Published in *Org. Lett.*

Scan QR Code For Link To Publication

Direct Minisci-Type C-H Amidation of Purine Bases

David T. Mooney (dtm2000@hw.ac.uk), Dr. Peter Moore and Dr. Ai-Lan Lee *
Institute of Chemical Sciences, School of Engineering and Physical Sciences, Heriot-Watt University, Edinburgh, EH14 4AS, Scotland, U.K.

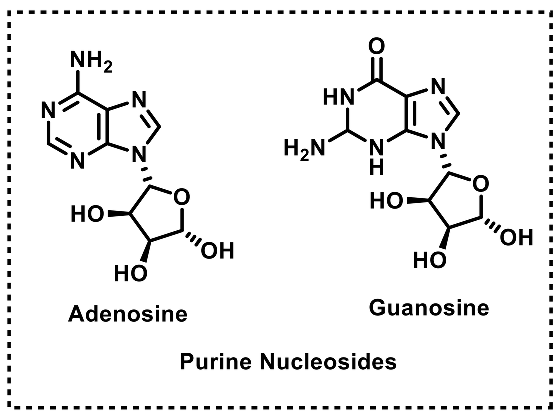
HERIOT WATT UNIVERSITY

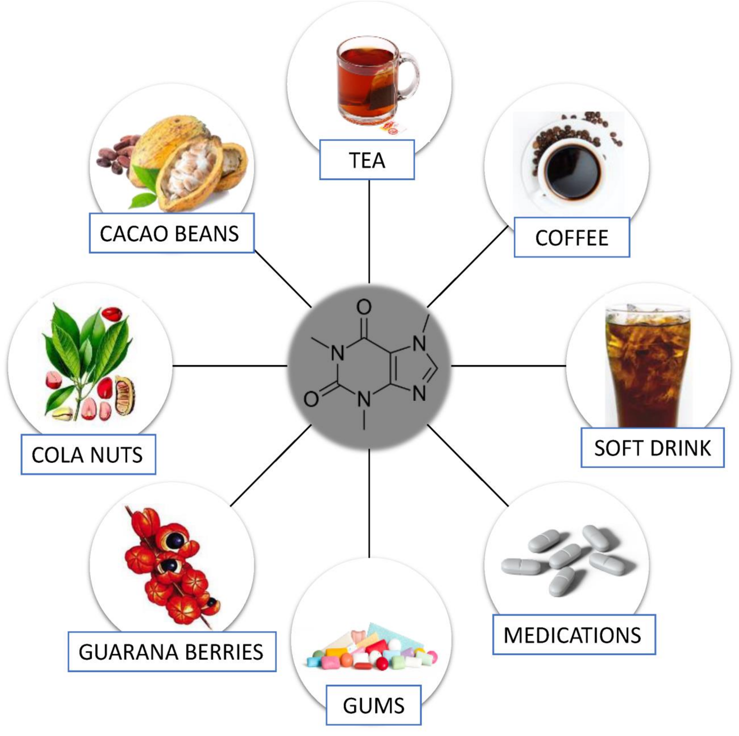
1. Aims:

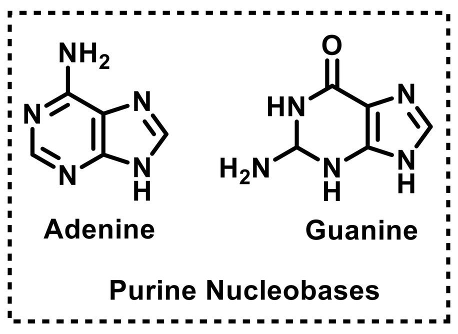
- ❑ Develop a metal-, light-, and catalyst-free C-H functionalisation of purine bases.
- ❑ Show that the operationally simple reaction can be performed on scale.
- ❑ Demonstrate the applicability of this reaction *via* the functionalisation of multiple drug molecules.

