A Convenient Method for the Preparation of Symmetrical or Unsymmetrical Ethers by The Coupling of Two Alcohols via A New Type of Oxidation–reduction Condensation Using Tetrafluoro-1,4-benzoquinone

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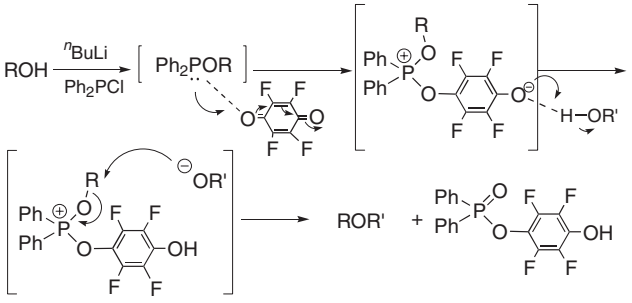
A new type of oxidation–reduction condensation by using tetrafluoro-1,4-benzoquinone (fluoranil), alcohols and alkoxydiphenylphosphines, in situ formed from ^{n}BuLi-treated alcohols and chlorodiphenylphosphine, proceeded smoothly to afford the corresponding symmetrical or unsymmetrical ethers in good to high yields.

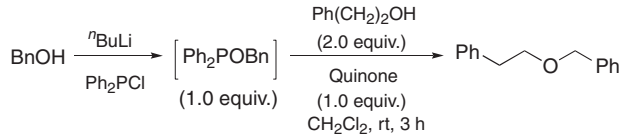
Preparation of ethers is one of the most fundamental and frequently used important reactions in synthetic organic chemistry. For example, several *O*-alkylation reactions are carried out by using alkyl halides (Williamson ether synthesis),[1] olefins,[2] dialkyl phosphates,[3] aldehydes,[4] nitro compounds,[5] *p*-toluene sulfonic acid,[6] and imidates.[7] Of these etherifications, however, to prepare ethers in high yields under mild conditions is still a challenging topic. As reported in our previous communications,[8] alkylation of various carboxylic acids or phenols with alkoxydiphenylphosphines, in situ formed from various ^{n}BuLi-treated primary, bulky secondary and tertiary alcohols, chlorodiphenylphosphine and 2,6-dimethyl-1,4-benzoquinone turned out to be a new type of oxidation–reduction condensation while *O*-alkylation reaction using 2,6-dimethyl-1,4-benzoquinone, alcohols, and in situ formed alkoxydiphenylphosphines was not successfully carried out. On treating with oxidants such as 2,6-dimethyl-1,4-benzoquinone, alkoxydiphenylphosphines are considered to form an important intermediate phosphonium salt quite effectively as the alkoxy part was introduced to phosphine in advance. However, thus formed intermediate phosphonium salt was not in turn converted smoothly to a so-called penta-valent phosphorus compound by abstracting one hydrogen atom from alcohols. In order to extend the scope of the above reaction, a new type of oxidation–reduction condensation by using more powerful oxidant such as fluoranil, alcohols, and alkoxydiphenylphosphines which were in situ formed from ^{n}BuLi-treated alcohols and chlorodiphenylphosphine, was tried. It was found then that the intermediate phosphonium salt was in turn converted smoothly to a so-called penta-valent phosphorus compound by catching one hydrogen atom from alcohols and the corresponding symmetrical or unsymmetrical ethers were successfully prepared in good to high yields (Scheme 1).

In the first place, *O*-alkylation reaction of 2 equiv. of 2-phenylethanol in CH_2Cl_2 with 1 equiv. of 2,6-dimethyl-1,4-benzoquinone and 1 equiv. of benzyloxydiphenylphosphine, in situ formed from ^{n}BuLi-treated benzyl alcohol and chlorodiphenylphosphine, was tried, however, the desired ether was not obtained (Table 1, Entry 1). When 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 1, Entries 2 and 3). Interestingly, the desired product was obtained in 72% yield at room temperature when an oxidant such as fluoranil was allowed to react under the above conditions for 3 h (Table 1, Entry 4).



Scheme 1.

Table 1. Effect of quinone derivatives on etherification of 2-phenylethanol

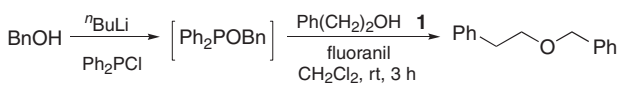


Entry	Quinone	Yield/%
1	2,6-dimethyl-1,4-benzoquinone	N.R.
2	DDQ	18
3	chloranil	6
4	fluoranil	72

After examination of reaction condition, it was revealed that the ether was obtained in 92% yield when 1.0 equiv. of Ph_2POBn and 1.2 equiv. of tetrafuluoro-1,4-benzoquinone were treated with 1.2 equiv. of 2-phenylethanol at room temperature for 3 h (Table 2, Entry 8).

