

Oxidation of oximes with hypervalent iodine reagents: opportunities, development, and applications

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Abstract

The paper reviews the oxidation of oximes to nitrile oxides with hypervalent iodine reagents, especially $\text{PhI}(\text{OAc})_2$, and the synthetic uses of such a transformation. Side reactions attending the process are also discussed.

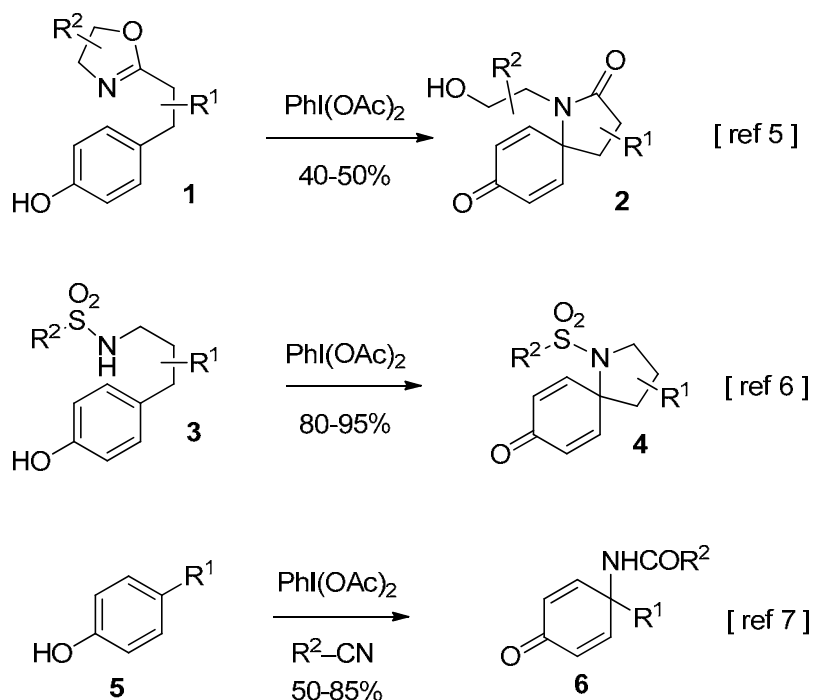
Keywords: Hypervalent iodine reagents, dipolar cycloaddition, nitrile oxides, oximes, heterocycles

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1. Introduction

Hypervalent organoiodine compounds¹ have emerged as uniquely capable oxidants in a number of noteworthy transformations, some of which are all but unachievable by the use of alternative reagents. For instance, $\text{PhI}(\text{OCOCH}_3)_2$ (DIB), or occasionally $\text{PhI}(\text{OCOCF}_3)_2$ (PIFA), serve as exquisite promoters of the oxidative amidation of phenols,² a special case of oxidative dearomatization of phenols³ exemplified in Scheme 1.⁴ Low toxicity and environmentally benign nature amplify the practical value of such oxidants.



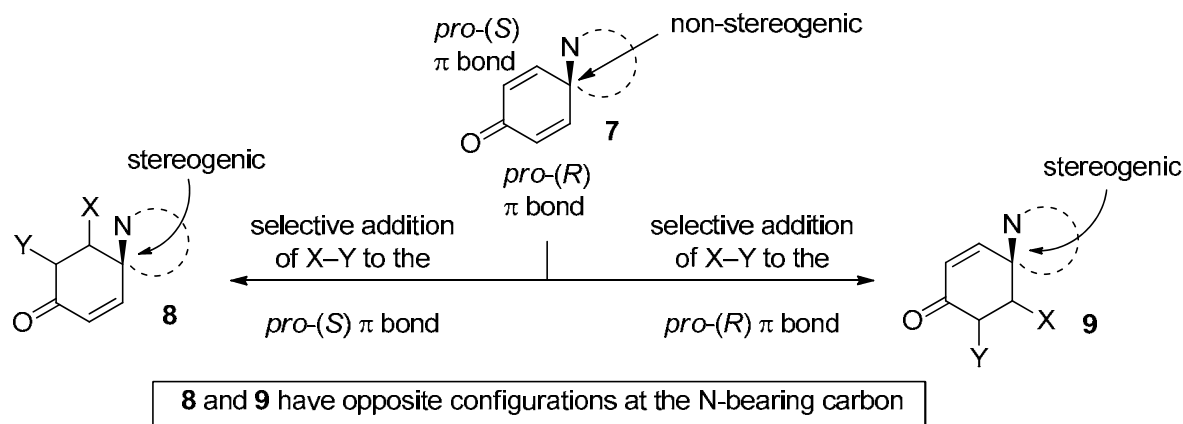
Scheme 1. The oxidative amidation of phenols.

Three modes of oxidative phenolic amidation are known at this time: the oxidative cyclization of phenolic oxazolines ($1 \rightarrow 2$)⁵ or sulfonamides ($3 \rightarrow 4$),⁶ both of which are intramolecular reactions, and the bimolecular Ritter-like amidation in the presence of nitriles ($5 \rightarrow 6$).⁷ Investigations centering on the application of these transformations to the synthesis of certain natural products revealed the desirability of engaging the emerging dienones in a nitrile oxide cycloaddition ("INOC") reaction,⁸ ideally, within the context of a tandem oxidative amidation / INOC sequence. A number of considerations induced us to focus on the oxidation of oximes with hypervalent iodine reagents as a means to generate nitrile oxides in a manner consonant with the foregoing objective. Research in that sense ultimately produced excellent solutions. In addition, it stimulated significant activity in other domains of chemical science, including bio-organic, main-group, and materials chemistry. The present contribution highlights key developments in these areas, and it covers literature published through June 2011.

2. Desymmetrization of Dienones obtained through Oxidative Amidation Reactions

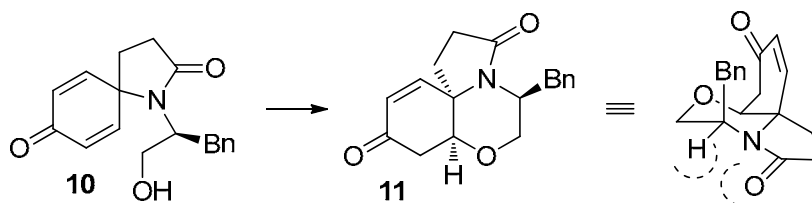
The incentive for revisiting the oxidation of oximes with hypervalent iodine reagents emanated from a desire to create a tetrasubstituted, N-bearing stereogenic carbon of a specific configuration in connection with a particular synthetic objective (*vide infra*). The stereoselective assembly of such carbon centers is generally difficult, but the desymmetrization of a "locally symmetrical" dienones

ensuing from an oxidative amidation reaction provides an effective and straightforward solution. As apparent from Scheme 2, this entails the selective addition of an.



