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# Design and Use of Electrophilic Thiocyanating and Selenocyanating Reagents: a New Trend for the Construction of SCN- and SeCN-containing Compounds

Mélissa Gao,<sup>[a]</sup> Martin Vuagnat,<sup>[a]</sup> Mu-Yi Chen,<sup>[a]</sup> Xavier Pannecoucke,<sup>[a]</sup> Philippe Jubault,<sup>[a]</sup> and Tatiana Besset\*<sup>[a]</sup>

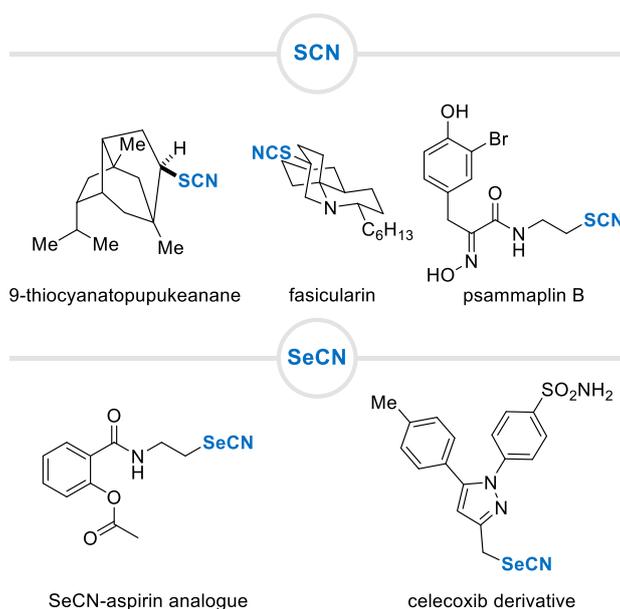
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**Abstract:** Organothiocyanate and organoselenocyanate compounds are of paramount importance in organic chemistry as they are key intermediates to access sulfur- and selenium-containing compounds. Therefore, among the different synthetic pathways to get SCN- and SeCN-containing molecules, original methodologies using electrophilic reagents has recently been explored. This Minireview will showcase the recent advances, which have been made. In particular, the design of several electrophilic sources and their applications for the thiocyanation and the selenocyanation of various classes of compounds will be highlighted and discussed.

## 1. Introduction

Organothiocyanate compounds and their selenated analogs are of high importance in organic chemistry and are found in agrochemicals, pharmaceuticals and materials.<sup>[1],[2]</sup> These key molecules are a linchpin in organic synthesis to access a large variety of molecules of interest (Figure 1).<sup>[1a],[1c],[2c],[3]</sup> Traditionally, they were synthesized by cyanation of sulfur- and selenium-containing molecules.<sup>[3],[4]</sup> A complementary and widespread approach relied on the direct introduction of the SCN<sup>[5]</sup> or the SeCN<sup>[6]</sup> moiety with a nucleophilic or a radical reagent.<sup>[3]</sup> In addition, the *in situ* generation<sup>[3h],[7]</sup> of an electrophilic reagent from a nucleophilic one was widely used. In sharp contrast, only a handful of electrophilic reagents was available until recently.



**Figure 1.** Selected examples of thiocyanated and selenocyanated compounds of interest.

Indeed, from the pioneer works, a regain of interest was showed to imagine and synthesize several original electrophilic SCN and SeCN sources as highlighted by the original reagents, which were successfully synthesized and applied in various transformations over the last years (Figure 2).

In this review, we intend to discuss and showcase the recent advances made for the direct introduction of a thiocyanate or a selenocyanate moiety using electrophilic sources. Note that the *in situ* generation of electrophilic sources will be out of the scope of the Minireview.<sup>[3h]</sup>

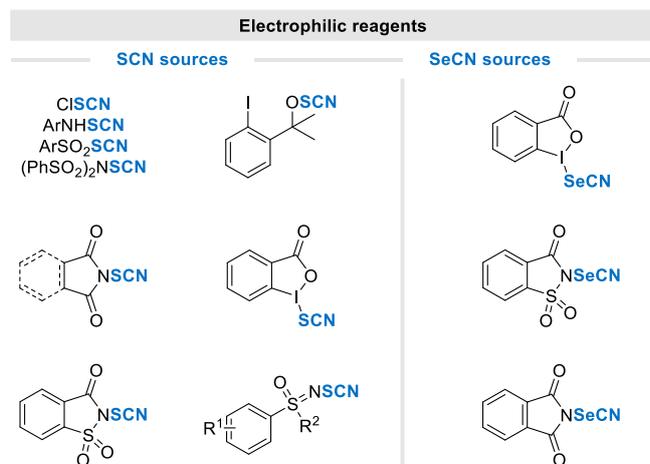
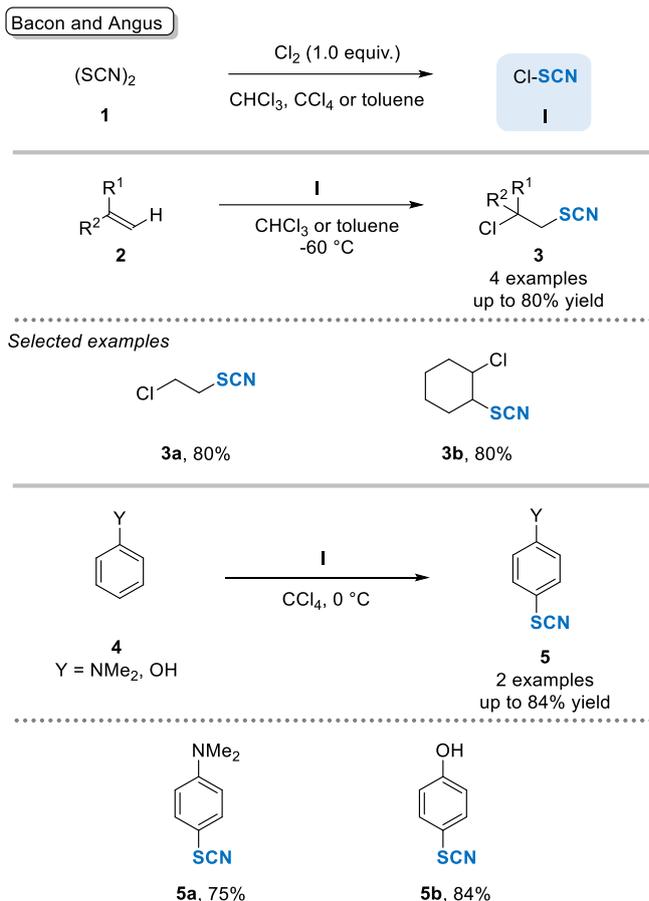


Figure 2. Electrophilic SCN and SeCN reagents.

