STEREORETENTIVE ENANTIOCONVERGENT REACTIONS OF AMINES

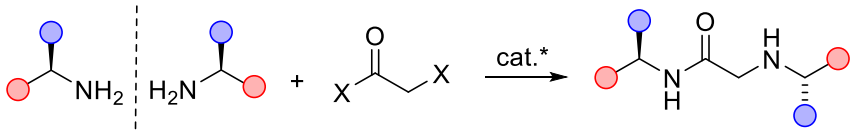
Jacob S. Bestwick, Andrew L. Lawrence*

EaStCHEM School of Chemistry, Joseph Black Building, David Brewster Road, Edinburgh, EH9 3FJ

j.bestwick@sms.ed.ac.uk

When using racemic substrates in asymmetric synthesis a yield of 100% can only be achieved through the use of enantioconvergent reactions (*cf*. kinetic resolutions (KR), maximum 50% yield). There are three established approaches for achieving enantioconvergency; stereomutation (*e.g.*, dynamic kinetic resolutions), stereoablation and stereodifferentiation.[1] These three concepts all have their own particular advantages. However, they all suffer from common limitations in their substrate scope. The stereogenic elements of the starting material must be labile towards mutation, ablation, or inversion. Additionally, substrates containing multiple stereogenic elements are generally not amenable to any of these established approaches.[2]

This presentation will describe our investigations into a new stereoretentive approach to enantioconvergent reactions. Stereoretention in enantioconvergent reactions is possible if the two enantiomers of a racemate are selectively coupled together to form a non-*meso* product. Uniquely, racemic substrates with robust and/or multiple stereogenic elements will be compatible with these enantioconvergent reactions. Our efforts to develop an enantioconvergent domino nucleophilic acyl substitution/S_N2 reaction sequence will be described. This multi-component approach can benefit from Horeau enantioamplification, meaning even a low *s* factor ($s = k_{fast}/k_{slow}$)[3] in the initial *in-situ* KR will be sufficient to produce products in exceptionally high enantiopurity.[4]



racemic *max 100% yield max 100% ee*

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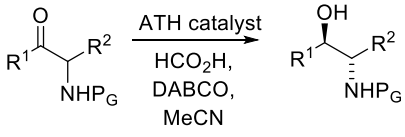
Asymmetric Transfer Hydrogenation: Dynamic Kinetic Resolution of α-Amino Ketones

Shweta K. Gediya, Guy Clarkson and Martin Wills*

Department of Chemistry, The University of Warwick, Coventry, CV4 7AL, UK.

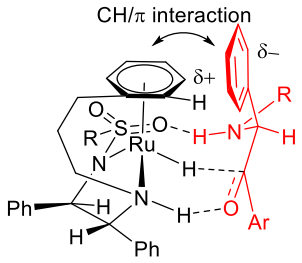
Shweta-Kamleshbhai.Gediya@warwick.ac.uk

Asymmetric transfer hydrogenation (ATH), using Noyori-Ikariya catalysts is a powerful method for the asymmetric reduction of ketones. ATH in combination with dynamic kinetic resolution (DKR) is used to generate two vicinal chiral centres. In this study, a series of α-amino ketones were synthesized and reduced to the corresponding amino-alcohol derivatives using an ATH-DKR process. A preliminary investigation including racemization kinetics and catalyst screening was carried out to find the best combination of *N*-protecting group and reducing agent. After reaction condition optimization, a series of substrates were investigated, giving products in high diastereoselectivity and enantioselectivity (over 99% ee in several cases) and full conversion. The preferential formation of the *anti*-diastereoisomer can be explained by a transition state for the hydride transfer, which is stabilized by a hydrogen bond between a N-H in the substrate and the sulfonamide group of the catalyst, coupled with a CH/π edge/face interaction as illustrated below. The methodology was applied to the enantioselective synthesis of a MDM2–p53 inhibitor precursor which had previously been prepared in an asymmetric form through a chiral resolution.

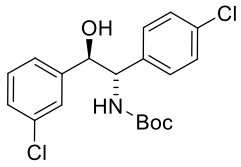


R^1, R^2 = *o.m,p* Cl-, MeO-phenyl, CH_3
P = Bz, Boc, Ts, Cbz
Selectivities in best cases:
dr >99.9:<0.1, >99% ee

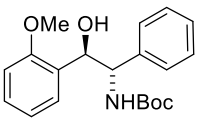
Transition state:



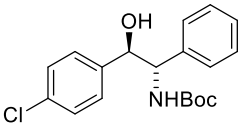
Application:



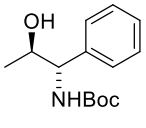
precursor of a reported MDM2-p53 Inhibitor:
100% conv, 89.2% yield,
dr 99.7:0.3, 96.4% ee



