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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 foremost choice for a carbon–carbon double bond disconnection. Despite this general utility, *de novo* routes to heteroaromatic compounds using the cross-metathesis (CM) reaction have only recently emerged as an efficient strategy. This approach allows a convergent union of simple, functionalised, three- to four-carbon olefinic core building blocks, to generate furans, pyrroles and pyridines with a high degree of control of substitution pattern 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 (Fig. 1a).[1] Synthetic approaches to substituted heteroaromatic compounds rely upon either the modification of a pre-existing aromatic core[2] (Fig. 1b) or the implementation of *de novo* synthetic technologies (Fig. 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 little substrate prefunctionalisation and generate minimal quantities of waste.

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Timothy J. Donohoe was an undergraduate in Chemistry at the University of Bath and then obtained his D.Phil. with Professor S. G. Davies at the University of Oxford (1992). Following a post-doctoral stay with Professor 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 a Lecturer in Chemistry and a 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

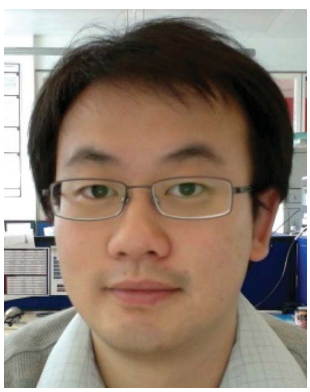
John F. Bower obtained his M.Sci. degree in Chemistry in 2003 from the University of Bristol. He then remained at Bristol to study for his Ph.D. degree (2007) under the guidance of Professor Timothy C. Gallagher. His first post-doctoral appointment (2007–2008) was with Professor Michael Krische at the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

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 generation[4] and Zhan 1B[5] catalysts (Fig. 2a) allow the union of two different olefins to provide a single more complex olefinic product.

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 (Fig. 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 wherein the metathesis precursor contains 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 our[7] (Scheme 1a–c) and other[8] 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 before or after elimination of the OBn group to provide either pyridine **2** or **3** in a regiodivergent manner (Scheme 1d).



Louis K. M. Chan

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 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.

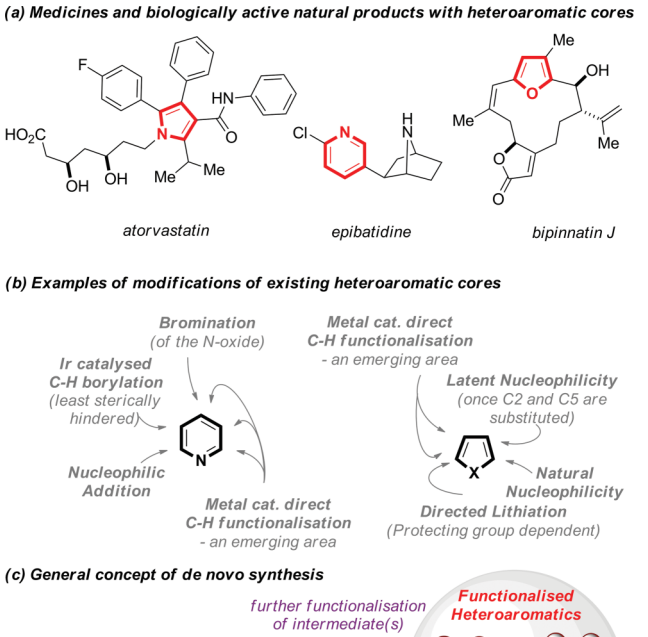


Fig. 1 Heteroaromatics in chemistry.

