Chem Soc Rev

TUTORIAL REVIEW

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Sulfur imidations: access to sulfimides and sulfoximines

Cite this: *Chem. Soc. Rev.*, 2015, **44**, 3378

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Received 9th March 2015

DOI: 10.1039/c5cs00208g

www.rsc.org/csr

Being mono-aza analogues of sulfoxides and sulfones, sulfimides and sulfoximines, respectively, are important compounds in asymmetric synthesis, crop protection and medicinal chemistry. For their preparation various methods have been developed. In the search for the optimal synthetic approach for a given target compound, several parameters have to be considered which also include safety issues and availability of starting materials. In this tutorial review, we present an overview of sulfur imidation methods, classified by imidating agents and compounds with a related behaviour. The aim of this survey is to provide a practical "tool box" for the synthetic chemist by mapping the advantages and disadvantages associated with the use of these compounds.

Key learning points

(1) Most imidating agents consist of the nitrogen atom to be transferred linked to a core fragment and a leaving group.

(2) Sulfur imidation involves either the reaction between an electrophilic sulfonium salt and a nucleophilic nitrogen, or the addition of an electrophilic nitren(oid) species to a nucleophilic sulfur.

(3) Toxicity and safety issues should be considered before choosing an imidation procedure.

(4) Use of a catalytic amount of transition metal can considerably improve the imidation efficiency and allows stereoselective syntheses of sulfimides and sulfoximines.

1. Introduction

Sulfimides and sulfoximines are mono-aza analogues of sulfoxides and sulfones, respectively. This one-atom modification is highly relevant for medicinal chemistry and crop protection, as the resulting products can reveal interesting bioactivities.[1] In this tutorial review a comprehensive overview of sulfide **1** and sulfoxide **3** imidations is presented, leading to sulfimides[2] **2** and sulfoximines[3] **4**, respectively, as depicted in Fig. 1. Noteworthy, the conversion of sulfoxide **3** into sulfimides **2** is not adressed herein.[4]

The first step in sulfur imidation is to choose the adequate imidating agent and suitable reaction conditions. Several questions have to be adressed before choosing the optimal procedure: is the substrate compatible with acid/basic conditions, or are neutral reaction conditions essential? Is it easier to isolate the corresponding imidated sulfur derivative as a salt or as a neutral product? Is a transition metal catalyst needed? How about safety and toxicity issues of the imidating agents?

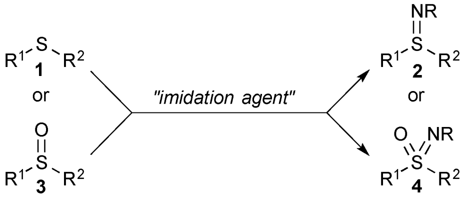

Fig. 1 Sulfide and sulfoxide imidations.

Interestingly, all imidating agents (R-N-LG) depicted in Fig. 2, have a recurrent structure consisting of first, a nitrogen atom (N) needed for the S–N bond, second, a remaining fragment (R) linked to the nitrogen before and after imidation which can be considered as a protecting group, and, third, a leaving group (LG) which is removed during the reaction. For a better understanding of the advantages and disadvantages of each imidation method, we have classified the examples reported in the literature according to the nature of the imidating agent: *N*-haloamides and associated derivatives such as chloramine-T and MSH, heterocyclic nitrene sources including oxaziridines and 1,4,2-dioxazol-5-ones, azides and iminoiodinane derivatives. This choice aims to highlight the general behaviour of such reagents in reactions with sulfides and/or sulfoxides by showing their reactivity, the substrate

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scope, the supposed mechanisms, and their use in stereoselective sulfur imidations. This tutorial review cannot be exhaustive, but our goal is to provide the reader a practical "tool box" discussing the main achievements in the development of efficient sulfide and sulfoxide imidation methods. As we recently devoted a tutorial review to the syntheses, properties and applications of fluorinated sulfoximines,[5] imidations of fluorinated sulfides and/or sulfoxides will not be addressed in this manuscript.

2. *N*-Haloamides and associated reagents (RNH-LG)

The common feature of *N*-haloamides and related compounds is that the nitrogen to be transferred is connected to a leaving group (a halogen or a RSO_3 moiety) and that the imidation process involves the formation of a sulfonium or sulfiliminium salt. These reagents are exclusively used for the nitrogen transfer onto sulfides providing sulfimides.

Vincent Bizet

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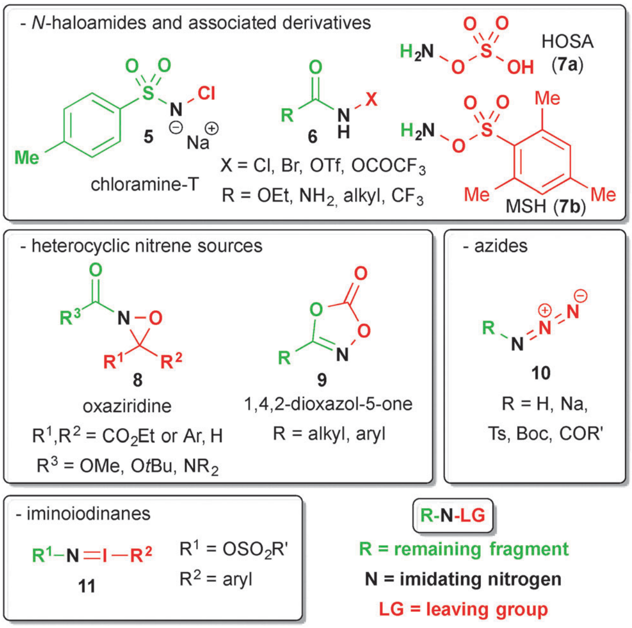

Fig. 2 Main imidation agents.

2.1. Imidations of sulfides with *N*-chloro sulfonamides

The first imidation reagent ever used in conversions of sulfides into sulfimides was chloramine-T (*N*-chloro tosylamide, sodium salt, **5**).[6] Using dry conditions with methanol as solvent at a pH of around 5 (adjusted by the addition of acetic acid) gave access to a variety of *N*-tosyl sulfimides **12** in moderate to high yields (Scheme 1). When water was present, the yields of **12** were lower due to the competing formation of the corresponding sulfoxides.

The proposed mechanism involves a protonation of **5** to give **13** that serves as chlorinating agent for sulfide **1**. The latter step is slow and rate-determining generating highly reactive sulfonium chloride **14** in combination with tosyl amidate **15**. Both ionic species react quickly with each other yielding **12** by

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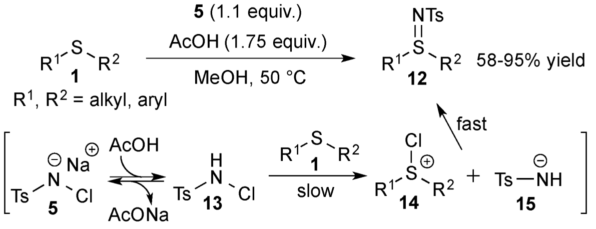
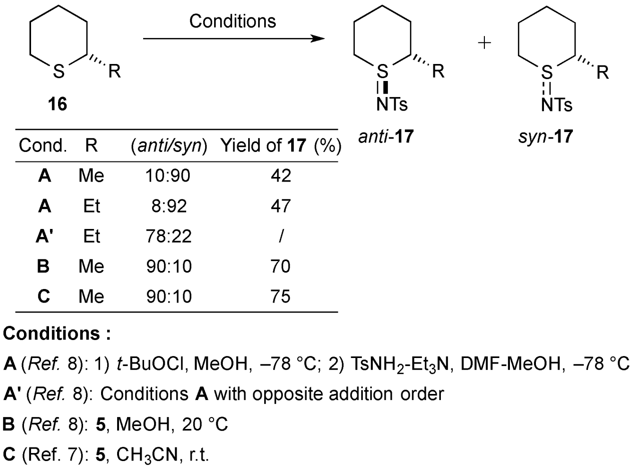
Carsten Bolm

Carsten Bolm studied chemistry at the TU Braunschweig in Germany and at the University of Wisconsin in Madison (USA). In 1987 he finished his doctoral work with Professor Reetz in Marburg (Germany). After postdoctoral studies at MIT, Cambridge (USA), with Professor Sharpless, Carsten Bolm began to work on his habilitation in Basel (Switzerland) in the group of Professor Giese. In 1993 he became Professor of Organic Chemistry at the University of Marburg (Germany), and since 1996 he has been full Professor of Organic Chemistry at the RWTH Aachen University (Germany). In 2012 he became an adjunct professor at WIT (Wuhan Institute of Technology), China.



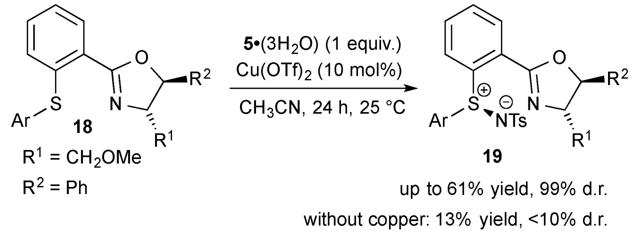
Scheme 1 Sulfide imidations with chloramine-T.



