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Oxidation

PPh_3·HBr-DMSO Mediated Expedient Synthesis of γ-Substituted β,γ-Unsaturated α-Ketomethylthioesters and α-Bromo Enals: Application to the Synthesis of 2-Methylsulfanyl-3(2*H*)-furanones

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Abstract: An efficient chemoselective general procedure for the synthesis of γ-substituted β,γ-unsaturated α-ketomethylthioesters from α,β-unsaturated ketones has been achieved through an unprecedented PPh_3·HBr-DMSO mediated oxidative bromination and Kornblum oxidation sequence. The newly developed reagent system serves admirably for the synthesis of α-bromoenals from enals. Furthermore, $AuCl_3$-catalyzed efficient access to 3(2*H*)-furanones from the above intermediates under extremely mild conditions are described.

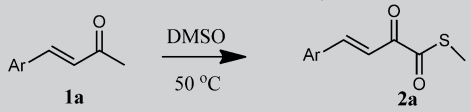
Oxygen-transfer reactions using DMSO, either through the activation of sulfoxides, such as Swern oxidation and its variants,[1] or through a non-activation pathway, such as the Kornblum oxidation, are of fundamental importance in chemical transformations.[2] On the other hand, addition of HX or X_2 (X = Br, I) to DMSO induce deoxygenation to generate dimethyl sulfide.[3] Taken together, a variety of unique oxidative transformations through oxidative halogenations followed by DMSO-based oxidation have been developed by using the X_2/HX-DMSO system.[4] Such reactions often lead to the formation of arylglyoxals, or their acids, in good yields through oxidative hydrolysis, and, occasionally, α-ketothioesters as minor products. Although α-ketothioesters find widespread applications as a synthetic intermediates, there is a lack of general methods to synthesize them; the few methods available involve the use of the pyrophoric reagent, *t*BuLi.[5] The related γ-substituted β,γ-unsaturated α-ketothioesters are also potentially important building blocks; however, their utility is very much underexplored owing to the paucity of methods available to access them.[6]

Herein, we report the synthesis of γ-substituted β,γ-unsaturated α-ketomethylthioesters under oxidative bromination[7] and Kornblum oxidation conditions, mediated by the hitherto unexplored reagent combination of PPh_3·HBr-DMSO and proceeding through conversion of ketomethyl groups into α-ketomethylthioesters. We also demonstrate that the newly developed reagent system is equally useful for the synthesis of α-bromoenals from enals. Furthermore, we demonstrate $AuCl_3$-catalyzed cyclization of 2-oxo-3-butynoic methylthioester into 2-methylsulfanyl-3(2*H*)-furanones.

In connection with our other projects dealing with α,β-unsaturated ketones and utilizing PPh_3·HBr as a reagent, we noticed the formation of some intriguing products when DMSO was used as the solvent instead of CH_2Cl_2.[8] Subsequently, we examined the reaction of **1a** with PPh_3·HBr (2.0 equiv) in DMSO.

Following the usual work-up and purification, we obtained β,γ-unsaturated α-ketothioester **2a** in 47% yield (entry 1, Table 1). Importantly, we did not observe any bromination at the aromatic ring or at alkenyl olefinic bond. Intrigued by our findings, we initiated a systematic study of this transformation and the scope of the reagent system towards other transfor-

Table 1. Reaction optimization for α-ketomethylthioesters.[a]



1a 2a

Entry	Reagent	Equiv	*t* [h]	Yield[b][%]
1	PPh_3·HBr	2.0	3	47
2	33% HBr-AcOH	2.0	15	n.d.[c]
3	pyridine·HBr	2.0	12	n.d.[c]
4	pyrrolidone hydrotribromide	2.0	2	n.d.[c]
5	pyridinium tribromide	2.0	2	n.d.[c]
6	dry HBr	2.0	12	19
7	PPh_3·HBr	0.5	17	6
8	PPh_3·HBr	1.0	8	28
9	PPh_3·HBr	3.0	1	53
10	PPh_3·HBr	2.0	4	43[d]
11	PPh_3·HBr	2.0	4	33[e]
12	PPh_3·HBr	2.0	15	n.d.[f]
13	PPh_3·HBr	2.0	15	n.d.[g]
14	PPh_3·HBr	2.0	4	42[h]

