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Efficient Methods for the Preparation of Alkyl−Aryl and Symmetrical or Unsymmetrical Dialkyl Ethers between Alcohols and Phenols or Two Alcohols by Oxidation−Reduction Condensation

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Abstract: Oxidation−reduction condensation via alkoxydiphenylphosphines (diphenylphosphinite esters) (**1**), generated in situ from chlorodiphenylphosphine (**2**) and alcohols, 2,6-dimethyl-1,4-benzoquinone (**3**), and phenols proceeds smoothly to afford alkyl−aryl ethers in good to high yields under neutral conditions. In a similar fashion, a new and efficient method for the preparation of symmetrical or unsymmetrical dialkyl ethers in good to high yields is established via tetrafluoro-1,4-benzoquinone (fluoranil) (**4**), alcohols, and **1** formed in situ from ^{n}BuLi-treated alcohols and **2**. This method is applicable also to the etherification of chiral secondary or tertiary alcohols with retention or inversion of configurations. The inverted ethers are afforded by treating chiral alkoxydiphenylphosphines and achiral alcohols, while the reaction of achiral alkoxydiphenylphosphines and chiral alcohols forms retained ethers.

Introduction

The preparation of ethers is one of the most fundamental and frequently used important reactions in synthetic organic chemistry. In 1850, the first examples of the formation of carbon−oxygen single bonds were reported via alkoxides and alkyl halides (Williamson ether synthesis).[1] The attack of alkoxides on alkyl halides, however, was synthetically effective only when the primary alkyl halide was used. When the secondary or tertiary alkyl halides were used, the desired ethers were obtained in low yields together with the corresponding olefins simultaneously formed by elimination reactions. Several O-alkylation reactions took place when olefins (in 1963),[2] dialkyl phosphates (in 1972),[3] aldehydes (in 1987),[4] nitro compounds (in 1987),[5] *p*-toluenesulfonic acid (in 1990),[6] or imidates (in 1998)[7] were allowed to react with alcohols. The trimethylsilyl triflate-catalyzed reaction of acetals and trialkylsilanes was also reported by Noyori et al. in 1979.[8] Another method of ether synthesis by treating carbonyl compounds such as aldehydes and triethylsilane in the presence of trityl perchlorate as a catalyst (in 1985) was reported from our laboratory.[9] Olah and co-workers also demonstrated trimethylsilyl iodide catalyzed reductive coupling of carbonyl compounds with trialkylsilanes (in 1987).[10] Recently, Nishiyama et al. reported ether synthesis via magnesium alkoxides and trifluoromethanesulfonic anhydride (in 1999).[11] Even after the above publications, the preparation of various ethers in high yields under mild conditions still remains a challenging topic in synthetic chemistry.

There are a number of examples for S_N2 displacement reactions of chiral secondary or tertiary centers with nucleophiles that form the inverted chiral substituted products.[12] Of these S_N2 displacement reactions via compounds which have a secondary carbon, a coupling reaction of chiral secondary alcohols with phenols in the presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine is most widely employed for the synthesis of alkyl−aryl ethers.[13] Ingold[14] first reported that the corresponding methyl ether, *tert*-aliphatic compound, was obtained with 34% inversion by S_N2 replacement when (*R*)-3-chloro-3,7-dimethyloctane was treated with methanol (1950). Doering[15] then reported the solvolysis of (+)-hydrogen 2,4-dimethyl-4-hexyl phthalate in refluxing MeOH which afforded the corresponding ether with 54% inversion and 46% racem-

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(3) Kashman, Y. *J. Org. Chem.* **1972**, *37*, 912.
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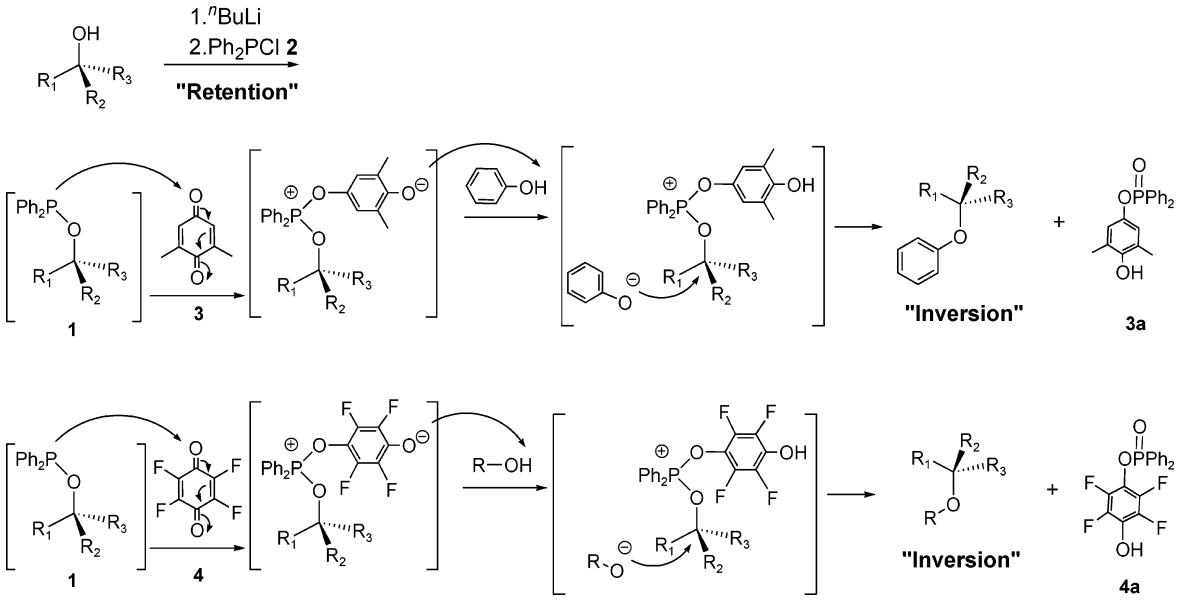
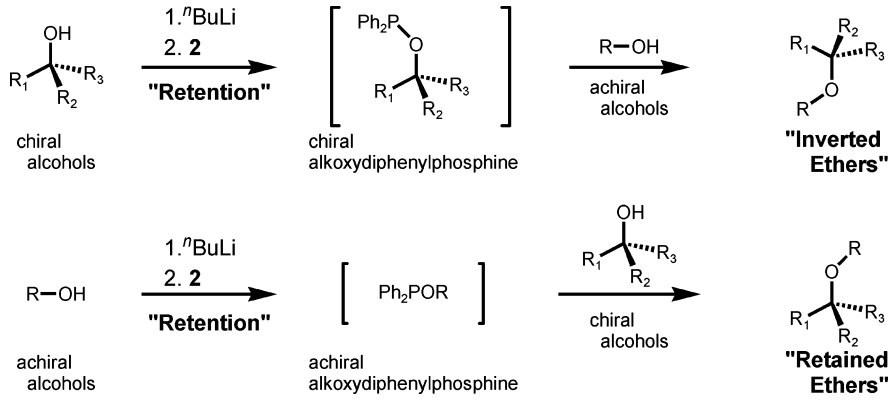
(15) Derling, W. von E.; Zeiss, H. H. *J. Am. Chem. Soc.* **1953**, *75*, 4733.

