REVIEWS

Catalytic C–H functionalization by metal carbenoid and nitrenoid insertion

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Novel reactions that can selectively functionalize carbon–hydrogen bonds are of intense interest to the chemical community because they offer new strategic approaches for synthesis. A very promising 'carbon–hydrogen functionalization' method involves the insertion of metal carbenes and nitrenes into C–H bonds. This area has experienced considerable growth in the past decade, particularly in the area of enantioselective intermolecular reactions. Here we discuss several facets of these kinds of C–H functionalization reactions and provide a perspective on how this methodology has affected the synthesis of complex natural products and potential pharmaceutical agents.

In 2006, 31 new chemical entities were introduced to the world pharmaceutical market and 2,075 molecules were in phase I or II of clinical development[1]. The majority of these were small-molecule (relative molecular mass <1,000) organic compounds[2]. As knowledge about the specific interactions of drugs *in vivo* increases, often so does the structural complexity of new drug targets. A major obstacle to the development of such drugs is the difficulty associated with synthesizing large quantities in an economical fashion, because complex multi-step syntheses are usually required. In the general media, it is often overlooked that the accessibility of the components required for these new treatments will often govern their eventual success or failure. Likewise, a design element of any pharmaceutical agent is the expectation that the target compounds can be made economically. Therefore, new strategies for synthesis can become enabling technologies, making available new targets and materials that would have been previously out of range. For example, new methodologies such as metal-catalysed cross-coupling[3] and olefin metathesis[4–6] have rapidly become central transformations in the synthesis of new pharmaceutical agents. Selective C–H functionalization is a class of reactions that could lead to a paradigm shift in organic synthesis, relying on selective modification of ubiquitous C–H bonds of organic compounds instead of the standard approach of conducting transformations on pre-existing functional groups. The reactive sites in each type of transformation are very different, as illustrated in Fig. 1.

The many opportunities associated with C–H functionalization has made this field an active area of research. Organometallic chemists have focused much attention on developing 'C–H activation' strategies, whereby a highly reactive metal complex inserts into a C–H bond, activating the system for subsequent transformations[7–9]. One of the major challenges associated with this chemistry has been to render it catalytic in the metal complex[10]. A partial solution to this problem has been to use neighbouring functionality to direct less reactive metal complexes to the site for functionalization. Numerous reviews have been written about this method for C–H functionalization[11–17]. Here, however, we highlight another approach, in which a divalent carbon (carbene)[18] or a monovalent nitrogen (nitrene)[19], coordinated to a metal complex, inserts into a C–H bond[20]. This alternative approach offers many advantages over the metal-induced C–H insertion because the reactions exhibit high turnover numbers and can lead to high levels of selectivity, both in terms of regioselectivity and stereoselectivity (Fig. 2).

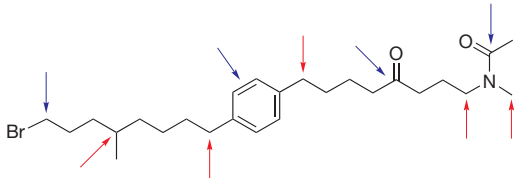

Figure 1 | Synthesis by functional group modification compared to C–H functionalization. Traditional sites for modification of organic molecules (indicated by blue arrows) rely on reactive (polarizable) functional groups. Such modes of reactivity include oxidation/reduction, aromatic substitution, and nucleophilic/electrophilic attack. Sites for direct functionalization of C–H bonds (red arrows) often have adjacent 'activating' groups, but can also occur at isolated positions.

C–H functionalization by metal carbenoids

The standard method for generating the transient metal carbenes is by metal-induced extrusion of nitrogen from diazo compounds[21].

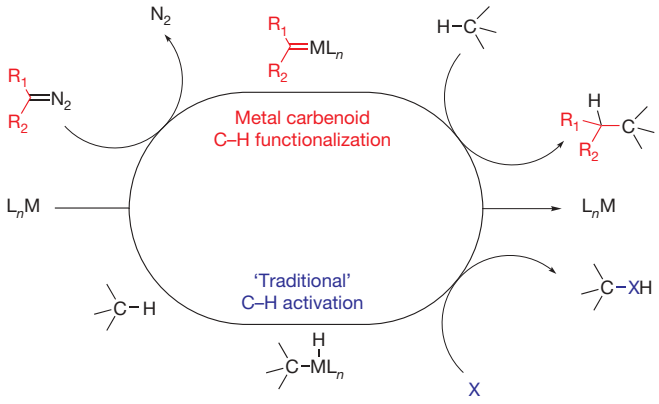

Figure 2 | Metal carbenoid C–H functionalization versus the 'traditional' C–H activation. In a traditional C–H activation manifold, the highly reactive metal complex (M = metal, L = ligand) inserts into a C–H bond. Regeneration of the active metal complex to form the C–H activation product has proved difficult. In contrast, C–H functionalization via a metal carbenoid approach typically uses a high-energy diazo compound and loss of nitrogen provides the driving force for the energetically unfavourable formation of the carbenoid. The highly reactive carbenoid species then inserts into a C–H bond to form the C–H activation product and liberates the metal catalyst for another cycle.