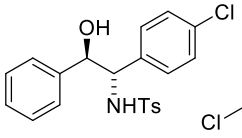
48h, 100% conv,
87.4% yield,
dr >99.9:0.1,
94.4% ee



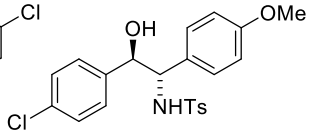
24h, 100% conv,
80.6% yield,
dr >99.9:0.1,
99.4% ee



24h,100% conv,
86.8% yield,
dr 98.3:1.7,
94.6% ee



24h, 100% conv,
84.8% yield,
dr 97.7:2.3,
92.4/>99% ee



48h, 100% conv,
88.2% yield,
dr >99.9:0.1,
97.6% ee

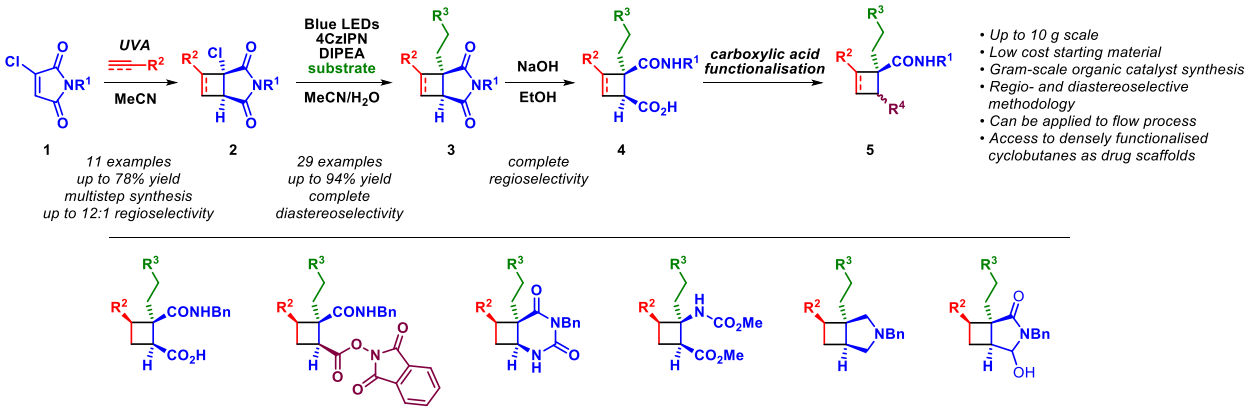
Photochemical Approaches to the Synthesis of Highly Functionalised Cyclobutanes

[a]**Mark Deeprose**, [b]Martin Lowe*, [a]Kevin I. Booker-Milburn*, [a]Varinder K. Aggarwal*

[a] *School of Chemistry, University of Bristol, Cantock's Close, Bristol, BS8 1TS*
[b]*Medicinal Chemistry Department, UCB, 216 Bath Road, Slough, SL1 3WE*

mark.deeprose@bristol.ac.uk

Photochemistry has grown into a diverse, integrative strategy that unlocks the ability to form complex molecular scaffolds from simple building blocks. Recent developments into photocatalysis have caused a rapid growth of interest into this area. Cyclobutane containing natural products are abundant in nature and therefore are a target for pharmaceuticals.[1] Using photochemical approaches, highly functionalised cyclobutane derivatives can be obtained via a [2+2] photocycloaddition to give **2**. Photoredox catalysed dehalogenation and functionalisation gives the stereo specific product **3**. Hydrolysis, and subsequent carboxylic acid functionalisation provides product **5**.[2,3] Developing these strategies may allow large scale production of regio- and diastereoselective functionalised cyclobutanes from simple building blocks.



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Electrochemical Manganese-Catalysed Deconstructive Chlorination of Cycloalkanols

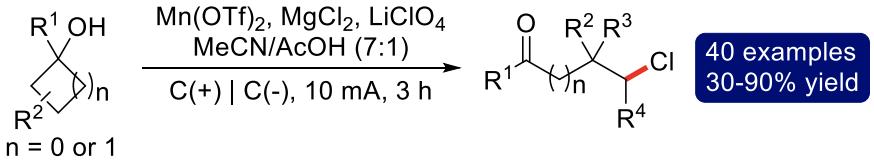
Alex C. Seastram, Benjamin D. W. Allen, Mishra Deepak Hareram, Tom McBride, Thomas Wirth, Duncan L. Browne,[a] and Louis C. Morrill*

Cardiff Catalysis Institute, Cardiff University, Park Place, Cardiff, CF10 3AT.
[a]UCL, 29-39 Brunswick Square, Bloomsbury, London, W1CN 1AX.

