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# Amino Acid-Derived Cyclic Phosphonamides as Potential HIV-Protease Inhibitors

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[Click here to start](#)

## **Table of Contents**

[Amino Acid-Derived Cyclic Phosphonamides as Potential HIV-Protease Inhibitors](#)

[Abstract](#)

[RCM Strategy to Phosphorus-Based Potential HIV Protease Inhibitors](#)

[RCM Strategy to Cyclic Phosphonamides](#)

[Phosphonamidic Anhydrides](#)

[Methyl, Vinyl, and Bicyclic Anhydrides](#)

[P-Heterocycles via RCM](#)

[Amino Acid-Derived P-Heterocycles](#)

[Utilization of P\(III\) Chemistry](#)

[Internal Amino Acid Centers on P-Heterocycles](#)

[Phosphonamides with Two External Amino Acids](#)

[1,4-Diamine Strategy](#)

[Synthesis of Amino Acid-Derived 1,4-Diamine](#)

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[Download presentation source](#)

[N,N- \$\alpha\$ -Branched Cyclic Phosphonamides](#)

[N,N- \$\beta\$ -Branched Cyclic Phosphonamides](#)

[Intermolecular Olefin Metathesis](#)

[Template Promoted RCM/Amide Hydrolysis  
Sequence En Route to 1,4-Diamines](#)

[Novel P-Heterocycles](#)

[Conclusion](#)

[Acknowledgements](#)

[References](#)

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Slide 1 of 21

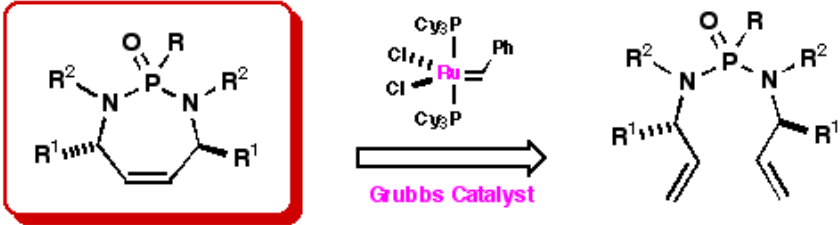


## Abstract

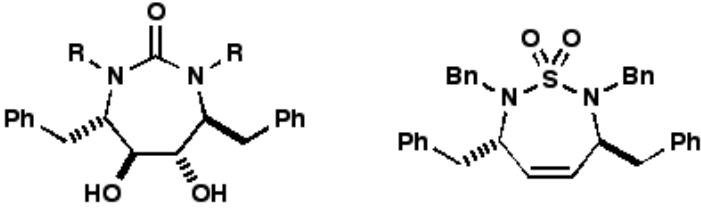
**Phosphorus containing compounds have gained considerable attention due to their diverse biological and chemical profiles.<sup>1</sup> A number of *P*-heterocycles have shown potent biological activity, and have become attractive targets as rationally designed small molecules.<sup>2</sup> We are interested in continuing to build a library of highly functionalized heterocyclic phosphorus-containing compounds of varied chemical and biological interests.**

**In our pursuit of novel *P*-heterocycles,<sup>3</sup> we have recently become interested in the synthesis of amino acid-based phosphorus containing compounds that may have potential as HIV-1 protease inhibitors.<sup>4</sup> Our efforts have largely been driven by the development of a number of cyclic urea-based HIV-1 protease inhibitors at Dupont-Merck that gave promising biological activity.<sup>5</sup>**