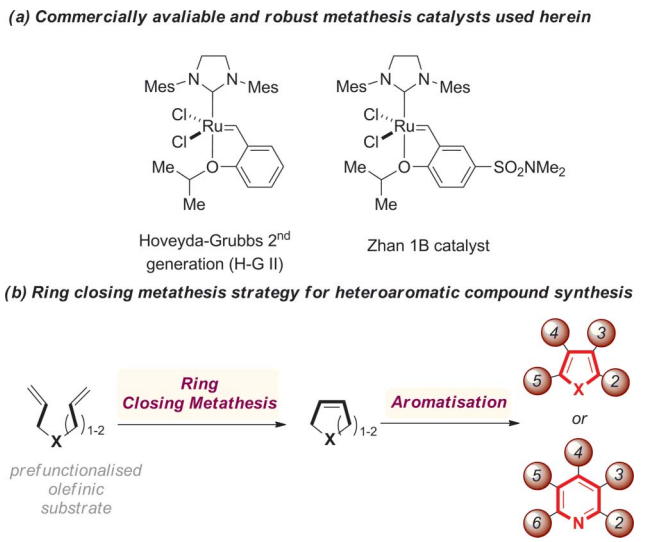
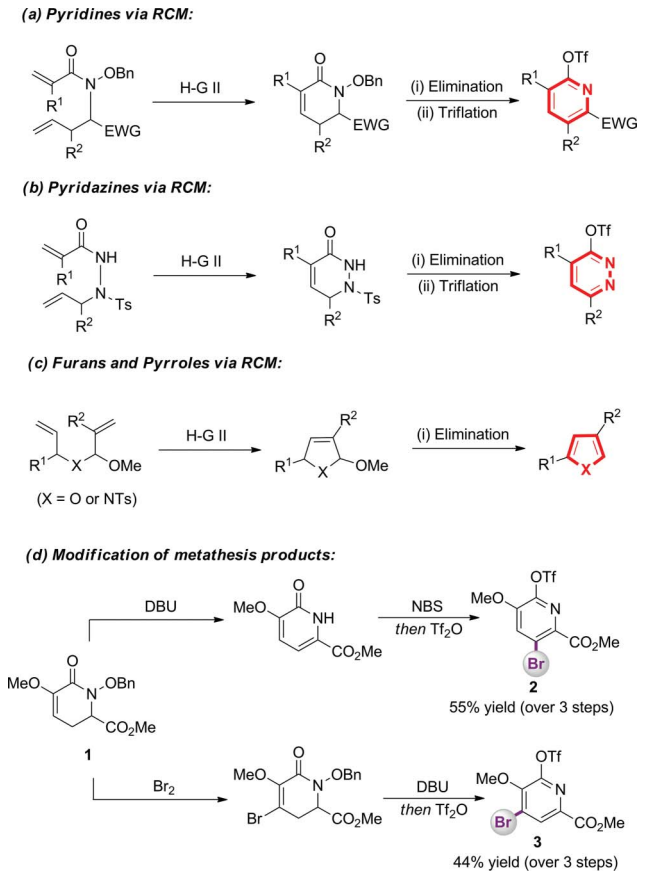


Fig. 2 Ring closing metathesis for heteroaromatic synthesis.

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 (Fig. 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



Scheme 1 Ring closing metathesis approaches to heteroaromatic compounds.

