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A Serendipitous Synthesis of Bis-Heterocyclic Spiro 3(*2H*)-Furanones

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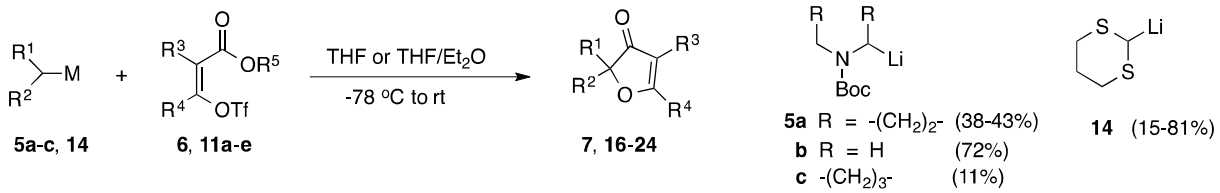


ABSTRACT

(*Z*) Enol triflates **6**, **11b-d**, (*E*) enol triflate **11e** and phenol triflate **11a**, derived from *β*-keto esters or 2-carboalkoxy phenols, respectively, react with *N*-Boc 2-lithiopyrrodidine (**5a**), *N*-Boc *N*-methylaminomethyllithium (**5b**) or 2-lithio-1,3-dithiane (**14)** to afford 3(*2H*)-furanones in modest to good yields (38-81%). Product and carbanion reagent studies suggest that the 3(2*H*)-furanone is formed in a cascade of reactions involving nucleophilic acyl substitution, enolate formation, trifluoromethyl transfer, iminium or sulfenium ion formation and subsequent ring closure to form the 3(2*H*)-furanone. The use of 2-lithio-1,3-dithiane affords a cyclic α-keto-*S*,*S*,*O*-orthoester in which the functionality can be selectively manipulated for synthetic applications.

INTRODUCTION

The 3(*2H*)-furanone core[1] (Figure 1, **1**) is present in several biologically active natural products such as Eremantholide A-C,[2] Geiparvarin,[3] and Bullatenone.[4] Jatrophone,[5] Pseurotin A,[6] Armeniaspirole A (**2**), B, and C[7a] are related natural products containing a spiro-furanone core and they and their derivatives[7b] are also of pharmaceutical interest.[7c] Pioneering work on the

syntheses of compounds containing the 3(*2H*)-furanone motif[1] was reported in the early 1980s by Smith and coworkers culminating in the synthesis of Jatrophone.[5b,c] A structurally related class of natural products contain a spirocyclic 3(2H)-benzofuranone moiety[8] illustrated by Griseofulvin.[8a] In the intervening years, synthetic methodologies have been developed for the regioselective introduction of varied substituents on the 3(*2H*)-furanone core,[9] the synthesis of 5-amino substituted derivatives,[10] the intramolecular condensation of α-acyloxy ketones at high temperature,[11] the application of Green Chemistry approaches[12] and the utilization of catalytic amounts of transition metals.[13]

The syntheses of spiro compounds has focused on carbocyclic spiro 3(2*H*)-furanones (e.g., **3,** Scheme 1) where one of the earliest reports came from Lehmann who prepared butenolides from cyclic *α*-acyloxy ketones via intramoleculare ester enolate addition to the ketone moiety.[14] Akita and co-workers[15] employed a similar protocol to convert *γ*-acetoxy-*β*-ketoesters derived from 1-alkynyl-1-acetoxy derviatives to spiro 3(2*H*)-furanones. Using transition metal catalysis in a protocol involving backbone rearrangement, the Kirsch group prepared C5-substituted spiro furanones from *α*-alkynyl-*α*-hydroxy ketones[16a] and C4-iodo C3-substituted spiro furanones from *α*-alkynyl-*α*-silyloxy ketones.[16b] More recent strategies include Au(I)-catalyzed intramolecular cyclization of *γ*-acyloxy-α,β-alkynyl ketones,[17] the intermolecular cyclization of *γ*-arylacyloxy[18a] or γ-alkylacyloxy-β-keto[18b] nitriles derived from γ-hydroxy-α,β-alkynyl nitriles and aryl or aliphatic carboxylic acids, and a copper mediated domino reaction between nitriles and propargylic alcohols induced by CO_2.[19]

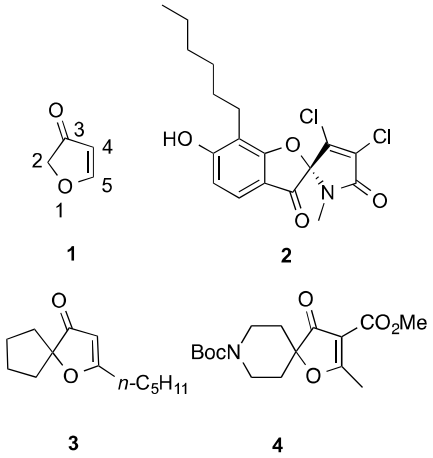
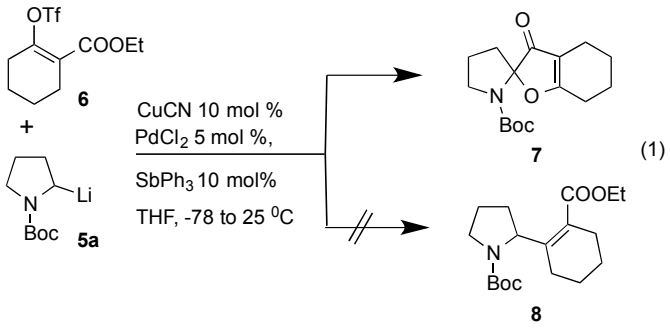


Figure 1. 3(*2H*)-Furanone (**1**), Armeniaspirole A (**2**),[7a] Carbocyclic Spiro Furanone (**3**),[17] and (**4**).[15]

Spiro furanones in which both rings of the spiro fused system are heterocyclic (e.g., **2**) are few in number and have only recently been reported;[7, 15,20] Among these compounds, the Armeniaspiroles A-C and their derivatives display antibiotic activity against Gram-positive bacteria.[7] During the course of our studies on the coupling of *α*-(*N*-Carbamoyl)-alkylcuprates[21] (e.g., **5a**) with enol triflates,[22] we observed the formation of spiro-furanone **7** instead of the expected coupling product **8** (eq. 1). We now report a detailed study of the scope and limitations in the reactions of organolithium reagents with (*Z*) enol triflates derived from *β*-keto esters as a synthetic protocol for the synthesis of 3(2*H*)-furanones.



RESULTS AND DISCUSSION

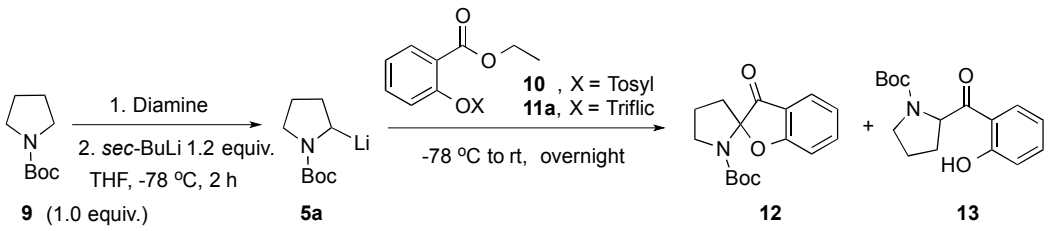
Initially, the attempted palladium promoted coupling of *N*-Boc-2-pyrrolidinyllithium **5a** with triflate **6** gave the 3(2*H*)-furanone derivative **7** instead of enoate **8** (eq. 1), which seemed uncharacteristic of a palladium promoted reaction pathway. Control experiments wherein the metals (i.e., CuCN, $PdCl_2$) and ligands (i.e., $SbPh_3$) were removed from the reaction mixture also afforded **7** in comparable yields. A study of substrate, diamine additive and solvent was then undertaken.

Tosylate **10,** prepared from ethyl salycilate, gave poor yields of spiro furanone **12** (Table 1, entries 1-6). Starting materials were the major components isolated from the crude reaction mixture, which also yielded phenol **13**. Switching from tosylate **10** to triflate **11a** increased the yield of **12** (Table 1, entries 7-16) and reduced considerably the amount of starting materials recovered. Here, the combined effect of the diamine and the solvent does not afford the high yields we observed when coupling α-(*N*-carbamoyl)-alkylcuprates with iodo vinylesters, enol triflates, or other electrophiles in which the best results were obtained with mixtures of THF/TMEDA or Et_2O/(-)-sparteine.[22-23] In these prior experiments, the α-(*N*-carbamoyl)alkylcuprate reagents were generated at -78 ^{o}C from the organolithium reagents and when the cuprates were generated at higher temperatures and for various periods of time lower and variable yields of products were obtained similar to those observed in the present reaction (Table 1). These observations are consistent with prior reports on the thermal instability of *N*-Boc 2-lithiopyrrolidine.[21,24]

The highest yields of **12** were obtained in THF using (-)-sparteine as an additive (entries 7 & 13), while lower yields were generally obtained with TMEDA (entries 8 & 12) and in less polar solvents (e.g., Et_2O, entry 15; ^{t}BuOMe, entry 9-10). It is intriguing that higher yields of **12**

were obtained with 2.2 equivalents of TMEDA in TBME than with 1.2 equivalents of (-)-sparteine in the same solvent (entries 9-10), while 6.0 equivalents of either diamine in THF gave comparable yields of **12** (entries 11-12) but lower than that obtained with 1.2 equivalents of (-)-sparteine in THF (entries 7 & 13). The yields of **12** obtained under these various conditions suggest the influence of multiple factors such as efficacy of deprotonation of **9** and the reactivity of **5a** with **11a**, which could be diminished by coordination of **5a** with diamine (i.e., entries 9-12). A diminished rate for reaction of **5a** with **11a** would allow for non-productive side reactions. The diamines are employed to facilitate deprotontion of the carbamate, and although Campos and co-workers[25] have reported the deprotonation of *N*-Boc heterocycles in THF without diamine, we could not reproduce or apply this diamine-free deprotonation protocol to this reaction. In general, spiro furanone **12** could be prepared in moderate yields accompanied by starting material and phenol **13** (approx. 20%).

