Highlight Review

Alkyl Phosphinites: Versatile Synthetic Intermediates for Dehydration Condensation Reactions

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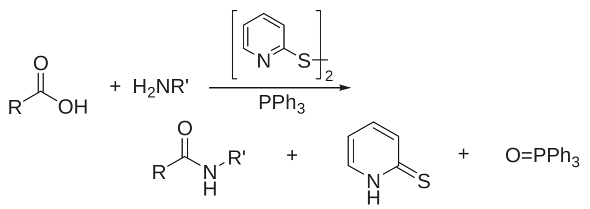
Abstract

Recent advances in the oxidation–reduction condensation reaction of alkyl phosphinites are described. The carbon–sulfur, carbon–carbon, or carbon–nitrogen bond forming reactions and cyanation, isocyanation reactions are established. These reactions proceed through inversion of configuration even when tertiary alkyl phosphinites are employed, providing thus, a novel route to chiral hydrosulfides, amines, nitriles, and isocyanides from easily available chiral alcohols.

◆ Introduction

The fundamental concept of "oxidation–reduction condensation" is to perform dehydration reaction by using a combination of weak reductants (oxygen acceptor) and oxidants (hydrogen acceptor), and thus to remove H_2O as in 2[H] and [O] under mild and almost neutral conditions without any assistance of acid or base. In 1963, the first example of oxidation–reduction condensation was reported by our group:[1] two moles of carboxylic acids were dehydrated to form the corresponding acid anhydrides in high yields by using a combination of (p-MeO-C_6H_4)$_2$Hg (hydrogen acceptor) and PBu_3 (oxygen acceptor) as described in Scheme 1.

It was also shown that the condensation reaction between Bz–L-Leu–OH and H–Gly–OEt successfully afforded dipeptide, Bz–L-Leu–Gly–OEt, in high yield by using a combination of triphenylphosphine (PPh_3) and di(2-pyridyl)disulfide (PySSPy) (eq 1).[2] On the other hand, Corey et al. developed an effective method of macrocyclic lactone synthesis by treating hydroxycarboxylic acid with PPh_3 and PySSPy,[3a] which was also applied to the syntheses of a number of important macrocyclic compounds including monensin,[3a] erythronolide B,[3b] vermiculine,[3c] enterobactin,[3d] and prostaglandins.[3a,3e]

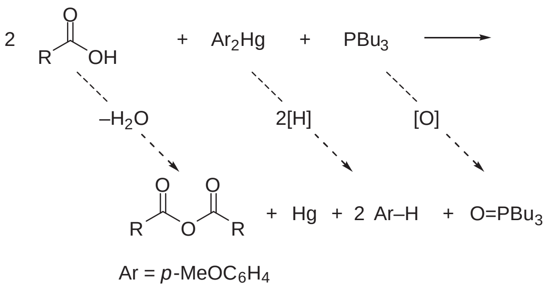


(1)

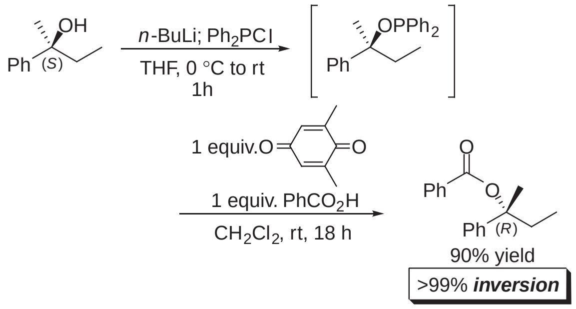
Phosphoric esters were also prepared by using allyl diethyl phosphite and diethyl azodicarboxylate (DEAD) in the presence of alcohols (1967).[4a] Later, Mitsunobu further applied this concept to an efficient dehydration condensation between alcohols and various nucleophiles such as carboxylic acids by the use of PPh_3 and DEAD in combination (Mitsunobu reaction).[4b] The scope of this PPh_3–DEAD system was expanded to the alkylation reactions of various acidic components including imides, sulfonamides, heterocycles, carbon acids, phenols, and inorganic substrates such as azide, cyanide, and halides.[4c]

Despite enormous efforts have been made on these condensation reactions, a problem still remained as a challenge, when bulky secondary or tertiary alcohols were employed as a substrate. 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 (Scheme 2).[5] It is noteworthy that almost complete stereochemical inversion was observed even when bulky tertiary alkyl phosphinites were employed.

