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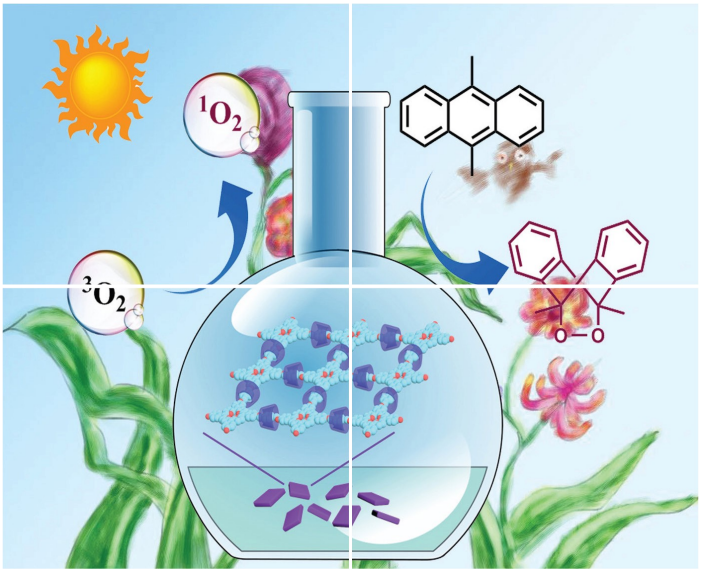

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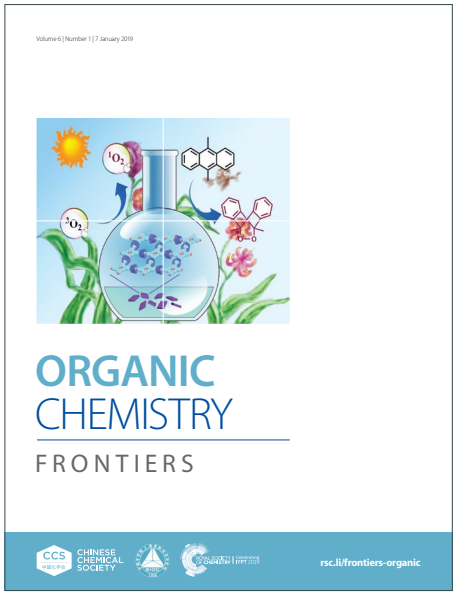

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Method

Iodonitrene: A Direct Metal-free Electrophilic Aminating Reagent

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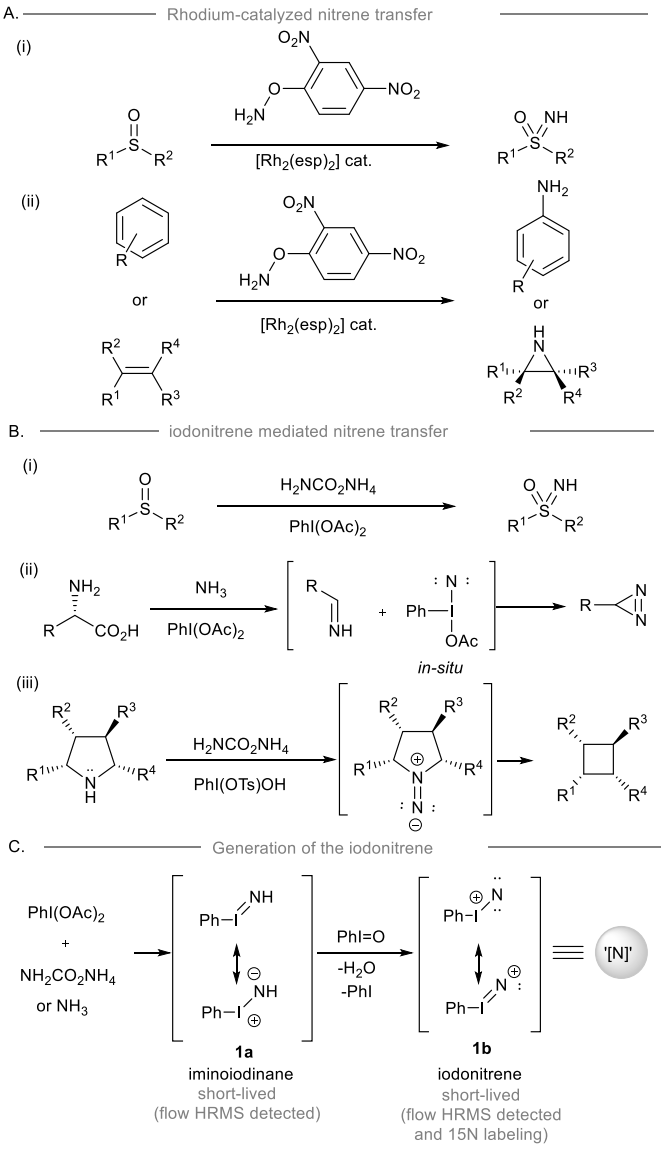
The use of conventional nitrenoids and/or metal–nitrenes as electrophilic aminating reagents requires a pre-activated nitrogen atom which makes transfer of an unprotected NH–group a difficult challenge. Iodonitrene, which is generated *in-situ* from phenyliodine(III) diacetate and ammonia surrogate, features a new class of reactive electrophilic aminating reagents. The novel reactivity of iodonitrene not only resulted in direct *NH*–group transfer to nucleophilic atoms such as sulfur and nitrogen but also led to new reaction development such as diazirines synthesis *via* decarboxylation and contractive synthesis of cyclobutanes *via* nitrogen extrusion. We highlight the contemporary advances in the application of iodonitrene and discuss the current limitations and future prospects.

