Tetrahedron 66 (2010) 5884–5892

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthetic aspects of the oxidative amidation of phenols

Huan Liang [†], Marco A. Ciufolini [*]

Department of Chemistry, University of British Columbia, 2036 Main Mall, Vancouver, BC, Canada V6T Oxford St., Cambridge, MA 02138, USA

ARTICLE INFO

Article history:
Received 6 April 2010
Received in revised form 6 May 2010
Accepted 7 May 2010
Available online 13 May 2010

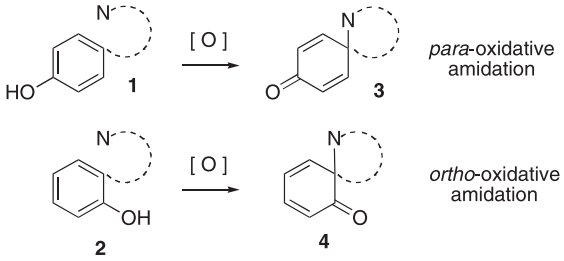
Keywords:
Hypervalent iodine
Oxidative amidation
Phenols
Amides
Alkaloids

ABSTRACT

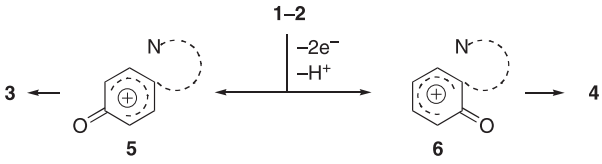
The oxidative amidation of phenols effects the conversion of appropriately substituted phenols into 4-amidodienones ('*para*-oxidative amidation') or 2-amidodienones ('*ortho*-oxidative amidation') by the action of hypervalent iodine reagents. The reagent, (diacetoxyiodo)benzene ('DIB') is especially effective in these transformations. This paper focuses on techniques for the desymmetrization of the dienoes thus obtained, leading to the stereocontrolled creation of *N*-substituted spiro carbons. The methodology creates new opportunities in alkaloid synthesis, as apparent from a number of examples.

1. Introduction

The oxidative amidation of phenols[1] entails the conversion of phenolic substrates such as **1** or **2** into aza-substituted dienones **3** or **4**, respectively. Group N in **1**–**2** represents a suitable nitrogen nucleophile, while in **3**–**4** it stands for an amide-type group. The dashed circles indicate that 'N' may be tethered to the phenolic ring or it may be independent. In the first case, the reaction will be intramolecular, in the second, bimolecular. Hypervalent iodine reagents,[2] especially $PhI(OCOCH_3)_2$ (DIB) but also $PhI(OCOCF_3)_2$ (PIFA), are uniquely competent in oxidative amidation chemistry, which constitutes a special case of oxidative dearomatization of phenols.[3] The reaction may be thought to proceed via electrophilic intermediates **5**–**6**, which are nucleophilically intercepted by the 'N' group (Scheme 2, but see Ref. 3 for a more detailed mechanistic discussion). Extensive precedent exists for the oxidation of a phenol to a transient electrophilic species such as **5** and for its capture by a suitable nucleophile.[4] Indeed, Barton[5] disclosed initial examples of this chemistry beginning in the late 1950s.[6] Over time, more effective oxidants steadily improved the efficiency of these reactions,[7] but it is the advent of hypervalent iodine reagents that permitted a veritable quantum leap in the field. Noteworthy contributions by Kita,[8] Pelter,[9] Barrett,[10] and Wipf,[11] speak eloquently to that effect.



Scheme 1. The oxidative amidation of phenols.



Scheme 2. Mechanistic hypothesis for the oxidative amidation of phenols.

We stress that oxidative amidation reactions proceeding as detailed in Scheme 2 differ at a mechanistic level from related transformations that predate them, and that involve the interaction of an electrophilic nitrogen atom with a nucleophilic aromatic nucleus. Such processes emanated from the work of Kikugawa,[12] Glover,[13] and Prabhakar[14] (Fig.1). Their full synthetic potential became apparent later thanks to the work of Wardrop.[15]

* Corresponding author. Tel.: +1 604 822 2417; fax: +1 604 822 8710; e-mail address: ciufi@chem.ubc.ca (M.A. Ciufolini).
† Current address: Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford St., Cambridge, MA 02138, USA

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.05.020

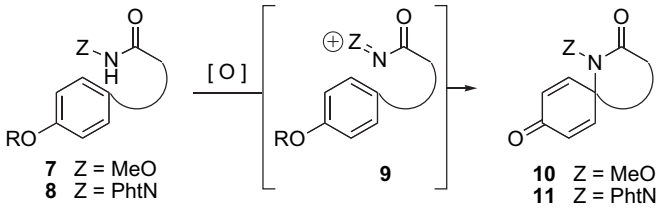
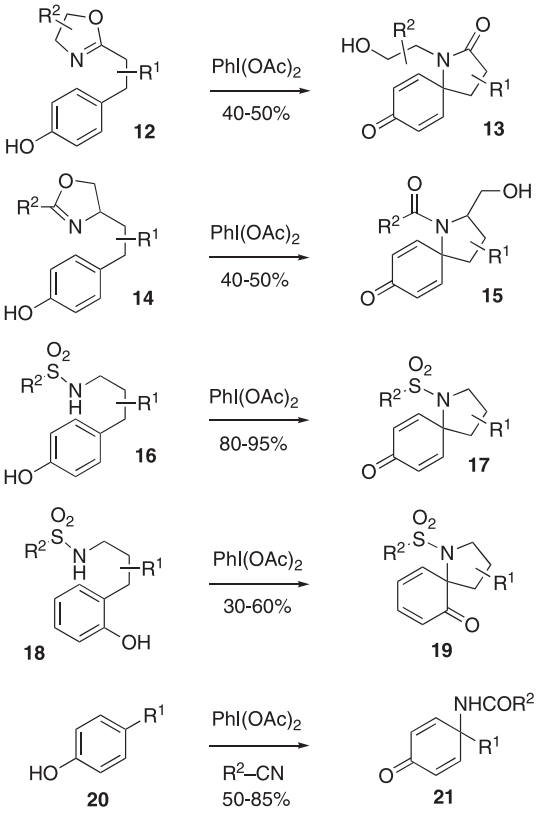


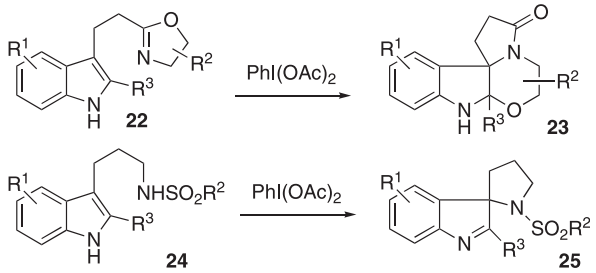
Figure 1. Kikugawa-Glover-type reactions.

Oxidative amidation according to the format of Scheme 1 was developed in our laboratory during research on the synthesis of azaspirocyclic natural products such as FR-901683[16] and TAN-1251C.[17] These efforts have been thoroughly reviewed.[1,18] Accordingly, we eschew further discussion of this chemistry and simply remind the reader that our investigations produced the modes of oxidative amidation outlined in Scheme 3; namely the cyclization



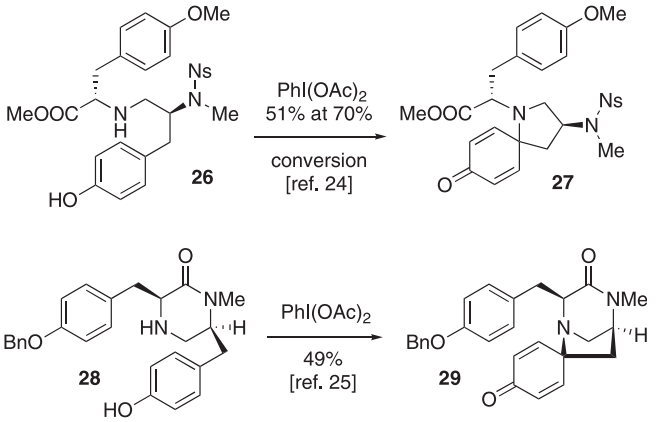
Scheme 3. Modes of oxidative amidation of phenols devised in the authors' laboratory.

of phenolic oxazolines[19] that of *para*- and *ortho*-phenolic sulfonamides,[20] and the bimolecular oxidative amidation of 4-substituted phenols in the presence of nitriles.[21] Related processes include the oxidative cyclization of indolic oxazolines[22] and sulfonamides[23] (Scheme 4). All these reactions are promoted by DIB. Independently,



Scheme 4. Oxidative cyclization of indolic oxazolines and sulfonamides.

Sorensen[24] and Honda[25] developed oxidative cyclizations of phenolic secondary amines (Scheme 5) in connection with their own total syntheses of FR-901683 and of TAN-1251 compounds.



Scheme 5. The Sorensen (Ref. 24) and Honda (Ref. 25) oxidative cyclization of phenolic secondary amines.

This article constitutes a personal account of recent developments in oxidative amidation chemistry. The recognition that the methodology could simplify the assembly of certain nitrogenous architectures to a significant degree, and the desire to adduce tangible proof of this in the form of total syntheses of various alkaloids, has encouraged us to expand the scope of oxidative amidation and to research appropriate refinements of original procedures. Such is the focus of this review.