Scheme 1. Etherification of Phenols or Alcohol with **3** or **4**



Scheme 2. Etherification with Retention or Invertion



ization (1953). In 2000, Müller[16] reinvestigated the methanolysis of (*R*)-3-chloro-3,7-dimethyloctane to study the solvent effects on steric course of solvolysis via thionyl chloride and pyridine. Tertiary-acyclic derivatives such as (*R*)-3-chloro-3,7-dimethyloctane in methanol or ethanol, etc., afforded the inverted ethers in 18−40% yields with 76−87% inversion. Recently, the stereospecific synthesis of chiral tertiary alkyl−aryl ethers by Mitsunobu reaction was introduced by Shi[17] et al. in which the complete inversion of configuration was attained with about 50% chemical yields (2003).

As shown in our previous reports, oxidation−reduction condensation using in situ-generated **1**, carboxylic acids, and **3**[18] or 1,4-benzoquinone[19] (**5**) provided a new and efficient method for the preparation of primary, inverted secondary, and tertiary alkyl carboxylates from the corresponding alcohols under mild and neutral conditions without any assistance from acids or bases. A reaction of alkoxydiphenylphosphine with a weak oxidant such as quinone was therefore considered to form a key intermediate, phosphonium salt, more smoothly than that of triphenylphosphine because of the increased reducing ability. In addition, alkoxydiphenylphosphine which was formed by the introduction of an alkoxy part to a trivalent phosphorus compound in advance worked more effectively in the formation of alkoxyphosphonium salt, an important key intermediate. To extend the scope of these reactions, condensation reactions of in situ-formed alkoxydiphenylphosphine from **2** and alcohols with phenols or alcohols were investigated.

This Article describes an efficient method for the preparation of alkyl−aryl ethers and symmetrical or unsymmetrical dialkyl ethers in good to high yields by oxidation−reduction condensation using **3** or **4**,[20] phenol or alcohols, and **1** in situ-formed from **2** and alcohols under mild conditions (Scheme 1). The present etherification of chiral secondary or tertiary alcohols proceeded with retention or inversion of configuration; that is, treatment of chiral alkoxydiphenylphosphines with phenols or achiral alcohols expectedly afforded the inverted ethers, and the reaction of achiral alkoxydiphenylphosphines with chiral alcohols afforded the retained ethers (Scheme 2).

Results and Discussion

Preparation of Alkyl−Aryl Ethers by Oxidation−Reduction Condensation Using Phenols. There are a number of

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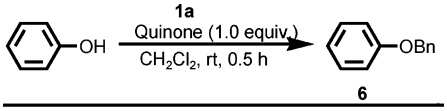
(20) Shintou, T.; Mukaiyama, T. *Chem. Lett.* **2003**, *32*, 984.

Table 1. Benzylation of Phenol with **1a** and Quinones



entry	**1a** (equiv.)	quinone	yield (%)
1	1.1	**5**	49
2	1.1	**3**	85
3	1.1		72[a]
4	1.2		85
5	1.5		92

[a] To a mixture of phenol and **3** was added **1a** in CH_2Cl_2 at 0 °C, and then it was reacted for 0.5 h at room temperature.

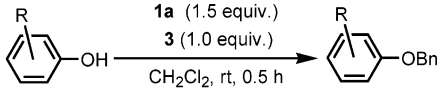
reactions that employ alkoxydiphenylphosphines **1**, for example, in peptide syntheses or Arbuzov reactions. Phosphines which have a primary, secondary, or tertiary alkoxy group are prepared easily from **2** and the corresponding alcohols in the presence of a base such as pyridine or triethylamine and are generally isolated by distillation. Alkoxydiphenylphosphines **1** are also prepared in situ by treating primary or secondary alcohols with aminodiphenylphosphine such as (*N*,*N*-dimethylamino)diphenylphosphine, while no corresponding alkoxydiphenylphosphine was detected in the case where tertiary alcohols were used. Alternatively, alkoxydiphenylphosphines **1** are in situ-generated from ^{n}BuLi-treated primary, secondary, or tertiary alcohols and **2**.

