# 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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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 $ClPPh_2$ by the combined use of $Et_3N$ 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 $LiAlH_4$ to afford the desired chiral thiol (*R*)-**5** in high yield.

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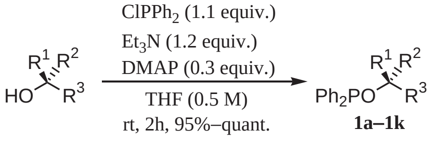
Nucleophilic substitution at quaternary carbon centers via $S_N2$-type displacement has been regarded as one of the most challenging topics in current organic synthesis, however, only a few successful examples have been reported.[1,2] Recently, it was shown from our laboratory that a new-type of oxidation–reduction condensation of *tert*-alkyl diphenylphosphinites **1**, prepared from *n*-BuLi-treated *tert*-alcohols and chlorodiphenylphosphine ($ClPPh_2$), 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 phophinite via $S_N2$ displacement.

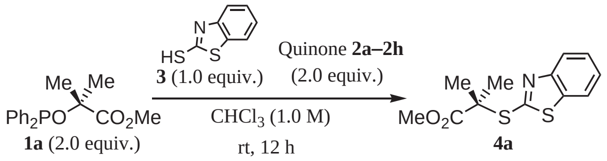
In order to establish a practical and convenient method of forming sulfur-containing quaternary centers, a condensation of *tert*-alkyl phosphinites **1** with 2-sulfanyl-1,3-benzothiazole (**3**) and a development of a preparative method of the phosphinite **1** under mild condensations were investigated 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.

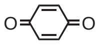
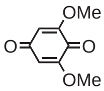
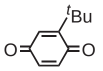
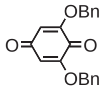
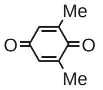
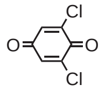
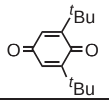
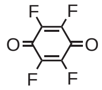
Phosphinites **1a**–**1k** were easily prepared from the corresponding *tert*-alcohols in excellent yields (95%-quant.) by simply adding chlorodiphenylphosphine ($ClPPh_2$) in the presence of triethylamine ($Et_3N$) and a catalytic amount of 4-(dimethylamino)pyridine (DMAP) as shown in Scheme 1.[3,4] 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*-BuLi[5] which afforded **1j** in only 8% yield.



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

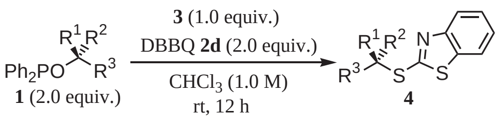
**Table 1.** Optimization of quinone derivatives



| 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. |

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 $\alpha$-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.[2e] 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 | $CO_2Bn$ | — | **4b** | 87 (78[d]) | — |
| **1c** | Me | Me | $CO_2{}^tBn$ | — | **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 | $(CH_2)_2Ph$ | — | **4g** | 34 (35[d,e]) | — |
| **1h** | Et | Me | $CO_2Bn$ | >99 (S) | **4h** | 73 | >99 (R) |
| **1i** | $CH_2Ph$ | Me | $CO_2Et$ | 78 (S) | **4i** | 61 | 76 (R) |
| **1j** | Ph | Me | $CO_2Me$ | >99 (S) | **4j** | 73 | 99 (R) |
| **1k** | Et | Me | Ph | 97 (S) | **4k** | 76 | 86[f] (R) |

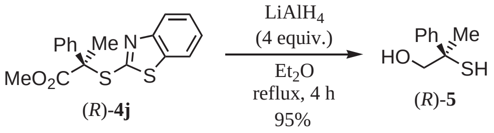
[a] Reactions were carried out on a 0.5 mmol scale. [b] Ee of alcohols. [c] Determined by HPLC using commercially available chiral columns. [d] DMBQ **2c** was used instead of DBBQ **2d**. [e] Data cited from Ref. 2a. [f] **4k** was obtained with 65% ee by DMBQ (See Ref. 2a).

(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 hydride[11] in refluxing diethyl ether for 4 h gave (*R*)-**5**[12] in 95% yield. The optical rotation of (*R*)-**5** $[\alpha]_D^{23}$ −32.6 (*c* 0.41, $CH_2Cl_2$) is in good agreement with that of the literature value[12] $[\alpha]_D^{20}$ −31.8 (*c* 0.36, $CH_2Cl_2$, ≥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 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.



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

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### References and Notes

1 For $S_N2$ reactions from *tert*-alcohols with various nucleophiles, see: a) A. Avenoza, J. H. Busto, F. Corzana, G. J. Osés, and J. M. Peregrina, *Chem. Commun.*, **2004**, 980. b) Y.-J. Shi, D. L. Hughes, and J. M. McNamara, *Tetrahedron Lett.*, **44**, 3609 (2003). c) N. D. Smith and M. Goodman, *Org. Lett.*, **5**, 1035 (2003). d) F. Effenberger and S. Gaupp, *Tetrahedron: Asymmetry*, **10**, 1765 (1999). e) J. Wachtmeister, A. Mühlman, B. Classon, and B. Samuelsson, *Tetrahedron*, **55**, 10761 (1999).

2 a) T. Mukaiyama and K. Ikegai, *Chem. Lett.*, **33**, 1522 (2004). b) T. Shintou, K. Fukumoto, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **77**, 1569 (2004). c) T. Shintou and T. Mukaiyama, *Chem. Lett.*, **32**, 1100 (2003). d) T. Mukaiyama, T. Shintou, and K. Fukumoto, *J. Am. Chem. Soc.*, **125**, 10538 (2003). e) T. Shintou and T. Mukaiyama, *J. Am. Chem. Soc.*, **126**, 7359 (2004).

3 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 $Et_3N$ (12 mmol) followed by $ClPPh_2$ (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.

4 G. Jones and C. J. Richards, *Tetrahedron: Asymmetry*, **15**, 653 (2004).

5 a) T. Shintou, W. Kikuchi, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **76**, 1645 (2003). b) T. Mukaiyama, W. Kikuchi, and T. Shintou, *Chem. Lett.*, **32**, 300 (2003). c) D. A. Evans, K. R. Campos, J. S. Tedrow, F. E. Michael, and M. R. Gangné, *J. Am. Chem. Soc.*, **122**, 7905 (2000).

6 F. G. Bordwell and W. T. Brannen, Jr., *J. Am. Chem. Soc.*, **5**, 4645 (1964).

7 T. Mukaiyama and H. Aoki, *Chem. Lett.*, **34**, 142 (2005).

8 a) N. Morita, *Chem. Pharm. Bull.*, **8**, 66 (1960). b) E. J. Tisdale, B. G. Vong, H. Li, S. H. Kim, C. Chowdhury, and E. A. Theodorakis, *Tetrahedron*, **59**, 6873 (2003).

9 T. Shintou and T. Mukaiyama, *Chem. Lett.*, **32**, 984 (2003).

10 A general procedure is as follows; to a stirred solution of phosphinite (1.0 mmol) in dry $CHCl_3$ (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.

11 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. Aurrecoechea, *J. Org. Chem.*, **52**, 844 (1987).

12 O. Stratmann, B. Kaiser, R. Fröhlich, O. Meyer, and D. Hoppe, *Chem.—Eur. J.*, **7**, 423 (2001).

13 The absolute configurations of **4h**, **4i**, and **4k** were deduced from the stereochemical outcome of the reaction of (*S*)-**1j** to (*R*)-**4j**.

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