Table 1. Solvent and Additive Effects on the Yield of 3(*2H*)-furanone 12.



entry	diamine (eq)	substrate (eq)	solvent[a]	yield of **12** (%)[b]	yield of **13** (%)[b]
1	TMEDA (2.2)	**10** (0.9)	THF	8	25
2	TMEDA (2.2)	**10** (0.5)	THF	10	23
3[c]	TMEDA (2.2)	**10** (0.5)	Et_2O	4	—
4	(-)-sparteine (1.2)	**10** (0.9)	THF	7	25
5	(-)-sparteine (1.2)	**10** (0.5)	THF	7	28
6[c]	(-)-sparteine (1.2)	**10** (0.5)	Et_2O	4	—
7	(-)-sparteine (1.2)	**11a** (0.5)	THF	65	11
8[c]	TMEDA (2.2)	**11a** (0.5)	THF	30	—
9[c]	(-)-sparteine (1.2)	**11a** (0.5)	TBME	31	—
10	TMEDA (2.2)	**11a** (0.5)	TBME	52	17
11[c]	(-)-sparteine (6.0)	**11a** (0.5)	THF	47	—
12[c]	TMEDA (6.0)	**11a** (0.5)	THF	44	—
13[d]	(-)-sparteine (1.2)	**11a** (0.5)	THF	65	24
14[c,e]	(-)-sparteine (1.2)	**11a** (0.5)	THF	42	—
15[c]	(-)-sparteine (1.2)	**11a** (0.5)	Et_2O	30	—
16[c]	—	**11a** (0.5)	THF	16	—

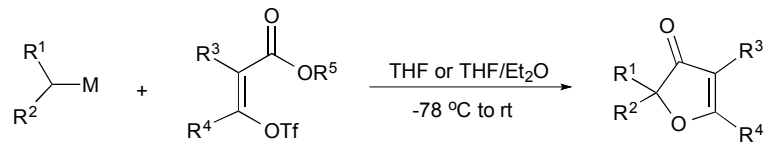
[a]Solvent with a composition for the reaction of 10/1 solvent/organometallic solvent (cyclohexane/hexane) unless otherwise noted. [b]Determined from isolated material purified by column chromatography. [c]The yield of product **13** was not determined. [d] Upon reaching room temperature, the reaction mixture was heated at reflux for 2 h. [e]$SbPh_3$ (0.15 equiv.) was added along with the diamine.

The scope of the reaction was briefly examined with a combination of carbanions and enol or phenol triflates (Table 2). Lithiocarbamate **5a** gave lower yields of furanones **7** and **16**, respectively, with cyclohexenyl triflate **6** and acyclic triflate **11b** (entries 1-2) than furnanone **12** with triflate **11a** (Table 1). Two additional α-lithiocarbamates derived from *N*-Boc-dimethylamine and *N*-Boc piperidine were then examined. These amines were *α*-lithiated with

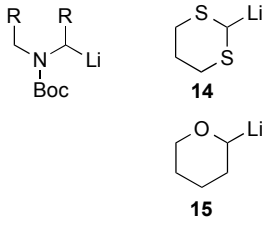
sec-BuLi in the presence of TMEDA or (-)-sparteine, to generate α-lithiated carbamates **5b-c**, respectively (Table 2, entries 3-5).

While the secondary α-lithiocarbamate **5c** afforded very low yields of furanone **18** (entry 5), the primary carbanion **5b** gave a good yield of the 2-carbamoylfuranone **17** when generated in the presense of (-)-sparteine (entry 3) but not with TMEDA (entry 4). Good yields of spiro-furanones could be obtained with 2-lithio-1,3-dithiane **14** and cyclic triflates **6**, **11a** (entries 6-7 & 9), although low yields of **19** were obtained in a THF/Et_2O solvent mixture (entry 8). For triflate **11a** and dithiane **14**, comparable yields of furnanone **19** were obtained with either 2.0 or 1.2 equivalents of 2-lithio-1,3-dithiane (i.e., **14**, entry 6 vs. 7). Recovery of starting sulfonate ester and low yields of **19** resulted when tosylate **10** or the corresponding mesylate were used in place of triflate **11a**. Carbanion **14** gave good yields of furanone **20** with cyclic triflate **6** (entry 9) but modest to low yields of furanones **21**-**22** (entries 10-11) with acyclic triflates **11b-c**, respectively. Closer examination of the product mixture from reaction of **14** with **11b** indicated that E2 elimination, nucleophilic acyl substitution, and ketone 1,2-nucleophilic addition reactions occurred competitively even when sequential reactions were involved in product formation (Table 3). The product distribution could be subtly altered by change of reaction conditions but no conditions were found to afford the furanone exclusively. The major product obtained with triflate **11c**, methyl 3-phenylproynoate, arises via a base induced elimination of triflic acid.

Table 2. Heterocyclic 3(*2H*)-furanones.

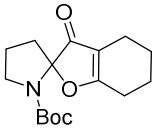
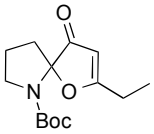
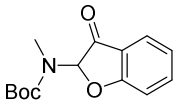
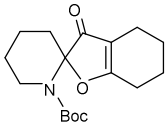
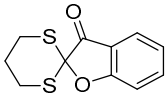


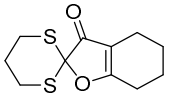
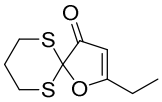
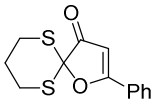
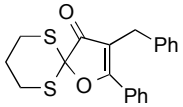
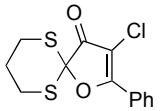
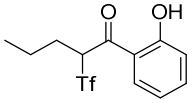
Carbanions (R^1R^2M)



Enol/phenol triflates

6 $R^3 = R^4 = -(CH_2)_4-$, R^5 = Et
11a $R^3 = R^4 = -(CH)_4-$, R^5 = Et
11b R^3 = H, R^4 = Et, R^5 = Me
11c R^3 = H, R^4 = Ph, R^5 = Et
11d $R^3 = PhCH_2$, R^4 = Ph, R^5 = Et
11e R^3 = Cl, R^4 = Ph, R^5 = Et

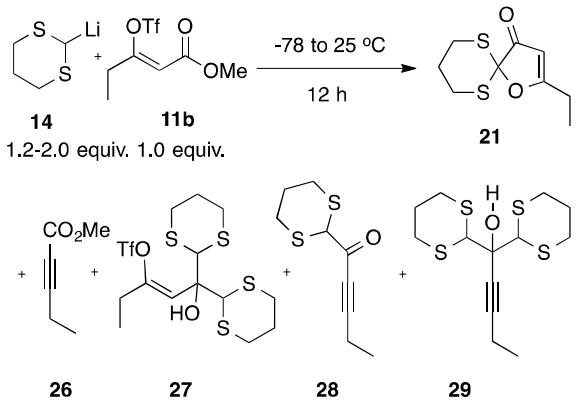
entry[a]	carbanion	enol/phenol triflate	product	yield (%)[b]
1	**5a**	**6**	 **7**	43
2	**5a**	**11b**	 **16**	38
3[c]	**5b**	**11a**	 **17**	72
4[d]	**5b**	**11a**	**17**	25
5[e]	**5c**	**6**	 **18**	11
6[f]	**14**	**11a**	 **19**	75
7[g]	**14**	**11a**	**19**	68
8[h]	**14**	**11a**	**19**	33

9	**14**	**6**	 **20**	68
10[i]	**14**	**11b**	 **21**	40
11[j]	**14**	**11c**	 **22**	15[k]
12	**14**	**11d**	 **23**	71
13[l]	**14**	**11d**	**23**	50
14[m]	**14**	**11e**	 **24**	68
15	[n]BuLi	**11a**	 **25**	68
16[n]	[n]BuLi	**11a**	**25**	40
17[o]	[n]BuMgCl	**11a**	—	—
18[p]	**15**	**11a**	—	—

[a]THF was used as solvent with a composition for the reaction of 10/1 solvent/organometallic solvent (hexanes) unless otherwise noted. Reactions were run from -78 °C for 2 h then slowly warmed up to 25 °C for a total of 8-12 h; with 2.0 equiv. of R^1R^2 M (M = Li, MgCl) and 1.0 equiv of enol or phenol triflate. When a protected amine was employed, 1.2 equiv. of (-)-sparteine was used unless otherwise noted. [b]Based upon isolated material purified by column chromatography unless otherwise noted. [c]Deprotonation for 1 h at -78 °C with 1.2 equiv. of (-)-sparteine. [d]Deprotonation

for 1.5 h at -78 °C with 2.4 equiv. of TMEDA. [e]Deprotonation for 4 h at -78 °C with 2.2 equiv. of TMEDA. [f]Byproducts formed included 1,3-dithian-2-yl 2-hydroxymethyl ketone (9%) and ethyl 2-hydroxybenzoate (2%). [g]Employing 1.22 equiv. of 2-lithio-1,3-dithiane, 1,3-dithian-2-yl 2-hydroxymethyl ketone (9%) and ethyl 2-hydroxybenzoate (3%) were formed as byproducts. [h]The solvent ratio THF:Et_2O was 1:2. Starting materials were recovered. [i]2-Lithio-1,3-dithiane **14** (1.2 equiv.) in a solvent mixture of THF:Et_2O (1/2) was employed. The elimination product, methyl 2-pentynoate (31%) was formed as a major byproduct. [j]1.2 equiv. of **14** was employed. [k]Molar ratio estimated from the ^{1}H-NMR spectrum of the crude reaction mixture. The major product formed was the elimination product ethyl 3-phenylpropynoate. Same result was obtained when the reaction mixture was quenched at -78 °C after 2 h. [l]2-Lithio-1,3-dithiane was employed at 1.2 equivalents. [m]2-Lithio-1,3-dithiane was employed at 1.0 equiv., reaction mixture was kept at -78 °C for 2.5 h and quenched with brine at -78 °C. [n]Employing 1.25 equiv. of ^{n}BuLi, triflate **11a** (35%) and ethyl 2-hydroxybenzoate (3%) were recovered. [o]Starting material **11a** was recovered in 85%. [p]2-Lithio tetrahydropyran was generated from 2-phenylthiotetrahyropyran with 1.0 equiv. of lithium napthalenide (LN) or 2.0 equiv. of lithium 1-(dimethylamino)naphthalenide (LNMAN) respectively.

