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EMERGING AREA

Olefin Cross-Metathesis for the Synthesis of Heteroaromatic Compounds

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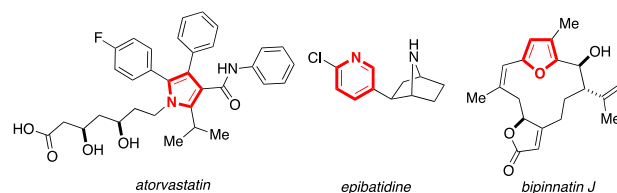
The olefin metathesis reaction has underpinned spectacular achievements in organic synthesis in recent years. Arguably, metathesis has now become the immediate choice for a carbon-carbon double bond connection. *De novo* routes to heteroaromatic compounds using the cross metathesis (CM) reaction have only recently emerged as an efficient strategy. This allows a convergent union of simple, but functionalised, three- to four-carbon olefinic core building blocks, to generate furans, pyrroles and pyridines with a high degree of control over the substitution patterns in the product.

Introduction

Heteroaromatic compounds play a pivotal role in drug discovery. Consequently, the ability to synthesise these motifs in a concise, efficient and regiocontrolled manner is of importance to medicinal chemistry and ultimately to the health and wellbeing of society (Figure 1a).¹ Synthetic approaches to substituted heteroaromatic compounds rely upon either the modification of a

pre-existing aromatic core² (Figure 1b) or the implementation of *de novo* synthetic technologies (Figure 1c).³ Although these approaches are often employed in isolation, in the case of *de novo* syntheses, subsequent modification of the aromatic product is still possible. As such, a natural synergy emerges between the development of *de novo* methodologies and recent advances in metal catalysed cross-coupling. A major challenge in identifying strategies for *de novo* heteroaryl construction lies in providing efficient and predictable methods for regiodefined C-C bond formation. The ideal method should be operationally simple, rely upon minimal substrate prefunctionalisation and generate minimal quantities of waste.

(a) Existing medicines and biologically active natural products with heteroaromatic cores



(b) Examples of modifications of existing heteroaromatic cores

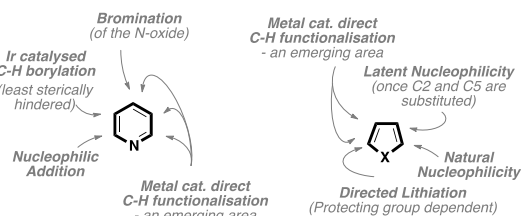
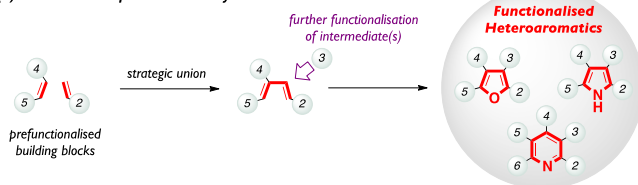
(c) General concept of *de novo* synthesis

Figure 1. Heteroaromatics in chemistry.

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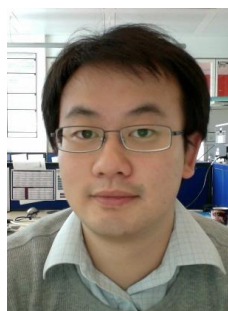
Timothy J. Donohoe was an undergraduate in Chemistry at the University of Bath and then obtained his D.Phil. with S. G. Davies at the University of Oxford (1992). Following a post-doctoral stay with P. D. Magnus in the USA, he joined the University of Manchester in 1994 as a lecturer and was promoted to Reader in 2000. In 2001, he joined the Dyson Perrins Laboratory, Oxford, as Lecturer in Chemistry and Fellow of Magdalen College. In 2004, he was appointed Professor of Chemistry at Oxford University. His research interests encompass asymmetric synthesis, the synthesis of aromatic compounds, total synthesis, catalysis and redox reactions.





