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

Teruaki Mukaiyama,*[1] Kiichi Kuroda,[2] and Yuji Maruyama[3]

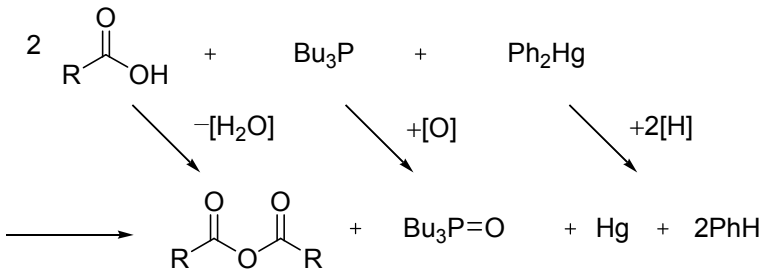
[1]Tokyo Chemical Industry Co., Ltd., 6-15-5 (TCI) Toshima, Kita-ku, Tokyo 114-0003, Japan
[2]Department of Applied Chemistry, Faculty of Science, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan
[3]Department of Industrial Chemistry, Faculty of Engineering, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan
E-mail; mukaiyam@abeam.ocn.ne.jp

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 diphenylphosphinite ($PhOPPh_2$) 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.

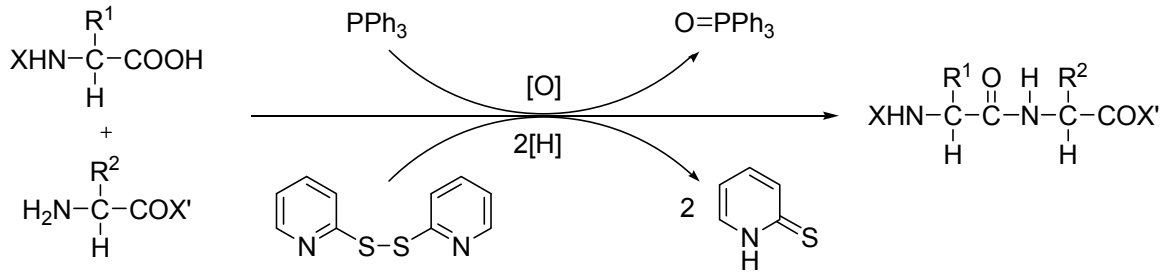
INTRODUCTION

The fundamental concept of oxidation–reduction condensation is to perform dehydration condensation between two molecules by removing H_2O 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 (Ar_2Hg) (hydrogen acceptor) and tributylphosphine ($^nBu_3P$) (oxygen acceptor) as shown in Scheme 1.[1]



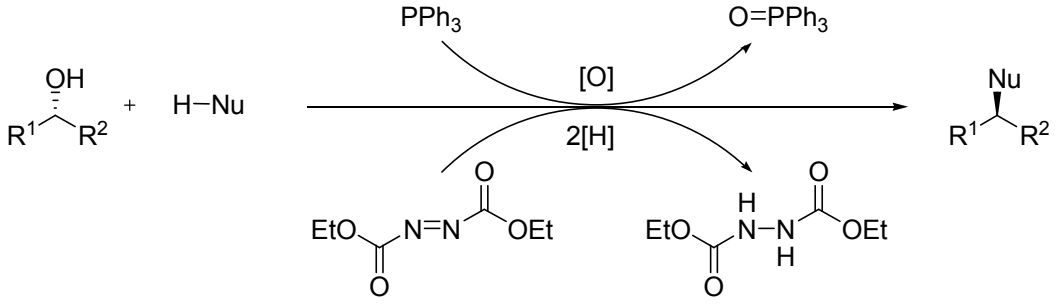
Scheme 1

It was reported also that the condensation reaction between Bz–$_L$-Leu–OH and H–Gly–OEt proceeded smoothly in the presence of triphenylphosphine (PPh_3) and di(2-pyridyl)disulfide (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 hydroxycarboxylic acid with PPh_3 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]



