A NEW TYPE OF OXIDATION–REDUCTION CONDENSATION BY THE COMBINED USE OF PHENYL DIPHENYLPHOSPHINITE AND OXIDANT

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Dedicated to Professor Dr. Akira Suzuki on the occasion of his 80th birthday.

Abstract – A new type of oxidation–reduction condensation of alcohols with sulfur, nitrogen, and oxygen nucleophiles by the combined use of phenyl diphenylphosphininite (PhOPPh2) and oxidants such as azides or diethyl azodicarboxylate (DEAD) are described. In these reactions, chiral secondary and tertiary alcohols are converted into the corresponding chiral sulfides, azides, esters and ethers under mild and neutral conditions with almost complete inversion of stereochemical configuration.

INTRODUCTION
The fundamental concept of oxidation–reduction condensation is to perform dehydration condensation between two molecules by removing H2O as 2[H] and [O] by a combined use of a weak reductant and an oxidant. The characteristic feature of this reaction is that it proceeds under mild and neutral conditions without any assistance of acidic or basic promoters. In 1963, the first example of oxidation–reduction condensation was reported from our laboratory that two moles of carboxylic acids were dehydrated to form the corresponding acid anhydrides in high yields by combined use of diphenyl- or bis (p-methoxyphenyl)mercury (Ar2Hg) (hydrogen acceptor) and tributylphosphine (Bu3P) (oxygen acceptor) as shown in Scheme 1.1
It was reported also that the condensation reaction between Bz–L-Leu–OH and H–Gly–OEt proceeded smoothly in the presence of triphenylphosphine (PPh₃) and di(2-pyridyl)disulphide (PySSPy) to afford dipeptide, Bz–L-Leu–Gly–OEt, in high yield (Scheme 2).² Corey et al. developed an effective method for a macrocyclic lactone synthesis by treating a hydroxy carboxylic acid with PPh₃ and PySSPy,³ which was also applied to the syntheses of a number of important macrocyclic compounds including, erythronolide B,⁴ vermiculine,⁵ and enterobactin.⁶

Phosphoric esters were prepared by treating allyl diethyl phosphite and diethyl azodicarboxylate (DEAD) in the presence of alcohols (1967).⁷ Later, Mitsunobu applied this concept to an efficient dehydration condensation between alcohols and various nucleophiles such as carboxylic acids by using PPh₃ and DEAD in combination (Mitsunobu reaction).⁸ The scope of this reaction system was expanded to the alkylation reactions of various acidic components including phenols, imides, hydrogen azide, active methylene compounds, and thiols (Scheme 3).⁹ In recent years, Tsunoda et al. also demonstrated dehydration reactions by using novel phosphorane reagents such as cyanomethylenetri butylphosphorane (CMBP), which was applied to the nucleophiles having the high pKₐ values.¹⁰ After the efforts on these condensation reactions, however, a challenging problem still remained when bulky secondary or tertiary alcohols were used as a substrate because the formation of a key reaction intermediate, alkoxyphosphonium salt, was strongly interfered by steric hindrance of alcohols.¹¹
It was reported from our laboratory that the oxidation–reduction condensation\textsuperscript{12–17} of alkyl diphenylphosphinites (ROPPh\textsubscript{2}), that were prepared from the corresponding alcohols and chlorodiphenylphosphine, with various nucleophiles (Nu–H) gave the dehydrated condensation products (R–Nu) in the presence of benzoquinone derivatives as oxidants. It is noteworthy that chiral tert-alkyl diphenylphosphinites are converted into the corresponding chiral products with inversion of configuration when carboxylic acids,\textsuperscript{13} diethyl cyanophosphonate,\textsuperscript{14} 2-sulfanyl-1,3-benzothiazole,\textsuperscript{15} or trimethylsilyl azide\textsuperscript{17} was used as a nucleophile (Scheme 4). Then, in order to improve the synthetic utility of this reaction system, it is important to develop a new method for a direct synthesis of products from tert-alcohols and nucleophiles without preparing alkyl diphenylphosphinites in advance.

