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One-Pot Synthesis of Alkyl Styryl Sulfides Free from Transition Metal/Ligand Catalyst and Thiols

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A new protocol for the one-pot synthesis of styryl alkyl sulfides was developed. This methodology involves the in situ generation of thiolate anions by nucleophilic substitution between potassium thioacetate and alkyl halides followed by fragmentation. Further reactions of these thiolate anions with substituted (*E*,*Z*)-β-styryl halides gave the corresponding sulfides with retention of stereochemistry in good to excellent yields. This procedure does not require a metal catalyst, it proceeds under mild conditions and in short times, and it is free from malodorous and air-sensitive alkyl thiols.

Introduction

Vinyl sulfides are important synthetic intermediates in organic chemistry.[1] They are frequently used as enolate ion equivalents,[2] Michael acceptors,[3] components of [2+2] cycloadditions,[4] intermediates in the stereoselective synthesis of functionalized alkenes[5] or heterocycles,[6] and substrates in transition-metal-catalyzed carbon–carbon bond-forming reactions.[7] Furthermore this functional group is a common feature in many natural products and compounds with attractive biological activities.[8]

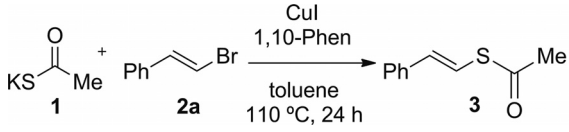
Different processes have been reported for the synthesis of vinyl sulfides.[9] Traditional methods involve the Wittig reaction,[10] the use of thiols in the nucleophilic substitution of activated vinyl halides by an addition–elimination mechanism,[11] or the nucleophilic addition of thiols to alkynes.[12] Both of these last two processes can also occur under transition metal catalysis. In the past few years, many new protocols involving Pd, Ni, and Cu complexes or nanoparticles have been reported for the preparation of vinyl sulfides.[13,14] Recently the iron-catalyzed cross-coupling reaction of alkyl vinyl halides with thiols has also been reported.[15] The main disadvantages of these methodologies arise from the low availability and effectiveness of auxiliary ligands, the air sensitivity of both catalysts and thiols, and the high temperatures (80–140 °C) and long reaction times (4–24 h) needed in the reactions.

On the other hand, potassium thioacetate is a versatile reagent. It is commercially available and easy to handle, and it has been used as a sulfur source in nucleophilic substitution with alkyl[16] and aryl[17] halides by S_N2 or $S_{RN}1$ mechanisms, respectively, and in Pd-catalyzed arylation reactions.[18]

As part of our ongoing research into sulfur chemistry,[17a,19] in this paper, we report a simple and convenient synthetic procedure for the preparation of alkyl arylvinyl sulfides, using potassium thioacetate (**1**) as a sulfide surrogate.

Results and Discussion

We selected (*E*)-β-bromostyrene (**2a**) as a model substrate and CuI (10 mol-%)/1,10-phenanthroline (20 mol-%) in toluene as the initial conditions. After 24 h at 110 °C, the reaction yielded only 25% of thioacetate derivative **3**; see Equation (1).



1 2a 3 (1)

Changing the solvent to the polar aprotic DMSO, divinyl sulfide (< 20%) was obtained under the same general conditions. No reaction was observed after only 4 h either in the presence or absence of CuI/1,10-phenanthroline when either DMSO or DMF was used as solvent.

In view of the low reactivity of the thioacetate anion towards the vinyl halide and, with the aim of synthesizing vinyl alkyl sulfides, we envisioned the possibility of a one-pot procedure by three consecutive reactions (Scheme 1). The in situ generation of alkyl thiolate anion **4** by reaction of **1** with the alkyl halide followed by fragmentation or hy-

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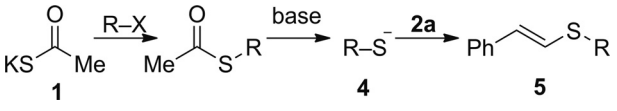
drolysis of the *S*-alkylthioacetate, and subsequent vinylation with (*E*)-β-bromostyrene (**2a**) should afford the alkyl vinyl sulfide (i.e., **5**).



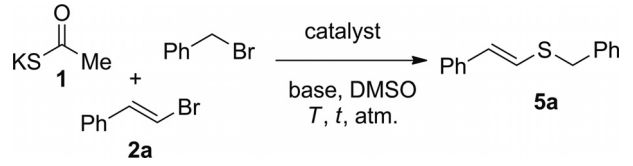
Scheme 1. One-pot synthesis of **5**.

Benzyl bromide was chosen as an alkylating agent, and the polar DMSO as solvent to start with the screening for optimized conditions (base, solvent, temperature, and time) (Table 1). First, we screened a variety of bases in both the presence and absence of copper/ligand and in both the presence and absence of a tiny amount of water to promote hydrolysis. The reaction of bromide **2a** with the thiolate anion was not copper-catalyzed, and the one-pot reaction only occurred in the presence of a base (Table 1, entries 1–4). As expected, better results were obtained with the stronger base, KO*t*Bu, than with other weak bases such as K_3PO_4, K_2CO_3, and KOH (Table 1, entries 4–7). When the reaction was performed in the presence of CuI/1,10-phenanthroline and a base, the yield of sulfide **5a** dropped by about 10% compared to when the reaction was carried out in the absence of copper and the ligand (Table 1, entries 3 and 4). Similar results were found for the combinations of other bases and CuI/1,10-phenanthroline, probably due to the formation of a complex between Cu^I and anion **4**, which would decrease its reactivity towards the vinyl bromide (results not shown). Surprisingly, when the reaction was performed without adding water, the yield of **5a** increased to 99%, suggesting that the alkyl thiolate anion is not formed by hydrolysis during the reaction, but by a base-assisted dethioacetylation (Table 1, entry 8, see below for further mechanistic elucidation). Time, temperature, and atmosphere were also optimized, and the reaction in DMSO with KO*t*Bu as a base also gave excellent results at 80 °C under air after 1 h (Table 1, entries 10–14).

