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# Practical synthesis of a highly functionalized thiazole ketone

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Abstract—Compound 1 is a uniquely substituted ketone prepared via addition of a thiazole anion to an aromatic nitrile in good overall yield. An exploration into the generality of the addition of thiazole anions to nitriles allowed us to make a variety of thiazole ketones in good to excellent yields. The non-odorous thiolate-mediated demethylation reaction used in the synthesis of 1 is also presented. © 2003 Elsevier Ltd. All rights reserved.

### 1. Introduction

Heterocyclic-aryl ketones appear in a wide range of compounds that have potential therapeutic uses and are also versatile reaction building blocks.<sup>1</sup> Thiazole-aryl ketones are no exception, however most of the literature describes the preparation of 2-(ketoaryl)thiazoles, and less is known about 5-(ketoaryl)thiazoles.<sup>2</sup>

In our laboratories, we required a robust and efficient synthesis of the 5-(ketoaryl)thiazole 1 (Scheme 1) to support our drug development program. This presented a unique challenge due to the compound's complex functionalization and unusual substitution pattern. In this paper we report our optimized synthesis of ketone 1 and describe the application of new methodologies used in the synthesis of 1 to the preparation of other substrates. As such, we summarize our investigations of non-odorous thiolate-mediated demethyl-



Scheme 1.

ation reactions and the addition of a variety of substituted thiazoles to a range of aromatic nitriles.

We anticipated that large quantities of ketone **1** would be required to support our drug development program, so our goals in designing a synthesis of this compound focused on both efficiency and the use of readily available starting materials and reagents. We envisioned that compound **1** could be assembled by addition of a deprotonated thiazole to an aromatic nitrile, followed by in situ hydrolysis of the resulting lithio imine intermediate. This approach was used in an efficient five-step sequence to ketone **1** (Scheme 1) starting from readily available materials, and was demonstrated on multi-gram scale with a good overall yield (56%). Notably, the route was amenable to scale up as it featured only two isolations and one low temperature reaction.

## 2. Discussion

## 2.1. Alkylation/elimination

Phenol 2 was a suitable starting material for the synthesis of ketone 1 since it already contained the desired regiochemistry on the aromatic ring. As the direct alkylation of phenols with a cyclopropyl group typically leads to low yields and rearranged products,<sup>3</sup> we envisioned installation of this functionality via cyclopropanation of the corresponding vinyl ether 3. Attempts to prepare vinyl ether 3 directly from the phenol were not successful,<sup>4</sup> so an alkylation/ elimination strategy was pursued (Scheme 2).

The alkylation was initially carried out using excess 1-bromo-2-chloroethane in the presence of potassium carbonate in acetonitrile at 80°C. Although this procedure afforded the desired compound **4**, significant amounts (up to

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Scheme 2. (i) pTsOCH<sub>2</sub>CH<sub>2</sub>Cl, Cs<sub>2</sub>CO<sub>3</sub>, Triton X-405, THF, reflux, 5 h, (ii) KOtBu, THF, 10°C, 1 h.

12%) of the alkylation dimer 5,<sup>5</sup> were formed. After some experimentation, it was found that the use of only 2 equiv. of 2-chloroethyl *p*-toluenesulfonate<sup>6</sup> and cesium carbonate<sup>7</sup> in refluxing tetrahydrofuran containing 5% Triton X-405 gave complete conversion of the starting material within 5 h (2.5% dimer **5** formed under these conditions). Although phase transfer conditions were employed it was found that the addition of water slowed the reaction rate, and reactions were typically run under anhydrous conditions.

The elimination to prepare vinyl ether **3** was carried out by direct addition of potassium *t*-butoxide in tetrahydrofuran to the crude alkylation mixture.<sup>8</sup> A small amount (typically 2%) of phenol **2** was regenerated in this reaction, and interestingly, this impurity was greater when potassium *t*-butoxide in toluene was used for the elimination.<sup>9</sup> The phenol was removed with a base wash providing a toluene solution of vinyl ether in 95% yield from phenol **2**.

# 2.2. Cyclopropanation

(Halomethyl)zinc reagents, commonly referred to as Simmons–Smith reagents,<sup>10</sup> were employed for the cyclopropanation of vinyl ether **3**. The reagent was generated using the conditions reported by Furukawa.<sup>11</sup> When vinyl ether **3** was subjected to these conditions (diethylzinc and diiodomethane) in non-polar solvents, a non-stirrable mixture formed; however, when polar solvents were employed, no reaction was observed. In an attempt to avoid these problems, the conditions reported by Y. Shi were investigated.<sup>12</sup> Hence, trifluoroacetic acid was added to diethylzinc prior to addition of the diiodomethane and the vinyl ether. This resulted in a homogeneous reaction mixture and complete conversion of starting material to cyclopropyl ether **6** (Scheme 3).

Significant reduction of the nitrile to aldehyde  $7^{13}$  (30%) was observed if the reaction was warmed to room temperature. When kept between 0 and 5°C, this reduction was minimized and compound **6** was obtained in good yield with formation of only 7% of aldehyde **7**. Unfortunately, the addition of the trifluoroacetic acid to the reaction mixture



was extremely vigorous and this proved problematic on scale up.

In an effort to prevent formation of the aldehyde and reduce reaction exotherms, other acids and zinc sources were investigated. The use of dimethylzinc in conjunction with trifluoroacetic acid gave reduced amounts of aldehyde 7, but the lack of availability of dimethylzinc in kilogram quantities did not offer a long-term solution. While screening combinations of other reagents, it was observed that reactions containing acetic acid did not reach completion, but a good reaction rate was obtained with trichloroacetic acid and diethylzinc. Although this latter acid-zinc source combination gave approximately 8% of aldehyde 7, the cost and availability of the diethylzinc and the ease of addition of trichloroacetic acid to the reaction mixture led us to pursue the use of this combination of reagents on scale up. The level of aldehyde 7 could be significantly reduced in the crystallization of 6 and eliminated through subsequent steps.

In practice, the cyclopropanation reaction involved complexing trichloroacetic acid with diethylzinc in dichloroethane at  $-10^{\circ}$ C, followed first by the addition of diiodomethane and then by a dichloroethane solution of vinyl ether **3**. When held at  $0-5^{\circ}$ C, the reaction was complete in 16 h with an assay yield of 90% product **6** and 8% aldehyde **7**. The work up involved an aqueous potassium hydroxide wash to remove trichloroacetic acid, and compound **6**<sup>14</sup> was isolated by crystallization in 85% yield from vinyl ether **3**.

