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Selective metal-halogen exchange of 4,4′-dibromobiphenyl mediated by lithium tributylmagnesiate

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Abstract—A selective metal–halogen exchange/electrophilic quench protocol on 4,4′-dibromobiphenyl **4** that proceeds under non-cryogenic conditions is reported. This method provides an economic alternative to traditional transition-metal catalyzed cross-coupling chemistry to prepare various biaryls **7a**–**g**. This novel route to functionalized biaryls was used as the basis for the kg-scale preparation of a biphenyl ketone **1**, a key intermediate in the synthesis of a potent cathepsin K inhibitor.

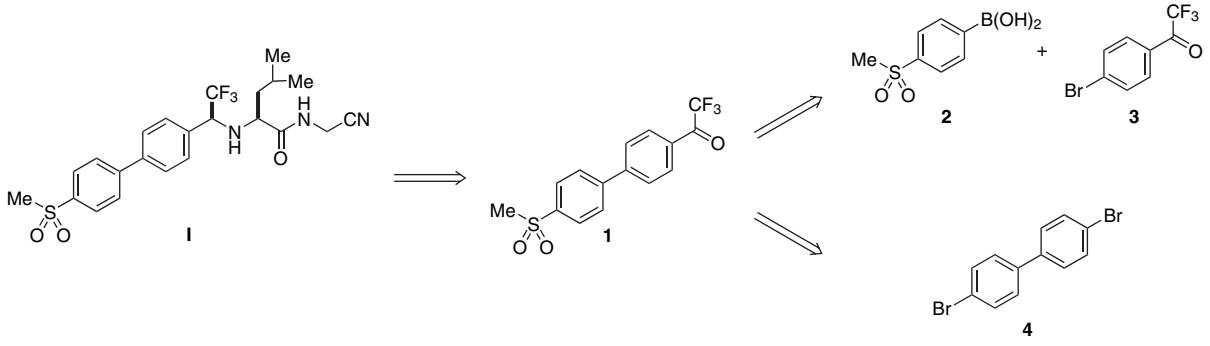
1. Introduction

Transition-metal catalyzed reactions represent some of the most widely used and powerful tools in synthetic organic chemistry.[1] Currently, these techniques are readily applied to various C–C bond constructions, including aryl–aryl bond formation.[2] In particular, the Suzuki–Miyaura[3] reaction has gained widespread use throughout preparative and medicinal chemistry due to the low toxicity and bench stability of organoboron species. Recent examples of pharmaceutically relevant molecules prepared utilizing this chemistry include VLA-4 antagonists,[4] angiotensin II antagonists,[5] and cathepsin K inhibitors.[6]

During the course of our investigations on cathepsin K inhibitors, we sought to develop a cost-efficient and practical synthesis of biphenyl ketone **1**, a precursor to potent cathepsin K inhibitor **I** (Scheme 1).[7] One obvious disconnection of biphenyl ketone **1** would be the aryl–aryl bond, which could be generated via a Suzuki–Miyaura[3] cross-coupling between boronic acid **2** and aryl bromide **3**. While these materials are commercially available, we felt that the price of the coupling partners was not justified for a simple molecule such as ketone **1**. The cost of these materials compelled us to develop an alternative strategy to ketone **1** that would avoid the use of metal-catalyzed cross-coupling.

2. Results and discussion

From the outset we aimed to use low-cost, commercial materials to avoid the use of cryogenic temperatures throughout



Scheme 1. Retrosynthetic analysis of cathepsin K inhibitor **I**.

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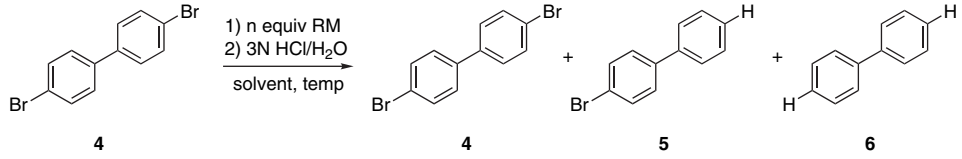
this process. We selected 4,4′-dibromobiphenyl (**4**) as starting material since it is a readily available, inexpensive commodity chemical. We sought to develop a protocol for stepwise functionalization of **4** via controlled, selective mono-metal–halogen exchange followed by electrophilic quench.

