Azidoindolines—From Synthesis to Application: A Review

Takumi Abe

Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Okayama City 700-8530, Japan; t-abe@okayama-u.ac.jp

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, which 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 azidiodinane 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.

Citation: Abe, T. Azidoindolines—From Synthesis to Application: A Review. Chemistry 2024, 6, 556–580. https://doi.org/10.3390/chemistry6040034

Academic Editors: Bartolo Gabriele, Damiano Tanini, Angelo Frongia and Alberto Martinez-Cuezva

Received: 2 July 2024
Revised: 16 July 2024
Accepted: 17 July 2024
Published: 18 July 2024

Copyright: © 2024 by the author. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).
A: 2,3-Diazidation of indoles using IN₃

\[
\begin{align*}
\text{R}^2 & \text{N}^2\text{R}^1 + [\text{IN}_3] \rightarrow \text{MeCN, rt} & \text{trans} & \text{N}_3 \text{N}_3 \\
\end{align*}
\]

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

B: 2,3-Diazidation of indoles using IN₃

\[
\begin{align*}
\text{R} & \text{N} & \text{R} \\
\end{align*}
\]

5 examples

\[
\begin{align*}
\text{R} = \text{Bz} & 63\% & 17\% \\
\text{R} = \text{Ts} & 49\% & 38\% \\
\end{align*}
\]

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

\[
\begin{align*}
\text{R} & \text{N} & \text{Ph} \\
\end{align*}
\]

2 examples

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 NaN₃ (Scheme 2) [25]. The homolytic cleavage of the iodine–nitrogen bond of hypervalent iodine PhI(N₃)₂ gives an azidyl radical and PhIN₃⁻ radical, which undergo abstractions of hydrogen bonding and azidation. In general, PhI(N₃)₂ generated from PhIO, Ph(OAc)₂/NaI, or TMSN₃ is highly reactive and unstable [26]. Thus, optimization of the reaction conditions may occasionally result in an insufficient outcome.

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.

In 2016, Sudalai found that a simple combination of molecular iodine and NaN₃ 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 I₂ and NaN₃.

In the system of TMSN₃, PhI(OAc)₂, and Et₃N, 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(N₃)₂], generated in situ. 3-substituted 3-azido-2-oxindoles participated in the H₂/Pd-C reduction and Cu-catalyzed 1,3-dipolar cycloaddition.

Scheme 5. Direct azidation of indoles using TMSN₃. PhI(OAc)₂ and Et₃N.

**Applications**

- **Scheme 4**: Umpolung direct azidation of indoles using I₂ and NaN₃.

- **Scheme 5**: Direct azidation of indoles using TMSN₃. PhI(OAc)₂ and Et₃N.
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$_2$.](image)

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)$_2$.](image)

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.
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 (EtCO₂)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 CH₂Cl₂, resulting in the isolation of N-H-triazole in a 95% yield with 90% ee.

In 2014, Jiao found that a merge of stable hypervalent cyclic iodine reagents (IBA-N₃, 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-oxindoles under mild conditions.

Scheme 8. Iron-catalyzed enantioselective azidation of indoles.

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-butoxy 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. tert-PrOH can promote the generation of an azidyl radical from TMSN₃ by the tert-butoxy radical.

\[
\text{Fe(NTf)}_2\text{ligand (5 mol %)} \\
\text{or Fe(OAc)}_2\text{ligand (10 mol %)} \\
\text{TBPP (1.2–1.4 equiv.)} \\
i\text{PrOH (1.2 equiv.)} \\
\text{CH}_2\text{Cl}_2/\text{MeCN, rt}
\]

30 examples 67–92% yields

**Examples of indoles**

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
</tr>
</thead>
<tbody>
<tr>
<td>N₃</td>
<td>N₃</td>
<td>Troc</td>
</tr>
<tr>
<td>N₃</td>
<td>Me</td>
<td>Troc</td>
</tr>
<tr>
<td>N₃</td>
<td>NHCO₂Me</td>
<td></td>
</tr>
<tr>
<td>N₂</td>
<td>CO₂Me</td>
<td></td>
</tr>
</tbody>
</table>

\[\text{N₃} \text{-N₃} \text{ Troc} \]
\[\text{N₃} \text{-Me} \text{ Troc} \]
\[\text{N₃} \text{-NHCO₂Me} \text{ Troc} \]
\[\text{N₂} \text{-CO₂Me} \text{ Troc} \]

\[\text{dr} > 20:1, 81\% \quad \text{dr} > 20:1, 78\% \quad \text{dr} > 20:1, 76\% \quad \text{dr} > 20:1, 74\%\]

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.

\[\text{R¹} \text{-R²} + \text{TMSN₃} \quad (2.4–2.5 \text{ equiv.)} \]

1. Fe(OAc)₃/ligand (10 mol %) \\
CH₂Cl₂/MeCN, rt

2. Pd-C (10 mol %) \\
H₂ (1 atm)

\[\text{H₂N} \text{-R¹} \text{-R²} \text{-CF₃} \]

then H₃TsOH (1.1 equiv.) \\
or Boc₂O (1.2 equiv.)

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHBoc</td>
<td>CF₃</td>
<td>Boc</td>
</tr>
<tr>
<td>NHBoc</td>
<td>Me</td>
<td>CF₃</td>
</tr>
<tr>
<td>BocHN</td>
<td>NHCO₂Me</td>
<td></td>
</tr>
</tbody>
</table>

\[\text{dr} > 20:1, 72\% \quad \text{dr} > 20:1, 83\% \quad \text{dr} > 20:1, 74\%\]


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 peroxy radical. Then, the peroxy radical underwent SET by Cu(I) and protonation by H₂O to yield a hydroperoxy intermediate. Finally, the reduction of the hydroperoxy intermediate by triethyl phosphate POE(t)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 O₂.