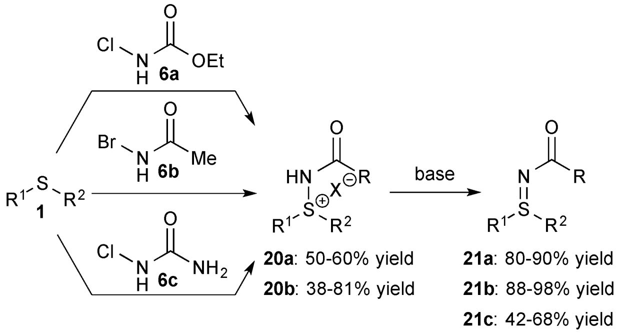
Cond.	R	(*anti*/*syn*)	Yield of **17** (%)
A	Me	10:90	42
A	Et	8:92	47
A'	Et	78:22	/
B	Me	90:10	70
C	Me	90:10	75

Conditions :
A (*Ref.* 8): 1) *t*-BuOCl, MeOH, –78 °C; 2) $TsNH_2$-Et_3N, DMF-MeOH, –78 °C
A' (*Ref.* 8): Conditions **A** with opposite addition order
B (*Ref.* 8): **5**, MeOH, 20 °C
C (Ref. 7): **5**, CH_3CN, r.t.

Scheme 2 Diastereoselective imidations of sulfides with chloramine-T.



Scheme 3 Copper-catalysed diastereoselective imidation of diarylsulfides.



Scheme 4 Imidations of sulfides with *N*-haloamides.

HCl elimination. Replacing methanol by acetonitrile as solvent proved to be highly beneficial.[7] Simple stirring of the sulfides with **5** in acetonitrile led to the corresponding *N*-sulfonyl sulfimides **12** in high to excellent yields (up to 99%). Even in the presence of water, the formation of sulfoxides has never been observed, making this procedure more convenient by using the hydrated form of **5**. The absence of sulfoxide led to doubts related to the proposed mechanism as it suggested that the reaction did not proceed through the intermediacy of **14**. This notion was supported by experiments with enantiopure 2-alkylthianes **16**. Forming the corresponding sulfonium chloride **14** with *t*-BuOCl and treatment of this intermediate with preformed tosyl amidate **15** (conditions **A**, Scheme 2) led to the expected *syn* selectivity (*anti*/*syn* = 10 : 90) for **17**, resulting from an *anti* electrophilic chlorination followed by an S_N2-type imidation. Inverting the addition order of the reagents (conditions **A′**) afforded the *anti* product predominantly, presumably by direct NTs imidation.[8] Interestingly, imidation of **16** with **5** in both methanol (conditions B)[8] and acetonitrile (conditions C)[7] resulted in the same *anti* selectivity (*anti*/*syn* = 90 : 10) implying a direct NTs transfer to the less-hindered face of the sulfide under these conditions as well. Thus, both the absence of sulfoxide formation under non-anhydrous reaction conditions and the *anti* selectivity rendered the initially proposed mechanism with the formation of **14** (Scheme 1) unlikely.

Higher diastereoselectivities were reached in imidations of diarylsulfides **18** with **5** in the presence of a catalytic amount of a copper salt. While the non-catalysed imidation gave *N*-tosyl sulfimide **19** in 13% yield with almost no diastereoselectivity, the use of 10 mol% of $Cu(OTf)_2$ afforded **19** with excellent 99% d.r. in up to 61% yield (Scheme 3).[9]

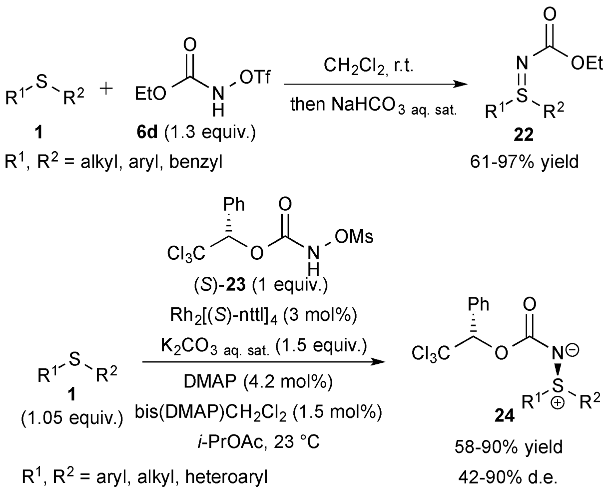
2.2. Imidations of sulfides with *N*-haloamides

Reactions between sulfides **1** and ethyl *N*-chlorocarbamate **6a** (Scheme 4) afforded iminosulfonium chloride salts **20a** in moderate yields (50–60%). Treatment of these salts with triethylamine provided the corresponding *N*-ethoxycarbonylsulfimides **21a** in high yields (80–90%).[10]

Similarly, *N*-carbonylsulfimides **21b** and **21c** were obtained by using *N*-bromoacetamide (**6b**),[11] or *N*-chlorourea (**6c**).[12] Imidation with **6b** proceeded only with dialkylsulfides affording sulfimides **21b** in yields ranging from 36 to 71% over two steps. The reaction failed, when applied to bulky dialkyl or aromatic sulfides. In contrast, with **6c** imidations of aryl-alkyl sulfides worked well leading to the corresponding products **21c** in yields between 42% and 68% after a basic workup. No reaction occurred with diarylsulfides. The mechanism was proposed to be similar to the one described for imidations with chloramine-T **5** as shown in Scheme 1.

2.3. Imidations of sulfides with N-OSO_2R carbamates

Reacting sulfides with *N*-[(methansulfonyl)oxy]carbamate (**6d**) as imidating agent was highly efficient, leading to the corresponding *N*-(ethoxycarbonyl) sulfimides **22** in good yields independent of the nature of R^1 and R^2 (Scheme 5, top).[13] Recently, this chemistry was extended by the development of a diastereoselective version of this reaction applying mesyloxycarbamate (*S*)-**23** as nitrogen source in combination with a chiral rhodium catalyst (Scheme 5, bottom).[14] The use of additives allowed to increase the diastereoselectivities in the formations of **24**,



Scheme 5 Imidations of sulfides with *N*-OSO_2R carbamates.

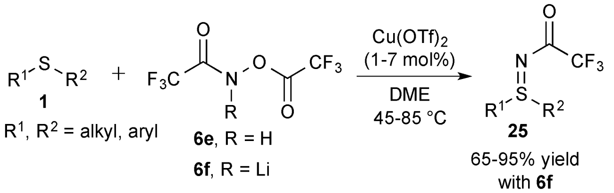
which could finally be isolated with a d.e. of up to 90% in good to high yields. Results from mechanistic and crystallographic investigations suggested the involvement of a Rh(II)–Rh(III) complex and the formation of a metal-nitrene intermediate.

2.4. Imidations of sulfides with *N*,*O*-bis(trifluoroacetyl)-hydroxylamine

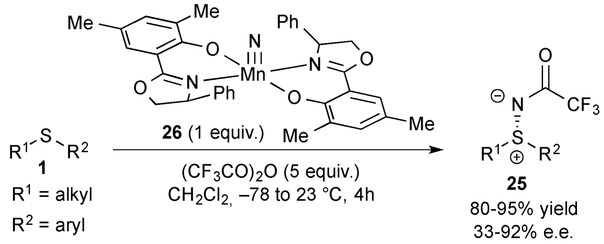
N,*O*-Bis(trifluoroacetyl)hydroxylamine (**6e**) is an inexpensive imidation agent obtained by reaction of hydroxylamine hydrochloride and trifluoroacetic anhydride (TFAA). However, it showed low reactivity in sulfide imidation under many reaction conditions. Interestingly, the corresponding lithium salt **6f** showed a higher efficiency along with an increased stability, allowing bench storage of this salt at room temperature under air. Finally, combining of **6f** with a catalytic amount of copper salt in dimethoxyethane (DME) led to sulfide imidations providing *N*-trifluoroacetyl sulfimides **25** in yields ranging from 65% to 95% (Scheme 6).[15]

Next, an enantioselective synthesis of **25** was demonstrated following an entirely different approach. (This case is discussed here due to structural similarity in the obtained products).

The asymmetric sulfide imidation was performed with chiral nitridomanganese(V) complex **26** that was activated by trifluoroacetic anhydride (Scheme 7).[16] The reaction proceeded smoothly leading to products with moderate to very good enantioselectivities in high yields. Despite the significant efficiency of this procedure, the chiral manganese complex had to be applied in a stoichiometric amount, which limited the synthetic applicability.



Scheme 6 Copper-catalysed imidations of sulfide with **6f**.



