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THURSDAY

EMERGING SYNTHETIC TECHNOLOGIES IN FRAGMENT-BASED DRUG DISCOVERY

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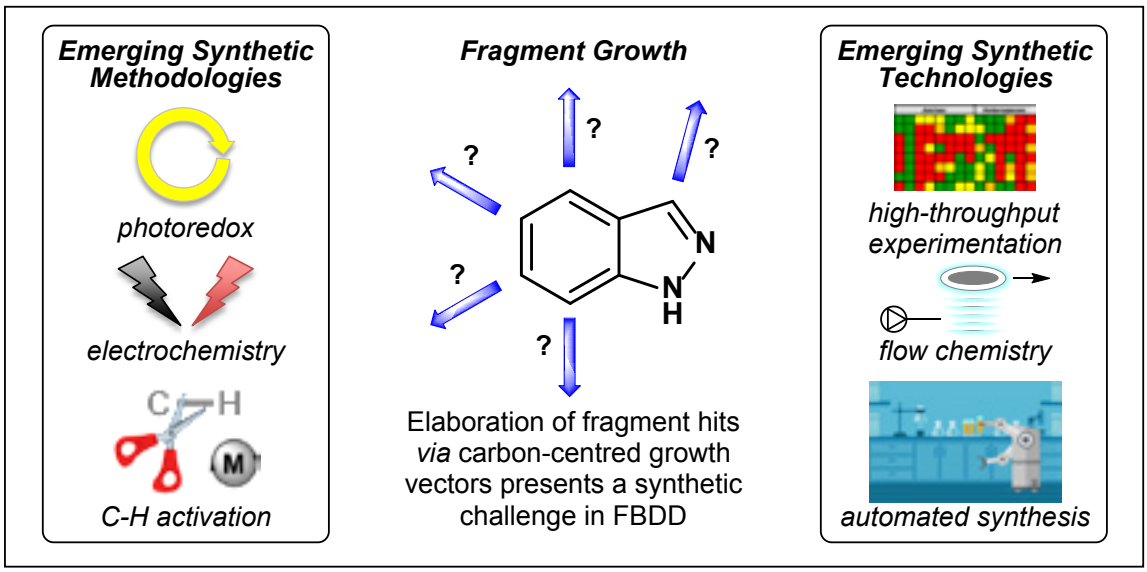
Fragment-based drug discovery (FBDD) requires robust synthetic methods to prepare and elaborate weakly binding small molecule hits (fragments), which typically have polar functionality to facilitate protein–fragment binding via hydrogen bonding. This polar functionality often presents synthetic challenges which slows down the drug discovery workflow, furthermore, some fragments are not progressed into optimisation due to synthetic intractability.[1-3]



Astex has addressed these challenges of fragment elaboration by establishing an in-house HTE workflow utilising emerging technologies and cutting-edge synthetic methodology.[4-6] This talk will show how these methods are used to expedite fragment-to-lead development at Astex.

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$H_2O{\cdot}B(C_6F_5)_3$-CATALYSED HYDROARYLATION OF ALKENES USING AROMATIC AMINES AND HETEROCYCLES

