Review

Azidoindolines—From Synthesis to Application: A Review

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Abstract: Azide-containing compounds, organic azides, showcases a variety of reactivities, making them highly convenient and chameleonic intermediates. An indoline derivative has been proven to be of great significance in drug discovery due to its sp^3-rich property. In this context, it is interesting to perform such vigorous azidation on medicinal-relevant indoles/indolines, resulting in the production of sp^3-rich azidoindolines. The potential biological activity, in combination with the sp^3-rich indoline bearing the azido moiety, makes azidoindolines an attractive synthetic target for medicinal and synthetic chemists. This review describes recent advances in the synthesis and application of azidoindolines: (1) iodine-mediated azidations, (2) metal-catalyzed azidations, (3) electrochemical azidations, (4) photochemical azidations, (5) azidation using a combination of an oxidant and an azide source, and (6) nucleophilic azidation.

Keywords: azidoindolines; indole; azido; synthesis; application

1. Introduction

Indoles and indolines are privileged structures that are found in natural products and pharmaceutical agents, exhibiting significant biological activities [1–6]. In particular, one indoline derivative has been proven to be of great significance in drug discovery due to its sp^3-rich property [7–9]. The construction of the sp^3-rich framework needs regio- and stereoselective methodologies, whic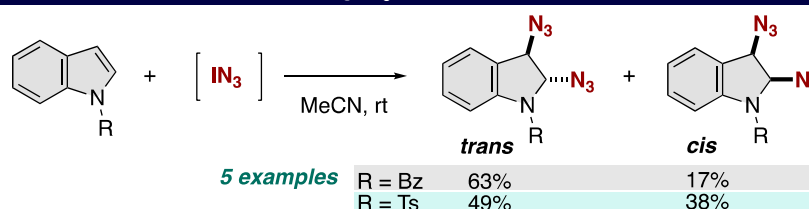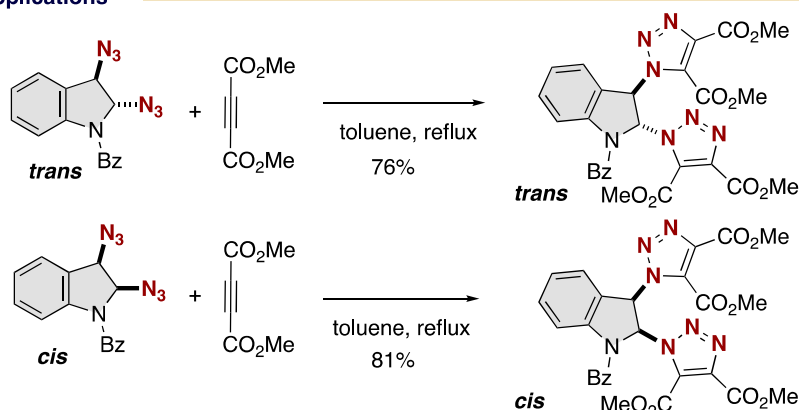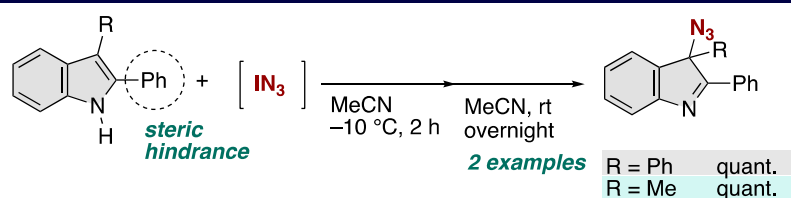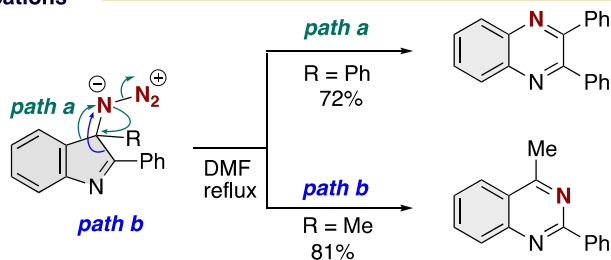h are difficult to realize. Therefore, efficient and divergent syntheses of added-value indolines are a pivotal challenge for medicinal and organic chemists [10–12].

Azide-containing compounds, organic azides, showcases a variety of reactivities, such as the Staudinger reaction [13], the aza-Wittig reaction [14], the click reaction [15], and C–H amination [16], making them highly convenient and chameleonic intermediates. Along with the recognition of azide radicals as a versatile species and the bloom of catalytic reactions, many protocols and precursors for azide radicals generated from NaN_3, XN_3, $TMSN_3$, and azidoiodinane have been developed [17–19].

In this context, it is interesting to perform a vigorous azidation on medicinal-relevant indoles/indolines, resulting in the production of sp^3-rich azidoindolines. The potential biological activity, in combination with the sp^3-rich indoline bearing the azido moiety, makes azidoindolines an attractive synthetic target for medicinal and synthetic chemists. This review describes recent advances in the synthesis and application of azidoindolines: (1) iodine-mediated azidations, (2) metal-catalyzed azidations, (3) electrochemical azidations, (4) photochemical azidations, (5) azidation using a combination of an oxidant and an azide source, and (6) nucleophilic azidation.

2. Azidation of Indoles Using Iodine Reagents

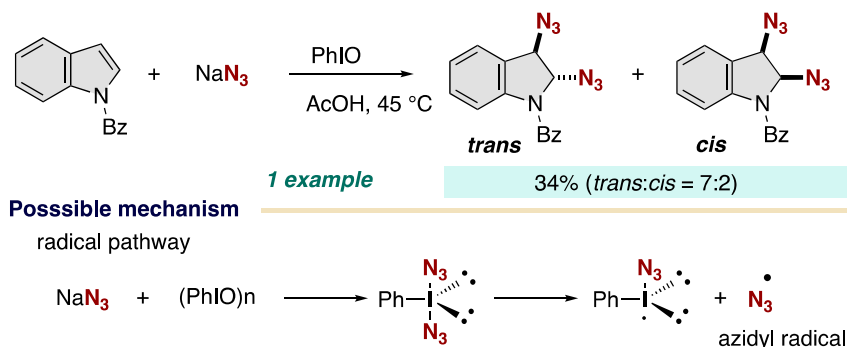In the past decades, diverse methodologies for the dearomatization of indoles have been developed. However, azides have rarely participated in the dearomatization of indoles [20,21]. Pioneering work on an azidoindoline synthesis was achieved by Ikeda's group in 1975 (Scheme 1A) [22]. By taking advantage of a homolytic cleavage of the iodine–nitrogen bond, the dearomatized azidation of indoles was accomplished.

A: 2,3-Diazidation of indoles using IN₃

6 examples   80–93% yields (*trans:cis* mixture)

B: 2,3-Diazidation of indoles using IN₃

5 examples	*trans*	*cis*
R = Bz	63%	17%
R = Ts	49%	38%

Applications

C: Azidation of 2,3-disubstituted indoles using IN₃

2 examples	
R = Ph	quant.
R = Me	quant.