1. Introduction

Direct access to nitrogen-containing functional groups is indispensable in the preparation of biological important molecules. Amination methods such as nucleophilic substitution, reductive amination, and metal-catalyzed amination reactions (e.g. allylic substitution, hydroamination, and C–N cross-coupling reactions) are widely used for amine synthesis.[1, 2] Electrophilic amination requires the use of electrophilic aminating reagents, such as metal–nitrene equivalents, or oxaziridines as nitrogen sources, resulting in a net addition of an amino group to the electron-rich functionalities of the substrate.[3-8] Conventionally, the dirhodium-nitrene chemistry enables intramolecular amination of inert C(sp^3)-H bond to form a C-N bond *via* intermolecular nitrene transfer,[9] that the condition was applied to the synthesis of *NH*-sulfoximine from sulfoxime[10], and the direct preparation of *NH*-aziridines and anilines from alkenes and arenes,[11, 12] which have been broadly applied to organic synthesis (**Scheme 1A**).[13] On the other hand, iodonitrene[14] generated *in-situ* from the reaction between hypervalent iodine(III) reagent and ammonia or its surrogate has recently been prompted as a promising electrophilic aminating reagent (**Scheme 1B**). The synthesis of *NH*-sulfoximine (Bull, Luisi and co-workers; 2016)[9], the synthesis of dizairines from unprotected amino acids (Reboul and coworkers; 2019)[15], and contractive synthesis of cyclobutanes from pyrrolidines (Antonchick and coworkers; 2021)[16] revealed the novel reactivity of iodonitrene distinguishing from the precedent metal-nitrene chemistry. The use of iodonitrene as an electrophilic aminating reagent



Scheme 1. (A) Rhodium catalyzed amination reactions involved dirhodium nitrene transfer[10-12]. (B) Some examples of amination reactions using iodonitrene as

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electrophilic aminating reagent[9, 15]. (C) The proposed mechanism of iodonitrene formation[9].

not only provides a reactive nitrene species ready for nitrogen transfer but also circumvents the use of metals and activated explosive reagents, such as *O*-mesitylenesulfonyl-hydroxylamine (MSH).[17] Bull and co-workers disclosed the evidence of iodonitrene and possible intermediates (PhI=NH), for instance, iminoiodinane **1a** and the unprecedented iodonitrene **1b** (PhI=N$^+$) *via* mass spectrometric analysis and isotopic labeling using ^{15}N,[18] (**Scheme 1C**). However, no evidence of any reactive intermediates was found throughout the NMR studies.[19]

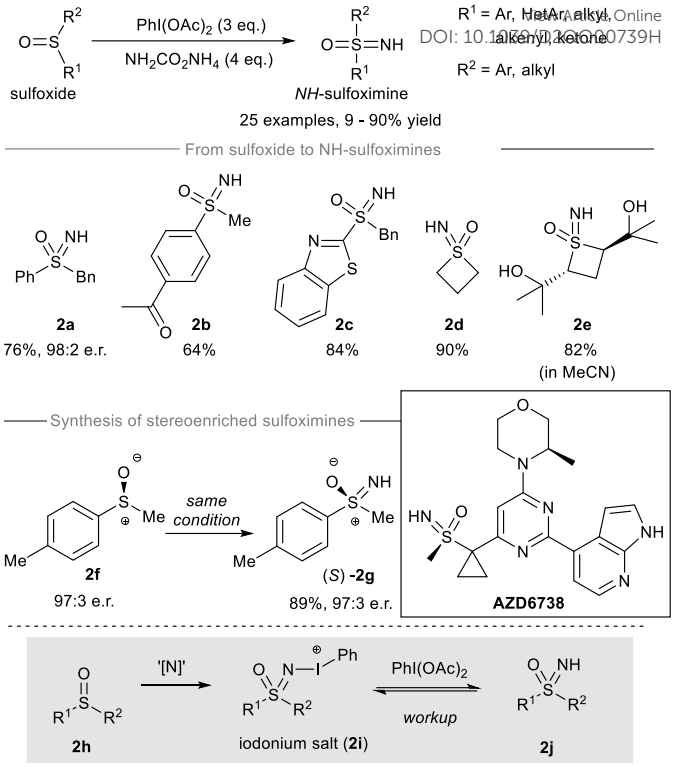
Our group[20-27] is engaged in the novel method development of hypervalent iodine(III) chemistry.[28-35] Despite a personal account and a review on *NH*-sulfoximines which was reported by Bull group and Luisi group[36-38] and *no review has been published, to the best of our knowledge, discussing the chemistry of iodonitrene*. We are motivated to provide a concise minireview, highlighting iodonitrene and its application in organic synthesis. This minireview could be useful to synthetic scientists in method development and natural product synthesis, and the pharmaceutical industry. Finally, we discuss the directions and prospects for the innovation of new reactions and potential applications in organic synthesis.

2. Electrophilic amination of sulfur-containing compounds

Sulfur-containing compounds possess significant biological profiles and appear as important elements in drug discovery.[39] For instance, sulfoximines are present as essential functional groups in drug candidates such as compound AZD6738 (**Scheme 2**, inset) from AstraZeneca.[40] Directing the transfer of the NH group from iodonitrene to sulfoxides gives *NH*–sulfoximines in one step. Accompanying the oxidizing power of hypervalent iodine(III) reagent, oxidation of the sulfur atom could take place before and/or after the nitrogen transfer from iodonitrene. In this section, the direct *NH*–group transfer to sulfoxides and sulfonamides is discussed. Moreover, the sequential *NH*–group transfer accompanying oxidation of sulfides, thiols, and sulfonamides are elaborated.

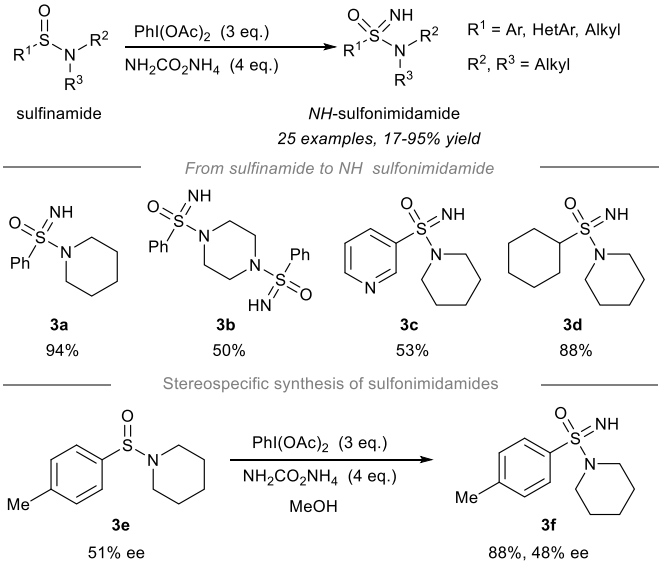
2.1 Direct *NH* transfer to sulfoxides

In 2016, Luisi and Bull and co-workers reported the direct transfer of the *NH*–group from iodonitrene to sulfoxide to afford *NH*–sulfoximine.[14] (**Scheme 2**) Under the standard conditions, the iodonitrene generated *in-situ* from the reaction between phenyliodine(III) diacetate (PIDA) and ammonium carbamate[41] promoted a *NH*–group transfer to produce various *NH*–sulfoximines. Both aryl-substituted and alkyl-substituted sulfoxides carrying different reactive groups, such as ketones, free alcohols, and benzothiazoles, gave sulfoxides **2a – 2e** from decent to good yield. When methyl *p*-tolylsulfoxide **2f** was used as starting material, the stereospecific *NH*–group transfer took place under standard conditions and gave sulfoximine (*S*)-**2g** in 89% yield with 97:3 e.r. Mechanistically, the authors proposed that the nitrene transfer from