## 2. Historical Context

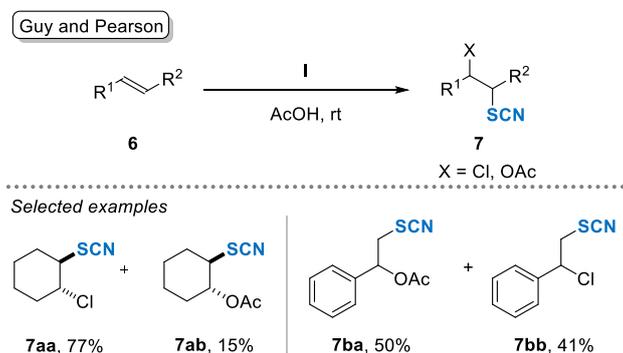
Since the emergence of the thiocyanogen chloride as an electrophilic thiocyanating reagent in 1958, several major contributions were reported in the last half of the century. In this section, the synthesis of this SCN source and a selection of its applications will be described.<sup>[8]</sup>

In 1958, Bacon and Angus reported the use of the thiocyanogen chloride **1** as an electrophilic thiocyanogen reagent (Scheme 1).<sup>[9]</sup> It was prepared from thiocyanogen **1** and gaseous chlorine and kept in solution as stable in a few solvents such as toluene,  $\text{CHCl}_3$  and  $\text{CCl}_4$ . Note that since it decomposed rapidly overtime, it was generally used in a short time after being made. When it was reacted on ethylene, the product **3a** resulting from the concomitant formation of a C-Cl and C-SCN bond was obtained in a 80% yield. The reaction was also carried out, at low temperature, on several olefins such as aliphatic ones, styrene and cyclohexene and in the last case, the compound **3b** was obtained in a high yield. The thiocyanation of *N,N*-dimethylaniline **4a** and phenol **4b** gave the thiocyanated products **5a** and **5b** in 75% and 84% yields, respectively.



**Scheme 1.** Synthesis of thiocyanogen chloride **I** and its application on the functionalization of alkene derivatives **2** as well as on *N,N*-dimethylaniline **4a** and phenol **4b**.

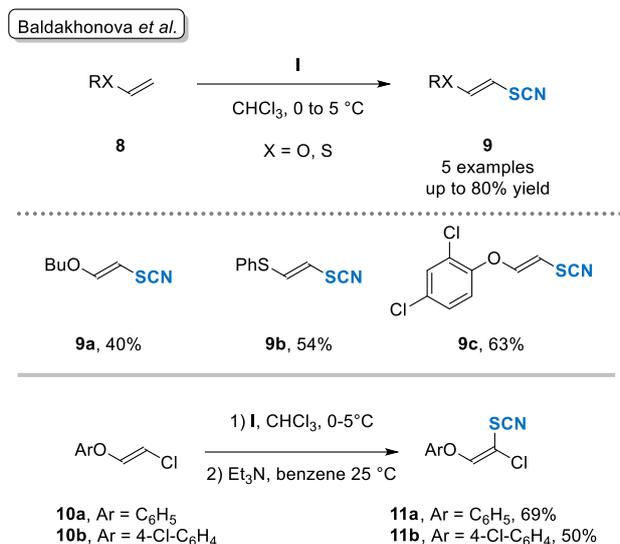
In 1973 and then in 1976, Guy and Pearson reported the thiocyanation of various alkenes **6** using the thiocyanogen chloride **I** in acetic acid (Scheme 2).<sup>[10]</sup> Depending on the alkenes, a mixture of chlorinated and acetoxyated products was obtained in different ratios. For instance, when the cyclohexene was engaged in these reaction conditions, the *trans*-1-chloro-2-thiocyanatocyclohexane was obtained as the major compound (**7aa**) in 77% yield along with the *trans*-1-acetoxy-2-thiocyanatocyclohexane (**7ab**, 15% yield). In case of the styrene, both the acetoxyated and the chlorinated products (**7ba** and **7bb**) were obtained.



**Scheme 2.** Thiocyanation of various alkenes using the thiocyanogen chloride **I** in acetic acid.

In 1991, Baldakhonova and co-workers used the thiocyanogen chloride, *in situ* generated from lead rhodanide and chlorine, for the direct thiocyanation of vinyl (thio)ethers **8**.<sup>[11]</sup> Note that when aryl chlorovinyl ethers (**10a** and **10b**) were engaged, a two-step process was necessary to afford the expected thiocyanated vinyl ethers (**11a** and **11b**) in up to 69%

yield over the two steps (Scheme 3). Note that another application of the thiocyanogen chloride was depicted by the group of Hey-Hawkins for the thiocyanation of a *nido*-dicarbaborate anion (*7,8-nido*-C<sub>2</sub>B<sub>9</sub>H<sub>12</sub><sup>-</sup>).<sup>[12]</sup>



