 31.3, 31.8, 70.1, 125.8, 128.2, 128.7, 129.5, 132.4, 139.2, 141.5, 152.9, 198.3; minor isomer: δ=13.9, 14.3, 22.8, 26.7, 29.6, 30.7, 31.3, 32.4, 69.3, 126.0, 128.3, 128.4, 128.5, 129.1, 131.0, 132.6, 138.4, 141.4, 149.6, 197.4. MS (70 eV) *m/z* 382 (M^+), 203, 118, 105, 91, 77. HRMS Found: *m/z* 382.1930. Calcd for $C_{24}H_{30}O_2S$: M, 382.1966. Anal. Found: C, 75.47; H, 7.77. Calcd for $C_{24}H_{30}O_2S$: C, 75.35; H, 7.90.

2-Butyl-3-ethylthio-1-phenyl-3-phenylthio-2-propen-1-one (4d) Compound **4d** was prepared by the method described for **4a** using **1a**, lithium ethanethiolate, and lithium benzenethiolate. Purification by thin layer chromatography on silica gel (hexane–AcOEt 10:1) gave **4d**. IR (neat) 2950, 1665, 1580, 1450, 1315, 1265, 1025, 740, 685 cm^{-1}. ^1H NMR ($CDCl_3$, for 3:2 *E/Z* mixture) δ=0.86 (1.2H, t, *J*=7.3 Hz), 0.90 (1.8H, t, *J*=7.3 Hz), 0.93 (1.2H, t, *J*=7.3 Hz), 1.24 (1.8H, t, *J*=7.3 Hz), 1.29–1.55 (4H, m), 2.53 (0.8H, q, *J*=7.3 Hz), 2.69–2.80 (2H, m), 2.75 (1.2H, q, *J*=7.3 Hz), 7.15–7.58 (8H, m), 7.88–7.95 (2H, m). ^{13}C NMR ($CDCl_3$) major isomer: δ=13.8, 15.2, 22.8, 26.9, 30.4, 34.2, 126.9, 128.6, 128.7, 128.9, 129.2, 129.5, 133.2, 134.4, 136.5, 152.6, 197.0; minor isomer: δ=13.8, 14.2, 22.7, 27.9, 30.6, 34.6, 127.0, 128.6,

129.0, 129.2, 129.8, 130.5, 133.2, 133.9, 136.5, 152.2, 197.1. MS (70 eV) *m/z* 356 (M^+), 327, 247, 105 (base peak), 77. Anal. Found: C, 70.47; H, 6.75. Calcd for $C_{21}H_{24}OS_2$: C, 70.74; H, 6.78.

2-Butyl-3-diethylamino-1-phenyl-3-phenylthio-2-propen-1-one (4e) Diethylamine (129 mg, 1.76 mmol) was added to the THF (2.5 mL) solution of **1a** (198 mg, 0.88 mmol) at 0 °C under a nitrogen atmosphere. The mixture was stirred for 30 min and then treated at 0 °C with lithium benzenethiolate generated from benzenethiol (117 mg, 1.06 mmol) and butyllithium (0.67 mL, 1.58 M in hexane, 1.06 mmol) in THF (1.5 mL). After 30 min at 0 °C, phosphate buffer (pH 7) was added to quench the reaction. Usual workup and purification by thin layer chromatography on silica gel (hexane–AcOEt 10:1) gave **4e** (291 mg, 90%). IR (neat) 2975, 1630, 1550, 1450, 1385, 1320, 1280, 1110, 1075, 940, 745, 695 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.52 (6H, br s), 0.87 (3H, t, *J*=7.3 Hz), 1.33 (2H, tq, *J*=7.3, 7.3 Hz), 1.38–1.47 (2H, m), 2.75 (2H, br s), 2.84 (4H, br q, *J*=6.7 Hz), 7.18–7.47 (8H, m), 7.72–7.80 (2H, m). ^{13}C NMR ($CDCl_3$) δ=12.2 (br), 14.0, 22.9, 32.4 (br), 33.4, 46.4, 125.4 (br), 127.2, 128.1, 128.4, 129.0, 131.3, 131.5, 134.9, 141.1, 155.2 (br), 199.3. MS (70 eV) *m/z* (rel intensity) 367 (M^+; 24), 258 (56), 105 (66), 100 (100), 77 (32), 72 (20). Anal. Found: C, 75.23; H, 8.26; N, 3.84. Calcd for $C_{23}H_{29}NOS$: C, 75.16; H, 7.95; N, 3.81.

