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First synthesis of P-chirogenic prophosphatranes

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ABSTRACT

Syntheses are reported for the novel P-chirogenic bicyclic prophosphatranes $P(RNCH_2CH_2)_2N(OCH_2CH_2)$— (**8**) in which the two R groups [i.e., 1-methylenenaphthyl and 1,2-methoxybenzyl (**8**)] and in its corresponding phosphine oxide (**9**) are different. Also synthesized was the transannulated protonated phosphatrane cation in the salt $[HP(RNCH_2CH_2)_3N]Cl$ in which the three R groups [i.e., 1-methylenenaphthyl, 1,2-methoxybenzyl, and (*S*)-1-phenethyl (**14**)] are different, and also in its corresponding deprotonated prophosphatrane form $P(RNCH_2CH_2)_3N$ (**15**). Good analytical resolution of racemic **9** is reported, whereas only partial resolution was achieved for diastereomeric **14**.

Nucleophilic organophosphorus catalysts enjoy wide use in organic reactions,[1] and many phosphine ligands are exceedingly effective in metal-assisted cross couplings.[2] Such transformations are of increasing interest in the synthesis of pharmaceuticals,[2] fine chemicals,[3] and compounds of biological interest.[4] Bulky electron-rich phosphines can be particularly useful for aryl chloride[5] and also for aromatic and heteroaromatic silanoate[6] substrates in cross coupling reactions. Prochiral olefins have been hydrogenated enantioselectively using chiral phosphites in the presence of a rhodium catalyst.[7] Allylation catalyzed by palladium/chiral phosphine ligand systems appears to be of considerable utility[8] and such a ligand has also been reported to efficiently facilitate an asymmetric Heck[8e,9] as well as other Heck-type reactions.[9b]

Chiral organophosphorus compounds catalyze a wide variety of useful enantiomeric transformations as organocatalysts.[10] Chiral phosphines catalyze the enantioselective acylation of alcohols to effect their kinetic resolution[10a,11] as well as desymmetrization of *meso* diols via acylation.[10a] Chiral phosphines also catalyze reactions of prochiral substrates as in MBH[10a,12] and aza-MBH reactions,[10a] formation of asymmetric quaternary carbon centers in the addition of nucleophiles to the γ-position of ethyl butynoate and ethyl 2,3-butadineate,[10a] and also in Steglich rearrangements.[10a] Cycloadditions of the [4 + 2] type are catalyzed by chiral phosphines as well as such reactions of the relatively rare [3 + 2] variety.[10a]

Non-chiral prophosphatranes of type **A** (with two or three identical R groups) in Figure 1 have been reported to catalyze a wide variety of important organic reactions[13] and to function as excellent ligands for palladium-catalyzed transformations.[14] Because a significant number of such reactions are carried out with prochiral substrates, it would be of interest to investigate the efficacy of P-chirogenic prophosphatranes in such reactions. P-chirogenic compounds[15] form a sizeable sub-class of chiral phosphines, but no examples of P-chirogenic prophosphatranes have been reported until now.

Prophosphatrane structures of types **A** and **B**, for example, feature a P-chiral 'pocket' for substrate activation by the nucleophilic phosphorus. Such a pocket in **A** and/or **B** may be anticipated to favor high product ee values since the R groups are held quite rigidly in place by the bicyclic framework and by the planarity of all four nitrogens.[1,2] This rigidity would be reasonably maintained by any changes in the N→P transannular distance that could potentially occur during the catalytic cycle.

Here we report initial results for the synthesis of chiral **8** and **9** in Scheme 1, and chiral **14** and **15** in Scheme 2.

The synthesis of racemic **8** was achieved by monoprotection of an NH_2 group in **2** with BOC to provide intermediate **3**, which was

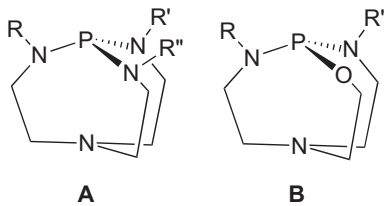

Figure 1. Prophosphatranes.