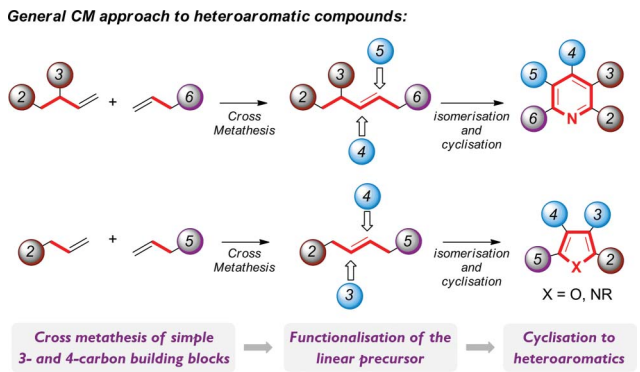


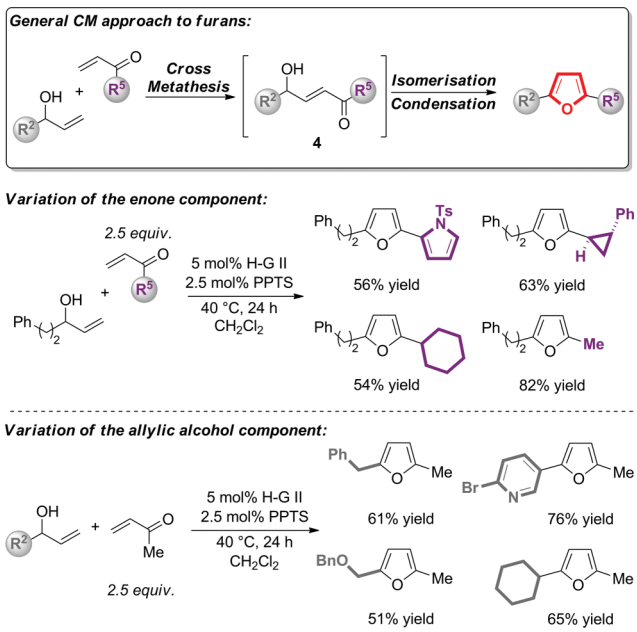
Fig. 3 CM as a key step in heteroaryl synthesis.

olefinic product which is then suitable for conversion into the target heteroaromatic.

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

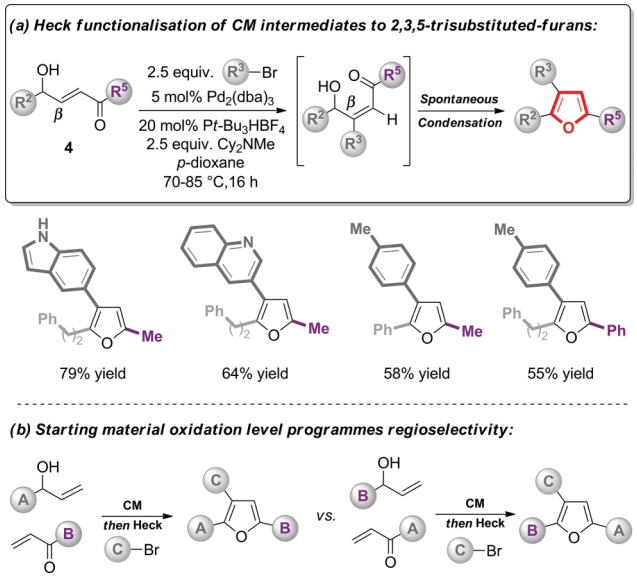
Our early studies involved developing effective CM-based entries to substituted furans.[11] Allylic alcohols have emerged as a special olefin class for metathesis, perhaps due to hydrogen bonding between the –OH and the chloride ligands associated with the ruthenium-based catalyst systems.[12] Accordingly, 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.

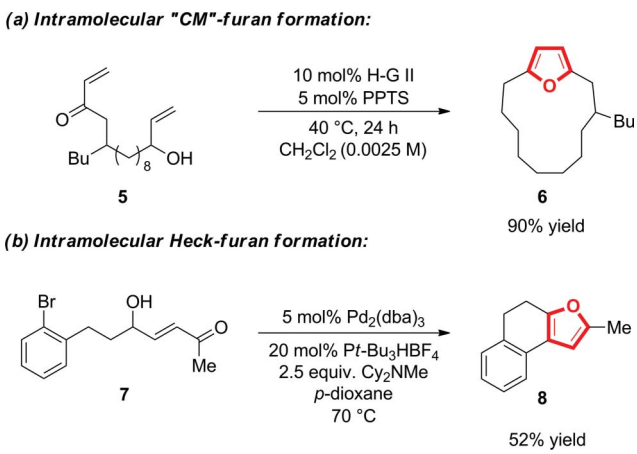
A more profitable strategy involves promoting isomerisation by using a protocol which facilitates concomitant introduction of further functionality. In this context, we have shown that the Heck reaction of δ-hydroxyenone intermediates **4** serves to introduce an aryl group onto the enone β-position and simultaneously effects olefin isomerisation to afford trisubstituted furans directly. 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).