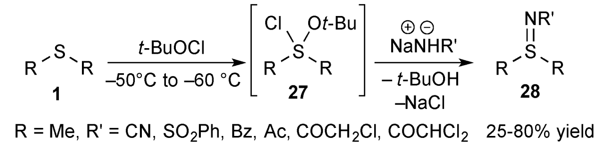
Scheme 7 Enantioselective imidations of sulfides with **26**.

2.5. Imidations of sulfides by halogenation/imidation

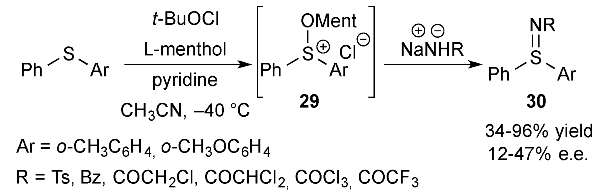
Even if some of the protocols described in the previous chapters implied a nucleophilic substitution in the reaction mechanism, all processes had in common that they involved a unique imidating reagent (RN-LG). Here, the imidation strategy is different as it relies on the use of at least two reagents performing an electrophilic halogenation/imidation sequence. These methods are presented here due to their mechanistic similarities.

tert-Butyl hypochlorite (*t*-BuOCl) is a well-known reagent used for electrophilic chlorination. In the presence of sulfides at low temperature, *t*-BuOCl yields tetravalent intermediate **27** which can react with amide anions to form the corresponding sulfimides **28** in moderate to good yields (Scheme 8).[17] The major drawback of this method lies in the choice of the amide anion which has to be acidic enough to avoid a competitive re-protonation by the generated *t*-BuOH. Consequently, aniline and methylamine cannot be used as amide sources in this reaction.

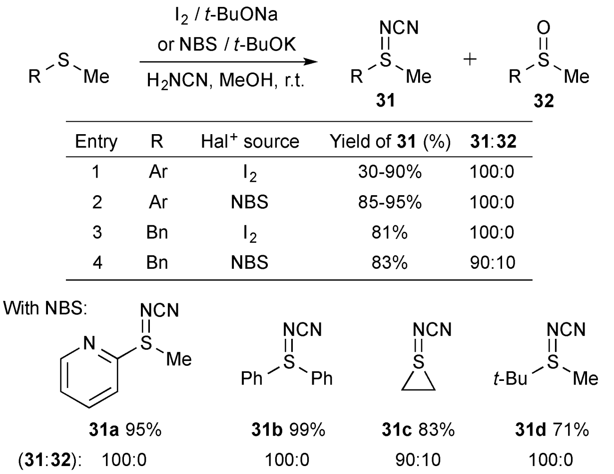
Following the same strategy with a combination of *t*-BuOCl and a chiral alcohol (L-menthol) allowed obtaining optically active sulfimides, albeit with only low to moderate enantioselectivities (Scheme 9).[18] Presumably, the reaction proceeded *via* L-menthyloxysulfonium chloride **29**, which reacted with the deprotonated amides to give diarylsulfimides **30**. The low asymmetric induction (up to 47% ee) was suggested to be a consequence of an insufficient control in the diastereoselective formation of **29** as revealed by the isolation of the perchlorate anion equivalent of **29** and its structural analysis by NMR spectroscopy. Finally,



Scheme 8 Imidations of sulfides with *t*-BuOCl and amide anions.



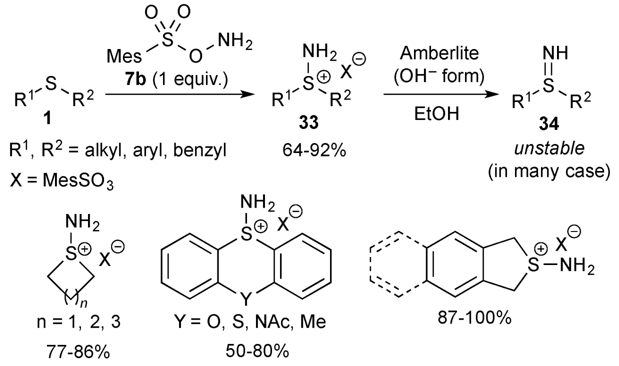
Scheme 9 Asymmetric sulfide imidations with L-menthol as chiral auxiliary.



Entry	R	Hal⁺ source	Yield of **31** (%)	**31**:**32**
1	Ar	I_2	30-90%	100:0
2	Ar	NBS	85-95%	100:0
3	Bn	I_2	81%	100:0
4	Bn	NBS	83%	90:10

	31a 95%	**31b** 99%	**31c** 83%	**31d** 71%
(**31**:**32**):	100:0	100:0	90:10	100:0

Scheme 10 Sulfide imidations with cyanogen amine and NBS or I_2.



Scheme 11 Sulfide imidations with MSH.

a mechanistic switch (inversion *versus* retention) in the conversion of **29** to **30** was discovered, which depended on the acidity of the amidate anion. Thus, ordinary amidate anions such as *N*-(chloroacetyl) and *N*-tosyl amidates substitute the L-menthyloxy group with inversion of the configuration while the more acidic *N*-(dichloroacetyl), *N*-(trichloroacetyl) and *N*-(trifluoroacetyl) imidates undergo substitution with retention of the configuration.

The sulfide activation by electrophilic halogenation can also be achieved by using other Hal⁺ sources. Iodine and *N*-bromosuccinimide (NBS) were applied in synthesising *N*-cyano sulfimides **31** starting from sulfides and cyanogen amine (Scheme 10).[19] Thus, with a combination of molecular iodine and sodium *tert*-butoxide as base, sulfimides **31** were obtained from *S*-aryl and *S*-benzyl-substituted *S*-methyl sulfides in moderate to high yields (Scheme 10, table entries 1 and 3). Using cyanogen amine with NBS and potassium *tert*-butoxide for the imidation led to higher yields of **31**, but the crude product mixture also contained significant amounts of sulfoxide **32** (Scheme 10, table entries 2 and 4 as well as below). The imidation of diaryl and dialkyl sulfides could only be achieved with the NBS/*t*-BuOK combination, while almost no reaction occurred with the I_2/*t*-BuONa system.

In a recent industrial study, a combination of 1,3-dibromo-5,5-dimethylhydantoin (as brominating agent), 2,2,2-trifluoroacetamide (as nitrogen source) and sodium hydride (as base) was applied affording the corresponding *N*-trifluoroacetyl sulfimides in yields ranging from 71 to 88%.[20]

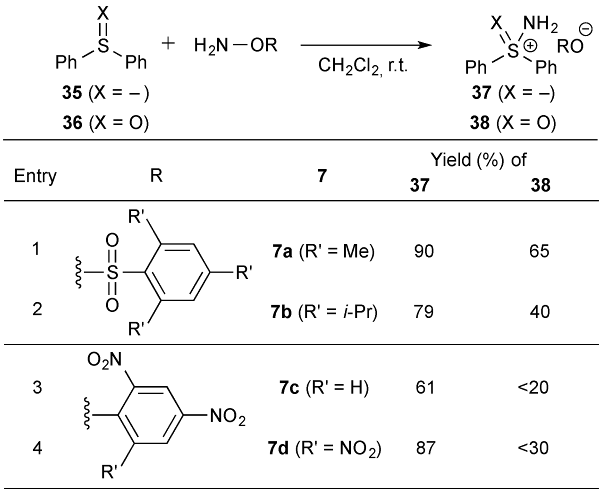
Recently, it has been demonstrated that alkyl amine–Br_2 mixtures allow sulfide imidations providing intermediates that can directly be converted to *N*-alkyl sulfoximines.[21] That is of particular interest for the synthesis of *N*-methylated sulfoximine derivatives.

2.6. Imidations with MSH and related reagents

Sulfur imidations with hydroxylamine-*O*-sulfonic acid (HOSA, **7a**) have been known since the early 1960ies,[22] but only with the introduction of *O*-mesitylensulfonylhydroxylamine (MSH, **7b**),[23] this sulfur imidation strategy became popular. MSH is a powerful aminating reagent able to react with many nucleophiles. In general, an equimolar mixture of sulfides **1** and **7b** in dichloromethane leads to the corresponding crystalline *S*-aminosulfonium salts **33** in moderate to excellent yields (Scheme 11). A subsequent basic workup transforms these salts into sulfimides **34.** The free NH sulfimides **34** can also be obtained by passing an ethanol solution of **33** through a column filled with amberlite (OH^- form) ion-exchange resin.[24] MSH can be applied for imidation of dialkyl, diaryl, alkyl-aryl or cyclic sulfides providing the corresponding sulfonium salts in good to high yields. The stability of the products is highly substrate dependent.[24]

The reactivity of MSH in reactions with diphenylsulfide (**35**) and diphenylsulfoxide (**36**) was compared to those of similar compounds **7** containing a H_2N–OR site (with variations of the OR leaving group). The results showed a slight superiority of MSH over its analogues **7b–c** in the synthesis of sulfiliminium salt **37** (Scheme 12, table entry 1 *vs.* entries 2–4). When sulfoximinium salts **38** were targeted, however, MSH was the only reagent that provided the products in good yields (Scheme 12, table entry 1 *vs.* entries 2–4).[25]

Interestingly, the reaction of enantiopure sulfoxides with MSH yields the corresponding enantiopure sulfoximines with retention of the configuration at the sulfur stereogenic centre.[26]



Entry	R	7	Yield (%) of 37	Yield (%) of 38
1		**7a** (R' = Me)	90	65
2		**7b** (R' = *i*-Pr)	79	40
3		**7c** (R' = H)	61	<20
4		**7d** (R' = NO_2)	87	<30

Scheme 12 Comparative study of sulfur imidations with MSH and its analogues.

