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Synthetic Studies Towards Spirocyclic Imine Marine Toxins Using *N*-Acyl Iminium Ions as Dienophiles in Diels–Alder Reactions

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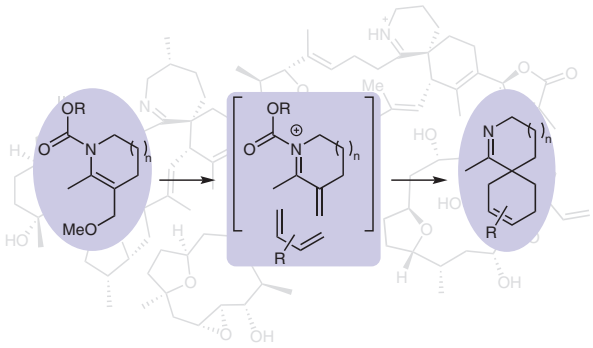

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Abstract Cyclic imine marine toxins have attracted considerable attention from the synthetic community in the past two decades due to their unique chemical structures and clinically relevant biological activities. This review presents recent efforts of our group in the development of various strategies to efficiently construct the common spirocyclic imine fragments of the cyclic imine toxins. In particular, the use of α,β-unsaturated *N*-acyl iminium ion dienophiles in Diels–Alder reactions are highlighted, whereby direct access to spirocyclic imine motifs was obtained and important mechanistic details were discovered. Alternative approaches to spirocyclic imine systems involving hydroamination of amino alkynes are also summarized. One such approach led to serendipitous access to *N*-vinyl amide products, while our most recently reported approach involving an intermolecular Diels–Alder/cross-coupling sequence using novel 2-bromo-1,3-butadienes to access 5,6-spirocyclic imines is also discussed. Additionally, the development of a novel method to construct another challenging motif present in the portimines is also introduced.

Key words spiroimines, Diels-Alder reaction, N-acyl iminium ions, Mukaiyama Michael addition, iminium dienophiles

1 Introduction

Oceanic microalgae can proliferate to concentrations of up to millions of cells per liter under favorable conditions, forming 'algal blooms' which are often visible as patches of red or brown on the ocean surface.[1] Often, the species of microalgae involved produce toxins which accumulate in the tissues of feeding shellfish and can then pass on to humans when they are ingested. Harmful algal blooms are responsible for the death of wildlife and human illness and are therefore considered an increasing global health concern.[2]

The toxins produced by marine dinoflagellates often display unique biological activities, rendering them potential pharmacological candidates. In particular, cyclic imine toxins have garnered particular interest from the synthetic community due to their synthetic complexity and potent activity. Named after their common structural motif (shaded in blue, Figure 1), these toxins can be further classified by the size of the cyclic imine ring, with either 7,6-spirocyclic systems (as in the spirolides, e.g. spirolide A (**1**), pinnatoxins, and pteriatoxins) or 6,6-spirocyclic systems (as in gymnodimine A (**2**) and recently isolated kabirimine (**3**)[3]) being the most common.[4] Portimine A (**4**), isolated in 2013, is an example of a cyclic imine toxin bearing a 5,6-spirocyclic imine system. Reviews regarding the classification and biological evaluation of these toxins are numerous.[5,6] In particular, the toxicity displayed by the pinnatoxins,[7,8] pteriatoxins,[9] and spirolides[10] stem from their ability to activate Ca^{2+} channels, while gymnodimine and members of the spirolide family have demonstrated affinity for nicotinic acetylcholine (nACh) receptors.[11] Meanwhile, portimine A (**4**) displays high *in vitro* cytotoxicity and promotes apoptosis *via* caspase-3 activation in P388 leukemia cells.[12,13]

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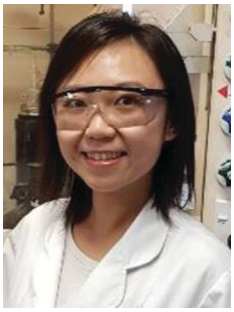
The spirocyclic imine motif is postulated to be an important component of the active pharmacophore of these toxins, since spirolides E and F (derivatives of spirolide A (**1**) possessing a hydrolyzed keto amine motif)[14] and a spirocyclic amine analogue of gymnodimine[15] all lacked biological activity. Work by Romo and co-workers suggests that the cyclic imine component acts as a masked enamine, and the mechanism of action may involve reaction of this latent nucleophile.[16] Therefore, there is immense value in these spirocyclic imine fragments as pharmacological probes, and convenient synthetic access to these systems is highly sought after.

Biographical sketches

Jared L. Freeman completed his PhD in 2019 from the University of Auckland under the supervision of Distinguished Professor Dame Margaret Brimble and Dr. Daniel Furkert. His PhD focused on the synthesis of an antibiotic macrocyclic natural product. He is currently undertaking a postdoctoral research position at Bayer AG in Frankfurt am Main, Germany, where his research interests currently include the synthesis of novel herbicides to address the issue of highly resistant weeds.



Freda F. Li received her PhD in 2017 from the University of Auckland in New Zealand under the supervision of Distinguished Professor Dame Margaret Brimble. She is currently a postdoctoral research fellow in Dame Brimble's research group at the University of Auckland. Her research interests include the synthesis of bioactive heterocycles, cell-imaging fluorophores, and anticancer peptide natural products. Her current research focuses on syntheses of spirocyclic imine natural toxin and related bioactive fragments.

Dr. Daniel Furkert is a senior research fellow at The University of Auckland, leading Professor Brimble's natural product synthesis and medicinal chemistry group in the School of Chemical Sciences. After undergraduate and doctoral degrees at The University of Auckland, he carried out postdoctoral fellowships in the synthesis of azaspiracid at Oregon State University (USA) and the medicinal chemistry of novel opioid receptor ligands at the University of Bath (UK). He returned to New Zealand take up his current role in 2010, where his current interests include asymmetric synthesis and medicinal chemistry applications of natural products, novel chemical reactivity, and drug discovery.

Dame Margaret Brimble is Director of Medicinal Chemistry and a Distinguished Professor at the University of Auckland where her research focuses on the synthesis of bioactive natural products and peptide chemistry. She has published over 500 papers and named as an inventor on more than 50 patents. She was inducted into the American Chemical Society Medicinal Chemistry Division Hall of Fame in 2019 and was elected a Fellow of the Royal Society (London) and awarded the RSC Sosnovsky Award in Cancer Therapy in 2018. She won the 2012 RSNZ Rutherford, MacDiarmid, and Hector Medals. She is past president of IUPAC Organic and Biomolecular Division III and an associate editor for Organic Letters. She discovered the first drug 'trofinetide' to treat Rett syndrome that is in phase III clinical trials with Neuren Pharmaceuticals (http://www.neurenpharma.com) and co-founded the company SapVax to develop self-adjuvanting cancer vaccines (https://sapvaxllc.com).

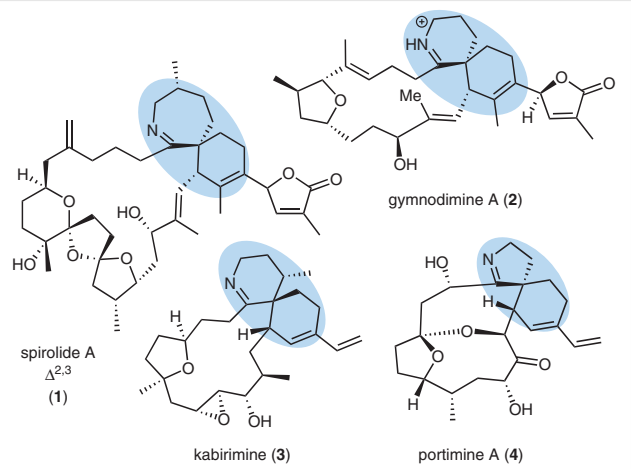


Figure 1 Representative examples of spirocyclic imine toxins

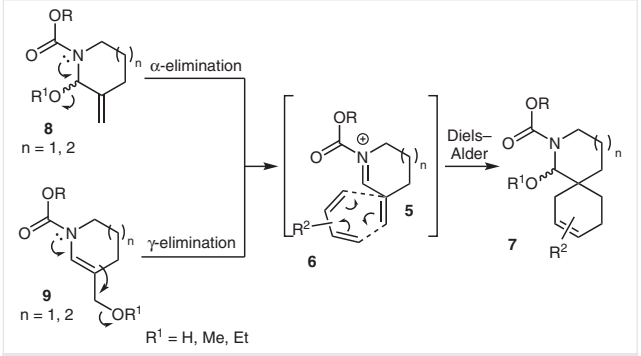
The synthesis of key members of this class of compounds has been the focus of a number of reviews,[17,18] and in recent times, a renewed interest has emerged, with five separate reports of synthetic strategies to access spirocyclic imine systems of the cyclic imine toxins since 2017.[19–23] Since the early 2000s, our group has remained interested in this unique structural motif and have previously published a review on selected synthetic efforts towards the spirocyclic imine unit of the spirolides prior to 2011.[24] Synthetic approaches detailed in that particular review include intermolecular Diels–Alder strategies,[25,26] alkylation–cyclization approaches[27–29] and an asymmetric Birch reductive alkylation.[30] Importantly, those approaches often involved targeting spirocyclic lactam fragments as precursors to spirocyclic imines. This review represents our recent efforts in the development of synthetic approaches towards cyclic imine toxins, which focus on providing direct access to spirocyclic imine fragments using *N*-acyl iminium chemistry, with serendipitous discoveries and new methodology developed along the way. Key relevant work from other research groups will also be described where appropriate.

