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Hypervalent iodine (III) reagents and ammonia as useful combination for highly chemoselective N-transfer to low-valent organosulfur compounds and amines

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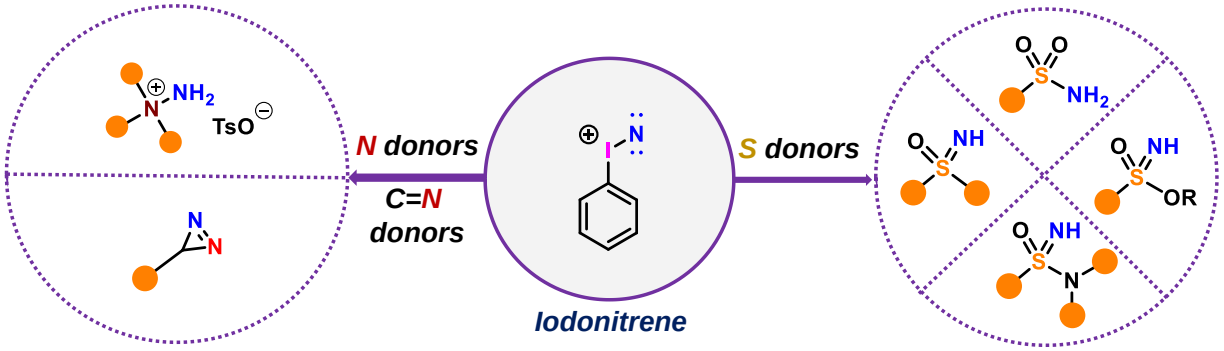
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Abstract

The combination of hypervalent iodine (III) reagents and source of ammonia allows the genesis of an iodonitrene species able to act as source of electrophilic nitrogen. Ammonia umpolung represents the net-result of this combination. Since the introduction of this method in 2016, important and unprecedented transformations have been discovered. In this short review we report the state of the art in the use of this type of iodonitrene in modern synthesis.



Keywords: Nitrogen transfer, hypervalent iodine, iodonitrene, iminoiodinane, sulfur compounds

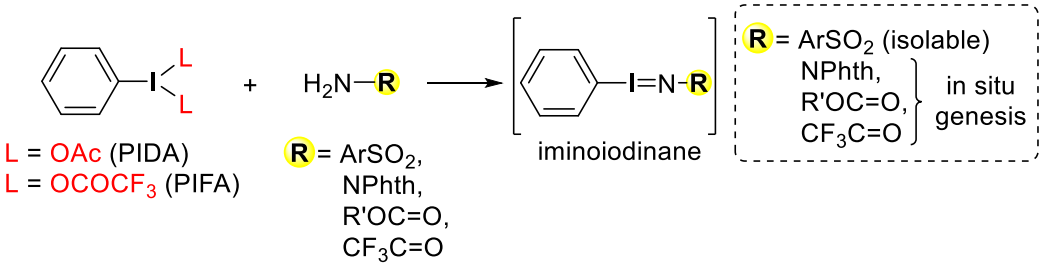
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1. Introduction

Electrophilic nitrogen species such as nitrenes play an important role in modern synthetic chemistry. With their ability to undergo insertion processes, nitrenes have been recognized as useful two-electron oxidants allowing selective C-N bond forming reactions. First described by Tiemann in 1891,[1] early developments in nitrene chemistry predominantly focused on inventing new types of nitrene-based transformations by exploiting organic azides, iminoiodinanes and N–O containing compounds as nitrene precursors. Nitrene-based transformations mainly include C–H amination/amidation, aziridination, addition to unsaturated bonds, sulfimidation, etc.[2] Recent studies have extended the scope of nitrene chemistry exploiting the corresponding metal-nitrenes species obtained from iminoiodinanes as N-donors. These methodologies typically require N-protected iminoiodinane species, easily generated from an hypervalent iodine (III) reagent and a suitable R-NH_2 partner. Among the hypervalent iodine reagents, phenyliodo diacetate (PIDA) or trifluoroacetate (PIFA) have been extensively used in combination with arylsulfonamides ($ArSO_2NH_2$), alkyl or arylcarbamates ($ROCONH_2$), N-aminophtalimide (H2NNPhth) and trifluoroacetamide (CF_3CONH_2) for the genesis of the corresponding putative iminoiodinane formally acting as a donor of electrophilic nitrogen (Scheme 1).

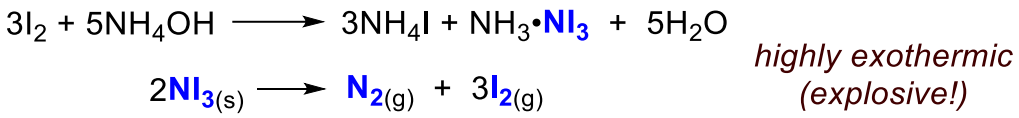


Scheme 1. General routes for the preparation of iminoiodinanes.

Iminoiodinanes have been mainly used for N-transfer reactions to double bonds or sulfur atom for the preparation of aziridines, amines, sulfilimines or sulfoximines.[3,4] However, the use of this type of iminoiodinanes is restricted to the use of electron deficient N-donors (R-NH_2 in Scheme 1) and provide N-protected products. The use of a more basic amine in combination with an hypervalent iodine (III) reagent (i.e. PIDA or PIFA) is reported to be a fast and exothermal reaction.[5] In fact, molecular Iodine/ammonia

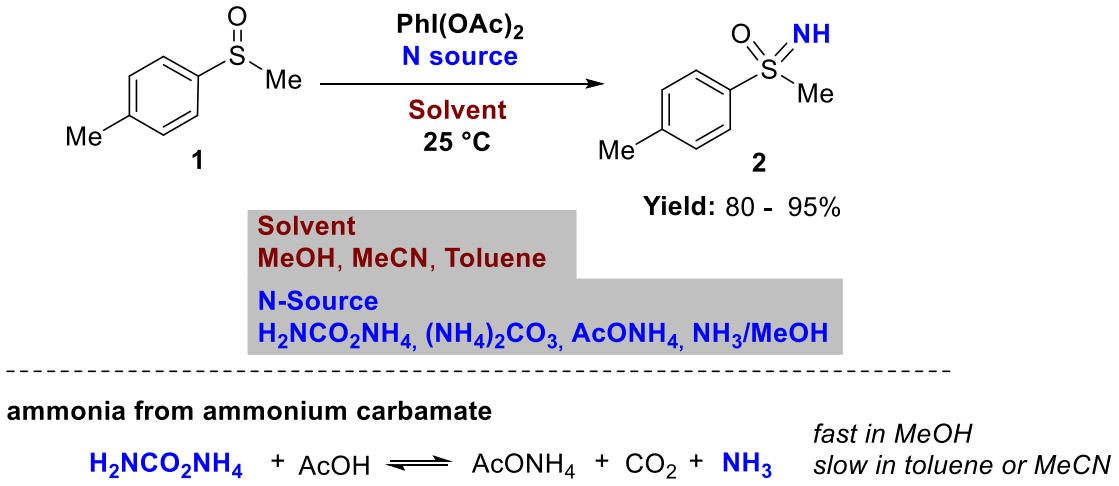
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combination is recognized as contact explosive, under solvent free condition, due to NI_3 formation (Scheme 2).[6] Similarly to ammonia-iodine combination, primary amines are also found to vigorously react with hypervalent iodine reagents.[7]



Scheme 2. Exothermal reaction between ammonia and molecular iodine.

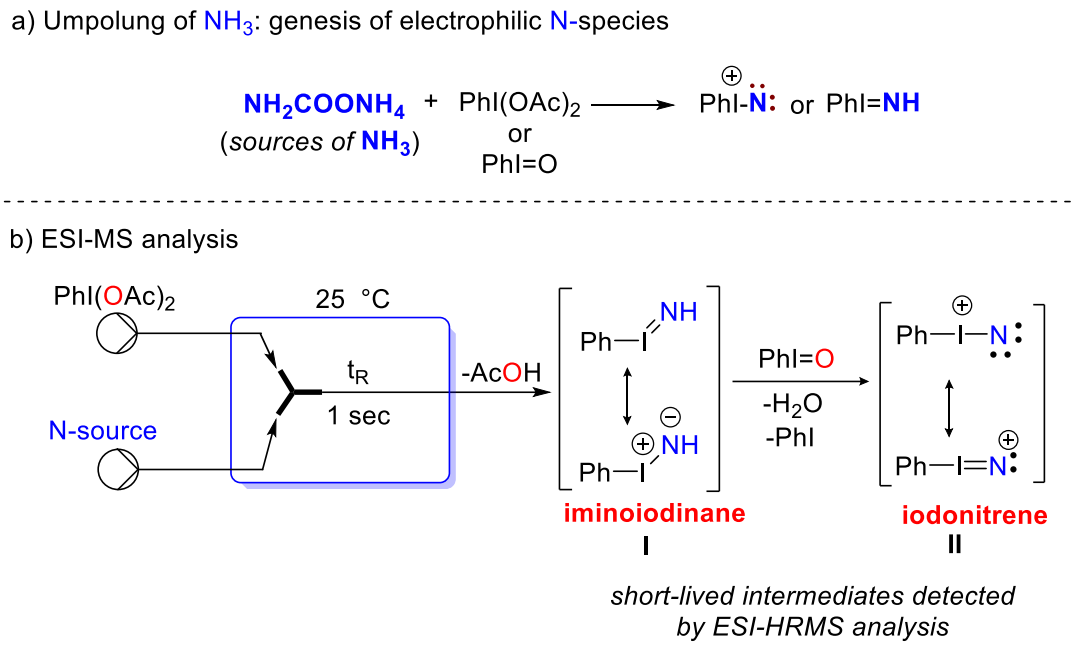
On this basis, the reaction between a hypervalent iodine reagent and ammonia could be disregarded, nevertheless, almost serendipitously, it was discovered that the reaction of PIDA with ammonia led to an unprecedented iodonitrene $[PhI\text{-}N]^+$ able to promote highly selective NH-transfer reactions.[8,9] In 2016, Luisi and Bull reported the first electrophilic metal-free NH transfer to sulfoxides for a direct preparation of NH-sulfoximines.[10] In this seminal work, a detailed mechanistic study, based on HRMS and NMR investigations, supported the involvement of an iodonitrene $[PhI\text{-}N]^+$ as the electrophilic N-specie. Detailed reactivity experiments demonstrated that the use of suitable sources of ammonia (NH_3), in the presence of PIDA, promoted the imination of model sulfoxide **1** furnishing high yields of NH-sulfoximine **2** (Scheme 3).