**Scheme 3.** Thiocyanation of vinyl (thio)ethers using the thiocyanogen chloride I.

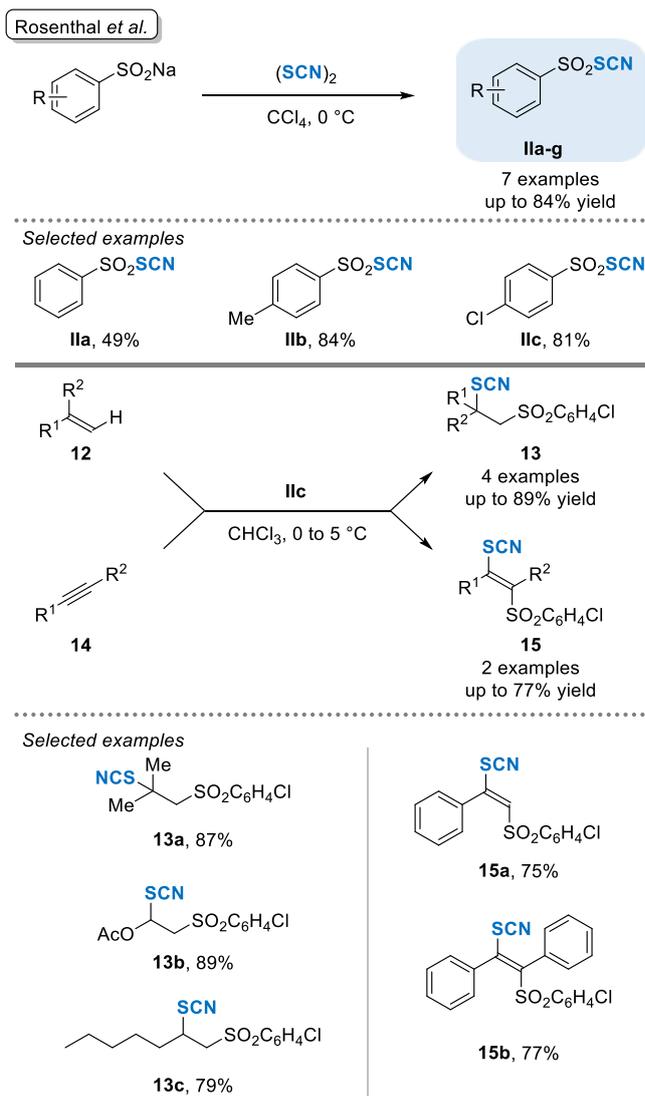
Using the thiocyanogen chloride as the SCN source, chemists developed interesting transformations, although restricted to the functionalization of alkenes, alkynes or few aromatic derivatives. Indeed, the use of the thiocyanogen chloride as a SCN source often required synthetic constraints due to its short-lived stability and the need to freshly prepare it. Therefore, to address these persisting challenges, new tools were needed to push the field further and among them, the design of electrophilic thiocyanation sources emerged as a powerful strategy.

### 3. Design of New Electrophilic Reagents: Synthesis and Applications

Even if this field has remained almost steady for more than 40 years, the design of original electrophilic SCN sources led recently to major milestones in the way to prepare organocyanate compounds. In this section, we will discuss how the chemists have managed to develop new electrophilic thiocyanating reagents and have applied them in various transformations.

#### 3.1 Electrophilic RSO<sub>2</sub>SCN Reagents

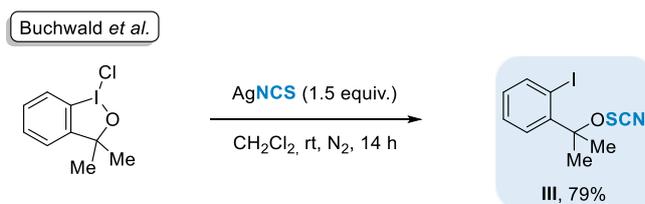
In 1964, Rosenthal and Goerdeler developed the synthesis of several arylsulfonyl thiocyanate reagents **II** starting from the corresponding sodium arylsulfonyl derivatives with thiocyanogen (SCN)<sub>2</sub> (Scheme 4).<sup>[13]</sup> Using the 4-chlorophenylsulfonyl-thiocyanate reagent **IIc**, the difunctionalization of alkenes was possible (4 examples) and the concomitant formation of C-SCN and C-SO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>Cl bonds occurred with a total control of the regioselectivity leading, for instance, to the corresponding thiocyanated alkanes (**13a-13c**) in good yields. This methodology was then applied to the functionalization of alkynes and the expected alkenes **15a** and **15b** were synthesized in 75% and 77% yields, respectively. More recently, another application of these reagents was reported. Indeed, in 2015, Somov and co-workers depicted the electrophilic thiocyanation of the 1-bromotricycloheptane using the methanesulfonyl thiocyanate and the benzenesulfonyl thiocyanate reagent.<sup>[14]</sup>



**Scheme 4.** Synthesis of the arylsulfonyl thiocyanate reagents **II** and the thiocyanation of alkene and alkyne derivatives using the 4-chlorophenylsulfonyl-thiocyanate **IIc**.

### 3.2 Synthesis of an Electrophilic Thioperoxocyanate Reagent

In 2014, the group of Buchwald reported the synthesis of the electrophilic source **III** derived from an hypervalent iodide derivative.<sup>[15]</sup> Indeed, the chlorobenziodoxole was reacted with AgNCS at room temperature offering an efficient access to the electrophilic thiocyanate source **III** as ascertained by X-ray analysis (Scheme 5).