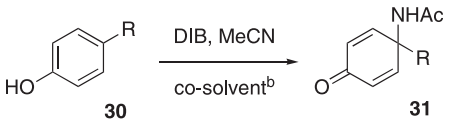
2. Trifluoroacetic acid as a solvent or co-solvent in the oxidative amidation of phenols

Our foremost objective has been the identification of a medium suitable for the conduct of oxidative amidation reactions on large scale. The transformations seen in Schemes 3 and 4 were initially carried out in solvents such as 2,2,2-trifluoroethanol (TFE) or 1,1,1,3,3,3-hexafluoroisopropanol (HFIP). The choice of these fluoroalcohols segued from the work of Kita,[8] who had shown that a number of DIB-promoted phenolic oxidations proceed best in such solvents. Unfortunately, TFE and HFIP are costly, and especially so the latter: the need for fluoroalcohol solvents had to be suppressed.

Bimolecular oxidative amidations stood to benefit the most from the development of a fluoro-alcohol-free protocol. The first-generation method for the conduct of these reactions entailed operating in dilute solutions using 1:1 HFIP/MeCN as the solvent.[21a] This is not an obstacle for runs involving less than 300 mg of substrate, but the cost of HFIP rapidly becomes prohibitive upon scale-up. Attempts to circumvent the problem by working at concentrations higher than about 0.05 M surrendered products contaminated with much polymeric matter, imposing the need for costly, impractical purifications that cause unacceptable losses.

The search for alternative solvents led to the identification of inexpensive trifluoroacetic acid (TFA) as a superb promoter. In virtually all cases examined to date, the reaction proceeded much better in MeCN containing 1.3–1.5 equiv of TFA relative to DIB.[21b] Table 1 compares representative examples of small-scale bimolecular oxidative amidation of phenols under the original and the new conditions. In some cases, a trebling of the yield was achieved. Only phenols incorporating a *para*-alkyl substituent of elevated migratory aptitude, such as an isopropyl group (**30h**) reacted less efficiently. This appears to be due to a more facile dienone/phenol rearrangement of the resultant **31h** in the presence of TFA.[21b] It is worthy of note that DIB was generally superior to the more reactive, but also more costly, PIFA. The reactions were best carried out by slow addition of the phenol to a solution of DIB in MeCN/TFA at room temperature. The examples listed in the table were run to a final

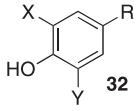
Table 1
Representative bimolecular oxidative amidations of *para*-alkylphenols with DIB in the presence of HFIP or TFA[a]



Entry	R	Yield[c] (%, HFIP)	Yield[c] (%, TFA)
a	CH_2CN	31	86
b	$(CH_2)_3CN$	71	81
c	$(CH_2)_2Br$	<10	57
d	$(CH_2)_2NHTs$	53	59
e	CH_2COOMe	58	86
f	Me	56	89
g	*n*-Pr	54	82
h	*i*-Pr	62	40[d]

[a] All reactions run at room temperature. See the Experimental section for representative procedures.
[b] Co-solvent=HFIP (50% vol/vol) or TFA (1.5 equiv vs DIB).
[c] After column chromatography.
[d] Chromatographic purification also afforded 4-acetamido-3-isopropyl- phenol (product of dienone/phenol rearrangement of **31h**) in 30% yield.

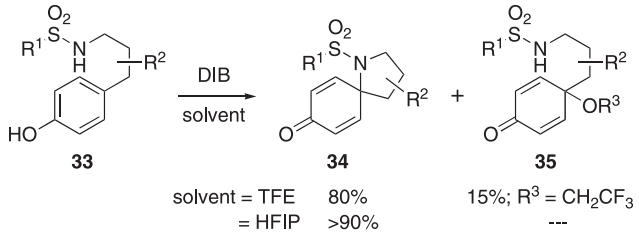
formal concentration of substrate equal to 8–10 mM. Of course, such dilute conditions are inappropriate for preparative work, but we found that the final substrate concentration could be increased up to about 0.15 M with minor erosion of yields. More importantly, the procedure was readily scalable and robust. For instance, compound **31e**, an important intermediate in one of our current projects, was consistently obtained in 65–70% yield from runs involving 10–30 g batches of starting phenol **30e**. On the other hand, phenols **32** (Scheme 6) reacted poorly. Substrates **32a**,**b** incorporate carbonyl groups that compete effectively with external nucleophiles (MeCN in this case) for the presumed electrophilic intermediate **5** (cf. Scheme 2). This shuts down the oxidative amidation pathway in favor of other outcomes.[26] Sterically demanding substituents at the phenolic *para*-position (entry **32d**) are damaging in two ways. First, they probably retard the nucleophilic attack of MeCN onto **5**. Second, after nucleophilic capture (i.e., at the stage of **21**) they are quite prone to dienone/phenol migration. Substitution at both *ortho*-phenolic positions with sterically demanding alkyls (entry **32h**) retards the interaction of DIB with the OH group. Phenols displaying carbonyl groups at the *para*-position (entries **32f**,**g**) were slowly converted into intractable mixtures containing none of the desired amidodienone. Finally, unlike bromide analog **30c**, iodide **32e** degraded rapidly in MeCN solution, possibly due to ionization anchimerically assisted by the electron-rich phenyl group.



entry	R	X	X
a	$(CH_2)_2CO_2Me$	H	H
b	$(CH_2)_2NPht$	H	H
c	$(CH_2)_2I$	H	H
d	*tert*-Bu	H	H
e	I	H	H
f	COOMe	H	H
g	$CON(CH_2)_4$	H	H
h	Me	*tert*-Bu	*tert*-Bu

Scheme 6. Poor substrates for the bimolecular reaction.

A second process that would greatly benefit from a fluoro-alcohol-free procedure is the oxidative spirocyclization of phenolic sulfonamides (Scheme 3, **16**→**17**). In its original form, the reaction was carried out with DIB in neat HFIP.[20] Only in this costly solvent were we able to suppress solvolysis of presumed intermediate **5** (Scheme 2). For instance, oxidative cyclization of **33** with DIB in TFE gave about 15% of **35** in addition to the desired **34**, while in HFIP only **34** was formed (Scheme 7).

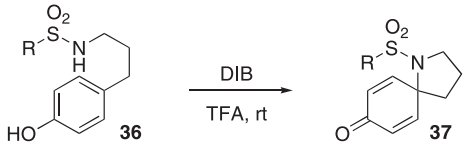


Scheme 7. Oxidative cyclization of sulfonamides in fluoroalcohol solvents.

A thorough study of the reaction[27] determined that one could achieve quantitative spirocyclization by adding the phenol to a solution of DIB in TFA at room temperature, to a final formal concentration of substrate equal to 0.3 M. Yields of purified products around 90% are common. Tables 2 and 3 summarize the results of a representative number of such experiments.[28] The electronic or steric properties of the sulfonyl group appear to have little or no influence on the course of the reaction. For instance, even substrates incorporating sterically demanding sulfonamides react in good yield (cf. **36c**, **36j**, Table 2). By contrast, bulky substituents on the side chain are not tolerated (cf. **38c**, **38g**, Table 3). Groups of small or moderate steric size are acceptable, and even aldehyde **38f** cyclized in high yield.

On a side note, the presence of a sulfonyl group on the N atom of products **37**–**39** raises legitimate concerns about the survival of the sensitive dienone during attempted N-deblocking, and by

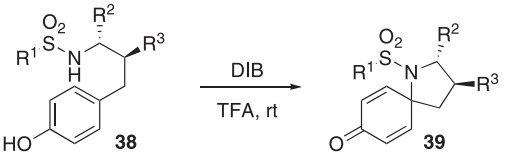
Table 2
Oxidative cyclization of phenolic sulfonamides[a]



Entry	R	Yield[b] %
a	Me	95
b	CF_3	94
c	*t*-Bu	85
d	*cyclo*-C_3H_6	90
e	4-Me–C_6H_4	94
f	2-O_2N–C_6H_4	95
g	4-Br–C_6H_4	93
h	4-NC–C_6H_4	93
i	4-MeO–C_6H_4	85
j	2,4,6-Triisopropylphenyl	83

[a] Representative procedures are provided in the Experimental section.
[b] After column chromatography.

Table 3
Oxidative cyclization of phenolic sulfonamides bearing substituents on the N–Ar tether[a]

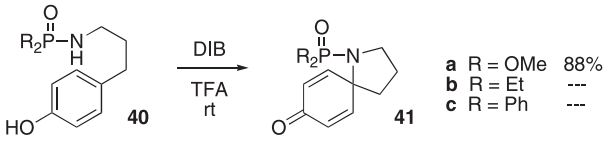


Entry	R^1	R^2	R^3	Yield[b] (%)
a	Me	H	NHTs	83
b	4-MeC_6H_4	H	NHTs	80
c	Me	Bn	H	—
d	Me	H	CH_2OH	95
e	Me	H	CH_2OMe	95
f	Me	H	CHO	94
g	Me	H	$CH_2OTBDPS$	—

[a] Representative procedures are provided in the Experimental Section.
[b] After column chromatography.

extension, about the synthetic usefulness of these spirocyclic intermediates. In fact, facile release of the sulfonyl group may be achieved using Fukuyama nitrosulfonamides.[29] Moreover, in a number of cases the sulfonamide becomes an integral part of the ultimate target, bypassing the need for N-deblocking at the stage of **37**–**39**. Examples will be detailed later.