A new combination of phosphorus compound and oxidants, benzoquinone derivatives for direct synthesis of the condensation products from alcohols and nucleophiles was first examined. By using the above combination, condensation of an alcohol with a sulfur nucleophile such as 2-sulfanyl-1,3-benzothiazole...
(BtzSH) was tried as a model. Then, a new type of oxidation–reduction condensation by the combined use of phenyl diphenyolphosphinite (PhOPPh₂) and benzoquinone derivatives was found, which in turn was applied effectively to the thioetherification of various alcohols.¹⁸,¹⁹ When chiral sec-alcohols were used, the corresponding sulfides were obtained in good to excellent yields with inversion of configuration. On the other hand, chiral tert-alcohols bearing α-ester groups were converted into the inverted sulfides in moderate yield via alkoxyphosphonium salt C along with undesired olefins (Scheme 5). In order to improve the yields of tert-alkyl sulfides, another type of oxidation–reduction condensation reaction was next considered in which organic azides were employed as oxidants in place of the above mentioned benzoquinone derivatives.

![Scheme 5](image)

A reaction of organic azides with trivalent phosphorus compounds that affords the corresponding iminophosphoranes (aza-ylides) is known as the Staudinger reaction.²¹ Although this iminophosphorane is a versatile synthetic intermediate,²² there are only few papers reported on the intermolecular dehydration condensation reactions between alcohols and acidic compounds. Thus, the use of azide compounds as oxidants was tried next to confirm if this iminophosphorane works as an intermediate in the oxidation–reduction condensation because iminophosphorane C would be expected to be equivalent to the betaine A or B (Scheme 6).

In this article, we would like to describe a new type of oxidation–reduction condensation by using PhOPPh₂ and the oxidants such as azides or DEAD that leads to novel C–S¹⁸,¹⁹,²⁴, C–N²⁵ and C–O bond forming reactions together with their applicabilities.
**CARBON–SULFUR BOND FORMING REACTION**

The carbon–sulfur bond forming reaction by way of Mitsunobu reaction (PPh₃–DEAD) is recognized as versatile preparative methods of various sulfides and thioesters from the corresponding alcohols and sulfur nucleophiles such as thiols or thioacetic acid.²⁶,²⁷ In this reaction, chiral sulfides and thioesters were formed from the corresponding chiral sec-alcohols with inversion of configuration. However, it is generally known that sterically-hindered tert-alcohols are not converted to the corresponding sulfides and thioesters. Therefore, the oxidation–reduction condensation by using a combination of PhOPPh₂ and azide compound, an oxidant, was examined so as to develop a method of converting tert-alcohols to the corresponding sulfides via SN₂ nucleophilic substitution.

In order to find the most suitable oxidant, commercially available various azides were examined in the first place by taking the condensation reaction of 4-phenylbutan-2-ol (1a) and BtzSH in the presence of PhOPPh₂ (Table 1). A condensation reaction using trimethylsilylmethyl azide afforded the desired product 2a in moderate yield while alkyl azides such as benzyl azide and ethyl azidoacetate gave 2a in good yields (Entries 1–3). When the reactions were carried out in toluene instead of 1,2-dichloropropane, the yields increased up to 81 and 84%, respectively (Entries 2 and 3). On the other hand, 1-azidoadamantane, diphenylphosphoryl azide, or trimethylsilyl azide did not work well (Entries 4–6).

Next, thioetherification of various tert-alcohols was tried in order to examine the scope of this reaction under the optimized conditions (Table 2). The reaction of tert-alcohol 1b having an α-ester group afforded the corresponding sulfide also in high yield, while the cases with 1c and 1d that bear α-ketone and α-phenyl groups were moderate (Entries 1–3). With an aliphatic substrate 1e, the yield of the desired sulfide markedly decreased because of the elimination reactions that accompanied to give undesired olefins (Entry 4).
Taking the above results into consideration, thioetherification of various chiral alcohols were next tried in order to examine the stereochemistry of this reaction (Table 3). A reaction of chiral sec-alcohol 1a proceeded smoothly to afford the corresponding sulfide in excellent yield with complete inversion of stereochemistry (Entry 1). Chiral benzylic alcohol 1f and propargylic alcohol 1g also gave the desired products in high yields with high enantiomeric excesses (Entries 2 and 3). The thioetherification of sterically-hindered (−)-(l)-menthol (1h) gave the inverted product in high yield without accompanying any other products (Entry 4). Further, more hindered tert-alcohols 1i–1l were tried as substrates in order
to find potential applicability of this reaction to the asymmetric construction of quaternary carbon. Then, a reaction of chiral tert-alcohol 1i having an \( \alpha \)-ester group was found to proceed smoothly and afforded the corresponding sulfide in good yield with complete inversion of stereochemistry (Entry 5). Similarly, chiral benzylic alcohol 1j gave the desired product in high yield with excellent enantiomeric excess (Entry 6). Also, thioetherification of chiral propargylic alcohol 1k gave the inverted product in high yield (Entry 7). On the other hand, the reaction of (R)-terpinen-4-ol (1l) did not take place under the above conditions and 1l was recovered, which is probably because its bulky isopropyl group interfered the attack of 1l on the positively charged phosphorus atom (Entry 8).