When working with MSH, strict safety rules have to be followed as the reagent is thermally unstable and explosive. It should be stored below 0 °C and/or in dichloromethane solution. Safety concerns have also led to a major alternation of the original MSH synthesis resulting in an industry-devised protocol being applicable on a kg scale.[27]

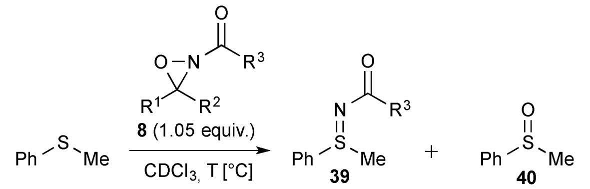
The *N*-methyl version of MSH (Me-MSH) has recently been used for the direct synthesis of *N*-methyl sulfoximines *via* the corresponding *N*-methyl sulfilimides.[28] Starting from an optically active sulfoxide, the imidation with Me-MSH was demonstrated to be stereospecific.

3. Heterocyclic nitrene sources

A poorly investigated approach for the imidation of sulfur derivatives is the use of nitrogen-containing heterocycles such as oxaziridines **8** and 1,4,2-dioxazol-5-ones **9**, as precursors for electrophilic imidating agents. Under specific reaction conditions those heterocycles degrade easily generating highly reactive neutral nitrene intermediates by releasing inert by-products.

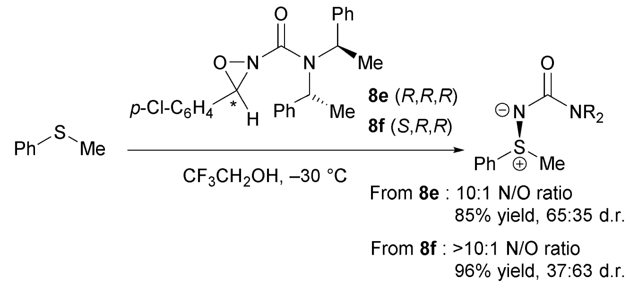
3.1. Imidation with oxaziridines

An oxaziridine **8** is a three-membered heterocycle containing a carbon, a nitrogen, and an oxygen atom. By varying the carbon and nitrogen substituents (R^1 to R^3) the heterocycle can be tuned becoming more reactive for sulfide imidation (Scheme 13). In the same manner, the imidation/oxidation selectivity can be influenced essentially avoiding the undesired oxygen transfer that results in sulfoxide formation. First attempts to obtain sulfimides **39** showed a higher selectivity with oxazirine **8a** (Scheme 13, table entry 1) compared to its analogues **8b–d**, which led mainly to sulfoxides **40** (Scheme 13, table entries 3, 4 and 6). Moreover, by decreasing the reaction temperature to −40 °C the selectivity increased up to >98% in favour of **39** (entry 2). A rather moderate substrate scope of this reaction with aryl-, benzyl-, and alkyl substituted sulfides gave the corresponding sulfimides in yields ranging from 49% to 95%.[29] Interestingly, replacement of $CDCl_3$ by trifluoroethanol at −40 °C significantly enhanced the N/O transfer selectivity up to 91 : 9 in favour of **39** for the oxaziridine **8c–d** (Scheme 13, table entries 5, 7 *vs.* 4, 6).



Entry	8	R^1	R^2	R^3	Solvent	T [°C]	**39:40 ratio**
1	**8a**	CO_2Et	CO_2Et	*t*-Bu	$CDCl_3$	19	90:10
2	**8a**	CO_2Et	CO_2Et	*t*-Bu	$CDCl_3$	–40	>98:2
3	**8b**	Ph	H	Me	$CDCl_3$	19	34:66
4	**8c**	*p*-CN-C_6H_4	H	*t*-Bu	$CDCl_3$	19	27:73
5	**8c**	*p*-CN-C_6H_4	H	*t*-Bu	CF_3CH_2OH	–40	91:9
6	**8d**	*p*-Cl-C_6H_4	H	NEt_2	$CDCl_3$	19	34:66
7	**8d**	*p*-Cl-C_6H_4	H	NEt_2	CF_3CH_2OH	–40	>91:9

Scheme 13 Imidations of thioanisole with oxaziridines **8**.



Scheme 14 Asymmetric imidations of thioanisole with oxaziridine **8e** and **8f**.

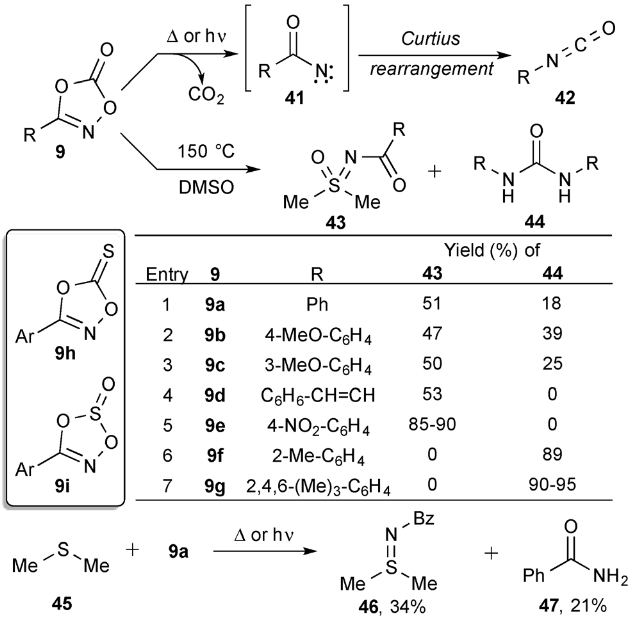
Unfortunately, this substantial selectivity improvement proved difficult to extend to other sulfides and low N/O selectivities (between 1 : 1 to 3 : 1) were obtained. The proposed mechanism implies an attack of the sulfur atom to the ring nitrogen or oxygen atom. In polar solvents the N-selectivity is believed to be enhanced by stabilization of unfavourable charge distributions. However, the significant improvement observed for the reaction in trifluoroethanol suggests that also the acidity of the latter can play a crucial role.

Applying diastereomerically pure chiral oxaziridines **8e** and **8f** led to good N/O transfer selectivities in the imidations of thioanisole (10 : 1 in favour of the nitrogen transfer). However, the diastereomeric ratios were low (*ca.* 2 : 1) (Scheme 14).[30] Noteworthy, the results show that the stereochemical path was predominantly controlled by the absolute configuration of the ring carbon.

3.2. Imidations with 1,4,2-dioxazol-5-ones

3-Substituted-1,4,2-dioxazol-5-ones **9** are five-membered heterocycles known to decarboxylate under thermal or photochemical conditions yielding highly reactive *N*-acyl nitrenes **41** which rearrange quickly to form isocyanates **42** by Curtius rearrangement (Scheme 15, top). When this reaction was performed in DMSO, the corresponding sulfoximines **43** were obtained in rather moderate yields along with symmetric ureas (Scheme 15, middle).[31] In this process, the R substituent of **9** played a crucial role (Scheme 15, table). While the selectivity in favour of **43** was generally moderate with yields ranging from 47% to 53% with heterocycles **9a–d**, the *p*-nitrophenyl derivative **9e** showed an optimal selectivity leading to sulfoximine **43e** in up to 90% yield. *ortho* substituents as in **9f** and **9g** (Scheme 15, table entries 6 and 7) had a detrimental effect leading exclusively to ureas **44f** and **44g** in high yields.