We investigated the selectivity of a variety of metal–halogen exchange reagents by examination of the ratio of di-, mono-, and non-brominated biphenyls (**4**, **5**, and **6**, respectively) resulting from direct quench with 3 N aqueous HCl (Table 1). Metal–halogen exchange using *n*-BuLi gave unsatisfactory ratios of mono- to di-metallation in THF at −46 °C, toluene at 22 °C, and toluene/THF (2:1) at −25 °C (Table 1, entries 1–3). Modest selectivity was observed with *n*-BuLi in MTBE, however a significant quantity of starting material remained (Table 1, entry 4). Grignard reagents have been used as an effective metal–halogen exchange reagents.[8] However, *i*-PrMgCl was completely ineffective in both THF and toluene, even after 16 h at 55 °C; the additive lithium chloride only marginally improved reactivity (Table 1, entries 5–7). The more reactive dibutylmagnesium[9] was also ineffective for metal–halogen exchange (Table 1, entry 8). While the Grignard reagent could be prepared by heating dibromide **4** with magnesium metal,[10] acceptable selectivity was not observed (Table 1, entry 10).

Lithium trialkylmagnesiates[11] have been used as metal–halogen exchange reagents for aryl and vinyl halides; the resultant magnesiates were successfully used as nucleophiles.[12] In fact, Oshima and co-workers have shown that addition of 1.0 equiv of *n*-Bu_3MgLi to dibromide **4**, followed by D_2O addition resulted in metal–halogen exchange and incorporation of deuterium at both the 4- and 4′-positions. Work within our own laboratories on 2,6-dibromopyridine has shown that all three alkyl groups on trialkylmagnesiates are active toward metal–halogen exchange and that direct addition of the dihalide to magnesiate, at −10 °C, afforded good mono- versus di-exchange selectivity.[13] We therefore examined the addition of dibromide **4** to 0.33 equiv *n*-Bu_3MgLi, but were disappointed to observe poor selectivity (Table 2, entry 1, **4**:**5**:**6**=47:36:17). Gratifyingly, by adding *n*-Bu_3MgLi to a solution of **4**, a substantial improvement in selectivity was observed (Table 2, entry 2, **4**:**5**:**6**= 24:73:3). In order to drive the reaction to completion, we tested the use of greater equivalents of reagent (Table 2, entries 3–4). As much as 0.43 equiv of *n*-Bu_3MgLi was needed in order to consume >98% dibromide **4**, however, at this point selectivity was significantly diminished (**4**:**5**:**6**= 1:89:10). We therefore settled upon the use of 0.40 equiv of magnesiate as the optimal stoichiometry, for which high conversion (94%) was obtained, and selectivity maintained

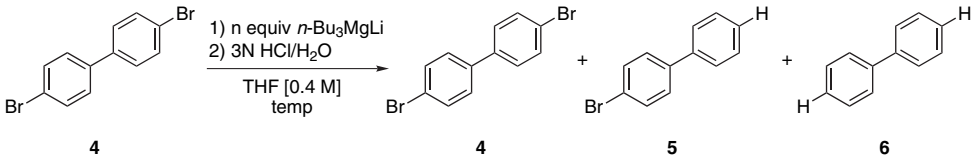
Table 1. Selectivity of various metal–halogen exchange reagents toward dibromobiphenyl **4**



4 **4** **5** **6**

Entry	Reagent	Solvent	*n* (equiv)	Temperature (°C)	Time (h)	HPLC area (%)		
						4	**5**	**6**
1	*n*-BuLi	THF	1.0	−46	0.1	32	41	27
2	*n*-BuLi	Toluene	1.0	22	0.1	10	43	47
3	*n*-BuLi	Toluene/THF	1.0	−25	0.1	23	50	27
4	*n*-BuLi	MTBE	1.0	−25	0.1	28	62	10
5	*i*-PrMgCl	THF	2.0	55	16	99	<1	0
6	*i*-PrMgCl	Toluene	2.0	55	16	99	<1	0
7	*i*-PrMgCl-LiCl	THF	1.1	22	24	83	16	1
8	*n*-Bu_2Mg	Toluene	1.0	22	1	99	<1	0
9	Mg	Toluene	1.5	80	24	99	<1	0
10	Mg	THF	1.5	55	24	64	16	18

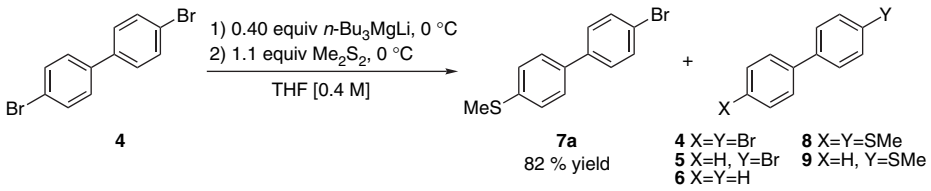
Table 2. Selectivity of *n*-Bu_3MgLi toward metal–halogen exchange of dibromobiphenyl[a]