Scheme 2. Desymmetrization of "locally symmetrical" dienones **7**

Appropriate agent, X–Y, either to the *pro*-(*R*) or the *pro*-(*S*) double bond. The various methods that were devised to that end were inspired by the observation that conformational effects can elicit selective reactivity at a particular diastereotopic π bond of the dienone. For instance, spiro lactam **10** undergoes highly stereoselective cyclization to **11** upon standing (Scheme 3).^{5b} Evidently, well-documented conformational effects direct the OH group selectively to the *pro*-(*R*)-double bond of **10**.⁹ This translates into a highly selective formation of the (*R*)-configuration of the spiro center in **11**.

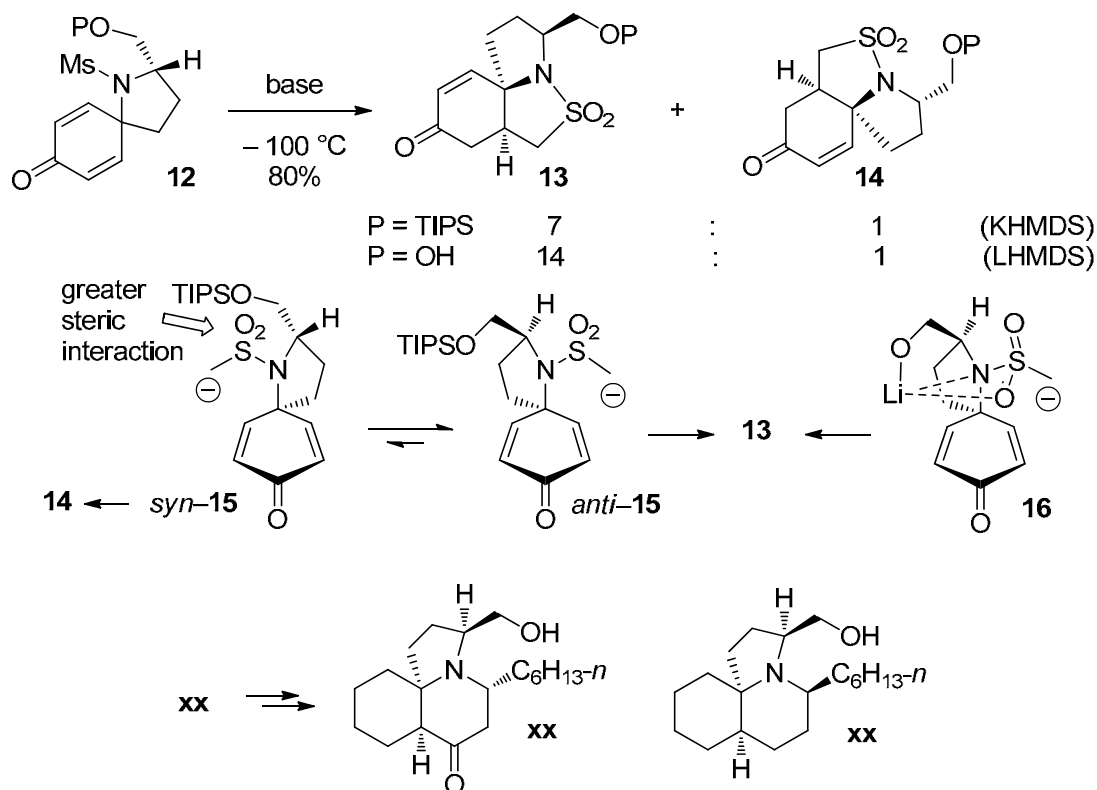


Scheme 3. Stereoselective Michael cyclization of **10**.

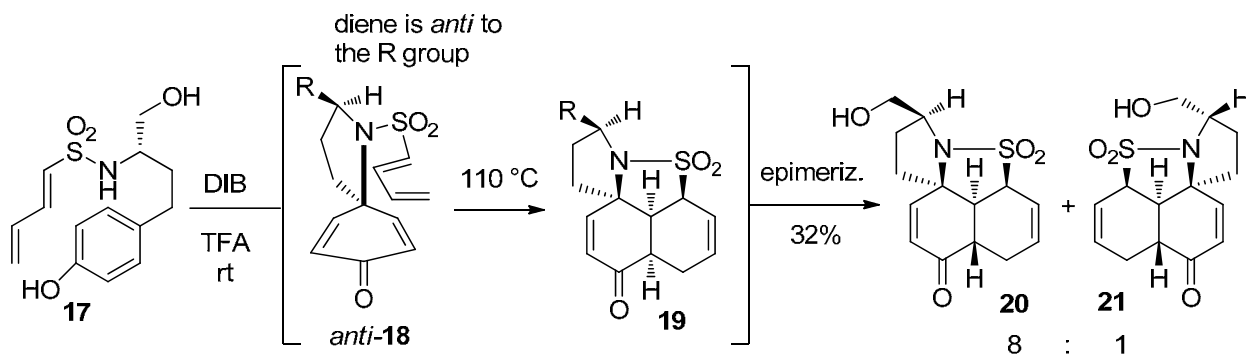
On the basis of the foregoing observation, we charted a synthesis of (–)-cylindricine C and putative (+)-lepadiformine^{6b-c} that relied on dienone desymmetrization via a stereocontrolled Michael cyclization of the anion of mesylamide **12** (Scheme 4). When compound **12**, P = TIPS, was deprotonated with KHMDS, products **13** and **14** were formed in a 7:1 ratio. The selectivity in favor of **13** increased to 14:1 when unprotected **12** (P = H) was treated with 2 equivalents of LHMDS. For TIPS-protected substrates, the stereochemical result may be explained by invoking preferential cyclization from conformer *anti*-**15**, in which the sulfonyl unit experiences a reduced degree of steric compression against the short side chain relative to conformer *syn*-**15**. In the unprotected

series, cyclization is likely to proceed from a Li-chelate such as **16**, wherein the anion of the sulfonamide is directed to add to the *pro-(R)* double bond of the dienone.

The reactions of Schemes 3-4 embody "nucleophilic" modes of dienone desymmetrization. A "pericyclic" variant of this process was recently demonstrated through intramolecular Diels-Alder (IMDA) chemistry. As detailed in Scheme 5, oxidative cyclization of sulfonamide **17** in trifluoroacetic acid (TFA) and *in situ* heating of the resultant **18** afforded an 8:1 mixture of products **20** (major, desired) and **21**. Clearly, the IMDA step occurs preferentially from the less sterically congested conformer *anti-18*, leading to the desired **20**. Interestingly, the primary adduct **19** underwent *in situ* acid-catalyzed epimerization of the stereocenter adjacent to the carbonyl group to produce the thermodynamically more favorable *trans* fusion between the two six-membered rings. Four stereogenic carbons, including a spiro center, are thus created stereoselectively in a single operation. Substance **20** is structurally related to the core of the unusual alkaloid, himandrine, albeit it possesses the antipodal configuration.¹⁰