[a] **1a** (0.05 g, 0.24 mmol, 1.0 equiv), reagent in dry DMSO (2 mL) under Ar atmosphere, 50 °C, employing time as mentioned. PPh_3·HBr (2.0 equiv) was used as optimized reaction conditions from an economical point of view. n.d. = not detected. [b] Yields of isolated product. [c] Complex reaction mixtures. [d] Reaction was carried out in open atmosphere. [e] DMSO was used without drying. [f] 10.0 equiv of H_2O was used. [g] 0.050 g of 4 Å molecular sieves was used. [h] 1 g (4.85 mmol) of **1a** batch size and DMSO (30 mL) were used. Ar = 3,4-$(OMe)_2$-C_6H_3

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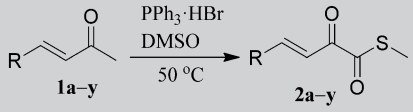
mations. As shown in Table 1, treating **1a** with 33% HBr-AcOH, py·HBr, pyrrolidone hydrotribromide, or pyridinium hydrotribromide in DMSO (entries 2–5, Table 1) did not result in **2a**, but the use of dry HBr in DMSO furnished **2a** in 19% yield (entry 6, Table 1). We observed that a catalytic amount of PPh_3·HBr was not enough to drive the reaction to completion (entries 7 and 8, Table 1). The use of PPh_3·HBr in stoichiometric ratios accelerated the transformation, and a higher yield was obtained with an excess of reagents (entry 9, Table 1). Interestingly, the reaction may be carried out in open atmosphere (43%; entry 10, Table 1) or with DMSO that hadn't been dried (33%; entry 11, Table 1), but with a lower yield and the necessity to conduct the reaction for a longer reaction time.

In order to explore the influence of water in the reaction system, as it was generated in situ in the reaction medium through an oxidation–reduction cycle, we conducted the reaction with 10.0 equiv of H_2O or 4 Å molecular sieves in dry DMSO; no product, **2a**, was formed even by conducting the reaction at 80 °C for several hours, only starting material being recovered (entries 12 and 13, Table 1). To demonstrate the PPh_3·HBr-DMSO mediated procedure on a large scale, we conducted the reaction with one gram of compound **1a** (4.85 mmol). We isolated **2a** in 42% yield (entry 14, Table 1) without compromising to the reaction efficiency. The use of other solvents (DMF, THF and CH_3CN) failed to deliver the required products.

Subsequently, we investigated the substrate scope and generality for this transformation. As shown in Table 2, several β-substituted α,β-unsaturated ketomethyl derivatives underwent methylthioesterification to give γ-substituted β,γ-unsaturated α-ketomethylthioesters with an excellent level of chemoselectivity. In general, the reaction is tolerant to variation in substituents in the aryl ring. It was found that the substrates containing an electron-donating (**2a**–**f**, 41–54%) and electron-neutral substituents (**2g**, 52%) on the aromatic ring or heteroaromatic substituent (**2w**, 56%) gave ketothioesters in moderate yields. Substrates containing strong electron-withdrawing (**2h**–**m**, 62–73%) and electron-deficient (**2n**–**u**, 51–65%) substituents on the aromatic ring or with a polynuclear aromatic hydrocarbon (**2v**, 70%) delivered the corresponding ketothioesters in moderate to good yields. An α,β-alkynyl derivative was also found to be compatible under the reaction conditions (**2z**; entry 26, Table 2). However, replacement of the β-aryl group with an alkyl group dramatically lowered the yield (**2x**–**y**, 16–22%), perhaps owing to the lack of aromatic conjugation, competitive allylic bromination, or both. The structure of **2g** was unambiguously established by single-crystal X-ray diffraction analysis (Figure 1).[9] Complete retention of the *trans*-alkene stereochemistry with respect to the double bond was observed in all products (**2a**–**y**, Table 2), as established by the large coupling constant for the olefinic protons ($^3J \sim 15$–16 Hz) in the ^{1}H NMR spectrum. The modest yields achieved in the reaction sequences (Table 2) were thought to be due to the formation of aldehyde (hydrated form) from the corresponding α-bromo intermediate through Kornblum oxidation (see Scheme 1). However, when the reaction was quenched midway, no such derivatives were isolated.

