Preparation of *tert*-Alkyl Azides from Tertiary Alcohols by Way of Benzoquinone-mediated Oxidation–Reduction Condensation

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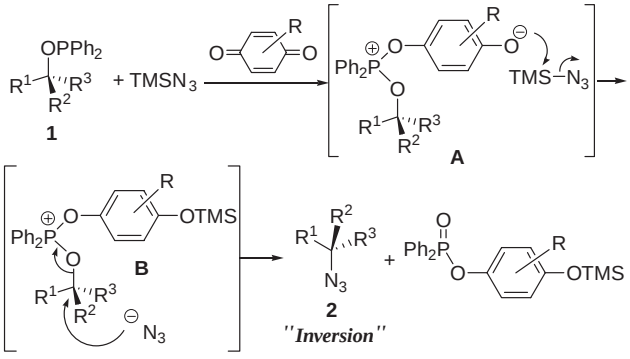
A novel method for the preparation of alkyl azides from alcohols by way of oxidation–reduction condensation is described. According to this reaction, the sterically hindered *tert*-alkyl phosphinites that are prepared from the corresponding alcohols are converted into *tert*-alkyl azides with almost complete inversions of their stereochemistries. On treatment with $LiAlH_4$ the obtained alkyl azides are then successfully reduced to afford the corresponding amines in good yields, thus, a versatile method for the preparation of chiral amines from the corresponding chiral alcohols was established.

As the preparation of azides[1] from alcohols by nucleophilic substitution with an azide anion is noted a useful reaction for introducing an amino-group, many trials have been made during the past decade. For instance, Mitsunobu-type azidation[2] such uses diphenyl phosphorazidate (DPPA)[3] or zinc azide/bis-pyridine complex[4] are good examples of versatile methods for the conversion of alcohols into the corresponding azides. It is known that the nucleophilic substitution proceeded via S_N2 manner, therefore, chiral secondary alkyl azides were formed from the corresponding chiral secondary alcohols with complete inversion of their stereochemistries. Although these methods have widely been applied to the primary and secondary alcohols, there are few reports on the sterically hindered ones to convert into the corresponding azides.[5]

Recently, a new type of oxidation–reduction condensation of carboxylic acids with alkyl phosphinites that were readily prepared from the corresponding alcohols in the presence of 2,6-dimethyl-1,4-benzoquinone (DMBQ) was reported from our laboratory,[6] where almost complete stereochemical inversion was observed even in the case of bulky *tert*-alkyl phosphinites. It was also reported that a C–N bond forming reaction of alkyl phosphinites with phthalimide was carried out by using 2,6-di-*tert*-butyl-1,4-benzoquinone (DBBQ).[7] In the cases of *tert*-alkyl phosphinites, however, the yield of the corresponding *N*-alkyl phthalimides was poor. It is therefore desired to develop a new and efficient method for the stereospecific conversion of *tert*-alkyl alcohols into the corresponding amine derivatives.

In order to perform this process successfully, the following oxidation–reduction condensation reaction by using benzoquinone derivatives and trimethylsilyl azide ($TMSN_3$) as an azide source was considered (Scheme 1). Reaction of alkyl phosphinite **1** with a benzoquinone derivative was supposed to lead to the formation of a zwitterionic intermediate **A** and subsequent O-silylation with trimethylsilyl azide would result in the formation of intermediate **B** and azide anion (N_3^-). Following nucleophilic attack of N_3^- on the phosphonium intermediate in S_N2 manner



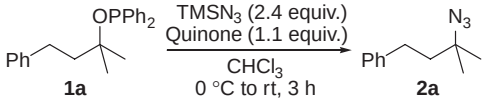
Scheme 1.

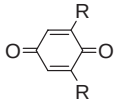
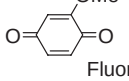
was expected to give the phosphinate derivative and the inverted azide **2**.

Based on these considerations, various 1,4-benzoquinone derivatives were examined by taking condensation reaction of *tert*-alkyl phosphinite **1a** with trimethylsilyl azide (Table 1). Phosphinite **1a** gave the corresponding azide **2a** in 56% yield when 1,4-benzoquinone was employed. The reaction with 2,6-disubstituted benzoquinone derivatives such as DMBQ and DBBQ afforded the desired product in lower yield (Entries 2 and 3). Benzoquinones possessing one or two electron-donating substituent(s) gave better results (Entries 4 and 5) while electron-withdrawing substituents retarded the reaction (Entries 7 and 8). Thus, it is noted that the result turned slightly better if the reaction started at a lower temperature (Entry 6).

Next, the molar ratio of **1a**, methoxybenzoquinone (MBQ) and $TMSN_3$ was examined, and the results are summarized in Table 2. As the amount of $TMSN_3$ increased, the yields of

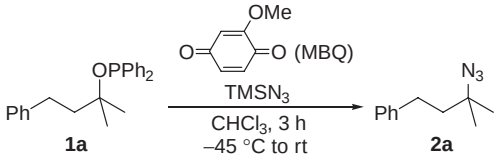
Table 1. Effect of quinone derivatives on azidation of **1a**



Entry	Quinone		Yield/%
1		R = H	56
2		R = Me	37
3		R = *t*-Bu	31[a]
4		R = OMe	57
5			58
6			63[b]
7	Fluoranil[c]		<7
8	DDQ		N. D.

