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Heterocyclic Symposium

MONDAY

THE RICH AND COLOURFUL CHEMISTRY OF AZULENE

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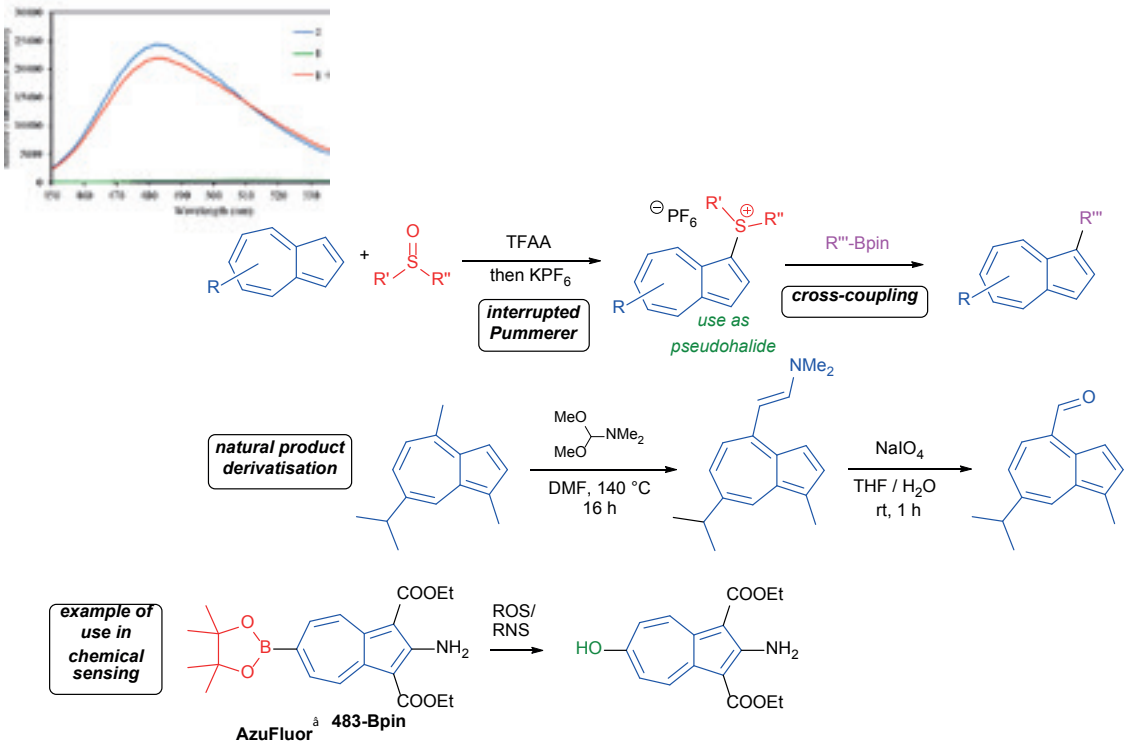
Azulene is a nonalternant bicyclic aromatic hydrocarbon, isomeric with naphthalene, yet with appreciably different properties, such as the blue colour for which it is named. Azulene is also often given as a textbook example of a system that exhibits "anomalous fluorescence", in violation of Kasha's rule. The azulene chromophore is sensitive to the electronic characteristics (EDG/EWG) of substituents on the ring, and may be "tuned" in a systematic fashion to access different absorption and emission maxima. We have developed several new synthetic methods for the functionalisation of the azulene core, including the use of sulfonium salts as *pseudo*halides in cross-coupling and selective manipulations of guaiazulene, a cheap azulene sesquiterpene. We have also developed the organoiron chemistry of azulene and used our methods to prepare azulenes for applications in ligand design, in dye-sensitized solar cells and (in particular) in chemical sensing. The properties of azulene described above also make it a versatile platform for the development of both colorimetric and fluorescent chemosensors/chemodosimeters. We have developed several "AzuFluor®» fluorescent probes for analytes of biological relevance such as peroxynitrite (ONOO–) and ADP. The use of these AzuFluor reagents in two-photon fluorescence microscopy has been demonstrated. In addition to applications in bioimaging, we have also exploited azulenes in colorimetric sensors with applications in drinking water sa[illegible]Sensors for F^- and Hg^{2+} have been demonstrated - these are both potential cc[illegible]mproved" water sources.