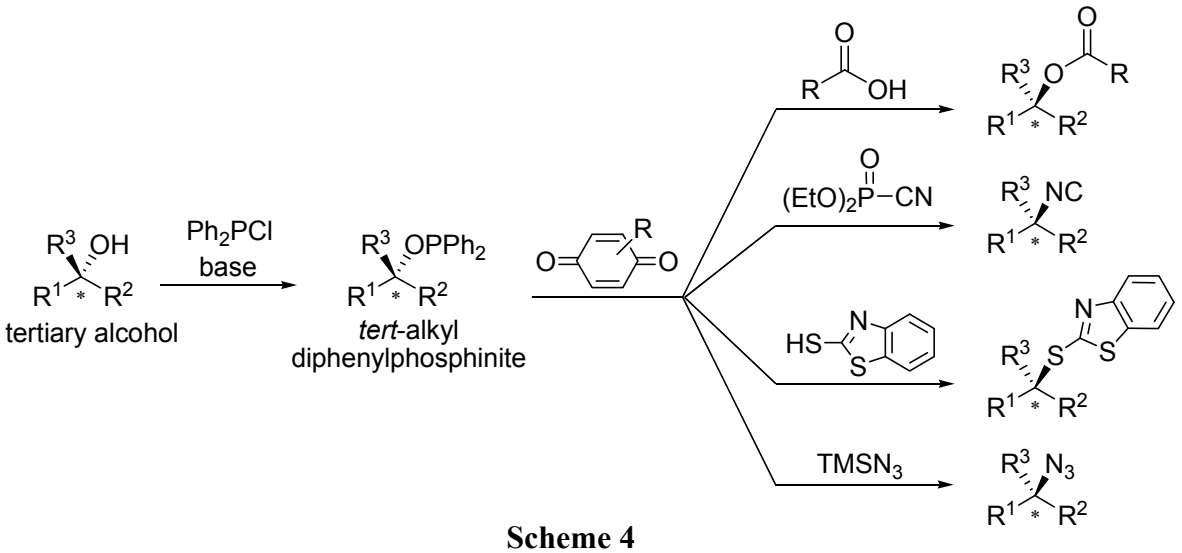
Scheme 2

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 PPh_3 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 cyanomethylenetributylphosphorane (CMBP), which was applied to the nucleophiles having the high pK_a 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]



Scheme 3

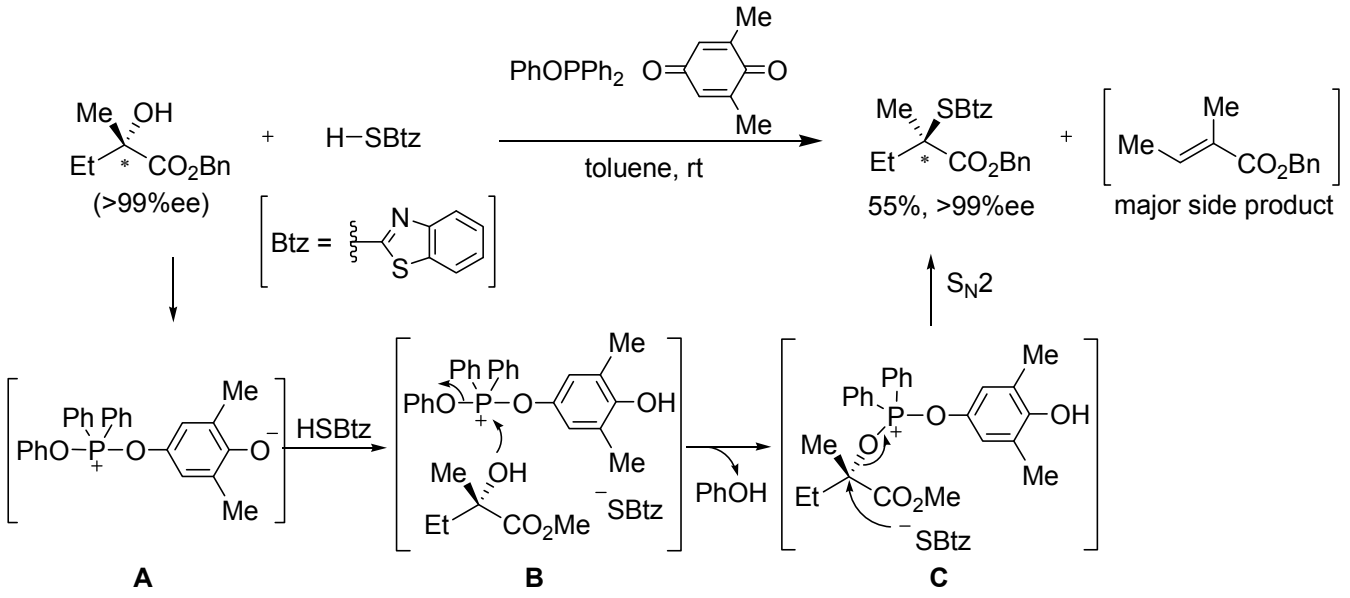
It was reported from our laboratory that the oxidation–reduction condensation[12–17] of alkyl diphenylphosphinites ($ROPPh_2$), that were prepared from the corresponding alcohols and chlorodiphenylphosphine, with various nucleophiles (Nu–H) gave the dehydrated condensation products (R–Nu) in the presence 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,[13] diethyl cyanophosphonate,[14] 2-sulfanyl-1,3-benzothiazole,[15] or trimethylsilyl azide[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.



Scheme 4

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

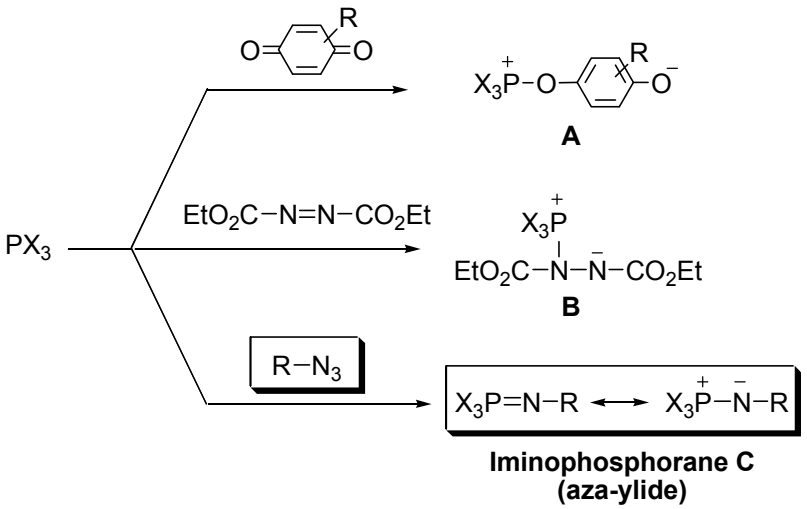
(BtzSH) was tried as a model. Then, a new type of oxidation–reduction condensation by the combined use of phenyl diphenylphosphinite ($PhOPPh_2$) and benzoquinone derivatives was found, which in turn was applied effectively to the thioetherification of various alcohols.[18,19] When chiral *sec*-alcohols 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

