

# Recent Advances in Phenol Dearomatization and Its Application in Complex Syntheses

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**Abstract:** As a powerful tool, the dearomatization of phenols has been explored extensively and utilized by organic chemists during the course of complex syntheses. This review highlights recent advances in phenol dearomatizations, especially those accomplished in an enantioselective manner, and the application of dearomatization strategies in complex syntheses.

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**Key words:** dearomatization, enantioselectivity, oxidation, phenols, tandem reaction

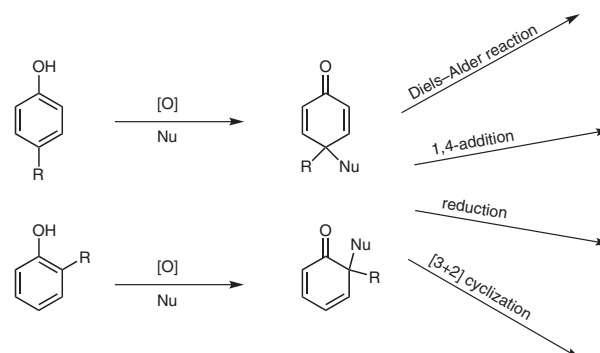
## 1 Introduction

Organic synthesis has reached a considerable level of maturity. Nowadays, almost any complex molecule can be synthesized, and selective functionalizations achieved. However, with ever-tighter resources, efficiency in organic synthesis is becoming more and more important. An ideal synthesis demands simplicity, safety, brevity, environmental friendliness, as well as high selectivity, yield and diversity.<sup>1</sup>

Phenols are the most frequently utilized substrates for dearomatization to access complex molecules. A number of dearomatization strategies have been used by organic chemists to construct fused, bridged and spiro structures. Owing to the high efficiency of these tactics, more and more investigations have focused on this field.<sup>2</sup>

The oxidation of *o*- and *p*-hydroquinones generally proceeds in methanol solution at room temperature, and the

yield of benzoquinones is almost quantitative.<sup>3</sup> Dearomatization of 4- or 2-substituted phenols in the presence of an appropriate nucleophile (Nu) leading to the respective 4,4- or 2,2-disubstituted cyclohexadienones is especially interesting and synthetically useful (Scheme 1). Various nucleophiles, such as water,<sup>4</sup> alcohols,<sup>3,5</sup> fluoride ion,<sup>6</sup> carboxylic acids,<sup>5d,7</sup> amides,<sup>8</sup> oximes,<sup>9</sup> and electron-rich aromatic rings<sup>10,11</sup> have been used successfully in dearomatization in either an inter- or an intramolecular mode. Besides, the resulting cyclohexadienones are good electrophilic substrates for various reactions, such as the Diels–Alder reaction, 1,4-addition, reduction and [3+2] cyclization. The following section of this report highlights some recent investigations on phenol dearomatizations, especially those accomplished in an enantioselective manner, and their application in complex syntheses.



**Scheme 1** Dearomatization of 4- or 2-substituted phenols

## 2 New Developments in Phenol Dearomatization

Besides electron-rich aromatic rings, other carbon resources can be introduced into the cyclohexa-2,5-dienone structure through an oxidative dearomatization process. Canesi and co-workers developed an iodine(III)-mediated oxidative Wagner–Meerwein transposition involving different functionalities (Scheme 2).<sup>12</sup> The reaction occurred rapidly in hexafluoroisopropanol (HFIP) using iodobenzene diacetate as oxidant. This transformation provides new strategic opportunities to prepare highly functionalized compounds containing a prochiral dienone and a quaternary carbon center connected to several sp<sup>2</sup> carbons.

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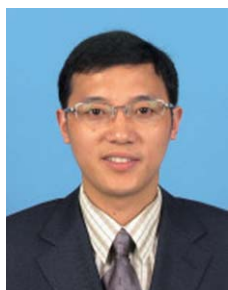
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One year later, the same research group reported a bimolecular oxidative process occurring with carbon–carbon bond formation that has been extended to allylsilanes (Scheme 3).<sup>13</sup> In this reaction, different 4-alkyl-2,6-disubstituted phenols **19** were successfully oxidized leading to an oxidative variant of the famous Hosomi–Sakurai allylation.<sup>11</sup> It is noteworthy that the first approach to this reaction was developed by Quideau and co-workers in aprotic solvents with phenyliodine(III) bis(trifluoroacetate) (PIFA), which provided some examples of oxidative allylation on substituted 1-naphthol.<sup>14</sup>

Canesi and co-workers also reported a dearomatization of phenol derivatives that promotes the formation of bicyclic and tricyclic products via a cationic cyclization process.<sup>15</sup> First, an oxidative vicinal-fused carbocycle formation was performed with a terminal alkyne on a lateral chain at the *meta*-position of phenol **21**. The authors speculated that a strained half-chair intermediate **22** was generated, and that this strongly favored nucleophile capture, leading to

the unsaturated decalin system **24** (Scheme 4). Vicinal-fused carbocycles were produced in good yields (43–91%). This new process could have application in asymmetric synthesis governed by the benzylic stereogenic center at the *meta* position (Scheme 5). Such scaffolds are present in numerous natural products such as anominine,<sup>16</sup> andrographolide,<sup>17</sup> or the decalin core of azadirachtin.<sup>18</sup> The cyclization reaction occurred with total stereocontrol in agreement with the configuration of the starting olefin, since a 2:1 mixture of diastereomers was obtained. To verify the high diastereoselectivity of this process, *cis*-**25** was prepared, and led exclusively to the tricyclic core **28** in a 43% yield. Recently, Canesi's research group also reported an oxidative *ipso*-rearrangement mediated by a hypervalent iodine reagent. A functionalized dienone system containing a quaternary carbon center connected to several sp<sup>2</sup> centers was constructed. This transformation was used in the total synthesis of sceletenone, a small alkaloid.<sup>19</sup>

## Biographical Sketches



**Qiuping Ding** was born in Jiangxi, China, in 1975. He received his Ph.D. from Fudan University under the su-

per vision of Professor Jie Wu in 2009. He is currently an associate professor at Jiangxi Normal University,

China. His research interest is focused on cascade reactions.



**Yang Ye** was born in Hunan, China, in 1985. In 2012, he received his Ph.D.

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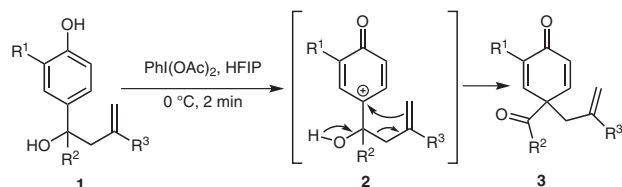
currently a technician in Pharmaron Beijing Co., Ltd.



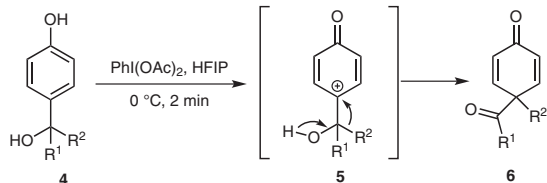
**Renhua Fan** was born in Jiangxi, China, in 1976. He received his Ph.D. from Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences under the supervision of Professor

Xuelong Hou in 2003. After postdoctoral studies (2003–2006) at Purdue University, USA with Professor Alexander Wei, he moved to Fudan University, China. He is currently a full professor of

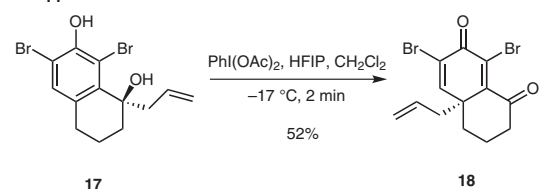
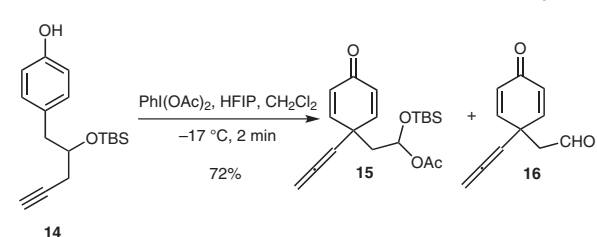
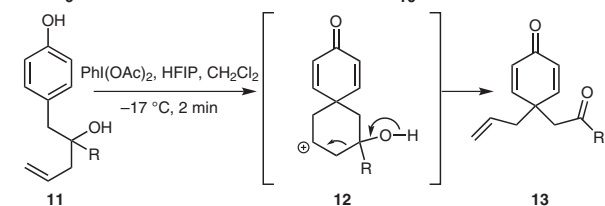
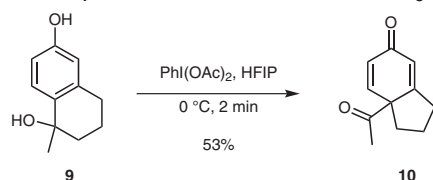
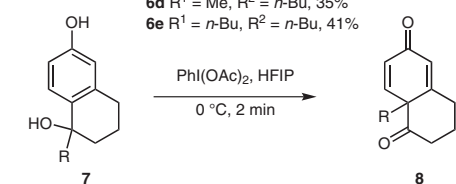
organic chemistry at the Department of Chemistry of Fudan University. His research interest is focused on hypervalent iodine chemistry.



