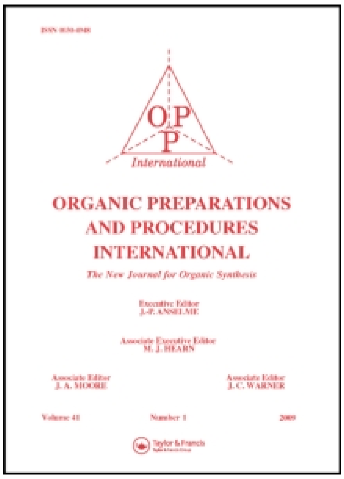

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A CONVENIENT PREPARATION OF DISSYMMETRIC TERTIARY PHOSPHINES VIA ALKYLATION OF DISSYMMETRIC LITHIUM PHOSPHIDES

Theodore E. Snider[a]; Don L. Morris[a]; W. Ronald Purdum[a]; G. A. Dilbeck[a]; K. D. Berlin[a]
[a] Department of Chemistry Oklahoma, State University, Stillwater, Oklahoma

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A CONVENIENT PREPARATION OF DISSYMMETRIC TERTIARY PHOSPHINES VIA ALKYLATION OF DISSYMMETRIC LITHIUM PHOSPHIDES[1]

Theodore E. Snider,[2a] Don L. Morris,[2b] W. Ronald Purdum,[2c]
G. A. Dilbeck,[2d] and K. D. Berlin*

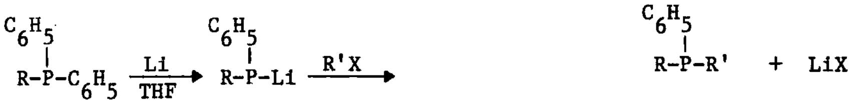
Department of Chemistry
Oklahoma State University
Stillwater, Oklahoma 74074

Many stereochemical and mechanistic investigations of phosphorus chemistry revolve about the accessibility of dissymmetric tertiary phosphines quite commonly prepared from dissymmetric phosphonium salts.[3] Most of the earlier methods are considered to be generally laborious.[4] Approaches to dissymmetric phosphines of recent origin deemed most promising are the reduction (with $LiAlH_4$) of quaternary, dibenzyl-substituted phosphonium salts[4] and alkylation[5] of unsymmetrically, disubstituted phosphinous chlorides. However, both methods have difficult experimental problems. The reduction of phosphonium salts involves the preliminary formation of the extremely air-sensitive, dibenzyl-substituted, tertiary phosphine which can be easily oxidized and thus a complex mixture can result. This can lead to ambiguous conclusions if the studies involve impure reactants.

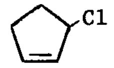
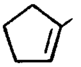
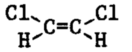
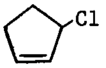
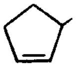
The utility of the second of the above methods is dependent upon the availability of the assymmetrical phosphinous chlorides. While the general preparation of phosphinous chlorides of the type R(R')PCl has been described by Maier,[6] this major route involves the utilization of highly hazardous tetraalkyl(aryl)lead reagents. The availability of tetrasubstituted lead compounds also limits the variation of alkyl (or aryl) substituents. Other synthetic schemes for R(R')PCl are time-consuming and devoid of flexibility for conversion of any intermediates to other useful, dissymmetric organophosphorus compounds.

Herein are presented the results of our investigations of a representative number of phneyl-substituted, tertiary phosphines in a lithium-cleavage reaction, a process followed by alkylation (Scheme I). Of course, one could oxidize, sulfurize, or quaternize any of the intermediate dissymmetric phosphines Since the reactions can be performed in a single vessel in a few hours, the yields are quite reasonable. We found the synthesis of the starting materials $(C_6H_5)_2PR$ to be most facile via a Grignard reaction on $(C_6H_5)_2PCl$.[3]

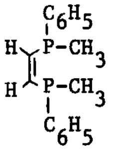
SCHEME I



$$R\text{-}\overset{C_6H_5}{\overset{|}{P}}\text{-}C_6H_5 \xrightarrow[THF]{Li} R\text{-}\overset{C_6H_5}{\overset{|}{P}}\text{-}Li \xrightarrow{R'X} R\text{-}\overset{C_6H_5}{\overset{|}{P}}\text{-}R' + LiX$$

R	R'-X	Cpd	R	R'	Yield (%)
CH_3	C_2H_5I	I	CH_3	C_2H_5	81[a]
CH_3	$CH_2{=}CHCH_2Br$	II	CH_3	$CH_2{=}CHCH_2$	66[a]
C_2H_5		III	C_2H_5		28
CH_3		IV[b]			53[c]
C_6H_5	$CH_2{=}CHCH_2Br$	V	C_6H_5	$CH_2{=}CHCH_2$	70[c]
C_6H_5		VI	C_6H_5		77[c]

[a] Excess alkyl halide used to quench phenyllithium.

