

HETEROCYCLES, Vol. 89, No. 9, 2014, pp. 2029 - 2052. © 2014 The Japan Institute of Heterocyclic Chemistry
Received, 7th May, 2014, Accepted, 20th June, 2014, Published online, 25th June, 2014
DOI: 10.3987/REV-14-798

SYNTHETIC ROUTES TOWARDS BENZOFURO[2,3-*b*]PYRROLES AND BENZOFURO[2,3-*b*]INDOLES

Yuta Ito, Masafumi Ueda,* and Okiko Miyata*

Kobe Pharmaceutical University, Motoyamakita, Higashinada, Kobe, 658-8558,
Japan, miyata@kobepharm-u.ac.jp, masa-u@kobepharm-u.ac.jp

Abstract – This review provides a summary of the synthetic methods currently available for the construction of benzofuro[2,3-*b*]pyrroles and benzofuro[2,3-*b*]indoles. The latter of these two scaffolds features as a key structural element in characteristic bioactive natural products.

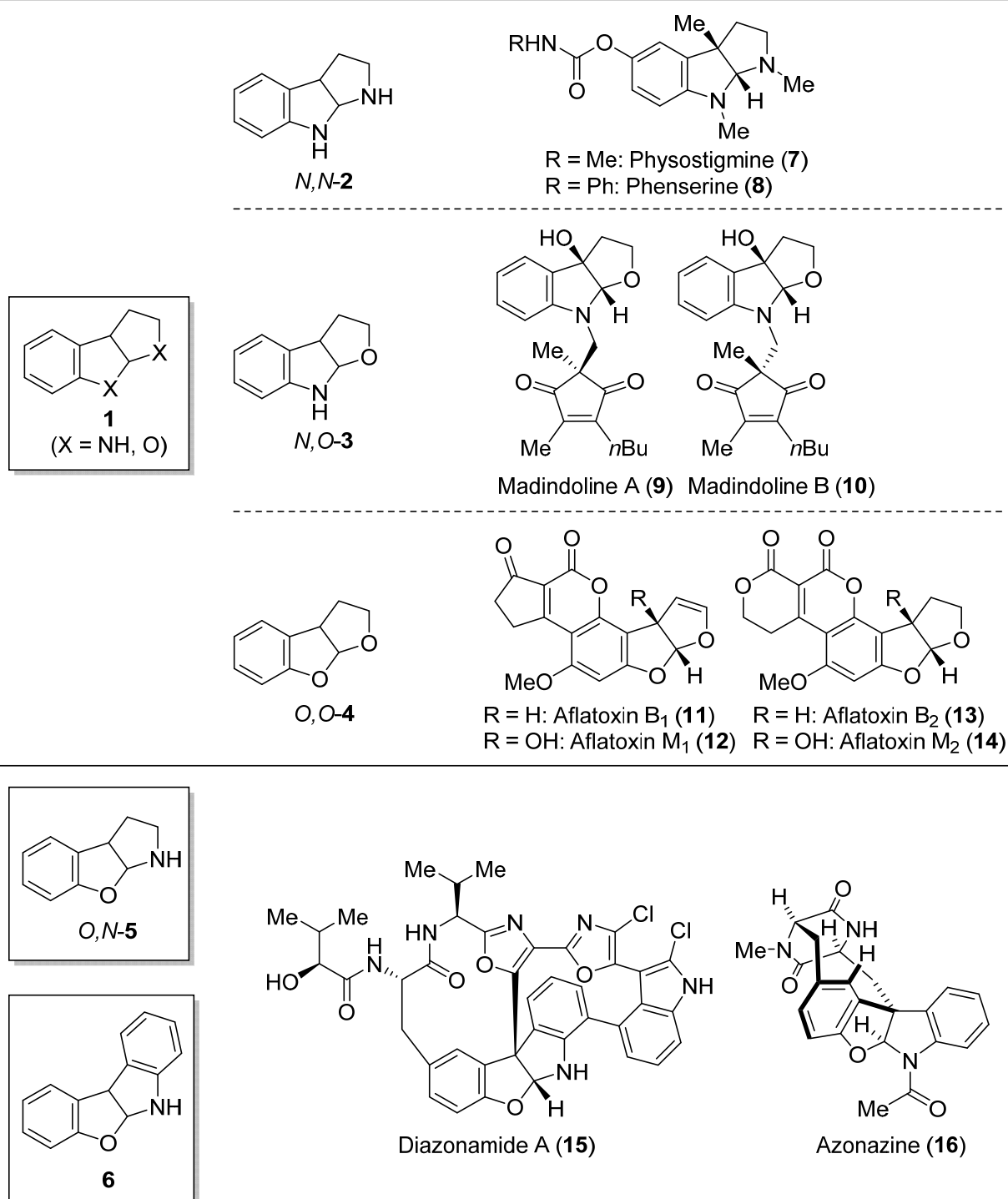
CONTENTS

1. Introduction
2. Synthesis of benzofuro[2,3-*b*]pyrrole
 - 2.1. Synthesis from benzofuran
 - 2.2. Synthesis from azirinocyclobutabenzofuran
 - 2.3. Synthesis from benzo[*f*]chromen-3-one
 - 2.4. Synthesis via 4-imino-3-(2-hydroxyphenyl)butanoate intermediate
 - 2.5. Synthesis via 2-(3,4-dihydro-2*H*-pyrrol-4-yl)phenol intermediate
3. Synthesis of benzofuro[2,3-*b*]indole
 - 3.1 Synthesis from indole
 - 3.2 Synthesis from oxindole
 - 3.3 Synthesis from indoline
4. Conclusion

1. INTRODUCTION

Tricyclic heterocycles **1** are key structural elements in a large number of natural and synthetic products that exhibit a wide range of bioactivities (Scheme 1). For example, the hexahydropyrrolo[2,3-*b*]indole¹ *N,N*-**2** can be found in compounds such as physostigmine (**7**) and phenserine (**8**), which are used to treat Alzheimer's disease and glaucoma,^{2,3} whereas the tetrahydrofuro[2,3-*b*]indole *N,O*-**3** can be found in madindolines A (**9**) and B (**10**), which have been reported to be selective inhibitors of interleukin-6.⁴ The

tetrahydrofuro[2,3-*b*]benzofuran *O,O*-**4** is present in the potent carcinogenic aflatoxins **11**–**14**.⁵ However, very few biological studies of tetrahydrobenzofuro[2,3-*b*]pyrrole *O,N*-**5** have been performed, despite their biological potential. Therefore, there is an urgent need for the development of synthetic methods capable of providing facile access to tetrahydrobenzofuro[2,3-*b*]pyrroles to allow for the effective evaluation of the biological properties.



Scheme 1

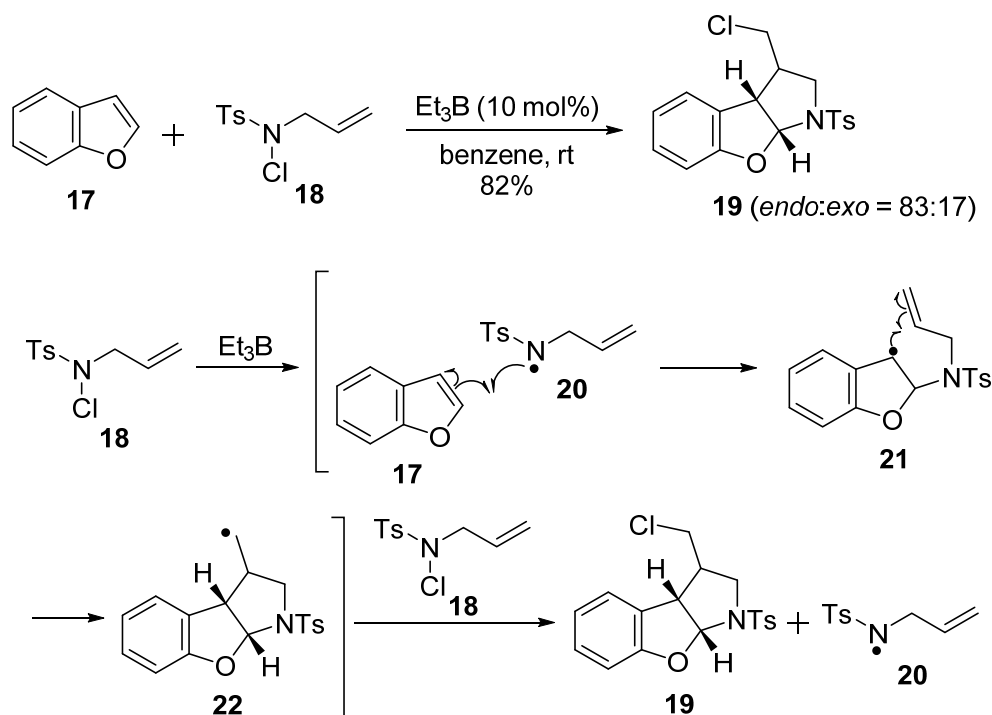
Furthermore, indole-fused benzofurans, such as dihydrobenzofuro[2,3-*b*]indole **6**, can be found in characteristic bioactive natural products such as diazomide A (**15**) and azonazine (**16**).^{6,7} For this reason, there has been a significant increase in research efforts directed towards the development of novel methods for the construction of dihydrobenzofuro[2,3-*b*]indoles. In this review, we have provided a summary of the existing methods for the synthesis of benzofuro[2,3-*b*]pyrroles and benzofuro[2,3-*b*]indoles.⁸

2. SYNTHESIS OF BENZOFURO[2,3-*b*]PYRROLE

The methods available for the synthesis of benzofuro[2,3-*b*]pyrroles can be divided into several categories, including (i) synthesis from benzofuran; (ii) synthesis from azirinocyclobutabenzofuran; (iii) synthesis from benzo[*f*]chromen-3-one; (iv) synthesis via 4-imino-3-(2-hydroxyphenyl)butanoate intermediate; and (v) synthesis via 2-(3,4-dihydro-2*H*-pyrrol-4-yl)phenol intermediate.

2.1 Synthesis from benzofuran

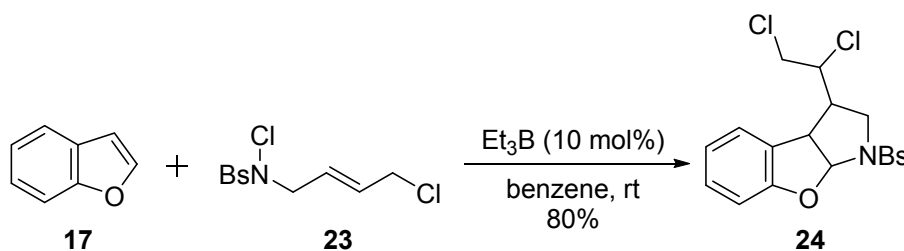
Oshima and Shinokubo⁹ developed a novel method for the preparation of a benzofuro[2,3-*b*]pyrrole from benzofuran that involved the radical [3 + 2] annulation reaction of *N*-allyl-*N*-chlorotosylamide (Scheme 2). The reaction of benzofuran (**17**) with *N*-allyl-*N*-chlorotosylamide (**18**) in the presence of 10 mol% of triethylborane afforded 3-chloromethylbenzofuro[2,3-*b*]pyrrole **19** in 82% yield (*endo:exo* = 83:17).



Scheme 2

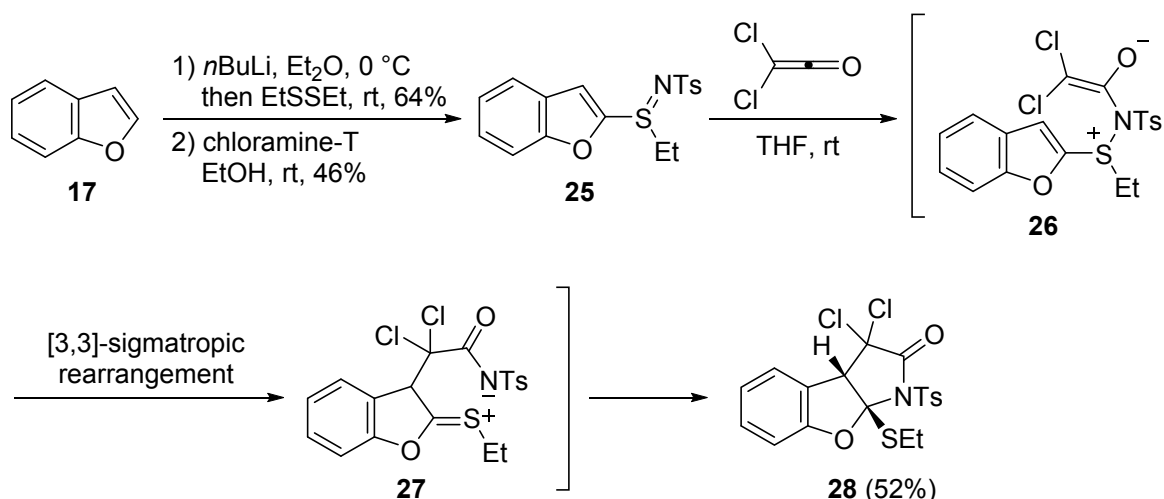
This radical reaction was initiated by the generation of the *N*-centered radical **20**, which reacted with benzofuran to form the alkyl radical **21**. Subsequent 5-*exo* radical cyclization would give the primary radical **22**, which would abstract a chlorine atom from **18** to afford 3-chloromethylbenzofuro[2,3-*b*]pyrrole **19** and regenerate the *N*-centered radical **20**.