SeastramAC@cardiff.ac.uk

Organic electrochemistry represents one of the cleanest possible chemical processing technologies,[1] and has recently undergone a renaissance in recent years, partly as a result of an increased availability of standardised batch and flow electrochemical reactors.[2] Despite this, the development of electrochemical methods for alkoxy radical generation has received little attention to date, with the majority of reports focusing on the generation of methoxy radicals at expensive boron-doped diamond or platinum anodes.[3,4] Within the Morrill Group, development of new electrochemical procedures for the generation of alkoxy radicals and their subsequent utilisation in a range of synthetic transformations is an ongoing research theme.

Within the group, a manganese-catalysed electrochemical deconstructive chlorination of cycloalkanols has been developed to furnish a diverse range of synthetically useful β- and γ-chlorinated ketones from cyclopropanols and cyclobutanols respectively via alkoxy radical intermediates.[5]



This work represents a new methodology for generating alkoxy radicals electrochemically and their subsequent utilisation in a synthetically useful transformation. In this work, a simple manganese (II) salt was employed together with magnesium chloride to form a redox mediator in-situ, allowing the formation of alkoxy radicals using inexpensive graphite electrodes. Mechanistic studies, supported by Cyclic Voltammetry (CV), enabled the proposal of a plausible reaction mechanism, whereby a catalytically active $Mn(III)X_2Cl$ species is anodically generated, facilitating the desired transformation. Furthermore, the combination of recirculating flow electrochemistry and continuous inline liquid-liquid extraction was employed for the first time to access products on a gram-scale.

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Isothiourea Catalysis for the Enantioselective α-Alkylation of Schiff Base Glycine Derivatives

R. S. Craik[a], A. D. Smith[a]*

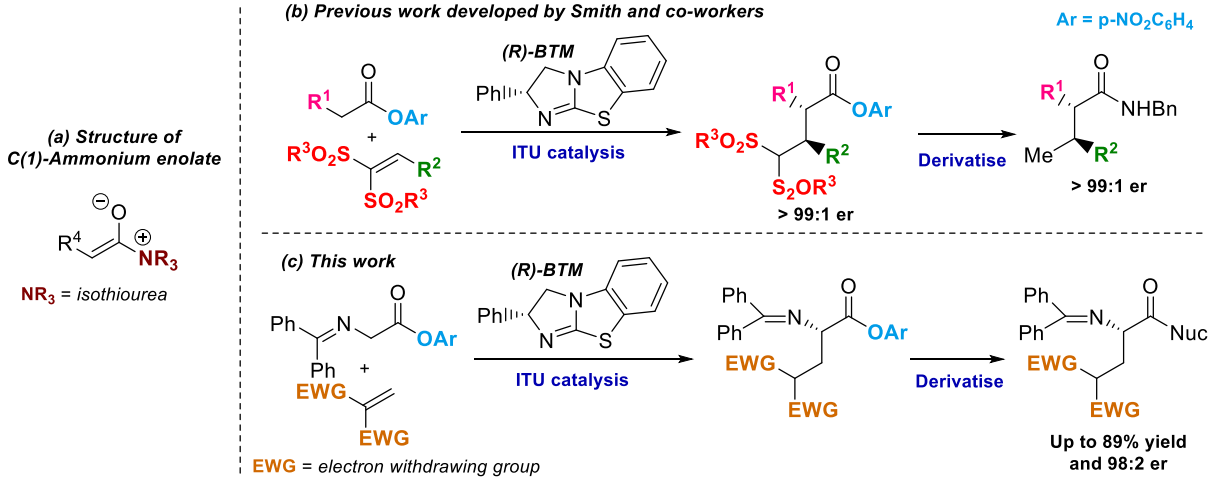
[a] School of Chemistry, University of St Andrews, North Haugh, St Andrews, Fife KY16 9ST, UK

rc244@st-andrews.ac.uk

Isothioureas (ITUs) have been extensively studied over the past decade as new Lewis base asymmetric catalysts. Pioneering work by Birman and coworkers first exemplified their efficiency in kinetic resolution of secondary benzylic and allylic alcohols.[1] Since then ITUs have been proven to be efficient acylation catalysts, even competing with the benchmark dimethylaminopyridine (DMAP) catalyst that is most often used for Steglich esterification[2]. ITUs are not only used as acyl transfer catalysts but also allow access to C(1)-ammonium enolates (Scheme 1a) which, in combination with a vast range of electrophiles, give a plethora of structurally diverse substrates[3,4].

Previous work by Smith and co-workers studied *para*-nitrophenol esters as starting material and C(1)-ammonium enolates precursors (Scheme 1b).[5] The *para*-nitrophenoxide anion released after nucleophilic attack of the catalyst acts as a base to form the ammonium enolate, and enables the catalyst to turnover at the end of the cycle. Previously the addition of an auxiliary base was needed to allow the formation of the ammonium enolate. However, the scope of this reaction was limited only to the use of the extremely reactive sulfonated alkenes.

