Developing a sustainable approach for the synthesis of Phosphorus-containing amino acids

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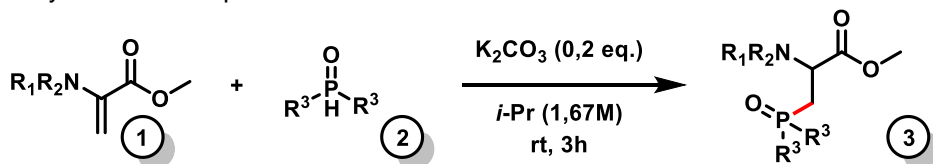*2) Department of Chemistry, Johannes Gutenberg University of Mainz, D-55128, Mainz, Germany*
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Keywords: *Phospha-Michael addition, stereoselective synthesis, amino acid functionalization.*
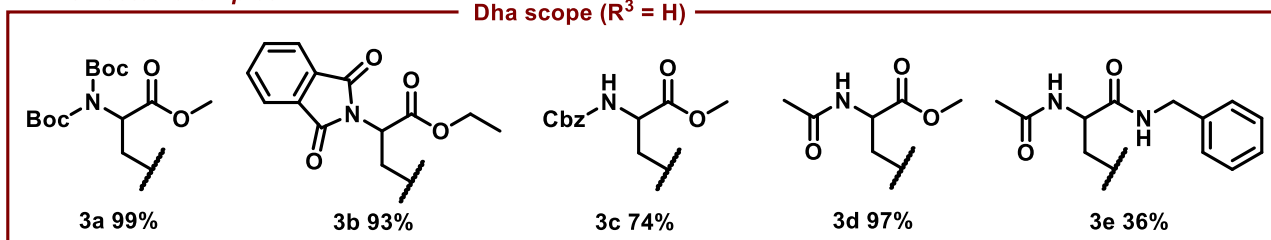
ABSTRACT

Amino carboxylic-phosphonic acids are prevalent in both natural products and synthetic bioactive molecules.[1] In this context, the artificial synthesis of non-hydrolyzable *C*-phosphorylated amino acids presents a significant area of research. The synthesis and utilization of α-amino acids bearing a phosphorus moiety have seen a resurgence of interest since the discovery of (*L*)-phosphinothricin in 1970. Notably, phosphorus-containing amino acids present a rich structural diversity, with functionalities that mimic carboxylates, thus serving as biologically active scaffolds.[2] Moreover, obtaining chiral products is crucial to the fine chemical industry, encouraging the development of asymmetric methodologies. This project focuses on the addition of derivatives of diphenylphosphine oxide and of phosphonates to dehydroalanine, yielding a range of phosphorus-containing amino acids under mild, base-catalyzed conditions with remarkable yields reaching up to 99%. An enantiomeric (using catalyst) and a diastereoisomeric (using chiral substrate) version of this reaction is currently under development.
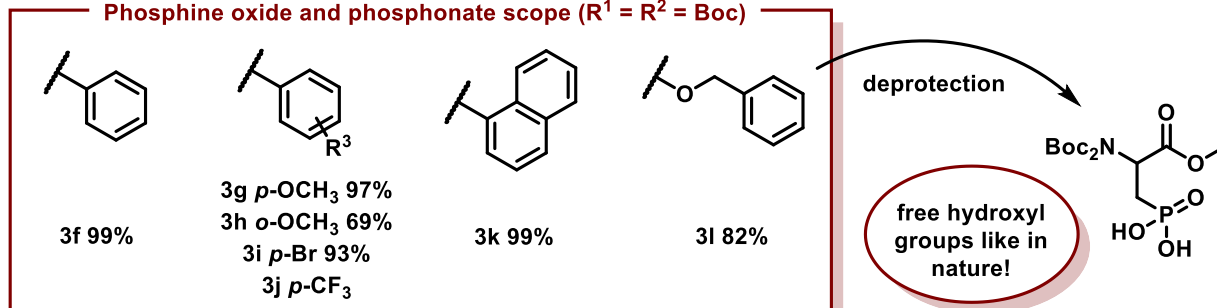
Selected examples:

Dha scope (R³ = H)

3a 99%   3b 93%   3c 74%   3d 97%   3e 36%

Phosphine oxide and phosphonate scope (R¹ = R² = Boc)

3f 99%

3g *p*-OCH₃ 97%
3h *o*-OCH₃ 69%
3i *p*-Br 93%
3j *p*-CF₃

3k 99%

3l 82%

deprotection

free hydroxyl groups like in nature!

ACKNOWLEDGEMENTS

REFERENCES

[1] Cao, H-Q.; Li, J-K.; Zhang, F-G.; Cahard, D.; Ma, J-A. *Adv. Synth. Catal.* **2021**, *363*, 688 – 729.
[2] Arribat, M.; Cavelier, F.; Remond, E. *RSC Adv.*, **2020**, *10*, 6678 – 6724.