Table 2. Synthesis of γ-substituted β,γ-unsaturated α-ketomethylthioesters.[a]



Entry	R	Product	*t* [h]	Yield[b][%]
1	3,4-$(OMe)_2$-C_6H_3	**2a**	3	47
2	3-OMe,4-OBn-C_6H_3	**2b**	3	45
3	2,3-$(OMe)_2$-C_6H_3	**2c**	3	47
4	4-OMe-C_6H_4	**2d**	5.5	46
5	4-OH-C_6H_4	**2e**	5	41
6	4-Me-C_6H_4	**2f**	3	54
7	C_6H_5	**2g**	4	52
8	4-NO_2-C_6H_4	**2h**	5	65
9	3-NO_2-C_6H_4	**2i**	2.5	64
10	2-NO_2-C_6H_4	**2j**	2.5	62
11	2,4-$(NO_2)_2$-C_6H_3	**2k**	2.5	73
12	4-CN-C_6H_4	**2l**	2	70
13	3-CN-C_6H_4	**2m**	1.5	71
14	4-Cl-C_6H_4	**2n**	4	56
15	3-Cl-C_6H_4	**2o**	2	58
16	2-Br-C_6H_4	**2p**	3	65
17	2,4-$(Cl)_2$-C_6H_3	**2q**	6	59[c]
18	2,6-$(Cl)_2$-C_6H_3	**2r**	3.5	64
19	2-Cl-6-F-C_6H_3	**2s**	5	51
20	4-OAc-C_6H_4	**2t**	18	56[c]
21	4-OBz-C_6H_4	**2u**	3	65
22	2-Naphthyl	**2v**	2	70
23	2-Thienyl	**2w**	3	56
24	$PhCH_2CH_2$	**2x**	6	22[d]
25	Cyclohexyl	**2y**	16	16[c]
26	PhC≡CCOMe (**1z**)→PhC≡CCOCOSMe (**2z**)		3	49

[a] Reactions were performed with **1a**–**y**, **z** (0.05 g, 1.0 equiv) and PPh_3·HBr (2.0 equiv) in dry DMSO at 50 °C under Ar atmosphere. [b] Yields of isolated product. [c] Reactions were performed at r.t. [d] Reaction was performed at 45 °C.

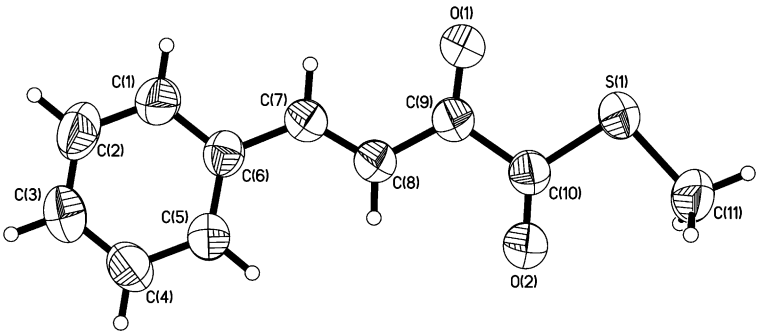
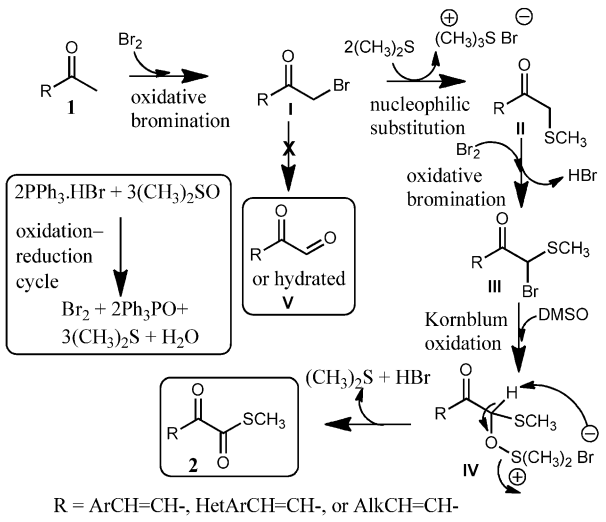


Figure 1. ORTEP diagram showing the molecular structure of **2g** at the 30% probability level.