# 2.3. Demethylation

Many standard demethylation conditions were screened for the transformation of **6** to **8** (Scheme 4). In several cases (i.e. boron tribromide), competing cleavage of the cyclopropyl ether was a problem. Fortunately, the use of a slight excess of sodium ethanethiolate in *N*,*N*-dimethylformamide<sup>15</sup> at 100°C effected clean demethylation of **6** with no detected cleavage of the cyclopropyl ether.<sup>16</sup>

Because the stench of sodium ethanethiolate and the reaction byproduct, ethyl methyl sulfide, made this reaction unpleasant to run on a large scale, we were interested in carrying out the same transformation under non-odorous conditions. Recent papers discuss the use of long chain thiols to minimize odor<sup>17,18</sup> so we used this work as a basis for choosing a long chain thiol for our demethylation reaction. Following a literature result, the use of mixtures of a thiol and various lewis acids was explored.<sup>19</sup> Unfortunately, these reactions were not successful on our substrate; however, employing the sodium salt of a thiol afforded clean demethylation.<sup>20</sup> Hence, the use of 1.7 equiv. of dodecanethiol and 1.7 equiv. of sodium methoxide in *N*,*N*-dimethyl-formamide at 100°C,<sup>21</sup> gave an almost quantitative yield of phenol **8**. Work up involved extraction of the product into



Scheme 4. (i) EtSNa or  $CH_3(CH_2)_{11}SH$  and NaOMe, DMF, 100°C, 1 h.

**Table 1**. Demethylation using sodium methoxide and 1-dodecanethiol in N,N-dimethylformamide at  $100^{\circ}C^{23}$ 



<sup>a</sup> 21% starting material recovered.

aqueous base with thiol byproducts left behind in the organic phase. The product was extracted from the aqueous layer simply by adjusting to acidic pH. This work up provided an odor free solution of compound  $\mathbf{8}$  that was used in the next reaction without further purification.

Due to our success with demethylation using a non-odorous long chain thiol, we explored the generality of the method with a few model compounds. Using the procedure described above for the conversion of 6 to 8, the compounds shown in Table 1<sup>22</sup> were readily demethylated by heating each substrate with sodium methoxide and dodecanethiol in N,N-dimethylformamide at 100°C. Demethylation of 4-methoxybenzonitrile and methyl 2-methoxybenzoate (Table 1, entries 1 and 2) proceeded in high yield. Demethylation of hindered 2,6-dimethylanisole (Table 1, entry 3) was sluggish and did not go to completion. Interestingly, selective (4.9:1) demethylation of 3,4dimethyoxybenzonitrile (Table 1, entry 4) was observed, with preference for demethylation para to the electron withdrawing nitrile substituent. Clearly, these results demonstrated that demethylation using a non-odorous long chain thiol and sodium methoxide was a viable alternative to sodium ethanethiolate for a range of anisole related substrates.

# 2.4. Difluoromethylation

With phenol **8** in hand, difluoromethylation to form compound **9** was next investigated (Scheme 5). This reaction typically employs chlorodifluoromethane<sup>24</sup> or sodium chlorodifluoroacetate.<sup>25</sup> The difficulty in handling gaseous chlorodifluoromethane made its use unappealing, so we focused on applications of sodium chlorodifluoroacetate. This reagent has been shown to be efficient in diffuoromethylations of a phenol with a *para* electron-



Scheme 5. (i) ClF<sub>2</sub>CCO<sub>2</sub>Na, Cs<sub>2</sub>CO<sub>3</sub>, DMF, 100°C, 3 h.

withdrawing group, making it potentially suitable for our substrate containing a nitrile group *para* to the phenol.<sup>20</sup>

The reaction of crude phenol **8**, obtained from the demethylation step, with sodium chlorodifluoroacetate could be carried out with a range of solvents and bases.<sup>26</sup> In all cases the major impurity generated was dimer **10** (Fig. 1).<sup>27</sup>





Exhaustive screening of reaction conditions led to several observations. First, although adding water to the reaction minimized the amount of dimer, use of more than 10% water led to sluggish reactions. Second, the choice of base impacted the level of dimer with 4% dimer present in reactions with cesium carbonate, 5% in reactions with potassium carbonate, and more than 10% in reactions with sodium or lithium carbonate. Third, the use of 1-methyl-2pyrrolidinone or dimethylacetamide instead of N,Ndimethylformamide led to a slight increase in dimer. Hence our optimized conditions were found to be addition of 2.5 equiv. of sodium chlorodifluoroacetate and 1.5 equiv. of cesium carbonate to a N,N-dimethylformamide solution of compound 8 containing 10 vol% water. Using this procedure, the reaction was complete within 3 h at 100°C (Scheme 5).

Concentrated hydrochloric acid was added to hydrolyze the dimer **10** to phenol **8** which allowed for its removal by basic extraction. After work up, the solution of **9** (86% yield) was used directly in the next reaction.

#### 2.5. Addition

Having prepared compound 9, we envisioned that addition of an anion of functionalized thiazole 11 to nitrile 9 would give an iminium intermediate, which on hydrolysis would offer ketone 1 (Scheme 6).



Scheme 6.

Functionalized thiazole 11 was prepared from thiazole via reaction with hexafluoroacetone and LHMDS followed by MOM protection of the resulting carbinol. Treatment of a low temperature THF solution of the above thiazole 11 with n-BuLi effected clean deprotonation at the 5-position, as demonstrated by deuterium quenching experiments. Subsequent addition of the nitrile resulted in complete conversion to the lithio imine intermediate. While studying this reaction, we observed that temperature control was crucial due to competitive decomposition of the iminium intermediate. Decomposition generally occurred at temperatures above  $-10^{\circ}$ C, while the addition reactions were sluggish at  $-50^{\circ}$ C. As a result, reactions were typically aged at temperatures between  $-35^{\circ}$ C and  $-20^{\circ}$ C to effect complete conversion to the lithio imine within a few hours, while minimizing decomposition. The reaction was quenched into either aqueous hydrochloric acid or aqueous acetic acid to generate the ketone immediately or into saturated aqueous ammonium chloride to give the imine (seen by <sup>1</sup>H NMR and LCMS). After work up, ketone **1** was crystallized from heptane in 87% isolated yield.

Based on the success of the thiazole addition to the nitrile the generality of this method for thiazole aryl ketone formation was explored. Notably, the majority of literature in this area focuses on the synthesis of 2-(ketoaryl)thiazoles, and the Hantzsch synthesis of 5-(ketoaryl)thiazoles<sup>28</sup> is limited in that it only produces thiazoles with an alkylamine group in the 2-position.<sup>29</sup> Using this new methodology we envisaged that a range of 5-(ketoaryl)thiazoles could be synthesized in a straightforward manner from commercially available aryl nitriles and with different substituents on the 2-position of the thiazole.<sup>30</sup>

Using conditions optimized for the synthesis of ketone **1** a variety of 2-substituted thiazoles were deprotonated and added to a number of electronically different aryl nitriles (Table 2). Clearly, the reaction was tolerant of electron withdrawing and donating groups on both reacting partners. The successful addition of several deprotonated 2-substituted thiazoles to many interesting aryl and heteroaryl nitriles (Table 3) demonstrates that a range of thiazole ketones can be prepared in good to excellent yield using this methodology. Notably the TBS group on the thiazole proved to be a versatile appendage, which could be

