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The deoxygenation of sulfoxide mediated by the Ph_3P/Lewis acid combination and the application to the kinetic resolution of racemic phosphines using optically active sulfoxide

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Abstract—It was found that the combination of $Ph_3P/TiCl_4$ was an effective promoter for the deoxygenation of sulfoxides and gave the corresponding sulfides in good yield (up to 97%) under mild conditions. This method was applied to the reaction between racemic phosphines and (*R*)-methyl *p*-tolyl sulfoxide, and it was found that the kinetic resolution was achieved in moderate selectivities.

1. Introduction

Sulfinyl group is one of the most important functional groups in organic synthesis and there are many reports of stereoselective reactions using sulfinyl group as a chiral auxiliary with high stereoselectivity.[1] The sulfinyl group is usually eliminated in two steps; first, the sulfoxide is deoxygenated to sulfide, and after that, the sulfide is removed by catalytic hydrogenation or other chemical means.[2] So, until now, many kinds of methods of the deoxygenation of sulfoxides have been developed; using metal hydride reagents ($LiAlH_4$, $NaBH_4$, etc.), low-valent metallic species ($SnCl_2$, VCl_2, $TiCl_3$ etc.), halide ions (HI, TMSI, TiI_4 etc.) and so on.[3,4] And phosphines were also known as reductants for sulfoxides.[4a,b] For example, the deoxygenation of diphenyl sulfoxide was mediated by Ph_3P, in the presence of $BF_3\cdot OEt_2$, under acetic acid reflux condition. However, in these cases, the drastic conditions were required and the ranges of substrates were limited. Therefore, it was desired the development of the deoxygenations using phosphines, which proceeded under mild conditions and had high generalities of substrates.

On the other hand, we have recently investigated the reaction mediated by the combination of phosphine and Lewis acid and it has been already reported that the several reactions proceeded in good yield with high stereoselectivity using this combination.[5,6] For example, the reduction of various α-bromocarboxylic acid derivatives proceeded in good yield under mild conditions,[5a] and the reduction of 1,2-dicarbonyl compounds was smoothly mediated by the $Ph_3P/AlBr_3$ combination.[5e] We herein would like to describe the deoxygenation of sulfoxides mediated by the phosphine and Lewis acid combination under mild conditions. Moreover, we would like to show the application to the kinetic resolution of racemic phosphines.

2. Results and discussion

2.1. The deoxygenation of sulfoxide

First, we examined the deoxygenation of diphenyl sulfoxide (**1a**) using the combination of Ph_3P and several Lewis acids, such as $AlCl_3$, $BF_3\cdot OEt_2$, $SnCl_4$ and $TiCl_4$, in CH_2Cl_2 at room temperature. Among Lewis acids examined, it was found that only $TiCl_4$ gave a good result. However, under these conditions, the deoxygenation of other aliphatic sulfoxides could not proceed in satisfied yield. So, we examined the effect of solvents in the deoxygenation of dibenzyl sulfoxide (**1b**) using Ph_3P and $TiCl_4$ combination. Then, it was found that THF was the most effectively solvent and the highest yield (96%) was achieved.

Under the optimized conditions, the deoxygenation of several kinds of sulfoxides was carried out. The results are summarized in Table 1.

As can be seen from Table 1, it was found that the deoxygenation of sulfoxides was effectively mediated by this combination. Moreover, it should be noted that even if

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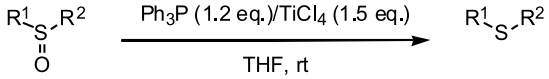
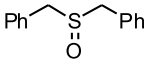
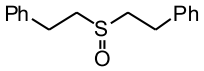
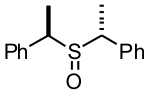
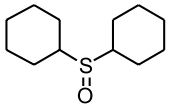
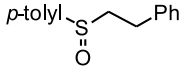
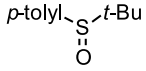
Table 1. The deoxygenation of sulfoxides using the combination of $Ph_3P/TiCl_4$



Entry	Substrate		Time (h)	Yield (%)[a]
1	**1a**		24	88
2	**1b**		2	96
3			24	88[b]
4	**1c**		1	92
5	**1d**		24	78
6	**1e**		2	67
7	**1f**		14	96
8	**1g**		2	97
9[c]	**1h**		14	90

[a] Isolated yields.
[b] Reaction was carried out using 0.5 equiv of $TiCl_4$.
[c] Reaction was carried out at 60 °C

the substrates possessed the bulky substituents, namely secondary or tertiary alkyl sulfoxides, the reaction proceeded smoothly in good yield (entries 5, 7, 9). And the reaction was also found to proceed in 88% yield using a catalytic amount of $TiCl_4$ (0.5 equiv) although the reaction rate was slower than that of the reaction using excess $TiCl_4$ (entries 2 and 3).