Applications

Scheme 1. Early report on direct azidations of indoles using IN₃.

In 1978, the [3 + 2] cycloaddition reaction of *trans*- or *cis*-diazidoindolines with acetylene dicarboxylate was reported by the same group (Scheme 1B) [23]. The two examples of sp³-rich triazoles construction can be obtained by this protocol.

In 1976, the Ikeda's group also found that 3-azidoindolenine participated in the switchable synthesis of a quinoxaline and a quinazoline in DMF under reflux conditions (Scheme 1C) [24]. The bulky phenyl group may contribute to the formation of 3-azidoindolenine through monoazidation at the C3 position of 2-phenylindoles. This IN₃ was quite unstable and explosive, and it must be used in situ. Thus, a mild protocol is necessary for expanding the scope of azidation of indoles via azide radical generation.
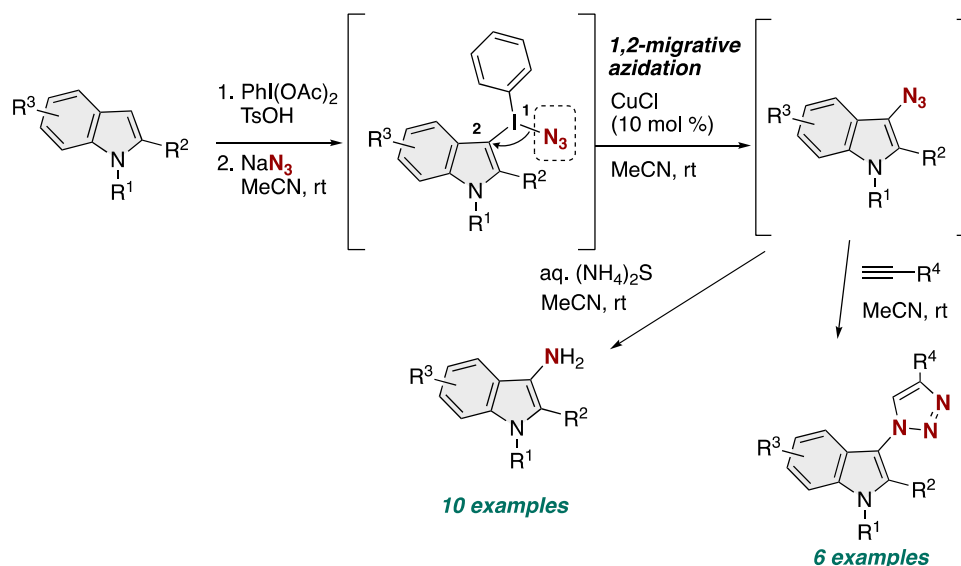
In 1986, Moriarty et al., reported the direct diazidation of indoles using a combination of PhIO and NaN_3 (Scheme 2) [25]. The homolytic cleavage of the iodine–nitrogen bond of hypervalent iodine $PhI(N_3)_2$ gives an azidyl radical and $PhIN_3^{\bullet}$ radical, which undergo abstractions of hydrogen bonding and azidation. In general, $PhI(N_3)_2$ generated from PhIO, $PhI(OAc)_2/NaN_3$, or $TMSN_3$ is highly reactive and unstable [26]. Thus, optimization of the reaction conditions may occasionally result in an insufficient outcome.

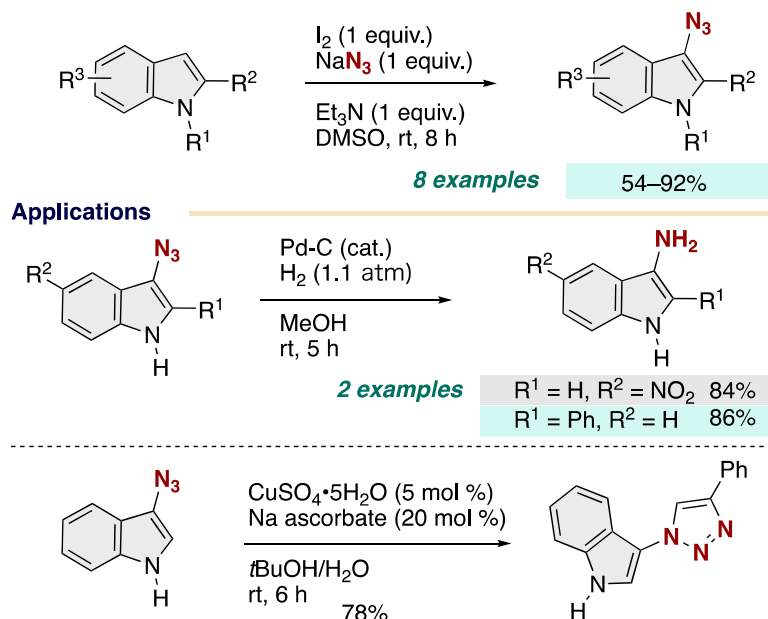**Scheme 2.** Diazidations of indoles using NaN_3 and PhIO.

Over the past decade, hypervalent iodine reagents have been shown to be useful reagents to achieve umpolung disconnections [27]. Various nucleophiles can be changed into electrophiles by these iodine reagents. The introduction of reactive yet stable indolyl iodonium salts has led to the development of broadly applicable reactions.

In 2011, applications of more stable indole-based iodonium reagents were introduced by Suna and co-workers (Scheme 3) [28]. The azide acted as not only as a group transfer reagent but also as a stabilizer against the iodonium reagents. However, the indolylazides are also unstable and the reaction should be performed on site and in situ. Consequently, a Cu(I)-catalyzed azidation/reduction and azidation/1,3-cycloadition have been conducted in a one-pot operation.
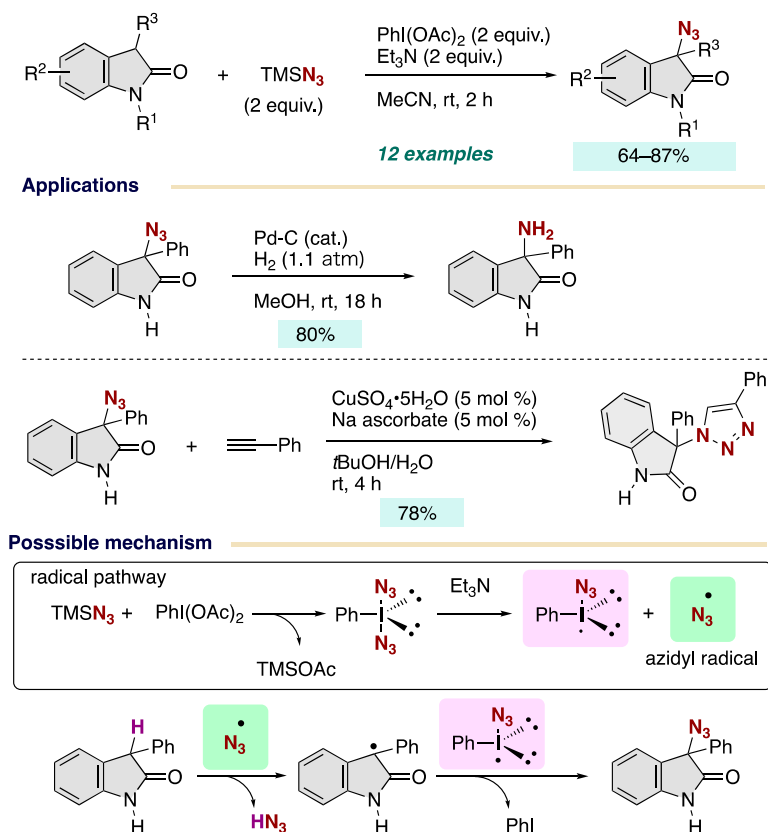

Scheme 3. Direct azidation of indoles through the in situ formation of indole-based iodonium intermediates.