# RCM Strategy to Phosphorus-Based Potential HIV Protease Inhibitors



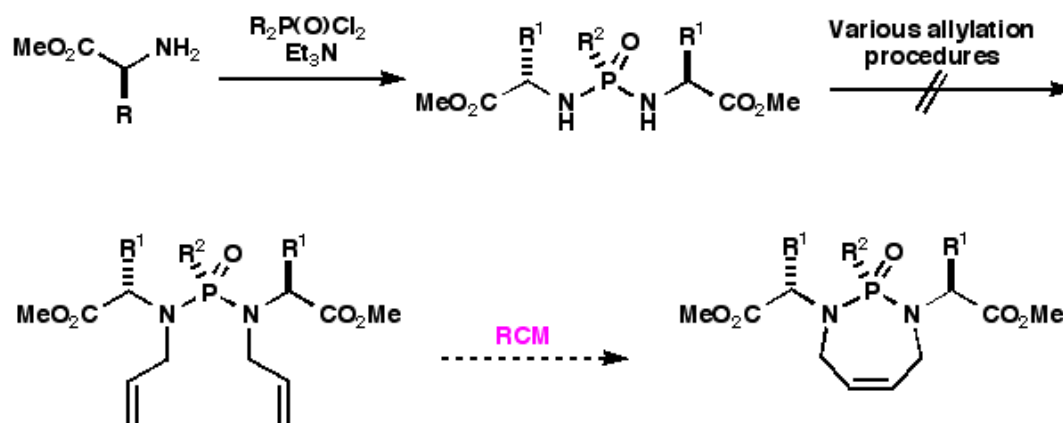
R<sup>2</sup> = Peptide Linkage



## DuPont-Merck HIV Protease Inhibitors

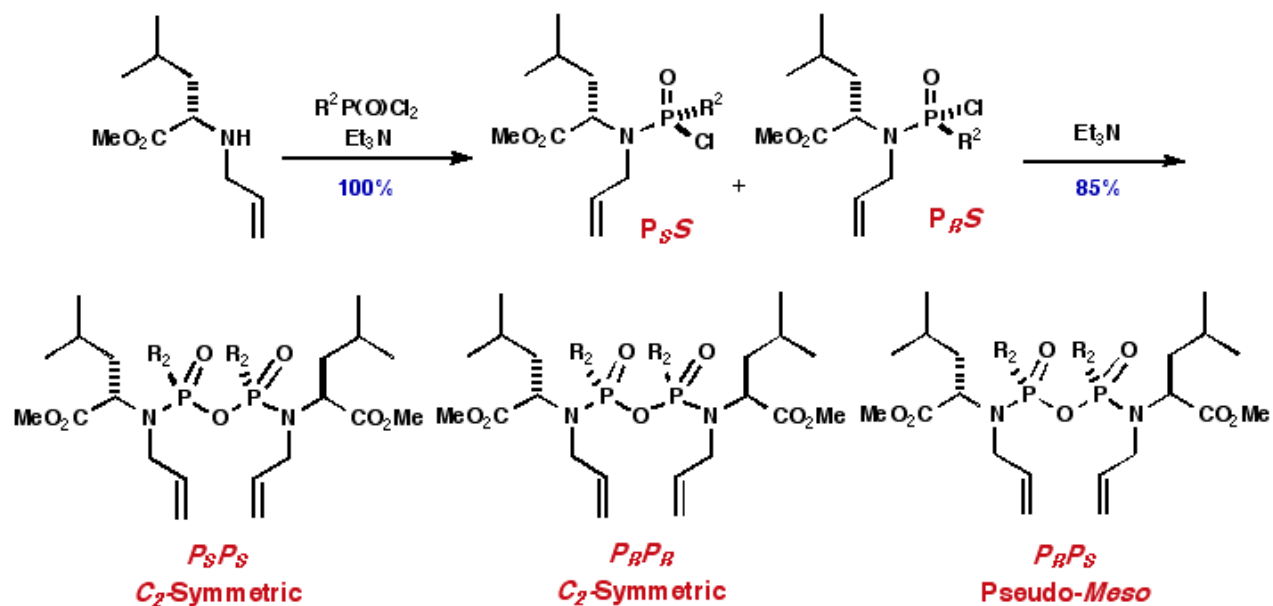


## RCM Strategy to Cyclic Phosphoramides

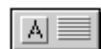
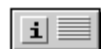