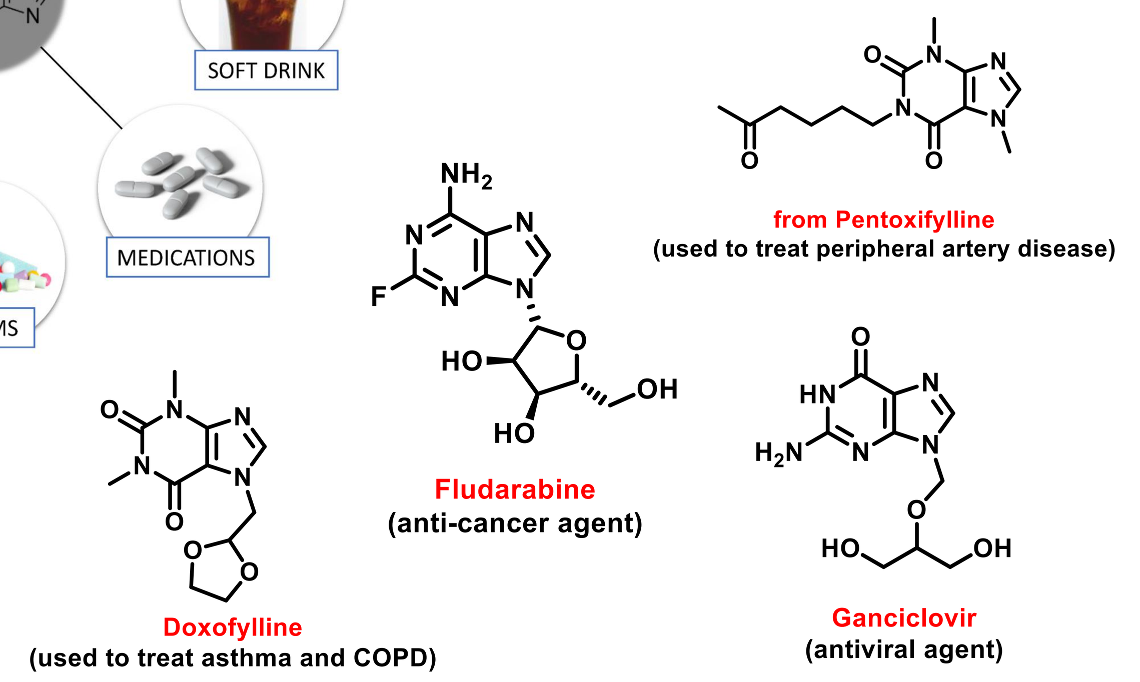
2. Introduction

Purines are one of the most widely occurring *N*-heterocycles in nature.[1] As well as forming the building blocks for DNA and RNA, they are also significant components of important biomolecules such as ATP, GTP, cAMP, CoA, and NADH.[1] Purine bases are therefore unsurprisingly prevalent in biological and pharmaceutical applications. The ability to directly and selectively C-H functionalise these purine motifs would therefore be highly advantageous. Hence we look to apply our metal-, light-, catalyst- and electrocatalytic-free Minisci protocol to purines.[2-4]

