

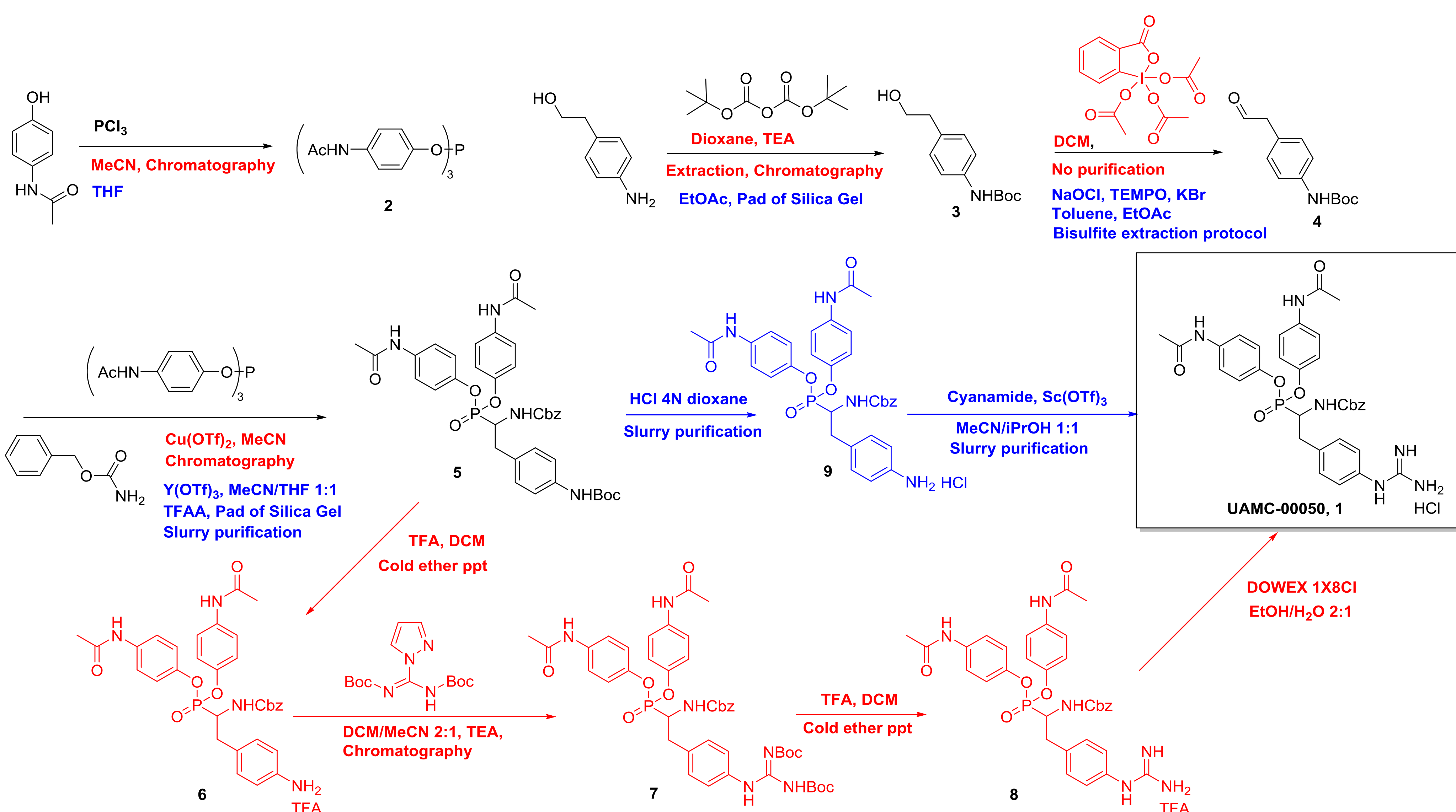
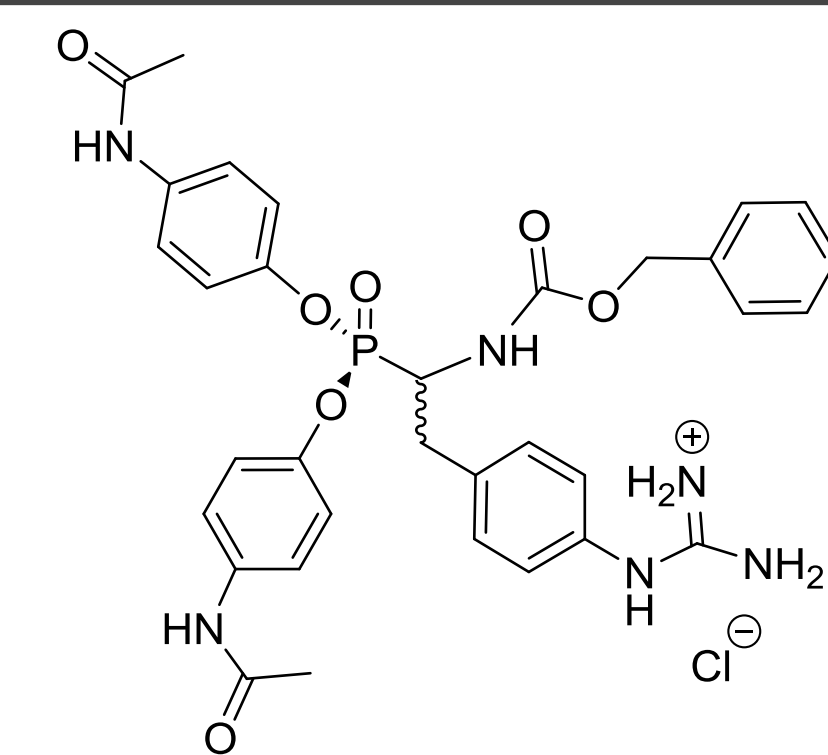
# Process optimization of the synthesis of UAMC-00050, a novel uPA inhibitor