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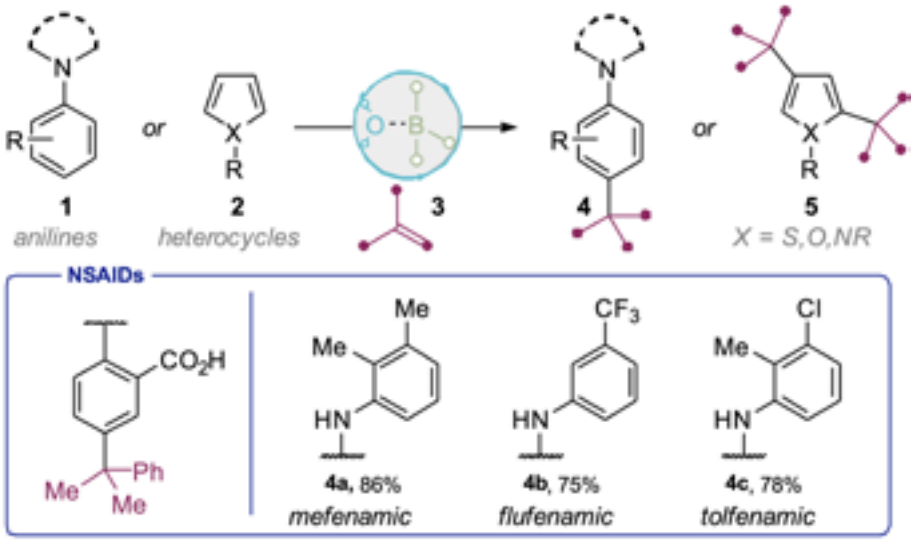
The aniline fragment is a building block for industrially relevant compounds including agricultural chemicals, dyes and pharmaceutical drugs.[1] Friedel-Crafts reactions are a classic example when considering the alkylation of aromatic compounds, although the coordination of basic substrates to the Lewis acid limits the use of anilines and its derivatives.[2]

Catalytic hydroarylation represents a direct and atom-economical approach to the derivatization of anilines with readily available alkenes. Although there have been various reports in the literature, hydroarylation of alkenes with anilines encounter challenges in the form of; *C*- (vs *N*) and *para*- (vs *ortho*) regiocontrol and limited substrate scope, in particular with the alkenes.[3]

Our approach[4] uses commercially available catalyst $H_2O{\cdot}B(C_6F_5)_3$, which can be handled in air and weighed on the open bench. $H_2O{\cdot}B(C_6F_5)_3$ has a pKa similar to HCl, but its unique weakly coordinating conjugate base has allowed us to develop a new catalytic hydroarylation process involving anilines. We have shown that the process tolerates primary, secondary and tertiary anilines and a diverse range of alkene partners, including styrenes, aliphatic alkenes, vinyl amides and allyl silanes. The reaction is completely p-selective and no N-alkylated by-products were observed. Functional groups such as halides, ether, nitro, amide, sulphide and carboxylic acids were well tolerated. We have also used $H_2O{\cdot}B(C_6F_5)_3$ to catalyse the hydroarylation of alkenes with heterocycles including thiophene, furan and pyrroles. We applied our methodology to the functionalisation of a family of non-steroidal anti-inflammatory drugs (NSAIDS).



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STEREOSELECTIVE SYNTHESIS AND CYCLISATION OF VINYL SILANES; MILD ACCESS TO AMBIPHILIC AZIRIDINE & OXETANE SCAFFOLDS

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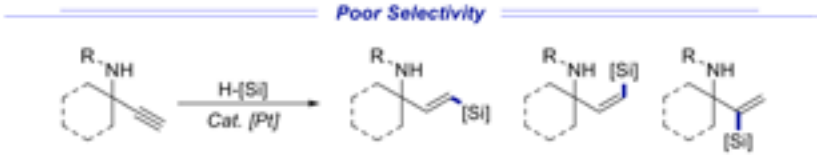
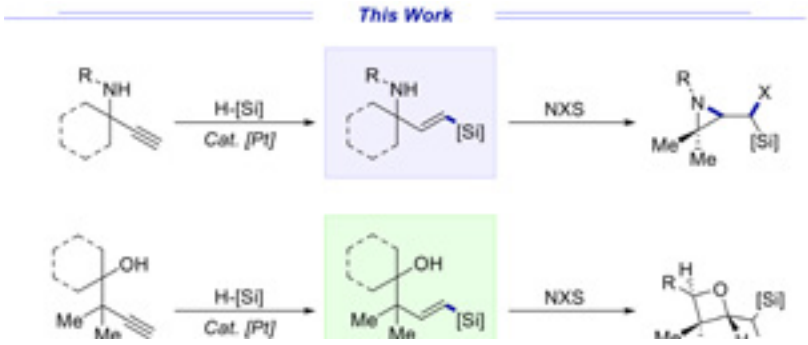
Modern organic chemistry relies heavily on the transition metal catalysed coupling of organometalloid reagents with electrophiles such as aryl halides. As such, development of methods which allow access to novel organometalloid compounds such as organosilanes remains of high importance to the synthetic chemistry community. Whilst hydrosilylation of unsaturated carbon-carbon bonds using transition metal catalysts has represented a highly successful method of accessing such compounds, introduction of co-ordinating functional groups into these substrates has proven to be difficult, with propargylic amines and their derivatives shown to act as highly effective inhibitors of traditional platinum hydrosilylation catalysts such as chloroplatinic acid and Karstedt's catalyst (Scheme 1.)