Scheme 3 CM–Heck approach to trisubstituted furans.

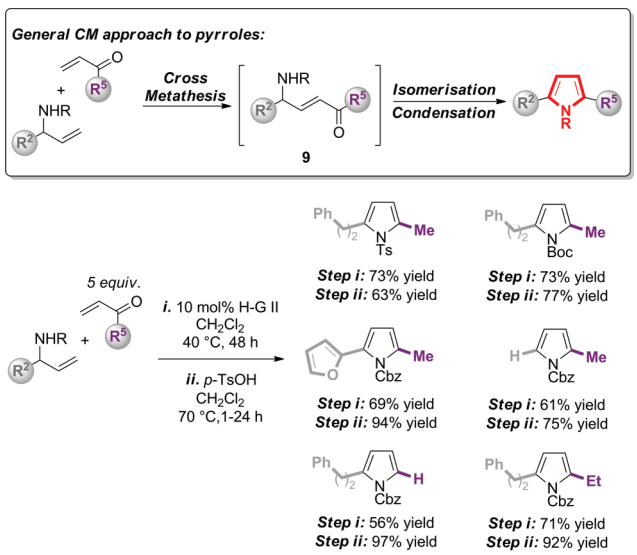
Both of these approaches towards furans can be used to synthesise more complex polycyclic systems by rendering the processes intramolecular. Accordingly, tandem CM-cycloaromatisation of tethered allylic alcohol–enone **5**, under high dilution conditions, afforded macrocyclic furan **6**, which is structurally related to the core of the furancembranolide family of natural products,[9] in excellent yield (Scheme 4a). This tandem macrocylisation–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).



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

Cross-metathesis based approaches to pyrroles

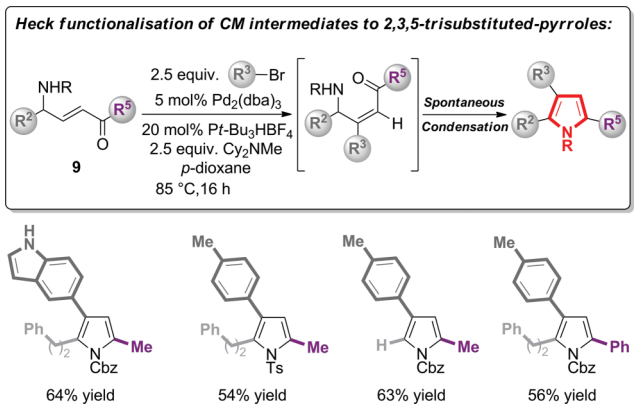
Extension of the chemistry discussed so far to the synthesis of pyrroles represents a natural progression. Here, we anticipated that CM between suitably protected allylic amine and enone components would provide efficient access to γ-aminoenones **9** which can then potentially be converted to pyrroles 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 stability and 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-aminoenone intermediates **9** (Scheme 5). These were then converted to the final pyrrole upon exposure to *p*-TsOH at 70 °C.



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

The more demanding nature of the CM process in these cases is evinced 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 alludes 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.

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 is also 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 a Lewis acid for promoting isomerisation of the olefin geometry, as well as the subsequent cyclisation.

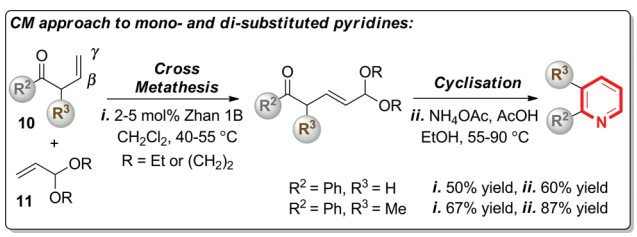


Scheme 6 CM–Heck approach to tri-substituted pyrroles.