We next examined different solvents in the model reaction under these last-mentioned conditions (i.e., KO*t*Bu, 80 °C, air, 1 h) (Table 2). Of the solvents screened, DMF and acetonitrile gave good yields, but the yields were lower than those obtained in DMSO (Table 2, entries 1–3). The non-polar or polar protic solvents tested gave a product yield of < 5% in the best case (Table 2, entries 4–9). We selected DMF to continue this study due to its qualities as a solvent for organic bases and other compounds, its lower cost than DMSO and acetonitrile, and its intermediate boiling point, all of which have made DMF a routine laboratory solvent. Finally, after the base:substrate ratio was increased to 3:1 and the temperature was reduced to 50 °C, the model reaction gave an excellent yield of sulfide **5a** after 1 h in DMF (Table 2, entries 10–11). When the reaction was performed starting with 6.5 mmol (1.20 g) of **2a** in 25 mL of DMF, 1.02 g of **5a** (69% isolated yield) was obtained.

Having successfully obtained benzyl styryl sulfide (**5a**) in a one-pot procedure, we next proceeded to explore the scope and limitations of this methodology with a variety of

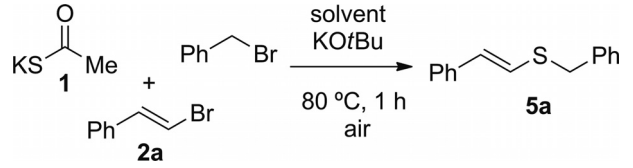
Table 1. Optimization of the conditions for the one-pot synthesis of benzyl (*E*)-styryl sulfide.[a]



Entry	*T*, *t*, atm.	Base [b]	Yield of **5a** [%][c]
1	110 °C, 7 h, N_2	–	–
2[d]	110 °C, 7 h, N_2	–	–
3[d]	110 °C, 7 h, N_2	KOH	39
4	110 °C, 7 h, N_2	KOH	49
5	110 °C, 7 h, N_2	K_3PO_4	27
6	110 °C, 7 h, N_2	K_2CO_3	28
7	110 °C, 7 h, N_2	KO*t*Bu	87
8[e]	110 °C, 7 h, N_2	KO*t*Bu	99
9[e,f]	110 °C, 1 h, N_2	KO*t*Bu	99
10[e,f]	60 °C, 1 h, N_2	KO*t*Bu	99
11[e,f]	r.t., 1 h, N_2	KO*t*Bu	74
12[e,f]	r.t., 1 h, air	KO*t*Bu	62
13[e,f]	60 °C, 1 h, air	KO*t*Bu	72
14[e,f]	80 °C, 1 h, air	KO*t*Bu	82

[a] Reaction conditions unless otherwise stated: (*E*)-β-bromostyrene (**2a**) (0.25 mmol), KSCOMe (**1**; 0.3 mmol), benzyl bromide (0.3 mmol), in solvent (2 mL), in the presence of water (25 μL). [b] Base: 0.35 mmol. [c] Determined by GC using the internal method, error < 5%. Starting vinyl bromide **2a** contained ca. 10% of the (*Z*) isomer, and this led to ca. 10% of the (*Z*) isomer in the product. [d] CuI (10 mol-%) and 1,10-phenanthroline (20 mol-%). [e] Without the addition of water. [f] (*E*)-β-Bromostyrene **2a** (0.25 mmol), KSCOMe (**1**; 0.38 mmol), benzyl bromide (0.38 mmol).

Table 2. Solvent screening for the one-pot synthesis of benzyl (*E*)-styryl sulfide.[a]

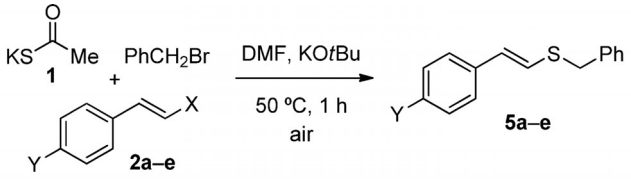


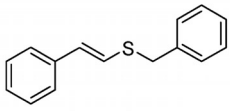
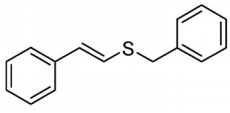
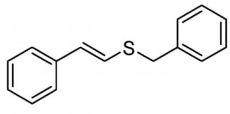
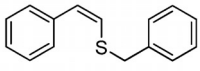
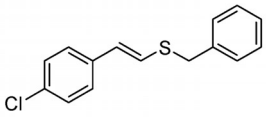
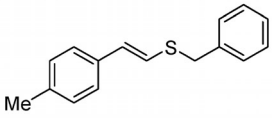
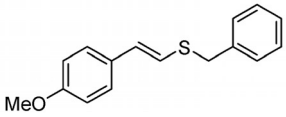
Entry	Solvent	Yield of **5a** [%][b]
1	DMSO	82
2	DMF	63
3	acetonitrile	68
4	ethanol	< 5
5	pyridine	< 5
6	PEG300	< 5
7	dioxane	< 5
8	THF	–
9	H_2O	–
10[c]	DMF	96
11[c,d]	DMF	93 (76)[e]

[a] Reaction conditions unless otherwise stated: (*E*)-β-bromostyrene **2a** (0.25 mmol), KSCOMe (**1**; 0.38 mmol), benzyl bromide (0.38 mmol), KO*t*Bu (0.38 mmol), in solvent (2 mL) at 80 °C for 1 h under air. [b] Determined by GC using the internal method, error < 5%. Starting vinyl bromide **2a** contained ca. 10% of the (*Z*) isomer, and this led to ca. 10% of the (*Z*) isomer in the product. [c] Base: 0.75 mmol. [d] Reaction performed at 50 °C. [e] Isolated yield.

substituted styryl and alkyl halides (Tables 3 and 4). Combinations of (*E*)-styryl bromide or chloride with benzyl bromide or chloride resulted in the formation of **5a** in good isolated yields (Table 3, entries 1–3). The (*Z*)-styryl bromide gave the corresponding (*Z*) isomer (i.e., **Z5a**) in 64% yield (Table 3, entry 4). We also tested the effect of the substituents on the styryl moiety. *p*-Chloro derivative **2c** afforded sulfide **5c** in yields comparable to those obtained with the unsubstituted styryl bromide (Table 3, entry 5), whereas styryl bromides bearing electron-donating methyl and methoxy substituents were less reactive and required longer times and higher temperatures to obtain good yields of the corresponding sulfides (Table 3, entries 6 and 7). The effect of the substituents on the styryl halides, the stereochemical outcome of the reaction (i.e., retention of configuration), and the occurrence of the reaction without catalysis suggest that the reaction of arylvinyl halides with thiolate anion **4** followed a classical vinylic nucleophilic substitution mechanism,[20] i.e., a concerted or stepwise addition–elimination mechanism with retention of stereochemistry by a perpendicular nucleophilic attack (Scheme 2).[11a,21]