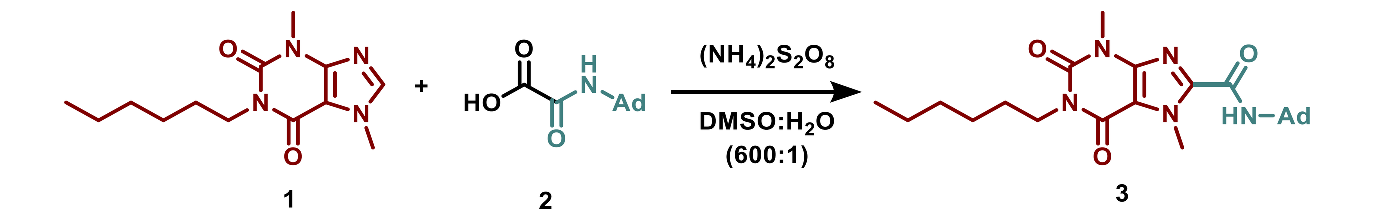








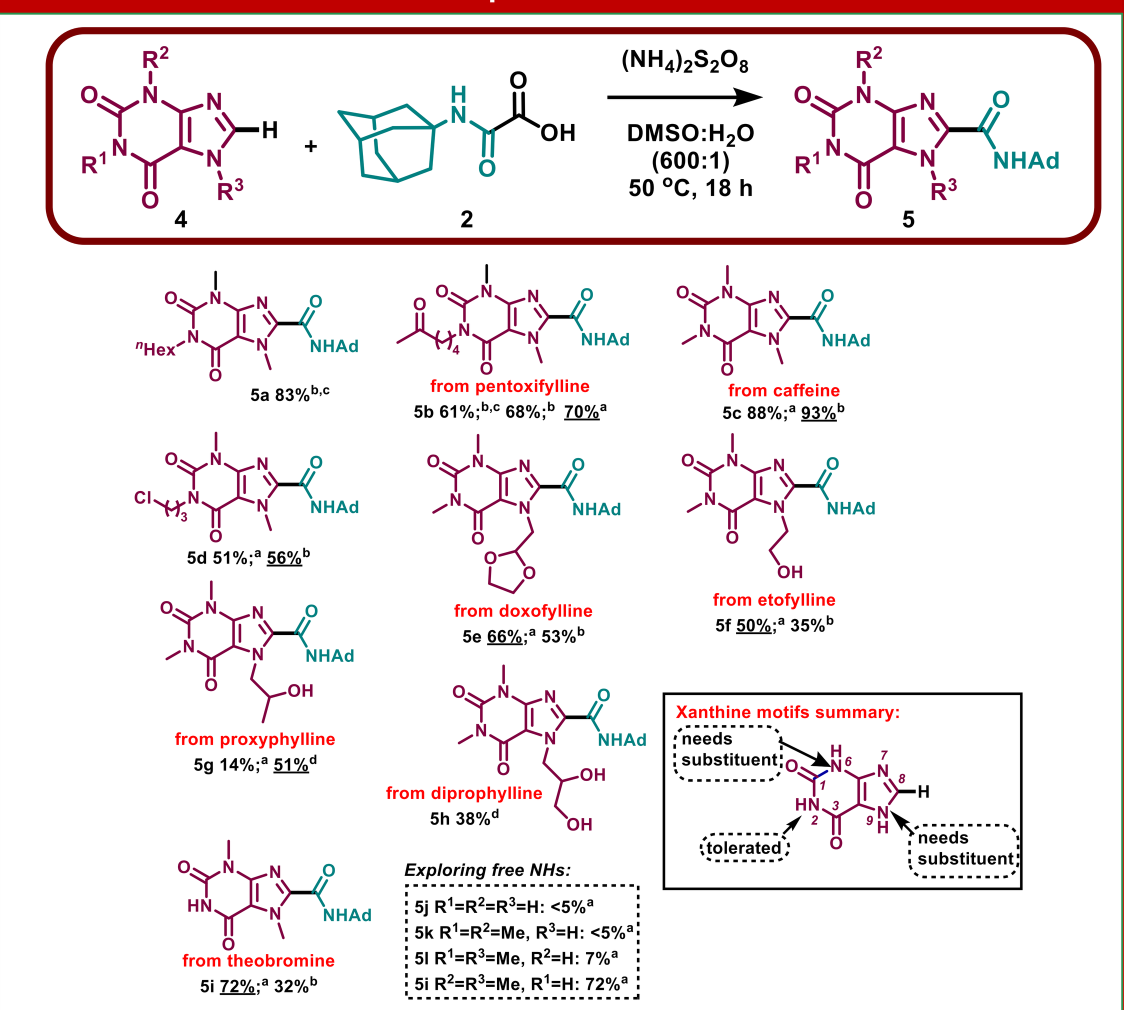
3. Reaction Optimisation



Entry	Temp. (°C)	Equiv. of 2	Equiv. of $(NH_4)_2S_2O_8$	M (mol/L)	Rxn Time (h)	Remaining 1 (%)[a]	Yield of 3 (%)[a]	Notes
1	50	2	6	0.15	18	0	(71)[b]	
2	40	2	6	0.15	18	8	75 (66)[b]	
3	50	2	3	0.15	18	7	79	
4	50	2	4	0.15	18	3	80	
5	50	2	5	0.15	18	0	84	
6	50	1.5	5	0.15	18	6	79	
7	50	3	5	0.15	18	1	69	