<table>
<thead>
<tr>
<th>Entry</th>
<th>ROH</th>
<th>1 (%ee)</th>
<th>Temp., Time</th>
<th>Product</th>
<th>2 Yield/%a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>1a (&gt;99)</td>
<td>40 °C, 24 h</td>
<td>Ph</td>
<td>2a 99 (99)</td>
</tr>
<tr>
<td>2c</td>
<td></td>
<td>1f (&gt;99)</td>
<td>rt, 12 h</td>
<td>Ph</td>
<td>2f 83 (97)</td>
</tr>
<tr>
<td>3c</td>
<td></td>
<td>1g (98)</td>
<td>rt, 24 h</td>
<td>Ph</td>
<td>2g 89 (98)</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>1h</td>
<td>80 °C, 6 h</td>
<td>Ph</td>
<td>2h 85</td>
</tr>
<tr>
<td>5d</td>
<td></td>
<td>1i (&gt;99)</td>
<td>40 °C, 48 h</td>
<td>Et</td>
<td>2i 76 (99)</td>
</tr>
<tr>
<td>6d</td>
<td></td>
<td>1j (&gt;99)</td>
<td>40 °C, 48 h</td>
<td>Me</td>
<td>2j 90 (99)</td>
</tr>
<tr>
<td>7c,d</td>
<td></td>
<td>1k (92)</td>
<td>27 °C, 48 h</td>
<td>Me</td>
<td>2k 87 (92)</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>1l</td>
<td>40 °C, 48 h</td>
<td>Ph</td>
<td>2l N.R.</td>
</tr>
</tbody>
</table>

*aIsolated yield. bDetermined by HPLC analysis. cThe solution of PhOPPh\(_2\) and ethyl azidoacetate was stirred at 80 °C for 20 min, followed by addition of alcohol and BtzSH at rt. dThe reaction was carried out by using BtzSH (4.0 equiv), PhOPPh\(_2\) (4.0 equiv) and ethyl azidoacetate (4.0 equiv).*
Next, reactions of various arenethiols with tert-alcohol 1b were examined in order to extend the scope of this reaction (Table 4). When benzenethiol derivatives were used as sulfur nucleophiles, the order of increase in the yields is as follows: 4-nitrobenzenethiol (pKₐ 5.11 in EtOH/H₂O, 5.5 in DMSO)²⁸ > benzenethiol (pKₐ 7.76 in EtOH/H₂O, 10.3 in DMSO)²⁸ > 4-methoxybenzenethiol (pKₐ 7.99 in EtOH/H₂O, 11.2 in DMSO)²⁸ (Entries 1–3). These results indicate that the yields are influenced by the pKₐ values of nucleophiles.¹²,¹⁶,²⁹ It is considered that deprotonation of thiol having low pKₐ value by iminophosphorane proceeds effectively to afford the desired product in high yield. Also, the reactivity of 5-nitro-2-sulfanylpyridine was shown to be higher than that of 2-sulfanylpyridine (Entries 4 and 5). Further, the reactions of various heteroarenethiols were examined (Entries 6–9). It was found then that 1-methyl-1H-tetrazole-5-thiol could also be used successfully in this reaction (Entry 6), and 2-sulfanyl-1,3-benzothiazole (BtzSH; pKₐ 7.00 in EtOH/H₂O)³⁰ was the most reactive of the heteroarene thiols (Entry 7). When thiobenzoic acid (pKₐ 5.3 in DMSO)³¹ was used, the yield of the desired product was poor though its acidity was sufficient (Entry 10).³²