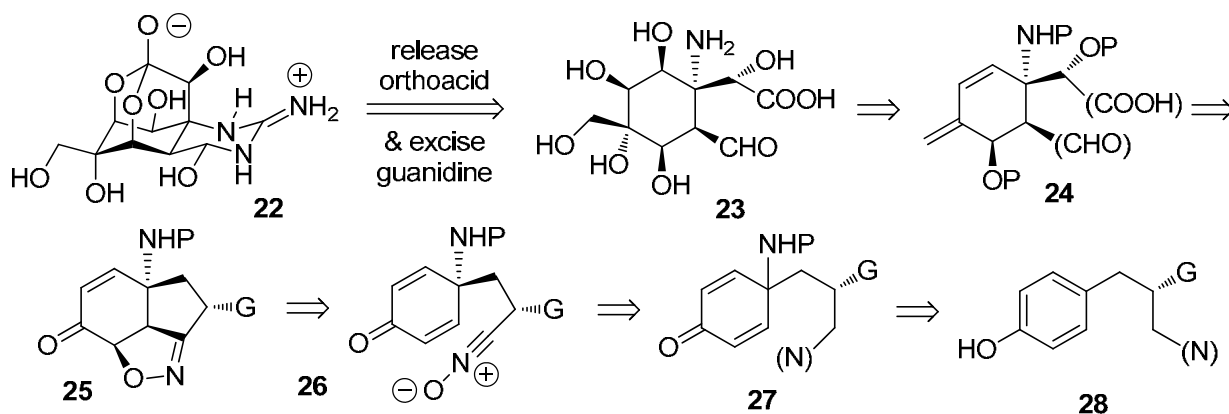
Scheme 4. Stereoselective Michael cyclization of sulfonamide **12**.



Scheme 5. Stereoselective IMDA cyclization of sulfonamide **18**.

3. Tandem Oxidative Amidation /Intramolecular Nitrile Oxide Cycloaddition Reactions

The desirability of dienone desymmetrization *via* 1,3-dipolar cycloaddition reactions of nitrile oxides materialized in connection with an ongoing synthesis of tetrodotoxin, **22** ("TTX", Scheme 6).¹¹ Simplification of the molecule leads to precursor **23**, which could be obtained by bis-dihydroxylation of diene **24**, wherein the groups in parentheses represent expressed or latent forms of the CHO and COOH functionalities. In turn, **24** may derive from **25** by fragmentation of the iso-oxazoline ring and Wittig reaction. The assembly of **25** may proceed via oxidative amidation of phenol **28** and intramolecular nitrile oxide cycloaddition¹² of **26**.



Scheme 6. Approach to tetrodotoxin, **22**.

Substituent (N) in **27-28** stands for a nitrogenous functionality suitable for the generation of a nitrile oxide, while G is a group that must fulfill a number of requirements. First, it must be sufficiently bulky to direct the nitrile oxide segment of **26** to the *pro*-(*S*) double bond, resulting in selective formation of the desired **25**. Indeed, a sterically demanding G would preferentially reside outside the developing bowl-shaped tricyclic product, favoring cyclization through transition state

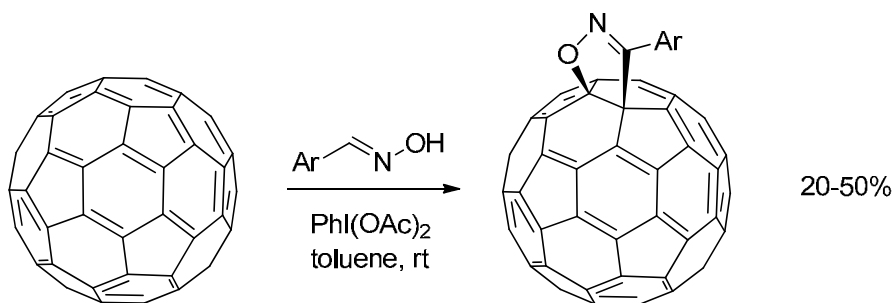
29, leading to the requisite **25** (Scheme 7). By contrast, transition state **30**, which leads to the undesired regioisomer of the product, would force G within the developing bowl, creating severe congestion. Second, G must enable oxazoline fragmentation as well as the elaboration of the α -hydroxyacid functionality found in intermediate **23**. Finally, it should be such that the starting **28** is readily available in enantiopure form. Interestingly, if group (N) were amenable to conversion into a nitrile oxide under the same conditions employed for the oxidative amidation step (reaction with hypervalent iodine agents), then **28** could be advanced to **25** by a tandem oxidative amidation / INOC reaction. The only proviso is that the rate of oxidation of (N) to a nitrile oxide should be slower than that of the oxidative amidation, so that the dienone may already be in place by the time that the nitrile oxide begins to form.



Scheme 7. Stereoselective INOC cyclization directed by substituent G.

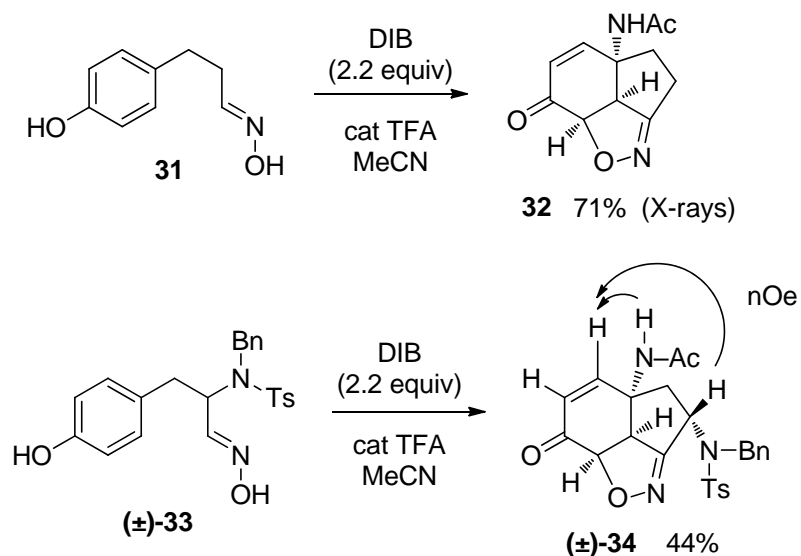
A logical choice for (N) appeared to be an aldoxime. Indeed, the literature records examples of oxidation of aldoximes to nitrile oxides with hypervalent iodine reagents, including PhICl_2 ,¹³ PhIO ,¹⁴ and, subsequent to the publication of the results we are about to describe, with $\text{PhI}(\text{OTs})\text{OH}$ (Koser's reagent).¹⁵ Especially relevant to our objectives was the pioneering work of Das, who had previously described the oxidation of aldoximes to nitrile oxides with DIB: the reagent of choice for the oxidative amidation of phenols.¹⁶ However, all such reactions employ conditions that are unsuitable for the conduct of a tandem oxidative amidation/INOC sequence. In particular, it was unclear whether the chemistry described in these reports would perform adequately in the solvents normally employed for oxidative amidation reactions, i.e. trifluoroethanol (TFE) or hexafluoroisopropanol (HFIP, oxidative cyclization of oxazolines and some sulfonamides), or neat TFA (most sulfonamides), or acetonitrile containing a catalytic amount of TFA (bimolecular oxidative amidation).