In summary, we found that the deoxygenation of sulfoxides smoothly proceeded in the presence of the Ph_3P and $TiCl_4$ combination in THF at room temperature and that this deoxygenation had high generalities.

2.2. Kinetic resolution of racemic phosphines

It is possible to consider this reaction, deoxygenation of sulfoxides, as the oxidation of the phosphine using the sulfoxide and Lewis acid combination. So, if the optically active sulfoxide is used with Lewis acid, it is assumed that this reaction can be applied to the asymmetric oxidation. Namely, it is expected that the kinetic resolution of racemic phosphines can be achieved to give the optically active phosphines. The optically active phosphines have many important roles in organic syntheses, especially in the transition metal catalyzed asymmetric reactions.[7] Therefore, a lot of methods for preparation of optically active phosphines have been developed. Recently, the kinetic resolution of planar chiral ferrocenyl phosphine was reported using selenoxide having an optically active binaphthyl skeleton.[8] But there were few reports to obtain the optically active phosphines using such a kinetic resolution. Then, we examined the kinetic resolution of racemic phosphines using optically active sulfoxides and Lewis acid combinations.

Initially, we carried out the kinetic resolution of racemic methyl(1-naphthyl)phenylphosphine using the combination of (*R*)-methyl *p*-tolyl sulfoxide (**2a**) and $TiCl_4$ in THF. Then, the reaction was found to proceed smoothly to give (*S*)-methyl(1-naphthyl)phenylphosphine in 32% yield with 18% ee.

Next, we screened a variety of optically active sulfoxides (Fig. 1) and $TiCl_4$ combination in the kinetic resolution of racemic methyl(1-naphthyl)phenylphosphine. Among the sulfoxides examined (**2a**–**e**), it was found that the highest enantioselectivity was achieved in the case of using (*R*)-methyl *p*-tolyl sulfoxide (**2a**). So, under these conditions, kinetic resolution of several sorts of racemic phosphines (**3a**–**e**) was carried out. The results are summarized in Table 2.

As shown in Table 2, the moderate enantioselectivity could be achieved in the reaction of P-chiral phosphine derivatives (**3a**, **3b**), the planer chiral phosphine (**3d**) and even the phosphine having a chiral center on neighboring carbon

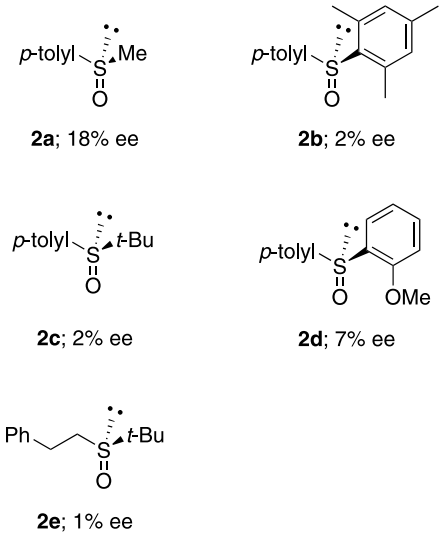


Figure 1. The used sulfoxide and the enantiomeric excess of methyl(1-naphthyl)phenylphosphine resolved by the sulfoxide.

atom (**3c**). Among them, it was noticed that the better results were obtained in the reaction of phosphines possessing the coordinating group (**3b**, **3d**).

