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**EMERGING AREA**

# Cascade polycyclisations in natural product synthesis

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The efficient, stereocontrolled construction of polycyclic ring systems has long presented a formidable challenge to synthetic chemists. Cascade reactions offer a 'quick fix'—building multiple rings in a single step—and often dramatically shorten a synthetic route. In this Emerging Area article, a selection of the most recent and impressive examples of applications of this tactic to natural product synthesis are discussed, which demonstrate the ambition and achievements of the modern synthetic chemist.

## Introduction

Cascade (or domino) processes, which achieve the sequential formation of multiple new bonds in a single synthetic operation, are among the most appealing of transformations to organic chemists.[1,2] They can comprise many different types of reaction, but all are linked by the concept of the *in situ* generation of a series of reactive intermediates able to undergo consecutive transformations, either spontaneously under a given set of reaction conditions, or through the influence of catalysts or other reagents present in the reaction mixture. Those cascade reactions which install multiple stereocentres and construct cyclic frameworks in a controlled manner are especially impressive, due to the obvious challenge and reward presented by this type of operation.

The beauty of cascade reactions lies in their associated step-efficiency, which can streamline an approach towards a target molecule, and in the increase in structural complexity which is intrinsically linked to the cascade. The successful incorporation of such strategies into total syntheses, in a manner which produces greater returns in molecular complexity in increasingly ambitious settings—but without the need for over-engineering of the reaction substrate—is perhaps the ultimate synthetic challenge.

This article highlights recent outstanding examples of cascade reactions involving *poly*cyclisations in natural product synthesis (*i.e.* the formation of multiple rings in the cascade step), with a particular focus on emerging strategies or areas which are ripe for further development, and on more classical tactics which have reached impressive levels of understanding and implementation. The review is divided into sections which highlight different cascade reaction themes, although it is important to recognise that as well as examples of cascades which contain a single reaction type, such as pericyclic or cationic processes, the linking of chemically orthogonal reactions is key to the design of creative cascades, and an area which provides clear opportunities for future cascade design. The selective coverage of an article of this nature means that many impressive examples of cascade processes in synthesis are unavoidably omitted; for more comprehensive discussions the reader is referred to a series of excellent reviews.[3–8]

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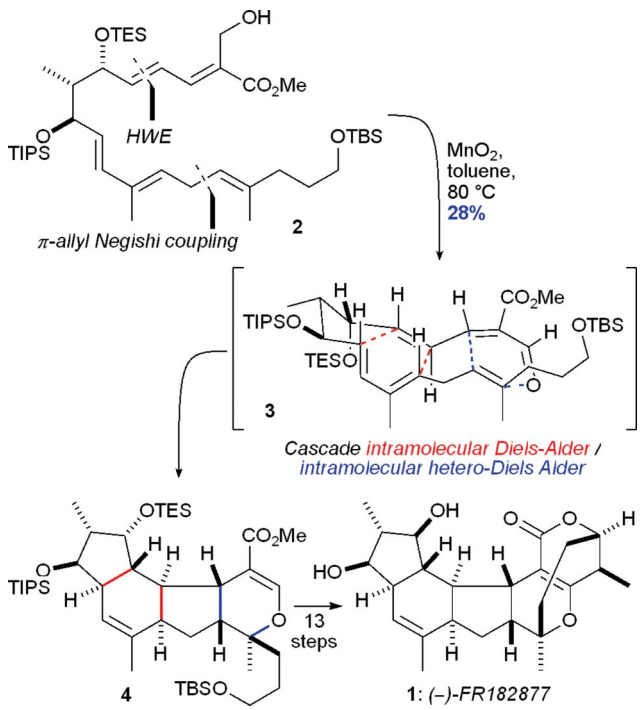
## Pericyclic cascades

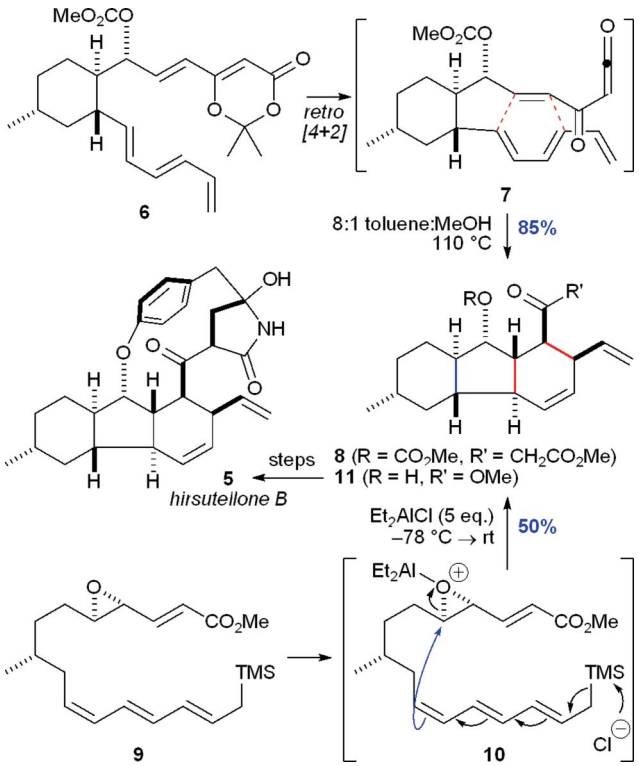
Pericyclic reactions have long formed the mainstay of cascade polycyclisations in natural product synthesis, tracing back to the landmark realisation of Black's hypothesis for the biosynthesis of the endiandric acids by Nicolaou *et al.* in 1982.[9] This 'biomimetic approach' to polycycle synthesis is a recurring theme of pericyclic cascades, and has inspired numerous total syntheses.[4] Electrocyclisations and cycloadditions, in particular the Diels–Alder reaction and its variants,[8] are particularly suited to the sequenced construction of multiple rings.

The biological properties, appealing structure, and proposed cascade biosynthesis[10] of the polyketide-derived anticancer natural product (–)-FR182877 (**1**, Scheme 1) have inspired several research groups to launch synthetic campaigns, culminating in two classic total syntheses by the Sorensen and Evans groups.[11–14] Recently, Nakada *et al.* have described a complementary approach to **1**,[15] in which the proposed biomimetic intramolecular Diels–Alder/hetero-Diels–Alder (IMDA/HDA) cascade could be achieved on an *acyclic* substrate, avoiding the need to prepare a macrocyclic precursor as used in the earlier syntheses. Pentaene **2**, prepared using a π-allyl Negishi cross-coupling and a Horner–Wadsworth–Emmons (HWE) olefination as key steps, could be activated towards the cascade cyclisation *via* allylic oxidation with $MnO_2$. The transiently-formed dienal **3** reacts with the remote diene and alkene components to effect firstly the IMDA, then intramolecular hetero-Diels–Alder (IMHDA) events. The resultant tetracycle **4** was formed in moderate yield, due to the occurrence of side reactions in the IMHDA. Nevertheless, the dramatic increase in complexity (4 rings and 7 stereocentres) offsets this, and the natural product **1** could be completed in a further 13 steps, which benefited from the endgame pursued by the Evans group.