A reaction of organic azides[20] 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[23] 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 $PhOPPh_2$ and the oxidants such as azides or DEAD that leads to novel C–S[18,19,24], C–N[25] and C–O bond forming reactions together with their applicabilities.



Scheme 6

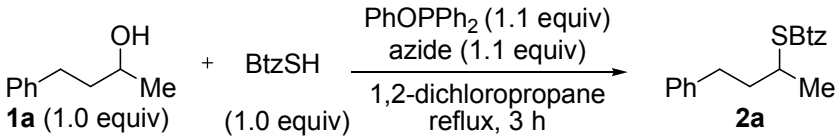
CARBON–SULFUR BOND FORMING REACTION

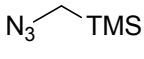
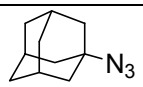
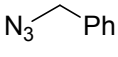
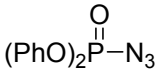
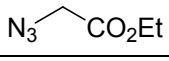
The carbon–sulfur bond forming reaction by way of Mitsunobu reation (PPh_3–DEAD) is recognized as versatile preparative methods of various sulfides and thioesters from the corresponding alcohols and sulfur nucleophiles such as thiols or thioacetic acid.[26,27] In this reaction, chiral sulfides and thioesters 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 $PhOPPh_2$ and azide compound, an oxidant, was examined so as to develop a method of converting *tert*-alcohols to the corresponding sulfides via S_N2 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 $PhOPPh_2$ (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).

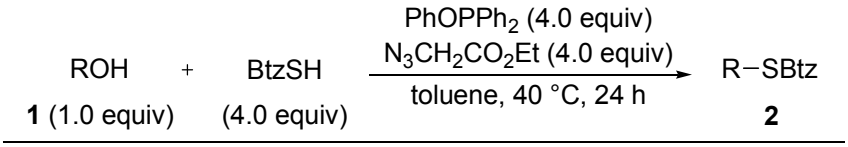
Table 1. Screening of azide compounds

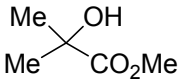
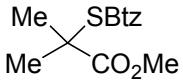
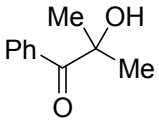
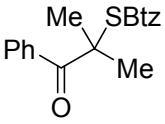
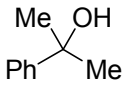
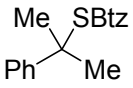
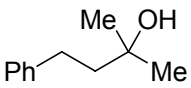
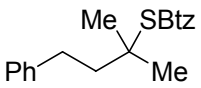


Entry	Azide	Yield/%[a]	Entry	Azide	Yield/%[a]
1		53	4		34
2		67 (81)[b]	5		N.D.
3		69 (84)[b]	6	$TMSN_3$	7

[a]Isolated yield. [b]Toluene was used instead of 1,2-dichloropropane.

Table 2. Thioetherification of various *tert*-alcohols



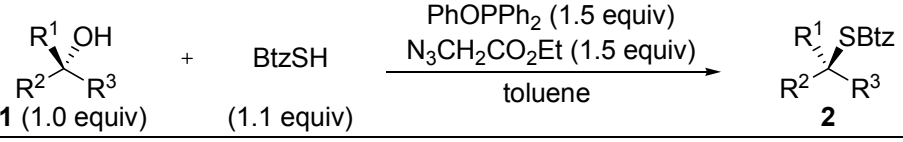
Entry	ROH	1	Product	2	Yield/%[a]
1[b]		**1b**		**2b**	94
2		**1c**		**2c**	42
3		**1d**		**2d**	53
4		**1e**		**2e**	17

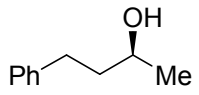
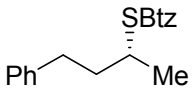
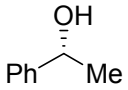
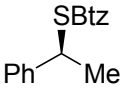
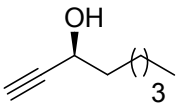
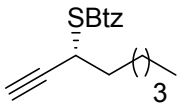
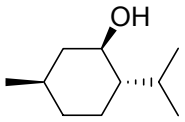
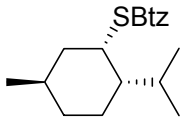
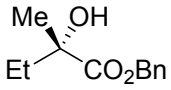
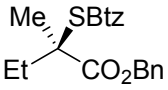
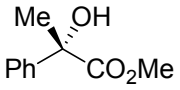
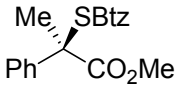
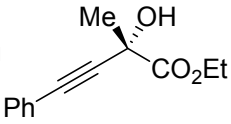
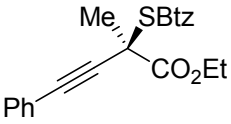
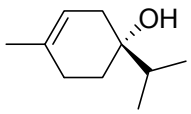
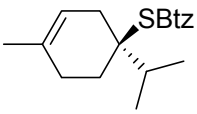
[a]Isolated yield. [b]The reaction was carried out by using BtzSH (2.0 equiv), $PhOPPh_2$ (2.0 equiv) and $N_3CH_2CO_2Et$ (2.0 equiv).

