Towards the development of DMAP-*N*-oxide derived kinase mimetics: rate and selectivity studies

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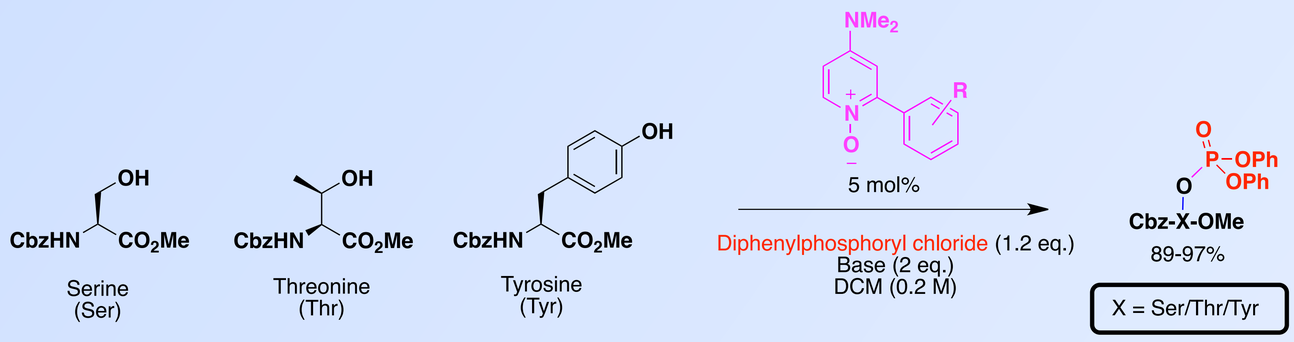
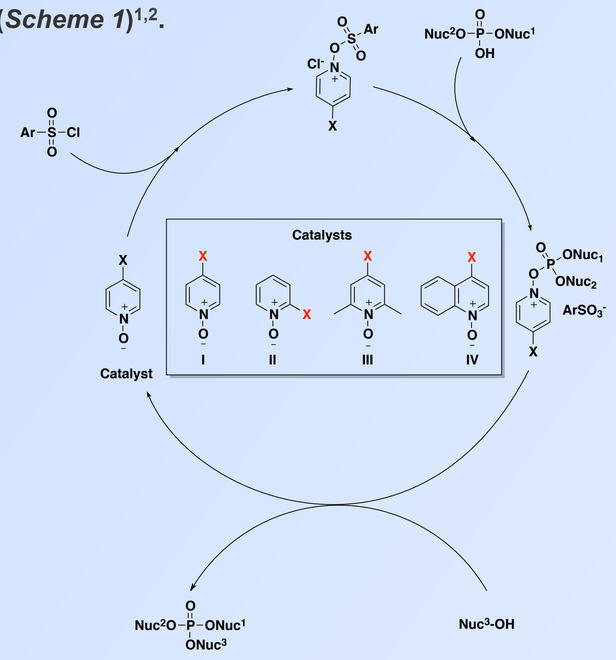
Abstract



The development of 4-dimethylamino-*N*-oxide (DMAP-*N*-oxide) derived kinase mimetics for selective phosphorylation of hydroxyl-containing amino acids is reported. The reaction proceeds in good to very good yields and good levels of selectivity for Ser *vs*. Thr *vs*. Tyr are achievable. Notably, reaction rates and substrate selectivities are highly dependent upon the choice of base and preliminary results indicate that increased selectivity may be achieved through fine-tuning of the 2-aryl substituent of the catalyst.

1. Introduction

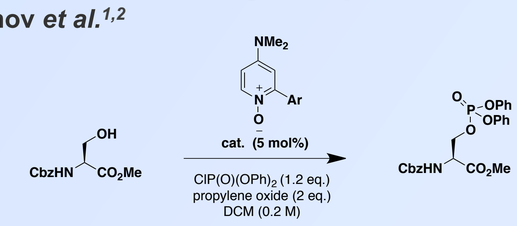
- Only previous example of organocatalytic P(*V*) phosphate transfer in oligonucleotide synthesis (*Scheme 1*)[1,2].