**Scheme 1** Nakada's biomimetic synthesis of (–)-FR182877 (**1**).

A second example of the use of pericyclic cascades is illustrated by two recent approaches to the hirsutellone family of natural products, which show pronounced bioactivity against tuberculosis. Of relevance to this discussion is the decahydrofluorene core of hirsutellone B (**5**, Scheme 2), which was independently recognised by the groups of Sorensen,[16] Liu,[17] and Nicolaou[18] as potentially arising through an IMDA reaction. The tactics of Liu and Sorensen are closely related, and the latter of these is illustrated in Scheme 2. Thus, thermolysis of dioxenone **6** (a process which itself formally corresponds to a retro-hetero-Diels–Alder reaction) leads to the acyl ketene-activated alkene **7**. A regioselective IMDA



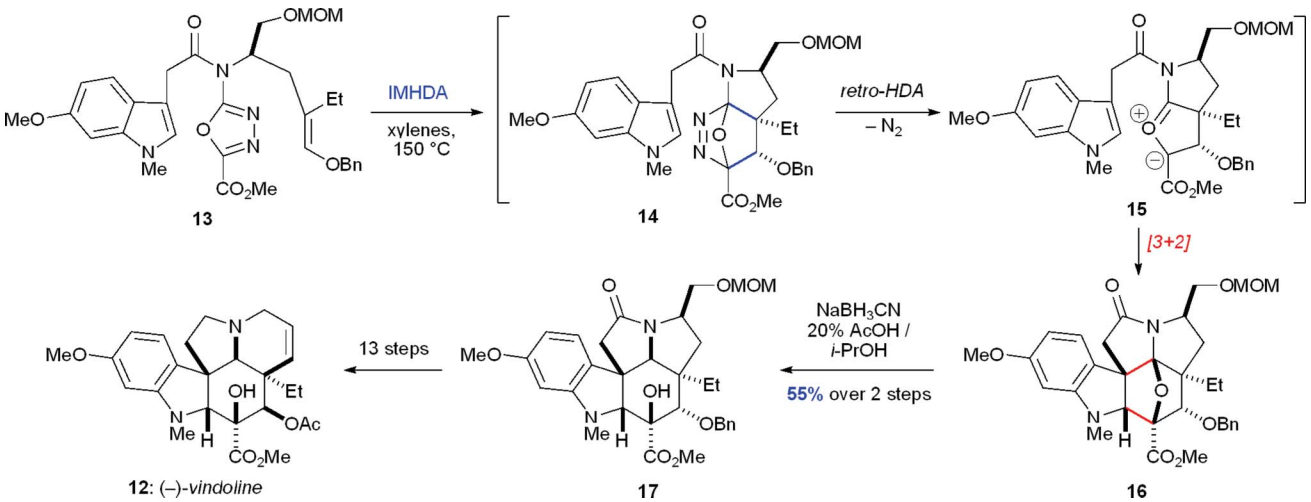

**Scheme 2** The Sorensen/Liu and Nicolaou routes to hirsutellenone B (**5**).

reaction with the tethered triene then generates the decahydrofluorene core **8** in 85% yield. The construction of two rings and four stereocentres in this key step lays a solid foundation for future efforts to realise a more ambitious cascade, which includes an *in situ* macrolactamisation to complete the hirsutellenone skeleton.[19]

In contrast to this thermally-initiated Diels–Alder route, Nicolaou *et al.* approached the key IMDA through an inventive intramolecular epoxide opening, with a trienyl allylsilane as nucleophile, which demonstrates the benefits of coupling of different reaction classes in a single cascade (Scheme 2).[18] Treatment of epoxide **9** with excess diethylaluminium chloride causes epoxide opening by the appended trienylsilane, a reaction which forms the first 6-membered ring of the hirsutellone core, and brings the resultant triene into closer proximity to the enoate. The ensuing IMDA reaction (**10** → **11**) constructs the remainder of the decahydrofluorene skeleton. The Nicolaou group was able to convert **11** into hirsutellone B in a further ten steps.

A final example of a more mature cascade pericyclic strategy, which has been used to great effect to construct a number of alkaloid natural products, is found in the recent enantioselective synthesis of (–)-vindoline (**12**, Scheme 3) by Boger *et al.*[20] In this work, the entire framework of the natural product was assembled in a single synthetic operation from oxadiazole **13** using a well-established but nevertheless noteworthy pericyclic cascade. This most recent iteration of the group's methodology features improved substrate-controlled diastereoselectivity in the initial IMHDA through a shortened diene–dienophile tether, and also profits from milder reaction conditions—rendering this approach both asymmetric and more efficient compared to a previous synthesis from the same group.[21] The cascade begins

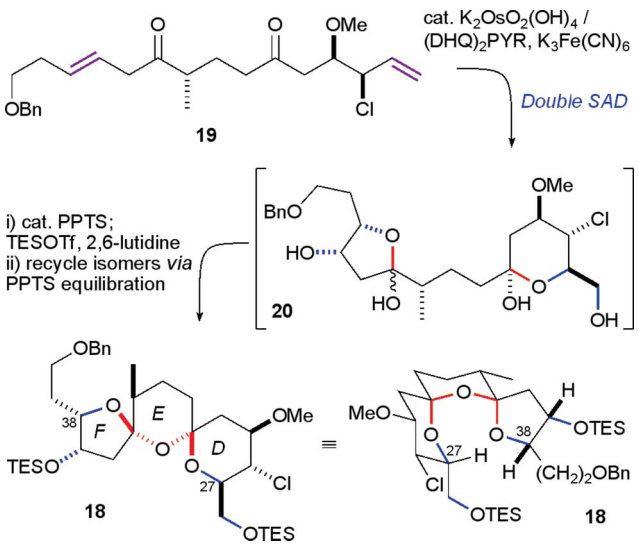
 




**Scheme 3** Cascade cycloaddition route to vindoline (**12**) (Boger *et al.*).

with an IMHDA reaction of the oxadiazole with the electron-rich enol ether, a reaction which crucially sets two stereocentres. The resultant oxadiazabicycloheptene cycloadduct **14** is primed to undergo a retro-HDA with loss of nitrogen, to generate the stabilised carbonyl ylid **15**. This engages in an intramolecular [3 + 2] cycloaddition with the pendant indole, installing an additional four stereocentres. For convenience, cycloadduct **16** is not purified, but instead directly subjected to mildly acidic reducing conditions, which lead to opening of the aminal and reduction of the transient *N*-acyliminium ion (**17**). The increase in complexity and exquisite stereocontrol achieved in this cascade is remarkable.

Despite these recent achievements and the mature state of the field, there is still room for further invention with pericyclic cascades. In particular, the use of sigmatropic rearrangements in purely pericyclic polycylisations has rarely been exploited, although impressive methodology developments in this area suggest much potential.[22–25]




**Scheme 4** Paterson's approach to the spirastrellolide A DEF rings.

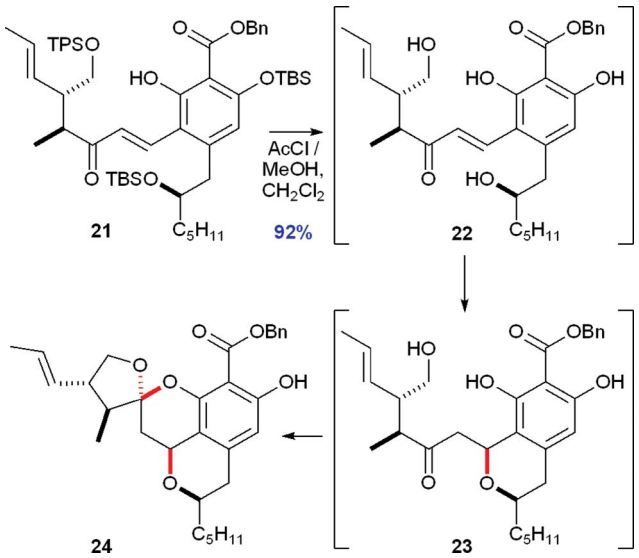
## Heteroatom-mediated cascades

Cascade heteroatom cyclisations to assemble poly-heterocyclic natural product skeletons have proved to be one of the most productive areas of cascade chemistry of recent years. In particular, the realisation of putative biosynthetic pathways in the laboratory has provided some striking demonstrations in this field. Two classes of heteroatom polycyclisations which have reached a high level of complexity are polyspiroacetal formation, and (arguably more impressive) cascade epoxide openings.