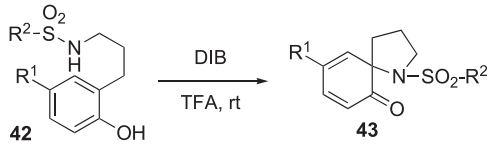
Phenolic phosphoramides such as **40a** also undergo oxidative cyclization[23,27] (Scheme 8), but curiously, structurally similar dialkyl phosphinamides **40b** and **40c** do not.[27]



Scheme 8. Oxidative cyclization of phosphoramides.

The oxidative cyclizations seen thus far occur at the *para*-position of a phenol, but as indicated earlier in Schemes 1 and 2, *ortho*-oxidative amidation is also viable (albeit less efficient). Neat TFA, as opposed to HFIP,[23] proved to be a good solvent for this reaction as well. Table 4 lists representative examples. Yields are lower than in the *para*-mode, normally hovering around 50%, and they drop further if electron-withdrawing groups are present on the aromatic nucleus (entry **b**). Sterically demanding sulfonamides may fail altogether to cyclize (entry **d**).

Table 4
ortho-Oxidative cyclization of phenolic sulfonamides[a]

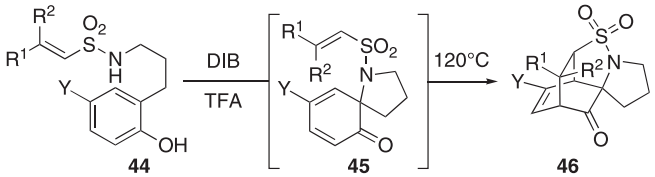


Entry	R^1	R^2	Yield[b] (%)
a	H	Me	60
b	Br	Me	29
c	Me	Me	47
d	H	4-O_2N–C_6H_4	—

[a] Representative procedures are provided in the Experimental section.
[b] After column chromatography.

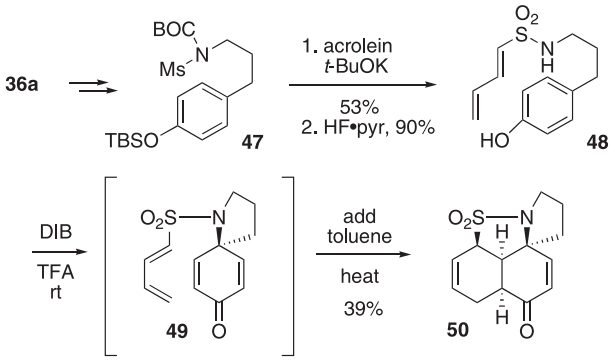
The moderate yields are partly attributable to the sensitive nature of dienones **43**, which, for instance, display poor tolerance of chromatographic operations. On the other hand, the *s-cis* arrangement of double bonds imparts marked Diels/Alder reactivity to these species.[30] This enables the conduct of tandem *ortho*-oxidative cyclizations/intramolecular Diels/Alder (IMDA)[31] reactions of substrates incorporating vinylsulfonamide moieties. Relevant examples appear in Table 5. Notice that the moderate yields obtained with Brr and Me-substituted dienones (entries **b**,**c**) reflects the substantially efficiency of the oxidative cyclization step, and not of the IMDA one. It is also worthy of note that dienic sulfonamides (entries **d**,**e**) expressed only dienophilic reactivity toward the dienone. A related transformation combines a *para*-oxidative cyclization of a 1-butadienyl-sulfonamide with an IMDA event (Scheme 9). Substrates **48** are readily made by Tozer-type condensation[32] on an *N*-Boc methanesulfonamide such as **47** with acrolein. Rather than isolating intermediate **49**, we found it expedient to dilute the reaction mixture resulting from the oxidative step with toluene, and to heat to reflux to trigger the conversion of **49** into **50**.[33]

Table 5
Tandem *ortho*-oxidative cyclization/intramolecular Diels–Alder reaction of phenolic sulfonamides[a]



Entry	R^1	R^2	Y	Yield[b] (%)
a	H	H	H	40
b	H	H	Br	31
c	H	H	Me	43
d	CH_2=CH–	H	H	34
e	H	CH_2=CH–	H	27

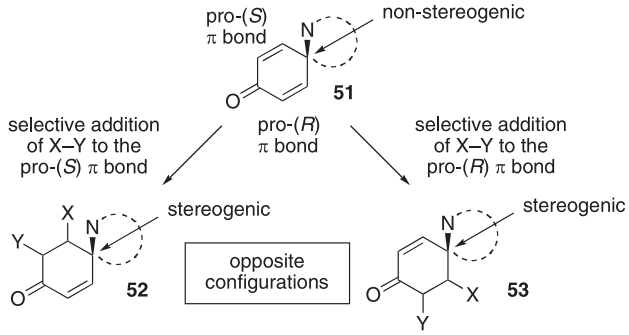
[a] Representative procedures are provided in the Experimental section.
[b] After column chromatography.



Scheme 9. Tandem *para*-oxidative cyclization/IMDA of phenolic sulfonamides.

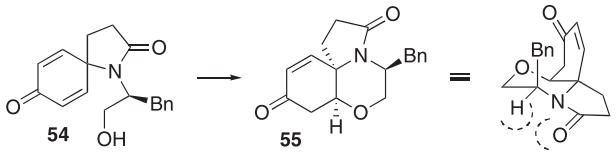
3. Desymmetrization of 'locally symmetrical' dienones obtained by oxidative amidation of phenols

A second objective of considerable import has been the exploration of artifices that permit the desymmetrization of dienones arising through *para*-oxidative cyclization of phenolic sulfonamides. As apparent from Scheme 10, such a transform enables the creation a tetrasubstituted nitrogen-bearing carbon atom of a specific configuration. Generally speaking, the stereoselective assembly of such carbon centers is difficult. In the present case, the stated goal is achievable through the selective addition of a generic agent X–Y either to the pro-(*R*) or the pro-(*S*) π bond of dienone **51**.



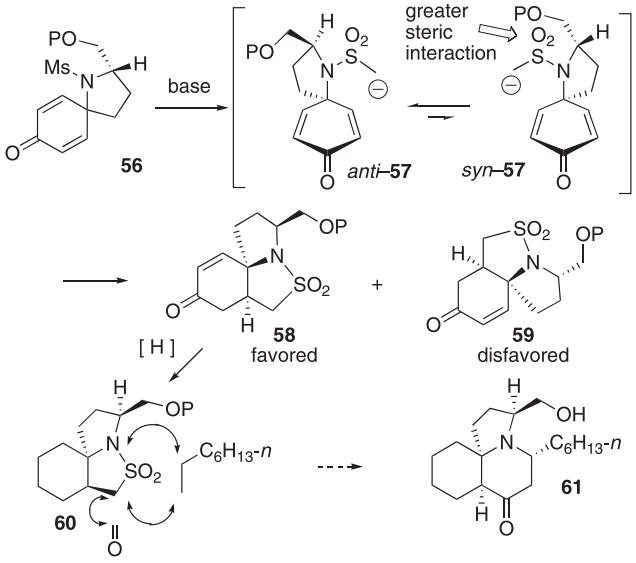
Scheme 10. Dienone desymmetrization.

What inspired us to pursue such an objective is an observation recorded during research on phenolic oxazolines. Specifically, we found that on standing, spirolactam **54** undergoes spontaneous, and highly diastereoselective, Michael cyclization to **55** (Scheme 11).[19b] The stereochemical outcome of this reaction is consistent with the known preference for an axial orientation for substituents occupying a position adjacent to the N atom in *N*-acylpiperidines and related structures, such as the *N*-acylmorpholine segment of **55**.[34] In the present case, this proclivity can be satisfied only if the OH group were to attack the *pro*-(*R*)-double bond of the dienone, thereby establishing the (*R*)-configuration of the spiro center. Thus, one can harness conformational effects to elicit selective reactivity at a particular diastereotopic π system of a 'locally symmetrical' dienone.



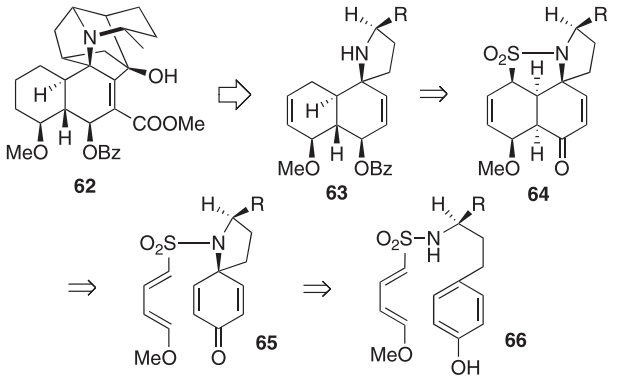
Scheme 11. Stereoselective Michael cyclization of **13d**.