The same authors also reported the synthesis of a benzofuro[2,3-*b*]pyrrole bearing a dichloroethyl group. Briefly, a mixture of benzofuran (**17**) and *N*-chloro-*N*-(4-chloro-2-butenyl)benzenesulfonamide (**23**) was treated with 10 mol% of triethylborane to give 3-(1,2-dichloroethyl)benzofuro[2,3-*b*]pyrrole **24** in 80% yield (Scheme 3).¹⁰



Scheme 3

Padwa's group^{11,12} reported that the reaction of 2-benzofuranylsulfilimine with dichloroketene afforded benzofuro[2,3-*b*]pyrrole. Benzofuran (**17**) reacted with *n*-butyllithium and diethyl disulfide to afford 2-ethylthiobenzofuran, which was then treated with chloramine-T to furnish the desired 2-benzofuranylsulfilimine **25** (Scheme 4). The subsequent reaction of **25** with dichloroketene afforded the 3,3-dichloro-8a-ethylthiobenzofuro[2,3-*b*]pyrrol-2-one **28** in 52% yield.

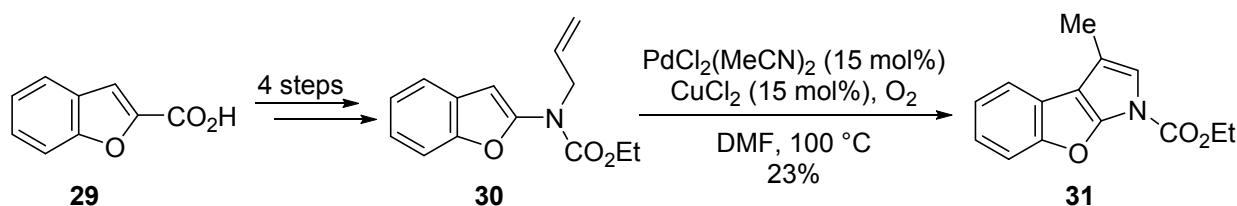


Scheme 4

This process involved the nucleophilic addition of the nitrogen atom to the highly electrophilic dichloroketene to generate the zwitterionic intermediate **26**. Intermediate **26** then underwent

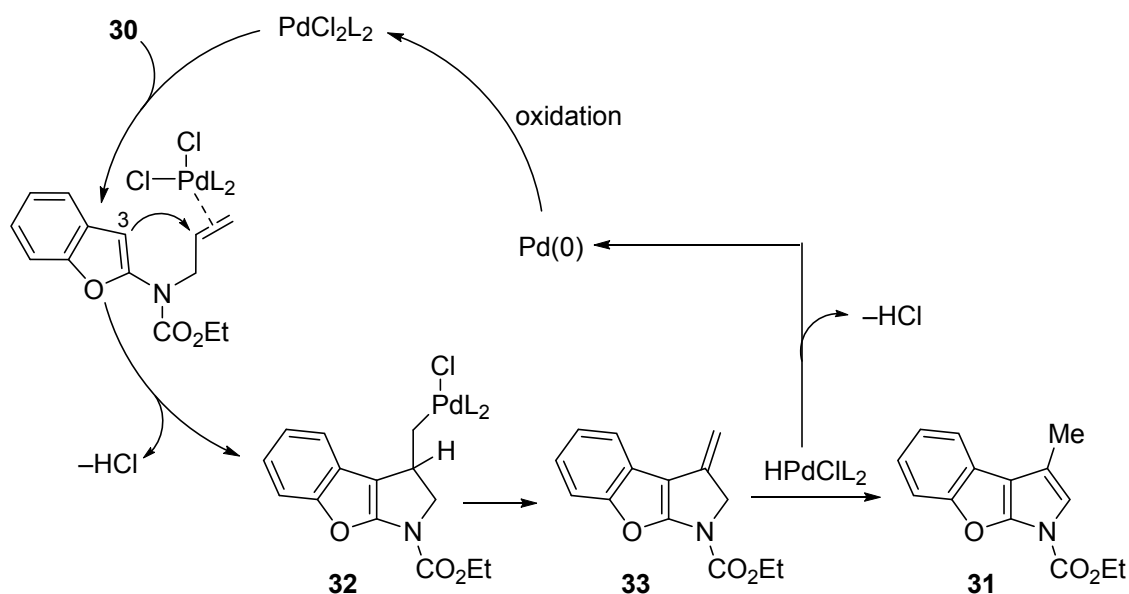
[3,3]-sigmatropic rearrangement to form the Pummerer cation **27**, which was trapped by the intramolecular attack of the amido anion to give benzofuro[2,3-*b*]pyrrole **28**.

Broggini and co-workers¹³ reported the intramolecular Pd(II)-catalyzed cyclization of 2-(*N*-allyl-*N*-carbethoxyamino)benzofuran as a method for the construction of benzofuro[2,3-*b*]pyrrole **31**. 2-(*N*-allyl-*N*-carbethoxyamino)benzofuran (**30**) was prepared in four steps from benzofuran-2-carboxylic acid (**29**) (Scheme 5). The cyclization of **30** was carried out in the presence of catalytic amount of PdCl₂(MeCN)₂ and CuCl₂ under oxygen atmosphere to give the aromatized benzofuro[2,3-*b*]pyrrole **31** in 23% yield.



Scheme 5

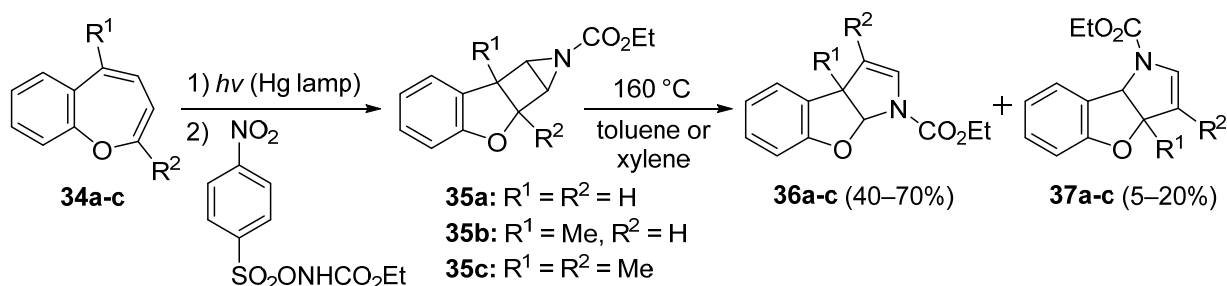
A plausible mechanism for this intramolecular Pd(II)-catalyzed cyclization is shown in Scheme 6. The intramolecular nucleophilic attack of benzofuran (C3) to the palladium(II)-activated olefin would afford the σ -complex **32**, which would undergo β -hydride elimination to give the cyclization product **33**. The exomethylene **33** would then readily isomerize to give the final product **31** together with Pd(II).



Scheme 6

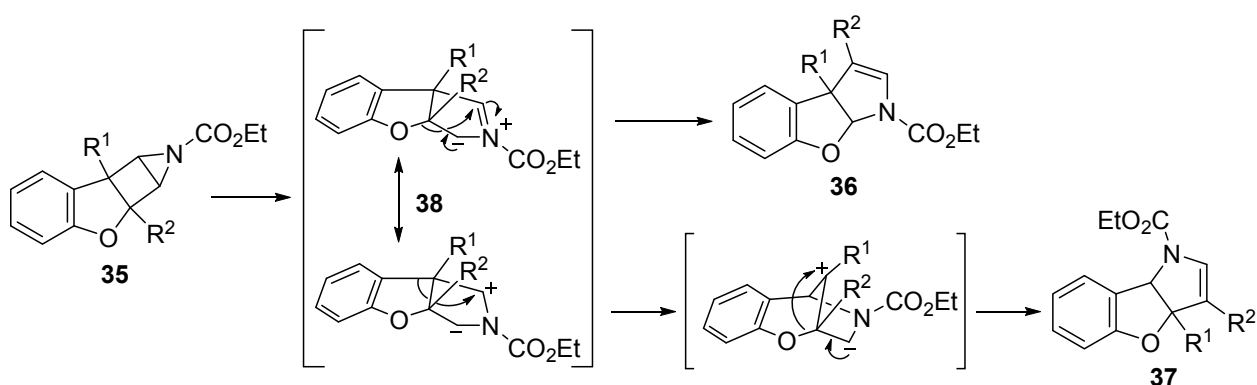
2.2. Synthesis from azirinocyclobutabenzofuran

Benzofuro[2,3-*b*]pyrroles have also been synthesized by the thermal skeletal rearrangement of the azirinocyclobutabenzofurans **35a-c**, which were prepared from the corresponding 1-benzoxepines **34a-c** by photocycloaddition followed by treatment with ethoxycarbonylnitrene generated *in situ* from ethyl nosyloxycarbamate (NsONHCO₂Et; Ns = 4-NO₂C₆H₄SO₂).¹⁴ Azirinocyclobutabenzofurans **35a-c** were then heated in a sealed tube at 160 °C, which resulted in a rearrangement reaction to give the corresponding benzofuro[2,3-*b*]pyrroles **36a-c** (40–70%) together with their [3,2-*b*]isomers **37a-c** (5–20%) (Scheme 7).



Scheme 7

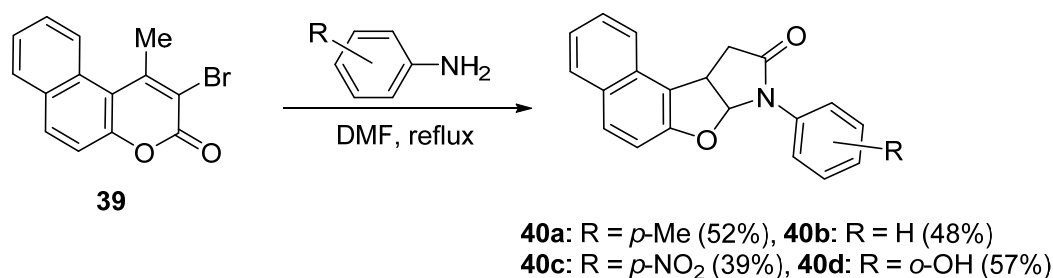
A plausible mechanism for the thermolysis reaction is shown in Scheme 8. The conversion of the ring system in **35** to the regioisomers **36** and **37** most likely proceeds via the cleavage of the C–C bond of the aziridine ring by electrocyclic reaction to afford the azomethine ylide intermediates **38**, which could undergo migration of the phenoxy group to give **36**. The other regioisomer **37** could also be formed from **38** by a Wagner-Meerwein type phenyl group migration followed by a shift of the phenoxy group.



Scheme 8

2.3. Synthesis from benzo[*f*]chromen-3-one

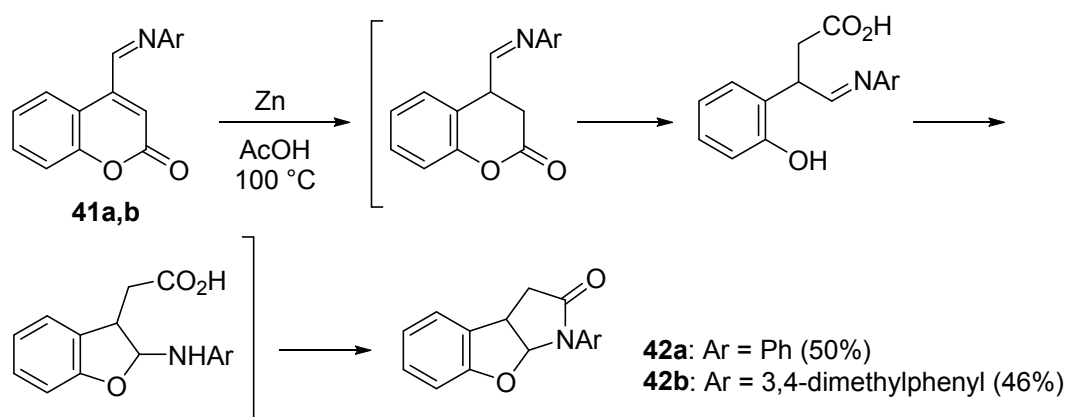
Soman and Thaker¹⁵ reported that the condensation of 2-bromo-1-methyl-3*H*-benzo[*f*]chromen-3-one (**39**) with a series of aromatic primary amines gave the tetracyclic naphthofuro[2,3-*b*]pyrroles **40a-d** (Scheme 9).