We note that nitrile oxide formation occurs in a range of solvents, even nonpolar ones like toluene. A relevant example drawn from the work of Yang is shown in Scheme 8.¹⁷ Our exploration of alternative media was dictated uniquely by a projected need to induce INOC reactions in tandem with oxidative amidation events and related transformations. It should also be emphasized that the feasibility of a tandem oxidative amidation / INOC reaction in protic solvents was not at all certain at the onset of the studies detailed below, because the action of DIB upon oximes may induce a number of side reactions.¹⁸



Scheme 8. Oxidation of aromatic oximes to nitrile oxides with DIB in toluene.

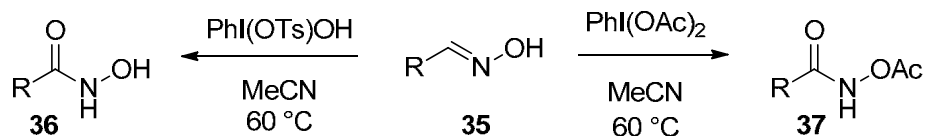
Initial experiments ascertained that DIB smoothly oxidizes aldoximes to nitrile oxides in solvents compatible with oxidative amidation chemistry.¹⁹ This enabled the conduct of the tandem processes adumbrated in Scheme 9. Thus, exposure of **31** to DIB (2.2 equiv) in MeCN in the presence of TFA afforded **32** (71% yield after chromatography), the structure of which was ascertained by X-ray diffractometry. More importantly, (\pm)-tyrosine-derived **33**, wherein the bulky *N*-benzyl tosylamide substituent functions now as group G in **28**, was converted into (\pm)-**34**, single diastereomer, as the sole identifiable product in 44% chromatographed yield. A NOESY-2D experiment unveiled strong dipolar coupling between the indicated protons, confirming the relative configuration shown. The genesis of this particular diastereomer of the product is entirely consistent with the hypothesis formulated earlier in Scheme 7.



Scheme 9. Tandem bimolecular oxidative amidation / INOC reaction.

We stress that a catalytic amount of TFA acts as an effective Bronsted acid promoter of oxime oxidation. In its absence, nitrile oxide formation may proceed inefficiently and side reactions are apt to occur, especially when operating in MeCN as the solvent. In that respect, Patel and collaborators

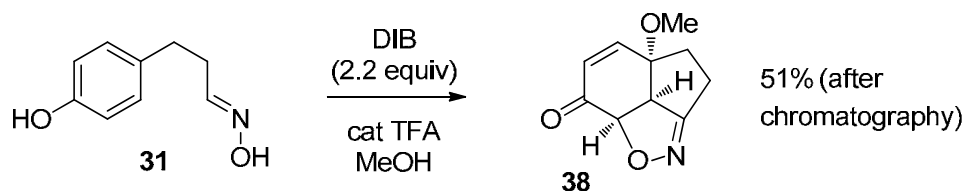
have shown that the reaction of aldoximes with Koser's reagent or DIB in MeCN at 60 °C, without added TFA, can lead to hydroxamic acids or the corresponding O-acetyl derivatives (Scheme 10).²⁰ While the authors correctly suggest that **36** and **37** could originate from a nitrile oxide intermediate, alternative mechanisms for the formation of the observed products may also be envisaged, and cannot be excluded at this time.



Scheme 10. Oxidation of aldoximes to hydroxamic acids in MeCN without added TFA.

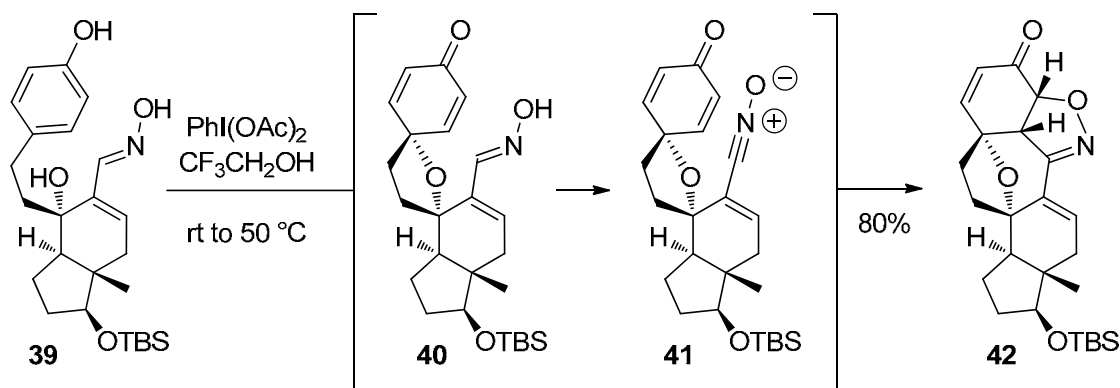
4. Other Processes Involving the Reactions of Oximes with Hypervalent Iodine Reagents

In the course of our investigations, we observed that methanol containing a catalytic amount of TFA is one of the best solvents for DIB-mediated nitrile oxide generation from oximes. It should be noted that MeOH is unsuitable for the conduct of oxidative amidation reactions, in that being nucleophilic, it will rapidly intercept electrophilic intermediates arising through DIB activation of phenols. For example, the reaction of **31** with DIB in MeOH / TFA produced compound **38** in 51% yield via a tandem oxidative methoxylation/INOC sequence (Scheme 11).¹⁹



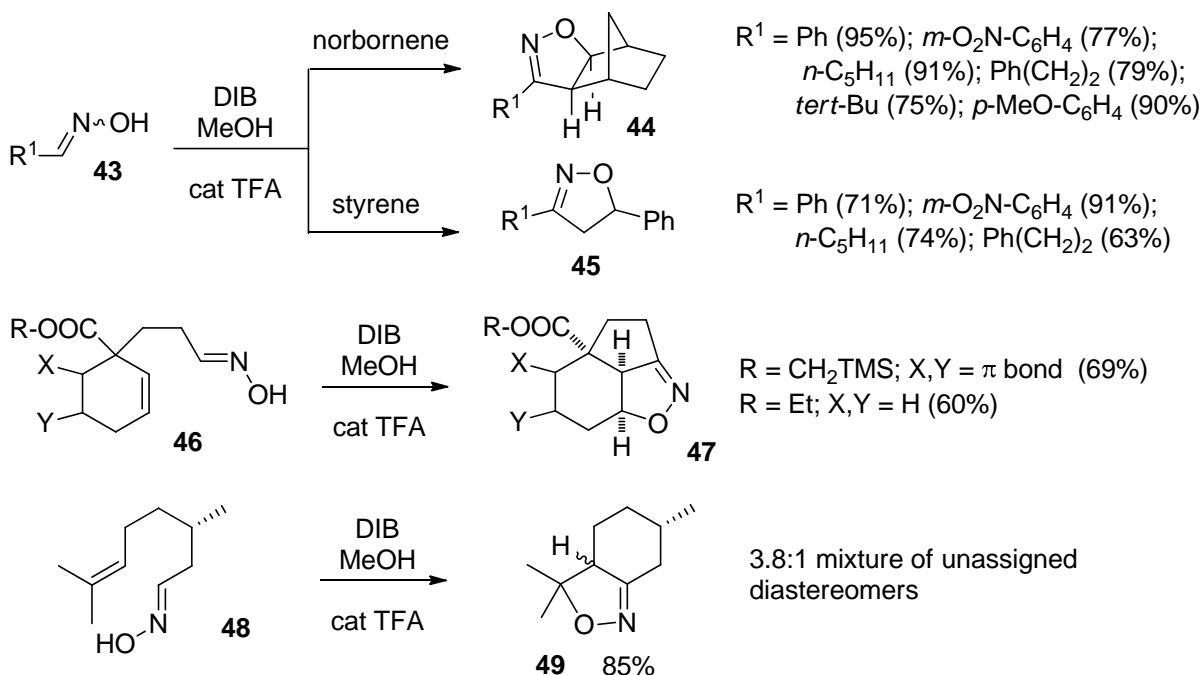
Scheme 11. Tandem bimolecular oxidative methoxylation / INOC reaction.