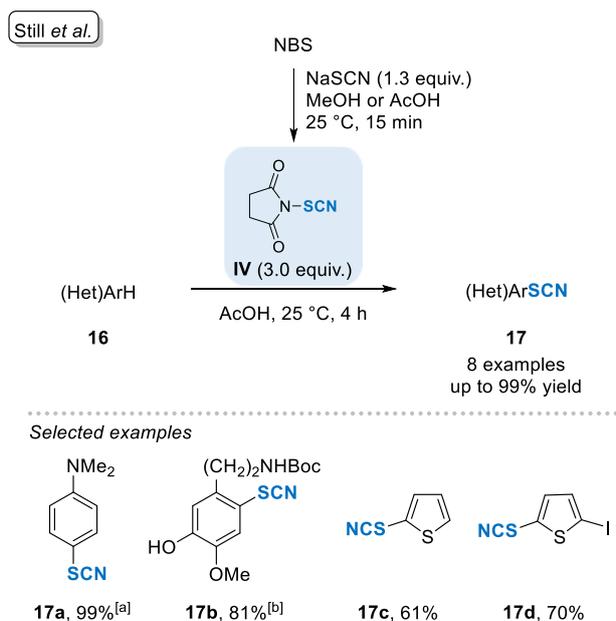
**Scheme 5.** Synthesis of the electrophilic source **III**.

### 3.3 Electrophilic N-Thiocyanating Reagents

Among all the available reagents for the thiocyanation reaction, a lot of efforts was devoted to the synthesis of electrophilic *N*-thiocyanating reagents.

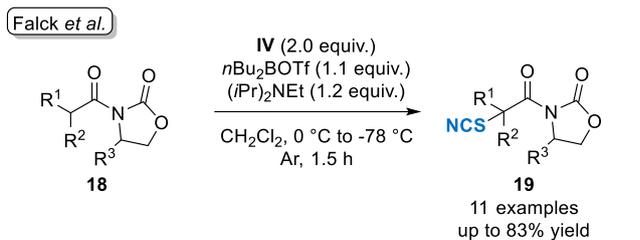
### 3.3.a The *N*-Thiocyanatosuccinimide and *N*-Thiocyanato-phthalimide Reagents

In 1995, the group of Still reported the thiocyanation of (hetero)arenes using the *N*-thiocyanatosuccinimide reagent **IV** from the commercially available NBS and NaSCN (Scheme 6).<sup>[16]</sup> The *N,N*-dimethylaniline was selectively functionalized at the *para* position and the product **17a** was obtained in a 99% yield. In addition, the thiocyanation of the electron-rich arene **16b** along with the thiophene derivatives **16c** and **16d** was also depicted.

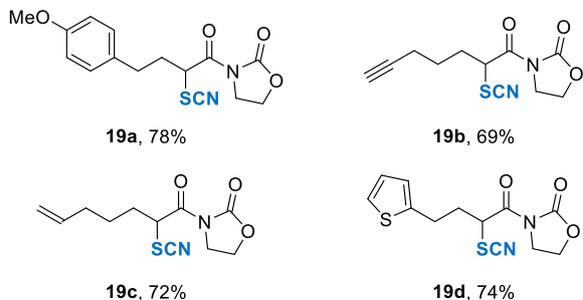


**Scheme 6.** Synthesis of the *N*-thiocyanatosuccinimide reagent **IV** and its applications. [a] MeOH, 0 °C, 2 h. [b] 2 h.

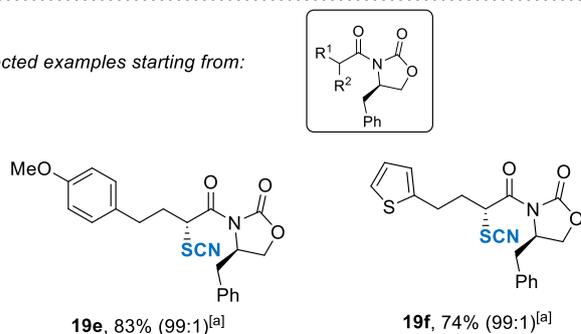
In 2008, the *N*-thiocyanatosuccinimide **IV** was applied for the  $\alpha$ -thiocyanation of (chiral) *N*-acyl imides, which were further used for the synthesis of 5-substituted and 5,5-disubstituted 2,4-thiazolidinediones (Scheme 7).<sup>[17]</sup> Indeed, using *n*Bu<sub>2</sub>BOTf as a Lewis acid and in the presence of the reagent **IV**, the  $\alpha$ -thiocyanation of *N*-acyl carboximides was depicted, leading to the corresponding products **19a-19d**. The reaction was tolerant to various functional groups such as a terminal alkyne (**18b**), an olefin (**18c**) and a heterocycle (**18d**), and the expected products (**19b-19d**) were obtained in good yields. This methodology was extended to the asymmetric  $\alpha$ -thiocyanation of 4-(*R*)-phenylmethyl-2-oxazolidinone derivatives leading to the compounds **19e** and **19f** in good yields and with an excellent diastereoselectivity (up to 99:1 d.r.).



Selected examples with  $R^3 = \text{H}$

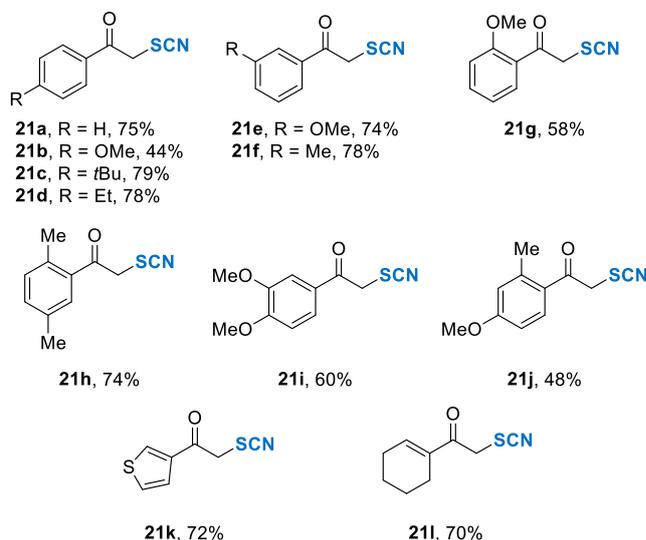
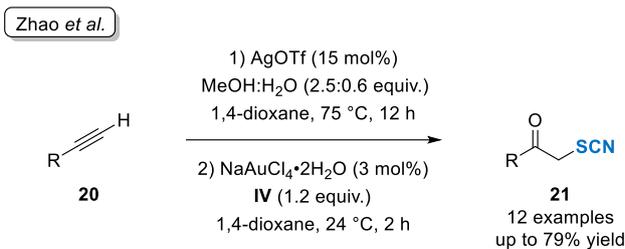