Based on success of the above results, alkylation reaction using various nitrogen-, carbon-, and sulfur-nucleophiles was considered next (Scheme 3). Now, we would like to describe



Scheme 1.



Scheme 2.

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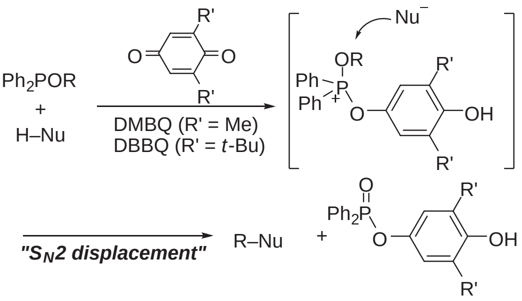


Scheme 3.

recent significant advances in the oxidation–reduction condensation reactions to show novel C–N, C–C, snd C–S bond forming reactions which appeared after the review published in 2004.[6]

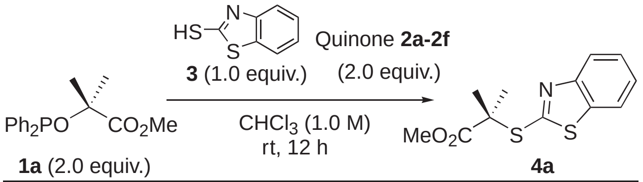
◆ Formation of Carbon–Sulfur Bond[7,8]

The carbon–sulfur bond forming reaction using PPh$_3$–DEAD system is considered to be a method versatile for preparation of various primary or secondary thioesters or thiols from the corresponding alcohols. Herein, alcohols are converted into the corresponding thioesters by reaction of an alcohol with PPh$_3$, DEAD, and thioacetic acid, followed by saponification or reduction of the thioester thus formed to give the corresponding thiol. However, this method is not applicable to the synthesis of tertiary alkyl hydrosulfide like other PPh$_3$–DEAD systems. Therefore, it is desirable to develop a method that allows conversion of tertiary alcohols to the corresponding thiols in an S$_N$2 manner. Thus, the oxidation–reduction condensation using phosphinites was next applied to the formation of carbon–sulfur bond.

In the first place, the reaction of tertiary alkyl phosphinite **1a** derived from methyl 2-hydroxyisobutyrate was tried by using benzo[*d*]thiazole-2-thiol (**3**) as a sulfur nucleophile in the presence of several 1,4-benzoquinones derivatives, and the results obtained are summarized in Table 1.

On the initial examination of simple 1,4-benzoquinone (**2a**), however, the desired tertiary alkyl sulfide was obtained in 34% yield only (Entry 1). On the other hand, introduction of bulky substituent(s) at 2- and/or 6-position of 1,4-benzoquinone increased yield of **4a** dramatically, which happened to be quantitative when DBBQ (**2d**) was used (Entries 2–4). Electron-donating 2,6-dialkoxy-substituted 1,4-benzoquinones also promoted the reaction to afford **4a** in high yields (Entries 5 and 6), while electron-withdrawing groups on benzoquinones retarded the reaction (Entries 7 and 8).

Table 1. Optimization of quinone derivatives



1a (2.0 equiv.) **4a**

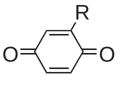
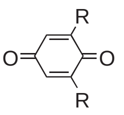
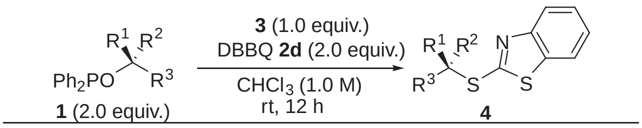
Entry	Quinone		Yield/%
1		R = H (**2a**)	34
2		R = *t*-Bu (**2b**)	51
3		R = Me (**2c**) (DMBQ)	84
4		R = *t*-Bu (**2d**) (DBBQ)	quant.
5		R = OMe (**2e**)	91
6		R = OBn (**2f**)	91
7		R= Cl (**2g**)	6
8	Fluoranil (**2h**) (2,3,5,6-tetrafluoro-1,4-benzoquinone)		N. D.