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 α-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 3. Thioetherfication of various chiral alcohols

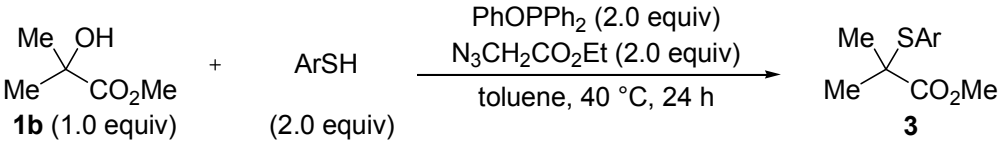


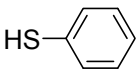
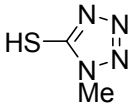
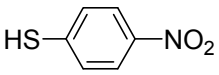
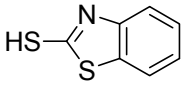
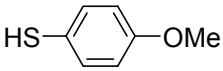
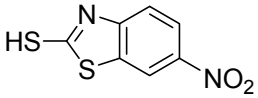
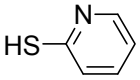
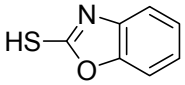
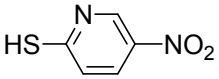
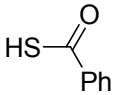
Entry	ROH	**1** (%ee)	Temp., Time	Product	**2**	Yield/%[a] (%ee)[b]
1		**1a** (>99)	40 °C, 24 h		**2a**	99 (>99)
2[c]		**1f**(>99)	rt, 12 h		**2f**	83 (97)
3[c]		**1g** (98)	rt, 24 h		**2g**	89 (98)
4		**1h**	80 °C, 6 h		**2h**	85
5[d]		**1i** (>99)	40 °C, 48 h		**2i**	76 (>99)
6[d]		**1j** (>99)	40 °C, 48 h		**2j**	90 (99)
7[c,d]		**1k** (92)	27 °C, 48 h		**2k**	87 (92)
8		**1l**	40 °C, 48 h		**2l**	N.R.

[a]Isolated yield. [b]Determined by HPLC analysis. [c]The solution of $PhOPPh_2$ and ethyl azidoacetate was stirred at 80 °C for 20 min, followed by addition of alcohol and BtzSH at rt. [d]The 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 (pK_a 5.11 in EtOH/H_2O, 5.5 in DMSO)[28] > benzenethiol (pK_a 7.76 in EtOH/H_2O, 10.3 in DMSO)[28] > 4-methoxybenzenethiol (pK_a 7.99 in EtOH/H_2O, 11.2 in DMSO)[28] (Entries 1–3). These results indicate that the yields are influenced by the pK_a values of nucleophiles.[12,16,29] It is considered that deprotonation of thiol having low pK_a 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-1*H*-tetrazole-5-thiol could also be used successfully in this reaction (Entry 6), and 2-sulfanyl-1,3-benzothiazole (BtzSH; pK_a 7.00 in EtOH/H_2O)[30] was the most reactive of the heteroarene thiols (Entry 7). When thiobenzoic acid (pK_a 5.3 in DMSO)[31] was used, the yield of the desired product was poor though its acidity was sufficient (Entry 10).[32]

Table 4. Condensation of tertiary alcohol **1b** with various ArSH



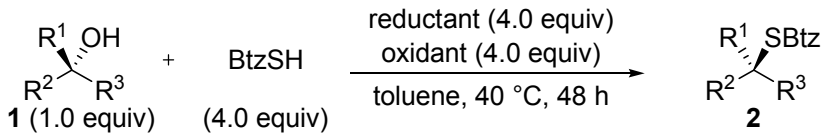
Entry	ArSH	Product **3**	Yield/%[a]	Entry	ArSH	Product **3**	Yield/%[a]
1		**3a**	44 (83)[b]	6		**3f**	83 (68)[b]
2		**3b**	85 (72)[b]	7		**2b**	94 (90)[b]
3		**3c**	19 (78)[b]	8		**3g**	91 (83)[b]
4		**3d**	72 (67)[b]	9		**3h**	89 (82)[b]
5		**3e**	97 (21)[b]	10		**3i**	34 (19)[b]

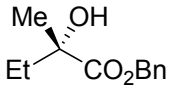
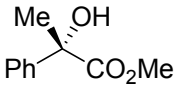
[a]Isolated yield. [b]2,6-Di-*tert*-butyl-1,4-benzoquione was used instead of ethyl azidoacetate. See ref. 19.