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, an 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]

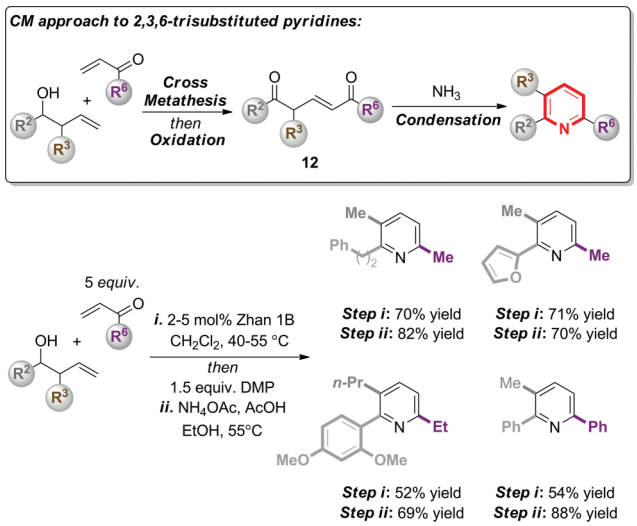
The preparation of mono- and di-substituted pyridines, without substitution at C6, is readily achieved. In these cases, CM between β,γ-unsaturated ketones **10** and acetal protected acrolein derivatives **11** was most efficient (Scheme 7). Direct conversion to the pyridine then occurs upon treatment 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.



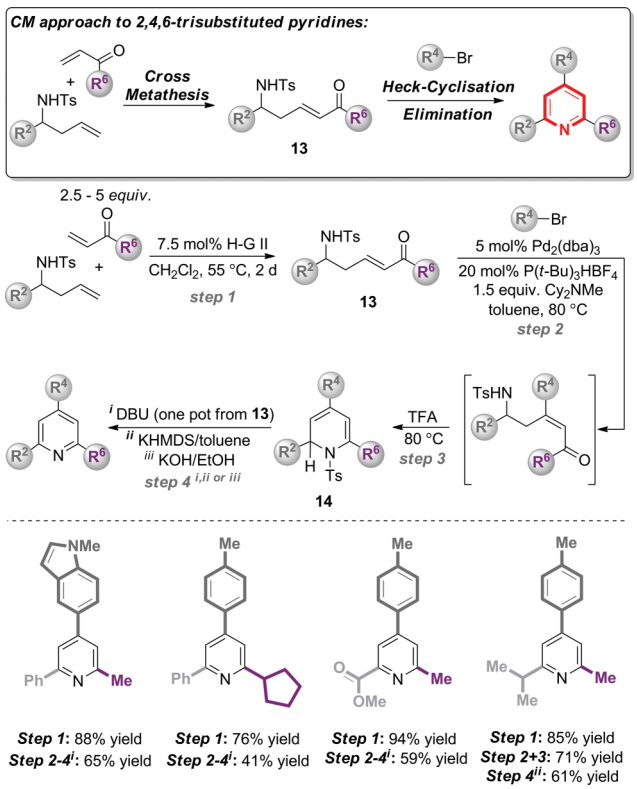
Scheme 7 CM approach to mono- and di-substituted pyridines.

Unsaturated 1,5-diketones are already established as efficient precursors to pyridines but have been under-utilised for this purpose. We have shown that cross-metathesis between homoallylic alcohols and vinylketones followed by DMP oxidation is possible (Scheme 8). The trisubstituted unsaturated 1,5-dicarbonyls **12** which resulted 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 presence of the dicarbonyl functionality.