Scheme 1 Propargylic amines typically show poor stereoselectivity and regioselectivity in hydrosilylation reactions

We have shown that through careful catalyst design these inhibitory effects can be mitigated, with PtCl2(XantPhos) proving to be a highly effective catalyst for the regioselective and stereoselective hydrosilylation of propargylic amines, amides and sulfonamides.[1] The resultant vinyl silanes can be readily transformed into aziridines upon electrophilic activation, owing to the well-established β-Silicon effect[2] with the cationic intermediate being trapped by the tethered nitrogen nucleophile, affording the corresponding aziridines in excellent yields. The same hydrosilylation/cyclisation sequence can be applied in a similar manner to the synthesis of oxetanes from homopropargylic alcohols, with the reaction notably affording the oxetanes with extremely high levels of diastereoselectivity (Scheme 2).[3]



Scheme 2 Hydrosilylation/Cyclisation of propargylic amines and homopropargylic alcohols

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PRACTICAL HYDROGEN-FREE eHYDROGENATION VIA ELECTROSYNTHESIS

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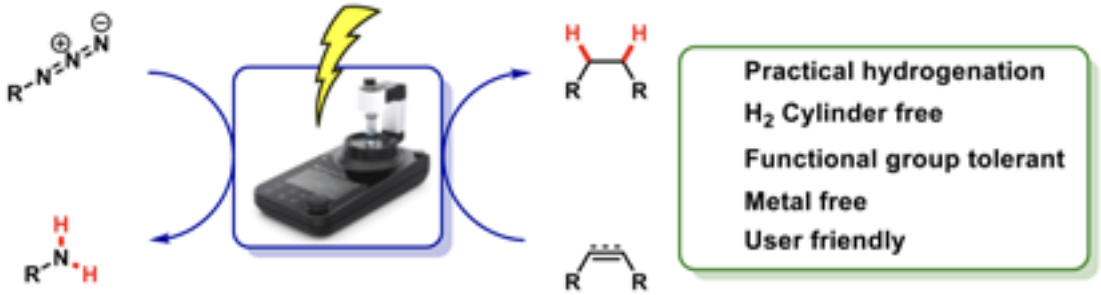
Hydrogenation is a cornerstone reaction in synthetic organic chemistry for the reduction of a vast array of unsaturated organic compounds,[1] however the necessity for specialist equipment to handle and store hydrogen and the need for a palladium catalyst limits its ease of use and sustainability. The use of compressed gasses can also pose significant logistical and safety concerns. Hydrogen-free methods for hydrogenation offer a practical alternative to traditional strategies by avoiding the need to handle gaseous hydrogen.[2,3] Electrochemistry has recently been undergoing a renaissance since the introduction of new more standardised and reproducible electrochemical equipment, such as the IKA Electrasyn 2.0.[4] As a tool in organic chemistry, electrosynthesis has proven to be of high utility in a diverse range of applications as a greener, safer, and inexpensive means of achieving both oxidative and reductive transformations. Through the electrolytic generation of diimide under ambient conditions, we have achieved the practical reduction of a wide range of unsaturated compounds, without the need for any metal catalysts or gaseous hydrogen. This user friendly approach to hydrogenation can be applied to a wide range of substrates bearing functional groups typically incompatible with common hydrogenation conditions and will be discussed.