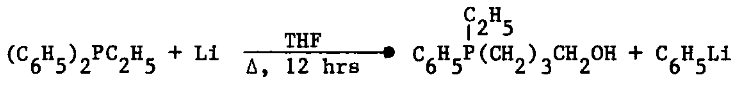
[b]  This phosphine was a heavy oil and very sensitive to oxidation and thus quaternization of IV to give the salt IX was effected. Some dioxide (<10%) could always be isolated even after care in in the distillation; Calcd. for $C_{16}H_{18}O_2P_2$: C, 63.16; H, 5.92; P, 20.39; Found: C, 63.23; H, 6.08; P, 20.33.

[c] *t*-Butyl chloride added to quench phenyllithium.

The formation and reactions of alkali metal phosphides were thoroughly reviewed in 1962,[7] but the favored starting material has been the commercially rare phosphinous halide. In contrast, many tertiary phosphines can be prepared easily[3] and are readily cleaved by alkali metals in both THF and dioxane.[7,8] The order of cleavage of C-P bonds in these P-Ar (or P-R) systems is α-naphthyl > phenyl > *p*-totyl > ethyl > cyclohexyl.[7-10] In view of the lack of available dissymmetric phosphinous halides R(Ar)PCl, very little work has been published on the synthesis of dissymmetric-tertiary phosphines by the type of cleavage discussed herein. It was conceived that P-aryl cleavage could be a valuable synthetic step in the preparation of dissymmetric, tertiary phosphines since diarylalkylphosphines are readily available,[3] stable to air oxidation, and P-Ar cleavage is known with triphenylphosphine.[11]

We have found that lithium metal in THF causes aryl-P cleavage in diarylalkylphosphines to occur in an efficient manner to produce dissymmetric arylalkyllithium phosphide reagents, R(Ar)PLi. The latter can be alkylated *in situ* to yield dissymmetric, tertiary phosphines. These phosphines (I-IV), along with pertinent physical and spectral data, are found in Table I (and supporting derivatives VII-IX are found in Table II) and in the Experimental. When desirable, the by-product phenyllithium may be preferentially quenched in the presence of the lithium phosphide by the addition of *t*-butyl chloride[11] with but a slight decrease in yield.

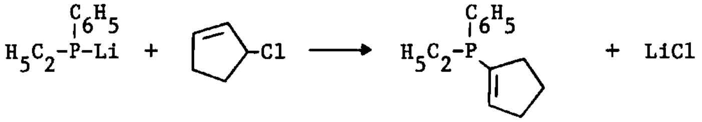
As also seen in Table I, cleavage[7,11] of triphenylphosphine yields a lithium phosphide capable of being alkylated. Thus, phosphines of the type Ar_2PAr', though commercially rare, could probably be used in the reaction. A considerable difference in reactivity exists, however, between diaryllithium phosphides and alkylaryllithium phosphides. The former may be readily formed in boiling THF. Surprisingly, with ethylphenyllithium phosphide in boiling THF over a 12-hour period, ring cleavage occurred to form the hydroxybutyl-substituted, tertiary phosphine XII. However, the general reaction with $C_6H_5(R)PLi$ proceeded smoothly in the formation of I



$$(C_6H_5)_2PC_2H_5 + Li \xrightarrow[\Delta,\ 12\ hrs]{THF} C_6H_5\overset{C_2H_5}{\overset{|}{P}}(CH_2)_3CH_2OH + C_6H_5Li$$

XII

and II, and only in the synthesis of III from a secondary haloalkene did the yield of phosphine, drop apparently because of competitive formation of XII. Interestingly, 3-chlorocyclopentene reacts with the diphenyllithium phosphide to give the predicted product VI but with the ethylphenyllithium phosphide to give a rearranged product, ethyl-1-cyclopentenylphenylphosphine (III). This rearrangement of allyl-type phosphorus compounds to