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



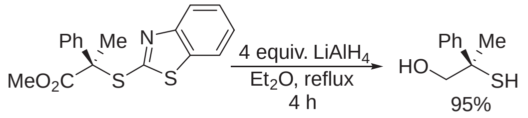
1 (2.0 equiv.) **4**

Ph$_2$POR	R^1	R^2	R^3	ee[b]/% (config.)	Product	Yield/%	ee[c]/% (config.)
1b	Me	Me	CO$_2$Bn	—	**4b**	87	—
1c	Me	Me	CO$_2$*t*-Bu	—	**4c**	90	—
1d	Me	Me	COPh	—	**4d**	52	—
1e	Me	Me	Ph	—	**4e**	90	—
1f	Me	–(CH$_2$)$_4$–		—	**4f**	53	—
1g	Me	Me	(CH$_2$)$_2$Ph	—	**4g**	34	—
1h	Et	Me	CO$_2$Bn	>99 (*S*)	**4h**	73	>99 (*R*)
1i	CH$_2$Ph	Me	CO$_2$Et	78 (*S*)	**4i**	61	76 (*R*)
1j	Ph	Me	CO$_2$Me	>99 (*S*)	**4j**	73	99 (*R*)
1k	Et	Me	Ph	97 (*S*)	**4k**	76	86 (*R*)

[a]Reactions were carried out on a 0.5 mmol scale. [b]Enantiomeric excess (ee) of alcohols. [c]Determined by HPLC using commercially available chiral columns.

Reactions with several substrates were studied by using DBBQ under the optimized conditions (Table 2). Phosphinites possessing ester, ketone, or phenyl groups at the quaternary centers were smoothly transformed into the corresponding sulfides **4b**–**4e** in high yields, while reactions of aliphatic tertiary alkyl phosphinites **1f** and **1g** afforded the tertiary alkyl sulfides in moderate yields. Chiral phosphinites **1h**–**1j** were also employed successfully in this reaction, and the enantiomerically enriched tertiary alkyl sulfides **4h**–**4j** were obtained in good yields with complete inversion at the quaternary centers. In the case of benzylic tertiary alkyl phosphinite **1k** in which S$_N$1 reaction is considered to take place readily, substantial decrease in enantiomeric excess was observed (97 to 86% ee).

The products, tertiary alkyl benzo[*d*]thiazol-2-yl sulfides, were converted into the corresponding thiols in excellent yields. For instance, treatment of chiral sulfide (*R*)-**4j** with lithium aluminum hydride (LAH) in Et$_2$O afforded chiral tertiary alkyl hydrosulfide (*R*)-**5j** without accompanying epimerization (eq 2). Thus, the first example of synthesis of chiral tertiary alkyl hydrosulfides was established from chiral tertiary alcohols via S$_N$2 substitution.



(*R*)-**4j** (*R*)-**5j** (2)

◆ Formation of Carbon–Carbon Bond[7,9]

Carbon–carbon bond forming reactions that use the PPh$_3$–DEAD system are limited to the case of carbon nucleophiles having a highly acidic C–H bond such as β-diketones, β-ketoesters, and α-cyanothioesters.[4c] To extend the scope of oxidation–

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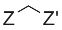
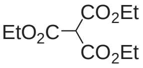
Table 3. Screening of carbon nucleophiles[a]

rac-**1l**

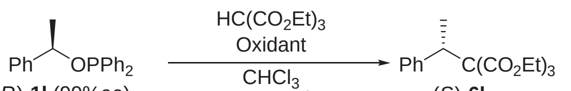
Entry	H–Nu		pK_a[b]	Yield/%
1		Z = CN, Z' = SO_2Ph	12.0	45
2		Z = Z' = CN	11.1	27
3		Z = Z' = SO_2Ph	12.2	N. D.
4		Z = Z' = CO_2Et	13.3	N. D.
5	 $EtO_2C{-}CH(CO_2Et)_2$		7.5	60

[a]The reactions were carried out by using *rac*-**1l** (1.0 equiv.), DBBQ (1.2 equiv.), and nucleophiles (1.2 equiv.). [b]Values in DMSO.

reduction condensation reaction to C–C bond formation, reaction of carbon-nucleophiles with secondary phosphinite **1l** was next examined in the presence of a DBBQ oxidant, and the results obtained are summarized in Table 3. Although very much alike in pK_a values, the reaction with (phenylsulfonyl)acetonitrile afforded the desired adduct in 45% yield (Entry 1) whereas the yield obtained with either malononitrile or bis(phenylsulfonyl)methane was unsatisfactory (Entries 2 and 3). Diethyl malonate could not be used in this transformation probably due to lack of acidity (Entry 4). On the other hand, more acidic triethyl methanetricarboxylate (pK_a = 7.5 in DMSO) was successfully converted to the desired product (60% yield, Entry 5).