2 Strategies towards the Spirocyclic Imine Fragment of Cyclic Imine Toxins

2.1 Diels–Alder Cycloadditions of α,β-Unsaturated *N*-Acyl Iminium Dienophiles

The spirocyclic imine fragments of cyclic imine toxins are largely purported to arise from intramolecular Diels–Alder cycloaddition reactions.[31] Indeed, this reflects the most convergent method for synthesizing the spirocyclic imine motif, given the ability to forge the precise stereochemical configuration of both the quaternary carbon center and the adjacent tertiary center in a single step. This factor justifies the prevalence of Diels–Alder strategies in reported syntheses of spirocyclic imine fragments by groups including Romo,[32] Murai,[33] Nakamura,[34] and White.[35,36] These methods often involved the use of α-*exo*-methylene lactam/lactone dienophiles, which ultimately afforded spirolactam/lactone ring systems and required further elaboration to the desired spirocyclic imine motif.

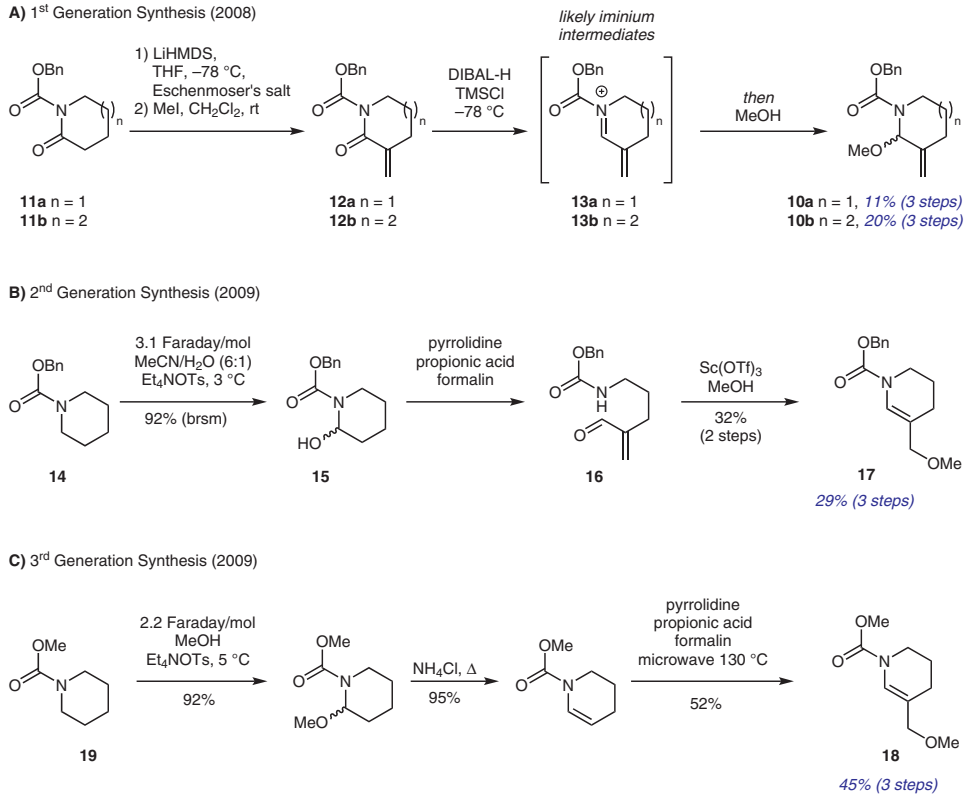
Alternatively, direct access to a spirocyclic imine could be achieved *via* a Diels–Alder reaction of an α,β-unsaturated iminium ion dienophile. From 2005 to 2007, intramolecular Diels–Alder approaches to gymnodimine A (**2**) and symbioimine involving α,β-unsaturated iminium ions were reported by Kishi,[37] Snider,[38] and Thomson.[39] In particular, both Snider and Thompson groups utilized a highly reactive *N*-acyl iminium dienophile which was generated *in situ* from Lewis acid activation of a stable *N*-acyl enecarbamate precursor. Intermolecular variants of the Diels–Alder reaction, however, were relatively unexplored prior to our initial investigations of *N*-acyl iminium ion chemistry in 2008.[40] Reaction of an exocyclic α,β-unsaturated *N*-acyl iminium ion **5** with an appropriate diene **6** could provide convenient access to spirocyclic imine fragment **7** similar to those found in the cyclic imine toxins (Scheme 1). It was rationalized that *in situ* iminium ion generation could occur through α- or γ-elimination of a nucleofuge from cyclic carbamates **8** and **9**, respectively, and a scalable synthesis of stable iminium ion precursors was the focus of our initial investigations.



Scheme 1 Possible pathways for *in situ* generation of α,β-unsaturated *N*-acyl iminium ion **5** and its use in Diels–Alder reactions

2.2 Early Studies Using *in situ*-Generated Iminium Ion Dienophiles

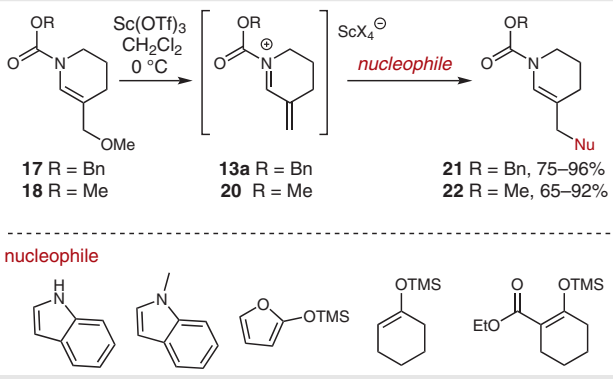
Our first-generation synthetic approach to iminium ion precursors **10a** and **10b** (Scheme 2, A), reported in 2008 involved base treatment of the corresponding six- or seven-membered *N*-CBz lactam **11a** and **11b**, followed by alkylation of the amide enolates with Eschenmoser's salt and Hofmann elimination.[40] Reduction of the α-methylenated lactams **12a** and **12b** with DIBAL-H/TMSCl and quenching with MeOH at low temperature afforded *N*,*O*-acetals **10a** and **10b** as iminium ion precursors, likely proceeding *via*



Scheme 2 Our first- (A), second- (B), and third-generation (C) syntheses of *N*-acyl iminium ion precursors **10**, **17**, and **18**[40,41]

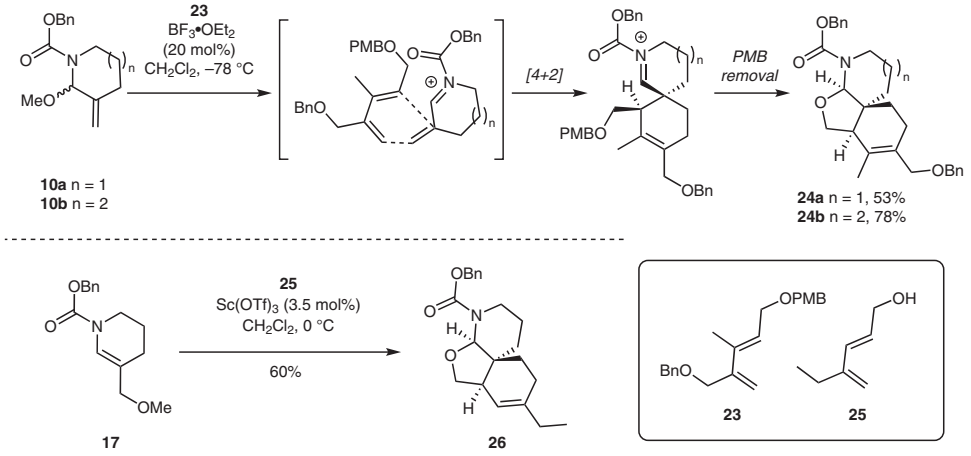
iminium intermediates **13a** and **13b**. The modest overall yield of this sequence warranted investigation of an alternative second-generation route to the six-membered iminium precursor **10a**. Later in 2009 it was discovered that an electrochemical oxidation of *N*-protected piperidine **14** could be employed to access hemiaminal **15** in greater yield (92% brsm) than conventional chemical oxidation methods (Scheme 2, B).[41] Pihko organocatalytic methylenation afforded ring-opened α,β-unsaturated aldehyde **16**, and subsequent treatment with catalytic amount of $Sc(OTf)_3$ in MeOH afforded enecarbamate **17** as an iminium ion precursor. Despite likely proceeding through identical iminium ion intermediate **13a**, it is noteworthy that **17** was formed under thermodynamic conditions, while kinetic conditions (i.e., DIBAL-H, –78 °C) afforded its constitutional isomer **10a**. This reaction sequence was then further modified in a third-generation approach to iminium ion precursor **18** while bypassing unstable aldehyde intermediates of the previous generation synthesis (Scheme 2, C).[41] Iminium ion precursor **18** was synthesized in a much improved yield through anodic α-oxidation of N-protected piperidine **19**, followed by NH_4Cl-mediated elimination and microwave-promoted organocatalytic alkylation.

