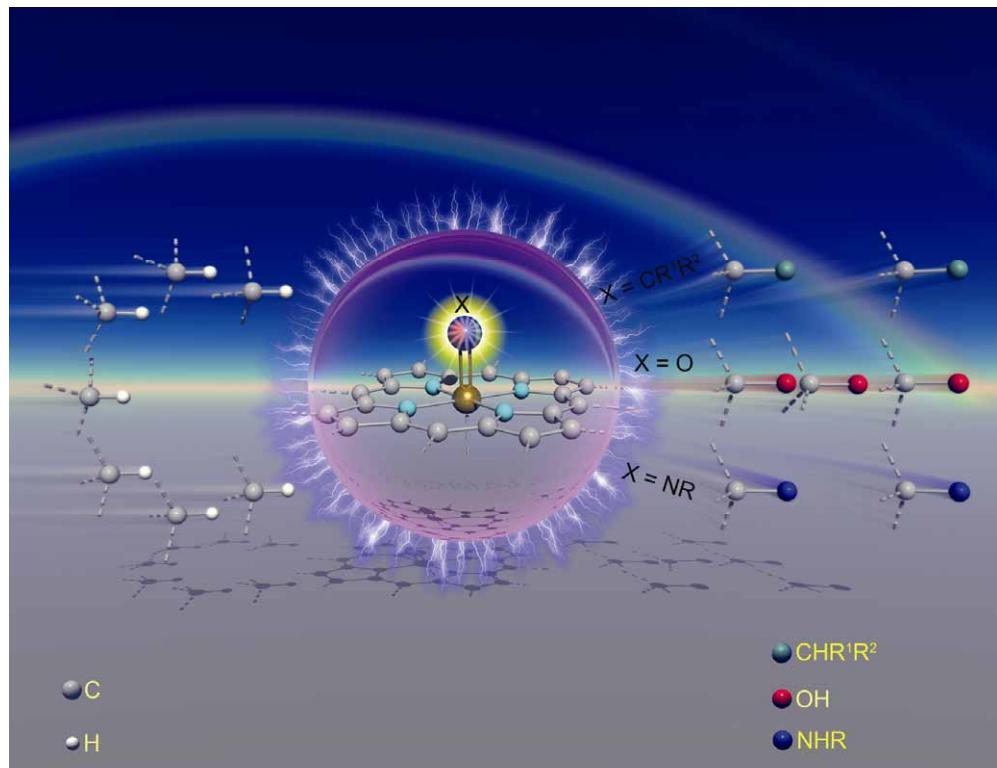


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## TUTORIAL REVIEW

# Recent developments in natural product synthesis using metal-catalysed C–H bond functionalisation<sup>†</sup>

Lindsay McMurray, Fionn O’Hara and Matthew J. Gaunt\*

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Metal-catalysed C–H bond functionalisation has had a significant impact on how chemists make molecules. Translating the methodological developments to their use in the assembly of complex natural products is an important challenge for the continued advancement of chemical synthesis. In this *tutorial review*, we describe selected recent examples of how the metal-catalysed C–H bond functionalisation has been able to positively affect the synthesis of natural products.

### Introduction and overview

The selective reactivity of functional groups (such as carbonyls, amines and alcohols) over the inert C–H and C–C bonds that make up the structural framework of organic compounds has underpinned the chemist’s ability to make molecules. Bond forming processes usually rely on manipulation of reactive groups, but molecules displaying these functional handles are not always readily available and need to be prepared through additional synthetic steps from the parent hydrocarbon building blocks. Inevitably, this takes time and leads to the formation of non-product waste material, so conventional synthesis can become inefficient and expensive, with a significant environmental footprint. The most common feature in organic molecules is the C–H bond, however, they are mostly considered to be inert and only useful in synthesis when in the vicinity of a

reactive group. If we could find ways to use C–H bonds as versatile functional groups we could revolutionise the rules that have influenced our strategies for assembling molecules over the last 100 years.

Nature often exploits ‘unreactive’ C–H bonds, installing C–OH bonds into molecules from the parent hydrocarbon via cytochrome P450 mediated C–H hydroxylation, beautifully exemplified by the cellular synthesis of baccatin III, the taxol precursor.<sup>1</sup> Despite this inspiring biosynthesis, chemists have rarely paralleled the generality of these pathways in synthetic molecule assembly.

The challenge associated with this way of making molecules is the *selective activation* of one C–H bond among many similar entities. The C–H bond is strong and of low polarity, making it fairly unreactive. The activation of C–H bonds using stoichiometric amounts of transition metals is known, but has never been economically sustainable. The use of catalytic quantities of metals has been realised only recently, resulting in a rapid expansion of the field;<sup>2</sup> but it is still in its infancy and there are many hurdles still to be overcome. Notably, many transformations often require harsh conditions to overcome

Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW, United Kingdom. E-mail: mjjg32@cam.ac.uk; Tel: +44 (0)1223 336318

† Part of a themed issue on C–H functionalisation in organic synthesis dedicated in memory of Keith Fagnou.



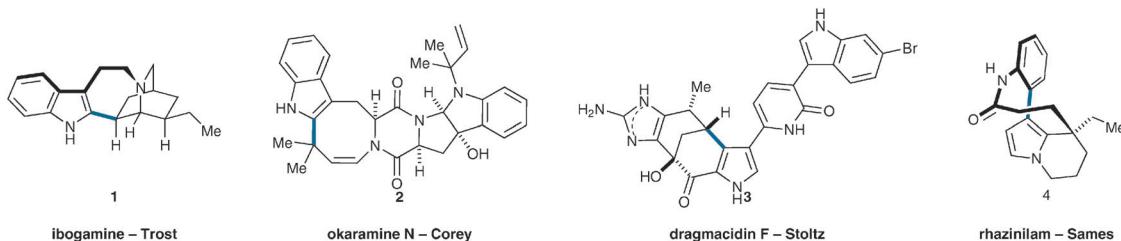
Lindsay McMurray

Lindsay McMurray received her BA/MSci in Natural Sciences from St Catharine’s College, University of Cambridge in 2008. She is currently a PhD student in the group of Dr Matthew J. Gaunt at the University of Cambridge where her research focuses on the development of novel copper-catalysed arylation reactions and the development of metal-catalyzed C–H functionalisation strategies for the synthesis of the natural products.



Fionn O’Hara

Fionn O’Hara graduated with a BA/MSci in Natural Sciences (Chemistry) from Trinity College, University of Cambridge in 2007. She is currently a PhD student in the group of Dr Matthew J. Gaunt at the University of Cambridge where her research focuses on the use of iterative metal-catalyzed C–H functionalisation strategies for the synthesis of natural products.



**Fig. 1** Natural products that exploit stoichiometric metal-mediated C–H bond functionalisation.

the low reactivity of the C–H bond; others often use auxiliary directing groups to control selectivity but these groups are frequently not part of the target molecule.

When considering how to implement metal-catalysed C–H functionalisation strategies in the synthesis of complex and structurally delicate natural products we must consider the limitations of the tools that we have at our disposal and design our routes carefully. Metal-catalysed C–H bond functionalisation is crucial to the future of synthesis, and it will form a new ally for the powerful synthetic strategies that we use everyday; to reach its full potential we must develop new reactions and processes that will help us meet these synthesis challenges.

This short review article is designed to give the reader an insight into how metal-catalysed C–H bond functionalisation has started to impact on complex molecule synthesis. Seminal contributions to natural product synthesis using metal mediated C–H bond functionalisation include Trost's synthesis of ibogamine, Corey's synthesis of okaramine N, Stoltz's synthesis of dragmacidin F, and Sames' synthesis of rhazinilam (Fig. 1).<sup>3</sup> While these syntheses represent landmarks in the field, we have chosen not to include examples of syntheses where stoichiometric amounts of the transition metal are used, as their synthesis has been covered in previous reviews.<sup>3</sup> However, where relevant we have referred to seminal methodological works, as their impact on the development of catalytic transformations cannot be underestimated. The overview is not exhaustive, but instead focuses on examples that we feel are instructive in explaining the potential of the field. We apologise

for not being able to include every example of where metal-catalysed C–H bond functionalisation has been used in a synthesis of a natural product.

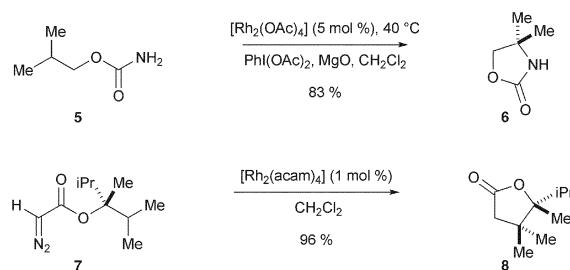
## The formation of C–O and C–N bonds in natural products *via* metal-catalysed C–H bond functionalisation

The direct formation of a C–O or C–N bond at a traditionally unreactive site of an intermediate or natural product can enable powerful alternative disconnection strategies that facilitate complex molecule synthesis. The following section reviews a selection of syntheses where the inclusion of a C–H bond functionalisation step was instrumental in allowing an interesting or unusual synthetic strategy.