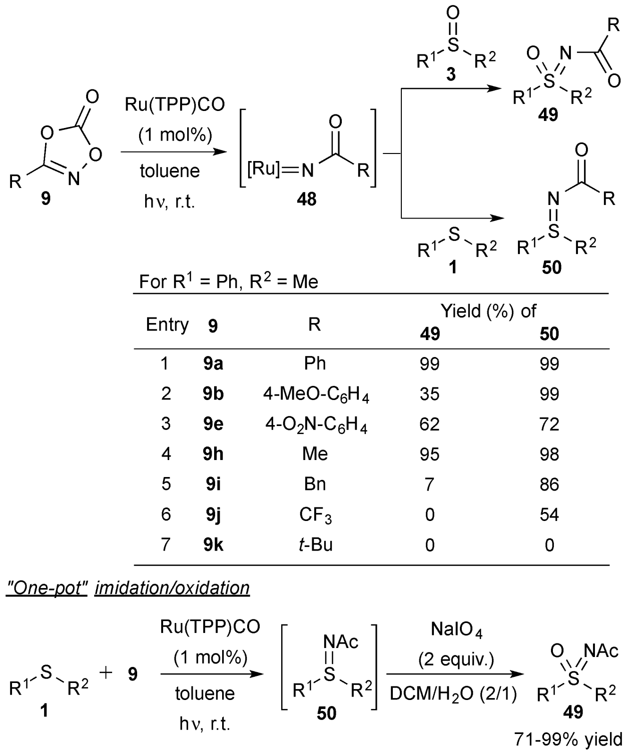
Surprisingly, the reaction of **9a** with sulfides under photochemical or thermal conditions was much more difficult. Among the sulfides tested, only dimethylsulfide **45** reacted with **9a** affording the corresponding sulfimide **46** in 34% yield along with benzamide **47** (Scheme 15, bottom). In the other cases, **47** was the only product. Varying the heterocycle and applying the C═S analogue of **9**, 1,4,2-dioxazol-5-thione **9h**, led to similar results as with **9**, albeit in lower yields (31–83%). The application of S═O analogue **9i** afforded urea **44** as the main product.



Entry	9	R	Yield (%) of 43	Yield (%) of 44
1	**9a**	Ph	51	18
2	**9b**	4-MeO-C_6H_4	47	39
3	**9c**	3-MeO-C_6H_4	50	25
4	**9d**	C_6H_6-CH=CH	53	0
5	**9e**	4-NO_2-C_6H_4	85-90	0
6	**9f**	2-Me-C_6H_4	0	89
7	**9g**	2,4,6-$(Me)_3$-C_6H_4	0	90-95

Scheme 15 Imidations of sulfoxides and sulfides with 1,4,2-dioxazol-5-ones.

Irradiation with visible light in the presence of a catalytic amount of Ru(TPP)CO allows the use of **9** in sulfur imidations under significantly milder reaction conditions (Scheme 16).[32] The proposed mechanism implies a light-induced decarboxylation of **9** and the formation of a rutheno *N*-acyl nitrene intermediate **48**.



For R^1 = Ph, R^2 = Me

Entry	9	R	Yield (%) of 49	Yield (%) of 50
1	**9a**	Ph	99	99
2	**9b**	4-MeO-C_6H_4	35	99
3	**9e**	4-O_2N-C_6H_4	62	72
4	**9h**	Me	95	98
5	**9i**	Bn	7	86
6	**9j**	CF_3	0	54
7	**9k**	*t*-Bu	0	0

Scheme 16 Light-induced ruthenium-catalysed imidations of sulfoxides or sulfides with 1,4,2-dioxazol-5-ones.

The latter species is highly electrophilic and reacts with both sulfoxides **3** and sulfides **1** giving *N*-acyl sulfoximines **49** and *N*-acyl sulfimides **50**, respectively.

Contrary to the thermally mediated sulfur imidation with **9**,[31] the photochemically induced ruthenium-catalysed version shows a preference of sulfide over sulfoxide imidations (Scheme 16, table entries 1–6), which is probably due to the higher nucleophilicity of the former compounds. A wide range of diaryl, dialkyl, aryl-alkyl and aryl-vinyl sulfides proved applicable leading to the corresponding sulfimides in yields ranging from 43% to 99%. The moderate reactivity of sulfoxides **3** in the imidation with **9** was overcome by the development of a one-pot imidation/oxidation sequence starting from sulfides catalysed by the same ruthenium complex (Scheme 16, bottom). In this process, the imidation of **1** gave **50**, which was subsequently treated with an oxidant under phase transfer conditions providing **49** from **50**. In this manner, various sulfides were successfully transformed into sulfoximines in high yields (71–99%).

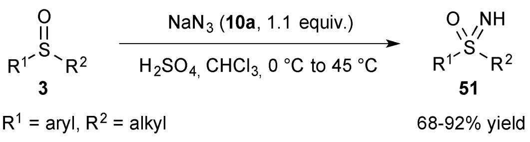
4. Imidations with azides

The main nitrene sources ever used in imidations of sulfides and sulfoxides are azides **10**. They can be applied by treatment of sodium azide with a strong acid, forming *in situ* highly reactive hydrazoic acid, or as organic azide such as TsN_3 or $BocN_3$. Although sulfur imidations with azides are frequently applied, safety issues concerning the toxicity and explosiveness of these reagents have to be taken into account, especially in large-scale reactions. Early reported methods do not require the addition of a catalyst. For achieving enantioselective sulfur imidations the use of a chiral activating agent is essential.

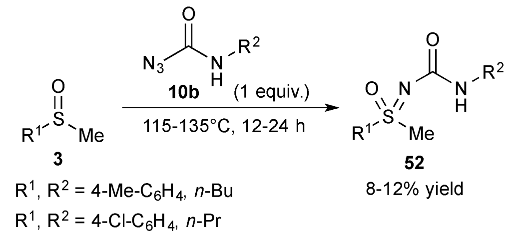
4.1. Metal-free imidations of sulfoxides

The discovery of sulfoximines as a new class of compounds in the early 1950ies is connected to the application of hydrazoic acid for sulfoxide imidation. Thus, methionine sulfoximine, the first example of a sulfoximine ever described, was isolated from freshly milled wheat that had been treated with nitrogen trichloride.[1] Since then, the imidation of sulfoxides with hydrazoic acid has been a frequently applied method for the synthesis of sulfoximines. Practically, sulfoxides **3** are mixed with sodium azide (**10a**) in chloroform in the presence of an excess of sulfuric acid at a temperature of 0 °C to 45 °C, and in most cases the resulting NH sulfoximines **51** are formed in good yields (Scheme 17).

Similarly, carbamoyl azides **10b** were used for transforming sulfoxides **3** into *N*-carbamoylsulfoximines **52** (Scheme 18).[33] However, despite the high reaction temperature and the long



Scheme 17 Sulfoxide imidations with *in situ* generated hydrazoic acid.



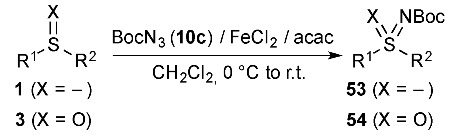
Scheme 18 Sulfoxide imidations with carbamoyl azides.

reaction times, very low yields were obtained showing the limitation of the metal-free sulfoxide imidation with azides.

4.2. Iron-catalysed sulfur imidations with azides

The lower reactivity of *N*-substituted azides in transition metal-free sulfur imidations was overcome by using iron(II) chloride.[34] An excess of sulfoxide and an equimolar amount of the iron salt and *tert*-butyloxycarbonyl azides (**10c**) were applied for obtaining the corresponding sulfoximines **54** in moderate to good yields (Scheme 19, table entry 1). Advantageously, the remaining starting material could be fully recovered after the reaction, which rendered the process more economic. Moreover, the reaction was shown to proceed with retention of the configuration, which is important when optically active products are targeted. Performing the sulfide imidation with **1**/BocN$_3$/FeCl$_2$ in a 1/1/0.5 ratio provided the corresponding *N*-Boc sulfimides **53** in moderate to good yields (Scheme 19, table entry 2). Addition of acetylacetone (acac) allowed to lower the reaction temperature from room temperature to 0 °C and to further decrease the quantity of catalyst to 25 mol% (Scheme 19, table entry 3). Generally, sterically demanding substrates led to lower yields. In terms of the mechanism the involvement of a (nitrene)Fe(IV) complex was suggested, but no experimental evidence was given.

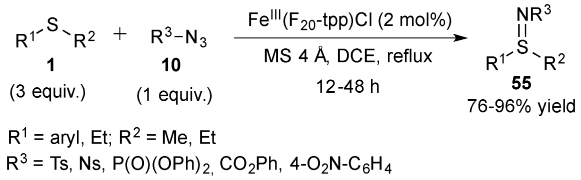
More recently, an interesting alternative was reported using an iron(III) porphyrin complex and *N*-protected azides **10**.[35] The sulfide imidation is catalysed by 2 mol% of [Fe^{III}(F$_{20}$-tpp)Cl] in 1,2-dichloroethane under reflux, leading to the corresponding sulfimides in high yields (Scheme 20).



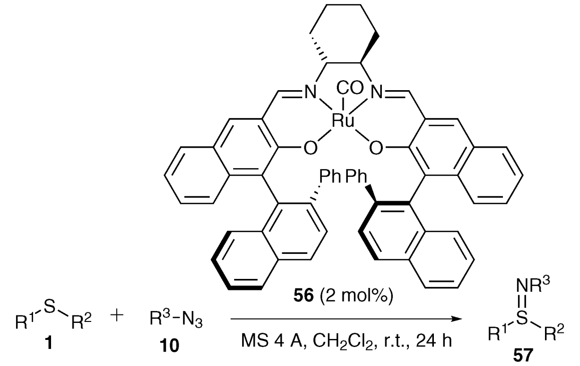
Entry	1[a]	3[a]	10c[a]	FeCl$_2$[a]	acac[a]	Yield (%) of 53	54
1	/	5	1	1	/	/	10-95
2	1	/	1	0.5	/	6-92	/
3	2.5	/	1	0.25	1.3	4-90	/

[a] Number of equivalents

Scheme 19 Iron-assisted sulfur imidations with *N*-Boc azide.



