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AZIDO, CYANO, AND NITRATO CYCLIC HYPERVALENT IODINE(III) REAGENTS IN HETEROCYCLE SYNTHESIS

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Abstract – In recent years, synthetic applications of cyclic hypervalent iodine reagents have undergone significant developments. Among them, benziodoxol(on)es containing azido, cyano, and nitrato ligands have been found to be useful synthetic tools for the preparation of functionalized heterocyclic compounds. This review aims to summarize recent synthetic applications of benziodoxol(on)es as effective heteroatom-introducing reagents.

Dedicated to Professor Yasuyuki Kita on the occasion of his 77th birthday

CONTENTS

1. INTRODUCTION

Over the past few decades, hypervalent iodine reagents have been widely recognized as versatile reagents for performing numerous environmentally friendly transformations, such as oxidations, rearrangements, and single-electron-transfer and radical reactions.[1] They have gained great importance as promising alternatives to toxic, heavy metal oxidants due to low toxicity, high stability, and easy handling. The increased stability of cyclic hypervalent iodine reagents with specific ligands has recently attracted attention (Figure 1).[2] 2-Iodoxybenzoic acid (IBX; **1**) and Dess-Martin periodinane (DMP; **2**) are the cyclic pentavalent iodine reagents extensively used and applied in the total synthesis or modification of biologically active natural products.[3,4] Regarding cyclic trivalent iodine reagents, structural studies of 2-iodosylbenzoic acid (IBA; **3**) and its acetate **4** and synthetic applications of Togni reagent (**5**) and ethynylbenziodoxolone (EBX; **6**) are well-developed, and utilities for these reagents have been frequently reviewed in detail.[5,6] However, synthetic applications of benziodoxol(on)es **7**–**9** containing azido, cyano, and nitrato ligands[7,8] received little attention until the 2010s. As benziodoxol(on)es **7**–**9** have been reported as an effective heteroatom-introducing reagent, transformations using benziodoxol(on)es **7**–**9** result in the efficient synthesis of highly functionalized heterocycles. Thus, this review highlights representative reactions using benziodoxol(on)es **7**–**9** related to heterocyclic synthesis based on currently available literature.

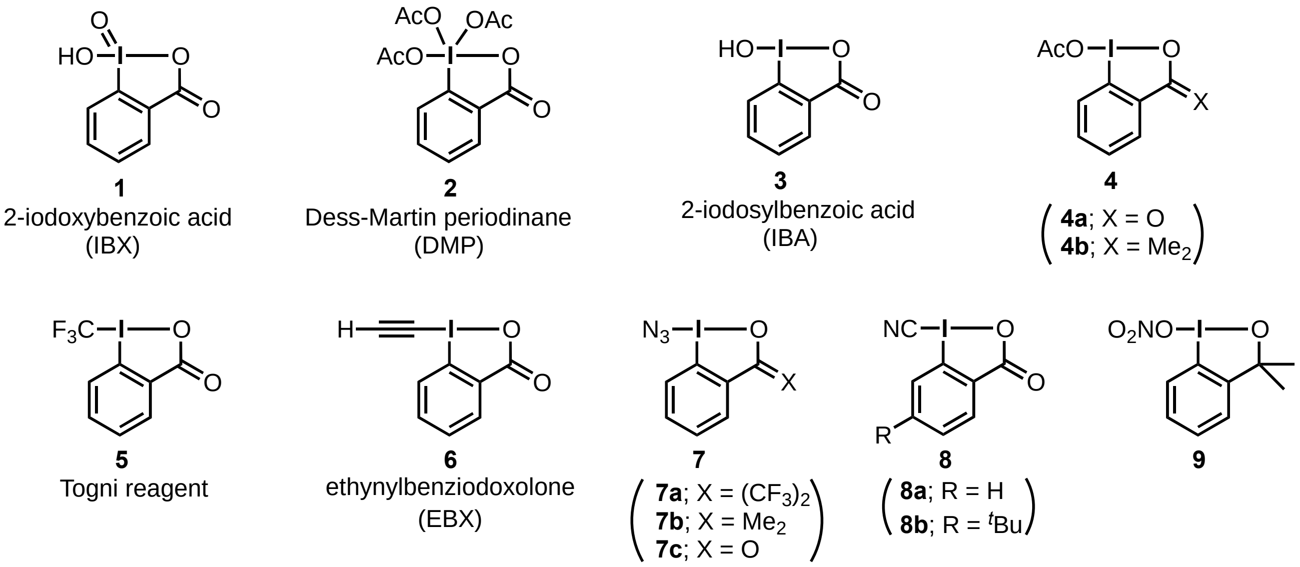
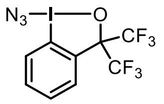


Figure 1. Cyclic hypervalent iodine reagents

2. CYCLIC HYPERVALENT IODINE AZIDE IN HETEROCYCLE SYNTHESIS

Organic azides are versatile compounds that are useful for the synthesis of heterocyclic compounds, such as triazoles and tetrazoles.[9] Acyclic hypervalent iodine species involving azido ligands are not stable and must be prepared *in situ* and used immediately. azidoiodanes, PhI(N_3)X (X = OAc, Cl, etc.) are reactive intermediates in azidation reactions[10,11] but difficult to isolate under ambient conditions. Thus, a noticeable suggestion was made in the mid-1990s, by Kita[7] and Zhdankin,[8] who independently demonstrated the synthesis and stability of cyclic azidobenziodoxol(on)es **7**. Kita reported that although the reaction of acetoxybenziodoxole **4b** with 1.5 equivalent of azidotrimethylsilane (TMSN_3) produces a complex mixture, the addition of a catalytic amount of trimethylsilyl triflate (TMSOTf) accelerated the desired transformation to yield azidobenziodoxole **7b** as pale-yellow crystals with 88% yield. In this study, the azidobenziodoxol(on)es **7** were prepared in similar manner and their structures were identified with satisfactory data, such as IR, NMR, microanalyses (within ±0.3% for C, H, N, and I), and high resolution mass spectroscopies; the IR data of compounds **7b** and **7c** showed the characteristic absorption of the azido groups from 2029–2070 cm^{-1}, respectively. Here, structure of the azidobenziodoxole **7a** was established by single-crystal X-ray analysis.[8d] The structural data disclosed distorted T-shaped geometry—typical of hypervalent iodine—with an N-I-O bond angle of 169.5°. The bond lengths around the iodine atom, I-N (2.18 Å), I-O (2.13 Å), and I-C (2.11 Å), have similar values and are generally within the range of typical single covalent bonds in organic derivatives of polyvalent iodine (Figure 2). The distinctive feature of azidobenziodoxol(on)es **7** is the considerably high stability based on heterocyclic structures compared to their acyclic analogues. This stabilization is usually explained by the occupation of the apical and the equatorial positions by the five-membered ring and by the better overlap of lone-pair electrons on the iodine atom with the π-orbitals of the benzene ring. In 1996, Zhdankin and co-workers reported that azidobenziodoxol(on)es **7** could be utilized as azidating agents for several organic substrates.[8d] However, further synthetic applications with azidobenziodoxol(on)es **7** did not appear until the 2010s.