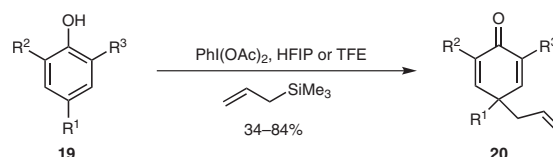
- 3a** R<sup>1</sup> = R<sup>3</sup> = H, R<sup>2</sup> = Me, 62%  
**3b** R<sup>1</sup> = R<sup>3</sup> = H, R<sup>2</sup> = CH<sub>2</sub>CH=CH<sub>2</sub>, 67%  
**3c** R<sup>1</sup> = R<sup>2</sup> = Me, R<sup>3</sup> = H, 63%  
**3d** R<sup>1</sup> = H, R<sup>2</sup> = R<sup>3</sup> = Me, 37%  
**3e** R<sup>1</sup> = R<sup>3</sup> = H, R<sup>2</sup> = CH<sub>2</sub>OTBS, 33%



- 6a** R<sup>1</sup> = Me, R<sup>2</sup> = CH=CH<sub>2</sub>, 34%  
**6b** R<sup>1</sup> = Me, R<sup>2</sup> = Ph, 51%  
**6c** R<sup>1</sup> = Et, R<sup>2</sup> = Ph, 35%  
**6d** R<sup>1</sup> = Me, R<sup>2</sup> = *n*-Bu, 35%  
**6e** R<sup>1</sup> = *n*-Bu, R<sup>2</sup> = *n*-Bu, 41%

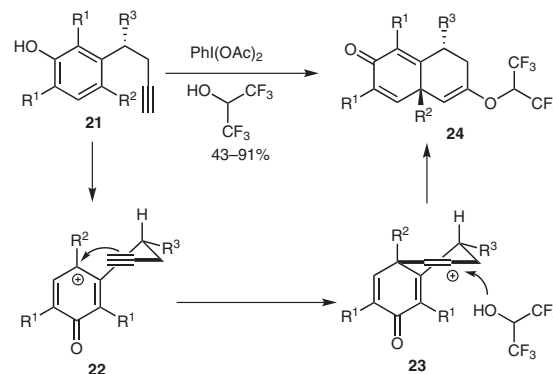


**Scheme 2** Wagner–Meerwein transposition by dearomatization of phenols

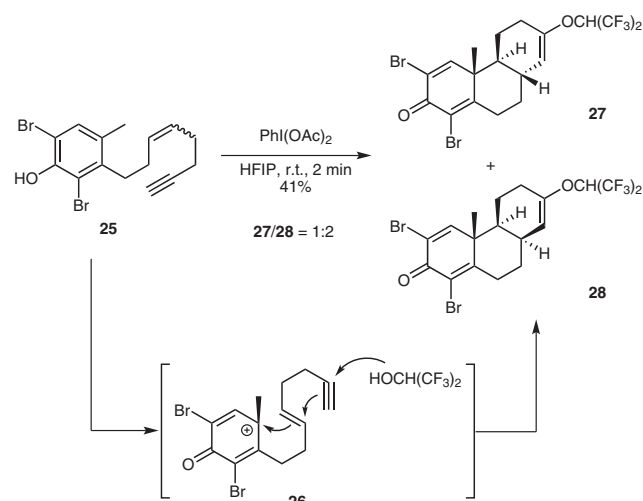


- R<sup>1</sup> = Me, Et, *n*-Bu, CH<sub>2</sub>CH<sub>2</sub>OH, *i*-Pr, Ph, CH<sub>2</sub>OTBDMS, CH<sub>2</sub>CO<sub>2</sub>Me  
 R<sup>2</sup> = *t*-Bu, TMS, Cl, Br, I  
 R<sup>3</sup> = *t*-Bu, TMS

**Scheme 3** Bimolecular oxidative process between phenols and allylsilanes

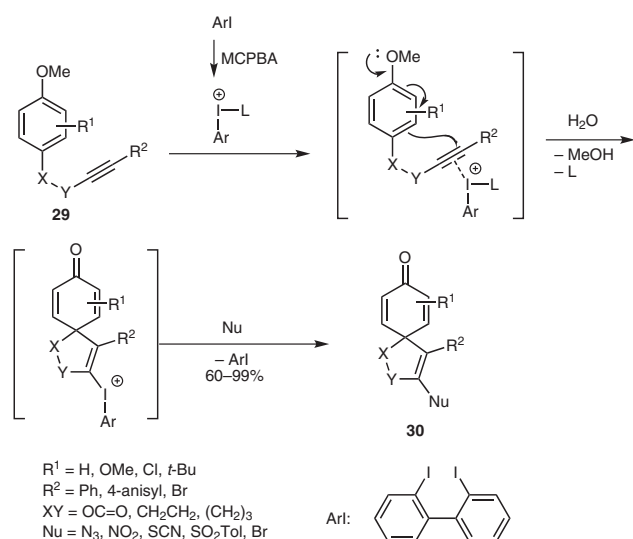


**Scheme 4** Oxidative formation of fused carbocycles



**Scheme 5** Asymmetric synthesis of a tricyclic scaffold

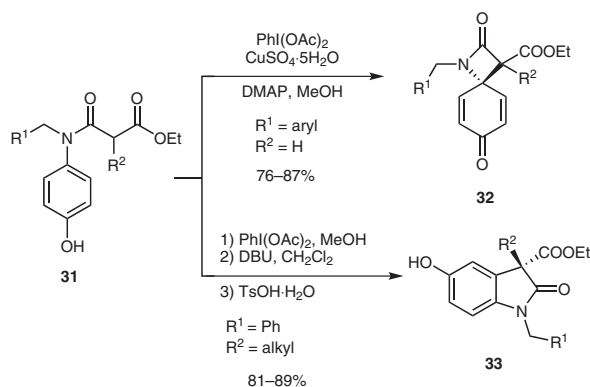
The substituted alkynyl group in **29**, where  $R^2 \neq H$ , also performed as a nucleophile in the carbon–carbon bond formation. Kita and colleagues developed a very effective spirocyclization procedure for installing nucleophiles ( $Nu = N_3, NO_2, SCN, SO_2Tol$ , and  $Br$ ) induced by iodonium(III) salts (Scheme 6).<sup>20</sup> The in situ generated cationic iodonium(III) species activates the alkynyl group and induces the *ipso*-cyclization of compound **29**, thereby leading to a spirocyclized iodonium(III) salt. The latter undergoes a reductive coupling<sup>21</sup> with nucleophiles to afford the functionalized spirocyclic compounds **30**.



**Scheme 6** Synthesis of spirocycles

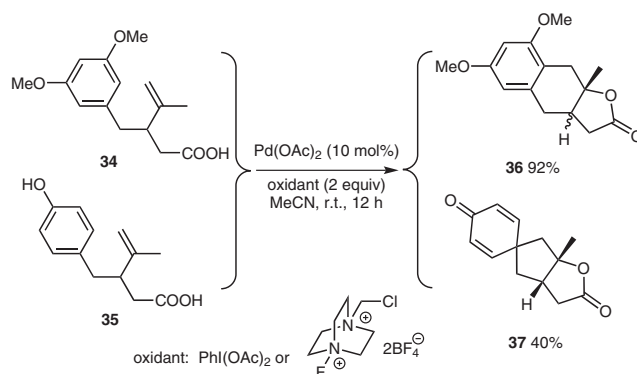
Zhang and co-workers reported a condition-controlled oxidative dearomatization of phenolic amides (Scheme 7).<sup>22</sup> In the presence of copper(II) sulfate pentahydrate and 4-dimethylaminopyridine (DMAP), the oxidation of phenolic amides with iodobenzene diacetate as oxidant gave rise to highly functionalized spiro  $\beta$ -lactams. In the absence of copper salts and DMAP, the oxidation provided 4-methoxycyclohexadienones in nearly quantitative yields. After base-catalyzed intramolecular Michael addition and acid-catalyzed rearomatization, oxindoles were formed.

In addition to oxidative dearomatization, a high-valent-palladium-mediated intramolecular cyclization cascade reaction developed by Stephenson and co-workers has been used to prepare spirocyclic cyclohexadienone structures from phenols (Scheme 8).<sup>23</sup> The resulting spirocyclic cyclohexadienone could be a precursor for a radical

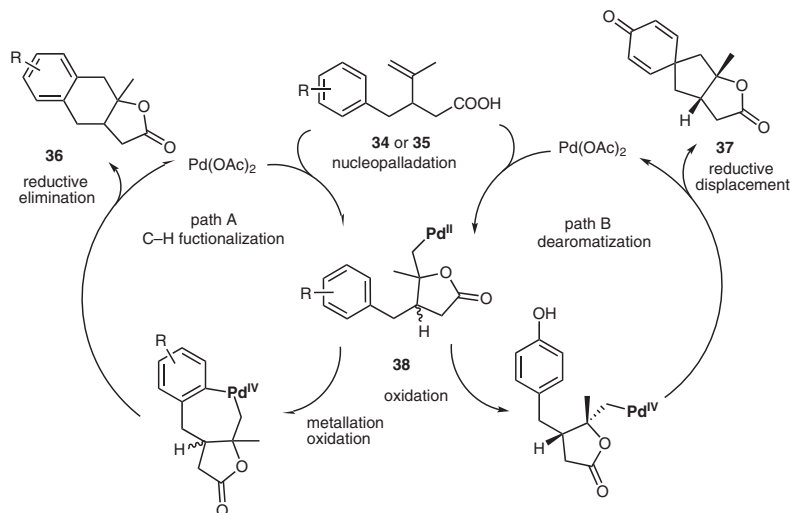


**Scheme 7** Synthesis of spiro lactams and oxindoles via oxidative dearomatization

conjugate addition to efficiently provide the bicyclic fragment of platensimycin.<sup>24</sup> A plausible catalytic cycle is outlined in Scheme 9. In path A, palladium(II) coordinates to the olefin of the substrate and induces an oxypalladation to form a Wacker intermediate.<sup>25</sup> Metallation of the carbon–hydrogen bond and subsequent oxidation by iodobenzene diacetate provides a palladacycle, which undergoes reductive elimination to produce the C–H insertion product **36**. For phenols, the catalytic cycle proceeds through a dearomatization pathway (path B). The resulting Wacker intermediate undergoes oxidation to form a highly electrophilic alkylpalladium(IV) intermediate. After reductive nucleophilic substitution by the phenol ring, spirocyclohexadienone product **37** is formed.



