Stereospecific Synthesis of *sec*- and *tert*-Alkyl Azides from Alcohols and Trimethylsilyl Azide by a New Type of Oxidation–Reduction Condensation Using Phenyl Diphenylphosphinite and Trimethylsilylmethyl Azide

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A novel method for the preparation of alkyl azides from alcohols and trimethylsilyl azide by a new type of oxidation–reduction condensation using phenyl diphenylphosphinite and trimethylsilylmethyl azide is described. Chiral secondary and tertiary alcohols are converted into the corresponding chiral azides with almost complete inversion of configuration under mild and neutral conditions.

Conversion of alcohols to their corresponding azides[1] is one of the most important functional group transformations in organic synthesis.[2] The most fundamental method known for azidation is the Mitsunobu reaction,[3] using hydrogen azide as an azide source.[4] The applicability of this reaction is limited owing to the use of highly toxic and explosive hydrogen azide and therefore alternative methods using diphenyl phosphorazidate (DPPA)[5] or zinc azide/bis-pyridine complex[6] are commonly used. Further, methods using DPPA/DBU,[7] p-NO_2DPPA/DBU,[8] and so forth[9] have been reported more recently. In these reactions, primary and secondary alcohols are the most suitable substrates, and chiral secondary alkyl azides are formed from chiral secondary alcohols with complete inversion of configuration by an S_N2 displacement. On the other hand, sterically hindered tertiary alcohols are known not to be converted to the corresponding tertiary alkyl azides.[10]

It was also reported from our laboratory that the oxidation–reduction condensation[11] of tertiary alkyl diphenylphosphinites ($ROPPh_2$), that were prepared from the corresponding *tert*-alcohols, with trimethylsilyl azide ($TMSN_3$) gave the corresponding azides ($R–N_3$) in the presence of methoxybenzoquinone.[12] It is noted that a chiral *tert*-alcohol is converted into the corresponding chiral *tert*-alkyl azide with inversion of configuration. However, in the case of *tert*-alcohol with an α-ester group, azidation that affords an α,α-disubstituted α-amino acid derivative does not proceed efficiently.

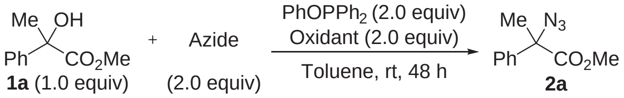
Recently, a newer type of oxidation–reduction condensation[13,14] by using a combination of phenyl diphenylphosphinite ($PhOPPh_2$) and an azide compound as oxidant[15] was reported from our laboratory, which was applied to the stereospecific synthesis of sulfides from alcohols and 2-sulfanyl-1,3-benzothiazole as a sulfur nucleophile. In this reaction, chiral *tert*-alcohols with an α-ester group are converted into the corresponding chiral *tert*-alkyl sulfides with inversion of configuration. In order to extend the utility of this type of reaction, stereospecific azidation of alcohols including *tert*-alcohols with an α-ester group was next studied.

In this communication, we would like to describe a new method for stereospecific synthesis of *sec*- and *tert*-alkyl azides from alcohols and trimethylsilyl azide by a new type of oxidation–reduction condensation using phenyl diphenylphosphinite and an azide compound as oxidant.

In order to find the most suitable azidation reagent, a reaction using tertiary alcohol **1a** in the presence of phenyl diphenylphosphinite ($PhOPPh_2$) and benzyl azide was first examined (Table 1, Entries 1–3). The reaction using tetrabutylammonium azide (Bu_4NN_3) did not afford the desired azide **2a** while **2a** was obtained in a low yield when DPPA was used. In the case of $TMSN_3$, the yield of **2a** increased up to moderate yield and therefore $TMSN_3$ was chosen as a reagent for this azidation. Next, various azide compounds were examined to find the suitable oxidant (Entries 4–6). Then, the use of ethyl azidoacetate and 1-azidoadamantane was shown to lower the yield of **2a** while trimethylsilylmethyl azide gave **2a** in high yield.