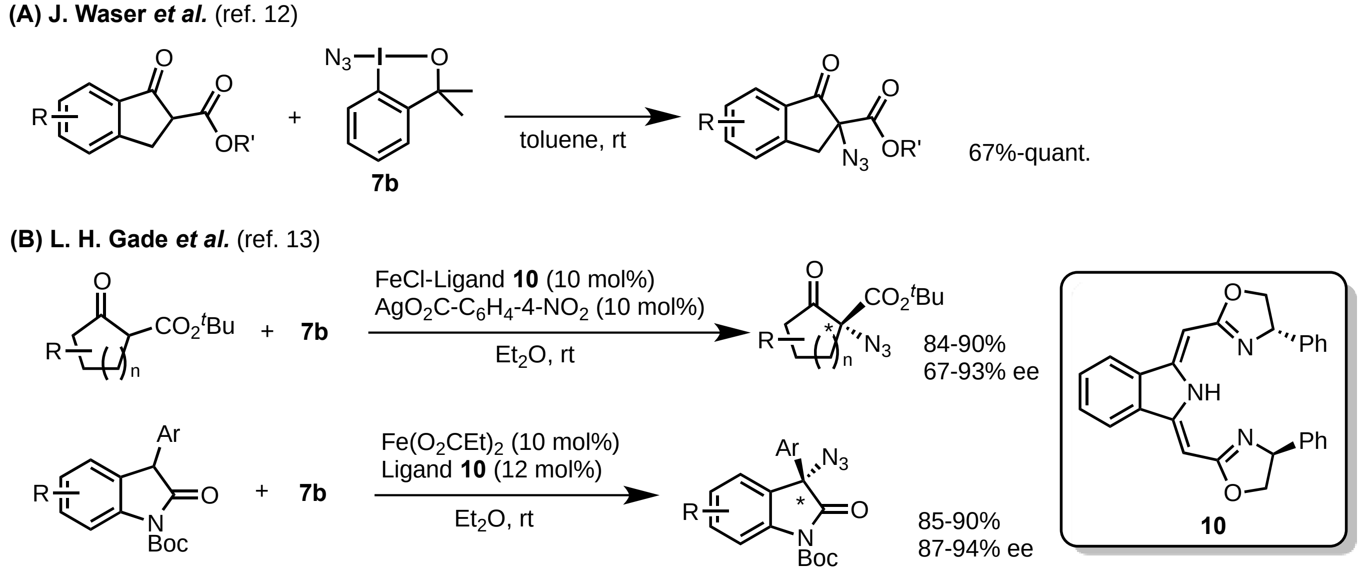


7a

bond length	angle
I—N : 2.18 Å	N—I—O : 169.5°
I—O : 2.13 Å	C—I—O : 78.9°
I—C : 2.11 Å	C—I—N : 90.6°

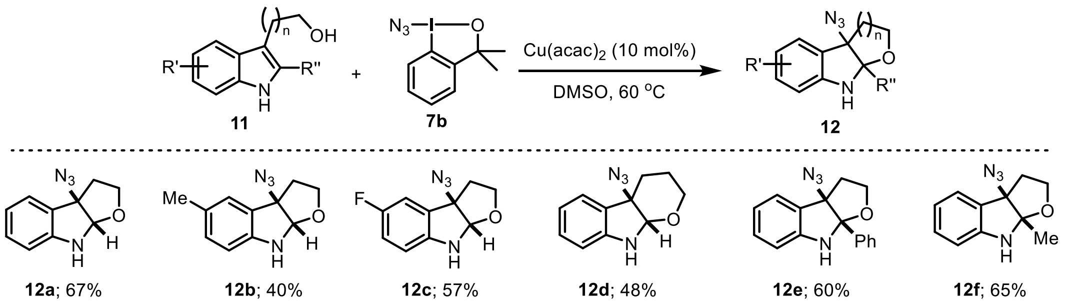
Figure 2. Selected bond lengths and angles of cyclic azidoiodinane **7a**

In 2013, Waser and Gade independently reported azidation of β-ketoesters by benziodoxole **7b**; Waser and co-workers demonstrated the azidation of β-ketoesters derived from indanone that did not require a catalyst or base (Scheme 1A),[12] and Gade et al. developed iron-catalyzed enantioselective azidation of β-ketoesters and oxindoles using chiral ligands **10** (Scheme 1B).[13] In these reactions, the catalysts played a key role for activation of the carbonyl group and furnished moderate to good enantioselectivities. Since then, azidobenziodoxol(on)es **7** have been recognized as excellent azide transfer agents, under metal-free[14] or metal-mediated[15] activation; and research work in this area is continuously expanding.

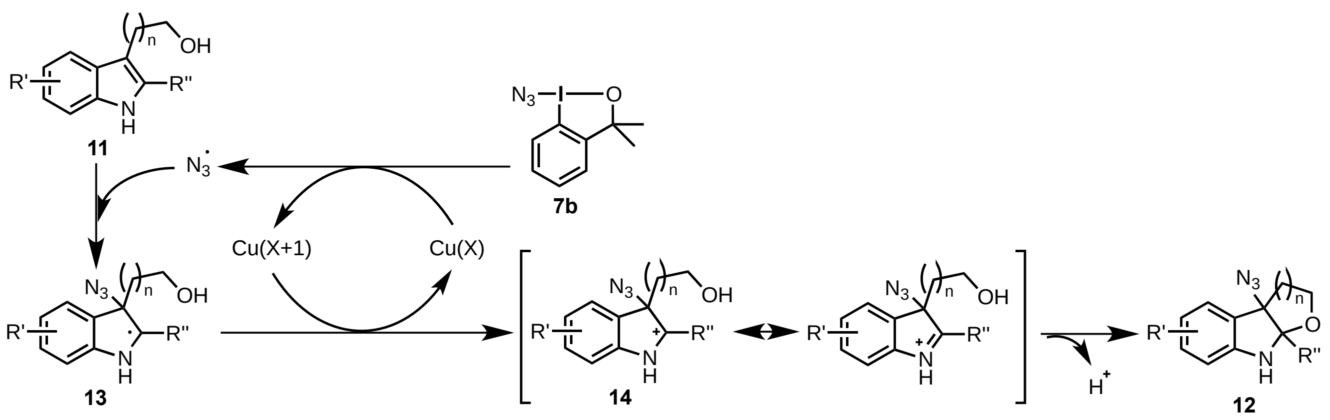


Scheme 1. Azidation of β-ketoesters with benziodoxolone reagent **7b**

In 2014, Jiao et al. reported Cu-catalyzed dearomatization of tryptophol derivatives **11** in the presence of cyclic azidoiodinane **7b** to afford azido tricyclic molecules **12** (Scheme 2)[16] and showed that azidoiodinane **7b** is a suitable azido source for this reaction; other types of azides, including NaN_3, $TMSN_3$, *p*-toluenesulfonyl azide (TsN_3), and diphenylphosphoryl azide (DPPA)—combined with equimolar amounts of phenyliodine(III) diacetate ($PhI(OAc)_2$; PIDA)—were ineffective in this reaction system. A plausible mechanism of this intramolecular cyclization is shown in Scheme 3. Copper is initially oxidized by azidoiodinane **7b** to generate azide radical, which is trapped by indoles **11** at the more nucleophilic 3-position to form radical intermediate **13**. The copper species then promotes single-electron oxidation of this intermediate **13**, forming the corresponding cationic intermediate **14**. Subsequently, the intramolecular nucleophilic attack of the pendent alcohol to this iminium moiety proceeds to produce the final product **12**.