Investigation into other pyridine forming sequences 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-aminoenone intermediates **13** (Scheme 9). Upon Heck arylation, olefin geometry switching occurs and this facilitates *in situ* acid promoted condensation to



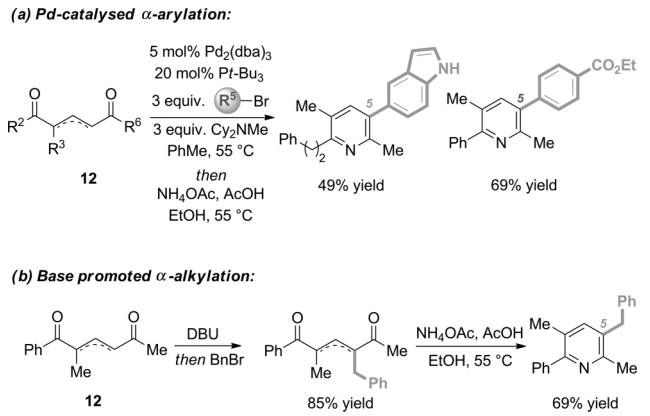
Scheme 8 CM approach to 2,3,6-trisubstituted pyridines.



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

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).

Finally, access to higher pyridine substitution patterns is achievable *via* modification of the key 1,5-dicarbonyl intermediates described earlier (see **12**, Scheme 8). 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



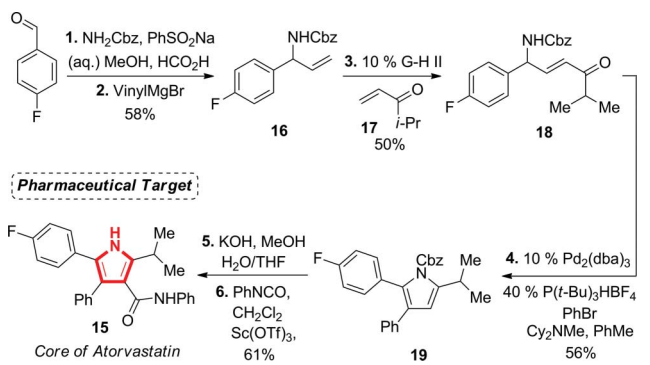
Scheme 10 Higher substituted pyridines *via* modification of the unsaturated 1,5-dicarbonyl intermediates.

observed and complex pyridine derivatives are available in a very short and modular manner.

Applications in synthesis

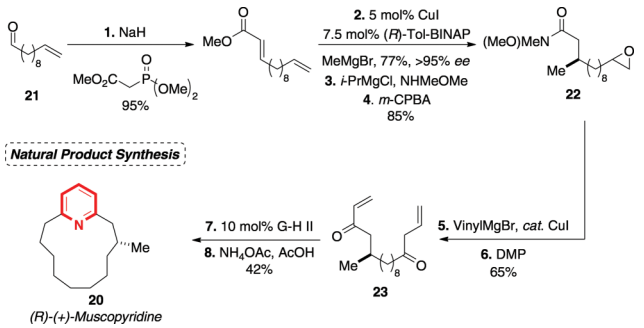
The validation of new methodologies in target directed settings is essential in demonstrating the true value and flexibility of the process. We have chosen to exemplify these new CM-based heteroaromatic methodologies by applying them to two distinct targets, one medicinal and one natural product.

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 the 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 a 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 approaches[19] 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. Thus, 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% ee), 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*)-(+)-musco-pyridine.

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.

Notes and references

1 (*a*) *Pharmaceutical Chemistry. Drug Synthesis*, Vol. 1., H. J. Roth and A. Kleemann ed., Prentice Hall Europe, London, 1988, p. 407; (*b*) V. Bonnet, F. Mongin, F. Trécourt, G. Breton, F. Marsais, P. Knochel and G. Queguiner, *Synlett*, 2002, 1008.

2 For reviews on functionalisation of heteroaryls: (*a*) J. C. Lewis, R. G. Bergman and J. A. Ellman, *Acc. Chem. Res.*, 2008, **41**, 1013; (*b*) I. J. S. Fairlamb, *Chem. Soc. Rev.*, 2007, **36**, 1036.