<table>
<thead>
<tr>
<th>Entry</th>
<th>ArSH</th>
<th>Product 3</th>
<th>Yield/%a</th>
<th>Entry</th>
<th>ArSH</th>
<th>Product 3</th>
<th>Yield/%a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HS-</td>
<td>3a</td>
<td>44 (83)b</td>
<td>6</td>
<td>HS-</td>
<td>3f</td>
<td>83 (68)b</td>
</tr>
<tr>
<td>2</td>
<td>HS-NO₂</td>
<td>3b</td>
<td>85 (72)b</td>
<td>7</td>
<td>HS-</td>
<td>2b</td>
<td>94 (90)b</td>
</tr>
<tr>
<td>3</td>
<td>HS-OMe</td>
<td>3c</td>
<td>19 (78)b</td>
<td>8</td>
<td>HS-NO₂</td>
<td>3g</td>
<td>91 (83)b</td>
</tr>
<tr>
<td>4</td>
<td>HS-N</td>
<td>3d</td>
<td>72 (67)b</td>
<td>9</td>
<td>HS-</td>
<td>3h</td>
<td>89 (82)b</td>
</tr>
<tr>
<td>5</td>
<td>HS-NO₂</td>
<td>3e</td>
<td>97 (21)b</td>
<td>10</td>
<td>HS-Ph</td>
<td>3i</td>
<td>34 (19)b</td>
</tr>
</tbody>
</table>

²Isolated yield. ᵃ²,6-Di-tert-butyl-1,4-benzoquione was used instead of ethyl azidoacetate. See ref. 19.

In order to confirm further the utility of the above results, condensation of chiral tert-alcohols 1i and 1j with BtzSH were examined with other oxidation–reduction systems (Table 5). Then, it was shown that the reaction using PhOPPh₂ and oxidants such as DEAD, DMBQ and N₅CH₂CO₂Et afforded the desired sulfides with inversion of configuration while the PPh₃–DEAD system (Mitsunobu conditions) did not. The yields of products 2i and 2j were found to increase in the order of PhOPPh₂–N₅CH₂CO₂Et >
PhOPPh₂–DMBQ > PhOPPh₂–DEAD > PPh₃–DEAD combination systems. Therefore, it is noted that PhOPPh₂ is an essential reductant for thioetherification of tert-alcohols.

Table 5. Yields and enantiomeric excesses (in parentheses) in thioetherification of tertiary alcohols

<table>
<thead>
<tr>
<th>ROH 1</th>
<th>Reagent</th>
<th>PPh₃ DEAD</th>
<th>PhOPPh₂ DEAD</th>
<th>DMBQ¹</th>
<th>N₂CH₂CO₂Et</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me₂CO₂Bn</td>
<td>1i</td>
<td>trace</td>
<td>43 (&gt;99)</td>
<td>55 (&gt;99)</td>
<td>76 (&gt;99)</td>
</tr>
<tr>
<td>Me₂CO₂Me</td>
<td>1j</td>
<td>N.D.</td>
<td>53 (&gt;99)</td>
<td>56 (&gt;99)</td>
<td>90 (99)</td>
</tr>
</tbody>
</table>

¹The reaction was carried out at rt for 24 h.

A plausible reaction mechanism is shown in Scheme 7: the Staudinger reaction of PhOPPh₂ with an azide compound initially affords an iminophosphorane followed by a successively deprotonation of BtzSH results in the formation of phosphonium salt A. A subsequent nucleophilic attack of an alcohol on the positively charged phosphorus atom leads to the formation of alkoxyphosphonium salt B which is a key intermediate, and the following nucleophilic attack of thiolate anion (BtzS⁻) on the carbon atom adjacent to an oxygen atom of alkoxy group via SN2 substitution gives the inverted sulfide.

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PhOPPh₂ + RN₃ → \[ \text{PhOPPh₂} + \text{RN₃} \rightarrow \text{PhO-P=N-R} \]
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Scheme 7

As the chiral tert-alkyl Btz sulfide 2j was converted to the corresponding chiral thiol in high yield on treatment with LiAlH₄,¹⁵ a concise method for the preparation of chiral thiols from the corresponding alcohols was established (Scheme 8).
Thus, a new type of oxidation–reduction condensation by using a combination of PhOPPh₂ and azide compounds was established. Chiral sec- and tert-alkyl sulfides were formed from the corresponding chiral alcohols with almost complete inversion of configuration under mild and neutral conditions. This is the first example of the direct and stereospecific synthesis of an inverted chiral tert-alkyl sulfide from a chiral tert-alcohol via an SN₂ displacement.