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H(O)P(OPH)$_2$-PROMOTED DEOXYGENATIVE HALOGENATION OF ALCOHOLS

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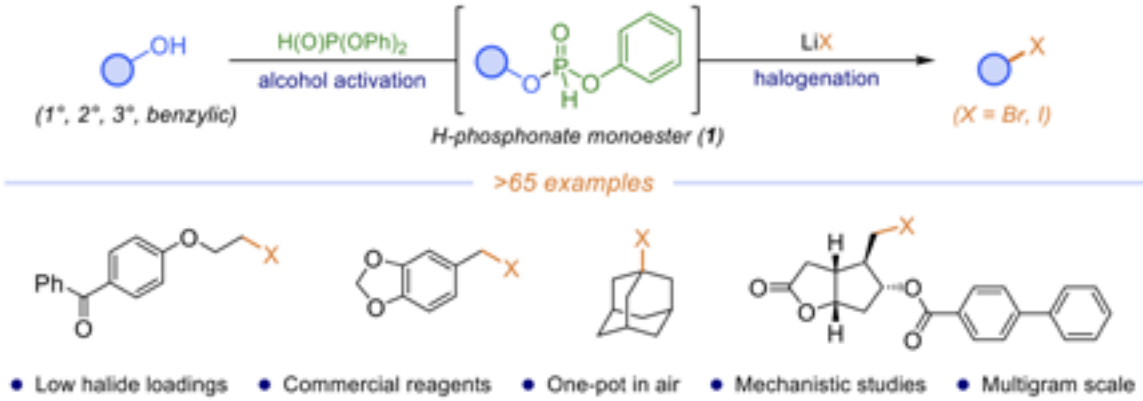
Organic halides are ubiquitous amongst target molecules such as pharmaceuticals, natural products and agrochemicals.[1–3] However, the use of these compounds is more often attributed to their inherent reactivity which is of the utmost importance in the formation of carbon–carbon and carbon–heteroatom bonds.[4] C(sp^3)–halogenated compounds in particular are synthetically useful reagents, as they enable molecular construction by nucleophilic substitution and can serve as precursors to organometallic reagents or carbon radicals. Alcohols are desirable starting materials due to their wide commercial availability with large structural variety and accessibility from renewable feedstocks,[5] their halogenation is reported to be the most prevalent functional group interconversion carried out amongst pharmaceutical companies.[6] Traditional means of preparing organic halides typically make use of high-energy reagents and generate stoichiometric quantities of halogenated waste, resulting in processes that are undesirable in the context of sustainable chemistry.



We report an operationally convenient protocol for the iodination and bromination of alcohols that exploits the inherent behaviour of a commercially available diaryl H-phosphonate promoter, H(O)P(OPh)$_2$.[7] Alcohol activation is achieved by a key transesterification event furnishing the reactive H-phosphonate monoester **(1)**, thus transforming the parent alcohol into an electrophilic intermediate. Lithium halide salts carry out the subsequent deoxygenative halogenation, circumventing the requirement for toxic molecular halogens or highly reactive halogenating agents. This approach culminates in improved safety and sustainability profiles for a universal transformation and enables lower loadings of halogenated material relative to the current state of the art. Mechanistic investigations have confirmed a distinctive pathway to other, traditional, phosphorus-promoted halogenation processes. This strategy has been applied in the synthesis of a variety of primary, secondary, tertiary and benzylic organic halides, demonstrating its synthetic utility as a novel halogenation protocol.