The reactivity of six-membered iminium precursors **17** and **18** was evaluated in a series of nucleophile trapping experiments, whereby reactive iminium ions **13a** and **20** were generated in the presence of a catalytic amount of $Sc(OTf)_3$, then quenched with various nucleophiles (Scheme 3). The corresponding alkylated products **21** and **22** were afforded in high yields for various nucleophiles such as indole and silyl enol ethers.



Scheme 3 Nucleophile trapping with six-membered *N*-acyl iminium ions **13a** and **20**[41]

Use of iminium precursors **10a**, **10b**, and **17** in Diels–Alder reactions to access spirocyclic systems was also reported in our 2008 study.[40] Both six- and seven-membered *N*-carboalkoxy-*N*,*O*-acetals **10a** and **10b** were reacted with diene **23** following iminium ion generation using $BF_3{\cdot}OEt_2$



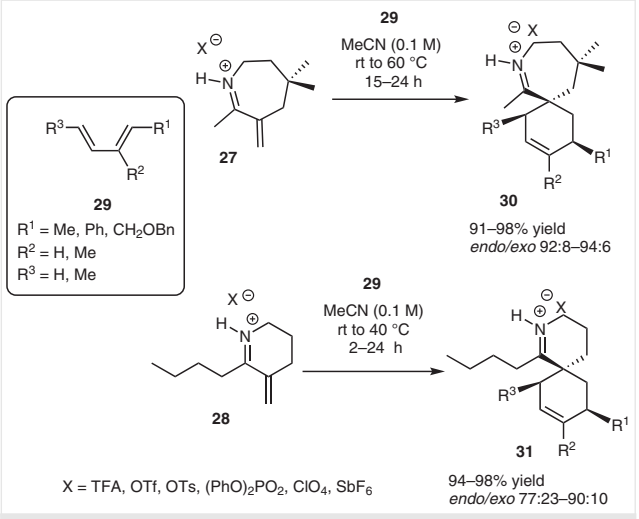
Scheme 4 Use of **10a**, **10b**, and **17** in iminium ion activated Diels–Alder cycloadditions[40]

to deliver tricyclic *N*,*O*-acetals **24a** and **24b** in good yields with high *endo* selectivity, although simple dienes such as isoprene failed to react with the generated six- or seven-membered iminium ions (Scheme 4). Meanwhile, enecarbamate **17** reacted similarly using diene **25** to afford tricycle **26**, suggesting that the reaction proceeds through *in situ* generation of an identical iminium ion species. These tricyclic adducts likely formed through Diels–Alder cycloaddition, *in situ* PMB ether deprotection, and intramolecular *N*,*O*-acetal formation through trapping of the resulting iminium intermediate. The precise order of these events, however, was unclear, as was the impact of intramolecular *O*-alkylation on the stereochemical outcome of the reaction. Typically, cyclic α-*exo*-methylene dienophiles provide *exo* adducts, due to a combination of steric and electronic factors associated with the *s*-*cis* dienophile configuration.[42,43] The exclusive formation of *endo* adducts in our study was confirmed on the basis of 2D NOESY NMR analysis, which was rationalized to be due to favorable secondary orbital overlap between the diene and the *s*-*trans*-configured iminium dienophile.

These investigations demonstrated that *in situ* generation of iminium ions in the presence of functionalized dienes could be a promising method for accessing spirocyclic systems resembling those of cyclic imine toxins. In particular, preventing *N*,*O*-acetal formation would be required in order to further elaborate the generated fragments towards the natural products. In addition, the moderate reaction yields could be attributed to instability of the iminium ion prior to cycloaddition.

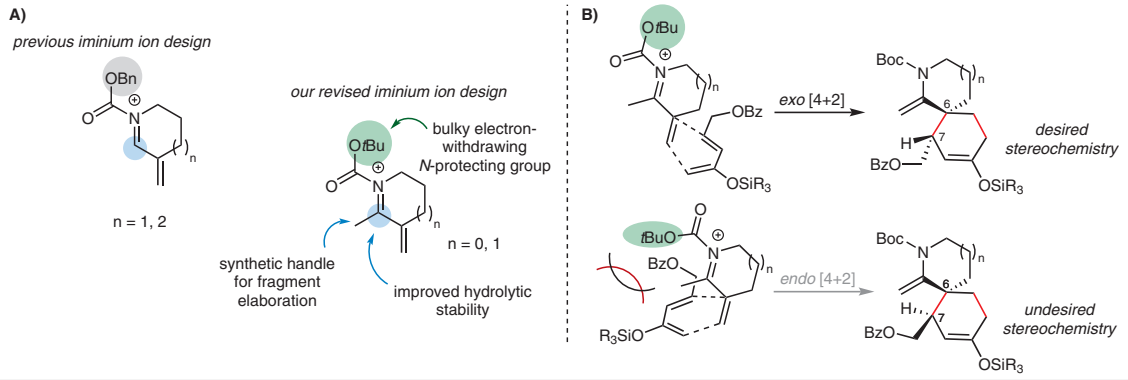
2.3 Use of More Stable Iminium Ion Dienophiles for Diels–Alder Reactions

Following these studies, in 2011, advances in intermolecular Diels–Alder reactions of iminium ions were reported by Evans and co-workers (Scheme 5).[44] Remarkably, seven- and six-membered *NH*-α,β-unsaturated iminium salts **27** and **28** were found to be isolable and stable to flash column chromatography. Iminium ions **27** and **28** were used in Diels–Alder reactions with simple dienes **29**, with spirocyclic adducts **30** and **31** afforded in excellent yields and high *endo* selectivities (>90:10) due to LUMO-lowering activation of the iminium dienophiles. The dienophilic counterion (X^-) was found to have a significant effect on the rate and diastereoselectivity of the reaction, with the noncoordinating hexafluoroantimonate (SbF_6^-) counterion resulting in substantial reaction-rate acceleration. Importantly, imine α-functionalization in the form of a methyl and *n*-butyl substituents appeared important for the hydrolytic stability of the iminium ions.



Scheme 5 Iminium ion Diels–Alder cycloadditions by Evans et al.[44]

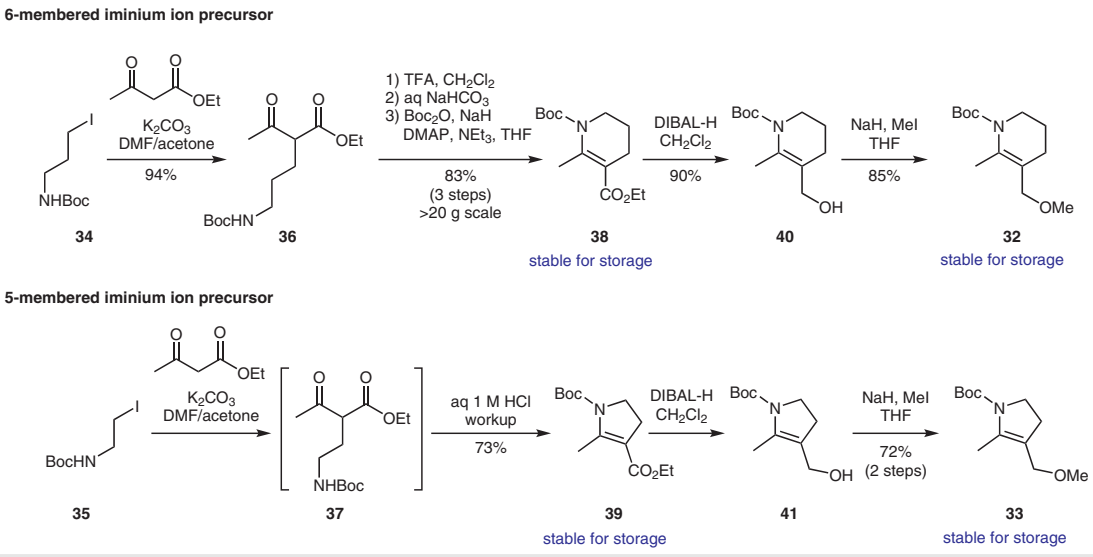
Evans' work therefore prompted a redesign of our iminium ion dienophile scaffold to incorporate a methyl substituent at the imine center (Scheme 6, A), which would serve