As shown in our previous reports, oxidation−reduction condensation using **1**, carboxylic acids, and **3** provided a new and efficient method for the preparation of primary, secondary, and tertiary alkyl carboxylates from the corresponding alcohols under almost-neutral conditions without any assistance from acids or bases. To extend the scope of these reactions, the formation of alkyl−aryl ethers via condensation between alcohols and phenols was examined via the above-mentioned **1**. In the first place, benzylation of phenol was examined using benzyloxydiphenylphosphine (**1a**), which was isolated by distillation. Benzyl phenyl ether was obtained in 49% yield within 0.5 h by treating phenol and 1.1 equiv of **1a** with 1.0 equiv of **5** in dichloromethane at room temperature (Table 1, entry 1). When quinone **3** was used under the same conditions, the desired product was obtained in 85% yield (Table 1, entry 2). However, the yield lowered to 72% when 1.1 equiv each of **3** and **1a** were allowed to react with phenol in dichloromethane at 0 °C and after stirring was continued for an additional 0.5 h at room temperature (Table 1, entry 3). Benzylation of phenol proceeded smoothly to afford the desired ether in 92% yield when 1.5 equiv of **1a** was used (Table 1, entry 5).

Next, benzylation of various phenols was examined via 1.5 equiv of **1a** and 1.0 equiv of **3** in dichloromethane (Table 2). Benzylation of phenols which have electron-donating or electron-withdrawing groups proceeded smoothly under mild conditions to afford the corresponding benzyl ethers in good yields (Table 2, entries 1−5). When an ortho-substituted phenol such as 2,6-dimethylphenol was used under the above conditions for 0.5 h at room temperature, the corresponding ether was obtained in 70% yield (Table 2, entry 6). Similarly, the desired products were obtained in 81% and 84% yields, respectively, when 1-naphthol or 2-naphthol was used (Table 2, entries 7 and 8).

Results of alkylations of phenols with **3** and **1** are shown in Table 3. When alkoxydiphenylphosphines **1** which have primary or secondary alkoxy groups were used, the corresponding alkyl

Table 2. Benzylation of Various Phenols with **1a** and **3**



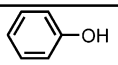
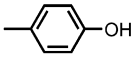
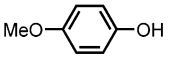
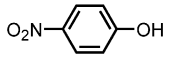
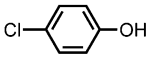
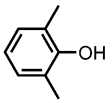
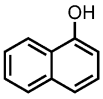
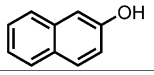
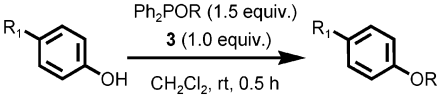
entry	PhOH derivative	product	yield (%)
1		**6**	92
2		**7**	82
3		**8**	78
4		**9**	88
5		**10**	84
6		**11**	70
7		**12**	81
8		**13**	84

Table 3. Alkylation of Phenol or *p*-Nitrophenol with **1** and **3**



entry	R^1	Ph_2POR	product	yield (%)
1	H	Ph_2POMe	**14**	88
2	H	Ph_2POEt	**15**	84
3	H	Ph_2PO^nBu	**16**	87
4	H	Ph_2PO^iPr	**17**	81
5	NO_2	Ph_2PO^tBu	**18**	62[a]

[a] The reaction mixture was refluxed for 10 h.

phenyl ethers were obtained in good yields (Table 3, entries 1−4). In the case of *tert*-butoxydiphenylphosphine which has a bulky substituent such as a *tert*-butyl group, however, the yield lowered to 62% even after the dichloromethane solution was refluxed for 10 h (Table 3, entry 5).

One-pot etherification of phenol by the present oxidation−reduction condensation that used **3** and in situ-formed alkoxydiphenylphosphine from (*N*,*N*-dimethylamino)diphenylphosphine and 1-phenylethyl alcohol at room temperature for 2.0 h also afforded the desired ether in 82% yield (Scheme 3).[21]

A new and efficient method for the preparation of primary, inverted secondary, and tertiary alkyl carboxylates from the corresponding alcohols under mild and neutral conditions was also established by the condensation using in situ-generated **1** from **2** and ^{n}BuLi-treated alcohols, various carboxylic acids, and **3** or 1.7 equiv of simple **5** as shown in previous communications. Reactions of alcohols with phenols forming alkyl−aryl ethers according to the present one-pot procedure were then further examined. First, benzylation of phenol with **3** or **5** was

(21) Effective one-pot esterifications of various carboxylic acids have been established by applying this type of oxidation−reduction condensation using a combination of **3** and **1** in situ-formed from (*N*,*N*-dimethylamino)-diphenylphosphine and primary or secondary alcohols.