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FROM STABLE N-HETEROCYCLIC CARBENES TO ORGANIC RADICALS

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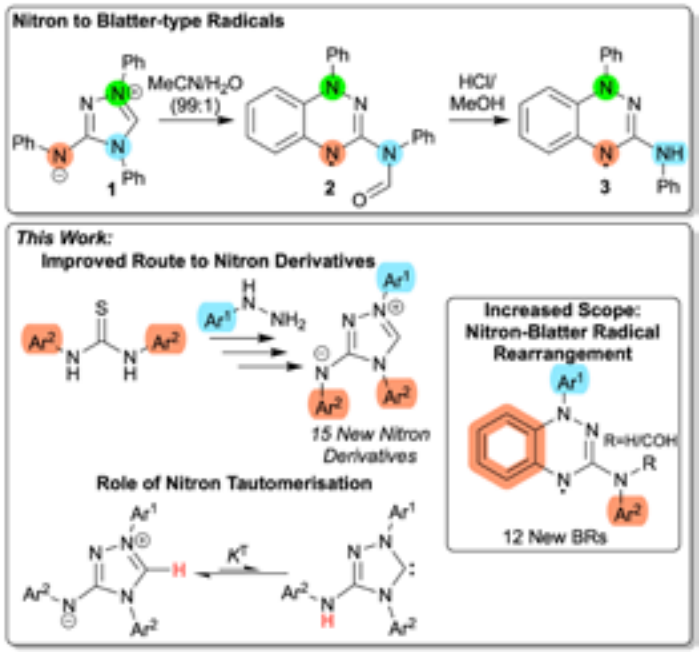
We recently reported the unusual rearrangement of a C(3)-anilino-1,2,4-triazolium ion, commonly known as Nitron **1**, to new C(3)-amido **2** and anilino **3** Blatter-type organic radicals.[1] These stable benzotriazinyl organic radicals have seen successful application as switchable signal enhancement agents for NMR spectroscopy.[2] Prior to this work, only the synthesis of the parent Nitron **1** was reported, which we used to access radical derivatives with simple alkyl substituents.[1] Nitron exists in both zwitterionic and N-heterocyclic carbene (NHC) tautomeric forms. We now report a new improved synthetic route to Nitron **1**, which permits access to a broader range of C(3)-anilino-1,2,4-triazolium derivatives encompassing both strong electron donating and withdrawing substituents. The range of Nitron derivatives was evaluated in the Nitron to Blatter radical rearrangement, with radical formation proving to be dependent on the zwitterion to carbene equilibrium position (K_T). Determination of NH and C(3)-H pK_as enabled access to K_T values for zwitterion-NHC tautomerization (K_T). We also report the initial evaluation of the series of Nitron derivatives as NHC organocatalysts of the archetypal benzoin condensation.



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3-D BUILDING BLOCKS: A MODULAR APPROACH FOR ELABORATING FRAGMENTS TO 3-D LEAD COMPOUNDS

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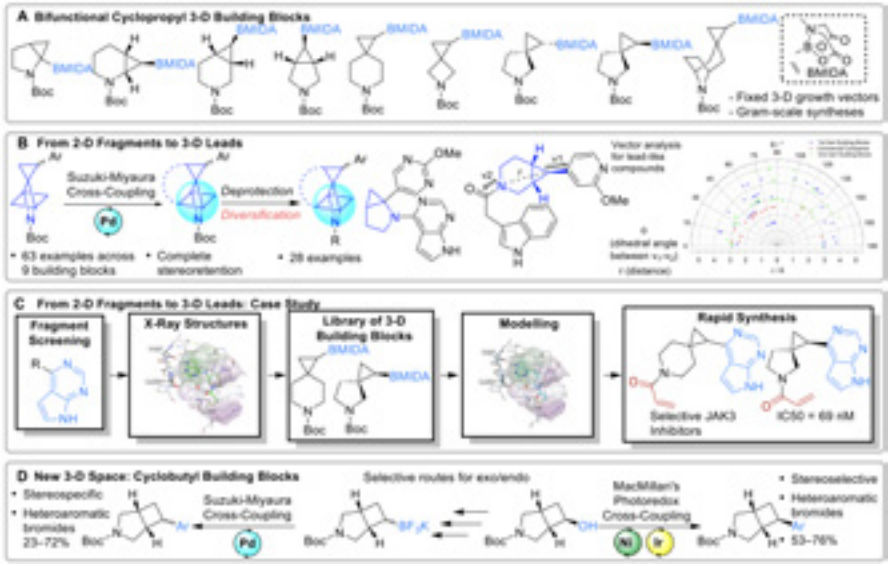
With the advent of Fragment Based Drug Discovery (FBDD) for the efficient sampling of chemical space, the overall rate of discovery of potential drug candidates starting from fragments has increased.[1] However, this increase has highlighted the need to further develop synthetic chemistry to support FBDD.[2] One of these needs is increasing the 3-D shape of current libraries due to its relationship with successful drug candidates.[3] To solve this, several approaches have been proposed and interest in 3-D shaped fragments has emerged.[4] Nonetheless, recognising that current libraries already possess many compounds with low 3-D shapes[5] and that such compounds need to be elaborated into higher molecular weight lead compounds, we now propose a new, modular approach for the conversion of 2-D fragments into 3-D lead-like compounds. Our technology platform will enable the rapid elaboration of 2-D fragments in three-dimensions. A series of bifunctional 3-D building blocks with defined elaboration vectors has been designed and synthesised **(A**, available from Redbrick Molecular). Utilising the cyclopropyl MIDA boronate handle, elaboration with medicinally relevant aryl bromides via Suzuki-Miyaura cross-coupling can be achieved. Additionally, a variety of N-functionalisation reactions are demonstrated to give access to a series of lead-like compounds by the use of precedented pharmacophores (**B**)[6,7] – this provides access to a wide range of 3-D vector space (B). The utility of our modular synthetic platform is further highlighted by the design and synthesis of selective JAK3 inhibitors utilising two of the designed 3-D building blocks (**C**). Finally, a new generation of 3-D building blocks comprising a cyclobutyl alcohol or BF_3K is showcased. Using Pd-catalysed Suzuki-Miyaura cross-coupling or a novel application of MacMillan's Ir/Ni-catalysed deoxygenative photoredox cross-coupling[8] allows access to new areas of chemical space not covered by the cyclopropyl building blocks (D). Full details will be presented.