Table 2. Varying electronics of thiazole and benzonitrile reaction partners

	$X \xrightarrow{\text{I. } n-\text{BuLi}} X \xrightarrow{\text{I. } n-\text{I. } n-$					
		3. aq. acid	×			
Entry	Х	R	Rxn time (h)	Yield <sup>a</sup>		
1	SMe	Cl	2	90		
2	SMe	Н	3	90		
3	SMe	OMe	4	94		
4	SitBuMe <sub>2</sub>	Cl	1.5	98 (98)		
5 <sup>31</sup>	$\text{Si}t\text{BuMe}_2^{\overline{3}2}$	H <sup>33</sup>	1.5	98 (95)		
6	SitBuMe <sub>2</sub>	OMe	8	88		
a .			1 14 7 1	1 37' 11 '		

Assay yields determined by HPLC, compared with a standard. Yields in parentheses are for X=H, TBS was removed in workup.

selectively removed or retained during reaction work-up allowing for further functionalization at the 2-position. During hydrolysis of the imine an overnight age in acetic acid retained the TBS group on the ketone product while an HCl quench removed it completely (entries 4 and 5 Table 2). In contrast when 2-(trimethylsilyl)thiazole was used, products were detected that arose from reaction at the 2-position, indicating that the TMS functionality was somewhat labile under reaction conditions.

In conclusion, a facile method for the preparation of 5-(ketoaryl)thiazoles from 2-substituted thiazoles and aryl nitriles was developed. This method is applicable to a broad range of substituted aryl and heteroaryl nitriles as well as functionalized thiazoles and affords the ketones in good to excellent yields. These ketone intermediates can provide a template on which pharmaceutically interesting compounds can be created.

# 2.6. Summary

In summary, an efficient, chromatography free, five-step synthesis of ketone 1 was developed and demonstrated on a multi-gram scale with a good overall yield (56%). The route features the addition of a thiazole anion to an aromatic nitrile which gives ketone 1 directly after hydrolysis.

We have also probed the utility of both a non-odorous thiolate-mediated demethylation reaction and the addition of thiazole anions to a variety of aromatic nitriles to afford a number of substituted biaryl ketones after acid hydrolysis. The demethylation reaction is a practical alternative to the use of sodium ethanethiolate, and the generality of the thiazole addition chemistry makes it attractive for the preparation of a range of 5-(ketoaryl)thiazoles.

## 3. Experimental

## 3.1. General

All manipulations were carried out under a positive atmosphere of dry nitrogen. Dry solvents were used (KF  $<300 \ \mu g/mL$ ). NMR data was obtained in CDCl<sub>3</sub> or in DMSO-d<sub>6</sub> using a Bruker AM400 spectrometer. Coupling constants are reported in Hertz. All chemicals were purchased from Aldrich Chemical Co. unless otherwise noted and were used without further purification.

**3.1.1. 4-Methoxy-3-(vinyloxy)benzonitrile 3.** To a solution of phenol **2** (50.0 g, 0.335 mol) in THF (500 mL) was added Cs<sub>2</sub>CO<sub>3</sub> (131 g, 0.402 mol), Triton X-405 (2.50 g), and ClCH<sub>2</sub>CH<sub>2</sub>OTs (122 mL, 0.670 mol). The light yellow slurry was heated to 65°C and aged for 5 h (monitoring by HPLC) to form *3-(2-chloroethoxy)-4-methoxybenzonitrile* **4** <sup>1</sup>H NMR (DMSO)  $\delta$  7.42–7.39 (m, 2H), 7.10 (d, *J*=8.2 Hz, 1H), 4.28–4.25 (m, 2H), 3.90–3.93 (m, 2H), 3.82 (s, 3H) ppm; <sup>13</sup>C NMR (DMSO)  $\delta$  153.5, 148.0, 127.5, 119.6, 116.6, 113.1, 103.1, 69.5, 56.4, 43.3 ppm; Anal. Calcd for C<sub>10</sub>H<sub>10</sub>ClNO<sub>2</sub>: C 56.75; H 4.76; N 6.62. Found C 56.60; H 4.72; N 6.30. The reaction was cooled to  $-10^{\circ}$ C and KO*t*Bu (1000 mL, 1.0 M THF, 1.00 mol) was added via addition funnel over 40 min, maintaining the temperature below

Table 3. Addition of 2-substituted thiazoles to a variety of aryl nitriles

Entry	ArCN	$ArCN + \bigvee_{X} \overset{N}{\searrow} \overset{S}{\searrow}$	Ar S X'	Reaction time (b)	Vield <sup>a</sup>
1		TBS		16 h	84
2	CN	TBS		5 h	92
3	CF <sub>3</sub> CN	TBS		2.5 h	84
4	OMe	TBS		3 h	90
5		TBS	MeO	3 h	87
6	OMe MeO CN	TBS	MeO Me	12 h	91
7	CN	F <sub>3</sub> C OMOM CF <sub>3</sub>	$\bigcup_{N \in \mathcal{F}_{3}}^{O} \bigcup_{N \in \mathcal{F}_{3}}^{OMOM}$	3 h	95
8	MeO	F <sub>3</sub> C OMOM CF <sub>3</sub>	MeO MeO MeO MeO N CF <sub>3</sub>	5 h	96
9	OMe MeO CN	F <sub>3</sub> C OMOM CF <sub>3</sub>	$MeO \xrightarrow{O} S \xrightarrow{OMOM} CF_3$	7 h	94
10	N CN	SMe	N S S	20 min	96
11	N CN	TBS		20 min	90
12		TBS	O S N	45 min	60

(continued on next page)

Table 3 (cd	1 able 3 (continued)						
Entry	ArCN	Х	Product	Reaction time (h)	Yield <sup>a</sup>		
13	CN			30 h	47		
14	CN			7.5 h	98		
15	CI	N N		45 min	93		
16	CN	Cl	S N N	7 h	69		

<sup>a</sup> Assay yield by HPLC, as compared to chromatographed standard.

20°C. The reaction was aged for 1 h at 10-20°C (monitoring by HPLC). NH<sub>4</sub>Cl (500 mL 50% saturated aqueous) was added to the reaction, followed by toluene (375 mL). The organic layer was concentrated to remove some THF, then washed with water to remove salts. The final organic layer (55.8 g, 95% yield of **3** as compared to a chromatographed sample) was azeotropically dried with toluene, diluted with DCE (98 mL total volume), and used directly in the cyclopropanation. Analytical data for a chromatographed sample: <sup>1</sup>H NMR (DMSO)  $\delta$  7.55 (dd, *J*=1.7, 8.5 Hz, 1H), 7.48 (d, J=1.7 Hz, 1H), 7.20 (d, J=8.5 Hz, 1H), 6.79 (dd, J=6.0, 13.5 Hz, 1H), 4.63 (dd, J=1.9, 13.5 Hz, 1H), 4.44 (dd, J=1.9, 6.0 Hz, 1H), 3.84 (s, 3H) ppm; <sup>13</sup>C NMR (DMSO) δ 154.2, 149.1, 145.5, 129.9, 121.1, 119.1, 114.0, 103.3, 95.6, 56.6 ppm; Anal. Calcd for C<sub>10</sub>H<sub>9</sub>NO<sub>2</sub>: C 68.56; H 5.18; N 8.00. Found C 68.19; H 5.13; N 7.84.1