Scheme 6 Our revised iminium ion scaffold and proposed outcome of their use in Diels–Alder reactions

to improve the hydrolytic stability of the resultant iminium ion while also providing a synthetic handle for natural product elaboration through methodology previously reported by our group.[45] Such a substituent at the α-position would also render the iminium center less susceptible to nucleophilic attack, prohibiting the previously observed intramolecular *N*,*O*-acetal formation. As an *exo*-Diels–Alder reaction was required to establish the natural C6–C7 relative stereochemical configuration, we postulated that increasing steric bulk of the dienophile through bulky protecting groups on both the diene and iminium dienophile components could direct Diels–Alder cycloaddition through an *exo* transition state (Scheme 6, B). An electron-withdrawing *N*-Boc protecting group would serve to enhance the reactivity of the resultant iminium ion, while also proving easy to remove and reveal the desired spirocyclic imine motif. Additionally, the isolation of portimine A (**4**, Figure 1) in 2013,[12] which possesses a 5,6-spirocyclic imine system, presented itself as an additional application for this chemistry through accessing an analogous five-membered iminium ion, which was previously unexplored.

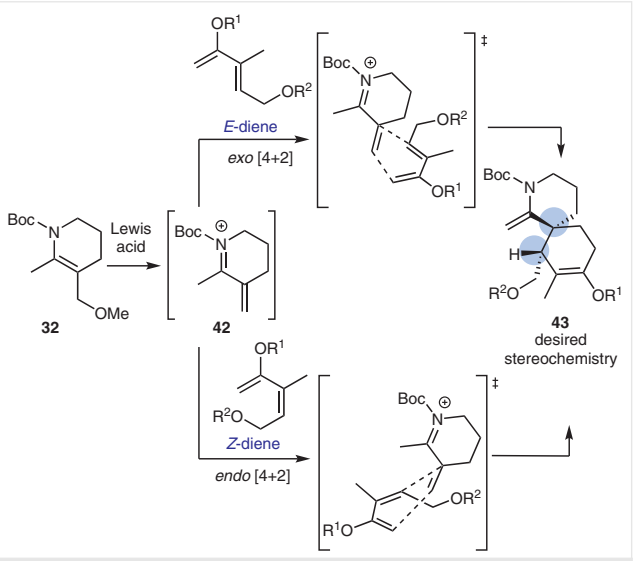
As a result, we reported our progress regarding the synthesis and reactivity of more stable six- and five-membered α,β-unsaturated *N*-acyl iminium ions in 2016[46] and 2019,[47] respectively. Robust syntheses of bench-stable six- and five-membered iminum ion precursors **32** and **33** were established in these studies (Scheme 7). Alkylation of iodides **34** and **35** using ethyl acetoacetate proceeded smoothly to afford β-keto esters **36** and **37**. Direct cyclization of β-keto ester **36** to form six-membered cyclic enecarbamate **38** proved problematic; however, it was found that *N*-Boc deprotection, cyclization, and subsequent amine reprotection were required to give stable six-membered cyclic enecarbamate ester **38** in high overall yield. Comparatively, direct cyclization of the analogous two-carbon-chain compound **37** to form cyclic five-membered enecarbamate **39**



Scheme 7 Synthesis of six- and five-membered *N*-Boc cyclic enecarbamates **32** and **33** as stable iminium ion precursors[46,47]

was successful, with facile cyclization of **37** occurring during the acidic workup following alkylation. DIBAL-H-mediated reduction of the ester motif of both **38** and **39** provided allylic alcohols **40** and **41** which were initially investigated as potential iminium precursors. However, instability and low reactivity led us to favoring methylation of alcohols **40** and **41**, delivering both methyl ethers **32** and **33** as convenient precursors of *N*-acyl iminium ions, which also proved stable long-term. Our newly developed route proved robust on gram-scale and overcame synthetic difficulties of previously reported methods, proceeding through stable intermediates (e.g., **38** and **39**) suitable for long-term storage if required.

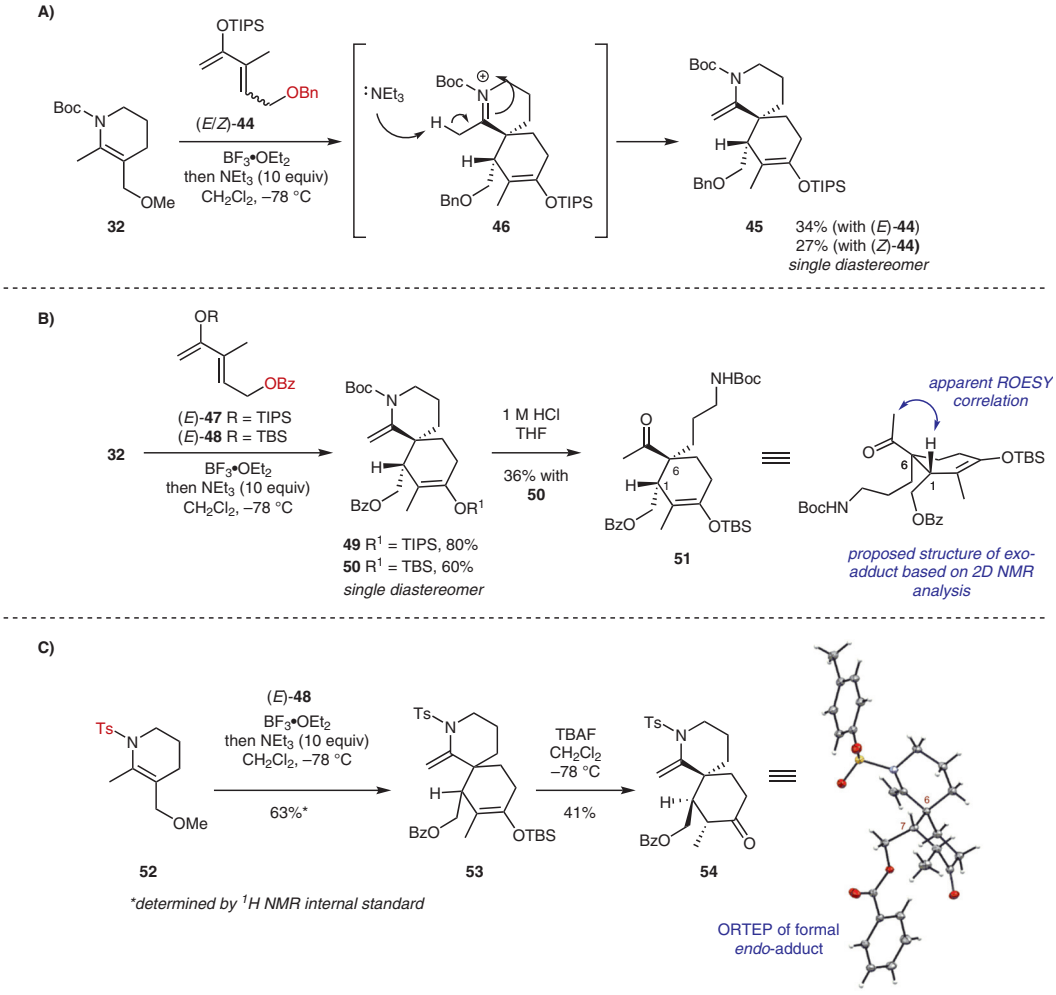
Use of precursors **32** and **33** to prepare the corresponding α,β-unsaturated *N*-acyl iminium ion dienophile **42** in the presence of the Lewis acid, which can then react with a range of silyloxy *E*/*Z*-dienes in the Diels–Alder reaction, were therefore investigated (Scheme 8). It was rationalized that a *Z*-diene configuration could also provide adducts **43** bearing the desired stereochemical orientation through a concerted cycloaddition *via* an *endo* reactivity mode.