Scheme 2. Direct *NH*–group transfer to sulfoxide producing *NH*–sulfoximine.[14]

iodonitrene (i.e. "[N]") to sulfoxide **2h** may generate an iodonium salt **2i**. Further oxidation of **2i** by free phenyliodine(III) diacetate followed by workup afforded *NH*–sulfoximines **2j**.



Scheme 3. Direct *NH*–group transfer in the synthesis of *NH*-sulfonimidamides from sulfinamides.[42]

2.2 Direct *NH* transfer to sulfinamides

Later, one-pot conversion of sulfinamides to sulfonimidamides *via* transfer of the electrophilic *NH*–group was reported by Stockman, Lücking, and co-workers (**Scheme 3**).[42] Under the optimized conditions, sulfonimidamides (**3a** to **3d**) were formed

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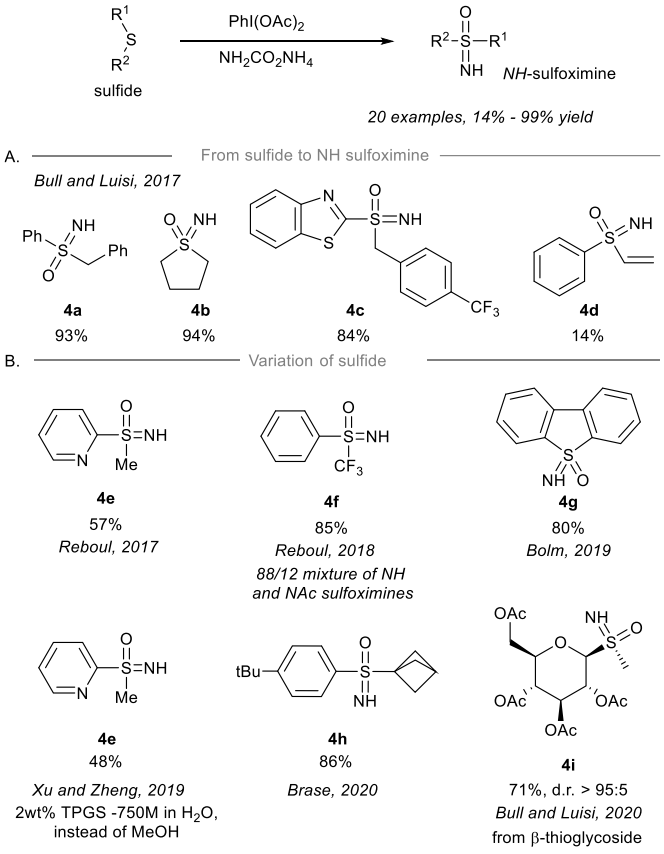
from sulfinamides in good to high yield. The replacement of the aryl substituents of tertiary sulfonamides by the 3-pyridinyl group **3c** or cyclohexyl group **3d** was tolerated. Importantly, the *NH*–group transfer to chiral sulfinamide **3e** (51% e.e.) proceeded stereospecifically to give *NH*-sulfonimidamide **3f** with 48% e.e.

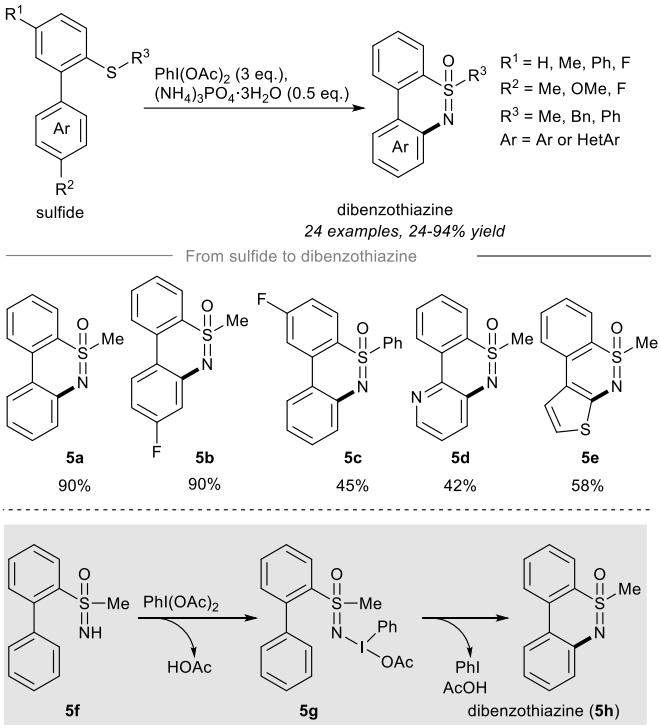
2.3 One-pot *NH*- and *O*- transfer to sulfides

After the pioneering synthesis of *NH*-sulfoximines from sulfides using iodonitrene as an electrophilic aminating reagent by Bull and Luisi in 2016[14], the synthesis of *NH*-sulfoximine from corresponding sulfides *via* a one-pot *NH*- and *O*- transfer were realized by several research groups using iodonitrene chemistry (**Scheme 4**). In 2017, Bull and Luisi first reported the one-pot *NH*- and *O*- transfer to sulfides to give *NH*-sulfoximines (**Scheme 4A**).[43] Aryl-, alkyl- and benzothiazole-substituted (R^1) sulfides gave the corresponding *NH*-sulfoximines in high yield (**4a – 4c**, 84%-94% yield). However, the low yield of vinyl substituent sulfoximine **4d** is suggested to be the result of a possible polymerization of the substrate.