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Csp³-H FUNCTIONALISATION OF HIGHER ALKYLAZOLES: STRATEGIES FOR HIGH PRODUCTIVITY AND EXPLOITING UNSTABLE INTERMEDIATES

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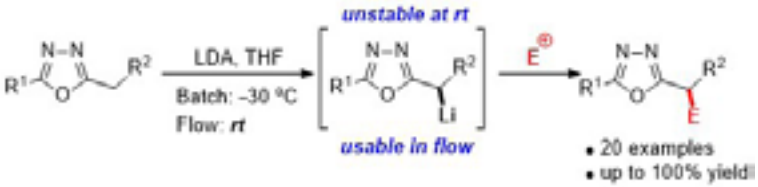
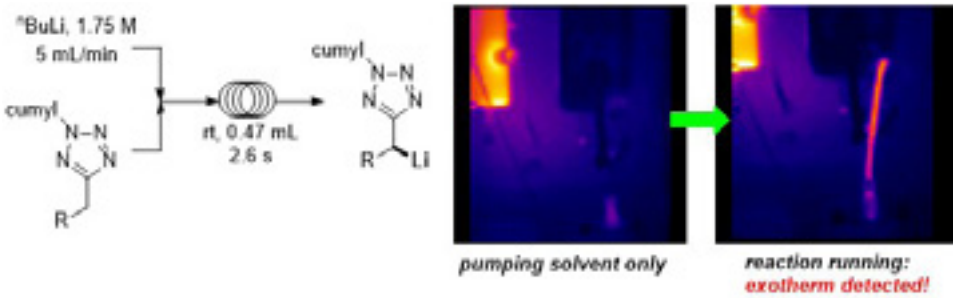
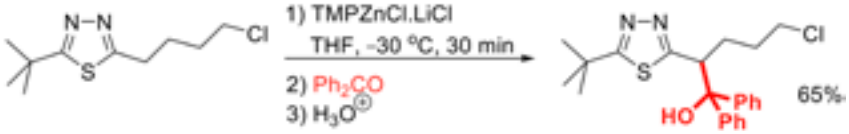


Higher azoles play a key role in medicinal chemistry, typically acting as bioisosteres for amides and carboxylates.[1,2] While many biologically active carboxylates and amides are derived from amino acids and bear adjacent stereocentres, higher azole analogues are underreported due to difficulty of synthesis using currently available methods. Commonly thought of as comparatively delicate motifs, late-stage functionalisations of higher azoles are also rare.



Using a metalation-substitution strategy, we have developed late-stage C-H functionalisations of alkyl-oxadiazoles and -tetrazoles.[3,4,5] The use of continuous flow technology enabled the interception of an unstable lithio-oxadiazole, allowing access to products in high yield which could not be obtained under analogous batch conditions. While the short reactor residence times necessary for unstable intermediate flow chemistry limit the possibilities for in-line reaction monitoring, we have pioneered the use of thermal imaging to identify exotherms which increase intermediate decomposition or pose a safety problem – this has allowed us to access productivity rates comparable to the early stages of API synthesis scale-up using entry-level academic laboratory equipment.

An alternative strategy for achieving C-H functionalisation without unwanted side reactions is to exploit the greater functional group tolerance of organozincs. We have developed the first example of non-enolic C-H zincation at an sp³ centre, enabling heterobenzylic derivatisation of alkylthiadiazoles bearing functional group incompatible with organo-lithium or -magnesium chemistry.



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STEREOSELECTIVE TWO-CARBON RING EXPANSION OF ALLYLIC AMINES VIA ELECTRONIC CONTROL OF PALLADIUM-PROMOTED EQUILIBRIA