Selected examples starting from:



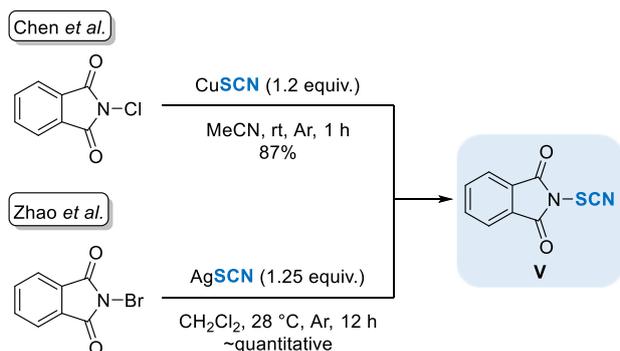
**Scheme 7.**  $\alpha$ -Thiocyanation of *N*-acyl imides with the reagent **IV**. [a] Diastereoisomeric ratios (d.r.) were given in parenthesis.

In 2018, during their study about the synthesis of alkynylthiocyanates, Zhao and co-workers reported the synthesis of  $\alpha$ -thiocyanoketones **21** (Scheme 8).<sup>[18]</sup> Indeed, under silver and gold catalysis, the hydrothiocyanation of terminal alkynes **20** with *N*-thiocyanosuccinimide **IV** was developed in a one pot two steps process (silver-catalyzed hydration of the alkyne followed by the subsequent gold-catalyzed thiocyanation of the resulted ketone derivative). Electron-rich aromatic alkynes were mainly functionalized in this process and substituents at the para, meta and ortho positions were well tolerated (**20b-20g**). Terminal alkynes bearing a disubstituted arene were converted into the  $\alpha$ -thiocyanoketones (**21h-21j**) in moderate to good yields. The transformation was also suitable for heteroaromatic alkyne **20k** and alkenyl-substituted compound **20l** and the expected products (**21k** and **21l**) were obtained in 72% and 70% yields, respectively.



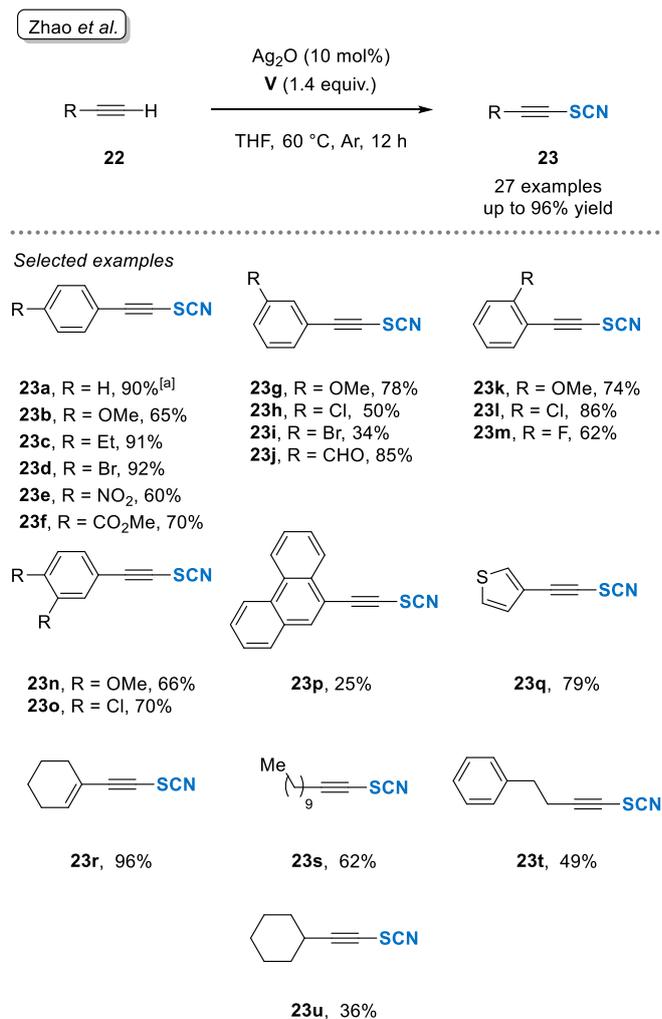
**Scheme 8.** Hydrothiocyanation of terminal alkyne **20** with the reagent **IV** under silver- and gold-catalysis.

In the same vein, the *N*-thiocyanophthalimide **V** was also studied as an electrophilic source of the SCN residue (Scheme 9). Its synthesis was described by Chen and co-workers.<sup>[19]</sup> Starting from the *N*-chlorophthalimide and copper thiocyanate, the expected product was isolated in a 87% yield. Note that the reagent **V** was also prepared using the *N*-bromophthalimide and silver thiocyanate.<sup>[18]</sup>