Scheme 4. (A) Direct *NH*-sulfoximination of sulfides by iodonitrene. (B) Variation of sulfides as starting material.[43-49]

Shortly after Bull and Luisi's work, other research groups reported variants of the transformation with modification of substrates and/or conditions (**Scheme 4B**),for instance, pyridinyl sulfides **4e** (Reboul's group)[44, 50], *S*-perfluoroalkylated sulfides **4f** (Reboul's group)[51], thiophene-derived sulfides **4g** (Bolm's group)[48], bicyclo[1.1.1]pentyl sulfides **4h** (Brase's group)[53], *β*-thioglycosides **4i** (Bull and Luisi's group)[54]. Besides, sulfoximination of sulfides could be achieved to afford **4e** in aqueous micellar conditions using surfactant TPGS-750-M as an additive.[49]



Scheme 5. Synthesis of dibenzothiazines from sulfides through tandem *NH*-sulfoximination/C(sp^2)-H amination[52].

After the report of direct sulfoximination of sulfides, a tandem *NH*–sulfoximination/C(sp^2)-H amination of sulfides to give dibenzothiazines[52] was developed by Chen and co-workers in 2018 (**Scheme 5**). Treatment of [1,1'-biaryl]-2-sulfides with PIDA and ammonium phosphate trihydrate afforded the *NH*- and *O*-transfer products *NH*–sulfoximines, which after intramolecular C(sp^2)-H functionalization provided dibenzothiazines.[55, 56] The variation of the substituents R^1 and R^2 gave the desired dibenzothiazine products **5a** and **5b** in high yield. A phenyl group on R^3 (**5c**) significantly reduced the yield of the reaction to 45% yield. Heterocyclic dibenzothiazines such as **5d** and **5e** are also compatible with the reaction condition. The authors proposed that the oxidation of newly formed *NH*-sulfoximines **5f** with PIDA gives **5g**, which cyclized to give dibenzothiazines **5h** (**Scheme 5**).

The proposed mechanism of one-pot synthesis of *NH*-sulfoximines from sulfides was suggested by Bull, Luisi, and co-workers (**Scheme 6**) and based on direct nitrene *NH*–group transfer to sulfides and subsequent *O*-transfer from PIDA to afford sulfoximines. [43] (**Scheme 6A**) Later, an investigation by Reboul and co-workers[44] revealed that iodonitrene could be generated when PIDA was reacted with either ammonium

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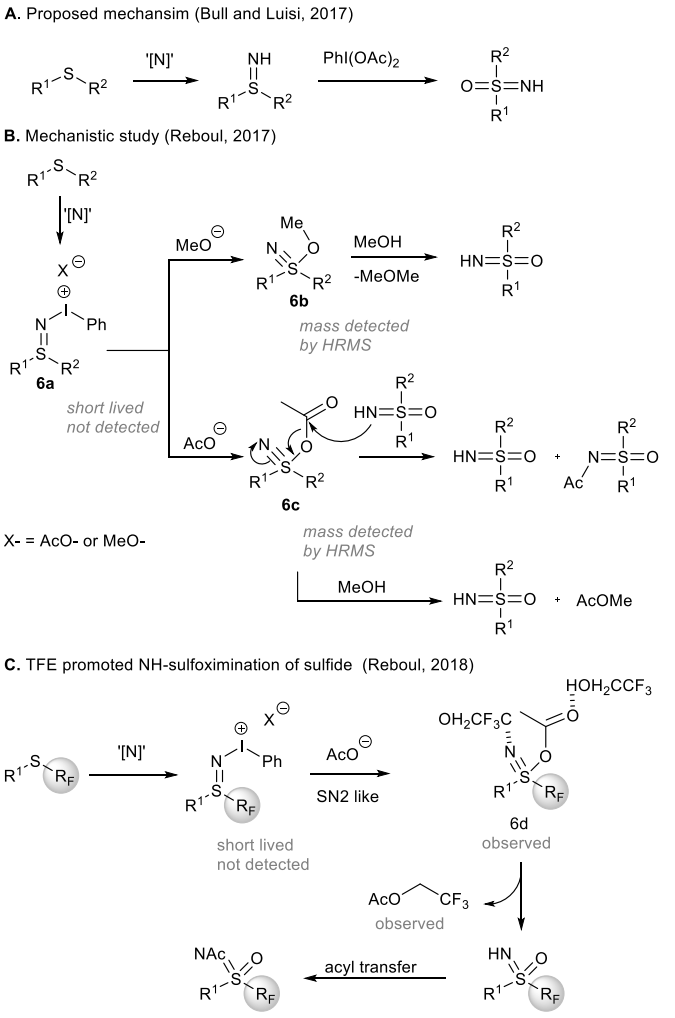
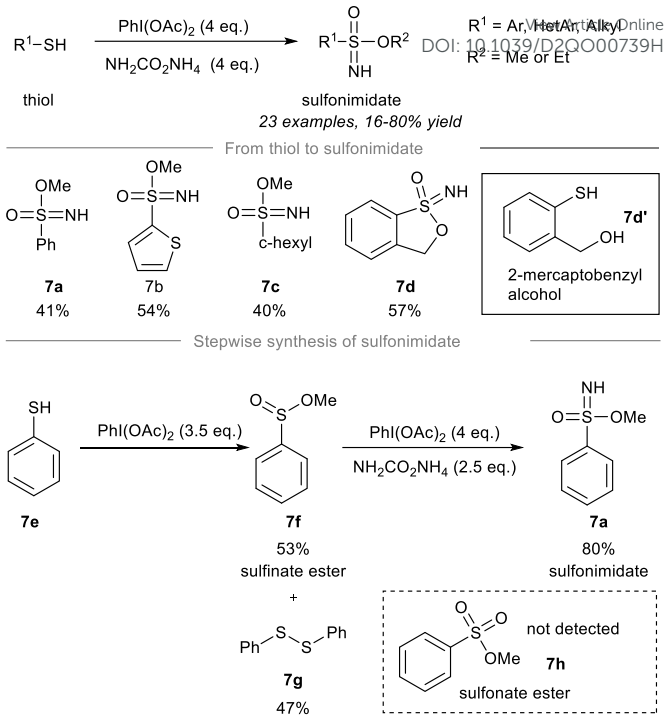


Scheme 6. Mechanistic investigation of direct *NH*-sulfoximination of sulfides. [42, 45, 46]