Table 3. Product Distribution from Reaction of 14 with 11b.



	14		products[b]
entry[a]	equiv.	solvent, ratio	**21**:**26**:**27**:**28**:**29**
1	1.2	THF	- :65: - : - : -
2	1.2	THF:Et_2O, 1:3	22:25:25: - : -
3	2.0	THF	13: - : - :30:33
4	2.0	THF:Et_2O, 1:2	40: - : - : 5:31
5	2.0	THF:Et_2O, 1:5	37: - : - : 5:33

[a]Solvent with a composition for the reaction of 10/1 solvent/organometallic solvent (hexanes). [b]Determined from isolated material purified by column chromatography

X-ray crystallographic data were obtained for compounds **7**, **12**, **19** and **20** confirming the structure of these heterocyclic spiro compounds and the ORTEP drawing for **19** is shown in Figure 2.

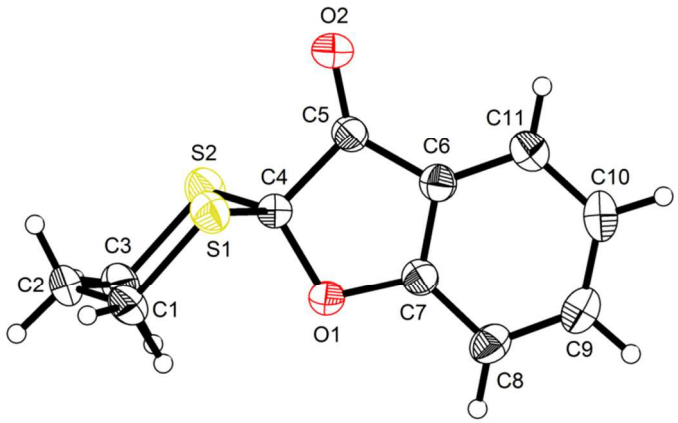
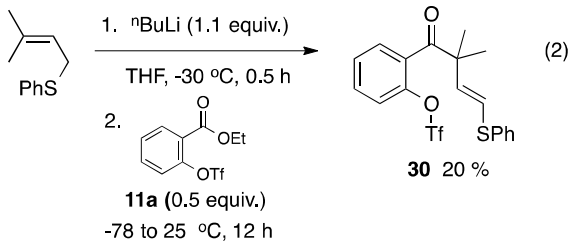
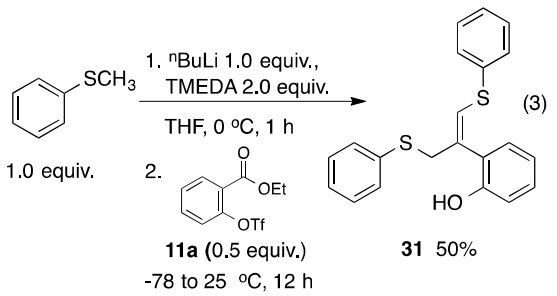


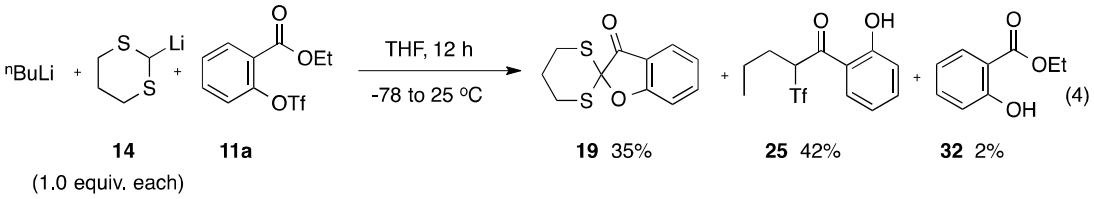
Figure 2. ORTEP Drawing of Spiro 3(2*H*)-furanone 19 at 50% ellipsoid contour.

Furanones were not obtained with several carbanions. Reaction of triflate **11a** with α-thio-stabilized carbanions did afford initial nucleophilic acyl substitution but with allylic rearrangement of the carbanion moiety (i.e., E2') (eq. 2) or olefination of the resultant phenylthiomethyl ketone via 1,2-nucleophilic addition and loss of water (eq. 3). When triflate **11a** was reacted with ^{n}BuLi, nucleophilic acyl substitution followed by intramolecular sulfonyl migration occurred to give ketone **25** (Table 2, entry 15) and the yield of **25** was diminished when only 1.25 equivalents of ^{n}BuLi was employed (entry 16). No major products were isolated upon reaction of ^{n}BuMgCl. In an attempt to expand this methodology to oxygen containing heterocycles, *α*-lithio ether **15** was prepared[26-27] by lithiation of 2-(phenylthio)tetrahydropyran[28] with lithium naphthalide or lithium dimethylaminonaphthalide.[29] Reaction of 2-lithiotetrahydropyran (**15**, entry 18) with triflate **11a** afforded PhS-SPh, recover starting materials, and unidentified by-broducts of high molecular weight even though **15** was successfully reacted with benzophenone to give the tertiary alcohol (50% yield).

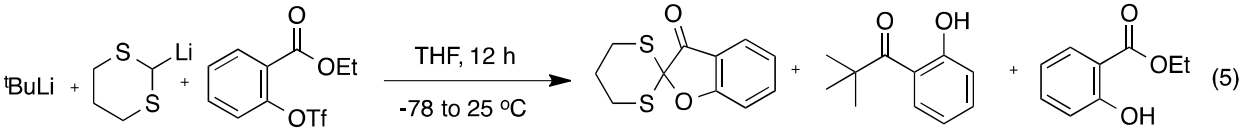




Several competition experiments were performed using two different nucleophiles. Reaction of triflate **11a** with equimolar amounts of **14** and ^{n}BuLi gave similar yields of furanone **19** and ketone **25** (eq. 4**)**, while equimolar amounts of **14** and ^{t}BuLi gave comparable yields of **19** and the *tert*-butyl ketone **33** (eq. 5). In both cases, very minor amounts of the desulfonated product **32** was obtained suggesting that intermolecular desulfonation is not competitive with the intramolecular pathway and that the nucleophilic acyl substitution reaction is only slightly sensitive to carbanion nucleophilicity and steric hindrance.



14 (1.0 equiv. each) **11a** **19** 35% **25** 42% **32** 2%

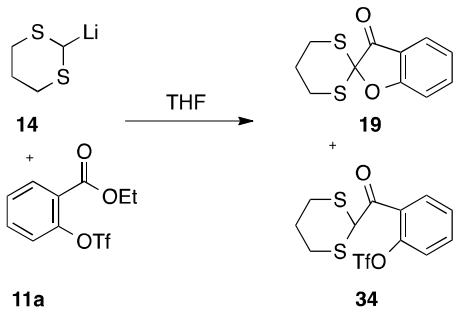


14 (1.0 equiv. each) **11a** **19** 44% **33** 31% **32** 2%

The reaction of **14** with triflate **11a** displayed an informative temperature profile (Table 4). As the temperature at which **11a** was added to **14** was raised, the yield of **19** decreased (entries 1-3). Surprisingly, the highest yield of **19** was obtained when the reaction mixture was quenched at -78 °C after 30 minutes (entry 5) and no diminution of yield was observed upon longer reaction times at -78 °C (entry 4). In these high yielding reactions, the 2-lithio-1,3-dithiane was generated at -40 to -20 °C. When **14** was generated at 0 °C, and the reaction mixture maintained at -78 °C a roughly 3:1 ratio of **34**:**19** was generated (entries 6-7) and the ratio shifted completely to product when the solution was warmed to room temperature (entry 8). These

results implicate the thermal stability of **14** and a role of the lithium ethoxide generated in the nucleophilic acyl substitution reaction.

Table 4. Temperature and Time Dependence in the Formation of 19



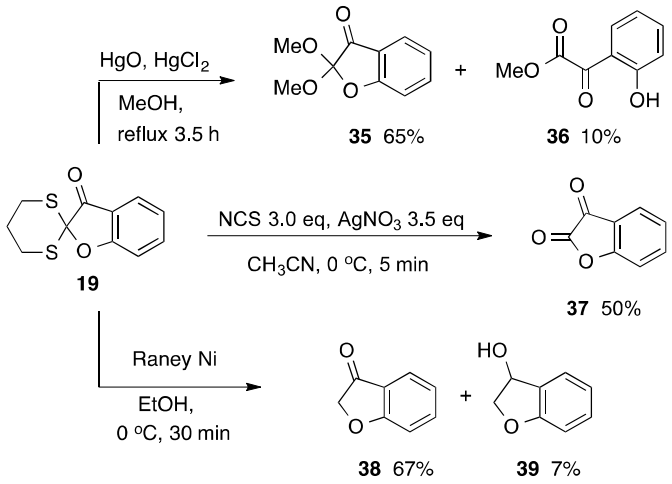
entry	rxn cond. °C (h)[a]	% yield **19** or **34**:**19**[b]
1	-78 (2), to 25 (12)	75
2	-40 (1), to 25 (12)	43
3	0 (1), to 25 (12)	38
4	-78 (1.33)	80[c]
5	-78 (0.5)	81[c]
6[d]	-78 (1.33)	72:28
7[d]	-78 (1.33)	68:32
8[d]	-78 (4), to 25 (12)	0:100

[a]The 2-lithio-1,3-dithiane was prepared at -40 to -20 °C for 40 min unless otherwise noted. [b]Yields are based upon isolated products purified by column chromatography. Product ratios were estimated from the ion-current trace obtained from GC-MS analysis. [c]The phenol derived from **34** was formed in 2-3%. [d]The 2-lithio-1,3-dithiane was prepared at 0 °C for 1 h.