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 $PhOPPh_2$ and oxidants such as DEAD, DMBQ and $N_3CH_2CO_2Et$ afforded the desired sulfides with inversion of configuration while the PPh_3–DEAD system (Mitsunobu conditions) did not. The yields of products **2i** and **2j** were found to increase in the order of $PhOPPh_2$–$N_3CH_2CO_2Et$ >

$PhOPPh_2$–DMBQ > $PhOPPh_2$–DEAD > PPh_3–DEAD combination systems. Therefore, it is noted that $PhOPPh_2$ is an essential reductant for thioetherification of *tert*-alcohols.

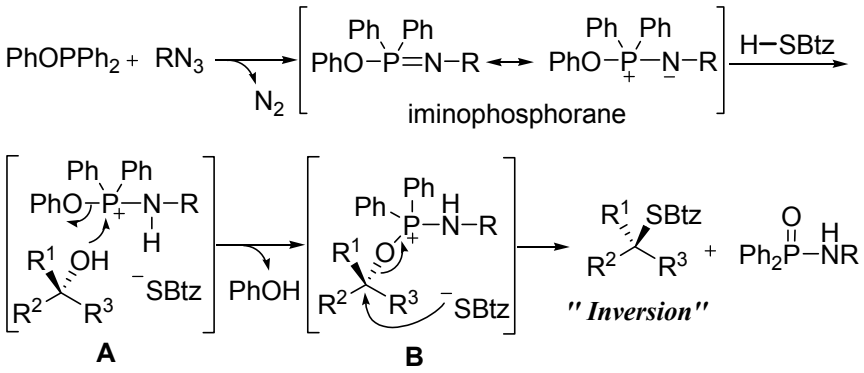
Table 5. Yields and enantiomeric excesses (in parentheses) in thioetherification of tertiary alcohols



Reagent / ROH **1**		PPh_3	$PhOPPh_2$		
		DEAD	DEAD	DMBQ[a]	$N_3CH_2CO_2Et$
	**1i**	trace	43 (>99)	55 (>99)	76 (>99)
	**1j**	N.D.	53 (>99)	56 (>99)	90 (99)

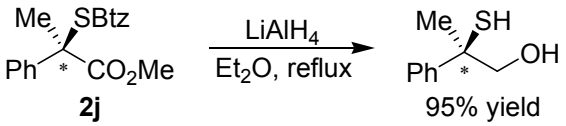
[a]The reaction was carried out at rt for 24 h.

A plausible reaction mechanism is shown in Scheme 7: the Staudinger reaction of $PhOPPh_2$ 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 S_N2 substitution gives the inverted sulfide.



Scheme 7

As the chiral *tert*-alkyl Btz sulfide **2j** was converted to the corresponding chiral thiol in high yield on treatment with $LiAlH_4$,[15] a concise method for the preparation of chiral thiols from the corresponding alcohols was established (Scheme 8).



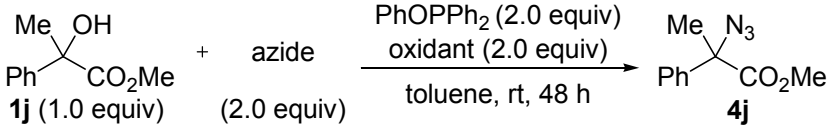
Scheme 8

Thus, a new type of oxidation–reduction condensation by using a combination of $PhOPPh_2$ 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 S_N2 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.[33] The most fundamental method known for azidation is the Mitsunobu reaction that uses hydrogen azide,[34] diphenyl phosphorazidate (DPPA)[35] or zinc azide/bis-pyridine complex.[36] More recently, methods using DPPA/DBU,[37] *p*-NO_2DPPA/DBU[38] and so forth[39] have been reported. In all these reactions, chiral *sec*-alkyl azides are formed from chiral *sec*-alcohols with complete inversion of configuration via S_N2 displacement. On the other hand, sterically-hindered *tert*-alcohols are not known to be converted to the corresponding *tert*-alkyl azides.[40] 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 $PhOPPh_2$ and an azide compound as oxidants.

Table 6. Optimization of reaction conditions[a]

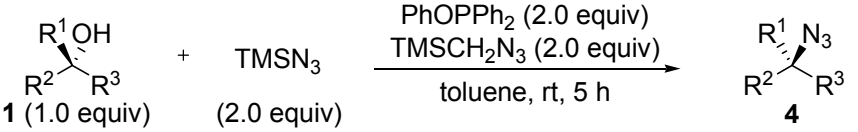


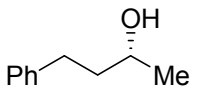
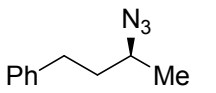
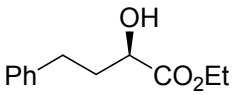
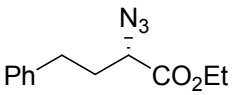
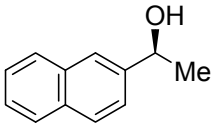
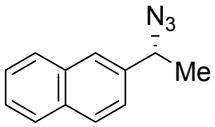
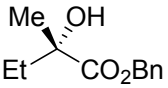
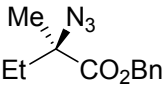
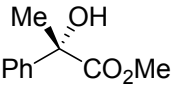
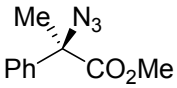
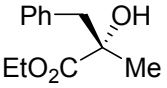
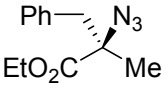
Entry	Azide	Oxidant	Yield/%[b]
1[c]	Bu_4NN_3	N_3CH_2Ph	N.D.
2[c]	DPPA	N_3CH_2Ph	34
3	$TMSN_3$	N_3CH_2Ph	57
4		$N_3CH_2CO_2Et$	9
5		AdN_3	12
6		N_3CH_2TMS	82

[a]The solution of $PhOPPh_2$ 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 $PhOPPh_2$ 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 $TMSN_3$, the yield of **4j** increased up to moderate yield and therefore $TMSN_3$ 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.

