Nicholas Kramer

Electrophilic Oxaziridines for N-Amination

Bowers Lab

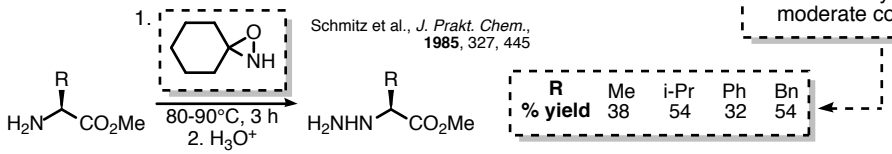
Oxaziridine; features a three-membered heterocycle containing oxygen, nitrogen, and carbon.

Electrophlic oxaziridine chemistry for N-aminations was initially studied by Schmitz and coworkers followed by extensive work from Vidal, Collet, and Armstrong. Most recently, Del Valle has established a method for efficient N-amination for applications including peptide synthesis.

Useful Reviews:

- Williamson, K. S.; Michealis, D. J.; Yoon, T. P. *Chem. Rev.*, **2014**, 114, 8016-8036
- Andreac, S.; Schmitz, E. *Synthesis*, **1991**, 327-341

Schmitz Electrophilic Amination Methodology:



Schmitz et al., *J. Prakt. Chem.*, **1985**, 327, 445

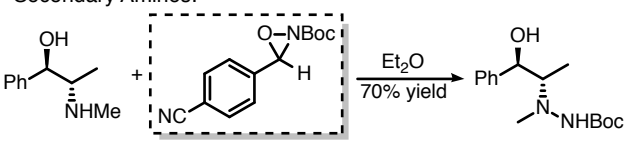
Initial studies yielded poor to moderate conversions.

R	Me	i-Pr	Ph	Bn
% yield	38	54	32	54

Limitations to the intial N-H oxaziridines employed by Schmitz included the necessity to form the reagents *in situ*, which propagated the design of oxaziridines with improved practicality.

Vidal & Collet's Electrophilic Amination Methodology:

Secondary Amines:

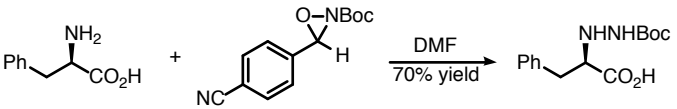


Vidal, J.; Drouin, J.; Collet, A. J. Chem. Soc., *Chem. Commun.*, **1991**, 435

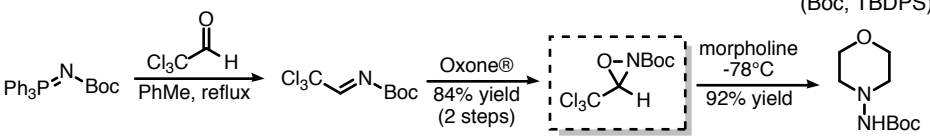
Vidal, J; Guy, L.; Sterin, S.; Collet, A.; *J.* Org. Chem., **1993**, 58, 4791

Vidal, J; Damestoy, S.; Guy, L.; Hannachi, J.-C.; Aubry, A.; Collet, A. *Chem.–Eur. J.*, **1997**, 3, 1691

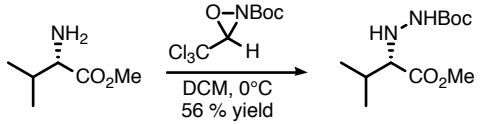
Primary Amines:



Vidal and Collet first developed electrophilic amination reagents that were capable of transferring nitrogen in a protected form (Boc, TBDPS).

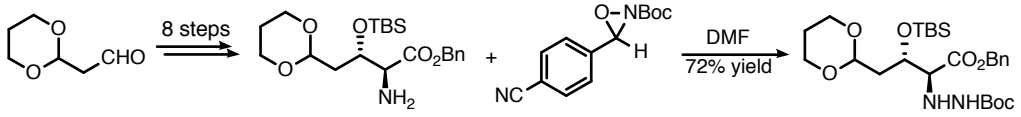


Vidal, J.; Hannachi, J.-C.; Hourdin, G.; Mulatier, J.-C.; Collet, A. *Tetrahedron Lett.*, **1998**, 39, 8845-8848



Collet and Vidal used protected nitrogen oxaziridines, which were not only stable and isolatable solids, but aminated nitrogen nucleophiles with increased effectiveness compared to Schmitz oxaziridines.

Applications of Vidal & Collet's Oxaziridine – Synthesis of Acyalic Precursors to Luzopeptin:



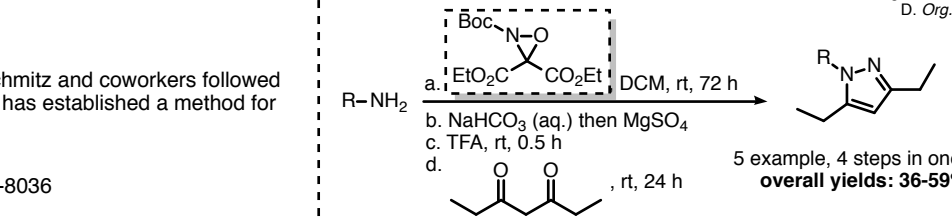
Boger, D. L.; Shüle, G.; *J. Org. Chem.*, **1998**, 63, 6421-6424

Limitations of Electrophilic Oxaziridine Chemistries for N-Amination:

- In situ generated aldehyde byproducts react with amine nucleophiles to give unwated imines.
- Undesired diaminated side products detract from yields due to both the inherent nucleophilicity of amine substrates and the high reactivity of oxaziridines.
- Poor solubility of substrates often necessitates the need for phase-transfer catalysts to induce reactions, often with moderate yields at best.
- With regard to amino acids, substrate scopes have been severely limited due to heteroatom-bearing side chain intolerance and the labile nature of some acid sensititve protecting groups (Boc, Trt, *t*-Bu, Pbf, etc).