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1,2-REDOX TRANSPOSITIONS OF TERTIARY AMIDES

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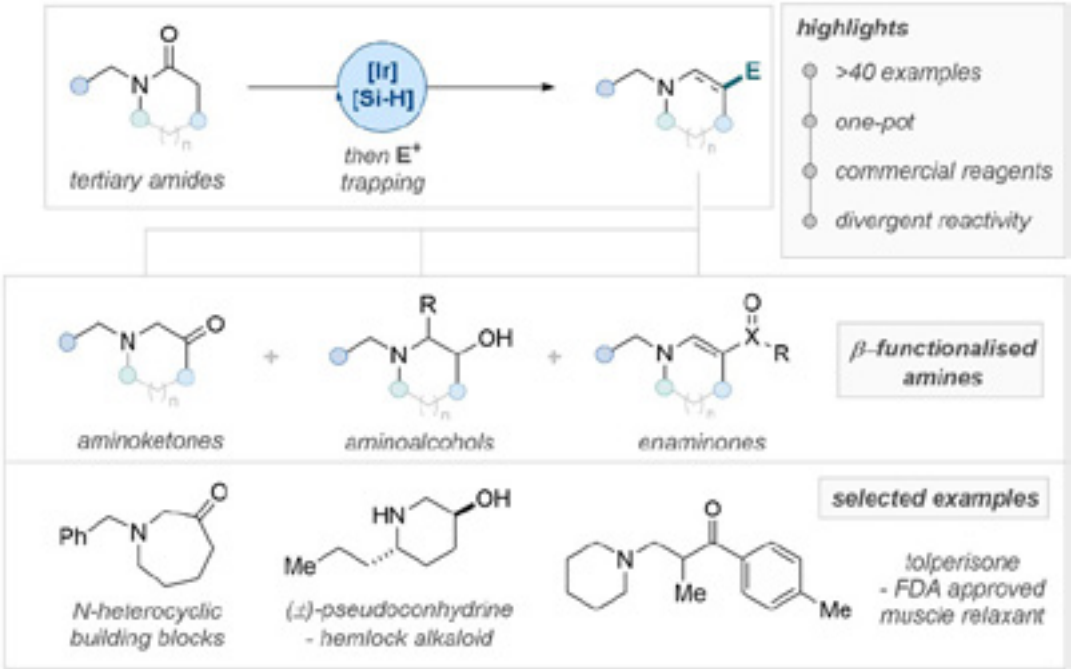
The transposition of a molecule's redox functionality represents a powerful yet underexplored paradigm for editing a molecule's reactivity profile, circumventing challenging functional group manipulations and expediting multi-step synthetic sequences.[1,2] This work investigates such a strategy in the direct 1,2-transposition of redox functionality in cyclic and acyclic tertiary amides, enabling the synthesis of aminoketones, aminoalcohols, enaminones and diverse β-functionalized amines.