**Scheme 8** Synthesis of spirocyclic cyclohexadienones and tricyclic scaffolds

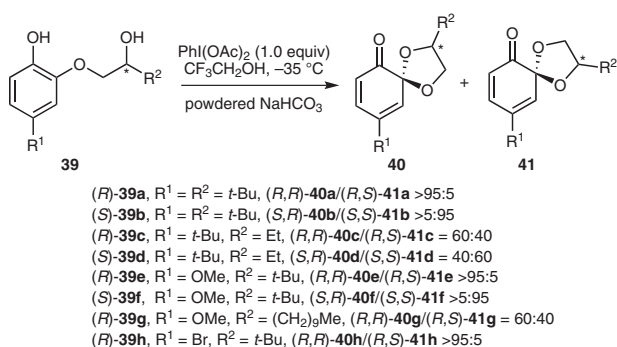


**Scheme 9** Mechanism of Pd-mediated cyclization reactions leading to spirocyclic cyclohexadienones and tricyclic scaffolds

### 3 Enantioselective Phenol Dearomatization

#### 3.1 Controlled by Chiral Substrate

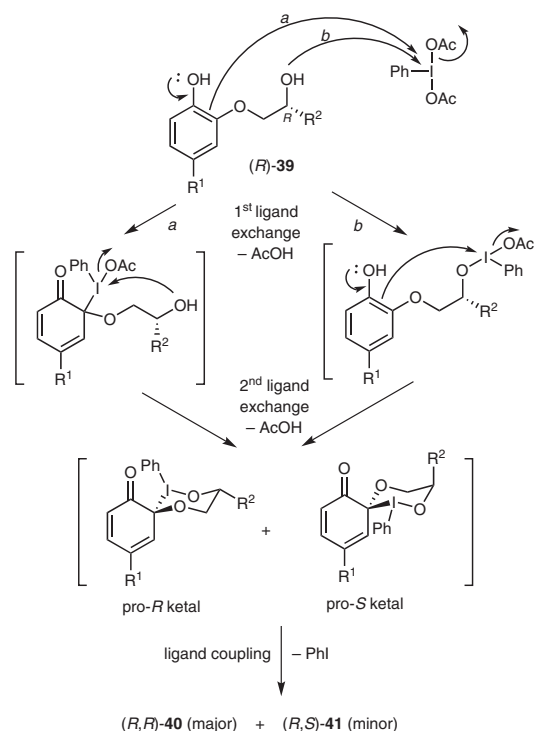
Quideau and co-workers reported a convenient and enantioselective route to access spiroketals through dearomatization of phenols (Scheme 10).<sup>5a,26</sup> Phenolic alcohols **39a,b,e,f,h**, with a *tert*-butyl substituent on the carbon atom attached to the hydroxy group in the side chain, underwent a highly diastereoselective transformation, in contrast to **39c,d,g**, which have an ethyl or *n*-decyl group at this position. The stereoselectivity is controlled by the chiral alkyl branch, and a density–functional theory (DFT) calculation was done to explain the stereoselectivity. The authors hypothesized that the spiroketals were formed via a tandem ligand-exchange and ligand-coupling reaction (Scheme 11). The ability of these chiral spiroketals to promote asymmetric induction was demonstrated during the synthesis of (+)-biscarvacrol,<sup>27</sup> a naturally occurring bridge-ring system (Scheme 12).



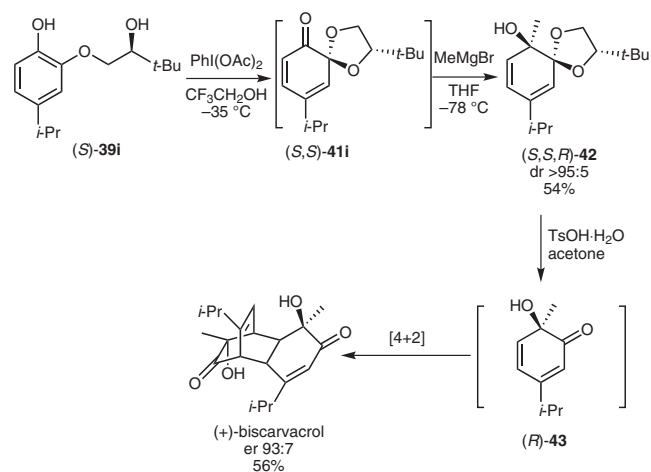
**Scheme 10** Dearomatization of phenolic alcohols **39** into orthoquinone monoketals **40** and **41**

Pettus and co-workers developed a diastereoselective dearomatization reaction and utilized it in the enantioselective synthesis of 4,6-dihydroxy-4-alkylcyclohexenone

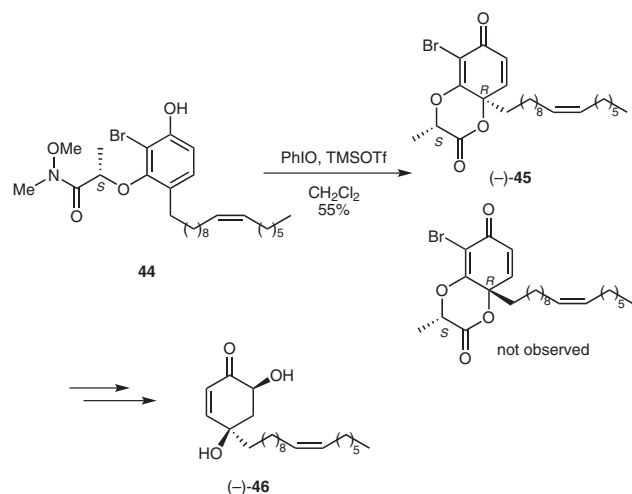
core structure with anticancer properties (Scheme 13).<sup>28</sup> This transformation was presumed to involve (1) in situ generation of PhI(OTf)OTMS, (2) oxidation of the phenol ring, (3) cyclization with the amide carbonyl, and finally (4) hydrolysis of the iminium species. The other diastereomer was not observed in the <sup>1</sup>H NMR spectrum of the crude product mixture. The modified conditions used here have significantly improved the versatility of this dearomatization process compared to their previous conditions, which used iodobenzene di(trifluoroacetate) as the oxidant.<sup>29</sup> Compound (–)-**45** is the precursor of *syn*-diol (–)-**46**, a structure with anticancer properties.



**Scheme 11** Plausible mechanism of the iodobenzene diacetate mediated spiroketalization of phenolic alcohols **39**



**Scheme 12** Enantioselective synthesis of (+)-biscarvacrol

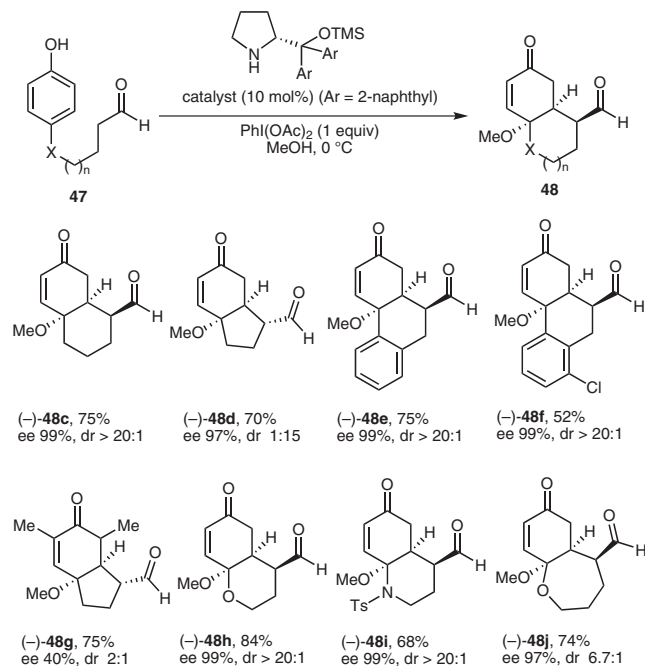


**Scheme 13** Dearomatization and diastereoselective synthesis of resorcinol-derived cyclohexadienone **45**

### 3.2 Controlled by Chiral Catalyst

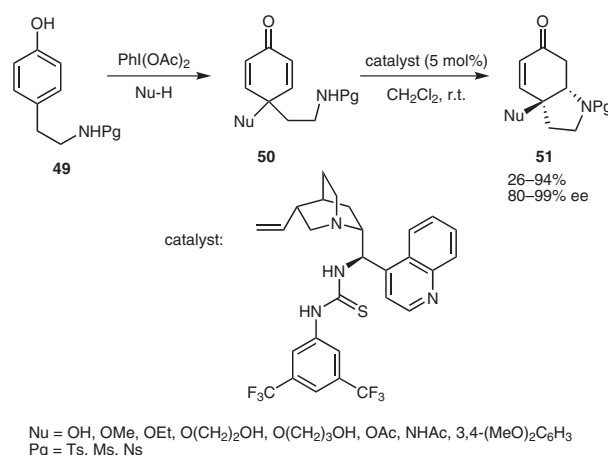
Gaunt and co-workers reported a process that directly converts *para*-substituted phenol **47** into the highly functionalized chiral molecule **48** via oxidative dearomatization and a desymmetrizing secondary-amine-catalyzed asymmetric intramolecular Michael addition (Scheme 14).<sup>30</sup> This one-step transformation constructs a complex structure with exquisite control of three new stereogenic centers. The corresponding decalin derivatives were formed with superb control of stereochemistry (up to >20:1 dr and 99% ee)

You and Gu developed an intramolecular aza-Michael reaction catalyzed by a cinchonine-derived thiourea

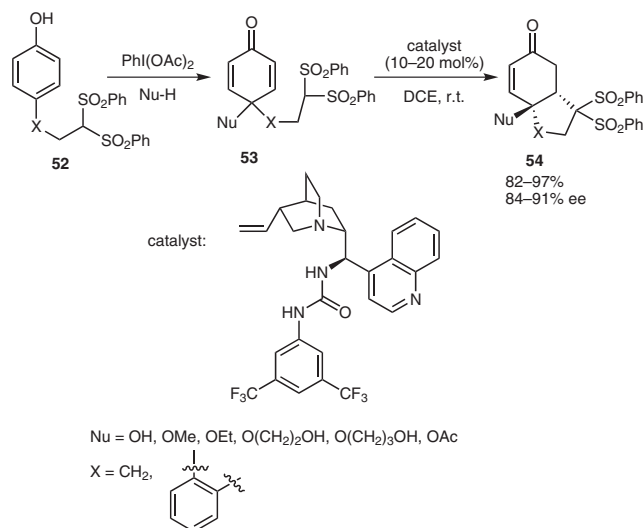


**Scheme 14** Catalytic enantioselective dearomatization

(Scheme 15).<sup>31</sup> With 5 mol% of the thiourea in dichloromethane at room temperature, cyclohexadienones **50** reacted smoothly to provide compounds **51** in excellent yields and enantiomeric excess. With this methodology, asymmetric total synthesis of (-)-mesembrine<sup>32</sup> was accomplished with high enantioselectivity (98% ee). The same catalyst was also used in the dearomatization of phenols **52** bearing a bis(phenylsulfonyl)methylene group (Scheme 16).<sup>33</sup> Various highly enantioenriched polycyclic cyclohexenones **54** were prepared.