The synthetic utility of **19** was briefly examined through functional group transformations (Scheme 1). Attempted deprotection of the *O*,*S*,*S*-orthoester in **19** with $HgO/HgCl_2$ afforded the *O*,*O*,*O*-orthoester **35** and minor amounts of α-ketoester **36** arising from ring opening, while utilization of *N*-chlorosuccinimide and $AgNO_3$ afforded α-ketolactone **37** in

modest yield. Desulfurization of **19** with Raney Nickel gave furanone **38** in moderate yield with minor amounts of alcohol **39** arising from over reduction. Ketolactone **37** (i.e., coumaran-2,3-dione) has previously been used in a variety of synthetic applications[30] and is generally prepared in four steps from isatin in 50% overall yield.

Scheme 1. Functional Group Transformations of 19

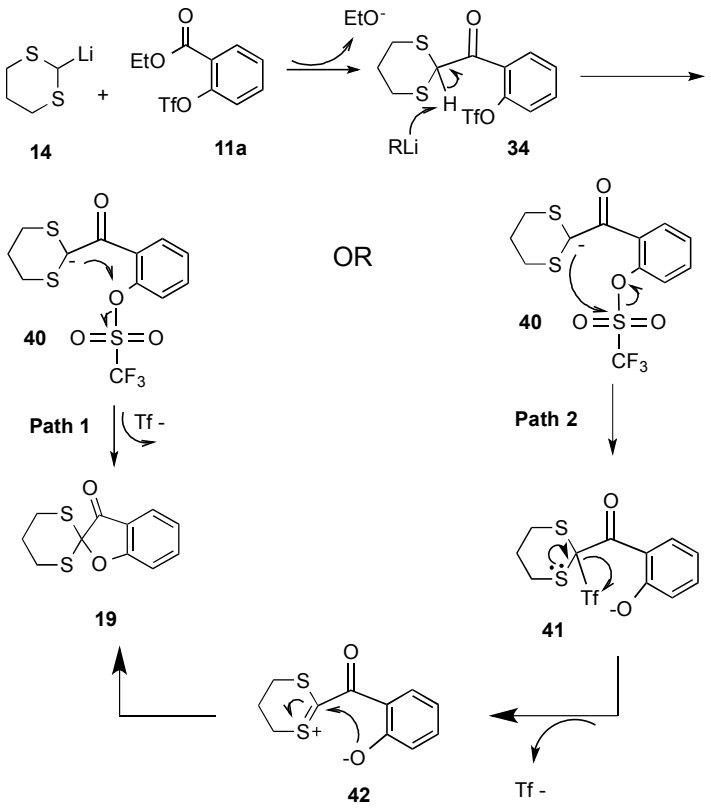


DISCUSSION

Plausible mechanistic pathways are outlined in Scheme 2 each of which begins with nucleophilic acyl substitution to give a ketone intermediate (e.g., **34**). The second equivalent of carbanion acts as a base to convert the intermediate ketone into an enolate (e.g., **40**), which can either attack the oxygen atom displacing the triflate anion directly forming the furanone (path 1) or attack the sulfur atom to transfer the trifluoromethylsulfonyl group from the oxygen atom to the carbon atom (path 2) forming an intermediate α-trifluoromethylsulfonylketone intermediate (i.e. **41**). The adjacent heteroatom can then expel the excellent leaving group affording a sulfenium (or iminium) cation **42** that is then trapped by the oxyanion (i.e., phenoxide or enolate). The experimental data is more consistent with the latter pathway. When ^{n}BuLi is employed as the nucleophile/base reactant the reaction stops at the α-trifluorosulfonylketone

stage (i.e., **25**) because there are no adjacent heteroatoms to assist in the displacement of the trifluorosulfonyl leaving group. Similarly, the low yields obtained with enol tosylates or mesylates reflect the poorer leaving group ability of the *p*-toluenesulfonyl or methanesulfonyl groups. The failure of ^{n}BuMgCl may reflect its lack of nucleophilicity and basicity. Reaction of phenylthiomethyllithium with triflate **11a** gives **31** (eq. 3) arising from successful nucleophilic acyl substitution followed by 1,2-nucleophilic addition to the resultant ketone and subsequent dehydration that could be aided by sulfonyl transfer from the phenol oxygen to the alkoxide. The utilization of 2-lithiotetrahydropyran (**15**) gives a complex mixture of products from which no major product was isolated. This pattern of reactivity suggests that a complex interplay of relative rates involving the sequential and/or competitive reactions of nucleophilic acyl substitution, enolization, 1,2-nucleophilic addition to intermediate ketones, intramolecular sulfonyl transfer, sulfenium or iminium ion formation and elimination reactions (e.g., substrates 11b-c) where possible play a crucial role in the eventual outcome of carbanion and triflate combinations. This perspective is supported by the competition experiments (eqs. 4-5) where 2-lithio-1,3-dithiane and the alkyllithium reagents give the respective products in roughly equimolar amounts across a range of basicities, nucleophilicities, and steric hindrance. It is also consistent with the temperature dependence observed for reaction of triflate **11a** with **14** where **11a** is sufficiently stable so that at higher temperatures the generated lithium ethoxide can function as the base to deprotonate **34** and drive the reaction to completion (Table 4, entries 6-8). Successful formation of **19** with 1.22 equivalents of **14** (Table 2, entry 7) also suggests deprotonation of the intermediate ketone by lithium ethoxide.

Scheme 2. Plausible Mechanistic Pathways for the Formation of Heterocyclic Spiro-furanone 19.



CONCLUSIONS

We have developed a new method for the one pot synthesis of heterocyclic spiro 3(*2H*)-furanones that can be prepared from triflates of β-keto esters or 2-carboalkoxy phenols and α-heteroatom stabilized carbanions containing either one nitrogen atom or two sulfur atoms. The product is most likely formed through a cascade of reactions involving nucleophilic acyl substitution, enolate formation, trifluoromethyl transfer, iminium or sulfenium ion formation and subsequent ring closure to form the 3(2*H*)-furanone. Consequently, the 3(2*H*)-furanone chemical yields are dependent upon the rates of the sequential reactions as well as competing side reactions and thus on temperature and solvent as well. For acyclic enol triflates (i.e., **11b-c)**, competitive E2 elimination of triflic acid arising from deprotonation of the *α*-hydrogen atom

(Table 2, entries 10-11) is faster than nucleophilic acyl substitution on the ester moiety, producing methyl 2-pentynoate and ethyl 3-phenylpropynoate respectively. This unwanted side reaction can be diminished by the use of THF/Et_2O mixtures, which increases the nucleophilic acyl substitution on **11b** or **11c** relative to the elimination reaction but increasing the Et_2O:THF ratio to more than 5 to 1 results in nucleophilic 1,2-addition of the lithiated nucleophile **14** to the intermediate ketone formed *in situ* from the initial nucleophilic acyl substitution reaction. Similarly, α-sulfur stabilized carbanions containing one sulfur atom lead to products arising from initial nucleophilic acyl substitution followed by nucleophilic 1,2-addition to the resultant ketone. Utilization of 2-lithio-1,3-dithiane affords α-keto-*O*,*S*,*S*-orthoesters in which the functionality can be manipulated for further synthetic applications.

EXPERIMENTAL SECTION

General. NMR spectra were recorded as $CDCl_3$ solutions on a 500 MHz or a 300 MHz instrument. The ^1H NMR chemical shits are reported as δ values in parts per million (ppm) relative to tetramethylsilane (TMS, δ = 0.00). The residual chloroform signal, $CHCl_3$ (δ = 7.28) was used as reference. ^{13}C NMR chemical shifts are reported as δ values in parts per million (ppm) relative to TMS and $CDCl_3$ signal (triplet, centerline δ = 77.0) as reference. Infrared (IR) spectra were recorded as neat samples (films on NaCl plates). Gas chromatography mass spectrometry (GC-MS) measurements were performed on equipment coupled to a mass spectrometer with a quadrupole detector at 70 eV. Analytical thin layer chromatography (TLC) was performed on silica gel plates, 200 μm with F254 indicator, visualization was accomplished by UV light (254 nm), 5% ethanol solution of ninhydrin or 3% ethanol solution of phosphomolybdic acid. Flash column chromatography was performed with 200-400 μm silica. Yields are reported as pure material after isolation by column chromatography. Compounds for

high resolution mass spectrometry (HRMS) were analyzed by positive mode electron ionization (EI) or electrospray ionization (ESI) using TOF detector.

Crystals were grown by slow evaporation of CH_2Cl_2 solutions. After microscopic evaluation, X-ray quality crystals were selected and mounted on glass fibers using epoxy glue. X-ray data were collected using a diffractometer equipped with a Mercury CCD area detector and Mo Kα radiation (λ = 0.7071 Å). Diffraction data were collected in 0.5 ° oscillations of ω at 200 K. Data were collected, processed and corrected for absorption and Lorentz and polarization effects using the CrystalClear software package.[31] The structures were solved by direct methods and refined by least squares refinement on F^2 using the SHELXL software package.[32] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were constrained to idealized geometries and treated as riding atoms.