Scheme 3. N-transfer by combining hypervalent iodine (III) reagent and ammonia.

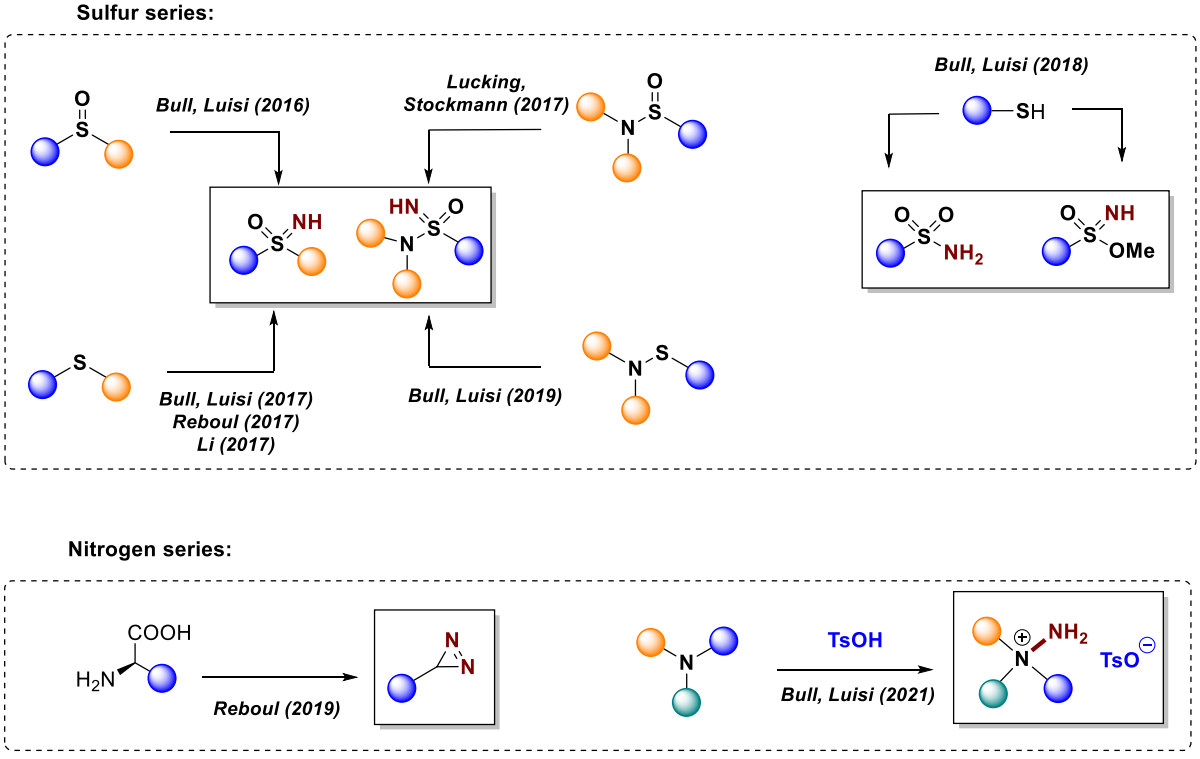
The reaction occurred effectively in several solvents such as acetonitrile, methanol, or toluene, and by using several sources of ammonia either as ammonium salts (ammonium carbamate, acetate, carbonate) or as methanolic solutions of ammonia. Ammonium carbamate was found the most versatile N-source releasing ammonia according to the reaction in Scheme 3. Further studies by using a continuous flow-MS set-up, revealed the HRMS signals of the short-lived iminoiodinane (PhI=NH) **I** and iodonitrene $[PhI\text{-}N]^+$ **II** (Scheme 4, b). Moreover, the use of ^{15}N-labeled ammonium acetate, as the N-source, resulted into the generation of the corresponding ^{15}N-labeled intermediates **I** and **II**.

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Scheme 4. In-flow ESI-HRMS evidence of short-lived iminoiodinane and iodonitrene formation from $PhI(OAc)_2$ and ammonia.

Since the introduction of this direct metal-free NH-transfer to sulfoxides, this strategy has been widely employed for the construction of novel functionalities and neglected structural motifs. In this account, we report the state of the art in the use of hypervalent iodine reagents and sources of ammonia for direct and highly chemoselective transfer of electrophilic nitrogen to organosulfur compounds as well as to nitrogenated compounds (Scheme 5), underlying the mechanistic rationale of these processes.

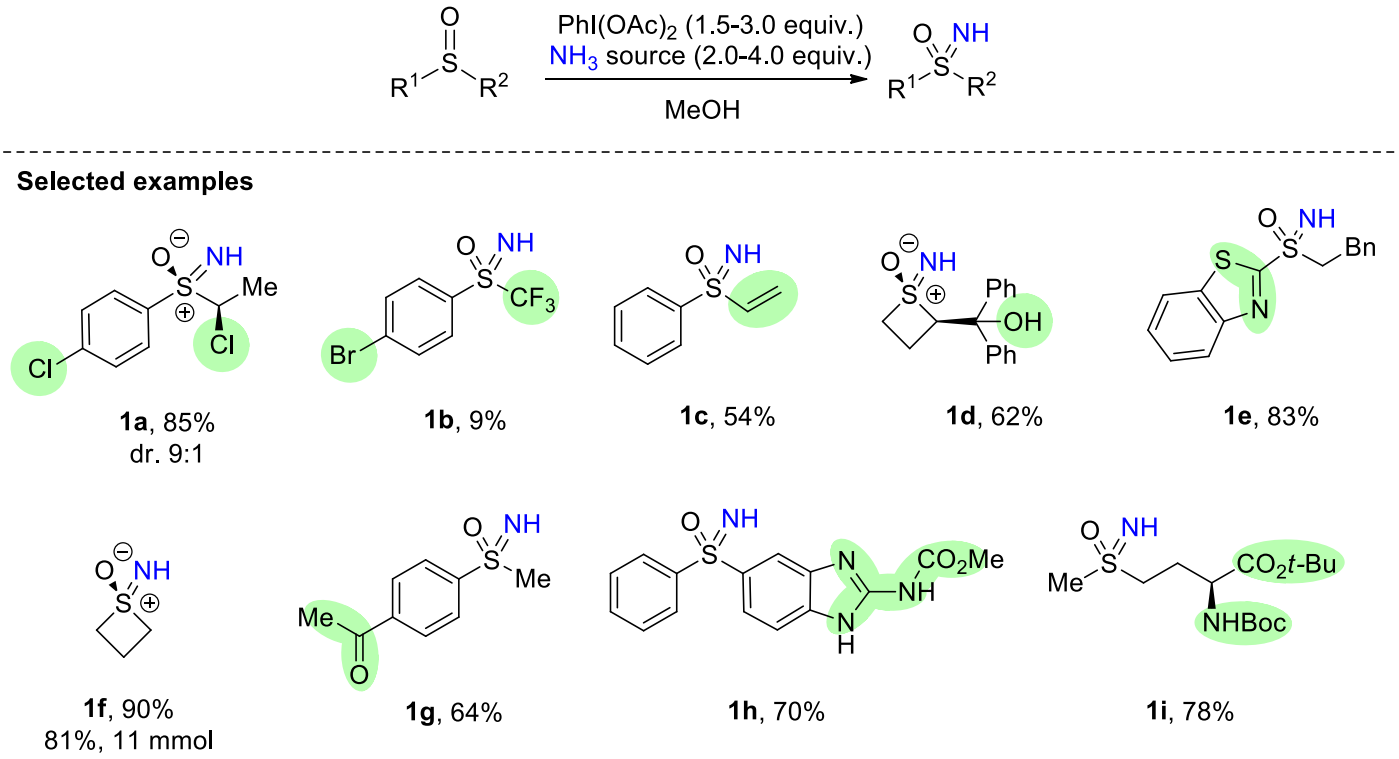


Scheme 5. Direct nitrogen transfer *via* iodonitrene to sulfur- and nitrogen-bearing compounds.

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2. Imination of Sulfoxides: Synthesis of Sulfoximines

As mentioned above, combination of ammonium carbamate and diacetoxyiodobenzene (PIDA) represents an extremely useful method for metal-free *NH*-transfer to organosulfur compounds such as sulfoxides.[10] The use of ammonium carbamate, as inexpensive and easy to handle nitrogen source, and PIDA in polar solvents, such as acetonitrile or methanol, as well as in nonpolar solvents such as toluene, provided excellent yields of the corresponding sulfoximines (Scheme 6). It was demonstrated that this simple protocol resulted compatible with a plethora of aryl and alkyl substituted sulfoxides as well as cyclic sulfoxides, and representative examples are depicted in Scheme 6. Slightly lower yields have been observed with vinyl-substituted sulfoxides such as **1c**, and trifluoromethyl sulfoxide such as **1b** likely due to a lower nucleophilicity of the corresponding sulfoxide.[11,12] Remarkably, the NH transfer is highly stereoselective as observed for example with cyclic sulfoximine **1d**. The functional groups compatibility of this NH-transfer method has been demonstrated via the Glorius' robustness screen.[13] In particular, for applications in medicinal chemistry, compatibility with heterocycles was verified (examples **1e**, **1h**, Scheme 6), and the conditions were shown to be tolerant of various functional groups (halogens, carbonyls) installed on the sulfoxide, including free hydroxyl groups (Scheme 6). Furthermore, protected methionine sulfoxide smoothly undergoes NH-transfer providing protected methionine sulfoximine (MSO) derivative in good yield. The scalability of the procedure was demonstrated with thietane sulfoximine **1f**, prepared on an 11 mmol scale in 81% yield. Interestingly, a continuous flow synthetic approach enabled the preparation of NH-sulfoximines from sulfoxides using PIDA and aqueous ammonia as a convenient nitrogen source.[14]



Scheme 6. Synthesis of sulfoximines from sulfides through NH-transfer (representative examples).