4 **4** **5** **6**

Entry	Mode of addition	Addition time (min)	*n* (equiv)	Temperature (°C)	Time (h)	HPLC area (%)		
						4	**5**	**6**
1	Direct	60	0.33	22	0.1	47	36	17
2	Inverse	60	0.33	22	0.1	24	73	3
3	Inverse	90	0.40	22	0.1	6	88	6
4	Inverse	120	0.43	22	0.1	1	89	10
5	Inverse	90	0.40	0	1.0	6	90	4

[a] Reaction conditions: for direct addition, a THF solution (0.4 M) of dibromide **4** was added to a slurry of *n*-Bu_3MgLi in THF. For inverse addition, *n*-Bu_3MgLi was added to a THF solution (0.4 M) of dibromide **4**.

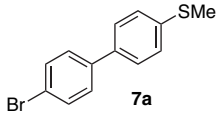
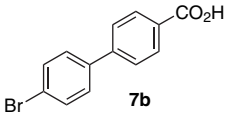
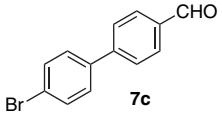
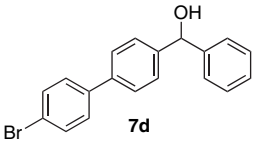
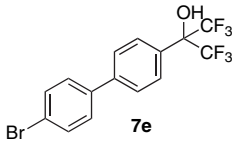
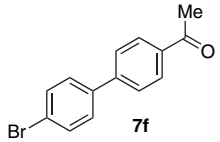
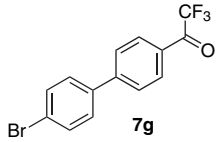


Scheme 2. Trialkylmagnesiate mediated mono-metal–halogen exchange followed by Me_2S_2 quench.

(**4**:**5**:**6**=6:88:6). Finally, we found that addition of magnesiate at 0 °C, followed by aging 1 h, provided optimal selectivity (Table 2, entry 5, **4**:**5**:**6**=6:90:4).

When addition of lithium tributylmagnesiate to dibromobiphenyl **4** was followed by addition of 1.1 equiv of methyl disulfide, biaryl **7a** was obtained in 82% yield (Scheme 2).[14] The crude organic stream was contaminated with several biphenyl impurities (**4**–**6**, **8**, and **9**), as indicated by HPLC analysis, however, these contaminants could be carried through the process sequence without detrimental effect.

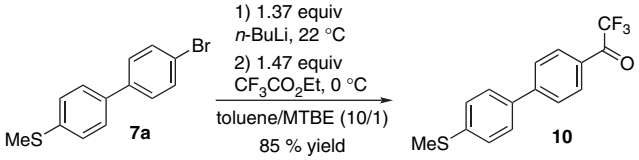
Table 3. Preparation of 4,4′-disubstituted biphenyls via magnesiate-mediated metal–halogen exchange and electrophilic quench[a]

Entry	Electrophile	Product	Yield[b] (%)
1	Me_2S_2	 **7a**	82 (73)[c]
2	CO_2	 **7b**	91 (73)[c]
3	DMF	 **7c**	83 (60)[c]
4	PhCHO	 **7d**	83 (55)[c]
5	$(CF_3)_2CO$	 **7e**	93 (59)[c]
6[d]	Ac_2O[d]	 **7f**	75 (63)[c]
7[d]	$(CF_3CO)_2O$[d]	 **7g**	79 (61)[c]

[a] Reaction conditions: 0.4 equiv *n*-Bu_3MgLi added over 90 min to a THF solution (0.4 M) of dibromide **4** at 0 °C. The reaction mixture was stirred 1 h, then 1.1 equiv of requisite electrophile was added.
[b] Assay yield determined by HPLC versus authentic standard.
[c] Isolated yield after column chromatography.
[d] Inverse addition was used: 0.4 equiv *n*-Bu_3MgLi added over 90 min to a THF solution (0.4 M) of dibromide **4** at 0 °C; then the crude reaction mixture was added over 60 min to a solution of the requisite electrophile in THF at −20 °C.