Table 7. Azidation of various chiral alcohols

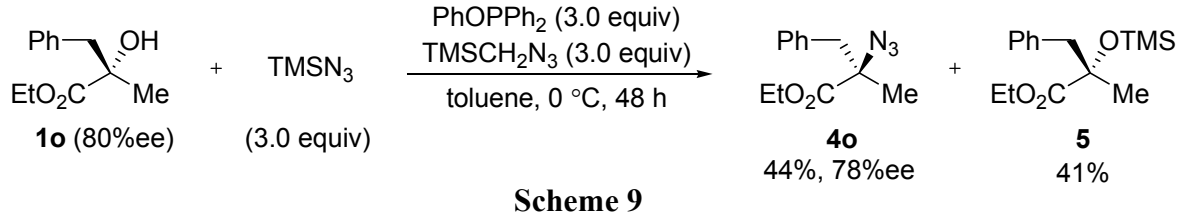


Entry	ROH	**1** (%ee)	Product	**4**	Yield/%[a] (%ee)
1		**1a** (>99)		**4a**	quant (>99)[b]
2		**1m** (>99)		**4m**	98 (>99)[c]
3		**1n** (>99)		**4n**	85 (97)[b]
4[d,e]		**1i** (>99)		**4i**	84 (96)[f]
5[d,g]		**1j** (>99)		**4j**	86 (>99)[b]
6[d,g]		**1o** (80)		**4o**	86 (61)[c]

[a]Isolated yield. [b]The ratio of enantiomer was determined by HPLC analysis after reducing the azide (**4a**, **4n**, **4j**) to the corresponding amines.[c]The ratio of enantiomer was determined by HPLC analysis. [d]$PhOPPh_2$(3.0 equiv), trimehylsilylmethyl azide (3.0 equiv), $TMSN_3$ (3.0 equiv) were used. [e]The reaction time was 24 h. [f]The ratio of enantiomer was determined by HPLC analysis after converting the azide to 1,4-disubstituted 1,2,3-triazole. [g]The reaction time was 48 h.

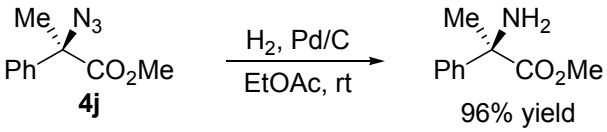
A suitable azidation reagent and an oxidant were then chosen and condensation reaction of various chiral alcohols with $TMSN_3$ was tried in order to examine the scope of this reaction under the optimized conditions (Table 7). A reaction of chiral *sec*-alcohol **1a** proceeded smoothly to afford the corresponding

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). Similary, 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).

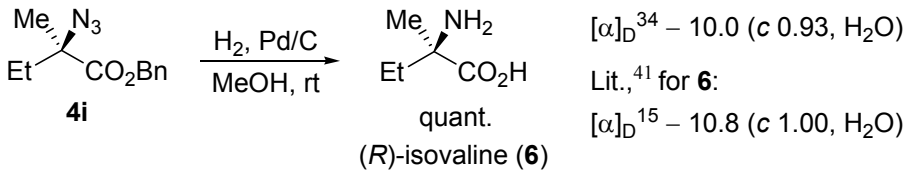


Scheme 9

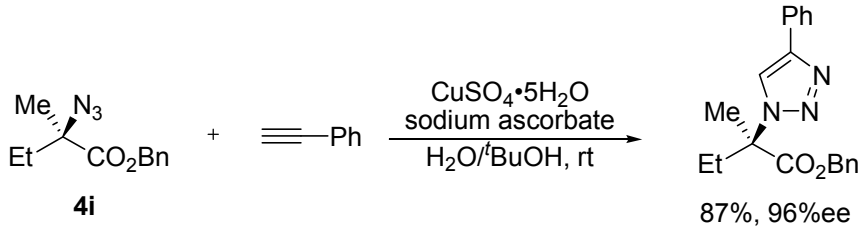
The chiral *tert*-alkyl azides **4j** is reduced into the corresponding chiral *tert*-alkyl amine in high yield by hydrogenation, therefore, a concise method for the preparation of chiral amines from the corresponding alcohols is established (Scheme 10). In hydrogenation process, *tert*-alkyl azides **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 value[41] (Scheme 11). Also, the azide **4i** is converted into 1,4-disubstituted 1,2,3-triazole on treatment with phenylacetylene in the presence of $CuSO_4 \cdot 5H_2O$ and sodium ascorbate (Scheme 12).