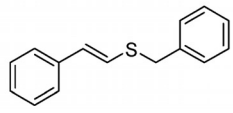
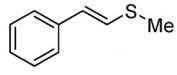
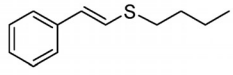
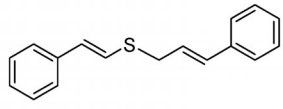
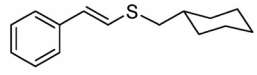
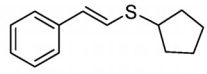
Table 3. One-pot synthesis of arylvinyl benzyl sulfides.[a]



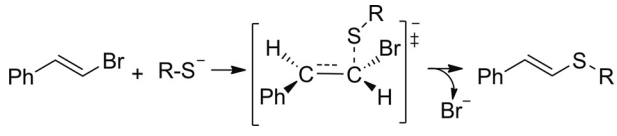
Entry	**2a-e** Y, X	Product **5a-e**, yield (%)[b,c]		
1	H, Br **2a**		**5a**	76
2[d]	H, Br **2a**		**5a**	72
3	H, Cl **2b**		**5a**	69
4	(*Z*)-H, Br[e]		**Z5a**	64[f]
5	Cl, Br **2c**		**5c**	77
6	Me, Br **2d**		**5d**	66[g]
7	MeO, Br **2e**		**5e**	72[h]

[a] Reaction conditions unless otherwise stated: (*E*)-vinyl halide (0.25 mmol), KSCOMe (**1**; 0.38 mmol), alkyl halide (0.38 mmol), KO*t*Bu (0.75 mmol) in DMF (2 mL) at 50 °C for 1 h under air. [b] Isolated yields. [c] The starting (*E*)-vinyl halide contained ca. 10% of the (*Z*) isomer, and this led to ca. 10% of the (*Z*) isomer in the product. [d] Benzyl chloride as alkylating reagent. [e] (*Z*)-styryl bromide. [f] The starting (*Z*)-vinyl halide contained ca. 10% of the (*E*) isomer, this led to ca. 10% of the (*E*) isomer in the product. [g] Reaction time: 2 h. [h] Reaction mixture was heated at 100 °C for 2 h.

Table 4. One-pot synthesis of alkyl (*Z*)-styryl sulfide.[a]

Entry	RX	Product, yield (%)[b,c]		
1	$PhCH_2Br$		**5a**	76
2	MeI		**5f**	95
3	*n*BuBr		**5g**	93
4	$PhCH{=}CHCH_2Br$		**5h**	61
5	Cy-CH_2Br		**5i**	55
6	*c*PenBr		**5j**	48

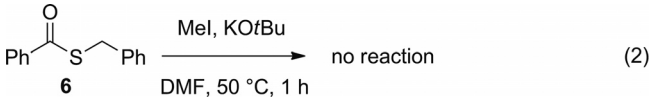
[a] Reaction conditions unless otherwise stated: (*E*)-β-bromostyrene (**2a**) (0.25 mmol), KSCOMe (**1**; 0.38 mmol), alkyl halide (0.38 mmol), KO*t*Bu (0.75 mmol) in DMF (2 mL) at 50 °C for 1 h under air. [b] Isolated yields. [c] The starting (*E*)-vinyl bromide **2a** contained ca. 10% of the (*Z*) isomer, and this led to ca. 10% of the (*Z*) isomer in the product.

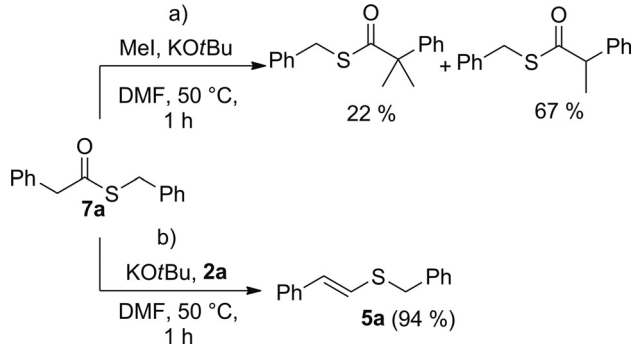


Scheme 2. Concerted vinylic nucleophilic substitution.

Finally, other alkyl bromides were tested (Table 4). As expected for an S_N2 reaction, the primary methyl, *n*-butyl, and cinnamyl bromides gave, together with the benzyl bromides, the best yields of the corresponding sulfides (Table 4, entries 1–4). However, the sterically hindered cyclohexylmethyl bromide and the secondary cyclopentyl bromide gave moderate yields (Table 4, entries 5 and 6, respectively). The tertiary *tert*-butyl chloride and cyclohexyl bromide failed to form the respective alkyl thiolate anions, as an E_2 elimination competed effectively with the nucleophilic substitution, and this represents the only limitation of this methodology.

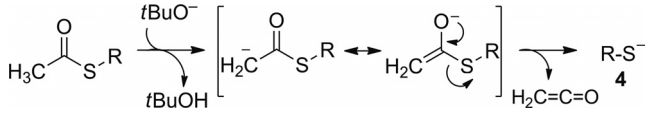
We also investigated the mechanism for the generation of thiolate anion **4** from the *S*-alkyl thioacetate. When a mixture of *S*-benzyl benzothioate (**6**), KO*t*Bu, and MeI was stirred for 1 h at 50 °C in DMF, benzyl methyl sulfide was not obtained, and unreacted **6** was recovered quantitatively; see Equation (2). Under the same conditions, *S*-benzyl-2-phenylethanethioate (**7a**), a compound with an acidic hydrogen α to the carbonyl group, was alkylated at the α position (Scheme 3, path a). Furthermore, the reaction of **7a** with KO*t*Bu and (*E*)-β-bromostyrene (**2a**) in DMF gave a 94% yield of (*E*)-styryl benzyl sulfide (**5a**, Scheme 3, path b). Finally, when the reactions of *S*-benzyl-2-phenylethanethioate (**7a**, *n* = 1) and *S*-phenyl-2-phenylethanethioate (**7b**, *n* = 0) were performed in two steps, i.e, deprotonation by the base and subsequent addition of MeI – see Equation (3) – benzyl methyl sulfide and phenyl methyl sulfide, respectively, were obtained as a major products (25%) together with (in both cases) methyl benzoate (28%), methyl 2-phenylacetate (30%), and a product of $[M]^+ = 250$, whose structure could be **8a** or **8b** (17%), as detected by GC-MS (yields determined by GC).