- Allylation of phosphoramidate problematic, presumably due to steric issues

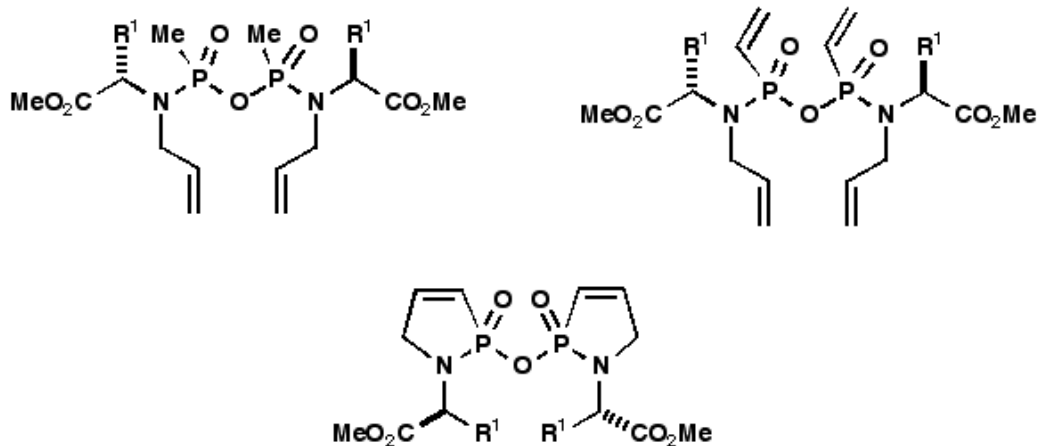
# Phosphonamidic Anhydrides



Sprott, K. T.; Hanson, P. R. *J. Org. Chem.* **2000**, *65*, 4721-4728.



## Methyl, Vinyl, and Bicyclic Anhydrides



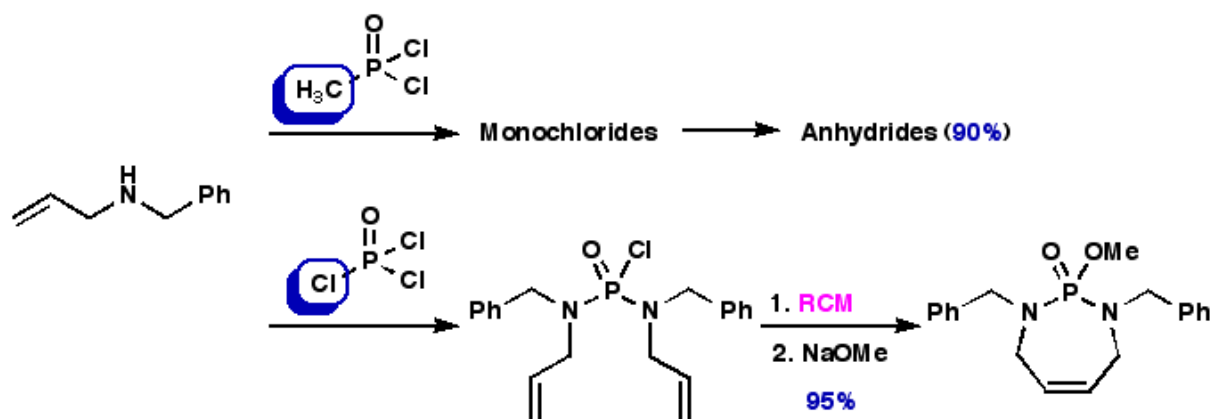
- **Bicyclic phosphonamidic anhydride synthesized via RCM (Grubbs catalyst) of vinyl phosphonamidic anhydrides**

Sprott, K. T.; Hanson, P. R. *J. Org. Chem.* **2000**, *65*, 4721-4728.





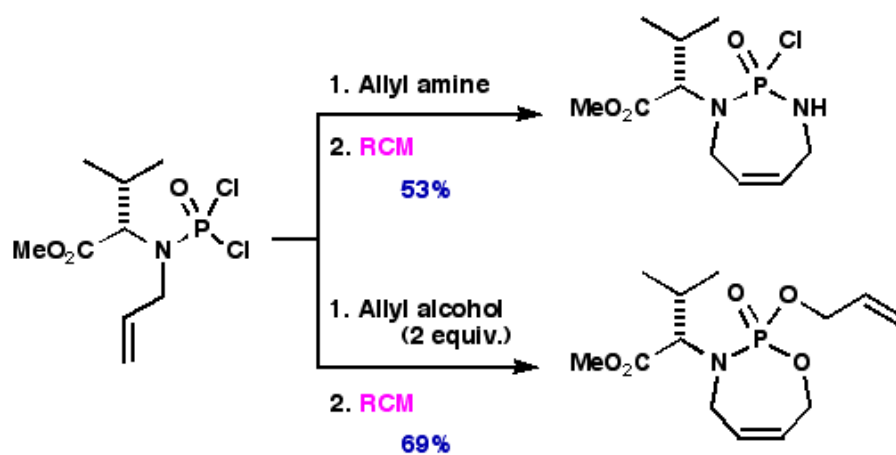
## P-Heterocycles via RCM



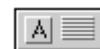
- Phosphorus oxychloride less bulky and more electrophilic
- RCM yields cyclic (non-amino acid bearing) phosphonamide