The effect of oxidants was investigated next; chiral phosphinite (*R*)-**1l** was allowed to react with $HC(CO_2Et)_3$ in the presence of various oxidants in $CHCl_3$, and the corresponding results are summarized in Table 4. When 1,4-benzoquinone derivatives are employed, the efficiency of this reaction was influenced dramatically by substituents on 2- and 6-positions (Entries 1–3). It was found that azodicarboxylate derivatives such as DEAD, diisopropyl azodicarboxylate (DIAD) or di-*tert*-butyl azodicarboxylate (DTBAD) gave the desired product in 67–72% yields with 96–97% ees (Entries 4–6). Stereochemically inverted product (*S*)-**6l** was obtained in 73% yield with 97% ee when the reaction was carried out by using DEAD at −63 °C (Entry 7).

Table 4. Optimization of reaction conditions[a]



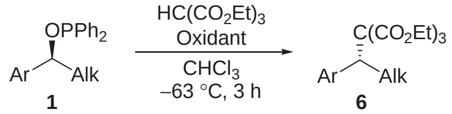
(*R*)-**1l** (99%ee) (*S*)-**6l**

Entry	Oxidant	Temp.	Yield/%	ee/%
1	1,4-benzoquinone	0 °C	ND	–
2	DMBQ	0 °C	36	97
3	DBBQ	0 °C	60	97
4	DEAD	0 °C	72	97
5	DIAD	0 °C	67	97
6	DTBAD	0 °C	72	96
7	DEAD	−63 °C	73	97
8	DIAD	−63 °C	69	97
9	DTBAD	−63 °C	74	97

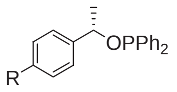
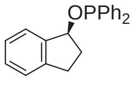
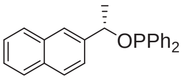
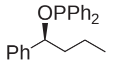
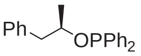
[a]The reactions were carried out by using **1l** (1.0 equiv.), oxidant (1.2 equiv.), and $HC(CO_2Et)_3$ (1.2 equiv.).

$R'O_2C{-}N{=}N{-}CO_2R'$ DEAD (R′ = Et)
DIAD (R′ = *i*-Pr)
DTBAD (R′ = *t*-Bu)

Table 5. Condensation reactions using various chiral phosphinites[a]



1 **6**

Phosphinite		Oxidant	Yield/%	ee/%
	R = Me **1m** (93% ee)	DEAD	79	88
		DIAD	81	88
		DTBAD	80	88
	R = Cl, **1n** (77% ee)	DEAD	58	75
		DIAD	56	75
		DTBAD	59	75
	R = OMe, **1o** (81% ee)	DEAD	87	38
		DIAD	89	42
		DTBAD	89	49
	**1p** (99% ee)	DEAD	71	96
		DIAD	63	96
		DTBAD	56	96
	**1q** (99% ee)	DEAD	78	97
		DIAD	57	79
		DTBAD	48	73
	**1r** (81% ee)	DEAD	54	81
		DIAD	56	81
		DTBAD	62	81
	**1s** (99% ee)	DEAD	8	99
		DTBAD	13	99

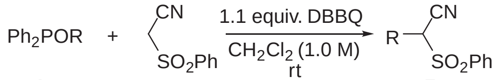
[a]The reactions were carried out by using **1m**–**1s** (1.0 equiv.), oxidant (1.2 equiv.), and $HC(CO_2Et)_3$ (1.2 equiv.). [b]Enantiomeric excess (ee) values were determined by chiral HPLC analysis.

With the optimal reaction conditions in hand, the scope of the reaction was studied by using various chiral alkyl aryl carbinols (Table 5); the condensation reaction was carried out by using dialkyl azodicarboxylates under the above-mentioned conditions ($CHCl_3$, −63 °C), and the corresponding triesters **6** were obtained in good yields with complete or almost complete inversion of their stereochemistries when benzylic phosphinites **1m**, **1n**, and **1p**–**1r** were used. Significant loss of enantiomeric excess was observed in the alkylation of **1o** that possessed a *p*-methoxy moiety, since this reaction competitively proceeded via S_N1 and S_N2 pathways. C-Alkylation of $HC(CO_2Et)_3$ with dialkyl carbinol **1s** gave the alkylated product **6s** in a poor yield. It is noted that the bulkiness of the substituent of azodicarboxylates had an influence on the stereochemical outcome when **1q** was used.