3. Oxo-Imination of Sulfides: Synthesis of Sulfoximines

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In 2017, Luisi and Bull expanded the applicability of the combination source of ammonia and hypervalent iodine (PIDA), realizing a direct conversion of sulfides into NH-sulfoximines.[15] This one-pot NH- and O-transfer resulted to be effective with several alkyl, aryl, benzyl, cycloalkyl, heteroaryl sulfides, leading to the corresponding sulfoximines **1j-w** with excellent yields and functional groups tolerance (Scheme 7). The method was further validated by using several sources of ammonia (ammonium acetate, NH_3 in methanol, ammonium carbonate) including the cheap and readily available ^{15}N-ammonium acetate, which afforded ^{15}N-labeled NH-sulfoximines of biologically relevant compounds such as biotin (**7**), methionine (**8**), and a dipeptide (**9**) (Scheme 7). Even in this case the use of microfluidic technology allowed the synthesis of sulfoximines employing aqueous ammonia as nitrogen source, and the process could be scaled up working under long-term continuous-flow regime.[14] In a similar fashion, Xu and coworkers developed an electrochemical method that enables the access to NH-sulfoximines from sulfides using ammonium acetate and a catalytic amount of an anodically generated iodoarene (III) intermediate. [16]

Substituted vinyl sulfoximines **2a-b** were also directly prepared from the corresponding vinyl sulfides, by NH and O transfer (Scheme 7), as reported by Craven, Bull and Armstrong very recently.[11] It is worth mentioning that this method represents a valid alternative for the synthesis of vinyl sulfoximines starting from the corresponding vinyl sulfoxides. Moreover, vinyl sulfoximines offer interesting potential as chiral electrophilic warheads in covalent inhibitors, that can also incorporate additional functionality through the nitrogen group to provide fully functionalized probes.

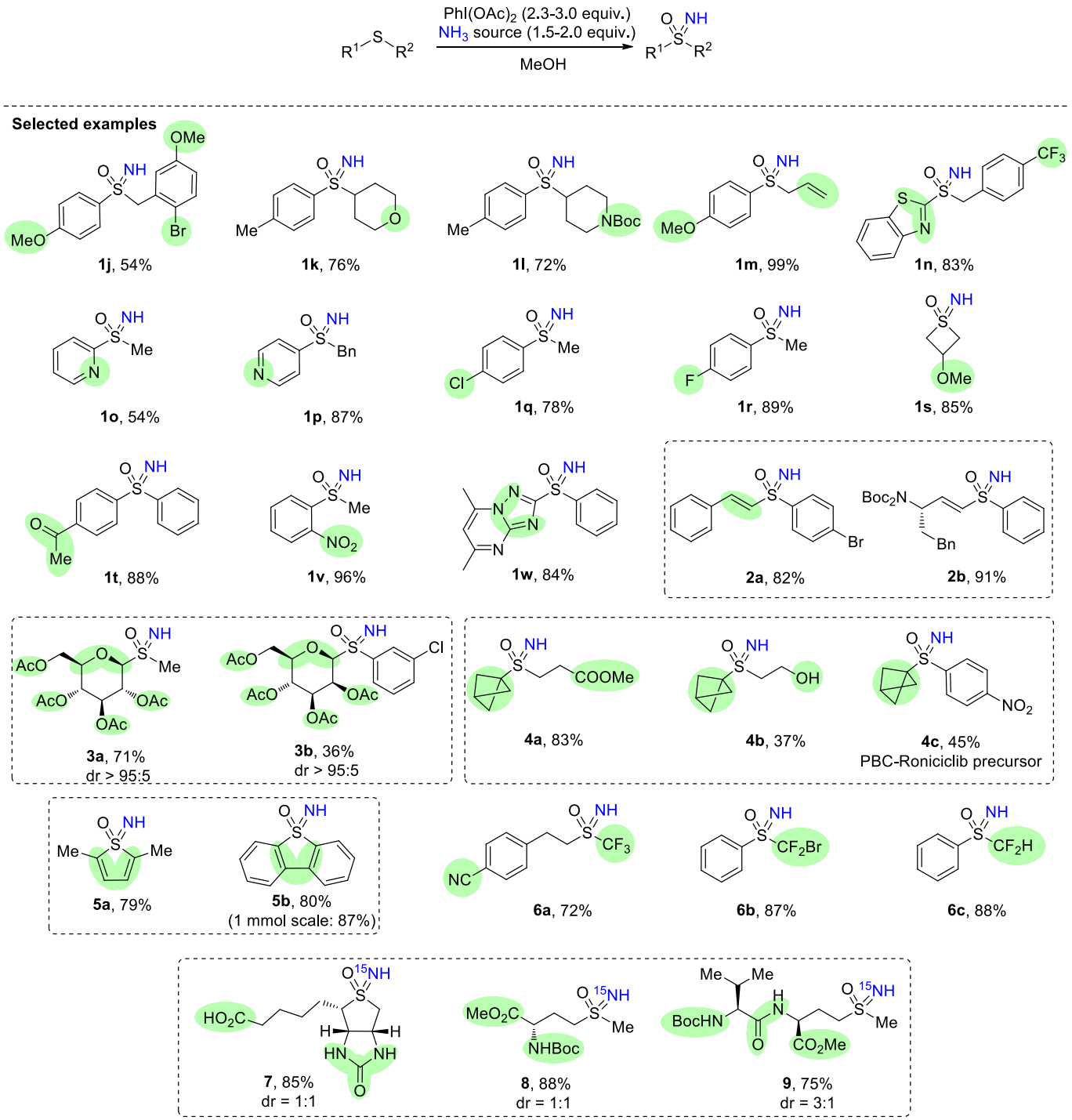
The protocol for oxo-imination of sulfides has been expanded by Luisi, Bull, and Rollin to prepare glycosyl sulfoximines trough the one-pot NH- and O- transfer to anomeric thioglycosides.[17] Peracetylated *S*-methyl-β-glucopyranoside was used as model substrate and could be transformed into the corresponding NH-sulfoximine **3a** by using 2.5 equiv. of PIDA, and 2 equiv. of ammonium carbamate, in ^{i}PrOH at room temperature for 3 hours. The use of methanol as solvent was avoided due to a competitive formation of the corresponding *O*-methyl glucopyranoside, reasonably resulting from displacement of the sulfonimidoyl group. The reaction showed a good tolerance for aryl and cycloalkyl S-substituents. Remarkably, the reaction proceeds with good to excellent stereoselectivity (dr up to 95:5), while a slight loss in stereoselectivity (dr = 70:30) was observed when electron-withdrawing substituents were installed on the aromatic ring S-substituent. X-ray analysis and computational models established the stereochemistry at the sulfur atom, and the structural variability was additionally explored by modifying the sugar portion, as for peracetylated mannose (**3b**, Scheme 7).

This one-pot NH- and O-transfer methodology has been applied by Bräse for the synthesis of bicyclo[1.1.1]pentyl sulfoximines (BCP-sulfoximines) **4a-c** starting from the corresponding sulfides.[18] In the Scheme 7 are reported selected examples of these new structural motifs that are of interest in drug discovery as 3D mimics of aromatic rings.[19] It is worth mentioning that the optimal reaction conditions required a large excess of the oxidant (3 equiv. of PIDA) and 2 equiv. of ammonium carbonate, and the reaction was tolerant to several functional groups furnishing good yields of the corresponding BCP sulfoximines including the synthesis of a BCP-analogue of Roniciclib.[20]

Bolm and co-workers investigated an oxo-imidation procedure on sp^2 hybridized sulfur of aromatic compounds.[21] In particular, applying the one-pot NH- and O-transfer methodology to thiophene derivatives, the corresponding NH-sulfoximines were easily prepared. In this case a large excess of PIDA (5 equiv.) and ammonium carbonate (3 equiv.) was necessary for the synthesis of the corresponding NH-sulfoximines in high yields and at larger scale as in the case of substituted thiophene sulfoximines **6a,b** (Scheme 7).

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In 2018, this protocol was extended to the synthesis of S-fluoroalkylated NH-sulfoximines **6a-c** (Scheme 7) from the corresponding fluoroalkylsulfides.[12] This metal-free strategy used ammonium carbamate (1.5 equiv.) as nitrogen source, PIDA (2.1 equiv.) as the oxidizing agent, and trifluoroethanol (TFE) as polar and hydrogen-bond donor solvent (Scheme 8). Under optimized conditions, high conversion of the sulfides was observed, and the formation of a mixture of NH-sulfoximines **6** and N-acetyl (N-Ac) sulfoximines **10** (Scheme 8 b). A final deprotection step by treatment with HCl provided the desired fluoroalkylated NH-sulfoximines **6**. Satisfactory results were obtained with several fluorinated alkyl and aryl sulfides, and the process was scalable up to 12 mmol. The protocol was effective with sulfides bearing a perfluorobutyl, CF_2Br, $CFCl_2$, CF_2H, and CH_2F groups.