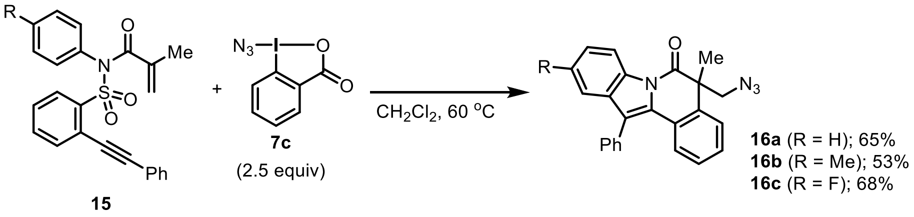


Scheme 2. Cu-Catalyzed de-aromatization of indoles with azidoiodinane **7b**

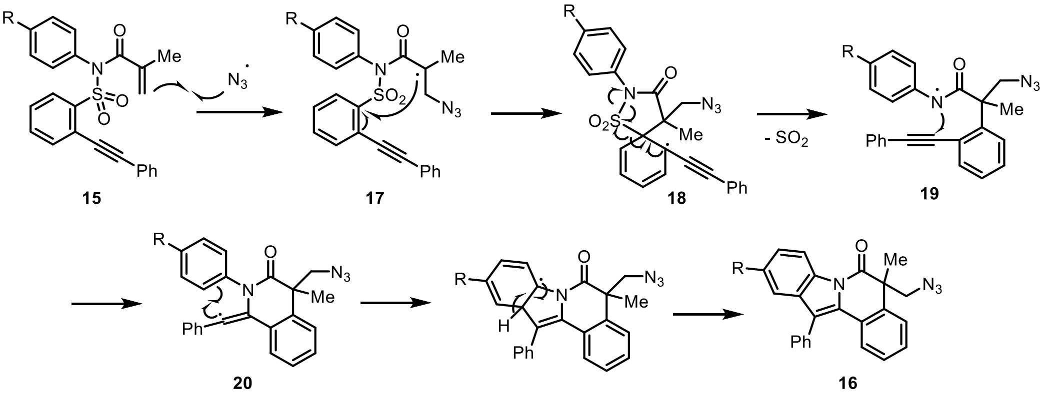


Scheme 3. Plausible mechanism for Cu-catalyzed radical cycloetherification of tryptophol derivatives **11**

Nevado et al. exploited the potential of azidobenziodoxolone **7c** for azide radical generation and demonstrated, in 2015, that the reaction of specifically functionalized substrates **15** with azidobenziodoxolone **7c** involved a complex cascade process to form tetracyclic heterocycle **16** (Scheme 4).[17] A mechanistic proposal for this transformation is described in Scheme 5. Initially, *in situ*-generated azide radical chemoselectively reacted with the acrylic moiety of *N*-acrylamides **15**, yielding an α-carbonyl radical intermediate **17**. The *ipso*-cyclization onto the Csp^2–SO$_2$ atom occurred next, forming a spirocyclic intermediate **18**, which was followed by re-aromatization and SO$_2$ elimination to generate amidyl radical **19**. A subsequent cyclization of amidyl radicals **19** to form a vinyl radical intermediate **20** generated the tetracyclic product **16** by additional cyclization.

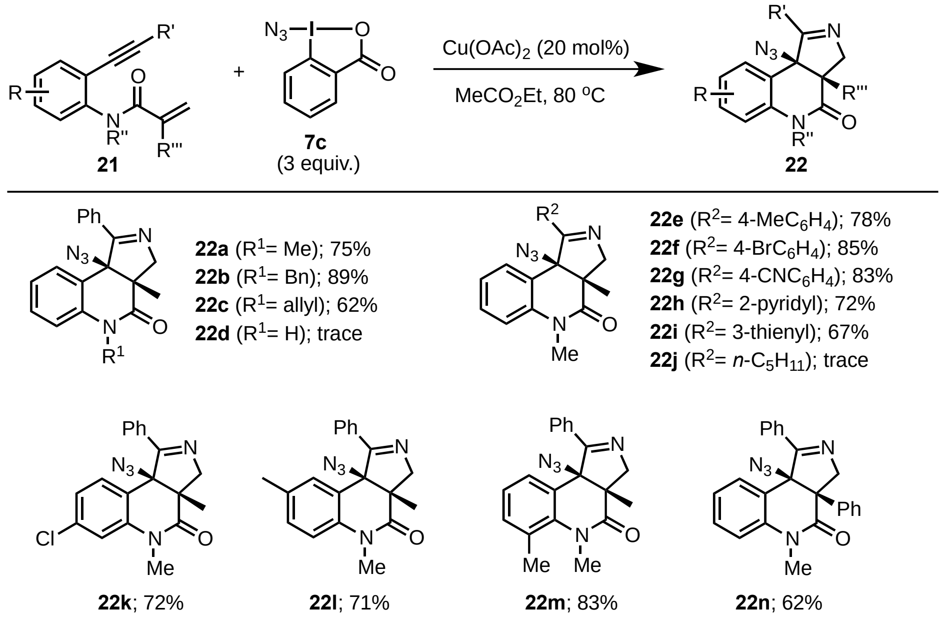


Scheme 4. Formation of tetracyclic heterocycle **16** using azidobenziodoxolone **7c**

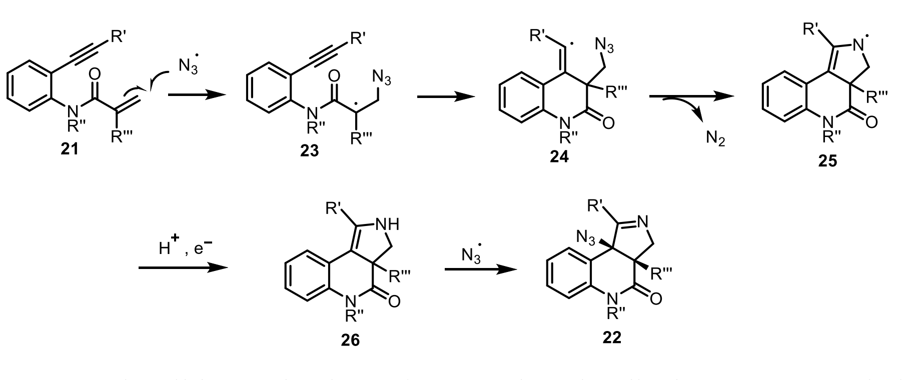


Scheme 5. Plausible tetracyclic heterocycle formation mechanism **16**

In 2015, Song and Li et al. developed Cu-catalyzed radical [2+2+1] annulation of benzene-linked 1,*n*-enynes **21** with azidobenziodoxolone **7c** to access fused pyrroline compounds **22** (Scheme 6).[18] In this system, the expected product **22** was not observed when using $TMSN_3$ or by replacing cyclic azidoiodinane **7c** with NaN_3. A variety of highly functionalized tricyclic pyrrolines **22** was obtained (Scheme 6), but the substrates with a free N-H group or aliphatic alkyne, such as **21d** and **21j**, were inert and did not form **22d** and **22j**. A possible mechanism for this [2+2+1] annulation reaction is shown in Scheme 7. Azide radical initially generated from **7c** was added to the alkene moiety of enyne **21** to yield alkyl radical **23**. The intermediate **23** readily underwent cyclization with the alkyne moiety to yield vinyl radical **24**, and an aminyl radical **25** was formed by the intramolecular addition of a vinyl radical to an azido group, followed by the elimination of N_2. The radical **25** was further transformed into intermediate **26** via H-abstraction or a reduction–protonation sequence. Subsequent addition of another azide radical to the alkene moiety of intermediate **26** furnished the tricyclic pyrrolines **22**.