The aim of the present work is to increase the scope of electrophiles used in previous work. To achieve this goal the ester was replaced by a Schiff base glycine derivative to increase the nucleophilicity of the ammonium enolate (Scheme 1c). This would also allow access to α-amino acids derivatives which are compounds of great interest often used as building blocks by the chemical industry. This work will show that we were able to develop such a procedure and synthesize a range of α-amino acids derivatives in up to 89% yield and up to 98:2 er.



Scheme 1. Michael Addition processes using Isothiourea Catalysis

References

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Heterogeneous Photocatalysis in Flow: Technologies for Accelerating Sustainable Synthesis

Christopher G. Thomson,[a] Ai-Lan Lee[a,*] and Filipe Vilela[a,*]

[a]Institute of Chemical Sciences, School of Engineering and Physical Sciences, Heriot-Watt University, Riccarton, Edinburgh, Scotland, EH14 4AS.

Email: ct261@hw.ac.uk.

Photocatalysis has emerged as a powerful methodology to achieve unique chemical transformations under mild conditions, enabling selective late-stage modification of complex and fragile compounds.[1,2] Development of efficient heterogeneous photocatalysts (HPCats) as a more sustainable alternative to state-of-the-art Ru and Ir transition metal complex (TMC) photocatalysts, has been described as one of the greatest challenges within the field of photocatalysis.[3] Flow chemistry can, to a large extent, mitigate the typical mass- and photon-transport limitations of HPCats to achieve efficiencies that rival TMC photocatalysts.[4]

In this talk, I will discuss our work developing Merrifield resins as solid-supports for organophotocatalysts, taking advantage of flow chemistry to enhance their synthesis, purification and application as HPCats (Figure 1A).[5] I will also discuss our development and application of emerging technologies within flow reactor systems, including 3D printing, in-line UV-Vis. absorption/emission spectroscopies and in-line NMR spectroscopy. The latter was utilised to greatly accelerate process optimisation of a flow photochemical process, achieving an three-fold increase in productivity.[5]

Finally I will discuss our recent work developing in-line integration of an automated flash chromatography system for continuous synthesis and purification (Figure 1B).[6] Our system was capable of isolating grams per hour quantities of product(s), directly from a flow reactor output stream. The system was also found to serve as a process analytical tool by monitoring the steady-state conversion of a flow process featuring and immobilised HPCat.

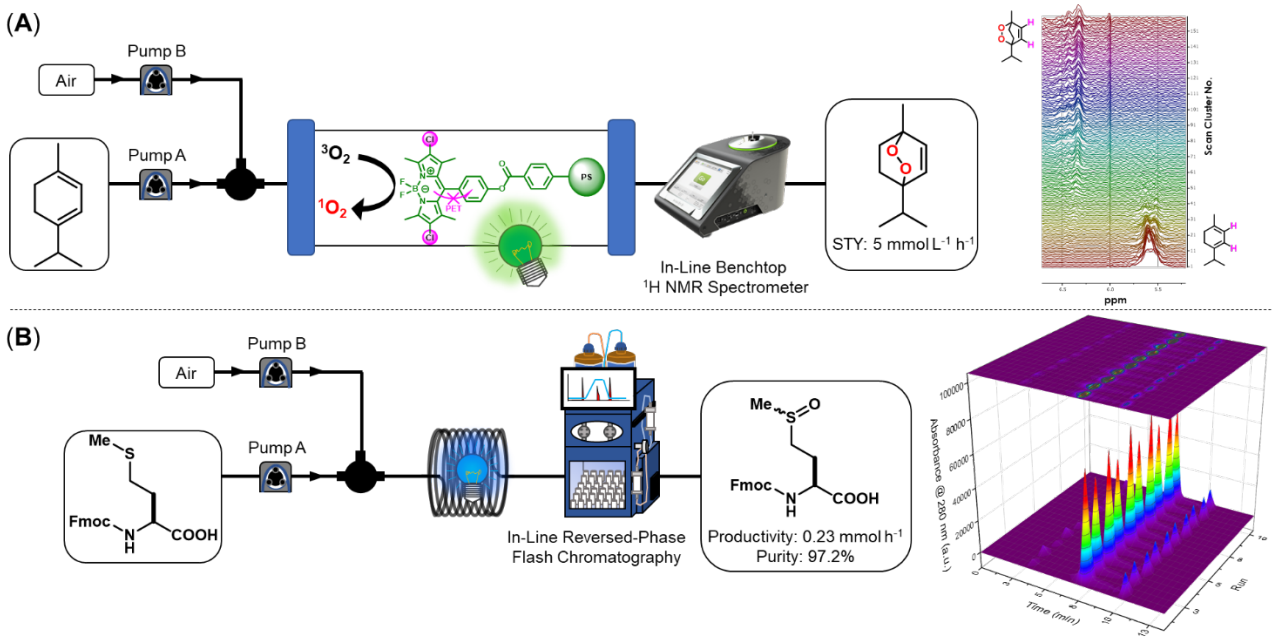

Figure 1. (**A**) Continuous heterogeneous photoxidation of *α*-terpinene, monitored by in-line ^{1}H NMR spectroscopy. (**B**) Continuous flow synthesis and purification of methionine sulfoxide *via* in-line reversed-phase flash chromatography.