3 Reviews on furan synthesis: (*a*) S. F. Kirsch, *Org. Biomol. Chem.*, 2006, **4**, 2076; (*b*) X. L. Hou, H. Y. Cheung, T. Y. Hon, P. L. Kwan, T. H. Lo, S. Y. Tong and H. N. C. Wong, *Tetrahedron*, 1998, **54**, 1955. For recent examples of furan synthesis; (*c*) C. K. Jung, J. C. Wang and M. J. Krische, *J. Am. Chem. Soc.*, 2004, **126**, 4118; (*d*) A. S. Dudnik and V. Gevorgyan, *Angew. Chem., Int. Ed.*, 2007, **46**, 5195; (*e*) J. Barluenga, L. Riesgo, R. Vicente, L. A. López and M. Tomás, *J. Am. Chem. Soc.*, 2008, **130**, 13528; (*f*) Y. Xiao and J. Zhang, *Angew. Chem., Int. Ed.*, 2008, **47**, 1903; (*g*) M. Zhang, H. F. Jiang, H. Neumann, M. Beller and P. H. Dixneuf, *Angew. Chem., Int. Ed.*, 2009, **48**, 1681. For recent reviews on pyridine synthesis; (*h*) G. D. Henry, *Tetrahedron*, 2004, **60**, 6043; (*i*) M. Hill, *Chem.–Eur. J.*, 2010, **16**, 12052. For recent pyridine synthesis; (*j*) O. G. Dediu, N. A. M. Yehia, T. Oeser, K. Polborn and T. J. J. Müller, *Eur. J. Org. Chem.*, 2005, 1834. For selected recent examples of pyrrole synthesis; (*k*) R. Martin, C. H. Larsen, A. Cucenca and S. L. Buchwald, *Org. Lett.*, 2007, **9**, 3379; (*l*) S. Shafi, M. Kędziorek and K. Grela, *Synlett*, 2010, **2011**, 124; (*m*) L. Ackermann, R. Sandmann and L. T. Kasper, *Org. Lett.*, 2009, **11**, 2031; (*n*) M. Yoshia, M. Al-Amin and K. Shishido, *Synthesis*, 2009, 2454; (*o*) P. W. Davies and N. Martin, *Org. Lett.*, 2009, **11**, 2293.

4 S. B. Garber, J. S. Kingsbury, B. L. Gray and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2000, **122**, 8168.

5 Z.-Y. J. Zhan, U. S. Patent, 2007, 20070043180.

6 For a comprehensive review: W. A. L. van Otterlo and C. B. de Koning, *Chem. Rev.*, 2009, **109**, 3743 and references therein.

7 (*a*) T. J. Donohoe, J. F. Bower, J. A. Basutto, L. P. Fishlock, P. A. Procopiou and C. K. A. Callens, *Tetrahedron*, 2009, **65**, 8969; (*b*) T. J. Donohoe, L. P. Fishlock, J. A. Basutto, J. F. Bower, P. A. Procopiou and A. L. Thompson, *Chem. Commun.*, 2009, 3008; (*c*) T. J. Donohoe, N. M. Kershaw, A. J. Orr, K. M. P. Wheelhouse (née Gosby), L. P. Fishlock, A. R. Lacy, M. Bingham and P. A. Procopiou, *Tetrahedron*, 2008, **64**, 809; (*d*) T. J. Donohoe, L. P. Fishlock and P. A. Procopiou, *Org. Lett.*, 2008, **10**, 285; (*e*) T. J. Donohoe, A. J. Orr and M. Bingham, *Angew. Chem., Int. Ed.*, 2006, **45**, 2664; (*f*) T. J. Donohoe, L. P. Fishlock and P. A. Procopiou, *Chem.–Eur. J.*, 2008, **14**, 5716; (*g*) T. J. Donohoe, L. P. Fishlock, A. R. Lacy and P. A. Procopiou, *Org. Lett.*, 2007, **9**, 953.