Materials. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium/benzophenone. All other solvents were dried over 4Å molecular sieves. Commercially available alkyllithium solutions were titrated with *sec*-butyl alcohol and 1,10-phenanthroline.[33] Commercially available Grignard solutions were titrated with menthol and 1,10-phenanthroline.[34] The glassware was flame-dried and cooled under nitrogen. Low-temperature baths (-78 °C) were made from dry ice and 2-propanol. All the reactions were carried out under positive pressure of N_2 passed over a trap of desiccant agent (Drierite). Trifluoromethanesulfonic anhydride (triflic anhydride), Sulfuryl chloride, Raney®-Nickel activated catalyst 50 % slurry in water (CAS 7440-02-0), Methanesulfonyl chloride, ethyl 2-cyclohexanonecarboxylate, methyl propionylacetate, ethyl salicylate, Ethyl benzoylacetate, and NaH 57-63% oil dispersion were purchased from commercial sources and used as received. Tosyl chloride and 1,3-dithiane were dried under vacuum over P_2O_5 into an Abderhalden's drying tube overnight. 3,4-Dihydro-2H-

pyran was dried over 4 Å molecular sieves. *N,N,N′,N′*-Tetramethylethylenediamine (TMEDA) was distilled and stored over 4 Å molecular sieves. (-)-Sparteine was distilled and stored over 4 Å molecular sieves and kept in the fridge at 4 °C. *N*-Chlorosuccinimide was purified by recrystallization in benzene. $AgNO_3$, HgO, $HgCl_2$ were used without any further purification. *N*-Boc protected amines were prepared according to the protocol from Varala.[35] (*Z*)-*β*-Enol/phenol triflates **6**, **11a-d** and (*E*)-*β*-enol triflate **11e** were prepared from *β*-keto esters: ethyl 2-cyclohexanone carboxylate, ethyl salicylate, methyl propionylacetate, ethyl benzoylacetate, ethyl 2-benzyl-3-oxo-3-phenylpropanoate and ethyl 2-chloro-3-oxo-3-phenylpropanoate respectively using the general protocol described below. (*Z*)-*β*-Enol tosylate **10** from ethyl salicylate was prepared adapting this procedure but using tosyl chloride instead triflic anhydride.

Compounds **6**,[22] **11a**,[22] **11b**,[36] **11c**,[37] **13**,[38] **26**,[39] **33**,[40] **35**,[41] **36**,[42] **37**,[43] **38**,[44] and **39**,[45] have been reported and characterized. Data reductions are included for **11d**,[46] **11e**,[47] **13**, **35**, **37**, **38**.

For new compounds **7**, **12, 16-25**, **27-31** and **34** ^{13}C-NMR, ^{1}H-NMR, ^{19}F-NMR, GC-MS, IR, elemental analysis or HRMS data reductions are reported.

General Synthesis of (*Z*)-*β*-enol/phenol triflates (6, 11a-d) and (*E*)-*β*-enol triflate 11e. NaH 60% oil dispersion (1.3 equiv, 6.5 mmol, 260mg) was weighted into a 100 ml round bottom flask, it was rinsed with hexanes (3 x 10 ml) and flushed with N_2, then a magnetic stirrer and 25 ml of CH_2Cl_2 were added, capped with rubber septa and provided with N_2. The flask was placed into an ice bath and after 5 minutes the *β*-keto ester (1.0 equiv, 5.0 mmol) was added dropwise in three portions over a 5 minutes period. This reaction mixture was stirred for 15-20 minutes at 0°C to complete deprotonation and then cooled down to -78°C. Trifluoromethanesulfonic anhydride (1.35 equiv, 6.75 mmol, 1.13 ml) were added dropwise while keeping a strong stirring then let to warm up slowly overnight from 8-12 h. It was quenched with brine, extracted with

CH_2Cl_2 three times, concentrated in vacuo and purified over silica gel with 5% Et_2O and 95% hexanes. For compounds **6**, **11b-d**, no mixtures of *Z* and *E* *β*-enol triflates were found with this methodology. The yields obtained for these substrates are as follow **6** (1.25 g, 83%), **11a** (1.35g, 90%), **11b** (1.15g, 88%), **11c** (1.38g, 85%), **11d** (1.55 g, 75%), **11e** (1.18g, 66%).

General procedure A. Synthesis of 3(*2H*)-furanone spiro from *N*-Boc protected amines (Table 1 and Table 2). A round-bottom flask with a magnetic stir bar and septum was flame-dried under N_2, *N*-Boc protected amine (1.0 equiv, 2.0 mmol), (-)-sparteine (1.2 equiv, 2.4 mmol, 560 mg) and THF (9.0 mL) were mixed at room temperature and stirred for 5 min, then the solution was cooled down to -78 °C and *sec*-BuLi (1.03 M, 1.2 equiv, 2.4 mmol, 2.35 mL) was added dropwise. The mixture was stirred at -78 °C for 2 h to complete the *α*-deprotonation of the protected amine and then the corresponding enol/phenol triflate **6**, **11a-b** (1.0 equiv, 1.0 mmol) was added in one portion. The reaction mixture was kept for 2 h at -78 °C and then warmed up slowly to room temperature for a total time of 8-12 h. It was quenched with a saturated aqueous solution of NH_4Cl, extracted with Et_2O three times, concentrated in vacuo and purified over silica gel.

General procedure B. Synthesis of 3(*2H*)-furanone spiro from 1,3-dithiane (Table 2). A round-bottom flask with a magnetic stir bar and septum was flame-dried under N_2. 1,3-Dithiane (2.0 equiv, 2.0 mmol, 240 mg) was added inside an AtmosBag®, and the flask was sealed with a rubber septum; the flask was then connected to a N_2 line and the solvent THF (9.0 mL) was added. This solution was cooled down to -40 °C and *n*-BuLi (2.50 M, 2.1 equiv, 2.1 mmol, 0.84 mL) was added dropwise and the mixture was stirred for 40 min from -40 to -20°C. The reaction mixture was then cooled down to -78 °C and the corresponding enol/phenol triflate **6**, **11a-e** (1.0 equiv, 1.0 mmol) was added in one portion. The mixture was kept for 2 h at -78 °C and then

warmed up slowly to room temperature for a total time of 8-12 h. It was quenched with brine, extracted with Et_2O three times, concentrated in vacuo and purified over silica gel.

Preparation of **14** at higher temperatures than -20 °C resulted in diminished yields.

***tert*-butyl 3-oxo-4,5,6,7-tetrahydro-1'*H*,3*H*-spiro[1-benzofuran-2,2'-pyrrolidine]-1'-carboxylate (7).** Prepared using general procedure A. After purification (silica gel, eluding first with 7% EtOAc / 93% hexanes followed by 20% EtOAc / 80% hexanes), a transparent solid was obtained (150 mg, 43%). Recrystallization was done from a CH_2Cl_2 solution which was left for slow evaporation of the solvent over 3 weeks period at room temperature. Melting point 146.0-148.5 °C. IR (neat) 2977 (m), 2935 (m), 2889 (m), 2856 (m), 1711(s), 1630 (s), 1383 (s), 1156 (m), 919 (m), 737 (w), 534 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (minor rotamer) δ 1.36 (1.44) (s, 9H), 1.60-1.90 (m, 4H), 1.95-2.45 (m, 8H), 3.50-3.60 (m, 1H), (3.68) 3.77 (t, J = 8.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) (minor rotamer) δ (18.1) 18.3, 21.5, 21.6, 21.8 (22.5), 25.5, 28.0 (28.2), (38.4) 39.1, 48.2 (48.6), (80.5) 80.9, 98.5 (98.9), 111.2 (111.8), (152.1) 152.2, 184.7, (198.2) 198.4; mass spectrum *m/z* (relative intensity) EI 293 (5, M^+), 237 (10), 193 (14), 176 (7), 86 (12), 70 (100), 57 (62), 41 (32). Elemental analysis calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90. Found: C, 65.51, H, 7.91.

Ethyl (2*Z*)-2-benzyl-3-phenyl-3-{[(trifluoromethyl)sulfonyl]oxy}prop-2-enoate (11d). Prepared using the general synthesis of β-enol triflates. Purification was done by filtration of the crude over silica with 5% Et_2O and 95% hexanes giving an pale orange liquid (solidifies after cooling in the fridge) and used without further purification (770 mg, 75%): IR (neat) 3060 (w), 2970 (m), 2915 (m), 1730 (s), 1618 (m), 1425 (s), 1220 (s), 1125 (m), 1062 (m), 760 (m), 680 (m), 580 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.14 (t, J = 7.3 Hz, 3H), 3.64 (s, 2H), 4.17 (q, J = 7.3 Hz, 2H), 7.09 (d, J = 7.8 Hz, 2H), 7.12-7.24 (m, 4H), 7.32-7.42 (m, 4H); ^{13}C NMR (125

MHz, $CDCl_3$) δ 13.7, 35.6, 61.9, CF_3 q (114.2, 116.7, 119.3, 121.8), 126.7, 128.0, 128.5, 128.6, 128.7, 129.0, 130.8, 131.0, 137.1, 148.7, 164.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ -74.3 (s, 3F); mass spectrum *m/z* (relative intensity) EI 355 (6), 281 (6), 264 (40), 191 (100), 165 (14), 94 (6).