The foregoing principle invites the exploration of previously uncharted strategies in alkaloid synthesis. An example is apparent in our synthesis of (−)-cylindricine C, **60**.[20b,23] A key step in this effort was the desymmetrization of the dienone in **56**. This objective appeared to be attainable by a stereocontrolled Michael cyclization of the anion of the methanesulfonamide (Scheme 12). This reaction was anticipated to favor formation of isomer **58**. Indeed, the metalated sulfonamide, **57**, may add to the enone from what may be described as an *anti* conformation [attack on the *pro*-(*R*) double bond] or a *syn* one [attack on the *pro*-(*S*) double bond], leading, respectively to **58** or **59**. Conformer *syn*-**57** suffers from greater steric compression between sulfonyl and CH_2OP groups. This should favor reaction from *anti*-**57**, translating into preferential formation of **58**. This is indeed the case. Furthermore, consistent with the model of Scheme 12, the selectivity for **58** improved with increasing steric demand of the protecting group P and with diminishing temperature, peaking at a 7:1 ratio when the P=TBDPS variant of **56** was cyclized at −100 °C.[20b,23] The emerging **58** was then reductively elaborated to **60**. The introduction of the remaining fragments of the molecule relied on the anionic chemistry of the cyclic sulfonamide. The C atom of the mesyl group thus became an integral part of the final target, suppressing any need to desulfonylate the sensitive dienone **56**.

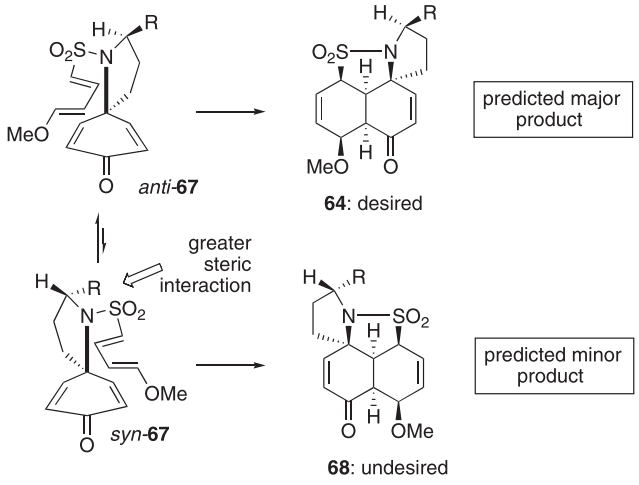


Scheme 12. Strategy for the synthesis of cylindricine.

More recent work has addressed dienone desymmetrization through cycloaddition chemistry. These studies were motivated by a desire to incorporate oxidative amidation technology in possible syntheses of himandrine[35] and of tetrodotoxin.[36] As seen in Scheme 13, the spirocyclic core of himandrine, **62**, contains subunit **63**. One could envisage **64** as a precursor of **63**. Relative to the natural product, **64** displays the *cis*-fusion of the decaline segment, but of course epimerization of the position adjacent to the C=O group at an appropriate juncture would presumably furnish the thermodynamically more favorable *trans*-isomer. The chemistry of Scheme 9 suggests that **64** may be accessible through a tandem oxidative amidation/IMDA reaction of **66**. In particular, the IMDA cyclization of **65** should occur diastereoselectively to furnish **64** for the reason delineated in Scheme 14. This diagram retraces the argument presented earlier in Scheme 12. Thus, the IMDA reaction of **65** may occur from either of two conformers: *anti*-**67** and *syn*-**67**. But conformer *syn*-**67** suffers from a greater degree steric compression between the sulfonyl group and the R substituent; therefore, it is disfavored relative to *anti*-**67**. Diels/Alder cyclization is thus more likely to occur from the latter, leading to the selective formation of the correct product **64**.

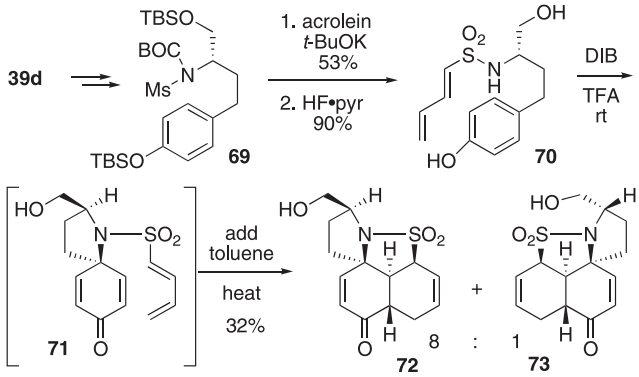


Scheme 13. Approach to the himandrine core.



Scheme 14. Predicted course of the IMDA step.

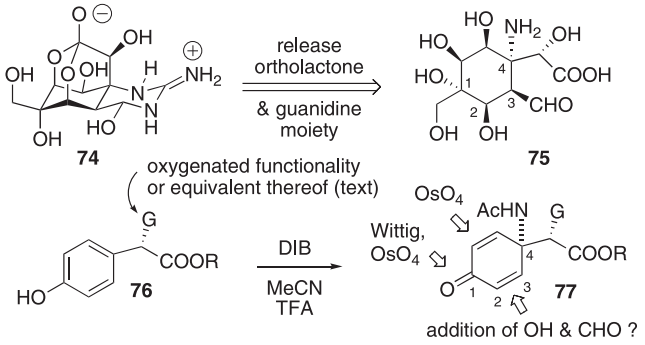
An investigation designed to address the foregoing hypothesis started with **39d** (Scheme 15), wherein the configuration of the N-bearing carbon is opposite that of **66**. But of course, here we are concerned with issues of diastereoselectivity, so the absolute configuration of the substrate is immaterial. Tozer condensation installed the dienic sulfonamide. A subsequent one-pot oxidative cyclization/IMDA sequence surrendered an 8:1 mixture of **72**



Scheme 15. Dienone desymmetrization via intramolecular Diels/Alder reaction.

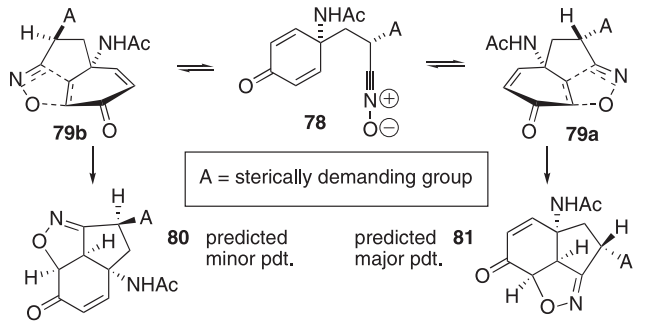
(desired)[37] and **73** in a moderate 32% yield. Interestingly, the products were obtained as the *trans*-fused isomers. Evidently, epimerization of the primary Diels/Alder adduct had occurred in situ, probably through acid-catalyzed enolization of the enone. Four new stereogenic carbons, including a spiro center, were thus created stereoselectively in a single operation.

The bimolecular oxidative amidation of phenols offers perhaps the widest range of possibilities in the synthesis of nitrogenous natural products. Tandem oxidative reactions that might elaborate a simple starting material into a product of considerable molecular complexity serve to multiply such tactical opportunities. To illustrate the point with a somewhat extreme example, imagine releasing both ortholactone and guanidine moieties in the molecule of tetrodotoxin, **74** (Scheme 16). The resultant **75** could be obtained from **77**, which is the product of oxidative amidation of **76** (G=oxygenated functionality or forerunner thereof). The 'northwestern' OH tetrad in **75** could be installed by osmylation chemistry once the keto group of **77** has been transformed into an exomethylene (Wittig reaction). A more interesting problem relates to the introduction of the C-2 OH and the C-3 CHO groups selectively onto the *pro-S* double bond of **77**, an operation that again would result in desymmetrization of a locally symmetrical dienone.



Scheme 16. Retrosynthetic hypothesis for tetrodotoxin.

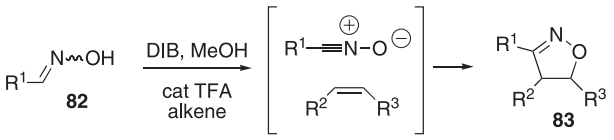
The simultaneous introduction of an OH and an equivalent of the formyl group—in the form of CN unit—may be achieved by an intramolecular nitrile oxide cycloaddition (INOC)[38] followed by isoxazoline cleavage. Selectivity for the *pro-S* double bond could be secured through a new incarnation of the principle delineated in Schemes 12 and 14. To illustrate, suppose that substituent A in nitrile oxide **78** (Scheme 17) were a sterically demanding group with a reactivity profile conducive to a subsequent fragmentation of the nascent isoxazoline ring. The INOC event can occur either from conformer **79a** or from **79b**. In the latter, the bulky A moiety is forced within the concavity of the developing bowl-shaped cycloadduct, thereby engendering significant steric congestion, whereas cyclization from **79a** occurs in such a way that A remains external to the developing tricyclic framework. This alleviates nonbonding interactions and promotes selectivity in favor of cycloadduct **81**.

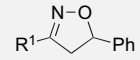
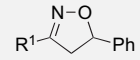
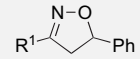
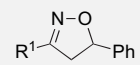
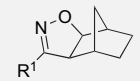
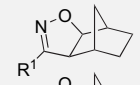
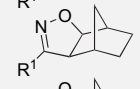
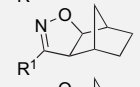
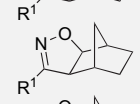
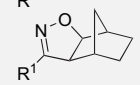
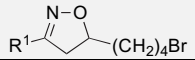


Scheme 17. Predicted course of the INOC reaction of **78**.