Non-solvolytic alkoxylation of the phenol prior to INOC reaction becomes possible by operating in non-nucleophilic protonic solvents such as TFE and HFIP. A noteworthy example of this chemistry has been described by Sorensen (Scheme 12).²¹ Specifically, attack of compound **39** with DIB in TFE resulted in cyclization to presumed intermediate **40**, which converged to the ultimate **42** after *in situ* oxidation of the oxime to a nitrile oxide and INOC cyclization. Substance **42** is structurally related to the interesting natural product, cortistatin.

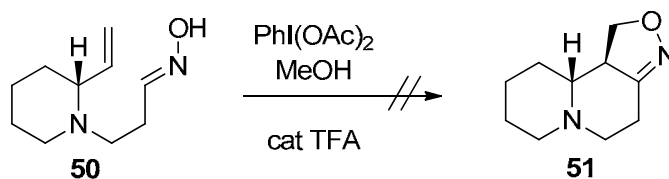


Scheme 12. Approach to cortistatin via tandem phenolic alkoxylation / INOC reaction.

In those cases where no oxidative phenolic amidation / alkoxylation steps are required prior to nitrile oxide generation, MeOH becomes a solvent of choice for DIB-mediated oxime oxidation. Pertinent examples appear in Scheme 13.¹⁹ As in the previous cases, a catalytic amount of TFA is essential for maximum efficiency. An instructive example of what might happen in the absence of protonic catalysis emerges from the work of Wang, Hu, and collaborators, who found that the treatment of oxime **50** with DIB in methanol / catalytic TFA failed to produce the desired **51** (Scheme 14; decomposition of **50**).²² It is likely that the basic amine neutralized the TFA, thereby denying protonic catalysis to the process and opening the door to side reactions.

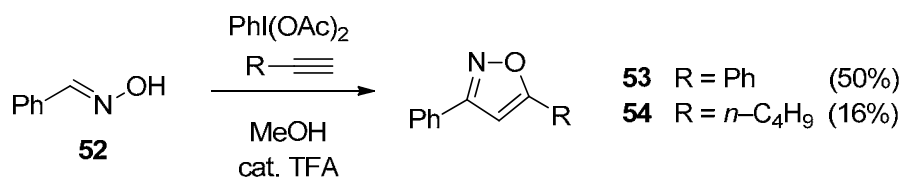


Scheme 13. Oxidation of aldoximes to nitrile oxides with methanolic DIB.

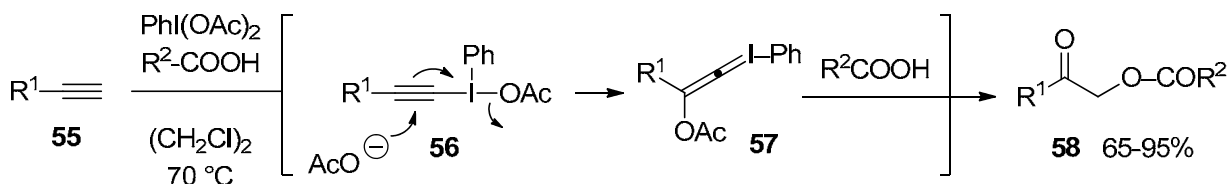


Scheme 14. Failure of oxime **50** to undergo DIB-mediated conversion into **51**.

A limitation of the above methodology is that the formation of isoxazoles from terminal alkynes is inefficient. For instance, the reaction of benzaldoxime with DIB in MeOH / TFA and in the presence of phenylacetylene furnished **53** in only 50% yield, while an analogous reaction with 1-hexyne provided **54** in a modest 16% yield (Scheme 15). In either case, much benzonitrile oxide dimer (3,4-diphenyl-1,2,5-oxadiazole-2-oxide) was formed, indicating that the poor yields were due to a side reaction that was subtracting the alkyne from the medium. All indications implicated a competing formation of reactive alkynyliodonium species,²³ which might then combine with various nucleophiles present in the medium, including MeOH, to form a host of different products. Interestingly, shortly after the appearance of our own work Hou described a method for the synthesis of α -acyloxy ketones (Scheme 16) by the reaction of terminal alkynes with DIB. A plausible mechanism indeed involves alkynyliodonium intermediates **56**.²⁴

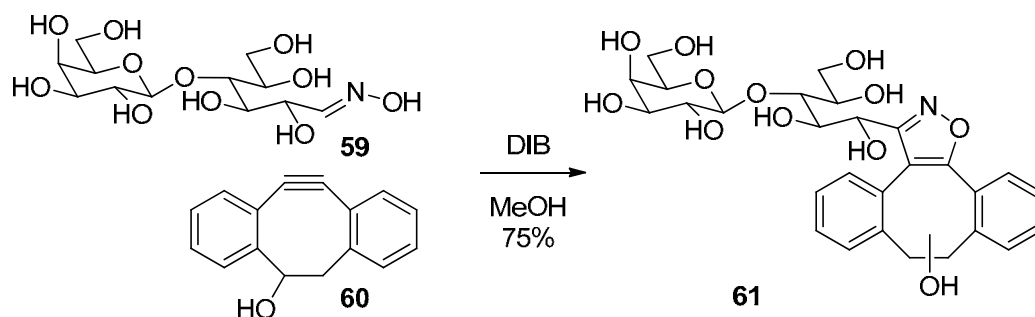


Scheme 15. Unsatisfactory isoxazole formation from terminal alkynes.