After a suitable azidation reagent and an oxidant were chosen, condensation reactions of various chiral alcohols with $TMSN_3$ were tried in order to examine the scope of this reaction under the optimized conditions (Table 2). A reaction of chiral secondary alcohol **1b** proceeded smoothly to afford the corresponding azide in quantitative yield with complete inversion of stereochemistry (Entry 1). The reaction of secondary alcohol with an α-ester group **1c** also afforded the inverted azide in high yield (Entry 2). When benzylic alcohol such as (S)-1-(2-naphthyl)ethanol (**1d**) was employed, the desired product was obtained in high yield with high enantiomeric excess though optical purity was lowered slightly (Entry 3). Further, more hindered tertiary alcohols were employed for substrates so as to investigate potential application of this reaction to the asymmetric construction of quaternary carbon (Entries 4 and 5). Then, the reaction of chiral *tert*-alcohol with an α-ester group **1e** proceeded smoothly to afford the corresponding azide in high yield with

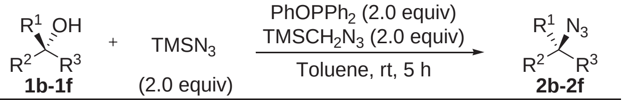
Table 1. Optimization of reaction conditions[a]

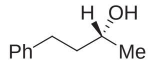
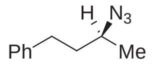
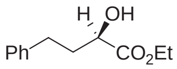
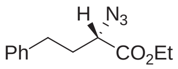
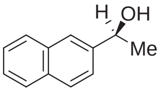
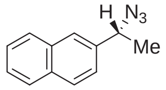
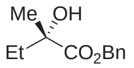
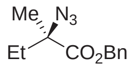
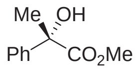
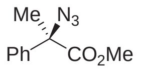


Entry	Azide	Oxidant	Yield/%[b]
1[c]	Bu_4NN_3	N_3CH_2Ph	N.D.
2[c]	DPPA	N_3CH_2Ph	34
3	$TMSN_3$	N_3CH_2Ph	57
4		$N_3CH_2CO_2Et$	9
5		AdN_3	12
6		N_3CH_2TMS	82

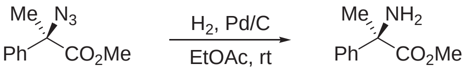
[a] The solution of $PhOPPh_2$ and oxidant was stirred at 80 °C for 20 min, followed by addition of alcohol and azide at rt. [b] Isolated yield. [c] The reaction time was 24 h.

Table 2. Azidation of various chiral alcohols



Entry	ROH	1	Product 2	Yield/%[a] (%ee)
1		1b		quant (>99)[b]
2		1c		98 (>99)[c]
3		1d		85 (97)[b]
4[d,e]		1e		84 (96)[f]
5[d,g,h]		1f		86 (>99)[b]

[a]Isolated yield. [b]The ratio of enantiomer was determined by HPLC analysis after reducing the azide to amine. [c]The ratio of enantiomer was determined by HPLC analysis. [d]$PhOPPh_2$ (3.0 equiv), trimethylsilylmethyl azide (3.0 equiv), $TMSN_3$ (3.0 equiv) were used. [e]The reaction time was 24 h. [f]Ref. 16. [g]The reaction time was 48 h. [h]Ref. 17.



2f

96%, >99%ee

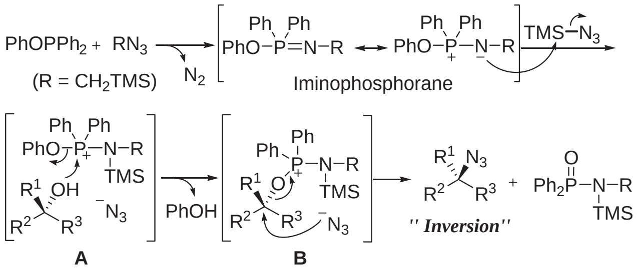
Scheme 1.

high enantiomeric excess (Entry 4). Similarly, chiral benzylic alcohol with an α-ester group **1f** gave the desired product in high yield with complete inversion of stereochemistry (Entry 5).

Since the chiral *tert*-alkyl azide **2f** was converted to the corresponding chiral α-tertiary amine in high yield by hydrogenation, a concise method for the preparation of chiral amines from the corresponding alcohols was established (Scheme 1).

A plausible reaction mechanism is shown in Scheme 2: a reaction of phenyl diphenylphosphinite ($PhOPPh_2$) and trimethylsilylmethyl azide gave initially the corresponding iminophosphorane which in turn resulted in the formation of intermediate **A** by subsequent N-silylation with trimethylsilyl azide. The following nucleophilic attack of an alcohol to the positively charged phosphorus atom led to an intermediate **B**. Finally, a nucleophilic attack of the azide anion (N_3^-) to its phosphonium part via S_N2 manner gave the inverted azide.

Thus, a new method for the preparation of *sec*- or *tert*-alkyl azides from the corresponding alcohols and trimethylsilyl azide by a new type of oxidation–reduction condensation using phenyl diphenylphosphinite and trimethylsilylmethyl azide is established. It is noted that chiral *tert*-alkyl azides 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 stereospecific synthesis of an inverted chiral *tert*-alkyl azide prepared directly from a chiral *tert*-alcohol by an S_N2 displacement.