John F. Bower obtained his M.Sci. degree in Chemistry in 2003 from the University of Bristol. He then remained at Bristol to study for his Ph.D. degree (2007) under the guidance of Professor Timothy C. Gallagher. His first postdoctoral appointment (2007-2008) was with Professor Michael Krische at the University of Texas at Austin. He then undertook a second postdoctoral

appointment with Professor Timothy J. Donohoe at the University of Oxford, where he focussed on the use of olefin cross metathesis for heteroaryl synthesis. In 2010, he was awarded a Royal Society University Research Fellowship and commenced his independent career at the University of Bristol.



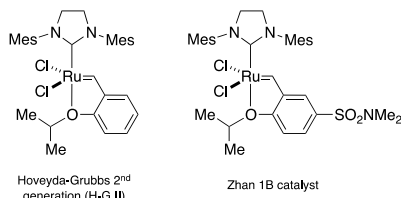
Louis K. M. Chan obtained his M.Sci. degree in Chemistry with a year in North America in 2006 from the University of Bristol, having carried out research with Professor James. P. Morken at the University of North Carolina at Chapel Hill, as well as with Professor Varinder K. Aggarwal at Bristol. He also obtained his Ph.D. degree (2010) under the supervision of Dr. Matthew J. Gaunt at the University

of Cambridge. He is currently carrying out post-doctoral research work in the laboratory of Professor Timothy J. Donohoe at Oxford, in the area of olefin metathesis for heteroaryl synthesis.

Ring Closing Metathesis Based Strategies

The olefin metathesis reaction is seemingly ideal as a key catalytic step for the construction of heteroaromatics, as it holds the criteria as a simple, yet powerful C-C double bond forming reaction. Commercially available and operationally robust catalysts such as Hoveyda-Grubbs 2nd generation⁴ and Zhan 1B⁵ catalysts (Figure 2a) allow the union of two different olefins to provide a single more complex olefinic product.

(a) Commercially available and robust metathesis catalysts relevant to these studies.



(b) A ring closing metathesis strategy for the synthesis of heteroaromatic compounds

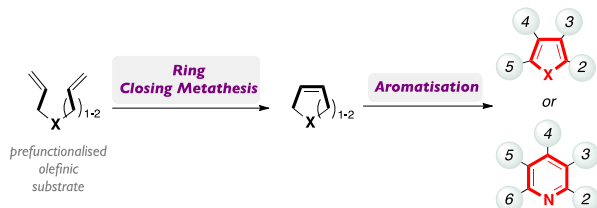
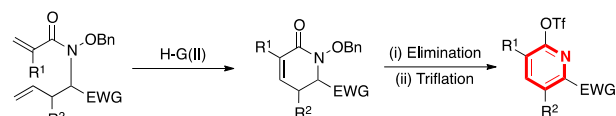


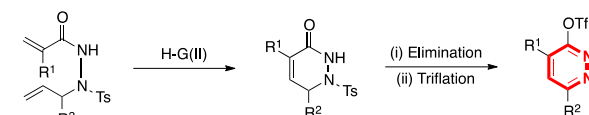
Figure 2. Ring closing metathesis for heteroaromatic synthesis.

Importantly, and of particular value to aryl synthesis, this method necessitates the provision of a product which possesses the unsaturation required for the eventual aryl target (Figure 2b). Despite this potential, heteroaryl methodologies that are reliant upon olefin metathesis have been slow to emerge. Although early, isolated examples of metathesis based heteroaryl syntheses were reported,^{3h,3i,6,} systematic studies into the employment of this reaction for heteroaryl construction have only been undertaken more recently. Studies from our laboratory have focused upon developing intramolecular olefin metathesis (termed Ring Closing Metathesis or RCM) based strategies

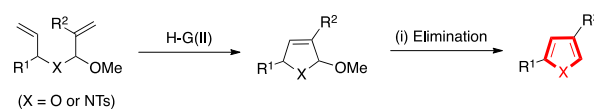
(a) Pyridines via RCM:



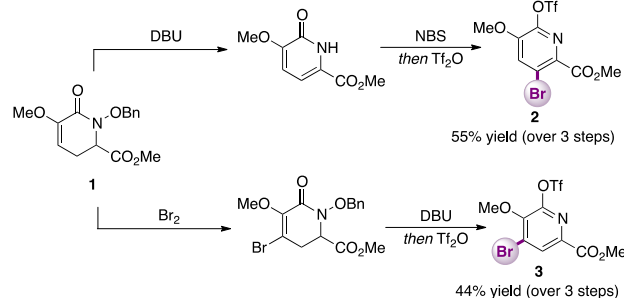
(b) Pyridazines via RCM:



(c) Furans and Pyrroles via RCM:



(d) Modification of metathesis products:



Scheme 1. Ring closing metathesis approaches to heteroaromatic compounds.

wherein the metathesis precursor embodies the oxidation level required for the eventual aromatic target. Accordingly, efficient protocols for the synthesis of pyridines, pyridazines, pyrroles and furans have been developed in our⁷ (Scheme 1a-c) and other⁸ laboratories.

In all of these cases, the key RCM event precedes aromatisation via elimination of a suitable leaving group under either acidic or basic conditions. This chemistry has evident

synthetic value as demonstrated by its application as a key step in the highly efficient synthesis of the furan cembranolide natural product (–)-deoxypukalide.⁹ A pertinent feature of these strategies is that further manipulation of the metathesis product, either prior to or after aromatisation, enables access to higher heteroaryl substitution patterns. This is most aptly demonstrated by considering RCM product **1** which can be brominated either prior to or after elimination of the OBn group to provide either pyridine **2** or **3** in a regiodivergent manner (Scheme 1d).

An Improved Approach Using Cross Metathesis

In principal, the use of selective intermolecular olefin metathesis (termed Cross Metathesis or CM) represents an even more powerful approach to heteroaryl construction. Here, there is no requirement for the design and preparation of a tethered metathesis precursor (Figure 3). Additionally, the key metathesis event is used both for the provision of the desired olefin and for the key fragment coupling step. As such, a scenario emerges wherein CM is used to selectively couple two relatively simple olefinic starting materials with the goal of providing a single, more highly functionalised olefinic product which is then suitable for conversion to the target heteroaromatic.

General CM approach to heteroaromatic compounds:

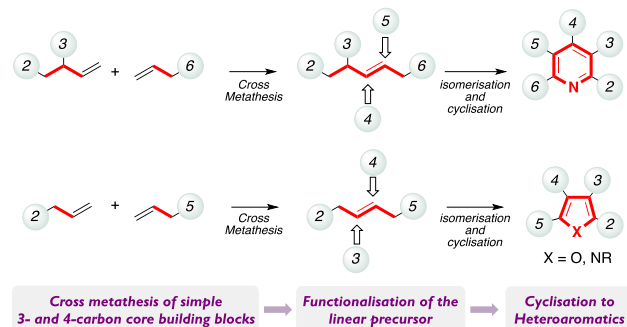


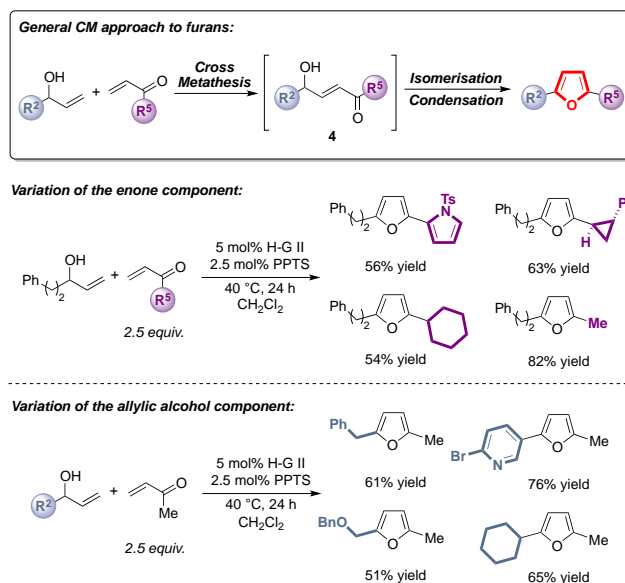
Figure 3. CM as an enabling approach to heteroaryl synthesis.