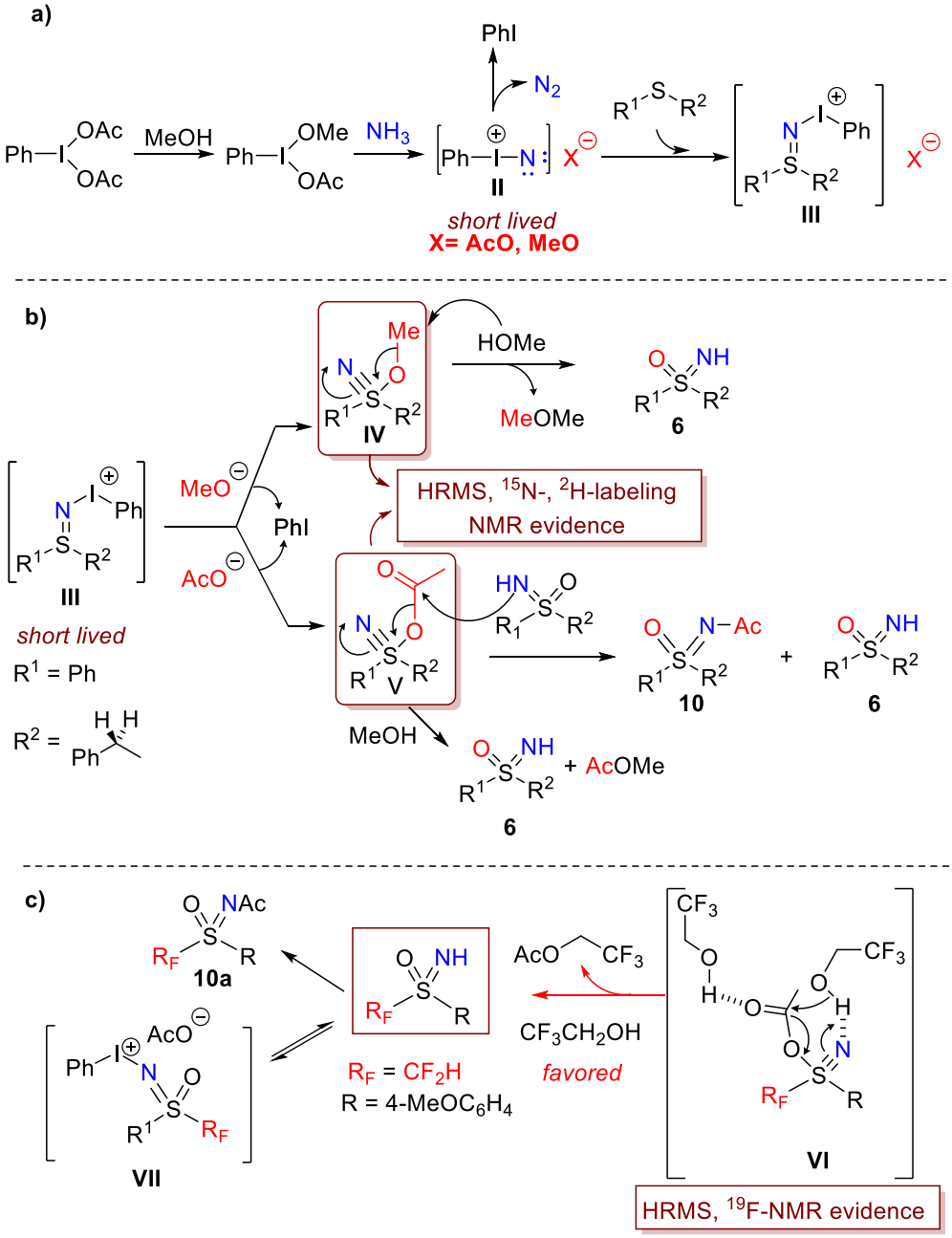


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Scheme 7. Preparation of sulfoximines from sulfides via one-pot NH and O transfer to sulfides.

Interestingly, Reboul and coworkers reported important mechanistic evidence on this one-pot NH- and O-transfer to alkyl and aryl sulfides,[22] and fluoroalkyl sulfides.[12] By multinuclear magnetic resonance and HRMS analysis, the authors were able to demonstrate that the oxygen is provided by the solvent or the acetate anion, and that a key intermediate is a sulfanenitrile specie. In fact, ^{15}N-, ^{13}C-, and ^{1}H-NMR and HRMS experiments, using phenylbenzylsulfide as model compound, supported the mechanism reported in Scheme 8. Similarly, ^{19}F-NMR and HRMS experiments, using (4-methoxyphenyl)difluoromethylsulfide as model substrate, further proved the proposed mechanism highlighting the role of the solvent in promoting sulfoximine release (Scheme 8). The process starts with the formation of the key iodonitrene **II** (Scheme 8, a) that reacts with the sulfide providing a postulated adduct **III**. Reaction of intermediate **III** with oxygen donors (i.e. MeOH or AcO^-) furnishes sulfanenitriles intermediates **IV** and **V** that undergo a solvent-promoted displacement releasing the sulfoximine **6** or the corresponding N-acyl sulfoximine **10** (Scheme 8, b). Similarly, the use of a fluoroalkylsulfide allowed to disclose the fluorinated sulfanenitrile **VI** as key intermediate for the NH- and O-transfer process on fluoroalkyl sulfides (Scheme 8, c). During this study, further evidence of the formation of iodonium salt **VII** and N-acyl sulfoximine **10a** were provided.

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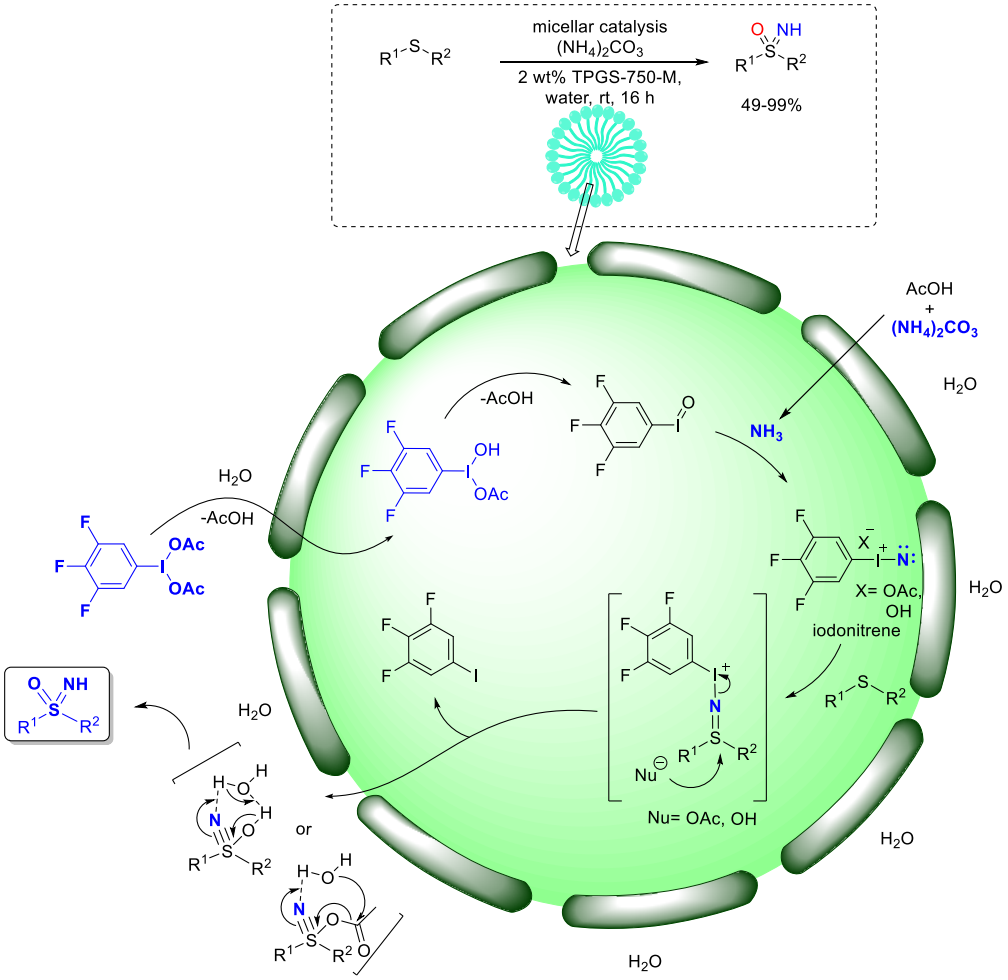


Scheme 8. Mechanistic details for the one-pot NH- and O-transfer to sulfides.

An interesting extension of the one-pot NH- and O-transfer reaction to sulfides was recently reported by Zheng and Xu, who performed the synthesis of NH-sulfoximines from sulfides in water, harnessing micellar catalysis (Scheme 9).[23] In this case, the generation of the iodonitrene intermediate was achieved from a fluorinated hypervalent iodine (III) reagent and ammonium carbonate as a water-soluble nitrogen source (Scheme 9). Among several surfactants, better yields were observed by using 2 wt% TPGS-750-M, and the sustainability of the process was assessed by recycling of the hypervalent iodine (III) reagent. In fact, trifluoroiodobenzene could be efficiently extracted with organic solvents and could be re-used after oxidation with sodium perborate tetrahydrate and trifluoromethanesulfonic acid in acetic acid, restoring the iodoarene(III) specie. This new protocol resulted effective with different aryl, heteroaryl, and alkyl sulfides providing the corresponding NH-sulfoximines in good to excellent yields. The scalability of the process and the

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application to biologically relevant compounds were also demonstrated. The proposed reaction mechanism recall that one previously reported (see Scheme 8, b), and involves an iodonitrene intermediate as described in Scheme 9. NH-Sulfoximines are obtained after permeation and decomposition, outside the micelle, of hydroxy or acetyl sulfanenitrile.



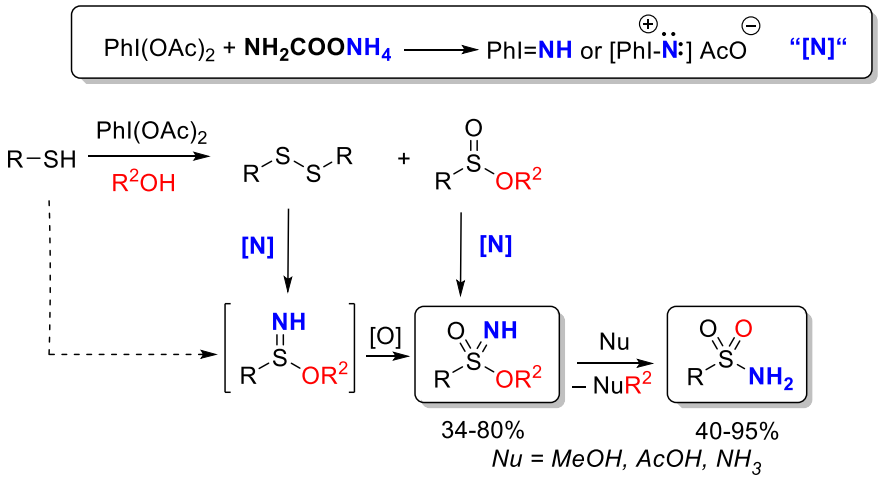
Scheme 9. Micellar catalysis for the synthesis of NH-sulfoximines from sulfides in water.