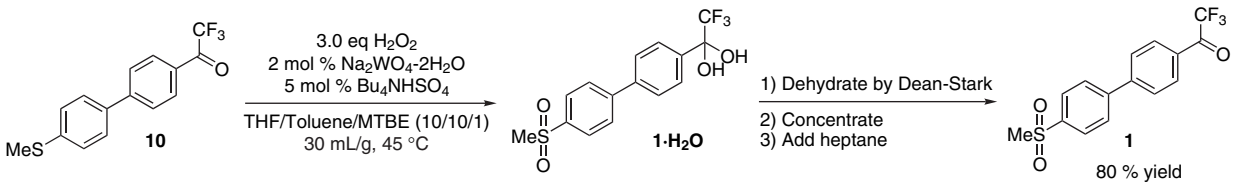
With a successful method for mono-metal–halogen exchange/electrophilic quench in hand, we briefly investigated the scope of addition to various electrophiles. We found that direct addition of carbon dioxide and DMF afforded high assay yields of the carboxylic acid and aldehyde derivatives, respectively (Table 3, entries 2 and 3). Non-enolizable ketones and aldehydes afforded both secondary and tertiary alcohols in good yield (Table 3, entries 4 and 5). Addition to acetic and trifluoroacetic anhydride necessitated the use of inverse addition to the electrophile at −20 °C to obtain good yields of the corresponding ketones (Table 3, entries 6 and 7).

In order to complete the synthesis of ketone **1**, we next investigated the introduction of the trifluoroacetyl moiety via aryllithium addition to ethyl trifluoroacetate, Scheme 3.[15] Metal–halogen exchange could be performed with *n*-BuLi at room temperature in a toluene/MTBE (10:1) solvent mixture. In the absence of MTBE as a co-solvent, exchange was sluggish (<15% conversion in 1 h at room temperature). The yield of thioketone **10** was found to be highly dependent upon the mode of electrophile addition. Direct addition of ethyl trifluoroacetate was not scalable; if the addition was completed in <5 s, thioketone **10** was obtained in ~80% yield on gram-scale. However upon scale-up to multigram, longer periods were needed for addition; greater amounts of unidentified impurities and variable yields were obtained. In contrast, slow addition of the aryllithium slurry to a solution of ethyl trifluoroacetate at 0 °C (inverse addition), consistently afforded material of higher purity and reproducibly in 85% yield on up to 50 g scale.



Scheme 3. Introduction of the trifluoroacetyl moiety.

The crude organic stream containing thioketone **10** was used directly for the tungstate-catalyzed oxidation[16] to sulfone **1**·$\mathbf{H_2O}$. Addition of 3.0 equiv H_2O_2 over 1.5–2 h to the reaction mixture at 45 °C, in the presence of 2 mol % $Na_2WO_4 \cdot 2H_2O$ and 5 mol % Bu_4NHSO_4, gave sulfone hydrate **1**·$\mathbf{H_2O}$ in 85% assay yield within 6 h (Scheme 4).[17] Azeotropic removal of water/toluene was used to drive the material to >99% ketone **1**, as determined by ^{19}F NMR



Scheme 4. Oxidation to sulfone and isolation.

spectroscopy. The material was then crystallized from toluene/heptane to afford desired ketone **1** in 80% yield from thioketone **10**.

In summary, we have developed a 3-step through process for the preparation of ketone **1** that proceeds in ~56% overall yield from inexpensive dibromobiphenyl **4**, without the use of cryogenic methods. The process features a selective mono-metal–halogen exchange of dibromobiphenyl **4**, mediated by lithium tributylmagnesiate. The metal–halogen exchange/electrophilic quench protocol provides access to a variety of functionalized biphenyls (**7a**–**g**) under non-cryogenic conditions and avoids the use of expensive transition-metal catalyzed cross-coupling chemistry.

3. Experimental

3.1. General

Reactions were carried out under an atmosphere of dry nitrogen. Reagents and solvents were used as received from commercial sources. ^{1}H NMR spectrum was recorded on a Bruker 400 (400 MHz) spectrometer. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent resonance as the internal standard (acetone-d_6: δ 2.06, DMSO-d_6: δ 2.49, THF-d_8: δ 3.65). Data are reported as follow: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, br=broad, m=multiplet), coupling constants (Hz) and integration. ^{13}C NMR spectrum was recorded on a Bruker 400 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in parts per million from tetramethylsilane with the solvent as the internal reference (acetone-d_6: δ 206.0, DMSO-d_6: δ 39.5, THF-d_8: δ 66.5). ^{19}F NMR spectrum was recorded on Bruker 400 (375 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in parts per million with α,α,α-trifluorotoluene added as an internal reference (δ −67.2). All compounds except **1**, **7g**, and **10** were characterized using the same HPLC conditions: Zorbax RX-C8 (4.6 mm×25.0 cm) column, gradient elution: (0.1% H_3PO_4/CH_3CN 50:10 to 10:90 over 7.5 min, hold 2.5 min), flow rate=2.0 mL/min, T=35 °C, UV detection at 220 nm. Compounds **1**, **7g**, and **10** were analyzed by GC: HP-1 (30 m, 0.32 mm, 0.25 μm film) column, gradient elution (100 °C–250 °C at 15 °C/min), flow rate=2.5 mL/min He, FID detection=300 °C. A 10 μL sample was injected at 250 °C.