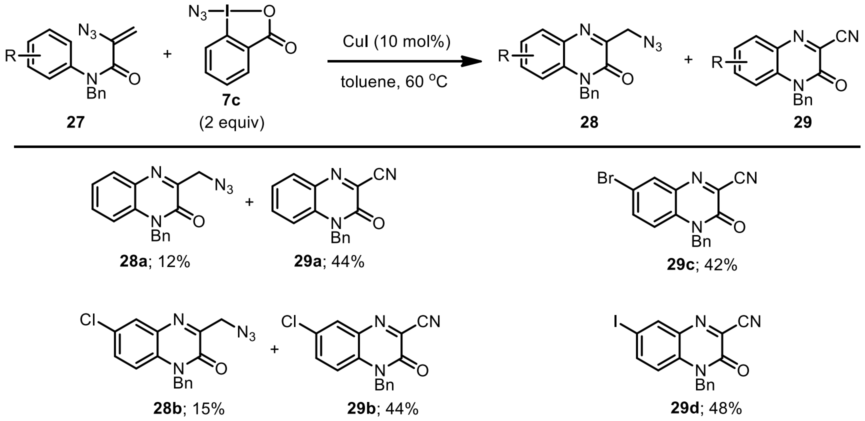


Scheme 6. Cu-Catalyzed radical [2+2+1] annulation of benzene-linked 1,*n*-enynes **21** with **7c**



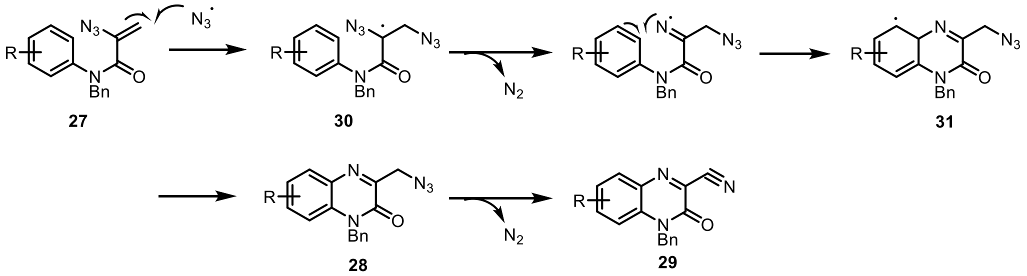
Scheme 7. Plausible mechanism of Cu-catalyzed radical [2+2+1] annulation

In 2016, Yu et al. investigated the reaction of 2-azido-*N*-acrylamides **27** with azide radical using cyclic azidoiodinane **7c** (Scheme 8).[19] Under the catalysis of CuI, the reaction produced a mixture of 3-azidomethyl and 3-cyano-subsituted quinoxalin-2(1*H*)-ones **28** and **29** in moderate yields. The cyanated compounds **29** were thought to be derived from azide products **28** by oxidation and denitrogenation.[20] Most of the *para-* and *meta*-substituted substrates **27** successfully reacted to yield quinoxalin-2-one products, but the reaction of *ortho*-substituted compounds failed under the same conditions. Among the *para*-substituted substrates, substrate **27a** and chloro-substituted **27b** reacted to form a mixture of the azide **28** and cyano products **29**, whereas substrates **27c** and **27d** involving other halogen substituents were exclusively converted to 3-cyano-substituted products **29**. For the *meta*-substituted compounds, the composition of the two products was further complicated because of the formation of regioisomers.



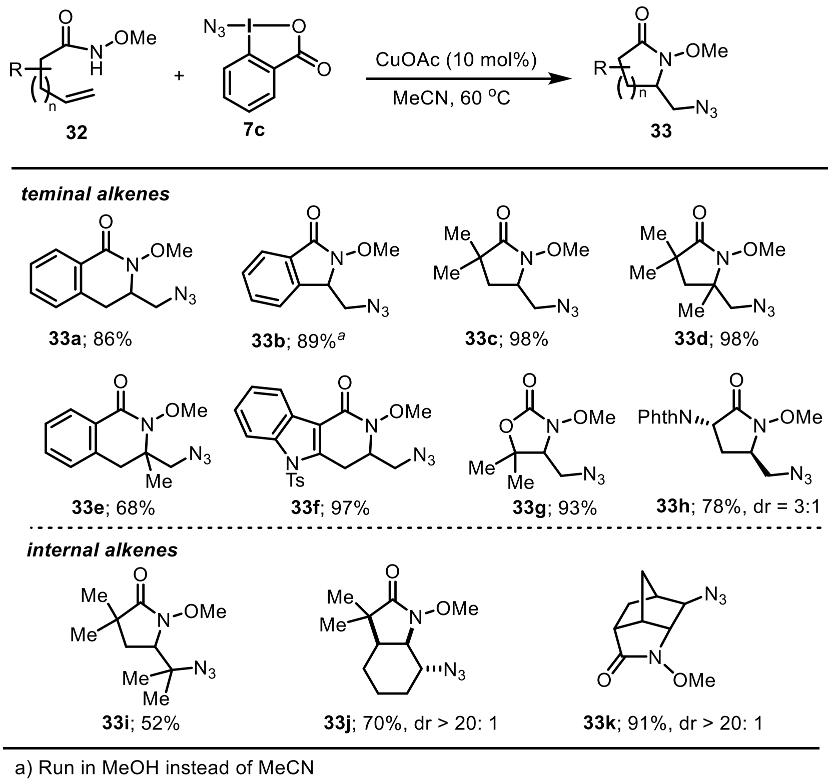
Scheme 8. Cu-Catalyzed cyclization of 2-azido-*N*-acrylamides **27** with azidobenziodoxolone **7c**

A possible mechanism for this transformation is shown in Scheme 9. An azide radical was initially added to the α,β-alkene moiety of amide **27** to form carbon radical **30**. Subsequent intramolecular cyclization and N_2 emission generated dearomatized intermediate **31**, followed by re-aromatization to yield 3-azidomethyl-subsituted quinoxalin-2(1*H*)-ones **28**. Finally, methyl azide **28** was decomposed to form nitrile **29** and N_2 by further oxidation.

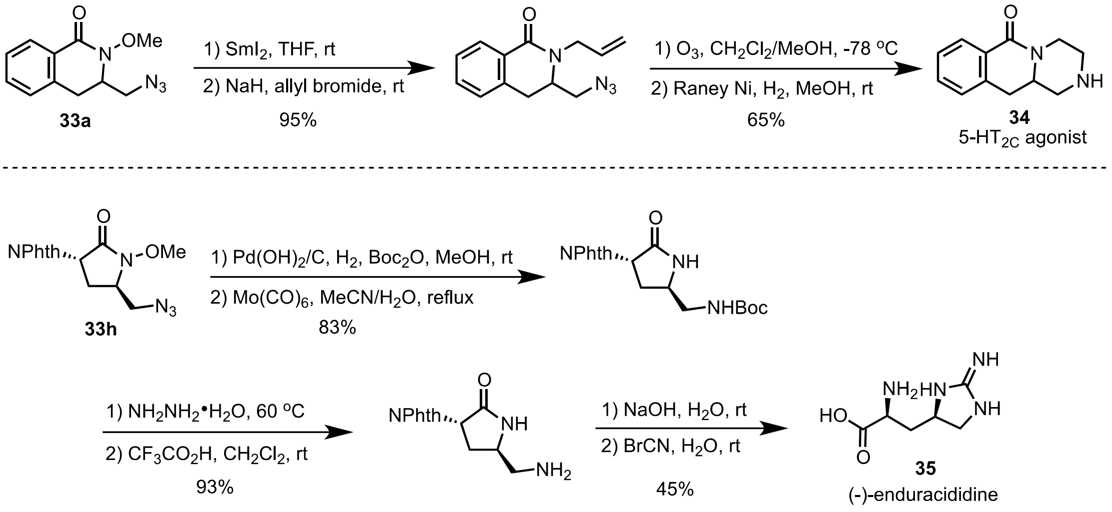


Scheme 9. Plausible mechanism for Cu-catalyzed cyclization of 2-azido-*N*-acrylamides **27**

In 2017, Wang et al. developed a copper-catalyzed aminoazidation of inactivated alkenes **32** with azidobenziodoxolone **7c** (Scheme 10).[21] This transformation offered an effective approach to simultaneously install the amide and azide group, two different amino precursors, onto terminal and internal alkenes, demonstrating the application of this method for the rapid synthesis of 1,2-diamine-containing bioactive compounds **34** and **35** from the obtained **33a** and **33h** (Scheme 11). These examples suggest the usefulness of the aminoazidation method for constructing diversely functionalized nitrogen-containing skeletons.