### Metal-catalysed insertion of carbene or nitrene species into C–H bonds

The use of carbene or nitrenes is a well established method for C–H functionalisation, with one of the first reported examples in complex molecule synthesis being Corey's synthesis of the penicillin core structure.<sup>4</sup> Although early examples required intramolecular carbene insertion to obtain selective reaction, greater control of reactivity has been achieved through the use of metal-nitrenoid (**5** to **6**) or carbenoid (**7** to **8**) species, which have significantly improved the efficacy of this type of process (Scheme 1).<sup>5,6</sup> The metal both catalyses the formation of the reactive species from the precursor—such as a diazo compound—and modulates the reactivity, resulting in enhanced selectivity.

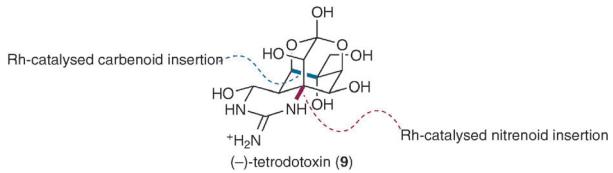
Careful selection of both the ligand and the substituents on the reactive centre can result in further tuning of the carbenoid or nitrenoid properties to allow high levels of both chemo- and stereoselectivity. This has made carbenoid and nitrenoid insertion a widely used method for the functionalisation of C–H bonds in complex systems. While strictly speaking, there is no C–M bond formed in this type of process, these transformations have facilitated a number of elegant syntheses, including



**Scheme 1** Rh-catalysed carbenoid and nitrenoid C–H insertions.



**Dr Matthew Gaunt** graduated from the University of Birmingham with a BSc honours degree in Chemistry. He was awarded a PhD from the University of Cambridge after studies with Dr Jonathan Spencer, before moving to the University of Pennsylvania for postdoctoral studies with Professor Amos B Smith III, as a GlaxoWellcome Fellow. He returned to the UK as a Junior College Research Fellow with Professor Steven Ley at the University of Cambridge in 2001. Dr Matthew Gaunt started his independent research career in October 2003 at the University of Cambridge and his laboratory is interested in the development of new catalytic strategies for chemical synthesis.



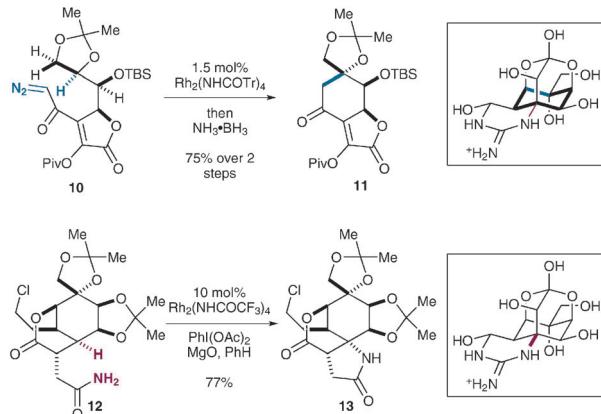
**Fig. 2** Tetrodotoxin and Du Bois' disconnections that exploit Rh-catalysed C–H bond functionalisation.

Davies' synthesis of elisapterosin B and columbasin A,<sup>7a</sup> Fukuyama's synthesis of ephedradine A<sup>7b</sup> and serotobenine,<sup>7c</sup> and Du Bois' synthesis of saxitoxin<sup>7d,e</sup> and the manzacidins.<sup>7f</sup> An illustrative example of the utility of this chemistry can be seen in Du Bois' stereoselective synthesis of (–)-tetrodotoxin (**9**)<sup>8</sup> which applies both an intramolecular carboid and nitrenoid insertion *en route* to the natural product (Fig. 2).

**Synthesis of (–)-tetrodotoxin.** Tetrodotoxin is a guanidinium poison from the Japanese blowfish which acts by blocking voltage-gated sodium channels.<sup>9</sup> The heavily functionalised bridged ring structure poses a formidable synthetic challenge. Du Bois' synthesis built up this complex structure using two key rhodium-catalysed C–H functionalisations.<sup>8</sup>

The first of these, a rhodium catalysed carboid insertion into a tertiary C–H bond, generated cyclohexane **11** from precursor **10** with simultaneous generation of the quaternary stereocentre.<sup>10</sup> Extensive screening identified the highly selective rhodium acetamide catalyst  $[\text{Rh}_2(\text{HCOCPh}_3)_4]$  to be optimal. This enabled exclusive generation of **11**, with the crude product being able to be carried directly into the next step without further purification. Fourteen further steps converted **11** into advanced intermediate **12** (Scheme 2).

The conversion of **12** into **13** aimed to apply a rhodium-catalysed carbamate-tethered nitrenoid insertion reaction previously developed by Du Bois.<sup>11</sup> Carbamates (**5**) were treated with  $\text{PhI}(\text{OAc})_2$  in the presence of a rhodium catalyst and an acid scavenger to generate oxazolidinones such as **6**. In addition to the potential efficacy of the C–H amination process, the mild conditions of this transformation also make this strategic bond disconnection highly amenable to natural product synthesis. For example, on application of the intramolecular C–H bond amination on the tetrodotoxin precursor **12** a slight modification of conditions, to use an increased



**Scheme 2** C–H functionalisation to build the core of tetrodotoxin.

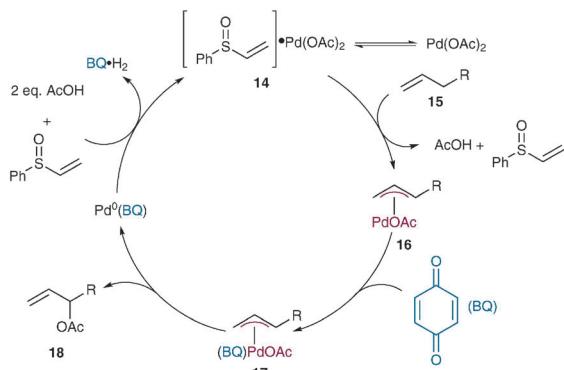
loading of the  $[\text{Rh}_2(\text{HCOCF}_3)_4]$  catalyst, allowed the reaction to proceed in an excellent 77% yield to give oxazolidinone **13** (Scheme 2). Seven further steps completed the stereoselective synthesis of (–)-tetrodotoxin.<sup>8</sup>

The use of rhodium-catalysed carboid and nitrenoid insertions into C–H bonds enabled the complex architecture of (–)-tetrodotoxin to be efficiently constructed in 32 steps. The structural and functional complexity of the substrates for these reactions underlines the remarkable selectivity of metal carboids and nitrenoids, and both reactions relay an effective method to generate fully substituted carbons. The synthesis compares well with Kishi's classic racemic synthesis which also requires 32 steps,<sup>12</sup> and Isobe's asymmetric synthesis which requires 39 steps,<sup>13</sup> but more importantly demonstrated that rhodium-catalysed C–H functionalisation *via* carboids or nitrenoids can be successfully applied to highly functionalised systems at various stages of a natural product synthesis.

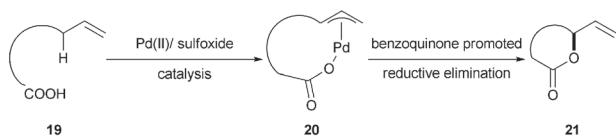
### Pd(II)-catalysed allylic C–H oxidation

White has developed a palladium-catalysed allylic C–H oxidation reaction which allows regioselective coupling of a carboxylic acid with the internal allylic position of a terminal olefin.<sup>14,15</sup> The reaction is proposed to proceed *via* a novel serial ligand catalysis mechanism where two different ligands interact sequentially with the palladium during the catalytic cycle. This allows the properties of the metal to subtly change, tuning the catalyst to be effective for different steps at subsequent stages of the catalytic cycle.

Initially palladium (II)/sulfoxide complex **14** enables C–H bond cleavage and formation of  $\pi$ -allyl palladium complex **16** from the terminal alkene. Loss of the sulfoxide ligand and interaction with benzoquinone changes the properties of the palladium centre such that C–O bond formation is promoted and reductive elimination from palladium–benzoquinone complex **17** generates the allylic ester **18** (Scheme 3).<sup>15b</sup> This process was successfully applied to streamlining the synthesis of a number of natural products by providing new and more efficient routes to intermediates.<sup>16</sup> The ability to directly install C–O bonds late in a synthesis reduced the need for functional group manipulations such as protection and deprotection, and also meant that commercially available alkenes could be rapidly converted into versatile synthetic intermediates.



**Scheme 3** Proposed catalytic cycle for Pd(II)-catalysed allylic C–H oxidation.



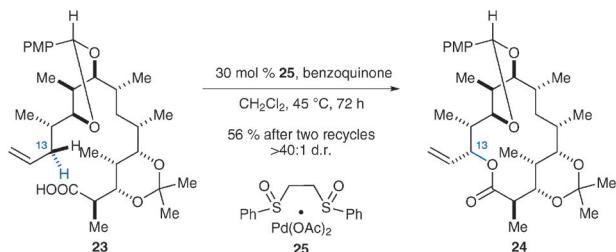
**Scheme 4** Macrocyclising Pd(II)-catalysed allylic C–H oxidation.