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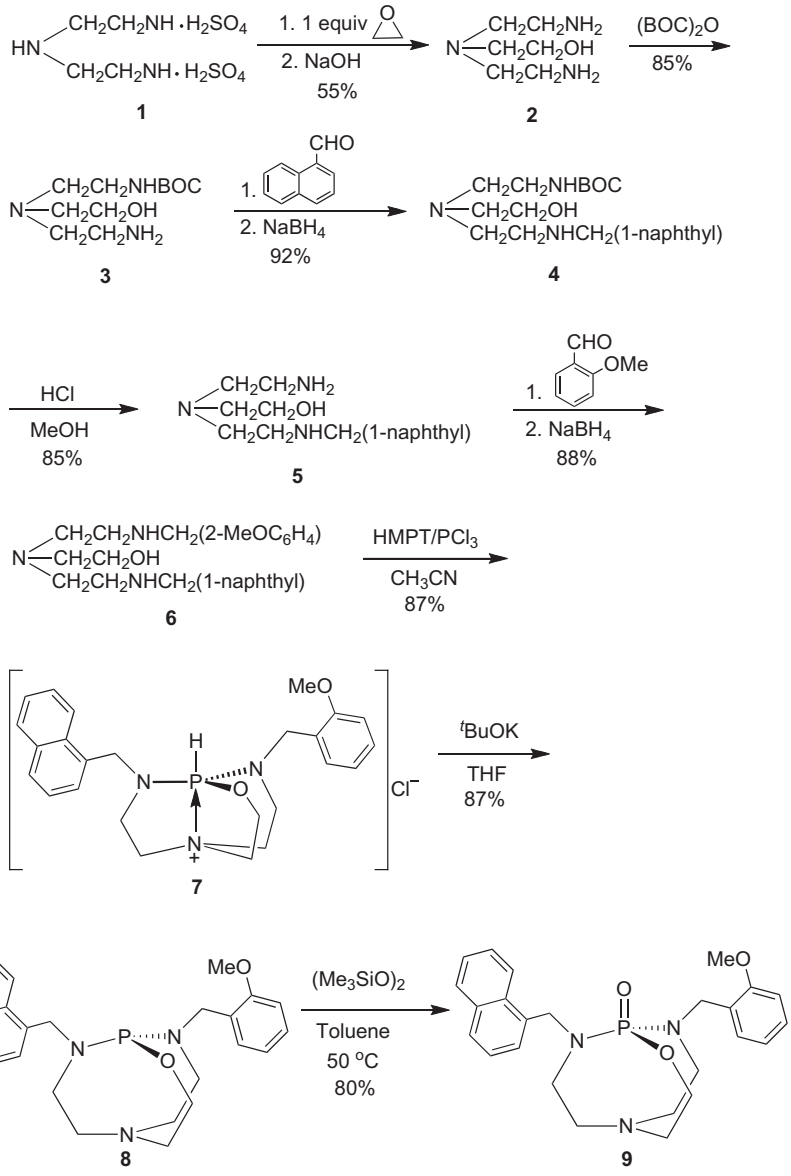
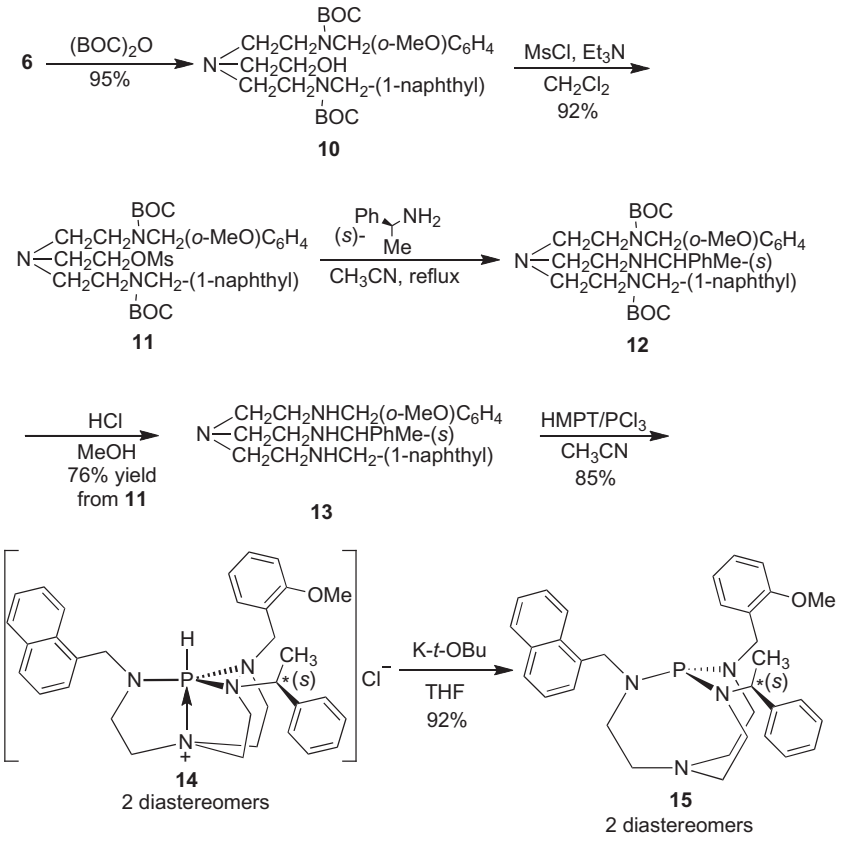