Scheme 3. Etherification of PhOH with 1-Phenylethyl Alcohol via Ph_2PNMe_2

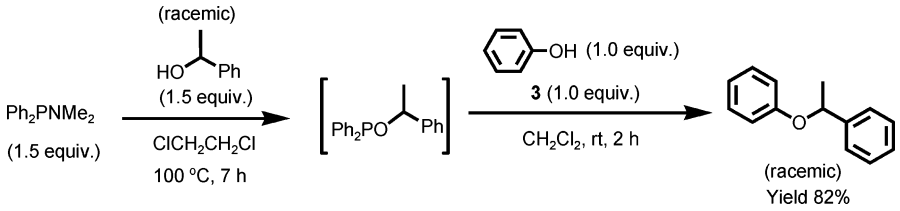
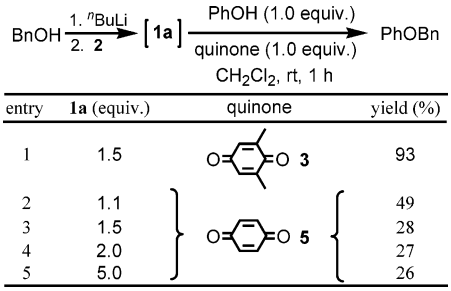


Table 4. Benzylation of Phenol with Quinones



entry	**1a** (equiv.)	quinone	yield (%)
1	1.5	O=⟨⟩=O **3**	93
2	1.1	O=⟨⟩=O **5**	49
3	1.5		28
4	2.0		27
5	5.0		26

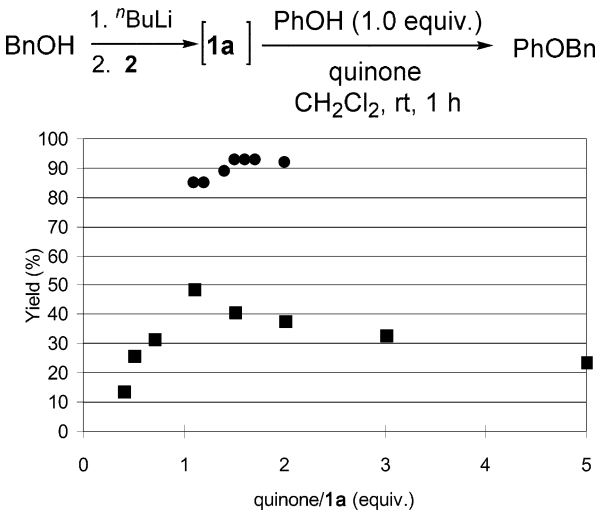
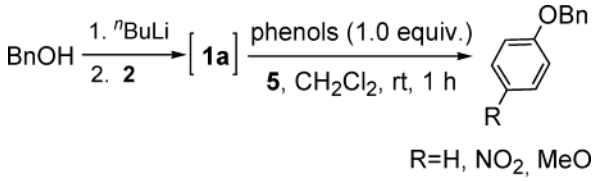


Figure 1. Benzylation of phenol (●, 1.0 equiv of **3**; ■, 1.5 equiv of **5**).

examined in CH_2Cl_2 at room temperature to find suitable conditions concerning the molar ratio of **1a**, in situ-formed from benzyl alcohol and **2**, and **5** (Table 4). The yield of the ether was not influenced by the amount of **1a** (1.5−5.0 equiv) when 1.0 equiv each of phenol and **5** were used (Table 4, entries 3−5). The reaction conditions that used **3** or **5** were further screened so as to improve the chemical yield, which showed the desired product in 49% (Figure 1).

The above benzyl ether was obtained in 93% yield when 1.5 equiv of in situ-formed **1a** and 1.0 equiv of **3** were treated with 1.0 equiv of phenol at room temperature for 1 h. In the case of using **5** under the same conditions, however, ether was obtained in 49% yield when a combination of 1.1 equiv each of in situ-formed **1a** and **5** were treated with 1.0 equiv of phenol. Next, etherifications of phenols which have electron-donating or electron-withdrawing groups such as 4-methoxyphenol or 4-nitrophenol with in situ-formed **1a** and **5** were examined under the above conditions; however, the corresponding ethers were obtained in low yields as shown in Figure 2.

Etherification of the above-mentioned phenols was further tried under the reaction conditions such that the stirring of the reaction mixture in toluene was continued for 1.0 h by keeping



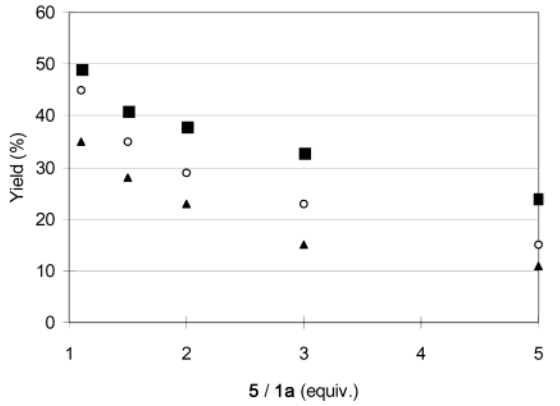
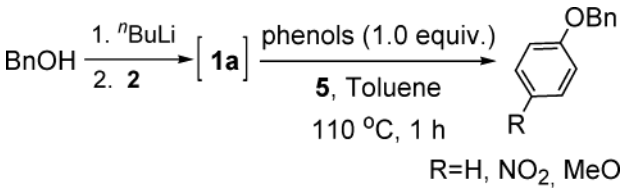


Figure 2. Benzylation of phenols via **5** at room temperature (■, phenol; ○, 4-nitrophenol; ▲, 4-methoxyphenol).