4. Imination of Thiols: Synthesis of Sulfonimidates and Sulfonamides

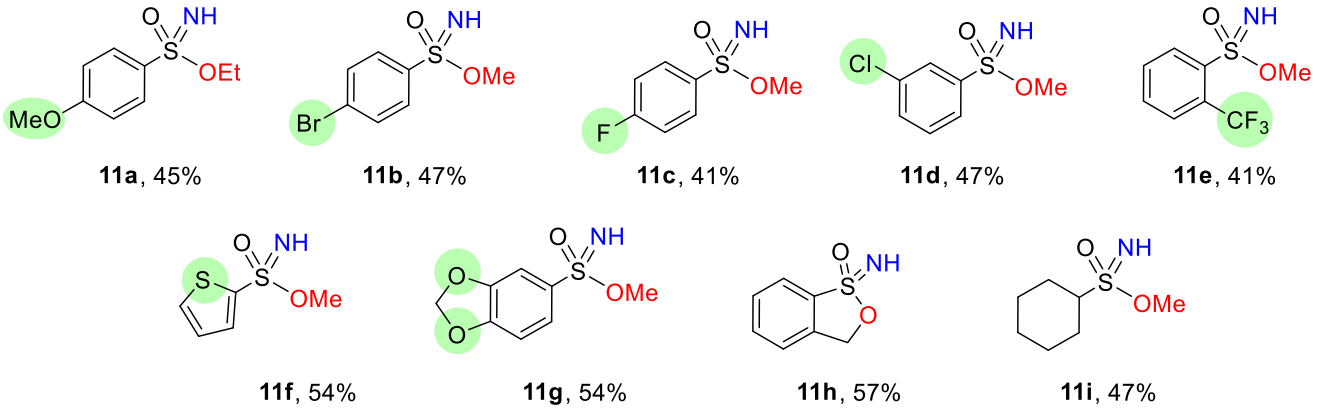
A straightforward and chemoselective synthesis of either sulfonimidates or sulfonamides was developed by Bull and Luisi by NH- and O-transfer to thiols under mild conditions.[24] Optimal conditions to form sulfonimidates **11** used 4 equiv. of ammonium carbamate and 4 equiv. of PIDA in alcoholic solvents. Various *para*-, *meta*- and *ortho*-substituted aryls as well as other aromatic thiols were found to be suitable for this transformation affording sulfonimidates **11a-e** and **11g** respectively in good yields (Scheme 10). Heterosubstituted electron-rich thiols such as thiophene-2-thiol led to the formation of the corresponding sulfonimidate **11f** in good yield. Cyclohexanethiol was also suitable, furnishing sulfonimidate **11h** in 40% yield. Interestingly, the use of 2-mercaptobenzylalcohol gave the cyclic sulfonimidate **11i**. In striking contrast, running the reaction in methanol with only 1 equiv of ammonium carbamate and extending the reaction time to 24 h, at 25 °C, provided full conversion of the thiol into the corresponding sulfonamide. Sulfonamides **12a–f**

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were easily obtained from the corresponding aromatic thiols, although the yields were dependent on the electronic nature of the substituent on the aromatic ring of the thiol. Even heteroaromatics and aliphatic thiols were converted in high yields to the corresponding sulfonamides **12g** and **12h**. To get insights on the mechanism of this reaction, and establish the order of events, a detailed mechanistic study was executed. Some diagnostic intermediates such as disulfide and sulfinate were detected by MS analysis. Based on the mechanistic results, the formation of sulfonimidate **11** was explained assuming initial oxidation (operated by PIDA) of the thiol into the corresponding disulfide and sulfinate, that react with electrophilic iodonitrene furnishing the sulfonimidate. Extending the reaction time, sulfonimidate undergoes a further nucleophilic attack by the solvent furnishing the sulfonamide **12** (Scheme 10).



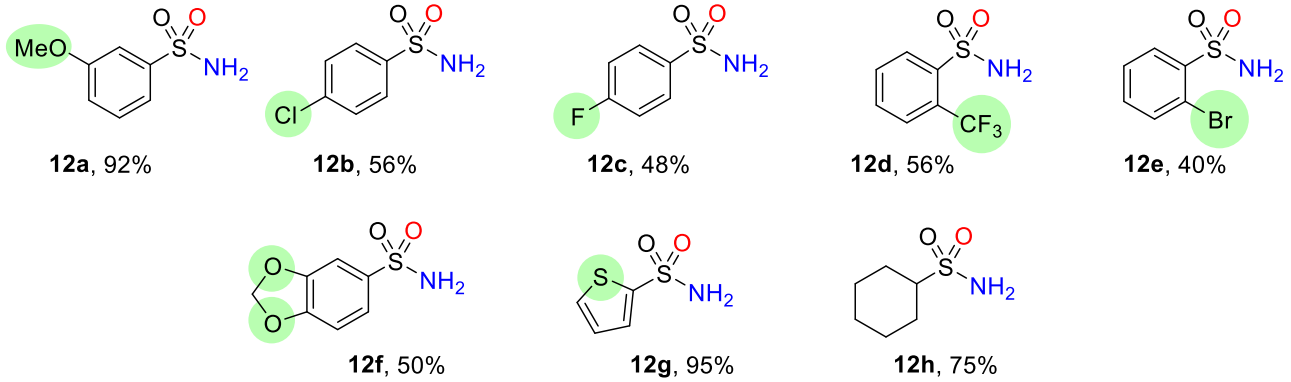
Selected examples for sulfonimidates



11a, 45% **11b**, 47% **11c**, 41% **11d**, 47% **11e**, 41%

11f, 54% **11g**, 54% **11h**, 57% **11i**, 47%

Selected examples for sulfonamides



12a, 92% **12b**, 56% **12c**, 48% **12d**, 56% **12e**, 40%

12f, 50% **12g**, 95% **12h**, 75%

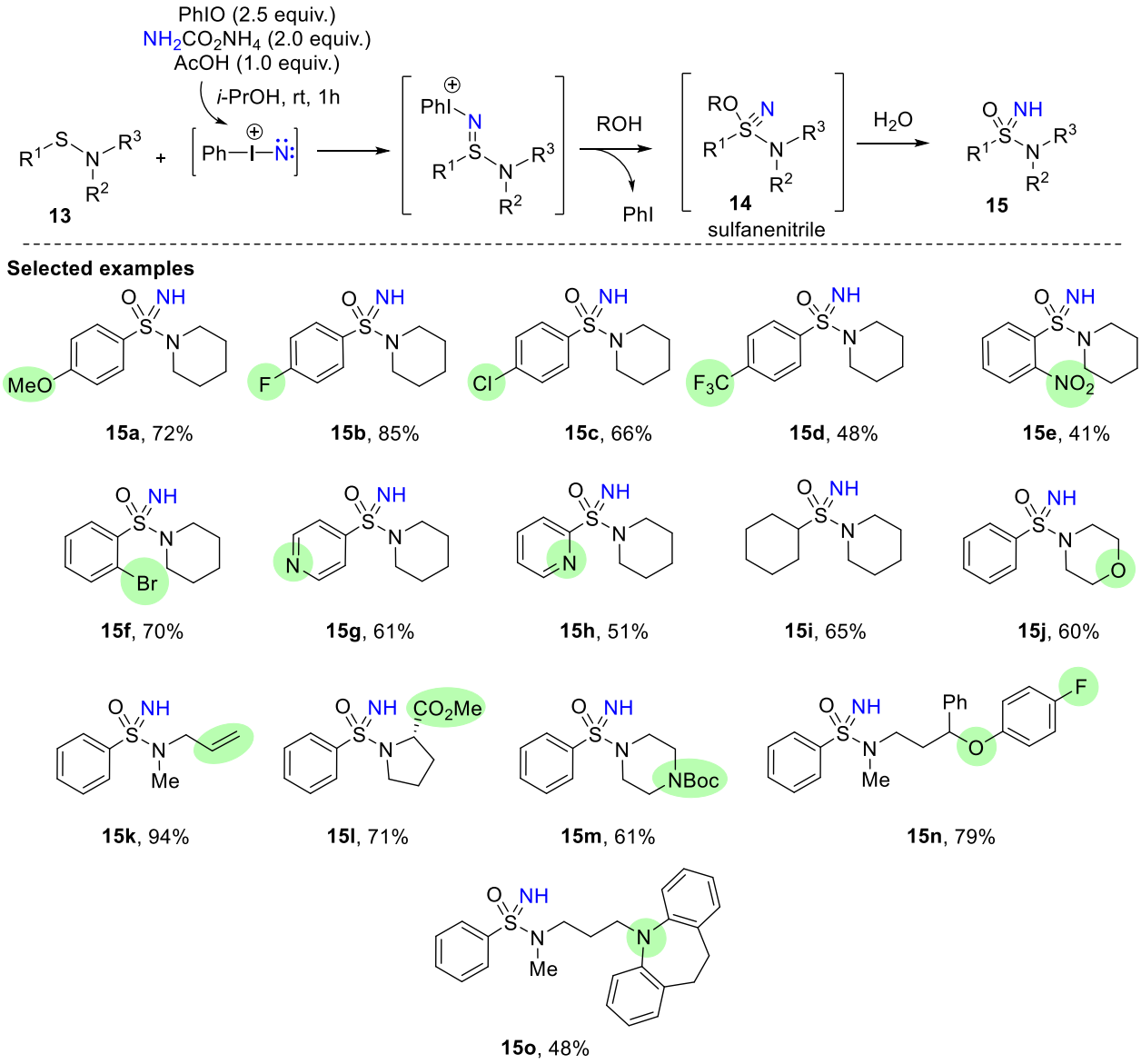
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Scheme 10. Divergent synthesis of sulfonamides and sulfonimidates from thiols.

5. Oxo-Imination of Sulfenamides: Synthesis of Sulfonimidamides

Sulfonimidamides, the aza-analogues of sulfonamides, have been demonstrated to be very useful for synthetic, medicinal, agrochemical, and material science applications.[25] Remarkably, the synthesis of NH-sulfonimidamides **15** has been achieved directly from sulfenamides **13**, readily formed in one step from amines and disulfides, by using the combination of hypervalent iodine reagent and a nitrogen source (Scheme 11). In 2019, Bull and Luisi developed a highly chemoselective one-pot NH- and O-transfer, mediated by PhIO in iPrOH, using ammonium carbamate as the N-source, and in the presence of 1 equiv. of acetic acid.[26] Under these mild conditions, a wide range of functional groups were tolerated such as various substituted aromatics (**15a-h**), heterocyclic compounds (**15j**, **15l,m**) and aliphatic compounds (**15i,k,n,o**) which also enables the functionalization of the antidepressants desipramine and fluoxetine and the preparation of an aza-analogue of the drug probenecid (Scheme 11). Moreover, Xu's electrochemical approach allows for the preparation of sulfonimidamides from sulfenamides in good yield using a catalytic amount of in situ prepared hypervalent iodine specie.[16] The reaction likely proceeds via different and concurrent mechanistic pathways, including the formation of an unprecedented sulfanenitrile specie **14** as key intermediate (Scheme 11). The authors also found optimal conditions to isolate some alkoxy-amino-λ^6-sulfanenitriles by treatment with different alcohols in the absence of acid. These newly formed alkoxyamino-λ^6-sulfanenitriles act as alkylating agents for a range of nucleophiles to release sulfonimidamide **15**.[26]

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Scheme 11. Preparation of sulfonimidamides from sulfenamides.