8	50	2	5	0.15	2	24	68	
9	50	2	5	0.15	4	3	76	
10	50	2	5	0.15	6	0	91 (83)[b]	
11	rt	2	5	0.15	18	80	9	
12	30	2	5	0.15	18	50	39	
13	50	2	5	0.15	6	0	86	In the dark
14	50	2	5	0.15	6	76	0	H_2O
15	50	2	5	0.15	6	99	0	MeCN
16	50	2	-	0.15	6	95	0	No persulfate

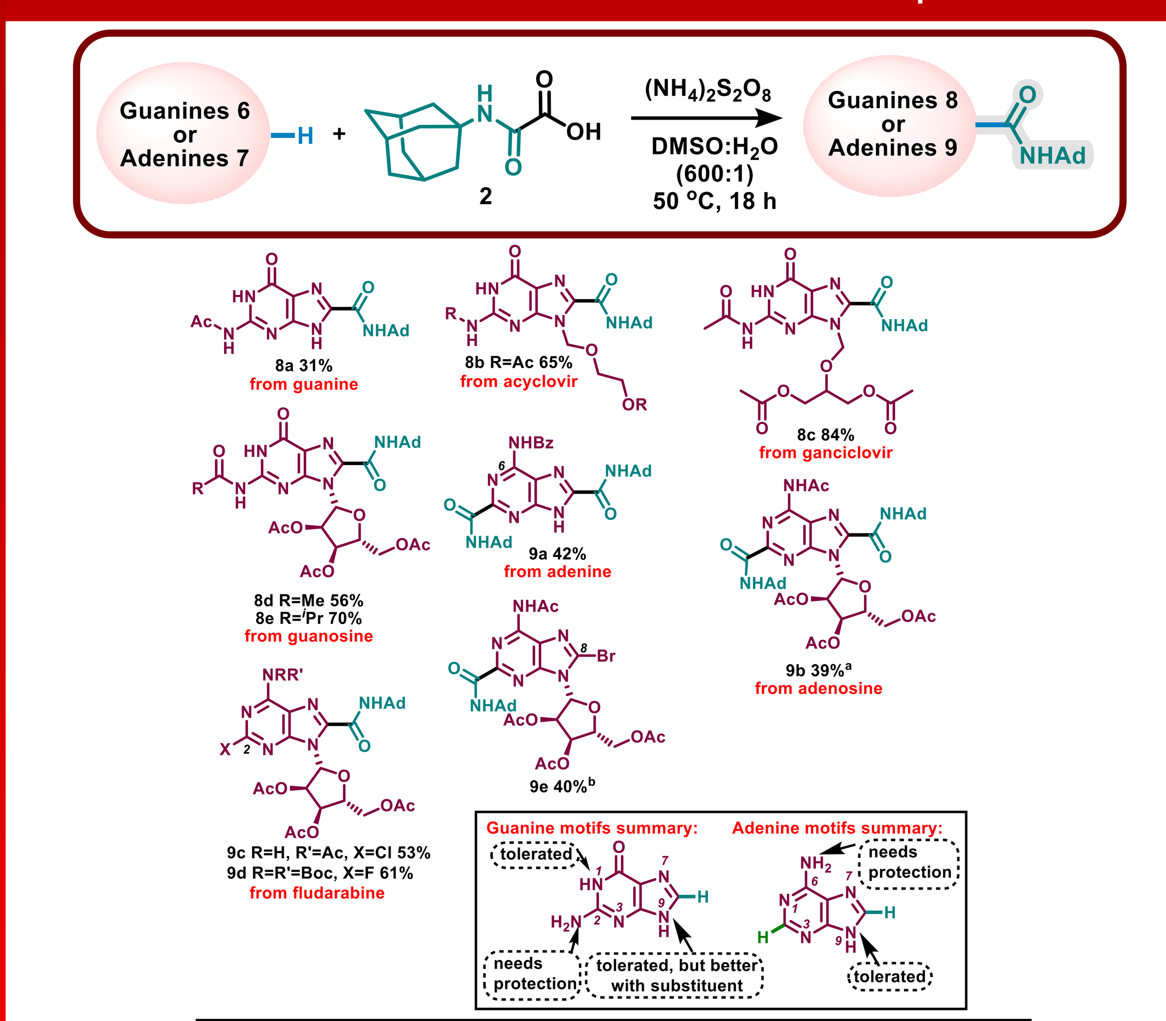
[a]Yield was determined by ^{1}H NMR analysis using trimethoxybenzene as an internal standard. [b]Isolated yield.