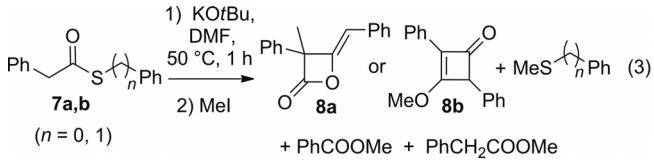


Scheme 3. Reactions of *S*-benzyl 2-phenylethanethioate (**7a**).

The lack of reaction in the absence of a base, the enhancement of the yield with increasing basicity of the base (Table 1, entries 1, 2, 4–8), and the requirement of an acidic hydrogen α to the carbonyl group support the mechanism suggested in Scheme 4 for the formation of thiolate anion **4** in the reaction media. This implies deprotonation of the methyl group α to the carbonyl, followed by elimination of a ketene with the concomitant generation of anion **4**. Evidence for the formation of phenylketene comes from the observation of a product **8a** or **8b** arising from phenylketene dimerization[22] after methylation, and the methyl 2-phenylacetate from hydration of phenylketene[23] during work-up or by traces of water present in DMF; see Equation (3).[24]



Scheme 4. Suggested mechanism for the generation of thiolate anion **4**.



Conclusions

In summary, we have developed a new one-pot methodology for the synthesis of alkyl arylvinyl sulfides in good to excellent yields, free of any metal/ligand systems and from malodorous and air-sensitive alkyl thiols. This procedure uses the commercially available potassium thioacetate, low temperatures, and short reaction times.

Experimental Section

General Information: KSCOMe, and alkyl and benzyl halides were all high purity commercially available compounds, and were used without further purification. (*E*) and (*Z*)-β-bromostyrenes were prepared from cinnamic acids following literature procedures.[25] Thioesters **6** and **7a**,**b** were prepared by standard procedures.[26] The commercially available CuI (> 98%) was used as received. DMF, acetonitrile, and DMSO absolute grade were stored over molecular sieves (4 Å) and used without further purification. Toluene, dioxane, THF, and pyridine were distilled by standard procedures and stored over molecular sieves (4 Å). PEG300 and ethanol were used without further purification. All the reaction products were isolated by radial chromatography (silica gel, petroleum/diethyl ether) from the reaction mixture and characterized by ^1H and ^{13}C NMR spectroscopy and mass spectrometry. ^1H and ^{13}C NMR spectra were recorded at 400.16 and 100.62 MHz, respectively, with a Bruker 400 spectrometer, and all spectra were reported in δ (ppm) relative to Me_4Si, with $CDCl_3$ as solvent. Gas chromatographic analyses were performed with an Agilent 5890 device with a flame-ionization detector, using a 30 m capillary column of 0.32 mm × 0.25 μm film thickness, with a 5% phenylpolysiloxane phase. GS-MS analyses were performed with an Agilent 7890 device using a 30 m × 0.25 mm × 0.25 μm with a 5% phenylpolysiloxane phase column. HRMS spectra were recorded with a GCT Premie orthogonal acceleration time-of-flight (oa-

TOF) GC mass spectrometer. Ionization was achieved by electron impact (70 eV), and detection was in positive mode.

General Procedure for the Reactions of (*E*)-β-Bromostyrene (2a) with Potassium Thioacetate (1): See Equation (1). The reactions were carried out in a 10 mL three-necked Schlenk tube, equipped with a nitrogen gas inlet, a condenser, and a magnetic stirrer bar. The tube was dried under vacuum, and filled with nitrogen, and then the dried solvent (2.0 mL) was added. (*E*)-β-Bromostyrene (45.7 mg, 0.25 mmol), CuI (4.7 mg, 0.025 mmol, 10 mol-%), 1,10-phenanthroline (9.9 mg, 0.055 mmol, 20 mol-%), and finally potassium thioacetate (57.1 mg, 0.5 mmol) were added to the degassed solvent under nitrogen, and the mixture was stirred at 110 °C for 24 h. The reaction mixture was then allowed to cool to room temperature. Diethyl ether (15 mL) and water (15 mL) were added, and the mixture was stirred. The organic phase was separated, and the aqueous phase was extracted with diethyl ether (2× 15 mL). The combined organic extracts were dried with anhydrous Na_2SO_4, and the product was isolated by radial chromatography (hexane) to give **3** (11.1 mg, 25%) as a pale yellow oil. The identity of the product, (*E*)-*S*-styryl ethanethioate (**3**),[27] was confirmed by ^{1}H and ^{13}C NMR spectroscopy and EI-MS: ^{1}H NMR (400.16 MHz, $CDCl_3$, 30 °C): δ = 2.41 (s, 3 H), 6.71 (d, J = 16.3 Hz, 1 H), 7.22 (d, J = 16.3 Hz, 1 H), 7.26 (d, J = 7.3 Hz, 1 H), 7.33 (t, J = 7.2 Hz, 2 H), 7.39 (d, J = 7.2 Hz, 2 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$, 30 °C): δ = 30.55, 117.17, 126.40, 128.14, 128.72, 131.64, 136.03, 192.70 ppm. MS (EI): *m*/*z* (%) = 178 (18) $[M]^+$, 137 (12), 136 (100), 135 (71), 134 (13), 91 (38), 43 (47).