In order to implement CM for heteroaryl synthesis, two key points require addressing. The first involves identifying olefinic cross-coupling partners which can undergo selective cross-metathesis. As the use of CM in synthesis has gained pace, the amount of empirical information available has reached levels where likely CM partners are readily identified. The likelihood of a successful CM can be predicted by considering which class an olefin belongs to as outlined in a key publication by Grubbs.¹⁰ The second point relates to identifying profitable strategies for the conversion of a *trans*-olefin (metathesis product) to a *cis*-olefin as required for the eventual aromatic target (*vide infra*).

Cross-Metathesis Based Approaches to Furans

Our early studies involved developing effective CM-based entries to substituted furans.¹¹ Allylic alcohols have emerged as a special olefin class for metathesis, perhaps due to hydrogen

bonding between the -OH and the chloride ligands associated with the ruthenium-based catalyst systems.¹² Accordingly, these species readily undergo CM with enones to provide γ -hydroxyenone intermediates **4** which are predisposed to cycloaromatise under acidic conditions. Using this chemistry as a basis, we developed a tandem protocol, that employs catalytic quantities of ruthenium and acid (PPTS) catalysts, to allow the direct conversion of an allylic alcohol-enone pair to a furan (Scheme 2). This protocol is amenable to the employment of a diverse range of allylic alcohol or enone partners and delivers complex 2,5-disubstituted furans in moderate to excellent yield. In the examples shown in Scheme 2, olefin isomerisation is promoted by an acid co-catalyst (PPTS).

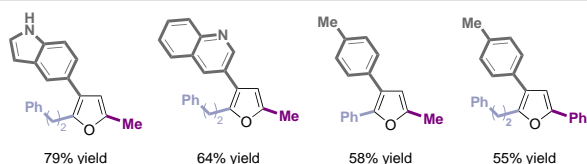
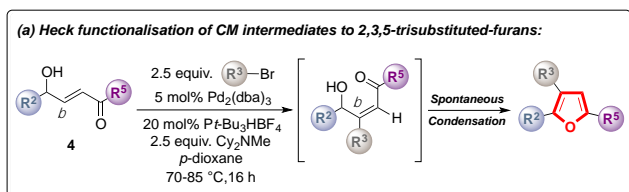


Scheme 2. CM approach to 2,5-disubstituted furans.

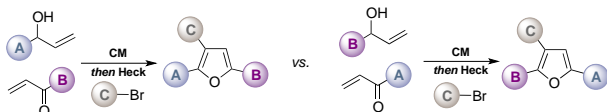
A more profitable strategy involves promoting isomerisation by using a protocol which facilitates concomitant introduction of further functionality. In this context, we have shown that Heck reaction of δ -hydroxyenone intermediates **4** serves to introduce an aryl group onto the enone β -position and simultaneously effects olefin isomerisation to directly afford trisubstituted furans. Isomerisation of the enone from *trans* to *cis* under Heck conditions is a result of the mechanistic requirements of the process (*syn*-carbopalladation followed by *syn*- β -hydride elimination), making the CM/Heck combination an ideal one for our purpose.¹³ The opportunity to further functionalise the δ -hydroxyenone metathesis products is of particular importance as CM between 1,1-disubstituted allylic alcohol or enone partners is not efficient and so direct metathetic entries to trisubstituted furans are currently precluded. Using this CM-Heck tandem protocol, a variety of trisubstituted furans are available in short order and with complete levels of regiocontrol (Scheme 3a). A powerful feature of this chemistry resides in the ability to dictate the final furan substitution pattern by programming the oxidation level of the allylic alcohol and enone CM precursors. Inversion of the oxidation level of this pair ultimately provides the alternative furan regioisomer (Scheme 3b).