In 2019, Wei, Liu, and co-workers reported the C(sp³)-H azidation of 2-oxindoles catalyzed by Cu(OAc)₂ with TMSN₃ 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(sp^3)-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.

In 2022, Liu and co-workers reported the first manganese-catalyzed site- and enantioselective C(sp^3)-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.
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.

In 2017, the Lin group reported the Earth-abundant manganese-catalyzed electrochemical diazidation of alkenes using NaN₃ 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-diazidoinodine 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 N3\textsuperscript{−}, yielding the 2,3-diazidoinodine. 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\textsubscript{3} as azide transfer reagents.

Scheme 21. Cont.
was performed to demonstrate the synthetic utilities. The click reaction of the spirocyclic
peptides by manganese-catalyzed diazidation/cyclization in aqueous buffer solution (Tris-
phosphoramidate-containing spirocyclic indoline in the presence of triethyl phosphite.
Approach to access 2-azido-spirocyclic indolines (Scheme 23) [54]. An azide-bound Mn(III)
metal catalyst.

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 ap-
proach to access 2-azido-spirocyclic indolines (Scheme 22) [53]. In similar to Vincent’s work, the reaction proceeds
doles. This protocol requires 5 equivalents of TMSN₃ as azide transfer reagents.

An example of indoles

Scheme 21. (A) Direct electrochemical diazidation of indoles. (B) Mechanism for the direct electro-
chemical 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 ap-
proach to access 2-azido-spirocyclic indolines (Scheme 23) [54]. An azide-bound Mn(III)
complex promotes the azidative dearomatization of indoles. A redox-active MnBr₂ 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

Mechanism for the direct electrochemical diazidation of indoles through radical cation intermediates.

Argon atmosphere. Reactions were performed in a standard electrochemical cell equipped
with a Pt anode (∼5 cm²). The cathode was a glassy carbon electrode and the electrolyte
was MeCN/MeOH (1:1, v/v) containing 0.1 M Et₄NOHT. The cell was pressurized with a
flowing mixture of argon (99.99%) and oxygen (99.99%). During the reaction, anodic
overpotentials were applied to maintain the potential at 0.7 V vs. Ag/AgCl. The reaction
 intermediates were monitored by HPLC and GC-MS. The products were identified by
NMR spectroscopy. The yield was determined by HPLC with a Waters 2695 Separation
Module and a Waters 996 Photodiode Array Detector. The purity of the isolated products
was checked by NMR spectroscopy.

Mechanistic studies

Proposed mechanism for the direct electrochemical diazidation of indoles through radical cation intermediates.

(A) Direct electrochemical diazidation of indoles. (B) Mechanism for the direct electro-
chemical diazidation of indoles through radical cation intermediates.

Proposed mechanism for the direct electrochemical diazidation of indoles through radical cation intermediates.

41 examples

N₃

22–81% yields

N₃

22%
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-alindole peptides.

In 2024, Ren and co-workers reported a C–H functionalization of 2-oxindoles by manganese-catalyzed azidation in CH$_3$CN/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.
Applications

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.
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 25](image)

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

**Photochemical radical generation**

\[ \text{azide source} \rightarrow N_3^* \]

\[ \text{1st Radical} \]

\[ \text{2nd Radical} \rightarrow \text{Rad} \]

**Scheme 26.** Concept of radical azidation in photochemistry.

In 2020, Xu, Ji, and co-workers reported a visible-light/acridine red-enabled multi-component cascade from indoles to 2-azidoindolin-3-yl 2-aminobenzoates using TMSN₃ as an azide-transferring reagent (Scheme 27A) [59]. This protocol can merge multiple components into one pot to produce sp³-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).
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 self-photocatalysts through excitation by LED irradiation. The excited substrate S* can undergo energy transfers with TMSN$_3$ 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
a self-photocatalyst through excitation by LED irradiation. The excited substrate $S^*$ can undergo energy transfers with TMSN$_3$ to generate an azidyl radical.

\[
\text{LED irradiation. (B) } \text{Scheme 28. Photocatalyst-free hydroxyazidation of indoles with TMSN}_3 \text{ under LED irradiation.}
\]

In 2021, Kashyap and co-workers reported a visible-light-enabled azido-oxygenation of alkenes using in situ-generated PhI(N$_3$)$_2$ from Ph(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.

\[
\text{Scheme 29. Photocatalyst-free azido-oxygenation of indoles with PhI(N}_3\text{)$_2$ under LED irradiation.}
\]

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).

\[
\text{Scheme 30. Azidation of indoles with CAN and NaN}_3.
\]
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-bromoidolines 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 NaN₃.](image)

In 2023, Li and co-workers reported the first hydroazidation of phenacylideneoxindoles 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 phenacylideneoxindoles, affording the silyl enol ether with the pendant of an azide group. Then, Claisen ([3,3]-sigamotropic) 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 TMSN₃ and TBAF.](image)
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].

Funding: This work was partly supported by JSPS KAKENHI (22K06503).
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.

**Funding:** This work was partly supported by JSPS KAKENHI (22K06503).

**Institution Review Board Statement:** Not applicable.

**Data Availability Statement:** Not applicable.

**Conflicts of Interest:** The author declares no conflicts of interest.

**Abbreviations**

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

**References**


33. Ge, L.; Chou, M.-F.; Li, Y.; Bao, H. Radical azidation as a means of constructing C(sp³)-N₃ bonds. *Green Synh. Catal.* 2020, 1, 86–120. [CrossRef]


Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.