III

TABLE I

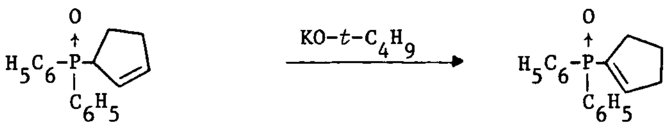
UNSYMMETRICAL PHOSPHINES

No.	bp (mm)	pmr (δ)/$DCCl_3$
I	101-105 (20 mm) lit[12] 95-97(15 mm)	1.08 (d, 3, J_{PCH} = 4 Hz, (CH_3) 0.9 (d of triplets, 3, J_{PCH} = 15 Hz, J_{HCCH} = 7 Hz, $CH_2C\mathit{H}_3$), 1.44 (m, 2, $C\mathit{H}_2CH_3$, 7.02-7.5 (m, 4, Ar*H*). Also converted to VII.
II	50(0.1 mm) lit[13]40(0.05 mm)	Converted to VIII.
III	107-107.5(0.2-0.4 mm) Calcd. for $C_{13}H_{17}P$: P, 15.19; Found, 15.21	0.98 (d of triplets, 3, J_{PCCH} = 16 Hz, J_{HCCH} = 6 Hz, $CH_2C\mathit{H}_3$), 1.48-1.85 (m, 3, $C\mathit{H}_2CH_3$ and $-CH_2C\mathit{H}_2CH_2-$), 2.1-2.4 (m, 4, $-C\mathit{H}_2CH_2C\mathit{H}_2-$), 5.86-6.02 (m, 1, $-C{=}C\mathit{H}$), 7.0-7.55 (m, 5, Ar*H*).
IV	Heavy oil	Converted to derivative IX.

TABLE I (Continued)

No.	bp (mm)	pmr (δ)/$DCCl_3$
V	124(0.1 mm) lit[14]150(4 mm)	2.74 (d, broad), 2, J_{PCH} = 7 Hz, PCH_2), 4.8-5.08 (m, 2, $CH{=}CH_2$), 5.5-5.95 (m, 1, $CH{=}CH_2$), 7.0-7.5 (m, 10, ArH). Also converted to X.
VI	146(0.1 mm) Calcd. for $C_{17}H_{17}P$: P, 12.30; Found, P, 12.00	1.72-2.3 (m, 4, $-CH_2CH_2-$), 3.3-3.56 (m, 1, PCH), 5.4-5.72 (m, 2, $-CH{=}CH-$), 6.9-7.6 (m, 10, ArH). Also converted to XI.

conjugated-vinyl-type derivatives has been previously recorded.[15] The assignment of position of the double bond in III was on the basis of pmr analysis which displayed only one vinyl proton. In contract, phosphine VI showed two vinyl protons in the pmr spectrum. In an ancillary experiment, diphenyl-3-cyclopentenylphosphine oxide (XIII) was rearranged by boiling with base[16] to form diphenyl-1-cyclopentenylphosphine oxide (XIV) thus confirming the original structure diagnosis for XIII.



XIII XIV

As further support for the validity of the overall sequence, a few of the tertiary phosphines were treated with various alkyl halides to form phosphonium salts (some known and some unrecorded) as shown in Table II.

TABLE II

PHOSPHONIUM SALTS

Alkylating Agent	Phosphonium Salt	Pmr (δ) (DCCl$_3$)	Elemental Analyses C	H	P
			(Calculated)		
$C_6H_5CH_2Br$	Benzylethylmethylphenylphosphonium bromide (VII) mp. 139-140° (lit.[17] 140°)				
$C_6H_5CH_2Br$	Allylbenzylmethylphenylphosphonium bromide (VIII) mp. 140-141° (lit.[12] 142°)				
$2CH_3I$	<u>cis</u>-1,2-Vinylene bis(dimethylphenylphosphonium) diiodide (IX) mp. 262-264°	2.85 (m, 12, CH_3) 8.03 (m, 8, ArH [a] and =CH)	39.06 (38.88	4.44 4.32	11.38 11.15)
$C_6H_5CH_2Br$	Allylbenzyldiphenylphosphonium bromide (X) mp. 201-203°	4.28 (d of quartets, J_{PCH} = 15 Hz, J_{HCCH} = 6 Hz, J_{HH} = 2 Hz, 2, $CH_2CH{=}CH_2$), 4.98 (d of doublets, J_{PCH} = 15 Hz, J_{HH} = 2 Hz, ArCH_2), 5.14-5.5 (m, 3, $CH{=}CH_2$), 7.12 (s, 5, ArHCH), 7.46-8.02 (m, 10, ArH)	66.17 (66.53	5.62 5.54	7.58 7.80)
$C_6H_5CH_2Br$	Benzyl-3-cyclopentenyldiphenylphosphonium bromide (XI) mp. 235-236°	1.3-2.5 (m, 4, $-CH_2CH_2-$), 4.8-5.1 (m, 1, P-CH), 5.00 and 5.14 (d of doublets, 2, J_{PCH} = 14 Hz, J_{HCCH} = 5 Hz, $-CH_2Ar$), 5.88 (m, 2, -CH=CH-), 7.05 (s, 5, $-CH_2ArH$), 7.4-8.0 (m, 10, ArH)	68.15 (68.12	5.84 5.67	7.20 7.32)

[a] In DMSO-d_6

EXPERIMENTAL[18]