Further studies demonstrated that this process could be used for C–H macrolactonisation when applied to alkenoic acids (**19**), generating large ring lactones (**21**) (Scheme 4).<sup>17</sup> The reaction mechanism is proposed to involve C–O bond formation from templated  $\pi$ -allylpalladium carboxylate complex **20**. Due to the requirement for the catalyst-mediated templating effect for reaction to occur, the maximum effective concentration of the reactive centres is reduced to the level of the catalyst loading, so the high dilutions frequently required for more conventional macrolactonisation strategies were not necessary.<sup>18</sup>

**Synthesis of 6-deoxyerythronolide B.**<sup>19</sup> 6-Deoxyerythronolide B (**22**) is the core structure of the erythromycin antibiotics,<sup>20</sup> and is a common structure in the larger family of the polyketide macrolide antibiotics. Many approaches towards structures of this type have been reported,<sup>21</sup> most of which rely on the formation of a large ring ester from a linear hydroxy acid precursor using classical macrolactonisation techniques. White's recent synthesis of this natural product applied a palladium-catalysed C–H oxidation/macrolactonisation reaction to install this key bond, which proceeded with remarkably high selectivity for such a conformationally flexible system (Fig. 3).<sup>19</sup>

White elected to deploy this macrocyclising C–H oxidation at a late stage in the synthesis of **22**; a strategy which precluded the need to carry a protected C13 hydroxyl group throughout the synthesis. Late stage precursor **23**, generated in eighteen steps using stereoselective aldol and alkylation reactions, was cyclised to macrolide **24** on heating to 45 °C in the presence of benzoquinone and catalyst **25**. A catalyst loading of 30 mol% gave a yield of 34%, with 45% recovered starting material. Recycling this recovered starting material twice through the same conditions gave a total of 56% isolated yield and 8% recovered starting material (Scheme 5).

Crucially, the reaction occurred with excellent selectivity;  $^1\text{H}$  NMR analysis of the crude reaction mixture showed only the desired diastereomer. This result had been predicted by computational study using the assumption that the transition structures resulting from palladium chelation would be similar in structure to the product, and could therefore be analysed by comparing the energies of the two diastereomeric macrolides that could be formed. The desired macrolide **24** was predicted to be considerably lower in energy due to the absence of an



**Scheme 5** Pd(II)-catalysed allylic C–H macrolactonisation.

unfavourable interaction between the exocyclic vinyl group and the PMP acetal, and this prediction was supported by the exceptionally high diastereoselectivity observed. Three further steps from **24** gave 6-deoxyerythronolide B **22**, in a total of 22 steps and 7.8% overall yield, slightly reducing the overall step count in comparison to other classic syntheses of this class of molecule.<sup>21</sup>

The synthesis of 6-deoxyerythronolide B **22** successfully demonstrated the applicability of White's C–H oxidation methodology to a considerably more complex late-stage natural product precursor. The tolerance of the reaction to the increase in substrate complexity, and the predictable high level of regio- and stereo-control make the inclusion of a C–H functionalisation step at the late stage of the synthesis a plausible strategy.

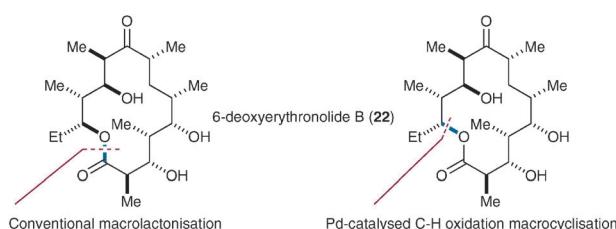
This work is particularly significant as it demonstrates that, with careful planning, C–H oxidation can be used for the late stage installation of reactive functional groups. As C–H functionalisation methodology continues to develop, and more is learnt about control of selectivity in C–H functionalisations on complex systems, this is likely to become a more common strategy for increasing efficiency in synthesis.

### Metal-catalysed remote oxidation of unactivated $sp^3$ C–H bonds

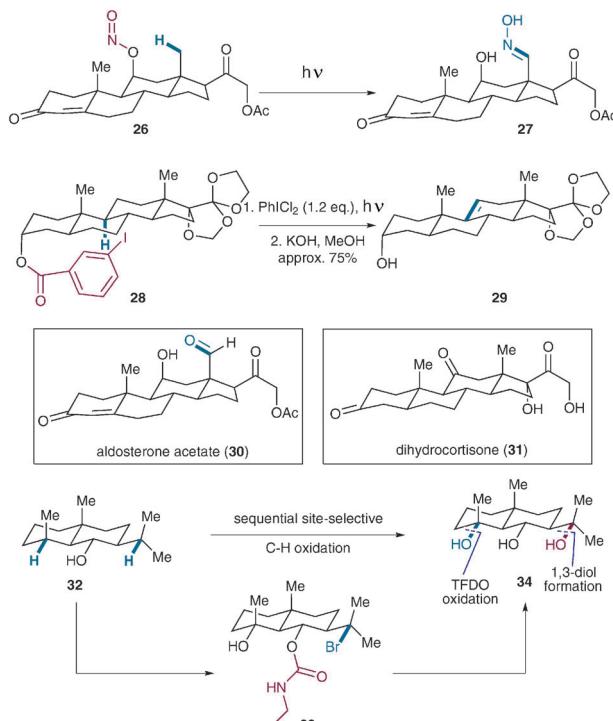
A common theme driving the development of  $sp^3$  C–H oxidation methodology is the desire to emulate the ease with which biological systems can convert relatively unfunctionalised molecules into a range of oxygenated derivatives by means of sequential oxidation by enzymes containing metal-porphyrin complexes.<sup>1</sup> These include the family of cytochrome p450 enzymes, which are responsible for C–H oxidation of a vast range of biological molecules, including many of the oxidation steps in the steroid synthesis pathway.

**'Classical' non-metal approaches to C–H oxidation.** Many of the recent developments in metal-catalysed C–H oxidation chemistry build upon seminal contributions made before the advent of metal catalysis. For example, before a detailed understanding of how enzymatic Fe-catalysed processes work was developed, chemists were trying to emulate the remarkably powerful oxidations that biological systems perform. The earliest examples of this were radical-mediated C–H functionalisations (Fig. 4), and the field has developed through biomimetic porphyrin methodology and the use of electrophilic reagents such as DMDO, to the discovery of new, selective, metal-based catalysts.<sup>22</sup>

The synthesis and functionalisation of steroids provided a driving force for much of the early work on C–H oxidation. Corey<sup>23</sup> and Buchschacher's<sup>24</sup> demonstration that the radical



**Fig. 3** Macrocyclising disconnections.

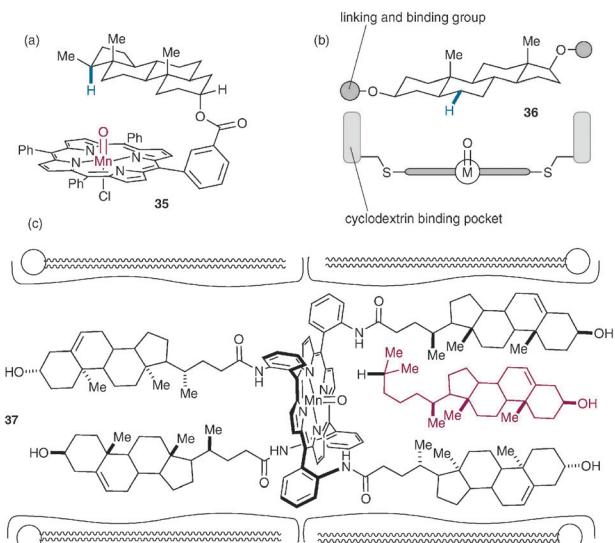


**Fig. 4** Remote radical mediated C–H functionalisation.

mediated Hoffmann–Löffler–Freytag reaction could be used in a complex setting to facilitate the synthesis of dihydroconessine, was rapidly followed by Barton's report of the application of a new radical-mediated C–H oxidation (**26** to **27**) in the synthesis of aldosterone acetate (**30**).<sup>25</sup> Breslow first proposed this concept of “remote functionalisation” through extensive work into the use of tethered reactive centres that could functionalise angular C–H bonds at remote sites on steroid frameworks.<sup>26</sup> This was exemplified by the installation of an iodine prior to elimination (**28** to **29**) in the synthesis of cortisone (**31**).

A more recent variant of remote radical functionalisation is Baran's Hoffmann–Löffler–Freytag inspired 1,3-diol synthesis that was used in the site-selective oxidation of the carbon framework of dihydrojunenol (**32**). This biomimetic process allowed the synthesis of four different members of the eudesmane terpenes, including pygmol.<sup>27</sup>

**C–H oxidation using metalloporphyrin systems.** A great deal of research has been directed at finding mimics for the cytochrome P450-haem system in order to facilitate C–H oxidation reactions. Based on Breslow's functionalisation concept, Grieco developed an oxidation strategy using metalloporphyrins tethered to steroids to generate reactive radicals that functionalised a remote C–H bond (**35**).<sup>28</sup> The use of biomimetic C–H bond oxidation on steroids was further developed by Groves<sup>29</sup> and Breslow,<sup>30</sup> both of whom investigated the possibility of selectively binding a substrate in proximity to a metalloporphyrin as a means to get selective and predictable C–H oxidation under catalytic conditions using a cyclodextrin derived system (**36**) or vesicle bilayer (**37**) based binding pocket (Fig. 5). These pioneering strategies enabled transformations that were unique at the time, but the size and



**Fig. 5** ‘Biomimetic P450-type’ C–H oxidations.

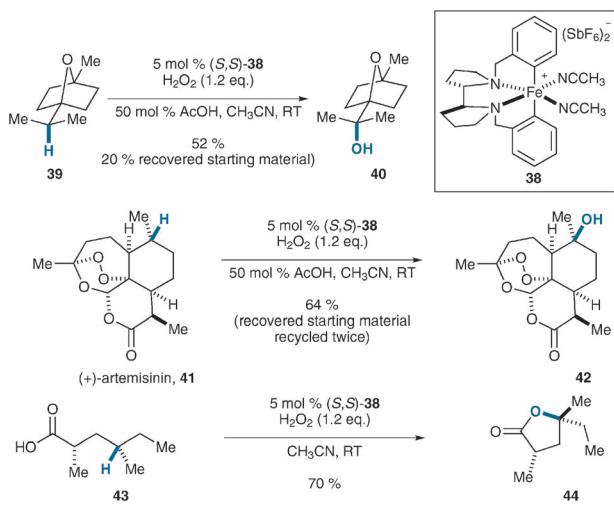
complexity of these systems precluded their practical use in synthesis, and a more general and broadly applicable method of obtaining regioselectivity was needed.