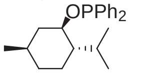
Further, C-alkylation of (phenylsulfonyl)acetonitrile with DBBQ was also examined by running the reaction of (phenylsulfonyl)acetonitrile with various phosphinites, and their results are summarized in Table 6. The condensation reactions of primary or secondary alkyl phosphinites proceeded smoothly to afford the alkylated acetonitriles in good yields (Entries 1–4). It is noted that the chiral phosphinite **1v** was completely converted to the inverted product. The use of more congested (–)-menthyl phosphinite (**1x**), however, did not give the desired condensation product (Entry 5).

The alkylated (phenylsulfonyl)acetonitrile derivatives produced in this way were converted to the corresponding alkylated acetonitriles by the reductive removal of a sulfonyl group: treatment of **7v** with SmI_2 in THF afforded chiral nitrile (*S*)-**8** in a good yield (eq 3). Therefore, this reaction is a concise method for preparation of chiral nitriles from chiral alcohols.

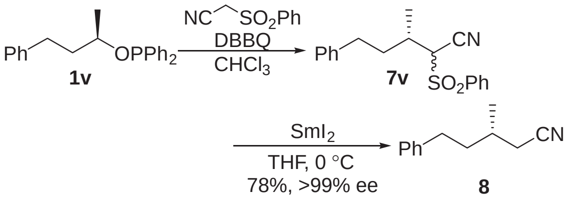
Table 6. Alkylation of (phenylsulfonyl)acetonitrile



1 (1.0equiv.) (1.5equiv.) 7

Entry	Phosphinite	Time/h	Yield/%
1	BnOPPh$_2$ (**1t**)	5	75[a]
2	 (**1u**)	12	85
3	 (**1v**)	5	70[b]
4	 (**1w**)	3	69
5	 (**1x**)	12	N.D.

[a]Dibenzylated product (25%) was obtained. [b]Stereochemistry of the product was inverted over 99%.



1v **7v** **8** (3)

◆ *Formation of Carbon–Nitrogen Bond*[7,10]

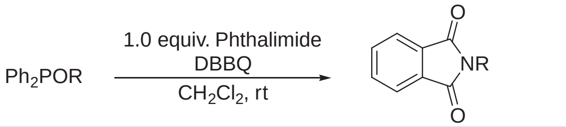
It is well known that the conversion of alcohols into amines with inversion is carried out by coupling a secondary alcohol with phthalimide using DEAD/PPh$_3$[4c] followed by hydrazinolysis of the resulting *N*-alkylphthalimide. However, there still remains a problem in performing the reaction of a sterically hindered tertiary alcohol with a nitrogen nucleophile in an S$_N$2 manner. Therefore, it is desired to develop a convenient method for the transformation of sterically hindered tertiary alcohols into inverted amines.

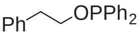
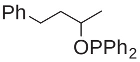
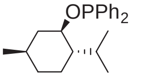
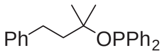
The next studied was a C–N bond forming reaction using alkyl phosphinites and nitrogen nucleophiles. In the first place, the reaction of various phosphinites with phthalimide as a nucleophile in the presence of DBBQ was examined, and the results are summarized in Table 7.

Primary and secondary alkyl phosphinites were converted into the corresponding *N*-alkylphthalimides in good yields (Entries 1–3). It is noteworthy that chiral phosphinite **1x** was converted into the corresponding *N*-alkylphthalimide with complete inversion of stereochemistry (Entry 3). However, when tertiary alkyl phosphinite **1g** was employed, the desired phthalimide was obtained in a poor yield (Entry 4).

Because the bulkiness of phthalimide retarded this reaction when tertiary alkyl phosphinite was used, less sterically demanding nitrogen nucleophile such as trimethylsilyl azide was examined next. The reaction of tertiary alkyl phosphinite **1g** with trimethylsilyl azide (2.4 equiv.) as a nucleophile was studied in the presence of various quinones (1.1 equiv.), and the results are summarized in Table 8.

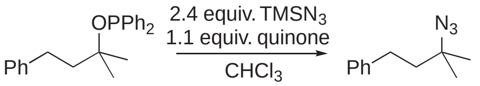
Table 7. Effect of quinone derivatives on N-alkylation of phthalimide



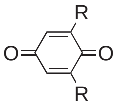
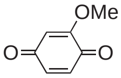
Entry	Ph$_2$POR (equiv.)	amt. of DBBQ	Time/h	Yield/%
1	 **1y** (1.1)	1.1 equiv.	1	88
2	 **1v** (1.1)	1.1 equiv.	1	75
3	 **1x** (2.0)	2.0 equiv.	1	72[a]
4	 **1g** (2.0)	2.0 equiv.	12	24

[a]The corresponding compound was obtained with perfect inversion.