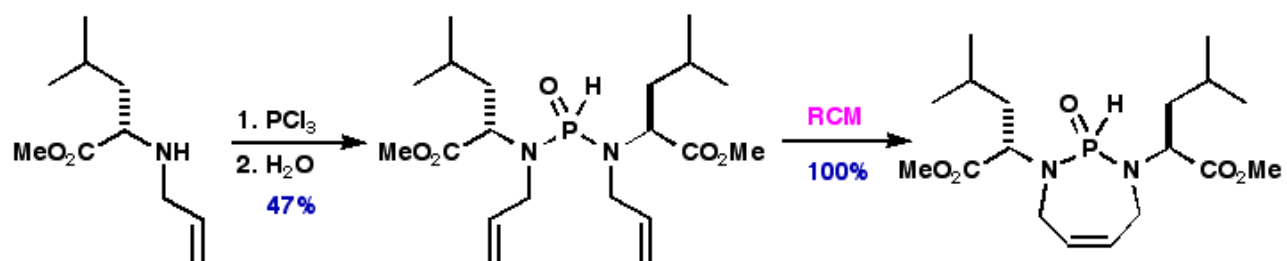
## Amino Acid-Derived *P*-Heterocycles



- Only a single allylated amino acid couples to phosphorus oxychloride



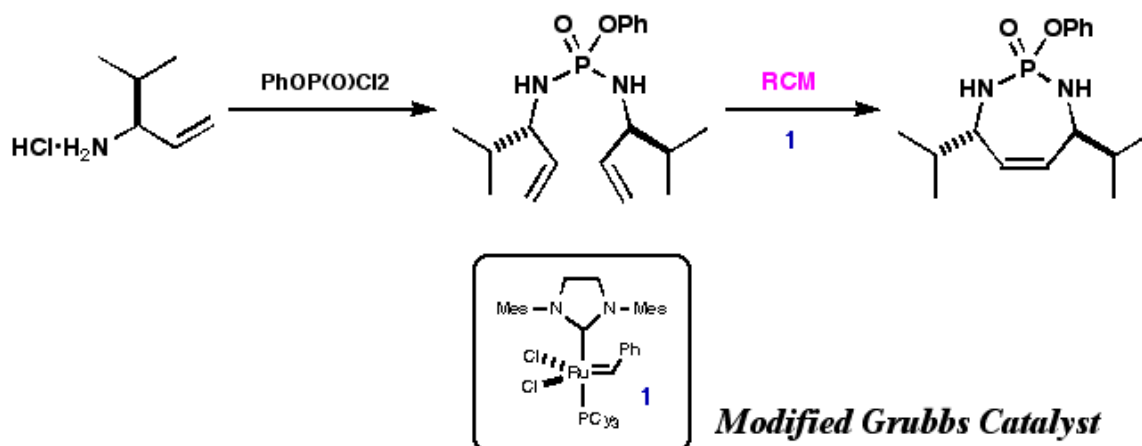
## Utilization of P(III) Chemistry



- $\text{PCl}_3$  was the only P(III) center to allow substitution of two allylated amino esters ( $\text{PhPCl}_2$ ,  $\text{MePCl}_2$ ,  $\text{MeOPCl}_2$ )

Sprott, K. T.; McReynolds, M. D.; Hanson, P. R. 2000, *submitted for publication*

