5th Syngenta Organic and Biological Chemistry Postdoc Symposium

ICL lecture theatre, Thursday 21st February 2019

Programme

1.15-3.00 pm

Introductory remarks

Dr Roly Armstrong (TJD group)
Borrowing hydrogen; returning it selectively – controlling relative and absolute stereochemistry in transition-metal catalyzed alkylation processes.

Dr Carole Bataille (AJR group)
Structure-based development of new small molecule inhibitors of RAS-effector protein interactions derived using an intracellular antibody fragment

Dr Alex Dürr (EAA group)
The first example of complete diastereocontrol in transition metal catalysed cycloisomerisation reactions: 'Privileged Interactions of the Active Site'

Dr Jamie Leitch (DJD group)
Photocatalytic construction of α-functionalised amines

3.00-3.30 pm: Tea break

3.30-5.00 pm

Dr James Eaton (AK group)
Engineering of anti-inflammatory cyclic peptides from tick salivary proteins

Dr Gabriele Pupo (VG group)
Asymmetric Nucleophilic Fluorination under Hydrogen Bonding Phase-Transfer Catalysis

Dr James Morris (Syngenta)
Herbicidally active 1,8-Naphthyridines: From one mode of action to another

5.00: *Closing remarks*

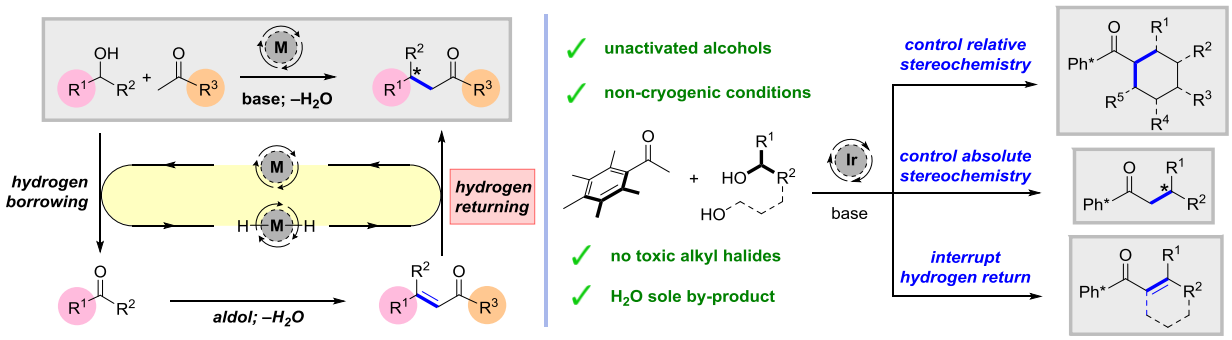
5.15 pm: Drinks reception and prizes

We thank Syngenta for generous sponsorship of this event

Dr Roly J. Armstrong

Borrowing hydrogen; returning it selectively – controlling relative and absolute stereochemistry in transition-metal catalyzed alkylation processes.

Hydrogen borrowing catalysis is rapidly emerging as a powerful tool for C–C bond formation enabling the direct alkylation of enolates with unactivated alcohols.[1] The key to unlocking this reactivity is a transition-metal catalyst, which "borrows" hydrogen from the alcohol, resulting in the formation of a reactive ketone intermediate that can condense with an enolate. The catalyst then returns hydrogen, leading to an alkylated product, along with water as the sole by-product. This process serves as a green alternative to classical enolate alkylation, but in order to become truly practical, the stereochemical outcome of the step in which hydrogen is returned must be controlled. This talk will begin by describing a highly diastereoselective [5+1] strategy for cyclohexane formation by two sequential Ir catalyzed C–C bond formations.[2] Additionally, we have recently found that chiral ligands can effectively control absolute stereochemistry within the hydrogen returning step, providing access to a range of cyclic and acyclic ketone products with high enantioselectivity. Finally, new conditions will be discussed in which the hydrogen returning step is disrupted entirely, allowing the isolation of high-value enone products.



[1] Corma, J. Navas, M. J. Sabater, *Chem. Rev*. **2018**, *118*, 1410.

[2] W. M. Akhtar, R. J. Armstrong, J. R. Frost, N. G. Stevenson, T. J. Donohoe, *J. Am. Chem. Soc*. **2018**, *140*, 11916.

Dr Carole J. R. Bataille

Structure-based development of new small molecule inhibitors of RAS-effector protein interactions derived using an intracellular antibody fragment

Mutation in RAS family members is among the most frequent in human cancer and the mutant RAS proteins are tumour-specific proteins for therapy. We have previously selected an **I**ntracellular single **d**omain **a**nti**b**ody fragment (designated **iDAb**) that binds to mutant forms of KRAS and HRAS[1] and used this antibody fragment to demonstrate that blocking RAS-effector interaction-dependent signal transduction prevents tumour initiation and overt tumour growth in mouse preclinical models.[2] However, intracellular antibodies are hard to implement as drugs because they do not penetrate cells, while compounds are considered to be unsuitable for inhibiting protein-protein interactions (PPIs).