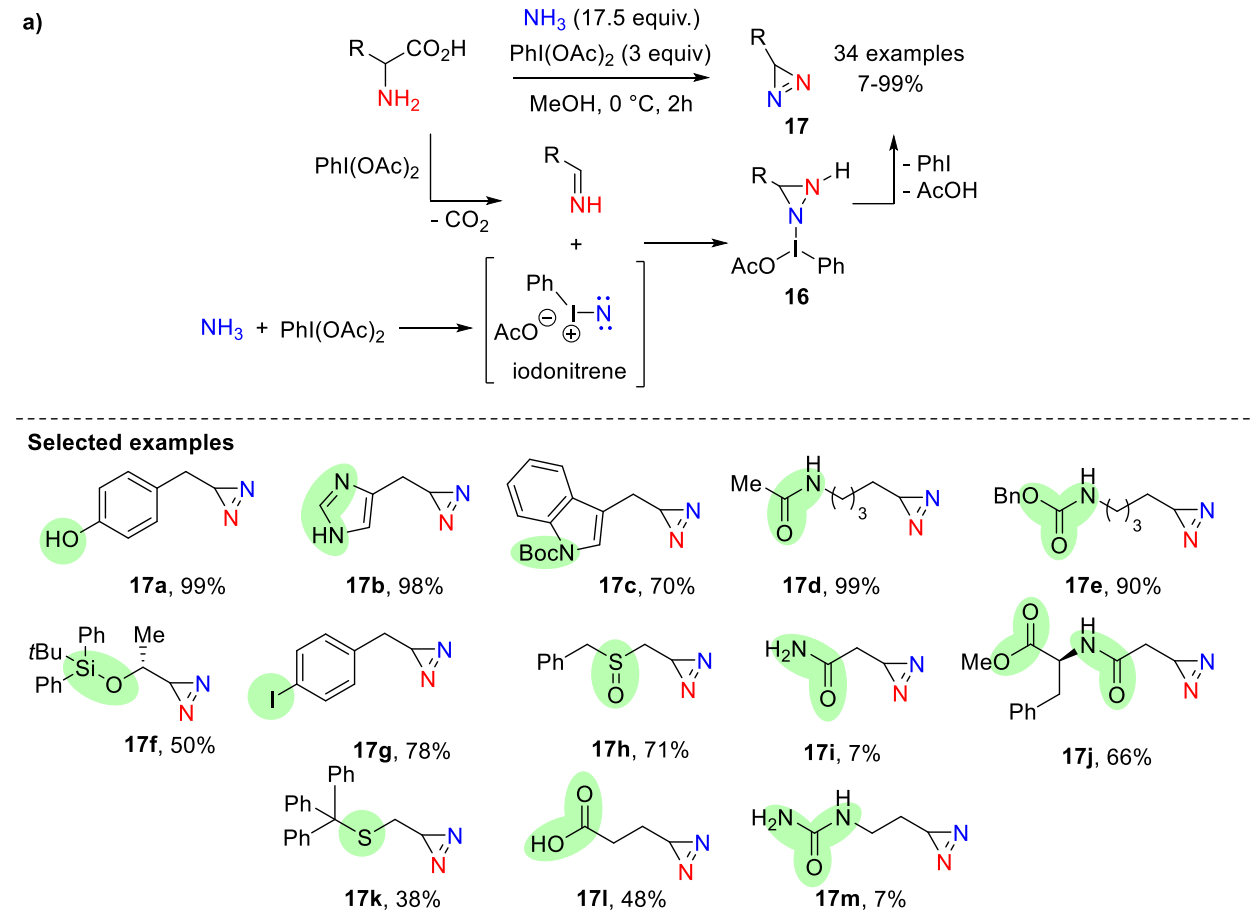
6. Imination of α-Aminoacids, Ketones, Aldehydes, and Imines: Synthesis of Diazirines

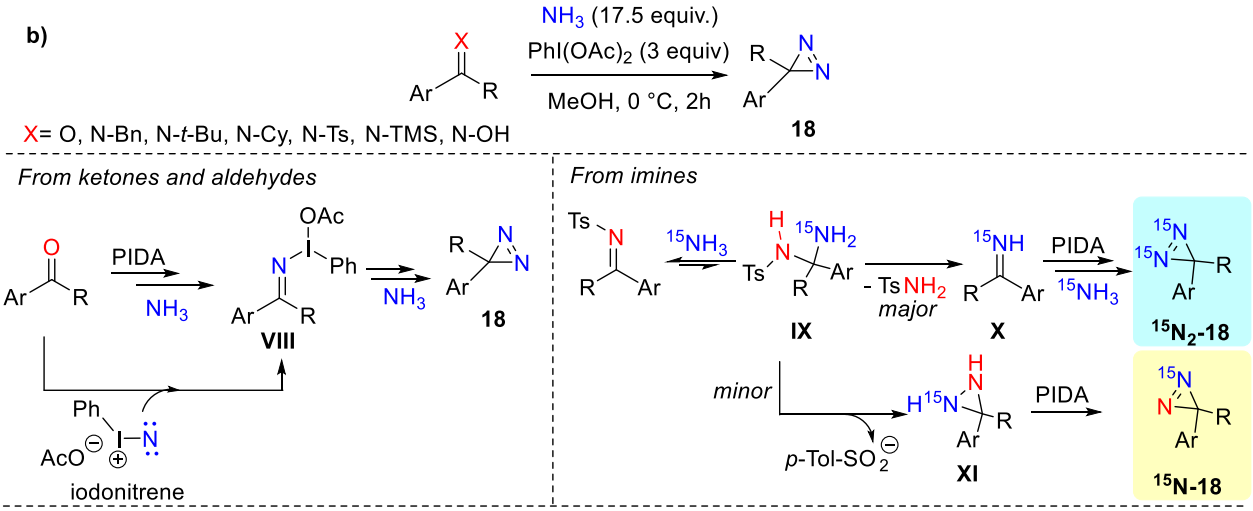
Hypervalent iodine reagents, such as phenyliodonium diacetate, are known to allow oxidative decarboxylation of α-amino acids, providing an imine intermediate that, in some cases, leads to the formation of nitriles.[27] In 2019, Reboul reported a one-pot metal-free conversion of unprotected amino acids into terminal diazirines using the combination phenyliodoniumdiacetate (PIDA) and ammonia.[28] This transformation occurred via three consecutive reactions, and again involved an iodonitrene intermediate. The successful formation of diazirine depends on the insertion reaction of the iodonitrene on the imine intermediate leading to the corresponding diaziridine precursor **16** that by subsequent oxidation, and release of iodobenzene and acetic acid, gave diazirine **17** (Scheme 12, a). This method was found to be efficient with several amino acids and tolerant to diverse functional groups, such as heteroarene (**17b,c**), carboxylic acid (**17l**), hydroxyl (**17a**), silyloxy group (**17f**), sulfide (**17k**), sulfoxide (**17h**), amide (**17i**), urea (**17m**), and ester groups (**17d,e,j**). Moreover, this procedure was operationally simple, high yielding, and provides rapid access to terminal diazirines, which is

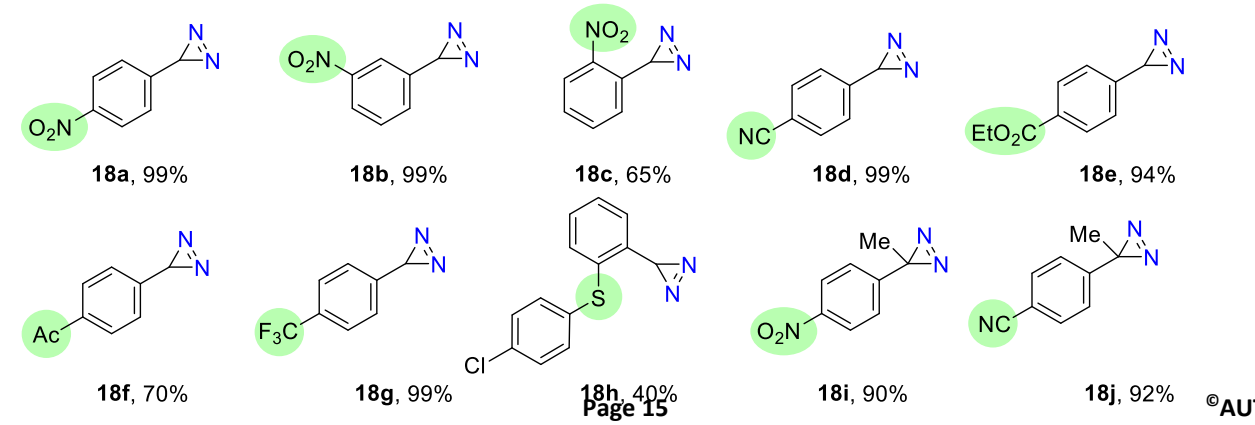
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not straightforward by other synthetic routes. Interestingly, it was also demonstrated that this transformation could be applied to dipeptides without observing racemization and can be scaled up to provide multigram quantities of diazirine (Scheme 12, a). More recently Franck, Reboul, Sabot, and co-workers reported the transformation of aromatic aldehydes, imines and ketones into diazirines upon treatment with PIDA and a solution of ammonia in methanol.[29] This interesting methodology is limited to electron poor aromatics, however the strategy allowed the preparation of diazirines carrying various functionalities, such as nitro (**18a-c,i**), cyano (**18d,j**), ester (**18e**), acetyl (**18f**), trifluoromethyl (**18g**), and sulfide (**18h**) (Scheme 12, b). Better yields were generally observed using N-tosyl imines as substrates, and ^{15}N diazirines with complete ^{15}N incorporation could be efficiently prepared. Interestingly, the reaction of substrates with labeled $^{15}NH_3$ helped to clarify the reaction mechanism. The authors suggest that the formation of diazirines **18** from ketones and aldehydes might involve the formation of intermediate **VIII** via a stepwise reaction with PIDA and ammonia, or directly from the *in situ* generated iodonitrene (Scheme 12, b). Intermediate **VIII** undergoes reaction with ammonia, affording product **18**. On the other hand, N-tosylimines are thought to furnish products **18** through a mixed mechanism, as suggested by the formation of both mono-and di-^{15}N-labeled diazirines when ^{15}N ammonia was used (Scheme 12, b). In more detail, intermediate **IX**, generated from the reaction of the starting imine and labeled ammonia, might follow two different pathways. First, a favored elimination of tosylamide could occur, forming NH-imine **X** that subsequently reacts with PIDA and labeled ammonia, affording doubly-labeled diazirines **$^{15}N_2$-18**. Alternatively, intermediate **X** could undergo an intramolecular cyclisation towards diaziridine **XI** that is suddenly oxidized from PIDA, releasing mono-labeled diazirine **^{15}N-18**. Interestingly, a complete incorporation of ^{15}N was observed when a N-*tert*-butyl imine was reacted, suggesting that with these substrates the transamination reaction towards **X** is highly favored.