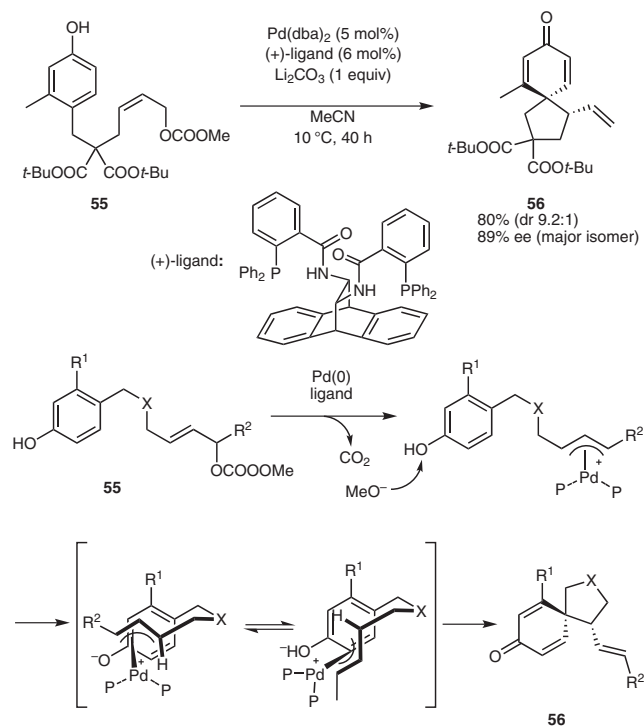


**Scheme 15** Synthesis of pyrrolidine derivatives via enantioselective intramolecular aza-Michael reaction



**Scheme 16** Asymmetric intramolecular Michael reaction

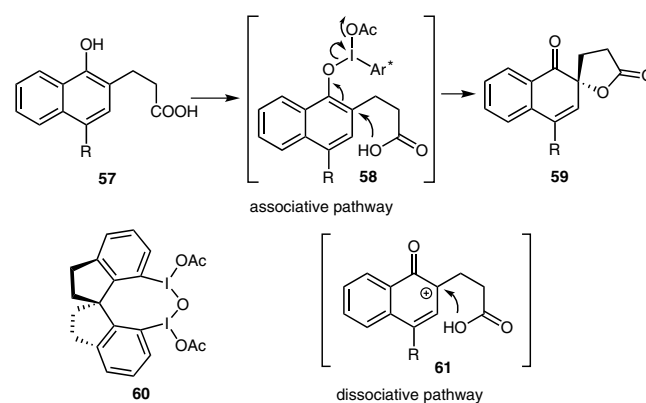
In an alternative to oxidation, the enantioselective dearomatization of phenols can also proceed in another way. Recently, Hamada and colleagues reported a palladium-catalyzed intramolecular *ipso*-Friedel-Crafts allylic alkylation of phenols **55** to afford spiro[4.5]cyclohexadienones **56** (Scheme 17).<sup>34</sup> The method was thus applied to the catalytic enantioselective construction of an all-carbon quaternary spirocenter.



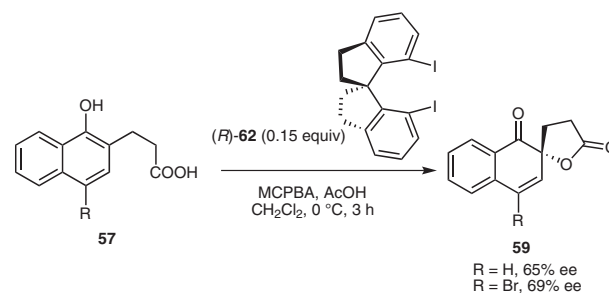
**Scheme 17** Enantioselective construction of an all-carbon quaternary spirocenter

### 3.3 Controlled by Chiral Hypervalent Iodine

Asymmetric dearomatization induced by chiral hypervalent iodine reagent is still a challenge in organic synthesis.<sup>35</sup> In 2008, Kita and co-workers developed the symmetric chiral iodine(III) reagent **60** and applied it in the tandem enantioselective oxidative dearomatization and spirocyclization reaction of naphthols (Scheme 18).<sup>36</sup> The enantiomeric excess values for the products reached 86%. The reaction might proceed through an 'associative'<sup>14,37</sup> or 'dissociative'<sup>38</sup> pathway. The higher levels of asymmetric induction were observed in those reactions carried out in nonpolar and moderately polar solvents such as carbon tetrachloride, dichloromethane, and chloroform, in contrast to the polar solvents such as hexafluoroisopropanol, and with substrates carrying electron-withdrawing substituents, rather than those with electron-donating substituents. These observations support an associative mechanism. A catalytic version of the same reaction afforded inferior enantioselectivity (up to 69% ee; Scheme 19).



**Scheme 18** Enantioselective spirocyclization and plausible reaction mechanisms

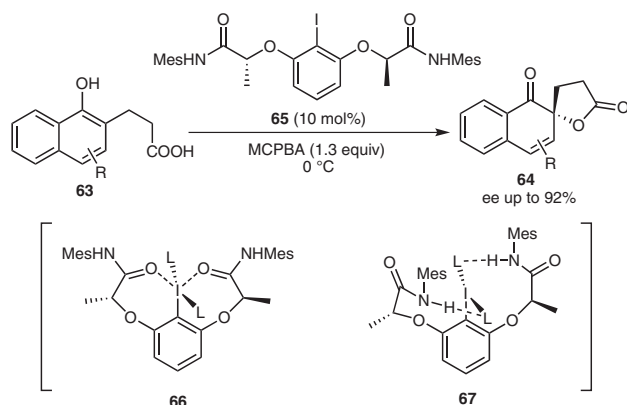


**Scheme 19** Catalytic application of the chiral hypervalent iodine(III) reagent (R)-62

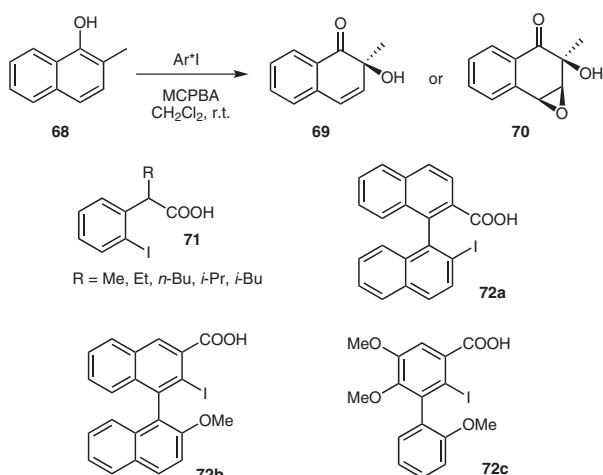
Ishihara and colleagues reported a similar spirocyclization reaction mediated by chiral iodoarenes **65** with *m*-chloroperoxybenzoic acid as co-oxidant (Scheme 20).<sup>39</sup> In the presence of 10 mol% of **65**, lactones **64** bearing an electron-donating or an electron-withdrawing group were formed in good to excellent yields (up to 92% ee). The active λ<sup>3</sup>-iodane catalyst may be stabilized by the electron donation from the carbonyl groups of the lactic amides to

the electron-deficient iodine(III) center, as in **66**, or may be activated by the hydrogen bonding between the mesityl-protected NH groups and the oxygen ligands connected to the iodine atom, as in **67**.

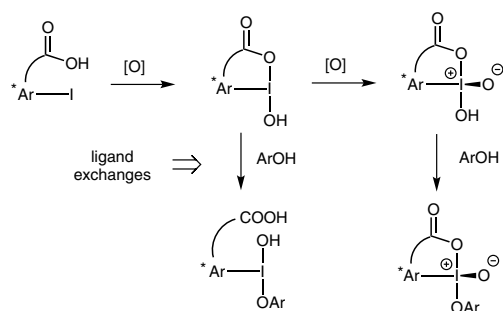
In 2009, Quideau et al. developed an asymmetric iodoarene-mediated hydroxylative dearomatization reaction (Scheme 21).<sup>40</sup> In the presence of 10–200 mol% of the chiral iodoarene, the enantioselectivities of *o*-quinol **69** or epoxide **70** were up to 50% ee. Both  $\lambda^3$ - and  $\lambda^5$ -iodane-mediated mechanisms were proposed (Scheme 22).