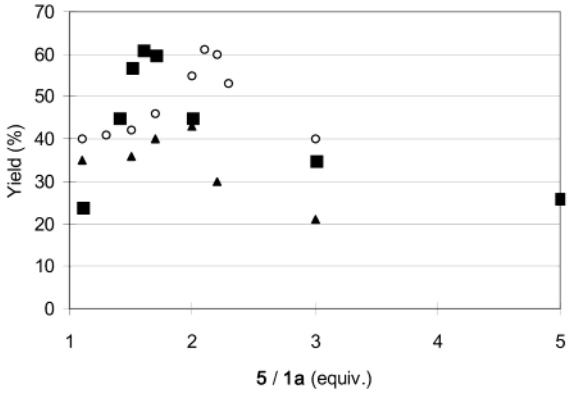


Figure 3. Benzylation of phenols via **5** at 110 °C (■, phenol; ○, 4-nitrophenol; ▲, 4-methoxyphenol).

the temperature of the oil bath at 110 °C. The outcome of the corresponding ethers is shown in Figure 3. These results indicate that reaction using **5**, in situ-formed **1a**, and phenols afforded the corresponding benzyl phenols in moderate yields and byproduct diphenylphosphonic acid 4-benzyloxyphenyl ester (**19**) was formed by competitive reaction between the two benzyloxydiphenylphosphonium salts (Scheme 4). The above results indicated that the concentration of the reaction mixture

Scheme 4. Mechanism of Formation or Inhibition of Byproduct with **3** or **5**

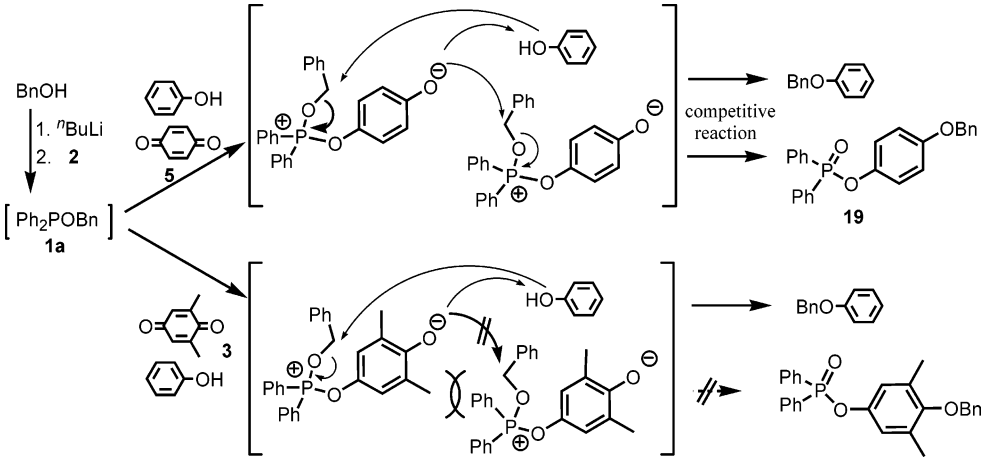
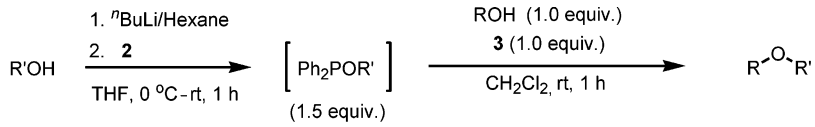
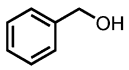
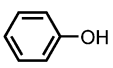
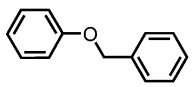
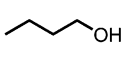
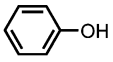
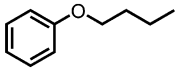
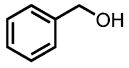
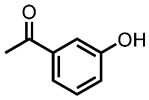
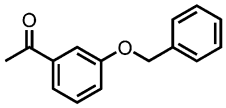
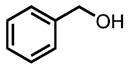
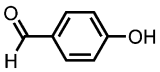
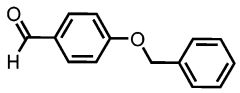
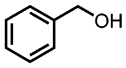
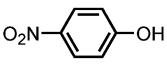
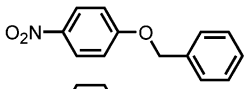
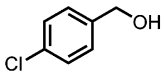
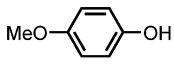
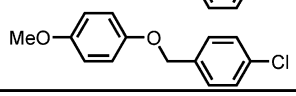


Table 5. Etherification of Various Phenols Using Several *n*BuLi-Treated Primary Alcohols



entry	R'OH	ROH	product		yield (%)
1				**6**	93
2				**16**	90
3				**20**	89
4				**21**	88
5				**9**	92
6				**22**	91

influenced the formation of byproduct. Thus, it is noted that a key intermediate, the phosphonium salt, was smoothly provided by an interaction of alkoxydiphenylphosphine with **3**, and benzyl phenyl, an alkyl aryl ether, was afforded in high yield by further reaction with phenols.

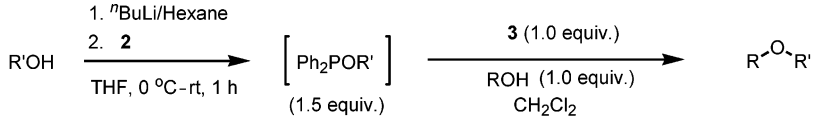
Next, etherifications of 1.5 equiv of in-situ generated **1** from **2** and several primary alcohols with 1.0 equiv each of various phenols and **3** were examined (Table 5). When phenols which have an electron-donating or electron-withdrawing group and primary alcohol were used, the corresponding alkyl−aryl ethers were obtained in high yields at room temperature (Table 5, entries 1−6).