Table 8. Effect of quinone derivatives on azidation of **1g**



1g **9g**

Entry	Quinone		Yield/%
1	 R = H	(**2i**)	56
2	R = Me	(**2c**)	37
3	R = *t*-Bu	(**2d**)	31[a]
4	R = OMe	(**2e**)	57
5		(**2j**)	58
6			63[b]
7	Fluoranil	(**2h**)	<7
8	DDQ	(**2k**)	

[a]The reaction was carried out for 17 h. [b]The reaction was carried out at −45 °C to room temperature.

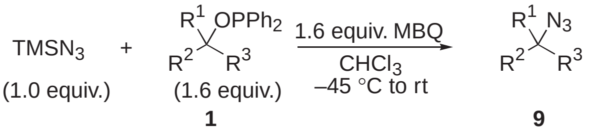
Expectedly, sterically hindered tertiary alkyl phosphinite **1g** was converted into the corresponding azide (**9g**) when 1,4-benzoquinone was employed. The reaction with 2,6-disubstituted benzoquinone derivatives DMBQ (**2c**) and DBBQ (**2d**) that gave the best results for C–O, C–S, and C–N bond forming reactions (vide supra) afforded the desired product in lower yields (Entries 2 and 3). Benzoquinones possessing electron-donating substituent(s) showed better results (Entries 4 and 5), while electron-withdrawing substituents retarded the reaction (Entries 7 and 8). The reaction starting from lower temperature gave slightly better result (Entry 6).

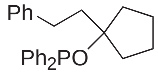
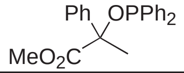
The reactions of several tertiary alkyl phosphinites were tried under the above optimized conditions, namely, 2-methoxy-1,4-benzoquinone (MBQ) at −45 °C to room temperature (Table 9).

When cyclopentyl phosphinite derivative **1z** was employed, the desired azide was obtained in 79% yield (Entry 1). The reaction of the chiral benzyl phosphinite **1A** gave the corresponding azide in a moderate yield (Entry 2), The product was obtained with almost complete inversion of stereochemistry when chiral phosphinite **1B** was employed as a substrate (Entry 3).

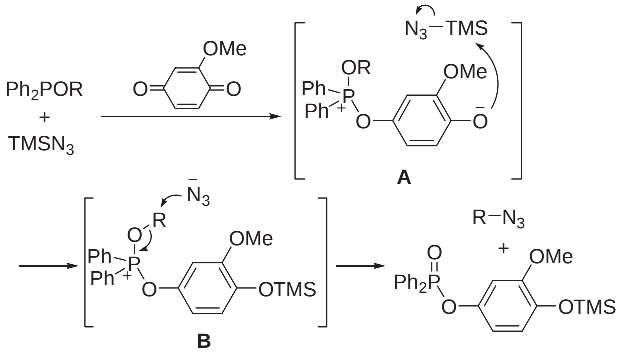
The mechanism of the present reaction is assumed as follows (Scheme 4): reaction of alkyl phosphinite with MBQ gives a zwitterionic intermediate **A** and following O-silylation by trimethylsilyl azide results in the formation of intermediate **B** and azide anion (N$_3$$^-$). Subsequent nucleophilic attack of

Table 9. Azidation of *tert*-alkyl phosphinites



Entry	Phosphinites		Yield[a]/%	Inversion/%
1		**1z**	79	—
2	 R = Ph	**1A** (98% ee)	57	60
3	R = $(CH_2)_2Ph$	**1B** (80% ee)	83	95
4		**1j** (racemic)	47	—

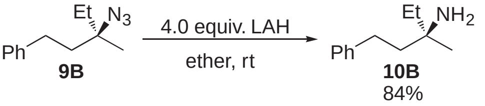
[a]Based on the amount of $TMSN_3$.



Scheme 4.

N_3^- to phosphonium part in an S_N2 manner gives the phosphinate derivative and the azide product with inversion.

The obtained chiral azide was converted to the chiral amine in a good yield by treatment of **9B** with LAH in diethyl ether (eq 4). Thus, a concise method for preparation of chiral amines from the corresponding alcohols was established.