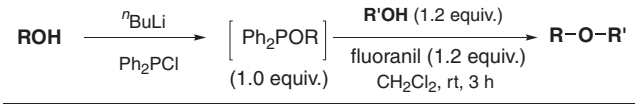
Next, *O*-alkylation reaction by using fluoranil, various alcohols and alkoxydiphenylphosohines in situ formed from several ^{n}BuLi-treated alcohols and chlorodiphenylphosphine was tried (Table 3). When benzyl alcohols having electron-donating or electron-withdrawing groups and primary, secondary, and tertiary alcohols were used, the corresponding symmetrical or unsymmetrical ethers were obtained in good to high yields (Table 3, Entries 1–13). On the other hand, the desired product was obtained in 63% yield by the coupling reaction between primary alcohol such as ^{n}BuOH and *p*-methoxybenzyl alcohol (Table 3, Entry 20). Ether-formation reaction between *t*-butoxydiphenylphosphine and *p*-methoxybenzyl alcohol did not take place at all (Table 3, Entry 22), while, the desired ether was obtained in 89% yield when *p*-methoxybenzyloxydiphenylphosphine was treated with

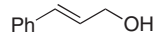
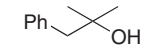
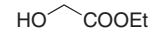
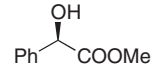
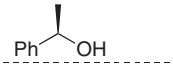
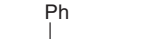
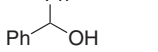
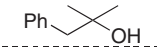
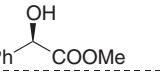
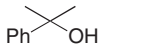
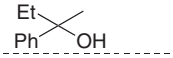
Table 2. Etherification of 2-Phenylethanol with Ph_2POBn and Fluoranil



Entry	R_2POBn/equiv.	**1**/equiv.	fluoranil/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

Table 3. Etherification using fluoranil, various alcohols and alkoxydiphenylphosphines in situ formed from alcohols, Ph_2Cl and ^{n}BuLi



Entry	ROH	R'OH	Yield /%
1	*p*-MeO-$C_6H_4CH_2OH$	$Ph(CH_2)_2OH$	95
2			90
3		Cyclohexanol	90
4		^{t}BuOH	89
5		(*L*)-Menthol	91
6		Neomenthol	90
7			94
8		*p*-MeO-$C_6H_4CH_2OH$	94
9[a]			86
10[a,b]			83
11	BnOH	$Ph(CH_2)_2OH$	92
12		BnOH	94
13	*p*-Cl-$C_6H_4CH_2OH$	$Ph(CH_2)_2OH$	75
14[c]		$Ph(CH_2)_2OH$	90
15		$Ph(CH_2)_2OH$	91
16			90
17[d]		*p*-MeO-$C_6H_4CH_2OH$	89
18		$Ph(CH_2)_2OH$	92
19		$Ph(CH_2)_2OH$	88
20	^{n}BuOH	*p*-MeO-$C_6H_4CH_2OH$	63
21[e]	L-Menthol	*p*-MeO-$C_6H_4CH_2OH$	30
22	^{t}BuOH	*p*-MeO-$C_6H_4CH_2OH$	N.R.

[a] 1.0 equiv. of fluoranil was used. [b] No racemiczation was observed by HPLC using DAICEL CHIRALCEL OD. [c] $[\alpha]_D^{26} = -125.7$ (c 0.80, $CHCl_3$). The corresponding ether was obtained with 69% inversion. [d] The corresponding ether was obtained with 95% inversion. [e] The corresponding ether was obtained with perfect inversion. Diastereoselectivities determined by ^{1}H NMR spectroscopy.

^{t}BuOH (Table 3, Entry 4). Alcohols having a hydroxy group at α-position of carboxylic esters such as ethyl glycolate or methyl (*R*)-(−)-mandelate also afforded the desired products in 86% yield or 83% yield (no racemization), respectively (Table 3, Entries 9 and 10). The etherification of several bulky secondary or tertiary alcohols with 2-phenylethanol or 2-methyl-1-phenyl-2-propanol smoothly proceeded to afford the corresponding unsymmetrical ethers in high yields when the reactions were carried out at room temperature for 3 h (Table 3, Entries 14–19). It is noted that the desired ether was obtained with 69% inversion when (*R*)-(+)-1-phenylethanol and 2-phenylethanol were used (Table 3, Entry 14). Also, when methyl (*R*)-(−)-mandelate and *p*-methoxybenzyl alcohol were allowed to react under the present condition, the corresponding ether was obtained in 89% yield (95% inversion) (Table 3, Entry 17). Thus, efficient methods for the etherification of chiral alcohols with retention or inversion, namely, treatment of chiral alkoxydiphenylphosphine and achiral alcohol afforded the inverted ether while that of achiral alkoxydiphenylphosphine and chiral alcohol afforded the ether with retention (Table 3, Entries 10 and 17). Also, in the etherification using secondary alkoxydiphenylphosphine such as L-menthol derivative and *p*-methoxybenzyl alcohol afforded the desired ether in 30% yield with perfect inversion (Table 3, Entry 21).

Typical experimental procedure is as follows: to a mixture of alkoxydiphenylphosphine[9] (0.60 mmol) and fluoranil (0.72 mmol) under argon atmosphere was added a dichloromethane (0.50 mL) solution of alcohol (0.72 mmol) at room temperature. After the reaction, that was monitored by TLC, was completed, the reaction mixture was quenched by adding water and the aqueous layer was extracted with dichloromethane. The organic layers were dried over anhydrous sodium sulfate. After filtration and evaporation, the resulted residue was purified by preparative TLC to afford the corresponding ether. The above reactions were also carried out by one-pot procedure and the same results were obtained even in the presence of lithium chloride.

Thus, a new and efficient method for the preparation of symmetrical or unsymmetrical ethers in good to high yields between various alcohols was established by way of a new type of oxidation–reduction condensation using in situ formed alkoxydiphenylphosphines, fluoranil, and alcohols. Further study on this type of condensation reaction is now in progress.

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References and Notes

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9 Preparation of various alkoxydiphenylphosphines. See Ref. 8.

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