**Scheme 20** Catalytic oxidative spirocyclization

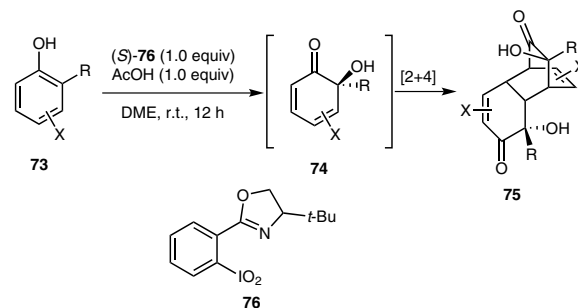


**Scheme 21** Enantioselective iodoarene-mediated hydroxylative dearomatization



**Scheme 22** Proposed mechanism of hydroxylative dearomatization

In the same year, Birman and Boppisetti developed a new class of chiral iodine(V) derivatives such as **76** with a chiral oxazoline group at the *ortho*-position (Scheme 23).<sup>41</sup> This kind of chiral polyvalent iodine reagent proved to be efficient in promoting the transformation of *o*-alkylphenols to *o*-quinol Diels–Alder dimers with significant asymmetric induction.

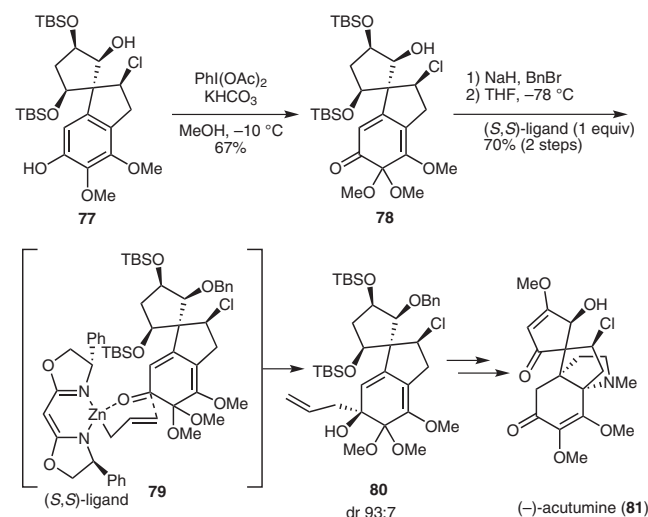


**Scheme 23** Asymmetric oxidation of isomeric dimethylphenols with **76**

## 4 Enantioselective Phenol Dearomatization Strategies in Complex Syntheses

### 4.1 With the Formation of a Carbon–Oxygen Bond

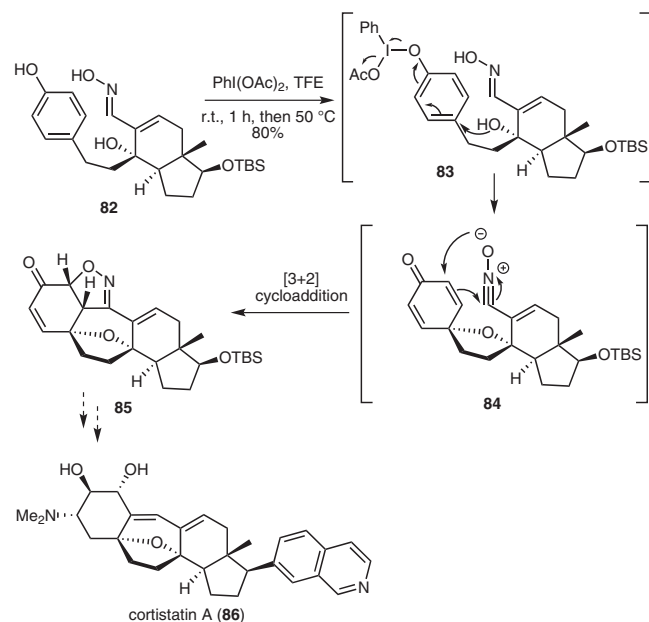
In the total synthesis of (–)-acutumine (**81**), which was originally isolated from the Asian vine *Menispermum dauricum* and possesses selective T-cell cytotoxicity and anti-amnesic properties, the iodobenzene diacetate mediated oxidative dearomatization was used as the key step to construct masked *o*-benzoquinone derivative **78** (Scheme 24).<sup>42</sup> This result highlighted the utility of iodine(III) reagents for the dearomatization of complex substrates.



**Scheme 24** Total synthesis of (–)-acutumine

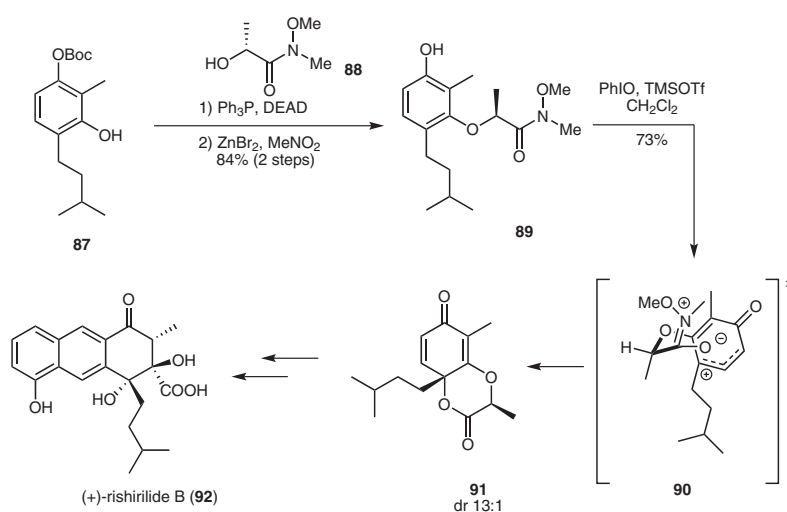


A cascade process involving a hypervalent iodine induced intramolecular oxidative dearomatization and an intramolecular dipolar cycloaddition<sup>43</sup> was reported by Sorensen and co-workers<sup>44</sup> for the construction of the pentacyclic core of cortistatin A (**86**; Scheme 25). The exposure of compound **82** to iodobenzene diacetate<sup>45</sup> in trifluoroethanol directly produced compound **85** as a single diastereomer through two oxidations and two ring formations.



**Scheme 25** Total synthesis of cortistatin A

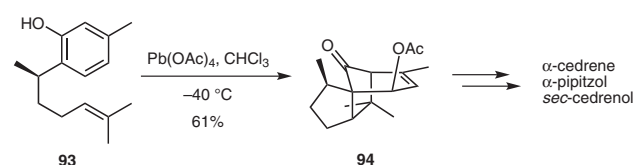
As shown in Scheme 26, a concise asymmetric synthesis of (+)-rishirilide B (**92**) was reported by Pettus and co-workers.<sup>46</sup> Resorcinol **87** was coupled with lactate derivative **88** through a Mitsunobu reaction and a deprotection. Diastereoselective oxidative dearomatization of **89** presumably proceeds via chair-like transition state **90** and leads to chirality transfer from the chiral auxiliary to af-



**Scheme 26** Total synthesis of (+)-rishirilide B

ford 1,4-dioxan-2-one **91** in high diastereoselectivity. Further transformations of **91** completed an efficient asymmetric total synthesis of (+)-rishirilide B (**92**) in 15 steps and a 12.5% overall yield.

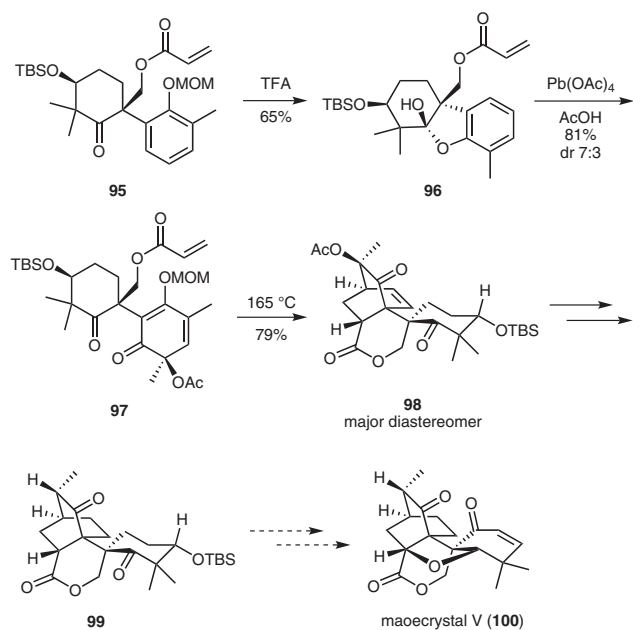
Recently, Pettus and colleagues also developed an oxidative dearomatization induced [5+2]-cascade reaction enabling the synthesis of  $\alpha$ -cedrene,  $\alpha$ -pipitzol, and *sec*-cedrenol (Scheme 27).<sup>47</sup> The benzylic stereocenter effectively guides the formation of the first two stereocenters during the intramolecular [5+2] cycloaddition of the respective phenoxonium intermediate across the tethered olefin.<sup>46</sup>



**Scheme 27** Synthesis of  $\alpha$ -cedrene,  $\alpha$ -pipitzol, and *sec*-cedrenol

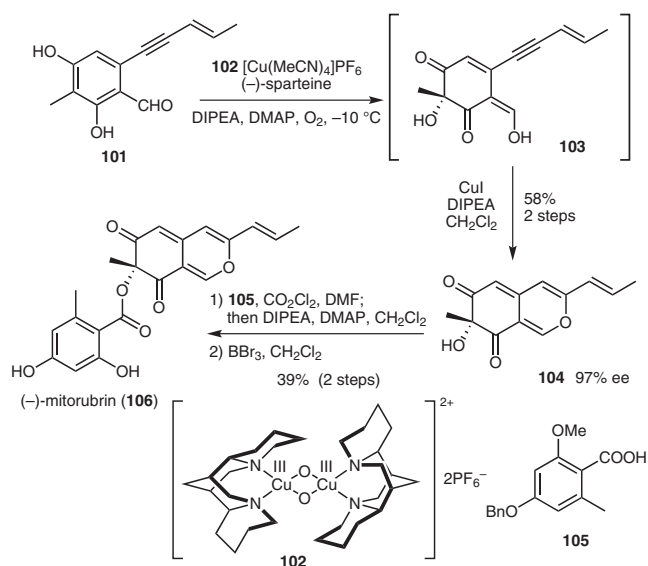
Baran and co-workers executed a sequential Barton arylation, Wessely oxidation and Diels–Alder strategy to create the core of the natural product, maecrystal V (Scheme 28).<sup>48</sup> A similar process was reported by Mehta and Maity in the preparation of the complete carbon framework present in tashironin-type sesquiterpenoid natural products.<sup>49</sup>