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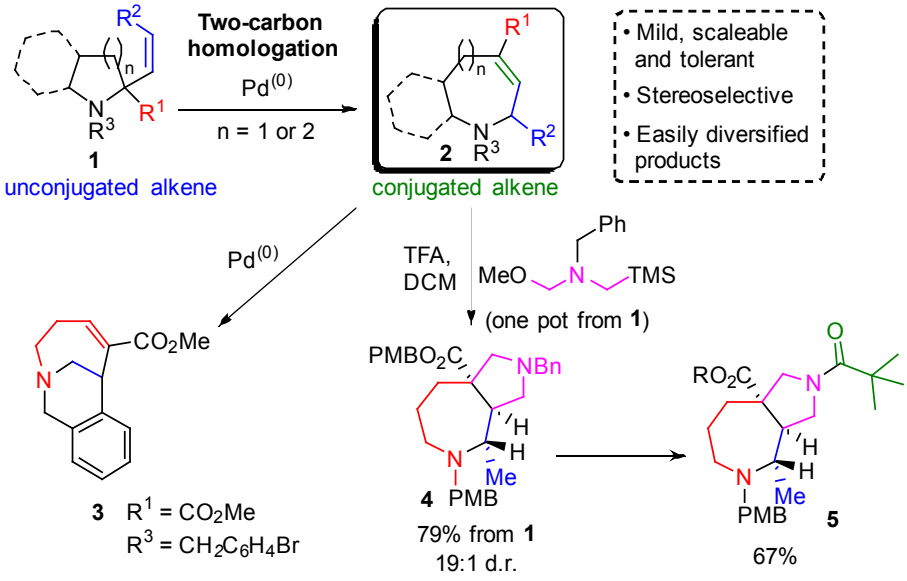
Nitrogen-containing heterocycles represent a key class of bioactive molecule, featuring widely both in natural products and drug discovery.[1] The development of novel methodologies which provide access to such compounds is therefore a key goal for synthetic chemists, especially where such approaches provide stereoselective access to novel ring systems and chemical space. Herein we report[2] that the palladium-catalysed ring expansion of allylic amines enables the two-carbon ring expansion of 5- and 6-membered compounds **1** into their azepane and azocane homologues **2**. Conditions are mild and tolerant of a range of functional groups, and the process can proceed with a high degree of enantio-retention. The products are ideally functionalised to undergo a range of chemo- and stereo-selective processes, thereby providing rapid access to a range of modifiable polycyclic scaffolds as exemplified by amines **3**, **4** and **5**.



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SYNTHESIS AND APPLICATIONS OF PYRROLYL SULFONIUM SALTS

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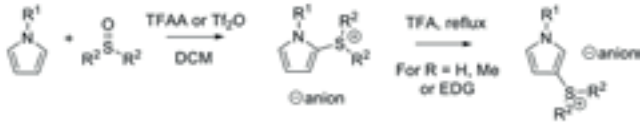
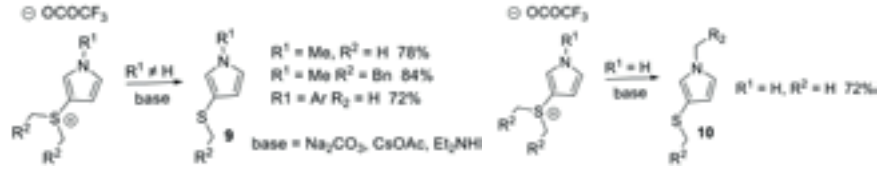
Sulfonium salts are important sulfur (IV) motifs due to their analogous reactivity with organohalides, and tendency to form uncharged sulfides[1,2]. Pyrrolyl sulfonium salts are of great interest due to the ubiquity of pyrrole in pharmaceuticals and natural products, as well as pyrrole halides being unstable and difficult to purify[3,4]. This study details the synthesis of sulfonium salts that are bench-top stable and synthesized efficiently without column chromatography. Electron rich pyrrole salts are unique in their ability for to undergo a [1,5]-sigmatropic shift of the sulfonium group in the presence of acid[5]. For electron poor pyrrolyl sulfonium salts, this rearrangement is disfavoured, and so both 2 and 3 position salts can be obtained depending on the nitrogen protecting group used. The salts can then be employed in a range of reactions, to give 2 and 3 position functionalized pyrroles.



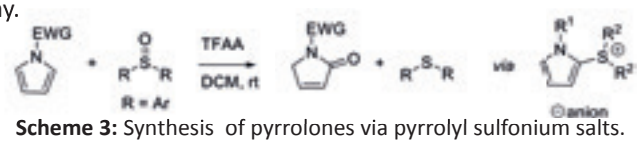
Scheme 1: Pyrrolyl salt synthesis from sulfoxide and anhydride activator

Pyrrole sulfides can be synthesized, in one pot reaction from pyrrole by the addition of base to the salt formation reaction.