Scheme 2.

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References and Notes

1 For a review of organic azides, see: S. Bräse, C. Gil, K. Knepper, V. Zimmermann, *Angew. Chem., Int. Ed.* **2005**, *44*, 5188.

2 a) B. M. Trost, I. Fleming, *Comprehensive Organic Synthesis*, Pergamon Press, New York, **1991**, Vol. VI, p. 76. b) S. Hanessian, *Preparative Carbohydrate Chemistry*, Marcel Dekker, New York, **1997**, Chap. 5, 90.

3 a) O. Mitsunobu, *Synthesis* **1981**, 1. b) D. L. Hughes, *Org. React.* **1992**, *42*, 335. c) R. Dembinski, *Eur. J. Org. Chem.* **2004**, 2763. d) T. Y. S. But, P. H. Toy, *Chem. Asian J.* **2007**, *2*, 1340.

4 H. Loibner, E. Zibral, *Helv. Chim. Acta* **1976**, *59*, 2100.

5 B. Lal, B. N. Pramanik, M. S. Manhas, A. K. Bose, *Tetrahedron Lett.* **1977**, *18*, 1977.

6 M. C. Viaud, P. Rollin, *Synthesis* **1990**, 130.

7 A. S. Thompson, G. R. Humphrey, A. M. DeMarco, D. J. Mathre, E. J. J. Grabowski, *J. Org. Chem.* **1993**, *58*, 5886.

8 M. Mizuno, T. Shioiri, *Chem. Commun.* **1997**, 2165.

9 a) A. Saito, K. Saito, A. Tanaka, T. Oritani, *Tetrahedron Lett.* **1997**, *38*, 3955. b) C. Yu, B. Liu, L. Hu, *Org. Lett.* **2000**, *2*, 1959. c) N. Iranpoor, H. Firouzabadi, B. Akhlaghinia, N. Nowrouzi, *Tetrahedron Lett.* **2004**, *45*, 3291.

10 For a recent example of preparation of *tert*-alkyl azides via the Markovnikov addition of an azide anion, see: J. Waser, B. Gaspar, H. Nambu, E. M. Carreira, *J. Am. Chem. Soc.* **2006**, *128*, 11693.

11 For reviews of oxidation–reduction condensation, see: a) T. Mukaiyama, H. Yamabe, *Chem. Lett.* **2007**, *36*, 2. b) T. Mukaiyama, K. Ikegai, H. Aoki, W. Pluempanupat, K. Masutani, *Proc. Jpn. Acad., Ser. B* **2005**, *81*, 103. c) T. Mukaiyama, *Angew. Chem., Int. Ed.* **2004**, *43*, 5590.

12 a) K. Kuroda, Y. Hayashi, T. Mukaiyama, *Tetrahedron* **2007**, *63*, 6358. b) K. Kuroda, N. Kaneko, Y. Hayashi, T. Mukaiyama, *Chem. Lett.* **2006**, *35*, 1432.

13 K. Kuroda, Y. Maruyama, Y. Hayashi, T. Mukaiyama, *Chem. Lett.* **2008**, *37*, 836.

14 K. Kuroda, Y. Hayashi, T. Mukaiyama, *Chem. Lett.* **2008**, *37*, 592.

15 For oxidation–reduction condensation using azides as oxidant, see: a) H. Aoki, K. Kuroda, T. Mukaiyama, *Chem. Lett.* **2005**, *34*, 1266. b) T. Mukaiyama, K. Kuroda, H. Aoki, *Chem. Lett.* **2005**, *34*, 1644. c) S. Torii, H. Okumoto, M. Fujikawa, M. A. Rashid, *Chem. Express.* **1992**, *7*, 933.

16 The ratio of enantiomer **2e** was determined by HPLC analysis after converting the azide to 1,4-disubstituted 1,2,3-triazole on treatment with phenylacetylene in the presence of $CuSO_4 \cdot 5H_2O$ and sodium ascorbate.

17 Typical experimental procedure is as follows (Table 2, Entry 5): to $PhOPPh_2$ (0.60 mmol) in dry toluene (0.30 mL) was added trimethylsilylmethyl azide (0.60 mmol) at rt under Ar atmosphere. After this mixture was stirred for 20 min at 80 °C, alcohol **1f** (0.20 mmol) in dry toluene (0.60 mL) and $TMSN_3$ (0.60 mmol) were added at rt. The reaction mixture was stirred at rt for 48 h and the crude product was purified by preparative TLC to afford the corresponding azide **2f** (86% yield).