3.2. Procedures

3.2.1. Preparation of lithium tri-*n*-butylmagnesiate. A 15-L round-bottom flask equipped with a dropping-funnel, thermocouple, mechanical stirrer, nitrogen inlet and outlet, was charged with anhydrous THF (3.21 L). *n*-BuMgCl (1.31 L, 2.0 M in THF, 2.63 mol, 100 mol %) was charged into the dropping-funnel, and added over 90 min at room temperature. The reactor's internal temperature rose from 20 °C to 31 °C during *n*-BuMgCl addition. Next *n*-BuLi (2.05 L, 2.5 M in hexane, 5.13 mol, 195 mol %) was charged to the dropping-funnel, and added to the reactor over 90 min. During the initial stages of *n*-BuLi addition the internal temperature rose from 30 °C to 34 °C, however, no external cooling bath was used. Upon complete addition of *n*-BuLi, a thin gray slurry formed, from which gray solids would settle if stirring was ceased. The slurry was stirred for 5 min, and then used to perform metal–halogen exchange. ^{1}H NMR (400 MHz, THF with an internal THF-d_8 standard) δ 1.49 (m, 2H), 1.22 (m, 2H), 0.81 (t, J=7.2, 3H), −0.79 (t, J=8.0, 2H). For comparison, the spectrum of *n*-BuMgCl is as follows: ^{1}H NMR (400 MHz, THF with an internal THF-d_8 standard) δ 1.34 (m, 2H), 1.67 (m, 2H), 0.68 (t, J=7.2, 3H), −0.80 (t, J=8.0, 2H).

3.2.2. Conversion of dibromobiphenyl 4 to 4-Bromo-4′-methylsulfanyl-biphenyl (7a). 4,4′-Dibromobiphenyl (2.00 kg, 6.41 mol, 100 mol %) was charged to a clean 50-L round-bottom flask equipped with a dropping-funnel, mechanical stirrer, thermocouple, nitrogen inlet and outlet. Anhydrous THF (16.0 L) was added with stirring, and the flask cooled to 0 °C in an ice/acetone bath. The dropping-funnel was charged with the *n*-Bu_3MgLi slurry (6.57 L, 2.63 mol, 40 mol %), which was added to the reaction flask over 2.25 h. The internal temperature rose from 0 °C to 4.4 °C during the addition of *n*-Bu_3MgLi (initial 4.0 L). The pale gray solution took on an amber color as *n*-Bu_3MgLi was added. Upon complete *n*-Bu_3MgLi addition, the internal temperature was 3.0 °C. The resultant yellow solution was aged for 60 min, while re-cooling to 0 °C. HPLC analysis of a crude aliquot (quenched into aqueous 3 N HCl/MTBE) showed a mixture of biphenyl, **6**, 4′-bromobiphenyl, **5**, and dibromobiphenyl, **4**. (**4**:**5**:**6**=6:84:3). A clean addition funnel was replaced for the used addition funnel, and charged with methyl disulfide (635 mL, 7.05 mol, 110 mol %), which was then added over 1.75 h. Addition of methyl disulfide caused an exotherm from 1.1 °C to 7.4 °C. The solution became a yellow-white slurry after 500 mL of methyl disulfide had been added. The slurry was aged for 15 h, then cooled with an external ice/acetone bath to −2.0 °C. Aqueous periodic acid (10 wt %, 4.04 L, 1.77 mol, 28 mol %) was added dropwise over 1 h into the reaction flask, and the resultant biphasic mixture stirred vigorously for 20 min. An exotherm was observed upon addition to aqueous periodic acid (internal temperature rose from −2.0 °C to 7.4 °C) and the mixture became deep-red. Aqueous 3 N HCl (4.04 L, 12.1 mol, 190 mol %) was then added dropwise over 1 h into the reaction flask, and the mixture stirred for 1 h, which raised the internal temperature