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a)
NH3 (17.5 equiv.)
PhI(OAc)2 (3 equiv)
MeOH, 0 °C, 2h
34 examples
7-99%
17
PhI(OAc)2
- CO2
- PhI
- AcOH
16
NH3 + PhI(OAc)2
iodonitrene
Selected examples
17a, 99%
17b, 98%
17c, 70%
17d, 99%
17e, 90%
17f, 50%
17g, 78%
17h, 71%
17i, 7%
17j, 66%
17k, 38%
17l, 48%
17m, 7%


b)
NH3 (17.5 equiv.)
PhI(OAc)2 (3 equiv)
MeOH, 0 °C, 2h
18
X= O, N-Bn, N-t-Bu, N-Cy, N-Ts, N-TMS, N-OH
From ketones and aldehydes
PIDA
NH3
VIII
iodonitrene
From imines
major
minor
IX
X
XI
p-Tol-SO2
15N2-18
15N-18


Selected examples of diazirines prepared from N-tosyl imines
18a, 99%
18b, 99%
18c, 65%
18d, 99%
18e, 94%
18f, 70%
18g, 99%
18h, 40%
18i, 90%
18j, 92%

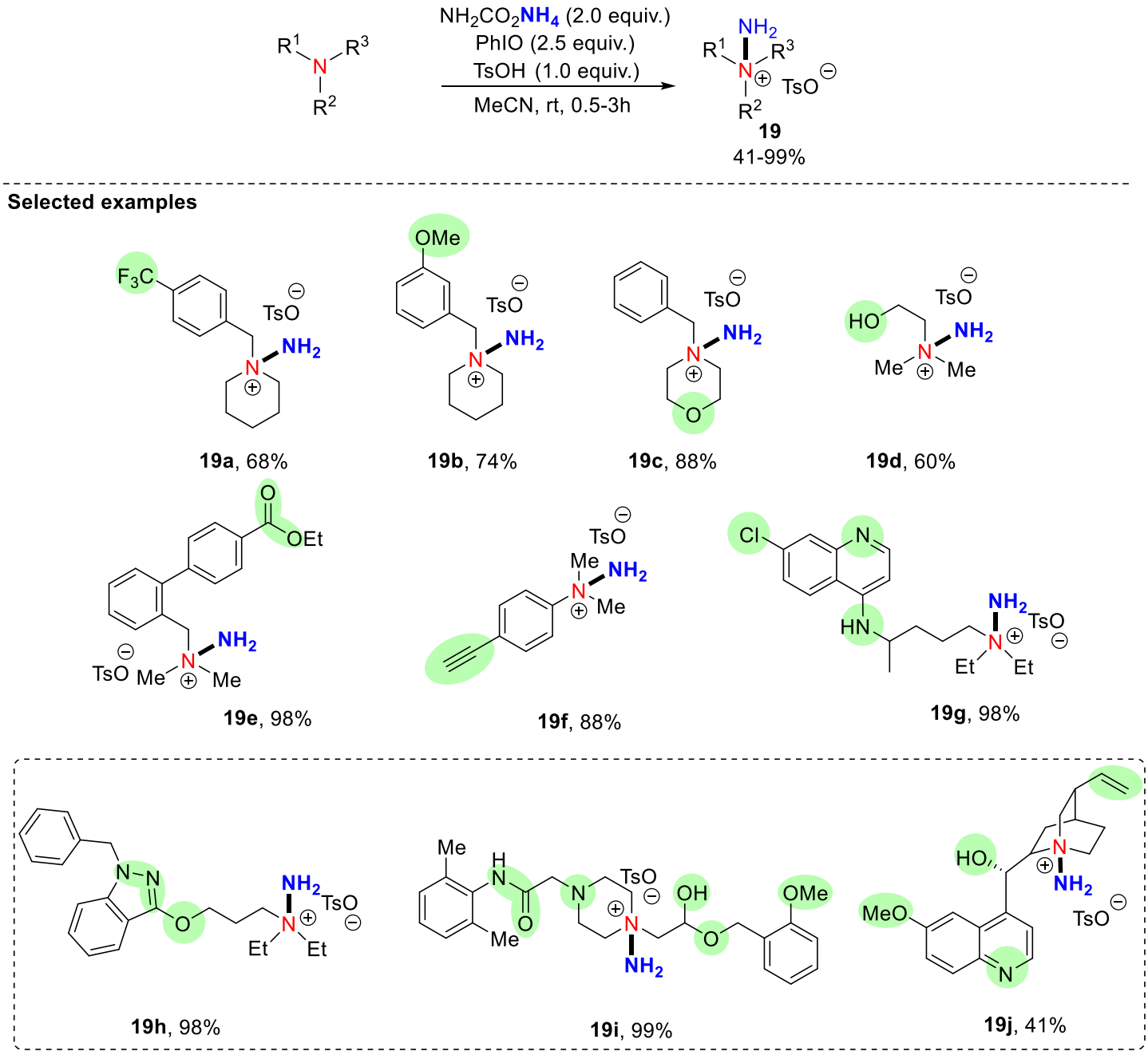
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Scheme 12. Synthesis of diazirines from α-amino acids, ketones, aldehydes, and imines.

7. Imination of Aliphatic amines: Synthesis of Hydrazinium Salts

The transfer of the amino group on tertiary aliphatic amines to form hydrazinium salts is a straightforward procedure and has been achieved in some old works using electrophilic nitrogen sources that involved toxic, explosive or harmful reagents.[30-37] Once again, the nitrene chemistry based on a versatile and easy combination of a nitrogen source and a hypervalent iodine reagent inspired Luisi and co-workers to develop a new approach for the formation of a N-N bond allowing for a direct synthesis of hydrazinium salts from tertiary amines.[38] Compared to other available methodologies, this method provides safer and milder conditions, and represents a strategy to avoid the use of hydrazine. The optimized conditions used PhIO (2.5 equiv.), NH_2COONH_4 (2 equiv.) in acetonitrile and required the addition of 4-methylbenzenesulfonic acid (TsOH) to the reaction mixture to render the tosylated hydrazinium salt an easily separable solid. The reaction worked well with other N-sources such as ammonium carbonate ($(NH_4)_2CO_3$), ammonium acetate (NH_4OA_c), and aqueous ammonia and in several solvents such as *i*-PrOH, CH_2Cl_2, DMF and toluene providing very good yields of hydrazinium salts. The authors investigated the scope of this method using various tertiary amines (Scheme 13). In particular, the reaction could be applied to different cyclic amines (selected examples **19a-c**), acyclic trialkyl amines (selected examples **19d**-**f**), some aromatic and heteroaromatic scaffolds (selected examples **19f-j**). In general, the presence of a hydroxyl group was tolerated as in the case of **19d** and **19j**, as well as the presence of carboxylic ester functionality or a triple bond as for **19e** and **19f**. Unfortunately, primary, and secondary amines and other nitrogen containing compounds such as sulfonamides were unreactive under the optimized conditions while the use of imines provided the corresponding nitriles. Remarkably, to demonstrate the selectivity of the N-transfer, some examples of poly-functionalized molecules and bioactive compounds have been presented. In the case of electrophilic nitrogen transfer to quinine **19j**, the amino group has been installed selectively on the nitrogen atom of the quinuclidine moiety. Similarly, no interference was observed in the amination of benzydamine **19h** as well as in the case of ranolazine **19i** in which the nitrogen transfer occurred selectively only at one nitrogen atom of the heterocycle. These late-stage amination of relevant bioactive molecules and APIs (examples **19i-j**) witnessed the potential of this N-transfer methodology.

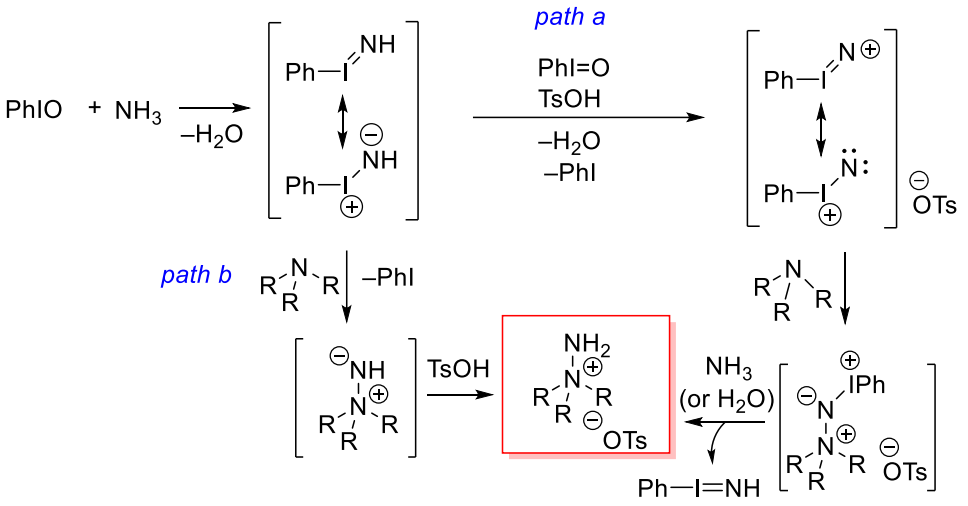
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Scheme 13. Preparation of hydrazinium salts from tertiary amines.

Concerning the mechanistic aspect of this transformation, two possible pathways involving either the iodonitrene (path a) or the iminoiodinane (path b) were proposed. Once generated the electrophilic species, the tertiary amine could attack the nitrene giving an ylide that generates the salt with the tosylate counter ion (path b). Alternatively, the formed iodonium salt (path a) could undergo to subsequent cleavage of the N-I bond after amination (Scheme 14).