Scheme 10

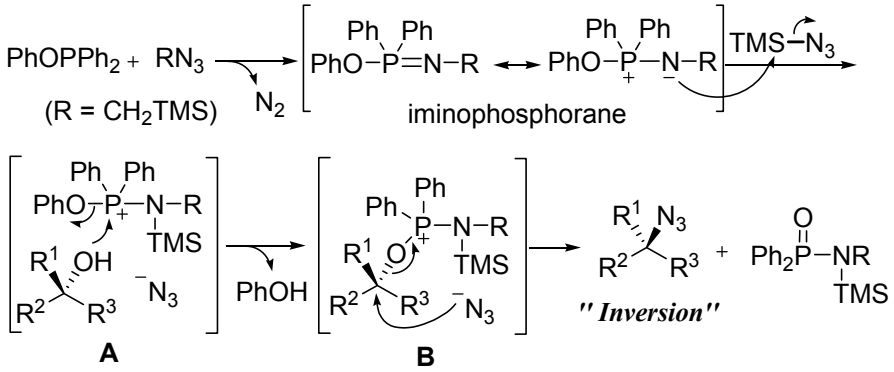


Scheme 11



Scheme 12

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 alkoxyphosphonium 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_N2 manner gave the inverted azide.



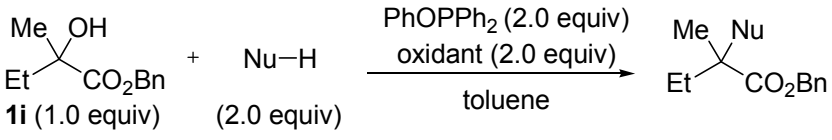
Scheme 13

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

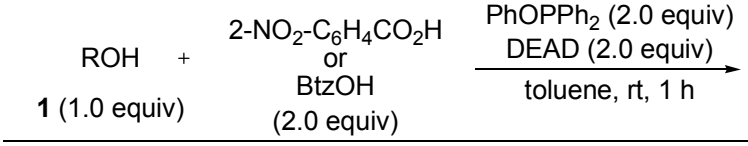
Table 8. Optimization of reaction conditions[a]

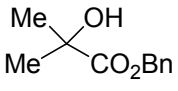
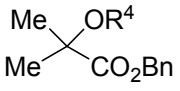
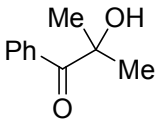
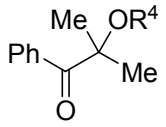
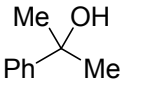
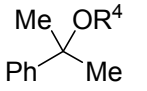
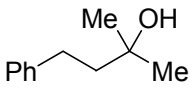
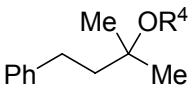


Entry	Nucleophile	Oxidant	Temp., Time	Yield/%[a]
1	$C_6H_5CO_2H$	N_3CH_2Ph	rt, 24 h	N.D.
2	$C_6H_5CO_2H$	DMBQ	rt, 24 h	trace
3	$C_6H_5CO_2H$	DEAD	rt, 24 h	5
4	2-$NO_2C_6H_5CO_2H$	DEAD	rt, 1 h	52
5	4-$NO_2C_6H_5CO_2H$	DEAD	rt, 72 h	24
6	2-$MeOC_6H_5CO_2H$	DEAD	rt, 24 h	N.D.
7	4-$MeOC_6H_5CO_2H$	DEAD	rt, 24 h	9
8	BtzOH	N_3CH_2Ph	40 °C, 24 h	trace
9	BtzOH	$N_3CH_2CO_2Et$	40 °C, 24 h	trace
10	BtzOH	DMBQ	0 °C, 24 h	49
11	BtzOH	DEAD	0 °C, 1 h	60

[a]Isolated yield.

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



Entry	ROH	1	Product	R^4	7 / 8	Yield/%[a]
1		**1b**		2-NO_2-C_6H_4CO	**7b**	76
2[b]				Btz	**8b**	70
3[c]		**1c**		2-NO_2-C_6H_4CO	**7c**	39
4[c]				Btz	**8c**	50
5		**1d**		2-NO_2-C_6H_4CO	**7d**	43
6[b,d]				Btz	**8d**	38
7		**1e**		2-NO_2-C_6H_4CO	**7e**	39
8[b]				Btz	**8e**	43

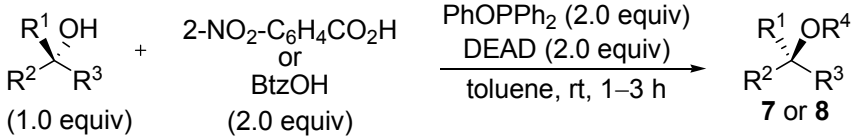
[a]Isolated yield. [b]The reaction was carried out at 0 °C. [c]The reaction was carried out at 80 °C. [d]The reaction time was 24 h.