Scheme 1. Synthesis of prophosphatrane **8** and its oxide **9**.

then followed by reductive amination of the second NH_2 group with α-naphthaldehyde, BOC deprotection, and reductive amination with *ortho*-benzaldehyde to afford compound **6** bearing different R groups attached to the two terminal NH groups. Under similar conditions for the synthesis of non-chiral prophosphatranes of type **A**,[16] compound **6** was converted into the oxa-prophosphatrane salt **7**, which was then deprotonated to afford oxa-prophosphatrane **8**. The overall yield of **8** through seven steps from **1** is 28%. This is the first report of the synthesis of a prophosphatrane featuring two different heteroatoms on the phosphorus. For purification and optical resolution of an air- and moisture-stable derivative of **8**, this type **B** product was converted into its corresponding oxide **9** in 80% yield via $CH_3SiOOSiCH_3$ oxidation.

Our synthesis of a P-chirogenic prophosphatrane of type **A** with three different R groups on the P–N nitrogens relied on the successful synthesis of the intermediate tetraamine **13** in Scheme 2. Starting with **6**, which was synthesized from **1** as shown in Scheme 1, the two terminal NH groups were protected by BOC, followed by protection of the OH group as the mesylate **11**, which was allowed to react with (*s*)-1-methyl benzylamine to provide **12**. Following BOC deprotection of **12**, **13** was afforded in very good overall yield (66% from **6** through four steps) and in 21% overall yield from **1** through nine steps. This represents the first synthesis of a tetraamine of type **13** with three different R groups on the terminal NH groups. Our methodology is amenable to scale-up and easy purification of the products of each step via column chromatography. Analogously to the synthesis of non-chiral prophosphatranes of type of **A**,[16] diastereomeric **15** was obtained by reaction of **13** with $ClP((NMe)_2)_2$, which was prepared in situ via the reaction of HMPT $\{P(NMe_2)_3\}$ with PCl_3, to form the salt **14** which was then deprotonated with *t*BuOK in THF. The ^{31}P NMR spectrum of **15** showed two peaks [δ 127.89 (s), 127.83 (s)] consistent with the presence of two diastereomers.

Results of chiral HPLC separation experiments with **9** and **14** are shown in Figures 2 and 3, respectively. Racemic prophosphatrane oxide **9** was successfully resolved into a pair of enantiomers on a Chiralpak IA column with a mobile phase of methyl *t*-butyl ether/methanol/acetic acid/triethylamine (85:15:0.3:0.2). The diastereomeric phosphatrane salt **14** was partially separated to a pair of diastereomers on a Chiralpak IC column with a mobile phase of



Scheme 2. Synthesis of diastereomeric prophosphatrane **15**.

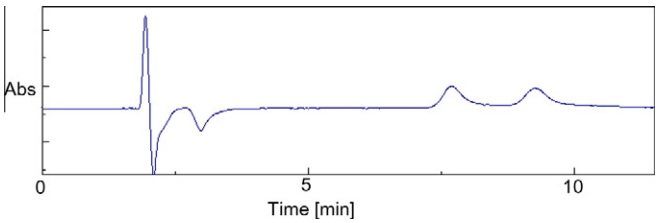


Figure 2. Enantiomeric separation of **9** on a Chiralpak IA column (15 cm).

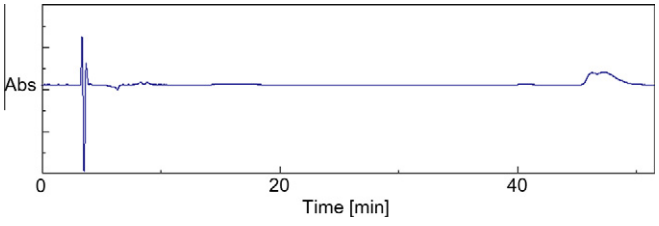


Figure 3. Partial diastereomeric separation of **14** on a Chiralpak IC column (25 cm).

methyl *t*-butyl ether/methanol/acetic acid/triethylamine (85:15:0.3:0.2).

In conclusion, we have successfully synthesized the first examples of P-chirogenic prophosphatranes. Thus $P(RNCH_2CH_2)_2N(OCH_2CH_2)$—(**8**) bearing two different R groups and its corresponding phosphine oxide (**9**) are reported, as well as $P(RNCH_2CH_2)_3N$ (**15**) featuring three different R groups. Good analytical resolution of racemic **9** and partial analytical resolution of diastereomeric prophosphatrane salt **14** was achieved. Our work sets the stage for further enantiomeric resolution and subsequent evaluation of compounds of the title type in inducing enantioselectivity in organic reactions.

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Supplementary data

Supplementary data (experimental details and characterizational data [NMR spectral (^{1}H, ^{13}C, ^{31}P) HRM spectral and HPLC conditions]) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.01.041.

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