Both of these approaches towards furans can be used to

synthesise more complex polycyclic systems by rendering the processes intramolecular. Accordingly, tandem CM-cycloaromatisation of tethered allylic alcohol-enone **5**, under high dilution conditions, afforded macrocyclic furan **6**, which is structurally related to the core of the furanembranolide family of



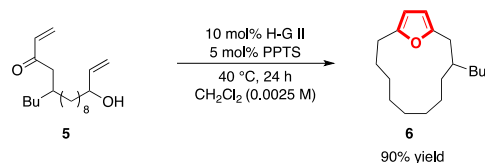
(b) Starting material oxidation level programmes regioselectivity:



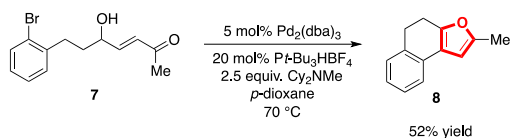
Scheme 3. CM-Heck approach to trisubstituted furans.

natural products,⁹ in excellent yield (Scheme 4a). This tandem macrocyclisation-aromatisation process unites the established utility of RCM for macrocycle synthesis with the heteroaryl methodology presented herein. Similarly, intramolecular Heck arylation of **7** affords furan **8** and potentially provides a blueprint for the construction of other complex, fused polycyclic ring systems (Scheme 4b).

(a) Intramolecular "CM"-furan formation:



(b) Intramolecular Heck-furan formation:



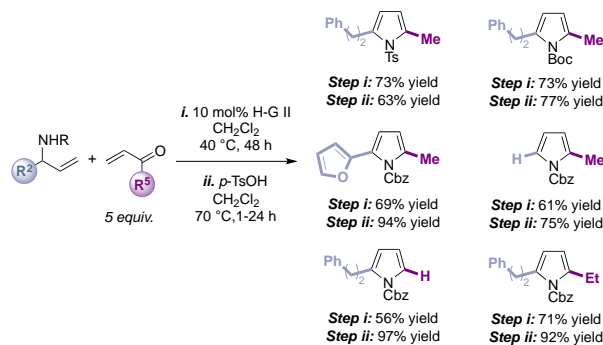
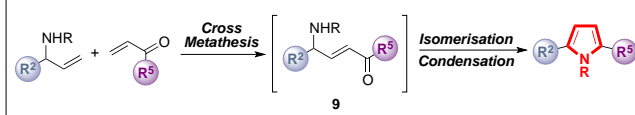
Scheme 4. Intramolecular "CM" or Heck reactions allow the formation of extra rings.

Cross-Metathesis Based Approaches to Pyrroles

Extension of the chemistry discussed so far to the synthesis of pyrroles represents a natural progression. Here, we anticipated that CM between suitably protected allylic amine and enone

components would provide efficient access to γ -amino enones **9** which can then potentially be converted to pyrroles either upon treatment with acid or with a discrete Heck arylation step.¹⁴ An added complication of this scenario lies in the requirement to protect the allylic amine component, which serves to prevent metathesis catalyst deactivation and also improves the synthetic accessibility and the utility of the final pyrrole. We observed that the CM of homoallylic amine derivatives with enones is more demanding than that involving the corresponding allylic alcohols. Nevertheless, a variety of amino components underwent efficient CM with a range of enones to provide γ -amino enone intermediates **9** (Scheme 5). These were then converted to the final pyrrole upon exposure to *p*-TsOH at 70 °C.

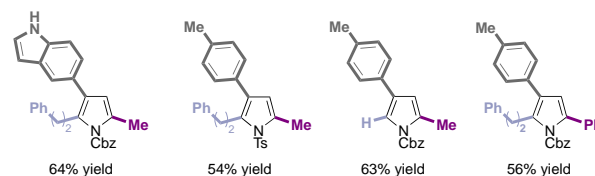
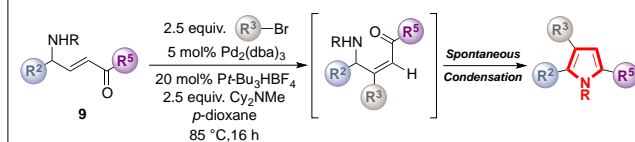
General CM approach to pyrroles:



Scheme 5. CM approach to mono- and di-substituted pyrroles.

The more demanding nature of the CM process in these cases is evidenced by the requirement for (i) longer reaction times, (ii) higher catalyst loadings and (iii) our inability to develop an efficient one pot CM-cycloaromatisation protocol. This latter point also eludes to the greater difficulty of cycloaromatisation of γ -aminoenones **9** compared to γ -hydroxyenones **4**; in the examples presented in Scheme 5 a stronger acid (*p*-TsOH vs. PPTS) and higher reaction temperatures (70 °C vs. 40 °C) are required.