Simple metal-porphyrin catalysts were also investigated, notably Groves's use of iron tetraphenyl porphyrin with PhIO as the oxidant,<sup>31</sup> and Tabushi's use of a manganese tetraphenyl porphyrin with oxygen from air.<sup>32</sup> Although these systems were capable of oxidising and epoxidising simple hydrocarbons, they did not in general provide sufficient yield or control of regioselectivity to give a synthetically useful process.<sup>33</sup>

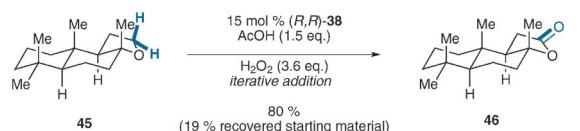
**C–H oxidation by small metal catalysts: synthesis of sclareolide.** A more broadly applicable approach to C–H oxidation is the use of small and easily accessible metal-based catalysts that allow the selective direct functionalisation of C–H bonds on molecules without any prerequisite directing groups.<sup>34</sup> A number of strategies have been investigated including Barton's Gif chemistry,<sup>35</sup> Crabtree's manganese catalyst<sup>36</sup> and Du Bois' recent report on ruthenium catalysed hydroxylations of tertiary C–H bonds,<sup>37</sup> but a key breakthrough was White's development of the non-haem iron Fe-PDP catalyst **38**.<sup>38</sup> Non-haem iron catalysts of this type have been proposed to function *via* a mechanism involving a high-valent iron-oxo species that is generated *in situ*. This is then thought to affect hydrogen abstraction to form a short-lived carbon-centred radical that undergoes hydroxyl rebound to produce the oxygenation products.<sup>39</sup>

The catalyst gave selective hydroxylation of tertiary C–H bonds on both simple and complex precursors (Scheme 6), and also enabled an acid-directed C–H oxidation procedure, which formed lactones. Extension of this methodology to methylene groups, and the elucidation of a set of predictable and reliable rules for the selectivity observed has resulted in it becoming a promising prospect for inclusion in synthesis. An indication of the potential of this methodology can be seen in the conversion of (−)-ambroxide (**45**) into (+)-sclareolide (**46**), which proceeded in 80% yield (Scheme 7).<sup>40</sup>

C–H oxidation is rapidly developing as a versatile strategy in synthesis, both for selective oxidation of natural products as



**Scheme 6** White's non-haem iron catalysed C–H oxidation.



**Scheme 7** Iron catalysed C–H oxidation of ambroxide to sclareolide.

exemplified by White's oxidation of artemisinin and Wender's late stage oxidation of bryostatin analogues,<sup>41</sup> and increasingly as fundamental steps in the synthesis of complex molecules. The continued establishment of guidelines<sup>42</sup> that enable the prediction of site of oxidation under different conditions should result in C–H oxidation becoming a much more widely used synthetic strategy.

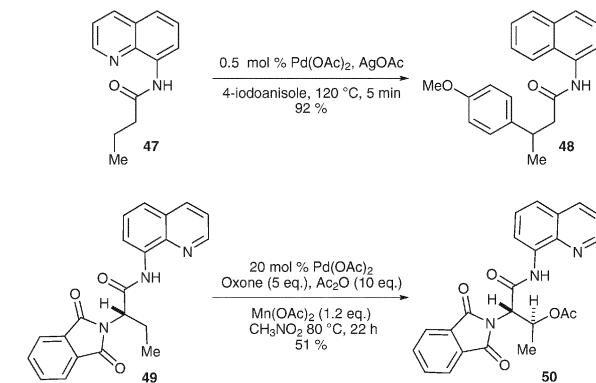
### The formation of C–C bonds in natural products via metal-catalysed C–H bond functionalisation

The previous sections have dealt with the transformation of C–H bonds to C–O or C–N bonds. However, the direct formation of C–C bonds from C–H bonds would provide a powerful direct coupling strategy that even Nature is rarely able to match. This section reviews the synthesis of a selection of molecules where C–C bond formation is enabled through metal-catalysed C–H bond functionalisation.

#### Coordination-directed metal-catalysed sp<sup>3</sup> C–H bond functionalisation

While metal-catalysed direct C–C bond formation from sp<sup>2</sup> hybridised C–H bonds has been widely developed,<sup>43</sup> the corresponding reactions for the functionalisation of sp<sup>3</sup> hybridised C–H bonds are less well established.<sup>44</sup>

A common strategy for functionalisation is using a coordinating group to bind a metal in proximity to a C–H bond, which is then functionalised. A well established example of this is Daugulis' amino-quinoline auxiliary which steers the Pd-catalyst to a particular position (Scheme 8, **47** to **48**).<sup>45</sup> This concept was applied by Corey in the development of diastereoselective Pd-catalysed, carboxamide directed C–H



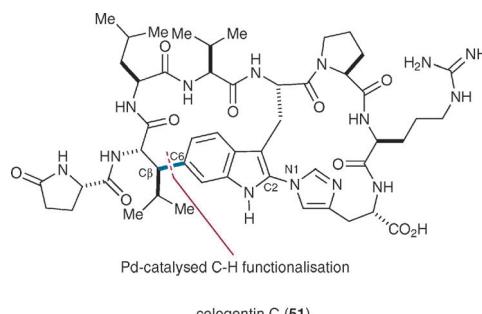
**Scheme 8** C–H bond functionalisation on quinoline derived amino acids.

acetoxylation or arylation at the β position of α-amino acids (Scheme 8, **49** to **50**).<sup>46</sup>

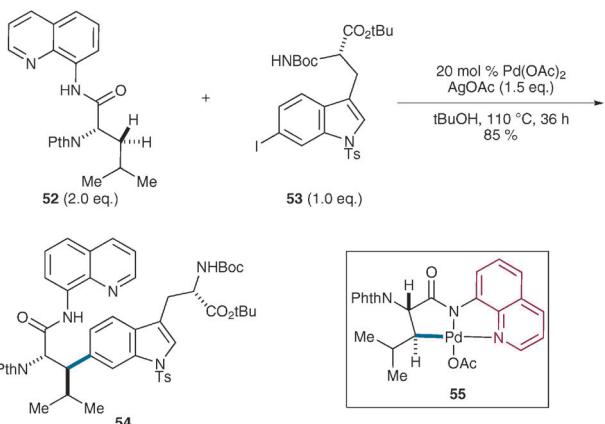
**Synthesis of celogentin C.** Celogentin C is a bicyclic non-ribosomal peptide isolated from the seeds of a Chinese herbal medicine, *Celosia argentea*, and has inhibitory activity against tubulin polymerisation ( $IC_{50} = 0.8 \mu\text{M}$ ).<sup>47</sup> Celogentin has an unusual structure, consisting of a peptide chain with direct linkages between the C6 position of tryptophan and the Cβ position of leucine, and also between the C2 position of tryptophan and the N1 position of histidine (Fig. 6). In Nature, these bonds have been proposed to be made by the enzyme catalysed oxidative linking of a much simpler peptide chain. Chen's recent synthesis of this natural product aimed to develop a C–H functionalisation strategy that would provide a synthetic equivalent to this process.<sup>48</sup>

Corey's sp<sup>3</sup> C–H arylation of amino acids was identified as a method that might facilitate the synthesis of celogentin C by enabling bond formation between two amino acid-derived fragments. This disconnection approach offered potential for the stereoselective formation of the required Trp C6 to Leu Cβ linkage in celogentin C, but a number of challenges had to be overcome. This transformation had only been demonstrated on simple aryl iodides such as iodo benzene,<sup>46</sup> and for successful synthesis the reaction would have to be extended to a considerably more complex 6-iodo-tryptophan derivative.

The stereoselective indolylation of N-phthaloyl leucine derivative **52** with a suitably protected 6-iodo-tryptophan derivative (**53**) was achieved by heating at 110 °C in the presence of silver acetate and catalytic palladium acetate (Scheme 9).



**Fig. 6** Structure of celogentin C and key disconnection.



**Scheme 9** C–H arylation in the synthesis of celogentin C.

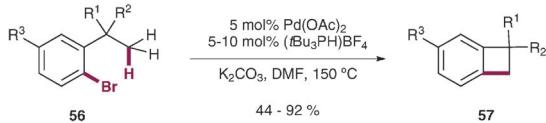
The reaction is thought to proceed *via* a palladacycle intermediate **55**,<sup>45,46</sup> in which the palladium is coordinated between the amide nitrogen and the quinoline moiety and directed to the C $\beta$  methylene group of the leucine residue. Exclusive functionalisation at one of these two diastereotopic C–H bonds is observed, which is thought to be due to preferential formation of the *trans*-palladacycle intermediate in which the bulky isopropyl group and *N*-phthaloyl group are on opposite sides of the ring. The product **54** was isolated in an excellent 85% yield and provided the key ‘Trp-Leu’ fragment of celogentin C.