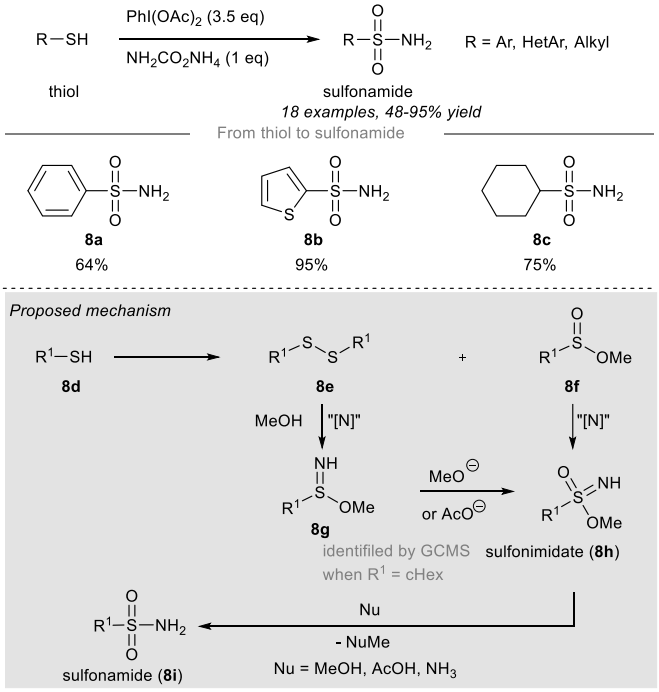
carbamate or ammonium carbonate (**Scheme 6B**). Although the sulfilimine **6a** formed initially was short-lived and not detected, nucleophilic addition of methoxide or acetate to sulfilimines gave **6b** and **6c**, respectively, and could be detected by HRMS. The rate enhancement of sulfoximination of *S*–perfluoroalkylated sulfides could be ascribed to the *H*–bonding between the 2,2,2-trifluoroethanol (TFE) and the observed sulfanenitrile intermediate **6d** (**Scheme 6C**)**.** The attack of TFE to the acetate on **6d** produced trifluoroethyl acetate. Acetyl group transfer from trifluoroethyl acetate to the reaction product *NH*-sulfoximines furnished *N*-Ac sulfoximines**.**

2.4 One-pot *NH*- and *O*- transfer to thiols

In 2018, Luisi and Bull and co-workers disclosed a one-pot chemoselective *NH*-, *O*- and *OR*- transfer to thiols using iodonitrenes to give sulfonimidates and sulfonamides[57] (**Scheme 7** and **8**). By reducing the amount of ammonium carbamate, the product distribution could be changed from sulfonimidate (4 equiv. of ammonium carbamate) (**Scheme 7**) to sulfonamide (1 equiv. of ammonium carbamate) (**Scheme 8**).

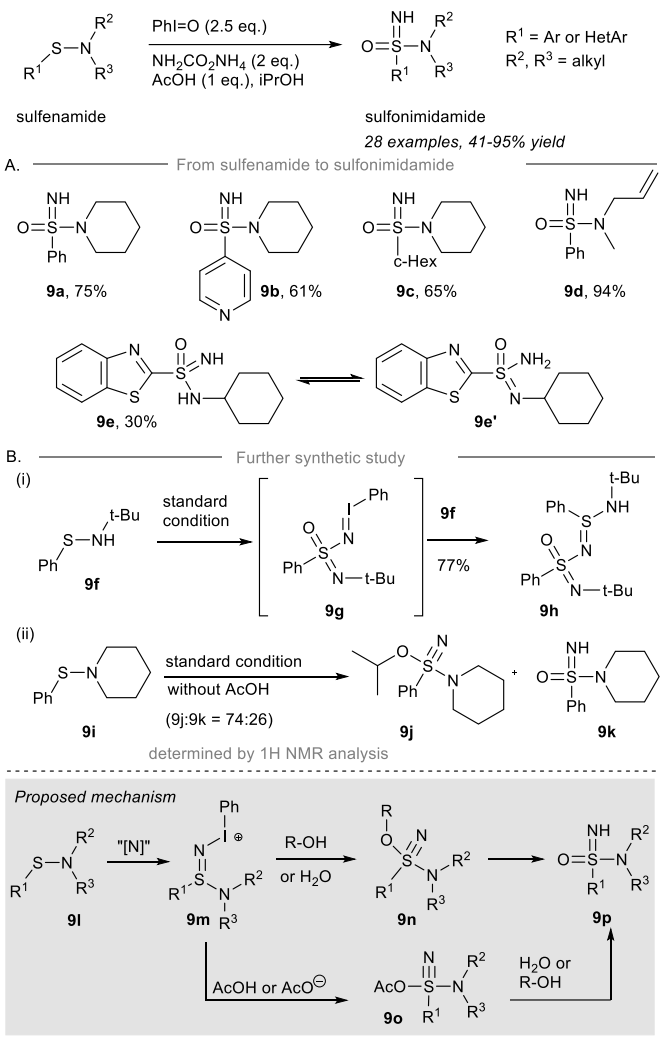


Scheme 7. Synthesis of sulfonimidates from thiols through a one-pot *NH*-, *O*-, *RO*-transfer.[57]



Scheme 8. Synthesis of sulfonimidates and sulfonamides from thiols through a one-pot *NH*-, *O*-, *RO*- transfer.[57]

To prepare *sulfonimidates*, phenylthiol, thiophene-2-thiol and cyclohexanethanol were converted to the corresponding sulfonimidates **7a** - **7c** in moderate yield under the standard conditions (**Scheme 7**). Interestingly, 2-mercaptobenzylalcohol **7d'** was transformed into cyclization product **7d** in 57% yield. Treatment of phenylthiol **7e** with an excess of phenyliodine(III) diacetate afforded a mixture of methyl sulfinate ester **7f** and diphenyl disulfide **7g**. However, sulfonate ester **7h** was not observed. Exposure of methyl benzenesulfinate **7f** to