General Procedure for the One-Pot Synthesis of Alkyl Vinyl Sulfides: See Table 3 and Table 4. The reactions were carried out in a 10 mL three-necked Schlenk tube, equipped with a magnetic stirrer bar. DMF (2.0 mL) was added to the tube, then potassium thioacetate (0.38 mmol), alkyl halide (0.38 mmol), and β-halostyrene (0.25 mmol) were added, and the mixture was stirred for some minutes at room temperature. Finally, base (0.75 mmol) was added, and the mixture was stirred at 50 °C for 1 h. The reaction mixture was then allowed to cool to room temperature. Diethyl ether (15 mL) and water (15 mL) were added, and the mixture was stirred. The organic phase was separated, and the aqueous phase was extracted with diethyl ether (2× 15 mL). The combined organic extracts were dried with anhydrous Na_2SO_4, and the products were isolated by radial chromatography from the crude reaction mixture or quantified by GC using the internal standard method (see Tables 3 and 4). The identities of all the products were confirmed by ^{1}H and ^{13}C NMR spectroscopy and EI-MS.

General Procedure for the Reactions Between Thioesters and KO*t*Bu: See Equation (2) and Scheme 3. The reactions were carried out in a 10 mL three-necked Schlenk tube, equipped with a magnetic stirrer bar. DMF (2.0 mL) was added to the tube. Thioester (**6** or **7a**, 0.38 mmol), methyl iodide (0.38 mmol) or β-halostyrene (0.25 mmol), and KO*t*Bu (0.75 mmol) were added, and the mixture was stirred at 50 °C for 1 h. The reaction mixture was then allowed to cool to room temperature. Diethyl ether (15 mL) and water (15 mL) were added, and the mixture was stirred. The organic phase was separated, and the aqueous phase was extracted with diethyl ether (2× 15 mL). The combined organic extracts were dried with anhydrous Na_2SO_4. The products were quantified by integration of a GC trace, and their identities were confirmed by EI-MS.

General Procedure for the Reactions Between Thioesters and KO*t*Bu Performed in Two Steps: See Equation (3). The reactions were carried out in a 10 mL three-necked Schlenk tube, equipped with a magnetic stirrer bar. DMF (2.0 mL) was added to the tube. Thioester (**7a** or **7b**, 0.38 mmol) and KO*t*Bu (0.75 mmol) were added, and the mixture was stirred at 50 °C for 1 h. The reaction mixture was allowed to cool to room temperature, and methyl iodide (excess) was added. After then, diethyl ether (15 mL) and water (15 mL) were added, and the mixture was stirred. The organic phase was separated, and the aqueous phase was extracted with diethyl ether (2× 15 mL). The combined organic extracts were dried with anhydrous Na_2SO_4. The products have been quantified by integration of a GC trace, and their identities were confirmed by EI MS.

(*E*)-Benzyl(4-methylstyryl)sulfane (5d): Following the general procedure for Table 3, using potassium thioacetate (**1**; 43.4 mg, 0.38 mmol), benzyl bromide (45 μL, 0.38 mmol), (*Z*)-1-(2-bromovinyl)-4-methylbenzene (**2d**, 49.3 mg, 0.25 mmol), and potassium *tert*-butoxide (84.2 mg, 0.75 mmol) for 2 h at 50 °C, and then purification by radial chromatography (hexane) gave **5d** (39.7 mg, 66%) as a white solid. m.p. 74–75 °C. ^{1}H NMR (400.16 MHz, $CDCl_3$, 30 °C): δ = 2.30 (s, 3 H), 3.98 (s, 2 H), 6.51 (d, J = 15.6 Hz, 1 H), 6.64 (d, J = 15.6 Hz, 1 H), 7.08 (d, J = 8.1 Hz, 2 H), 7.14 (d, J = 8.1 Hz, 2 H), 7.32–7.35 (m, 5 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$, 30 °C): δ = 21.2, 37.5, 123.1, 125.6, 127.3, 128.4, 128.7, 128.9, 129.3, 134.2, 136.9, 137.4 ppm. MS (EI): *m*/*z* (%) = 240 (41) $[M]^+$, 149 (27), 148 (12), 134 (23), 91 (100), 65 (15). HRMS (GC-MS, EI): calcd. for $C_{16}H_{16}S$ $[M]^+$ 240.0973; found 240.0972.

(*E*)-Cinnamyl(styryl)sulfane (5h): Following the general procedure for Table 4, using potassium thioacetate (**1**; 43.4 mg, 0.38 mmol), cinnamyl bromide (74.9 mg, 0.38 mmol), (*E*)-β-bromostyrene (**2a**, 45.7 mg, 0.25 mmol), and potassium *tert*-butoxide (84.2 mg, 0.75 mmol), and then purification by radial chromatography (hexane) gave **5h** (38.5 mg, 61%) as a yellow solid. m.p. 93–95 °C. ^{1}H NMR (400.16 MHz, $CDCl_3$, 30 °C): δ = 3.59 (dd, J = 7.2 and 1.2 Hz, 2 H), 6.27 (dt, J = 15.6 and 7.2 Hz, 1 H), 6.57 (d, J = 15.6 Hz, 2 H), 6.73 (d, J = 15.6 Hz, 1 H), 7.26–7.38 (m, 10 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$, 30 °C): δ = 35.6, 124.0, 125.0, 125.7, 126.5, 127.1 and 127.8, 128.3, 128.6, 128.7, 133.0, 136.6, 137.0 ppm. MS (EI): *m*/*z* (%) = 117 (100) $[M - 135]^+$, 116 (11), 115 (39), 91 (23). HRMS (GC-MS, EI): calcd. for $C_{17}H_{16}S$ $[M]^+$ 252.0973; found 252.0963.

(*E*)-(Cyclohexylmethyl)(styryl)sulfane (5i): Following the general procedure for Table 4, using potassium thioacetate (**1**; 43.4 mg, 0.38 mmol), (bromomethyl)cyclohexane (53 μL, 0.38 mmol), (*E*)-β-bromostyrene (**2a**, 45.7 mg, 0.25 mmol), and potassium *tert*-butoxide (84.2 mg, 0.75 mmol), and then purification by radial chromatography (hexane) gave **5i** (31.9 mg, 55%) as a colorless oil. ^{1}H NMR (400.16 MHz, $CDCl_3$, 30 °C): δ = 0.98–1.28 (m, 5 H), 1.65–1.90 (m, 6 H), 2.69 (d, J = 6.8 Hz, 2 H), 6.44 (d, J = 15.6 Hz, 1 H), 6.72 (d, J = 15.6 Hz, 1 H), 7.15–7.29 (m, 5 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$, 30 °C): δ = 26.1, 26.3, 32.8, 37.9, 40.2, 125.4, 126.2, 126.3, 126.7, 128.6, 137.2 ppm. MS (EI): *m*/*z* (%) = 232 (62) $[M]^+$, 137 (13), 136 (100), 135 (54), 134 (10), 97 (17), 91 (30), 55 (54), 41 (19). HRMS (GC-MS, EI): calcd. for $C_{15}H_{20}S$ $[M]^+$ 232.1286; found 232.1322.