In 2016, Sudalai found that a simple combination of molecular iodine and NaN_3 could be used for the direct umpolung azidation of indoles, affording 3-azidoindoles (Scheme 4) [29]. Reduction and 1,3-dipolar cycloaddition have been conducted.
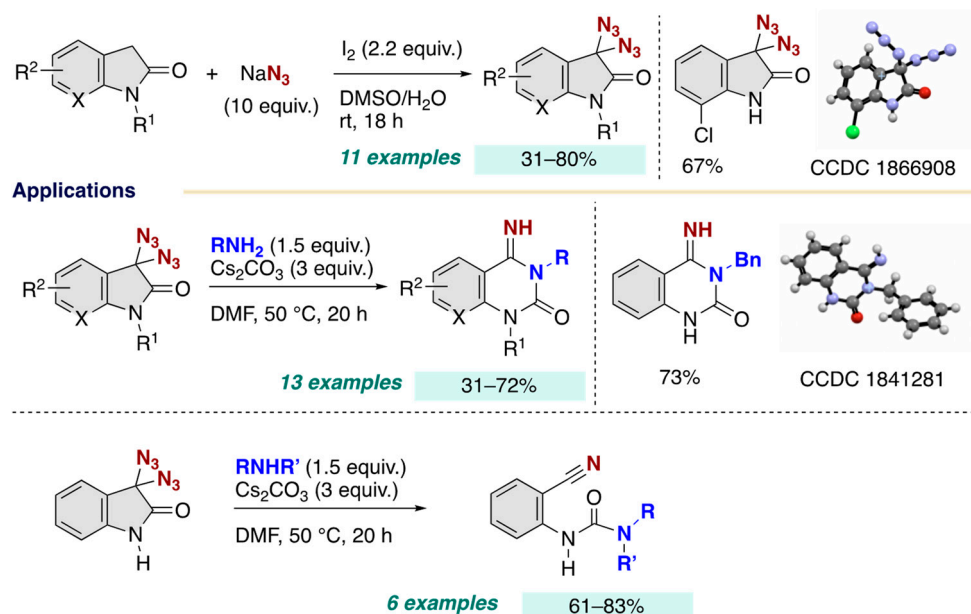
Scheme 4. Umpolung direct azidation of indoles using I_2 and NaN_3.

In the system of $TMSN_3$, $PhI(OAc)_2$, and Et_3N, radical coupling of 3-substituted 2-oxindoles with an azidyl radical takes place in the absence of a transition metal catalyst (Scheme 5) [30]. To promote this transformation, the C3-aryl group plays an important role. It is proposed that the azidyl radical generates through a cleavage of the iodine–nitrogen bond of diazidoiodine(III) [$PhI(N_3)_2$], generated in situ. 3-substituted 3-azido-2-oxindoles participated in the H_2/Pd-C reduction and Cu-catalyzed 1,3-dipolar cycloaddition.
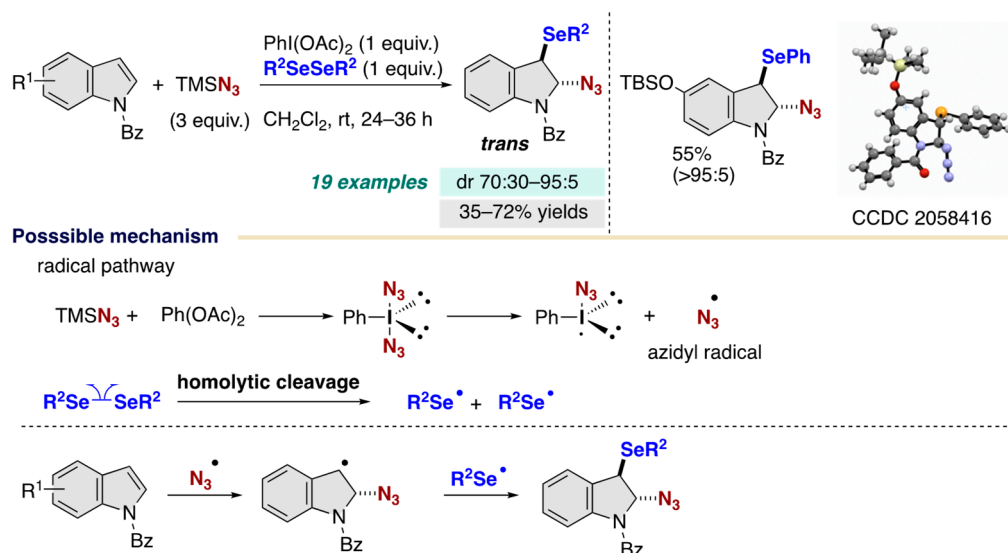

Scheme 5. Direct azidation of indoles using $TMSN_3$. $PhI(OAc)_2$ and Et_3N.

In the system of NaN_3 and I_2, the radical coupling of 2-oxindoles with an azide radical takes place in the absence of a transition metal catalyst (Scheme 6) [31]. The 3,3-diazido-2-oxindoles showed new reactivities against amine nucleophiles, with a release of N_2, affording quinazolinone derivatives and cyanophenylureas. The structure of a quinazolinone derivative was determined by using X-ray crystallography (CCDC 1841281).

Scheme 6. Metal-free direct azidation of 2-oxindoles using NaN_3 and I_2.

In 2023, a metal-free radical coupling of indoles with an azidyl radical and a selenyl radical was reported (Scheme 7) [32]. 3-alkyl- and aryl selenyl indolines bearing the azide moieties can be obtained by this protocol. The structure of aryl selenyl indoline was determined by using X-ray crystallography (CCDC 2058416).