4. Xanthine Scope



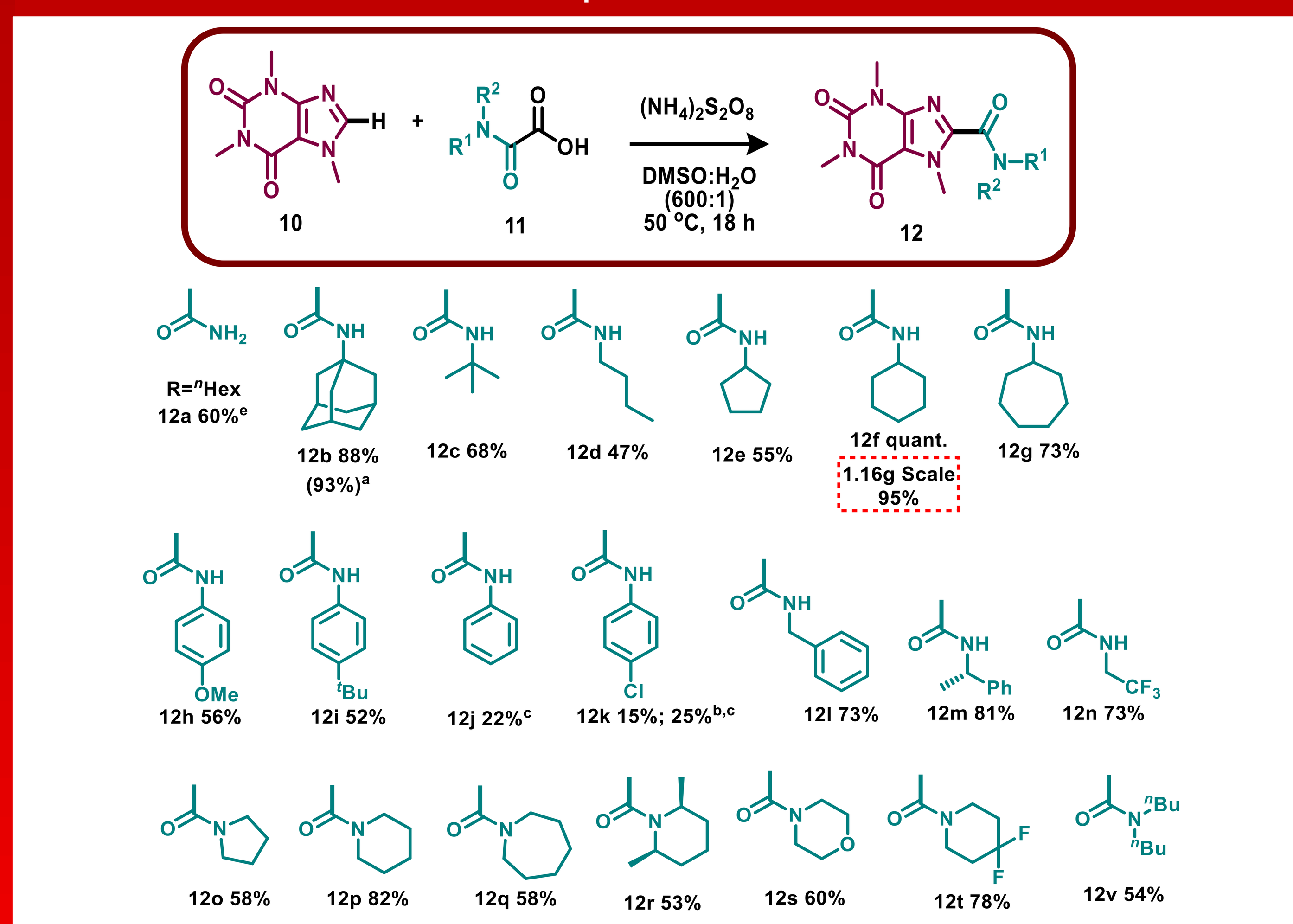
Isolated yield reported using 0.2 mmol of 4, 0.4 mmol of 2. [a]3 equiv. of $(NH_4)_2S_2O_8$. [b]5 equiv. of $(NH_4)_2S_2O_8$. [c]6 h. [d]40 °C.