Scheme 20 Fe^{III}-catalysed imidations of sulfides using sulfonyl, phosphoryl, carboxyl and aryl azides.



10d: R^3 = Ts; R^1 = aryl, benzyl; R^2 = Me, Et

10e: R^3 = CO$_2$C(CCl$_3$)(CH$_3$)$_2$;
R$_1$ = aryl; R$_2$ = Me, Et

	Yield (%)	e.e. (%)
10d	36-99	66-99
10e	74-99	92-99

Scheme 21 Ru-catalysed enantioselective sulfide imidations.

4.3. Ru-catalysed enantioselective sulfide imidations with azides

Enantioselective sulfide imidations are of interest, as the resulting products are valuable compounds and intermediates for the synthesis of sulfoximines. A high-yielding enantioselective sulfimidation was developed using a combination of Ru(CO)(salen) **56** as catalyst and azides **10** as nitrene precursors (Scheme 21).[36]

Both sulfonyl and carboxyl azides **10** were investigated in this stereoselective transformation, and it quickly became obvious that a bulky and electron-withdrawing R^3 group was essential to reach high yields and enantioselectivities. Thus, tosyl azide (**10d**) and 2,2,2-trichloro-1,1-dimethylethoxycarbonyl azide (**10e**) proved to be the best reagents, providing the corresponding sulfimides **57** with good to excellent enantioselectivities in moderate to high yields. Practically, the reaction proceeds at room temperature in dichloromethane in the presence of molecular sieves. From spectroscopic studies it was deduced that the imidation involved a ruthenium-salen azide adduct which interacted with the sulfides to yield the corresponding sulfimides.

Enantioselective biocatalytic sulfimidations have recently been reported for the first time.[37] Enzymes of the iron porphyrin-containing cytochrome P450 family were tested in sulfur imidations with substituted azides. Surprisingly, only the use of TsN$_3$ (**10d**) led to satisfactory results. The enzyme screening showed that P411$_{BM3}$-CIS T438S was the most active enzyme with a total turnover number (TTN) up to 300, affording the *N*-Ts sulfimides with an e.r. of 74 : 26. After the introduction of a mutation the resulting enzyme provided the opposite enantiomer of the product. In this series, P411$_{BM3}$-CIS I263A T438S proved best, having a TTN of 320 and leading to a product with an e.r. of 18 : 82. The reaction proceeded with 0.2 mol% of the enzyme in buffered water at room temperature. However, both reactivity and stereoselectivity appeared highly substrate dependent, and a competitive reduction of the azide was observed lowering the overall efficiency of this novel biocatalytic approach.

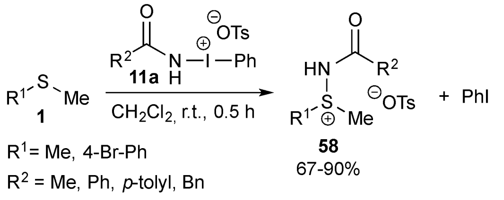
5. Imidations with iminoiodinanes (RN═IR′)

Iminoiodinanes are powerful imidating agents that can be employed under mild reaction conditions with or without metal catalyst. Furthermore, they are very easy and safe to handle. Their field of application is broad since many different reagents varying by the R-group, connected to the nitrogen atom, are applicable in reaction with both sulfides and sulfoxides. If the formation of phenyl iodide as by-product can be tolerated, they are often the reagents of choice. Iminoiodinanes are added as preformed reagents to the reaction mixture, or advantageously, they are generated *in situ* by combining an oxidizing iodine species such as phenyliodine diacetate (PIDA) or iodosobenzene (PhI═O) with an appropriate amine.

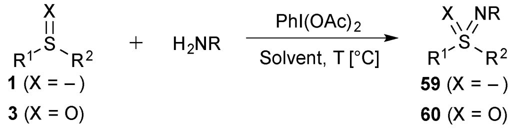
5.1. Non-catalysed imidation of sulfides and sulfoxides

The early discovery of the high potency of iodine(III) species in sulfimidation was made by analogy to sulfoxidation with (hydroxy)iodine(III) compounds. Thus, mixing sulfides with *N*-phenyliodonio carboxamide tosylates **11a** in dichloromethane at room temperature, led quickly to the formation of amidosulfonium tosylates **58**, as sulfimide precursors, in good to high yields (Scheme 22).[38]

More straightforward approaches were then described employing $PhI(OAc)_2$ and amines to generate the corresponding iminoiodinanes **11** *in situ*. This method is a simple one-step procedure, applicable to wide variety of sulfides and sulfoxides (Scheme 23).



Scheme 22 Syntheses of amidosulfonium tosylates using *N*-phenyliodonio tosylates.



Entry	Amine	**1** or **3**	Solvent	T [°C]	Yield (%) of **59**	Yield (%) of **60**
1[a]	$R'SO_2NH_2$	**1**	CH_2Cl_2	r.t.	45-64	/
2	$NsNH_2$	**1, 3**	CH_3CN	82 °C	71-75	79-82
3	$NCNH_2$	**1**	CH_3CN	0 °C	77-98	n.r.

[a] R' = *p*-CH_3-C_6H_4, Ph, *p*-Cl-C_6H_4

Scheme 23 Metal-free imidations of sulfides and sulfoxides.

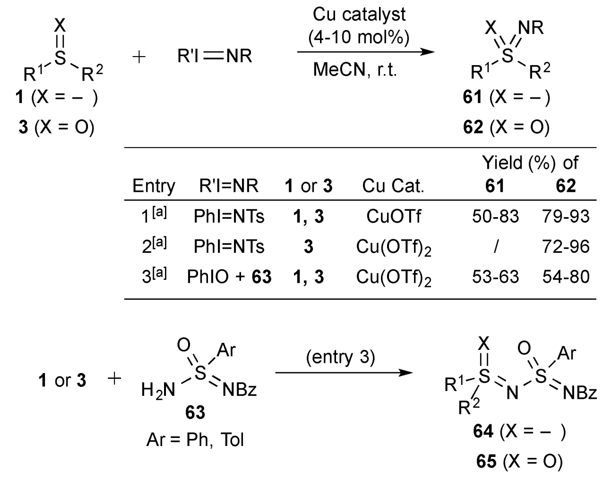
In first attempts, sulfonamides were combined in equimolar ratio with $PhI(OAc)_2$ in the presence of an excess of sulfide (Scheme 23, table entry 1). At room temperature in dichloromethane the corresponding *N*-sulfonyl sulfimides **59** were obtained in moderate to good yields.[39] Subsequent experiments led to process improvements and allowed to apply it to both sulfides **1** and sulfoxides **3**. A slight excess of 4-nitrobenzensulfonamide and $PhI(OAc)_2$ in refluxed acetonitrile proved to be optimal providing both sulfimides and sulfoximines with *N*-nosyl groups in good yields (Scheme 23, table entry 2).[40] One limitation, a partial epimerization (from 83% ee to 43% ee) was observed in the imidation of an enantioenriched sulfoxide, probably due to high reaction temperature for a long period of time (16 h). As an extension, the preparation of *N*-cyano sulfimides and sulfoximines was investigated using a combination of cyanogen amine and $PhI(OAc)_2$. Imidation of sulfides in acetonitrile at 0 °C proceeded well affording the corresponding *N*-cyano sulfimides in high yields, while no reaction occurred with sulfoxides.[41]

As an aside, instead of using an iodine-based oxidant, an electrochemical oxidation can be performed and in this case, *N*-aminophtalimide was reported as nitrene precursor.[42] The corresponding *N*-phtalimido sulfoximines were obtained in yields ranging from 62% to 88%, and the subsequent removal of the *N*-phtalimido group by N–N-cleavage providing NH-sulfoximines was also achieved by electrochemistry.

5.2 Metal-catalysed imidations of sulfides and sulfoxides

The use of a metal catalyst in the imidation with an iodinane offers various synthetic possibilities. In order to choose a suitable metal, several aspects should be considered: which nitrogen-protecting group is relevant? Is a preformed iodinane needed? What are the benefits for using metal catalysis? Below, the examples are classified by the type of the metal catalyst applied in reactions with iodinanes.