[a]The reaction was carried out for 17 h. [b]The reaction temperature was −45 °C to room temperature. [c]Tetrafluoro-1,4-benzoquinone.

Table 2. Optimaization of reaction condition



1a **2a**

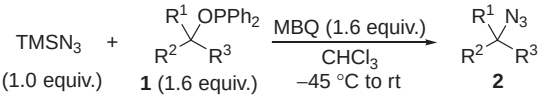
Entry	**1a** (equiv.)	$TMSN_3$ (equiv.)	MBQ (equiv.)	Yield/%
1	1.0	1.8	1.1	56
2	1.0	2.4	1.1	63
3	1.0	3.0	1.1	60
4	1.0	5.0	1.1	65
5	1.0	2.4	1.1	53[a]
6	1.0	2.4	1.1	20[b]
7	1.6	1.0	1.6	90[c]

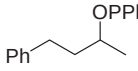
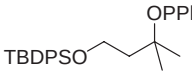
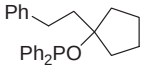
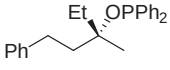
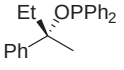
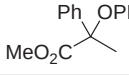
[a]MBQ was slowly added to the reaction mixture for 1 h at room temperature. [b]**1a** was slowly added to the reaction mixture for 3.5 h. [c]Yield based on $TMSN_3$.

2a became slightly better (Entries 1–4). It is noted that there were formed substantial amounts of the dehydrated alkenes, 4-phenyl-2-methylbut-2-ene and 4-phenyl-2-methylbut-1-ene, under these conditions. Further, slow addition of either MBQ (Entry 5) or $TMSN_3$ (Entry 6) was examined so as to suppress the formation of these alkenes. However, no substantial effect on the formation of dehydrated alkenes was observed irrespective of the rates of addition: i.e. **2a** was obtained in 53 and 20% yields, respectively. Then, **2a** was finally obtained in 90% yield when 1.6 molar amount of **1a** was used (Entry 7).

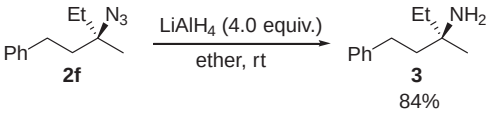
Next, the reactions of several secondary and tertiary alkyl phosphinites were examined under the optimized conditions[8] (Table 3): the secondary phosphinite **1b** afforded the azide in high yield (Entry 1). Tertiary alkyl phosphinites **1c**, **1d**, and **1f** were succsessfully converted into the corresponding azides in

Table 3. Generality of the azidation by $TMSN_3$



Entry	Phosphinite		Yield/%	Inversion[f]/%
1		*rac*-**1b**	92[a]	—
2		**1c**	67[b]	—
3		**1d**	79[b]	—
4		**1f** (80% ee)	83[b,c,d]	94
5		**1e** (98% ee)	57[b,c,e]	60
6		*rac*-**1g**	47[a]	—

[a]1.0 equiv. of **1**, 2.4 equiv. of $TMSN_3$, and 1.1 equiv. of MBQ was used. [b]Yield was based on $TMSN_3$. [c]The ratio of enantiomer was determined by HPLC analysis after reducing the azide to amine with $LiAlH_4$. [d]The desired product was obtained in 75% ee. [e]The desired product was obtained in 59% ee. [f]Inversion (%) was defined as (% ee of **2**)/(% ee of SM).



Scheme 2.

good yields (Entries 2–4) while the reaction of benzylic phosphinite **1e** or phosphinite having ester part (**1g**) gave the product in moderate yields (Entries 5 and 6). It is noteworthy that the inverted products **2f** were obtained with almost complete inversion of stereochemistry when the chiral phosphinite **1f** was employed as a substrate.

This reaction proceeded as presumed at the beginning (Scheme 1). The effect of the substituent of quinone derivatives on the reaction is considered as follows: since O-silylation of the intermediate **A** in Scheme 1 is irreversible and is playing an important role in carrying out this transformation, an electron-donating substituent of the quinone derivative enhances the nucleophilicity of the intermediate **A**.

Since the chiral azide **2f** was converted to the chiral amine **3** in good yield when **2f** was treated with lithium aluminum hydride in ether (Scheme 2), a concise method for the preparation of chiral amines from the corresponding alcohols was established.

Thus, it is noted that *tert*-alkyl azides are synthesized under neutral conditions by treating *tert*-alkyl phosphinites with $TMSN_3$ and MBQ. Chiral *tert*-alkyl azides were formed from the corresponding chiral *tert*-alcohols with almost complete inversion of configuration.

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References and Notes

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8 Typical experimental procedure for the preparation of **2f** is shown in the following; to a stirred solution of **1f** (232 mg, 0.64 mmol) in dry $CHCl_3$ (1.28 mL) were added 2-methoxy-1,4-benzoquinone (88.4 mg, 0.64 mmol) followed by trimethylsilyl azide (54.6 μL, 0.40 mmol) at −45 °C under argon atmosphere. The reaction mixture was allowed to warm to room temperature and was stirred for 3 h. The reaction mixture was directly purified by preparative TLC to afford **2f** (67.8 mg, 83%).

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