A plausible reaction mechanism is outlined in Scheme 1. Based on earlier reports,[4,10a] we presumed that PPh_3·HBr in presence of DMSO would generate Br_2, Ph_3PO, $(CH_3)_2S$, and H_2O through an oxidation–reduction cycle.[10b] The initial oxidative bromination of **1** could then lead to the corresponding α-

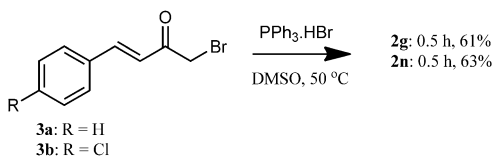


Scheme 1. Possible reaction mechanism pathway leading to **2**.

bromo derivative **I**, followed by immediate formation of **II** through nucleophilic substitution with dimethyl sulfide and concomitant release of trimethylsulfonium bromide salts (Scheme 1). Further bromination of intermediate **II** would lead to **III**, and subsequent DMSO-mediated Kornblum oxidation to the β-γ-unsaturated-α-ketomethylthioesters **2** via **IV**. However, DMSO-mediated direct oxidation of **I** to **V** was not observed.[4]

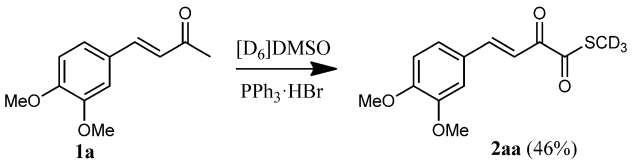
Since, HBr was regenerated at the end of the reaction in the proposed reaction pathway (Scheme 1), we expected PPh_3·HBr could be used in catalytic amount. However, we observed that a catalytic amount of PPh_3·HBr was not sufficient to drive the reaction to completion (entries 7–8, Table 1). Whereas, the use of PPh_3·HBr in stoichiometric ratios only accelerated the transformations, and we isolated **2a** in good yield. Further, we observed that use of dry HBr in DMSO only furnished **2a** in 19% yield (entry 6, Table 1). As a result, although HBr was regenerated at the end of the reaction (Scheme 1), upon addition of catalytic PPh_3·HBr, the product was obtained in only a poor yield owing to the inefficiency of regenerated HBr reacting with DMSO. We are also not sure about the role, if any, played by Ph_3PO in this proposed mechanistic cycle and further investigations are ongoing to settle this.

To determine if the corresponding α-bromoketone is an intermediate, **3a** and **3b** were prepared following the literature procedure,[11a] and subjected to PPh_3·HBr-DMSO reaction conditions (Scheme 2). Corresponding α-ketothioesters **2g** and **2n** were obtained in 61% and 63% yield, respectively, thus suggesting that the transformation of α-ketothioesters **2a–z** proceed through the corresponding α-bromoketone intermediates.



Scheme 2. Control experiments with α-bromo styryl ketones.

To gain further mechanistic insights on this transformation, an NMR experiment was carried out with **1a** (0.01 g, 0.048 mmol), [D_6]DMSO (0.4 mL), and PPh_3·HBr (0.097 mmol) at 50 °C for 3 h (Scheme 3). Exclusive formation of **2aa** with incorporation of -CD_3 confirmed that the methyl group originated from DMSO and not from any other source (for details, see the Supporting Information).



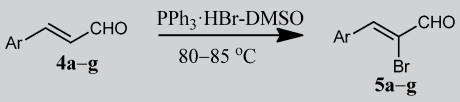
Scheme 3. Synthesis of α-keto deutrated-methylthioester with [D_6]DMSO.

To determine whether substrates with a conjugated double bond are necessary, we performed experiments with acetophenone/*p*-nitroacetophenone and PPh_3·HBr-DMSO. However, we did not observe any expected α-ketothioester from acetophenone even upon heating the reaction mixture for several hours; the use of *p*-nitroacetophenone did lead to product, but only in 13% yield. The poor yield obtained in the reaction may be due to the lack of a conjugated double bond in the substrate (see the Supporting Information).