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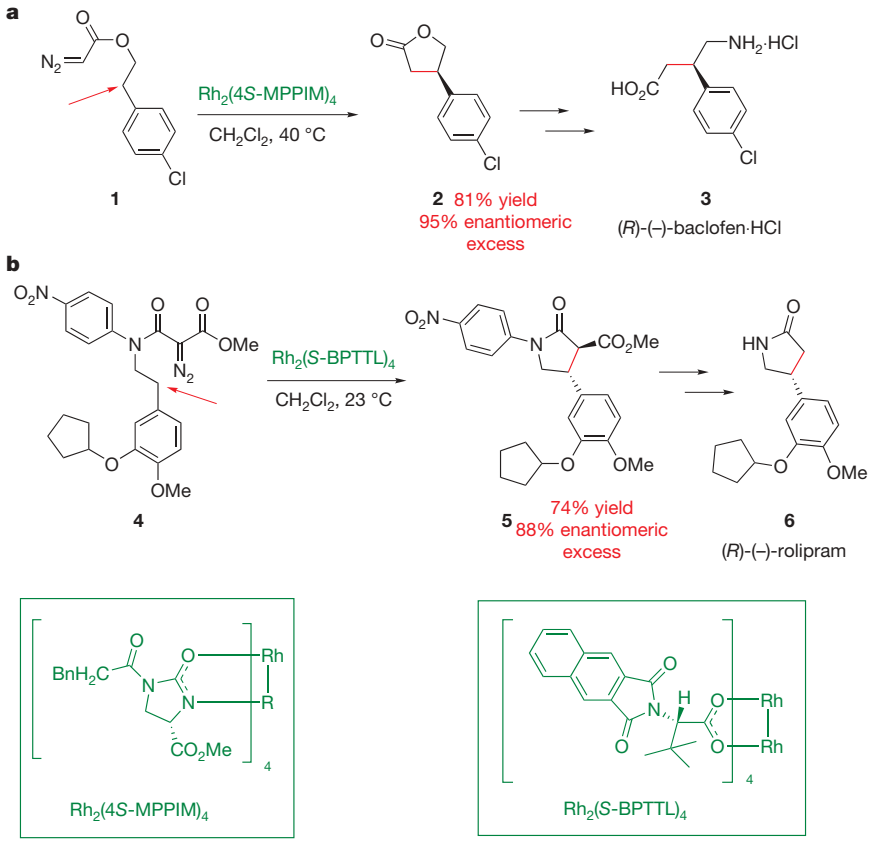

Figure 3 | Intramolecular C–H insertions. a, The intramolecular C–H insertion of an acceptor substituted carbenoid catalysed by the chiral rhodium carboxamidate catalyst $Rh_2(4S\text{-MPPIM})_4$ is the key step in an enantioselective synthesis of the $GABA_B$ receptor agonist (*R*)-(–)-baclofen (ref. 24). **b**, The intramolecular C–H insertion of an acceptor/acceptor-substituted carbenoid catalysed by the chiral rhodium carboxylate catalyst $Rh_2(S\text{-BPTTL})_4$ results in a concise synthesis of the phosphodiesterase type IV inhibitor (*R*)-(−)-rolipram (ref. 25).

The challenges of regioselectivity associated with the carbene-induced C–H functionalization meant that most of the early advances in this field were achieved in systems capable of intramolecular reactions[21–23]. Because the rhodium carbenoid and the reacting C–H bond are connected by a suitable tether, they are brought into close proximity, leading to a favourable regioselective transformation. By using a chiral catalyst, the C–H insertion can be made enantioselective, favouring the formation of one mirror image of the product over the other. This type of approach has been used in the synthesis of various pharmaceutical agents, such as (*R*)-(−)-baclofen[24] (**3**) and (*R*)-(−)-rolipram[25] (**6**) (Fig. 3).

In terms of strategic reactions, controllable intermolecular transformations would be much more powerful because the sequence of steps required to make the substrate for an intramolecular reaction would no longer be needed. Controlling the regioselectivity of intermolecular C–H insertions, however, has been challenging, particularly in the case of the most commonly used metal carbenoids derived from acceptor-only substituted diazoacetates[22,26]. The metal carbenoids behave as very electrophilic species and the electron-withdrawing ester group reinforces the high reactivity, generating a system characterized by poor regioselectivity between different C–H bonds[27–29]. In recent years, extensive efforts have been made to attenuate the carbenoid reactivity by altering the nature of the catalysts, with some improvements having been made by using very bulky ligands with copper[30] and silver[31] complexes. The major breakthrough in this field, however, was the discovery that carbenoids functionalized with both donor and acceptor groups were much more chemoselective than the traditional carbenoids, as shown in Fig. 4[18,32,33].