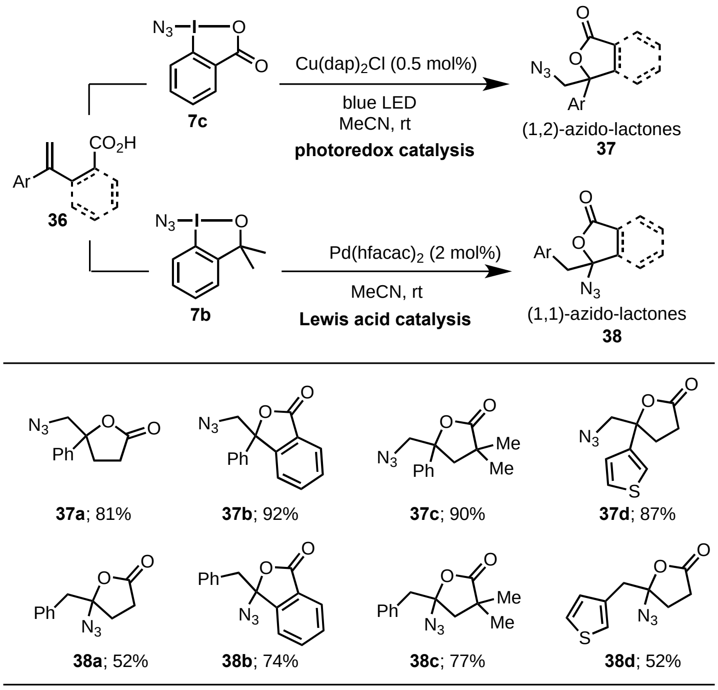


Scheme 10. Cu-Catalyzed aminoazidation of inactivated alkenes **32** with azidobenziodoxolone **7c**

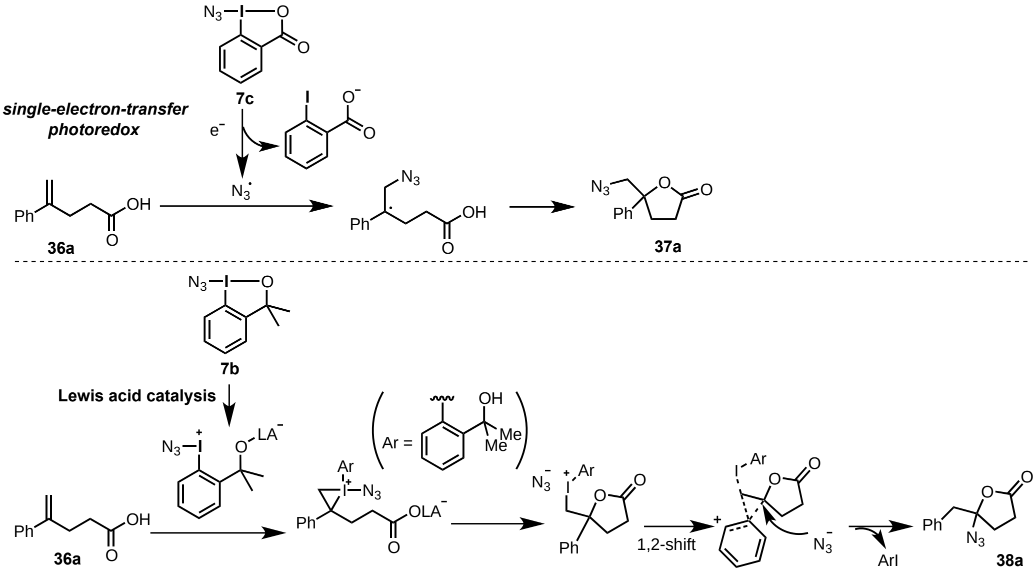


Scheme 11. Synthesis of 1,2-diamine-containing bioactive compounds

In 2017, Waser et al. developed a versatile synthesis of azidolactones through cyclization of alkene-containing carboxylic acids **36** triggered by cyclic azidoiodinane (Scheme 12)[22] and selectively synthesized (1,1) and (1,2) azidolactones based on photoredox[23] or palladium catalysis. Thus, the photoredox activation of azidobenziodoxolone **7c** resulted in the formation of an azide radical, which reacted with the alkenes to form 1,2-azidolactones **37a**–**d**. However, the radical was not formed from the weaker oxidizing agent, azidobenziodoxole **7b**, and the use of $Pd(hfacac)_2$ as a Lewis acid yielded 1,1-azidolactones **38a**–**d**, through iodination, a 1,2-aryl shift, and an azidation sequence (Scheme 13).



Scheme 12. The 1,2- and 1,1-azido-lactonizations of styrene derivatives controlled by photoredox and Lewis acid catalysts



Scheme 13. Mechanistic differences between photoredox and Lewis acid catalysis

3. HETEROCYCLE SYNTHESIS USING CYCLIC HYPERVALENT IODINE CYANIDE

Five-membered cyclic hypervalent iodine(III) compounds are more stable than their acyclic analogs.[24] In the mid-1990s, Kita[7] and Zhdankin[8b] independently reported the preparation of stable cyanobenziodixoxlone **8a**. The one-step transformation to cyanobenziodoxolone **8a** was made possible by treatment of acetoxybenziodoxolone **4a** with trimethylsilylcyanide at room temperature. The colorless crystalline **8a** was obtained in 65% yield with a fully characterized structure;[7] in IR data, **8a** showed the characteristic absorption of the cyano group at 2161 cm^{-1}. Moreover, Kita et al. determined the stereostructure of cyanoiodinane by single-crystal X-ray analysis (Figure 3),[7] revealing that—similar to those of other reported cyclic iodinanes[24b,e,f]—cyanobenziodoxoxlone **8a** is approximately T-shaped around the iodine atom, whereas the exocyclic C-I bonds (2.11 and 2.13 Å) are slightly shorter than the endocyclic I-O bonds (2.218 and 2.221 Å). Zhdankin et. al. showed several examples that cyanobenziodioxoxlone **8a** could be used as a cyanating agent,[8b] but new synthetic applications first appeared in the literature in 2015.[25,26]

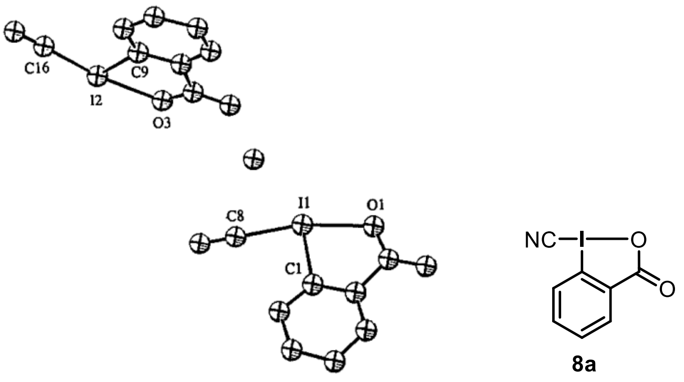
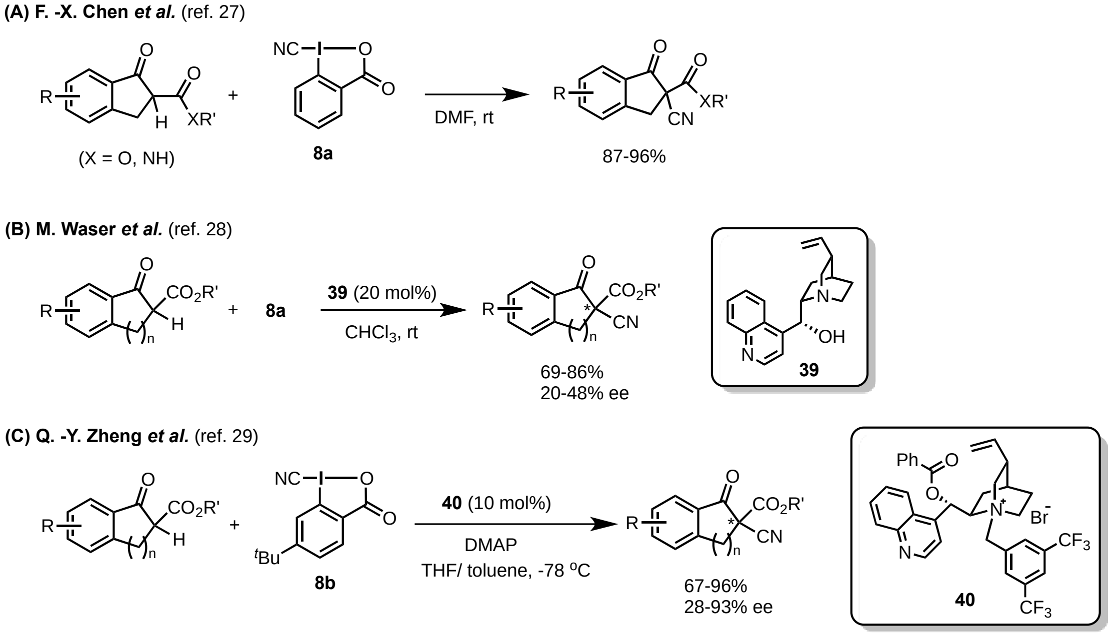