3.1.2. 3-(Cyclopropyloxy)-4-methoxybenzonitrile 6. ZnEt<sub>2</sub> (637 mL, 1.0 M heptane, 637 mmol) was diluted with DCE (475 mL) and cooled to  $-20^{\circ}$ C. A solution of Cl<sub>3</sub>CCO<sub>2</sub>H (10.6 g, 637 mmol) in DCE (100 mL) was added slowly (30-40 min) so that the internal temperature remained below 0°C. After a 20 min age at 0°C, CH<sub>2</sub>I<sub>2</sub> (51.3 mL, 637 mmol) was added and aged 10 min. A solution of the vinyl ether 3 (55.8 g, 319 mmol) in toluene-DCE (27% toluene, 98 mL total) was added and the mixture aged for 17 h (monitoring by HPLC). The reaction was quenched into 2N HCl (745 mL) and iPAc (175 mL) was added. The quench was warmed to RT and the orange aqueous layer was removed. The dark orange organic layer was washed with 2.5N KOH (265 mL, 1 equiv. relative to Cl<sub>3</sub>CCO<sub>2</sub>H) then with pH 7 buffer (260 mL). The organic layer was solvent switched to 99% heptane at 6.5 vol. The resulting slurry was cooled and filtered and the solid was dried under vacuum (52.4 g, 79% isolated yield of 6). Material left behind in the crystallization flask and funnel accounted for an additional 3.06 g (5%). Analytical data for a chromatographed sample: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.48 (d, J=1.9 Hz, 1H), 7.30 (dd, J=1.9, 8.4 Hz, 1H), 6.90 (d, J=8.4 Hz, 1H), 3.91 (s, 3H), 3.76 (m,

1H), 0.88 (m, 4H);  ${}^{13}$ C NMR (CDCl<sub>3</sub>)  $\delta$  152.8, 148.6, 126.6, 119.3, 116.2, 111.5, 103.8, 56.1, 51.9, 6.3; Anal. Calcd for C<sub>11</sub>H<sub>11</sub>NO<sub>2</sub>: C 69.83; H 5.86; N 7.40. Found C 69.54; H 5.85; N 7.08.

3.1.3. 3-(Cyclopropyloxy)-4-hydroxybenzonitrile 8. To a solution of 6 (47.7 g, 0.252 mol) in DMF (450 mL) was added 1-dodecanethiol (104 mL, 0.432 mol) followed by NaOMe (23.4 g, 0.432 mol). The mixture was heated to 100°C and aged for 1 h (monitoring by HPLC). After cooling to RT, iPAc (404 mL), water (518 mL), and 5N NaOH (45 mL) were added and the layers mixed well. The aqueous layer was washed with iPAc (350 mL) to remove more thiol byproducts. The aqueous layer was neutralized to pH 6 by addition of conc HCl (45 mL), and the product was extracted into iPAc (518 mL). The aqueous layer was extracted with iPAc (278 mL then 150 mL). The organic layers were concentrated and flushed with 160 mL DMF (43.7 g, 99% yield of 8 as compared to a chromatographed standard) before being used directly in the difluoromethylation. Analytical data for a chromatographed sample: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  10.16 (s, 1H), 7.51 (d, J=1.9 Hz, 1H), 7.24 (dd, J=1.9, 8.2 Hz, 1H), 6.87 (d, J=8.2 Hz, 1H), 3.88 (septet, J=2.9 Hz, 1H), 0.79–0.63 (m, 4H) ppm; <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) δ 151.9, 147.7, 127.2, 120.0, 117.5, 116.8, 101.4, 52.0, 6.4 ppm; Anal. Calcd for C<sub>10</sub>H<sub>9</sub>NO<sub>2</sub>: C 68.56; H 5.18; N 8.00. Found C 68.33; H 4.92; N 7.87.

**3.1.4. 3-(Cyclopropyloxy)-4-(diffuoromethoxy)benzonitrile 9.** A DMF solution of phenol **8** (5.08 g, 29.0 mmol) from the demethylation step was diluted to 32.3 mL using DMF, and 7.3 mL water was added. CIF<sub>2</sub>-CCO<sub>2</sub>Na (10.6 g, 66.7 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (13.2 g, 40.6 mmol) were charged, and the slurry was heated to 100°C for 3 h (monitoring by HPLC). Caution was taken to provide appropriate venting since CO<sub>2</sub> evolution was rapid at high temperature. The reaction was cooled, and conc HCl (12.1 mL) was added. After an overnight age, water (25 mL) and iPAc (100 mL) were added and the layers separated. The organic was washed with 1N NaOH (62 mL) then with

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water (3×34 mL). The organic was solvent switched into toluene to give 5.60 g **9** (86% yield compared to a chromatographed sample). Analytical data for a chromatographed sample: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.57 (d, *J*=1.7 Hz, 1H), 7.25 (dd, *J*=1.7, 8.3 Hz, 1H), 7.18 (d, *J*=8.3 Hz, 1H), 6.58 (t, *J*=74.0 Hz, 1H), 3.81 (m, 1H), 0.84 (m, 4H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  150.9, 143.4 (t, *J*=3.2 Hz), 125.8, 122.3, 118.2, 118.0, 115.5 (t, *J*=262.4 Hz), 110.0, 52.3, 6.3 (2C); Anal. Calcd for C<sub>11</sub>H<sub>9</sub>F<sub>2</sub>NO<sub>2</sub>: C 58.67; H 4.03; N 6.22. Found C 58.74; H 3.86; N 6.17.

3.1.5. 2-[2,2,2-Trifluoro-1-(methoxymethoxy)-1-(trifluoromethyl)ethyl]-1,3-thiazole 11. (Also see Table 3, entries 7–9). Under nitrogen, thiazole (22.6 g, 266 mmol) was dissolved in MTBE (448 mL), the solution was cooled to -40°C, and CF<sub>3</sub>COCF<sub>3</sub> (51.1 g, 299 mmol) was bubbled slowly through the cold solution. LiHMDS (1.0 M in THF, 271 mL, 271 mmol) was added via addition funnel over 30 min while the reaction temperature was kept below -40°C. After addition of LiHMDS, the resulting solution was brought up to rt. Both the deprotonation and nucleophilic addition reaction were instantaneous. The carbinol was not isolated: 1,1,1,3,3,3-hexafluoro-2-(1,3thiazol-2-yl)propan-2-ol:<sup>34</sup> <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.93 (d, J=3.2 Hz, 1H), 7.68 (d, J=3.2 Hz, 1H), 6.05 (s, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 157.2, 141.3, 124.4, 121.5 (q, J=287.4 Hz, 2C), 76.9 (q, J=32.0 Hz). The reaction mixture was concentrated under vacuum to remove HN(SiMe<sub>3</sub>)<sub>2</sub> and solvent switched from MTBE to THF. MOMCl (26.4 mL, 342 mmol) and NEt<sup>i</sup>Pr<sub>2</sub> (9.22mL, 52.9 mmol) were added at rt. The reaction mixture was aged at 40°C for 2 h (monitoring by HPLC), cooled to 0°C, and then charged with MTBE (660 mL) and water (66 mL). The layers were separated and the organic layer was washed with 1.0N NaOH (165 mL) and water (165 mL×3). The organic layer was concentrated and flushed with MTBE under vacuum to give 11 as a light yellow oil (69.2 g, 97% yield as compared to a chromatographed standard). Analytical data for a chromatographed sample: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.98 (d, J=3.2 Hz, 1H), 7.60 (d, J=3.2 Hz, 1H), 5.07 (s, 2H), 3.55 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 158.0, 143.6, 122.7, 121.6 (q, J=290.3 Hz, 2C), 94.9, 80.7 (m), 57.0; Anal. Calcd for C<sub>8</sub>H<sub>7</sub>F<sub>6</sub>NO<sub>2</sub>S: C 32.55; H 2.39; N 4.74. Found C 32.19; H 2.23; N 4.52.