The synthetic potential of the donor/acceptor carbenoids is illustrated in a direct enantioselective synthesis of the most active enantiomer of *threo*-methylphenidate (Ritalin) (compound **9**).

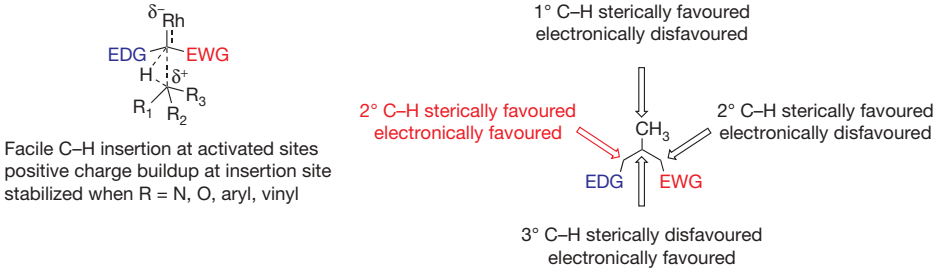

Figure 4 | Controlling factors of carbenoid reactivity. The substituents attached to the carbenoid help to modulate its reactivity. The presence of both an electron-donating group (EDG) and an electron-withdrawing group (EWG) is necessary to reduce carbene dimerization pathways and increase selectivity for intermolecular reactions. During the C–H activation event, a partial positive charge build-up occurs at the carbon undergoing C–H functionalization. Sites adjacent to functionality that can stabilize this polarization are considered to be electronically 'activated' towards carbenoid reactions (1°, 2° and 3° represent primary, secondary or tertiary sites, indicating the number of substituents at a particular carbon site).

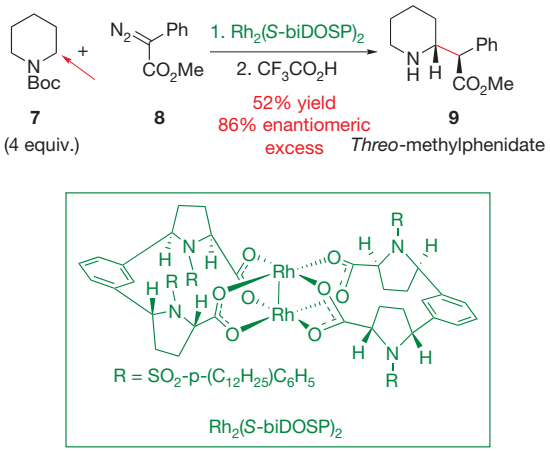

Figure 5 | Ritalin synthesis. A concise, stereoselective synthesis of the biologically active enantiomer of the pharmaceutical agent Ritalin (*threo*-methylphenidate) was achieved using the bridged, chiral rhodium catalyst Rh_2(*S*-biDOSP)$_2$ (ref. 38). Boc, *tert*-butoxycarbonyl.

Ritalin is an important drug for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) and, as an old drug, is sold as a racemate. The most active enantiomer of Ritalin has been marketed as an independent therapeutic agent[34]. Its synthesis using conventional functional group manipulations requires multiple steps[35,36]. The C–H functionalization approach to Ritalin, conversely, is direct[37,38]. The Rh_2(*S*-biDOSP)$_2$[39] catalysed reaction of *N*-protected piperidine (compound **7**) with methyl phenyldiazoacetate (compound **8**) followed by removal of the protecting group leads to the rapid synthesis of (*R*,*R*′)-(+)-methylphenidate (compound **9**) in 86% enantiomeric excess (Fig. 5)[38].

C–H functionalization can provide complementary approaches to achieve transformations equivalent to some of the classic reactions of organic synthesis[40–45]. For example, C–H functionalization adjacent to oxygen can lead to products that would be commonly derived from an aldol reaction (Fig. 6)[44,46]. In the specific example used to illustrate this concept, other key elements that control the selectivity of this chemistry are demonstrated. The carbenoid has an electronic preference to functionalize C–H bonds in which the carbon can stabilize positive charge build-up because the C–H insertion has the partial characteristic of a hydride abstraction event[47,48]. In this case, selective functionalization occurs adjacent to the siloxy group rather than the more electron-withdrawing acetoxy group in compound **10**. Additionally, if there is good steric differentiation at the C−H insertion site, high levels of diastereoselectivity can be achieved. Thus, compound **11** is formed in 92% yield, >94% diastereomeric excess and 72% enantiomeric excess[44].