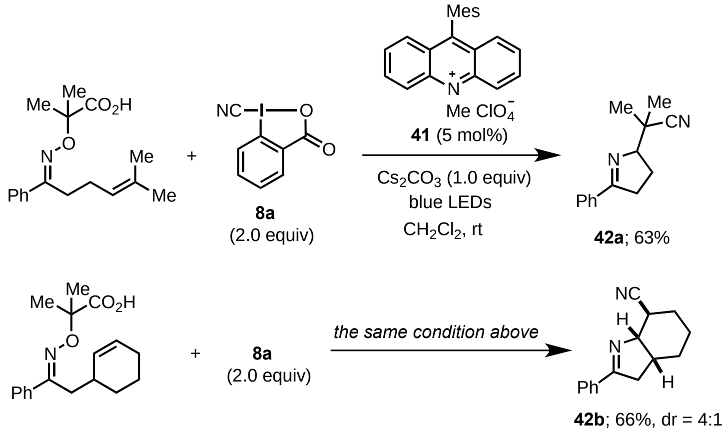
Figure 3. The first X-ray crystallographic structure of cyanobenziodoxolone **8a**·1/2H_2O
(Two molecules of **8a** and one molecule of H_2O are shown. This figure is extracted from reference 7;
S. Akai, T. Okuno, M. Egi, T. Takada, H. Tohma, and Y. Kita, *Heterocycles*, 1996, **42**, 47.)

In 2015, Chen et al. reported the α-cyanation of cyclic β-ketoesters in high yields by using cyanobenziodoxolone **8a** (Scheme 14A).[27] An asymmetric version was almost simultaneously achieved by Waser et al. using cinchona alkaloid **39** as a chiral orgnocatalyst (Scheme 14B).[28] Additionally, Zheng et al. reported the application of benziodoxolone **8b** in the highly enantioselective α-cyanation of β-ketoesters using a modified cinchona phase-transfer catalyst **40**. The introduction of the *tert*-butyl group in benziodoxolone **8b** was crucial to enhance the solubility of the organic solvents, enabling rapid reaction progress at low temperatures and improving enantioselectivity (Scheme 14C).[29] The obtained cyanoketone derivatives are the useful synthetic precursors for preparing functionalized heterocyclic compounds.[30]

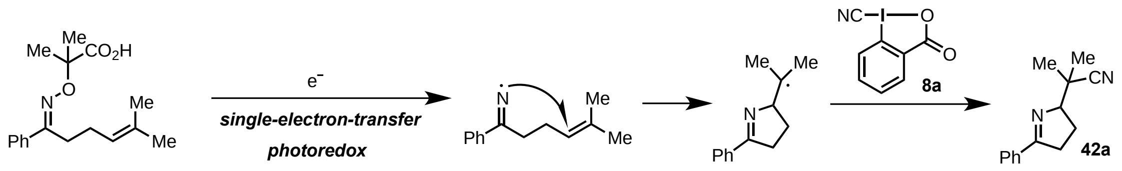


Scheme 14. α-Cyanation of ketoesters with benziodoxolone reagents **8**

In 2017, Leonori et al. developed the photoredox imino functionalization of olefins in the presence of methyl acridinium perchlorate **41**[31] to synthesize highly functionalized nitrogen heterocycles. For example, the formation of **42** was reported by using cyanobenziodoxolone **8a** (Scheme 15).[32] In this reaction, oxidative generation of iminyl radicals and subsequent cyclization/radical trapping allowed the effective construction of polyfunctionalized heterocycles, which are valuable building blocks (Scheme 16).

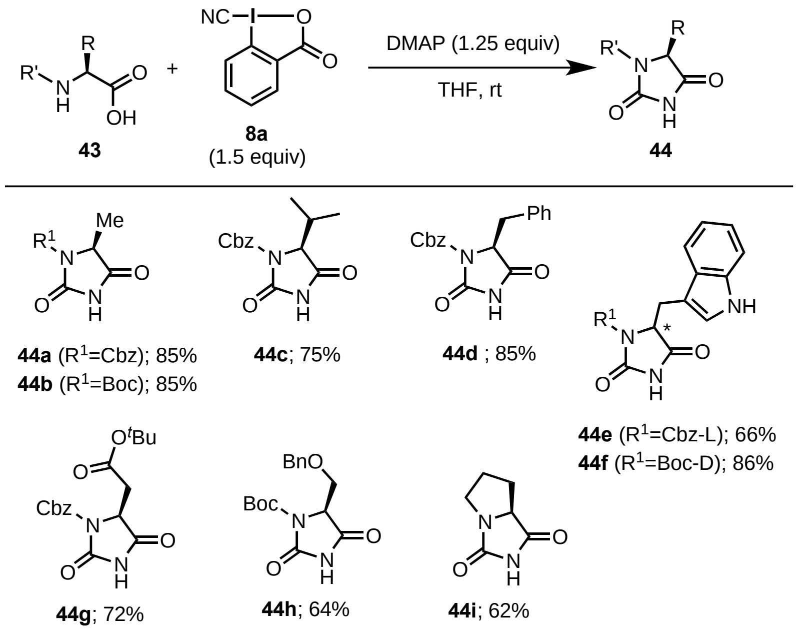


Scheme 15. Photoredox imino functionalization of olefins with cyanobenziodoxolone **8a**

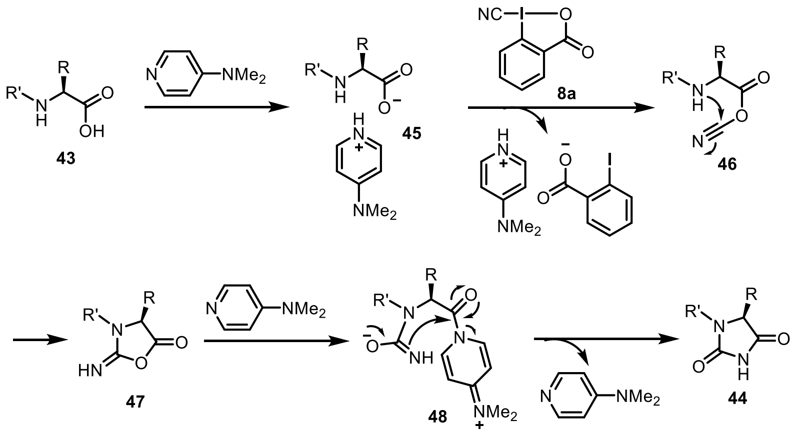


Scheme 16. Plausible mechanism involving imidyl radical formation

In 2019, Waser et al. developed the synthesis of enantiopure 1,5-substituted hydantoins **44** from commercially available chiral-protected amino acids **43** without epimerization by utilizing cyanobenziodoxolone **8a** as an electrophilic carbon source in the presence of DMAP (Scheme 17).[33] Screening of other cyanating agents, such as BrCN, ICN, and 1-cyano-4-dimethylaminopyridinium tetrafluoroborate (CDAP)—instead of cyanoiodinane **8a**—resulted in inferior yields. The mechanism is conceptualized in Scheme 18. The deprotonation of amino acid **43** by DMAP led to the formation of carboxylate **45**. Cyanation with cyanoiodinane **8a** yielded *O*-cyano intermediate **46**, which then underwent cyclization and possibly generated the corresponding 2-iminooxazolidin-5-one **47**. Subsequent rearrangement of **47** to a more stable hydantoin **44** might be accelerated by DMAP as a nucleophilic catalyst for the ring-opening intermediate **48**, although several alternative pathways were proposed related to the reaction processes and cyano transfer steps.