Porco and co-workers described the synthesis of (–)-mitorubrin (**106**) and related azaphilone natural products using copper-mediated enantioselective oxidative dearomatization of resorcinols (Scheme 29).<sup>50</sup> Dearomatization of the resorcinol aldehyde **101** using complex **102** was achieved in a regioselective manner with high enantioselectivity to afford vinylogous acid **103**. Enyne **103** was subjected to copper(I) iodide catalyzed cycloisomerization to afford the mitorubrin core structure **104** (58% yield and 97% ee for two steps). Further esterification with acid **105** and final deprotection afforded the desired azaphilone (–)-mito-



Scheme 28 Total synthesis of maoecrystal V

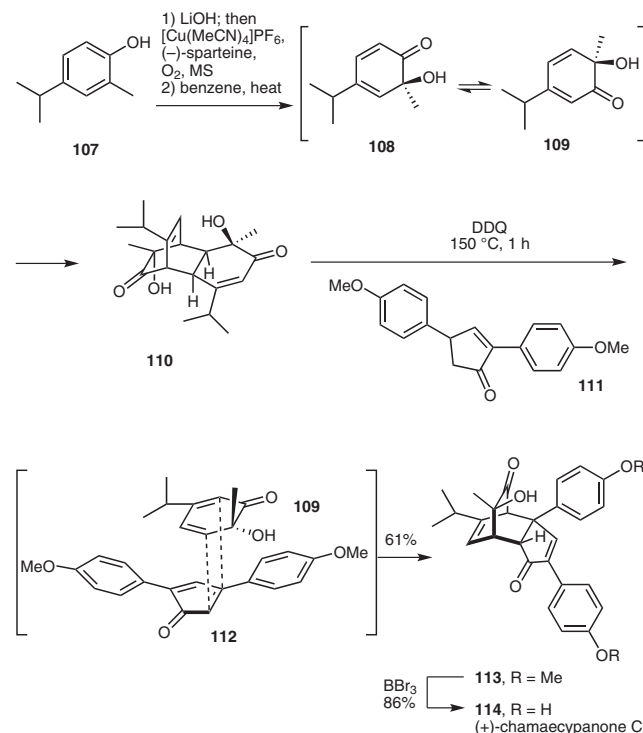
rubrin (**106**). This convergent synthesis features the highly enantioselective oxidative dearomatization of resorcinol aldehyde using a readily accessible chiral bis- $\mu$ -oxodicopper complex.



Scheme 29 Total synthesis of (-)-mitorubrin

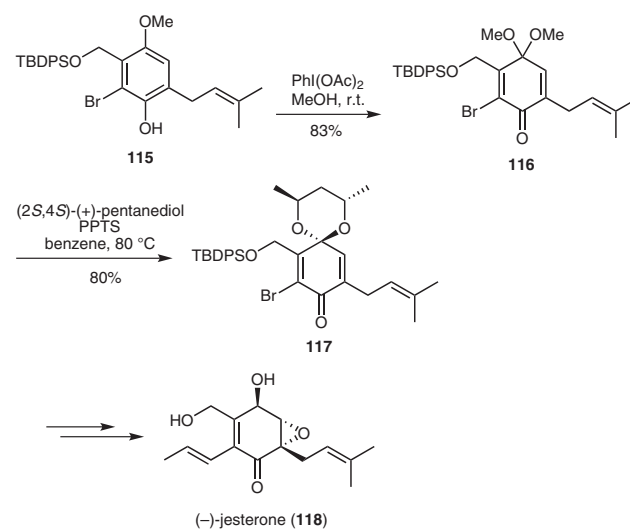
This oxidation system was also used in the enantioselective synthesis of (+)-chamaecypanone C, a novel microtubule inhibitor (Scheme 30).<sup>51</sup> In the presence of copper bis(oxo) complex derived from (-)-sparteine, the chemoselective *ortho*-dearomatization of 2,4-disubstituted lithium phenolate led to *o*-quinol **108** which equilibrated by means of a [1,2]-ketol shift to isomer **109**. The latter underwent a Diels–Alder dimerization to generate bicyc-

lo[2.2.2]octenone **110** (>99% ee). After a retro-Diels–Alder reaction and a subsequent Diels–Alder cycloaddition with the in situ generated diarylcyclopentadienone, the desired enantiopure cycloadduct **113** was obtained in 61% yield.



Scheme 30 Total synthesis of (+)-chamaecypanone C

Dimethylketal **116**, generated from the corresponding oxidative dearomatization of *o*-prenylphenol **115**, underwent a transketalization with (2*S*,4*S*)-pentanediol to form chiral quinone monoketal **117**. The latter is a key intermediate in the total synthesis of **118**, the epoxyquinoid natural product (-)-jesterone (Scheme 31).<sup>52</sup>

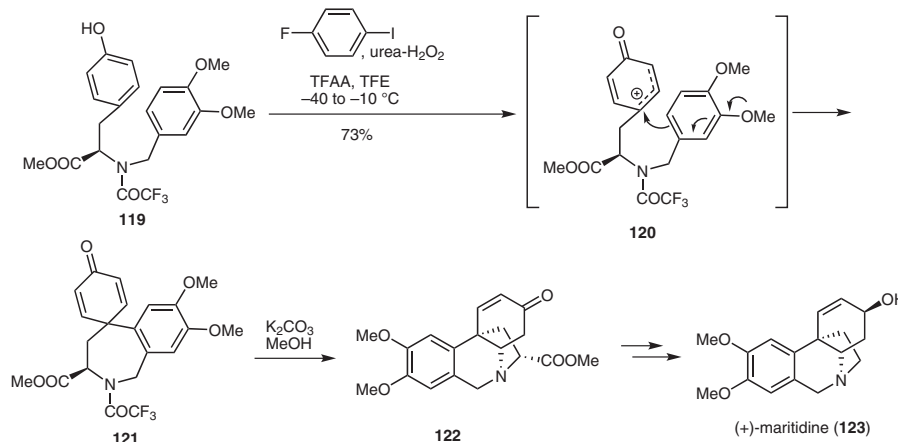


Scheme 31 Total synthesis of (-)-jesterone

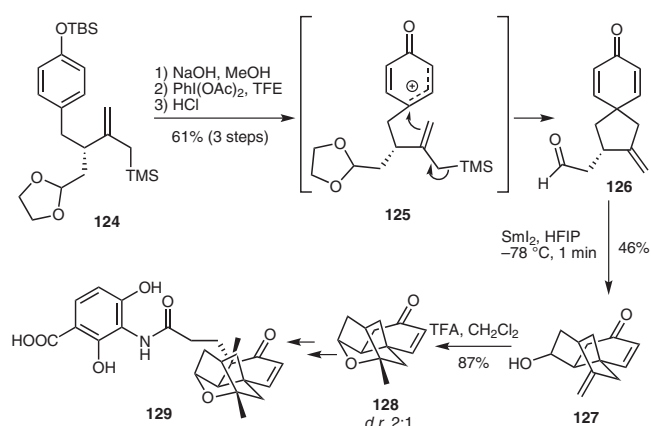
## 4.2 With the Formation of a Carbon–Carbon Bond

As highlighted in the previous section, many oxidative dearomatizations involve soft carbon nucleophiles. The carbon–carbon bond formation during the oxidative dearomatization is of significant interest in complex natural product synthesis. Kita and co-workers reported the first versatile iodoarene-catalyzed carbon–carbon bond-forming reaction (Scheme 32).<sup>53</sup> With the in situ generated active catalytic iodine(III) species, the oxidative dearomatization of compound **119** produced the discrete carbocation intermediate **120**, which was selectively trapped by the pendant aromatic ring to afford the desired spirocyclic amino ester **121**. This reaction was used in the key synthetic process of producing biologically important amaryllidaceae alkaloids, such as (+)-maritidine (**123**).

An important example of the oxidative dearomatization of a phenolic substrate with concomitant carbon–carbon bond formation in the context of complex total synthesis was reported by Nicolaou and colleagues in their enantioselective synthesis of (–)-platensimycin (Scheme 33).<sup>54</sup> The authors employed oxidative dearomatization with an intramolecular *para*-spiroannulation of a pendant allylsilane<sup>13,14,37e,55</sup> using hypervalent iodine activation to assemble the first two rings of the natural product. Activation of the free phenol moiety by iodobenzene diacetate in a polar solvent (trifluoroethanol) afforded the activated intermediate **125** bearing a delocalized carbocation which reacted internally with the allylsilane to furnish the desired spirocyclic dienone. Subsequent removal of the ethylene acetal group led to the free aldehyde substrate **126**, which was ready to undergo a radical-mediated cyclization and an acid-mediated etherification to efficiently produce the tetracyclic core of platensimycin (**129**). Danishefsky and Dai developed an alkylative *para*-dearomatization of compound **130** to synthesize **131**, the core matrix of the steroidal alkaloid cortistatin A (Scheme 34).<sup>56</sup>



