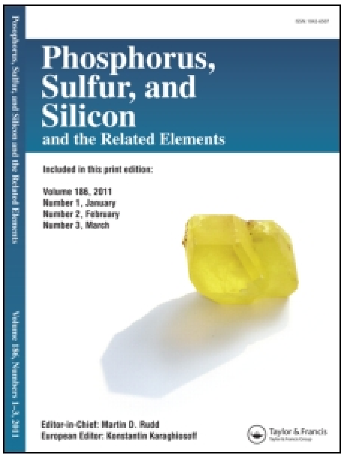

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Preparation of (2S*, 5S*) -2,5-Dibenzyl Phospholanic Acid

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PREPARATION OF (2S*,5S*)-2,5-DIBENZYL PHOSPHOLANIC ACID.

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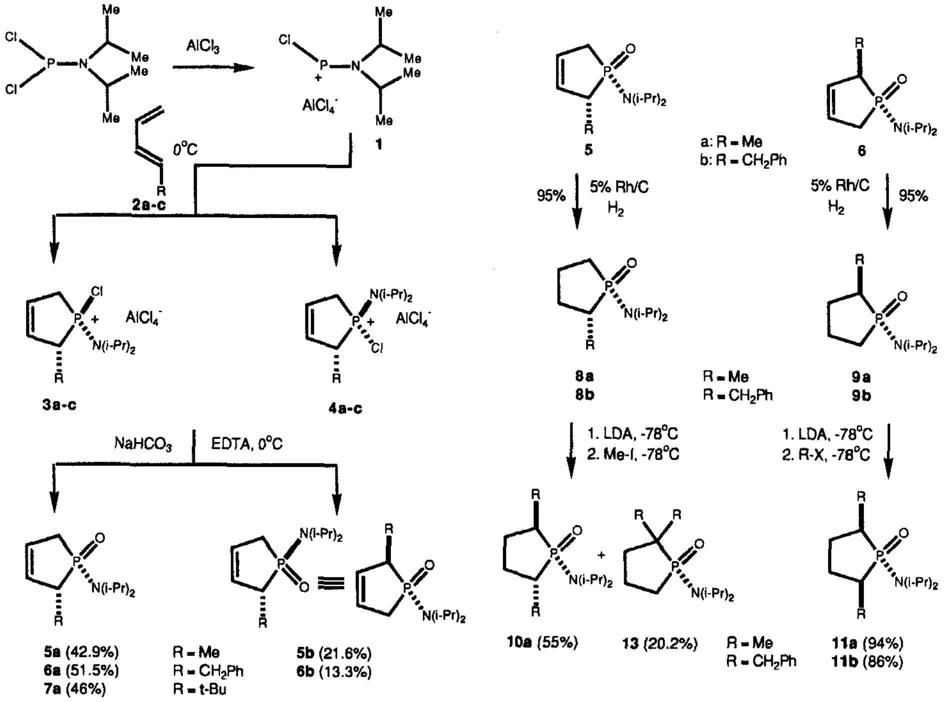
Abstract Phosphenium ion **1** underwent cheletropic cycloaddition with *E*-1-benzylbutadiene **2b** to afford cyclic phosphonium salts **3b** and **4b**. *In situ* hydrolysis of the phosphonium salts produced phosphinamides **6a** and **6b** in a 3:1 ratio. Three chemical steps coverted phosphinamide **6a** to the title compound **12b**.

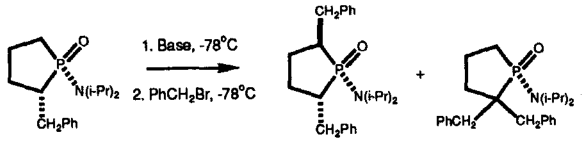
Recently, the potential utility of *trans*-2,5-disubstituted derivatives of phospholane as chiral reagents in organic[1,2] and organometallic[3,4] chemical transformations has been recognized by ourselves[1] and three other groups.[2-4] We report herein an improved method for the preparation of (2*R**,5*R**)-2,5-dimethyl- and (2*S**,5*S**)-2,5-dibenzyl phospholanic acids (**12a** and **12b**).