The phthaloyl protection proved to be crucial for this reaction, and substrates with alternative protecting groups including mono-carbamates, dibenzylamines and azides failed to react. This steric bulk of the *N*-phthaloyl group imposed a further challenge on the synthesis, as subsequent cleavage of the quinoline carboxamide group proved to be problematic with the bulky and labile *N*-phthaloyl group in place. A solution to this problem required conversion of the *N*-phthaloyl group of **54** into the sterically smaller azide group prior to quinoline carboxamide cleavage. The resultant azido acid could be converted to an intermediate that intercepted the Castle synthesis of celogentin C *via* five peptide coupling steps.<sup>49</sup>

The transmission of stereoinformation from the leucine chiral centre in the C–H arylation step avoided the need to employ lengthy or poorly diastereoselective sequences to install this stereocentre.<sup>49b,50</sup> Despite the multistep functional group manipulation required to cleave the directing auxiliary, this synthesis provides a proof of concept of how C–H functionalisation can enable complex structures to be built up efficiently from the most appropriate available precursors, and exploit pre-existing stereocentres to install chiral information into complex structures.

### Synthesis of ( $\pm$ )-coralydine

**sp<sup>3</sup> C–H activation for the synthesis of benzocyclobutanes.** Functionalised benzocyclobutanes are versatile intermediates in organic synthesis, however there have been few general and chemoselective methods reported for their preparation.<sup>51</sup> One possible route to these structures would be the oxidative coupling of a homobenzylic methyl group to the arene nucleus through C–H activation of sp<sup>3</sup> C–H bonds.



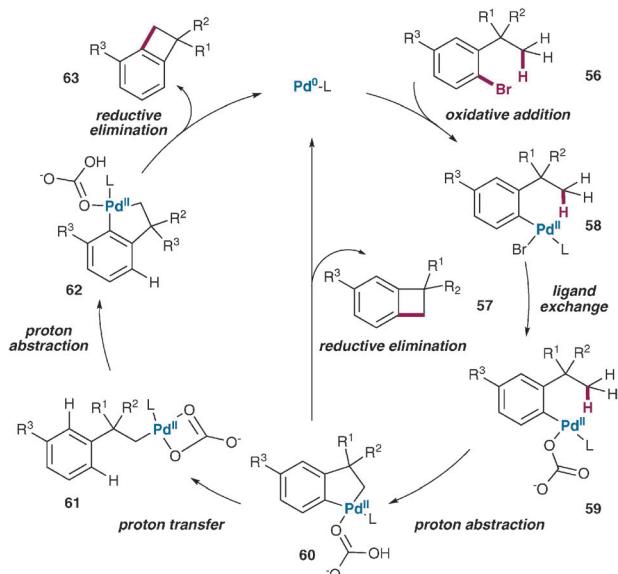
**Scheme 10** Pd(0)-catalysed synthesis of benzocyclobutanes.

In 2008 Baudoin *et al.* described a general method for the preparation of substituted benzocyclobutanes **57** from bromo-arene **56** *via* Pd(0)-catalysed C–H activation of sp<sup>3</sup> C–H bonds (Scheme 10).<sup>52</sup> Optimal results for the cyclisation were obtained with DMF as solvent, K<sub>2</sub>CO<sub>3</sub> as the base, and the bulky electron-rich (tBu<sub>3</sub>PH)BF<sub>4</sub> as the ligand. The nature of the base was important as coordination to the metal is crucial for C–H activation. The carbonate anion proved to be superior to both bicarbonate and acetate anions. This sp<sup>3</sup> C–H activation strategy tolerates a range of functional groups, however it is limited to substrates bearing a quaternary benzylic group.

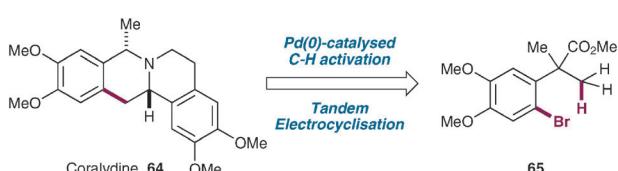
Extensive computational studies into the mechanism of this Pd(0)-catalysed cyclisation have been reported.<sup>52</sup> The proposed mechanism starts with an oxidative addition of the Pd(0) species into the C–Br bond to generate intermediate **58**. Ligand exchange affords the reactive species **59** which undergoes immediate C–H insertion to form the 5-membered palladacycle **60**. Reductive elimination of Pd(0) then yields the desired benzocyclobutane **57**. Interestingly, it was found that with substrates where R<sub>3</sub> was small (and *para* to the bromide group) an unexpected regioisomer (**63**) was formed. This is thought to arise from 1,4 migration of the palladium, where a proton can be transferred to the aromatic ring, yielding an alkyl intermediate **61**. This proton transfer is reversible, and therefore leads to the desired benzocyclobutane **57** as the major product along with a small quantity of the more strained regioisomer (**63**) (Scheme 11).

**Application to synthesis of ( $\pm$ )-coralydine.**<sup>53</sup> Baudoin *et al.* have recently applied their Pd(0)-catalysed cyclisation methodology in the synthesis of coralydine, a tetrahydroprotoberberine alkaloid containing a tetrahydroisoquinoline core.<sup>53</sup> These tetrahydroisoquinolines are easily accessible from dihydro-quinolines; structural motifs found commonly in many natural products. Baudoin used a tandem process involving electrocyclic ring-opening of a benzocyclobutane, followed by 6 $\pi$ -electrocyclisation to access the dihydroquinoline core of coralydine **64** (Scheme 12).

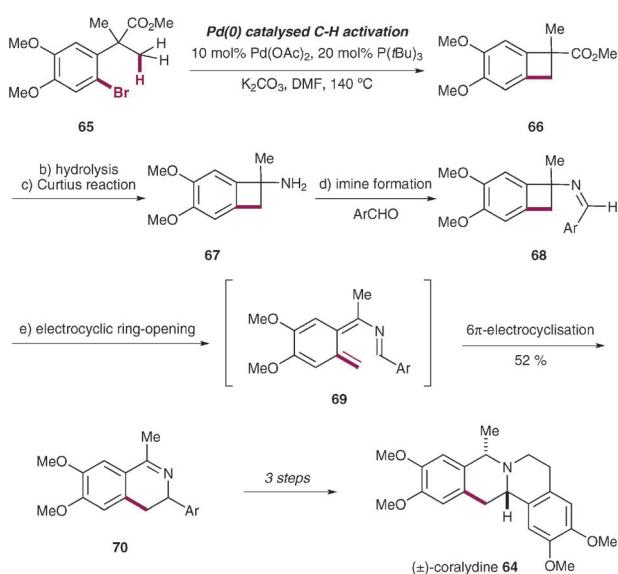
Starting from bromoarene **65**, benzocyclobutane **66** was synthesised *via* the described sp<sup>3</sup> C–H activation strategy (Scheme 13). Hydrolysis of the ester, followed by Curtius rearrangement afforded the amino-benzocyclobutane **67**. Reaction of this amine with a benzaldehyde derivative formed the corresponding imine **68**, which underwent the tandem electrocyclic ring-opening/ring-closing process (*via* **69**) to afford the dihydroisoquinolone **70** in 52% yield from the benzocyclobutane **66** over 4 steps. Reduction of the imine followed by desilylation and Mitsunobu reaction afforded racemic coralydine **64**, completing the synthesis in an overall 6.2% yield, and representing a novel approach to the synthesis of tetrahydroisoquinolines.



**Scheme 11** Proposed catalytic cycle for Pd(0)-catalysed synthesis of benzocyclobutanes.



**Scheme 12** Key disconnections *en route* to coralydine.



**Scheme 13** Baudouin's synthesis of coralydine.

### The synthesis of complanadine A

The Lycopodium alkaloids are a skeletally diverse family of natural products which have attracted a large amount of interest due to their complex molecular architectures and their potentially useful biological properties, such as the ability to stimulate nerve growth factor production.<sup>54</sup> Complanadine A (71), which

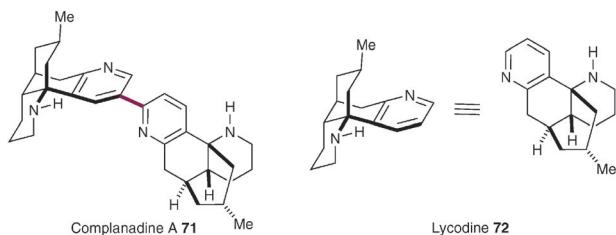
was isolated from the club moss *Lycopodium complanatum*<sup>55</sup> has a structure consisting of two molecules of lycodine 72 joined by a C2–C3' linkage (Fig. 7). Although this dimeric structure provides an obvious disconnection strategy, uniting these two lycodine molecules is a challenging task, as complanadine A is an unsymmetrical dimer of lycodine and therefore requires control of regioselectivity in the dimerisation step.