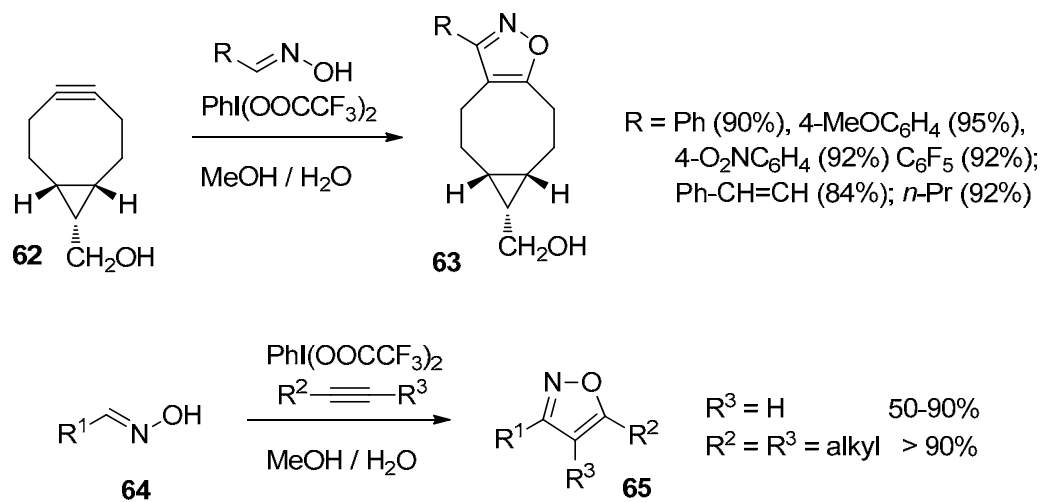


Scheme 16. DIB-mediated conversion of terminal alkynes into α -acyloxyketones.

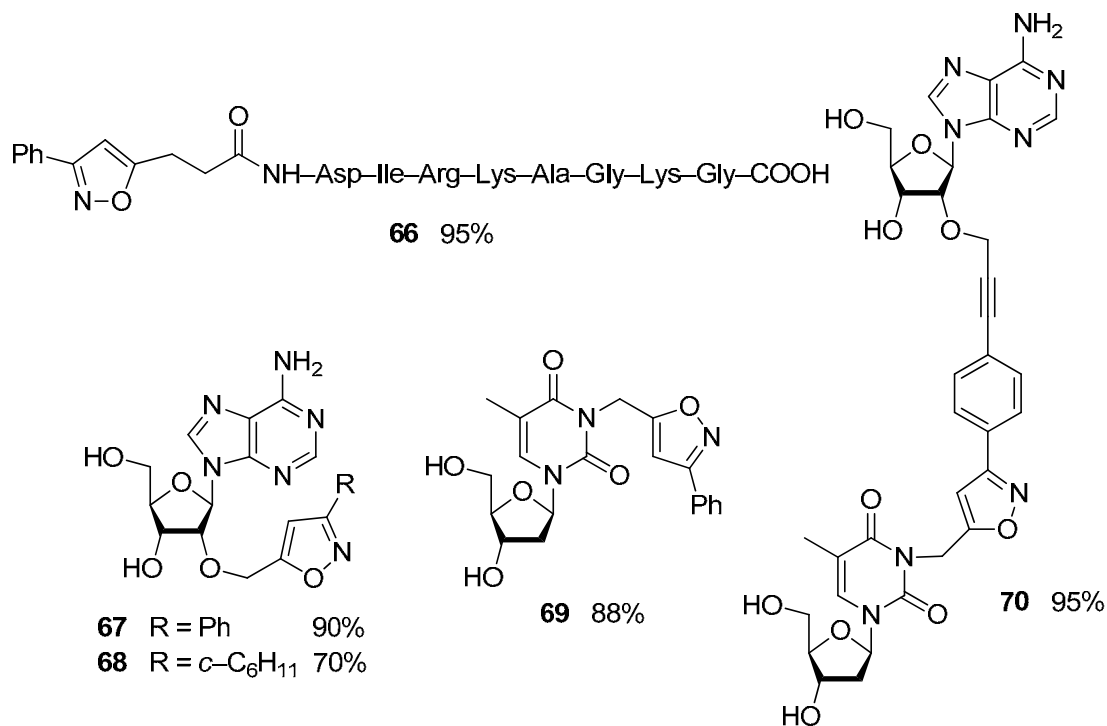
One may conclude from the foregoing that an internal alkyne should participate more efficiently in such DIB-mediated reactions; a surmise that finds confirmation in recent work by Boons and collaborators.²⁵ Strained cycloalkynes such as **60** are especially effective trapping agents for nitrile oxides so generated (Scheme 17).



Scheme 17. Internal alkynes as traps for nitrile oxides obtained by DIB oxidation of oximes

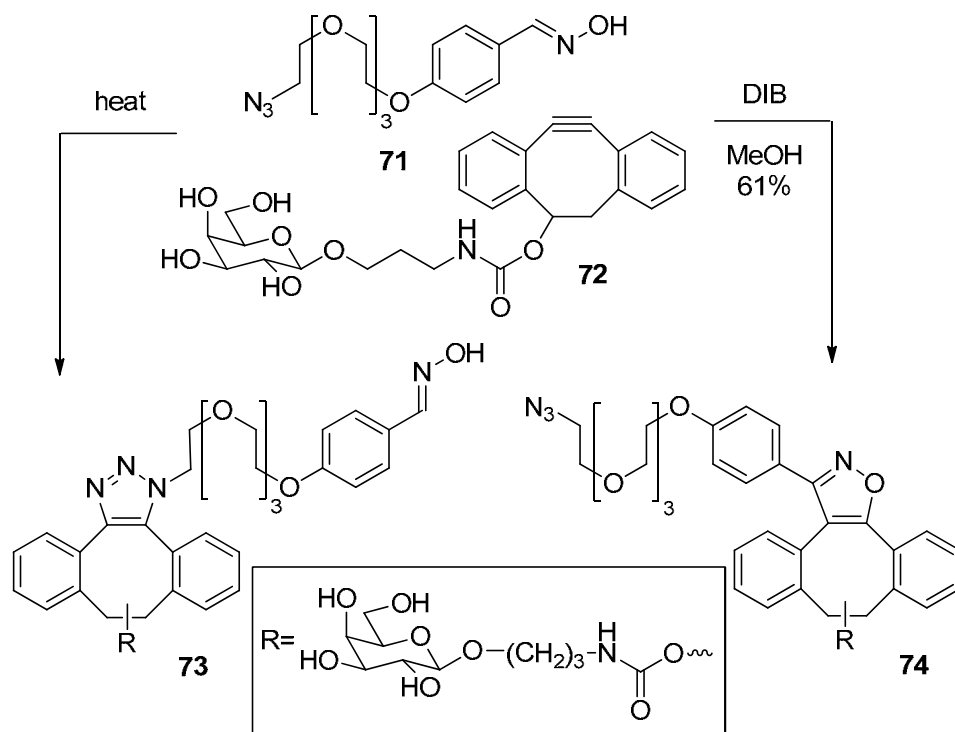


Scheme 18. Isooxazoles obtained by oxidation of oximes with PIFA in aqueous MeOH.