5. Guanine and Adenine Scope



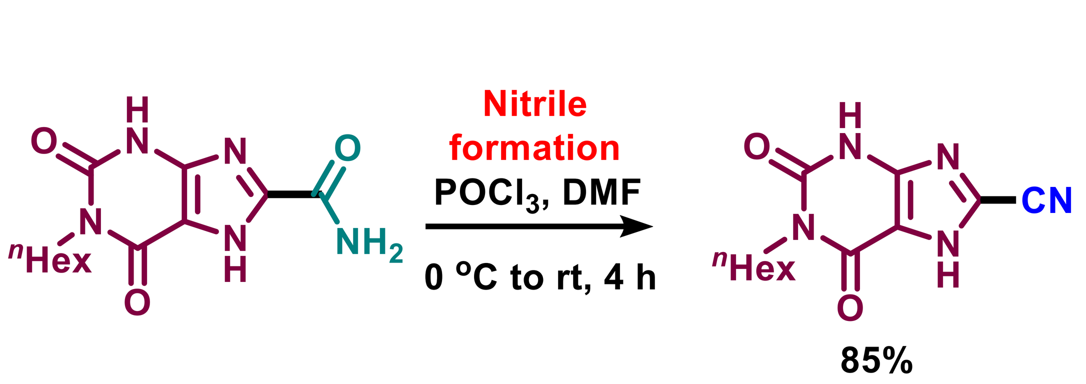
Isolated yield reported using 0.2 mmol of 6/7, 0.4 mmol of 2 and 0.6 mmol of $(NH_4)_2S_2O_8$ unless otherwise stated. [a]<5% 9 when 2 and reagents were doubled. [b]70 °C; 32% at 50 °C.