3.1.6. [3-(Cyclopropyloxy)-4-(difluoromethoxy)henyl]{2-[2,2,2-trifluoro-1-(methoxymethoxy)-1-(trifluoromethyl)ethyl]-1,3-thiazol-yl}methanone 1. A toluene solution of 2-substituted thiazole 11 (15.8 mL, 550 mg/ mL, 29.5 mmol) was diluted with THF (27.6 mL). The solution was cooled to -70°C. n-BuLi (1.6 M, 18.4 mL, 29.5 mmol) was slowly added to the thiazole solution, maintaining the reaction temperature below  $-55^{\circ}$ C. The solution grew very dark. The level of deprotonation was checked with an aliquot of the anion solution quenched into deuterated methanol. NMR indicated that 97% of the thiazole was deprotonated. A toluene solution (11 mL) of the nitrile 9 (5.54 g, 24.6 mmol) was added to the anion via canula over 10 min, and the reaction was warmed to  $-20^{\circ}$ C over 4 h (monitoring by HPLC). The reaction was transferred via canula into 2N HCl (59 mL) at 10-25°C. Toluene (11 mL) was added and the organic layer was washed with pH 7 buffer (22 mL). The organic layer was

concentrated, diluted to 5 volumes with toluene, and silica gel (6.4 g) was added for an overnight age. After filtration and washing with toluene, the filtrate was concentrated to a low volume and diluted with heptane. Upon concentration, a brown slurry formed. After several heptane flushes the toluene was reduced to 2%, and at approx. 3 vols., the slurry was filtered and dried to give a brown solid. The isolated yield of ketone 1 was 87% (11.2 g). Analytical data for a chromatographed sample: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  8.35 (s, 1H), 7.86 (d, J=1.99 Hz, 1H), 7.53 (dd, J=2.0, 8.3 Hz, 1H), 7.28 (d, J=8.1 Hz, 1H), 6.64 (t, J=74.2 Hz, 1H), 5.16 (s, 2H), 3.89 (m, 1H), 3.57 (s, 3H), 0.88 (m, 4H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 185.3, 164.7, 150.9, 147.8, 144.1 (t, J=2.9 Hz), 141.8, 134.8, 123.0, 121.6, 121.3 (q, J=291.2 Hz, 2C), 115.6 (t, J=262.1 Hz), 115.2, 95.4, 80.8 (q, J=30.3 Hz), 57.3, 52.1, 6.4 (2C); Anal. Calcd for  $C_{19}H_{15}F_8NO_5S$ : C 43.77; H 2.90; N 2.69. Found C 43.39; H 2.67; N 2.62.

# 3.2. Synthesis of 2-substituted thiazoles

**3.2.1.** 2-(*tert*-Butyldimethylsilyl)thiazole. (Table 2, entries 4–6, Table 3, entries 1–6, 11–12): Thiazole (10.0 g, 118 mmol) was dissolved in THF (100 mL) and cooled to  $<-50^{\circ}$ C. *n*-BuLi (74 mL) was added slowly followed by a solution of TBSCI (17.7 g) in THF (30 mL). After 4 h, the reaction was quenched into saturated aq. NH<sub>4</sub>Cl (75 mL) and diluted with EtOAc (60 mL). The organic layer was concentrated and chromatographed (98:2 hexanes/EtOAc) to give 18.0 g of product (77% yield): HR-MS calcd for C<sub>9</sub>H<sub>17</sub>NSSi (M+) *m/z* 200.0929, found *m/z* 200.0925. The spectral data of the isolated product matched that found in the literature.<sup>35</sup>

**3.2.2.** 2-Methylthio-1,3-thiazole. (Table 2, entries 1–3, Table 3, entry 10): 2-Mercaptothiazole<sup>36</sup> (15.0 g, 128 mmol) was dissolved in DMF (150 mL).  $K_2CO_3$  (21.2 g) was added followed by a 30 min age. MeI (8.1 mL) was added slowly and the reaction aged 20 min. The mixture was diluted with EtOAc (150 mL) and water (100 mL). The organic was washed with water (3×100 mL) and then concentrated to give 14.0 g of product (76% yield). The spectral data of the isolated product matched that found in the literature.<sup>37</sup>

**3.2.3. 2-(2-Methyl-1,3-dioxolanyl)thiazole.** (Table 3, entries 13 and 14): prepared following a literature procedure.<sup>38</sup> The spectral data of the isolated product matched that found in the literature.

**3.2.4. 2-(2,5-Dimethyl-1***H***-pyrrol-1-yl)-1,3-thiazole. (Table 3, entry 15): 2-Aminothiazole (5.00 g, 49.9 mmol) was slurried in toluene (80 mL). Powdered sieves (2.5 g) were added followed by acetonylacetone (7 mL) and POCl<sub>3</sub> (4.7 mL). The reaction was heated to 100°C for 4 h and then EtOAc (50 mL) and 2N HCl (50 mL) were added. The organic layer was concentrated and chromatographed (96:4 hexanes/EtOAc) to give 0.27 g (<5% yield) of the product. The spectral data of the isolated product matched that found in the literature.<sup>39</sup>** 

**3.2.5. 2-Chloro-1,3-thiazole.** (Table 3, entry 16): a literature procedure was followed (although yield was much lower than that reported in the paper).<sup>40</sup> The spectral

data of the isolated product matched that found in the literature.<sup>41</sup>

3.2.6. Synthesis of ketones from thiazoles and aryl nitriles. Representative procedure for ketones presented in Tables 2 and 3 is given here. {2-[tert-butyl(dimethyl)silyl]-1,3-thiazol-5-yl}(pyridin-4-yl)methanone (Table 3, entry 11): 2-(t-Butyldimethylsilyl) thiazole (1.27 g, 9.60 mmole) was dissolved in THF (15 mL) and cooled to  $-60^{\circ}$ C. n-BuLi (6.0 mL, 9.60 mmole, 1.6 M in hexanes) was added at such a rate as to keep the reaction temperature below  $-40^{\circ}$ C, forming a deep red solution, which became a slurry. 4-Cyanopyridine (500 mg, 4.80 mmole) was dissolved in THF (3 mL) and added to the reaction, and the temperature was held between -35°C and -20°C for 20 min (monitoring by HPLC). Aqueous AcOH (1 M, 28.8 mmole) was added, and the hydrolysis was aged overnight. The solution was diluted with EtOAc and H<sub>2</sub>O, and the organic was washed with a 50% aq.  $K_2CO_3$  solution (2×20 mL). After drying over Na<sub>2</sub>SO<sub>4</sub>, the solution was filtered and concentrated to an orange oil. The ketone was purified by column chromatography (80:20 hexanes/EtOAc) and isolated as a yellow oil. To remove TBS, the reaction was poured into 2N HCl and THF, aged for 1 h, and worked up in a similar manner. Characterization data given below.