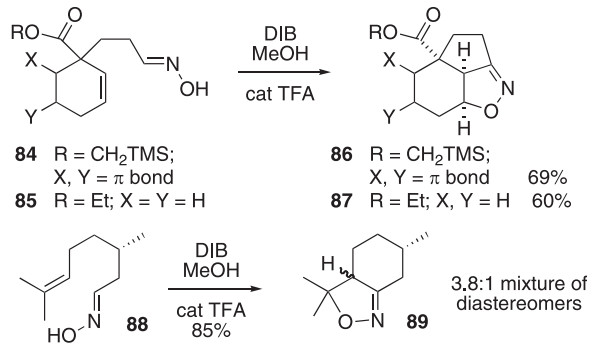
Considering that nitrile oxides are available by oxidation of oximes, we questioned whether DIB could promote a tandem oxidative amidation/INOC sequence of appropriately tailored oximinophenols. The success of this process is conditional to the occurrence of the oxidative amidation step at a rate much faster than that of oxime oxidation. Indeed, the nascent nitrile oxide must undergo instant intramolecular capture by the preformed dienone, otherwise it will rapidly dimerize. We knew that the oxidative amidation of the phenol occurs very rapidly (minutes) but we had no knowledge of whether DIB (or PIFA) would oxidize oximes to nitrile oxides, and at which rate. We were also cognizant that the conversion of oximes into nitrile oxides with PhIO[39] and $PhICl_2$[40] had been documented, but these reagents are unsuitable for oxidative amidation chemistry. Fortunately, DIB proved to be quite effective for the oxidation of oximes into nitrile oxides.[41] The reaction was best run in MeOH containing a catalytic amount of TFA. Pertinent examples appear in Table 6, while Scheme 18 illustrates three cases of INOC processes. Happily, oxime oxidation was relatively slow (ca. 1 h at rt), engendering optimism for the feasibility of the tandem sequence. Indeed, exposure of **90** to DIB in MeOH/TFA produced **91** in 51% yield,[42] while treatment with DIB in MeCN/TFA furnished **92** in 71% yield (Scheme 19). More importantly, (±)-**93** reacted with DIB in MeCN/TFA to afford (±)-**94** in moderate yield (44%), but as a single diastereomer. The stereochemical outcome of this reaction is consistent with the logic of Scheme 17.

Table 6
DIB oxidation of oximes to nitrile oxides and cycloaddition thereof to alkenes[a]

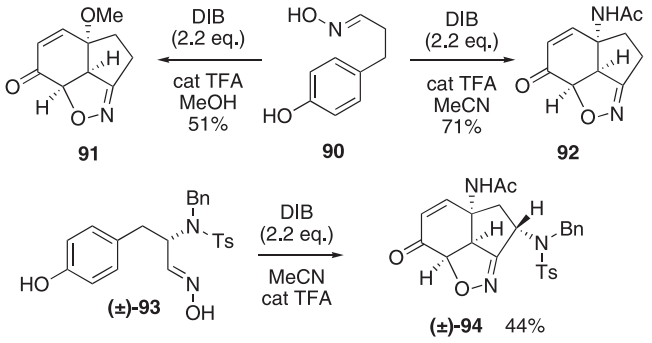


Entry	R^1	Alkene	Product type	Yield[b] (%)
a	Ph			71
b	3-O_2N–C_6H_4			91
c	*n*-C_5H_{11}			74
d	$Ph(CH_2)_2$			63
e	Ph			95
f	3-O_2N–C_6H_4			77
g	*n*-C_5H_{11}			91
h	$Ph(CH_2)_2$			79
i	*t*-Bu			75
j	4-MeO–C_6H_4			90
k	Ph			83

[a] Representative procedures are provided in the Experimental section.
[b] After column chromatography.

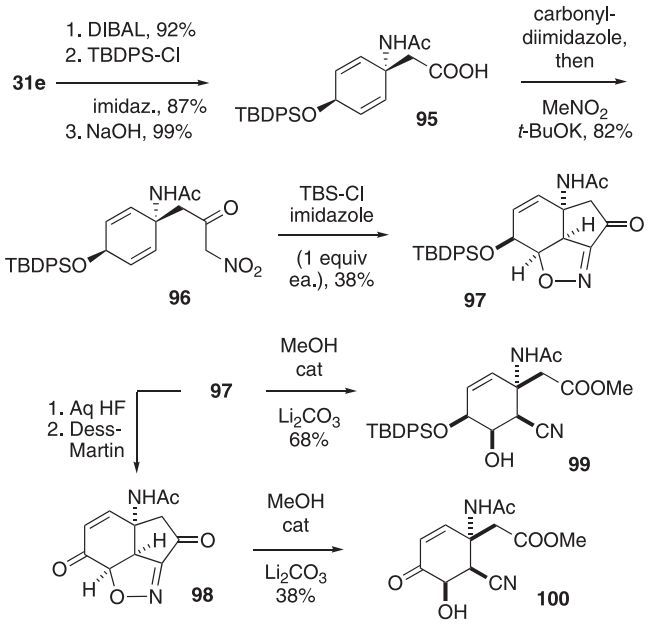


Scheme 18. DIB-promoted INOC reactions.



Scheme 19. Tandem oxidative dearomatization/INOC reaction of phenols promoted by DIB.

A possible mode of isoxazoline fragmentation was demonstrated by the use of intermediate **97**, which was prepared from dienone **31e** as detailed in Scheme 20. A key step in this sequence was a Torssell cyclization[43] of nitroketone **96**. Treatment of **97** or its



Scheme 20. Keto-isoxazoline fragmentation with methanolic Li_2CO_3.

congener **98** with Li_2CO_3/MeOH provided **99** and **100**, respectively.[44] This observation suggests that an enantioselective route to **99**–**100**, and consequently to **74**, may be possible starting with enantioenriched **93**, available in turn from L-tyrosine. Oxidative conversion into scalemic **94**, elaboration of the *N*-benzylsulfonamide into a carbonyl group, and ensuing isoxazoline fragmentation would deliver nonracemic **99**–**100**. Such a goal is being actively pursued as of this writing.

4. Conclusion

This article has highlighted key aspects of the oxidative amidation of phenols, a technique that encompasses a suite of reactions devised in our laboratory in response to specific synthetic problems. The new methodology provides access to valuable enantioenriched building blocks for nitrogenous substances. Numerous applications in natural product synthesis and in medicinal chemistry may be envisaged. We emphasize that the driving force behind this effort was—and remain—the élan toward efficient syntheses of architecturally intriguing natural products through previously unexplored strategies.

5. Experimental section

5.1. Experimental protocols

Unless otherwise noted, NMR spectra were recorded in $CDCl_3$ at 300 MHz for ^1H and 75 MHz for ^{13}C. Chemical shift (δ) are in parts per million, and coupling constants (J) are in hertz. Multiplicities are reported as: 's' (singlet), 'd' (doublet), 't' (triplet), 'q' (quartet), 'm' (multiplet), 'br' broad. IR spectra (cm^{-1}) were measured on a Perkin/Elmer 1720-X FTIR from $CHCl_3$ solutions. Low- and high resolution mass spectra (m/e) were obtained in the CI (isobutane), EI (70 eV), LSIMS (Cs^+), or ESI mode, as specified. Optical rotation were measured in $CHCl_3$, with concentrations (c) expressed in g/100 mL. All reactions were run under argon, and monitored by TLC. Reagents and solvents were commercial products and were used as received, except: THF (freshly dist. Na/benzophenone); CH_2Cl_2, Et_3N (dist. CaH_2).

5.2. Representative procedure for small-scale bimolecular oxidative amidation of phenols using DIB in MeCN/TFA: compound 31e[21b]

A MeCN (20 mL) solution of **30e** (53 mg, 320 μmol, 1 equiv) was added over 10 min (syringe pump) to a solution of DIB (123 mg, 380 μmol, 1.2 equiv) and TFA (47 mg, 400 μmol, 1.3 equiv vs DIB) in MeCN (20 mL), at room temperature with good stirring. The final concentration was equal to 8 mmol of substrate/L. At the end of the addition, the solution was light yellow. Solid $NaHCO_3$ (107 mg, 1.3 mmol, 4 equiv) was added and the mixture was stirred for 15 min, then it was filtered through Celite and concentrated. Chromatographic purification (1% MeOH in EtOAc) gave 61 mg (280 μmol, 86%) of **31e**, off-white solid, mp 100–102 °C.

5.3. Representative procedure for preparative-scale bimolecular oxidative amidation of phenols using DIB in MeCN/TFA: compound 31e[21b]

A MeCN (20 mL) solution of **30e** (9.1 g, 55.0 mmol, 1 equiv) was added over 3 h (syringe pump) to a solution of DIB (23.9 g, 74.0 mmol, 1.3 equiv) and TFA (6.4 mL, 82.5 mmol, 1.5 equiv vs DIB) in MeCN (480 mL), at rt with good stirring (final concentration=0.11 M). The progress of the reaction was monitored by ^1H NMR. At the end of the addition, the solution had become light brown. The mixture was evaporated (rotavap) and the residue was taken up with toluene (10 mL). The suspension was concentrated (rotavap) and the procedure was repeated to azeotropically remove all residual TFA. The brown residue was filtered through a silica pad (45 g) using first 300 mL of Et_2O (removal of brown tar and iodobenzene) and then 300 mL Et_2O/CH_3CN (2.5:1, elution of product).