Ethyl (2*E*)-2-chloro-3-phenyl-3-{[(trifluoromethyl)sulfonyl]oxy}prop-2-enoate (11e). Prepared using the general synthesis of β-enol triflates, with the following modifications: after the addition of trifluoromethanesulfonic anhydride, the reaction mixture was allowed for slow warm up from -78 °C to 0 °C for 4 h and quenched at this temperature. This procedure gives a mixture of 75:25 *E* to *Z* stereoisomers of the β-enol triflate. Purification of the *E*-stereoisomer **11e** was done over silica with 5% Et_2O and 95% hexanes giving a pale liquid (235 mg, 66%): IR (neat) 3068 (w), 2983 (m), 2942 (w), 2905 (w), 1735 (s), 1627 (m), 1431 (s), 1222 (s), 1138 (s), 1062 (m), 991 (s), 809 (s), 766 (m), 697 (s), 598 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.34 (t, J = 7.3 Hz, 3H), 4.36 (q, J = 7.3 Hz, 2H), 7.38-7.46 (m, 3H), 7.50 (d, J = 6.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 63.5, CF_3 q (114.2, 116.7, 119.2, 121.7), 121.3, 128.5, 129.1, 130.3, 131.4, 149.4, 160.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ -73.7 (s, 3F); mass spectrum *m/z* (relative intensity) EI 358 (34, M^+), 313 (8), 265 (5), 197 (18), 169 (18), 125 (15), 105 (100), 77 (58), 51 (17).

***tert*-butyl 3-oxo-1'*H*,3*H*-spiro[1-benzofuran-2,2'-pyrrolidine]-1'-carboxylate (12).** Prepared using general procedure A. After purification (silica gel, eluding first with 15% EtOAc / 85% hexanes followed by 25% EtOAc / 75% hexanes), a transparent solid was obtained (70 mg, 65%). Recrystallization was done from a CH_2Cl_2 solution which was left for slow evaporation of the solvent over 3 weeks period at room temperature. Melting point 112.6-115.0 °C. IR (neat) 2979 (m), 2962 (w), 2890 (w), 1709 (s), 1616 (s), 1464 (m), 1381 (s), 1322 (w), 1244 (m), 1154 (s), 918 (m), 757 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (minor rotamer) δ 1.07 (1.42) (s, 9H),

2.03-2.33 (m, 4H), 3.54-3.64 (m, 1H), (3.75) 3.85 (t, J = 8.7 Hz, 1H), 7.00-7.10 (m, 2H), 7.58-7.73 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) (minor rotamer) δ 22.2 (22.9), 27.5 (28.2), (37.7) 38.5, 48.0 (48.3), (81.0) 81.7, 98.9 (99.6), 112.7, 120.5, 121.5 (121.6), 124.4 (124.5), (137.9) 138.1, 152.1 (152.5), (169.4) 169.7, (197.5) 198.1; mass spectrum *m/z* (relative intensity) EI 289 (17, M^+), 233 (33), 189 (33), 161 (83), 121 (18), 106 (78), 57 (100), 41 (46). Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62. Found: C, 66.35, H, 6.62.

***tert*-butyl 2-(2-hydroxybenzoyl)pyrrolidine-1-carboxylate (13).** Prepared using general procedure A. After purification (silica gel, 30% EtOAc / 70% hexanes and preparative TLC-silica with 20% EtOAc / 80% hexanes), a pale yellow solid was obtained (73 mg, 25%). Melting point 108.2-111.6 °C. IR (neat) 2972 (w), 2917 (w), 2864 (w), 1699 (s), 1643 (m), 1613 (w), 1446 (w), 1401 (s), 1292 (w), 1156 (m), 1120 (w), 768 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) (minor rotamer) δ 1.28 (1.45) (s, 9H), 1.90-2.04 (m, 3H), 2.33-2.50 (m, 1H), 3.47-3.72 (m, 2H), 5.21-5.28 (m, 0.5H), 5.35-5.42 (m, 0.5H), 6.86-6.96 (m, 1H), 6.97-7.07 (m, 1H), 7.46-7.56 (m, 1H), 7.74-7.82 (m, 1H), (12.11) 12.19 (s, 0.7H); ^{13}C NMR (125 MHz, $CDCl_3$) (minor rotamer) δ 23.7 (24.2), 28.1 (28.4), (30.4) 31.4, 46.6 (46.8), (60.5) 60.7, (79.9) 80.0, 117.5 (117.6), (118.6) 118.7, (118.9) 119.0, 129.1 (129.5), (136.4) 136.5, 153.6 (154.4), 162.8 (162.9), (204.2) 204.9; mass spectrum *m/z* (relative intensity) EI 291 (0.5, M^+), 235 (2.5), 218 (7), 170 (25), 114 (71), 70 (100), 57 (57), 41 (22).

***tert*-butyl 2-ethyl-4-oxo-1-oxa-6-azaspiro[4.4]non-2-ene-6-carboxylate (16).** Prepared using general procedure A. After purification (silica gel, 10% Et_2O / 90% hexanes), a pale yellow oil was obtained (102 mg, 38%): IR (neat) 2978 (s), 2939 (m), 2881 (w), 1700 (s), 1397 (s), 1163 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) (minor rotamer) δ 1.15 (t, J = 7.5 Hz, 3H), 1.34 (s, 6H), 1.39 (s, 3H), 1.53-2.03 (m, 3H), 2.03-2.28 (m, 1H), 2.31 (q, J = 5.1 Hz, 2H), 3.46 (t, J = 6.6 Hz, 2H),

4.14 (4.31) (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) (minor rotamer) δ 12.6, 23.5 (24.0), 28.0, 28.3, 29.0, 30.1, 46.4 (46.6), (66.3) 66.5, (79.6) 80.1, (97.1) 97.7, 153.6 (154.0), (188.0) 188.2; mass spectrum *m/z* (relative intensity) EI 195 (1), 179 (0.8), 170 (17), 150 (5), 70 (100), 57 (70). Anal. Calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92. Found: C,62.75; H, 7.90.

***tert*-butyl methyl(3-oxo-2,3-dihydro-1-benzofuran-2-yl)carbamate (17).** Prepared using general procedure A. After purification (silica gel, eluding first with 7% EtOAc / 93% hexanes followed by 20% EtOAc / 80% hexanes), a white solid was obtained (180 mg, 72%). Melting point 86.8-89.4 °C. IR (neat) 2979 (m), 2934 (w), 1717 (s), 1616 (s), 1464 (s), 1318 (s), 1151 (s), 1004 (w), 928 (m), 760 (m), 507 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) (minor rotamer) δ 1.30 (1.52) (br s, 9H), 2.80 (2.98) (br s, 3H), 5.40-6.30 (br s, 1H), 7.08-7.14 (m, 2H), 7.63-7.71 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) (minor rotamer) δ 27.8, 28.0, (81.7) 82.2, 89.6 (90.6), 113.0 (113.3), 120.3, 122.0, 124.5, 138.6, 154.0 (155.3), 170.9 (171.5), 195.7 (196.3); mass spectrum *m/z* (relative intensity) EI 263 (1, M^+), 207 (58), 163 (10), 134 (59), 121 (29), 94 (47), 57 (100), 42 (53). HRMS (ESI) calcd for $[C_{14}H_{17}NO_4+H]^+$ 264.1159, found 264.1151.

tert-butyl 3-oxo-4,5,6,7-tetrahydro-1'H,3H-spiro[1-benzofuran-2,2'-piperidine]-1'-carboxylate (18). Prepared using general procedure A. After purification (silica gel, 25% EtOAc / 85% hexanes), a white solid was obtained (34 mg, 11%). Melting point 141.1-142.5 °C. IR (neat) 2983 (w), 2947 (m), 2869 (w), 1705 (s), 1633 (m), 1368 (m), 1151 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 9H), 1.50-1.75 (m, 7H), 1.75-1.94 (m, 3H), 2.06-2.25 (m, 2H), 2.25-2.47 (m, 2H) 2.97-3.22 (m, 1H), 3.75-3.93 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 18.5, 18.8, 21.7, 21.8, 23.3, 25.5, 28.1, 33.8, 42.7, 81.6, 93.9, 110.4, 154.4, 183.0, 199.4; mass spectrum *m/z* (relative intensity) EI 307 (12, M^+), 251 (16), 234 (12), 207 (35), 190 (15), 178 (19), 164 (54), 84 (100), 57 (64). Anal. calcd for $C_{17}H_{25}NO_4$: C, 66.43; H, 8.20. Found: C, 66.24, H, 8.17.

3*H*-spiro[1-benzofuran-2,2'-[1,3]dithian]-3-one (19). Prepared using general procedure B. After purification (silica gel, 10% Et_2O/90% hexanes) a white solid was obtained (50 mg, 75%). Recrystallization was done from a CH_2Cl_2 solution which was left for slow evaporation of the solvent over 3 weeks period at room temperature. Melting point 105.7-108.0 °C. IR (neat) 2920 (m), 1719 (s), 1612 (s), 1476 (m), 1461 (m), 1298 (m), 1197 (m), 920 (m), 883 (m), 749 (m), 518 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.20-2.36 (m, 2H), 3.20-3.27 (m, 2H), 3.36-3.44 (m, 2H), 7.12-7.19 (m, 2H), 7.69 (t, J = 8.7 Hz, 1H), 7.76 (d, 7.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.9, 27.2, 91.0, 113.7, 118.7, 122.9, 125.7, 138.6, 169.1, 194.2; mass spectrum *m/z* (relative intensity) EI 238 (74, M^+), 205 (27), 173 (100), 163 (87), 121 (37), 104 (33), 76 (47), 41 (22). HRMS (ESI) calcd for $[C_{11}H_{10}O_2S_2 + H]^+$ 239.0200, found 239.0204.