## Internal Amino Acid Centers on *P*-Heterocycles

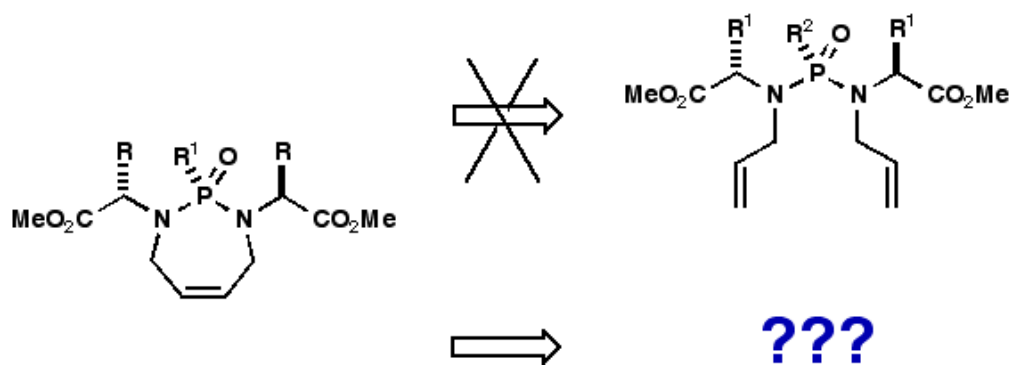


- Grubbs catalyst yielded **33%** product; modified catalyst, **87%**

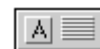
Sprott, K. T.; McReynolds, M. D.; Hanson, P. R. **2000**, *submitted for publication*



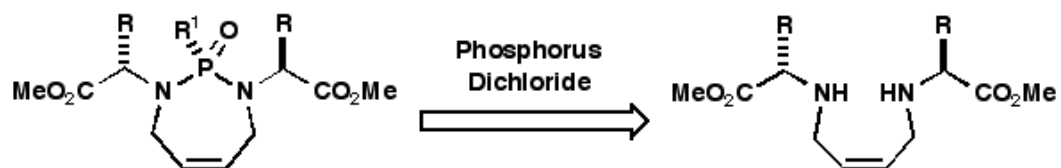
## Phosphoramides with Two External Amino Acids



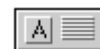
- Steric congestion prohibits synthesis of the RCM precursor



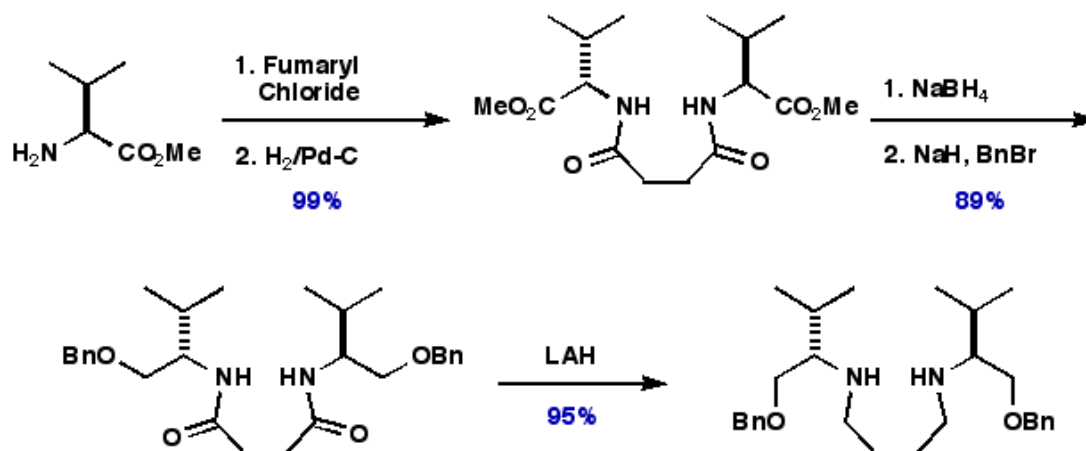
## 1,4-Diamine Strategy



- Utilizing a presynthesized 1,4-diamine may overcome be entropically favorable enough to overcome steric problems and promote ring closure.