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Transition metal-free, visible light-mediated radical cyclisation of malonyl radicals onto 5-ring heteroaromatics

Pol Hernández-Lladó;[a] Daniel C. Schmitt;[b] Jonathan W. Burton*[a]

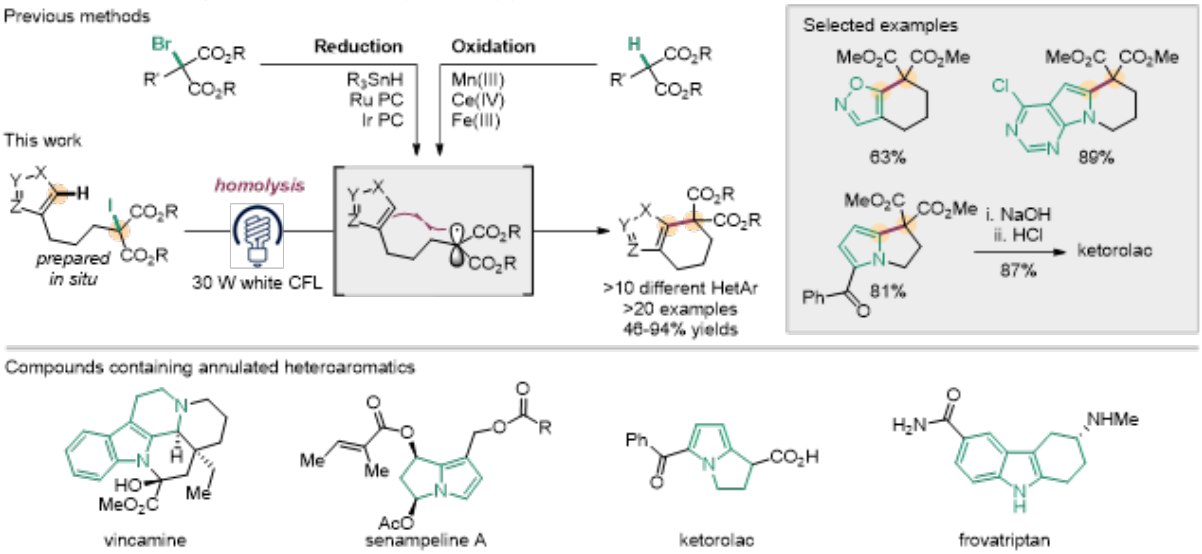
[a]Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford OX1 3TA, UK.
[b]Medicine Design, Pfizer Worldwide Research, Development and Medical, Groton, Connecticut 06340, United States

pol.hernandezllado@chem.ox.ac.uk

Annulated heteroaromatics are common in nature and medicinal chemistry. For example, the natural products vincamine and senampeline A contain such motifs, as well as the marketed drugs ketorolac and frovatriptan. These ring systems can be accessed through the cyclisation of carbon-centred radicals onto heteroaromatics.[1]

Malonyl radicals are particularly useful in this approach due to their stability and easy derivatisation. They have been previously generated via reduction of halomalonates with tin hydrides[2,3] and photoredox catalysts;[4,5] or oxidation of malonates with Mn(III), Ce(IV), or Fe(III) reagents (Scheme 1).[6] However, these methods were reliant on tin or transition metals, and were limited to a small number of electronically similar heteroaromatics.

We have developed a metal-free, visible light-mediated method for the cyclisation of malonyl radicals onto heteroaromatics that addresses these limitations. This reaction is based on the *in situ* preparation and homolysis of iodomalonates, which happens in the absence of any photocatalyst. Under these mild conditions, malonyl radicals cyclise onto a wide variety of heteroaromatics, and tolerate arene and malonate substitution. The utility of this transformation was further showcased through the synthesis of the anti-inflammatory drug ketorolac in 5 steps from pyrrole.



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Stereoselective Palladium Catalysed C(sp3)–H mono-Arylation of Piperidines and Tetrahydropyrans with a C(4) Directing Group