Employing an iridium-catalyzed reduction,[3] transiently formed silylated hemiaminals were converted cleanly to the corresponding enamines which reacted efficiently with numerous electrophiles. Most notably, when treated with the oxidant mCPBA, the enamine converted to the desired aminoketone, constituting a formal carbonyl transposition in a manner reminiscent of the Amadori and α-iminol rearrangements.

The scope of this transformation, and related reactions with alternative electrophiles, has been explored with respect to the amide, highlighting the subtle factors affecting both the reductive dehydration stage and the electrophile trapping stage. The carbonyl transposition was scaled to 5 mmol following minor modification to the conditions and the product aminoketones were shown to be multi-faceted and valuable synthetic intermediates.

It is hoped that this work will stimulate further development of such redox-editing approaches.



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THE 19 STEPS: MULTI-KG MANUFACTURE OF AZD5462, AN RXFP1 AGONIST FOR THE TREATMENT OF HEART DISEASE

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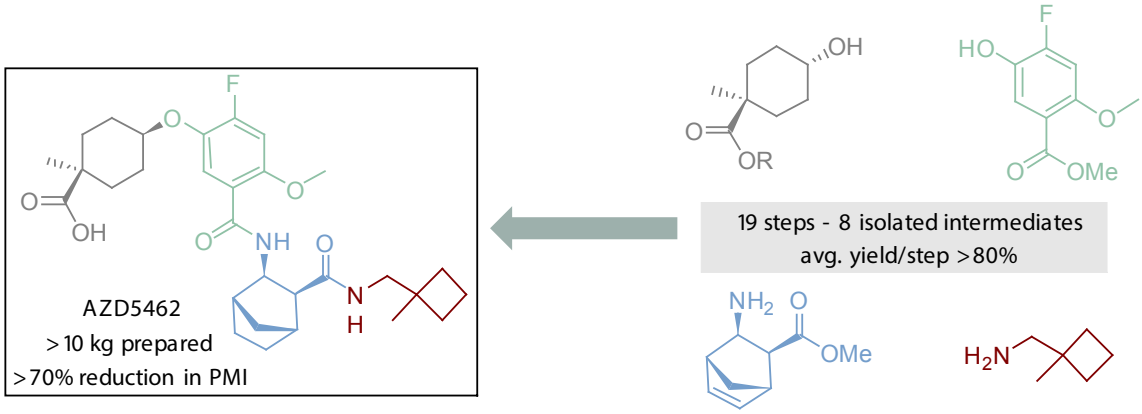
AZD5462, an oral agonist of the relaxin family peptide receptor 1 (RXFP1) is currently under investigation for the treatment of heart disease. Its complex structure represents a formidable challenge to the fast, yet also efficient and environmentally conscious manufacture, required to support early phase clinical studies. This talk will outline the synthetic chemistry story from route and process development to multi-Kg scale manufacture, encompassing twists, turns, failure, but ultimate success. Key synthetic achievements include the introduction of an iridium borylation/oxidation sequence, a critical enzymatic reduction, and a Curtius rearrangement conducted safely at multi-kg scale. 2.5 Kg of AZD5462 was prepared within 9 months and >10 Kg overall through 19 steps, with only 8 isolated intermediates in >80% avg. yield per stage. The environmental impact of manufacture was also significantly reduced, with a >70% reduction in process mass intensity (PMI).



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ADVENTURES IN CATALYSIS

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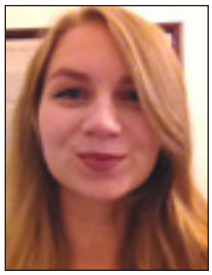
Chemical catalysis is a key technology in chemical synthesis, including pharmaceutical manufacture. Application to manufacturing processes requires understanding of a range of factors beyond the reaction itself, from sourcing the specific catalyst required to understanding of the equipment, separation of the catalyst residues from the product and the equipment train and eventual recovery of the precious metal. This talk will cover two case studies from GSK where difference in oxygen levels between lab development and the plant resulted in a difference in performance, necessitating careful selection of the equipment for lab experiments to generate appropriate data to predict what would happen for future plant campaigns.