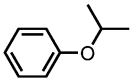
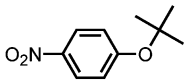
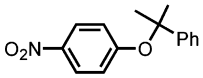
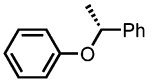
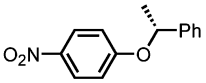
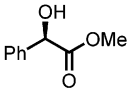
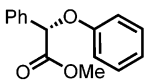
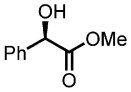
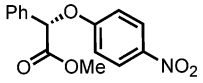
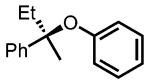
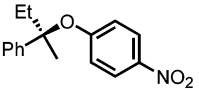
Next, etherifications of various in situ-formed chiral and achiral secondary or tertiary alkoxydiphenylphosphine **1** with phenol or 4-nitrophenol were examined (Table 6). The desired ethers were obtained in 72−86% yields at room temperature in the case when several achiral secondary or tertiary alcohols and phenols were used (Table 6, entries 1−3). Etherifications of chiral secondary alcohols such as (*R*)-(+)-1-phenylethanol or methyl (*R*)-(−)-mandelate with phenol or 4-nitrophenol proceeded smoothly in dichloromethane at room temperature to afford the corresponding ethers in good yields with almost complete inversion of configuration (Table 6, entries 4−7). Similarly, the desired ethers were obtained in 84% yield with 99% inversion or 88% yield with 99% inversion, respectively, when a chiral tertiary alcohol such as (*S*)-2-phenyl-2-butanol was treated with phenol or 4-nitrophenol (Table 6, entries 8 and 9).

Thus, an effective one-pot etherification of various phenols was established via the oxidation−reduction process via a combination of **3** and in situ-formed **1** from **2** and *n*BuLi-treated primary, secondary, or tertiary alcohols.

Preparation of Symmetrical or Unsymmetrical Ethers by Oxidation−Reduction Condensation Using Two Alcohols. The O-alkylation reaction of 2.0 equiv of 2-phenylethanol in dichloromethane with 1.0 equiv of **3** and 1.0 equiv of **1a**, in situ-formed from *n*BuLi-treated benzyl alcohol and **2**, did not afford the desired ether (Table 7, entry 1). An important

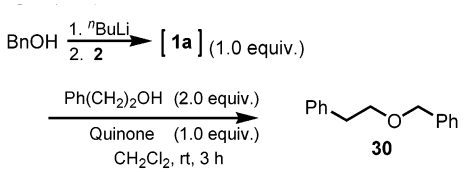
Table 6. Etherification of Phenol or 4-Nitrophenol Using Various ^{n}BuLi-Treated Secondary or Tertiary Alcohols



entry	R'OH	ROH	time (h)	product		yield (%)	inversion (%)
1		PhOH	3		**17**	86	—
2		4-NO_2-C_6H_4-OH	12		**18**	72	—
3		4-NO_2-C_6H_4-OH	6		**23**	86	—
4[a]		PhOH	3		**24**	85	98
5[b]		4-NO_2-C_6H_4-OH	3		**25**	88	99
6[c]		PhOH	3		**26**	90	>99
7[c]		4-NO_2-C_6H_4-OH	3		**27**	91	>99
8[c]		PhOH	6		**28**	84	99
9[c]		4-NO_2-C_6H_4-OH	6		**29**	88	99

[a] DAICEL CHIRALCEL OD column was used for HPLC analysis. [b] DAICEL CHIRALCEL OJ column was used for HPLC analysis. [c] DAICEL CHIRALCEL OB column was used for HPLC analysis.

Table 7. Effect of Quinone Derivatives on Etherification of Phenylethyl Alcohol



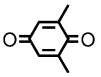
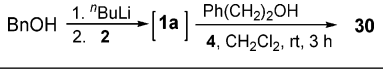
entry	quinone	yield (%)
1		N.R.
2		18
3		6
4		72

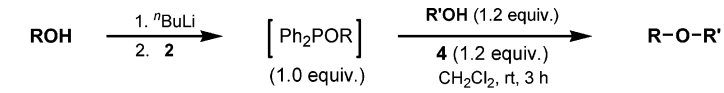
Table 8. Etherification of Phenylethyl Alcohol with **1a** and **4**

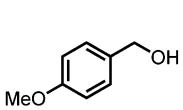
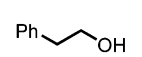
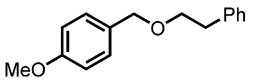
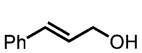
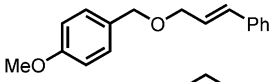
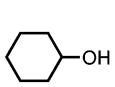
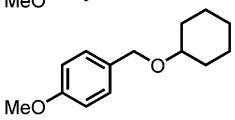
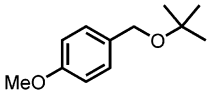
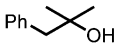
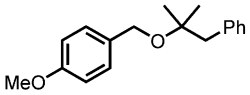
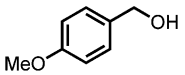
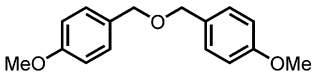
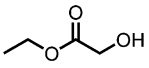
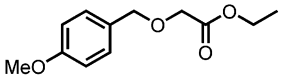
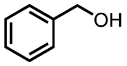
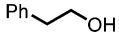
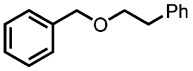
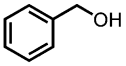
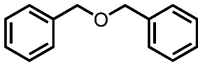
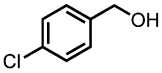
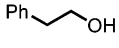
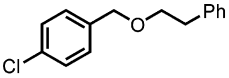
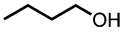
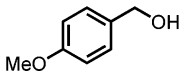
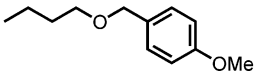