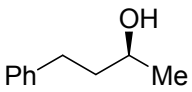
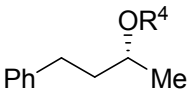
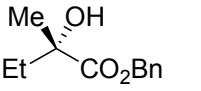
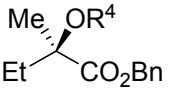
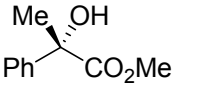
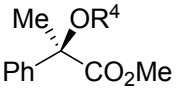
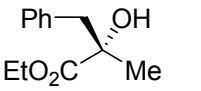
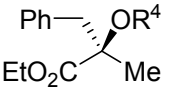
of the influence of substituents on the aromatic carboxylic acid in the presence of DEAD, the desired product was found to obtain in 52% yield when 2-nitrobenzoic acid was used as a nucleophile (Entry 4). Because 2-sulfanyl-1,3-benzothiazole (BtzSH) showed high nucleophilicity as a sulfur nucleophile 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



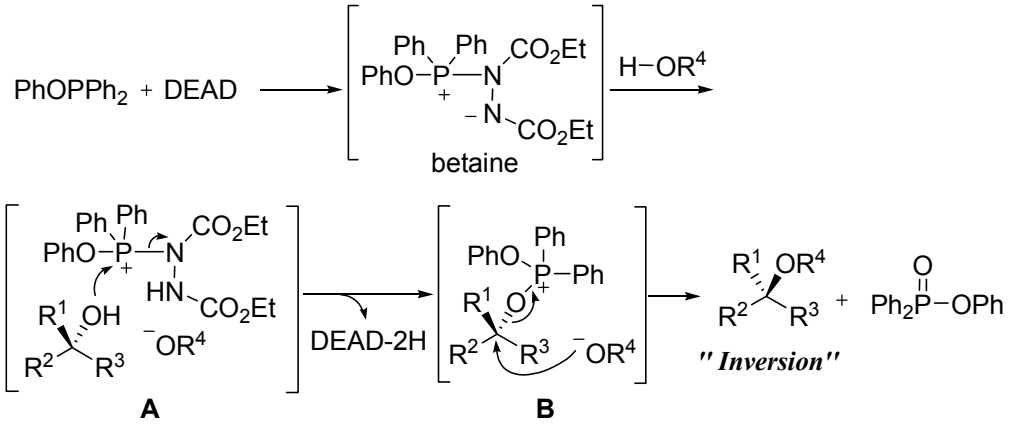
Entry	ROH	1 (%ee)	Product	R^4	7 8	Yield/%[a]	ee/%[b]
1		**1a** (>99)		2-NO_2-C_6H_4CO	**7a**	91	>99
2		**1i** (>99)		2-NO_2-C_6H_4CO	**7i**	52	96
3[c]				Btz	**8i**	60[d]	96
4		**1j** (>99)		2-NO_2-C_6H_4CO	**7j**	42	85
5[c]				Btz	**8j**	54	94
6		**1o** (80)		2-NO_2-C_6H_4CO	**7o**	32	78
7[c]				Btz	**8o**	46	79

[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.

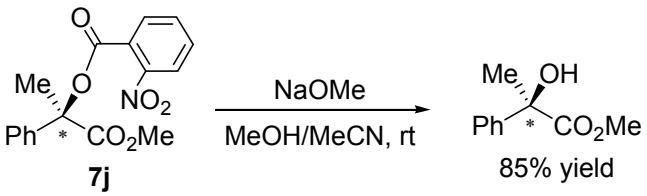
Taking the above results into consideration, reactions of various chiral alcohols were next tried in order to examine the stereochemistry of this reaction (Table 10). The esterification of *sec*-alcohol **1a** proceeded smoothly to afford the corresponding ester in excellent yield with complete inversion 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 $PhOPPh_2$ 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_N2 substitution gives the inverted product.

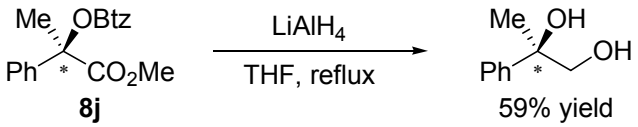


Scheme 14



7j

Scheme 15



8j

Scheme 16

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 stereoinverion of chiral *tert*-alcohols was established.

In summary, a new type of oxidation–reduction condensation by the combined use of $PhOPPh_2$ 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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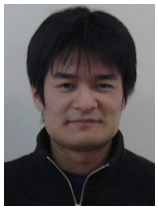
Teruaki Mukaiyama was born in 1927. He received his B.Sc. from the Tokyo Institute of Technology (T.I.T) in 1948, and Ph.D. from the University of Tokyo in 1957. He first became Assistant Professor at Gakusyuin University in 1953 and then at T.I.T in 1958. He was appointed Full Professor at TIT in 1963 and moved to the University of Tokyo in 1974. In 1987 he became Professor of Chemistry at Science University of Tokyo and moved to the Kitasato Institute in 2002. Since 2009 he supervises basic research on new synthetic reactions at TCI; as well as Emeritus Professor at the University of Tokyo, the T.I.T, and the Science University of Tokyo. He is a recipient of many major awards and is currently a member of the Japan Academy as well as a foreign member of the Academy of Sciences in American, France and Poland.



Kiichi Kuroda was born in 1981 and received B.Sc. (2004) and Ph.D. degree (2009) from Tokyo University of Science. He was a JSPS research fellow during 2006-2009.

Yuji Maruyama was born in 1984 and received B.Sc. (2007) and M.S degree (2009) from Tokyo University of Science.