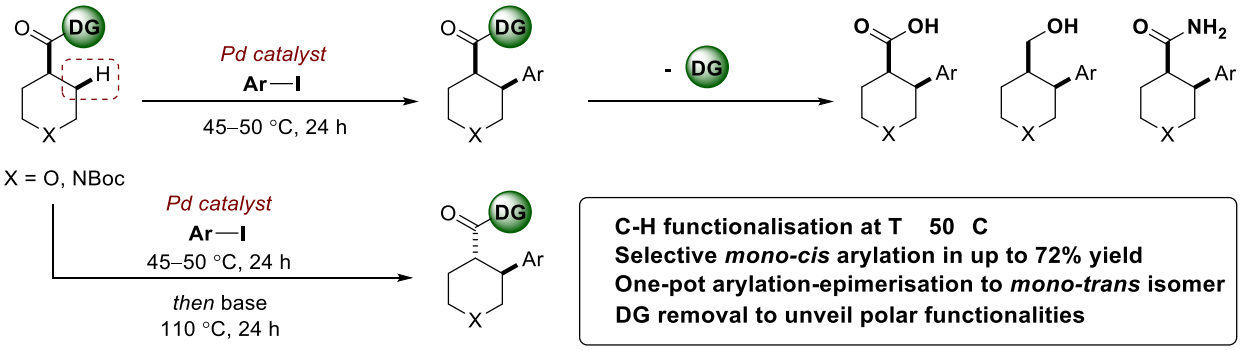
Amalia-Sofia Piticari; Dr. James A. Bull*; Dr. Matthew Webster[a]

Molecular Sciences Research Hub, Imperial College London, London W12 0BZ, UK
[a]AbbVie Inc., 1 North Waukegan Road, North Chicago, IL 60064-6101, United States

Email: ap3714@imperial.ac.uk

In fragment-based drug discovery, saturated heterocyclic rings are advantageous starting points for hit identification due to their low molecular weight, polarity and presence of defined 3D exit vectors along the C(sp^3)–H bonds.[1-3] However, there are few synthetic methods that enable fragment "growth" from intact rings, by probing exit vectors in a selective fashion.[4,5] The ability to generate a variety of defined substitution patterns is extremely valuable, allowing chemists to increase the topological variety of drug precursors and analogues, as well as expanding the accessible chemical space. Our approach is to achieve efficient divergent synthesis of fragments through C–H functionalisation.[6]

We have previously reported the stereoselective directed C–H arylation of N- and O-heteroaliphatic rings at unactivated positions. We used C(2) directing groups to arylate at C(3),[7] as well as C(3) directing groups to react at the C(4) position of piperidines and pyrrolidines.[8] This work presents a palladium-catalysed methodology for accessing a 3,4-disubstitution pattern on 6-membered heterocycles, by C(3) functionalisation in the presence of a C(4) directing group that can itself be further derivatised. Reaction optimisation using a DoE approach gave highly selective mono functionalisation and cis-stereochemistry in the unbiased symmetrical substrate. Isolated yields of up to 72% were obtained of single diastereoisomer products. Temperature was key to the observed selectivity, this constituting the first heterocycle C–H functionalisation remote from the heteroatom that can be conducted below 50 °C. Additionally, direct access to the corresponding mono-trans isomers was possible *via* a facile one-pot arylation-epimerisation protocol. Directing group removal strategies unveiled a range of free polar functionalities and allowed the preparation of a fragment collection.



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Ambruticins: Tetrahydropyran Ring Formation and Total Synthesis

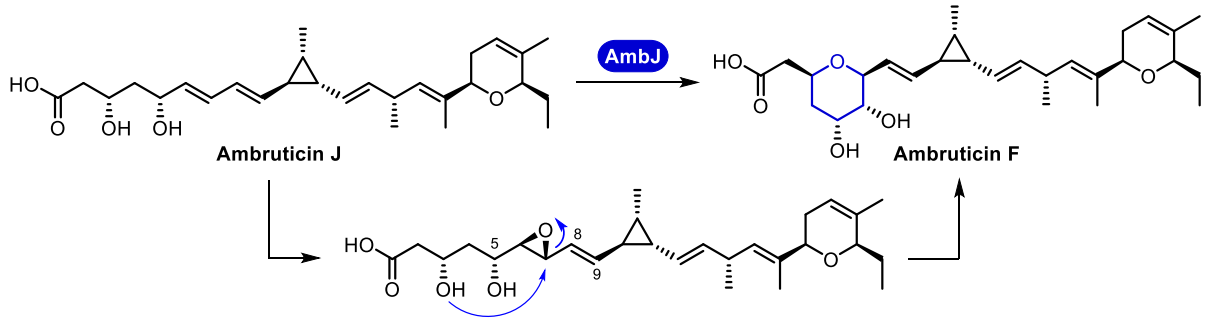
James I. Bowen,[a] Luoyi Wang,[b] Matthew P. Crump[a] and Christine L. Willis*[a]

[a]School of Chemistry, University of Bristol, Cantock's Close, Bristol, BS8 1TS, UK
[b]Institute of Microbiology, Chinese Academy of Sciences, NO. 1 Beichen West Road, Chaoyang District, Beijing, 100101, China