Heck functionalisation of CM intermediates to 2,3,5-trisubstituted-pyrroles:



Scheme 6. CM-Heck approach to tri-substituted pyrroles.

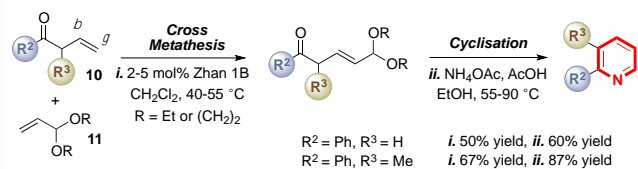
Extension to the corresponding trisubstituted pyrroles using a

tandem Heck-aromatisation process is also possible. Accordingly, diverse and highly complex trisubstituted pyrroles are available in short order and with complete levels of regiocontrol (Scheme 6). Note that this process also is tolerant of a range of protecting groups at nitrogen (e.g. Cbz, Boc, Ts). Grela and co-workers have further demonstrated a one-pot synthesis of substituted pyrroles using CM.¹⁵ This was made possible with the use of B(OPh)₃ as Lewis Acid for promoting isomerisation of the olefin geometry, as well as the subsequent cyclisation.

10 Cross-Metathesis Based Approaches to Pyridines

As previously discussed, a powerful aspect of CM-based *de novo* heteroaryl synthesis is the ability to control the final substitution patterns during fabrication of the olefin precursors. In the case of pyridines, appropriate choice of the starting CM partners, reaction conditions and reaction sequence allows the selective synthesis of mono-, di-, 2,3,6-tri-, 2,4,6-tri-, and 2,3,5,6-tetra-substituted pyridines.¹⁶

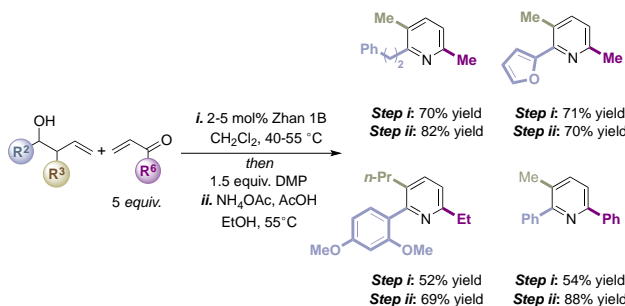
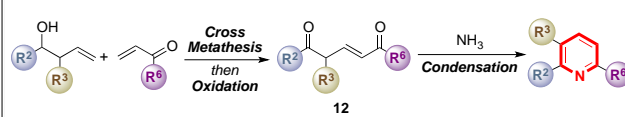
CM approach to mono- and di-substituted pyridines:



Scheme 7. CM approach to mono- and di-substituted pyridines.

The preparation of mono- and di-substituted pyridines, without substitution at C6, is readily achieved. In these cases, CM between β,γ-unsaturated ketones **10** and acetal protected acrolein derivatives **11** was most efficient (Scheme 7). Conversion directly to the pyridine then occurs upon treatment with ammonia under mildly acidic conditions (which also effects acetal hydrolysis). Protection of the acrolein partner is important to circumvent stability issues associated with aldehydic unsaturated 1,5-dicarbonyls.

CM approach to 2,3,6-trisubstituted pyridines:

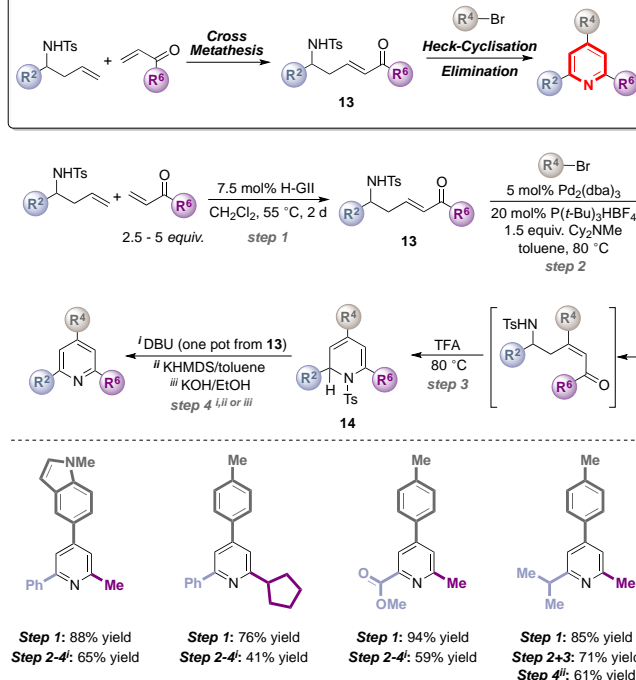


Scheme 8. CM approach to 2,3,6-trisubstituted pyridines.

Unsaturated 1,5-diketones are already established as efficient precursors to pyridines but have been underutilised for this purpose. We have shown that cross metathesis between homoallylic alcohols and vinylketones follow by DMP oxidation is possible (Scheme 8). The trisubstituted unsaturated 1,5-dicarbonyls **12** which were then converted to the final 2,3,6-trisubstituted pyridines targets by exposure to ammonia. Note that during condensation, isomerisation of the double bond established during the CM event is facilitated by the acidity of the dicarbonyl intermediates.

Investigation into other pyridine formation led to a route for the regiodefined synthesis of 2,4,6-trisubstituted pyridines. CM between a homoallylic sulfonamide and a vinylketone partner provided access to δ-amino enone intermediates **13** (Scheme 9). Upon Heck arylation, olefin geometry switching occurs and this facilitates *in situ* acid promoted condensation to **14**. Subsequent base induced aromatisation (by elimination of the sulfinate group) then provides the target pyridines.¹⁷ This latter process is substrate dependant and the final elimination is either conducted *in situ* (with DBU) or in a separate step (with KHMDS or KOH/EtOH).

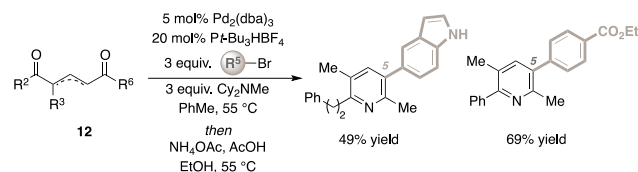
CM approach to 2,4,6-trisubstituted pyridines:



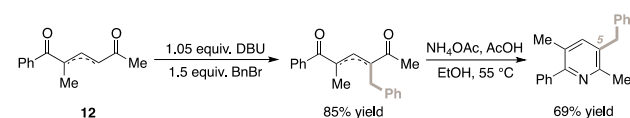
Scheme 9. CM-Heck approach to 2,4,6-trisubstituted pyridines.

Finally, access to higher pyridine substitution patterns is achievable *via* modification of the key 1,5-dicarbonyl intermediates described earlier. Accordingly, tetrasubstituted pyridines are available *via* Pd-catalysed α-arylation (Scheme 10a) or base promoted α-alkylation (Scheme 10b) of the key 1,5-dicarbonyl **12**. In both cases, complete levels of regiocontrol are observed and complex pyridine derivatives are available in a very short and modular manner.

(a) Pd-catalysed α -arylation:



(b) Base promoted α -alkylation:

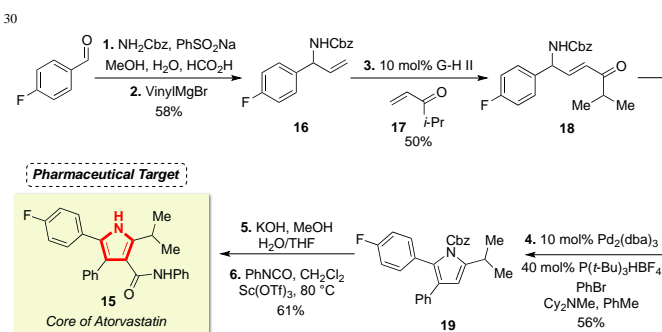


Scheme 10. Higher substituted pyridines *via* modification of the unsaturated 1,5-dicarbonyl intermediates.