- Rate studies by Effimov *et al.*[1,2] demonstrated 4-DMAP-*N*-oxide to be most efficient catalyst.
- Steric hinderance around reactive *O*-centre resulted in decreased catalyst activity.

2.1 Serine Phosphorylation

- Initial reactions focused on phosphorylation of serine derivative using catalysts described by Effimov *et al.*[1,2]



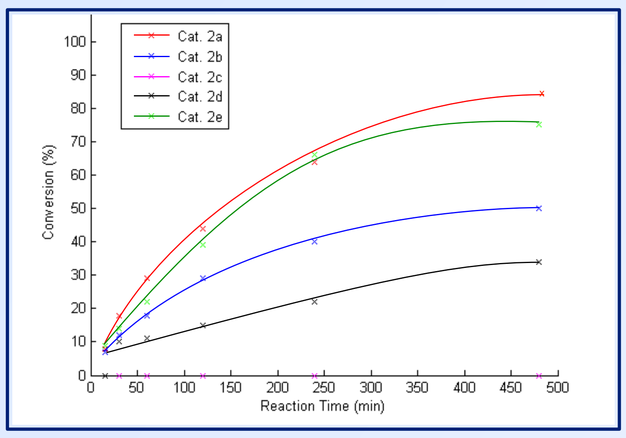


Figure 1 – Serine phosphorylation: initial catalyst evaluation Conversion determined by crude ^{1}H NMR.

Catalysts

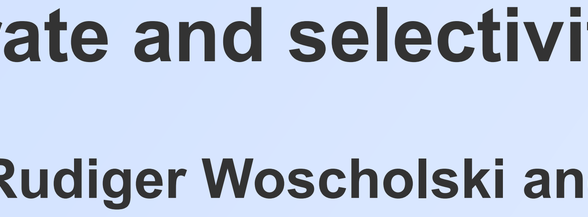


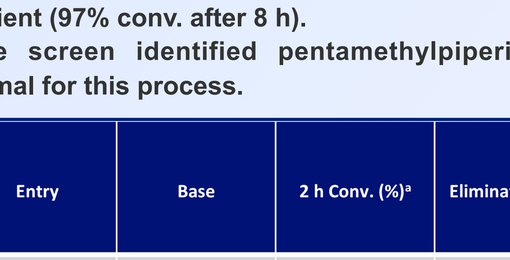
Figure 2 – Serine phosphorylation: further catalyst evaluation. Conversion determined by crude ^{1}H NMR.

- Electron withdrawing 2-aryl substituents found to accelerate reaction rate. Catalyst 2j proved most efficient (97% conv. after 8 h).
- Base screen identified pentamethylpiperidine as optimal for this process.

Entry	Base	2 h Conv. (%)[a]	Elimination (%)[b]
1	Proton Sponge®	89	0
2	DBU	9	83
3	pentamethyl-piperidine	>99	0
4	NEt_3	46	54
5	None	0	0

2.2 Threonine Phosphorylation

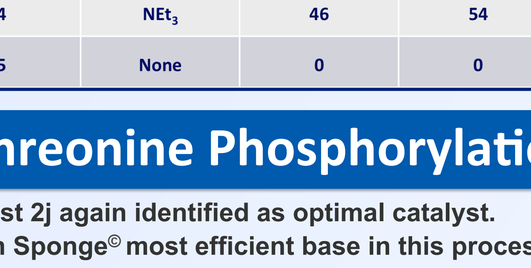
- Catalyst 2j again identified as optimal catalyst.
- Proton Sponge© most efficient base in this process.



- Early indication of base controlling substrate selectivity.

2.3 Tyrosine Phosphorylation

- NEt_3/PMP/DBU resulted in quantitative conversion within 1 h.