BRØNSTED ACID-CATALYSED FRIEDEL-CRAFTS ALKYLATION OF INDOLES WITH ELECTRON-DEFICIENT ALKENES IN WATER



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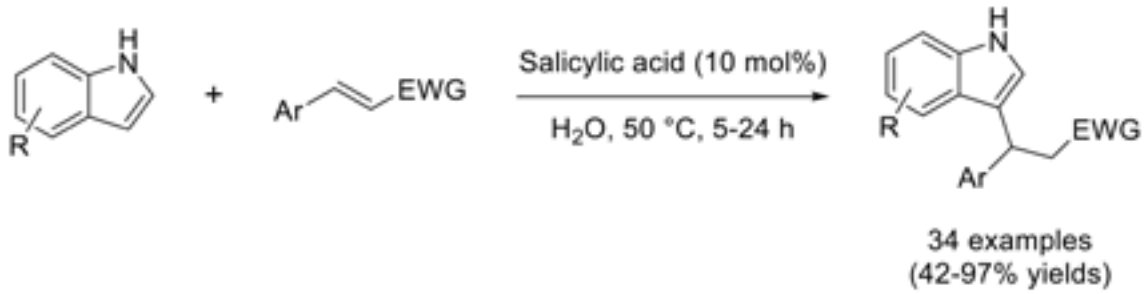
A low cost, environmentally benign method has been developed for the Friedel-Crafts alkylation of indoles using readily available salicylic acid as a hydrogen-bonding catalyst and water as the reaction medium (Scheme 1). The mild conditions are compatible with a wide variety of substituted indoles and nitroalkenes, including acid-sensitive groups such as Bocprotected amines and pinacol boronic esters. The applicability to different Michael acceptors and heterocycles has also been explored. The Friedel-Crafts alkylation products were obtained in good to excellent yields (42-97%).



Scheme 1: Salicylic acid catalysed Friedel-Crafts alkylation of substituted indoles.

BRØNSTED BASE CATALYSED ENANTIOSELECTIVE [2,3]- AND [1,2]-REARRANGEMENT OF ALLYLIC ETHERS

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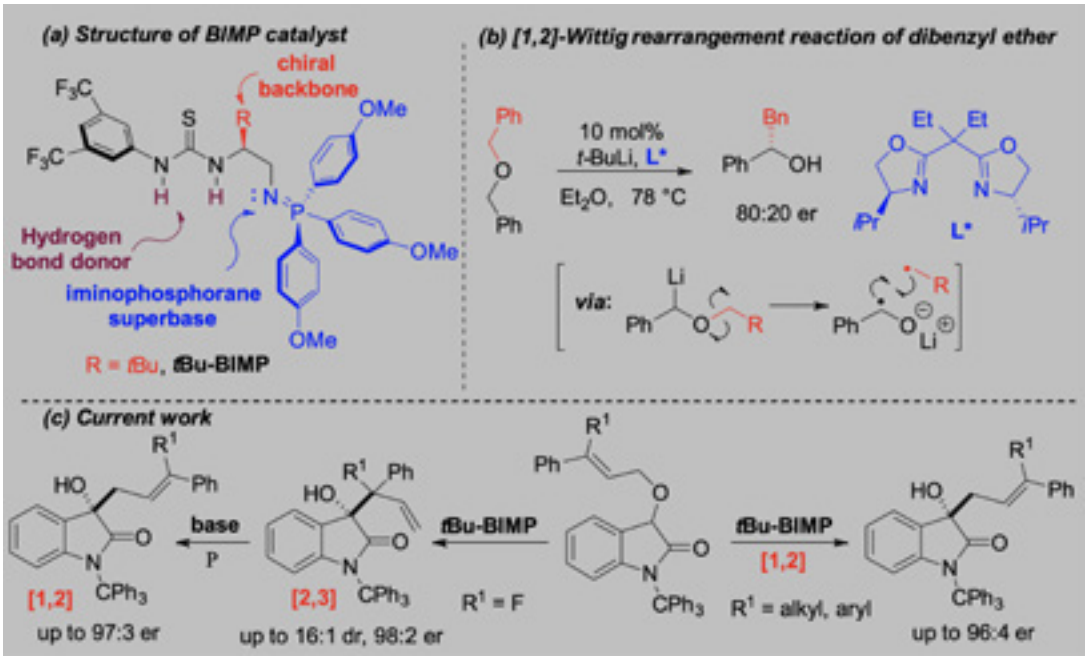
Bifunctional iminophosphoranes (BIMPs) (Scheme 1a), originally developed by Dixon,[1] have been extensively studied as novel Brønsted base catalysts in many stereoselective transformations over the past decade, as they possess a Brønsted superbasic moiety and an H-bond donor moiety for stereocontrol. However, to date, such catalysts have not been used to promote sigmatropic rearrangement reactions. Sigmatropic rearrangements are appealing as they show high reliability and atom-economy, usually combined with inherently high stereocontrol for the construction of carbon-carbon and carbon-heteroatom bonds. In particular, [2,3]-sigmatropic rearrangements have widely been employed in the synthesis of bioactive molecules and natural products, with a range of catalytic enantioselective [2,3]-Wittig rearrangements developed.[2] In comparison, the [1,2]-Wittig rearrangement, first reported in 1942,[3] is a recognised challenge in terms of both enantiocontrol and functional group tolerance. To date, there is only one example of an enantioselective [1,2]-Wittig reaction reported by Tomooka and Nakai in 1999 that proceeds with moderate yield and enantioselectivity (Scheme 1b).[4]