4,5,6,7-tetrahydro-3*H*-spiro[1-benzofuran-2,2'-[1,3]dithian]-3-one (20). Prepared using general procedure B. After purification (silica gel, eluding first with 10% EtOAc / 90% hexanes followed by 25% EtOAc / 75% hexanes) a transparent solid was obtained (165 mg, 68%). Recrystallization was done from a CH_2Cl_2 solution which was left for slow evaporation of the solvent over 3 weeks period at room temperature. Melting point 183.0-186.6 °C (decomposition). IR (neat) 2938 (m), 2854 (w), 1703 (s), 1628 (s), 1425 (m), 1411 (m), 1204 (m), 912 (m), 816 (w), 467 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.68-1.75 (m, 2H), 1.84-1.91 (m, 2H), 2.21-2.31 (m, 4H), 2.49 (t, J = 6.0 Hz, 2H), 2.99-3.06 (m, 2H), 3.37-3.45 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.4, 21.5, 21.6, 23.7, 25.9, 27.2, 91.1, 111.6, 185.5, 195.2; mass spectrum *m/z* (relative intensity) EI 242 (34, M^+), 209 (30), 117 (100), 118 (53), 85 (50), 79 (37), 42 (62). HRMS (EI) calcd for $[C_{11}H_{14}O_2S_2]^+$ 242.0435, found 242.0433.

2-ethyl-1-oxa-6,10-dithiaspiro[4.5]dec-2-en-4-one (21). Prepared using general procedure B. After purification (silica gel, 10% EtOAc / 90% hexanes), a clear liquid was obtained (86 mg,

40%). IR (neat) 2974 (w), 2920 (w), 1703 (s), 1593 (s), 1421 (w), 1275 (w), 1018 (w), 910 (m), 802 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.27 (t, J = 7.3 Hz, 3H), 2.20-2.28 (m, 2H), 2.56 (q, J = 7.3 Hz, 2H), 3.00-3.80 (m, 2H), 3.34-3.42 (m, 2H), 5.56 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.9, 23.7, 24.2, 27.1, 91.6, 101.0, 191.9, 196.9; mass spectrum *m/z* (relative intensity) EI 216 (27, M^+), 183 (13), 159 (24), 151 (100), 118 (60), 85 (64), 71 (35), 42 (90). HRMS (ESI) calcd for $[C_9H_{12}O_2S_2 + H]^+$ 217.0357, found 217.0360.

2-phenyl-1-oxa-6,10-dithiaspiro[4.5]dec-2-en-4-one. (22). Prepared using general procedure B. After purification (silica gel, 10% EtOAc / 90% hexanes) a pale orange solid was obtained (25 mg, 9%): Melting point 115.7-118.5 °C. IR (neat) 2956 (w), 2921 (w), 1700 (s), 1605 (s), 1562 (s), 1450 (w), 1346 (m), 1285 (w), 1045 (w), 768 (w), 689 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.27-3.35 (m, 2H), 3.09-3.16 (m, 2H), 3.46-3.54 (m, 2H), 6.15 (s, 1H), 7.51-7.56 (m, 2H), 7.61 (t, J = 7.3 Hz, 1H), 7.86-7.90 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.7, 27.4, 92.2, 99.3, 127.4, 128.3, 128.9, 133.2, 182.1, 196.2; mass spectrum *m/z* (relative intensity) EI 264 (20, M^+), 231 (16), 199 (70) 118 (22), 102 (100), 77 (25), 42 (30). HRMS (ESI) calcd for $[C_{13}H_{12}O_2S_2+H]^+$ 265.0357, found 265.0359.

3-benzyl-2-phenyl-1-oxa-6,10-dithiaspiro[4.5]dec-2-en-4-one (23). Prepared using general procedure B. After purification (silica gel, eluding first with 10% EtOAc / 90% hexanes followed by 25% EtOAc / 75% hexanes) a pale orange solid was obtained (100 mg, 71%). Melting point 127.7-130.5 °C. IR (neat) 3061 (w), 3027 (w), 2920 (w), 1698 (s), 1610 (s), 1493 (m), 1423 (m), 1386 (s), 1131 (m), 918 (m), 726 (m), 695 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.22-2.36 (m, 2H), 3.11-3.20 (m, 2H), 3.43-3.51 (m, 2H), 3.85 (s, 2H), 7.15-7.21 (m, 3H), 7.25-7.31 (m, 2H), 7.44 (t, J = 7.3 Hz, 2H), 7.51 (t, J = 7.3 Hz, 1H), 7.74 (t, J = 7.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.9, 27.4, 27.6, 89.3, 112.1, 126.3, 127.8, 128.1, 128.6, 128.7, 129.3,

132.1, 138.3, 177.8, 197.7; mass spectrum *m/z* (relative intensity) EI 354 (14, M^+), 321 (20), 289 (80), 192 (100), 165 (11), 119 (10), 105 (29), 77 (32), 42 (24); HRMS (ESI) calcd for $[C_{20}H_{18}O_2S_2 + H]^+$ 355.0826, found 355.0819.

3-chloro-2-phenyl-1-oxa-6,10-dithiaspiro[4.5]dec-2-en-4-one (24). Prepared using general procedure B with the following modifications: 1.0 equiv. of **14** and 1.05 equiv of **11e** were used. **11e** was dissolved in 1.0 ml of THF and cooled to -78 °C before adding it by a cannula over the reaction flask. The reaction mixture was kept at -78 °C for 2.5 h and quenched with brine at this temperature. After purification (silica gel, 10% Et_2O/90% hexanes) an orange solid was obtained (65 mg, 68%). Melting point 128.5-131.0 °C. IR (neat) 2950 (w), 2921 (w), 2900 (w), 1716 (s), 1602 (m), 1588 (m), 1568 (s), 1346 (s), 1045 (m), 891 (m), 687 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.24-2.34 (m, 2H), 3.13-3.23 (m, 2H), 3.40-3.50 (m, 2H), 7.56 (t, J = 7.8 Hz, 2H), 7.63 (t, J = 7.3 Hz, 1H), 8.19 (d, J = 7.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.5, 27.3, 90.1, 107.1, 127.6, 128.3, 128.7, 133.3, 173.9, 190.7; mass spectrum *m/z* (relative intensity) EI 298 (14, M^+), 265 (16), 233 (100), 193 (12), 136 (89), 105 (52), 77 (55), 42 (65); HRMS (ESI) calcd for $[C_{13}H_{11}ClO_2S_2+H]^+$ 298.9967, found 298.9967.

1-(2-hydroxyphenyl)-2-[(trifluoromethyl)sulfonyl]pentan-1-one (25). Prepared using general procedure B, using 2.0 equiv of *n*-BuLi instead **14**. After purification (silica gel, eluding first with 7 % EtOAc / 93% hexanes followed by 10% EtOAc / 90% hexanes), a white solid was obtained (63 mg, 68%). Melting point 80.4-81.4 °C. IR (neat) 2967 (m), 2879 (w), 1636 (s), 1453 (w), 1361 (s), 1194 (s), 1116 (s), 959 (w), 753 (m), 496 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.98 (t, J = 7.3 Hz, 3H), 1.32-1.47 (m, 2H), 2.18-2.28 (m, 1H), 2.48-2.58 (m, 1H), 5.25 (dd, J = 11.0, 3.2 Hz, 1H), 7.02 (t, J = 7.3 Hz, 1H), 7.09 (d, J = 8.7 Hz, 1H), 7.63 (t, J = 7.3 Hz, 1H), 7.70 (d, J = 8.7 Hz, 1H), 11.72 (s, 0.8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6, 20.2, 29.4,

64.8, CF_3 q (115.7, 118.3, 120.9, 123.6), 119.3, 119.5, 119.8, 129.9, 138.6, 163.6, 193.8. ^{19}F NMR (282 MHz, $CDCl_3$) δ -74.3 (s, 3F); mass spectrum *m/z* (relative intensity) EI 310 (9, M^+), 268 (8), 199 (5), 147 (7), 134 (9), 121 (100), 93 (14), 65 (18); HRMS (EI) calcd for $[C_{12}H_{13}F_3O_4S]^+$ 310.0487, found 310.0488.

(2*Z*)-1,1-di(1,3-dithian-2-yl)-1-hydroxypent-2-en-3-yl trifluoromethanesulfonate (27). Prepared using general procedure B, with a ratio of solvents THF/Et_2O : 1/2. After purification (silica gel, eluding first with 7 % Et_2O / 93% hexanes followed by 12% Et_2O / 88% hexanes), a pale solid was obtained (55 mg, 25%). Melting point 142.5-145.9 (decomposition) °C. IR (neat) 3011 (w), 2923 (w), 2875 (w), 1699 (w), 1417 (s), 1207 (s), 1142 (s), 901 (m), 591 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.20 (t, J = 7.3 Hz, 3H), 1.94-2.03 (m, 2H), 2.03-2.12 (m, 2H), 2.44 (q, J = 7.3 Hz, 2H), 2.73-2.83 (m, 4H), 3.07-3.17 (m, 4H), 3.51 (s, 1H), 4.43 (s, 2H), 5.32 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.1, 25.3, 28.0, 29.0, 29.2, 53.4, 83.4, 119.0, 153.1. ^{19}F NMR (282 MHz, $CDCl_3$) δ -74.7 (s, 3F); mass spectrum *m/z* (relative intensity) EI 320 (1), 213 (7), 201 (23), 173 (1), 159 (1), 119 (100), 85 (5), 75 (7), 45 (14); HRMS (ESI) calcd for $[C_{14}H_{21}F_3O_4S_5+Na]^+$ 492.9893, found 492.9891.

1-(1,3-dithian-2-yl)pent-2-yn-1-one (28). Prepared using general procedure B. After purification (silica gel, 5 % Et_2O / 95% hexanes), a pale yellow solid was obtained (30 mg, 30%): Melting point 91.4-94.0 (decomposition) °C. IR (neat) 2924 (m), 2853 (w), 2208 (m), 1670 (s), 1656 (s), 1259 (w), 1144 (w), 1001 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.24 (t, J = 7.5 Hz, 3H), 1.98-2.20 (m, 2H), 2.43 (q, J = 7.5 Hz, 2H), 2.55-2.65 (m, 2H), 3.19-3.31 (m, 2H), 4.29 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.5, 12.9, 24.9, 25.8, 48.3, 78.9, 97.1, 179.1; mass spectrum *m/z* (relative intensity) EI 200 (8, M^+), 172 (1), 144 (2), 119 (100), 85 (8), 75 (10), 53 (15), 45 (18); HRMS (EI) calcd for $[C_9H_{12}OS_2]^+$ 200.0330, found 200.0336.