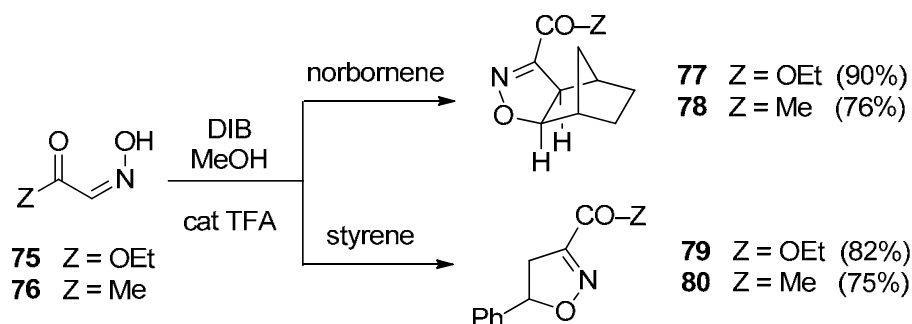
Scheme 19. Isoxazoles obtained from biomolecules incorporating terminal alkynes.

No TFA is required in this case. Van Delft and coworkers subsequently discovered that PIFA in aqueous MeOH is superior to DIB for this general reaction (Scheme 18).²⁶ Even terminal alkynes provide isoxazoles efficiently under the new conditions. Evidently, the rate of oxime oxidation by PIFA is so fast that side reactions such as the one outlined in Scheme 16 no longer compete. Furthermore, the examples listed in Scheme 19 indicate that the methodology is exceptionally tolerant of spectator functionality: even substrates incorporating basic (lysine and arginine) or acidic (aspartic acid) aminoacids, nucleotides, and aminopurines (e.g., adenine) react efficiently. These reactions embody a new form of "click" technology, and under this rubric, a noteworthy application of the Boons methodology²⁵ is the tunable click reactivity of azidooxime **71**. Thus, reaction of the latter with **72** under thermal conditions leads to triazole **73**, but oxidation of **71** with DIB in MeOH in the presence of **72** gives isoxazole **74** (Scheme 20). The reactions shown in Schemes 19-20 presage many significant applications in bio-organic chemistry.

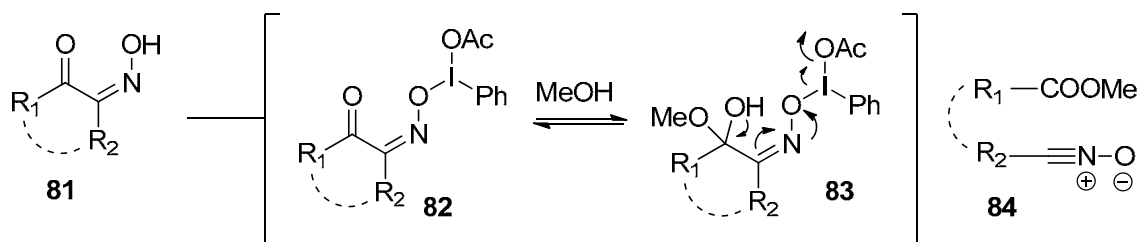


Scheme 20. Tunable click reactivity of oxime **71**.

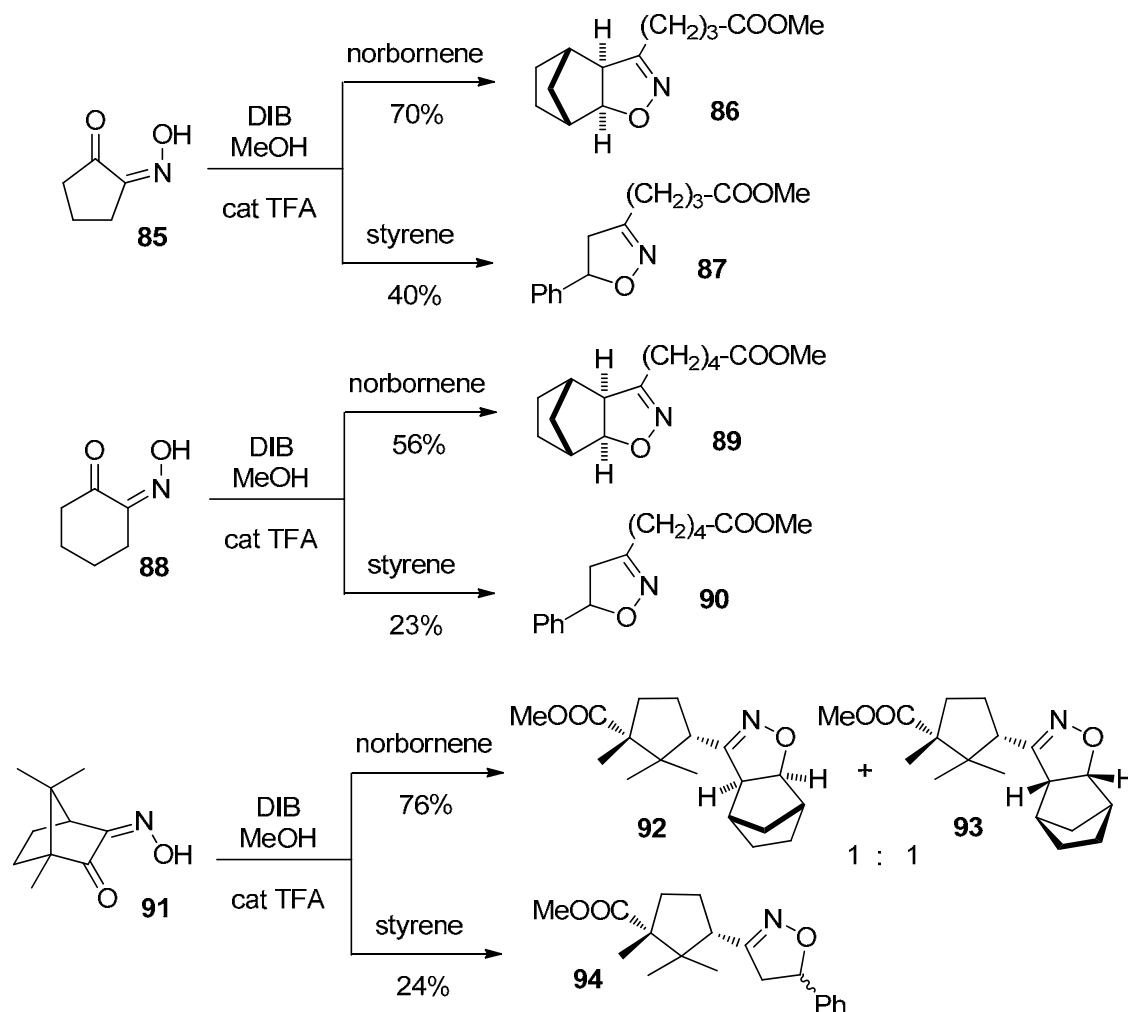
The foregoing developments encouraged us to broaden the scope of the reaction of oximes with hypervalent iodine reagents. A synthetically appealing opportunity materialized in the form of an oxidation of **75**, leading to carboxyformonitrile oxide (CEFNO):²⁷ a useful (and safe) fulminic acid equivalent.²⁸ Happily, methanolic DIB in the presence of TFA smoothly converted **75** into CEFNO, which was efficiently trapped *in situ* with norbornene and styrene (Scheme 21).²⁹ Analogous reactions of oximinoacetone, **76** also proceeded in a satisfactory manner, albeit the yields of products **79-80** were lower than those obtained from **75**. Regardless, the oxidation of oximes **75-76** nicely complements other methods for the generation of α -oxo-nitrile oxides.³⁰



Scheme 21. Oxidation of α -oxo-aldoximes with DIB in MeOH - TFA.