8 (*a*) K. Yoshida, F. Kawagoe, K. Hayashi, S. Horiuchi, T. Imamoto and A. Yanagisawa, *Org. Lett.*, 2009, **11**, 515; (*b*) O. Fujimura, G. C. Fu and R. H. Grubbs, *J. Org. Chem.*, 1994, **59**, 4029; (*c*) C. Theeraladanon, M. Arisawa, A. Nishida and M. Nakagawa, *Tetrahedron*, 2004, **60**, 3017; (*d*) K. Yoshida, K. Hayashi and A. Yanagisawa, *Org. Lett.*, 2011, **13**, 4762.

9 T. J. Donohoe, A. Ironmonger and N. M. Kershaw, *Angew. Chem., Int. Ed.*, 2008, **47**, 7314.

10 A. K. Chatterjee, T.-L. Choi, D. P. Sanders and R. H. Grubbs, *J. Am. Chem. Soc.*, 2003, **125**, 11360.

11 (*a*) T. J. Donohoe and J. F. Bower, *Proc. Natl. Acad. Sci. U. S. A.*, 2010, **107**, 3373; (*b*) T. J. Donohoe, J. F. Bower and J. A. Basutto, *Nat. Protoc.*, 2010, **5**, 2005.

12 A. H. Hoveyda, P. J. Lombardi, R. V. O'Brien and A. R. Zhugralin, *J. Am. Chem. Soc.*, 2009, **131**, 8378.

13 Geometric inversion of the alkene during the Heck reaction has previously been reported: A. F. Littke and G. C. Fu, *J. Am. Chem. Soc.*, 2001, **123**, 6989.

14 T. J. Donohoe, N. J. Race, J. F. Bower and C. K. A. Callens, *Org. Lett.*, 2010, **12**, 4094.

15 S. Shafi, M. Kędziorek and K. Grela, *Synlett*, 2010, **2011**, 124.

16 (*a*) T. J. Donohoe, J. A. Basutto, J. F. Bower and A. Rathi, *Org. Lett.*, 2011, **13**, 1036; (*b*) T. J. Donohoe, J. F. Bower, D. B. Baker, J. A. Basutto, L. K. M. Chan and P. Gallagher, *Chem. Commun.*, 2011, **47**, 10611.

17 (*a*) L. Alcaraz, J. J. Hamett, C. Mioskowski, J. P. Madel, T. Le Gall, D.-S. Shin and J. R. Falck, *Tetrahedron Lett.*, 1994, **35**, 5449; (*b*) A. Fürstner, M. D. B. Fenster, B. Fasching, C. Godbout and K. Radkowski, *Angew. Chem., Int. Ed.*, 2006, **45**, 5510; (*c*) H. Benakki, E. Colacino, C. Andre, F. Guenoun, J. Martinez and F. Lamaty, *Tetrahedron*, 2008, **64**, 5949; (*d*) M. Arisawa, C. Theeraladanon, A. Nishida and M. Nakagawa, *Tetrahedron Lett.*, 2001, **42**, 8029.

18 B. D. Roth, U. S. Patent, 5 273 995.

19 (*a*) A. Fürstner and A. Leitner, *Angew. Chem., Int. Ed.*, 2003, **42**, 308; (*b*) H. Hagiwara, T. Katsumi, V. P. Kamat, T. Hoshi, T. Suzuki and M. Ando, *J. Org. Chem.*, 2000, **65**, 7231.

20 (*a*) S.-Y. Wang, S.-J. Ji and T.-P. Loh, *J. Am. Chem. Soc.*, 2007, **129**, 276; (*b*) S.-Y. Wang, T.-K. Lum, S.-J. Ji and T.-P. Loh, *Adv. Synth. Catal.*, 2008, **350**, 673.