To confirm Br_2 as the active reagent formed in situ through an oxidation–reduction cycle, we conducted control experiments with 1-tetralone/6-methoxytetralone/7-methoxytetralone and PPh_3·HBr-DMSO separately under the standard reaction conditions. We isolated only α′-monobrominated products in high yields, thus confirming that Br_2 is generated in situ (see the Supporting Information).[11b]

Inspired by the above results and to further exploit the potential of the PPh_3·HBr-DMSO reagent system, we became interested in investigating the scope and feasibility of these reagent systems with β-substituted enal derivatives. As indicated in Table 3, electron-donating (entries 1–4, Table 3), electron-neutral (entry 5, Table 3), and strong electron-withdrawing (entry 6, Table 3) substituents on the aromatic ring, as well as a heteroaromatic substituent (entry 7, Table 3) were well-tolerated, and produced the corresponding *Z*-α-bromoenal derivatives with moderate to excellent yields (61–94%).[2b,12] However, the presense of an alkyl group on the β-position did not result in any α-bromoenal derivative, ostensibly owing to lack of aromatic conjugation. The mechanism of the transformation may involve an initial oxidative dibromination of the olefinic double bond, followed by the displacement of the bromine atom at the β-position by DMSO to form alkoxysulfonium intermediate, and finally elimination of the α hydrogen atom, thus leading to dehydrobromination.[2b,13a] Or, the intermediate bromonium derivative eliminates a proton from the α-carbon atom to directly give the product.[13b] Synthesis of such aromatic α-bromoenal derivatives generally involves two steps with highly corrosive and toxic Br_2, followed by base treatment. We

Table 3. PPh_3·HBr-DMSO catalyzed synthesis of *Z*-α-bromoenal derivatives.[a]



Entry	Ar	Product	*t* [h]	Yield[b][%]
1	4-OMe-C_6H_4	**5a**	6	94
2	3,4-$(OMe)_2$-C_6H_3	**5b**	11	85
3	3-OMe,4-OBn-C_6H_3	**5c**	20	74
4	4-Me-C_6H_4	**5d**	12	82
5	C_6H_5	**5e**	12	81
6	4-NO_2-C_6H_4	**5f**	21	68
7	2-furyl	**5g**	6	61[c]

[a] Reactions were performed with **4a–g** (1.0 equiv) and PPh_3·HBr (2.0 equiv) in dry DMSO (2 mL) under Ar atmosphere. [b] Yields of isolated product. [c] Reaction was carried out at 70–75 °C.

envision that our one-step PPh_3·HBr-DMSO method will be a viable alternative to the existing method. Another interesting feature is the base-free reaction conditions, thus suggesting new opportunities for the synthesis of base-sensitive and highly substituted compounds. More importantly, the yields reported in Table 3 are comparable with the precedent results reported by other research groups.[12,13a]

To demonstrate the potential utility of the current γ-substituted β,γ-unsaturated α-ketomethylthioester intermediate, we have shown the synthesis of 3(2*H*)-furanones under extremely mild conditions (Table 4). 3(2*H*)-Furanones are a key structural unit in medicines and biologically active natural products. Their diverse arrays of pharmacological significance includes antibiotic, anticancer, antiulcer, and antiallergical activities.[14] Owing to their potential applications, several methods including transition-metal-catalyzed cyclization have been developed for their synthesis.[15] On the other hand, cationic gold(III) species have been reported as a powerful catalysts for the activation of alkynes toward addition of a variety of nucleophiles.[16] We envisioned that the highly activated 2-oxo-3-butynoic methylthioester might also undergo a gold(III)-catalyzed cyclization and offer an easy access to 3(2*H*)-furanones.

Subsequently, when we treated **2z** (0.15 mmol) with $AuCl_3$ (2 mol%) and MeOH in CH_2Cl_2 at room temperature, the corresponding 2-methylsulfanyl-3(2*H*)-furanone was isolated in 72% yield (entry1, Table 4). The structure of **6a** was unambiguously established by single-crystal X-ray diffraction analysis (Figure 2).[9]

The mechanism of the reaction can be explained on the basis of the formation of an activated alkyne–gold complex intermediate, followed by either a domino nucleophilic attack/*anti-endo-dig* cyclization or the formation of cyclic oxonium ion with subsequent nucleophilic attack, as described in the literature.[14b,16a] Similarly, when we used other alcohols, for example, ethanol (entry 2, Table 4), isopropanol (entry 3, Table 4; Figure 3),[9] benzyl alcohol (entry 4, Table 4), allyl alcohol (entry 5, Table 4), and cinnamyl alcohol (entry 6, Table 4), the respective 3(2*H*)-furanones (**6b–f**) were isolated in high yields.