The former of these has been fruitfully employed in approaches towards such complex natural products as the azaspiracids and the spirastrellolides, with control over multiple spiroacetal stereocentres being mediated through a balance of anomeric effects, disposition of substituents, and, in certain cases, intramolecular hydrogen bonding. The stereocontrolled assembly of an entire polyspiroacetal system in a single step is therefore somewhat challenging.

The Paterson synthesis of spirastrellolide A provides a notable demonstration,[26,27] particularly the approach used to assemble the DEF ring system (**18**, Scheme 4).[28] The group recognised that embedded within the D and F rings of the natural product are two diols of the same relative and absolute configuration, which could be installed in a single step using a double Sharpless asymmetric dihydroxylation of an appropriate diene (**19**). In practice, *in situ* cyclisation of the resultant tetraol **20** under acidic conditions leads to the predominant formation of the tricyclic spiroacetal product **18**, possessing the desired configurations at the newly-formed spiroacetal centres; separation of the minor EF-anomer and acid-mediated equilibration/recycling gave **18** in an overall yield of 65% from the acyclic precursor **19**, with three rings and eight carbon–oxygen bonds being formed in a single step.

A further example of spiroketal synthesis through cascade heteroatom-mediated bond formation is the recent synthesis of berkelic acid by the Fürstner group.[29,30] This slightly unusual cascade (Scheme 5) involves an acid-mediated triple deprotection of the three silyl ethers of substrate **21**, under which conditions oxy-Michael cyclisation of the secondary alcohol occurs onto the enone **22**. This process now permits spiroketalisation of the




**Scheme 5** Cascade cyclisation *en route* to berkelic acid (Fürstner *et al.*).

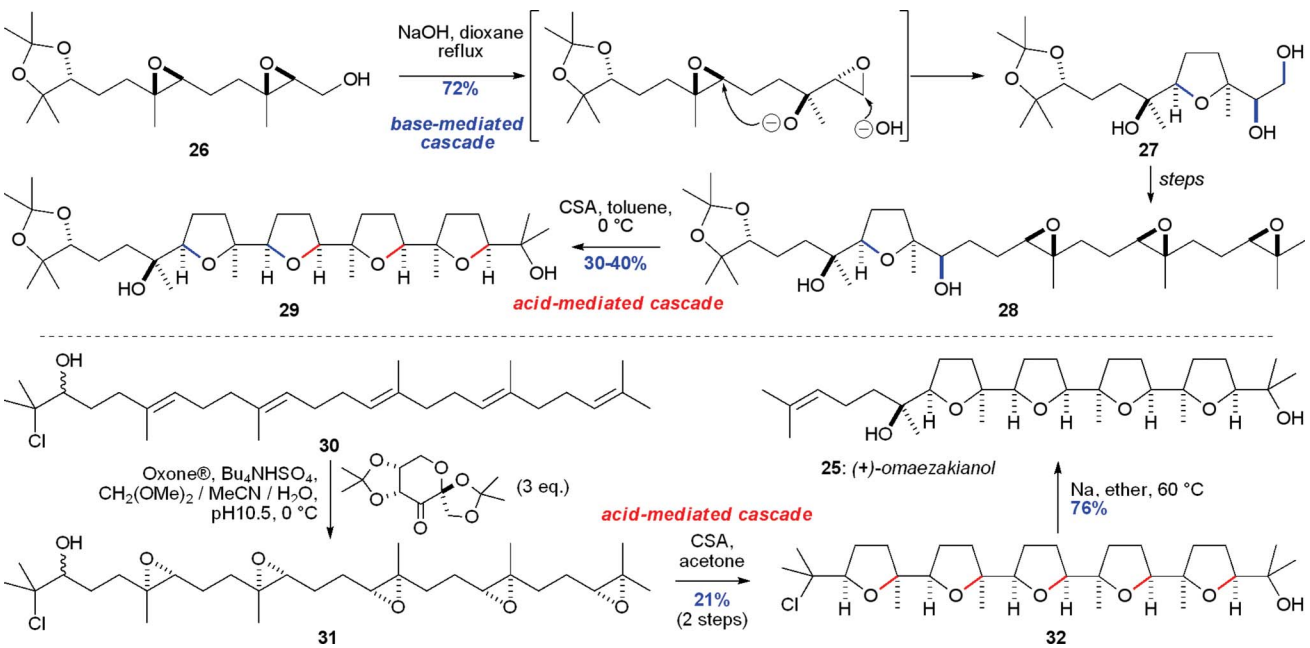
phenolic and aliphatic hydroxyls onto ketone **23**. The order of events is not clear, and the reaction may well proceed *via* a number of degenerate pathways; the overall yield (of **24**) for this highly effective transformation is 92%.

No discussion of heteroatom-mediated cascades can omit the field of cascade epoxide openings, which presents an additional challenge: control over the regioselectivity of epoxide opening by the nucleophile in an *exo* or *endo* sense. These two outcomes lead to linked-ring and fused-ring polyethers respectively, with both modes having been proposed in natural product biosynthetic pathways; this topic has been the subject of a recent outstanding review.[31] The *exo*-opening cascade gives rise to the polyether ionophore, annonaceous acetogenin, and oxasqualenoid classes of natural products, and is the kinetically preferred outcome based on Baldwin's rules.

(+)-Omaezakianol (**25**, Scheme 6) represents the latest target to have succumbed to this biomimetic cascade synthesis. Isolated in 2008, omaezakianol is likely to possess ionophoric bioactivity, and has been the subject of two recent total syntheses. The first of these, from Morimoto *et al.*,[32] is an instructive example which makes use of both basic and acidic conditions to initiate the cascade epoxide *exo*-opening processes. Firstly, a base-promoted Payne rearrangement/cascade epoxide opening sequence, based on early work by Hoye and Jenkins,[33] is used to convert *bis*-epoxide **26** into furan **27**. A series of manipulations including a cross-metathesis union of the left-hand and right-hand portions of the molecule lead to *tris*- epoxide **28**, the substrate for an acid-promoted epoxide opening cascade. The opening of these three epoxides affords tetrafuran **29**, an advanced intermediate *en route* to (+)-omaezakianol.

Although Morimoto's synthesis does afford the natural product with some efficiency, a considerable amount of synthetic effort is directed towards the preparation of the cascade cyclisation substrates, which results in a longest linear sequence of 20 steps from farnesol. This step count is dramatically reduced in the second total synthesis, from the Corey group,[34] and it is not without coincidence that this latter work uses a more ambitious cascade polycyclisation. The synthesis begins with racemic chlorohydrin **30**, available in three steps from the classic terpene building block squalene. Subjection of **30** to exhaustive Shi asymmetric epoxidation leads to the pentaepoxide **31**, the polycyclisation substrate. The natural product is completed in just two further steps: polycyclisation to **32** under acidic conditions, then reductive olefination. This elegant and concise synthesis — just six steps from squalene—underlines the benefits of cascade (*versus* stepwise) strategies.