5 Applications in Synthesis

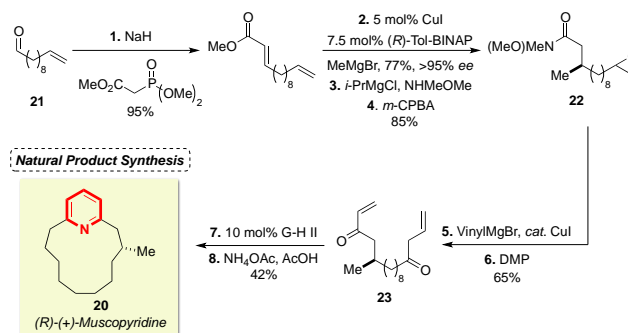
The validation of new methodologies in target directed settings is essential in demonstrating the true value and flexibility of the process. We have chosen to exemplify these new CM-based heteroaromatic methodologies by applying them to two distinct targets, one medicinal and one natural product.

The first target is the core of the world's largest selling drug Atorvastatin **15** (or Lipitor) (Scheme 11).¹⁸ The key aromatic portion of this molecule possesses a fully substituted pyrrole core and provides the ideal test rig for CM-based pyrrole forming methodologies. Accordingly CM of allylic amine derivative **16**, which is available in two steps, with enone **17**, afforded aminoenone **18**. γ -Arylated enones of this type have proven to be challenging substrates for Heck-aromatisation. Nevertheless, after optimisation trisubstituted pyrrole **19** was procured in 56% yield. Cbz deprotection then enabled further functionalisation of the remaining pyrrole C-H by Friedel-Crafts acylation with phenyl isocyanate. Thus, the fully functionalised pyrrole core of Atorvastatin **15** is available with complete regiocontrol and in 6 steps from commercial materials. While this approach is, of course, not comparable to commercial routes to **15**, one should recognize that highly flexible, modular and predictable entries to diverse pyrroles, and indeed many heteroaromatics, are likely to be of high utility in medicinal chemistry.



Scheme 11. CM-Heck approach to the pyrrole core of Atorvastatin.

The second target we have studied is the macrocycle (*R*)-(+)-muscopyridine which possesses an pyridine core embedded in a 13-membered macrocycle (Scheme 12). Here, we have employed an intramolecular variant of our CM-condensation pyridine methodology which facilitates the concomitant formation of the key macrocycle and pyridine portions. Given the utility of olefin metathesis for macrocycle formation it is unsurprising that this reaction has been employed previously for syntheses of **20**. However, in all previous approaches¹⁹ the element of unsaturation established during RCM (i.e. the olefin) was later reduced and not incorporated into the more natural site of the pyridine. Commercially available undecenal **21** was subjected to Wadsworth-Emmons olefination and then asymmetric copper catalysed conjugate addition of MeMgBr ,²⁰ which gave excellent levels of enantioenrichment ($>95\%$ e.e.), before advancing to the key metathesis precursor **23**. Metathetic macrocyclisation under high dilution conditions and treatment of the crude product with ammonia then afforded directly (*R*)-(+)-muscopyridine **20** in 42% yield. The overall route to **20** comprises 8 steps and proceeds in 17% overall yield.



Scheme 12. Intramolecular “CM”-condensation approach to (*R*)-muscopyridine.

Conclusions and Outlook

Heteroaromatic compounds continue to provide a major synthetic challenge to the organic chemist and this has inspired a variety of creative methods for their regiocontrolled preparation. Stimulated by the synthetic power of the olefin cross-metathesis reaction, we have delineated versatile strategies for the synthesis of a range of heteroaromatics, namely furans, pyrroles and pyridines. In all of these cases, the CM reaction provides the key by allowing the rapid and regiocontrolled union of simple precursors to provide a single more complex product. This CM product may then be advanced directly to the aromatic target or further modified to provide access to more highly substituted derivatives. It is clear that as the power of the CM reaction increases then so will the number of potential CM-based avenues to heteroaromatic derivatives. Studies towards this broad goal will be a focus of continuing efforts within our laboratory.

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