**CARBON–NITROGEN BOND FORMING REACTION**

Conversion of alcohols to their corresponding azides is one of the most important functional group transformations in organic synthesis. The most fundamental method known for azidation is the Mitsunobu reaction that uses hydrogen azide, diphenyl phosphorazidate (DPPA) or zinc azide/bis-pyridine complex. More recently, methods using DPPA/DBU, p-NO₂DPPA/DBU and so forth have been reported. In all these reactions, chiral sec-alkyl azides are formed from chiral sec-alcohols with complete inversion of configuration via SN₂ displacement. On the other hand, sterically-hindered tert-alcohols are not known to be converted to the corresponding tert-alkyl azides. Therefore, it is desired to develop a convenient method for tert-alcohols to be transformed into the inverted azides. Next the application of the above oxidation–reduction condensation to stereospecific azidation of alcohols was studied by using a combination of PhOPPh₂ and an azide compound as oxidants.

![Scheme 8](image)

**Table 6. Optimization of reaction conditions**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Azide</th>
<th>Oxidant</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1c</td>
<td>Bu₄N₃</td>
<td>N₃CH₂Ph</td>
<td>N.D.</td>
</tr>
<tr>
<td>2c</td>
<td>DPPA</td>
<td>N₃CH₂Ph</td>
<td>34</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>N₃CH₂Ph</td>
<td>57</td>
</tr>
<tr>
<td>4</td>
<td>TMSN₃</td>
<td>N₃CH₂CO₂Et</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>AdN₃</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>N₃CH₂TMS</td>
<td>82</td>
</tr>
</tbody>
</table>

*a*The solution of PhOPPh₂ and oxidant was stirred at 80 °C for 20 min, followed by addition of alcohol and Azide at rt. *b*Isolated yield. *c*The reaction time was 24 h.
In order to find the most suitable azidation reagent, a reaction using tert-alcohol 1j in the presence of PhOPPh2 and benzyl azide was first examined (Table 6, Entries 1–3). The reaction using tetrabutylammonium azide did not afford the desired azide 4j while DPPA gave 4j in low yield. In the case with TMSN3, the yield of 4j increased up to moderate yield and therefore TMSN3 was chosen as the reagent for the present azidation. Next, various azide compounds were examined to find which was the suitable oxidant (Entries 4–6). The use of ethyl azidoacetate and 1-azidoadamantane was then shown to lower the yield while trimethylsilylmethyl azide gave 4j in high yield.

A suitable azidation reagent and an oxidant were then chosen and condensation reaction of various chiral alcohols with TMSN3 was tried in order to examine the scope of this reaction under the optimized conditions (Table 7). A reaction of chiral sec-alcohol 1a proceeded smoothly to afford the corresponding

Table 7. Azidation of various chiral alcohols

<table>
<thead>
<tr>
<th>Entry</th>
<th>ROH</th>
<th>1 (%ee)</th>
<th>Product</th>
<th>4 Yield/%a (%ee)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>1a (&gt;99)</td>
<td>Ph</td>
<td>quant (&gt;99)b</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>1m (&gt;99)</td>
<td>Ph</td>
<td>98 (&gt;99)c</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>1n (&gt;99)</td>
<td>Ph</td>
<td>85 (97)b</td>
</tr>
<tr>
<td>4d,e</td>
<td>Me</td>
<td>1i (&gt;99)</td>
<td>Me</td>
<td>84 (96)f</td>
</tr>
<tr>
<td>5d,g</td>
<td>Ph</td>
<td>1j (&gt;99)</td>
<td>Me</td>
<td>86 (&gt;99)b</td>
</tr>
<tr>
<td>6d,g</td>
<td>Et</td>
<td>1o (80)</td>
<td>Et</td>
<td>86 (61)c</td>
</tr>
</tbody>
</table>