Recently, Sarpong and co-workers have completed the synthesis of (+)-complanadine A *via* a C–H functionalisation strategy.<sup>56</sup> They employed an Ir(i)-catalysed C–H borylation reaction, developed by the Smith/Maleczka<sup>57</sup> and Hartwig/Miyaura/Ishiyama<sup>58</sup> laboratories, that enabled the dimerisation of the two lycodine derived fragments.

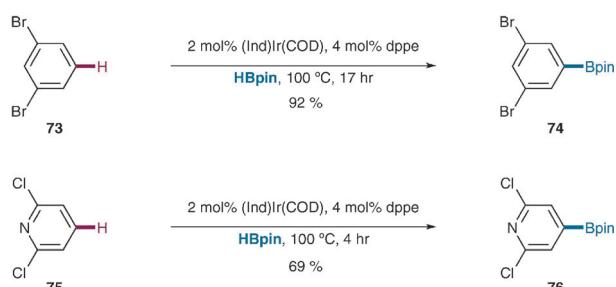
**Iridium(i)-catalysed C–H borylation.** Organoboron compounds are highly versatile intermediates in organic synthesis, and therefore direct borylation of hydrocarbons is a powerful synthetic strategy. The Smith/Maleczka and Hartwig/Miyaura/Ishiyama laboratories have developed a highly efficient C–H activation strategy for the synthesis of organoboron compounds.<sup>57,58</sup> This process uses air-stable, commercially available iridium(i) precursors in conjunction with 2,2'-bipyridine ligands to form complexes that catalyse the direct borylation of arenes with B<sub>2</sub>pin<sub>2</sub> or HBpin, generating pinacol arylboronates under relatively mild conditions.

The regiochemistry of the borylation is controlled by steric factors and often a single regioisomer is obtained, with borylation usually occurring at the sterically least hindered position. Interestingly, aromatic C–H bonds are selectively borylated in the presence of C–halogen bonds (73). Pyridines (75) have also been shown to be tolerant to these conditions, with borylation occurring selectively at the sterically least hindered C–H bond (Scheme 14).<sup>57,58</sup> Both electron rich and electron poor arenes undergo borylation, further demonstrating the broad scope of this methodology.

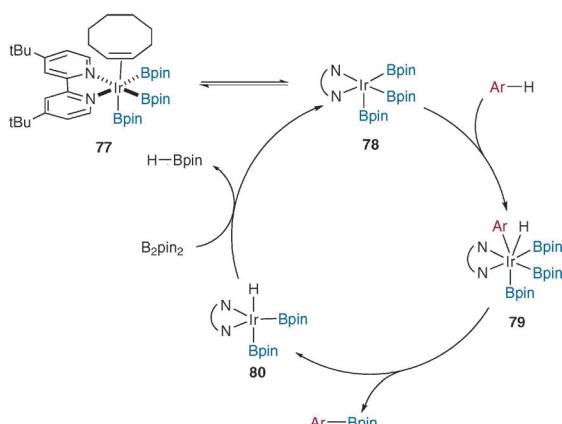
The proposed catalytic cycle is thought to start with the generation of the active tris(boryl)Ir(III) catalyst 78. Oxidative addition of an arene C–H bond to this intermediate yields the Ir(V) species 79. Reductive elimination then gives the desired product, ArBpin, and generates the Ir(III) hydride complex 80. Oxidative addition of B<sub>2</sub>pin<sub>2</sub> followed by reductive elimination of HBpin regenerates the active catalyst 78 (Scheme 15). The resulting HBpin can also participate in the regeneration of the active catalytic species *via* oxidative addition to 80 followed by reductive elimination of hydrogen. This direct borylation strategy provides a simple and efficient route for the synthesis of useful arylboronate intermediates, especially due to the reliable and predictable selectivity of this transformation.



**Fig. 7** Disconnection strategy to complanadine A 71.



Scheme 14 Ir(i)-catalysed direct borylation of arenes.



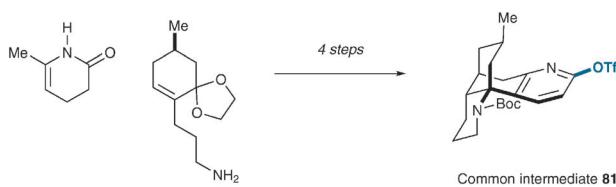
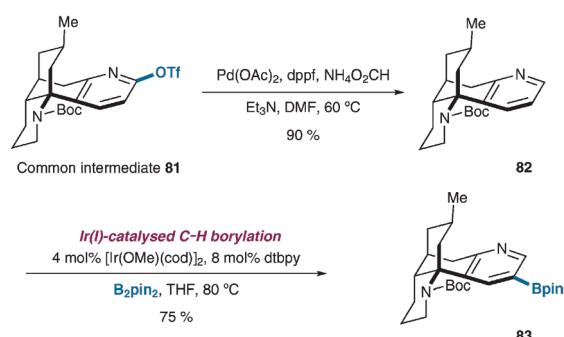
Scheme 15 Proposed mechanism for the Ir(i)-catalysed borylation.

**Sarpong's synthesis of complanadine A.**<sup>56</sup> Sarpong identified a key disconnection that views complanadine A as a dimer of a common intermediate, triflate **81** (Scheme 16). The key triflate **81** can be readily assembled in 4 steps.

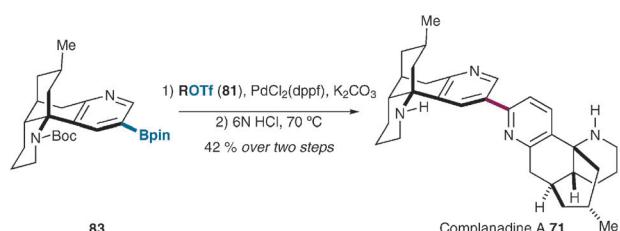
Removal of the triflate group under Pd-catalysed reducing conditions provided the unfunctionalised lycodine derivative **82** for the Ir(i)-catalysed borylation. Treatment of **82** with [Ir(OMe)(cod)]<sub>2</sub>, dtbpy and bis(pinacolato)diboron in THF at 80 °C for 5.5 h gave **83** in 75% yield (Scheme 17).

The selectivity is consistent with that predicted, with borylation occurring at the sterically least hindered position. Suzuki cross-coupling of boronic ester **83** with triflate **81**, followed by cleavage of the Boc protecting groups afforded complanadine A **71** in an overall yield of 42% over the two steps (Scheme 18).

Identification of symmetry elements in molecules has always provided a disconnection strategy that rapidly breaks down molecular complexity, however even just a small break in symmetry results in a significantly more challenging synthesis. Sarpong's use of Ir(i)-catalysed borylation to desymmetrise the common lycodine intermediate enabled an efficient, streamlined synthesis whilst still utilising the inherent symmetry of this natural product.

Scheme 16 Synthesis of the common intermediate **81**.

Scheme 17 Synthesis of the key coupling partners.



Scheme 18 Complanadine A endgame.

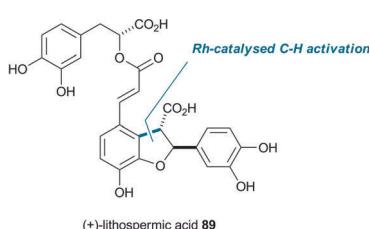
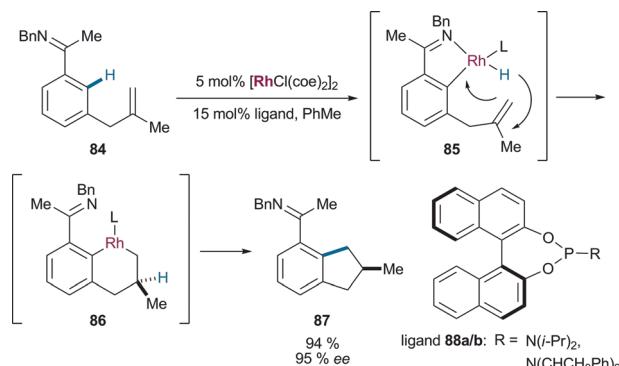
### Rh(i)-catalysed directed C–H bond activation in the synthesis of natural products

**Rh(i)-catalysed directed C–H bond activation.** Bergman and Ellman have demonstrated that Wilkinson's catalyst could be effectively employed in intramolecular C–H alkylation processes towards the synthesis of functionalised indane, tetralane, dihydrobenzofuran and dihydroindole derivatives.<sup>59</sup> As part of the further development of a catalytic enantioselective reaction, a range of chiral phosphorus ligands were investigated.<sup>60</sup> In the reaction of imine **84** with rhodium (i) catalysts, excellent enantioselectivities and conversions to **87** were obtained with the (S)-BINOL-derived phosphoramidites **88**. Interestingly, the amine stereochemistry was found to be insignificant, with the enantioselectivity being controlled by the BINOL backbone. The reaction proved tolerant to a range of substrates, and proceeded at room temperature in some cases (Scheme 19).

This reaction proceeds *via* a hydrometallation-type mechanism, resulting in 100% atom efficiency, further demonstrating the elegance of this reaction.<sup>61</sup> The high enantioselectivities are thought to be a result of a highly diastereoselective migratory insertion of the olefin into the Rh–H bond after C–H activation.