(4)

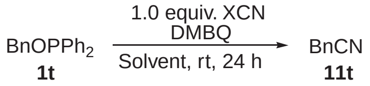
◆ *Cyanation and Isocyanation*[7,11]

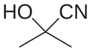
Nucleophilic substitution reaction with a cyanide anion (CN^-) was next studied. Cyanide anion is known as an ambident nucleophile that reacts at either C- or N-position depending on reaction conditions. Thus, alkylation of cyanide anion at its C- or N-position results in the formation of nitriles or isocyanide, respectively.

In the first place, reaction of benzyl phosphinite **1t** with several cyanide sources in the presence of DMBQ (**2c**) was examined (Table 10).

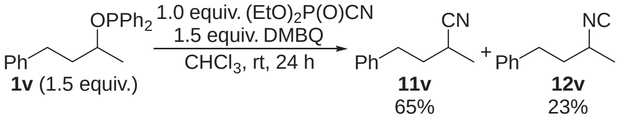
In the above reaction, it was found that trimethylsilyl cyanide (TMSCN) did not react at all and acetone cyanohydrin gave desired nitrile **11t** in a poor yield (Entries 1 and 2). However, yield increased when diethyl cyanophosphonate was used (Entry 3). After screening the reaction conditions, nitrile **11t** was eventually obtained in 82% yield when 1.5 equiv. of benzyl phosphinites was treated with 1.5 equiv. of DMBQ in $CHCl_3$ (Entry 5).

Table 10. Reaction of **1t** with vairous cyanide souces

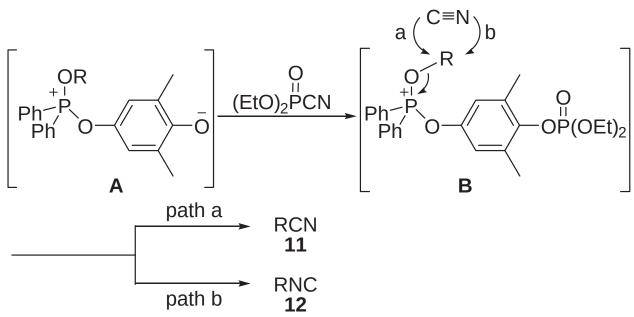


Entry	$BnOPPh_2$ (equiv.)	XCN	DMBQ (equiv.)	Solvent	Yield[a]/%
1	1.0	TMSCN	1.0	CH_2Cl_2	—
2	1.0		1.0	CH_2Cl_2	20
3	1.0	$(EtO)_2P(O)CN$	1.0	CH_2Cl_2	35
4	1.0	$(EtO)_2P(O)CN$	1.0	$CHCl_3$	49
5	1.5	$(EtO)_2P(O)CN$	1.5	$CHCl_3$	82

[a]Since a small amount of DMBQ was contamined, yield was determined by ^1H NMR analysis.



Scheme 5.

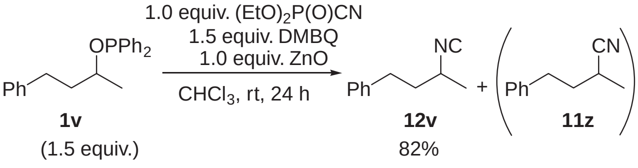


Scheme 6.

As diethyl cyanophosphonate was found effective, reaction of secondary alkyl phosphinite **1v** with $(EtO)_2P(O)CN$ was then tried in the presence of DMBQ. When diethyl cyanophosphonate was treated with **1v** in $CHCl_3$ at room temperature, an unexpected isocyanide **12v** was formed in 23% yield along with aimed nitrile **11v** as shown in Scheme 5.

In Scheme 6, a cyanide anion works as an ambident nucleophile as expected. To the best of our knowledge, no formation of isocyanide from secondary alcohols with cyanide anion has yet been reported. In order to establish a versatile method for the preparation of isocyanide from alcohols, the reaction conditions were therefore re-examined. Then, the nucleophilic attack of a cyanide anion at its N-position was found to be promoted by the addition of ZnO and the isocyanide **12z** was formed exclusively (Scheme 7).

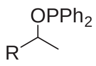
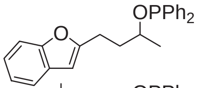
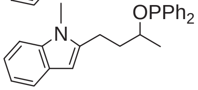
Next, the isocyanation of several secondary alcohols was examined under the optimized conditions. As shown in Table 11,



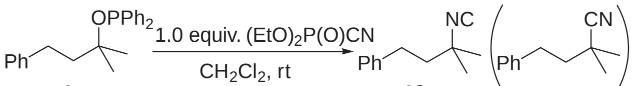
Scheme 7.