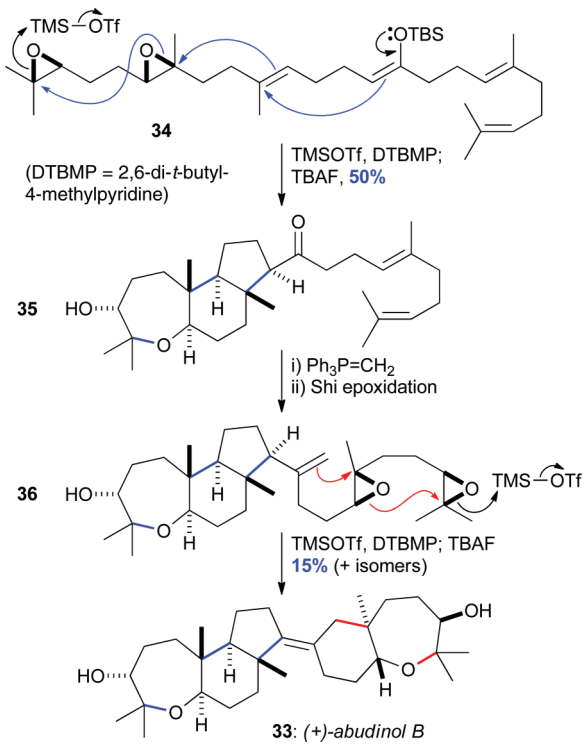
Analogous *endo*-selective epoxide openings, leading to thermodynamically-preferred pyranyl products but also proceeding under




**Scheme 6** *Exo*-selective epoxide opening cascades: Morimoto's and Corey's recent syntheses of (+)-omaezakianol (**25**).

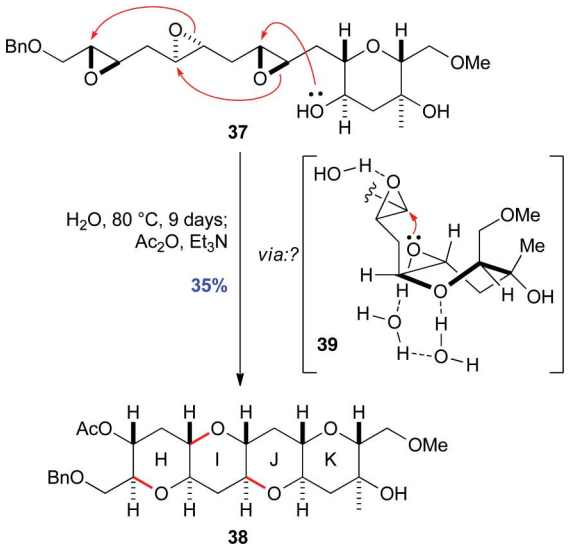
 

kinetic control, present a significant challenge. One inventive solution to this problem is to use a directing group to control the regioselectivity of epoxide opening, the most common mode of direction being through stabilisation of the *endo* ring-opening transition state (for example by alkenyl, alkynyl, alkyl or silyl substituents).[31] With the exception of alkyl (methyl) groups, this tactic inevitably leaves behind functionality that must be subsequently modified or removed, and therefore represents something of an inefficient solution.[35,36] However, the use of methyl groups as *endo*-directing substituents has been particularly successful, with one recent noteworthy example being the synthesis of (+)-abudinol B (**33**, Scheme 7) by McDonald and co-workers,[37,38] which employs two beautiful Lewis acid-promoted *endo*-selective cascades. The first involves the cyclisation of silyl enol ether **34** to give tricycle **35**, which is converted in two steps (olefination/asymmetric epoxidation) to *bis*-epoxide **36**. Cyclisation of this epoxide under identical conditions to those used previously leads directly to abudinol B, albeit in moderate yield due to the formation of several byproducts.




**Scheme 7** McDonald's synthesis of (+)-abudinol B (**33**).

Of much greater challenge is control over *endo*-selectivity in epoxide opening cascades which do not benefit from directing effects. Here, the outstanding work of Jamison has revealed that such cascades can be achieved specifically using water (or other hydroxylic) solvent, under neutral conditions (pH 7). Under acidic or basic conditions, either aqueous or non-aqueous, significantly greater proportions of *exo*-opening were observed.[39,40] In a synthetic context, these results have been applied to the HIJK rings of the ladder polyether toxin gymnocin A.[41] Thus, subjection of *tris*-epoxide pyran **37** (Scheme 8) to thermal aqueous ring-opening conditions leads, over a prolonged period, to HIJK



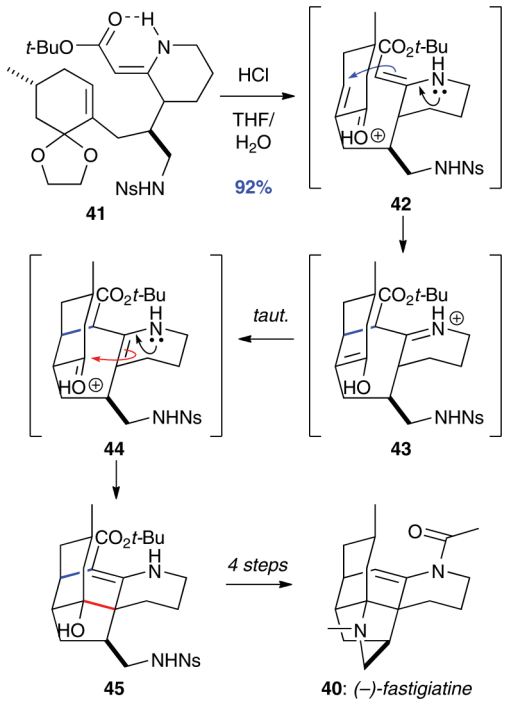

**Scheme 8** Jamison's water-promoted *endo*-selective cascade epoxide opening towards gymnocin A.

tetracycle **38** (38% yield), a reaction which may initiate *via* the templated intermediate **39**.[42] This highly impressive example of reaction control in a non-electronically-biased system provides new insight into *endo*-selective epoxide opening cascades, and a useful synthetic entry to these polyethers. Further recent results from the Jamison group suggest this water-promoted reaction to be a sequence of single epoxide-opening processes rather than a concerted mechanism, with the intriguing finding that both the rate and regioselectivity increases for sequential ring-opening steps.[43]

## Cationic cascades

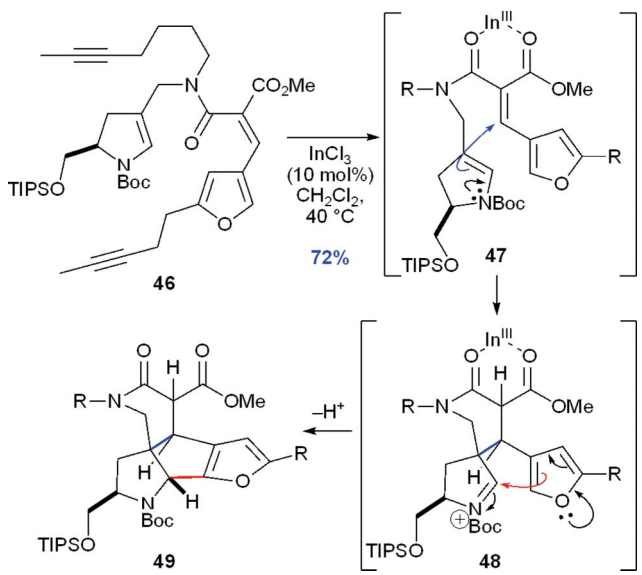
From a complexity-inducing perspective, alkene cyclisations promoted by proximal cations are among the most popular routes to cyclic structures, and lend themselves well to cascade processes. The seminal works of Johnson in the field of biomimetic steroid synthesis, and Heathcock, Overman and many others in the area of alkaloid synthesis, have lent confidence and ambition to modern cascade reaction design involving cation-promoted cyclisations. Two recent examples are described here, both of which employ enamine/iminium ion reactivity in key ring-forming steps.

The first total synthesis of the *Lycopodium* alkaloid (–)-fastigiatine (**40**, Scheme 9) reported by Shair *et al.* uses a powerful formal [3 + 3] cycloaddition reaction to construct the densely functionalised core of the natural product.[44] This cascade process is effected simply through the treatment of ketal **41** with aqueous acid, which reveals the activated enone **42**—the substrate for the first carbon–carbon bond formation through attack of the proximal enamine. The resultant iminium ion **43** undergoes tautomerisation in readiness for a second nucleophilic attack on the carbonyl **44**, forming the fastigiatine core **45** in an outstanding 92% yield. Just four further steps were required to complete this synthesis, which proceeded in 30% overall yield from a readily available starting material.




