

Preparation of *tert*-Alkyl Aryl Sulfides from *tert*-Alcohols via Quinone-mediated Oxidation–Reduction Condensation between *tert*-Alkyl Diphenylphosphinites and 2-Sulfanyl-1,3-benzothiazole

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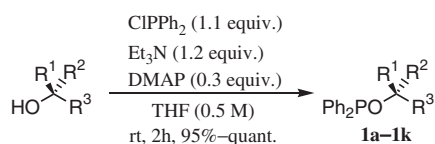
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A convenient two-step procedure for the construction of sulfur-containing quaternary centers from *tert*-alcohols involving chiral ones is established. *tert*-Alkyl diphenylphosphinites **1** were easily prepared in excellent yields from *tert*-alcohols and ClPPh₂ by the combined use of Et₃N and a catalytic amount of DMAP. Subsequent condensation of **1** with thiol **3** smoothly proceeded in the presence of quinone **2d** to afford the corresponding *tert*-alkyl sulfides **4** in good to high yields via S_N2 displacement. Removal of benzothiazol-2-yl group of (*R*)-**4j** was achieved with LiAlH₄ to afford the desired chiral thiol (*R*)-**5** in high yield.

Nucleophilic substitution at quaternary carbon centers via S_N2-type displacement has been regarded as one of the most challenging topics in current organic synthesis, however, only a few successful examples have been reported.^{1,2} Recently, it was shown from our laboratory that a new-type of oxidation–reduction condensation of *tert*-alkyl diphenylphosphinites **1**, prepared from *n*-BuLi-treated *tert*-alcohols and chlorodiphenylphosphine (ClPPh₂), with heteroaryl thiols proceeded smoothly by the promotion of 2,6-dimethyl-1,4-benzoquinone (DMBQ; **2c**) under neutral and mild conditions to afford various *tert*-alkyl aryl sulfides in moderate to good yields.^{2a} In a similar fashion, preparation of chiral tertiary alkyl sulfides was also achieved using chiral benzylic *tert*-alkyl phosphinite via S_N2 displacement.

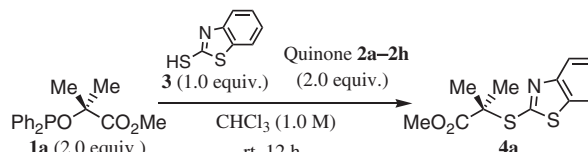
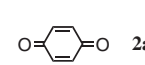
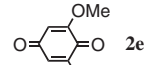
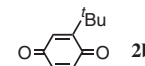
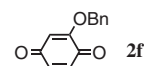
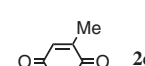
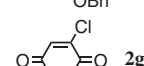
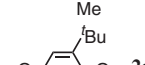
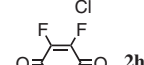
In order to establish a practical and convenient method of forming sulfur-containing quaternary centers, a condensation of *tert*-alkyl phosphinites **1** with 2-sulfanyl-1,3-benzothiazole (**3**) and a development of a preparative method of the phosphinite **1** under mild condensations were investigated in detail. Now, we would like here to describe an effective method for the synthesis of *tert*-alkyl benzothiazol-2-yl sulfides **4** from *tert*-alcohols by the oxidation–reduction condensation of **1** with thiol **3** using 2,6-di-*tert*-butyl-1,4-benzoquinone (DBBQ; **2d**) as an oxidant.

Phosphinites **1a–1k** were easily prepared from the corresponding *tert*-alcohols in excellent yields (95%–quant.) by simply adding chlorodiphenylphosphine (ClPPh₂) in the presence of triethylamine (Et₃N) and a catalytic amount of 4-(dimethyl-



Scheme 1. Preparation of *tert*-alkyl diphenylphosphinites.

Table 1. Optimization of quinone derivatives

					
Entry	Quinone	Yield/ %	Entry	Quinone	Yield/ %
1	 2a	34	5	 2e	91
2	 2b	51	6	 2f	91
3	 2c	84	7	 2g	6
4	 2d	quant.	8	 2h	N.D.

amino)pyridine (DMAP) as shown in Scheme 1.^{3,4} The reactions completed within 2 h at room temperature and pure phosphinites were obtained just by filtration through a pad of alumina using an eluent of hexane/ethyl acetate (v/v = 9/1) under the conditions resisting to air-oxidation of phosphinites. It should be noted that the above conditions are obviously milder than those of the previously reported procedure of using a strong base as *n*-BuLi⁵ which afforded **1j** in only 8% yield.

Since sufficient amounts of phosphinites are available by the above procedure, the screening of 1,4-benzoquinone derivatives was tried in order to choose an excellent one for the condensation of phosphinite **1a** with thiol **3** (Table 1). It was considered that **1a** is one of most suitable substrates for S_N2 substitution because the reaction center of **1a** is activated by the α-carboxylic ester group.^{1a–1d,6} The reaction was tried first by using simple 1,4-benzoquinone (**2a**) which was successfully employed in our previous papers,^{2b–2c} but the desired sulfide **4a** was obtained in only 34% yield (Entry 1). The use of 2-*tert*-butyl-1,4-benzoquinone (**2b**) or DMBQ **2c**,² on the other hand, dramatically improved the yield of **4a** up to 84% (Entries 2, 3). This suggests that substituents at 2- and 6-positions of **2a** effectively suppress the undesired competitive E2 elimination^{1b} caused by the phenolic anion generated from 1,4-benzoquinone.^{2c} Further experiments concerning the above substituent effects finally led to the use of bulky DBBQ **2d**⁷ and it afforded **4a** in a quantitative yield