5.2.1 Copper-catalysed imidations of sulfides and sulfoxides. The early discovery of metal-catalysed sulfur imidation was made with copper catalysts by analogy with nitrene transfer to alkenes. Both copper(I) and copper(II) proved to be effective in the nitrogen transfer from imidoiodinanes to sulfides and sulfoxides (Scheme 24). Using 5 mol% of CuOTf (Scheme 24, table entry 1), the reaction proceeded smoothly at room temperature affording the corresponding *N*-Ts sulfimides **61** in moderate to good yields.[43] Although long reaction times (26–48 h) were needed, those conditions were also efficient for imidations of sulfoxides providing sulfoximines **62** in good yields (Scheme 24, table entry 1).[44] The switch from Cu(I) to 10 mol% of $Cu(OTf)_2$ (Scheme 24, table entry 2) allowed to shorten the reaction times to few minutes. The imidation was stereospecific occurring with retention of configuration at the stereogenic sulfur of enantiomerically enriched sulfoxide. It tolerated oxygen and water and was also suitable for acetylenic and sterically hindered sulfoxides. Advantageously, the amount of catalyst could be reduced to 3 mol% without a major decrease in yields.[44] The catalytic system worked equally if the nitrene source was generated *in situ* (Scheme 24, table entry 3). For example, using sulfonimidamide **63** and PhI═O provided access



Entry	R'I=NR	1 or 3	Cu Cat.	Yield (%) of 61	Yield (%) of 62
1[a]	PhI=NTs	1, 3	CuOTf	50-83	79-93
2[a]	PhI=NTs	3	$Cu(OTf)_2$	/	72-96
3[a]	PhIO + 63	1, 3	$Cu(OTf)_2$	53-63	54-80

Scheme 24 Copper-catalysed imidations of sulfoxides and sulfides.

to *N*-sulfonimidoyl sulfilimines **64** and sulfoximines **65** in moderate to good yields.[45]

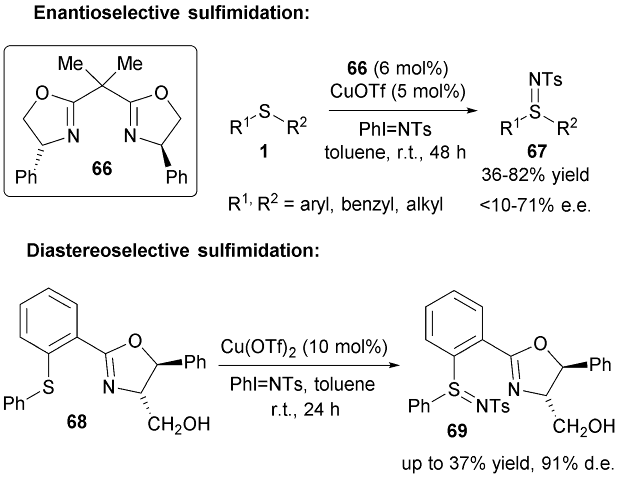
In addition to the good reactivity observed in the copper-catalysed sulfur imidations, an additional advantage of using such metal catalysts was the possibility to perform stereoselective transformations. For example, 4,4′-disubstituted bis(oxazoline) **66** combined with CuOTf gave sulfimides **67** with similar reactivity than without the ligand and with up to 71% ee. The replacement of Cu(I) by Cu(II) led to good yields, but was detrimental for the enantioselectivity (Scheme 25, top).[43]

Using PhI=NTs in a copper-catalysed diastereoselective imidation of sulfide **68** (Scheme 25, bottom) led to **69** with 91% d.e. in moderate yield. Note that compared to the analogous reaction with chloramine-T as imidating agent (Scheme 3),[9] the d.e. obtained here was slightly lower.

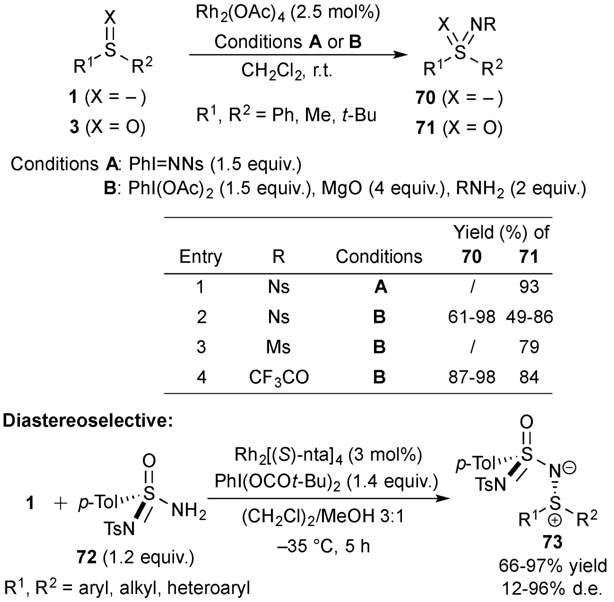
5.2.2 Rhodium-catalysed imidations of sulfides and sulfoxides.

The copper-catalysed imidation opens access to a variety of products, but the scope is limited with regard to the nitrogen substituent. Most common is the *N*-tosyl group, which is difficult to remove in order to prepare the synthetically attractive *N*H-sulfoximines. This problem can be overcome by an imidation with $Rh_2(OAc)_4$ as catalyst. It proceeds under mild and safe reaction conditions at room temperature, using either preformed PhI=NR **11** or the corresponding reagent generated *in situ* by reaction of $PhI(OAc)_2$ and an amine in the presence of MgO (Scheme 26, top).[46] Following this route, imidations leading to products with easy-to-cleave R-groups such as nosyl and $COCF_3$ have been performed, giving the corresponding sulfimides **70** and sulfoximines **71** in good to high yields. The imidation of enantioenriched sulfoxides proceeded stereospecifically with retention of the configuration.

Enantioselective sulfimidation:



Scheme 25 Enantioselective and diastereoselective imidations of sulfides.



Conditions **A**: PhI=NNs (1.5 equiv.)
B: $PhI(OAc)_2$ (1.5 equiv.), MgO (4 equiv.), RNH_2 (2 equiv.)

Entry	R	Conditions	Yield (%) of 70	Yield (%) of 71
1	Ns	A	/	93
2	Ns	B	61-98	49-86
3	Ms	B	/	79
4	CF_3CO	B	87-98	84

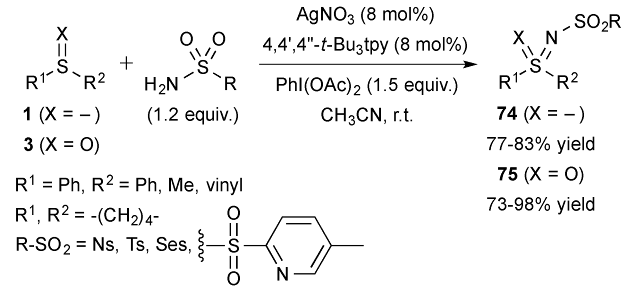
Scheme 26 Rhodium-catalysed imidations of sulfides and sulfoxides.

An extension of this chemistry now allows the direct preparation of *N*-unprotected sulfoximines.[47]

With 3 mol% of $Rh_2[(S)\text{-nta}]_4$ as catalyst in combination with (*S*)-*N*-(*p*-toluenesulfonyl)-*p*-toluene sulfonimidamide (**72**) as chiral nitrene source and $PhI(OCOt\text{-}Bu)_2$ as oxidant diastereoselective sulfide imidations have recently been achieved (Scheme 26, bottom).[48] The reaction was carried out in a dichloroethane/methanol 3 : 1 mixture at −35 °C affording sulfimides **73** in high yields with moderate to high diastereoselectivities. Subsequent stereospecific oxidation of **73** followed by deprotection through S–N-bond cleavage gave the corresponding optically active *N*H-sulfoximines.

5.2.3 Silver-catalysed imidations of sulfides and sulfoxides.

Efforts to replace the highly expensive rhodium catalysts were successfully achieved by introducing a silver(I) catalyst (Scheme 27).[49] The procedure utilises 8 mol% of $AgNO_3$ and 4,4′,4″-tri-*tert*-butyl-2,2′:6′,2″-terpyridine as ligand and is applicable to various sulfonylamides such as nosyl-, tosyl-, 2-trimethylsilylethyl-sulfonylamide ($SesNH_2$) and 5-methylpyridine-2-sulfonamide. Using this system at room temperature in acetonitrile, the corresponding sulfimides **74** and sulfoximines **75** were obtained in good yields. In some cases, long reaction times (between 16 h and 7 d) were required to reach satisfactory yields. The imidation

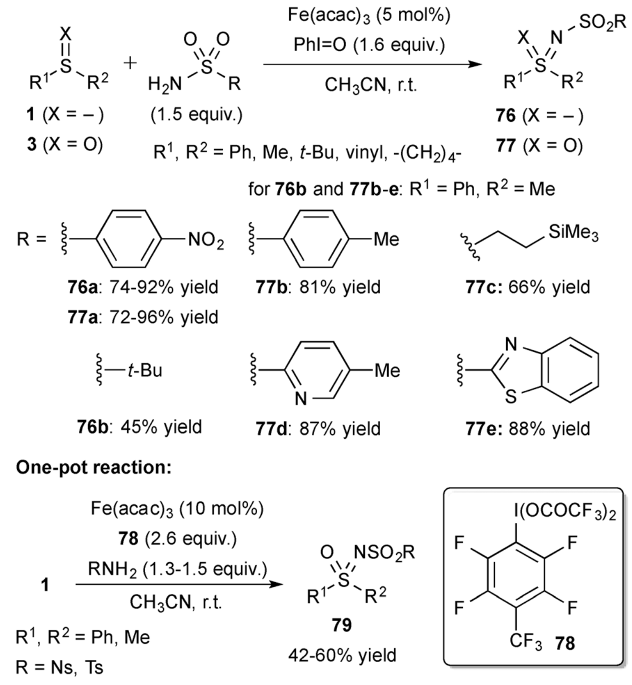


Scheme 27 Silver-catalysed imidations of sulfoxides and sulfides.

was stereospecific providing enantiomerically sulfoximines from the corresponding sulfoxides.