from 3.6 °C to 11.1 °C. Agitation was stopped and the mixture was transferred to a 50 L extractor; the flask was washed with 1.0 L THF, which was added to the extractor. The mixture was vigorously stirred, then allowed to settle for 5 min. The bottom (aqueous) layer was removed. Aqueous sodium thiosulfate (10 wt %, 8.1 L) was added to the extractor, causing the internal temperature to rise from 10 °C to 23 °C, the mixture was vigorously stirred for 5 min, which became pale-yellow. After agitation was stopped, the aqueous layer was cut. Aqueous sodium thiosulfate (10 wt %, 4.0 L) and toluene (5.0 L) were added to the extractor, and after vigorous stirring for 5 min, the aqueous layer was separated. The organic layer was then washed with water (2×4.0 L) and collected. HPLC analysis showed **7a** (15.95 kg at 9.16 wt % for a total of 1.46 kg, 5.24 mol, 82% assay yield). The crude solution was concentrated in vacuo, flushed with toluene (20 L), and re-concentrated to a thick beige slurry of 3.537 kg. Approximately 155 g of this slurry was dissolved in toluene and used for the subsequent transformation. An analytically pure sample was prepared by chromatography on silica gel, eluting with 5% MTBE in hexane. ^{1}H NMR (400 MHz, acetone-d_6) δ 7.62 (m, 6H), 7.38 (d, J=8.0, 2H), 2.54 (s, 3H); mp=144.0–146.4 °C (lit.[18] 148–150 °C). HPLC retention time: 6.79 min. Anal. Calcd for $C_{13}H_{11}BrS$: C, 55.92; H, 3.97. Found: C, 55.65; H, 3.73.

3.2.3. 2,2,2-Trifluoro-1-(4′-methylsulfanyl-biphenyl-4-yl)-ethanone (10). A 2-L round-bottom flask equipped with a magnetic stirrer, thermocouple, nitrogen inlet and outlet, was charged with crude bromosulfide **7a** (8.76 wt % in toluene, 731 g, 230 mmol, 100 mol %) and MTBE (80 mL). *n*-BuLi (130 mL, [2.5 M] 322 mmol, 140 mol %) was via syringe pump over 0.5 h. The initial internal temperature was observed as 20.7 °C and increased to 37.7 °C during *n*-BuLi addition. Upon completion, a dark orange slurry formed, from which white solids would settle very slowly if stirring was ceased. HPLC analysis of a crude aliquot after *n*-BuLi was added (quenched into aqueous 3 N HCl/MTBE) showed >97% conversion to the aryllithium species. The slurry was stirred for 2 h, and then transferred to the apparatus described as follows. A second 2-L round-bottom flask, equipped with a magnetic stirrer, thermocouple, addition funnel, nitrogen inlet and outlet, was charged with ethyl trifluoroacetate (41 mL, 345 mmol, 150 mol %) and toluene (40 mL), and cooled in an ice/acetone bath. The prepared slurry of aryllithium was charged to the addition funnel, and added to the reaction flask over 1.0 h. An exotherm (internal temperature started at 4.4 °C and rose to 19.9 °C) was observed during aryllithium addition. Upon completion, a bright yellow-orange solution formed. GC analysis of an aliquot immediately after addition was complete indicated ~81% conversion to the thioketone (59.3 A% thioketone **10**, 10.4 A% sulfide **9** by GC). The slurry was aged for 30 min, then aqueous 3 N HCl (350 mL) and THF (350 mL) were added into the reaction flask. The resultant biphasic mixture stirred vigorously for 15 min, then allowed to settle. The bottom (aqueous) layer was removed and the bright yellow organic phase washed with aqueous 3 N HCl (200 mL) and collected. GC analysis showed thioketone **10** (1.2 kg at 4.84 wt % for a total of 58.11 g, 85.9% assay yield). The crude organic solution was concentrated in vacuo to 327 g of a yellow solution. An analytically pure sample was prepared by chromatography on silica gel, eluting with 25% MTBE in hexane. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.18 (d, J=7.6, 2H), 7.98 (d, J=7.6, 2H), 7.77 (d, J=8.4, 2H), 7.43 (d, J=8.4, 2H), 2.57 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 180.3 (q, $^2J_{CF}$=34), 148.2, 141.5, 135.7, 131.4, 129.1, 128.4, 128.0, 127.2, 117.7 (q, $^1J_{CF}$=289), 14.9; ^{19}F NMR (375 MHz, acetone-d_6) δ−76.2; mp=114.6–116.2 °C. GC retention time: 13.24 min. Anal. Calcd for $C_{15}H_{11}F_3OS$: C, 60.80; H, 3.74; F, 19.24. Found: C, 60.56; H, 3.44; F, 19.19.