Scheme 9

2.4. Synthesis via 4-imino-3-(2-hydroxyphenyl)butanoate intermediate

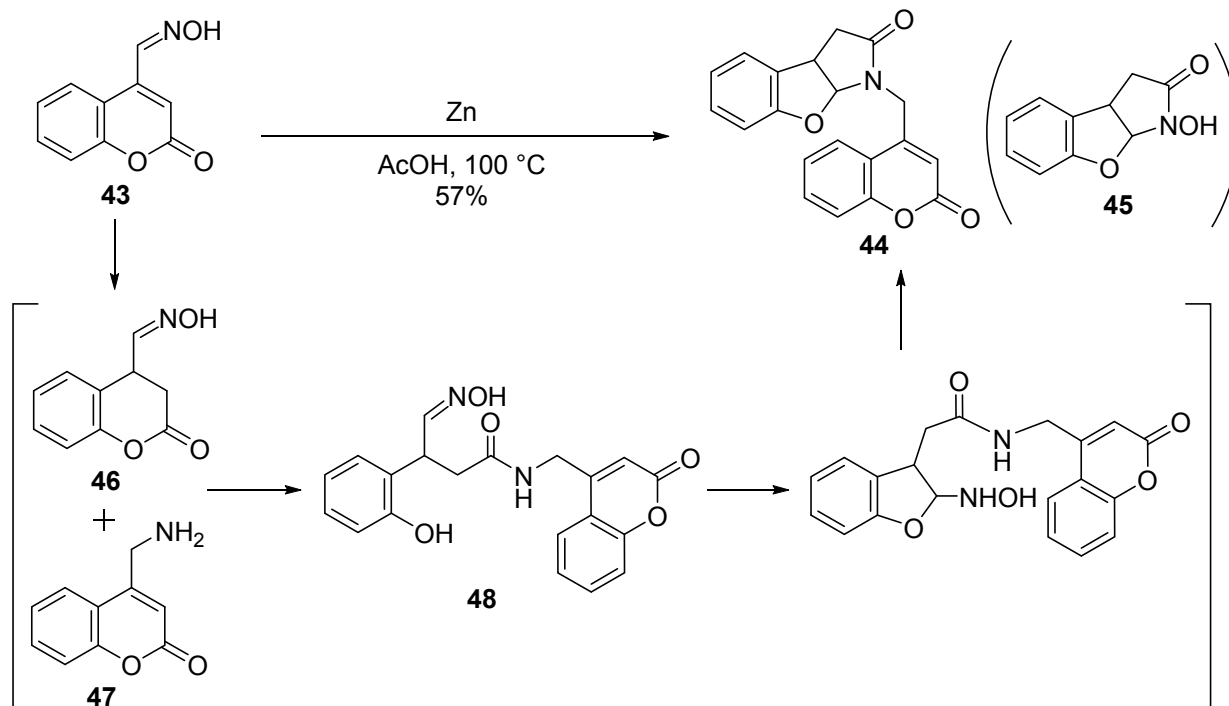
The first documented synthesis of a benzofuro[2,3-*b*]pyrrole was reported by Connor and Strandtmann in 1973.¹⁶ The treatment of imines **41a** and **41b** with zinc in acetic acid gave the benzofuro[2,3-*b*]pyrrol-2-ones **42a** and **42b** via the reduction of the C–C double bond followed by a transannulation reaction (Scheme 10).



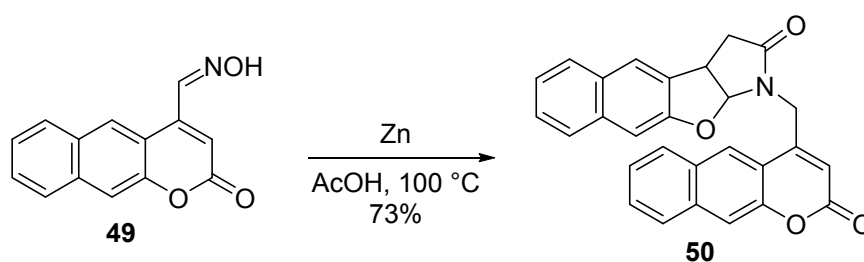
Scheme 10

In contrast, the application of the same conditions to oxime **43** afforded the condensation product **44** instead of the *N*-hydroxybenzofuro[2,3-*b*]pyrrole **45**. The reaction mechanism proposed for this transformation is shown in Scheme 11. There is an equal probability for the reduction of either C–C or C–N double bond resulting in the production of approximately equal amounts of **46** and **47**. These compounds could then condense with each other to give **48**, which would undergo a double cyclization reaction to afford **44**.

The application of these conditions to the oxime derivative **49** also afforded the corresponding naphthofuro[2,3-*b*]pyrrol-2-one **50** in 73% yield (Scheme 12).

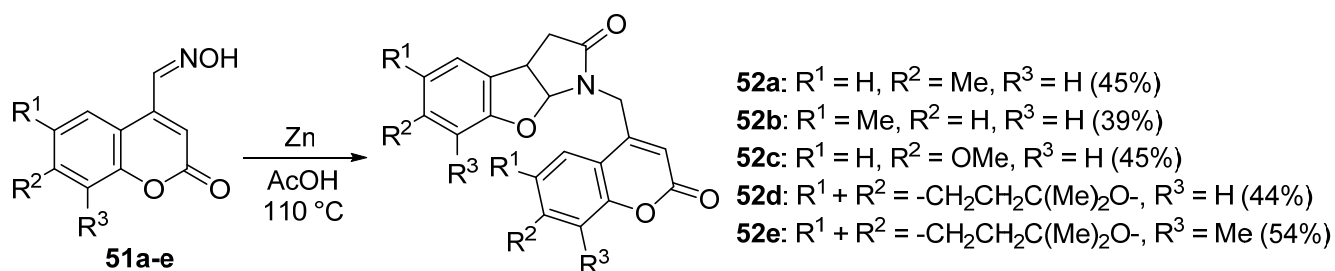


Scheme 11



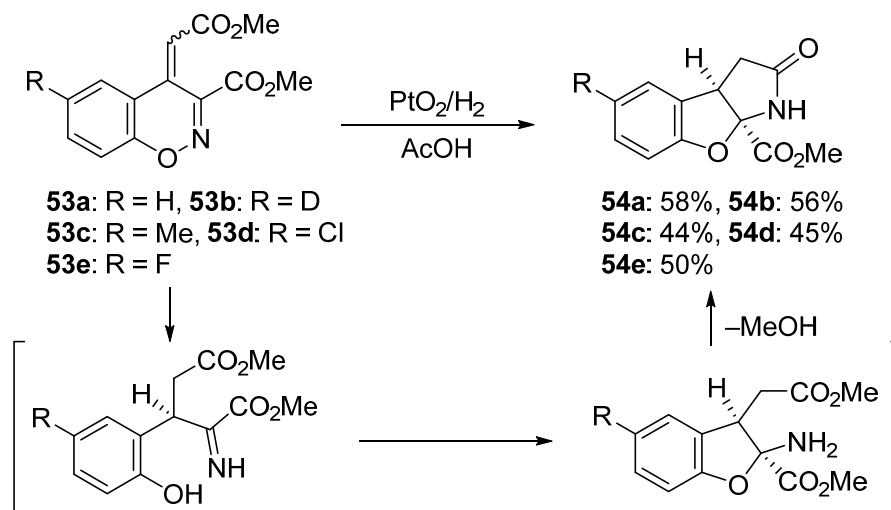
Scheme 12

Usgaonkar's group^{17,18} expanded on this work when they reported that benzofuro[2,3-*b*]pyrroles bearing a variety of different substituents could be synthesized by the reductive transannulation of oximes **51a–e** (Scheme 13).



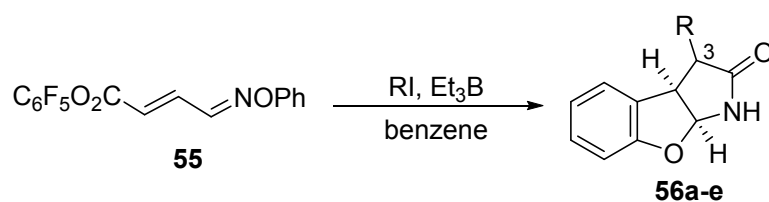
Scheme 13

Harada et al.¹⁹ reported that the hydrogenation of the 4-methoxycarbonylmethylidene-1,2-benzoxazines **53a–e** with PtO₂ in acetic acid produced the benzofuro[2,3-*b*]pyrrol-2-ones **54a–e** in moderate yields (Scheme 14). This transformation was presumably initiated by the reductive cleavage of the 1,2-oxazine ring followed by a double cyclization sequence to give **54**.



Scheme 14

Our research group²⁰ recently reported the development of a facile method for the construction of benzofuro[2,3-*b*]pyrroles using a novel domino reaction. Treatment of the *O*-phenyl conjugated oxime ether **55** with triethylborane as an ethyl radical source afforded the desired 3-ethylbenzofuro[2,3-*b*]pyrrol-2-one **56a** in 95% yield as a 1:1 mixture of diastereomers at the C3 position (Table 1, entry 1).

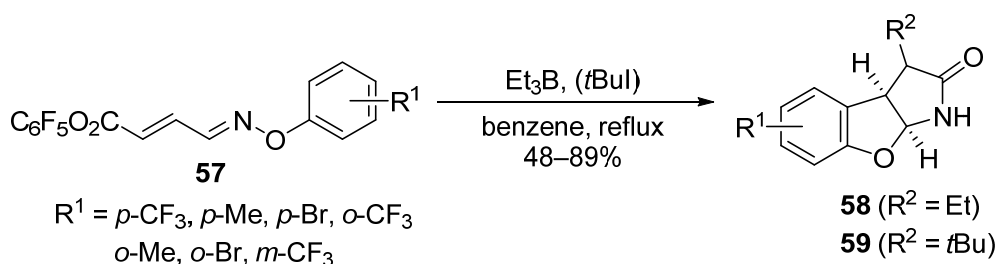
Table 1. Et₃B-mediated domino reaction of *O*-phenyl conjugated oxime ether **55**

entry	RI	temp.	product	yield (%)	selectivity (<i>exo:endo</i>)
1	none	rt	56a (R = Et)	95	1:1
2	EtO ₂ CCH ₂ I	reflux	56b	67	1:1
3	<i>i</i> PrI	reflux	56c	81	2:1
4	<i>c</i> -C ₅ H ₉ I	reflux	56d	62	2:1
5	<i>t</i> Bul	reflux	56e	66	>10:1
6 ^[a]	<i>t</i> Bul	reflux	56e	98	>10:1

[a] In the presence of Na₂S₂O₃.

Pleasingly, the use of secondary alkyl radicals in this reaction led to a significant improvement in the stereoselectivity (Table 1, entries 3 and 4). Interestingly, the use of a *tert*-butyl iodide led to the formation of the corresponding *exo*-product **56e** as a single stereoisomer (Table 1, entries 5 and 6).

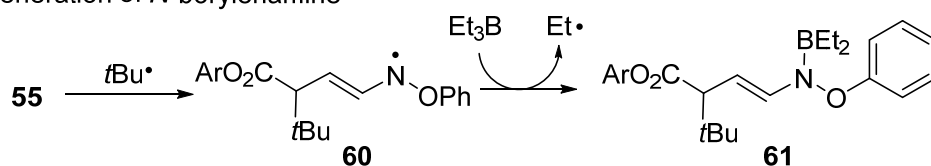
We then proceeded to investigate the impact of different substituents on the phenyl group, with respect to the domino reaction initiated by the addition of the ethyl and *tert*-butyl radicals (Scheme 15). The results of this investigation revealed that trifluoromethyl, methyl and bromo substituents were well tolerated under these reaction conditions. Particularly, domino reactions conducted with the *tert*-butyl radical gave the corresponding *exo*-3-*tert*-butylbenzofuro[2,3-*b*]pyrroles **59** in good yields with excellent stereoselectivities.