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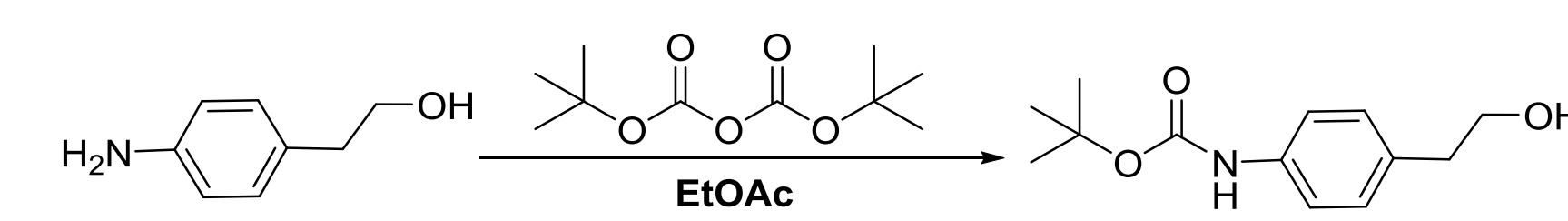
## Introduction

The  $\alpha$ -aminophosphonate UAMC-00050, a newly developed trypsin-like serine protease inhibitor, has shown promising results for the treatment of dry eye syndrome and ocular inflammation.<sup>1</sup> A laboratory scale synthetic route was initially developed at University of Antwerp. Preparation of larger amounts of UAMC-00050, required in the advanced steps of the project, proved to be difficult, due to the usage of environmentally unfriendly solvents and hazardous reagents. A new process was developed with greener alternatives and less toxic reagents. Every reaction was investigated in order to obtain the maximum yield, all the flash chromatography were replaced with plug filtration and slurry purifications. The overall yield was increased from a 7% of the discovered route to a 32% of the process development route.



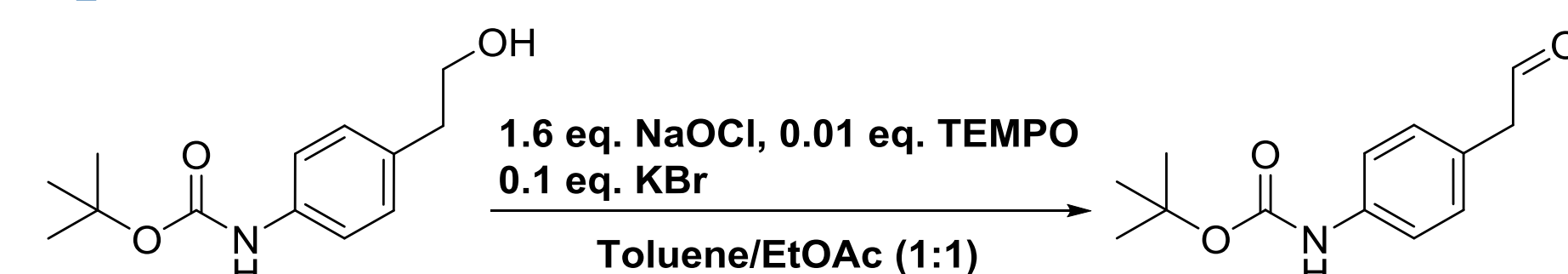
Discovery route to UAMC-00050, overall yield 7%  
 Process development route to UAMC-00050, overall yield 32%