Scheme 8 Proposed outcome of Diels–Alder reactions of iminium ion **42** with *E*- or *Z*-silyloxy dienes

To probe the reactivity of six-membered *N*-acyl iminium ions as dienophiles in Diels–Alder reactions, an initial reaction involved the generation of the iminium ion dienophile from precursor **32** using $BF_3{\cdot}OEt_2$ prior to reaction with silyloxydiene (*E*)-**44** to provide adduct **45** as a single diastereomer in 34% yield (Scheme 9, A). Use of an excess amount of triethylamine was required to convert iminium adduct intermediate **46** into the observed enamine adduct **45**. Interestingly, unpublished results from our group involved an analogous reaction using *Z*-diene (*Z*)-**44** with six-membered iminium precursor **32** which afforded the same adduct diastereomer **45** in 27% yield. This appeared to corroborate a similar observation reported by Romo and co-workers in 2000, whereby Diels–Alder reaction of a six-membered α-*exo*-methyl lactam resulted in a single adduct diastereomer obtained, irrespective of the diene configuration.[48] In their case, they reasoned that a formal Diels–Alder reaction, proceeding stepwise via sequential Michael additions was in fact occurring, and it was conceivable that a similar process was occurring in our reaction. Further investigation of diene protecting groups revealed that replacement of benzyl with a benzoyl group on the primary alcohol of the diene [(*E*)-**47** and (*E*)-**48**] improved the yield of the cycloaddition products **49** and **50** significantly (Scheme 9, B). Stereochemical elucidation was enabled through hydrolytic ring opening of the *N*-heterocycle **50**, affording keto amine **51** which displayed a plausible through-space correlation between the C-6 acetyl substituent and H-1 in a 2D ROESY spectrum. This correlation corresponded to the desired natural configuration, which would have arisen from a formal *exo* cycloaddition. More recently, unpublished results from these ongoing studies within our group involved iminium Diels–Alder reactions using *N*-Ts enecarbamate precursor **52** which could be readily prepared through an analogous reaction sequence to previously reported *N*-Boc enecarbamate precursor **32** (Scheme 9, C). The desired iminium Diels–Alder reaction proceeded smoothly, however, stereochemical elucidation of adduct **53** through 2D NMR experiments proved ambiguous. Silyl group removal using TBAF provided crystalline ketone **54**, which possessed formal *endo* configuration as determined by X-ray crystallography. At this stage, whether or not there was a stereochemical discrepancy between the Diels–Alder reaction products of *N*-Boc and *N*-Ts iminium ions is yet to be confirmed unambiguously, and further work will be required to determine the factors controlling the stereochemical outcome of this reaction.

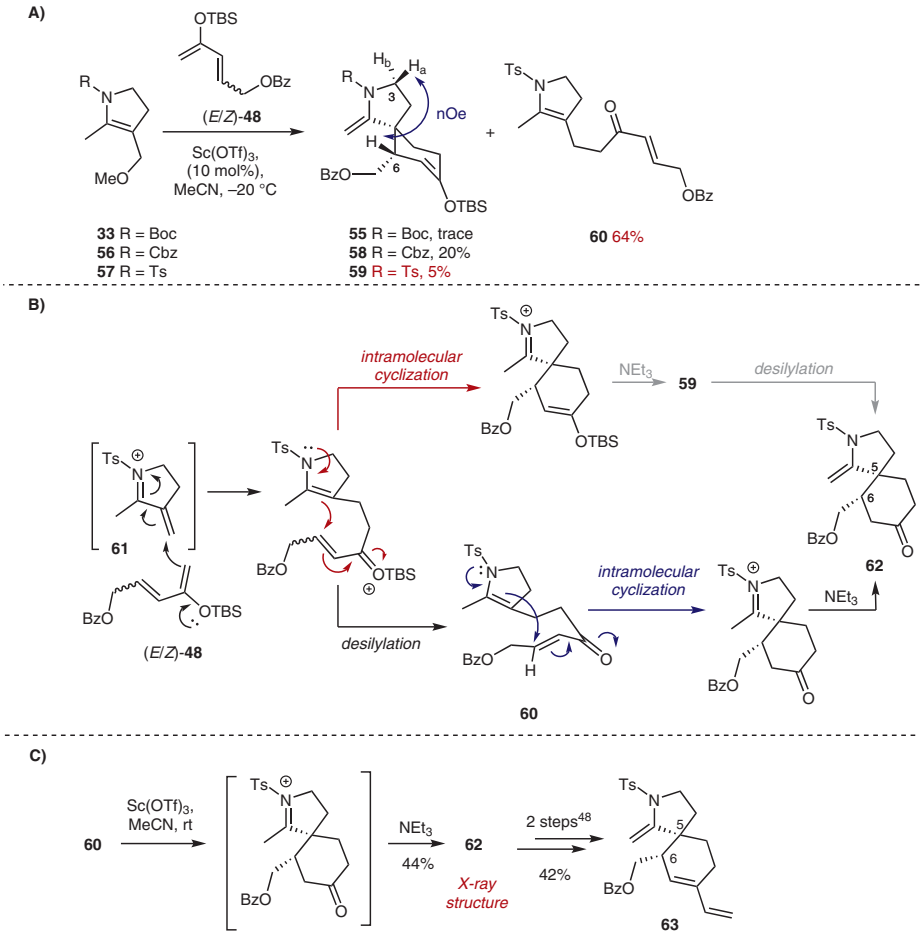
The discrepancy between the reactivity of five- and six-membered iminium ions was noted when investigating the Diels–Alder reaction with diene (*E*/*Z*)-**48** in our 2019 study,[47] with the *N*-protecting group also playing a major role (Scheme 10). The Diels–Alder reaction of five-membered *N*-Boc enecarbamate **33** with diene (*E*/*Z*)-**48** was initially attempted using conditions previously optimized for six-membered **32** (Scheme 10, A). Extensive decomposition was observed, and subsequent investigation of an extensive range of reaction conditions failed to afford more than a trace amount of bicyclic adduct **55**. It was soon realized that the five-membered *N*-Boc acyl iminium ion was unstable, and modification of the *N*-acyl substituent appeared as a promising method to modulate the reactivity of the resulting iminium ion. *N*-CBz and *N*-Ts enecarbamates **56** and **57** were therefore synthesized using similar sequences to those used to prepare **33**. In the case of *N*-CBz enecarbamate **56**, the desired bicyclic adduct **58** was afforded in a 20% yield, and a 2D NOESY experiment revealed a through-space correlation between H-3 and H-6, suggesting the for-



Scheme 9 Studies of **32** and **52** as precursors of six-membered iminium ion dienophiles in Diels–Alder reactions

mation of an *endo*-cycloaddition adduct. Meanwhile, an analogous reaction using *N*-Ts enecarbamate **57** provided the expected bicyclic adduct **59** in 5% yield, alongside a major quantity (64%) of enone **60**, which likely forms through Mukaiyama–Michael addition of diene **48** to the five-membered *N*-Ts iminium ion **61** (Scheme 10, B). This marked the first instance that such an intermediate had been detected and isolated throughout our extensive investigation of reactive iminium ions. It was expected that enone **60** could undergo intramolecular cyclization to afford bicyclic adduct **62**, and this was indeed the case, with exposure of **60** to $Sc(OTf)_3$ facilitating cyclization to afford adduct **62** as a single diastereomer (Scheme 10, C). The configuration of **62** was determined to be the formal *endo*-cycloaddition product through X-ray crystallography, and **62** could be further elaborated to natural product like fragment **63**, albeit with non-natural C5–C6 configuration. The isolation of enone **60** and its ability to cyclize to bicyclic compound **62** appeared to suggest that the iminium Diels–Alder reactions were in fact proceeding through a stepwise mechanism involving initial Mukaiyama–Michael addition of diene (*E*/*Z*)-**48** to iminium ion **61**, followed by Lewis acid mediated intramolecular cyclization. In support of this conclusion, the same adduct diastereomer was obtained irrespective of the diene geometry employed in the reaction, with use of a mixture of dienes (*E*)-**48** and (*Z*)-**48** affording the same, single diastereomer **62**.