*aIsolated yield. bThe ratio of enantiomer was determined by HPLC analysis after reducing the azide (4a, 4n, 4j) to the corresponding amines. cThe ratio of enantiomer was determined by HPLC analysis. dPhOPPh2 (3.0 equiv), trimethylsilylmethyl azide (3.0 equiv), TMSN3 (3.0 equiv) were used. eThe reaction time was 24 h. fThe ratio of enantiomer was determined by HPLC analysis after converting the azide to 1,4-disubstituted 1,2,3-triazole. gThe reaction time was 48 h.
azide in quantitative yield with complete inversion of stereochemistry (Entry 1). The reaction of sec-alcohol 1m having an α-ester group also afforded the inverted azide in high yield (Entry 2). When benzylic alcohol such as (S)-1-(2-naphthyl)ethanol (1n) was employed, the desired product was obtained in high yield with almost complete inversion (Entry 3). Further, tert-alcohols were tried as substrates so as to investigate potential application of this reaction to the asymmetric construction of quaternary carbon. Then, the reaction of chiral tert-alcohol 1i having an α-ester group was found to proceed smoothly to afford the corresponding azide in high yield with high enantiomeric excess (Entry 4). Similarly, chiral benzylic alcohol 1j with an α-ester group gave the desired product in high yield with complete inversion of stereochemistry while enantiomeric excess of the desired product was lowered if chiral tert-alcohol 1o with an α-ester group was used (Entries 5 and 6). When azidation of tert-alcohol 1o (80%ee) was performed at 0 ºC, the desired product was obtained with almost complete inversion (78%ee) though the yield was lowered to 44% because of the undesired trimethylsilyl ether 5 produced (Scheme 9).

![Scheme 9](image)

The chiral tert-alkyl azides 4j is reduced into the corresponding chiral tert-alkyl amine in high yield by hydrogenation, therefore, a concise method for the preparation of chiral amines from the corresponding alcohols is established (Scheme 10). In hydrogenation process, tert-alkyl azides 4i is converted into the corresponding α,α-disubstituted α-amino acid 6 (isovaline) and the optical rotation of 6 was also in good agreement with the reported value concerning sign and absolute value41 (Scheme 11). Also, the azide 4i is converted into 1,4-disubstituted 1,2,3-triazole on treatment with phenylacetylene in the presence of CuSO₄·5H₂O and sodium ascorbate (Scheme 12).

![Scheme 10](image)

![Scheme 11](image)
A plausible reaction mechanism is shown in Scheme 13: a reaction of PhOPPh$_2$ and trimethylsilylmethyl azide affords initially the corresponding iminophosphorane which in turn results in forming of phosphonium salt A by subsequent N-silylation with trimethylsilyl azide. The following nucleophilic attack of an alcohol to the positively charged phosphorus atom leads to alkoxycarboxonium salt B which is a key intermediate. Finally, a nucleophilic attack of the azide anion (N$_3^-$) to the carbon atom adjacent to an oxygen atom of alkoxy group via S$_{N}2$ manner gave the inverted azide.

**Scheme 13**

**CARBON–OXYGEN BOND FORMING REACTION**

Stereoinversion of a chiral sec-alcohol is a versatile method for constructing a new chiral center and is commonly carried out by condensation of a sec-alcohol with a carboxylic acid under Mitsunobu conditions followed by hydrolysis of the resulting ester. However, it is also known that Mitsunobu reaction is not applicable to the sterically-hindered tert-alcohols. Then, the application of the above oxidation–reduction condensation to oxygen nucleophiles was next studied in order to develop a new method for stereoinversion of a chiral tert-alcohol.

In order to find a most reactive oxygen nucleophile and a suitable oxidant, reactions of tert-alcohol 1i with various carboxylic acids were first examined in the presence of PhOPPh$_2$ and various oxidants (Table 8, Entries 1–7). The esterification of tert-alcohol 1i with benzoic acid did not give good results under any oxidants such as benzyl azide, DMBQ or DEAD (Entries 1–3). As a result of the examination...
Table 8. Optimization of reaction conditions\textsuperscript{a}

\begin{tabular}{cccccc}
Entry & Nucleophile & Oxidant & Temp., Time & Yield/%\textsuperscript{a} \\
1 & \(\text{C}_6\text{H}_5\text{CO}_2\text{H}\) & \(\text{N}_3\text{CH}_2\text{Ph}\) & rt, 24 h & N.D. \\
2 & \(\text{C}_6\text{H}_5\text{CO}_2\text{H}\) & \(\text{DMBQ}\) & rt, 24 h & trace \\
3 & \(2\text{-NO}_2\text{C}_6\text{H}_5\text{CO}_2\text{H}\) & \(\text{DEAD}\) & rt, 24 h & 5 \\
4 & \(4\text{-NO}_2\text{C}_6\text{H}_5\text{CO}_2\text{H}\) & \(\text{DEAD}\) & rt, 1 h & 52 \\
5 & \(2\text{-MeOC}_6\text{H}_5\text{CO}_2\text{H}\) & \(\text{DEAD}\) & rt, 72 h & 24 \\
6 & \(4\text{-MeOC}_6\text{H}_5\text{CO}_2\text{H}\) & \(\text{DEAD}\) & rt, 24 h & N.D. \\
8 & \(\text{BtzOH}\) & \(\text{N}_3\text{CH}_2\text{Ph}\) & 40 °C, 24 h & trace \\
9 & \(\text{BtzOH}\) & \(\text{N}_3\text{CH}_2\text{CO}_2\text{Et}\) & 40 °C, 24 h & trace \\
10 & \(\text{BtzOH}\) & \(\text{DMBQ}\) & 0 °C, 24 h & 49 \\
11 & \(\text{BtzOH}\) & \(\text{DEAD}\) & 0 °C, 1 h & 60 \\
\hline
\end{tabular}