## Synthesis of Amino Acid-Derived 1,4-Diamine

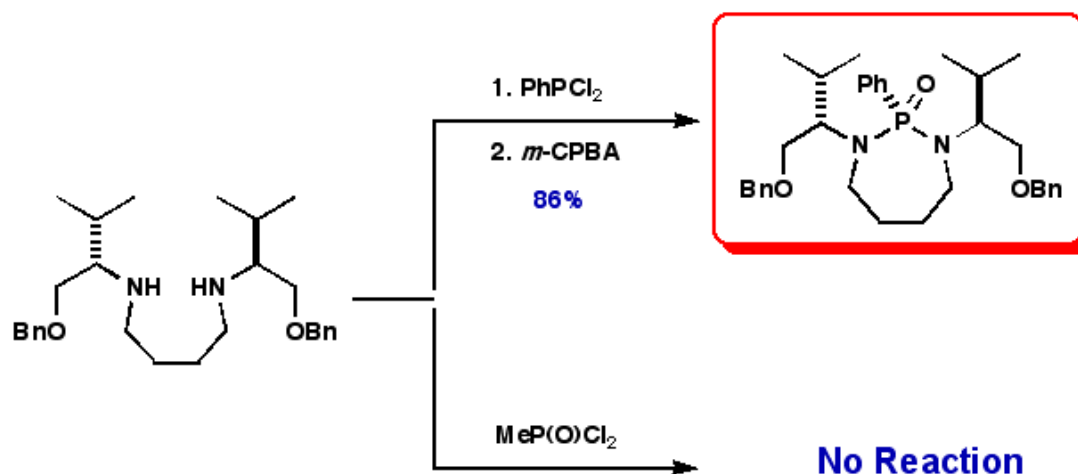


• 5-step synthesis: overall yield, **84%**

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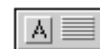


## $N,N'$ - $\alpha$ -Branched Cyclic Phosphonamides

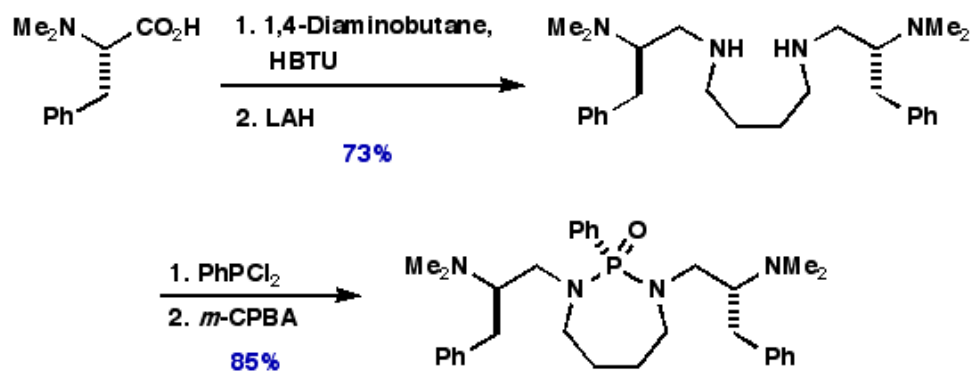


- Supports premise that these phosphonamides have significant steric demand





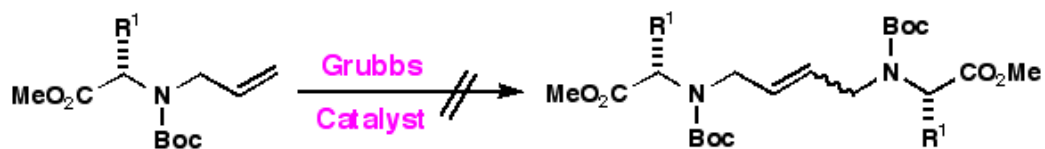
## $N,N'$ - $\beta$ -Branched Cyclic Phosphonamides



- Amino acid center one atom removed from previously synthesized cyclic phosphonamide