**Scheme 32** Total synthesis of (+)-maritidine

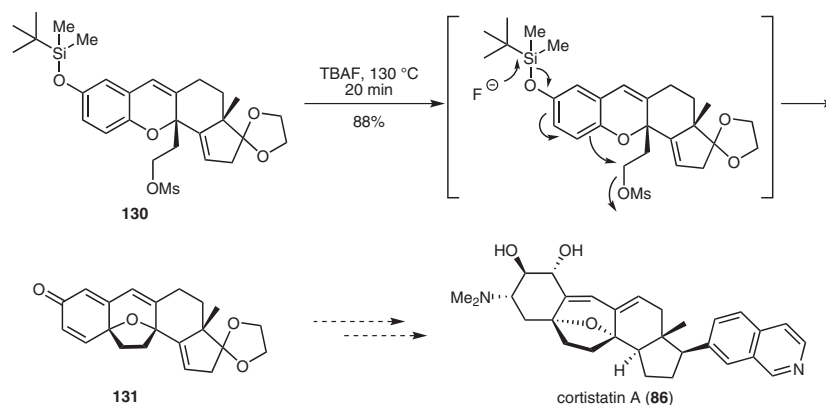


**Scheme 33** Total synthesis of (–)-platensimycin

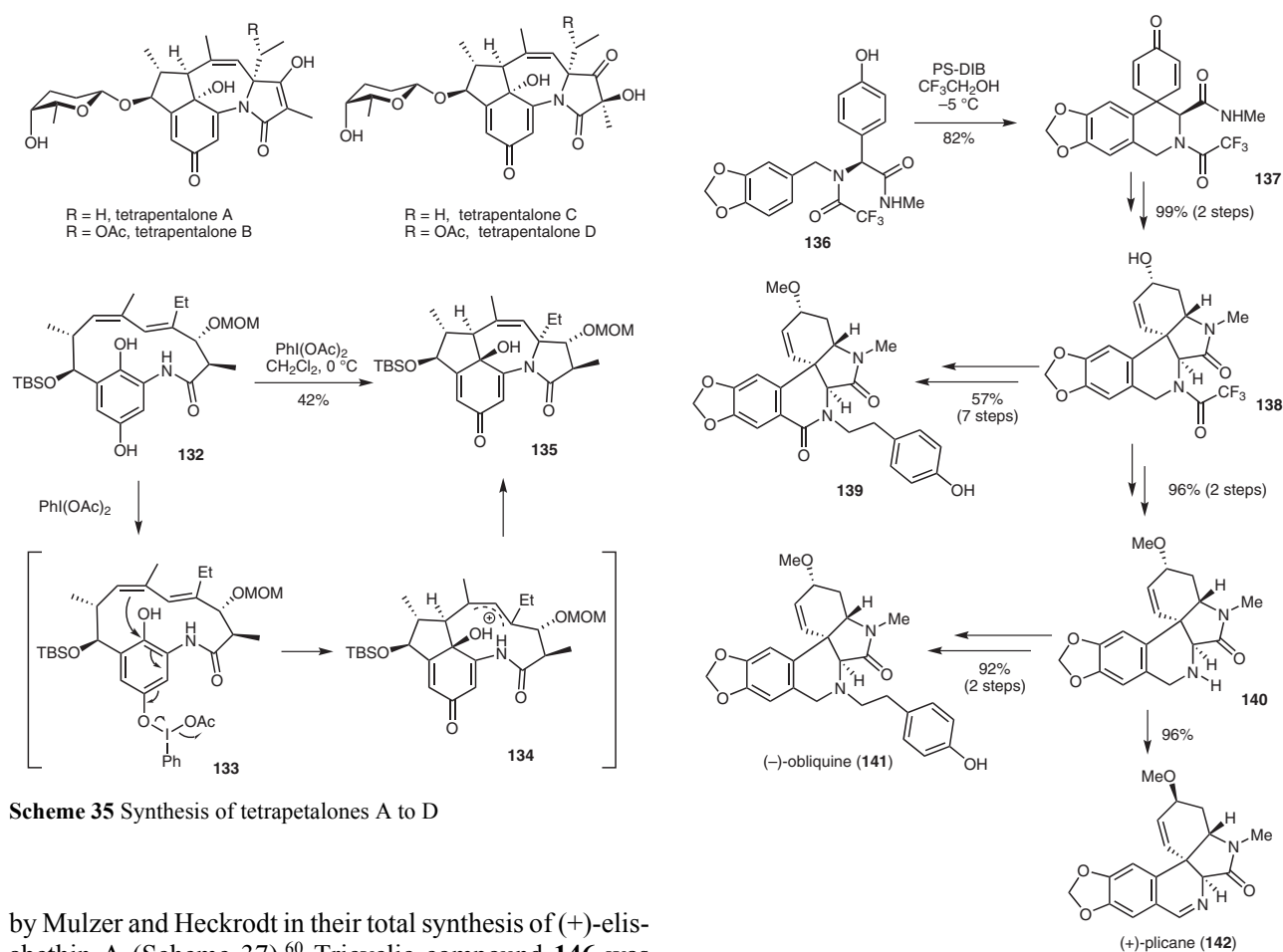
Porco and Wang made efforts toward the synthesis of the soybean lipoxygenase inhibitors, tetrapetalones A to D (Scheme 35).<sup>57</sup> Treatment of macrocyclic hydroquinone **132** with iodobenzene diacetate led to a diastereoselective transannular [4+3] cyclization and formed the tetracyclic core of the targeted molecules. The attack of the electron-rich diene unit at the oxidatively activated hydroquinone moiety generated an intermediate with an allylic cation, which could rotate to form a suitable conformation (**134**) for reaction with the amide nitrogen atom. The *para*-quinolonic tetracycle **135** was obtained in 42% yield from **132** via this one-pot process.

In the first total synthesis of the amaryllidaceae alkaloid (+)-plicamine (**139**), Ley and co-workers used a solid-supported iodobenzene diacetate (PS-DIB) to mediate the spirocyclization of **136** (Scheme 36).<sup>58</sup> The resulting advanced intermediate **138** was also exploited for the synthesis of both (–)-obliquine (**141**) and (+)-plicane (**142**) via the common secondary amine precursor **140**.<sup>59</sup>

An iron(III)-mediated cascade oxidative dearomatization and intramolecular Diels–Alder reaction was developed



Scheme 34 Total synthesis of cortistatin

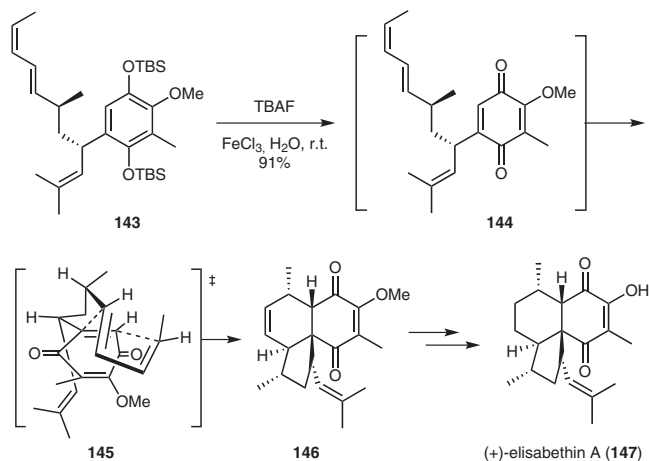


Scheme 35 Synthesis of tetrapetalones A to D

by Mulzer and Heckrodt in their total synthesis of (+)-elisabethin A (Scheme 37).<sup>60</sup> Tricyclic compound **146** was formed via *endo* transition state **145**. This cascade process relied on the *Z*-configuration of the terminal olefin to induce the desired stereochemistry. The facial selectivity of the diene–quinone cycloaddition is presumably dictated by the minimization of allylic strain between the substituents at C9 and the quinone carbonyl moiety in *endo* transition state **145** such that cycloadduct **146** is produced as a single diastereoisomer. The required chemoselective re-

Scheme 36 Polymer-supported approach to the total synthesis of amaryllidaceae alkaloids

moval of the endocyclic alkene, epimerization at C2, and deprotection afforded (+)-elisabethin A (**147**).

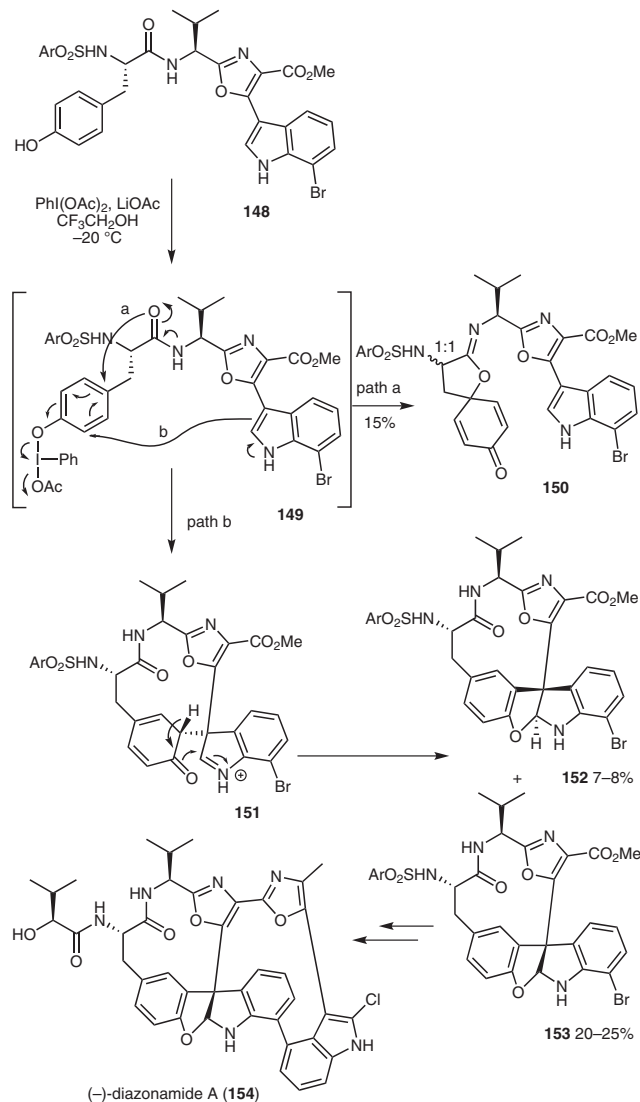


Scheme 37 Total synthesis of (+)-elisabethin A

In the total synthesis of the antimetabolic natural product (–)-diazonamide A (**154**), Harran and co-workers subjected the advanced phenolic–indolic amide intermediate **148** to reaction with iodobenzene diacetate in the presence of lithium acetate in trifluoroethanol at  $-20\text{ }^{\circ}\text{C}$  (Scheme 38).<sup>61</sup> This treatment led to the formation of an undesired dearomatized and spiroannulated cyclohexa-2,5-dienone product **150** in 15% yield (path a). Nevertheless, the two diastereomeric macrolactams **152** and **153** were fortunately also obtained in a 1:3 ratio (ca. 30% yield) according to the proposed path b, through which the transient intermediate **149** is trapped intramolecularly by the nucleophilic indolic moiety, followed by rearomatization of the resulting cyclohexa-2,4-dienone intermediate **151** with a concerted oxocyclization onto its iminium unit leading to the observed benzofurans. Finally, the major benzofuran product **153** was further transformed to afford (–)-diazonamide A (**154**) after 14 additional steps.

