



## Metal-catalyzed phosphinyl ester forming reaction of alcohols and phenols with diphosphine disulfides and a dioxide

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### ABSTRACT

Transition metal complexes catalyzed the dialkylphosphinothioation reaction of alcohols and phenols with tetraalkyldiphosphine disulfides in high yields. Phenols were reacted in the presence of RhH(PPh<sub>3</sub>)<sub>4</sub> and 1,2-bis(dimethylphosphino)ethane under THF reflux, and alcohols with Pd(OAc)<sub>2</sub> and 1,2-bis(diphenylphosphino)benzene under chlorobenzene reflux. Primary alcohols reacted faster than secondary alcohols under these conditions, and protected tyrosine and serine were phosphinothioated with minimal racemization. Tetraphenyldiphosphine dioxide also underwent the P–O bond formation reaction.

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Synthetic organophosphorus esters derived from phosphinic acid, phosphonic acid, and their sulfur analogs have attracted much interest with regard to their function as biologically active substances and materials.<sup>1</sup> In general, such esters are synthesized from alcohols and phenols by treatment with organophosphorus reagents possessing highly reactive leaving groups, typically chloride, in the presence of stoichiometric amounts of a base.<sup>1–4</sup> Because the method employs basic reaction conditions and inevitably forms salts as a byproduct, it is desirable that the P–O bond formation be conducted without using a base. It was considered that the development of an appropriate combination of a catalyst and a phosphorus reagent could provide an efficient method for phosphorus ester formation.

The P–P bond-containing compounds in general were not reactive with alcohols and phenols. An occasional example of the phosphorus ester formation is known using compounds possessing polarized P–P bonds in the presence of a large excess of simple alcohols or alkoxides,<sup>6</sup> and photolysis of diphosphines and polyphosphines in alcohol give phosphorus esters.<sup>7</sup> We have been examining transition-metal-catalyzed methods for the synthesis of organophosphorus compounds, and have showed that rhodium complexes can cleave P–P bonds and transfer the phosphorus group to other molecules.<sup>5</sup> The results of this study shows that transition metal complexes can catalyze the effective phosphinyl ester formation reaction of alcohols and phenols using diphosphine disulfides and a dioxide. It should be noted that the P–O bonds were formed employing stoichiometric amounts of hydroxy compounds and diphosphines. In addition, we show that transition metal complexes can catalytically promote the esterification reaction of alcohols and phenols without a base.

When an equimolar mixture of *p*-methoxyphenol and tetramethyldiphosphine disulfide<sup>8</sup> in THF was heated at reflux for 3 h in the presence of RhH(PPh<sub>3</sub>)<sub>4</sub> (1 mol %) and 1,2-bis(dimethylphosphino)ethane (dmpe, 2 mol %), *O*-(*p*-methoxyphenyl) dimethylphosphinothioate was obtained in 100% yield; it was accompanied by PHSMe<sub>2</sub> in 72% yield (Table 1, entry 1). No reaction occurred in the absence of the rhodium complex. Other metal complexes exhibiting similar activity in the presence of dmpe were RhH(CO)(PPh<sub>3</sub>)<sub>3</sub> and Rh(acac)(CH<sub>2</sub>=CH<sub>2</sub>). In contrast, RhCl(PPh<sub>3</sub>)<sub>4</sub>, Rh(acac)<sub>3</sub>, [Rh(cod)(PPh<sub>3</sub>)<sub>2</sub>]PF<sub>6</sub>, and [Rh(OAc)<sub>2</sub>]<sub>2</sub> were less effective. The effect of the phosphine ligand was also critical, and other bidentate ligands with phosphino groups separated by two carbon atoms such as 1,2-bis(diethylphosphino)ethane (depe), 1,2-bis(diphenylphosphino)ethane (dppe), and 1,2-bis(diphenylphos-

**Table 1**  
Rhodium-catalyzed phosphinothioation reaction of phenols

Entry	R'	Ar substituent	Yield (%)
1	Me	<i>p</i> -Me	100
2	Me	<i>p</i> -( <i>t</i> -Bu)	98
3	Me	<i>p</i> -MeO	99
4	Et	<i>p</i> -MeO	99
5	Me	<i>p</i> -Cl	98
6	Me	<i>p</i> -Ph	96
7	Me	<i>m</i> -Me	97
8	Me	<i>m</i> -Ph	97
9	Me	<i>o</i> -Me	86
10	Me	<i>o</i> -Ph	97
11	Me	( <i>S</i> )- <i>p</i> -C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> CH(NHBoc)CO <sub>2</sub> Me	98, 99% ee

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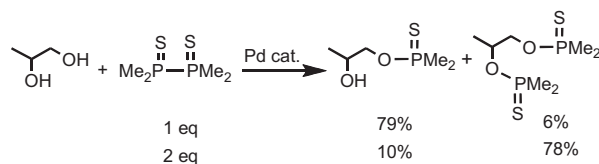
phino)benzene (dppBz) exhibited modest catalytic activity forming the product in 30–60% yield.

The reaction proceeded with substituted phenols, as summarized in Table 1, giving the aryl esters in high yields. The electronic effect of the *p*-substituent was small (entries 1, 3, and 5). Tetraethyldiphosphine disulfide reacted as well as the tetramethyl derivative (entry 4). The dimethylthiophosphination reaction of protected tyrosine proceeded effectively without racemization (entry 11).