Scheme 2: Pyrrolyl sulfide synthesis from alkyl sulfoniums

Pyrrolones can be synthesised in an S_NAr type mechanism via pyrrolyl sulfonium salts, these are highly valuable synthetic precursors, and found in a range of drug molecules[6]. This method is a convenient one pot reaction from commercially available starting materials, and the products can be purified without column chromatography.



Scheme 3: Synthesis of pyrrolones via pyrrolyl sulfonium salts.

The salts can also be employed in Suzuki-Miyaura cross couplings, and due to their crystalline and stable nature, the salts are a desirable alternative for industrial use.

Scheme 4: Applications of pyrrolyl salts in Suzuki-Miyaura cross-couplings

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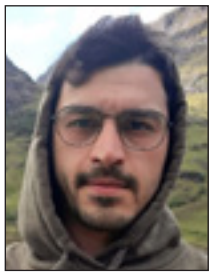
TRANSITION METAL-FREE ARYNE-ENABLED ARYLATION OF ANILINES



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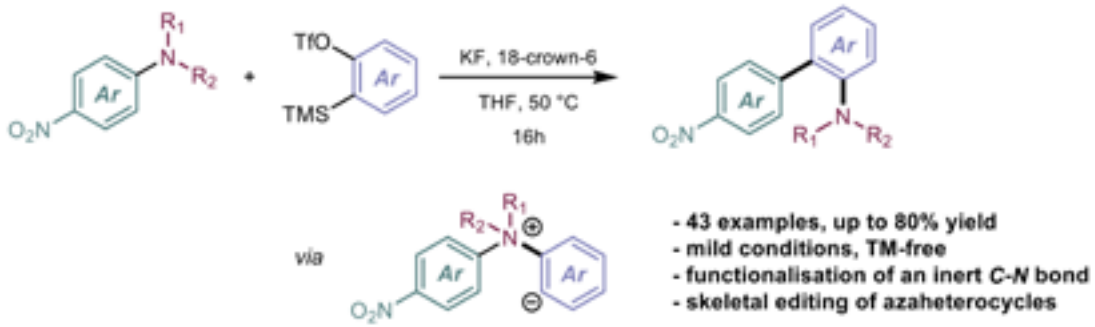
Anilines have played a key role in kickstarting the British chemicals industry and are widely used as feedstocks, with applications ranging from commodity chemicals to pharmaceuticals and agrochemicals.[1] Despite their prevalence, the amino group itself is rarely considered as a functional handle due to the high bond dissociation energy (BDE) of the *C-N* bond.[2] Accordingly, current strategies of *C-N* arylation of anilines necessitate either tedious installation of directing groups or pre-activation of the *C-N* bond, eventually coalescing into transition metal (TM) catalysis. These strategies are characterised by harsh conditions, multi-step processes, and limited substrate scope,[3] revealing mild and functional group-tolerant C-N arylation as a key challenge. To address this challenge, we have developed a TM-free arylation of easily accessible tertiary anilines enabled by the bifunctional character of arynes. Our proposal proceeds via nucleophilic attack of anilines to *in situ* formed arynes, leading to a zwitterionic quaternary ammonium species that subsequently undergoes a Truce-Smiles rearrangement to furnish synthetically valuable and densely substituted biaryls. The transformation proceeds under mild conditions and in the absence of any precious metals, forging two $C(sp)_2$-$C(sp)_2$ bonds at the expense of an inert $C(sp_2)$-*N* bond, thus unmasking the amino group as a functional handle. This approach can be applied to a variety of different anilines, including complex drug scaffolds, and is tolerant of a variety of functional groups such as esters, acetals, nitriles, olefins, and halides, illustrating its orthogonality with TM-catalysed cross couplings. Additionally, various aryne precursors can be used with remarkable regioselectivity, affording otherwise inaccessible atropisomeric biaryls. Skeletal editing on indoline and tetrahydroisoquinoline scaffolds is also achieved under the same protocol, providing access to medium size azaheterocycles via a formal *n+2* carbon insertion. We hope that our approach will stimulate the development of further ways for the functionalisation of what is considered to be an inert bond.