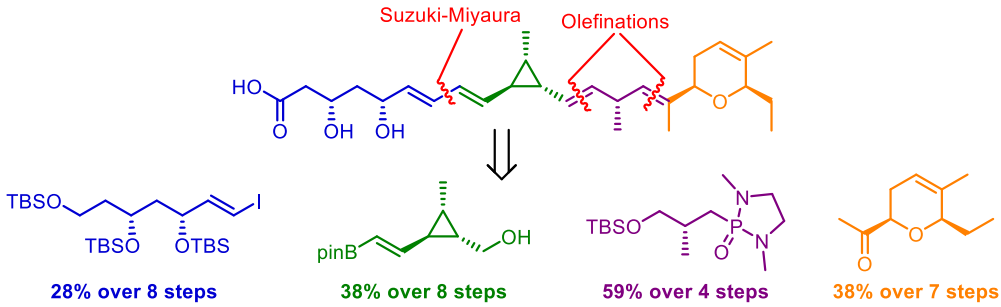
James.bowen@bristol.ac.uk

The ubiquitous use of antifungal agents in agriculture, veterinary, and human healthcare has resulted in the development of drug-resistant fungal pathogens such as *Candida auris*.[1,2] The limited variety of treatments alongside a changing climate has exacerbated the problem.[3] Natural products, such as the ambruticins, are a source of inspiration for new antimycotics.

Gene knockout experiments are in accord with the proposal that the tetrahydropyran ring of the ambruticins is formed *via* the AmbJ-catalysed epoxidation of the unsaturated 3,5-dihydroxy acid, ambruticin J, followed by regioselective cyclisation to ambruticin F.[4] Investigations towards understanding this biosynthetic transformation may facilitate the exploitation of nature's biological machinery to generate variants of the ambruticins. Furthermore, this could lead to novel biocatalysts to perform challenging synthetic transformations cleanly and efficiently.



To investigate THP ring formation in ambruticin biosynthesis, we have conducted model studies involving chemical epoxidation and cyclisation of unsaturated hydroxy esters. These studies indicate that both the C-5 alcohol and 8,9-alkene of epoxy-ambruticin J may be responsible for selective cyclisation to give ambruticin F. Furthermore, we have accessed the putative biosynthetic intermediate, ambruticin J, through a highly modular total synthesis, where four fragments are united *via* a thallium-accelerated Suzuki-Miyaura cross-coupling and two olefinations.[5] *In vitro* and *in vivo* investigations using heterologously expressed AmbJ are currently underway for the selective oxidation of ambruticin J.



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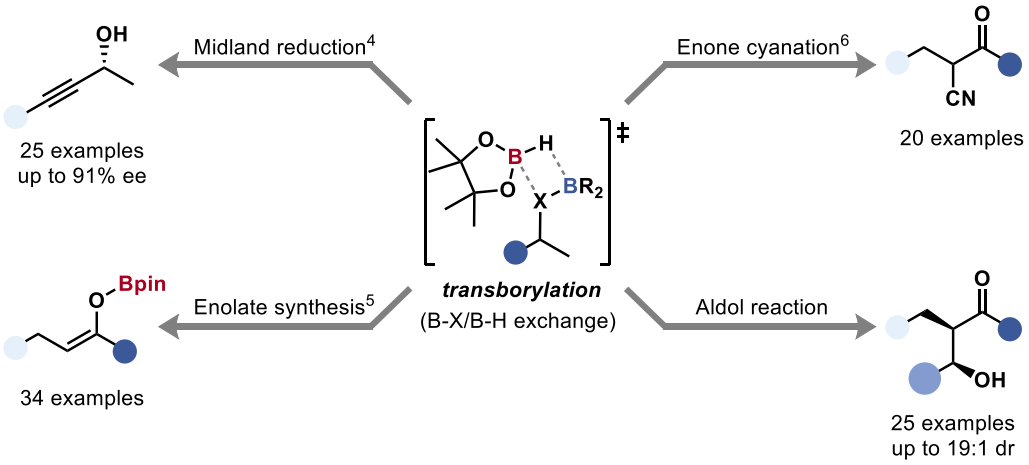
Transborylation as General Turnover Strategy for Main-group Catalysis

Kieran Nicholson[a]; Thomas Langer[b]; Stephen P. Thomas[a]*

[a]EaStCHEM School of Chemistry, Joseph Black Building, The University of Edinburgh, Edinburgh, EH9 3FJ.
[b]Pharmaceutical Technology & Development, Chemical Development UK, AstraZeneca, Silk Road, Macclesfield, SK10 2NA.

K.nicholson-3@sms.ed.ac.uk

The main-group offers an underutilised and sustainable alternative to transition metal catalysis; however, the redox chemistry of transition metals is not readily translated to p-block species and examples of oxidative addition and reductive elimination remain limited.[1] Here, we report transborylation, a redox-neutral turnover strategy for main-group catalysis which enables the use of previously stoichiometric organoborane reagents as catalysts.[2-3] This new turnover pathway has been exemplified in catalysis as a generalisable strategy through catalytic Midland reduction,[4] the chemoselective reduction of enones,[5] reductive cyanation of enones,[6] and reductive coupling of esters to give aldol-type products.