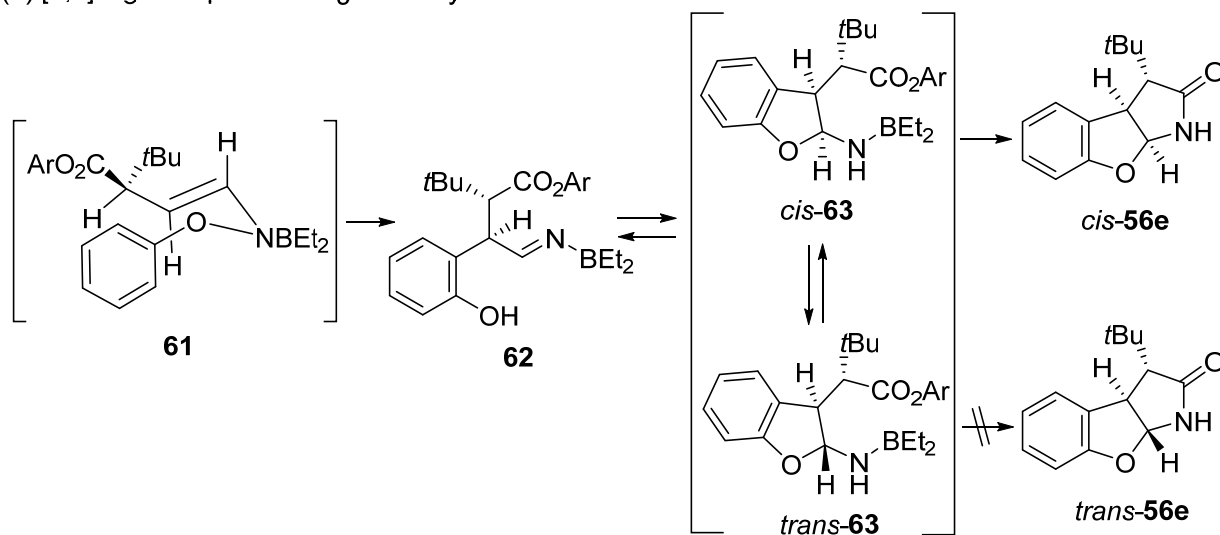
Scheme 15

A possible reaction pathway for this transformation that accounts for the formation of **56e** is shown in Scheme 16. This mechanism involves the regioselective addition of a *tert*-butyl radical to the C–C double bond of **55** to afford the aminyl radical **60**, which is then trapped by Et_3B to form the *N*-borylenamine **61** (Scheme 16-(a)). The *N*-boryl-*N*-phenoxyenamine **61** then undergoes a [3,3]-sigmatropic rearrangement via a six-membered transition state, which minimizes the steric repulsion between the *tert*-butyl and phenyl groups, to allow for the stereoselective formation of the *syn*- α -arylimine **62** (Scheme 16-(b)). Given that the subsequent cyclization of **62** would be reversible, an equilibrium would exist between the *cis*- and *trans*-isomers of **63**. The irreversible lactamization would then push the equilibrium towards the formation of the sterically favored *cis*-fused tricycle **56e**.

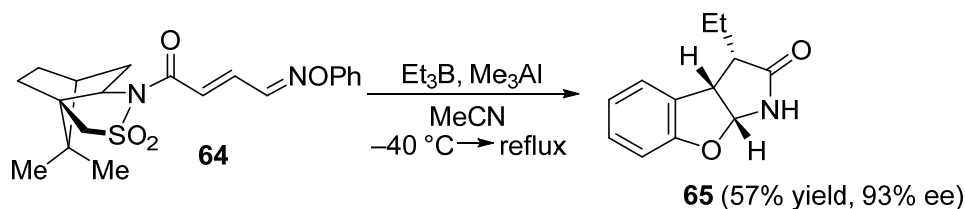
Furthermore, we demonstrated the asymmetric synthesis of benzofuro[2,3-*b*]pyrroles via the traceless cleavage of a chiral auxiliary (Scheme 17). Triethylborane was added to a solution of the chiral conjugated oxime ether **64** and trimethylaluminum in acetonitrile at -40°C , and the resulting mixture was heated at reflux. In contrast to the reaction involving the oxime ether **55** bearing a pentafluorophenyl ester, this reaction afforded the *endo*-isomer **65** as the major product in 57% yield with 93% ee. This result therefore confirmed that the [3,3]-sigmatropic rearrangement had proceeded in such a way as to avoid the occurrence of a steric interaction of the camphorsultam moiety with the phenyl group in the six-membered transition state.

(a) generation of *N*-borylenamine

(b) [3,3]-sigmatropic rearrangement/cyclization/lactamization



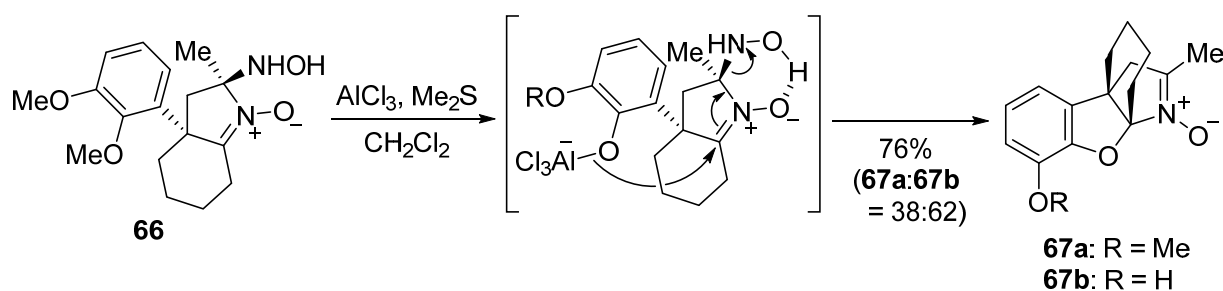
Scheme 16



Scheme 17

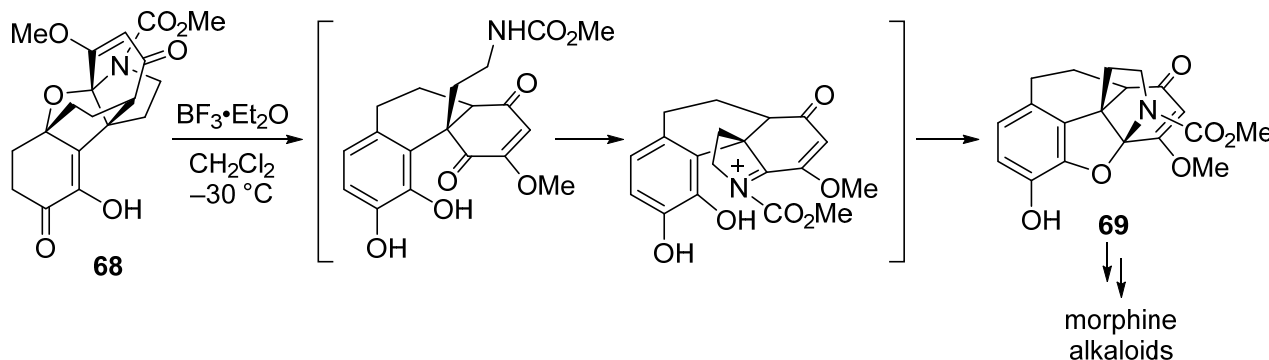
2.4. Synthesis via 2-(3,4-dihydro-2*H*-pyrrol-4-yl)phenol intermediate

Benzofuro[2,3-*b*]pyrrole-1-oxides were synthesized to explore the reactivity and utility of the nitrene **66**.²¹ The treatment of nitrene **66** with AlCl_3 and Me_2S led to the formation of the benzofuro[2,3-*b*]pyrrole-1-oxides **67a** and **67b** in a combined yield of 76% (Scheme 18).



Scheme 18

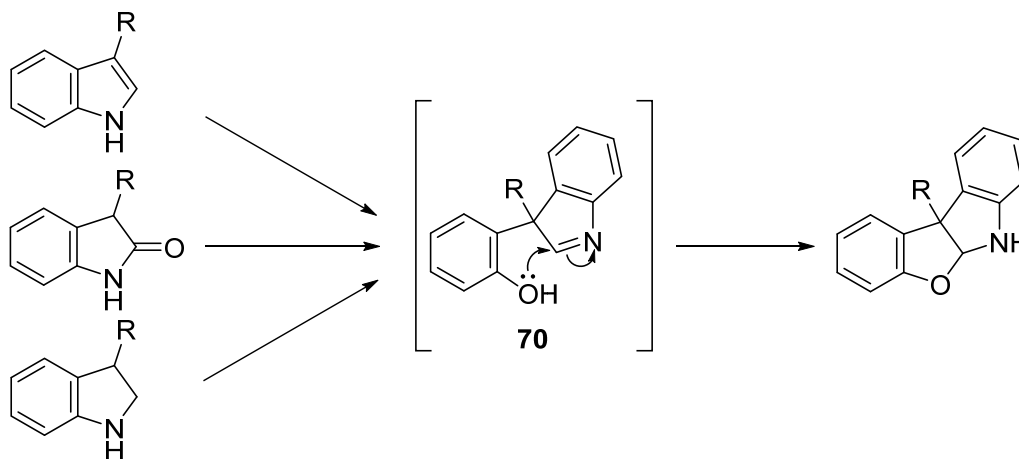
Tius and Kerr²² reported the preparation of benzofuro[2,3-*b*]pyrrole as an intermediate in the synthesis of a series of morphine alkaloids. Exposure of **68** to boron trifluoride etherate at $-30\text{ }^{\circ}\text{C}$ led to the formation of **69** via sequential aromatization and hemiaminalization reactions (Scheme 19). This method has also been used for the synthesis of dihydrobenzofuro[2,3-*b*]indoles, and this work will be discussed in the following chapter.



Scheme 19

3. SYNTHESIS OF DIHYDROBENZOFURO[2,3-*b*]INDOLE

One of the most commonly used strategies for the synthesis of dihydrobenzofuro[2,3-*b*]indoles involves the cyclization of 3-(2-hydroxyphenyl)indolenine **70** or indolenium, which can be prepared from the corresponding indoles, oxindoles and indolines (Scheme 20).

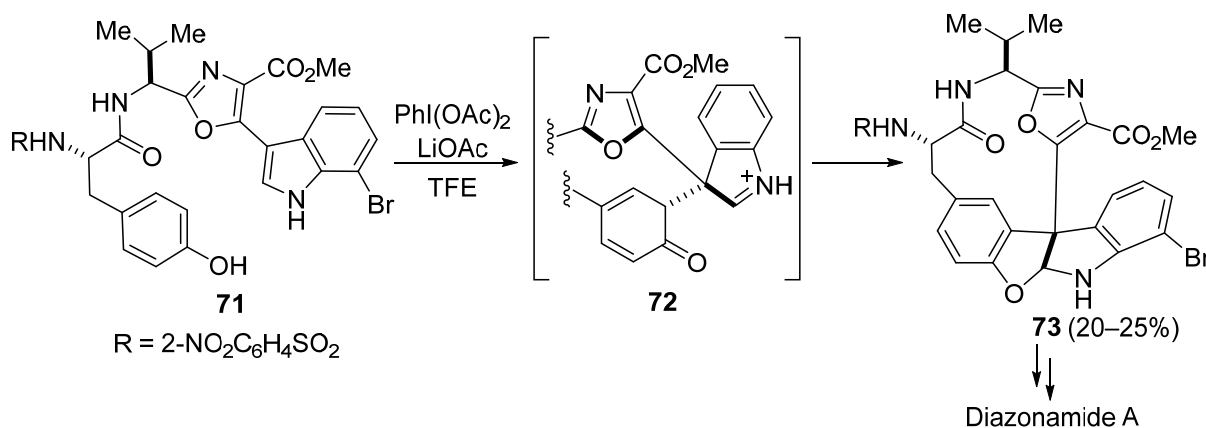


Scheme 20

3.1. Synthesis from indole

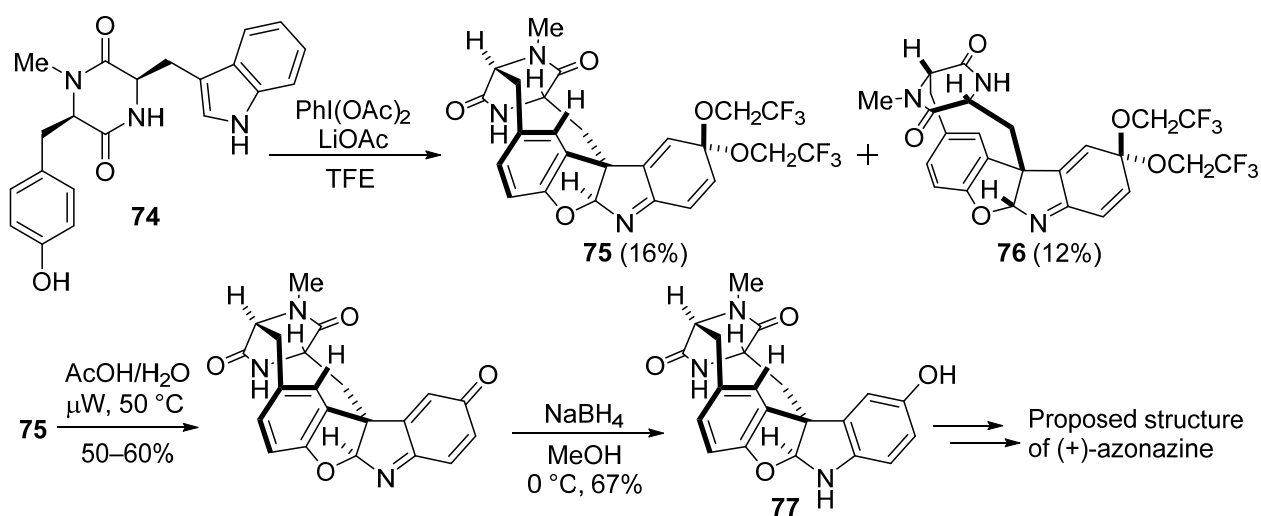
As part of synthetic studies towards the total synthesis of diazonamide A, Harran's group²³ reported the intramolecular oxidative cycloaddition of a hydroxyphenyl group with an indole. In this case, **71** reacted with $\text{PhI}(\text{OAc})_2$ and LiOAc to give the benzofuro[2,3-*b*]indoles **73** in 20–25% yield (Scheme 21). Mechanistically, oxidation of the phenol would initiate an annulation reaction between the phenoxenium

ion and the tethered indole to give the cyclohexadienone-linked indolenium species **72**, which would undergo a ring closing reaction to give **73**. The possibility that the reaction was initiated by the single electron oxidation of the indole subunit, however, cannot be excluded.