## Optimization Boc protection



	Solvent	Base
Initial condition	Dioxane	Triethylamine
1 <sup>st</sup> optimization	DCM	No base
2 <sup>nd</sup> optimization	EtOAc	No base
	Work up	Purification
Initial condition	HCl 2N / extraction	Flash chromatography
1 <sup>st</sup> optimization	No work up	Plug filtration EtOAc/PE
2 <sup>nd</sup> optimization	No work up	Plug filtration EtOAc/PE

## Optimization aldehyde synthesis

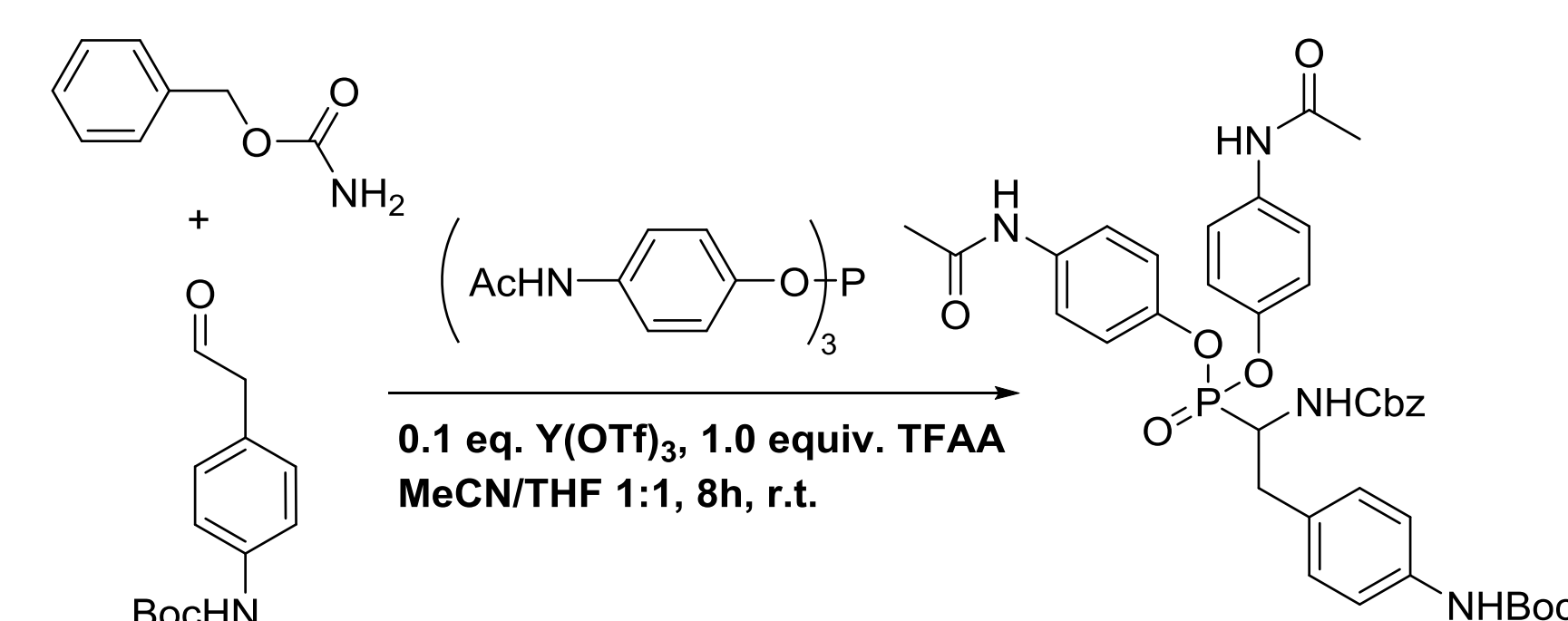


	Oxidant	Solv.	Time	Purification	Yield
Start	2.0 eq. DMP	DCM	3 h	Flash chrom. PE/EA	58%
Optimized	1.6 eq. NaOCl/TEMPO	EtOAc/toluene	15 min.	Bisulfite purification	71%

Atom economy: DMP (36%), NaOCl/TEMPO (76%)