**Bergmann and Ellman's synthesis of (+)-lithospermic acid.**<sup>62</sup> This methodology was effectively applied in the first total synthesis of (+)-lithospermic acid (Fig. 8).<sup>62</sup> Lithospermic acid **89** has attracted considerable attention as a result of its impressive anti-HIV activity whilst still being non-toxic. It has been shown to suppress HIV production by inhibition of the viral integration process.<sup>63</sup>

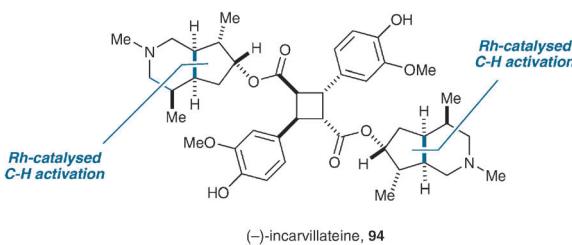
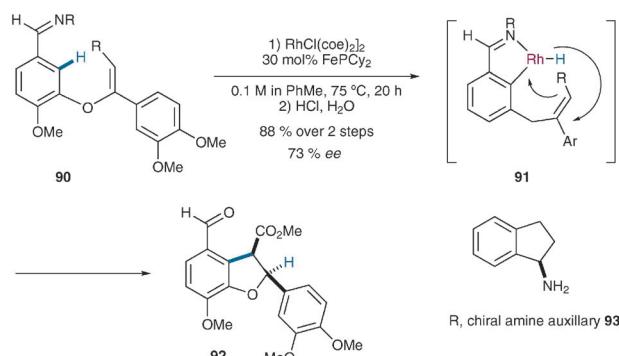
It was initially hoped that the highly functionalised dihydrobenzofuran core of lithospermic acid could be synthesised *via* the Rh(i)-catalysed intramolecular C–H bond activation strategy described above. However, no chiral catalyst could be identified that provided satisfactory yields and/or



enantioselectivities in the cyclisation. Instead, chiral imine auxiliaries were employed in order to achieve a diastereoselective insertion of the prochiral olefin. It was found that the imine formed from (*R*)(–)-aminoindane **93** led to the optimum yield and diastereoselectivity in the C–H alkylation step. Following auxiliary hydrolysis, the dihydrobenzofuran product was obtained in 88% yield, with 73% *ee* (Scheme 20),<sup>62</sup> four further steps completed the synthesis of (+)-lithospermic acid.

**Bergmann and Ellman's synthesis of (–)-incavillateine.**<sup>65</sup> This Rh(i)-catalysed C–H bond activation strategy has been extended to the alkylation of olefinic C–H bonds, which has successfully been applied in the synthesis of (–)-incavillateine **94**.<sup>64,65</sup> (–)-Incarvillateine is a monoterpene alkaloid, first isolated from *Incarvillea sinensis* (Fig. 9). Since its isolation it has attracted significant attention due to its potent analgesic properties, displaying a significant antinociceptive effect.<sup>66</sup>

Bergman and Ellman have reported the concise synthesis of (–)-incavillateine **94** using conditions developed from their recently reported Rh(i)-catalysed C–H alkenylation

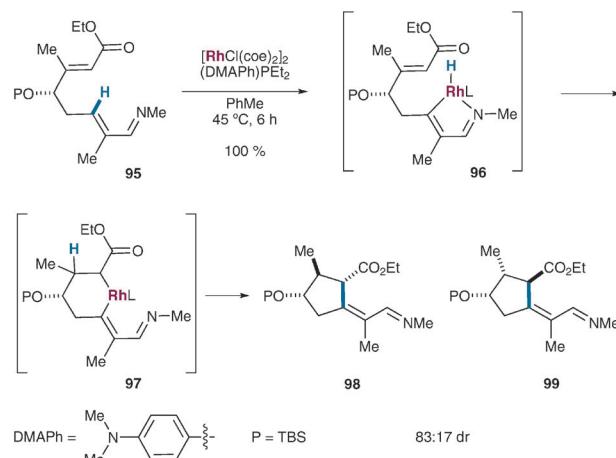


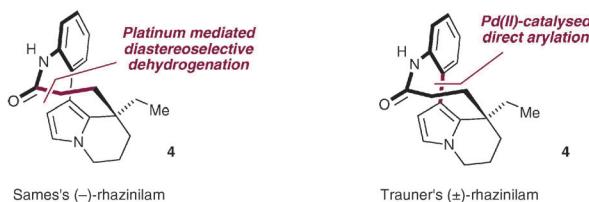
of  $\alpha,\beta$ -unsaturated imines with alkynes.<sup>67</sup> Ferrocenyl dialkyl phosphines and 4-(dimethylamino)phenyl (DMAPh) based phosphines were investigated and whilst many of these were found to be active, (DMAPh)-PEt<sub>2</sub> was found to be the most selective ligand. Therefore, imine **95** provided the diastereomers **98** and **99** in a  $\sim 5:1$  ratio with catalyst loading reduced to just 2.5 mol% (Scheme 21), forming the core of the target natural product.

The synthesis of (–)-incavillateine was completed in 6 steps following the cyclisation with an overall 15.4% yield. The use of Rh-catalysed alkylation installed two of the five stereocentres in the bicyclic piperidine as well as stereospecifically installing the tetrasubstituted, exocyclic alkene. The rapid assembly of stereocentres demonstrates the power of this methodology.

### The rhazinilam alkaloids

Rhazinilam **4** was first isolated in 1965 from the plant species *Melodinus australis*,<sup>68</sup> and was found to interfere with tubulin polymerisation dynamics and consequently mitosis in cell division. Rhazinilam displays the effect of both vinblastine and taxol anti-cancer compounds in that it not only induces the non-reversible assembly of tubulin, but also inhibits the cold-induced disassembly of the microtubule (Fig. 10).<sup>69</sup> As a result of these interesting anti-cancer properties, and the synthetic challenge posed by its novel architecture, rhazinilam and related structures have attracted considerable attention in the search for anti-cancer treatments. Both racemic and enantioselective syntheses have been completed, several of which involve one or more C–H functionalisation steps to install key bonds. Sames' approach to (–)-rhazinilam involved an impressive late stage diastereoselective dehydrogenation



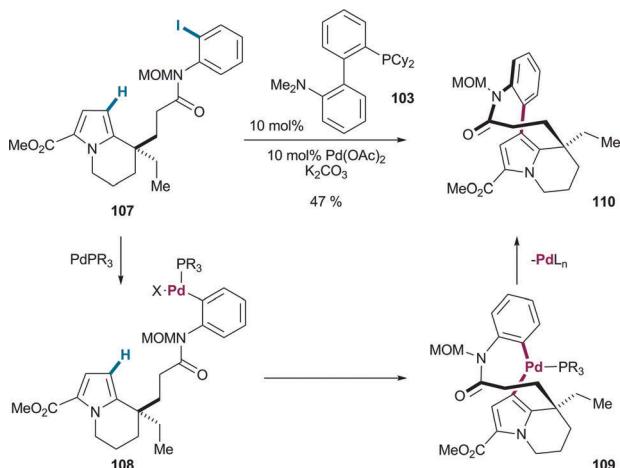


**Fig. 10** The rhazinilam alkaloids and associated disconnection strategies.

step *via* C–H bond activation.<sup>3d</sup> Here, a stoichiometric amount of a platinum salt was used to functionalise an isolated sp<sup>3</sup> C–H bond in the presence of many other functional groups. In 2005 Trauner *et al.* reported the concise synthesis of (±)-rhazinilam *via* a palladium(II)-catalysed cyclisation reaction.<sup>70a</sup> This synthesis featured an intramolecular direct arylation as the key step to assemble the nine-membered ring of rhazinilam.

**Biaryl synthesis *via* direct arylation.** The intramolecular biaryl forming step in Trauner's rhazinilam synthesis was based on a Pd-catalysed coupling, first developed by Fagnou *et al.*, between an aryl halide and a donor Ar–H species, **100** (Scheme 22).<sup>71</sup> A catalytic Pd(0) species is generated from Pd(OAc)<sub>2</sub> and ligand **103**. This subsequently undergoes oxidative addition to the aryl halide to form the Pd(II)-aryl species. A ligand assisted C–H deprotonation pathway (concerted metallation deprotonation, CMD) facilitates the activation of the aryl C–H donor to assemble the biaryl–Pd(II) intermediate prior to reductive elimination, forming the product (**104–106**).<sup>71,72</sup> Fagnou later applied this direct coupling in the synthesis of allocolchicine **102**, highlighting the utility of this process.<sup>74</sup>

**Trauner's synthesis of rhazinilam.**<sup>70</sup> This methodology has since been elegantly employed in the synthesis of rhazinilam to install the nine-membered lactam ring, directly assembling the framework of the natural product (Scheme 23). Treatment of **107** with 10 mol% of Buchwald's 'DavePhos' ligand **103**, 10 mol% Pd(OAc)<sub>2</sub> and K<sub>2</sub>CO<sub>3</sub> formed the strained, nine-membered lactam **110** in a moderate yield. Trauner and co-workers proposed the mechanism proceeded through intramolecular nucleophilic attack of the pyrrole moiety onto



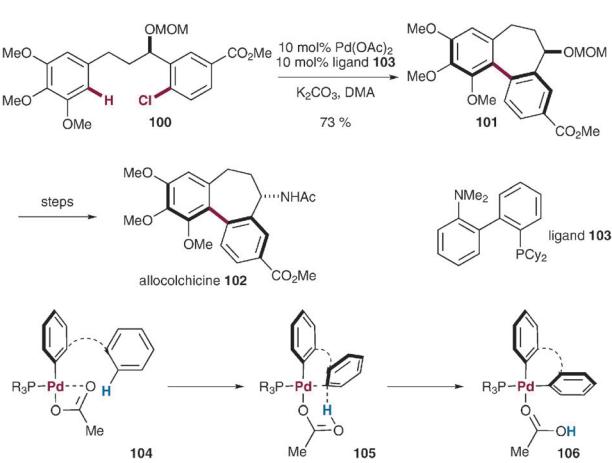
**Scheme 23** Trauner's synthesis of rhazinilam.

the Pd(II) centre *via* an S<sub>E</sub>Ar pathway, followed by a slow deprotonation step. They postulated that the electron-rich DavePhos ligand **103** not only facilitated oxidative addition but also the formation of a more reactive cationic palladium (II) species by dissociation of the halide. An alternative mechanism could proceed through a mechanism in line with a concerted metalation deprotonation pathway (opinion of the review authors).<sup>72,73</sup> Nevertheless, this remarkable 9-membered ring forming reaction represents a novel and highly useful method to generate the core architecture of rhazinilam, and will likely find widespread use throughout complex molecule synthesis.