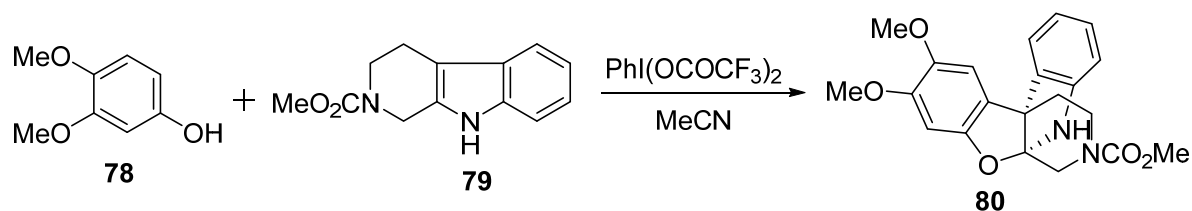
Scheme 21

Yao and co-workers²⁴ have successfully accomplished the first total synthesis of (–)-azonazine using a biomimetic oxidative cyclization as a key step for the construction of the benzofuro[2,3-*b*]indole core. Treatment of the diketopiperazine **74** with PhI(OAc)₂ led to the formation of two diastereomeric products **75** and **76** bearing the hexacyclic core structure of azonazine in 16 and 12% yields, respectively (Scheme 22). The poor yields of the cyclized products suggested that there was severe ring strain in the congested hexacyclic core, and that this strain was making it particularly difficult for cyclization to take place in a rapid and efficient manner. Subsequent hydrolysis of ketal **75** followed by reduction with NaBH₄ afforded the benzofuro[2,3-*b*]indole **77**, which was then converted to originally proposed structure of (+)-azonazine. This structure, however, was later revealed to be a diastereomer of natural (+)-azonazine. The total synthesis of (–)-azonazine was also accomplished in the same way using **76**.



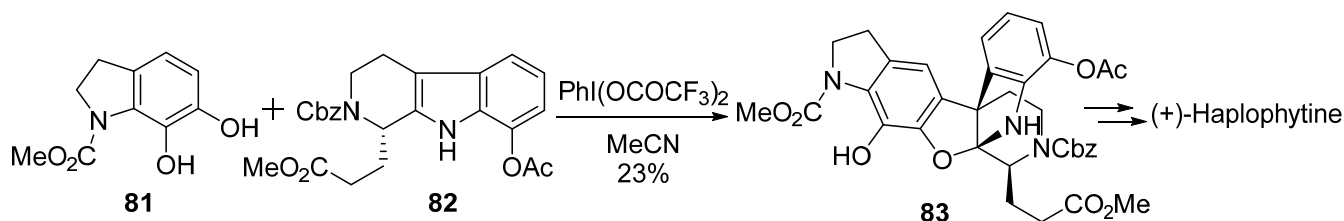
Scheme 22

In studies toward the total synthesis of phalarine using biomimetic coupling strategies, Danishefsky et al.²⁵ reported the intermolecular oxidative cycloaddition of the tetrahydro- β -carboline with phenol. Phenol **78** was treated with $\text{PhI}(\text{OCOCF}_3)_2$ followed by addition of tetrahydro- β -carboline **79** to give the benzofuro[2,3-*b*]indole **80** (Scheme 23).



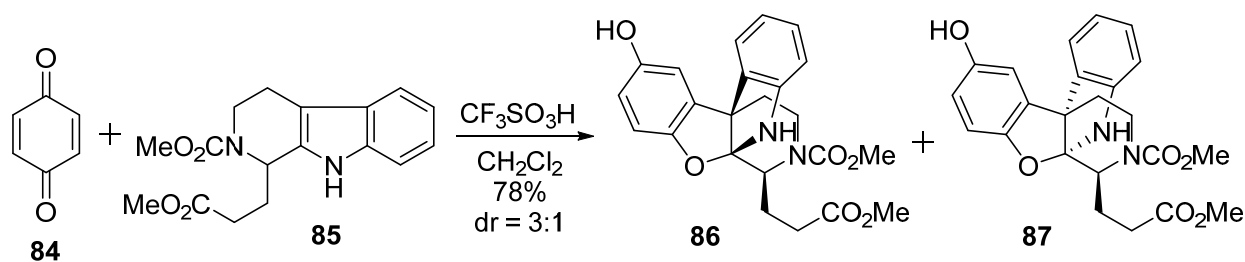
Scheme 23

Nicolaou and Chen^{26,27} achieved the total synthesis of (+)-haplophytine via an intermolecular oxidative cycloaddition reaction. Treatment of a mixture of dihydroxyindoline **81** and tetrahydro- β -carboline **82** with $\text{PhI}(\text{OCOCF}_3)_2$ provided the benzofuro[2,3-*b*]indole **83** in 23% yield (Scheme 24).



Scheme 24

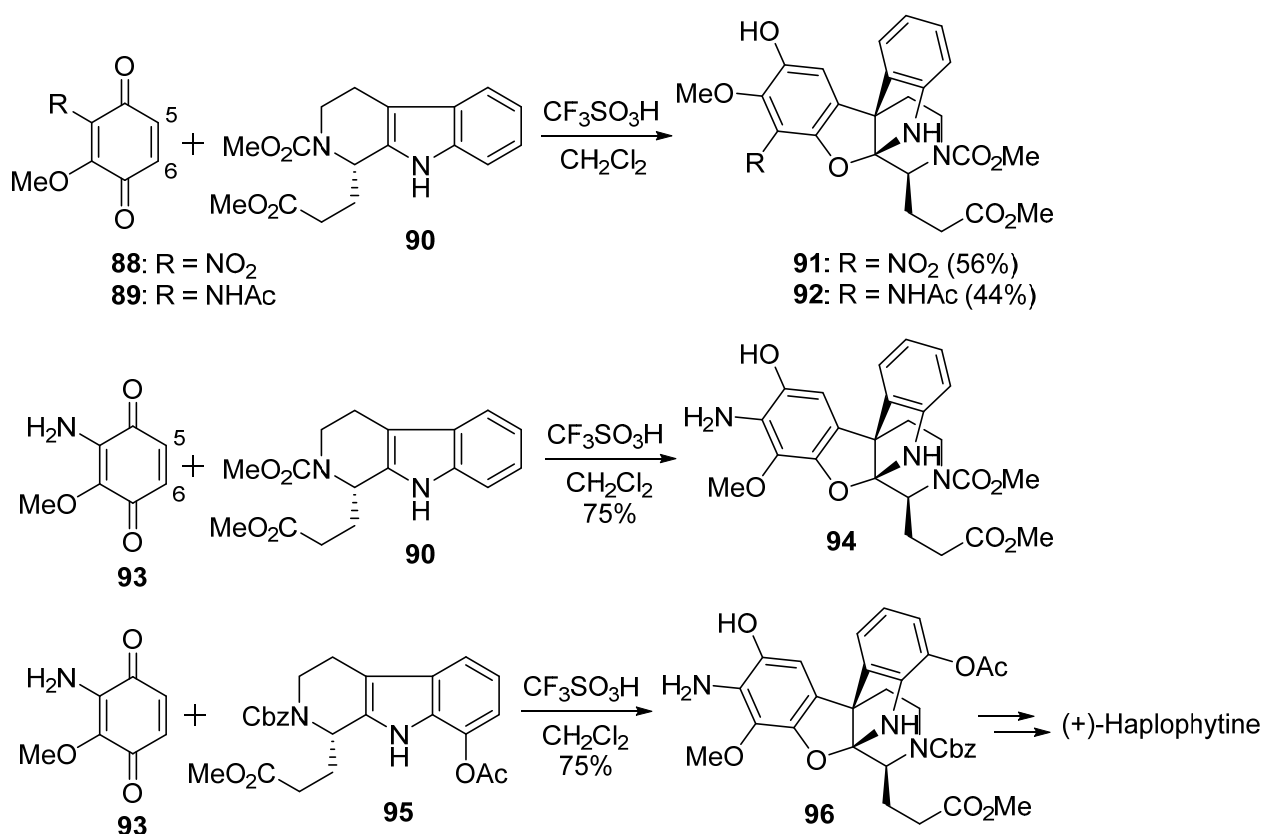
Although the hypervalent iodine-mediated oxidative cycloaddition reaction provides rapid and efficient access to benzofuro[2,3-*b*]indoles from phenols and indoles, the overall utility of this method has been limited by low yields. Based on these limitations, Chen's group²⁸ reported the development of an improved strategy for the synthesis of benzofuro[2,3-*b*]indoles via a 1,4-addition/cyclization reaction in their second-generation formal synthesis of (+)-haplophytine. In this study, the authors began by conducting a model study involving the reaction of *p*-quinone **84** with β -carboline **85** in the presence of $\text{CF}_3\text{SO}_3\text{H}$, which gave the benzofuro[2,3-*b*]indoles **86** and **87** as a 3:1 mixture of diastereomers (Scheme 25).



Scheme 25

The preferential formation of **86** was attributed to a transition state where the steric interaction between **84** and the methyl propanoate side chain of **85** was minimized.

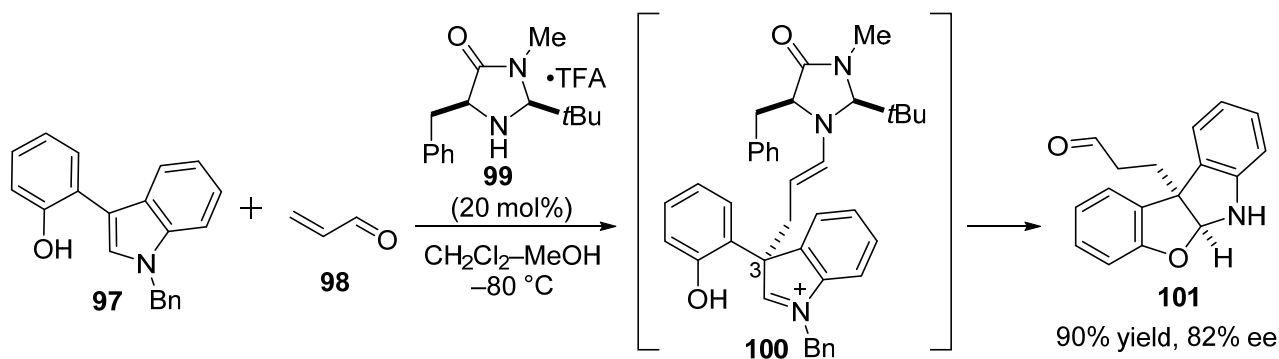
The 1,4-addition/cyclization reactions of several other functionalized *p*-quinone were also investigated in terms of their application to the synthesis of haplophytine (Scheme 26). When the *p*-quinones **88** and **89** were reacted with β -carboline **90**, the 1,4-addition proceeded at the 5-position of the quinone ring to afford the benzofuro[2,3-*b*]indoles **91** and **92** in 56 and 44% yields, respectively. In contrast, when *p*-quinone **93** was used as the substrate, the addition reaction proceeded at the 6-position of the quinone ring to give benzofuro[2,3-*b*]indole **94** in 75% yield. Furthermore, the reaction of 3-amino-2-methoxy-*p*-quinone **93** with β -carboline **95** furnished benzofuro[2,3-*b*]indole **96** in 75% yield as a single stereoisomer, which proved to be an enabling intermediate in the formal synthesis of (+)-haplophytine.