C–H functionalization adjacent to nitrogen can lead to products that would be typically formed from a Mannich reaction, as illustrated in the direct synthesis of β-amino ester **13** (ref. 42). This example illustrates the important controlling influences in steric factors, because the electronically most activated site in compound **12**, the benzylic carbon, is sterically inaccessible and selective functionalization occurs at the *N*-methyl group[42,49,50].

A further advantage of the carbenoid-induced C–H functionalization is the possibility of the C−H insertion step initiating a cascade sequence. A spectacular example of such an event is termed the 'combined C–H activation/Cope rearrangement'[51–56]. One of the earliest examples of this reaction is shown between the vinyldiazoacetate **15** and 1,3-cyclohexadiene in Fig. 7. Before the C–H functionalization is complete, a rearrangement occurs to form a 1,4-cyclohexadiene derivative **16** with exceptional enantiocontrol. The entire process is believed to occur via a concerted, ordered transition state that leads to higher stereoselectivity than is normally observed in a direct C–H insertion. This transformation has been used in a very concise enantioselective formal synthesis of the antidepressant sertraline (Zoloft, Fig. 7)[51].

An even more elaborate sequence of events has been developed for the enantioselective synthesis of 4-substituted indoles. Indoles are present in a number of pharmaceutical agents[57] and there has been much interest in the enantioselective synthesis of 1-aryl-1-indolylalkyl derivatives. Normally the indole is functionalized at the 2- or 3-position because these are the most reactive sites using conventional chemistry[58–60]. In contrast, the C–H functionalization strategy results in a very efficient method for generating 4-substituted indoles with high enantioselectivity (Fig. 8)[56]. These types of

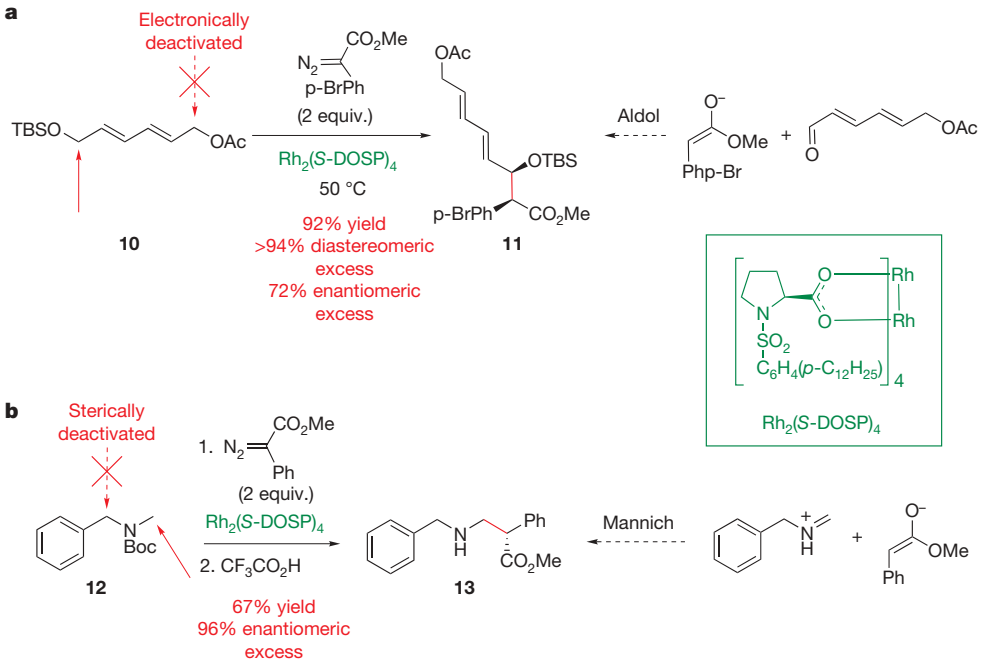

Figure 6 | C–H functionalization as a strategic reaction. a, C–H insertion α to oxygen generates products that would classically be formed via an aldol reaction. The insertion occurs preferentially at the site adjacent to the more electron-rich siloxy-protected oxygen (ref. 44) **b**, C–H insertion α to nitrogen generates the products formally derived from a Mannich reaction, with high levels of enantiocontrol (ref. 42). TBSO, *tert*-butyldimethylsiloxy.