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A NEW GAS-PHASE SYNTHESIS OF CHIRAL β-LACTAMS

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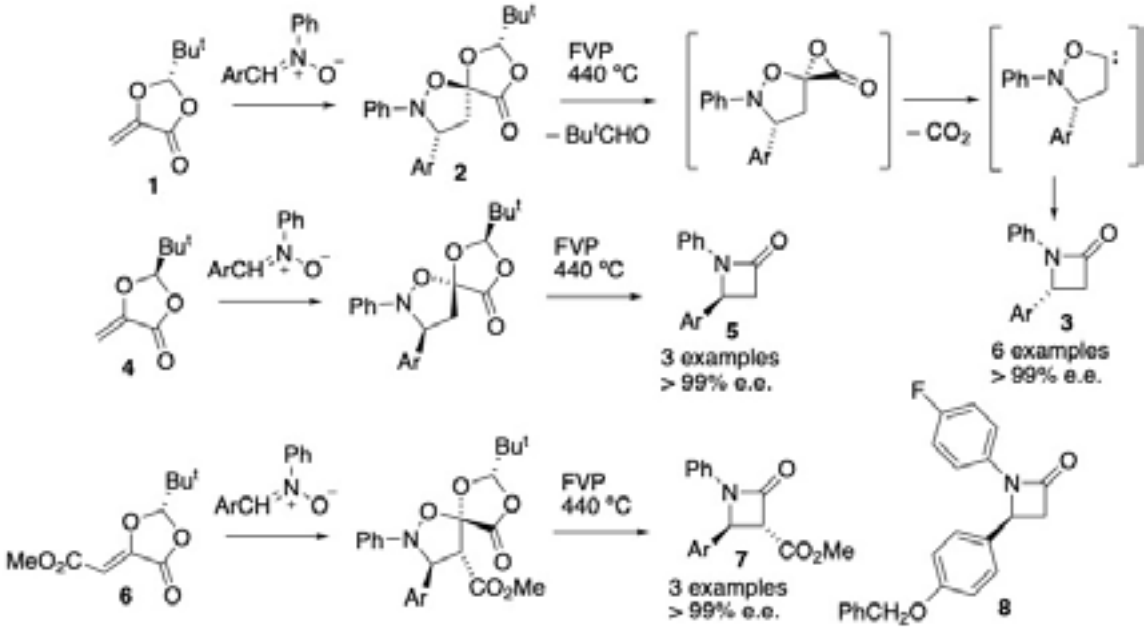
Although the chiral methylenedioxolanone **1**, readily available in 3 steps from (*S*)-lactic acid, has been used in a few Diels Alder reactions, its behaviour towards 1,3-dipolar cycloaddition remains unexplored. We have now found that it undergoes cycloaddition with nitrones to give readily separable diastereomeric adducts. When the major products **2** are subjected to flash vacuum pyrolysis at 440 °C, there is sequential extrusion of pivalaldehyde and CO_2, via the spiro α-lactone and oxacarbene intermediates shown, to give β-lactams **3**. By starting from the enantiomeric methylenedioxolanone **4** derived from (*R*)-lactic acid1 products **5** of the opposite enantiomeric series are readily obtained.



The ester-functionalised methylenedioxolanone **6** is readily available from (*S*)-malic acid and this allows formation of β-lactams **7** with an extra stereogenic centre. Although the key pyrolytic step proceeds in modest yield to give products in 15-30% isolated yield after chromatographic purification, they are obtained in essentially enantiomerically pure form.

The utility of the process, as well as the ability to vary the *N*-substituent, is illustrated by formation of β-lactam **8** (and its enantiomer) by FVP of the appropriate nitrone adducts of **4** (and **1**) in 36% isolated yield. Compound **8** is a known precursor[2] of Ezetimibe, thus constituting a formal total synthesis of this important cholesterol-lowering agent.

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