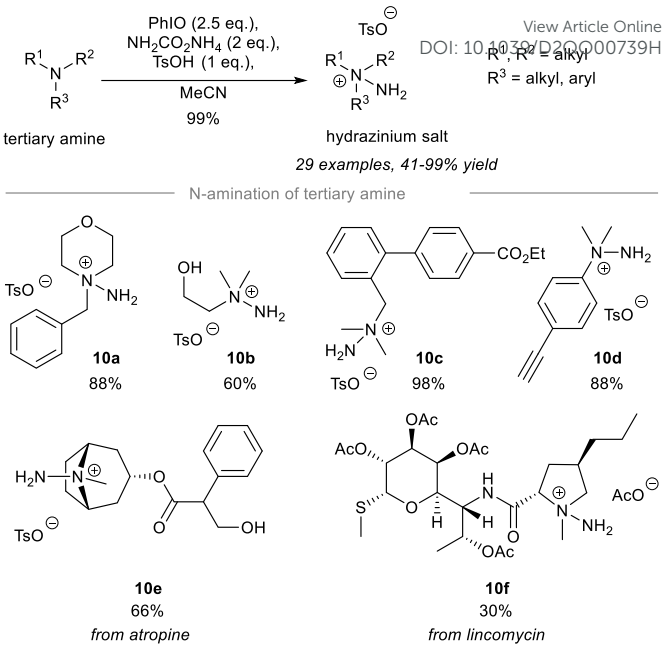


Scheme 9. Synthesis of sulfonimidamides from sulfonamides through one-pot *NH*- and *O*- transfer[58]

in-situ generated iodonitrene in acetonitrile afforded sulfonimidate **7a**. To prepare sulfonamides, phenylthiol, thiophene-2-thiol and cyclohexanethiol afforded the corresponding sulfonamides **8a – 8c** in good to excellent yield (**Scheme 8**).

Based on the experimental evidence, the authors suggested a possible mechanism of these reactions (**Scheme 8,** *grey box*). Intermediate **8g** was detected by GCMS when R is a cyclohexyl group, which was reacted with methoxide or acetate to give sulfonimidate **8h** as the product. Sulfonimidate **8h** could be converted to sulfonamide **8i** by reaction with existing nucleophiles, including methanol, acetic acid, and ammonia.

In 2019, Bull and co-workers reported the direct one-pot *NH*- and *O*- transfer from sulfonamide to sulfonimidamides (**Scheme 9A**).[58] Treatment of sulfonamides with 2.5 equivalents of iodosylbenzene and 2 equivalents of ammonium carbamate in the presence of 1 equivalent of AcOH as additive gave sulfonimidamides in good yield. Phenyl-sulfenamide, 4-pyridinyl-sulfenamide, and cyclohexyl-sulfenamide performed well under the standard conditions to give the corresponding sulfonaimidamides **9a – 9c** in decent yield. Secondary sulfenamides containing an *NH* moiety gave sulfonimidamide



Scheme 10. Chemoselective electrophilic amination of tertiary amines.[59]

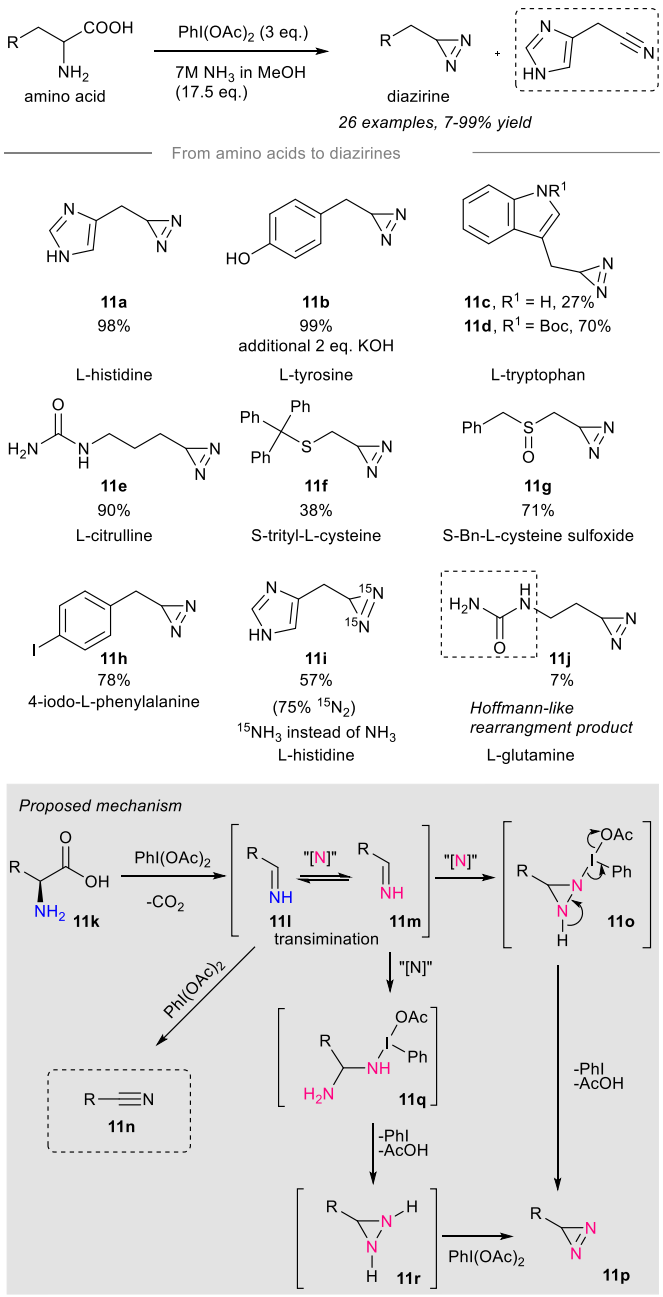
9e in 30% isolated yield, along with the corresponding sulfinamide as the major side product.

Unexpectedly, *tert*-butylphenylsulfenamide **9f** was converted to **9h** in 77% yield under the standard conditions (**Scheme 9B**). It is rationalized that direct one-pot *NH*- and *O*- transfer to **9f** followed by activation by an excess of iodosylbenzene leads to the formation of iminoiodinane intermediate **9g**. Imination of **9g** by another equivalent of sulfenamide **9f** produced **9h**. When the reaction was performed in the absence of acid, sulfenamide **9i** was converted into λ^6-sulfanenitrile **9j** and sulfonimidamide **9k** in a ratio of 74:26 determined by ^{1}H NMR. The λ^6-sulfanenitrile **9j** was fully characterized through HRMS, ^{1}H- and ^{13}C-NMR and IR.

The proposed mechanism is depicted (**Scheme 9**, grey box). Sulfonamide **9l** is reacted with the iodonitrene to afford sulfinamidine salt **9m**. Elimination of iodobenzene from **9m** forming the S≡N triple bond may occur before or at the same time as an attack of a nucleophile, being either R-OH/H_2O to give alkoxy-amino-λ^6-sulfanenitrile **9n** or AcOH to give sulfonimidamide **9o**. Finally, **9n** is converted to the desired sulfonimidamide **9p**. Alternatively, sulfonimidamide **9o** reacts with water from solvent or the solubilization of iodosylbenzene to produce sulfonimidamide **9p** under the standard conditions to give the corresponding sulfonaimidamides **9a – 9c** in decent yield, respectively.