A solution to these problems is to first select intracellular antibody fragments to block PPIs[3] and then to derive compounds overlapping the antibody-binding site. We have achieved this using the inhibitory RAS-binding intracellular antibody fragment (iDAb Y6) to select compounds that bind to mutant RAS, a major target for cancer treatment since it is mutated in over 30% of all human cancers.[4] X-ray crystallography showed that anti-RAS iDAb interacts with HRAS & KRAS with an analogous binding mode to the natural effector proteins such as CRAF and PI3K but binds with an affinity up to ~1000 times higher than natural RAS-effector interaction. Because of this potent binding Kd, we were able to employ the anti-RAS intracellular antibody fragment as a competitor in a small molecule library screen.

We have identified compounds that bind to mutant RAS where the antibody fragment binds and, using crystal soaking of $KRAS^{Q61H}$ and X-ray crystallography, we show that the binding of the compounds overlaps with that of the iDAb. With this X-ray crystallography strategy, we carried out a medicinal chemistry programme with the crystal structures driving the chemical evolution. Accordingly, we have employed this structure-based design to develop potent RAS-binding compounds that interact with RAS inside cells, prevent RAS-effector PPI and inhibit endogenous RAS-dependent signaling.[5,6] These compounds form the basis of RAS-dependent cancer drug development, and our results demonstrate a general approach for developing compounds from high affinity intracellular antibody fragments that can be applied to any PPI of interest.

(1) Tanaka, T.; Williams, R. L.; Rabbitts, T. H. *EMBO J* **2007**, *26*, 3250.

(2) Tanaka, T.; Rabbitts, T. H. *Oncogene* **2010**, *29*, 6064.

(3) Tanaka, T.; Rabbitts, T. H. *Nat Protoc* **2010**, *5*, 67.

(4) Downward, J. *Nat Rev Cancer* **2003**, *3*, 11.

(5) Quevedo, C. E.; Cruz-Migoni, A.; Bery, N.; Miller, A.; Tanaka, T.; Petch, D.; Bataille, C. J. R.; Lee, L. Y. W.; Fallon, P. S.; Tulmin, H.; Ehebauer, M. T.; Fernandez-Fuentes, N.; Russell, A. J.; Carr, S. B.; Phillips, S. E. V.; Rabbitts, T. H. *Nat. Commun.* **2018**, *9*, 12.

(6) Cruz-Migoni, A.; Canning, P.; Quevedo, C. E.; Bataille, C. J. R.; Bery, N.; Miller, A.; Russell, A. J.; Phillips, S. E. V.; Carr, S. B.; Rabbitts, T. H. *PNAS* **2019**, *early article*.

Dr Alexander B. Dürr

The first example of complete diastereocontrol in transition metal catalysed cycloisomerisation reactions: 'Privileged Interactions of the Active Site'

Abstract: The synthesis of new molecules for agrochemical, pharmaceutical, and materials applications is crucially dependent on methods for the stereoselective formation of C–C bonds. Among many such processes, transition metal-catalyzed cycloisomerization reactions hold a privileged position due to their high atom efficiency of ring synthesis, mild reaction conditions, and the structural diversity of products that can arise from a single starting material, depending on the choice of catalyst.[1] Within this large field, a few methods have been reported where prochiral, unsaturated substrates undergo cyclization in an enantioselective fashion, employing a transition metal catalyst bearing chiral ligands.[2] In such processes, the stereochemical outcome is determined by powerful conformational influences of the chiral catalyst.

When the substrate and catalyst backbone are *both* chiral, the transition metal complex can bind to different diastereotopic faces of the substrate in the stereodetermining cyclization step, leading to the possibility of matched and mismatched interactions.[3] While the matched reaction (reinforcing stereoinduction from substrate and catalyst) is likely to proceed efficiently, the mismatched reaction (opposing stereoinduction) presents the catalyst with a significant challenge, particularly where strong substrate stereoinduction is shown In an era of organic synthesis where complete control over the formation of new stereocentres is a priority, the design of cycloisomerisation catalysts that dictate the formation of new stereocentres *irrespective of substrate preference* is a key but yet unmet aim.

This presentation reports the first example of complete diastereocontrol in cycloisomerisation reactions depending solely on the enantiomer of the chiral ligand. An in depth DFT study of the conditions necessary for such a process to occur will be presented. We were able to identify which interactions in the TS structures of the stereodetermining step (electronic / steric / stereoelectronic) are crucial for high *ee*s and diastereoselectivities, by carrying out extensive computational investigations linked to a panel of experimental results. By classifying a hierarchy of key interactions among those structures, we characterised a catalyst 'active site', leading to a privileged TS responsible for excellent diastereoselectivities.