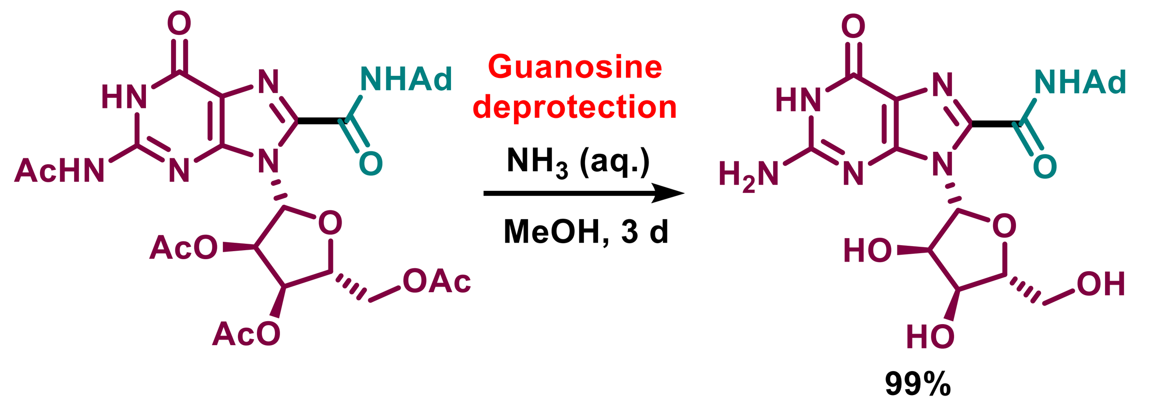
6. Oxamic Acid Scope

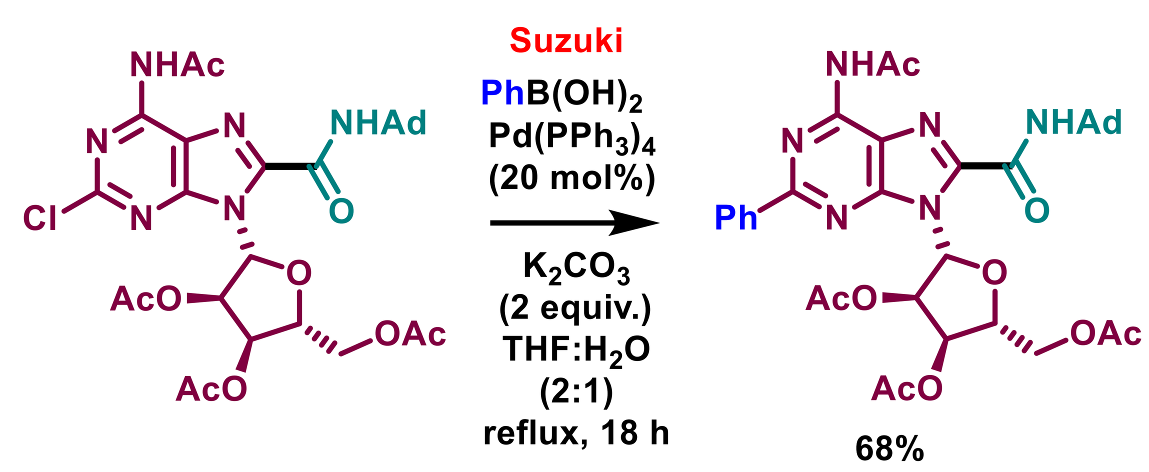


Isolated yield reported using 0.2 mmol of 10, 0.4 mmol of 11 and 0.6 mmol of $(NH_4)_2S_2O_8$ unless otherwise stated. [a]5 equiv. of $(NH_4)_2S_2O_8$. [b]Conversion based on starting material. [c]70 °C. [d]Homocoupling of the carbamoyl radical observed. [e]4a used due to solubility issues of product with 4c.