**Scheme 9.** Synthesis of the *N*-thiocyanophthalimide **V** by means of two synthetic routes.

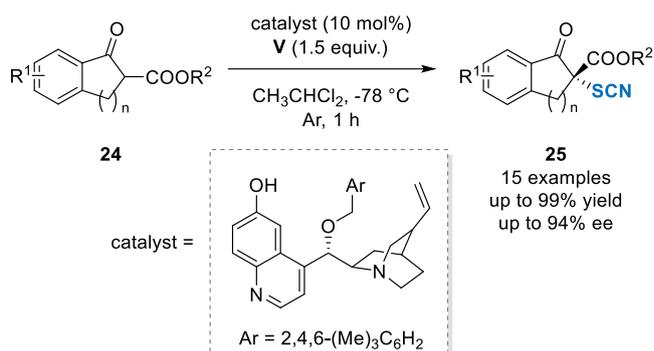
Interested by the functionalization of terminal alkynes with SCN sources, Zhao and co-workers developed a silver-catalyzed thiocyanation of terminal alkynes **22** with the *N*-thiocyanophthalimide **V** to access the corresponding alkynylthiocyanates **23** (Scheme 10).<sup>[18]</sup> This transformation was applied to a wide range of terminal alkynes (27 examples). Aromatic alkynes substituted with electron-donating groups, electron-withdrawing ones and halogens were thiocyanated in moderate to good yields (**23b-23m**). Moreover, the reaction was tolerant to various functional groups such as ester (**22f**) and aldehyde (**22j**). Disubstituted aromatic alkynes (**22n-22o**), 9-ethynylphenanthrene **22p** and a thiophene derivative **22q** were smoothly functionalized. In addition, alkenyl- and alkyl-substituted alkynes (**22r-22u**) were also suitable in this transformation.



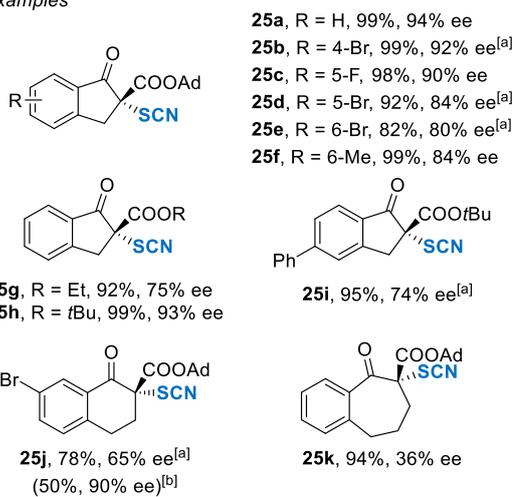
**Scheme 10.** Thiocyanation of terminal alkynes with the reagent **V**. [a] Reaction on 1 mmole scale.

The *N*-thiocyanatophthalimide reagent **V** was further applied in the enantioselective  $\alpha$ -thiocyanation of cyclic  $\beta$ -ketoesters **24** by a bifunctional cinchona alkaloid catalysis (Scheme 11).<sup>[19]</sup> From this approach, a panel of SCN-containing molecules were obtained in good to excellent yields (up to 99%) with high enantioselectivity (up to 94% ee).  $\beta$ -Ketoesters (**24a-i**) derived from indanone with substituents (mainly halogens) at various positions on the aromatic ring were thiocyanated. Other esters were also smoothly functionalized (**24g-i**). When a  $\beta$ -ketoester derived from tetralone or possessing a seven-membered ring was used as a substrate, the expected products (**25j** and **25k**) were obtained in good to excellent yields with 65% and 36% ee, respectively.

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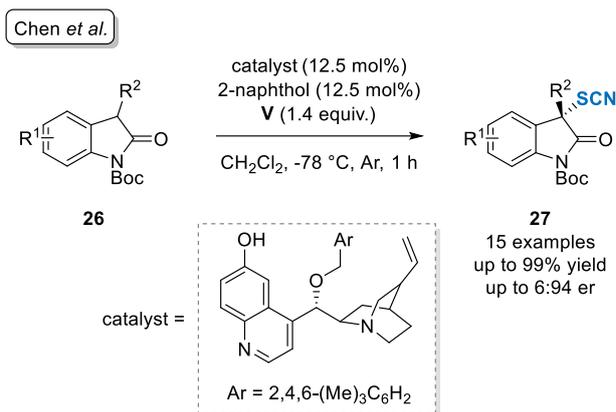


Selected examples

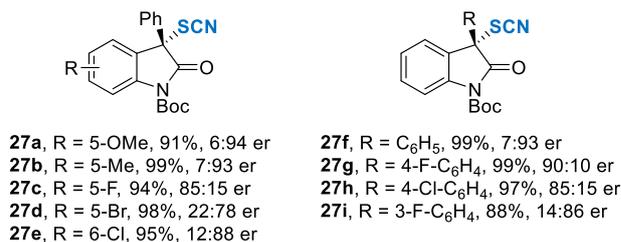


**Scheme 11.** Enantioselective  $\alpha$ -thiocyanation of cyclic  $\beta$ -ketoesters with the reagent **V**; ee values were determined by chiral HPLC analysis. [a]  $\text{CH}_2\text{Cl}_2$  instead of  $\text{CH}_3\text{CHCl}_2$ . [b] After a single recrystallization.

One year later, the same group reported an extension of their methodology to the  $\alpha$ -thiocyanation of 3-substituted oxindoles **26** (Scheme 12).<sup>[20]</sup> Indeed, using a similar catalytic system and the 2-naphthol as a co-catalyst, the expected thiocyanated products **27** were afforded in excellent yields (er up to 94:6). Note that the stereoselectivity outcome of the reaction was substrate-dependent.