(1) Michelet, V.; Toullec, P. Y.; Genet, J. P. *Angew. Chem. Int. Ed.* **2008**, *47*, 4268-4315.

(2) (a) Marinetti, A.; Jullien, H.; Voituriez, A. *Chem. Soc. Rev.* **2012**, *41*, 4884-4908; (b) Fairlamb, I. J. S. *Angew. Chem. Int. Ed.* **2004**, *43*, 1048-1052; (c) Watson, I. D. G.; Toste, F. D. *Chem. Sci.* **2012**, *3*, 2899-2919.

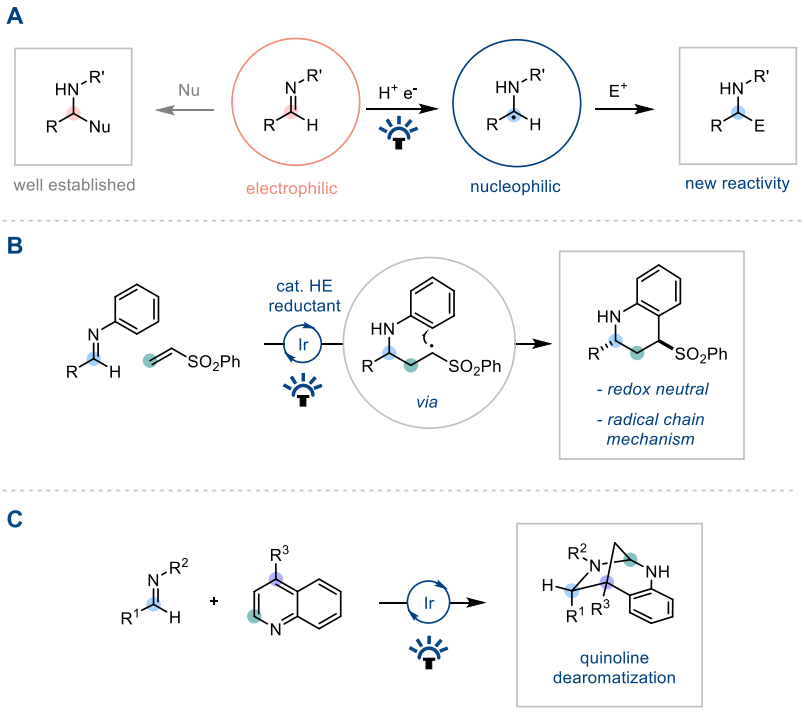
(3) For a classic review on this topic, see: Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem. Int. Ed.* **1985**, *24*, 1-30.

Dr Jamie A. Leitch

Photocatalytic construction of α-functionalised amines

Photoredox catalysis has come to the forefront of modern catalytic development due to burgeoning potential reactivity from the mild generation and manipulation of open shell radical intermediates. These methods have been shown to be a vital tool in unlocking new reactivity of classical functional groups, such as imines, whereby single electron reduction can transform an electrophilic imine into a pseudo-nucleophilic α-amino radical.[1]

This concept has been applied to a selection of reaction manifolds including; a Povarov-type radical cyclisation (Scheme 1B)[2] as part of a wider project on α-C-H functionalisation of amines,[3] and in the photocatalytic dearomatization/cyclisation of quinolines (Scheme 1C).[4]



(1) (a) Qi, L.; Chen, Y. *Angew. Chem., Int. Ed.* **2016**, *55*, 13312−13315. (b) Fuentes de Arriba, A. L.; Urbitsch, F.; Dixon, D. J. *Chem. Commun*. **2016**, *52*, 14434−14437.

(2) Leitch, J. A.; Fuentes de Arriba, A. L.; Tan, J.; Hoff, O.; Martinez, C. M.; Dixon, D. J. *Chem. Sci.* **2018**, *9*, 6653-6658.

(3) Vasu, D.; Fuentes de Arriba, A. L.; Leitch, J. A.; de Gombert, A.; Dixon, D. J. *Manuscript Submitted, Chem Rxiv* **2018**, DOI: 10.26434/chemrxiv.6653381.

(4) *Manuscript in preparation*

Dr James R. O. Eaton

Engineering of anti-inflammatory cyclic peptides from tick salivary proteins

Designing therapeutic molecules with novel binding modalities, such as being able to engage multiple targets in a specified manner, is particularly challenging and deviates from the “one-drug-one-target” paradigm that is typically associated with modern medicinal chemistry. Chemokines are small, secreted proteins that are validated targets for a number of inflammatory diseases due their key role in immune cell trafficking and recruitment. However, chemokines are challenging to inhibit as they signal through a robust network where a single chemokine can bind multiple receptors and *vice versa* meaning that the inhibition of a single chemokine (e.g. with an antibody which binds a single chemokine) is not sufficient to prevent chemokine driven inflammation.