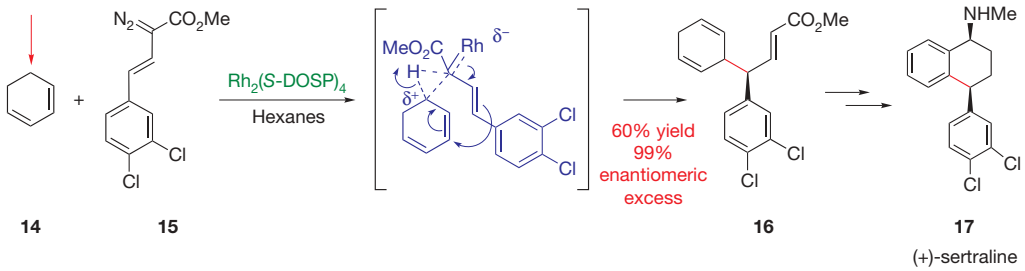

Figure 7 | Combined C–H activation/Cope rearrangement. The C–H functionalization with a vinyldiazoacetate begins at the allylic C–H bond, but is interrupted when a Cope rearrangement occurs (see blue intermediate) to give the combined C–H activation/Cope rearrangement product with exceptionally high enantioselectivity (ref. 51).

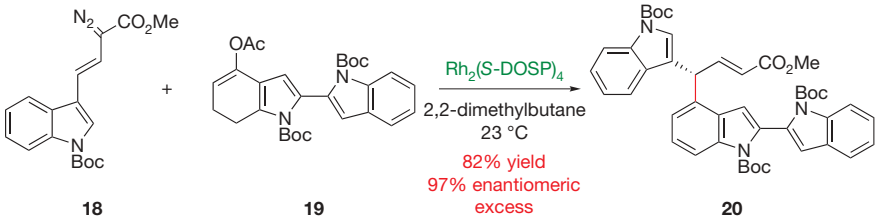

Figure 8 | *Tris*-indole synthesis. The product of the combined C–H activation/Cope rearrangement between the vinyldiazoacetate **18** and the 4-acetoxy-6,7-dihydroindole **19** undergoes loss of acetic acid to generate the aromatized *tris*-indole compound **20** in good yield and in high enantiomeric excess (ref. 56).

compounds and related structures have not been extensively studied as potential therapeutic agents, presumably because they were not readily accessible.

A powerful enabling synthetic methodology should greatly simplify the total synthesis of complex natural products. Notable examples of this have been illustrated in the synthesis of the natural products derived from the West Indian gorgonian coral *Pseudopterogorgia elisabethae* (Fig. 9)[61]. Previous syntheses have struggled with controlling the stereochemistry at the three stereocentres indicated in red, primarily because the natural products lack