Scheme 22. Possible solvolytic nitrile oxide formation from α -oxo-ketoximes.

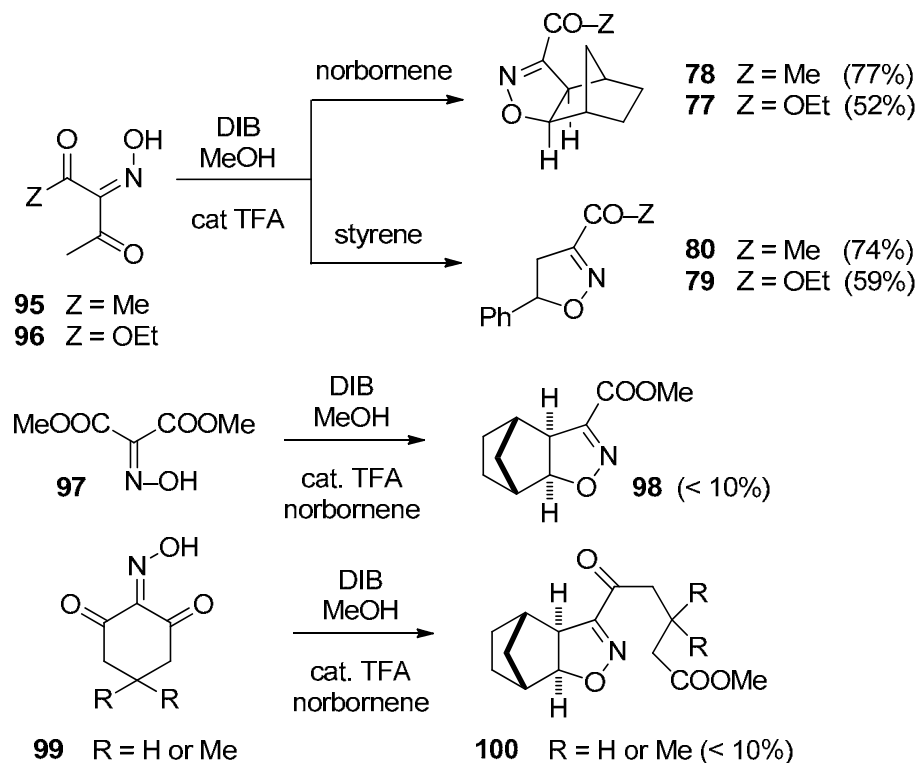


Scheme 23. Oxidation of α -oxo-ketoximes with methanolic DIB.

Contrary to an aldoxime, an ordinary ketoxime cannot produce a nitrile oxide directly upon oxidation. However, a nitrile oxide could form as a result of the oxidation of an α -oxo-ketoxime in a nucleophilic solvent such as MeOH, through solvolytic fragmentation of the carbonyl-imino C–C bond, perhaps through the mechanism depicted in Scheme 22. This is indeed the case. As seen in Scheme 23, the oxidation of representative α -oxo-ketoxime **85**, **88**, and **91** with DIB in methanol

proceeded in a satisfactory manner, although consistently higher yields of cycloadducts were obtained when norbornene, rather than styrene, was employed as a trap. The reasons for this remain unclear. It should be noted that norbornene adducts of the type **89** have been employed as building blocks for the synthesis of prostaglandin analogs.³¹ The methodology outlined in Scheme 23 offers a particularly direct avenue to these materials. Also worthy of note is the fact that the nitrile oxide arising from camphor-derived **91** reacted with norbornene to yield an essentially 1:1 mixture of diastereomeric adducts **89** and **90**, which arise from the two possible *exo*-topologies of the cycloaddition step, while its styrene adduct **94** emerged as a 1:1 mixture of diastereomers. Evidently, cycloaddition reactions of this chiral nitrile oxide proceed with no stereoselection whatsoever.

A limitation of this chemistry is that α,α' -dioxoketoximes are generally poor substrates for solvolytic DIB oxidation (Scheme 24). To wit, oxime **95** yielded **78** as efficiently as did **76** (cf. Scheme 21), but **96** gave **77** in lower yield than **75**, while the oxidations of **97** and **99** were no longer preparatively useful. As detailed elsewhere,²⁹ inductive, resonance, and steric effects conspire to retard the rate of oxidation of α,α' -dioxo substrates and of nucleophilic cleavage of the resulting reactive intermediates, hampering nitrile oxide formation and diminishing overall yields.



Scheme 24. Generally unsatisfactory oxidation of α,α' -dioxo-ketoximes with methanolic DIB.

5. Conclusions

The oxidation of oximes to nitrile oxides by the use of hypervalent iodine reagents provides new tactical opportunities for the synthesis of nitrogenous substances, natural or otherwise. While the first examples of this reaction^{13,14,17} predate our own contributions, the appearance of our 2009 paper¹⁹ seems to have rekindled interest in this noteworthy transformation. Indeed, numerous applications in natural product, bio-organic, heterocyclic, and materials chemistry have been described since. The method complements existing avenues to nitrile oxides, the usefulness of which in preparative operations is likely to make this chemistry of interest to a broad cross section of synthetic and medicinal chemists. In closing, we would be remiss not to underscore that the incentive to research the reactions discussed herein originated exclusively from a perceived need for new synthetic technology: Synthesis is, and will always be, the engine that drives chemical invention.

6. Acknowledgements

We thank the NSERC, CIHR, CFI, BCKDF, the Canada Research Chair Program (M.A.C.) and the University of British Columbia for support of our research program.

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Marco A. Ciufolini: is a native of Rome, Italy. He received a B.S. (1978) from Spring Hill College, Mobile, AL, and a Ph.D. (1981) from the University of Michigan, under the direction of Prof. M. Koreeda. After postdoctoral studies in the group of Prof. S. Danishefsky, at Yale University, he started his independent career (1984) at Rice University, where he rose to the rank of Professor of Chemistry. At the end of 1997, he left Rice to accept a Chair of organic chemistry at the Ecole Supérieure de Chimie, Physique et Electronique de Lyon and the University of Lyon, France, but in mid-2004 he returned to North America as the holder of the Canada Research Chair in Synthetic Organic Chemistry at the University of British Columbia, Vancouver, BC. His research interests are in organic and medicinal chemistry, with focus on the development of new methods for the preparation of nitrogenous substances and on the application of these techniques to the synthesis of heterocyclic natural products.