(*E*)-Cyclopentyl(styryl)sulfane (5j): Following the general procedure for Table 4, using potassium thioacetate (**1**; 43.4 mg, 0.38 mmol), 1-bromocyclopentane (53 μL, 0.38 mmol), (*E*)-β-bromostyrene (**2a**, 45.7 mg, 0.25 mmol), and potassium *tert*-butoxide (84.2 mg, 0.75 mmol), and then purification by radial chromatography (hexane) gave **5j** (24.5 mg, 48%) as a colorless oil. ^{1}H NMR (400.16 MHz, $CDCl_3$, 30 °C): δ = 1.61–2.1 (m, 8 H), 3.42–3.49 (m, 1 H), 6.50 (d, J = 15.6 Hz, 1 H), 6.77 (d, J = 15.6 Hz, 1 H), 7.16–7.21 (m, 1 H), 7.28–7.29 (m, 4 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$, 30 °C): δ = 24.9, 33.6, 44.7, 125.2, 125.5, 126.8, 127.6, 128.6, 137.3 ppm. MS (EI): *m*/*z* (%) = 204 (58) $[M]^+$, 137 (13), 136

(100), 135 (92), 91 (35), 69 (10), 41 (25). HRMS (GC-MS, EI): calcd. for $C_{13}H_{16}S$ $[M]^+$ 204.0973; found 204.0978.

(*E*)-Benzyl(styryl)sulfane (5a):[28] Following the general procedure for Table 3, using potassium thioacetate (**1**; 43.4 mg, 0.38 mmol), benzyl bromide (45 μL, 0.38 mmol), (*E*)-β-bromostyrene (**2a**, 45.7 mg, 0.25 mmol), and potassium *tert*-butoxide (84.2 mg, 0.75 mmol), and then purification by radial chromatography (hexane) gave **5a** (43.0 mg, 76%) as a white solid. ^{1}H NMR (400.16 MHz, $CDCl_3$, 30 °C): δ = 4.00 (s, 2 H), 6.51 (d, J = 15.6 Hz, 1 H), 6.70 (d, J = 15.6 Hz, 1 H), 7.24–7.35 (m, 10 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$, 30 °C): δ = 37.4, 124.4, 125.6, 127.0, 127.4, 128.0, 128.66, 128.71, 128.9, 137.0, 137.3 ppm. MS (EI): *m*/*z* (%) = 226 (27) $[M]^+$, 135 (14), 134 (11), 91 (100), 65 (13).

(*Z*)-Benzyl(styryl)sulfane (Z5a):[29] Following the general procedure for Table 3, using potassium thioacetate (**1**; 43.4 mg, 0.38 mmol), benzyl bromide (45 μL, 0.38 mmol), (*Z*)-β-bromostyrene (**2a**, 45.7 mg, 0.25 mmol), and potassium *tert*-butoxide (84.2 mg, 0.75 mmol), and then purification by radial chromatography (hexane) gave **Z5a** (36.2 mg, 64%) as a colorless oil. ^{1}H NMR (400.16 MHz, $CDCl_3$, 30 °C): δ = 3.99 (s, 2 H), 6.24 (d, J = 10.8 Hz, 1 H), 6.41 (d, J = 10.8 Hz, 1 H), 7.19–7.46 (m, 10 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$, 30 °C): δ = 39.6, 125.9, 126.0, 126.8, 127.4, 128.3, 128.7 and 128.7, 129.0, 136.9, 137.4 ppm. MS (EI): *m*/*z* (%) = 260 (21) $[M]^+$, 91 (100), 65 (12).

(*E*)-Benzyl(4-chlorostyryl)sulfane (5c):[30] Following the general procedure for Table 3, using potassium thioacetate (**1**; 43.4 mg, 0.38 mmol), benzyl bromide (45 μL, 0.38 mmol), (*Z*)-1-(2-bromovinyl)-4-chlorobenzene (**2c**, 54.3 mg, 0.25 mmol) and potassium *tert*-butoxide (84.2 mg, 0.75 mmol), and then purification by radial chromatography (hexane) gave **5c** (50.2 mg, 77%) as a white solid. ^{1}H NMR (400.16 MHz, $CDCl_3$, 30 °C): δ = 4.01 (s, 2 H), 6.45 (d, J = 15.6 Hz, 1 H), 6.69 (d, J = 15.6 Hz, 1 H), 7.15 (d, J = 8.4 Hz, 2 H), 7.23 (d, J = 8.4 Hz, 2 H), 7.25–7.35 (m, 5 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$, 30 °C): δ = 37.3, 125.3, 126.4, 126.7, 127.4, 128.7, 128.8, 128.9, 132.5, 135.5, 137.0 ppm. MS (EI): *m*/*z* (%) = 260 (21) $[M]^+$, 91 (100), 65 (11).

(*E*)-Benzyl(4-methoxystyryl)sulfane (5e):[31] Following the general procedure for Table 3, using potassium thioacetate (**1**; 43.4 mg, 0.38 mmol), benzyl bromide (45 μL, 0.38 mmol), (*Z*)-1-(2-bromovinyl)-4-methoxybenzene (**2e**, 53.3 mg, 0.25 mmol), and potassium *tert*-butoxide (84.2 mg, 0.75 mmol) for 2 h at 100 °C, and then purification by radial chromatography (hexane) gave **5e** (46.2 mg, 72%) as a white solid. ^{1}H NMR (400.16 MHz, $CDCl_3$, 30 °C): δ = 3.79 (s, 3 H), 3.98 (s, 2 H), 6.49 and 6.54 (d, J = 15.2 and 15.6 Hz, 2 H), 6.81 (d, J = 8.8 Hz, 2 H), 7.18 (d, J = 8.8 Hz, 2 H), 7.24–7.35 (m, 5 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$, 30 °C): δ = 37.7, 55.3, 114.1, 121.5, 126.9, 127.3, 128.5, 128.6, 128.8, 129.9, 137.5, 158.9 ppm. MS (EI): *m*/*z* (%) = 257 (23), 256 (90) $[M]^+$, 165 (77), 151 (21), 150 (87), 121 (24), 91 (100), 65 (35).