Scheme 7. Metal-free selenyl azidation of indoles using $TMSN_3$ and $PhI(OAc)_2$.
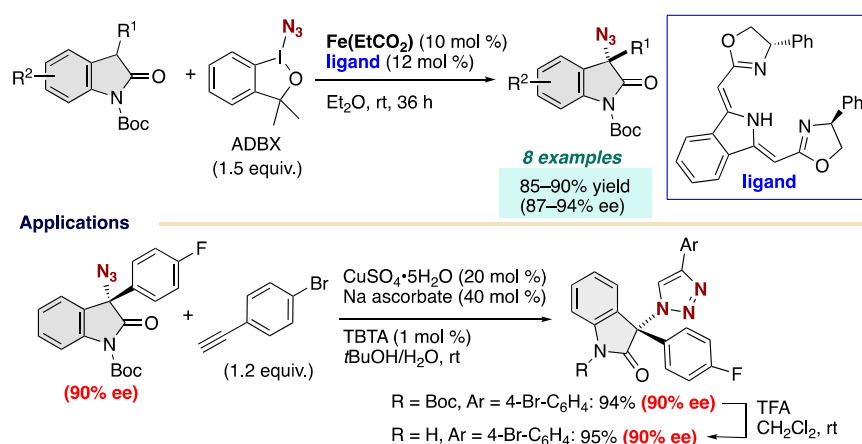
A possible reaction mechanism was also proposed. First, an azidyl radical is generated from $TMSN_3$ and $PhI(OAc)_2$. Then, azidyl radical addition at the C2 position of the indoles occurs, generating a C3 radical. The C3 radical intermediates simultaneously are

captured by the selenyl radical (generated by homolytic cleavage of RSe-SeR) to afford 2-azido-3-selenylindolines with high diastereoselectivity.
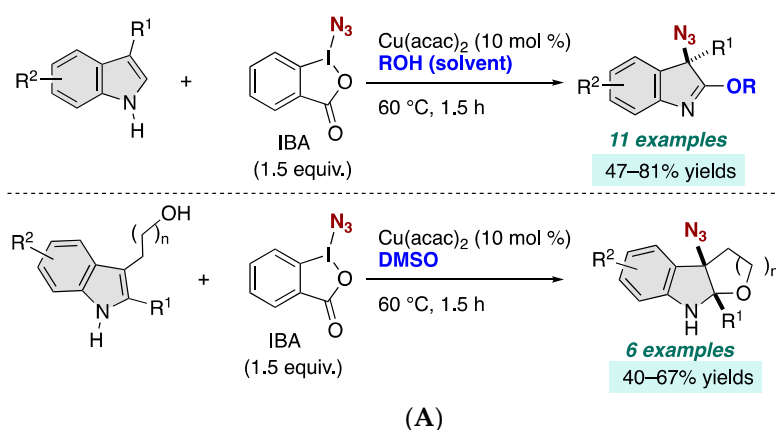
3. Metal-Catalyzed Azidation of Indoles

Transition metals such as Mn, Fe, and Cu have a pivotal role in the radical azidation process by generating the azide radical or metal–azide species [33–37].

In 2013, the Gade group reported the $(EtCO_2)_2Fe$-catalyzed enantioselective azidation of β-ketoesters and oxindoles using azidobenziodate ABDX as an azide transfer reagent (Scheme 8) [38]. A combination of iron propionate/chiral pincer-type tridentate ligand/azidobenziodate gave a high isolated yield with high enantioselectivity. By subjecting the Cu-catalyzed azide-alkyne 1,3-dipolar cycloaddition (click reaction), 3-azido-2-oxindoles (90% ee) gave a 94% triazole yield, with 90% ee. Subsequently, the Boc group was removed by TFA in CH_2Cl_2, resulting in the isolation of N-H-triazole in a 95% yield with 90% ee.

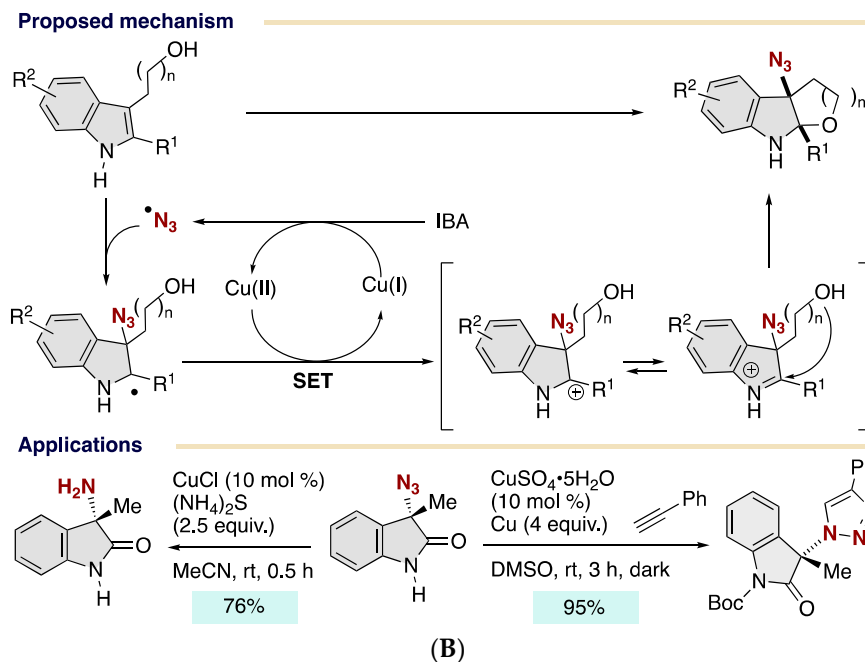**Scheme 8.** Iron-catalyzed enantioselective azidation of indoles.

In 2014, Jiao found that a merge of stable hypervalent cyclic iodine reagents (IBA-N_3, Zhdankin reagents) and $Cu(acac)_2$ can be used as a source of azide radicals for the direct azidation of indoles (Scheme 9A) [39]. This protocol afforded 3-azidoindolenine and 3-azido-2-oxiindoles under mild conditions.
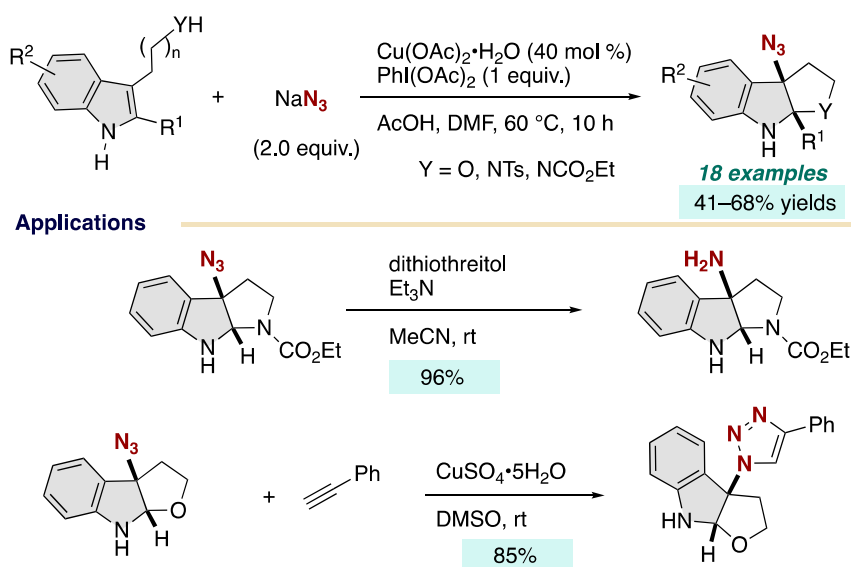

(A)

Scheme 9. *Cont.*

Scheme 9. (**A**) Copper-catalyzed oxyazidation of indoles. (**B**) Possible mechanism for the copper-catalyzed oxyazidation of indoles.