1,1-di(1,3-dithian-2-yl)pent-2-yn-1-ol (29). Prepared using general procedure B. After purification (silica gel, 15 % Et_2O / 85% hexanes), a pale yellow solid was obtained (45 mg, 30%): Melting point 122.5-125.3 (decomposition) °C. IR (neat) 2948 (w), 2922 (s), 2854 (w), 2236 (w), 1657 (s), 1421 (w), 1317 (m), 1277 (s), 1053 (w), 703 (s), 638 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.19 (t, J = 7.3 Hz, 3H), 2.00-2.10 (m, 4H), 2.32 (q, J = 7.3 Hz, 2H), 2.60-2.72 (m, 4H), 3.25-3.35 (m, 4H), 3.56 (bs, 0.55H), 4.41 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.7, 12.9, 25.0, 27.3, 27.5, 50.4, 78.9, 80.9, 90.1; mass spectrum *m/z* (relative intensity) EI 320 (1, M^+), 281 (0.5), 213 (6), 201 (22), 127 (2), 119 (100), 85 (6), 75 (7), 45 (12); HRMS (ESI) calcd for $[C_{13}H_{20}OS_4+Na]^+$ 343.0295, found 343.0298.

2-[(3*E*)-2,2-dimethyl-4-(phenylsulfanyl)but-3-enoyl]phenyl trifluoromethanesulfonate (30). After purification (silica gel, 3% Et_2O / 97% hexanes), a clear liquid was obtained (40 mg, 20%): IR (neat) 3062 (w), 2977 (w), 2934 (w), 2867 (w), 1699 (s), 1478 (m), 1425 (s), 1215 (s), 1140 (s), 1093 (m), 886 (s), 741 (m), 593 (m) cm^{-1}: ^1H NMR (500 MHz, $CDCl_3$) δ 1.39 (s, 6H), 5.91 (d, J = 15.6 Hz, 1H), 6.31 (d, J = 15.6 Hz, 1H), 7.22-7.32 (m, 5H), 7.34-7.40 (m, 2H), 7.44 (dd, J = 1.8, 7.8 Hz, 1H), 7.50 (td, J = 1.8, 7.3 Hz, 1H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.7, 51.5, CF_3 q (114.7, 117.1,119.7, 122.2), 122.0, 125.2, 127.1, 127.5, 128.4, 129.2, 130.0, 131.4, 133.3, 134.4, 135.1, 145.4, 203.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ -73.5 (s, 3F); mass spectrum *m/z* (relative intensity) EI 430 (3, M^+), 321 (1), 253 (3), 177 (100), 161 (2), 144 (6), 135 (13), 120 (8), 99 (7), 91 (6); HRMS (ESI) calcd for $[C_{19}H_{17}F_3O_4S_2+H]^+$ 431.0599, found 431.0595.

2-[(1*E*)-1,3-bis(phenylsulfanyl)prop-1-en-2-yl]phenol (31). After purification (silica gel, 10% Et_2O / 90% hexanes), a thick pale yellow liquid was obtained (85 mg, 50%): IR (neat) 3060 (w), 3019 (w), 2931 (w), 1579 (s), 1477 (s), 1279 (w), 1181 (w), 1082 (w), 833 (w), 739 (s), 690 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.12 (s, 2H), 6.43 (s, 1H), 6.77-6.83 (m, 2H), 7.04 (dd, J =

1.4, 7.3 Hz, 1H), 7.08-7.27 (m, 10H), 7.33-7.37 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 37.1, 116.1, 120.6, 126.9, 127.0, 127.4, 128.9, 129.1, 129.2, 129.4, 129.5, 130.8, 134.1, 135.0, 135.1, 152.9; mass spectrum *m/z* (relative intensity) EI 350 (10, M^+), 241 (82), 208 (12), 163 (11), 147 (15), 131 (95), 107 (100), 91 (58), 77 (42), 45 (18); HRMS (EI) calcd for $[C_{21}H_{18}OS_2]^+$ 350.0799, found 350.0806.

2-(1,3-dithian-2-ylcarbonyl)phenyl trifluoromethanesulfonate (34). After purification (silica gel, 8% Et_2O/92% hexanes), a pale solid was obtained (83 mg, 64%): Melting point 103.8-106.5 °C. IR (neat) 2928 (w), 2917 (w), 1694 (s), 1605 (m), 1425 (s), 1210 (s), 1138 (s), 1108 (m), 994 (w), 890 (s), 594 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.00-2.10 (m, 1H), 2.16-2.26 (m, 1H), 2.60-2.70 (m, 2H), 3.39 (t, *J* = 12.4 Hz, 2H), 4.88 (s, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.62 (dt, *J* = 1.4, 7.8 Hz, 1H), 7.76 (dd, *J* = 1.4, 7.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.8, 25.7, 44.7, CF_3 q (114.7, 117.3, 119.8, 122.4), 122.5, 128.4, 130.1, 130.8, 133.4, 146.9, 190.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ -73.3 (s, 3F); mass spectrum *m/z* (relative intensity) EI 372 (0.02, M^+), 238 (72), 205 (28), 173 (100), 163 (93), 137 (10), 121 (44), 92 (44), 76 (74), 41 (43); HRMS (ESI) calcd for $[C_{12}H_{11}F_3O_4S_3+H]^+$ 372.9850, found 372.9837.

2,2-dimethoxy-1-benzofuran-3(2*H*)-one (35). Prepared adapting the procedure from Bestmann.[48] Substrate **19** (1.0 equiv, 0.55 mmol, 130 mg) was dissolved in 7.5 ml of MeOH 85% in water. Then $HgCl_2$ (2.2 equiv, 1.21 mmol, 328 mg) and HgO (red) (1.1 equiv, 0.61 mmol, 131 mg) were added. The dispersion was strongly stirred and refluxed for 3.5 h at 83-85 °C (external temperature). Upon cooling to room temperature, the solids were filtered off and most of the solvent removed under reduced pressure. After purification (silica gel, 10% Et2O / 90% hexanes) a clear liquid was obtained (70 mg, 65%): IR (neat) 2981 (w), 2950 (m), 2842 (w), 1735 (s), 1615 (s), 1462 (m), 1326 (m), 1260 (m), 1202, 1148 (s), 986 (m), 932 (m), 754 (s) cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.56 (s, 6H), 7.07-7.13 (m, 2H), 7.64-7.69 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 51.5, 113.1, 113.2, 119.3, 122.6, 125.1, 139.2, 169.0, 192.2; mass spectrum *m/z* (relative intensity) EI 194 (66, M^+), 163 (80), 135 (19), 121 (35), 107 (78), 90 (84), 77 (100), 63 (48), 50 (27).

1-benzofuran-2,3-dione (37). Prepared by a modified procedure from Seebach.[49] *N*-Chlorosuccinimide (3.0 equiv, 1.11 mmol, 147mg) and $AgNO_3$ (3.5 equiv, 1.29 mmol, 218 mg) and 7.0 ml of CH_3CN were loaded into an 50 ml round bottom provided with magnetic stirrer and rubber septa. This mixture was cooled into an ice bath. In another flask, substrate **19** (1.0 equiv, 0.37 mmol, 88 mg) was dissolved in 1.5 ml of CH_3CN and this solution was transferred by cannula over the previous flask. The reaction mixture was strongly stirred for 5 min at 0 °C, and then 30 ml of Et_2O were added to precipitated salts. The solvents were partially evaporated under reduced pressure, another portion of Et_2O was added and the solids were filtered off over cotton. Solvent was evaporated under reduced pressure. After purification by distillation under reduced pressure at 150 °C, a yellow oil that solidifies upon receiving was obtained (30 mg, 50%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, J = 8.2 Hz, 1H), 7.34 (t, J = 7.8 Hz, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.80 (t, J = 7.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 113.7, 119.0, 125.7, 125.8, 140.6, 155.8, 163.7, 177.1.

The CH_3CN used as solvent no molecular sieves were added. **37** could not be purified by column chromatography over SiO_2 or Al_2O_3. It also decomposed after filtration over Celite. It decomposed over standing on the bench.

1-benzofuran-3(*2H*)-one (38). A 100 ml round bottom flask provided with a magnetic stir bar was loaded with substrate **19**, 20 ml of EtOH and approximately 3 ml of the Raney-Nickel slurry (50 % in water); it was capped with rubber septa and placed into an ice bath, then a balloon with

H_2 was attached. This mixture was strongly stirred for 30 min at 0° C (higher temperatures, larger amounts of Raney-Nickel or longer reaction times yielded higher amounts of alcohol **39**). Solid were filtered off and the solvent partially removed under reduced pressure. After purification (silica gel, 7% Et_2O / 93% hexanes) a pale yellow solid was obtained (33 mg, 67%). IR (neat) 2958 (w), 2919 (w), 2850 (w), 1735 (m), 1611 (s), 1588 (m), 1464 (s), 1299 (m), 1190 (m), 990 (m), 835 (m), 762 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.65 (s, 2H), 7.12 (t, J = 7.3 Hz, 1H), 7.17 (d, J = 8.3 Hz, 1H), 7.64 (t, J = 8.3 Hz, 1H), 7.70 (d, J = 7.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 74.6, 113.7, 121.2, 122.1, 124.2, 138.0, 174.1, 200.0, mass spectrum *m/z* (relative intensity) EI 134 (100, M^+), 105 (86), 76 (70), 63 (8), 50 (49). Small amounts (5-7%) of the alcohol **39** were also found.

ASSOCIATED CONTENT

Supporting Information

^1H, ^{13}C and ^{19}F NMR spectra and X-ray crystallographic data are provided. This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

The authors declare no competing financial interest.

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