3. Selective electrophilic amination of tertiary amines

In 2021, Bull and Luisi disclosed the electrophilic amination of tertiary amines to give the corresponding hydrazinium salts (**Scheme 10**).[59] Treatment of tertiary amines with 2.5 equivalent of iodosylbenzenes and 2 equivalents of ammonia carbamate in the presence of *p*-methylbenzenesulfonic acid gave hydrazinium salts. The study of the substrate scope revealed



Scheme 11. Synthesis of terminal diazirines from amino acids through a tandem decarboxylation /iodonitrene transfer.[60]

that many reactive functional groups are well-tolerated under the standard conditions.

For instance, hydrazinium salts of primary alcohol **10b**, ethyl ester **10c**, alkyne **10d** were prepared successfully in good yield under the reported protocol. Importantly, chemoselective electrophilic amination of the tertiary amino group on atropine and a lincomycin derivative took place to give the corresponding hydrazinium salts **10e** and **10f**, respectively.

4. Synthesis of terminal diazirines from amino acids through tandem decarboxylation/ iodonitrene transfer

In 2019, Reboul and co-workers disclosed the synthesis of terminal diazirines from amino acids through a tandem decarboxylation/iodonitrene transfer[59] (**Scheme 11**). Treatment of amino acids with phenyliodine(III) diacetate and 7M ammonia solution produces terminal diazirines as major products accompanied by a small number of undesired nitriles that resulted from over-oxidation. Amino acids such as *L*-histidine, *L*-tyrosine, *N-Boc-L*-tryptophane, *L*-citrulline, and 4-iodo-*L*-phenylalanine were converted to the corresponding diazirines **11a**, **11b**, **11d**, **11e,** and **11h** in high yield. However, unprotected *L*-tryptophane resulted in a volatile diazirine **11c** in 27% yield, which was not accurate for quantification. Besides, sulfurated amino acids such as cysteine (Cys)[57] and methionine (Met)[50] were incompatible with the reaction conditions due to possible side reactions with PIDA. Prior protection of the sulfur, for instance, (*S*)-trityl-*L*-cysteine and (*S*)-Bn-L-cysteine sulfoxide gave the corresponding terminal diazirines **11f** and **11g** in poor to moderate yield. Noteworthy, no sulfoximination[45] product was observed when the sulfoxides above were subjected to the standard conditions.

Treatment of *L*-histidine with PIDA and ^{15}N-labeled ammonia afforded $^{15}N_2$-diazirine **11i** in 57% yield with 75% ^{15}N-label incorporated. This implied that both nitrogen atoms of the newly installed diazirine group originated from the ammonia solution. Primary amides, such as *L*-glutamine, gave diazirines in low yield due to sublimation. In particular, a Hofmann-like rearrangement of *L*-glutamine took place to give urea **11j** in 7% yield. This rearrangement could be alle*via*ted by prior *N*-ethylation of *L*-glutamine.

The authors proposed a possible reaction mechanism (**Scheme 11**, grey box). Amino acid **11k** is subjected to decarboxylation upon treatment with phenyliodine(III) diacetate to give an imine **11l**.[61, 62] The imine **11l** formed could be oxidized to nitrile **11n** in the presence of excess oxidant. Transimination[63] of imine **11l** takes place with iodonitrene to give **11m**[14], which reacts with the second moiety of iodonitrene *via* insertion to give the diaziridine intermediate **11o**.[64] Subsequent oxidation with the release of iodobenzene and acetic acid, affords the desired diazirine **11p**.[65] Another possible pathway involves nucleophilic addition of $^{15}NH_3$ to give **11q**,[66] followed by cyclization into diaziridine **11r**. Oxidation of diaziridine **11r** by phenyliodine(III) diacetate afforded diazirine **11p**.

Very recently, Reboul's chemistry on direct diazirine synthesis from amino acids was used to prepare a diazirine tag for chemical proteomics.[67]

5. Stereoselective and contractive synthesis of cyclobutanes from pyrrolidines

In 2021, stereoselective and contractive synthesis of cyclobutanes from the corresponding pyrrolidines was reported by Antonchick and co-workers [59] (**Scheme 12**). Iodonitrene, which was generated *in-situ* from the reaction between 2.5 equivalents of hydroxy(tosyloxy)iodobenzene (HTIB) and 8 equivalents of ammonium carbamate, acts as an electrophilic aminating reagent and converted the pyrrolidines into the corresponding cyclobutanes in a stereoselective manner. *Meso*-cyclobutanes carrying α-aryl and/or α-heterocyclic substituents, such as **12a** and **12b**, could be prepared in decent yield from the corresponding pyrrolidines under the standard conditions. The pyrrolidine possessing α-quaternary center could be converted