Product Table 2, entry 1: Following the general procedure given above the reaction was aged for 2 h to reach completion. Assay Yield of (4-chlorophenyl)[2-(methylthio)-1,3-thiazol-5-yl]methanone was 90%. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  8.23 (s, 1H), 7.85 (m, 2H), 7.60 (m, 2H), 2.75 (s, 3H); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>)  $\delta$  185.1, 176.8, 150.3, 138.3, 138.1, 136.1, 131.2, 129.5, 16.9; Anal. Calcd for C<sub>11</sub>H<sub>8</sub>CINOS<sub>2</sub>: C 48.97; H 2.99; N 5.19. Found C 48.93; H 2.82; N 5.23.

Product Table 2, entry 2: Following the general procedure given above the reaction was aged for 3 h to reach completion. Yield of [2-(methylthio)-1,3-thiazol-5-yl](phe-nyl)methanone was 89%. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  8.20 (s, 1H), 7.82 (m, 2H), 7.66 (m, 1H), 7.54 (m, 2H), 2.75 (s, 3H); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>)  $\delta$  186.2, 176.5, 150.0, 138.4, 137.5, 133.5, 129.4, 129.3, 16.9; Anal. Calcd for C<sub>11</sub>H<sub>9</sub>NOS<sub>2</sub>: C 56.14; H 3.85; N 5.95. Found C 55.97; H 3.60; N 5.88.

Product Table 2, entry 3: Following the general procedure given above the reaction was aged for 4 h to reach completion. Yield of (*4-methoxyphenyl*)[2-(*methylthio*)-1,3-thiazol-5-yl]methanone was 94%. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  8.21 (s, 1H), 7.85 (d, J=8.8, 2H), 7.07 (d, J=8.8, 2H), 3.84 (s, 3H), 2.74 (s, 3H); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>)  $\delta$  184.6, 175.4, 163.7, 149.0, 138.7, 131.8, 129.9, 114.7, 56.1, 16.8; HR-MS Calcd for C<sub>12</sub>H<sub>11</sub>NO<sub>2</sub>S<sub>2</sub> (M+) *m*/*z* 266.0309, found *m*/*z* 266.0308.

Product Table 2, entry 4: Following the general procedure given above the reaction was aged for 1.5 h to reach completion. Yield of  $\{2-[tert-butyl(dimethyl)silyl]-1,3-thia-zol-5-yl\}(4-chlorophenyl)methanone was 98%. <sup>1</sup>H NMR (CDCl<sub>3</sub>) <math>\delta$  8.48 (s, 1H), 7.85 (d, J=8.4 Hz, 2H), 7.49 (d, J=8.2 Hz, 2H), 1.00 (s, 9H), 0.43 (s, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  186.0, 181.8, 150.7, 140.7, 139.5, 136.4, 130.6,

129.0, 26.3, 17.0, -5.5; HR-MS calcd for C<sub>16</sub>H<sub>20</sub>ClNOSSi (M+) *m*/*z* 338.0802, found *m*/*z* 338.0811.

Product Table 2, entry 4 without TBS: Following the general procedure given above the reaction was aged for 1.5 h to reach completion. Aqueous HCl was used to remove the TBS group. Yield of (4-chlorophenyl)(1,3-thiazol-5-yl)methanone was 98%. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  9.09 (s, 1H), 8.36 (s, 1H), 7.86 (d, *J*=8.6 Hz, 2H), 7.53 (d, *J*=8.5 Hz, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  185.9, 159.4, 148.9, 139.7, 139.0, 135.8, 130.5, 129.1; Anal. Calcd for C<sub>10</sub>H<sub>6</sub>CINOS: C 53.70; H 2.70; N 6.26. Found C 53.38 H 2.58 N 6.11.

Product Table 2, entry 5: Following the general procedure given above the reaction was aged for 1.5 h to reach completion. Yield of {2-[tert-butyl(dimethyl)silyl]-1,3-thia-zol-5-yl](phenyl)methanone was 98%. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  8.53 (s, 1H), 7.90 (m, 2H), 7.63 (m, 1H), 7.52 (m, 2H), 1.01 (s, 9H), 0.44 (s, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  187.4, 181.4, 150.9, 141.1, 138.2, 133.0, 129.2, 128.7, 26.3, 17.0, -5.5; HR-MS calcd for C<sub>16</sub>H<sub>21</sub>NOSSi (M+) *m*/*z* 304.1191, found *m*/*z* 304.1204.

Product Table 2, entry 6: Following the general procedure given above the reaction was aged for 8 h to reach completion. Aqueous HCl was used to remove the TBS group. Yield of (*4-methoxyphenyl*)(1,3-thiazol-5-yl)methanone was 88%. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  9.03 (s, 1H), 8.35 (s, 1H), 7.93 (dd, *J*=1.9, 7.0 Hz, 2H), 7.01 (dd, *J*=1.8, 7.2 Hz, 2H), 3.91 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  185.7, 163.9, 158.5, 148.2, 139.5, 131.7, 130.3, 114.1, 55.6; Anal. Calcd for C<sub>11</sub>H<sub>9</sub>NO<sub>2</sub>S: C 60.26; H 4.14; N 6.39. Found C 60.33 H 4.08 N 6.24.

Product Table 3, entry 1: Following the general procedure given above the reaction was aged for 16 h to reach completion. Aqueous HCl was used to remove the TBS group. Yield of (2-methylphenyl)(1,3-thiazol-5-yl)methanone was 84%. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  8.99 (s, 1H), 8.04 (s, 1H), 7.42 (d, *J*=7.5 Hz, 1H), 7.34 (t, *J*=7.5 Hz, 1H), 7.22 (m, 2H), 2.33 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  189.4, 159.8, 149.9, 140.7, 137.7, 136.9, 131.4, 131.1, 128.3, 125.4, 19.8; HR-MS calcd for C<sub>11</sub>H<sub>9</sub>NOS (M+) *m*/*z* 204.0483, found *m*/*z* 204.0482.

Product with TBS: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.81 (s, 1H), 7.30 (m, 4H), 2.26 (s, 3H), 1.00 (s, 9H), 0.41 (s, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  178.4, 171.5, 149.2, 142.5, 139.9, 134.3, 130.8, 129.4, 127.1, 126.0, 26.3, 19.6, 17.0, -5.5.