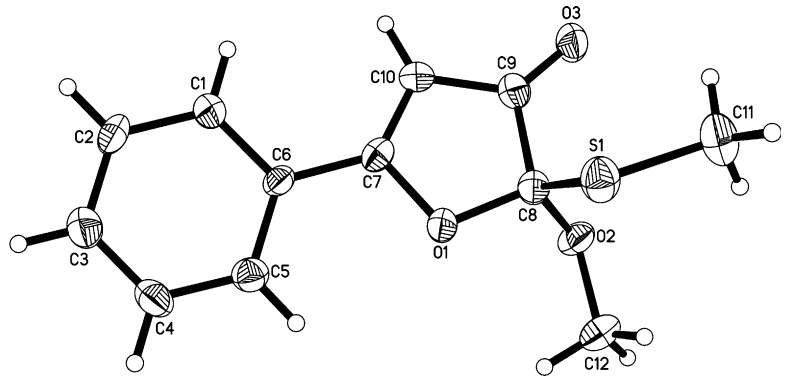
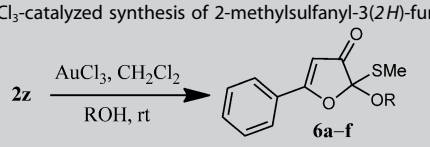


Figure 2. ORTEP diagram showing the molecular structure of **6a** at the 30% probability level.

Table 4. $AuCl_3$-catalyzed synthesis of 2-methylsulfanyl-3(2*H*)-furanones.[a]



Entry	R	Product	*t* [h]	Yield[b][%]
1	Me	**6a**	4	72
2	Et	**6b**	3	82
3	$CH(CH_3)_2$	**6c**	4	77
4	CH_2Ph	**6d**	2	78
5	CH_2-CH=CH_2(*E*)	**6e**	2	88
6	CH_2-CH=CHPh(*E*)	**6f**	3	80

[a] Reactions were performed with **2z** (0.15 mmol), ROH (0.30 mmol), $AuCl_3$ (2 mol%) in CH_2Cl_2 (4 mL) at r.t. [b] Yields of isolated product.

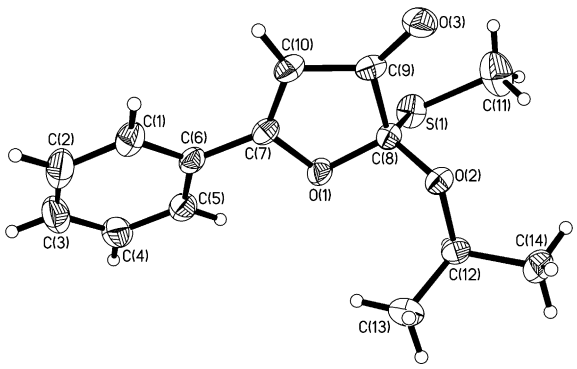


Figure 3. ORTEP diagram showing the molecular structure of **6c** at the 50% probability level.

In conclusion, we have successfully developed an efficient chemoselective general route to γ-substituted β,γ-unsaturated α-ketomethylthioesters from α,β-unsaturated ketones through an unprecedented PPh_3·HBr-DMSO mediated oxidative bromination followed by Kornblum oxidation in moderate to good yields. We further demonstrate that the newly developed reagent system is equally useful for the synthesis of α-bromoenals from enals. Furthermore, $AuCl_3$-catalyzed highly efficient access to 3(2*H*)-furanones from 2-oxo-3-butynoic methylthioester with different alcohols under mild reaction conditions are described. We believe that it opens up a splendid opportunity for exploiting γ-substituted β,γ-unsaturated α-ketothioesters as versatile synthons in both metal- and organocatalyzed asymmetric synthesis towards biologically active heterocycles.