3.2.4. 2,2,2-Trifluoro-1-(4′-methylsulfonyl-biphenyl-4-yl)-ethanone (1). The crude thioketone **10** (18.0 wt % in toluene, 327 g, 198 mmol, 100 mol %) was charged into a visually clean, 2-L round-bottom flask equipped with a magnetic stirrer, reflux condenser, internal temperature probe, nitrogen inlet and outlet. Toluene (300 mL), THF (600 mL), $Na_2WO_4\cdot 2H_2O$ (22.8 g, 0.07 mol, 2 mol %), and Bu_4NHSO_4 (58.2 g, 0.17 mol, 5 mol %) were added to the reactor and the resultant mixture heated to 45 °C in an oil bath while stirring vigorously. Hydrogen peroxide (67 mL, 30% aqueous, 594 mmol, 300 mol %) was then added via syringe pump over 1.5 h, the resultant mixture was stirred with heating for an additional 2 h and then cooled to room temperature. (The internal temperature remained below 59 °C during peroxide addition.) Aqueous $Na_2S_2O_3\cdot 5H_2O$ (10 wt %, 300 mL) was added to the flask over 60 min (temperature remained <25 °C) and the mixture stirred for 5 min. At this point, starch-paper test indicated <10 mg/L of peroxide remained. Methyl ethyl ketone (750 mL) was added, and after 5 min stirring was stopped. The mixture was transferred to a separatory funnel, the cloudy bottom (aqueous) layer removed, and the organic solution collected. GC analysis indicated ketone-hydrate **1·H$_2$O** (3.66 wt % of 1.68 kg, 61.5 g, 95.2% assay yield). The solution was concentrated and solvent-switched to toluene. Analysis by ^{19}F NMR spectroscopy indicated a 10:1 mixture of **1·H$_2$O** (−88.7 ppm) & **1** (−76.3 ppm). The material was diluted to ~1.0 L toluene, then dehydrated by water/toluene azeotrope in a Dean–Stark apparatus. After 1 h only the ketone **1** remained (^{19}F NMR analysis). The toluene solution was concentrated in vacuo to ~643 g, whereupon white solids began to form in the orange solution. The material was transferred to a 3-neck round-bottom flask equipped with mechanical stirrer and addition funnel, then diluted with toluene (12 mL). Heptane (675 mL) was added dropwise over 1 h to the vigorously stirred slurry. After stirring for an additional 45 min, the material was filtered to afford sulfone **1** (68.8 g at 75 wt % for 51.6 g, 80% assay yield, 91.9 A% by GC). An analytically pure sample was prepared by chromatography on silica gel, eluting with 15% ethyl acetate in hexane. ^{1}H NMR (400 MHz, acetone-d_6) δ 8.23 (d, J=7.4, 2H), 8.11 (d, J=8.2, 2H), 8.05 (m, 4H), 3.20 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6) δ 180.3 (q, $^2J_{CF}$=34), 146.6, 144.3, 142.2, 131.3, 130.0, 128.9, 128.7, 117.4 (q, $^1J_{CF}$=289), 116.7, 44.0; ^{19}F NMR (375 MHz, acetone-d_6) δ−76.3; mp=157.9–158.8 °C. GC retention time: 15.91 min. Anal. Calcd for $C_{15}H_{11}F_3O_3S$: C, 54.88; H, 3.38; F, 17.36. Found: C, 53.37; H, 3.60; F, 15.00.

3.2.5. 4′-Bromo-biphenyl-4-carboxylic acid (7b). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.00 (br s, 1H), 8.01 (d, J=8.0, 2H), 7.79 (d, J=8.0, 2H), 7.68 (m, 4H); mp=300.3–302.2 °C

(lit.[19] 301.5–302.5 °C). HPLC retention time: 3.96 min. Anal. Calcd for $C_{13}H_9BrO_2$: C, 56.34; H, 3.27. Found: C, 56.46; H, 3.34.

3.2.6. 4′-Bromo-biphenyl-4-carboxaldehyde (7c). ^{1}H NMR (400 MHz, acetone-d_6) δ 10.12 (s, 1H), 8.05 (d, J=8.0, 2H), 7.92 (d, J=7.6, 2H), 7.73 (m, 4H); mp=159.1–161.4 °C (lit.[20] 158 °C). HPLC retention time: 5.27 min. Anal. Calcd for $C_{13}H_9BrO$: C, 59.80; H, 3.47. Found: C, 45.33; H, 2.65.