Armstrong Oxaziridine Chemistry:

Armstrong, A.; Jones, L. H.; Knight, J. D.; Kelsey, R. D. *Org. Lett.*, **2005**, 7, 713-716

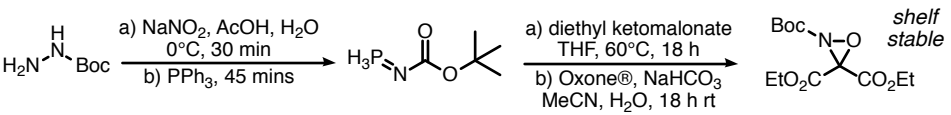


5 example, 4 steps in one pot
overall yields: 36-59%

Armstrong sought to troubleshoot the problematic imine and diaminated side products that often hindered the Schmitz, Vidal, and Collet oxaziridine reactions.

A new oxaziridine reagent was generated.

Gram-Scale Synthesis:

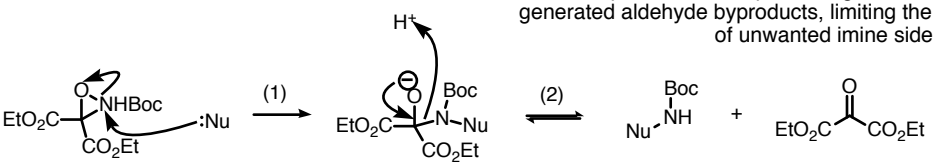


40% yield (2 steps)

- Yields multigram quantities of shelf-stable product.
- Requires only one chromatographic purification.
- Accessable in 48 hours from start of synthesis.

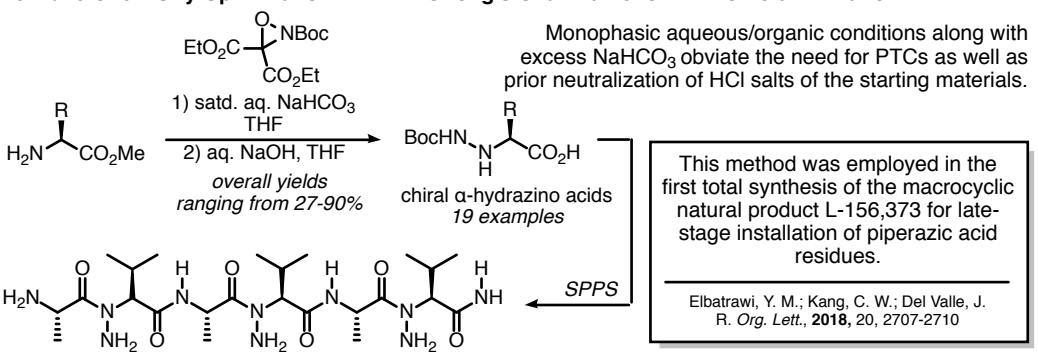
Kang, C. W.; Sarnowski, M. P.; Elbatrawi, Y. M.; Del Valle, J. R. *J. Org. Chem.*, **2017**, 82, 1833-1841

Mechanism:



The ketone byprodct is less reactive toward nucleophiles than the previous generation's in situ-generated aldehyde byproducts, limiting the formation of unwanted imine side products.

Del Valle Chemistry Optimization with Armstrong's Oxaziridine for Amino Acid Amination:



Monophasic aqueous/organic conditions along with excess $NaHCO_3$ obviate the need for PTCs as well as prior neutralization of HCl salts of the starting materials.

This method was employed in the first total synthesis of the macrocyclic natural product L-156,373 for late-stage installation of piperazic acid residues.

Elbatrawi, Y. M.; Kang, C. W.; Del Valle, J. R. *Org. Lett.*, **2018,** 20, 2707-2710

***N*-amino peptide (NAP)**

Kang, C. W.; Sarnowski, M. P.; Elbatrawi, Y. M.; Del Valle, J. R. *J. Org. Chem.*, **2017**, 82, 1833-1841

- Compatible with commercially available and inexpensive α-amino ester hydrochloride salts.
- Acid-labile protecting groups are stable through both steps (amination & saponification).
- Reactions proceed with moderate to excellent conversions.
- α-hydrazino ester intermediates are easy to purify, making the stepwise procedure attractive.
- Previously limited scope drastically expanded to support heteroatom side chain-bearing amino acids as well as acid-labile protecting groups.
- Optional one-pot synthesis as well as on-resin N-amination, making the method amenable for SPPS.

Future Directions:

The Del Valle group has established new conditions using Armstrong's oxaziridine and expanded the scope to canonical amino acids. With access to α-hydrazino peptides, which is demonstrated in the total synthesis of L-156,373, organic chemists may use this strategy for late stage piperazic acid residue formation, garnering synthetic access to many Piz-containing natural products.