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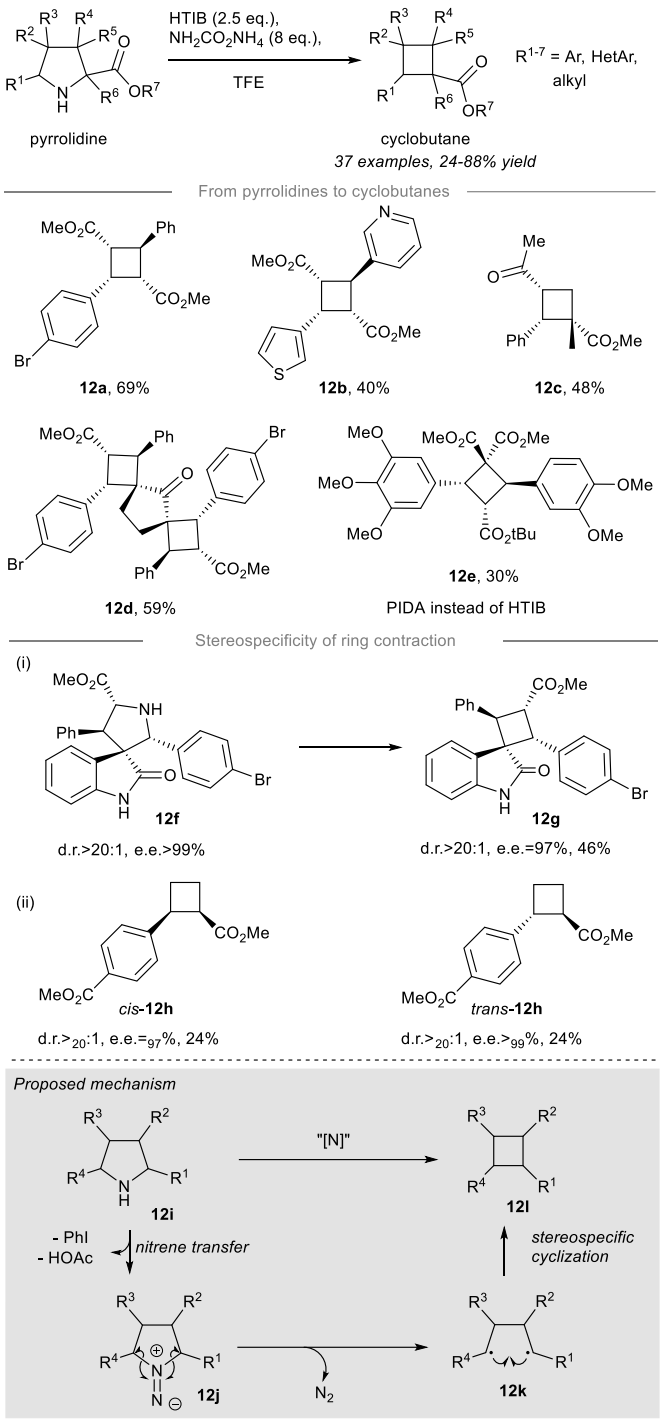

Scheme 12. Stereospecific contraction synthesis of cyclobutanes from pyrrolidines. [59]

to the corresponding cyclobutane **12c** in 48% yield. Furthermore, double ring contraction of bipyrrolidines under additional amounts of HTIB (i.e. 5 equiv.) provided polyspirocyclobutane **12d** in 59% yield. The contractive synthesis of cyclobutane **12e** effected by HTIB instead of PIDA served as an essential intermediate to the preparation of the cytotoxic cyclobutane natural product piperarborenine B. [68-70]

When optically-pure spirooxindole **12f** was subjected to the standard conditions, spirocyclobutane **12g** formed with excellent stereocontrol (*d.r.*>20:1, *e.e.*=97%) validating the stereospecificity of the ring contraction. More importantly, the stereospecific nature of the ring contraction was further substantiated by the formation of cyclobutanes *cis*-**12h** and *trans*-**12h**. Although both ring contractions afforded low yields (i.e. 24%), the outstanding diastereo- and enantiocontrol for *cis*-**12h** (*d.r.*>20:1, *e.e.*>97%) and *trans*-**12h** (*d.r.*>20:1, *e.e.*>99%) indicated a memory of chirality for the developed novel ring contraction allowing access to enantiopure novel cyclobutane derivatives.

The proposed reaction mechanism is depicted (**Scheme 12**, grey box). Treatment of pyrrolidine **12i** with the *in-situ* generated iodonitrene species leads to electrophilic amination affording 1,1-diazene **12j** as a possible intermediate. The reactive 1,1-diazene **12j** proceeds further to give 1,4-biradical **12k** *via* dinitrogen extrusion. Intramolecular cyclization of 1,4-biradical **12k** leads to C-C bond formation to give cyclobutane **12l.**

6. Summary and Outlook

This review provides an overview of iodonitrene chemistry and illustrates its development since 2016. Through the discovery of iodonitrene as an *in-situ* generated reactive species from the reaction between hypervalent iodine(III) and ammonia, iodonitrene has been used extensively as an electrophilic aminating reagent on the amination of sulfides and sulfoxides. Until 2019, the unprecedented synthesis of diazirenes from unprotected amino acids was achieved by Reboul making use of hypervalent iodine(III) as an oxidant for decarboxylation and the iodonitrene as a source of nitrogen. Diazirenes generated by this method can be served as a tag once they are incorporated into bioactive compounds and could be used for various biological investigations. Later, our group reported the stereospecific contractive synthesis of cyclobutanes from pyrrolidines featuring iodonitrene-promoted electrophilic amination of the N-atoms of pyrrolidines followed by nitrogen extrusion. Taking into account the reaction we described above, iodonitrene not only serves as an electrophilic aminating reagent but also shows oxidation properties of hypervalent iodine(III). This makes iodonitrene a very interesting reagent for the development of new methods.

Iodonitrene, acts as a convenient and easily manageable reagent in organic synthesis. Besides its metal-free nature, the use of iodonitrene provides comparable reactivity to rhodium-carbene in the synthesis of *N*H-sulfoximines from sulfoxides but requires no use of transition metal. This provides a fascinating opportunity that rhodium-catalyzed nitrene transfer reactions might be accomplished by iodonitrene chemistry, for instance, in the amination of arenes and alkenes. One major issue that needs to be addressed is the stoichiometric amounts of hypervalent iodine(III) reagent necessary to react with ammonia or its surrogate in order to generate iodonitrene. Inspired by the organocatalytic reactions developed by us and others, hypervalent iodine(III) formed from catalytic quantities of aryl iodide and *m*-CPBA as stoichiometric oxidant might react with ammonia to give iodonitrene, avoiding the use of stoichiometric amounts of hypervalent iodine(III). Furthermore, the prospect of asymmetric iodonitrene transfer might be enabled by iodonitrenes prepared from chiral hypervalent iodine(III) compounds. New method development involving the usage of iodonitrene continues to be an active research area. We envision that synthetic application of the reported iodonitrene chemistry, such as the preparation of diazirene tags

and the synthesis of bioactive natural products, will be flourished as practically useful chemistry applied widely in the synthetic communities and the pharmaceutical industry.

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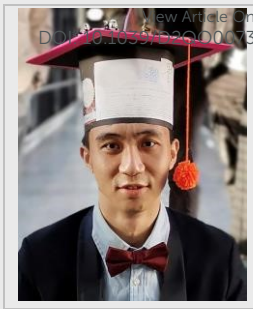

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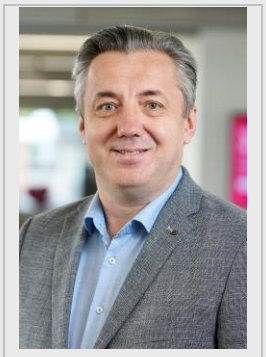

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