\textsuperscript{a}Isolated yield.

Table 9. Reactions of various tert-alcohols with oxygen nucleophiles

\begin{tabular}{cccccc}
Entry & ROH & \(\text{1}\) (1.0 equiv) & \(2\text{-NO}_2\text{C}_6\text{H}_5\text{CO}_2\text{H}\) or \(\text{BtzOH}\) (2.0 equiv) & \(\text{PhOPPPh}_2\) (2.0 equiv) & \(\text{DEAD}\) (2.0 equiv) & \(\text{R}^4\text{OR}^4\) \\
1 & \(\text{Me}_3\text{OH}\) & \(\text{Me}_3\text{CO}_2\text{Bn}\) & \(\text{BtzOH}\) & rt, 1 h & 7 or 8 & Yield/%\textsuperscript{a} \\
2\textsuperscript{b} & \(\text{Me}_3\text{OH}\) & \(\text{Me}_3\text{CO}_2\text{Bn}\) & \(\text{BtzOH}\) & rt, 1 h & 7 or 8 & Yield/%\textsuperscript{a} \\
3\textsuperscript{c} & \(\text{Ph}_3\text{OH}\) & \(\text{Ph}_3\text{CO}_2\text{Bn}\) & \(\text{BtzOH}\) & rt, 1 h & 7 or 8 & Yield/%\textsuperscript{a} \\
4\textsuperscript{c} & \(\text{Ph}_3\text{OH}\) & \(\text{Ph}_3\text{CO}_2\text{Bn}\) & \(\text{BtzOH}\) & rt, 1 h & 7 or 8 & Yield/%\textsuperscript{a} \\
5 & \(\text{Me}_3\text{OH}\) & \(\text{Me}_3\text{CO}_2\text{Bn}\) & \(\text{BtzOH}\) & rt, 1 h & 7 or 8 & Yield/%\textsuperscript{a} \\
6\textsuperscript{b,d} & \(\text{Me}_3\text{OH}\) & \(\text{Me}_3\text{CO}_2\text{Bn}\) & \(\text{BtzOH}\) & rt, 1 h & 7 or 8 & Yield/%\textsuperscript{a} \\
7 & \(\text{Ph}_3\text{OH}\) & \(\text{Ph}_3\text{CO}_2\text{Bn}\) & \(\text{BtzOH}\) & rt, 1 h & 7 or 8 & Yield/%\textsuperscript{a} \\
8\textsuperscript{b} & \(\text{Ph}_3\text{OH}\) & \(\text{Ph}_3\text{CO}_2\text{Bn}\) & \(\text{BtzOH}\) & rt, 1 h & 7 or 8 & Yield/%\textsuperscript{a} \\
\hline
\end{tabular}

\textsuperscript{a}Isolated yield. \textsuperscript{b}The reaction was carried out at 0 °C. \textsuperscript{c}The reaction was carried out at 80 °C. \textsuperscript{d}The reaction time was 24 h.

of the influence of substituents on the aromatic carboxylic acid in the presence of DEAD, the desired product was found to obtain in 52% yield when 2-nitrobenzoic acid was used as a nucleophile (Entry 4). Because 2-sulfanyl-1,3-benzothiazole (BtzSH) showed high nucleophilicity as a sulfur nucleophile as
shown in Table 3, etherification using 2-hydroxy-1,3-benzothiazole (BtzOH) as an oxygen nucleophile was further examined (Entries 8–11). A reaction of tert-alcohol 1i and BtzOH in the presence of azide compounds as an oxidant scarcely afforded the desired product while the use of DMBQ gave the corresponding product in 49% yield (Entries 8–10). On the other hand, the yield of the desired product increased to 60% in the case of using DEAD (Entry 11). Thus, it is apparent that 2-nitrobenzoic acid and BtzOH were suitable nucleophiles in this reaction system.