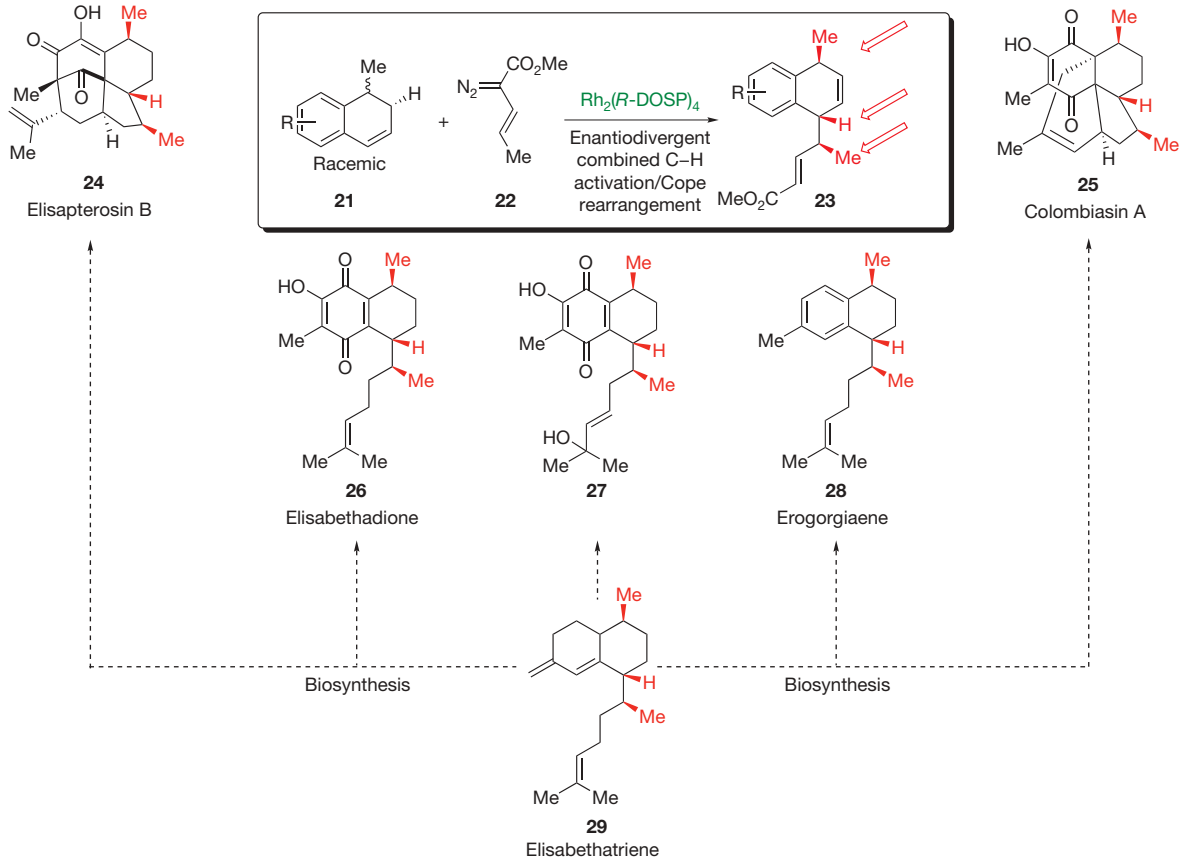

Figure 9 | Application of C–H functionalization to natural product synthesis. A series of diterpene natural products have been isolated from the gorgonian coral *Pseudopterogorgia elisabethae*. All are derived biosynthetically from (+)-elisabethatriene and share the same configuration at the three stereocentres shown by red arrows (ref. 61). One of the most challenging aspects in synthesizing these molecules is controlling the stereochemistry at these sites because of the lack of neighbouring functional groups. A powerful feature of the combined C–H activation/Cope rearrangement is the ability of the chiral catalyst Rh_2(*R*-DOSP)$_4$ to differentiate between the enantiomers of a racemic substrate to generate all three stereocentres in a single step.