The radical mechanism involving the redox system between Zhdankin reagents and $Cu(acac)_2$ was also proposed (Scheme 9B). By subjecting the reaction of the obtained 3-azidoindolines to phenylacetylene, triazole can obtain in a 95% yield.
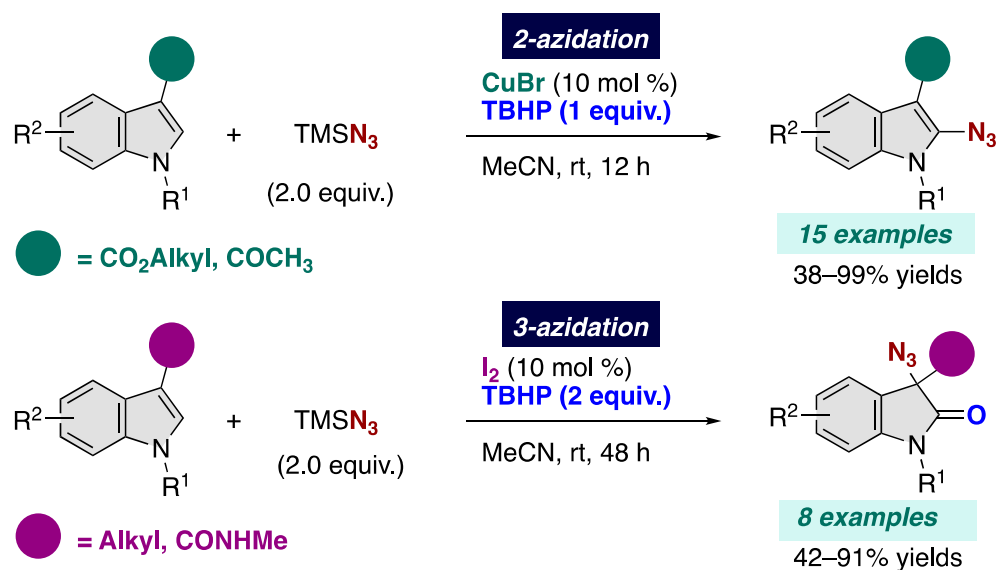
Based on the above precedent, an alternative protocol using $PhI(OAc)_2$-NaN_3 instead of Zhdankin reagents was reported by Hong, Wang, and co-workers (Scheme 10) [40]. The reaction mechanism is similar to that proposed in Scheme 8. The obtained 3-azidopyrroloindoline was converted to an amine derivative. In addition, the click reaction of 3-azidofuroindoline with phenylacetylene provided the triazole-containing furoindoline in an 85% yield.

Scheme 10. Copper-catalyzed oxyazidation of indoles using $PhI(OAc)_2$ and NaN_3.
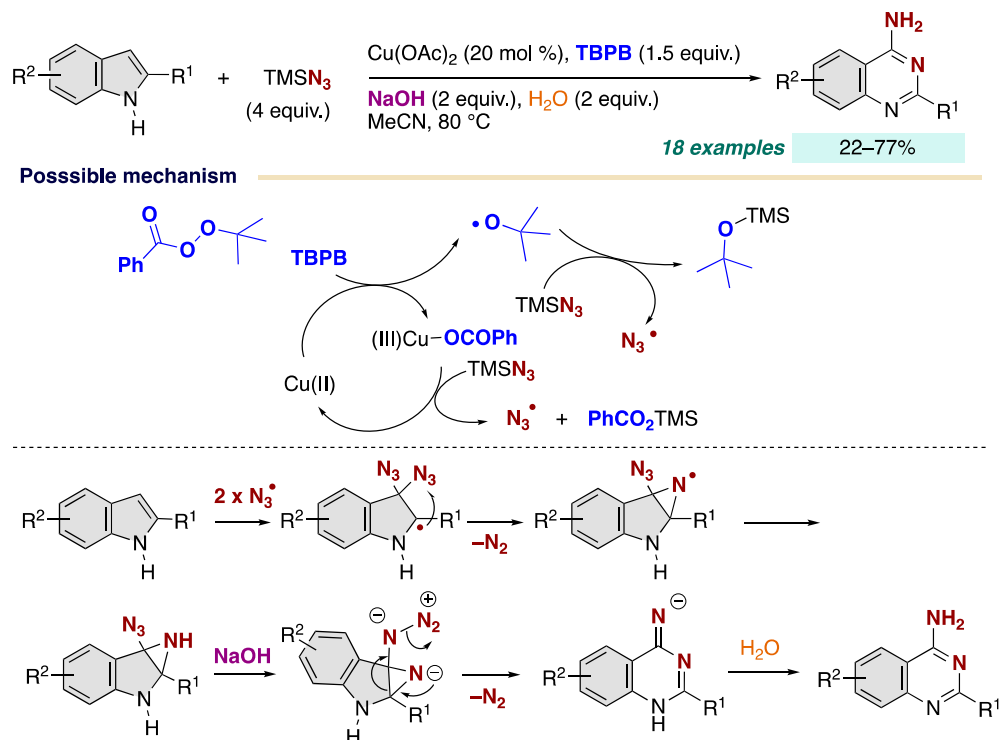
The radical azidation involving the redox system can also participate in a switchable synthesis of 3-azidoindoles and 2-azidoindoles (Scheme 11) [41]. A radical less-stabilizing group, such as an alkyl or amide at the C3 position of indoles, results in C3 azidation

through a C2 radical intermediate, while an ester or ketone at the C3 position of indoles leads to 2-azidoindoles through the C3 radical intermediate. All of the obtained products possess the pharmaceutically important pharmacophore, which may lead to drug discovery.

Scheme 11. Switchable synthesis of 3-azido- or 2-azidoindoles.

In 2018, Ji and co-workers reported the efficient synthesis of 2-arylquinazolin-4-amines through ring expansion triggered by the 3,3-diazidation of indoles (Scheme 12) [42]. TBPB (*tert*-butyl peroxybenzoate) plays an important role in generating the *tert*-buthoxy radical. The novel ring rearrangements can be explained, as the cascade process involves C3-selective diazidation, cyclization, and ring expansion.

Scheme 12. Copper-catalyzed 3,3-diazidation, cyclization, and ring expansion sequence.