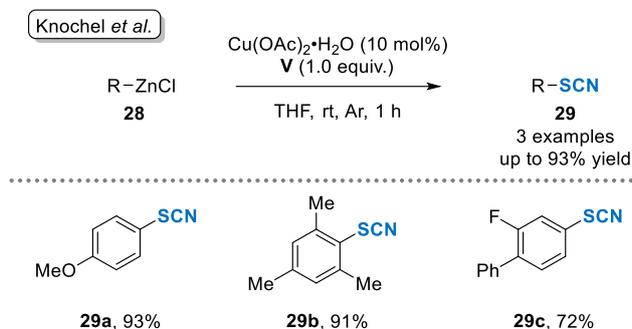


Selected examples



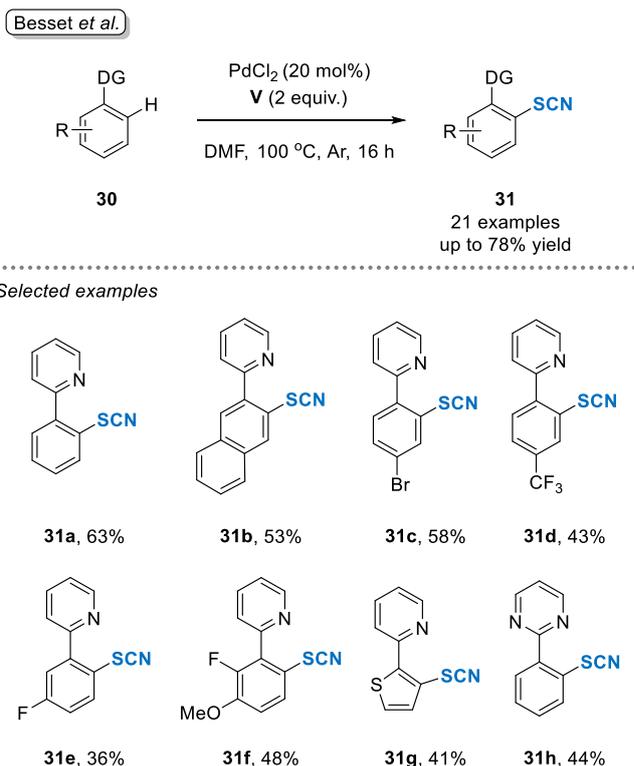
**Scheme 12.** Asymmetric  $\alpha$ -thiocyanation of 3-substituted oxindoles using the *N*-thiocyanophthalimide **V**.

In 2019, the group of Knochel developed a methodology for the electrophilic thiolation of organozinc chlorides by copper-catalysis. During this study, they successfully extended their approach to the thiocyanation of three arylzinc chlorides (**28a-28c**) with the reagent **V**, offering an access to the corresponding products **29a-29c** in high yields (Scheme 13).<sup>[21]</sup>



**Scheme 13.** Copper-catalyzed thiocyanation of arylzinc chlorides with the reagent **V**.

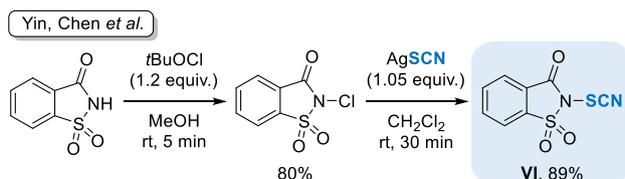
This year, a palladium-catalyzed directed mono-thiocyanation of (hetero)arenes by C-H bond activation was reported by the group of Besset (Scheme 14).<sup>[22]</sup> With this ligand- and additive-free approach, a panel of SCN-containing products was selectively synthesized using the reagent **V** in up to 78% yield. The 2-phenylpyridine **30a** and the naphthalene analogue **30b** were smoothly functionalized. The thiocyanation reaction was suitable with 2-aryl-pyridines with various substituents at the *para* position such as a halogen **30c** or a fluorinated group **30d**, at the *meta* position **30e** and even with the disubstituted derivative **30f**. When the 2-(2-thienyl)pyridine **30g** was reacted under these reaction conditions, the SCN-containing product **31g** was obtained in a 41% yield. Moreover, by changing the nature of the directing group (pyrimidine vs pyridine), the corresponding product **31h** was obtained in a 44% yield.



**Scheme 14.** Palladium-catalyzed *ortho* thiocyanation of (hetero)arenes by C-H bond activation using the reagent **V** as the SCN source.

### 3.3.b The *N*-Thiocyanatosaccharin Source

Recently, a new electrophilic thiocyanating reagent has emerged, namely the *N*-thiocyanatosaccharin **VI**. The first synthesis and application of this original source was reported by Yin, Chen and co-workers in 2018.<sup>[23]</sup> The *N*-thiocyanatosaccharin **VI** was prepared in a 71% yield over two steps: chlorination of the saccharin with *tert*-butyl hypochlorite followed by a treatment with AgSCN. Note that the reagent **VI** is sensitive to light and air and therefore, should be stored at low temperature under an inert atmosphere (Scheme 15).