Table 2. DBBQ-mediated condensation of **1** with **3**^a

Phosphinite	R ¹	R ²	R ³	% ee ^b (config.)	Product	Yield /%	% ee ^c (config.)
1b	Me	Me	CO ₂ Bn	—	4b	87 (78 ^d)	—
1c	Me	Me	CO ₂ ^t Bn	—	4c	90 (66 ^d)	—
1d	Me	Me	COPh	—	4d	52 (22 ^d)	—
1e	Me	Me	Ph	—	4e	90 (78 ^d)	—
1f	Me	—	—(CH ₂) ₄ —	—	4f	53 (48 ^{d,e})	—
1g	Me	Me	(CH ₂) ₂ Ph	—	4g	34 (35 ^{d,e})	—
1h	Et	Me	CO ₂ Bn	>99 (S)	4h	73	>99 (R)
1i	CH ₂ Ph	Me	CO ₂ Et	78 (S)	4i	61	76 (R)
1j	Ph	Me	CO ₂ Me	>99 (S)	4j	73	99 (R)
1k	Et	Me	Ph	97 (S)	4k	76	86 ^f (R)

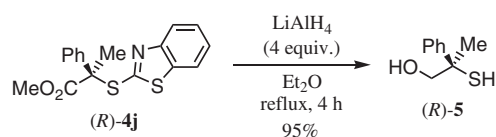
^aReactions were carried out on a 0.5 mmol scale. ^bEe of alcohols. ^cDetermined by HPLC using commercially available chiral columns. ^dDMBQ **2c** was used instead of DBBQ **2d**. ^eData cited from Ref. 2a. ^f**4k** was obtained with 65% ee by DMBQ (See Ref. 2a).

(Entry 4). Interestingly, dialkoxy derivatives **2e** and **2f**⁸ were also found to be effective oxidants and **4a** was obtained in 91% yield in both cases (Entries 5, 6). In contrast, the use of electron-deficient dichloro derivative **2g** or fluoranil **2h**^{2e,9} gave the desired products in quite low yields (Entries 7, 8).

After reaction conditions of using DBBQ **2d** were optimized,¹⁰ the generality of this reaction was examined by using various *tert*-alkyl phosphinites (see Table 2). Phosphinites **1b–1e** bearing ester, ketone, or phenyl group at the quaternary centers were smoothly transformed into the corresponding sulfides **4b–4e** in good to high yields (52–90%). It is noted that the use of **2d** instead of **2c** fairly improved the yields in the coexistence of such reactive phosphinites **1b–1e** while good results were not obtained when phosphinites **1f–1g** were used. Chiral phosphinites **1h–1j** were also successfully employed in this reaction, and the enantiomerically enriched *tert*-alkyl sulfides **4h–4j** were afforded in good yields with either perfect or nearly complete inversion at the quaternary centers. Condensation of benzylic *tert*-alkyl phosphinite **1k**, which was considered to proceed via S_N1 reaction, also gave the inverted sulfide **4k** in 76% yield with high ee (86% ee).

The absolute stereochemistry of **4j** was determined after reductive cleavage of the benzothiazol-2-yl group as described in Scheme 2; that is, treatment of (*R*)-**4j** (99% ee) with lithium aluminum hydride¹¹ in refluxing diethyl ether for 4 h gave (*R*)-**5**¹² in 95% yield. The optical rotation of (*R*)-**5** [α]_D²³ –32.6 (c 0.41, CH₂Cl₂) is in good agreement with that of the literature value¹² [α]_D²⁰ –31.8 (c 0.36, CH₂Cl₂, ≥99% ee).¹³ Thus, the first example of synthesis of chiral *tert*-thiol from chiral *tert*-alcohol via S_N2 substitution was established.

It is important to note that construction of sulfur-containing chiral quaternary centers from chiral *tert*-alcohols was achieved

**Scheme 2.** Deprotection of benzothiazol-2-yl group.

via inversion of configuration by S_N2 displacement. Subsequent removal of benzothiazol-2-yl group of thus formed **4** provides a new and convenient route to the synthesis of chiral *tert*-thiols from chiral *tert*-alcohols.

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References and Notes

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- A general procedure is as follows; to a stirred solution of alcohol (10 mmol) and DMAP (3 mmol) in dry THF (20 mL) were added Et₃N (12 mmol) followed by ClPPh₂ (11 mmol) under Ar atmosphere. After stirring at rt for 2 h, TLC showed complete consumption of the alcohol, and the resulted white slurry was concentrated by a rotary evaporator. After the dilution of the residue with hexane/EtOAc (v/v = 9/1, 100 mL), the mixture was filtered through a pad of alumina (activated, 300 mesh; purchased from Wako Pure Chemical Industries, Ltd.) and Celite. The filtrate was concentrated under reduced pressure to give the desired phosphinites in >95% yields. Since *tert*-alkyl phosphinites were moderately sensitive to air and moisture, they should be stored at <10 °C under dry Ar atmosphere.
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- A general procedure is as follows; to a stirred solution of phosphinite (1.0 mmol) in dry CHCl₃ (0.5 mL) were successively added thiol **3** (0.5 mmol) and DBBQ (1.0 mmol) at rt under Ar atmosphere. After 12 h, the crude product was purified using preparative TLC to afford the corresponding sulfide.
- For deprotection of benzothiazol-2-yl group using alkyl metals, see: a) V. Calò, F. Scordari, A. Nacci, E. Schingaro, L. D'Accolti, and A. Monopoli, *J. Org. Chem.*, **68**, 4406 (2003). b) A. R. Katritzky, W. Kuzmierkiewicz, and J. M. Aurecoechea, *J. Org. Chem.*, **52**, 844 (1987).
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- The absolute configurations of **4h**, **4i**, and **4k** were deduced from the stereochemical outcome of the reaction of (*S*)-**1j** to (*R*)-**4j**.