entry	**1a** (equiv)	$Ph(CH_2)_2OH$ (equiv)	**4** (equiv)	yield (%)
1	1.0	2.0	1.0	72
2	2.0	1.0	1.0	70
3	1.0	2.0	1.5	87
4	1.0	1.5	1.5	88
5	1.0	1.2	1.5	92
6	1.0	1.0	1.5	87
7	1.0	1.2	1.3	92
8	**1.0**	**1.2**	**1.2**	**92**
9	1.0	1.2	1.1	85
10	1.0	1.2	1.0	72

intermediate, phosphonium salt, was considered to be formed effectively by application of oxidants such as **3** because the alkoxy part was introduced to phosphine in advance, but the phosphonium salt was not converted to the pentavalent phosphorus intermediate because the key step of abstraction of one hydrogen atom from the alcohols did not take place smoothly under the conditions. An employment of a more powerful oxidant such as fluoranil was then considered, and the reaction with alcohols and **1**, in situ-formed from ^{n}BuLi-treated alcohols and **2**, was examined. It was considered that the intermediate phosphonium salt would be in turn converted successfully to the so-called pentavalent phosphorus compound by catching one hydrogen atom from alcohols and the corresponding symmetrical

Table 9. Etherification via **4**, Various Alcohols, and **1** in Situ-Formed from Primary Alcohols, **2**, and ^{n}BuLi



entry	ROH	R'OH	product		yield (%)
1				**31**	95
2				**32**	90
3				**33**	90
4				**34**	89
5				**35**	94
6				**36**	94
7[a]				**37**	86
8				**30**	92
9				**38**	94
10				**39**	75
11				**40**	63

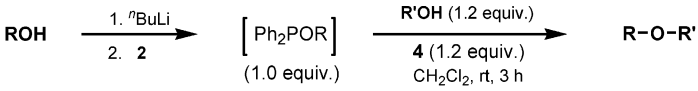
[a] 1.0 equiv of fluoranil was used.

or unsymmetrical ethers would be formed in good to high yields by just starting from two free alcohols (Scheme 1). When a more powerful oxidizing agent such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or tetrachloro-1,4-benzoquinone (chloranil) was used, the corresponding ether was obtained in 18% and 6% yields, respectively (Table 7, entries 2 and 3). Interestingly, the desired product was obtained in 72% yield at room temperature when an oxidant such as **4** was allowed to react under the same conditions for 3 h (Table 7, entry 4). After the reaction conditions were screened, it was revealed that the ether was obtained in 92% yield when 1.0 equiv of **1a** and 1.2 equiv of **4** were treated with 1.2 equiv of 2-phenylethanol at room temperature for 3 h (Table 8, entry 8).

Next, the O-alkylation reaction via **4**, various alcohols, and **1**, in situ-formed from ^{n}BuLi-treated primary alcohols and **2**, was examined (Tables 9−11). When benzyl alcohols which have electron-donating or electron-withdrawing groups and primary, secondary, and tertiary alcohols were used, the corresponding symmetrical or unsymmetrical ethers were obtained in good to high yields (Table 9, entries 1−10). It should particularly be noted that alcohols which have a hydroxyl group at the α-position of carboxylic esters such as ethyl glycolate afforded the desired products also in 86% yield (Table 9, entry 7). However, the yield of the coupling reaction lowered to 63% when *p*-methoxybenzyl alcohol and alkoxydiphenylphosphine in situ-formed from a ^{n}BuLi-treated primary alcohol such as *n*-butanol were used (Table 9, entry 11).

Etherification of **1** in situ-formed from several ^{n}BuLi-treated bulky secondary or tertiary alcohols with 2-phenylethanol or 2-methyl-1-phenyl-2-propanol proceeded smoothly to afford the corresponding unsymmetrical ethers in high yields when the reaction mixture was kept standing at room temperature for 3 h (Table 10, entries 1−4). Attempted reaction between *p*-methoxybenzyl alcohol and in situ-formed *tert*-butoxydiphenylphosphine from *tert*-butyl alcohol and **2** for preparation of *tert*-butyl 4-methoxybenzyl ether did not take place at all (Table 10, entry 5), while the desired product was obtained in 89% yield when in situ-generated *p*-methoxybenzyloxydiphenylphosphine from *p*-methoxybenzyl alcohol and **2** was treated with *tert*-butanol (Table 9, entry 4).

Table 10. Etherification via **4**, Several Alcohols, and **1** in Situ-Formed from Secondary or Tertiary Alcohols, **2**, and ^{n}BuLi



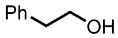
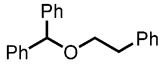
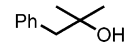
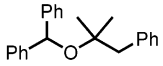
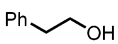
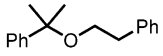
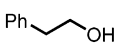
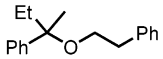
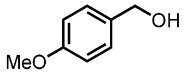
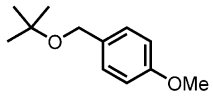
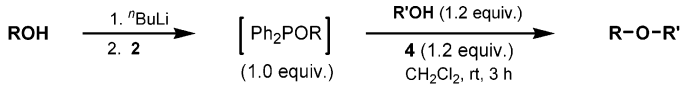
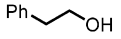
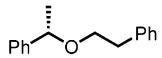
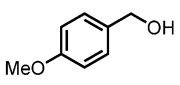
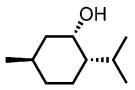
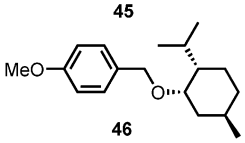
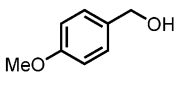
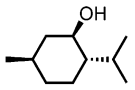
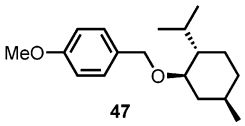
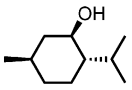
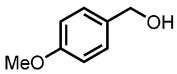
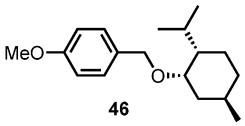
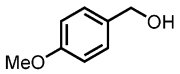
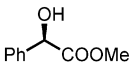
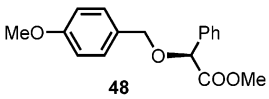
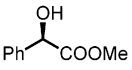
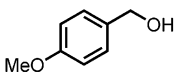
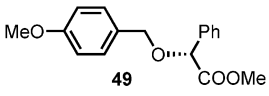
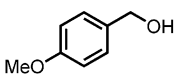
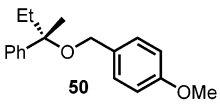
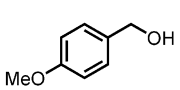
entry	ROH	R'OH	product		yield (%)
1				**41**	91
2				**42**	90
3				**43**	92
4				**44**	88
5				**34**	N.R.