Concentration (rotavap) afforded a brown solid, which was re-filtered through fresh silica gel using the same procedure (complete removal of polymeric material). The solid residue was taken up with 20 mL of EtOAc and kept at −20 °C for 5 h. The resulting precipitate was essentially pure product. Concentration of the mother liquor afforded a second crop of crystalline material. A total of 8.2 g (36.3 mmol, 66.0%) of product was obtained. A sample recrystallized from 2:1 EtOAc/hexanes had mp 100–102 °C. ^{1}H (acetone-d_6): 7.54 (br, 1H); 7.17 (d, J=10.3, 2H); 6.15 (d, J=10.3, 2H); 3.62 (s, 3H); 3.02 (s, 2H); 1.88 (s, 3H). ^{13}C (acetone-d_6): 184.3; 169.4; 169.0; 148.8; 128.1; 53.3; 51.1; 41.7; 22.5. IR: 3200, 1738, 1666. HRMS: calcd for $C_{11}H_{13}NO_4Na$ $[M+Na]^+$ 246.0737; found 246.0742. EA calcd for $C_{11}H_{15}NO_4$ C 59.19, H 5.87, N 6.27; found C 58.96, H 5.80, N 6.18.

5.4. Representative procedure for *para*-oxidative cyclization of phenolic sulfonamides with DIB in TFA: compound 39d[27]

Solid DIB (1.5 g, 4.8 mmol, 1.1 equiv) was added slowly and portionwise at rt to a well stirred 0.3 M solution of **38d** (1.0 g, 4.4 mmol, 1.0 equiv) in TFA. Upon completion of the reaction (TLC), the mixture was evaporated (rotavap). Silica gel (ca. 30 g) chromatography of the residue (1% MeOH in AcOEt) afforded 942 mg (4.2 mmol, 95%) of **39d**, low-melting, pale yellow solid, $[\alpha]_D^{22}$ −20.3 (*c* 1.10, acetone). IR: 3417; 2929; 1667; 1328. ^{1}H (acetone-d_6): 7.26 (dd, J=9.8, 3.0, 1H); 7.04 (dd, J=9.9, 3.0, 1H); 6.16 (dd, J=9.9, 2.3, 1H); 6.10 (dd, J=10.1, 2.1, 1H); 4.15 (br, 1H); 4.12–4.04 (m, 1H); 3.82–3.72 (m, 2H); 3.00 (s, 3H); 2.61–2.33 (m, 2H); 2.24–2.13 (m, 1H); 1.99–1.89 (m, 1H). ^{13}C (acetone-d_6): 184.4; 152.7; 148.7; 127.7; 127.3; 64.2; 63.9; 63.1; 39.3; 37.7; 26.5. HRMS: calcd for $C_{11}H_{15}NO_4SNa$ $[M+Na]^+$ 280.0619; found 280.0619.

5.5. Representative procedure for *para*-oxidative cyclization of phenolic phosphoramides with DIB in TFA: compound 41[27]

The above procedure was applied to the oxidative cyclization of **40**, whereupon compound **41**, pale yellow oil, was obtained in 88.0% yield after chromatography (100:6 EtOAc/MeOH). IR: 3450; 1662; 1251; 1016. ^{1}H: H NMR: 6.84 (d, J=10.1, 2H); 6.16 (d, J=10.1, 2H); 3.66 (s, 3H); 3.62 (s, 3H); 3.54–3.47 (m, 2H); 2.09–2.01 (m, 4H). ^{13}C: 185.3; 151.5; 127.1; 62.0 overlapping with 61.9; 53.43 overlapping with 53.36; 48.94 overlapping with 48.87; 40.4, 40.3; 25.1, 25.0. HREIMS: calcd for $C_{11}H_{16}NO_4P$ 257.0817 $[M]^+$; found 257.0821.

5.6. Representative procedure for *ortho*-oxidative cyclization of phenolic sulfonamides with DIB in TFA: compound 43a[27]

Solid DIB (151 mg, 470 μmol, 1.1 equiv) was added slowly at rt to a well stirred solution of **42a** (98 mg, 427 μmol, 1 equiv) in TFA (1.3 mL). Upon completion of the reaction, the mixture was evaporated (rotavap). Chromatography of the residue (2:1 EtOAc/hexanes) afforded 58 mg (255 μmol, 60%) of **43a**, pale yellow oil. IR: 1655; 1318; 1147. ^{1}H: 7.01 (ddd, J=9.8, 5.8, 1.7, 1H); 6.55 (ddd, J=9.6, 1.7, 0.8, 1H); 6.16 (ddd, J=9.6, 5.8, 1.0, 1H); 6.05 (dt, J=9.8, 0.8, 1H); 3.78–3.57 (m, 2H); 2.96 (s, 3H); 2.27–1.97 (m, 4H). ^{13}C: 201.6; 146.1; 142.0; 124.9; 119.8; 73.2; 49.4; 39.7; 39.5; 22.8. HRMS: calcd for $C_{10}H_{13}NO_3SNa$ $[M+Na]^+$ 250.0514; found 250.0512.

5.7. Representative procedure for tandem *ortho*-oxidative cyclization/IMDA of phenolic sulfonamides: compound 46a[33]

Solid DIB (1.1 equiv) was added slowly and portionwise to a well stirred 0.3 M TFA solution of **44a** (1 equiv). The reaction was monitored by TLC and upon disappearance of the substrate the mixture was diluted with twice the volume of toluene (final formal concentration of substrate=0.1 M) and heated to reflux. Upon the completion of the reaction (several hours), the mixture was evaporated (rotavap). Silica gel chromatography of the residue (1:1:3 EtOAc/hexanes/toluene) afforded **46a** (40%) as a pale yellow solid, mp 121–122 °C. IR: 1735; 1304; 1133. ^{1}H (acetone-d_6): 6.55–6.48 (m, 1H); 6.39–6.32 (m, 1H); 3.77–3.63 (m, 2H); 3.47–3.38 (m, 2H); 3.04–2.92 (m, 1H); 2.87 (dt, J=14, 2.5, 1H); 2.32–2.19 (m, 1H); 2.16–1.93 (m, 3H); 1.64–1.54 (m, 1H). ^{13}C (acetone-d_6): 202.4; 134.2; 130.0; 71.2; 56.8; 46.3; 44.8; 43.9; 30.8; 27.2; 27.0. HRMS: calcd for $C_{11}H_{13}NO_3SNa$ $[M+Na]^+$ 262.0514; found 262.0515.

5.8. Representative procedure for tandem *para*-oxidative cyclization/IMDA of phenolic sulfonamides: compound 72[33]

Solid DIB (70 mg, 216 μmol) was added slowly at rt to a 0.2 M TFA (0.9 mL) solution of **70** (54 mg, 180 μmol) at room temperature. After 30 min, toluene (2.5 mL) was added and the mixture was heated to reflux for 10 h, whereupon the IMDA reaction was complete. The mixture was evaporated to dryness (rotavap) and the residue was chromatographed over silica gel (ca. 3 g) with 3:1 EtOAc/hexanes to give 17 mg (58 μmol, 32%) of an 8:1 a mixture of **72** and **73**. A fraction enriched in **72** deposited crystals suitable for an X-ray study that confirmed the structure. Compound **72**. IR: 3290; 1709; 1358; 1219. ^{1}H: 6.72 (d, J=10.3, 1H); 6.41–6.32 (m, 1H); 6.13 (d, J=10.3, 1H); 5.93–5.85 (m, 1H); 4.35–4.23 (m, 1H); 3.99–3.91 (m, 1H); 3.86 (dd, J=11.8, 2.8, 1H); 3.68–3.46 (m, 2H); 2.77–2.59 (m, 2H); 2.38–1.88 (m, 6H). ^{13}C: 197.8; 145.1; 135.7; 128.1; 115.3; 66.9; 66.0; 64.6; 58.0; 40.7; 40.4; 40.0; 26.0; 24.3. HRMS: calcd for $C_{14}H_{17}NO_4SNa$ $[M+Na]^+$ 318.0776; found 318.0782.

5.9. Representative procedure for DIB oxidation of oximes to nitrile oxides with bimolecular capture: compound 83a[41]

A solution of benzaldoxime (**82a**, 109 mg, 1 mmol) in MeOH (1 mL) was added slowly (syringe pump, 1 h) at room temperature to a stirred solution of DIB (354 mg, 1.1 equiv) and styrene (115 mg, 126 μL, 1.1 equiv) in MeOH (2 mL) containing TFA (15 μL). A white precipitate formed immediately and then slowly redissolved as the reaction progressed. Upon consumption of starting oxime (TLC, ca. 1 h), the mixture was evaporated (rotavap). The residue was purified by column chromatography (step gradient: 5%–10%–20% ethyl acetate/hexanes) to afford 158 mg (71%) of the known isoxazoline **83a**, colorless crystals, mp 72–73 °C.[45] ^{1}H: 7.70 (m, 2H), 7.40 (m, 8H), 5.75 (dd, J=11.2, 8.4, 1H), 3.79 (dd, J=16.4, 11.2, 1H), 3.35 (dd, J=16.4, 8.2, 1H). ^{13}C: 156.2, 141.1, 130.3, 129.6, 128.9, 128.9, 128.3, 126.9, 126.0, 82.7, 43.3. ESI-MS: 224 $[M+H]^+$, 246 $[M+Na]^+$. HRMS: calcd for $C_{15}H_{13}NONa$ $[M+Na]^+$ 246.0895; found 246.0894.