(*E*)-Methyl(styryl)sulfane (5f):[21] Following the general procedure for Table 4, using potassium thioacetate (**1**; 43.4 mg, 0.38 mmol), iodomethane (24 μL, 0.38 mmol), (*E*)-β-bromostyrene (**2a**, 45.7 mg, 0.25 mmol), and potassium *tert*-butoxide (84.2 mg, 0.75 mmol), and then purification by radial chromatography (hexane) gave **5f** (35.6 mg, 95%) as a colorless oil. ^{1}H NMR (400.16 MHz, $CDCl_3$, 30 °C): δ = 2.38 (s, 3 H), 6.31 (d, J = 15.4 Hz, 1 H), 6.79 (d, J = 15.4 Hz, 1 H), 7.18 (m, 1 H), 7.28–7.29 (m, 4 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$, 30 °C): δ = 14.85, 124.75, 125.41, 125.82, 126.69, 128.67, 137.16 ppm. MS (EI): *m*/*z* (%) = 150 (100) $[M]^+$, 135 (83), 134 (25), 102 (11), 91 (68), 77 (12), 51 (10).

(*E*)-Butyl(styryl)sulfane (5g):[32] Following the general procedure for Table 4, using potassium thioacetate (**1**; 43.4 mg, 0.38 mmol), 1-bromobutane (41 μL, 0.38 mmol), (*E*)-β-bromostyrene (**2a**, 45.7 mg, 0.25 mmol), and potassium *tert*-butoxide (84.2 mg, 0.75 mmol), and then purification by radial chromatography (hexane) gave **5g** (44.7 mg, 93%) as a colorless oil. ^{1}H NMR (400.16 MHz, $CDCl_3$, 30 °C): δ = 0.94 (t, J = 7.2 Hz, 3 H), 1.45 (sex, J = 7.6 Hz, 2 H), 1.68 (q, J = 7.2 Hz, 2 H), 2.80 (t, J = 7.2 Hz, 2 H), 6.46 (d, J = 15.6 Hz, 1 H), 6.72 (d, J = 15.6 Hz, 1 H), 7.17–7.29 (m, 5 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$, 30 °C): δ = 13.7, 22.0, 31.6, 32.3, 125.4, 125.5, 126.6, 126.8, 128.6, 137.2 ppm. MS (EI): *m*/*z* (%) = 192 (83) $[M]^+$, 137 (10), 136 (66), 135 (100), 134 (15), 115 (12), 91 (45), 41 (12).

Supporting Information (see footnote on the first page of this article): NMR spectra (^{1}H and ^{13}C) for all the products (**3**, **5a**, **Z5a**, and **5c**–**j**).

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[1] a) S. Oae, *Organic Sulfur Chemistry: Structure and Mechanism*, CRC Press, Boca Raton, FL, **1991**; b) R. J. Cremlyn, *An Introduction to Organosulfur Chemistry*, Wiley & Sons, New York, **1996**; c) C. A. Woodland, G. C. Crawley, R. C. Hartley, *Tetrahedron Lett.* **2004**, *45*, 1227–1231.
[2] B. M. Trost, A. C. Lavoie, *J. Am. Chem. Soc.* **1983**, *105*, 5075–5090.
[3] a) V. Aucagne, C. Lorin, A. Tatibouët, P. Rollin, *Tetrahedron Lett.* **2005**, *46*, 4349–4352; b) R. D. Miller, R. Hassig, *Tetrahedron Lett.* **1985**, *26*, 2395–2398.
[4] K. Narasaka, Y. Hayashi, H. Shimadzu, S. Niihata, *J. Am. Chem. Soc.* **1992**, *114*, 8869–8885.
[5] J. V. Comasseto, *J. Organomet. Chem.* **1983**, *253*, 131–181.
[6] a) M. Yar, S. P. Fritz, P. J. Gates, E. M. McGarrigle, V. K. Aggarwal, *Eur. J. Org. Chem.* **2012**, 160–166; b) C. Quinet, L. Sampoux, I. E. Markó, *Eur. J. Org. Chem.* **2009**, 1806–1811.
[7] a) S. R. Dubbaka, P. Vogel, *Angew. Chem.* **2005**, *117*, 7848–7859; *Angew. Chem. Int. Ed.* **2005**; *44*, 7674–7684; b) H. Lin, X. Dong, Y. Li, Q. Shen, L. Lu, *Eur. J. Org. Chem.* **2012**, 4675–4679.
[8] a) N. Muraoka, M. Mineno, K. Itami, J. I. Yoshida, *J. Org. Chem.* **2005**, *70*, 6933–6936; b) H. S. Sader, D. M. Johnson, R. N. Jones, *Antimicrob. Agents Chemother.* **2004**, *48*, 53–62; c) M. Ceruti, G. Balliano, F. Rocco, P. Milla, S. Arpicco, L. Cattel, F. Viola, *Lipids* **2001**, *36*, 629–636; d) P. Johannesson, G. Lindeberg, A. Johansson, G. V. Nikiforovich, A. Gogoll, B. Synnergren, M. Le Greves, F. Nyberg, A. Karlén, A. Hallberg, *J. Med. Chem.* **2002**, *45*, 1767–1777; e) E. Marcantoni, M. Massaccesi, M. Petrini, G. Bartoli, M. C. Bellucci, M. Bosco, L. Sambri, *J. Org. Chem.* **2000**, *65*, 4553–4559.
[9] N. V. Zyk, E. K. Beloglazkina, M. A. Belova, N. S. Dubinina, *Russ. Chem. Rev.* **2003**, *72*, 769–786.
[10] V. Aucagne, A. Tatibouët, P. Rollin, *Tetrahedron* **2004**, *60*, 1817–1826.
[11] a) C. F. Bernasconi, Z. Rappoport, *Acc. Chem. Res.* **2009**, *42*, 993–1003; b) M.-Y. Lei, Y.-J. Xiao, W.-M. Liu, K. Fukamizu, S. Chiba, K. Ando, K. Narasaka, *Tetrahedron* **2009**, *65*, 6888–6902.
[12] a) J. R. Cabrera-Antonino, A. Leyva-Pérez, A. Corma, *Adv. Synth. Catal.* **2012**, *354*, 678–687; b) C. J. Weiss, T. J. Marks, *J. Am. Chem. Soc.* **2010**, *132*, 10533–10546; c) M. S. Silva, R. G. Lara, J. M. Marczewski, R. G. Jacob, E. J. Lenardao, G. Perin,