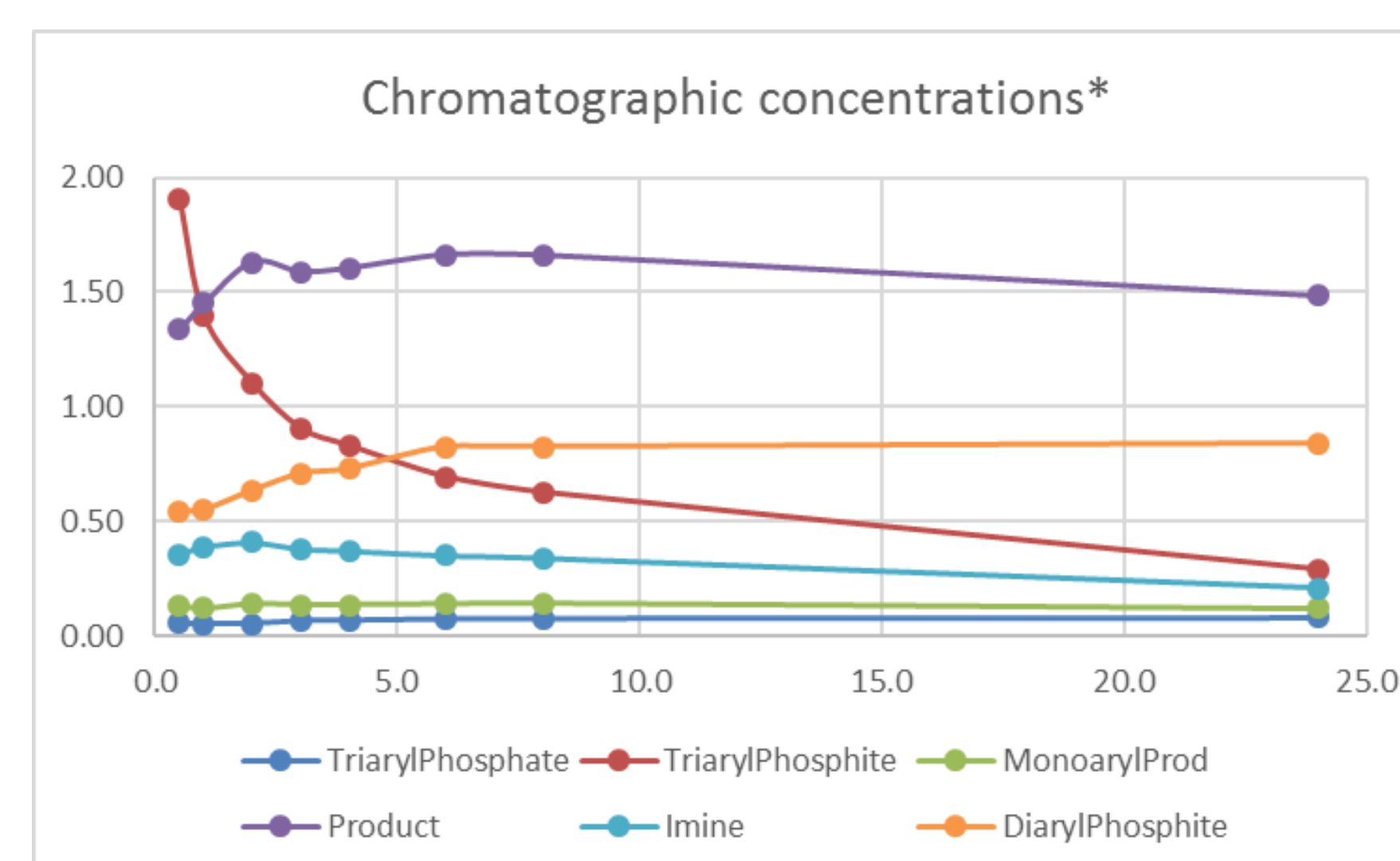
## Optimization Birum-Oleksyszyn reaction

The Birum-Oleksyszyn step represent an important bottle neck in the process, since with initial conditions of synthesis it was possible to obtain only a yield of 11%, after a screening of 17 different catalysts, yttrium triflate was able to provide a yield of 42% of phosphonate. After further development, testing different conditions and additive, we were able to achieve a yield of 52%, an important input was the use of trifluoroacetic anhydride that allow the reaction byproduct, diarylphosphite, to react with the imine, increasing the yield.<sup>2</sup>