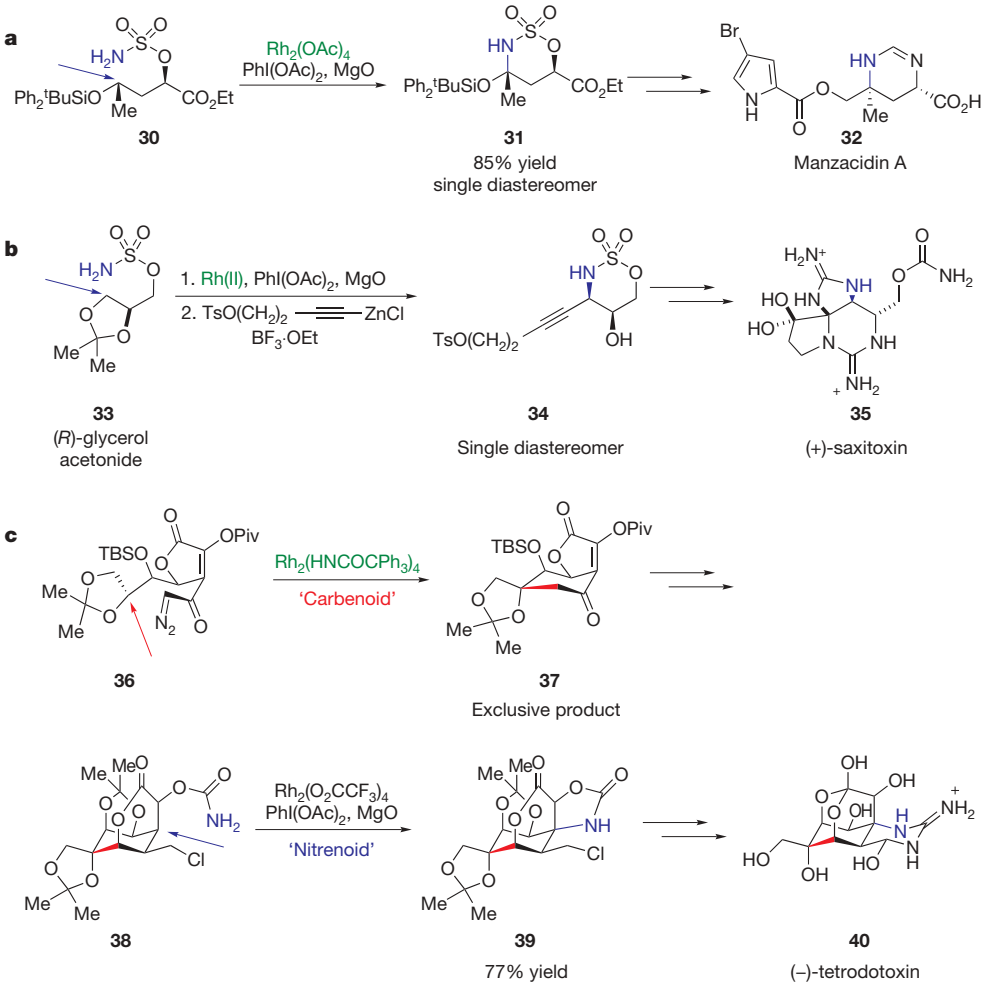

Figure 10 | Application of C–H amination to natural product synthesis. **a**, **b**, Sulphamate esters provide excellent precursors to nitrenes that can undergo highly diastereoselective intramolecular insertions into tertiary C–H bonds. Du Bois has shown the potential of this methodology with syntheses of the marine alkaloid manzacidin A (ref. 74) and the natural product (+)-saxitoxin, an ion channel blocker (ref. 75). **c**, An elegant synthesis of the potent marine poison (±)-tetrodotoxin by Du Bois and colleagues illustrates the utility and complementarity of C–H functionalization by metal carbenoids and nitrenoids (ref. 76). $Ph_2{}^tBuSiO$, diphenyl-*tert*-butylsiloxy; Piv, pivalate.

suitable functional groups as handles in the synthetic transformations[62–67]. In contrast, an enantiodivergent C–H functionalization of racemic dihydronaphthalenes **21** generates the core structures **23** with high stereoselectivity at all three stereocentres. In the presence of the chiral catalyst Rh_2(*R*-DOSP)$_4$ (ref. 68), the other enantiomer of the dihydronaphthalene **21** reacts in an entirely different manner to form cyclopropanation products[69]. This reaction can be conducted with a variety of dihydronaphthalene derivatives and has been applied to very efficient syntheses of a range of natural products including elisapterosin B[70] (compound **24**), colombiasin A[70] (compound **25**), elisabethadione[71] (compound **26**), the *p*-benzoquinone **27**[71] and erogorgiaene (compound **28**)[69].

C–H functionalization by metal nitrenoids

In recent years, metal nitrenoid complexes have also been shown to be capable reagents for C–H functionalization, a reaction that is usually called C–H amination[14,72,73]. Some spectacular intramolecular examples have been reported by Du Bois and colleagues for the synthesis of complex natural products such as manzacidin A[74] (compound **32**), (+)-saxitoxin[75] (compound **35**) and (−)-tetrodotoxin[76] (compound **40**) (Fig. 10). These transformations illustrate how, by judicious choice of substrates, the C–H amination can be conducted in the presence of a range of functional groups. Generally, the most broadly used precursors to the transient metal nitrenes have been aryliminoiodinanes, which are decomposed by a suitable metal complex[77]. In the syntheses described here, the aryliminoiodinanes are produced *in situ* from the corresponding amine, which makes the overall transformations even more attractive[78,79].

Lebel and colleagues have shown that *N*-tosyloxyamides such as compound **41** are also efficient precursors to transient metal

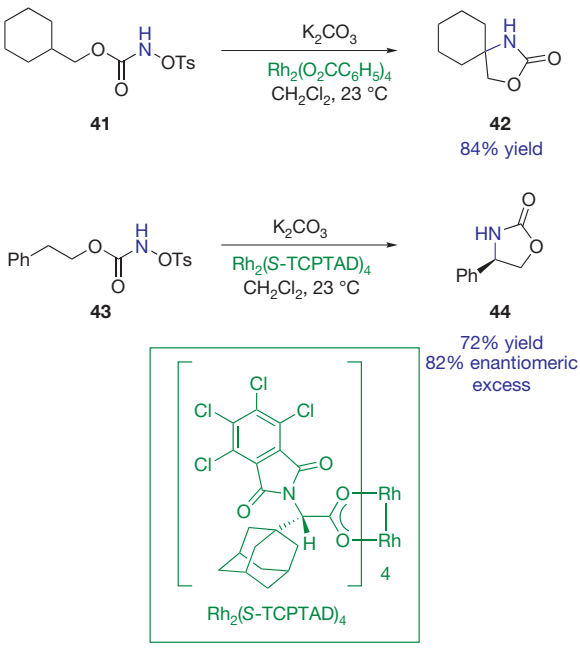

Figure 11 | Enantioselective C–H amination. Lebel and colleagues have developed an alternative method for the *in situ* generation of metal nitrenoids using *N*-tosyloxycarbamates as the precursors. This method avoids the generation of a stoichiometric amount of iodobenzene, a drawback to the use of hypervalent iodine reagents that are commonly used to generate nitrene precursors *in situ*. Lebel's method proceeds with high efficiency (ref. 80), and when the chiral catalyst Rh_2(*S*-TCPTAD)$_4$ is used, good levels of enantioselectivity can be achieved (ref. 82).