In 2018, Xu and co-workers reported a new iron-catalyzed diazidation of indoles via the tridentate nitrogen–ligand-promoted activation of peroxyester TBPB as a *tert*-butoxy radical source (Scheme 13) [43]. This work revealed that the combination of TMSN₃ and an iron catalyst suppressed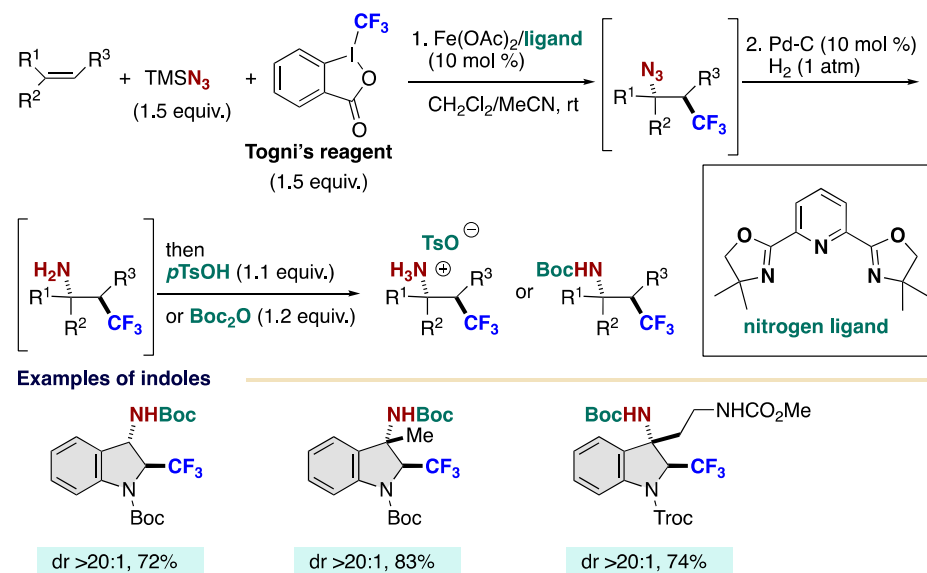 the non-productive oxidant decomposition pathway, unlike the cyclic hypervalent iodine reagent method. *i*PrOH can promote the generation of an azidyl radical from TMSN₃ by the *tert*-butoxy radical.

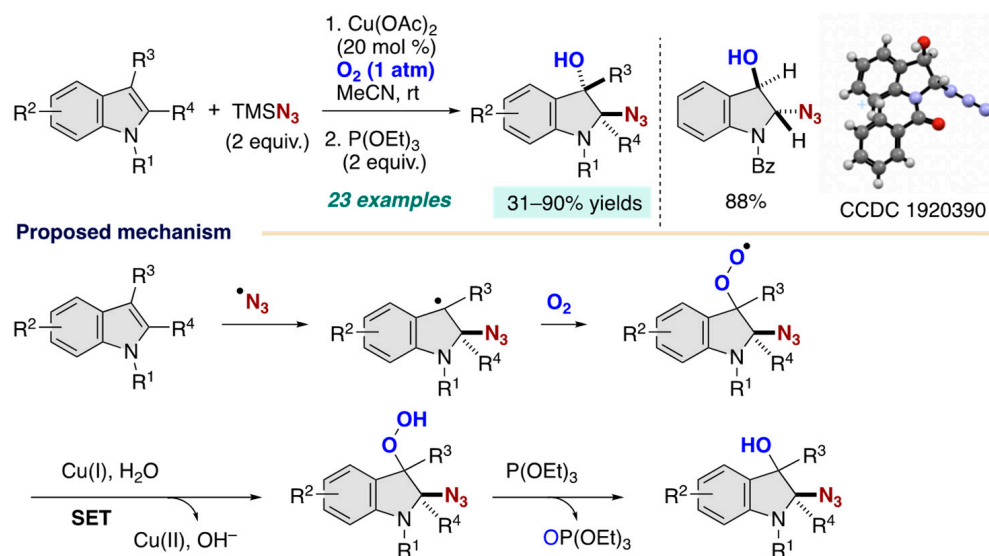**Scheme 13.** Iron-catalyzed 2,3-diazidation of indoles.

In order to extend their iron–azide chemistry, an iron-catalyzed azidotrifluoromethylation of indoles was developed by Xu and co-workers in 2018 (Scheme 14) [44]. The iron-catalyst plays a dual role in the generation of an azido radical from TMSN₃ and a trifluoromethyl radical from Togni's reagent. This work also revealed that TMSN₃ is necessary for iron catalyst regeneration through TMSN₃-mediated anion metathesis.

Scheme 14. Iron-catalyzed azidotrifluoromethylation of indoles.

In 2019, Ji and co-workers reported the copper-catalyzed oxidative hydroxyazidation of indoles (Scheme 15) [45]. The reaction was initiated by the addition of an azidyl radical at the C2 position, and subsequent O₂-trapping to afford a peroxyradical. Then, the peroxyradical underwent SET by Cu(I) and protonation by H₂O to yield a hydroxyperoxy intermediate. Finally, the reduction of the hydroxyperoxy intermediate by triethyl phosphite P(OEt)₃ afforded the 3-hydroxy-2-azidoindolines. The origin of the high trans-

selectivity is unknown, although this reaction features a broad substrate scope with quite high regio- and diastereoselectivities.

Scheme 15. Copper-catalyzed oxidative hydroxyazidation of indoles under O_2.

In 2019, Wei, Liu, and co-workers reported the C(sp^3)-H azidation of 2-oxindoles catalyzed by Cu(OAc)$_2$ with TMSN$_3$ in MeCN at 40 °C (Scheme 16) [46]. Interestingly, the reaction pathway involves the addition of an azido radical to the enol tautomer. This protocol is convenient because of the mild reaction conditions, with a short reaction time and broad substrate scope that includes biologically important products.

Scheme 16. Copper-catalyzed azidation of 2-oxindoles.

In 2020, Zhu and co-workers reported the copper-catalyzed 2,3-diazidation of indoles with the assistance of N1-directing groups (Scheme 17A) [47]. This protocol exhibits wide functional group compatibility and enables the further synthesis of vicinal diamines, triazoles, and benzotriazoles (Scheme 17B). The directing group can be removed by sodium ethoxide in DMSO after the reaction.

Scheme 17. (**A**) Copper-catalyzed 2,3-diazidation of indoles with the assistance of directing groups. (**B**) Follow-up chemistry of the copper-catalyzed 2,3-diazidation of indoles with the assistance of directing groups.

In 2022, Liu and co-workers reported the first manganese-catalyzed site- and enantioselective C(sp³)-H azidation of indolines (Scheme 18) [48]. The obtained optically pure azidoindolines allows for the installation of a variety of nitrogen-based functional groups, including pharmaceutically relevant scaffolds.

Scheme 18. Manganese-catalyzed C(sp^3)-H azidation of indolines.

4. Electrochemical Azidation of Indoles

The old and new electrochemistry mechanisms are compatible with redox transformations [49,50]. They offer the use of electrons instead of toxic oxidants and reductants, and also allow for chemo-selective reactions by changing the electrochemical conditions. These merits make them attractive and sustainable protocols to substitute for traditional azidations (Scheme 19). Electrochemical radical generation does not require the use of oxidants.

Scheme 19. Concept of radical azidation in electrochemistry.

In 2017, the Lin group reported the Earth-abundant manganese-catalyzed electrochemical diazidation of alkenes using NaN$_3$ as an azide transfer reagent (Scheme 20) [51]. Among various substrates, they reported one example of the reaction with N-Ts indole,

affording 2,3-diazidoindoline at a 69% yield, with a high diastereomeric ratio. The mechanistic experiments revealed that the metal-mediated azidyl radical transfer enabled a dual-azidation reaction. In general, an inorganic azide radical is highly reactive and unstable, while the reactivity of the metal–azide complexes can be controlled by the reaction conditions.

Scheme 20. Manganese-catalyzed electrochemical diazidation of unactivated alkenes.