General Procedure for the Preparation of Tertiary Phosphines I-VI. An alkyldiphenylphosphine (0.1 mol) and lithium shavings (0.2 g-atom) were mixed and stirred in 250 ml of anhydrous THF. Immediate indications of reaction were noted as the mixture became warm and discolored (reddish-brown). The reaction was easily moderated by an ice-water cooling bath to maintain a reaction temperature of *ca.* 40°. After 3 hr, *ca.* 30% of the lithium remained unreacted. Cooling was discontinued and the reaction mixture was stirred at ambient temperatures for an additional hour. The alkyl halide[19] (0.2 mol) was added dropwise to the stirred solution (the color is discharged), and the mixture was boiled for 30 min. The mixture was subsequently cooled, hydrolyzed with water, and the aqueous layer was extracted (ether). All organic portions were than combined, dried ($MgSO_4$), evaporated to an oil, and distilled. The physical and spectral data are summarized in Table I.

Phosphonium Salts VII-XI. These salts were prepared in the standard manner.[3] The tertiary phosphine and alkyl halide were boiled in a toluene solution. The solution was evaporated and the resultant oil was recrystallized from ethanol or H_2CCl_2:ether (2:1). The physical and spectral data are summarized in Table II.

Ethyl-4-hydroxybutylphenylphosphine (XII). Diphenylethylphosphine (21.4 g, 0.10 mol) and lithium shavings (1.4 g, 0.20 g-atom) in 200 ml of THF were stirred and boiled for 12 hr. The mixture was then cooled, hydrolyzed (H_2O), and extracted (ether). The etheral extracts were dried ($MgSO_4$) and evaporated upon a rotary evaporator; the resultant oil was distilled under vacuum to give XII (bp 127-134°/0.02 mm, 16 g, 76%); pmr ($DCCl_3$) δ 0.99 (2-*t*, J_{PCH} = 15 Hz, J_{HCCH} = 7 Hz, 3, CH_2CH_3), 1.34-1.75 (m, 8, CH_2CH_3 and $CH_2CH_2CH_2CH_2OH$), 1.97 (s, broad, 1, O*H*), 3.44 (*t*, J_{HCCH} = 5 Hz, 2, CH_2OH)

7.02-7.64 (m, 5, Ar*H*).

Anal. Calcd. for $C_{12}H_{19}OP$: P, 14.76

Found: P, 14.65

<u>*2-Cyclopentenyldiphenylphosphine Oxide*</u> (XIII). 2-Cyclopentenyldiphenylphosphine (VI) (2.52 g, 0.010 mol) was oxidized by hydroxylamine as described by Martz and Quin.[20] The product was recrystallized from ethyl acetate/hexane to give XIII (2.21 g, mp 124-126° s.t., 82%): pmr ($DCCl_3$) δ 2.0-2.44 (m, 4, CH_2CH_2), 3.5-3.86 (m, 1, P-CH), 5.47-5.66 (m, 1, C*H*=CH), 5.70-8.01 (m, 1, C*H*=CH), 7.3-7.8 (m, 10, Ar*H*).

Anal. Calcd. for $C_{17}H_{17}OP$: P, 11.56

Found: P, 11.55

<u>*1-Cyclopentenyldiphenylphosphine Oxide*</u> (XIV). A mixture of 2-cyclopentenyldiphenylphosphine oxide (XIII) (1.0 g, 0.0038 mol) and potassium *t*-butoxide (3.0 g, 0.03 mol) in 50 ml of dry toluene was boiled for 14 hr. After cooling, the reaction mixture was hydrolyzed (50 ml of H_2O). The layers were separated and the aqueous layer was extracted ($HCCl_3$). The combined organic portions were dried ($MgSO_4$) and evaporated to a residual oil. The oil was chromatographed through an alumina column using $HCCl_3$ as an eluent. The solvent was evaporated and the residue was recrystallized (ethyl acetate/hexane) to give XIV (0.7 g, mp 110-111°, 62%): pmr ($DCCl_3$) δ 2.0 (pent, J_{HCCH} = 7 Hz, 2, $CH_2CH_2CH_2$), 2.4-2.7 (m, 4, $CH_2CH_2CH_2$), 6.35 (m, 1, C=C*H*), 7.3-7.8 (m, 10, Ar*H*).

Anal. Calcd. for $C_{17}H_{17}OP$: P, 11.56

Found: P, 11.87

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16. As an analogy, it has been found that 1-methyl-3-phospholene 1-oxide rearranges in basic solution to 1-methyl-2-phospholene 1-oxide in 90%

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19. If desirable, 0.1 mole of *t*-butyl chloride may be added to quench the phenyllithium by-product. If so, the amount of alkyl halide should be appropriately reduced.

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