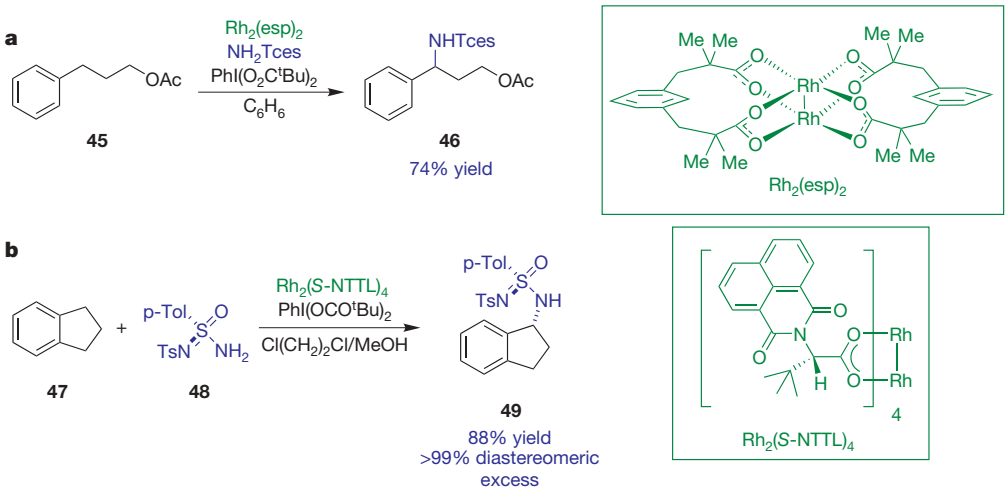

Figure 12 | *In situ* generation of metal nitrenoid precursor. a, The bridged, achiral rhodium catalyst $Rh_2(esp)_2$, developed by Du Bois and co-workers specifically for nitrenoid reactions, has demonstrated remarkable efficiency in both intra- and intermolecular reactions with catalyst loadings as low as 2 mol.% (ref. 84). **b**, Exceptionally high diastereoselectivity can be achieved in intermolecular C–H amination reactions when a 'matched' reaction is carried out using a chiral sulphonamide as the nitrene precursor and a chiral rhodium catalyst (ref. 87). 'esp' is a trivial name for the catalyst (structure shown). Tces, 2,2,2-trichloroethoxysulphonyl.

nitrenoids[80,81]. By conducting this nitrene insertion with chiral dirhodium catalyst $Rh_2(S\text{-TCPTAD})_4$, enantioselective transformations can be achieved, as illustrated in Fig. 11[82]. The site for C–H amination is governed by the length of the tether and in general five-membered rings are preferred.

Du Bois and colleagues have developed a bridged achiral rhodium catalyst $Rh_2(esp)_2$ that has performed well at low catalyst loadings in both intra- and intermolecular C−H amination reactions (Fig. 12)[83–85]. Enantioselective intermolecular reactions of metal nitrenes are less developed than the parallel reactions of metal carbenes, although some significant examples have been reported[81,82,86,87]. A conceptually interesting approach to stereoselective intermolecular nitrene chemistry involves the use of a chiral sulphonamide (compound **48**) as the amine source in the reactions. Exceptionally high diastereoselectivity can be obtained in matched reactions between the appropriate enantiomers of a chiral sulphonamide and a chiral rhodium catalyst[87]. Given the ubiquity of nitrogen atoms in biologically active compounds, C−H amination as an enabling technology in pharmaceutical synthesis has broad potential. A number of efficient transformations have been achieved at benzylic positions, but broad application of this chemistry is still relatively limited.

Future directions

C–H functionalizations by means of metal carbenoids and metal nitrenoids are rapidly becoming very general strategic reactions for the synthesis of natural products and pharmaceutical targets. The intramolecular C−H insertion of metal carbenoids is now a well-established transformation, while the corresponding intramolecular C−H amination has, in the last few years, been shown to be applicable to the synthesis of highly complex natural product targets. The recognition that donor/acceptor functionalized carbenoids are highly selective intermediates has opened up enantioselective intermolecular C–H insertion as a powerful transformation. Enantioselective intermolecular C−H amination is also developing well and is likely to see broad synthetic application. During the next few years this field is likely to undergo rapid expansion as improved chiral catalysts and even more selective reagents are developed. It has already been shown that these reactions can be considered as complementary to some of the classic reactions of organic synthesis and this will be further emphasized as additional ingenious applications of this chemistry to total synthesis are described. As the synthetic uses of C–H functionalization become more fully appreciated, its application as an enabling technology for drug discovery and synthesis will become a common practice.

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Acknowledgements The research conducted in the Davies laboratories was supported by the National Institutes of Health and the National Science Foundation.

Author Contributions This was a collaborative writing project between H.M.L.D. and J.R.M., in which both contributed equally.

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