The reaction of alcohols and the diphosphine disulfide exhibited a slightly different nature. Benzyl alcohol and tetramethyldiphosphine disulfide in chlorobenzene were heated at reflux for 3 h in the presence of Pd(OAc)<sub>2</sub> (1 mol %) and dppBz (2 mol %), and *O*-benzyl dimethylphosphinothioate was obtained in 99% yield (Table 2, entry 1). Higher temperature was required for the reaction of the alcohol compared with that of the phenols and 21% of the product was obtained at 80 °C. Use of RhH(PPh<sub>3</sub>)<sub>4</sub> in place of Pd(OAc)<sub>2</sub> gave a modest yield of the product, probably because of catalyst deactivation. The ligand effect was again examined, and only 6% yield of the product was obtained without dppBz. It was confirmed that dppBz itself did not catalyze the reaction.

The method using Pd(OAc)<sub>2</sub> and dppBz was applied to primary alcohols giving phosphinothioates in high yield (entries 1, 3, 4, 5, and 7). Tetraethyldiphosphine disulfide reacted at slower rates, and required 16 h for completion (entries 2 and 6). Because the palladium complex catalyzed the reaction of *p*-methoxyphenol in refluxing chlorobenzene giving the phosphinothioate quantitatively (entry 8), phenol could be reacted using either catalyst. The reactions of secondary and tertiary alcohols were slow, as indicated by the reactions of 2- and 1-adamantanol (entries 9 and 11). 1,2-Propanediol gave a mono-phosphinothioated product in 79% yield accompanied by a bis-product in 6% yield, when 1 equiv of the diphosphine was employed (Scheme 1). The use of 2 equiv of the reagent gave predominantly a bis-phosphinylated product. The exceptional reactivity of cyclopentanol can probably be ascribed to less steric congestion of the substrate (Table 2, entry 10). A serine derivative was dimethylphosphinothioated with minimal racemization despite the relatively high reaction temperature (entry 12). A protected sugar also reacted smoothly (Scheme 2). Although some differences in the reactivity were observed in rhodium- and palladium-catalyzed reactions, both catalyzed the phosphinothioation reaction. Such metal effects appear to be general in the reactions of organophosphorus compounds.<sup>9</sup>

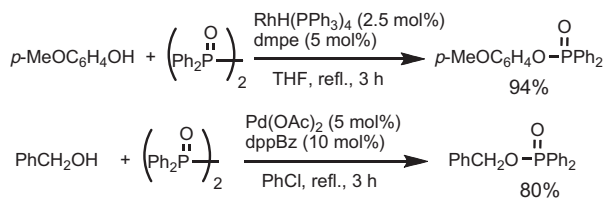
In addition to tetraalkyldiphosphine disulfides, tetraphenyldiphosphine dioxide reacted with an alcohol and a phenol giving



Scheme 1.



Scheme 2.



Scheme 3.

phosphinates in high yields (Scheme 3). Thus, the P=S and P=O bonds in the diphosphine exert a small effect on the catalytic phosphinothioation reaction.

In summary, rhodium and palladium complexes catalyzed the phosphinyl ester formation reaction of alcohols and phenols with diphosphine disulfides and a dioxide in high yields. It should be emphasized that the transition metal catalysis can be used for the esterification reaction of O–H compounds, and such methodology has an advantage of avoiding the use of a base. The catalysts probably participated both in the generation of reactive metal phosphorus intermediates and in the activation of the O–H group. An oxidative addition reaction of a polyphosphine with a rhodium(I) complex has recently been reported.<sup>10</sup> Depending on the ligand, palladium and rhodium complexes can react with free alcohols and phenols either as acids or bases,<sup>11</sup> and such an activated species could also react with activated phosphorus intermediates.

## Typical experimental procedures

In a two-necked flask equipped with a reflux condenser were placed RhH(PPh<sub>3</sub>)<sub>4</sub> (1.0 mol %, 11.5 mg), tetramethyldiphosphine disulfide (1.0 mmol, 186.2 mg), and *p*-methoxyphenol (1.0 mmol, 124.1 mg) under an argon atmosphere. Dry THF (2 mL) and dmpe (2.0 mol %, 3.4 μL) were added, and the solution was heated at reflux for 3 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel giving *O*-(*p*-methoxyphenyl) dimethylphosphinothioate (212.8 mg, 99%) as a colorless solid and dimethylphosphine sulfide (67.3 mg, 72%) as a pale yellow oil.

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**Table 2**  
Palladium-catalyzed phosphinothioation reaction of alcohols

Entry	R'	R	Yield (%)
1	Me	PhCH <sub>2</sub>	99
2	Et	PhCH <sub>2</sub>	91 <sup>a</sup>
3	Me	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	98
4	Me	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	72
5	Me	<i>n</i> -C <sub>8</sub> H <sub>17</sub>	83
6	Et	<i>n</i> -C <sub>8</sub> H <sub>17</sub>	81 <sup>a</sup>
7	Me	1-Adamantylmethyl	82
8	Et	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	99
9	Me	2-Adamantyl	23
10	Me	<i>cyclo</i> -C <sub>5</sub> H <sub>9</sub>	71
11	Me	1-Adamantyl	7
12	Me	( <i>S</i> )-MeO <sub>2</sub> CCH(NHBoc)CH <sub>2</sub>	93, 95 <sup>ee</sup>

<sup>a</sup> Reaction time: 16 h.

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### Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.040.

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