Experimental Section

Representative procedure

PPh_3·HBr (0.20 g, 0.58 mmol, 2.0 equiv) was placed in a 25 mL two-neck round bottom flask under Ar with condenser. Dry DMSO (2.0 mL) was added dropwise at room temperature. **1m** (0.05 g, 0.29 mmol, 1.0 equiv) was introduced into the reaction mixture, and the resulting mixture was stirred at 50 °C for 1.5 h. After completion of the reaction (TLC), saturated ammonium chloride solution was added, and the product was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure to get a residue. The crude residue was purified over silica gel (230–400 mesh) flash column chromatography to obtain **2m** (0.048 g, 71%); eluent, EtOAc/hexane (20%); yellow amorphous solid; m.p. 150 °C; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 7.87$–7.92 (m, 3H), 7.73 (d, $J = 7.2$ Hz, 1H), 7.57 (t, $J = 7.8$ Hz, 1H), 7.47 (d, $J = 16.2$ Hz, 1H), 2.42 ppm (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 192.7$, 182.4, 145.6, 135.4, 134.3, 132.6, 132.3, 130.0, 119.9, 117.9, 113.7, 11.5 ppm; IR (KBr): $\tilde{\nu} =$ 2230, 1677, 1671, 1605 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{12}H_9NO_2S$: 231.0354 $[M]^+$; found: 231.0359.

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Keywords: chemoselectivity · cyclization · gold · oxidative bromination · triphenylphosphine hydrobromide

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[8] The details will be reported in due course.

[9] **2g**: $C_{11}H_{10}O_2S$, $M = 206.25$, monoclinic, $P2_1/n$, $a = 9.281(2)$, $b = 5.417(1)$, $c = 21.152(4)$ Å, $\beta = 102.47(1)^\circ$, $V = 1038.3(4)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.319$ g cm^{-3}, $\mu = 0.281$ mm^{-1}, $F(000) = 432$, $\lambda(Mo_{K\alpha}) = 0.71073$ Å, yellow block, crystal size: 0.26×0.1×0.04 mm, 14222 reflections measured ($R_{int} = 0.0511$), 1551 unique reflections, $wR(F^2) = 0.1367$ for all data and conventional $R = 0.0349$ for 1320 *F* values with $I > 2\sigma(I)$, $(\Delta/\sigma)_{max} = 0.001$, $S = 1.116$ for all data and 129 parameters, $\Delta\rho_{max,min}$ (e/Å^3) = 0.197, −0.165; **6a**: $C_{12}H_{12}O_3S$, $M = 236.28$, monoclinic, $P2_1/n$, $a = 7.332(2)$, $b = 9.937(2)$, $c = 16.090(3$ Å, $\beta = 100.96(3)^\circ$, $V = 1150.9(4)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.364$ g cm^{-3}, $\mu = 0.269$ mm^{-1}, $F(000) = 496$, $\lambda(Mo_{K\alpha}) = 0.71073$ Å, colorless block, crystal size: 0.23×0.23×0.13 mm, 2841 reflections measured ($R_{int} = 0.087$), 1871 unique reflections, $wR(F^2) = 0.1620$ for all data and conventional $R = 0.0437$ for 682 *F* values with $I > 2\sigma(I)$, $S = 0.635$ for all data and 147 parameters, $\Delta\rho_{max,min}$ (e/Å^3) = 0.208, −0.220; **6c**: $C_{14}H_{16}O_3S$, $M = 264.33$, monoclinic, $P2_1/c$, $a = 11.979(5)$, $b = 10.808(5)$, $c = 11.992(5$ Å, $\beta = 115.946(8)^\circ$, $V = 1396.1(11)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.258$ g cm^{-3}, $\mu = 0.229$ mm^{-1}, $F(000) = 560$, $\lambda(MoK_\alpha) = 0.71073$ Å, colorless block, crystal size: 0.23×0.21×0.2 mm, 11382 reflections measured ($R_{int} = 0.0374$), 2919 unique reflections, $wR(F^2) = 0.2177$ for all data and conventional $R = 0.0736$ for 2544 *F* values with $I > 2\sigma(I)$, $(\Delta/\sigma)_{max} = 0.000$, $S = 1.281$ for all data and 166 parameters, $\Delta\rho_{max,min}$ (e/Å^3) = 0.552, −0.814. CCDC 960814 (**2g**), 960815 (**6a**), and 967757 (**6c**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif; for more details see the Supporting Information.

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