In 2019, a direct anodic oxidation method of N-substituted indoles was reported by Vincent and co-workers (Scheme 21A) [52].

The reaction proceeds through the anodic oxidation of indoles into a radical cation (Scheme 21B). The radical cation undergoes nucleophilic attack by N_3^-, yielding the 2,3-diazidoindoles. This protocol does not rely on stoichiometric oxidants and proceeds smoothly under environmentally benign conditions.

In 2022, a direct anodic oxidation method of the 2-oxindoles was reported by Maulide and co-workers (Scheme 22) [53]. In similar to Vincent's work, the reaction proceeds through the anodic oxidation of 2-oxindoles into a radical cation, which undergoes nucleophilic attack by nucleophiles, yielding the 3-alkoxy-2-oxindoles and 3-diazido-2-oxindoles. This protocol requires 5 equivalents of $TMSN_3$ as azide transfer reagents.

(A)

Scheme 21. *Cont.*

Proposed mechanism

(B)

Scheme 21. (**A**) Direct electrochemical diazidation of indoles. (**B**) Mechanism for the direct electrochemical diazidation of indoles through radical cation intermediates.

Scheme 22. Electrochemical umpolung C–H functionalization of 2-oxindoles in the absence of a metal catalyst.

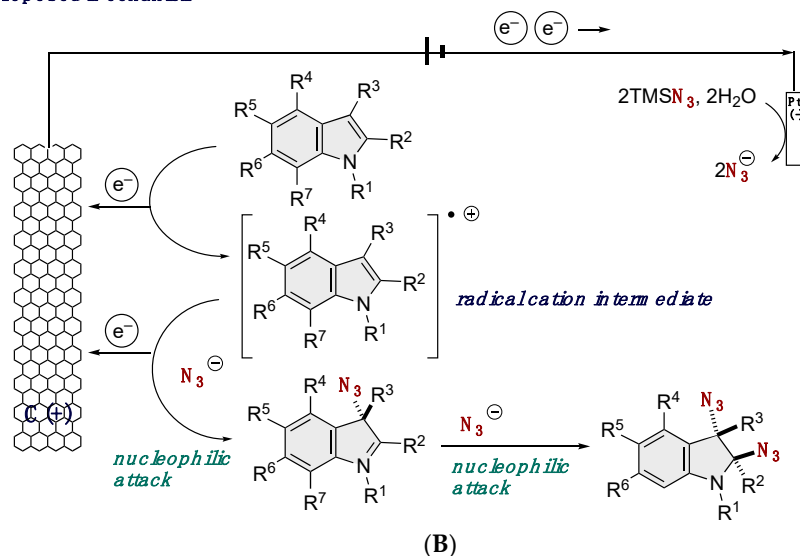In 2022, Wu and co-workers developed a manganese-mediated electrochemical approach to access 2-azido-spirocyclic indolines (Scheme 23) [54]. An azide-bound Mn(III) complex promotes the azidative dearomatization of indoles. A redox-active MnBr$_2$ can tune the reactivity of the azidyl radical species. Synthetic application of the spirocyclic indolines was performed to demonstrate the synthetic utilities. The click reaction of the spirocyclic indoline afforded the corresponding 1,2,3-triazole. The azido group was converted into a phosphoramidate-containing spirocyclic indoline in the presence of triethyl phosphite.

In 2022, Weng and co-workers reported a late-stage functionalization of Trp-containing peptides by manganese-catalyzed diazidation/cyclization in aqueous buffer solution (Tris-AcOH) (Scheme 24A) [55]. This methodology provides access to C3-azide-containing tetrazolo[1,5-a]indole peptides with broad functional group tolerance. Mechanistic experi-

ments revealed that the diazidation/heterocyclization of Trp-containing peptides proceeds through a radical pathway rather than the previously known radical cation pathway.

Trp-containing peptides with C3-azide and tetrazole moieties were derivatized to a series of 1,2,3-triazole peptides by a click reaction of alkynes with azides (Scheme 24B). BODIPY-derived alkyne was also applicable for the click reaction of C3-azide-containing tetrazolo[1,5-a]indole peptides.

In 2024, Ren and co-workers reported a C–H functionalization of 2-oxindoles by manganese-catalyzed azidation in CH_3CN/HFIP (Scheme 25) [56]. The cyclic voltammetry experiments exclude the possibility of the direct oxidation of N_3^- into an azide radical. The azidyl radical $Mn(III)$-N_3 species generated in situ seems to be an azide transfer reagent. Enantioselective azidation using a Jacobsen-(*R*,*R*)-Mn(salen) catalyst was also discovered, although the enantioselectivities were low (30% ee and 43% ee).

Scheme 23. Manganese-mediated electrochemical azidation of indoles to afford azide-containing spirocyclic indolines.

Scheme 24. (**A**) Manganese-catalyzed electrochemical diazidation/cyclization of tryptophan-containing peptides. (**B**) Follow-up chemistry of the C3-azide-containing tetrazolo[1,5-a]indole peptides.

Scheme 25. Manganese-catalyzed electrochemical C–H azidation of 2-oxindoles. Asterisk (*) indicates stereocenter.

5. Photochemical Azidation of Indoles

The photochemical approach is also old and less-explored due to its complex nature. However, photocatalysis, light-emitting diodes (LEDs), and photoreactors make it a privileged field. Photochemistry can play a role in the sustainable and environmentally benign process, with reduced chemical waste. Thus, the photochemical approach has gained much attention [57,58]. In this section, a direct bifunctionalization of alkenes using photochemistry is introduced (Scheme 26). The key feature is an efficient generation of an azidyl radical under visible-light irradiation in the presence or absence of a photocatalyst. Due to the mild reaction conditions, successive 2nd radical additions by another radical species can be undertaken.

Scheme 26. Concept of radical azidation in photochemistry.

In 2020, Xu, Ji, and co-workers reported a visible-light/acridine red-enabled multicomponent cascade from indoles to 2-azidoindolin-3-yl 2-aminobenzoates using $TMSN_3$ as an azide-transferring reagent (Scheme 27A) [59]. This protocol can merge multiple components into one pot to produce sp^3-rich, complicated indolines. Interestingly, two types of reactions, such as azido-3-hydroxylation/ring-opening, proceed in one pot under visible-light irradiation. An interesting structure was determined by using X-ray crystallography (CCDC 1965932).

Scheme 27. (**A**) Organocatalyst-enabled multicomponent cascade of indoles with TMSN$_3$ under LED irradiation. (**B**) Mechanism for multicomponent cascade of indoles with TMSN$_3$ under LED irradiation.

The mechanism of the formation of the products was proposed (Scheme 27B). First, the 2-azido-3-hydroperoxyindolines are converted into 2-azido-3-oxindoles **A** with the assistance of PhSeSePh as a reductant. Next, the 2-azido-3-hydroperoxyindolines are reduced to 2-azido-3-hydroxyindolines **B** by PhSeSePh, which can attack the carbonyl group of the intermediate **A** with the help of Et$_3$N. Finally, the ring opening takes place to afford 2-azido-indolin-3-yl 2-benzamide derivatives, with a release of HCHO and HN$_3$.