Product Table 3, entry 2: Following the general procedure given above the reaction was aged for 5 h to reach completion. Aqueous HCl was used to remove the TBS group. Yield of (4-methylphenyl)(1,3-thiazol-5-yl)methanone was 92%. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  9.06 (s, 1H), 8.37 (s, 1H), 7.82 (d, J=8.2 Hz, 2H), 7.34 (d, J=8.2 Hz, 2H), 2.47 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  186.9, 158.8, 148.7, 144.2, 139.5, 135.0, 129.5, 129.4, 21.7; Anal. Calcd for C<sub>11</sub>H<sub>9</sub>NOS: C 65.00; H 4.46; N 6.89. Found C 64.61 H 4.34 N 6.83.

Product Table 3, entry 3: Following the general procedure given above the reaction was aged for 2.5 h to reach

completion. Aqueous HCl was used to remove the TBS group. Yield of *1,3-thiazol-5-yl[2-(trifluoromethyl)phenyl]-methanone* was 84%. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  9.11 (s, 1H), 8.02 (s, 1H), 7.83 (m, 1H), 7.69 (m, 2H), 7.55 (m, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  186.9, 160.5, 150.6, 139.8, 137.1 (q, *J*=1.7 Hz), 131.7, 130.7, 128.1 (q, *J*=32.4 Hz), 128.0, 127.0 (q, *J*=4.7 Hz), 123.4 (q, *J*=274.2 Hz); HR-MS calcd for C<sub>11</sub>H<sub>6</sub>F<sub>3</sub>NOS (M+) *m/z* 258.0201, found *m/z* 258.0186.

Product Table 3, entry 4: Following the general procedure given above the reaction was aged for 3 h to reach completion. Yield of *[2-[tert-butyl(dimethyl)silyl]-1,3-thia-zol-5-yl](3-methoxyphenyl)methanone* was 90%. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  8.53 (s, 1H), 7.45 (m, 3H), 7.17 (m, 1H), 3.88 (s, 3H), 1.01 (s, 9H), 0.44 (s, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  187.1, 181.4, 159.8, 150.8, 141.0, 139.3, 129.6, 121.8, 119.4, 113.5, 55.5, 26.2, 16.9, -5.5; HR-MS calcd for C<sub>17</sub>H<sub>23</sub>-NO<sub>2</sub>SSi (M+) *m/z* 334.1297, found *m/z* 334.1314.

Product Table 3, entry 5: Following the general procedure given above the reaction was aged for 3 h to reach completion. Aqueous HCl was used to remove the TBS group. Yield of (*3-methoxyphenyl*)(1,3-thiazol-5-yl)methanone was 87%. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  8.59 (s, 1H), 8.40 (s, 1H), 7.47 (m, 3H), 7.19 (m, 1H), 3.89 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  186.9, 159.9, 159.2, 149.1, 139.3, 138.8, 129.8, 121.7, 119.5, 113.7, 55.5; HR-MS calcd for C<sub>11</sub>H<sub>9</sub>NO<sub>2</sub>S (M+) *m/z* 220.0432, found *m/z* 220.0425.

Product Table 3, entry 6: Following the general procedure given above the reaction was aged for 12 h to reach completion. Aqueous HCl was used to remove the TBS group. Yield of (3,4-dimethoxyphenyl)(1,3-thiazol-5-yl)methanone was 91%. <sup>1</sup>H NMR (CDCl<sub>3</sub>) & 9.05 (s, 1H), 8.39 (s, 1H), 7.59 (dd, *J*=2.0, 8.4 Hz, 1H), 7.49 (d, *J*=2.0 Hz, 1H), 6.97 (d, *J*=8.4 Hz, 1H), 3.99 (s, 3H), 3.97 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) & 185.6, 158.5, 153.7, 149.4, 148.2, 139.3, 130.3, 124.2, 111.6, 110.3, 56.2, 56.1; Anal. Calcd for C<sub>12</sub>H<sub>11</sub>NO<sub>3</sub>S: C 57.82; H 4.45; N 5.62. Found C 57.44 H 4.26 N 5.53.

Product Table 3, entry 7: Following the general procedure given above the reaction was aged for 3 h to reach completion. Yield of *phenyl*{2-[2,2,2-triffuoro-1-(methoxy-methoxy)-1-(triffuoromethyl)ethyl]-1,3-thiazol-5-yl]-methanone was 95%. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.34 (s, 1H), 7.92 (d, *J*=7.6 Hz, 2H), 7.69 (t, *J*=7.2 Hz, 1H), 7.57 (t, *J*=7.5 Hz, 2H), 5.17 (s, 2H), 3.59 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 186.7, 164.3, 148.0, 142.1, 136.9, 133.5, 129.2, 128.9, 121.3 (q, *J*=290.9 Hz, 2C), 95.4, 80.7 (m), 57.1; Anal. Calcd for C<sub>16</sub>H<sub>15</sub>F<sub>6</sub>NO<sub>3</sub>S: C 45.12; H 2.78; N 3.51. Found C 44.99 H 2.59 N 3.47.

Product Table 3, entry 8: Following the general procedure given above the reaction was aged for 5 h to reach completion. Yield of (4-methoxyphenyl)[2-[2,2,2-trifluoro-1-(methoxymethoxy)-1-(trifluoromethyl)ethyl]-1,3-thiazol-5-yl]methanone was 96%. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  8.32 (s, 1H), 7.95 (dd, J=2.0, 6.8 Hz, 2H), 7.03 (dd, J=2.0, 6.9 Hz, 2H), 5.16 (s, 2H), 3.93 (s, 3H), 3.59 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$ 185.0, 164.1, 163.7, 147.1, 142.3, 131.8, 129.5, 121.3 (q, J=291.1 Hz, 2C), 114.2, 95.3, 80.7 (m), 57.2, 55.6; HR-MS calcd for  $C_{16}H_{13}F_6NO_4S$  (M+) m/z 430.0548, found m/z 430.0554.

Product Table 3, entry 9: Following the general procedure given above the reaction was aged for 7 h to reach completion. Yield of  $(3,4-dimethoxyphenyl){2-[2,2,2-tri-fluoro-1-(methoxymethoxy)-1-(trifluoromethyl)ethyl]-1,3-thiazol-5-yl]methanone was 94%. <sup>1</sup>H NMR (CDCl<sub>3</sub>) <math>\delta$  8.34 (s, 1H), 7.60 (dd, *J*=2.0, 8.4 Hz, 1H), 7.49 (d, *J*=1.9 Hz, 1H), 6.98 (d, *J*=8.4 Hz, 1H), 5.17 (s, 2H), 4.00 (s, 3H), 3.98 (s, 3H), 3.59 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  185.0, 163.7, 154.0, 149.5, 147.1, 142.2, 129.6, 124.4, 121.3 (q, *J*=291.9 Hz, 2C), 111.4, 110.2, 95.3, 80.3 (m), 57.2, 56.2, 56.1; Anal. Calcd for C<sub>17</sub>H<sub>15</sub>F<sub>6</sub>NO<sub>5</sub>S: C 44.45; H 3.29; N 3.05. Found C 44.17 H 3.00 N 3.02.