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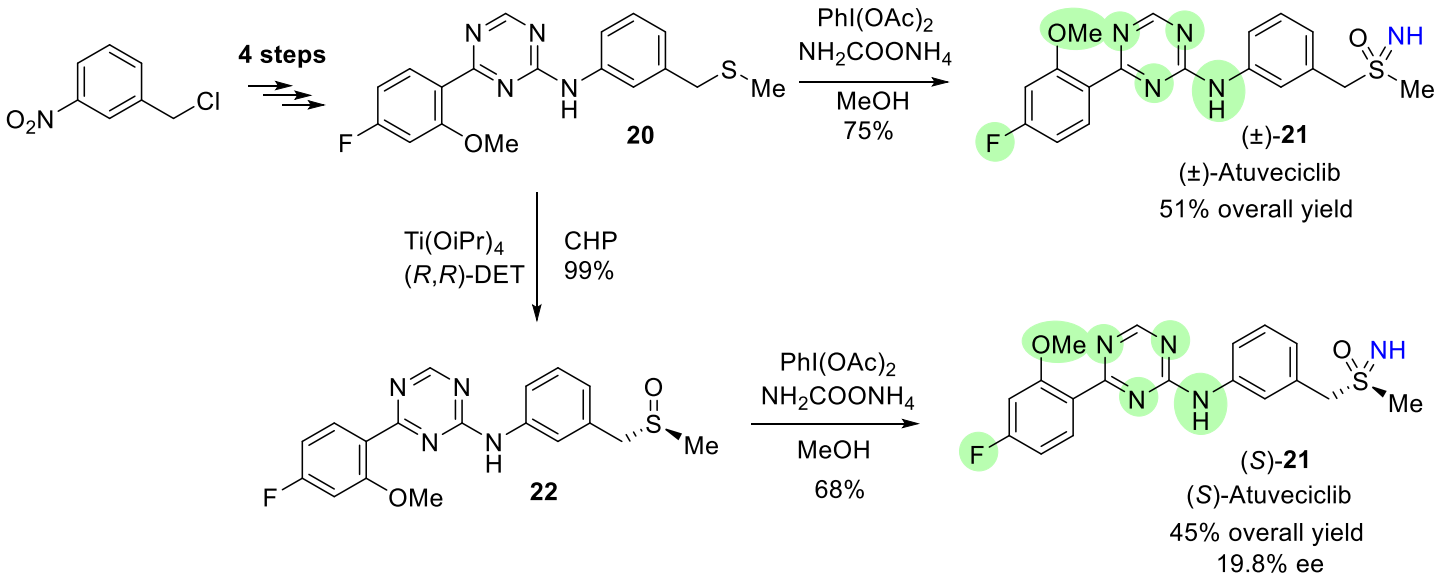


Scheme 14. Mechanistic hypotheses for hydrazinium salts formation.

8. One-pot NH and O transfer for the Synthesis of Biologically active Compounds

The one-pot NH- and O-transfer *en route* to biologically active compounds witness the potential of this method. Methionine sulfoximine, a potent glutamine synthetase inhibitor, showed activity in animal models for the treatment of hepatic encephalopathy, inflammation leading to the liver failure and amyotrophic lateral sclerosis.[39] The ^{15}N labeled methionine sulfoximine precursor **8**, as aforementioned, was efficiently synthetized from protected L-methionine as reported by Luisi and Bull (Scheme 7).[13] Recently, Reboul reported the preparation of the anticancer drug candidate Atuveciclib **21**, which acts as a potent and highly selective PTEFb18/CDK9 inhibitor.[40] In 2012,[41] and 2017,[42] Lücking reported two different multistep syntheses of this compound obtaining respectively 16.8% (9 steps) and 13.9% (6 steps) overall yields. The premature installation of the sulfoximine moiety is probably responsible for the low yields in these two approaches. Reboul proposed a revised strategy based on late-stage one-pot NH- and O-transfer (Scheme 15). Consequently, the authors embarked on the preparation of sulfide **20** which was subjected to a standard oxo-imination protocol obtaining the desired compound (±)-**21** with a noteworthy 51% overall yield (in 5 steps). Furthermore, an enantioenriched version of this synthesis was accomplished by imination reaction on the sulfoxide **22**, affording optically active Atuveciclib (*S*)-**21** in good yield although with a low enantioselectivity (19.8% ee) due to the weakly asymmetric sulfoxidation reaction of **20** to **22**.

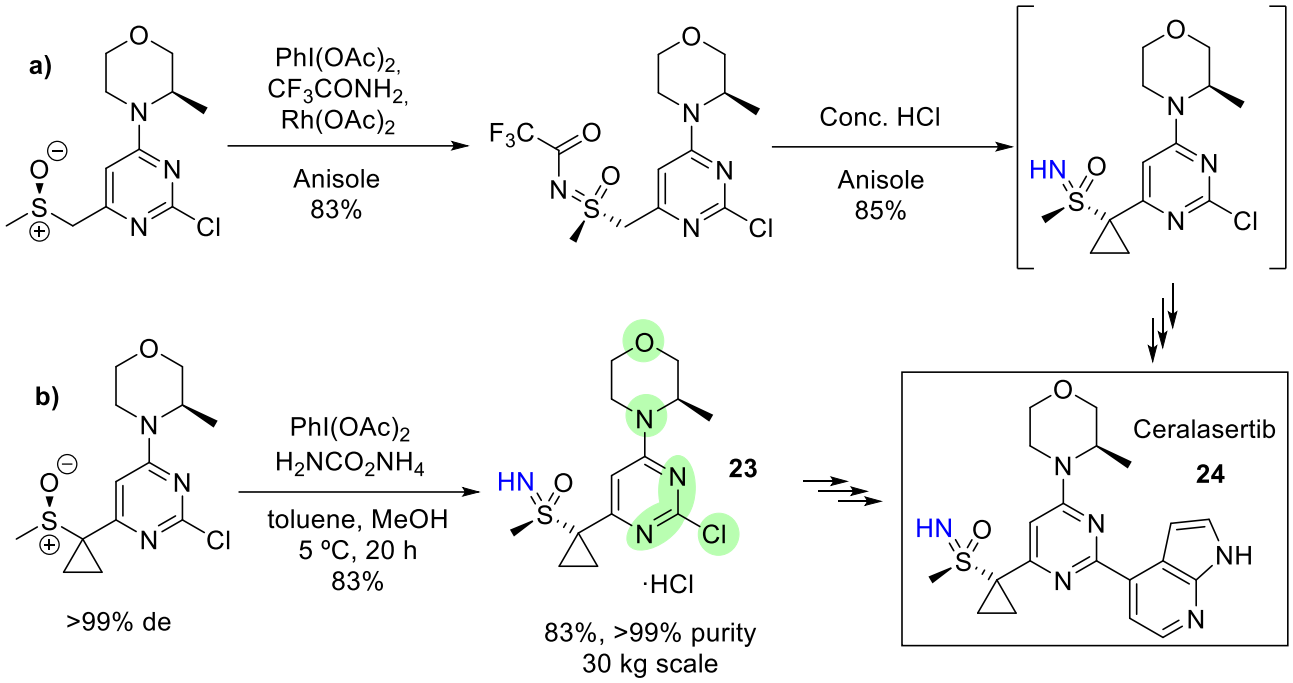
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Scheme 15. Preparation of Atuveciclib via iodonitrene-mediated nitrogen transfer to sulfide and sulfoxide precursors.

Ceralasertib (AZD6738) **24** has been discovered by AstraZeneca as a potent ATR inhibitor which is currently being evaluated in phase II as an antitumor drug.[43] A key step for the synthesis of this compound is the installation of the sulfoximine group. In the early development route (Scheme 16, a), this moiety was introduced by a rhodium acetate catalyzed process by using PIDA as the oxidant and trifluoroacetamide as the nitrogen source.[44] However, drawbacks such as the need for the hydrolysis of the acetamide and the cost of rhodium acetate prompted Graham and coworkers to propose an alternative strategy based on the imination of sulfoxide developed by Bull and Luisi but with few modifications (Scheme 16, b).[45] In particular, the reaction was performed at 5 °C and by decreasing the equivalents of PIDA (2.1 instead of 3 equivalents) to control the impurities formation. Moreover, a mixture of methanol and toluene was adopted as a suitable reaction solvent for this transformation. Hence, the intermediate **23** was produced as hydrochloride salt in 83% yield on 30 kg scale and high purity.

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Scheme 16. Preparation of Ceralasertib precursor via nitrogen transfer to sulfur.

9. Conclusions

In conclusion, in this short review the state of the art on the use of iodonitrene in modern synthesis has been discussed. Since the first introduction of this method in 2016, several researchers from academia and industry have used the combination hypervalent iodine (III) reagents and sources of ammonia as a straightforward methodology for the N- and O-transfer as well as the N-transfer to sulfur- and nitrogen-bearing compounds. Remarkably, the methodology has been adopted in large scale industrial synthesis, and it is becoming a first in class method for the preparation of a plethora of NH-sulfoximines. Mechanistic investigation supported the involvement of an iodonitrene species as key intermediate. Nevertheless, the fleeting nature of this intermediates hampered its isolation and full characterization. However, the synthetic potentials of such electrophilic nitrogen donor are enormous, and further developments of hypervalent iodine reagents able to control the lifetime of this specie are required.

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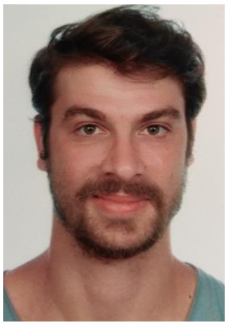
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Marco Colella obtained the M.Sci. (summa cum laude) in Chemistry and Pharmaceutical Technology at the University of Bari (Italy) in 2016. In 2020, he obtained the Ph.D. in Chemical and Molecular Sciences under the supervision of Prof. Renzo Luisi. His research activity is focused on the use of flow microreactor technology applied to organometallic chemistry. In 2019, he has been a visiting scholar at the Department of Synthetic Chemistry and Biological Chemistry, Kyoto University (Japan), working in the group of Prof. Aiichiro Nagaki. He is recipient of the 2020 CINMPIS award for the best Ph.D. thesis.



Leonardo Degennaro obtained the master degree in Chemistry and Pharmaceutical Technology in 1999 and the PhD in Applied Chemical and Enzymatic Synthesis in 2003. In 2002 he was "visiting scholar" at the University of Groningen under the supervision of Prof. B. L. Feringa. In 2006 he was appointed assistant professor in Organic Chemistry at the Department of Pharmacy of University of Bari. In 2011 he has been "visiting assistant professor" at the University of Kyoto working in the group of Prof. J.-i. Yoshida. The research activity is aimed at developing new stereocontrolled synthesis by using small heterocycles and organometallic species, and microreactor technology.



Renzo Luisi is full professor of Organic Chemistry at the University of Bari (Italy). The research activity focuses on organometallic chemistry, sulfur and fluorine chemistry and the use of flow technologies for the development of new synthetic methodologies. He obtained the PhD in 2000 under the guidance of Professor Saverio Florio. He has been visiting student at the Roger Adams Lab at Urbana Champaign in the group of Prof. Peter Beak, and visiting professor at the University of Manchester in the group of Jonathan Clayden. He is RSC

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