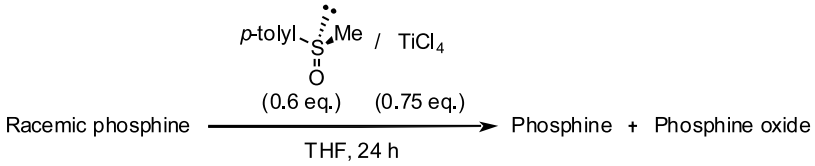
2.3. Mechanism

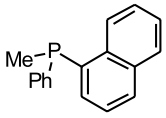
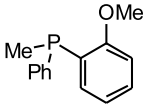
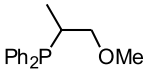
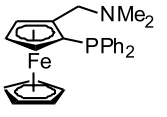
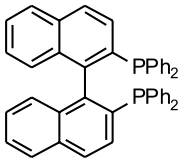
The mechanism of the kinetic resolution of methyl-(1-naphthyl)phenylphosphine (**3a**) could be explained as follows (Scheme 1): first, $TiCl_4$ coordinated the oxygen atom of (*R*)-methyl *p*-tolyl sulfoxide (**2a**). After that, phosphine (**3a**) attacked sulfur atom from behind the lone pair and then the intermediate (**4a**) and (**4b**) were formed. However, the formation of the intermediate (**4b**) was more disadvantageous than the formation of the intermediate (**4a**) because of the steric repulsion between naphthyl substituent and *p*-tolyl substituent. So, the reaction prefers to go through the intermediate (**4a**) to give the intermediate (**5**) and the (*S*)-methyl(1-naphthyl)phenylphosphine oxide was formed preferably.

3. Conclusion

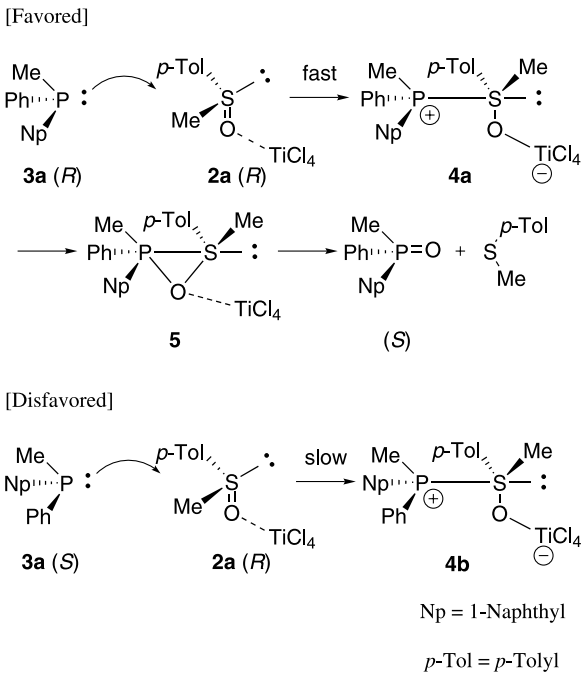
We found that the deoxygenation of many kinds of sulfoxides was effectively promoted by the combination of

Table 2. The kinetic resolution of several racemic phosphines mediated by the combination of (*R*)-methyl *p*-tolyl sulfoxide and $TiCl_4$



Entry	Substrate		Temperature (°C)[a]	Phosphine		
				Yield (%)[b]	ee (%)	Ref.
1	**3a**		−40	32	18 (*S*)[c,d]	18b
2	**3b**		0	37	23 (*S*)[e]	19
3	**3c**		0	21	12 (*S*)[f]	20
4	**3d**		0	34	26 (*R*)[f]	21
5	**3e**		rt	49	4 (*S*)[f]	22a

[a] These were the lowest temperatures to be able to carry out the reaction.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis (Daicel Chiralcel OJ).
[d] The corresponding phosphine oxide was obtained in 59% yield with 14% (*S*) ee.
[e] Determined by chiral HPLC analysis (Daicel Chiralcel OJ) of the corresponding phosphine–borane.
[f] Determined by optical rotation.



Scheme 1.

Ph_3P and $TiCl_4$ under mild conditions in good yield. This reaction was found to be a very useful reaction in organic synthesis because of the easy operation, mild conditions and high generalities of substrates. Moreover, it was found that the (*R*)-methyl *p*-tolyl sulfoxide/$TiCl_4$ combination was the effective promoter for the kinetic resolution of several types of racemic phosphines. Further examination of the kinetic resolution is now in progress.