3.2.7. (4′-Bromo-biphenyl-4-yl)-phenyl-methanol (7d). ^{1}H NMR (400 MHz, acetone-d_6) δ 7.58 (m, 6H), 7.53 (d, J=8.0, 2H), 7.48 (d, J=7.2, 2H), 7.33 (t, J=7.6, 2H), 7.24 (t, J=7.4, 1H), 5.90 (d, J=3.8, 1H), 4.97 (d, J=3.8, 1H); mp=136.0–138.6 °C (lit.[21] 115–116 °C). HPLC retention time: 5.76 min. Anal. Calcd for $C_{19}H_{15}BrO$: C, 67.27; H, 4.46. Found: C, 67.22; H, 4.17.

3.2.8. 2-(4′-Bromo-biphenyl-4-yl)-1,1,1,3,3,3-hexafluoro-propan-2-ol (7e). ^{1}H NMR (400 MHz, acetone-d_6) δ 7.91 (d, J=8.4, 2H), 7.84 (d, J=8.4, 2H), 7.69 (m, 4H), 7.58 (s, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 142.0, 139.3, 132.5, 130.7, 129.4, 128.0, 127.4, 123.7 (q, $^1J_{CF}$=286), 122.4, 77.9 (q, $^2J_{CF}$=30); ^{19}F NMR (375 MHz, acetone-d_6) δ−79.5; mp=44.8–45.5 °C. HPLC retention time: 6.40 min. Anal. Calcd for $C_{15}H_9F_6BrO$: C, 45.14; H, 2.27; F, 28.56. Found: C, 44.53; H, 2.10; F, 27.24.

3.2.9. 1-(4′-Bromo-biphenyl-4-yl)-ethanone (7f). ^{1}H NMR (400 MHz, acetone-d_6) δ 8.09 (d, J=8.4, 2H), 7.82 (d, J=8.4, 2H), 7.70 (m, 4H), 2.63 (s, 3H); mp=124.9–127.5 °C (lit.[22] 121–122.5 °C). HPLC retention time: 5.38 min. Anal. Calcd for $C_{14}H_{11}BrO$: C, 61.11; H, 4.03. Found: C, 61.29; H, 3.82.

3.2.10. 1-(4′-Bromo-biphenyl-4-yl)-2,2,2-trifluoroethanone (7g). ^{1}H NMR (400 MHz, acetone-d_6) δ 8.22 (d, J=8.4, 2H), 8.02 (d, J=8.4, 2H), 7.79 (d, J=8.4, 2H), 7.75 (d, J=8.4, 2H); ^{19}F NMR (375 MHz, acetone-d_6) δ−76.2; mp=72.5–74.8 °C (lit.[23] 75–77 °C). GC retention time: 11.47 min. Anal. Calcd for $C_{14}H_8F_3BrO$: C, 51.09; H, 2.45; F, 17.32. Found: C, 50.72; H, 2.38; F, 16.94.

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14. Reaction between n-Bu$_3$MgLi, dibromide **4** and Me$_2$S$_2$ leads to the formation of a stoichiometric amount of methanethiol. In order to control emissions and odor during work-up, we investigated the use of various adsorbents. We found that DARCO (KB and G60), Ecosorb (905, 908, 941, 962, 971, and 981),

silica and alumina powders were ineffective at odor removal, even at 1 g/g loadings. Treatment of the crude solution with aqueous copper salts ($CuSO_4$, $CuCl_2$, and $CuCO_3$) or KOH was also unsuccessful. Odor was effectively removed by treatment with either 10% aqueous HIO_3 or 1% aqueous NaOCl, however oxidation of **7a** to the corresponding sulfoxide (5–10%) was observed. Treatment with 10% aqueous H_5IO_6 removed virtually all odor, with <2% oxidation to sulfoxide. Therefore, the crude reaction was quenched by the direct addition of aqueous periodic acid.

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17. Initial studies showed that a strong, delayed exotherm occurred when this oxidation was performed at room temperature, even with slow addition (1 h) of peroxide. We attributed this to a slow initiation step, which is difficult to control due to the biphasic nature of the reaction mixture. Furthermore, the exotherm was not always observed (particularly on smaller scale) resulting in extended reaction times and incomplete conversion to the sulfone. By performing the oxidation at 45 °C, the reaction was complete within 6 h, and the internal temperature was maintained below 62 °C.
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