5.2.4 Iron-catalysed imidations of sulfides and sulfoxides. As described earlier in this review (chapter 3.2), iron salts can be applied as activators in sulfur imidations with azides. However, safety concerns related to azides requested exploring alternative nitrene sources such as iminoiodinanes (Scheme 28, top). A first protocol involved 5 mol% of Fe(acac)$_3$ and a variety of *in situ* generated sulfonimidoiodinanes. The imidation proceeded smoothly with sulfoxides at room temperature, giving the corresponding sulfoximines **77** in high yields.[50] Moreover, the reaction worked stereospecifically with retention of the configuration. Competition experiments using a 1 : 1 mixture of sulfide **1** and sulfoxide **3** showed that **1** was much more reactive than **3**. This notion was further supported by the substrate scope, where imidations of sulfoxides with bulky substituents (such as 2,4,6-trimethylphenyl) failed to react, whereas the analogous reaction with the corresponding sulfide proceeded well (yielding 74% of the product). Similarly, the sterically demanding *tert*-butylsulfonamide was only reactive as imidating agent in the sulfimidation (45% yield). Attempts to apply it on sulfoxides failed.

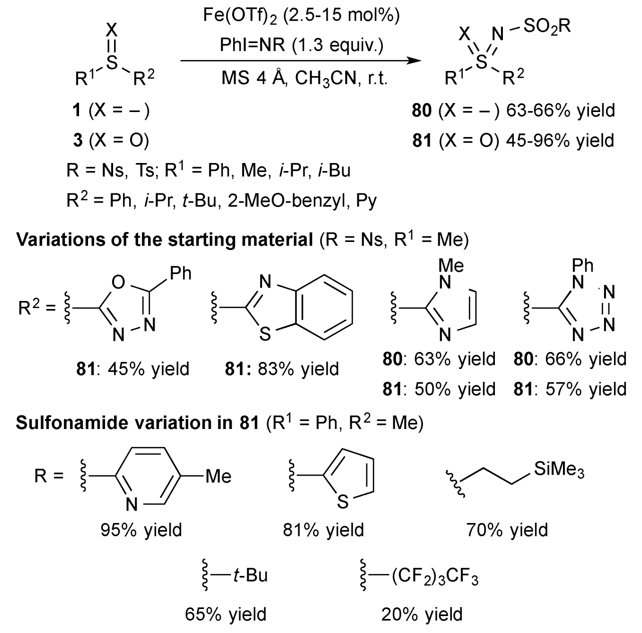
In a worry of step economy, a one-pot synthesis of sulfoximines **79** from the corresponding sulfides **1** catalysed by Fe(acac)$_3$ was reported making use of polyfluorinated hypervalent iodine(III) reagent **78** as oxidant (Scheme 28, bottom).[51] Interestingly, **78** showed a higher oxidative power than its C_6F_5- or C_6H_5-analogues allowing first to oxidise sulfonamides *in situ* to form the corresponding sulfonimidoiodinane as active species for the sulfimidation. Then, second, another equivalent of **78** oxidised the resulting sulfimides, leading to corresponding sulfoximines **79** in moderate yields.



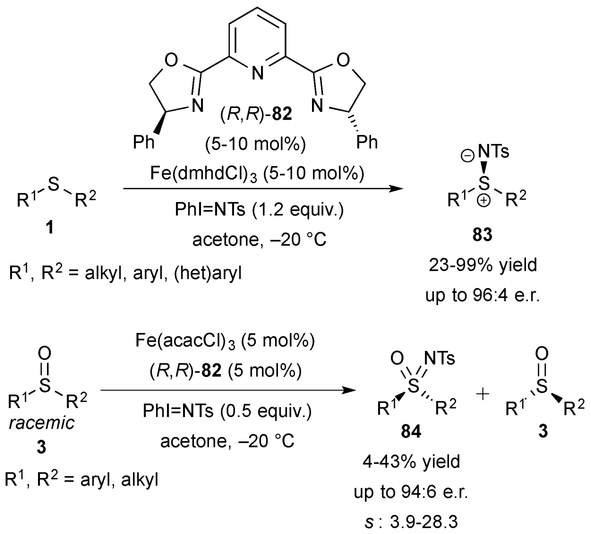
Scheme 28 Fe(acac)$_3$ catalysed imidations of sulfoxides and sulfides.

The limitations observed with Fe(acac)$_3$ (acac = acetylacetonate) in sulfur imidations have been addressed by switching the catalyst for Fe(OTf)$_2$.[52] The catalyst loading could be decreased down to 2.5 mol%, and the reaction was efficient either with pre-formed or *in situ* generated sulfinimidoiodinane (Scheme 29). The substrate scope was broadened and even sulfoxides with sterically demanding substituents, such as *tert*-butyl, and highly valuable heterocyclic substrates, such as oxadiazole, benzothiazole, imidazole or tetrazole gave the corresponding sulfoximines **81** in yields ranging from 45% to 96%. Interestingly, variations of the sulfonamide component were also allowed, and compounds with pyridinyl, thiophenyl, silylethyl, *tert*-butyl or perfluorobutyl substituents worked well. Noteworthy, this catalytic system could also be applied in sulfimidations providing **80** in good yields.

Recently, a considerable improvement in the enantioselective synthesis of sulfimides and sulfoximines has been achieved by using a catalyst consisting of an iron(III) salt combined with a PyBOX ligand.[53,54] The investigation of enantioselective sulfimidations showed that 5–10 mol% of Fe(dmhdCl)$_3$ (dmhd = 4-chloro-2,6-dimethyl-3,5-heptanedionate) along with 5–10 mol% of (*R*,*R*)-Ph-PyBOX **82** and PhI=NTs as nitrene source was the



Scheme 29 Fe(OTf)$_2$-catalysed imidations of sulfoxides and sulfides.



Scheme 30 Iron(III)-catalysed enantioselective sulfur imidation.

best combination providing sulfimides **83** in high yields and enantiomeric ratios of up to 96 : 4 for a broad substrate scope (Scheme 30, top).

Noteworthy, the reactions proceeded smoothly in acetone (cheap, low toxicity) at low temperature, without exclusion of air and moisture. Both enantiomers of the product were accessible by choosing the adequate chiral ligand. Subsequent stereospecific oxidations of the initial products allowed preparing optically active sulfoximines with retention of configuration.[53] Furthermore, chiral sulfoxides **3** reacted stereoselectively allowing an efficient kinetic resolution.[54] Thus, with 5 mol% of Fe(acacCl)$_3$, 5 mol% of (*R*,*R*)-**82**, and 0.5 equiv. of PhI=NTs as nitrene source racemic sulfoxides **3** were converted into the corresponding optically active sulfoximines **84** in yields up to 43%, with enantiomeric ratios up to 94 : 6, and selectivity factors *s* up to 28.3 (Scheme 30, bottom).[54]

6. Conclusion and perspectives

Sulfur imidations can be addressed by several synthetic approaches, depending on the nature of the starting sulfide or sulfoxide. A wide range of imidating agents has been developed including *N*-haloamides and related reagents, azides, heterocyclic nitrene precursors, and iodinanes.[55] All are characterised by their specific properties and reactivities. Most of the imidation procedures have been developed for sulfide imidation, while only a few are efficient for sulfoxide conversions. This is particularly true for metal-free variants of imidation reactions. Importantly, the nature of the nitrogen-protecting group has to be considered early for following deprotection or functionalization. In this context, the development of a late-stage imidation leading to *N*H- or specifically *N*-functionalised products would be desirable. From a stereochemistry point of view, several methods are available for the direct synthesis of optically active sulfimides, which can then be oxidised stereospecifically providing the corresponding enantiomerically enriched sulfoximines. In contrast, stereoselective imidations of sulfoxides are rare. Finding an asymmetric imidation of racemic sulfoxides with concomitant *in situ* racemisation of the remaining sulfoxide enantiomer is a valuable target in this context. Despite all of the synthetic advances highlighted in this tutorial review, many improvements are still possible. Challenges to address relate to specific substitution pattern of the starting materials and products, the reaction conditions, which often are inapplicable for large-scale syntheses, and safety concerns, in particular, with respect to the imidating agents.

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