**Scheme 9** Shair's synthesis of (–)-fastigiatine (**40**).

Funk *et al.* have described a total synthesis of (–)-nakadomarin A which features an appealing Michael/Mannich cascade to forge the tetracyclic core of the natural product (Scheme 10).[45] This transformation begins with the treatment of enoate **46** with catalytic indium trichloride, a Lewis acid which activates the enoate to intramolecular attack by the enamide (**47**). The resultant *N*-acyliminium ion **48** is then trapped through nucleophilic addition of the furan, completing the tetracyclic core **49** and setting three crucial contiguous stereocentres. The stereocontrol in this remarkable transformation is dictated by a single substituent on the dihydropyrrole (enamide) ring of **47**.

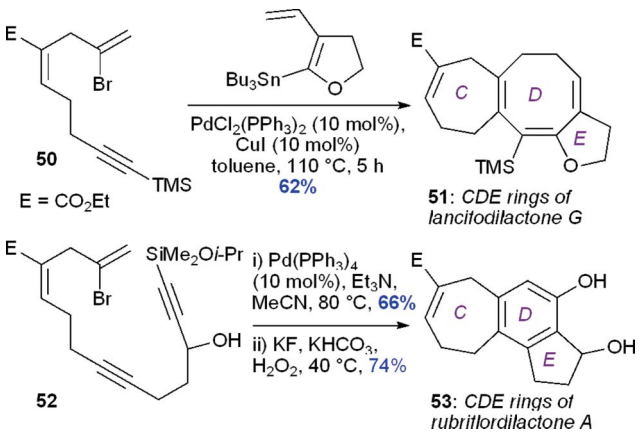



**Scheme 10** Funk's approach to nakadomarin A.

Tetracycle **49** was advanced to nakadomarin A in a further 11 steps.

## Metal-mediated cascades

Metal-mediated cascade reactions have historically centred on palladium-catalysed processes, due to the ability of palladium to effect multiple and diverse carbon–carbon bond formations in a regio- and stereocontrolled manner.[2] Whilst this strategy is well-established as a route to polyalkenes and related structures, the coupling of additional, chemically orthogonal processes to the palladium-mediated cascade represents an appealing means to diversify the product scope. A recent example from our own laboratory which illustrates this idea is the assembly of the CDE ring systems of the *Schisandra* natural products lancifodilactone G and rubriflordilactone A (Scheme 11).[46] The former natural product core could be assembled in a single step using a palladium-catalysed carbopalladation/Stille cross-coupling process to construct a tetraene from bromoenyne **50**, which undergoes an *in situ* 8π-electrocyclisation to give the tricyclic product **51**.[47,48] In contrast, the rubriflordilactone CDE rings were assembled using a 'fully-intramolecular' variant of the palladium-mediated cascade cyclisation as originally developed by Negishi[49] and de Meijere,[50–52] but which to date has not been applied in total synthesis, with the cyclisation of bromoenediyne **52** leading to 7,6,5-tricycle **53** under these conditions. Both reactions effect the efficient formation of three rings and three carbon–carbon bonds in a single synthetic operation, and provide a general means to access related bi- and tricyclic ring systems.[53]

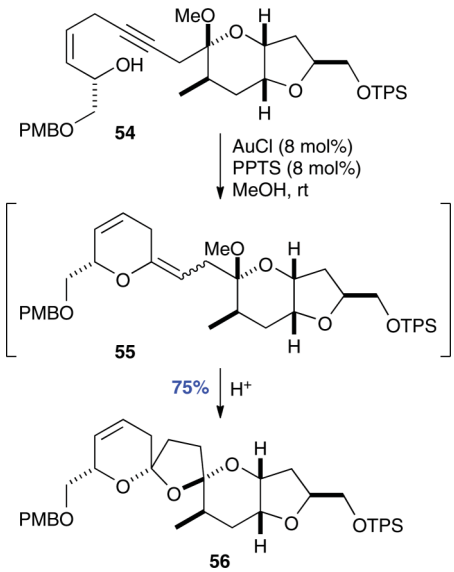



**Scheme 11** Palladium-mediated cascades to the *Schisandra* natural product CDE-cores **51** and **53** (Anderson *et al.*).

The recent popularisation of π-acid organometallic catalysis using late transition metals has led to an explosion of methodologies including cyclisation processes.[54–57] Despite these advances, relatively few examples of *poly*cyclisations using π-acid catalysis have been reported. One area in which this mode of reactivity has proved useful is the synthesis of spiroketals, in which an alkyne serves as a ketone surrogate in the cyclisation of a dihydroxyalkyne.

An example of this method, from the Forsyth group, is illustrated in Scheme 12.[58] Treatment of the ynol **54** with catalytic gold(I) chloride leads to the presumed formation of the enol

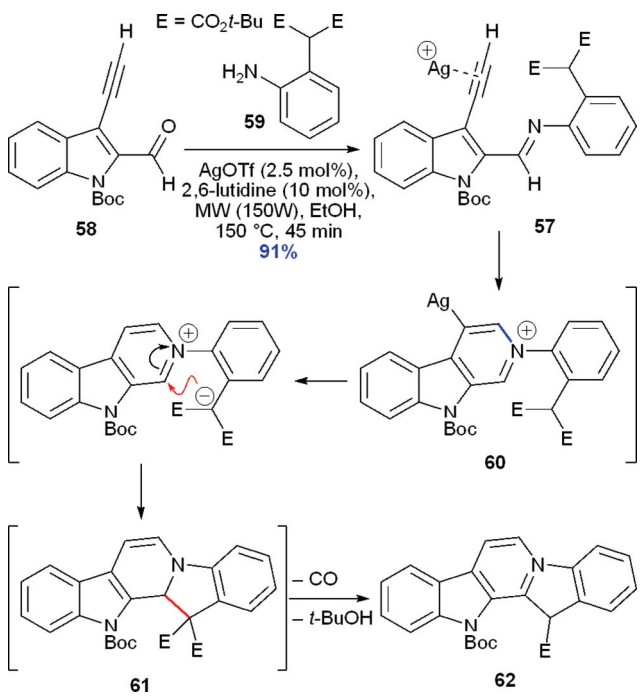
 




**Scheme 12** Gold-catalysed spiroketalisation towards the azaspiracid ABCD rings (Forsyth *et al.*).

ether **55**; under the acidic reaction conditions, this intermediate undergoes a second cyclisation reaction to form the AB spiroketal **56** of azaspiracid. In light of the efficiency of this and related reactions,[59] it is likely that the use of transition metals in such spiroketalisation processes will continue to be of great appeal in synthesis.