5.10. Representative procedure for tandem DIB oxidation of oximes to nitrile oxides/INOC: compound 87[41]

A solution of oxime **85** (99 mg, 440 μmol) in MeOH (1 mL) was slowly added to a solution of DIB (156 mg, 484 μmol) and TFA (15 μL) in MeOH (1 mL). The mixture was stirred at room temperature for 45 min, then it was quenched with 5% aqueous $NaHCO_3$ (1 mL) and 10% aqueous $NaHSO_3$ (1 mL), and extracted with ether (3×5 mL). The combined extracts were washed with water (2×7 mL), dried ($MgSO_4$), filtered, and evaporated (rotavap). Purification of the residue by flash chromatography (20% EtOAc in hexanes) afforded **87** (58 mg, 60%) as a colorless oil. ^{1}H: 4.74 (dt, J=9.0, 8.1, 1H), 4.17 (q, J=4.2, 2H), 4.07 (d, J=9.0, 1H), 2.64–2.45 (m, 3H), 2.34–2.26 (m, 1H), 2.16–2.09 (m, 1H), 2.04–1.93 (m, 1H), 1.54–1.44 (m, 1H), 1.41–1.19 (m, 2H), 1.26 (t, J=7.2, 3H). ^{13}C: 175.2, 170.7, 77.8, 61.2, 58.8, 48.5, 40.5, 30.5, 28.5, 19.8, 18.6, 14.2. ESI-MS: 446.3 $[M+Na]^+$. HRMS calcd for $C_{12}H_{17}NO_3Na$ $[M+Na]^+$ 246.1106; found 246.1106.

5.11. Representative procedure for tandem bimolecular oxidative amidation—INOC of phenolic oximes: compound 92[41]

A solution of **90** (62 mg, 375 μmol) in MeCN (5 mL) was slowly added at rt to a well stirred solution of DIB (226 mg, 825 μmol) and TFA (15 μL) in acetonitrile (20 mL). The reaction was complete after 1 h at room temperature. The mixture was evaporated (rotavap) and the residue was purified by flash column chromatography (step gradient: 25%–50%–100% ethyl acetate/hexanes) to afford 58 mg (266 μmol, 71%) of **126**, colorless crystals, mp 162–163 °C. ^{1}H (acetone-d_6): 7.84 (br s, 1H), 6.41 (dd, J=10.3, 2.0, 1H), 6.15 (dd, J=10.3, 0.5, 1H), 4.72 (dd, J=9.7, 0.5, 1H), 4.28 (ddd, J=9.7, 2.0, 1.6, 1H), 2.69 (m, 1H), 2.64 (m, 2H), 2.37 (m, 1H), 1.84 (s, 1H). ^{13}C (acetone-d_6): 191.1, 170.4, 169.3, 146.5, 132.7, 79.8, 63.6, 53.5, 42.2, 42.1, 23.1, 19.3. ESI-MS: 243.3 $[M+Na]^+$. HRMS calcd for $C_{11}H_{12}N_2O_3Na$ $[M+Na]^+$ 243.0746; found 243.0752.

Acknowledgements

We thank the University of British Columbia, the Canada Research Chair Program, NSERC, CIHR, CFI, BCKDF, and MerckFrosst Canada for support of our research. Portions of this work were carried out at the Ecole Supérieure de Chimie, Physique, Electronique de Lyon and the Université Claude Bernard Lyon 1, France, with support from the CNRS and the MRT. H.L. is the recipient of a Laird Graduate Fellowship.