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Nickel-Catalyzed Cross-Coupling of Alkyl Carboxylic Acid Derivatives with Pyridinium Salts via C–N Bond Cleavage

Feba Thomas Pulikottil Ramadevi Pilli, Rohith Valavil Suku, and Ramesh Rasappan*

*School of Chemistry, Indian Institute of Science Education and Research Thiruvananthapuram, Thiruvananthapuram, Kerala 695551, India.

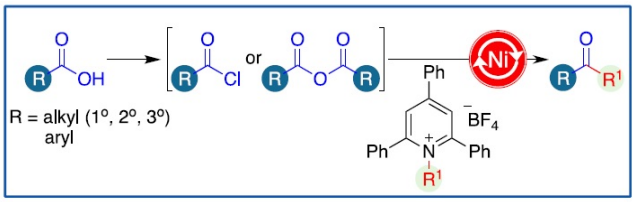
Email address of presenter: feba16@iisertvm.ac.in

The transition metal-mediated cross-electrophile coupling *via* cleavage of C(sp^3)–N bonds to offer unsymmetrical diakyl ketones from various alkyl pyridnium salts and acyl chlorides was developed.[1] $NiBr_2$·bpy catalyst, co-solvent system CH_3CN:DMA and Mn as reductant was the optimized condition. In substrate scope apart from 1°, 2° and 3° acid chlorides, carboxylic acids were also employed as acylating agents which enabled the incorporation of acid-sensitive functional groups such as MOM, BOC and acetal to offer the acylated products in good yields.

The mechanistic studies in the preceding Ni catalyzed cross-coupling suggests (i) sequential reduction and (ii) radical chain process as the two most probable pathways for the complete catalytic cycle. In sequential reduction (i) oxidative addition of acyl chloride takes place as the initial step and then subsequent generation of alkyl radical from the pyridinium salts with the aid of Mn reduced nickel species occurs. In radical chain process (ii) there is a generation of alkyl radical by the low valent nickel catalyst as the first step and thereafter oxidative addition of the acid chloride takes place. Eventually, it leads to alkyl radical recombination on to the nickel centre and reductive elimination to complete the catalytic cycle. The radical scavenger Tempo and radical inhibitor 2,4-Dinitrochlorobenzene corroborate the presence of radical intermediate.

This protocol gains its attention by accommodating no additives, cheap bipyridine ligand, proceeds at rt and by synthesis of vital compounds.

Scheme 1. Cross-coupling of 2,4,6-triphenylpyridinium salts and acid derivatives to obtain dialkyl ketones



- Inexpensive bpy ligand
- No additive
- 37 examples
- Ambient temperature
- Abundant nickel catalyst
- Broad substrate scope

[1]. Pulikottil, F. T.; Pilli, R.; Suku, R. V.; Rasappan, R. *Org. Lett.* **2020,** *22* (8), 2902-2907.

meta-Arylation of Phenols

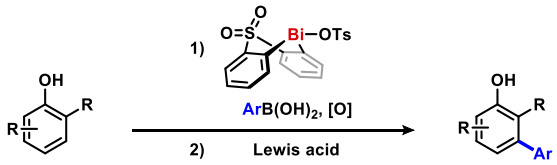
Aaron Senior[a], Katie Ruffell[a], Dr Liam T. Ball*[a]

[a]School of Chemistry, The University of Nottingham, Nottingham, NG7 2RD

aaron.senior@nottingham.ac.uk

Phenol functionalization strategies are dominated by *ortho*- and *para*-selective electrophilic aromatic substitution and *ortho*-directed catalytic C-H activation.[1] Access to the *meta*-position remains challenging and demands elaborate directing 'templates' or 'blocking' groups, superstoichiometric additives, and high catalyst loadings.[2,3] Additionally, current *meta*-functionalisation strategies cannot be applied to *ortho*-substituted phenols. We have developed a general, directing group-free strategy for the *meta*-selective C-H arylation of phenols mediated by a bismuth heterocycle that tolerates mono- and di-*ortho*-substitution of the substrate.

Starting from a versatile bismuth(III) precursor that can be synthesised on a decagram scale,[4] we show that *meta*-selective C-H arylation of *ortho*-substituted phenols is achieved in good to excellent yields. The reaction tolerates a wide range of electronically diverse substrates and is compatible with functionality that is orthogonal to conventional cross-coupling methods. In this way it is now possible to access both the elusive *meta*- position of phenols, and 1,2,3,4-tetrasubstituted benzenoids which are under-represented in current drug libraries.[5]



In-depth mechanistic studies provide evidence for an unexpected reaction pathway and enable reliable *a priori* prediction of reaction outcome. This convenient, efficient, and general chemistry opens the door to previously unexplored chemical space.

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