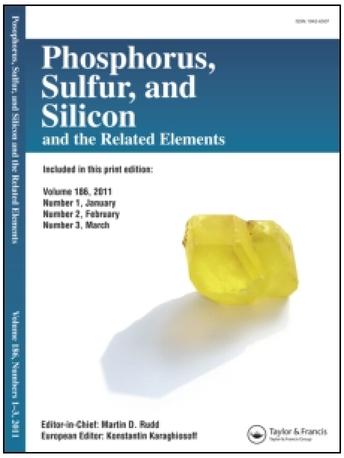

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Ring-Closing Metathesis Strategies to P -heterocycles

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RING-CLOSING METATHESIS STRATEGIES TO *P*-HETEROCYCLES

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A general approach to the synthesis of P*-heterocycles using the ring-closing metathesis reaction is described. We have developed a new method utilizing phosphorus nuclei as suitable temporary tethers for the coupling of non-racemic allylic amines. This approach allows for the generation of symmetric and unsymmetric 1,4-diamines. Subsequent coupling of these 1,4-diamines with various nuclei produces an array of 7-membered heterocycles.*

Keywords: 1,4-Diamine; *P*-heterocycle; ring-closing metathesis cyclic phosphonamide; temporary phosphorus tether

Phosphorus containing compounds have gained considerable attention due to their diverse biological and chemical profiles.[1] A number of *P*-heterocycles have shown potent biological activity[2] and have thus become attractive targets as rationally designed small molecules. We are interested in continuing to build a library of highly diverse *P*-heterocycles of varied chemical and biological interests. We and others have recently shown that the ring-closing metathesis (RCM) reaction[3] catalyzed by the Grubbs benzylidene catalyst[4] is an effective method for the construction of *P*-heterocycles.[5] We recently have directed our efforts to a class of amino acid-based seven-membered heterocycles **1–8** (Scheme 1), due to their geometrical and structural similarity to potent HIV-1 protease inhibitors described by DuPont Merck Laboratories.[6] We herein report the scope and utility of the RCM reaction in the construction of an array of amino acid-derived *P*-heterocycles.

An expedient method of utilizing phosphorus-III [P(III)] and phosphorus-V [P(V)] as convenient temporary tethers for the generation of nonracemic symmetric and unsymmetric *Z*-olefinic 1,4-diamines is described. Our new method employs intermediate phosphinamide and

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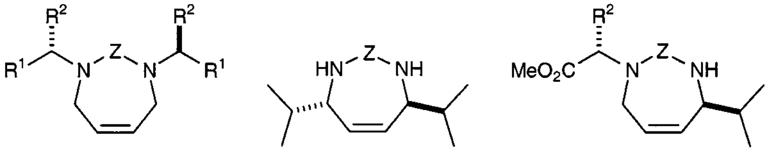

1–3
$Z = P(O)R_3$, SO, CO

4, 5
$Z = P(O)R_3$, CO

6–8
$Z = P(O)R_3$, SO_2, CO

SCHEME 1

phosphonamide species containing both P(III) and P(V) nuclei as the central lynch pins for subsequent ring-closing metathesis (RCM) to generate the *P*-heterocycles. The temporary *P*-tethers can be quantitatively hydrolyzed under mild acidic conditions to derive the 1,4-diamines.[7] Insertion and manipulation of a number of nuclei generates an array of cyclic phosphonamides ($Z{=}P(O)R^3$), sulfimides (Z=SO), sulfamides ($Z{=}SO_2$), and ureas (Z=CO). RCM strategies to an array of symmetric and unsymmetric phosphonamides are also described.

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