Product Table 3, entry 10: Following the general procedure given above the reaction was aged for 20 min to reach completion. Yield of [2-(methylthio)-1,3-thiazol-5-yl](pyridin-4-yl)methanone was 96%. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  8.81 (dd, J=1.6, 4.4, 2H), 8.29 (s, 1H), 7.74 (dd, J=1.6, 4.4, 2H), 2.79 (s, 3H); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>)  $\delta$  185.4, 177.9, 151.2, 151.0, 143.9, 137.5, 122.5, 16.9: Anal. Calcd for C<sub>10</sub>H<sub>8</sub>N<sub>2</sub>OS<sub>2</sub>: C 50.82; H 3.41; N 11.85. Found C 50.78; H 3.11; N 11.72.

Product Table 3, entry 11: Following the general procedure given above, the reaction was aged for 20 min to reach completion to obtain {2-[tert-butyl(dimethyl)silyl]-1,3-thiazol-5-yl](pyridin-4-yl)methanone in 90% yield: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  8.83 (dd, J=1.7, 4.3, 2H), 8.67 (s, 1H), 7.77 (dd, J=1.7, 4.3, 2H), 0.95 (s, 9H), 0.40 (s, 6H); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>)  $\delta$  186.4, 182.2, 152.4, 151.0, 144.4, 140.4, 122.6, 26.5, 17.0, -5.2.

Product Table 3, entry 12: Following the general procedure given above the reaction was aged for 8 h to reach completion. Aqueous HCl was used to remove the TBS group. Yield of 2-furyl(1,3-thiazol-5-yl)methanone was 60%. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  9.06 (s, 1H), 8.91 (s, 1H), 7.74 (dd, *J*=0.6, 1.5 Hz, 1H), 7.47 (d, *J*=3.6 Hz, 1H), 6.67 (dd, *J*=1.7, 3.6 Hz, 1H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  172.7, 158.9, 152.1, 148.5, 147.0, 138.0, 119.4, 112.9; HR-MS calcd for C<sub>8</sub>H<sub>5</sub>NO<sub>2</sub>S (M+) *m/z* 180.0119, found *m/z* 180.0114.

Product with TBS: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  9.00 (s, 1H), 7.72 (dd, *J*=0.7, 1.6, 1H), 7.45 (dd, *J*=0.7, 3.6, 1H), 6.65 (dd, *J*=1.6, 3.6, 1H), 1.01 (s, 9H), 0.44 (s, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  181.0, 172.8, 152.2, 150.2, 146.8, 139.6, 119.2, 112.8, 26.2, 16.9, -5.5.

Product Table 3, entry 13: Following the general procedure given above the reaction was aged for 30 h to reach completion. Yield of *cyclopropyl[2-(2-methyl-1,3-dioxo-lan-2-yl)-1,3-thiazol-5-yl]methanone* was 47%. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  8.40 (s, 1H), 4.10 (m, 4H), 2.49 (m, 1H), 1.84 (s, 3H), 1.28 (m, 2H), 1.08 (m, 2H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  192.8, 178.8, 146.8, 141.0, 106.9, 65.6, 25.1, 18.9, 11.8; Anal. Calcd for C<sub>11</sub>H<sub>13</sub>NO<sub>3</sub>S: C 55.21; H 5.48; N 5.85. Found C 54.90 H 5.30 N 5.83.

Product Table 3, entry 14: Following the general procedure given above the reaction was aged for 7.5 h to reach

completion. Yield of [2-(2-methyl-1,3-dioxolan-2-yl)-1,3-thiazol-5-yl](phenyl)methanone was 98%. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  8.21 (s, 1H), 7.88 (dd, J=3.3, 5.2 Hz, 2H), 7.64 (m, 1H), 7.53 (m, 2H), 4.12 (m, 4H), 1.87 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  187.5, 179.2, 149.3, 139.6, 137.6, 133.1, 129.2, 128.8, 107.0, 65.7, 25.1; HR-MS calcd for C<sub>14</sub>H<sub>13</sub>NO<sub>3</sub>S (M+) *m*/z 276.0694, found *m*/z 276.0692.

Product Table 3, entry 15: Following the general procedure given above the reaction was aged for 45 min to reach completion. Yield of (4-chlorophenyl)[2-(2,5-dimethyl-1H-pyrrol-1-yl)-1,3-thiazol-5-yl]methanone was 93%. <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  8.12 (s, 1H), 7.88 (d, J=8.6 Hz, 2H), 7.54 (d, J=8.5 Hz, 2H), 5.96 (s, 2H), 2.38 (s, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  185.8, 164.8, 146.6, 139.5, 137.5, 135.6, 130.4, 130.2, 129.1, 109.8, 14.2; Anal. Calcd for C<sub>16</sub>H<sup>13</sup>ClN<sub>2</sub>OS: C 60.66; H 4.14; N 8.84. Found C 60.42; H 3.91; N 8.74.

Product Table 3, entry 16: Following the general procedure given above the reaction was aged for 7 h to reach completion. Yield of (2-chloro-1,3-thiazol-5-yl)(phenyl)-methanone was 69%. Characterization data given in footnote 2a.

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- Reducing the ClCH<sub>2</sub>CH<sub>2</sub>OTs charge to 1.2 equiv. required an overnight age for the reaction to reach completion.
- No reaction was observed with Na<sub>2</sub>CO<sub>3</sub>, and was very slow with K<sub>2</sub>CO<sub>3</sub> (with or without phase transfer reagents, and with 0–5 equiv. water). Use of Cs<sub>2</sub>CO<sub>3</sub>: Lee, J. C.; Yuk, J. Y.; Cho, S. H. *Synth. Commun.* **1995**, *25*(9), 1367–1370.
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- 13. 3-(Cyclopropyloxy)-4-methoxybenzaldehyde 7: <sup>1</sup>H NMR (DMSO) δ 9.82 (s, 1H), 7.64 (d, J=1.9 Hz, 1H), 7.54 (dd, J=1.9, 8.3 Hz, 1H), 7.13 (d, J=8.3 Hz, 1H), 3.87 (septet, J=2.9 Hz, 1H), 3.81 (s, 3H), 0.80-0.62 (m, 4H) ppm. <sup>13</sup>C NMR (DMSO) δ 191.8, 154.6, 149.0, 130.1, 127.0, 112.0, 111.8, 56.3, 51.7, 6.3 ppm. Anal. Calcd for C<sub>11</sub>H<sub>12</sub>O<sub>3</sub>: C 68.74; H 6.29. Found C 68.58; H 6.09.
- 14. The solid contained 5% aldehyde 7.
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a 1:1 mixture of starting material **8** and product **9** to  $100^{\circ}$ C in DMF in the presence of base (no ClCF<sub>2</sub>CO<sub>2</sub>Na) did not generate any of the dimer.

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