#### 4.3 With the Formation of a Carbon–Nitrogen Bond

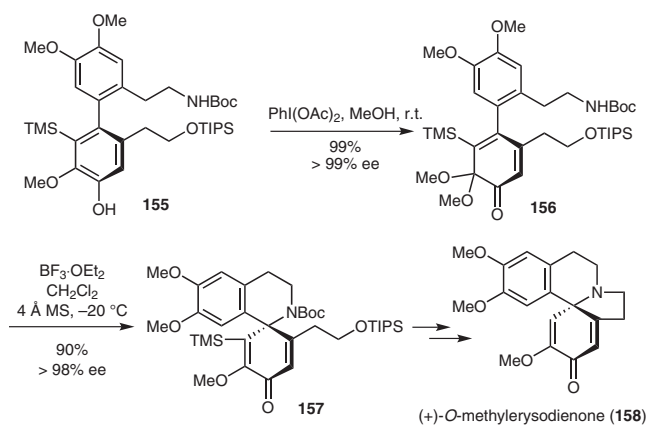
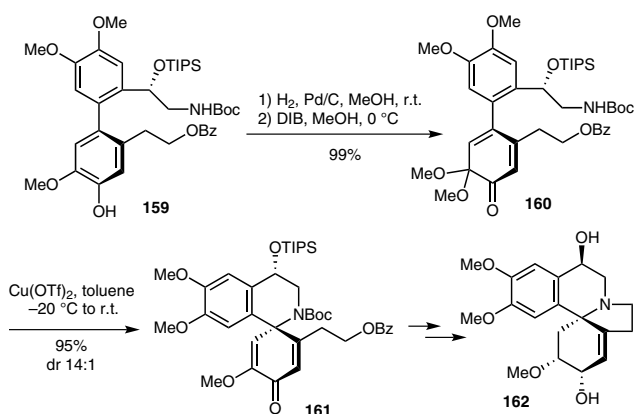
Matsumoto and co-workers<sup>62</sup> relied on 6,6-dimethoxycyclohexa-2,4-dienone derivatives as key intermediates in the synthesis of the erythrinan skeleton, an indolo[7a,1- $\alpha$ ]isoquinoline core common to alkaloids isolated from many plant species of the Erythrina family. These unique tetracyclic amino structures were shown to exhibit curare-like, sedative, hypotensive and central-nervous-system-depressant activities. The atropisomerically pure biphenylic phenol **155** was successfully dearomatized into the desired *o*-quinone monoketal **156** upon treatment with iodobenzene diacetate in methanol at room temperature (Scheme 39).<sup>62</sup> Subsequent Lewis acid promoted aza-spirocyclization converted compound **156** into **157**. Both cyclohexa-2,4-dienone and the spiro-isoquinoline product proved to be enantiomerically pure, thus demonstrating the efficacious transmission of the axial chirality of the biphenyl **155** to the  $\text{sp}^3$ -center chirality of the spirocycle **157** during this focal  $\text{S}_{\text{N}}2'$ -type reaction of the synthesis.<sup>62a</sup> The total synthesis of (+)-*O*-methylerysodienone (**158**)



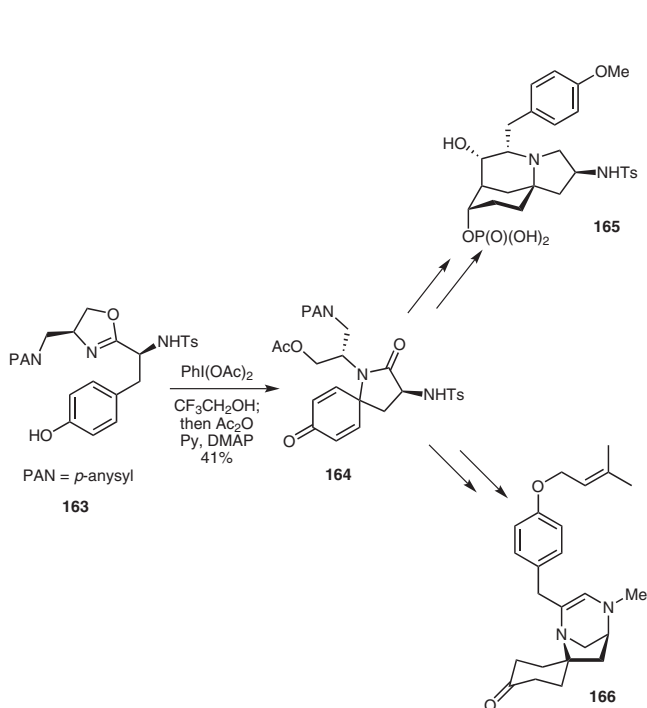
Scheme 38 Total synthesis of (–)-diazonamide A

was next completed through three additional steps.<sup>62b</sup> More recently, this strategy was followed by the same research group to achieve the total synthesis of (+)-11-hydroxyerythratidine (**162**), a C-11 oxygenated erythrinan alkaloid (Scheme 40).<sup>63</sup>

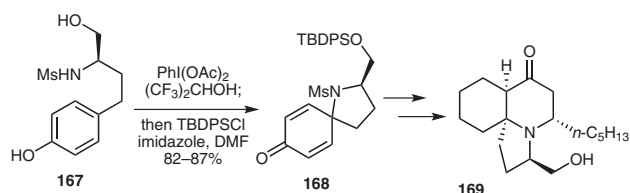
Ciufolini and co-workers reported a synthesis of the cyclohexa-2,5-dienone spiroactam **164** by treating the L-tyrosine-derived oxazoline **163** with iodobenzene diacetate in trifluoroethanol, following immediately with an acetylation (Scheme 41).<sup>64</sup> This spiroactam then served as a common intermediate for the synthesis of (+)-FR901483 (**165**)<sup>8a,65</sup> and (+)-TAN1251C (**166**).<sup>61</sup> Further investigations led them to work with phenolic sulfonamides that turned out to be much better substrates than oxazolines for aza-spirocyclization.<sup>66</sup> For example, sulfonamide **167** was converted into the cyclohexa-2,5-dienone spirocycle **168**, which is the key synthetic intermediate for the total synthesis of the ascidian *Clavelina cylindrica* metabolite (–)-cylindricine C (**169**) (Scheme 42).<sup>67</sup>

Scheme 39 Total synthesis of (+)-*O*-methylerysodienone

Scheme 40 Total synthesis of (+)-11-hydroxyerythratidine

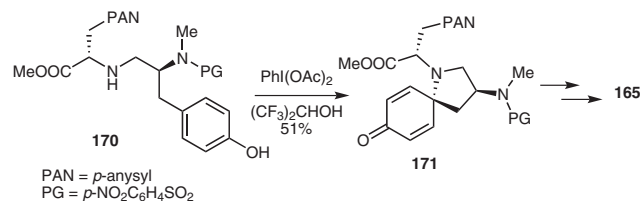


Scheme 41 Synthesis of (+)-FR901483 (165) and (+)-TAN1251C (166)



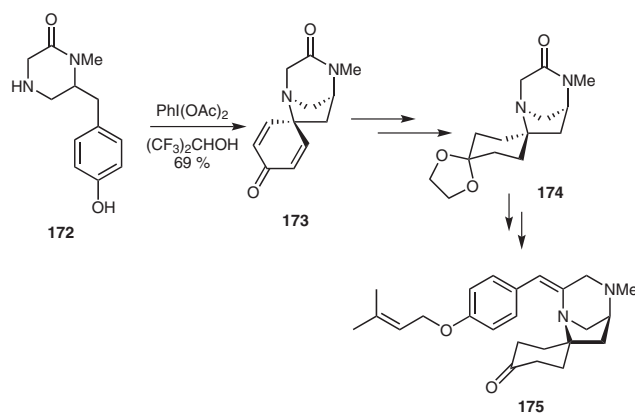
Scheme 42 Synthesis of (-)-cylindricine C (169)

Sorensen and co-workers also accomplished an enantioselective synthesis of the potent immunosuppressant (+)-FR901483 (165) by relying on a  $\lambda^3$ -iodane-mediated oxidative phenol dearomatization reaction to cast the azaspiro system (Scheme 43).<sup>68</sup> In this case, phenolic secondary amine 170 was used as substrate to afford azaspiro[4.5]decadienone 171. Eight additional transformations completed the synthesis of the targeted (+)-FR901483 (165).



Scheme 43 Synthesis of (+)-FR901483 (165)

A similar strategy was used by Honda and colleagues as the key step in the synthesis of (-)-TAN1251A (175), isolated from a culture of *Penicillium thomii* RA-89 (Scheme 44).<sup>69</sup>



Scheme 44 Synthesis of (-)-TAN1251A (175)

## 5 Conclusions

A large number of papers have been published since the beginning of the century on the investigation of phenol dearomatizations, both in natural product synthesis and methodology development. This review highlights some recent advances in the phenol dearomatization reactions, especially those carried out in an enantioselective manner, and the application of dearomatization strategies in com-

plex syntheses. Future research in this area should lead to additional strategies and methods for the use of new and efficient chiral reagents and catalysts which should be of great value to the field of natural products total synthesis.

### Acknowledgment

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