A Temporary Phosphorus Tether/Ring-Closing Metathesis Strategy to Functionalized 1,4-Diamines

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The synthesis of 1,4-diamines containing the (2)-1,4-diaminobut-2-ene subunit via a temporary phosphorus tether/RCM strategy is described. We have developed a new method utilizing phosphorus nuclei as suitable temporary tethers for the coupling of nonracemic aliphatic amines. This approach allows for the generation of \( \mathrm{C}_2 \)-symmetric and unsymmetric 1,4-diamines 1–3, which may have considerable synthetic and biological utility. This represents the first synthetic pathway for the expedient coupling of two amines via a temporary tether approach.

Recently, nonracemic 1,4-diamines have served as key synthetic intermediates in the development of potent cyclic HIV protease inhibitors. In addition, the potential of nonracemic 1,4-diamines to serve as biologically active agents and asymmetric ligands warrants continued efforts toward an efficient route to their synthesis. Previous methods reported for the generation of nonracemic 1,4-diamines include intermolecular pinacol coupling of \( \alpha \)-amino aldehydes and several chiral pool syntheses starting from tartrate or mannitol. Our interest in the ring-closing metathesis (RCM) reaction on phosphorus templates has led us to investigate a temporary phosphorus tether (P-tether)/RCM strategy to the synthesis of 1,4-diamines.

Although temporary tethers have been extensively utilized in organic synthesis, examples of P-tethers have been


limited. We now report a new strategy that allows for the rapid coupling of nonracemic allylic amines via a P-tether/RCM sequence to derive Z-olefinic, C₂-symmetric 1,4-diamines 1 and 2 and unsymmetric, differentially substituted 1,4-diamines 3 (Scheme 1).

Our new method employs both intermediate phosphorous acid diamide 4 and phosphonamide species 5 and 6 containing P(III)- and P(V)-nuclei, respectively, as the central lynchpins for subsequent RCM (Scheme 1). The temporary cyclic P-tethers can be quantitatively hydrolyzed under mild acidic conditions to derive the title 1,4-diamines 1–3 containing the (Z)-1,4-diaminobut-2-ene subunit.

Our primary interest in C₂-symmetric 1,4-diamines 1 was rooted in our efforts to synthesize amino acid-derived 1,3,2-diazaphosphine 2-oxides such as A and B (Figure 1). These compounds and analogues thereof are similar in structure to DMP-323 and other potent HIV-1 protease inhibitors developed at DuPont Merck Laboratories. We determined that in order to generate phosphonamides such as A (R³ = alkyl, aryl), containing exocyclic α-amino substitution, it is necessary to overcome steric congestion imposed by an α-branched secondary amine by first synthesizing the 1,4-diamine 1, coupling it with R³PCl₂, and oxidizing at phosphorus.

Our initial strategy for the synthesis of A was to couple 2 equiv of an α-branched secondary allylic amine, such as 7, with either a P(V)- or P(III)-dichloride, followed by RCM (Scheme 2). However, we found that, due to steric congestion imposed by 7, the only phosphorus reagent which allowed the bis-coupling event to occur was phosphorus trichloride. The compounds and analogues thereof are similar in structure to DMP-323 and other potent HIV-1 protease inhibitors developed at DuPont Merck Laboratories.

Figure 1.

### Scheme 1

\[
\begin{align*}
\text{R}^1\text{N} = \text{N} & \quad \Rightarrow \\
\text{R}^2\text{P}=\text{Cl} & \quad \Rightarrow \\
\text{Phosphorous acid diamide 4} &
\end{align*}
\]

\[
\begin{align*}
\text{R}^1\text{N} = \text{N} & \quad \Rightarrow \\
\text{R}^2\text{PCl} & \quad \Rightarrow \\
\text{Phosphonamide 5} &
\end{align*}
\]

\[
\begin{align*}
\text{R}^1\text{N} = \text{N} & \quad \Rightarrow \\
\text{R}^2\text{PCl} & \quad \Rightarrow \\
\text{Phosphonamide 6} &
\end{align*}
\]

### Scheme 2

\[
\begin{align*}
\text{R}^1\text{O} = \text{N} & \quad \Rightarrow \\
\text{R}^2\text{O} & \quad \Rightarrow \\
\text{Phosphonamide 8} &
\end{align*}
\]

\[
\begin{align*}
\text{R}^1\text{O} = \text{N} & \quad \Rightarrow \\
\text{R}^2\text{O} & \quad \Rightarrow \\
\text{Phosphonamide 10} &
\end{align*}
\]

### Figure 1.

\[
\begin{align*}
A & \\
B & \\
\text{DMP-323 (Ar = p-OH-C₆H₄)} &
\end{align*}
\]

\[
\begin{align*}
\text{1a, R}^1 = \text{Me}, R^2 = \text{CH₂CH(CH₃)₂} & \\
\text{1b, R}^1 = \text{Me}, R^2 = \text{Bn} & \\
\text{1c, R}^1 = \text{Bn}, R^2 = \text{CH₂CH(CH₃)₂} & \\
\text{1d, R}^1 = \text{Bn}, R^2 = \text{Bn} &
\end{align*}
\]