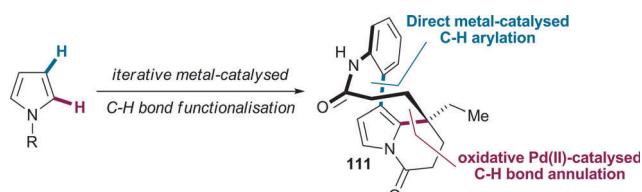
In the case of rhazinilam, the C3 position of the pyrrole has been selectively functionalised without the need for prior installation of functional groups, leading to a concise synthesis, demonstrating the synthetic power of direct coupling reactions of nucleophilic arenes and heteroarenes.

**Synthesis of rhazinicine.** The synthesis of another member of the rhazinilam alkaloid natural products, rhazinicine **111**, has recently been completed by Gaunt and co-workers.<sup>75</sup> Here, an Ir(I)-catalysed C–H borylation/Suzuki coupling sequence<sup>57,58</sup> and an oxidative Pd(II)-catalysed C–H bond annulation<sup>76</sup> were employed to install the key architecture of the natural product (Scheme 24).

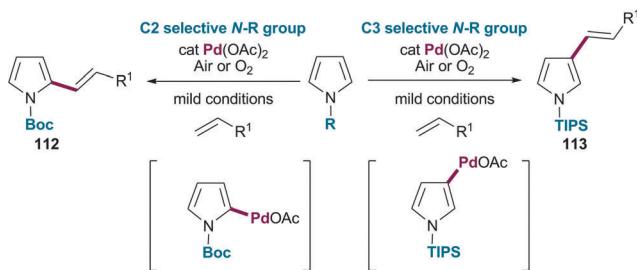
**C–H alkenylation of pyrroles.** Pyrroles are ubiquitous in natural products and medicinal agents,<sup>77</sup> however instability towards acidic and oxidative conditions has limited their utility in metal catalysed C–H transformations. Gaunt *et al.* developed an efficient aerobic palladium system for the C–H bond functionalisation of these sensitive molecules under ambient conditions.<sup>76</sup> This methodology has been used to generate a



**Scheme 22** Fagnou's synthesis of allocolchicine.



**Scheme 24** Gaunt's iterative C–H functionalisation strategy to rhazinicine.



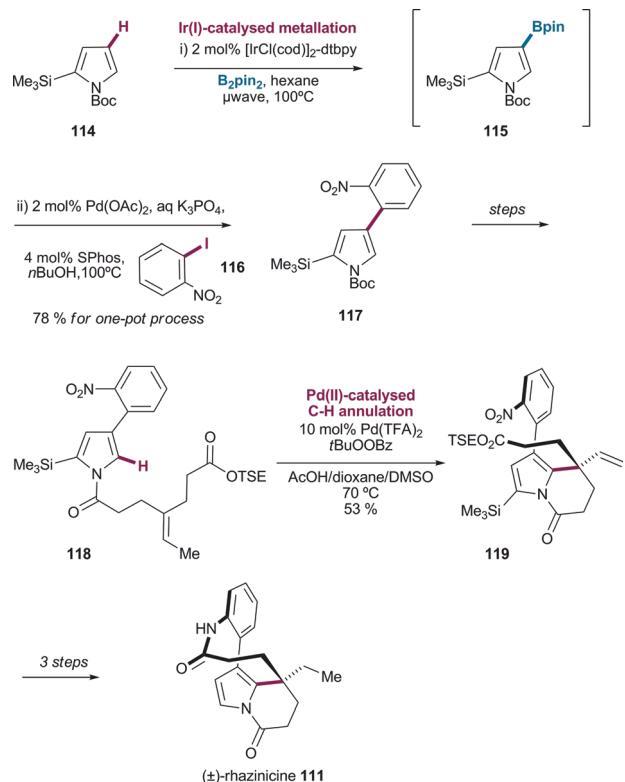
**Scheme 25** Gaunt's site-selective functionalisation strategy of pyrroles.

range of functionalised pyrrole architectures. It was found that it was possible to control the regioselectivity *via* sterically and electronically tuned *N*-pyrrole protecting groups. *N*-Boc pyrroles afforded the C2 product **112**, in line with the natural reactivity of pyrroles. However, *N*-TIPS pyrrole selectively formed only the C3 product **113**. It is thought that both reactions proceed *via* an electrophilic palladation step, followed by Heck type coupling with the olefin. The switch in selectivity is attributed to the sterically demanding nature of the TIPS group, which shields the C2 position from reaction with the palladium catalyst, forcing the reactive pyrrole to palladate at the C3 position (Scheme 25).

**Gaunt's synthesis of ( $\pm$ )-rhazinicine.<sup>75</sup>** This highly selective methodology was employed in the synthesis of rhazinicine **111** and allows the key structural architecture to be directly installed from a simple pyrrole nucleus *via* iterative metal-catalysed C–H bond functionalisation.

The use of multiple C–H activation steps in a synthesis has great potential to dramatically reduce the total step count because it precludes the need for pre-functionalisation at various stages throughout the route.<sup>71</sup> Although directly functionalising the C–H bonds to give the desired functional group would be highly effective, such a strategy can be complicated by selectivity issues in the functionalisation step and the increasing complexity of the substrates that would be required. Gaunt *et al.* showed that they could orchestrate the synthesis of rhazinicine through two key C–H activation steps.<sup>75</sup> First, a one-pot iridium (I)-catalysed borylation–Suzuki reaction<sup>57,58</sup> was used to couple pyrrole **114** with aryl iodide **116**, installing the heterobiaryl fragment **117** in excellent yields (Scheme 26). This is particularly useful in pyrroles, where installation of a large group on the nitrogen results in borylation selectively at the sterically less hindered C3 position **115**. Furthermore, these iridium catalysts are highly selective for aromatic C–H bonds and the by-products from this iridium reaction do not usually interfere in subsequent reactions of the arylboron products, such as Pd-mediated cross-couplings.

Coupling of the heterobiaryl fragment **117** with the hydrocarbon portion of the molecule afforded the key cyclisation precursor **118**. Using conditions adapted from the intermolecular alkenylation studies (Scheme 25), it was found that when **118** was treated with 10 mol% Pd(TFA)<sub>2</sub> and *t*BuOOBz as the oxidant, ( $\pm$ )-**119** was formed in 53% yield, installing the tetrahydroindoline ring system and all quaternary carbon centres as a single regioisomer at the desired C2 position of the pyrrole. A substituent at the C5 position was found to be crucial to prevent reaction at this more reactive position,



**Scheme 26** Iterative C–H functionalisation to access rhazinicine **111**.

and also to avoid competing oxidative pyrrole dimerisation reactions. The more active Pd(TFA)<sub>2</sub> catalyst was found to provide superior results compared to Pd(OAc)<sub>2</sub>, perhaps reflecting the lower reactivity of the sterically hindered C2 position of the pyrrole. They completed the synthesis to afford ( $\pm$ )-rhazinicine **111** in a total of 11 steps from commercial materials. Trauner has since used this oxidative Heck cyclisation in the synthesis of ( $\pm$ )-rhazinal,<sup>70b</sup> where catalytic Pd(OAc)<sub>2</sub> is used in preference.

This synthesis elegantly demonstrates how C–H functionalisation can be used in an iterative fashion to assemble complex molecular architecture. While iterative C–H functionalisation strategies have great potential in synthesis, before this can become a widely implemented method of synthesis significant development in both the selectivity and reactivity of C–H bond functionalisations in complex systems is necessary.

## Conclusions

This review has highlighted selected examples of the use of metal-catalysed C–H bond functionalisation in the synthesis of natural products. Although the use of these methods are still in their infancy, these selected examples demonstrate the potential of these strategies to streamline synthesis and provide novel approaches to complex architectures. To fully realise the potential of these strategies we must address a number of challenges that include the development of more new reactions that expand the C–H toolbox available, to discover reactions that work under mild reaction conditions, to address the problems of deploying C–H activation in complex systems, and to target the development of catalytic enantioselective

C–H activation strategies. The future of metal-catalysed C–H activation holds many exciting challenges and new developments will continue to push forward the frontiers of chemical synthesis.

## Acknowledgements

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