Table 11. Isocyanation reaction of secondary alkyl phosphinites

$$\underset{\substack{\mathbf{1}\\(1.5\ \text{equiv.})}}{\mathrm{ROPPh_2}} \xrightarrow[\mathrm{CH_2Cl_2},\text{rt, 24 h}]{\substack{1.0\ \text{equiv.}\ (\mathrm{EtO})_2\mathrm{P(O)CN}\\1.5\ \text{equiv. DMBQ}\\1.0\ \text{equiv. ZnO}}} \underset{\mathbf{12}}{\mathrm{RNC}}$$

Entry	Phosphinite			Yield/%
1		R = Ph	**1C**	40
2		R = CH_2Ph	**1D**	63^a
3		R = $(CH_2)_2Ph$	**1v**	89^b
4		R = $(CH_2)_2OPMB$	**1E**	63
5		R = $(CH_2)_2OTBDPS$	**1F**	72
6			**1G**	78
7			**1H**	81

^{a}The reaction time was 3 h. ^{b}The corresponding isocyanide was obtained with complete inversion of its stereochemistry.



1g **12g**

(1.5 equiv.) 1.5 equiv. DMBQ, 1.0 equiv. ZnO 40%
1.5 equiv. DMBQ 44%
2.0 equiv. DMBQ 70%

Scheme 8.

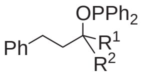
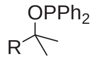
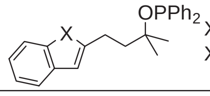
the reactions of secondary alkyl phosphinites having various substituents proceeded smoothly in an S_N2 manner.

Finally, reaction of tertiary alkyl phosphinites was studied. When tertiary alkyl phosphinite **1g** was employed, isocyanide **12g** was obtained exclusively regardless of the presence or absence of ZnO (Scheme 8).

This cyanation was further applied to various phosphinites under the optimized conditions (Table 12). The alkyl phosphinites derived from 3-methyl-1-phenylpentan-3-ol and 3-ethyl-1-phenylpentan-3-ol provided the corresponding isocyanides in good yields (Entries 1 and 2), while the use of a phosphinite having a *tert*-butyldiphenylsilyl or benzo[*b*]furan-2-yl group gave the corresponding product in a high yield (Entries 4 and 5). On the other hand, yield turned out to be moderate when a phosphinite having a 1-methyl(indol-2-yl) or benzylic *tert*-alkyl group was employed (Entries 3 and 6).

Table 12. Isocyanation reaction of *tert*-alkyl phosphinites

$$\underset{\substack{\mathbf{1}\\(1.5\ \text{equiv.})}}{\mathrm{ROPPh_2}} \xrightarrow[\mathrm{CH_2Cl_2},\text{ rt}]{\substack{1.0\ \text{equiv.}\ (\mathrm{EtO})_2\mathrm{P(O)CN}\\2.0\ \text{equiv. DMBQ}}} \underset{\mathbf{12}}{\mathrm{RNC}}$$

Entry	Phosphinite			Time/h	Yield/%
1		R^1 = Me, R^2 = Et	**1I**	7	59
2		R^1 = R^2 = Et	**1J**	3	60^a
3		R = Ph	**1e**	3	33
4		R = $(CH_2)_3OTBDPS$	**1K**	7	71
5		X = O	**1L**	3	67
6		X = NMe	**1M**	7	43^a

^{a}2.0 equiv. of $ROPPh_2$ was used.

Thus, a new type of oxidation–reduction condensation of cyanide anion with various phosphinites was successfully provided. Whereas the nitriles in this reaction were obtained by the use of primary alkyl phosphinites, isocyanides were formed exclusively when secondary alcohols were treated with ZnO or tertiary alkyl phosphinites in the absence of an additive. As for stereochemistry, inversion of configuration takes place in cyanation of optically active phosphinites.

♦ Summary

Novel oxidation–reduction condensation reactions are described. In these reactions, alkyl phosphinites that are readily prepared from alcohols and chlorodiphenylphosphine are converted into inverted substitution product. These methods provide new routes toward chiral hydrosulfides, amines, nitriles, or isocyanides from easily available chiral alcohols.

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