Scheme 26

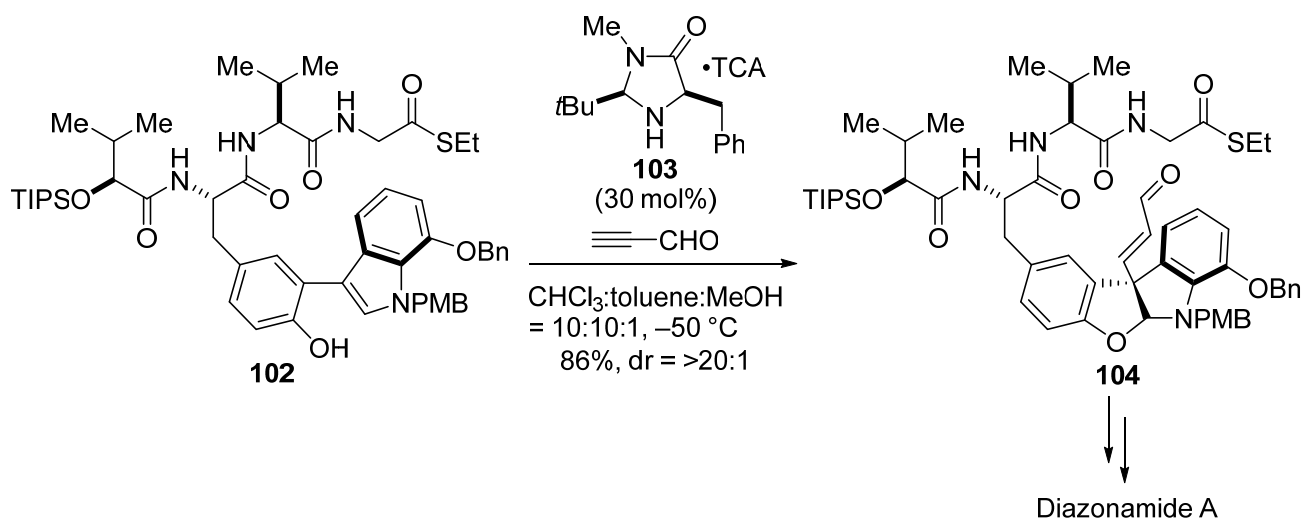
MacMillan et al.²⁹ developed a chiral imidazolidinone-catalyzed enantioselective alkylation-cyclization cascade reaction for the asymmetric synthesis of a benzofuro[2,3-*b*]indoles. The reaction of 3-(2-hydroxyphenyl)indole **97** with acrolein **98** in the presence of the imidazolidinone catalyst **99**•TFA (20 mol%) gave the benzofuro[2,3-*b*]indole **101** in 90% yield with 82% ee (Scheme 27). The authors suggested that the addition of indole **97** to the activated iminium ion resulting from the reaction of

catalyst **99** with acrolein **98** would lead to the formation of the C(3)-quaternary carbon-substituted indolenium ion **100**, which would be trapped through an intramolecular reaction with the phenol moiety to afford the benzofuro[2,3-*b*]indole **101**.



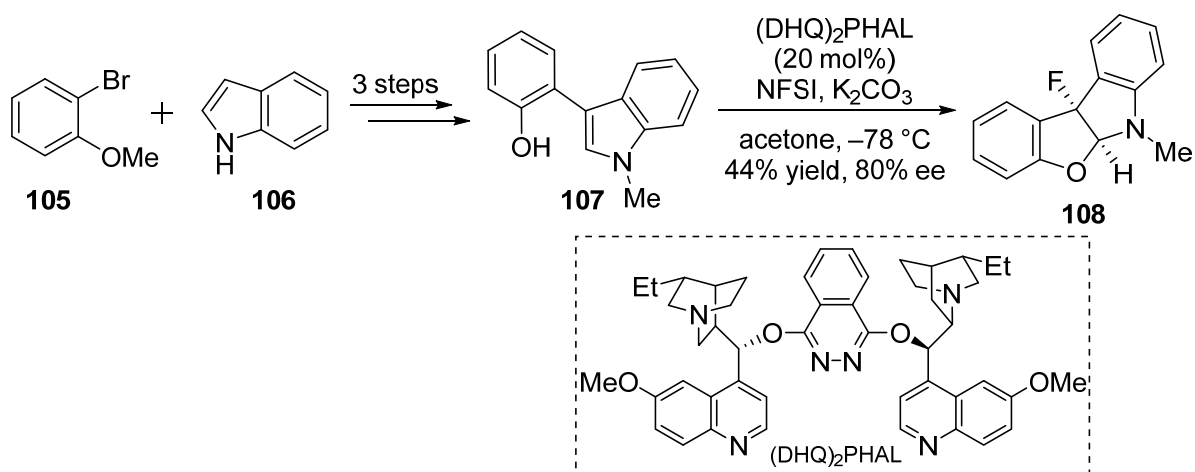
Scheme 27

This cascade reaction was subsequently applied as one of the key transformations in the total synthesis of diazonamide A.³⁰ Indole **102** was reacted with an excess of propynal in the presence of the imidazolidinone catalyst **103**·TCA (30 mol%) in a ternary solvent mixture consisting of toluene, chloroform and methanol to give the benzofuro[2,3-*b*]indole core **104** of diazonamide A (Scheme 28).



Scheme 28

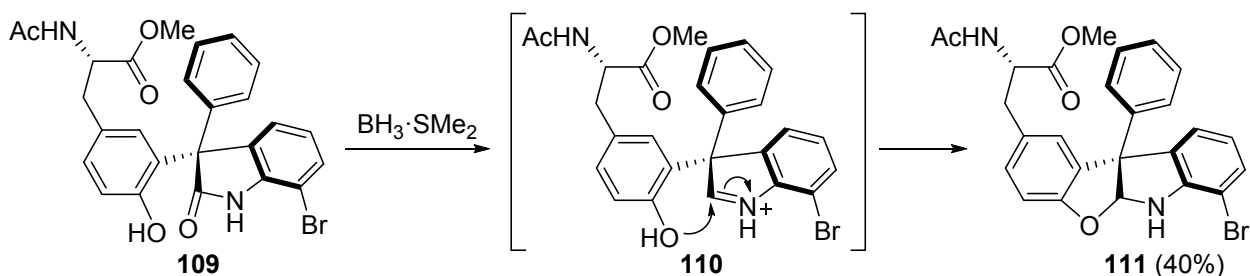
Gouverneur and co-workers³¹ have developed a synthetic method for the construction of the fluorinated benzofuro[2,3-*b*]indole **108** using a catalytic asymmetric fluorocyclization reaction. The 3-(2-hydroxyphenyl)indole **107** was prepared in three-steps from 2-bromoanisole (**105**) and indole (**106**) (Scheme 29). The treatment of **107** with *N*-fluorobenzenesulfonimide and K₂CO₃ in the presence of a catalytic amount of (DHQ)₂PHAL afforded **108** in 44% yield and 80% ee.



Scheme 29

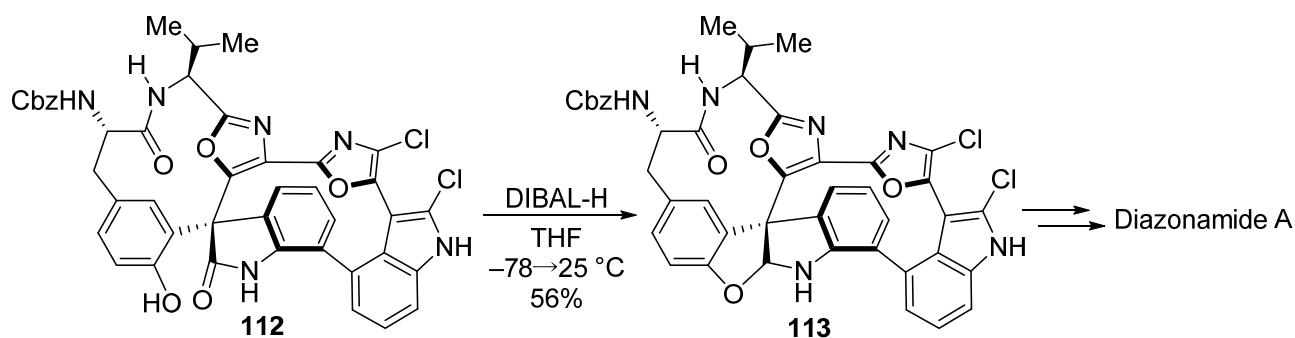
3.2. Synthesis from oxindole

In studies towards the first and second total syntheses of diazonamide A, Nicolaou's group³²⁻³⁵ developed a synthetic approach to the benzofuro[2,3-*b*]indole structure of this natural product via the reductive cyclization of an oxindole. Oxindole **109** was selected as a model substrate for this reaction and treated with borane dimethyl sulfide to give the desired benzofuro[2,3-*b*]indole **111** via the formation of the indolenium intermediate **110** (Scheme 30).



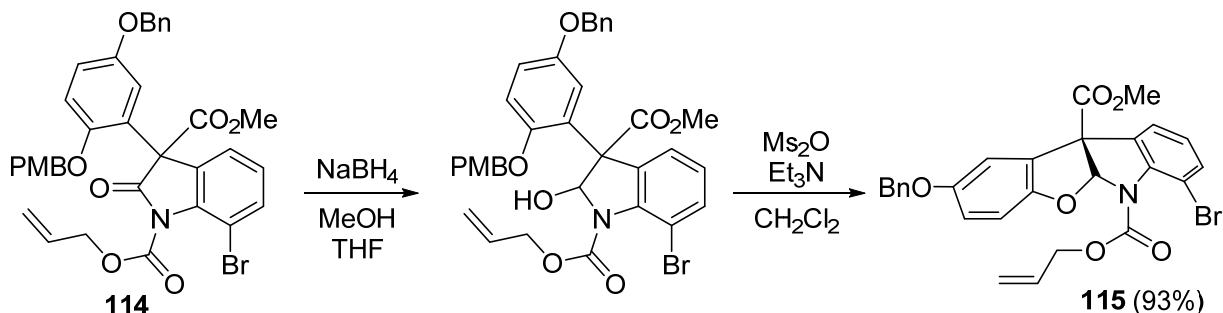
Scheme 30

The authors went on to apply this method to the total synthesis of diazonamide A. Thus, the treatment of **112** with DIBAL-H afforded benzofuro[2,3-*b*]indole **113** in 56% yield (Scheme 31).



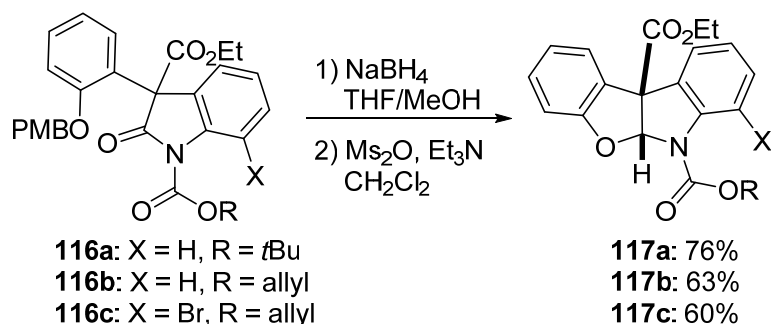
Scheme 31

Vedejs and Zajac³⁶ reported the stepwise construction of benzofuro[2,3-*b*]indole **115** in excellent yield by the reduction of the *N*-alloc activated oxindole **114** with NaBH₄ followed by the dehydration of the resulting hemiaminal with Ms₂O and Et₃N (Scheme 32).



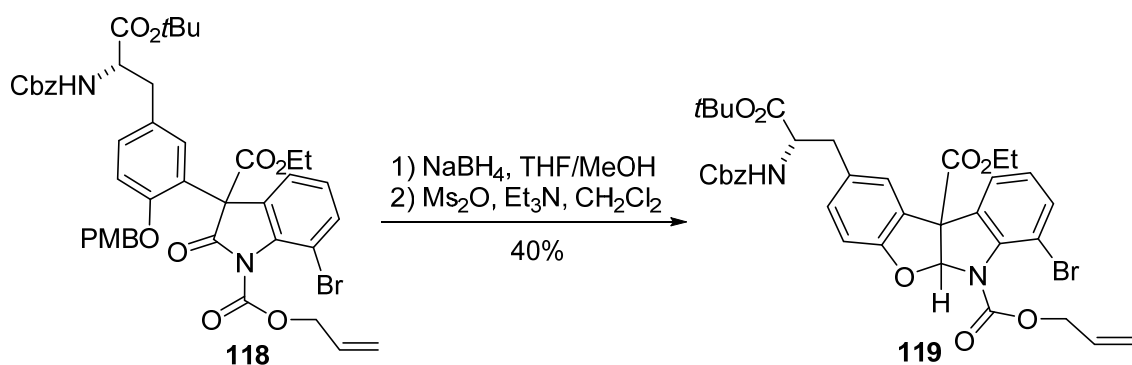
Scheme 32

Using similar conditions, Moody and co-workers³⁷ reported the synthesis of the benzofuro[2,3-*b*]indoles **117a–c** from the *N*-Boc or Alloc protected oxindoles **116a–c** (Scheme 33).