N-Acyl iminium ions are well established as versatile intermediates for the synthesis of nitrogen-containing compounds, and their chemistry remains a promising area of research, particularly towards complex alkaloid synthesis, with extensive reviews regarding this field have been reported.[49,50] Taken together, these findings appeared to strongly suggest that the originally hypothesized concerted Diels–Alder cycloadditions of α,β-unsaturated *N*-acyl iminium ions may in fact proceed through a stepwise mechanism. Despite providing adducts bearing non-natural relative stereochemical configuration, we demonstrated easy



Scheme 10 Studies of **33**, **56**, and **57** as precursors of five-membered iminium ion dienophiles in Diels–Alder reactions

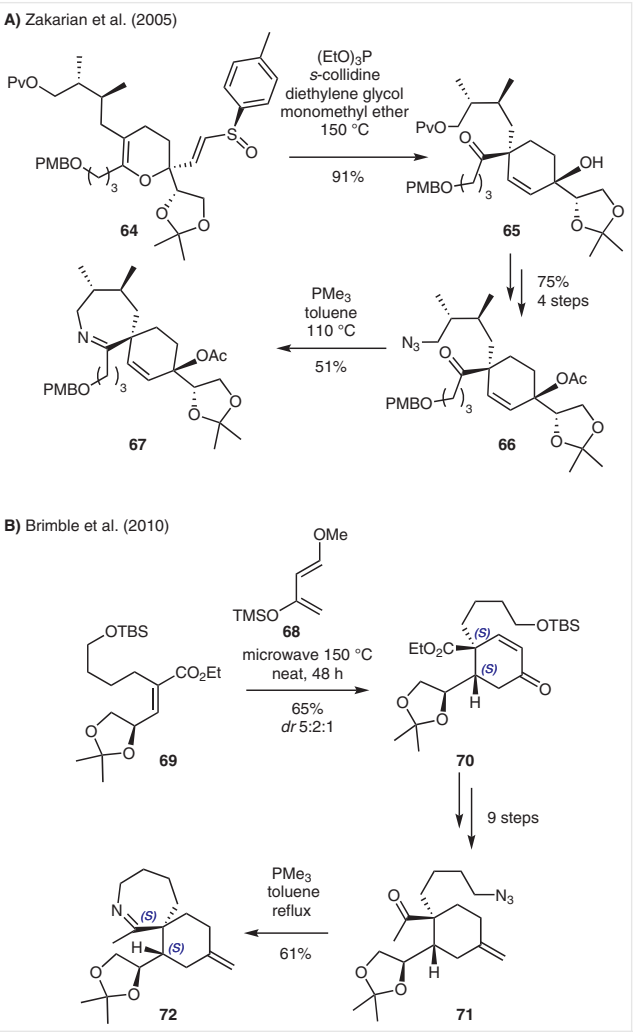
access to highly reactive iminium ions from stable precursors and their use in a highly convergent approach to access spirocyclic systems. Additionally, the ability to access intermediate enone **60** in the recent study (Scheme 10) offers the possibility for asymmetric control of the subsequent cyclization step, which is an ongoing area of investigation by our group.

2.4 Other Notable Strategies towards Spirocyclic Imines

Although Diels–Alder cycloadditions were utilized as the most efficient strategy to construct the spirocyclic imine fragments, other synthetic methods, developed by our group and others, have been utilized to construct the spirocyclic ring systems of members of the spirolides,[26] gymnodimine,[51] and, more recently, portimines.[21] As an alternative, indirect approach to forge spirocyclic imine fragments, these methods often involve construction of the 'lower' cyclohexene ring bearing the required stereochemistry at the quaternary center, with tethered side chains installed to later form the nitrogen-containing 'upper' ring.

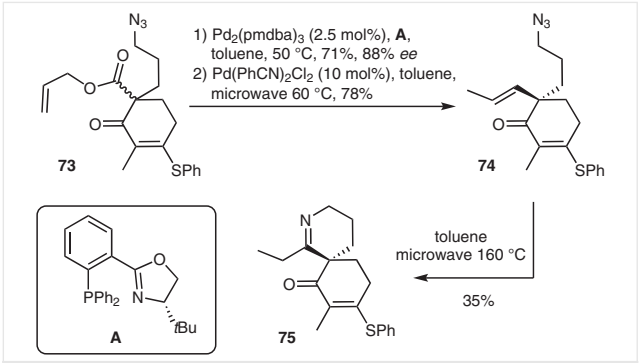
In 2005, Zakarian and co-workers reported a synthetic approach to the spirocyclic imine ring system of the pinnatoxins, whereby dihydropyran **64** underwent a cascade sigmatropic rearrangement to afford chiral ketone **65**, thus constructing the chiral quaternary center present in the pinnatoxins (Scheme 11, A). Subsequent elaboration of ketone **65** to azide **66** was followed by an aza-Wittig reaction, which facilitated cyclization of the seven-membered imine ring of **67**.[52] In 2010, our research group reported the synthesis of the spirocyclic imine fragment of members of the spirolides, whereby the cyclic imine formation was also achieved using a late-stage aza-Wittig cyclization (Scheme 11, B). The synthesis involved a microwave-assisted Diels–Alder cycloaddition between Danishefsky's diene (**68**) and α,β-unsaturated ester **69**, affording cyclohexenone **70** in 65% yield as a mixture of three diastereomers (5:2:1). Following successful formation of the 'lower' ring, subsequent transformations of the desired (*S*,*S*)-adduct **70** to keto-azide

71 was followed by an aza-Wittig cyclization reaction, affording spirocyclic imine **72** possessing the same relative stereochemistry as members of the spirolide family.[26]



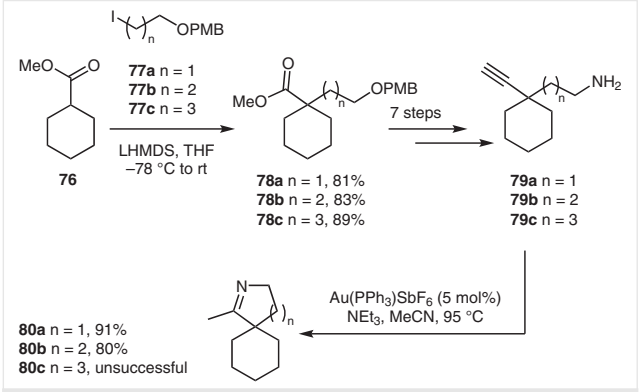
Scheme 11 Use of aza-Wittig reaction to construct spirocyclic imine fragments[26]

The Guillou group has reported several synthetic approaches to the 6,6-spirocyclic imine motif of the gymnodimine family since 2011.[51,53] Their most recent work in 2014 hinged on a palladium-catalyzed decarboxylative allylation reaction of **73** to forge the required quaternary stereocenter in high yield and enantioselectivity (Scheme 12). This was followed by a microwave-assisted alkene isomerization to afford azidoalkene **74** which subsequently underwent a [3+2] cycloaddition to afford spirocyclic imine **75** in moderate yield. Importantly, 6,6-spirocyclic imine **75** incorporates the requisite functional handles to be further elaborated to a viable spirocyclic imine intermediate for the synthesis of the gymnodimines.



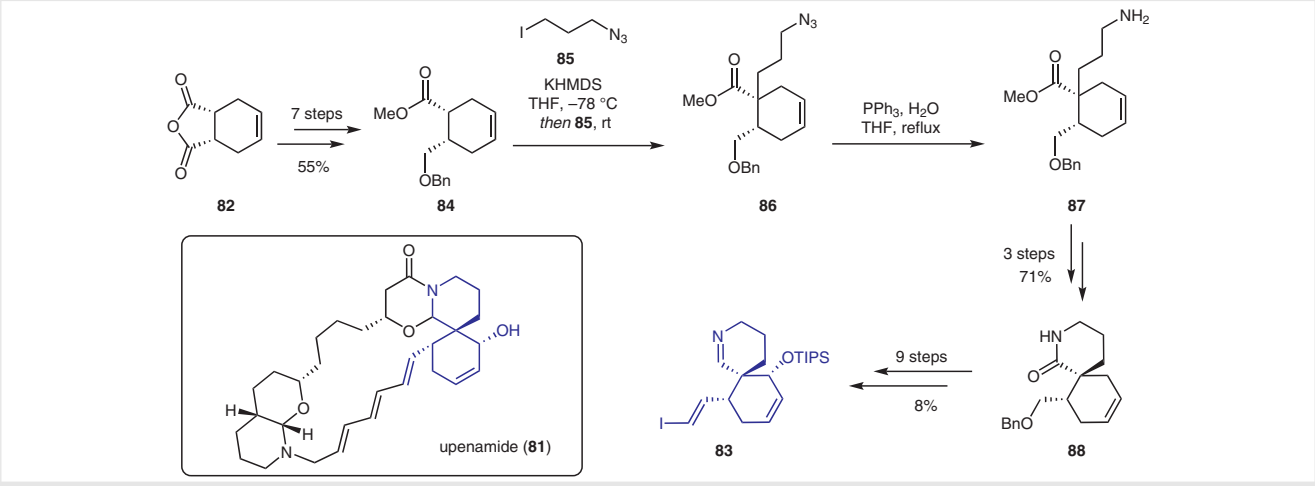
Scheme 12 Synthesis of 6,6-spirocyclic imine **75** by Guillou et al.[51]

Also in 2011, our research group reported a new approach to model spirocyclic imines which relied on quaternary center construction *via* an alkylation reaction, followed by a gold-catalyzed intramolecular hydroamination reaction to construct the cyclic imine system (Scheme 13).[54] This mild chemical transformation appeared ideally suited for late-stage construction of spirocyclic imine motifs. Alkylation of methyl cyclohexanecarboxylate (**76**) using alkyl iodides **77a–c** afforded the corresponding alkylated adducts **78a–c** which were subsequently functionalized to afford amino alkynes **79a–c** in good overall yield. With amino alkynes **79a–c** in hand, a large range of cyclization conditions were trialed, culminating in successful hydroamination of amines **79a** and **79b** through reaction with $Au(PPh_3)SbF_6$ and triethylamine at high temperature, generating spirocyclic imines **80a** and **80b** in good yield. However, hydroamination proved unsuccessful for amine **79c**, with complex mixtures generated instead, thus this approach was not feasible for accessing 7,6-spirocyclic imine fragments (e.g., **80c**).