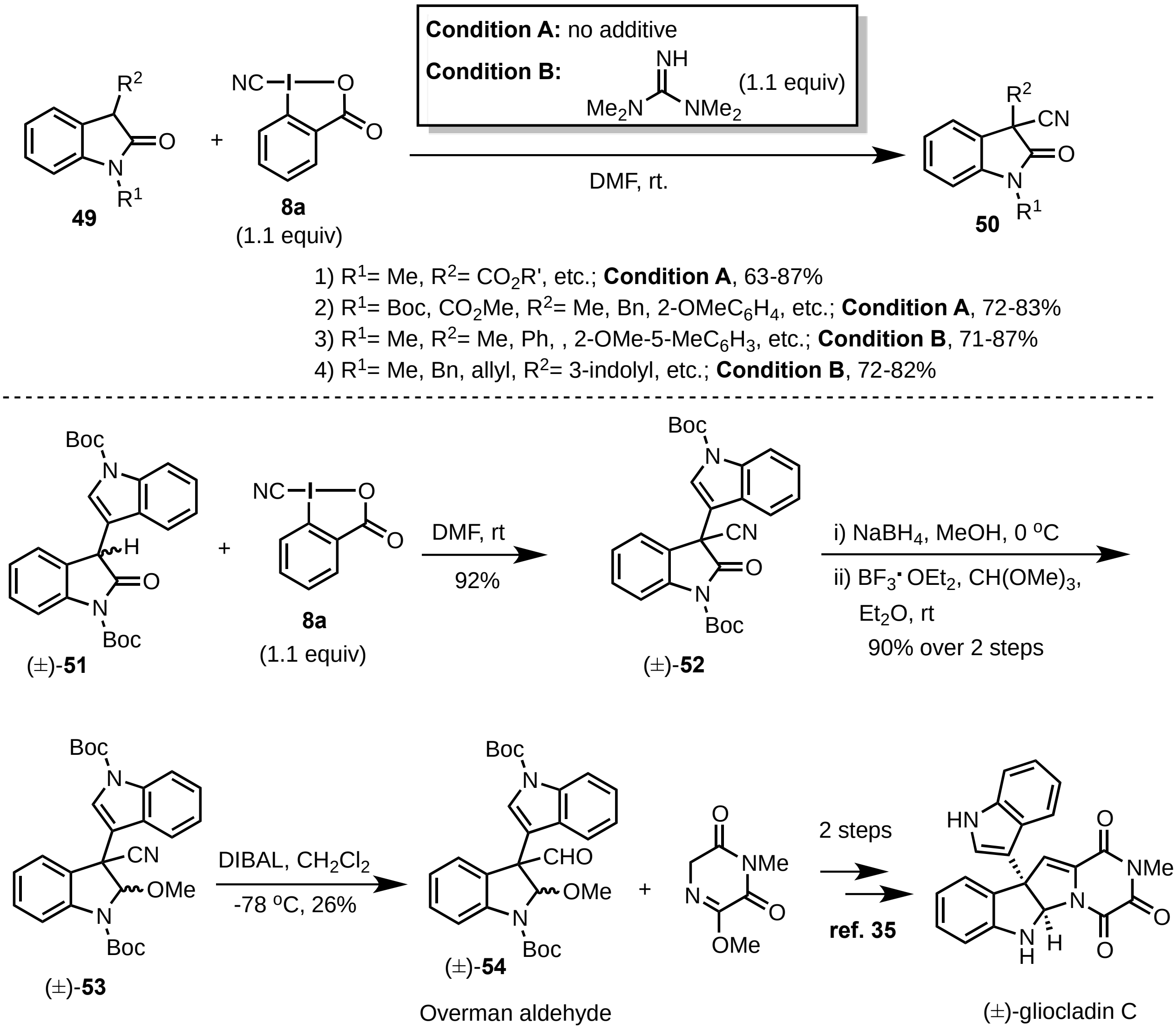


Scheme 17. Synthesis of enantiopure 1,5-substituted hydantoins **44** with cyanobenziodoxolone **8a**



Scheme 18. Plausible mechanism for the hydantoin formation

In 2020, Bisai and co-workers reported the efficient cyanation of 3-alkyl/aryl 2-oxindoles **49** using cyanobenziodoxolone **8a** under transition metal-free conditions to synthesize a wide variety of 3-cyano 3-alkyl/aryl 2-oxindoles **50** (Scheme 19).[34] As an application of this process, they also demonstrated the formal total synthesis of (±)-gliocladin C[35,36] in a few steps. The oxidative cyanation of dimeric indolinone **51** was performed on a gram-scale to yield **52** with 92% yield. The cyanated product **52** could be then converted to the Overman aldehyde **54**[35] in 3 steps; in other words, $NaBH_4$ reduction of indolinone followed by a reaction with $HC(OMe)_3$ in the presence of $BF_3 \cdot OEt_2$ to produce compound **53** with 90% overall yield in two steps. The cyanide functionality of **53** was reduced using DIBAL-H to obtain Overman aldehyde **54**, which was used as a common intermediate for the total synthesis of (±)-gliocladin C.



Scheme 19. Formal total synthesis of (±)-gliocladin C utilizing cyanobenziodixoxlone **8a**

4. RECENT APPLICATIONS OF CYCLIC HYPERVALENT IODINE NITRATE

In 1996, Kita et al. prepared and isolated cyclic iodinane bearing a nitrato ligand for the first time and demonstrated that the reaction of acetoxybenziodoxole **4b** with trimethylsilyl nitrate ($TMSONO_2$) produced nitratobenziodoxole **9** with 74% yield; however, this method was not preferable, because $TMSONO_2$ is somewhat unstable. A more effective and convenient synthesis of this compound was thus established by the ligand exchange reaction of chlorobenziodoxole with three equivalent $AgNO_3$, without a catalyst. Benziodoxole **9**—obtained with 98% yield—is very stable and can be stored under ambient conditions for up to one year without observing decomposition. Figure 4 shows that single-crystal X-ray analysis of nitratobenziodoxole **9** displayed typically distorted T-shaped geometry.[7] The exocyclic O-I bonds (2.26 Å) are slightly longer than the endocyclic I-O and I-C bonds (2.00 and 2.08 Å). This bond relationship is reversed when compared to the cyano analogue **8a** and should be related to the differences in the electron negativity of these two ligands. Benziodoxole **9**, a stable and easy-to-handle hypervalent iodine compound that seems to be applicable as a unique source of the nitrooxy functional group, was not exploited in organic synthesis until 2020.