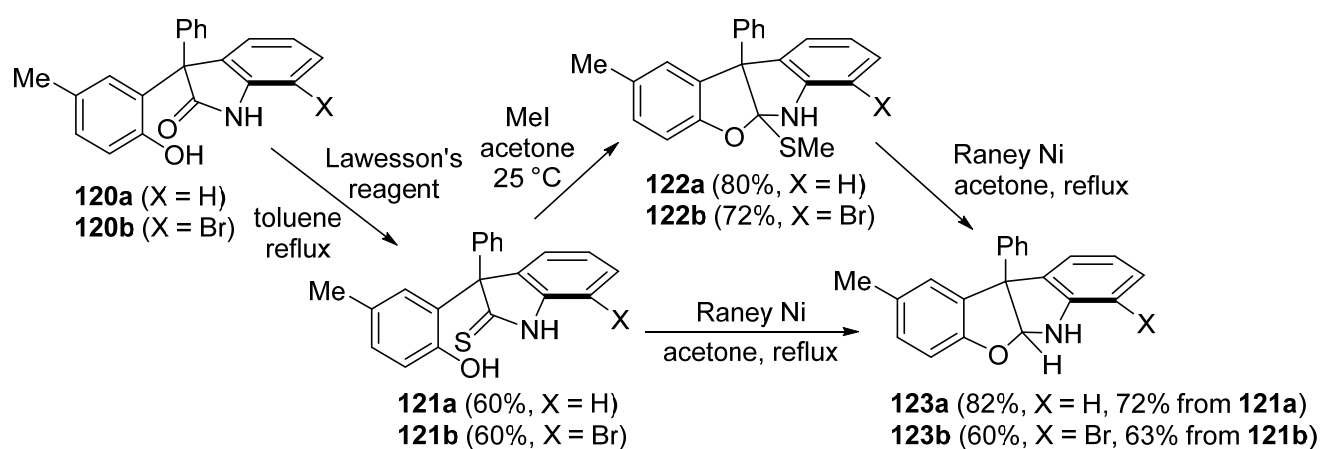
Scheme 33

This methodology was successfully applied to the synthesis of the benzofuro[2,3-*b*]indole core **119** of diazonamide A (Scheme 34).



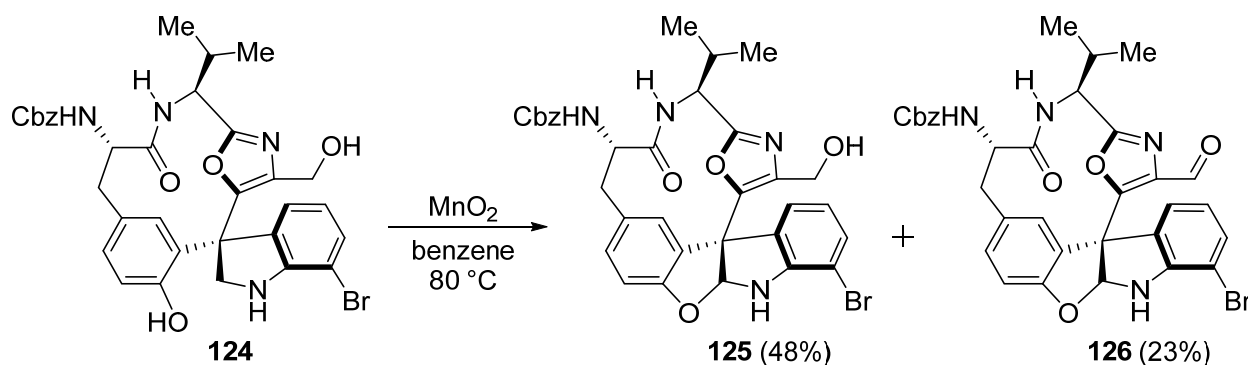
Scheme 34

Magnus and Turnbull³⁸ attempted to apply this methodology to the reductive cyclization of oxindole **120**, but their reactions proved to be unsuccessful because of over reduction to the indoline rather than the benzofuro[2,3-*b*]indole. In light of this failure, the authors went on to develop a mild and selective procedure from indoline-2-thione **121** prepared by thionation with Lawesson's reagent. The indoline-2-thione **121a** was treated with iodomethane to give **122a** in 80% yield. Subsequent exposure of **122a** to Raney nickel resulted in a clean desulfurization reaction to provide **123a** in 82% yield (Scheme 35). The indoline-2-thione **121b** was converted to **122b** in a similar manner and then desulfurized to give **123b** in 60% yield. The indoline-2-thiones **121a** and **121b** were also treated directly with Raney nickel to afford **123a** and **123b** in 72 and 63% yields, respectively.

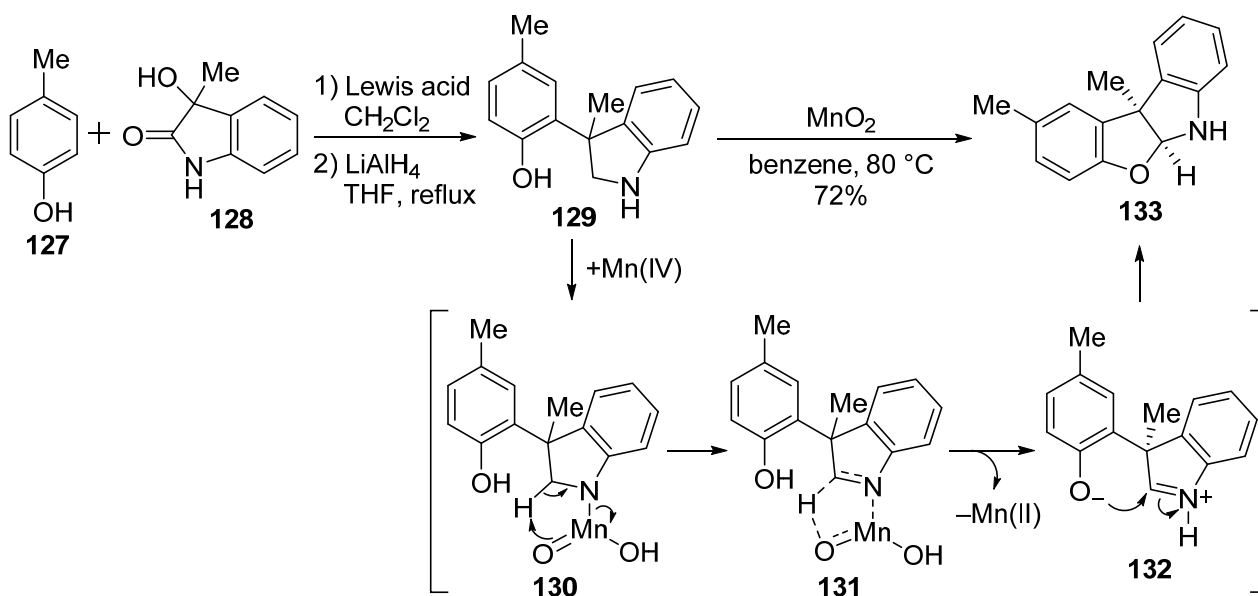


3.3. Synthesis from indoline

Benzofuro[2,3-*b*]indoles can also be prepared by the oxidative cyclization of 3-(2-hydroxyphenyl)indolines. Nicolaou's group³⁵ reported that the oxidation of 3-(2-hydroxyphenyl)indoline **124** with MnO_2 led to the formation of the benzofuro[2,3-*b*]indoles **125** and **126** for the synthesis of diazonamide A analogues (Scheme 36).



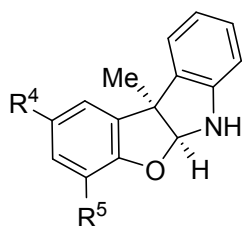
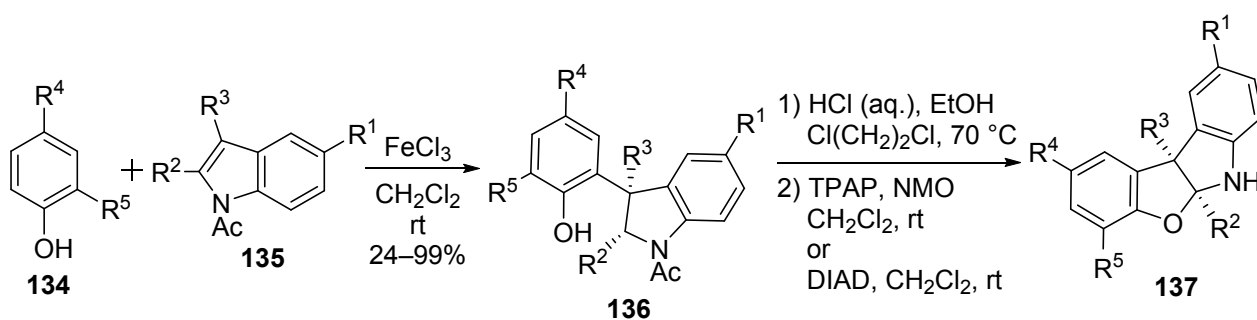
Bisai et al.³⁹ reported the development of a similar process for the oxidative cyclization of 3-(2-hydroxyphenyl)indolines. Indoline **129** was prepared by the Lewis acid-catalyzed Friedel-Crafts alkylation of *p*-cresol (**127**) with 3-hydroxy-3-methyl-2-oxindole (**128**) followed by a reduction step. The subsequent treatment of indoline **129** with MnO₂ afforded benzofuro[2,3-*b*]indole **133** in 72% yield. The authors proposed a mechanism for this transformation, which is shown in Scheme 37. α -Elimination reaction of the intermediate Mn(IV)-complex **130** under an oxidative environment would lead to the formation of indolenium intermediate **132** via the intermediacy of **131**. The phenoxide **132** would then undergo an intramolecular reaction to afford the benzofuro[2,3-*b*]indole **133**.



Scheme 37

Vincent and co-workers⁴⁰ reported that the regioselective C3-hydroarylation of a 3-substituted *N*-acetylindoles with phenols led to the formation of 3,3-disubstituted indolines, which could be oxidized to the corresponding benzofuro[2,3-*b*]indoles. The treatment of *N*-acetylindole **135** with *para*-substituted phenol **134** in the presence of iron(III) chloride afforded the indolines **136** in 24–99% yield (Scheme 38). Subsequent removal of the *N*-acetyl substituent of **136** under acidic conditions followed by oxidation of the resulting indoline using either tetrapropylammonium perruthenate (TPAP) or diisopropyl azodicarboxylate (DIAD) gave the benzofuro[2,3-*b*]indoles **137a–q** in 50–86% yields.

To access enantioenriched benzofuro[2,3-*b*]indoles, *N*-mesyl-protected proline was employed as a chiral auxiliary and attached to the nitrogen atom of skatole (Scheme 39). The hydroarylation of **138** with *p*-cresol (**127**) afforded indolines **139a** and **139b** as a 2.8:1 mixture of C3-epimers. Hydrolysis of **139a** followed by DIAD oxidation allowed for the isolation of (–)-**137a** in 94% ee.