In this work we realize the enantioselective [2,3]- and [1,2]-Wittig rearrangement of allylic ethers using BIMP catalysts (Scheme 1c). Mechanistic studies and DFT calculations indicate that the current formal [1,2]-Wittig rearrangement described herein proceeds via a stepwise [2,3]-/ [1,3]-Wittig rearrangement cascade, with ionic fragmentation-recombination of the latter showing retention of configuration rather than the generally accepted radical fragmentation pathway.



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CATALYTIC SYNTHESIS OF HETEROCYCLES FROM YNDIAMIDES

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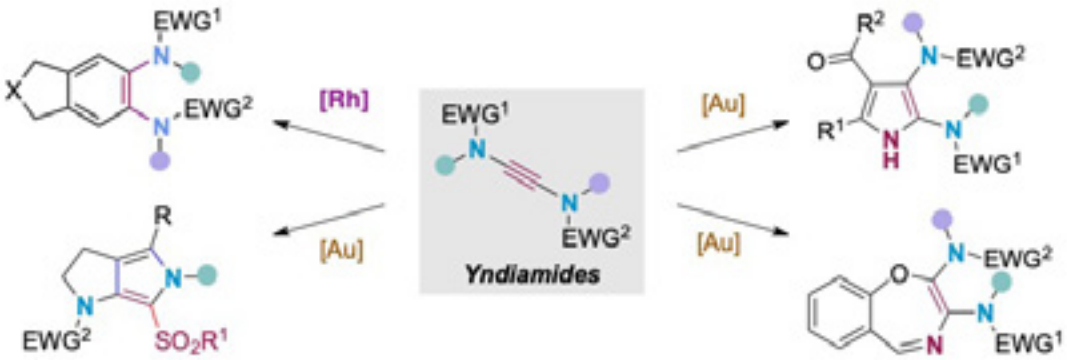
Yndiamides are a novel class of alkyne featuring nitrogen substituents at both ends of the triple bond.[1] These nucleophilic species are able to engage with a variety of transition metal catalysts to achieve heterocycle synthesis with 1,2-diamination. This presentation will discuss recent discoveries in gold- and rhodium-catalyzed cyclizations of yndiamides for the *de novo* synthesis of highly-substituted heterocycles.[2,3] A particular focus will be on how regiocontrol could be achieved in the reactions of *pseudo-symmetric* yndiamides, using subtle steric or electronic effects, and the mechanistic basis for this selectivity. A novel class of *N*-aryl yndiamide will also be presented.



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FLIPPING THE SWITCH: REVERSIBLE REACTIONS IN CATALYSIS

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A 1997 report by Catellani (1) outlining a novel C-H functionalization reaction stimulated our interest in reversible reactions, since a key step is reversible carbopalladation with norbornene (1). We subsequently explored improved reaction conditions, and the synthetic potential of the Catellani reaction, including its application in the synthesis of natural products (2-6).

This lecture will discuss how our research program evolved in the exploration of other metal catalyzed reversible reactions, including C-C and C-X bonds (7-10).

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