Next, esterification and etherification of various tert-alcohols was tried in order to examine the scope of this reaction under the optimized conditions (Table 9). The reactions of tert-alcohol 1b having an α-ester group afforded either ester and ether in good yields (Entries 1 and 2) while it was moderate in the cases with 1c bearing α-ketone (Entries 3 and 4). Also, the reactions of benzylic alcohol 1d or aliphatic substrate 1e afforded the corresponding products in moderate yields along with undesired olefins (Entries 5–8).

**Table 10. Reactions of various tert-alcohols with oxygen nucleophiles**

| Entry | ROH | Product  | R^4  | 7 or 8 Yield/% | ee/%
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>PhOH</td>
<td>MePh</td>
<td>2-NO_2-C_6H_4CO</td>
<td>7a</td>
<td>91 &gt;99</td>
</tr>
<tr>
<td>2</td>
<td>MeOH</td>
<td>MeMe</td>
<td>2-NO_2-C_6H_4CO</td>
<td>7i</td>
<td>52 96</td>
</tr>
<tr>
<td>3</td>
<td>EtCO_2Bn</td>
<td>EtCO_2Bn</td>
<td>Btz</td>
<td>8i</td>
<td>60^d 96</td>
</tr>
<tr>
<td>4</td>
<td>MeOH</td>
<td>MeMe</td>
<td>2-NO_2-C_6H_4CO</td>
<td>7j</td>
<td>42 85</td>
</tr>
<tr>
<td>5</td>
<td>PhCO_2Me</td>
<td>PhCO_2Me</td>
<td>Btz</td>
<td>8j</td>
<td>54 94</td>
</tr>
<tr>
<td>6</td>
<td>PhetO_2C</td>
<td>PhetO_2C</td>
<td>2-NO_2-C_6H_4CO</td>
<td>7o</td>
<td>32 78</td>
</tr>
<tr>
<td>7</td>
<td>MePh</td>
<td>MeMe</td>
<td>2-NO_2-C_6H_4CO</td>
<td>7o</td>
<td>32 78</td>
</tr>
</tbody>
</table>

*a*Isolated yield. *b*Determined by HPLC analysis. *c*The reaction was carried out at 0 °C. *d*When the reaction was carried out at 100 °C for 24 h under Mitsunobu conditions (PPh_3/DEAD), the desired product was scarcely obtained.

Taking the above results into consideration, reactions of various chiral alcohols were next tried in order to examine the stereochemistry of this reaction (Table 10). The esterification of sec-alcohol 1a proceeded smoothly to afford the corresponding ester in excellent yield with complete inversion of stereochemistry (Entry 1). The esterification and etherification of chiral tert-alcohol 1i having an α-ester group afforded
the corresponding products (7i and 8i) in moderate yield with high enantiomeric excess while 8i was scarcely obtained under Mitsunobu condition (Entries 2–3). Chiral benzylic alcohol 1j gave the desired products also in moderate yield but with slightly lowered optical purity (Entries 4 and 5). In the case of chiral tert-alcohol 1o, the corresponding products were obtained in moderate yield with almost complete inversion (Entries 6 and 7).

A plausible reaction mechanism is shown in Scheme 14: a reaction of PhOPPh2 and DEAD initially affords the corresponding betaine followed by successive deprotonation of 2-nitrobenzoic acid or BtzOH to result in the formation of phosphonium salt A. A subsequent nucleophilic attack of an alcohol on the positively charged phosphorus atom leads to the formation of alkoxyphosphonium salt B which is a key intermediate, and the following nucleophilic attack of carboxylate anion or aryloxy anion (BtzO–) on the carbon atom adjacent to an oxygen atom of alkoxy group via S$_2$2 substitution gives the inverted product.

As the chiral ester 7j or ether 8j treated by NaOMe or LiAlH$_4$ was converted to the corresponding chiral alcohol in high or moderate yield, respectively, (Scheme 15 and 16), a new method for stereoinversion of chiral tert-alcohols was established.
In summary, a new type of oxidation–reduction condensation by the combined use of PhOPPh₂ and oxidants such as azides or DEAD was established. It is noted that this reaction system was applicable to stereospecific C–S, C–N and C–O bond forming reaction from chiral sec- and tert-alcohols under mild and neutral conditions.

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