2-Butyl-3-diethylamino-3-ethylthio-1-phenyl-2-propen-1-one (4f) Compound **4f** was prepared by the method described for **4e** using **1a**, diethylamine, and ethanethiolate. Purification by thin layer chromatography on silica gel (hexane–AcOEt 10:1) gave **4f**. IR (neat) 2975, 1630, 1550, 1450, 1385, 1320, 1280, 1215, 1110, 1075, 940, 725, 695 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.78 (6H, t, *J*=7.1 Hz), 0.88 (3H, t, *J*=7.2 Hz), 1.16 (3H, t, *J*=7.3 Hz), 1.33 (2H, tq, *J*=7.2, 7.2 Hz), 1.37–1.46 (2H, m), 2.53 (2H, q, *J*=7.3 Hz), 2.61 (2H, t, *J*=7.9 Hz), 3.04 (4H, q, *J*=7.1 Hz), 7.33–7.46 (3H, m), 7.68–7.73 (2H, m). ^{13}C NMR ($CDCl_3$) δ=12.8, 14.0, 14.9, 22.9, 27.6, 32.1, 33.3, 45.9, 125.8 (br), 128.0, 128.3, 131.2, 141.6, 155.2 (br), 199.4. MS (70 eV) *m/z* (rel intensity) 319 (M^+; 14), 290 (16), 276 (25), 214 (52), 105 (100), 100 (60), 77 (39), 72 (26). Anal. Found: C, 71.40; H, 9.17; N, 4.08. Calcd for $C_{19}H_{29}NOS$: C, 71.43; H, 9.15; N, 4.38.

***N*-(2-Butyl-3-oxo-3-phenyl-1-phenylthiopropylidene)benzylamine (4g)** Compound **4g** was prepared by the method described for **4e** using **1a**, benzylamine, and benzenethiolate. Purification by thin layer chromatography on silica gel (hexane–AcOEt 8:1) gave **4g**. IR (neat) 2950, 1690, 1625, 1450, 1345, 1230, 1000, 930, 730, 695 cm^{-1}. ^1H NMR ($CDCl_3$) δ=0.81 (3H, t, *J*=7.2 Hz), 1.14–1.25 (4H, m), 1.85–1.99 (2H, m), 4.18 (1H, t, *J*=6.3 Hz), 4.70 (1H, d, *J*=16.3 Hz), 4.74 (1H, d, *J*=16.3 Hz), 7.16–7.39 (10H, m), 7.46–7.57 (3H, m), 7.63–7.67 (2H, m). ^{13}C NMR ($CDCl_3$) δ=13.9, 22.6, 30.1, 30.3, 55.0, 56.6, 126.4, 127.4, 128.2, 128.3, 129.6, 129.6, 130.0, 132.6, 136.2, 136.7, 139.4, 161.0, 196.6. MS (70 eV) *m/z* 402 (M^++H), 292, 110, 105, 91, 77. HRMS Found: *m/z* 402.1883. Calcd for $C_{26}H_{28}NOS$: M+H, 402.1891.

2-Butyl-N^1,N^1-diethyl-3-oxo-3,N^2-diphenylpropanamidine (4h) Diethylamine (91 mg, 1.24 mmol) was added to the THF (2.5 mL) solution of **1a** (139 mg, 0.62 mmol) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred for 1 h, and then aniline (127 mg, 1.36 mmol) was added. After 2 h stirring at room temperature, the solvent was removed under reduced pressure without quenching. The residue was purified by flash column chromatography on silica gel (hexane–AcOEt 10:1) to give **4h** (184 mg, 85%). IR (neat) 2950, 1680, 1585, 1450, 1425, 1255, 1190, 1070, 935, 775, 700 cm^{-1}. ^1H NMR (C_6D_6) δ=0.85 (3H, t, *J*=7.3 Hz), 0.85 (6H, t, *J*=6.7 Hz), 1.14–1.43 (4H, m), 1.65–1.74 (1H, m), 2.49–2.60 (1H, m), 3.13–3.25 (4H, m), 4.36 (1H, dd, *J*=9.2, 2.5 Hz), 6.93–7.13 (6H, m), 7.24–7.30 (2H, m), 7.94–7.99 (2H, m). ^{13}C NMR (C_6D_6) δ=13.0, 14.1, 23.1, 30.3, 30.7, 42.1, 51.5, 122.0, 123.1, 128.4, 128.7, 129.3, 132.9, 137.5, 151.8, 156.2, 197.9. MS (70 eV) *m/z* (rel intensity) 350 (M^+; 11), 294 (14), 245 (48), 172 (15), 130 (16), 105 (100), 77 (76). HRMS Found: *m/z* 350.2331. Calcd for $C_{23}H_{30}N_2O$: M, 350.2358.

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12. In some cases, α-oxoketene imines can be isolated, which results will be presented in due course.

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