### Scheme 2

\[
\begin{align*}
\text{Scheme 2} & \\
\text{a Reagents and conditions: (a) i. PCl₃, Et₃N, DMAP, CH₂Cl₂, reflux, ii. H₂O, 80–90%; (b) i. 9, benzene, reflux, >95%, ii. methanolic HCl, rt, >95%.}
\end{align*}
\]

\[
\begin{align*}
\text{(14) We have reported the synthesis of 1,4-diamine 1a (Scheme 2) via a phosphaldehyde tether/RCM/hydrolysis sequence: RCM yielded predominantly the Z-isomer (10:1 Z/E), see ref 12c.}
\end{align*}
\]
Due to the lability of the $P-N$ bond to hydrolysis in cyclic species 10,16 we reasoned that we could employ the phosphorous acid diamide moiety as a P(VI)-temporary tether in a one-pot RCM/hydrolysis procedure (Scheme 2). Optimization of the previously reported conditions6b provides acyclic RCM precursors 8 in 80–90% yield. Subsequent RCM utilizing the second generation Grubbs catalyst 915c,17 in refluxing benzene, followed by facile cleavage18 of the $P$-tether with methanolic HCl, results in quantitative yields of $C_2$-symmetric 1,4-diamine 1 with complete stereochemical and geometrical integrity. Furthermore, the RCM reaction is complete within several minutes, reaction scale is a nonissue, and the RCM/hydrolysis sequence is a single-pot event.

A number of other temporary tethers were also investigated,19 including various metals2a-c (Cu, Fe, Mn, Mg, and Ni), as well as carbon (CO) and boron2b (BPh). Thus far, none have allowed this facile “di-amine” binding/metathesis sequence to occur. Our group previously reported an RCM strategy to generate cyclic sulfamides analogous to 10,20 however, the inability to effectively cleave the sulfamide linkage (RNNSO2NR) under mild conditions limits their utility in the production of 1,4-diamines such as 1–3.

Moreover, while temporary silicon tethers11 have been employed in the RCM reaction to access 1,4-diols, all of our attempts to prepare 1 from 7 utilizing silicon tethers (SiPh2, SiMe2, and SiCl2) have been unsuccessful. We have found that not only does phosphorus appear to be the sole nucleus in which this 1,4-diamine chemistry is successful but the efficiency and ease of the sequence is extraordinary.

With this temporary bridging strategy in hand, we turned our attention to the synthesis of $C_2$-symmetric 1,4-diamine 2, containing branching at the allylic positions (Scheme 3). Previously, we found that less sterically encumbering $alpha$-branched primary amines, such as l-valine-derived 11,21 readily couple twice with P(V)-dichloride 12a to give 13a in high yield. In addition, we and others22 have shown that the reaction between phosphorus oxychloride (POCl3) and 3 equiv of an $alpha$-branched primary amine, such as 11, is facile to afford the corresponding phosphoramidic monochloridates, see ref 6b.

Prior work in our laboratory revealed that only 1 equiv of an N-allylated, $alpha$-branched primary amine, such as 7a, couples with P(V)-dichlorides, such as methylphosphonic dichloride (14), to give an $sim 1:1:1$ diastereomeric mixture of phosphonamidic monochloridates 15.24 We reasoned that this monochloridate, 15, would serve as an ideal intermediate in the production of the differentially substituted 1,4-diamine 3. Therefore, addition of primary amine 11 to the diaste-
omeronic mixture of 15 produces the unsymmetric metathesis precursor 16 in high yield and with good to high diastereoselectivity (ds 6.6–13.2:1.0). Metathesis utilizing the first generation Grubbs catalyst 17, followed by in situ acid-mediated methanolic cleavage of the P(V)-tether, affords unsymmetric 1,4-diamine 3 in near quantitative yield.

The strengths of this new P-tether strategy are reflected in the ease in which the chiral, nonracemic 1,4-diamines can be synthesized. Not only is the RCM/hydrolysis sequence a single-pot event but chromatography is required only after the initial phosphorus/amine coupling. Moreover, the 1,4-diamines 1–3 can be obtained in high purity by simple acid/base extraction following the cleavage of the temporary P-tether (>99% purity as determined by GC and >95% purity as determined by 1H, 13C, and 31P NMR analysis). We have demonstrated the efficacy of this sequence by generating as much as 10 g of 1,4-diamines 1b in a single afternoon starting from N-allylated amino esters 7b.

In summary, we have developed an efficient method to synthesize C2-symmetric and unsymmetric, nonracemic 1,4-diamines 1–3 via a P-tethered RCM/hydrolysis sequence, of which the P(III)-tether represents the first of its kind. To our knowledge, this approach represents the first synthetic pathway that allows for the expedient coupling of two amines via a facile temporary tether approach. Furthermore, we have demonstrated the P-tether strategy to be an effective route to the synthesis of unsymmetric, differentially substituted 1,4-diamines. The synthetic and biological potential of the 1,4-diamines and analogues thereof is currently being investigated and will be reported in due course.

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Supporting Information Available: Experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) The unambiguous assignment of the major diastereomer, as well as mechanistic rationale for the observed selectivity, is currently being investigated.