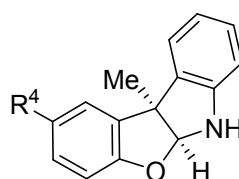
137a: R⁴ = Me, R⁵ = H (56%, TPAP; 63%, DIAD)

137b: R⁴ = *n*Pr, R⁵ = H (65%, TPAP)

137c: R⁴ = *i*Pr, R⁵ = H (72%, TPAP)

137d: R⁴ = Bn, R⁵ = H (85%, DIAD)

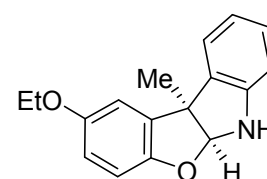
137e: R⁴ = Me, R⁵ = Me (61%, TPAP)



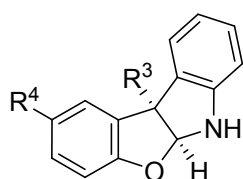
137f: R⁴ = F (79%, DIAD)

137g: R⁴ = Cl (65%, TPAP)

137h: R⁴ = Br (81%, DIAD)



137i: (82%, DIAD)

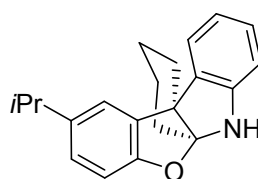


137j: R³ = *n*Bu, R⁴ = Me (50%, TPAP)

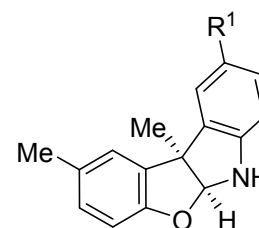
137k: R³ = *n*Bu, R⁴ = *i*Pr (50%, TPAP)

137l: R³ = Bn, R⁴ = Me (68%, DIAD)

137m: R³ = Ph, R⁴ = Me (53%, DIAD)



137n: (62%, DIAD)

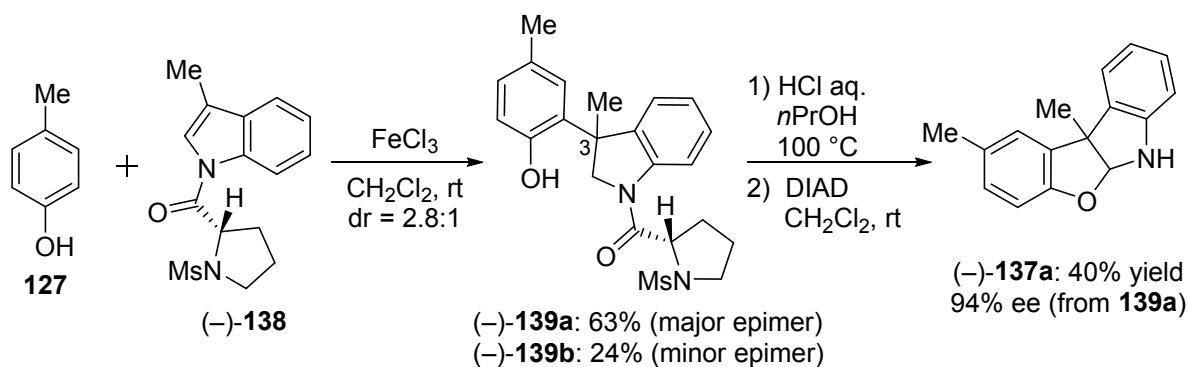


137o: R¹ = Br (86%, DIAD)

137p: R¹ = CO₂Et (66%, DIAD)

137q: R¹ = OMe (70%, DIAD)

Scheme 38



Scheme 39

4. CONCLUSION

We have described a variety of synthetic methods for the construction of benzofuro[2,3-*b*]pyrroles and benzofuro[2,3-*b*]indoles. Although effective synthetic approaches have been reported for the preparation of benzofuro[2,3-*b*]indoles, reports pertaining to the facile and efficient synthesis of benzofuro[2,3-*b*]pyrroles are relatively scarce. To study on the biological activity of benzofuro[2,3-*b*]pyrroles, the development of new methodologies for the construction of benzofuro[2,3-*b*]pyrrole skeleton will be further requested in the future.

ACKNOWLEDGEMENTS

This work was supported by Grants-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology of Japan (MEXT), the MEXT-Supported Program for the Strategic Research Foundation at Private Universities, and Takeda Science Foundation.

REFERENCES

1. (a) P. Ruiz-Sanchis, S. A. Savina, F. Albericio, and M. Álvarez, *Chem. Eur. J.*, 2011, **17**, 1388; (b) M. A. Schmidt and M. Movassaghi, *Synlett*, 2008, 313; (c) D. Crich and A. Banerjee, *Acc. Chem. Res.*, 2007, **40**, 151.
2. J. Liu, T. Ng, Z. Rui, O. Ad, and W. Zhang, *Angew. Chem. Int. Ed.*, 2014, **53**, 136.
3. A. W. Schammel, G. Chiou, and N. K. Garg, *J. Org. Chem.*, 2012, **77**, 725.
4. M. Hayashi, M.-C. Rho, A. Enomoto, A. Fukami, Y.-P. Kim, Y. Kikuchi, T. Sunazuka, T. Hirose, K. Komiyama, and S. Omura, *Proc. Natl. Acad. Sci. U.S.A.*, 2002, **99**, 14728.
5. S. Bräse, A. Encinas, J. Keck, and C. F. Nising, *Chem. Rev.*, 2009, **109**, 3903.
6. (a) N. Lindquist, W. Fenical, G. D. Van Duyne, and J. Clardy, *J. Am. Chem. Soc.*, 1991, **113**, 2303; (b) J. Li, A. W. G. Burgett, L. Esser, C. Amezcua, and P. G. Harran, *Angew. Chem. Int. Ed.*, 2001, **40**, 4770.
7. Q.-X. Wu, M. S. Crews, M. Draskovic, J. Sohn, T. A. Johnson, K. Tenney, F. A. Valeriote, X.-J. Yao, L. F. Bjeldanes, and P. Crews, *Org. Lett.*, 2010, **12**, 4458.
8. Although benzofuro[3,2-*b*]pyrroles and benzofuro[3,2-*b*]indoles are found in natural products and bioactive compounds, we will not discuss in this review. For selected example, see: (a) H. J. Kim, S. H. Cho, and S. Chang, *Org. Lett.*, 2012, **14**, 1424; (b) H. Ding and D. Y.-K. Chen, *Angew. Chem. Int. Ed.*, 2011, **50**, 676; (c) J. D. Trzupsek, D. Lee, B. M. Crowley, V. M. Marathias, and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2010, **132**, 8506; (d) I. Kim, H.-K. Na, K. R. Kim, S. G. Kim, and G. H. Lee, *Synlett*, 2008, 2069.
9. T. Tsuritani, H. Shinokubo, and K. Oshima, *Org. Lett.*, 2001, **3**, 2709.

10. T. Tsuritani, H. Shinokubo, and K. Oshima, *J. Org. Chem.*, 2003, **68**, 3246.
11. Q. Wang, S. Nara, and A. Padwa, *Org. Lett.*, 2005, **7**, 839.
12. A. Padwa, S. Nara, and Q. Wang, *J. Org. Chem.*, 2005, **70**, 8538.
13. E. M. Beccalli, E. Borsini, G. Broggin, M. Rigamonti, and S. Sottocornola, *Synlett*, 2008, 1053.
14. J. Kurita, H. Sakai, S. Yamada, and T. Tsuchiya, *J. Chem. Soc., Chem. Commun.*, 1987, 285.
15. S. S. Soman and T. H. Thaker, *J. Chem. Res.*, 2010, 502.
16. D. T. Connor and M. von Strandtmann, *J. Org. Chem.*, 1973, **38**, 3874.
17. S. D. Joshi and R. N. Usgaonkar, *Indian J. Chem.*, 21B, 1982, 399.
18. P. Waykole and R. N. Usgaonkar, *Indian J. Chem.*, 21B, 1982, 707.
19. K. Harada, E. Kaji, K. Takahashi, and S. Zen, *Chem. Pharm. Bull.*, 1994, **42**, 1562.
20. M. Ueda, Y. Ito, Y. Ichii, M. Kakiuchi, H. Shono, and O. Miyata, *Chem. Eur. J.*, 2014, **20**, 6763.
21. J.-L. Avril, B. Marçot, M. Coquillay, C. De Rango, H. Moskowitz, and J. Mayrargue, *New J. Chem.*, 1999, **23**, 743.
22. M. A. Tius and M. A. Kerr, *J. Am. Chem. Soc.*, 1992, **114**, 5959.
23. A. W. G. Burgett, Q. Li, Q. Wei, and P. G. Harran, *Angew. Chem. Int. Ed.*, 2003, **42**, 4961.
24. J.-C. Zhao, S.-M. Yu, Y. Liu, and Z.-J. Yao, *Org. Lett.*, 2013, **15**, 4300.
25. C. Chan, C. Li, F. Zhang, and S. J. Danishefsky, *Tetrahedron Lett.*, 2006, **47**, 4839.
26. K. C. Nicolaou, S. M. Dalby, S. Li, T. Suzuki, and D. Y.-K. Chen, *Angew. Chem. Int. Ed.*, 2009, **48**, 7616.
27. K. C. Nicolaou, U. Majumder, S. P. Roche, and D. Y.-K. Chen, *Angew. Chem. Int. Ed.*, 2007, **46**, 4715.
28. W. Tian, L. R. Chennamaneni, T. Suzuki, and D. Y.-K. Chen, *Eur. J. Org. Chem.*, 2011, 1027.
29. J. F. Austin, S.-G. Kim, C. J. Sinz, W.-J. Xiao, and D. W. C. MacMillan, *Proc. Natl. Acad. Sci. U.S.A.*, 2004, **101**, 5482.
30. R. R. Knowles, J. Carpenter, S. B. Blakey, A. Kayano, I. K. Mangion, C. J. Sinz, and D. W. C. MacMillan, *Chem. Sci.*, 2011, **2**, 308.
31. O. Lozano, G. Blessley, T. Martinez del Campo, A. L. Thompson, G. T. Giuffredi, M. Bettati, M. Walker, R. Borman, and V. Gouverneur, *Angew. Chem. Int. Ed.*, 2011, **50**, 8105.
32. K. C. Nicolaou, M. Bella, D. Y.-K. Chen, X. Huang, T. Ling, and S. A. Snyder, *Angew. Chem. Int. Ed.*, 2002, **41**, 3495.
33. K. C. Nicolaou, D. Y.-K. Chen, X. Huang, T. Ling, M. Bella, and S. A. Snyder, *J. Am. Chem. Soc.*, 2004, **126**, 12888.
34. K. C. Nicolaou, P. B. Rao, J. Hao, M. V. Reddy, G. Rassias, X. Huang, D. Y.-K. Chen, and S. A. Snyder, *Angew. Chem. Int. Ed.*, 2003, **42**, 1753.

35. K. C. Nicolaou, J. Hao, M. V. Reddy, P. B. Rao, G. Rassias, S. A. Snyder, X. Huang, D. Y.-K. Chen, W. E. Brenzovich, N. Giuseppone, P. Giannakakou, and A. O'Brate, *J. Am. Chem. Soc.*, 2004, **126**, 12897.
 36. M. A. Zajac and E. Vedejs, *Org. Lett.*, 2004, **6**, 237.
 37. C. Poriel, M. Lachia, C. Wilson, J. R. Davies, and C. J. Moody, *J. Org. Chem.*, 2007, **72**, 2978.
 38. P. Magnus and R. Turnbull, *Tetrahedron Lett.*, 2006, **47**, 6461.
 39. S. Ghosh, L. K. Kinthada, S. Bhunia, and A. Bisai, *Chem. Commun.*, 2012, **48**, 10132.
 40. R. Beaud, R. Guillot, C. Kouklovsky, and G. Vincent, *Angew. Chem. Int. Ed.*, 2012, **51**, 12546.
-



Yuta Ito is a Ph. D. student of Kobe Pharmaceutical University. He received his B. Sc. from Kobe Pharmaceutical University in 2012. He received Best Presentation Award for students at the 134th Annual Meeting of the Pharmaceutical Society of Japan in 2012. His research interests are in the areas of synthetic organic chemistry and medicinal chemistry.



Masafumi Ueda is Associate Professor of Kobe Pharmaceutical University. He received his B. Sc. (1999) from Kobe Pharmaceutical University and Ph. D. degree (2006) from Osaka University. He became appointed research assistant of Kobe Pharmaceutical University in 2000 and was promoted to Assistant Professor in 2001 and Associate Professor in 2013. He joined the group of Professor Peter Wipf at Pittsburgh University as a postdoctoral associate for one year from 2007. He has received several awards, including the Pharmaceutical Society of Japan Kinki-Branch Award for Young Scientists in 2004, the Fuji Photo Film Award in Synthetic Organic Chemistry, Japan in 2005, the Mitsubishi Chemical Award in Synthetic Organic Chemistry, Japan in 2012, and the Pharmaceutical Society of Japan Award for Young Scientists in 2014. His research interests include the development of new synthetic methodologies using radical chemistry and transition metal catalysis, as well as the design and synthesis of bioactive compounds with potential pharmaceutical applications.



Okiko Miyata is Professor of Kobe Pharmaceutical University. She received her B. Sc. (1973) from Kobe Pharmaceutical University and Ph. D. degree (1979) from Osaka University. She became an Assistant Professor of Kobe Pharmaceutical University in 1976 and was promoted to Associate Professor in 2001 and Professor in 2008. She worked as a postdoctoral fellow of Alexander von Humboldt-Stiftung (AvH) with Professor R. R. Schmidt at Konstanz University for one year from 1981. She received The Society of Synthetic Organic Chemistry, Japan Kansai-Branch Award in 2005. Her research interests are in the areas of synthetic organic chemistry, medicinal, and bioorganic chemistry.