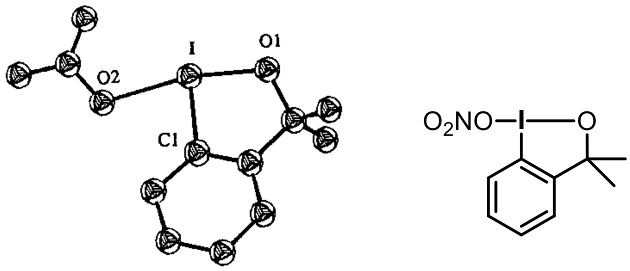


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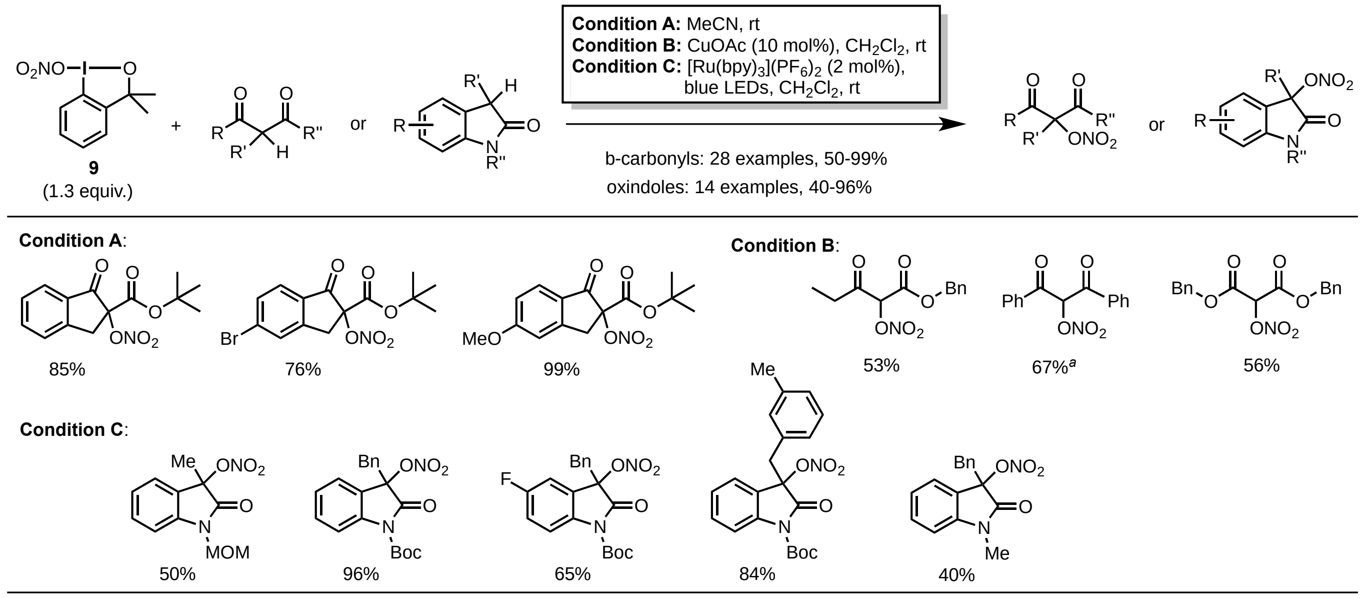
Figure 4. The first X-ray crystallographic structure of nitratobenziodoxole **9**
(This figure is extracted from reference 7; S. Akai, T. Okuno, M. Egi, T. Takada, H. Tohma, and Y. Kita, *Heterocycles*, 1996, **42**, 47.)

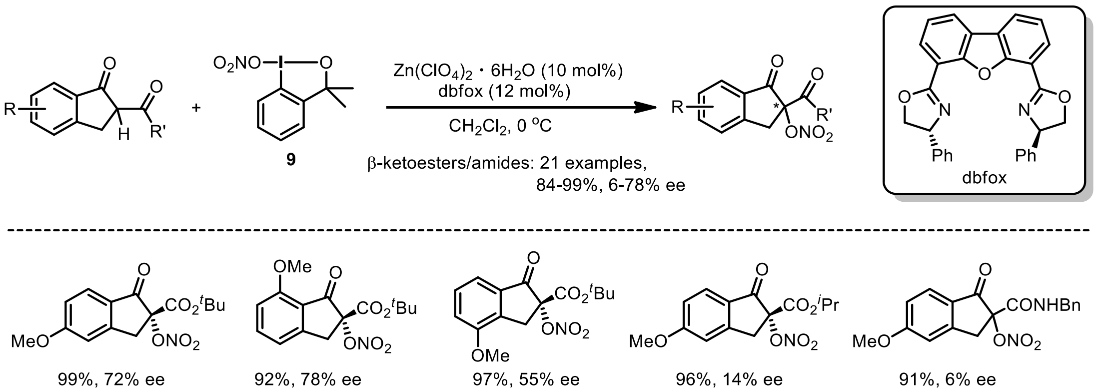
In 2020, Katayev et al. demonstrated that benziodoxole **9** enabled a direct and selective nitrooxylation of enolizable C-H bonds to access a broad range of organic nitrate esters (Scheme 20).[37] Activation of benziodoxole **9** by adding Brønsted and Lewis acids was effective for the synthesis of nitrooxylated β-ketoesters, 1,3-diketones, and malonates, whereas activation under photoredox catalysis was utilized for the synthesis of nitrooxylated oxindoles.



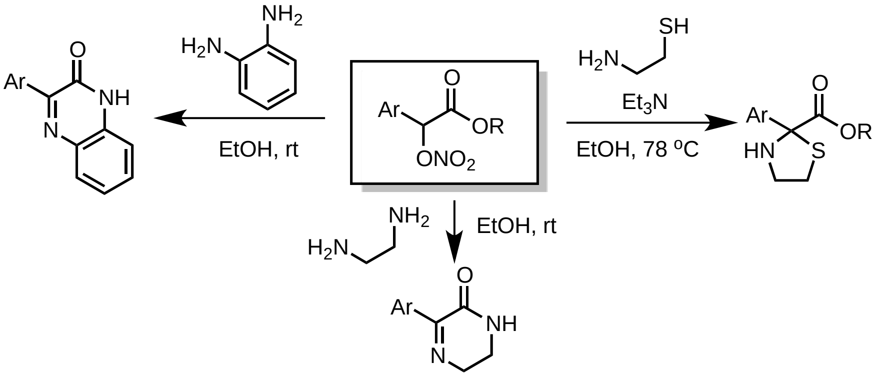
a) 3 Equivalents of substarate employed.

Scheme 20. Nitrooxylation of enolizable C-H bonds with nitratobenziodoxole **9**

Deng and co-workers very recently reported the first asymmetric nitrooxylation of cyclic β-ketoesters/amides using benziodoxole **9** with a chiral Zn-dbfox catalyst (Scheme 21).[38] A series of chiral α-nitrooxy β-ketoesters/amides were prepared in high yields with low to moderate enantioselectivities. For the preparation of chiral α-nitrooxy β-ketoesters, the *tert*-butyl group on the ester was crucial for stereocontrol; thus, small groups of methyl, ethyl, and isopropyl showed only low ee values. Additionally, β-ketoamides were smoothly reacted under standard reaction conditions to access the desired products with high yields and low stereoselectivities (6–20% ee). It should be noted that all these obtained nitrooxylated compounds can be used as useful synthetic intermediates in heterocyclic synthesis (Scheme 22).[39]



Scheme 21. Asymmetric nitrooxylation of cyclic β-ketoesters/amides



Scheme 22. Nitrooxylated compounds as useful synthetic intermediates in heterocyclic synthesis

5. CONCLUSION

The preparation and high stability of cyclic hypervalent iodine(III) compounds involving azido, cyano, and nitrato ligands was suggested in the mid-1990s but there were not exploited in organic synthesis until this decade. These obscure hypervalent iodine compounds are being recognized as efficient and powerful agents for the formation of a variety of highly functionalized heterocyclic compounds. The synthetic utility of cyclic hypervalent iodine(III)-mediated protocols have been demonstrated by the preparation of several bioactive compounds. Further developments of new synthetic transformations in this area by applying these cyclic azido, cyano, and nitrato-iodanes are highly expected in future studies.

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