Table 11. Etherification with Inversion or Retention of Stereochemistry via **4**, Various Alcohols, and **1** in Situ-Formed from Various Alcohols, **2**, and ^{n}BuLi



entry	ROH	R'OH	product	yield (%)	inversion/ retention (%)
1[a]			 **45**	90	Inversion 69
2[b]			 **46**	90	Retention >99
3[b]			 **47**	91	Retention >99
4[b]			 **46**	30	Inversion >99
5[c,d]			 **48**	83	Retention >99
6[d]			 **49**	89	Inversion 95
7[e]			 **50**	88	Inversion 99%
8[e]			**51**	86	Retention >99

[a] DAICEL CHIRALCEL OJ column was used for chiral HPLC analysis. [b] Diastereoselectivities were determined by ^{1}H NMR spectroscopy. [c] 1.0 equiv of fluoranil was used. [d] DAICEL CHIRALCEL OD column was used for HPLC analysis. [e] DAICEL CHIRALCEL OB column was used for HPLC analysis.

Further, etherifications of in situ-formed **1** from ^{n}BuLi-treated various alcohols and **2** with inversion or retention of stereochemistry were investigated under the above-mentioned conditions (Table 11). It is noted that the desired ether was obtained in 90% yield with 69% inversion when alkoxydiphenylphosphine in situ-formed from ^{n}BuLi-treated (*R*)-(+)-1-phenylethanol and (*R*)-(+)-1-phenylethanol were used (Table 11, entry 1). Etherifications of alkoxydiphenylphosphine in situ-formed from ^{n}BuLi-treated *p*-methoxybenzyl alcohol with (1*S*,2*S*,5*R*)-(+)-neomenthol or (1*R*,2*S*,5*R*)-(−)-(*l*)-menthol also proceeded to afford the desired ethers in more than 90% yields without racemization (Table 11, entries 2 and 3), while the corresponding ether was obtained in 30% yield with perfect inversion by the reaction between alkoxydiphenylphosphine in situ-formed from ^{n}BuLi-treated (1*R*,2*S*,5*R*)-(−)-(*l*)-menthol and *p*-methoxybenzyl alcohol (Table 11, entry 4). Similarly, the corresponding ether was obtained in 83% yield with complete retention of configuration when alkoxydiphenylphosphine in situ-formed from ^{n}BuLi-treated *p*-methoxybenzyl alcohol was allowed to react with methyl (*R*)-(−)-mandelate (Table 11, entry 5). However, the yield of the desired ether was 89% with 95% inversion when alkoxydiphenylphosphine in situ-formed from a ^{n}BuLi-treated secondary alcohol such as methyl (*R*)-(−)-mandelate and *p*-methoxybenzyl alcohol were treated under the same conditions (Table 11, entry 6). Further, etherification of alkoxydiphenylphosphine in situ-formed from a ^{n}BuLi-treated tertiary alcohol such as (*S*)-2-phenyl-2-butanol with *p*-methoxybenzyl alcohol proceeded smoothly to afford the corresponding unsymmetrical ethers in 88% yields with 99% inversion (Table 11, entry 7). The desired ether was obtained in 86% yield without racemization when alkoxydiphenylphosphine in situ-formed from *p*-methoxybenzyl alcohol and (*S*)-2-phenyl-2-butanol were used (Table 11, entry 8).

Thus, an effective method for the etherification of chiral alcohols with retention or inversion was established: that is, reaction between chiral alkoxydiphenylphosphine and achiral alcohol afforded the inverted ether, while that between achiral alkoxydiphenylphosphine and chiral alcohol afforded the ether with retention of configuration (Table 11, entries 3−8).

Summary

Alkyl−aryl ethers were obtained in good to high yields by oxidation−reduction condensation using alkoxydiphenylphosphines, generated in situ from chlorodiphenylphosphine and alcohols, 2,6-dimethyl-1,4-benzoquinone, and phenols (Scheme 1). Similarly, a new and efficient method was introduced for the preparation of symmetrical or unsymmetrical dialkyl ethers in good to high yields via fluoranil, alcohols, and alkoxydiphenylphosphine, in situ-formed from ^{n}BuLi-treated alcohols and chlorodiphenylphosphine (Scheme 1). It is interesting to note that this method enabled the etherification of chiral secondary or tertiary alcohols with retention or inversion of configurations; that is, by treating chiral alkoxydiphenylphosphines and achiral alcohols, the inverted ethers were successfully obtained, while the reaction of achiral alkoxydiphenylphosphines and chiral alcohols afforded the retained ethers only.

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Supporting Information Available: Experimental procedures and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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