4. Experimental

4.1. General

The starting materials (**1a**, **1b**, **1e**) and reagents, purchased from commercial suppliers, were used after standard purification. Solvents were dried over sodium or molecular sieves, and were distilled before use. The reaction flasks were flame-dried under a steam of argon. Preparative TLC (PTLC) was carried out with Wakogel B-5F. ^{1}H NMR spectra were recorded on a Varian Mercury 300 at 300 MHz using tetramethylsilane as an internal standard. Optical rotations were recorded on a JASCO DIP-360. Analytical HPLC was performed using a Daicel Chiralcel OJ column with the detector wavelength at 254 nm. Sulfoxides (**1c**,[9] **1d**,[10] **1f**,[11] **1g**,[12] **1h**[13]), enantiomerically pure sulfoxides (**2a**,[14] **2b**,[15] **2c**,[13] **2d**,[16] **2e**[17]) and phosphines (**3a**,[18] **3b**,[19] **3c**,[20] **3d**,[21] **3e**[22]) were prepared according to the literature procedures. $TiCl_4$ was used as a 3 mol/L solution in hexane.

4.2. General procedure for the deoxygenation of sulfoxide

To a solution of sulfoxide (0.20 mmol) and $TiCl_4$ (0.3 mmol) in THF (2.5 mL) was added a solution of triphenylphosphine (0.24 mmol) in THF (1.5 mL) and the mixture was stirred at appropriate temperature under an argon atmosphere. The reaction was quenched with saturated sodium hydrogencarbonate (10 mL), and the mixture was extracted with ether (3×10 mL). The combined ether layers were washed with brine (1×10 mL) and dried over Na_2SO_4. This organic layer was filtered and evaporated under reduced pressure, and then the crude product was purified by preparative TLC to give the corresponding sulfide. All sulfides are known compounds and were characterized by a comparison of their spectral data with those of authentic samples prepared or those from the literature (Table 1).[9–11,23,24]

4.3. General procedure for kinetic resolution

To a solution of (*R*)-methyl *p*-tolyl sulfoxide (0.12 mmol) and $TiCl_4$ (0.15 mmol) in THF (2 mL) was added a solution of racemic phosphine (0.2 mmol) in THF (1 mL) and the mixture was stirred at appropriate temperature under an argon atmosphere. The reaction was quenched with aqueous 1 N NaOH (10 mL) and the mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over Na_2SO_4. This organic layer was filtered and evaporated under reduced pressure, and then the crude product was purified by preparative TLC to give the desired chiral phosphines. Absolute configurations and enantiomeric excess of all products were determined by a comparison of their optical rotation or HPLC analysis with those of the literature (Table 2).[18b–22a]

4.3.1. (*S*)-Methyl(1-naphthyl)phenylphosphine (3a). The enantiomeric excess was determined as 18% by an HPLC analysis using chiral column: Daicel Chiralcel OJ, hexane: 2-propanol=93:7, 0.6 mL/min, 10.3 min (*R*), 13.9 min (*S*). The absolute configuration was determined as *S* by a comparison of their optical rotation with that of the literature.[25]

4.3.2. (*S*)-Methyl(1-naphthyl)phenylphosphine oxide.[18b] The enantiomeric excess and absolute configuration were determined as 14% (*S*) by an HPLC analysis using chiral column: Daicel Chiralcel OJ, hexane:2-propanol=90:10, 0.6 mL/min, 19.4 min (*S*), 24.0 min (*R*).

4.3.3. (*S*)-2-Methoxyphenyl(methyl)phenylphosphine (3b). The enantiomeric excess and absolute configuration were determined as 23% (*S*) by an HPLC analysis of the corresponding phoshphine–borane using chiral column: Daicel Chiralcel OJ, hexane:2-propanol=90:10, 0.5 mL/min, 17.2 min (*S*), 32.9 min (*R*).[18b]

4.3.4. (*S*)-(2-Methoxy-1-methylethyl)diphenylphosphine (3c). The enantiomeric excess was determined as 12% by an optical rotation; $[\alpha]_D=-2.8$ (*c* 0.432, CH_2Cl_2). Lit;[20] $[\alpha]_D=+23.5$ (*c* 1, CH_2Cl_2) of an (*R*)-isomer.

4.3.5. (*R*)-[2-(*N*,*N*-Dimethylaminomethyl)ferrocenyl]diphenylphosphine (3d). The enantiomeric excess was determined as 26% by an optical rotation; $[\alpha]_D=+84$ (*c* 0.3, $CHCl_3$). Lit;[21] $[\alpha]_D=+324$ (*c* 0.5, $CHCl_3$).

4.3.6. (*S*)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl (3e). The enantiomeric excess was determined as 4% by

an optical rotation; $[\alpha]_D = -8.5$ (*c* 0.15, benzene). Lit;[22a] $[\alpha]_D = -229$ (*c* 0.31, benzene).

Acknowledgements

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