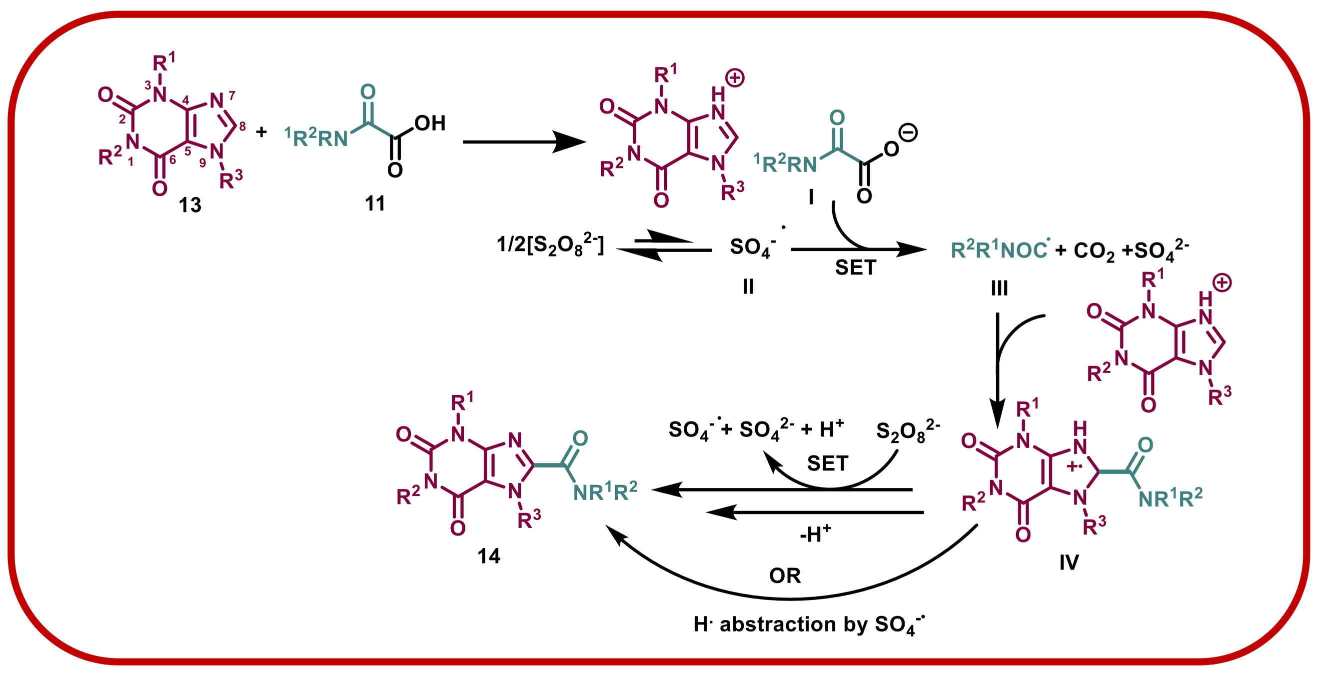
7. Further Modifications







9. Proposed Mechanism



10. Summary and Conclusions

- ❖A mild, metal-, catalyst- and light-free Minisci-type carbamoylation of xanthines, guanines and adenines has been developed.
- ❖Primary, secondary and tertiary amides where successfully installed.
- ❖Further modifications could be applied to the products synthesised to make high-value products.

11. Acknowledgements

I would like to thank: Dr. Ai-Lan Lee, for giving me the opportunity to be a part of her research group as well as for the invaluable support and guidance she has given during this project; the Lee group and the reading room for their support in and out of the lab; Dr. Dave Ellis for his support with NMR; Dr. Peter Moore (AstraZeneca) for helpful discussions and AstraZeneca (ICASE, EP/V519522/1) and the EPSRC for funding.

AstraZeneca EPSRC Engineering and Physical Sciences Research Council

12. References

1) H. Rosemeyer, *Chem. Biodivers.*, 2004, **1**, 361-401. 2) D. T. Mooney, P. R. Moore and A.-L. Lee, *Org. Lett.*, 2022, **24**, 8008-8013. 3) D. T. Mooney, B. D. T. Donkin, N. Demirel, P. R. Moore and A.-L. Lee, *J. Org. Chem*, 2021, **86**, 17282-17293. 4) E. B. McLean, D. T. Mooney, D. J. Burns and A.-L. Lee, *Org. Lett.*, 2022, **24**, 686-691.