Tetrahedron Lett. **2008**, *49*, 1927–1930; d) V. P. Ananikov, N. V. Orlov, I. P. Beletskaya, *Organometallics* **2006**, *25*, 1970–1977; e) A. Kondoh, K. Takami, H. Yorimitsu, K. Oshima, *J. Org. Chem.* **2005**, *70*, 6468–6473; f) O. Arjona, R. Medel, J. Rojas, A. M. Costa, J. Vilarrasa, *Tetrahedron Lett.* **2003**, *44*, 6369–6373; g) M. Beller, J. Seayad, A. Tillack, H. Jiao, *Angew. Chem.* **2004**, *116*, 3448–3479; *Angew. Chem. Int. Ed.* **2004**, *43*, 3368–3398; h) F. Alonso, I. P. Beletskaya, M. Yus, *Chem. Rev.* **2004**, *104*, 3079–3159; i) I. P. Beletskaya, V. P. Ananikov, *Eur. J. Org. Chem.* **2007**, 3431–3444.

[13] a) I. P. Beletskaya, V. P. Ananikov, *Chem. Rev.* **2011**, *111*, 1596–1636; b) T. Kondo, T. Mitsudo, *Chem. Rev.* **2000**, *100*, 3205–3220.

[14] For examples of the copper-catalyzed synthesis of vinyl sulfides from alkenyl halides, see: a) M. S. Kabir, M. Lorenz, M. L. Van Linn, O. A. Namjoshi, S. Ara, J. M. Cook, *J. Org. Chem.* **2010**, *75*, 3626–3343; b) M. S. Kabir, M. L. Van Linn, A. Monte, J. M. Cook, *Org. Lett.* **2008**, *10*, 3363–3366; c) W. Bao, Y. Liu, X. Lv, *Synthesis* **2008**, 1911–1917; d) Z. Wang, H. Mo, W. Bao, *Synlett* **2007**, 91–94; e) C. G. Bates, P. Saejueng, M. Q. Doherty, D. Venkataraman, *Org. Lett.* **2004**, *6*, 5005–5008.

[15] Y.-Y. Lin, Y.-J. Wang, C.-H. Lin, J.-H. Cheng, C.-F. Lee, *J. Org. Chem.* **2012**, *77*, 6100–6106.

[16] T.-C. Zheng, M. Burkart, D. E. Richardson, *Tetrahedron Lett.* **1999**, *40*, 603–606.

[17] a) L. C. Schmidt, V. Rey, A. B. Peñéñory, *Eur. J. Org. Chem.* **2006**, 2210–2214; b) G. Petrillo, M. Novi, G. Garbarino, M. Filiberti, *Tetrahedron* **1989**, *45*, 7411–7420; c) S. M. Soria-Castro, *Synlett* **2012**, 2997–2998, and references therein.

[18] a) C. Lai, B. J. Backes, *Tetrahedron Lett.* **2007**, *48*, 3033–3037; b) N. Park, K. Park, M. Jang, S. Lee, *J. Org. Chem.* **2011**, *76*, 4371–4378.

[19] a) J. E. Argüello, L. C. Schmidt, A. B. Peñéñory, *ARKIVOC* **2003**, 411–419; b) J. E. Argüello, L. C. Schmidt, A. B. Peñéñory, *Org. Lett.* **2003**, *5*, 4133–4136; c) J. E. Argüello, L. C. Schmidt, A. B. Peñéñory, *J. Org. Chem.* **2007**, *72*, 2936–2944.

[20] While we were working on this manuscript, a paper was published with the same observation, see: H.-L. Kao, C.-F. Lee, *Org. Lett.* **2011**, *13*, 5204–5207.

[21] X. Chen, Z. Rappoport, *J. Org. Chem.* **1998**, *63*, 5684–5686.

[22] The base-catalyzed rearrangement of a neutral phenylketene dimer of the lactone type (corresponding to **8a**) to its acidic isomer (corresponding to **8b**) has been reported, see: J. E. Baldwin, J. D. Roberts, *J. Am. Chem. Soc.* **1963**, *85*, 2444–2445.

[23] Y. Chiang, A. V. Fedorov, A. J. Kresge, I. Onyido, T. T. Tidwell, *J. Am. Chem. Soc.* **2004**, *126*, 9382–9386.

[24] The origin of the methyl benzoate is not clear. All the control experiments of reagents and products did not afford methyl benzoate, as judged by analysis by GC-MS.

[25] a) S. Chowdhury, S. Roy, *J. Org. Chem.* **1997**, *62*, 199–200; b) C. Kuang, H. Senboku, M. Tokuda, *Tetrahedron Lett.* **2001**, *42*, 3893–3896.

[26] M. B. Smith, J. March, *March's Advanced Organic Chemistry*, 6th ed., John Wiley & Sons, New Jersey, **2007**, p. 1425.

[27] J. H. Wang, Q. Xu, X. Huang, *Chin. Chem. Lett.* **2000**, *11*, 1–2.

[28] Y. Yatsuminji, O. Okada, A. Tsubouchi, T. Takeda, *Tetrahedron* **2006**, *62*, 9981–9987.

[29] S. Ranjit, Z. Duan, P. Zhang, X. Liu, *Org. Lett.* **2010**, *12*, 4134–4136.

[30] M. V. R. Reddy, E. P. Reddy, S. C. Bell, WO2006US06698, **2006**.

[31] S. Shoai, P. Bichler, B. Kang, H. Buckley, J. A. Love, *Organometallics* **2007**, *26*, 5778–5781.

[32] C. G. Bates, P. Saejueng, M. Q. Doherty, D. Venkataraman, *Org. Lett.* **2004**, *6*, 5005–5008.

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