Scheme 13 Intramolecular hydroamination towards spirocyclic imine fragments by Brimble et al.[54]

The proposed structure of upenamide (**81**) contains a 6,6-spirocyclic imine derived fragment (Scheme 14). In 2013, Taylor and co-workers reported a 19-step linear sequence from commercially available *meso*-anhydride **82** for



Scheme 14 Synthesis of the spirocyclic imine fragment **83** of upenamide (**81**) by Taylor et al.[55]

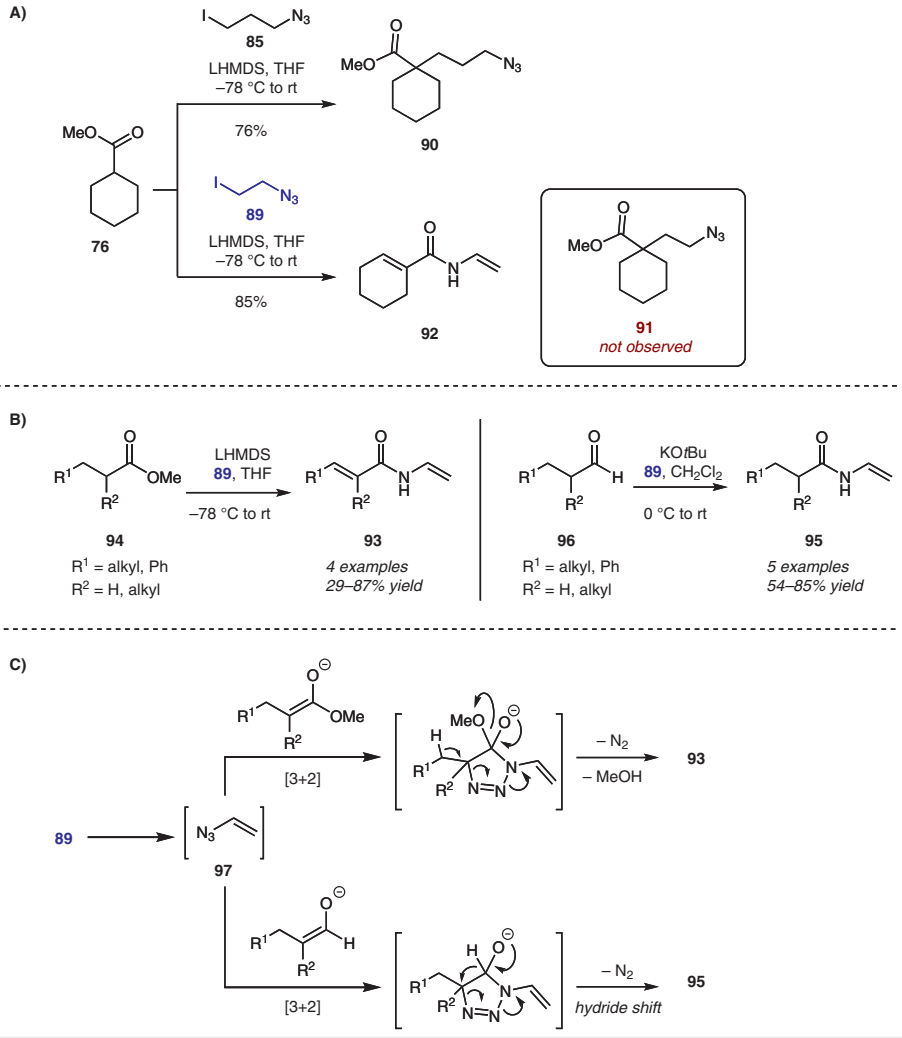
the synthesis of 6,6-spirocyclic imine **83** as a key fragment of upenamide (**81**, Scheme 14).[55] To this end, **82** was converted into *syn*-methyl ester **84** over 7 steps in 55% yield. The subsequent construction of the spirocyclic imine ring system involved a base-mediated alkylation of cyclohexene **84** with iodoazide **85**, Staudinger reduction of azide **86**, and lactam formation from amine ester **87** afforded bicyclic compound **88**, which was eventually elaborated to spirocyclic imine **83**.

In particular, the alkylation of cyclohexyl methyl ester **84** using iodoazide **85** reported by Taylor and co-workers appeared relevant for our own investigations as a means to streamline our previously reported synthesis of spirocyclic imine ring systems through the direct alkylation of ester **76** with iodoazides **85** and **89** (Scheme 15, A). Indeed, alkylation of **76** using iodide **85** provided the desired alkylated adduct **90** in high yield. Interestingly, the analogous reaction using iodoazide **89** failed to deliver the expected alkylated adduct **91**, instead affording α,β-unsaturated *N*-vinyl amide **92**. Following this observation, our study expanded the substrate scope to confirm this unexpected result and soon realized this reaction to be a remarkable and direct synthesis of industrially important α,β-unsaturated *N*-vinyl amides **93** from esters **94** and *N*-vinyl amides **95** from aldehydes **96** (Scheme 15, B). The reaction most likely proceeds through the *in situ* formation of an *N*-vinyl azide **97**, which undergoes facile azide–enolate [3+2] cycloaddition, followed by rearrangement and nitrogen extrusion (Scheme 15, C). This work was published in 2017[56] and remains an ongoing area of research within our group, using differentially substituted iodoazides and their reaction with aldehydes and esters to construct unique *N*-vinyl amide building blocks.

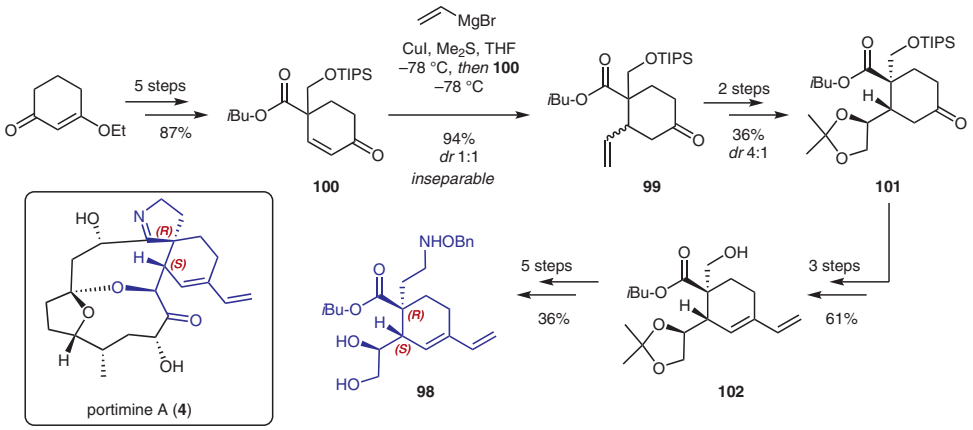
2.5 Recent Efforts towards the 5,6-Spirocyclic Imine Marine Toxin Portimine A

Among the cyclic imine marine toxin family, portimine A (**4**) represents the smallest member (5,6-spirocyclic imine) identified to date with a unique biological profile. It exhibits high *in vitro* cytotoxic activity (P388 cells, EC_{50} = 2.7 nM), yet low *in vivo* toxicity, setting it apart from the rest of cyclic imine toxin families which exhibit less specific toxicity.[57] In 2019, Fujiwara and co-workers reported the first synthetic study towards portimine A (**4**, Scheme 16), in which the synthesis of the cyclohexene fragment **98** of the natural toxin was achieved in 6.5% overall yield over 16 steps. The sequence involved the construction of the tertiary center of **99** through conjugate addition of vinylmagnesium bromide to α,β-unsaturated ketone **100**, followed by diastereoselective dihydroxylation of the vinyl group and acetal formation to provide acetal **101**. Installation of the diene moiety through a Grignard addition–dehydration sequence afforded diene **102**, which was subsequently elaborated to provide racemic cyclohexene fragment **98**.[21]