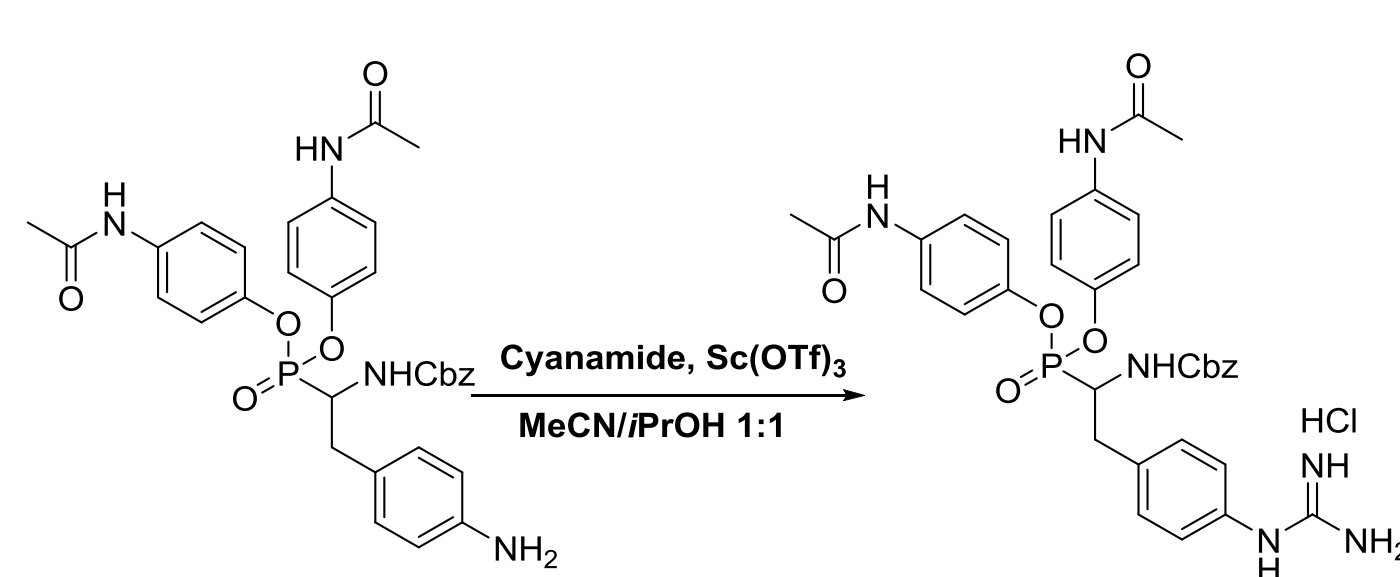
Catalyst <sup>(a)</sup>	Yield	Catalyst <sup>(a)</sup>	Yield
TiCl <sub>4</sub>	8%	Et <sub>2</sub> O-BF <sub>3</sub>	16%
ZrCl <sub>4</sub>	8%	Bi(NO <sub>3</sub> ) <sub>3</sub> ·5H <sub>2</sub> O	19%
Cu(OTf) <sub>2</sub>	11%	Yb(OTf) <sub>3</sub>	20%
BiCl <sub>3</sub>	13%	SnCl <sub>4</sub>	22%
Triflic acid	13%	ZnCl <sub>2</sub>	22%
Mg(OTf) <sub>2</sub>	14%	La(OTf) <sub>3</sub>	25%
FeCl <sub>3</sub>	15%	Bi(OTf) <sub>3</sub>	31%
LiOTf	15%	Y(OTf) <sub>3</sub>	42%
Sc(OTf) <sub>3</sub>	16%	(a) 0.1 equiv. of catalyst	

L.A.	Equiv.	Solvent	Conc.	Time	Additive	Yield
Cu(OTf) <sub>2</sub>	0.1 eq.	MeCN	0.07 M	4 h	None	11%
Y(OTf) <sub>3</sub>	0.1 eq.	MeCN	0.07 M	4 h	None	42%
Y(OTf) <sub>3</sub>	0.1 eq.	MeCN/THF	0.07 M	8 h	None	43%
Y(OTf) <sub>3</sub>	0.1 eq.	MeCN/THF	0.07 M	16 h	None	34%
Y(OTf) <sub>3</sub>	0.1 eq.	MeCN/THF	0.07 M	4 h	None	45%
Y(OTf) <sub>3</sub>	0.1 eq.	MeCN/THF	0.17 M	4 h	None	48%
Y(OTf) <sub>3</sub>	0.1 eq.	MeCN/THF	0.30 M	4 h	None	41%
Y(OTf) <sub>3</sub>	0.1 eq.	MeCN/THF	0.17 M	4 h	1.0 eq. TFAA	52%