References and notes

1. Previous review: Ciufolini, M. A.; Braun, N. A.; Canesi, S.; Ousmer, M.; Chang, J.; Chai, D. *Synthesis* **2007**, 3759.
2. Reviews: (a) Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893; (b) Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3656; (c) Hamamoto, H.; Anilkumar, G.; Tohma, H.; Kita, Y. *Chem.—Eur. J.* **2002**, *8*, 5377; (d) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523; (e) Moriarty, R. M. *Org. React.* **2001**, *57*, 327; (f) Varvogolis, A. *Hypervalent Iodine in Organic Synthesis*; Academic: San Diego, CA, 1997; (g) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **1996**, *96*, 1123.
3. Review: Pouységu, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 2235.
4. Yamamura, S. In *Chemistry of Phenols*; Rappoport, Z., Ed.; John Wiley & Sons: Chichester, UK, 2003; Vol 2, pp 1153–1346.
5. (a) Barton, D. H. R.; Deflorin, A. M.; Edwards, O. E. *J. Chem. Soc.* **1956**, 530; (b) Barton, D. H. R.; Kirby, G. W. *J. Chem. Soc.* **1962**, 806 Review; (c) Barton, D. H. R. *Pure Appl. Chem.* **1964**, *9*, 35.
6. Significant contributions by other groups: (a) Kametani, T.; Fukumoto, K. *Yakugaku Kenkyu* **1963**, *35*, 426; (b) Scott, A. I.; McCapra, F.; Buchanan, R. L.; Day, A. C.; Young, D. W. *Tetrahedron* **1965**, *21*, 3605.
7. For a summary of the various oxidants that have been employed for the activation of phenols see: Rodríguez, S.; Wipf, P. *Synthesis* **2004**, 2767.
8. (a) Tamura, Y.; Yakura, T.; Haruta, J.; Kita, Y. *J. Org. Chem.* **1987**, *52*, 3927; (b) Kita, Y.; Tohma, H.; Kikuchi, K.; Inagaki, M.; Yakura, T. *J. Org. Chem.* **1991**, *56*, 435; (c) Kita, Y.; Fujioka, H. *Pure Appl. Chem.* **2007**, *79*, 701.
9. Pelter, A.; Elgendy, S. *Tetrahedron Lett.* **1988**, *29*, 677.
10. Barret, R.; Daundon, M. *Tetrahedron Lett.* **1991**, *32*, 2133.
11. (a) Wipf, P.; Jung, J.-K. *Chem. Rev.* **1999**, *99*, 1469; (b) Wipf, P.; Spencer, S. R. *J. Am. Chem. Soc.* **2005**, *127*, 225 See also Ref. 7.
12. (a) Kikugawa, Y.; Kawase, M. *J. Am. Chem. Soc.* **1984**, *106*, 5728; (b) Kawase, M.; Kitamura, T.; Kikugawa, Y. *J. Org. Chem.* **1989**, *54*, 3394; (c) Kikugawa, Y.; Kawase, M. *Chem. Lett.* **1990**, 581; (d) Kikugawa, Y.; Shimada, M.; Matsumoto, K. *Heterocycles* **1994**, *37*, 293; (e) Kikugawa, Y.; Nagashima, A.; Sakamoto, T.; Miyazawa, E.; Shiiya, M. *J. Org. Chem.* **2003**, *68*, 6739.
13. (a) Glover, S. A.; Goosen, A.; McCleland, C. W.; Schoonraad, J. L. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2255; (b) Glover, S. A.; Scott, A. P. *Tetrahedron* **1989**, *45*, 1763.
14. (a) Clemente, D.-T.; Lobo, A. M.; Prabhakar, S.; Marcelo-Curto, M. J. *Tetrahedron Lett.* **1994**, *35*, 2043 Review; (b) Prata, J. V.; Clemente, D.-T. S.; Prabhakar, S.; Lobo, A. M.; Mourato, I.; Branco, P. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 513.
15. (a) Wardrop, D. J.; Burge, M. S. *J. Org. Chem.* **2005**, *70*, 10271; (b) Wardrop, D. J.; Zhang, W.; Landrie, C. L. *Tetrahedron Lett.* **2004**, *45*, 4229; (c) Wardrop, D. J.; Burge, M. S. *Chem. Commun.* **2004**, 1230; (d) Wardrop, D. J.; Landrie, C. L.; Ortiz, J. A. *Synlett* **2003**, 1352; (e) Wardrop, D. J.; Burge, M. S.; Zhang, W.; Ortiz, J. A. *Tetrahedron Lett.* **2003**, *44*, 2587; (f) Wardrop, D. J.; Zhang, W. *Org. Lett.* **2001**, *3*, 2353; (g) Wardrop, D. J.; Basak, A. *Org. Lett.* **2001**, *3*, 1053.
16. Ousmer, M.; Braun, N. A.; Ciufolini, M. A. *Org. Lett.* **2001**, *3*, 765 See also Refs. 1,17,18.
17. Ousmer, M.; Braun, N. A.; Bavoux, C.; Perrin, M.; Ciufolini, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 7534 See also Refs. 1,18.
18. (a) Ciufolini, M. A.; Canesi, S.; Ousmer, M.; Braun, N. A. *Tetrahedron* **2006**, *62*, 5318; (b) Ciufolini, M. A.; Liang, H. In *Biomimetic Organic Synthesis*; Poupon, E., Nay, B., Eds.; Wiley-VCH: Weinheim, 2010.
19. (a) Braun, N. A.; Ciufolini, M. A.; Peters, K.; Peters, E.-M. *Tetrahedron Lett.* **1998**, *39*, 4667; (b) Braun, N. A.; Ousmer, M.; Bray, J. D.; Bouchu, D.; Peters, K.; Peters, E.-M.; Ciufolini, M. A. *J. Org. Chem.* **2000**, *65*, 4397.
20. (a) Canesi, S.; Belmont, P.; Bouchu, D.; Rousset, L.; Ciufolini, M. A. *Tetrahedron Lett.* **2002**, *43*, 5193; (b) Canesi, S.; Bouchu, D.; Ciufolini, M. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4336 See also Ref. 23.
21. (a) Canesi, S.; Bouchu, D.; Ciufolini, M. A. *Org. Lett.* **2005**, *7*, 175; (b) Liang, H.; Ciufolini, M. A. *J. Org. Chem.* **2008**, *73*, 4299.
22. Braun, N. A.; Bray, J.; Ciufolini, M. A. *Tetrahedron Lett.* **1999**, *40*, 4985 See also Ref. 19b.
23. Canesi, S. Ph.D. Dissertation, Université Claude Bernard Lyon 1, 2004.
24. (a) Scheffler, G.; Seike, H.; Sorensen, E. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 4593; (b) Seike, H.; Sorensen, E. J. *Synlett* **2008**, 695.
25. (a) Mizutani, H.; Takayama, J.; Soeda, Y.; Honda, T. *Tetrahedron Lett.* **2002**, *43*, 2411; (b) Mizutani, H.; Takayama, J.; Soeda, Y.; Honda, T. *Heterocycles* **2004**, *62*, 343; (c) Mizutani, H.; Takayama, J.; Honda, T. *Synlett* **2005**, 328.
26. The capture of electrophilic intermediates of the type **5** with carbonyl nucleophiles forms the basis of some noteworthy transformations: (a) Wong, Y.-S. *Chem. Commun.* **2002**, 686; (b) Peuchmaur, M.; Wong, Y.-S. *J. Org. Chem.* **2007**, *72*, 5374; (c) Peuchmaur, M.; Wong, Y.-S. *Synlett* **2007**, 2902; (d) Peuchmaur, M.; Saidani, N.; Botte, C.; Marechal, E.; Vial, H.; Wong, Y.-S. *J. Med. Chem.* **2008**, *51*, 4870; (e) Li, C.; Danishefsky, S. J. *Tetrahedron Lett.* **2006**, *47*, 385; (f) Chang, J.; Chan, B.; Ciufolini, M. A. *Tetrahedron Lett.* **2006**, *47*, 3599.
27. Liang, H. Ph.D. Dissertation, University of British Columbia, 2009.
28. Liang, H.; Ciufolini, M.A., unpublished.
29. Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353 Ref. 23 describes some implementations of this technology.
30. E.g.: (a) Drutu, I.; Njardson, J.; Wood, J. *Org. Lett.* **2002**, *4*, 493; (b) Bérubé, A.; Drutu, I.; Wood, J. L. *Org. Lett.* **2006**, *8*, 5421 For Diels/Alder reactions of structurally similar quinone monoketals see: (c) Breuning, M.; Corey, E. J. *Org. Lett.* **2001**, *3*, 1559; (d) Yu, M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 2783; (e) Hayden, A. E.; DeChancie, J.; George, A. H.; Dai, M.; Yu, M.; Danishefsky, S. J.; Houk, K. N. *J. Org. Chem.* **2009**, *74*, 6770; (f) Dory, Y. L.; Roy, A.-L.; Soucy, P.; Deslongchamps, P. *Org. Lett.* **2009**, *11*, 1197.
31. Review: Ciganek, E. *Org. React.* **1984**, *32*, 1.
32. Tozer, M. J.; Woolford, A. J. A.; Linney, I. D. *Synlett* **1998**, 186.
33. Liang, H.; Ciufolini, M. A. *Org. Lett.* **2010**, *12*, 1760.
34. (a) Chow, Y. L.; Colon, C. J.; Tan, J. N. S. *Can. J. Chem.* **1968**, *46*, 2821; (b) Lunazzi, L.; Cerioni, G.; Foresti, E.; Macciantelli, D. *J. Chem. Soc., Perkin Trans. 2* **1980**, 717; (c) Johnson, F. *Chem. Rev.* **1968**, *68*, 375.
35. Isolation: (a) Brown, R. F. C.; Drummond, R.; Fogerty, A. C.; Hughes, G. K.; Pinhey, J. T.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1956**, *9*, 283 Bioactivity; (b) Cobbin, L. B.; Thorp, R. H. *Aust. J. Exptl. Biol. Med. Sci.* **1957**, *35*, 15 Structural work: (c) Guise, G. B.; Mander, L. N.; Prager, R. H.; Rasmussen, M.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1967**, *20*, 1029; (d) Willis, A. C.; O'Connor, P. D.; Taylor, W. C.; Mander, L. N. *Aust. J. Chem.* **2006**, *59*, 629; O'Connor, P. D.; Mander, L. N.; McLachlan, M. M. W. *Org. Lett.* **2004**, *6*, 703; Total synthesis: Synthetic studies: Movassaghi, M.; Tjandra, M.; Qi, J. *J. Am. Chem. Soc.* **2009**, *131*, 9648.
36. First total synthesis: (a) Kishi, Y.; Fukuyama, T.; Aratani, M.; Nakatsubo, F.; Goto, T.; Inoue, S.; Tanino, H.; Sugiura, S.; Kakaoi, H. *J. Am. Chem. Soc.* **1972**, *94*, 9219 Recent syntheses: (b) Ohyabu, N.; Nishikawa, T.; Isobe, M. *J. Am. Chem. Soc.* **2003**, *125*, 8798; (c) Nishikawa, T.; Urabe, D.; Isobe, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4782; (d) Urabe, D.; Nishikawa, T.; Isobe, M. *Chem.—Asian J.* **2006**, *1*, 125; (e) Isobe, M.; Ohyabu, N.; Nishikawa, T. *Yuki Gosei Kagaku Kyokaishi* **2007**, *65*, 492; (f) Hinman, H.; DuBois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510; (g) Sato, K.-I.; Akai, S.; Shoji, H.; Sugita, N.; Yoshida, S.; Nagai, Y.; Suzuki, K.; Nakamura, Y.; Kajihara, Y.; Funabashi, M.; Yoshimura, J. *J. Org. Chem.* **2008**, *73*, 1234; (h) Sato, K.; Akai, S.; Sugita, N.; Ohsawa, T.; Kogure, T.; Shoji, H.; Yoshimura, J. *J. Org. Chem.* **2005**, *70*, 7496 Synthetic studies: (i) Taber, D. F.; Storck, P. H. *J. Org. Chem.* **2003**, *68*, 7768 Reviews; (j) Narahashi, T. *Proc. Jpn. Acad., Ser. B* **2008**, 84; (k) Koert, U. *Angew. Chem., Int. Ed.* **2004**, *43*, 5572.
37. The structure of this compound was confirmed by X-ray crystallography.
38. Reviews: (a) Mulzer, J. In *Organic Synthesis Highlights*; Mulzer, J., Altenbach, H. J., Braun, M., Krohn, K., Reissig, H. U., Eds.; VCH: Weinheim, Germany, 1990; Vol. I, p 77; (b) Nair, V.; Suja, T. D. *Tetrahedron* **2007**, *63*, 12247 See especially p. 12255.
39. Tanaka, S.; Ito, M.; Kishikawa, K.; Kohmoto, S.; Yamamoto, M. *Nippon Kagaku Kaishi* **2002**, *3*, 471.
40. Radhakrishna, A. S.; Sivaprakash, K.; Singh, B. B. *Synth. Commun.* **1991**, *21*, 1625.
41. Mendelsohn, B.; Lee, S.; Kim, S.; Teyssier, F.; Aulakh, V. S.; Ciufolini, M. A. *Org. Lett.* **2009**, *11*, 1539.
42. For an interesting application of this chemistry see: Frie, J. L.; Jeffrey, C. S.; Sorensen, E. J. *Org. Lett.* **2009**, *11*, 5394.
43. (a) Andersen, S. H.; Das, N. B.; Joergensen, R. D.; Kjeldsen, G.; Knudsen, J. S.; Sharma, S. C.; Torssell, K. B. G. *Acta. Chem. Scand. B* **1982**, *36*, 1; (b) Torssell, K. B. G. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; VCH: New York, NY, 1988.
44. Mendelsohn, B. A.; Ciufolini, M. A. *Org. Lett.* **2009**, *11*, 4736.
45. Literature mp's for this compound range from a low of 71–72 °C (Cecchi, L.; De Sarlo, F.; Machetti, F. *Eur. J. Org. Chem.* **2006**, 4852) to a high of 75–76 °C; D'Alcontres, G. S.; Grunanger, P. *Gazz. Chim. Ital.* **1950**, *80*, 831.