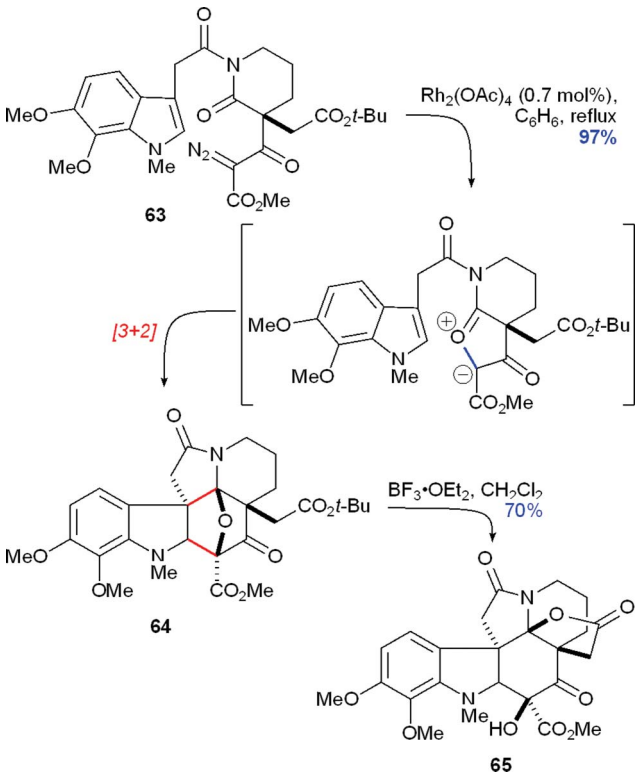
A further recent example of π-acid catalysis in cascade polycyclisation is the silver(I)-promoted condensation/cyclisation of aldehydes and anilines reported by Waldmann (Scheme 13).[60] This reaction uses a silver catalyst to promote cyclisation of imine **57** (derived from starting materials **58** and **59**) onto the indolyl alkyne,




**Scheme 13** Waldmann's route to homofascaplysin C.

leading to a pyridinium ion **60** which, after protodemetallation, is subject to a second cyclisation by the pendant malonate nucleophile to form **61**. A final rearomatisation step delivers the pentacyclic indolylpyridine **62**, a precursor to homofascaplysin C, in an impressive 91% yield.

Finally, one of the most productive classes of metal-promoted cascade polycyclisations has involved the initial formation of 1,3-dipoles from diazocarbonyl compounds using rhodium (or other metal) catalysis. The Padwa group has recently reported a highly efficient total synthesis of aspidophytine using this mature strategy,[61] in which the core of the natural product is assembled from diazoacetate **63** by treatment with catalytic $Rh_2(OAc)_4$ (Scheme 14). The metal catalyst effects diazo decomposition followed by intramolecular [3 + 2] cycloaddition (97%); subsequent Lewis acid-mediated rearrangement/cyclisation of intermediate **64** provides **65**. This methodology has been extensively reviewed,[62] and is included here for comparison to Boger's approach to similar carbonyl ylid intermediates (see **16**, Scheme 3).



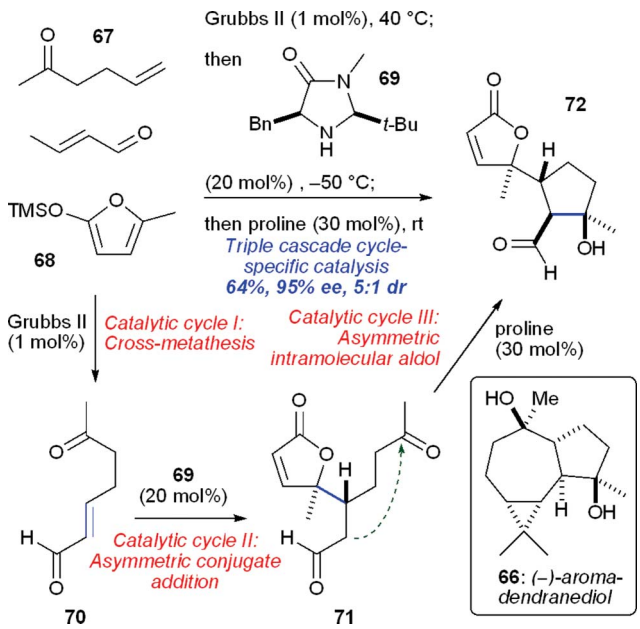

**Scheme 14** Padwa and Meija-Oneto's route to aspidophytine.

It is clear that cascades involving metal-mediated reactions, in totality or as component events, are likely to continue as a mainstay of polycyclisation processes. Areas such as 'coinage' metal-catalysed reactions, and olefin or alkyne metathesis chemistry, remain somewhat unexploited in the context of true cascade polycyclisation reactivity (although the latter is well-established as a means to construct multiple rings in a single step)[63–65] and provide real opportunities for further discovery and invention.

## Organocatalytic cascades

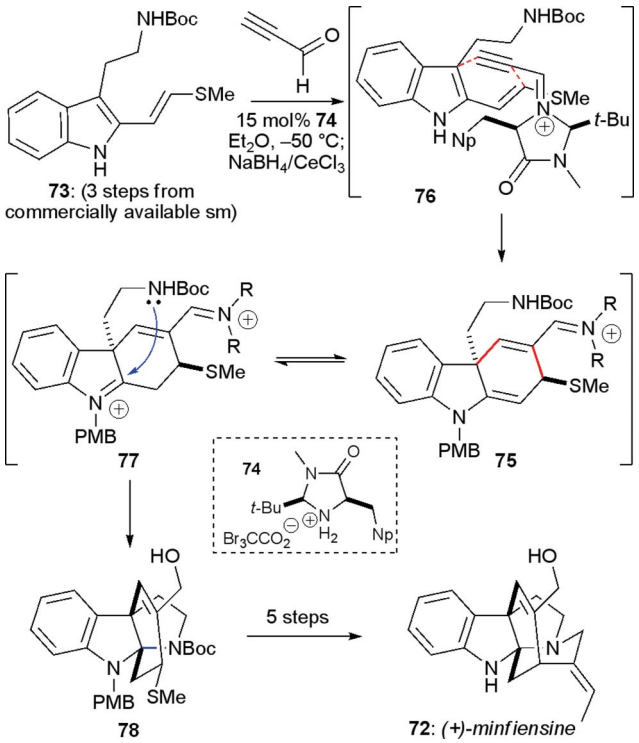
The exponential rise in publications in the field of organocatalysis has inevitably led to the development of impressive cascade processes, particularly in the area of sequential organocatalysed reactions leading to heavily substituted ring systems.[66–68] However, these organocatalysed polycyclisations have yet to be generally applied to natural product synthesis, and the area remains ripe for further innovation. The MacMillan group has been a leading force in the field, having recently reported two appealing examples of cascade organocatalysis directed towards total synthesis.[69,70]

The first of these is a synthesis of the marine sesquiterpene (–)-aromadendranediol (**66**, Scheme 15),[71] in which the first, key step of the synthesis involves the combination of ketone **67**, crotonaldehyde, and furan **68** under the influence of three catalysts: the Grubbs second generation metathesis catalyst, imidazolidinone **69**, and proline. In what the authors term a 'triple-catalysis-cycle-specific mechanism' these reagents are combined *via* an initial cross-metathesis of **67** with crotonaldehyde, then an asymmetric conjugate addition of furan **68** to the iminium ion derived from enal **70** and imidazolidinone **69**, and finally an asymmetric intramolecular aldol reaction between the proline enamine derived from aldehyde **71** and the ketone. This transformation (64% yield, 95% *ee*, 5 : 1 *dr*) not only forms two rings, but also simultaneously installs the four most challenging stereocentres of the natural product in the first step of the total synthesis—which stands in marked contrast to the usual later-stage implementation of cascade processes. This dual organometallic/organocatalytic cascade highlights the complexity and control that can be achieved with carefully designed reaction systems.