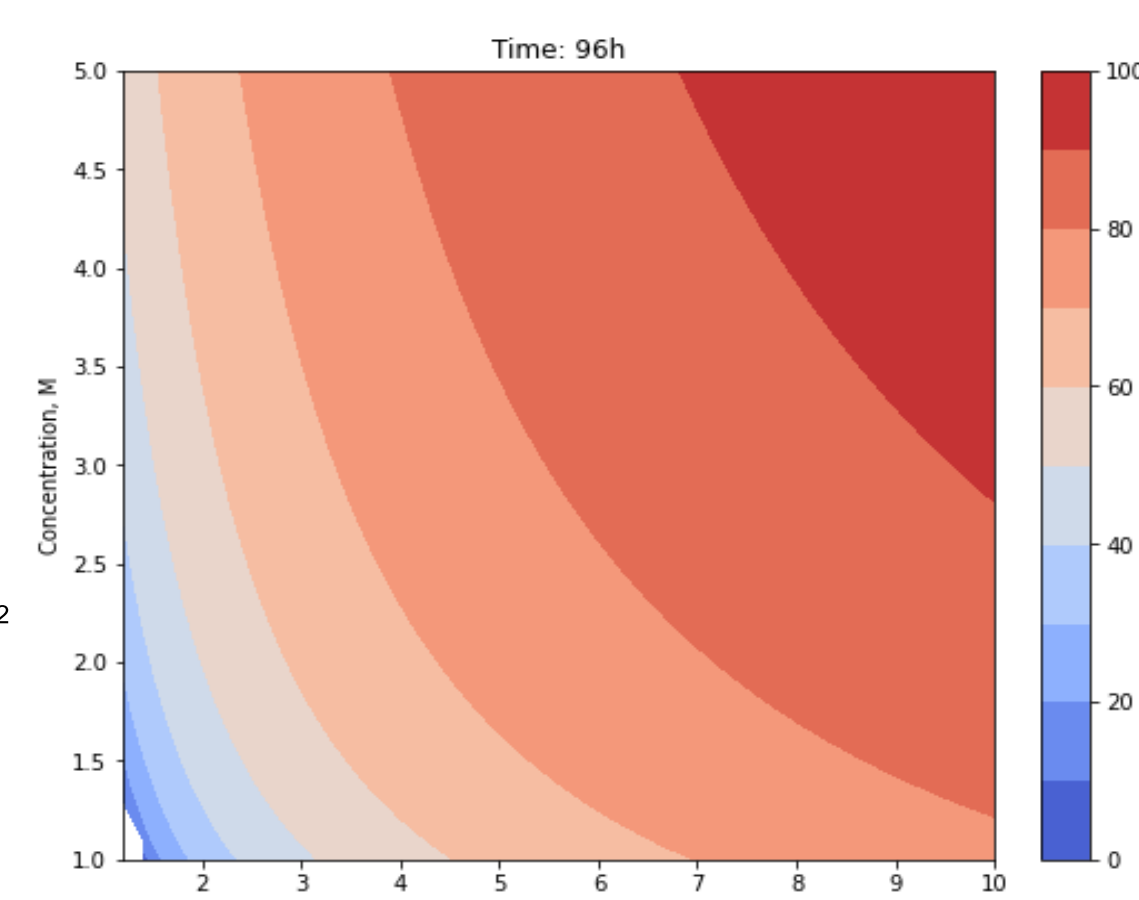


## Optimization guanylation

The N,N'-Di-Boc-1H-pyrazole-1-carboxamide protocol was substituted with a cyanamide guanylation. With the initial condition reported by Tsubokura et al.<sup>3</sup> we got only 25% of product. A Design of experiment optimization of the variables: cyanamide equivalents, concentration and reaction time allow us to achieve a yield of 89% of final product.



### Predicted yield



## References

- [1] Joossen, C., Bañ, A., Moreno-Cinos, C. *et al.* A novel serine protease inhibitor as potential treatment for dry eye syndrome and ocular inflammation. *Sci Rep* **10**, 17268 (2020).
- [2] Ragulin, V., V. *et al.* New opinion on the amidalkylation of hydrophosphorylic compounds. *Tetrahedron Letters* **51**, 2613-2616 (2010)
- [3] Tsubokura, K., Iwata, T., Taichi, M., Kurbangaliev, A., Fukase, K., Nakao, Y., Tanaka, K., *SYNLETT* **2014**, 25, 1302-1306