3. Comparison of Phosphorylation rates

- Choice of base governs substrate selectivity

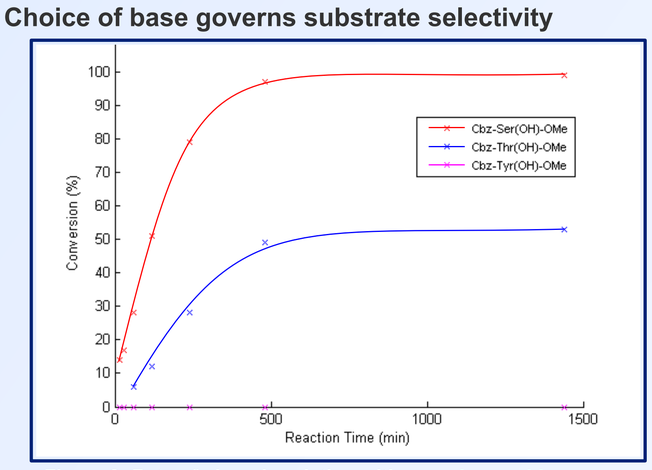


Figure 3: Rate of phosphorylation with propylene oxide

- Propylene oxide should allow selective phosphorylation of serine over threonine/tyrosine.

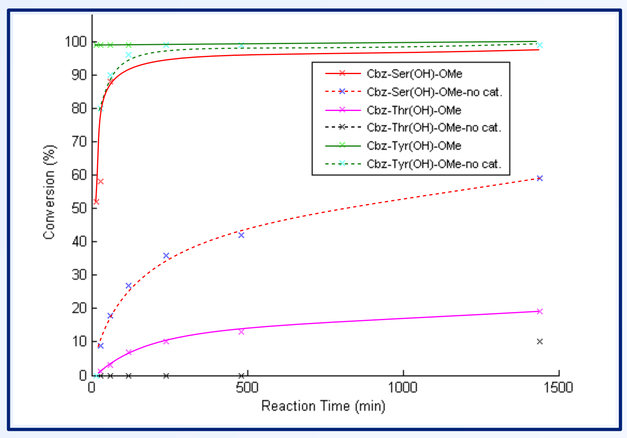
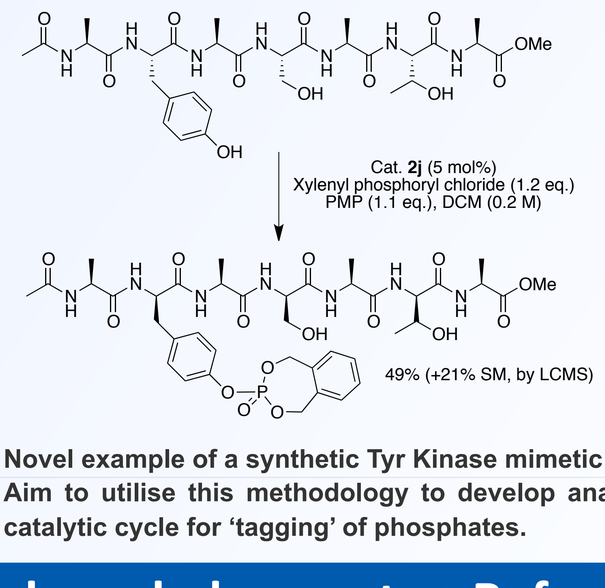


Figure 3: Rate of phosphorylation with pentamethylpiperidine

- Pentamethylpiperidine should allowed selective phosphorylation of tyrosine over threonine/serine.

4. Synthetic 'Tyr kinase mimetic'

- Selective *mono*-phosphorylation of heptapeptide
- Use of novel 'xylenyl phosphoryl choride' for facile, tyrosine compatible deprotection (H_2, Pd/C)
- Moderate yield (49% + 21% SM recovery)



- Novel example of a synthetic Tyr Kinase mimetic
- Aim to utilise this methodology to develop analagous catalytic cycle for 'tagging' of phosphates.

Acknowledgements + References

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[1] V. A. Efimov *et al. Nucleic Acids Res.* 1985, *13*, 3651-3666
[2] V. A. Efimoc *et al. Nucleic Acids Res.* 1986, *14*, 6525-6540.