N,N-Diisopropylamino dichlorophosphine has been shown to undergo chloride ion abstraction by aluminum trichloride to form phosphenium ion[5] **1**. Cowley[6] and Baxter[7] have independently demonstrated that phosphenium ions undergo cycloaddition reactions with 1,3-dienes. We have found that cheletropic cycloaddition of the *N,N*-diisopropylamino chloro phosphenium ion **1** with *trans*-piperylene at 0°C afforded a 5:1 mixture of diastereomeric *P*-chloro-*P*-(*N,N*-diisopropylamino)-Δ3-phospholenium tetrachloroaluminates. Aqueous hydrolysis of the phospholenium ions at 0°C afforded a 2:1 mixture of 1-(*N,N*)-diisopropylamino-1-oxo-Δ3-phospholenes **5a** and **5b**. These compounds possess a phosphinic amide moiety, and such entities will hereafter be referred to as Δ3-phospholene amides. In a similar fashion *trans*-1-benzyl-1,3-butadiene[8] reacted with phosphenium ion **1** at 0°C to afford a 10:1 mixture of *P*-chloro-*P*-(*N,N*-diisopropylamino)-Δ3-phospholenium ions which upon aqueous hydrolysis afforded a 3:1 mixture of Δ3-phospholene amides **6a** and **6b**. *E*-1-*t*-Butyl-1,3-butadiene[9] underwent cycloaddition with **1** to afford a single Δ3-phospholenium ion. The Δ3-phospholenium ion then underwent a stereospecific hydrolysis to afford 2-*t*-butyl-Δ3-phospholene amide **7a**.



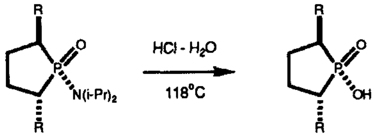
The Δ3-phospholene amide diastereomers **5a-b** and **6a-b** were readily separated by flash chromatography on silica gel. The combined yield of diastereomers produced in each reaction was good, being on the order of 65%. The isolated yield of **6a** was 51%, and that of **5a** was 43%. The carbon-carbon double bond of each pure diastereomer in each series was catalytically reduced over 5% rhodium on carbon. The average yield for this transformation was 95%.

Deprotonation of 1-(*N*,*N*)-diisopropylamino-1-oxo-2-alkyl phospholane **9a** or **9b** under kinetic conditions with lithium diisopropylamide followed by alkylation with methyl iodide or benzyl bromide, respectively, afforded phosphinamides **11a** and **11b**. A similar deprotonation/alkylation sequence carried out on phosphinamide **8a** resulted in the formation of 2,5-dimethyl phosphinamide **10a** and regioisomer **13** in a ratio of 2.8:1. The isolated yield of the desired isomer **10a** was 55%.



8b

	10b	**14**
LTMP	0	100
LDA	18	82
n-BuLi	80 (70% isolated)	20



10a R = Me **12a** (68%)
10b R = CH$_2$Ph **12b** (70%)

The deprotonation/alkylation behavior of phosphinamide **8b** resembled that of **8a**. Deprotonation of **8b** with lithium tetramethylpiperidide (LTMP) in THF at -78°C under standard kinetic conditions, followed by addition of benzyl bromide in the usual manner produced dibenzyl phosphinamide **14** exclusively. When deprotonation was effected with the less hindered base LDA, both the desired phosphinamide **10b** and regioisomer **14** were produced in a ratio of 1:4.5. When *n*-BuLi was used as the base, the ratio of **10b** to **14** inverted, **10b** now being favored over **14** by a 4:1 margin. The isolated yield of *trans*-2,5-dibenzyl *N,N*-diisopropyl phospholanic amide **10b** was 70%.

We had anticipated that phosphinamides **10a** and **10b** would serve as ideal precursors of the corresponding phospholanic acids since, phosphinic amides are in general, readily hydrolyzed.[10] In the event, the hydrolysis required heating the phosphinic amides in concentrated HCl for several hours. The phosphinic acids themselves are very robust and were isolated in good yield. It is conceivable that the reluctance of amides **10a** and **10b** toward hydrolysis was due to steric congestion in the vicinity of the phosphinyl moiety which must necessarily undergo nucleophilic attack by water. Presumably, a significant amount of the steric hindrance originates from the diisopropylamino moiety directly attached to phosphorus.

We have thus established a general method for the preparation of *trans*-2,5-dialkyl derivatives of phospholanic acid. Studies directed toward further elucidating the mechanistic details and improving the preparative aspects of the reactions are underway and will be reported in due course.

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