**Scheme 15** Triple cascade catalysis (MacMillan *et al.*).

The second example from the same group is the total synthesis of the *Strychnos* alkaloid (+)-minfiensine (**72**, Scheme 16).[72] In an extremely concise approach to this pentacyclic natural product, the conceptually simple and highly atom economic *endo*-selective Diels–Alder reaction of propynal with thioalkenyl indole **73**, catalysed by imidazolidinone **74**, presumably leads to an




**Scheme 16** MacMillan's concise synthesis of minfiensine (**72**).

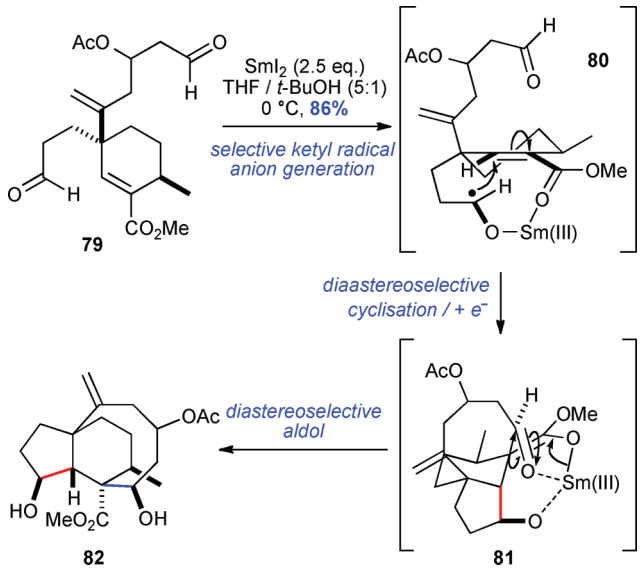
intermediate 1,4-cyclohexadiene **75** *via* the proposed transition state **76**. This compound is in equilibrium with the corresponding iminium ion **77**, which undergoes nucleophilic trapping by the pendant amine sidechain to provide the tetracyclic core **78** of minfiensine in a single step, in 87% yield and 94% *ee*. **78** was advanced in a further five steps to (+)-minfiensine.

These two examples represent the state-of-the-art for applications of organocatalytic polycyclisations in synthesis, and in these cases display two additional benefits: both syntheses employ readily available starting materials in the cascade step (with the implication of reduced cost and scalability), and it is the cascade itself which first introduces asymmetry into the synthesis, removing the traditional reliance on substrate stereocontrol.

## Radical cascades

The use of radical cascades to construct polycyclic ring systems is well-established. Samarium diodide provides a particularly useful contemporary method to initiate such reactions in complex frameworks, as it can provide a highly selective route to ketyl radical anions from carbonyl derivatives. A recent example which highlights the exquisite chemo- and regioselectivity that may be achieved in such processes is found in the synthetic studies towards pleuromutilin reported by Proctor *et al.* (Scheme 17).[73,74] In this work, treatment of dialdehyde **79** with $SmI_2$ leads to the selective reduction of the aldehyde proximal to the enoate functionality, a reaction which could be explained through a pre-complexation of the aldehyde and ester groups to the samarium(II) reducing agent. The stereoselective cyclisation of the resultant radical anion **80** onto the enoate double bond is followed by a second electron transfer to generate an intermediate enolate




**Scheme 17** Proctor's radical cascade approach to pleuromutilin.

**81**. Finally, this enolate undergoes a further stereoselective C–C bond formation *via* aldol reaction with the remaining aldehyde (→**82**), with the stereochemistry again explained through the coordinating effects of the samarium(III) cation. This outstanding transformation proceeded in 86% yield, and although these efforts have not yet led to a total synthesis of pleuromutilin, the ability of $SmI_2$ to mediate the formation of four contiguous stereocentres and two rings, including the ansa bridge, is particularly notable.[72]

## Summary and outlook

The field of cascade cyclisations is both a classical and contemporary area—it holds an unparalleled fascination for organic chemists in both the mimicry of Nature and the more general increase in molecular complexity it engenders. Nevertheless, it is not a mature field. Many areas of synthetic methodology remain to be incorporated into genuine complexity-inducing polycyclisation pathways, and this will rely on the recognition of orthogonal, or at the least mutually compatible, reaction manifolds. Examples include the use of organocatalysis, for which few examples have been reported beyond those described above, and many transition-metal catalysed processes such as C–H activations and cycloisomerizations. In both of these fields, the idea of asymmetric cascade cyclisations (with the catalyst(s) rather than the substrate being the origin of new stereochemistry) is likely to emerge as an important area. Given the well-established nature of these classes of reaction as powerful synthetic methods, their coupling with each other[75] or with other reaction types[76] will surely continue to provide almost limitless opportunities for efficiency, complexity, step-efficiency, and above all creativity in cascade reaction design and realisation.

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## Notes and references

1 L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115–136.
2 L. F. Tietze, G. Brasche and K. M. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, 2006.
3 K. C. Nicolaou and J. S. Chen, *Chem. Soc. Rev.*, 2009, **38**, 2993–3009.
4 K. C. Nicolaou, D. J. Edmonds and P. G. Bulger, *Angew. Chem., Int. Ed.*, 2006, **45**, 7134–7186.
5 T. Newhouse, P. S. Baran and R. W. Hoffmann, *Chem. Soc. Rev.*, 2009, **38**, 3010–3021.
6 J. Kim and M. Movassaghi, *Chem. Soc. Rev.*, 2009, **38**, 3035–3050.
7 B. B. Toure and D. G. Hall, *Chem. Rev.*, 2009, **109**, 4439–4486.
8 M. Juhl and D. Tanner, *Chem. Soc. Rev.*, 2009, **38**, 2983–2992.
9 K. C. Nicolaou, N. A. Petasis and R. E. Zipkin, *J. Am. Chem. Soc.*, 1982, **104**, 5560–5562.
10 C. D. Vanderwal, D. A. Vosburg, S. Weiler and E. J. Sorensen, *Org. Lett.*, 1999, **1**, 645–648.
11 D. A. Vosburg, C. D. Vanderwal and E. J. Sorensen, *J. Am. Chem. Soc.*, 2002, **124**, 4552–4553.
12 C. D. Vanderwal, D. A. Vosburg, S. Weiler and E. J. Sorensen, *J. Am. Chem. Soc.*, 2003, **125**, 5393–5407.
13 D. A. Evans and J. T. Starr, *Angew. Chem., Int. Ed.*, 2002, **41**, 1787–1790.
14 D. A. Evans and J. T. Starr, *J. Am. Chem. Soc.*, 2003, **125**, 13531–13540.
15 N. Tanaka, T. Suzuki, T. Matsumura, Y. Hosoya and M. Nakada, *Angew. Chem., Int. Ed.*, 2009, **48**, 2580–2583.
16 S. D. Tilley, K. P. Reber and E. J. Sorensen, *Org. Lett.*, 2009, **11**, 701–703.
17 M. Z. Huang, C. Huang and B. Liu, *Tetrahedron Lett.*, 2009, **50**, 2797–2800.
18 K. C. Nicolaou, D. Sarlah, T. R. Wu and W. Q. Zhan, *Angew. Chem., Int. Ed.*, 2009, **48**, 6870–6874.
19 A report of this ambitious cascade is contained within the following review: K. P. Reber, S. D. Tilley and E. J. Sorensen, *Chem. Soc. Rev.*, 2009, **38**, 3022–3034.
20 D. Kato, Y. Sasaki and D. L. Boger, *J. Am. Chem. Soc.*, 2010, **132**, 3685–3687.
21 H. Ishikawa, G. I. Elliott, J. Velcicky, Y. Choi and D. L. Boger, *J. Am. Chem. Soc.*, 2006, **128**, 10596–10612.
22 S. Arns and L. Barriault, *Chem. Commun.*, 2007, 2211–2221.
23 R. Clement, C. M. Grise and L. Barriault, *Chem. Commun.*, 2008, 3004–3006.
24 N. A. Miller, A. C. Willis, M. N. Paddon-Row and M. S. Sherburn, *Angew. Chem., Int. Ed.*, 2007, **46**, 937–940.
25 For a review, see: E. A. Ilardi, C. E. Stivala and A. Zakarian, *Chem. Soc. Rev.*, 2009, **38**, 3133–3148.
26 I. Paterson, E. A. Anderson, S. M. Dalby, J. H. Lim, J. Genovino, P. Maltas and C. Moessner, *Angew. Chem., Int. Ed.*, 2008, **47**, 3016–3020.
27 I. Paterson, E. A. Anderson, S. M. Dalby, J. H. Lim, J. Genovino, P. Maltas and C. Moessner, *Angew. Chem., Int. Ed.*, 2008, **47**, 3021–3025.
28 I. Paterson, E. A. Anderson, S. M. Dalby, J. H. Lim, P. Maltas and C. Moessner, *Chem. Commun.*, 2006, 4186–4188.
29 P. Buchgraber, T. N. Snaddon, C. Wirtz, R. Mynott, R. Goddard and A. Fürstner, *Angew. Chem., Int. Ed.*, 2008, **47**, 8450–8454.
30 T. N. Snaddon, P. Buchgraber, S. Schulthoff, C. Wirtz, R. Mynott and A. Furstner, *Chem.–Eur. J.*, 2010, **16**, 12133–12140.
31 I. Vilotijevic and T. F. Jamison, *Angew. Chem., Int. Ed.*, 2009, **48**, 5250–5281.
32 Y. Morimoto, T. Okita and H. Kambara, *Angew. Chem., Int. Ed.*, 2009, **48**, 2538–2541.
33 T. R. Hoye and S. A. Jenkins, *J. Am. Chem. Soc.*, 1987, **109**, 6196–6198.
34 Z. M. Xiong, R. Busch and E. J. Corey, *Org. Lett.*, 2010, **12**, 1512–1514.
35 For an elegant solution to this problem involving a silyl substituent as a 'disappearing' directing group, see: G. L. Simpson, T. P. Heffron, E. Merino and T. F. Jamison, *J. Am. Chem. Soc.*, 2006, **128**, 1056–1057.
36 T. P. Heffron, G. L. Simpson, E. Merino and T. F. Jamison, *J. Org. Chem.*, 2010, **75**, 2681–2701.
37 R. B. Tong and F. E. McDonald, *Angew. Chem., Int. Ed.*, 2008, **47**, 4377–4379.
38 M. A. Boone, R. B. Tong, F. E. McDonald, S. Lense, R. Cao and K. I. Hardcastle, *J. Am. Chem. Soc.*, 2010, **132**, 5300–5308.
39 I. Vilotijevic and T. F. Jamison, *Science*, 2007, **317**, 1189–1192.
40 C. J. Morten, J. A. Byers, A. R. Van Dyke, I. Vilotijevic and T. F. Jamison, *Chem. Soc. Rev.*, 2009, **38**, 3175–3192.