In 2021, Lu, Wang, and co-workers reported a visible-light-enabled hydroxyazidation of indoles using TMSN$_3$ as an azide-transferring reagent and bis(pinacolato)diboron as a reductant (Scheme 28) [60]. Surprisingly, the N-pyrimidyl indole substrates can act as

a self-photocatalyst through excitation by LED irradiation. The excited substrate S* can undergo energy transfers withTMSN$_3$ to generate an azidyl radical.

Scheme 28. Photocatalyst-free hydroxyazidation of indoles with TMSN$_3$ under LED irradiation.

In 2021, Kashyap and co-workers reported a visible-light-enabled azido-oxygenation of alkenes using in situ-generated PhI(N$_3$)$_2$ from PhI(OAc)$_2$/TMSN$_3$ as an azide-transferring reagent and TEMPO as another radical (Scheme 29) [61]. The LED irradiation enables a homolytic cleavage of the iodine–nitrogen bond to generate an azide radical. Thus, this transformation does not require a photocatalyst. In this work, one example of indoles as a substrate is presented.

Scheme 29. Photocatalyst-free azido-oxygenation of indoles with in situ-generated PhI(N$_3$)$_2$ under LED irradiation.

6. Azidation of Indoles Using a Combination of an Oxidant and an Azide Source

In 2014, Shi and co-workers demonstrated that ceric ammonium nitrate (CAN) can generate an azide radical from NaN$_3$ in the azidative spirocyclization of 3-substituted indoles (Scheme 30) [62]. Diazidation at the C2 position of an indole ring was also achieved in the case of a reaction with N-Boc tether-substituted substrates. The indicated stereochemistry was determined by using X-ray analysis (CCDC 1015318). Furthermore, the structure of the diazide spirocycle was also confirmed by the X-ray analysis (CCDC 1015373).

Scheme 30. Azidation of indoles with CAN and NaN$_3$.

7. Nucleophilic Azidation of Indoles

One of the most reliable methods to access alkyl azide is a Finkelstein-type (S_N2-type) nucleophilic substitution of alkyl halide with the highly nucleophilic NaN_3 [17]. However, their application to indoline halides has not been reported due to the possibilities of competition with the elimination reaction powered by the aromatization of indolines.

In 2021, Abe and co-workers reported a concise synthesis of 2-alkoxy-3-azidoindolines (AZINs) from 2-RO-3-bromoindolines and NaN_3 in DMF (Scheme 31) [63]. With the help of an O–N_β bonding stabilization (X-ray analysis: CCDC 2107262), an unprecedented production of *cis*-2-alkoxy-3-azidoindolines was dominant. The AZINs are a stable and versatile synthon for the synthesis of 2-monosubstituted 3-oxindoles through a formal umpolung process [64] and of 2-alkoxy-3-(quinazolin2,4-dione)idolines through the aza-Wittig reaction/cyclization [65].

Scheme 31. Nucleophilic substitution of bromoindolines with NaN_3.

In 2023, Li and co-workers reported the first hydroazidation of phenacylideneoxin-doles using *n*-tetrabutylammonium fluoride (TBAF) and $TMSN_3$ (Scheme 32) [66]. In this transformation, $TMSN_3$ is activated by TBAF, generating *n*-tetrabutylammonium azide (BNN_3) and TMSF [67]. This BNN can attack the carbonyl group of phenacylideneoxin-doles, affording the silyl enol ether with the pendant of an azide group. Then, Claisen ([3.3]-sigamtropic) rearrangement of the allylic azide vinyl silyl ethers results in hydrolysis to afford 3-azido-2-oxindoles.

Scheme 32. Addition/Claisen-type rearrangement of phenacylideneoxindoles with $TMSN_3$ and TBAF.

Very recently, Abe and co-workers reported a switchable synthesis of two different medicinally relevant backbones with the merge of Grignard reagents and AZIHY (3-azido-2-hydroxyindolines) (Scheme 33) [68]. The newly designed AZIHY, bearing both indoline hemiaminal and an azide functional group, can be harnessed as a novel denitrogenative cascade. This property enabled the switchable synthesis under a tautomeric control of hemiaminals.

Scheme 33. Synthesis of 3-azido-2-hydroxyindolines.

8. Conclusions

Both organic azides and indole/indolines are privileged motifs in organic and medicinal chemistry. This review focused on advances and applications made with the azidation of indolines and indoles. Recent developments have demonstrated that the azidation of indoles/indolines have predominantly been discovered under radical technologies, including hypervalent iodine, electro-, and photochemistry. There are some drawbacks to hypervalent iodine: one is the high cost of manufacturing due to its multi-step production process. After the reaction, iodosobenzene is also produced as a byproduct. The advantages of methodologies using hypervalent iodine are environmentally friendly chemistry due to its low toxicity. In this line, the protocols utilizing electro- and photochemistry are also employ green chemistry as there is no need for any extra oxidants and the simple set-ups/work-ups.

Surprisingly, traditional approaches such as the S_N2 reaction by N_3^- and alkyl halides are quite scarce. Nucleophilic substitution is a straightforward reaction due to the intrinsic polar match, while the electro- and photochemistry processes require umpolung reactivities. Thus, they are suitable for the control of stereochemistry depending on the choice of starting material. Among the control of stereochemistry, the *cis*-selective synthesis of azidoindolines is rather limited. It is expected that a stereoselective synthesis will develop through a novel reaction pathway to expand the unexplored chemical space, leading to unique sp^3-rich heterocycles [69,70].

Although many synthetic applications of azidoindolines are found, most of them are related to the reaction of alkyl azides, such as the click reaction and amine synthesis. There have been a few examples of the bio-orthogonal azidation of tryptophans reported to date [71,72]. I expect that a variety of bio-orthogonal applications of azidoindolines will appear in the future.

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Abbreviations

MeCN	acetonitrile
Bz	benzoyl
DMF	*N*,*N*-dimethylformamide
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl
DMSO	dimethyl sulfoxide
TBS	*tert*-butyldimethylsilyl
ADBX	azidodimethylbenziodoxole
IBA	2-iodosobenzoic acid
TFA	trifluoroacetic acid
acac	acetylacetonate
TBTA	tris(benzyltriazolyl)methylamine
SET	single electron transfer
TBHP	*tert*-butyl hydroperoxide
TBPB	*tert*-butyl peroxibenzoate
Boc	*tert*-butoxycarbonyl
Troc	2,2,2-trichloroethoxycarbonyl
DG	directing group
1,10-phen	1,10-phenanthroline
Cbz	benzyloxycarbonyl
LED	light emitting diode
PC	photocatalyst
HFIP	1,1,1,3,3,3-hexafluoropropan-2-ol
CAN	ceric ammonium nitrate
TEMPO	2,2,6,6-tetramethylpiperidine 1-oxyl
DMA	*N*,*N*-dimethylacetamide
AZIN	2-alkoxy-3-azidoindoline
TBAF	*n*-tetrabutylammonium fluoride
BNN3	*n*-tetrabutylammonium azide
AZIHY	3-azido-2-hydroxyindoline
CCDC	Cambridge crystallographic data centre

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