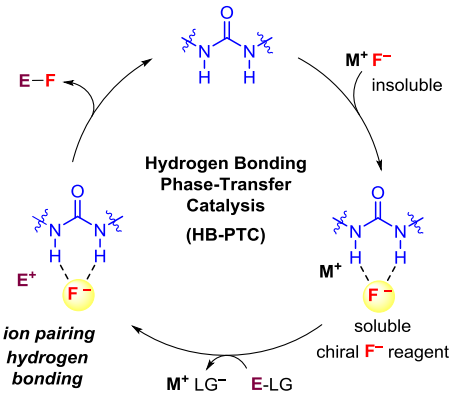
Evasins are proteins found in tick saliva that have evolved to inhibit the chemokine system utilising a “one-to-many” binding mechanism where a single evasin can bind multiple chemokines. Using biolayer interferometry, cell migration assays, native and hydrogen- deuterium exchange mass spectrometry, homology modelling and domain swap experiments we have characterized the interaction between the novel evasin P672 and its target chemokines, and have designed a linear 16-mer peptide that possesses the "one-to- many" chemokine binding activity found in evasins.

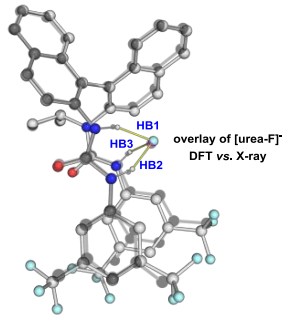
We have studied the interaction of this peptide with its target chemokines and we found that head-to-tail cyclisation increased the binding affinity, efficacy and metabolic stability of this peptide. This work shows that through the characterisation of a protein-protein interaction it is possible to design peptides that can mimic the action of a larger protein structure to possess novel binding modes.

Dr Gabriele Pupo

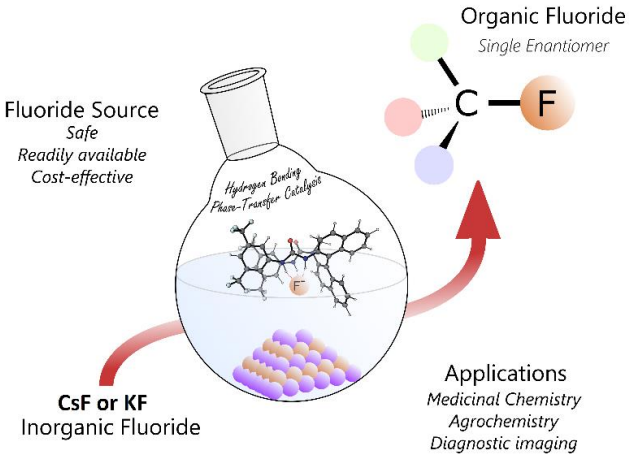
Asymmetric Nucleophilic Fluorination under Hydrogen Bonding Phase-Transfer Catalysis

Common anionic nucleophiles such as those derived from inorganic salts have not been used for enantioselective catalysis because of their insolubility in organic solvents. We herein present the successful development of a novel activation mode for these nucleophiles which relies on the merge between hydrogen bonding and phase-transfer catalysis (HB-PTC).[1] By employing readily available alkali metal fluorides as fluorinating reagents, we disclose a class of organocatalysts whose main role is to render the anion soluble and reactive while simultaneously providing an asymmetric environment. Following a brief introduction on nature's only known fluorinase, this novel bio-inspired catalytic manifold will be presented. By using a chiral *bis*-urea catalyst to form a tridentate hydrogen bonding complex with fluoride from its alkali metal salt, we desymmetrized *in situ* formed *epi*sulfonium ions using CsF up to 98% yield and 97:3 e.r. Experimental and computational mechanistic insight will be presented thus highlighting the key features of the catalytic system.





Finally, we will focus on our recent advances in the activation of safe, easy-to-handle and low-cost KF for asymmetric fluorinations. These will include novel scalable methods (up to 50g) for the asymmetric synthesis of fluorinated analogues of bioactive molecules.[2]



1) G. Pupo, F. Ibba, D. M. H. Ascough, A. C. Vicini, P. Ricci, K. E. Christensen, L. Pfeifer, J. R. Morphy, J. M. Brown, R. S. Paton, V. Gouverneur, *Science* **2018**, *360*, 638.

2) G. Pupo, A. C. Vicini, D. M. H. Ascough, F. Ibba, K. E. Christensen, A. L. Thompson, J. M. Brown, R. S. Paton, V. Gouverneur, *submitted manuscript*.