## Intermolecular Olefin Metathesis

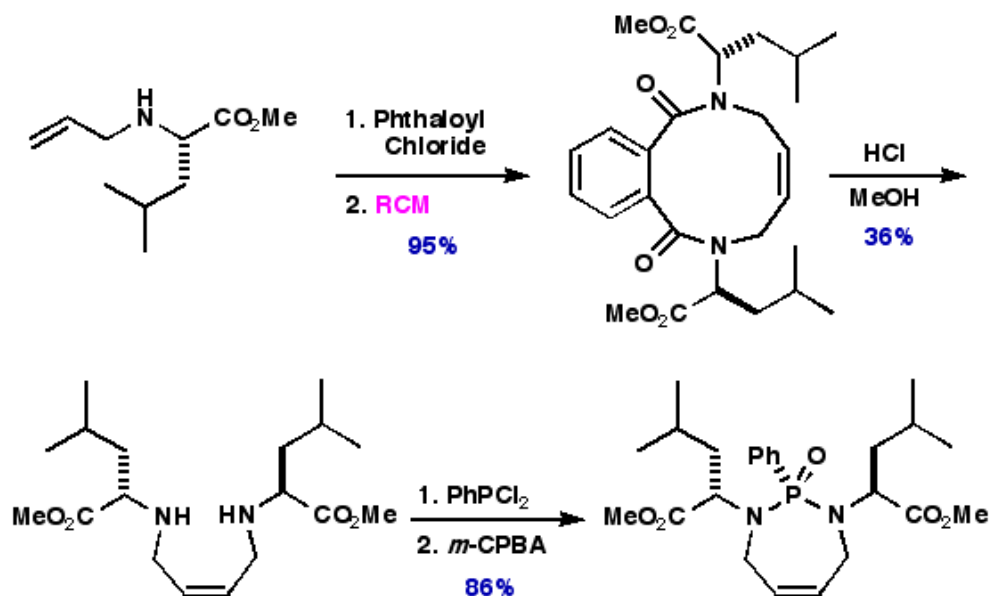


- Intermolecular cross-metathesis of allylated amino esters is unsuccessful, as consistent with the previous findings of Grubbs<sup>a</sup>

<sup>a</sup>(O'Leary, D. J.; Miller, S. J.; Grubbs, R. H. *Tetrahedron Lett.* 1998, *39*, 1689-1690)



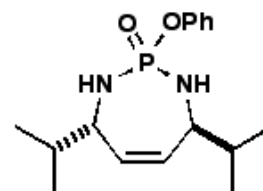
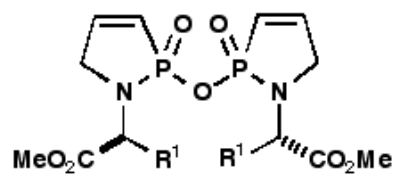
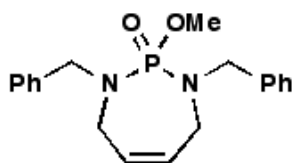
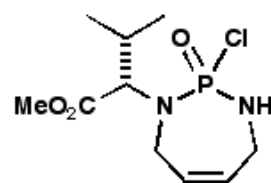
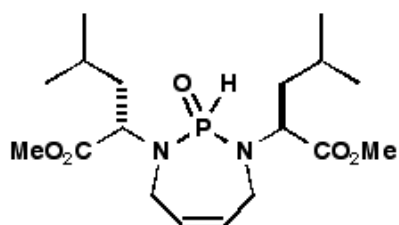
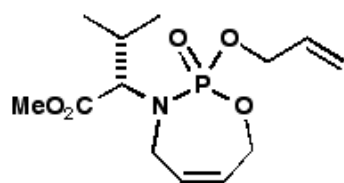
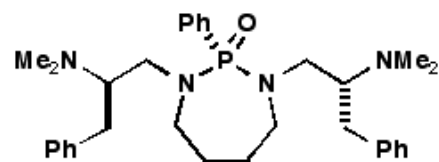
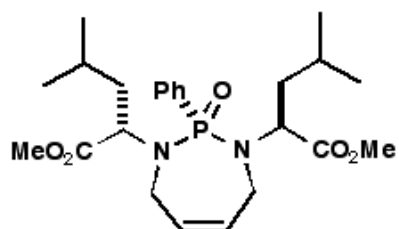
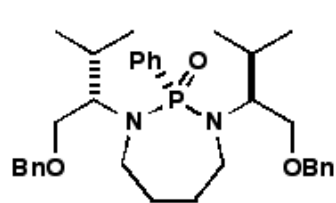
## Template Promoted RCM/Amide Hydrolysis Sequence En Route to 1,4-Diamines



Sprott, K. T.; Hanson, P. R. *J. Org. Chem.* **2000**, *in press*



## Novel *P*-Heterocycles





## Conclusion

- **Addition of allylated amino esters to phosphorus (V) yields phosphonamidic anhydrides**
- **Development of *P*-heterocycles with a single amino acid center via RCM strategy**
- **Development of amino acid derived cyclic P-H compounds via RCM strategy**
- **Cyclic phosphonamides with two internal amino acid centers via RCM strategy**
- **Development of cyclic phosphonamides and coupling of presynthesized amino acid-derived 1,4-diamines**
- **Phosphonamides in both C- and N- terminus of a peptide chain**
- **Synthesis of 1,4-diamine via template promoted RCM/amide hydrolysis sequence**



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