41 A. R. Van Dyke and T. F. Jamison, *Angew. Chem., Int. Ed.*, 2009, **48**, 4430–4432.
42 J. A. Byers and T. F. Jamison, *J. Am. Chem. Soc.*, 2009, **131**, 6383–6385.
43 C. J. Morten, J. A. Byers and T. F. Jamison, *J. Am. Chem. Soc.*, 2011, **133**, 1902–1908.
44 B. B. Liau and M. D. Shair, *J. Am. Chem. Soc.*, 2010, **132**, 9594–9595.
45 M. G. Nilson and R. L. Funk, *Org. Lett.*, 2010, **12**, 4912–4915.
46 M.-C. A. Cordonnier, S. B. J. Kan and E. A. Anderson, *Chem. Commun.*, 2008, 5818–5820.
47 For leading references to the development of this strategy, see: C. Hulot, S. Amiri, G. Blond, P. R. Schreiner and J. Suffert, *J. Am. Chem. Soc.*, 2009, **131**, 13387–13398.
48 J. Suffert, B. Salem and P. Klotz, *J. Am. Chem. Soc.*, 2001, **123**, 12107–12108.
49 E. Negishi, L. S. Harring, Z. Owczarczyk, M. M. Mohamud and M. Ay, *Tetrahedron Lett.*, 1992, **33**, 3253–3256.
50 F. E. Meyer and A. de Meijere, *Synlett*, 1991, 777–778.
51 W. M. Tokan, F. E. Meyer, S. Schweizer, P. J. Parsons and A. de Meijere, *Eur. J. Org. Chem.*, 2008, 6152–6167.
52 S. Schweizer, W. M. Tokan, P. J. Parsons and A. de Meijere, *Eur. J. Org. Chem.*, 2010, 4687–4699.
53 S. B. J. Kan and E. A. Anderson, *Org. Lett.*, 2008, **10**, 2323–2326.
54 For a recent thematic issue highlighting the use of coinage metals in synthesis, see: B. H. Lipshutz and Y. Yamamoto, *Chem. Rev.*, 2008, **108**, 2793–2795.
55 A. S. K. Hashmi, *Chem. Rev.*, 2007, **107**, 3180–3211.
56 A. Furstner and P. W. Davies, *Angew. Chem., Int. Ed.*, 2007, **46**, 3410–3449.
57 N. D. Shapiro and F. D. Toste, *Synlett*, 2010, 675–691.
58 Y. F. Li, F. Zhou and C. J. Forsyth, *Angew. Chem., Int. Ed.*, 2007, **46**, 279–282.
59 J. K. D. Brabander, B. Liu and M. Qian, *Org. Lett.*, 2008, **10**, 2533–2536.
60 H. Waldmann, L. Eberhardt, K. Wittstein and K. Kumar, *Chem. Commun.*, 2010, **46**, 4622–4624.
61 J. M. Mejia-Oneto and A. Padwa, *Helv. Chim. Acta*, 2008, **91**, 285–302.
62 A. Padwa, *Chem. Soc. Rev.*, 2009, **38**, 3072–3081.
63 For a recent enyne RCM cascade towards natural product synthesis, see: R. S. Nandurdikar, A. V. Subrahmanyam and K. P. Kaliappan, *Eur. J. Org. Chem.*, 2010, 2788–2799.
64 For a recent outstanding example of enyne RCM in a sequenced reaction, see: J. Ramharter, H. Weinstabl and J. Mulzer, *J. Am. Chem. Soc.*, 2010, **132**, 14338–14339.
65 M. Porta and S. Blechert, in *Metathesis in Natural Product Synthesis*, ed. J. Cossy, S. Arseniyadis and C. Meyer, Wiley-VCH, Weinheim, 2010, pp. 313–342.
66 D. Enders, M. R. M. Huttl, C. Grondal and G. Raabe, *Nature*, 2006, **441**, 861–863.
67 For a recent example and leading references, see: D. Enders, C. Wang, M. Mukanova and A. Greb, *Chem. Commun.*, 2010, **46**, 2447–2449.
68 Y. Wang, D. F. Yu, Y. Z. Liu, H. Wei, Y. C. Luo, D. J. Dixon and P. F. Xu, *Chem. Eur. J.*, 2010, **16**, 3922–3925.
69 For reviews on organocatalysis in total synthesis, see: E. Marques-Lopez, R. P. Herrera and M. Christmann, *Nat. Prod. Rep.*, 2010, **27**, 1138–1167.
70 C. Grondal, M. Jeanty and D. Enders, *Nat. Chem.*, 2010, **2**, 167–178.
71 B. Simmons, A. M. Walji and D. W. C. MacMillan, *Angew. Chem., Int. Ed.*, 2009, **48**, 4349–4353.
72 S. B. Jones, B. Simmons and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2009, **131**, 13606–13607.
73 M. D. Helm, M. Da Silva, D. Sucunza, T. K. Findley and D. J. Procter, *Angew. Chem., Int. Ed.*, 2009, **48**, 9315–9317.
74 For an additional example of this strategy, see: C. Beemelmanns and H. U. Reissig, *Angew. Chem., Int. Ed.*, 2010, **49**, 8021–8025.
75 Z. H. Shao and H. B. Zhang, *Chem. Soc. Rev.*, 2009, **38**, 2745–2755.
76 J. Zhou, *Chem.–Asian J.*, 2010, **5**, 422–434.

 