Meanwhile, the most recent study from our group in 2019 has demonstrated 2-bromo-1,3-butadiene systems (e.g., **103**, Scheme 17) as highly effective substrates for tandem Diels–Alder–transition-metal cross-coupling reaction sequences.[58] Intermolecular cycloaddition of 2-bromodiene **103** with a variety of activated dienophiles was shown to proceed in generally high yield, with good to excellent *endo* diastereoselectivity. The resulting vinyl bromide cycloadducts **104** readily underwent subsequent Stille and Suzuki cross-couplings under standard conditions to provide access to novel substituted cyclohexene products **105**. Of particular importance to this review is our application of this study to successfully assemble the spirocyclic imine motif **106** of portimine A (**4**), whereby the Diels–Alder reaction of diene **103** and enal dienophile **107** was used to forge the



Scheme 15 Unexpected formation of *N*-vinyl amide **92** and related study by Brimble and Furkert et al.[56]

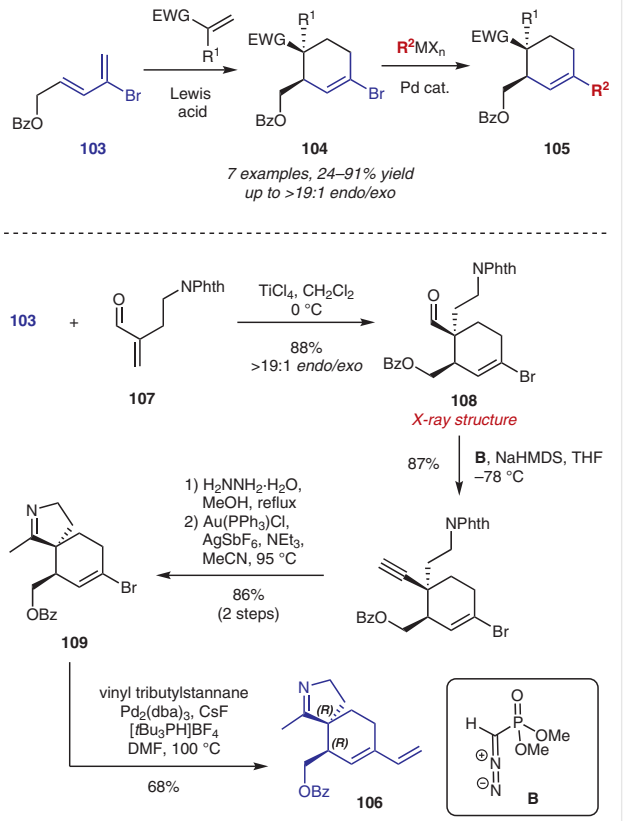


Scheme 16 Synthesis of the cyclohexene fragment **98** of portimine A (**4**) by Fujiwara et al.[21]

cyclohexene quaternary center. Adduct **108** then underwent Seyferth–Gilbert homologation, *N*-phthalimide deprotection, and gold-catalyzed hydroamination, employing conditions previously developed by our group,[54] to afford bicyclic imine **109**. Subsequent Stille coupling successfully installed a vinyl substituent to construct bicyclic fragment **106** resembling the 5,6-spirocyclic imine system of portimine A (**4**), albeit with non-natural (*R*,*R*)-relative stereochemical configuration. Future efforts will focus on understanding factors governing the diastereoselectivity of Diels–Alder reactions using 2-bromo-1,3-butadienes, and methods to reverse the inherent *endo* selectivity and favor adducts bearing the same stereochemical configuration seen in the cyclic imine toxins.

2.6 Construction of Another Challenging Motif of Portimine A

While the spirocyclic imine fragments of cyclic imine toxins command particular attention from synthetic chemists, each toxin of the family also bears a complex polyketide motif, representing another formidable synthetic task. At the time of Fujiwara and co-workers' synthesis of the cyclohexene fragment of portimine A (**4**), the polyketide portion of the natural product remained a challenging target, with the *syn*-1,3-dihydroxyketone motif in particular (shaded in blue of **4**, Scheme 18), identified by our group as an important synthetic issue to address before a total synthesis could be realized. The *syn*-dihydroxyketones are embedded in a wide range of biologically active natural products, however, development of stereoselective synthetic methods to assemble these structures has proven a challenging task. In 2019, we reported our development of a highly stereoselective synthesis of *syn*-dihydroxyketone motifs **110** from readily available propargylic alcohols **111** (Scheme 18).[59] The reaction sequence involved regioselective cyclization of propargylic alcohols **111** with incorporation of triketone **112** to give enol dioxolanes **113** that then underwent highly diastereoselective epoxidation to give spiroepoxide intermediates **114**. Hydrolysis or acetolysis of the spiroepoxides **114** then cleanly afforded *syn*-dihydroxyketones **110** or the corresponding monoacetylated dihydroxyketones **115** as single diastereomers. This methodology also included a telescoped one-pot protocol with no loss of overall yield or diastereoselectivity comparing to the three-step sequence, with wide scope for application in the stereoselective synthesis of complex molecular architectures.

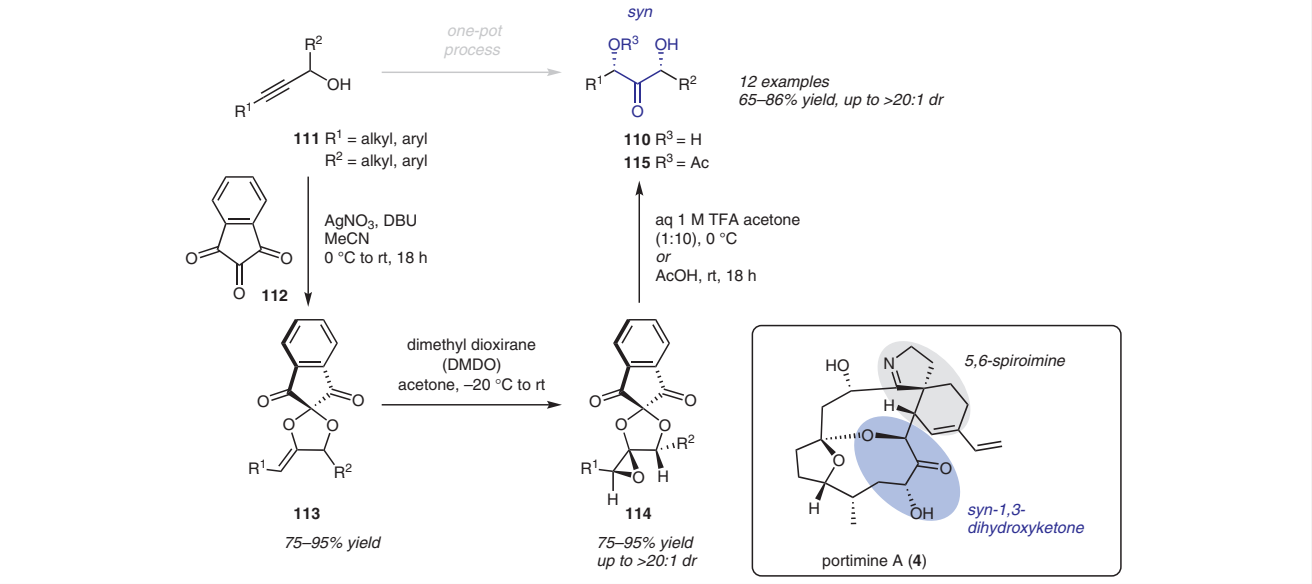


Scheme 17 Use of 2-bromodiene **103** in Diels–Alder cycloadditions to access 5,6-spirocyclic imine **106** by Brimble and Furkert et al.[58]

3 Conclusion and Future Perspectives

Taken together, this review details multiple synthetic investigations by our research group towards cyclic imine toxins. In particular, iminium chemistry has been investigated and has proved to be an efficient method for direct access to spirocyclic imine fragments, albeit bearing non-natural relative stereochemical configuration. In parallel, we also investigated alternative approaches to spirocyclic imine fragments, including alkylation–hydroamination sequences and Diels–Alder–hydroamination sequences. Along the way, an efficient method to synthesize *N*-vinyl amide building blocks was serendipitously discovered, and recently, a novel approach to access the challenging 1,3-*syn*-dihydroxyketone motif present in many bioactive natural products, including portimines, was established.

Recent years have seen a resurgence in interest in the spirocyclic imine fragment of cyclic imine toxins, with multiple new reports since 2017 validating the importance of these structural motifs. Diels–Alder approaches appear the most efficient means of accessing spirocyclic imine fragments, with the iminium Diels–Alder reaction in particular providing rapid access to spirocyclic imine systems. Further work is required to investigate the factors governing the stereochemical outcome of iminium Diels–Alder reactions, since the means with which to precisely control this will enable access to adducts bearing the natural stereochemical configuration.



Scheme 18 Diastereoselective synthesis of *syn*-1,3-dihydroxyketone motifs **110** by Furkert and Brimble et al.[59]

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