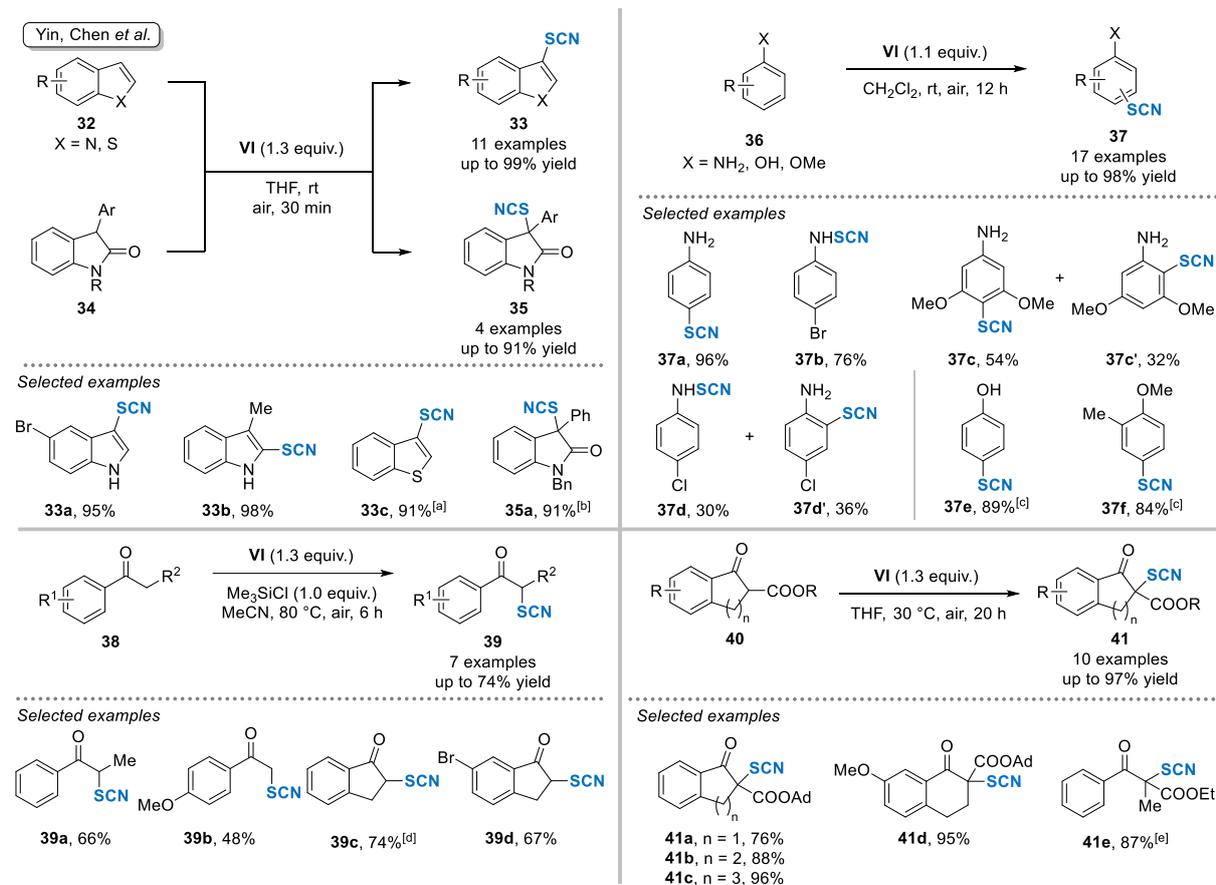


**Scheme 15.** Synthesis of *N*-thiocyanatosaccharin **VI**.

The potential of this reagent as an electrophilic SCN source was investigated with the direct thiocyanation of a panel of nucleophiles (Scheme 16).<sup>[23]</sup> Firstly, on the 5-bromoindole **32a**, the thiocyanation gave selectively the expected 3-thiocyanated product **33a** in a 95% yield. When the 3-methyl indole was used as a substrate, the 2-thiocyanation occurred with a remarkably high yield (**33b**). The transformation was also performed on the benzothiophene **32c** and the oxindole **34a** leading to the corresponding thiocyanated compounds with high yields (**33c** and **35a**, respectively).

Aniline, phenol and anisole derivatives were also investigated. On aniline, the thiocyanated product was obtained with a particularly good yield (**37a**). When the *para* position was functionalized by a bromine atom, only the *N*-functionalization was observed with a good yield (**37b**). In contrast, 3,5-dimethoxyaniline led to a mixture of *para* and *ortho* thiocyanated products (**37c**, **37c'**). A mixture of *N*-functionalization and *ortho*-functionalization was observed with the 4-chloroaniline (**36d**, **36d'**). On phenol and anisole derivatives (**36e** and **36f**), only the *para*-functionalization was observed with high yields (**37e** and **37f**). On acyclic aromatic ketones (**38a** and **38b**), the transformation gave the corresponding thiocyanated products with moderate to good yields (**39a** and **39b**). However, the reaction was more efficient in case of the indanones **38c** and **38d**. Finally, the thiocyanation reaction was also conducted on  $\beta$ -ketoesters derived from indanone and tetralone

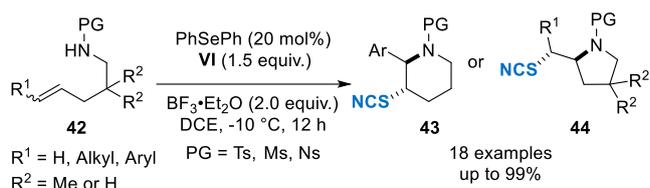
leading to the corresponding products **41a-41d** in good yields. Note that in case of the acyclic  $\beta$ -ketoester **40e**, the reaction was possible under slightly modified reaction conditions.



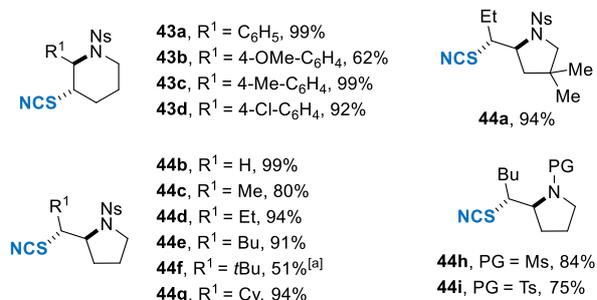
**Scheme 16.** Application of the electrophilic *N*-thiocyanatosaccharin reagent **VI** for the direct thiocyanation of various nucleophiles. [a] TfOH (1.0 equiv.) in MeCN. [b] 12 h. [c] **VI** (1.0 equiv.). [d] Zn(BF<sub>4</sub>)<sub>2</sub>·H<sub>2</sub>O (0.2 equiv.) instead of Me<sub>3</sub>SiCl (1.0 equiv.). [e] DMAP (4.0 equiv.), toluene, 30 °C, 20 h.

One year later, Zhao and co-workers developed a selenide-catalyzed thiocyanaminocyclization of the alkene derivatives **42** using the electrophilic *N*-thiocyanatosaccharin **VI** as the SCN source (Scheme 17).<sup>[24]</sup> In the presence of a catalytic amount of diphenyl selenide and a Lewis acid (BF<sub>3</sub>·Et<sub>2</sub>O), an access to SCN-containing azaheterocycles was achieved with a good regioselectivity and an excellent diastereoselectivity (> 19:1). When the reaction was carried out with alkenes bearing an aromatic moiety as the R<sup>1</sup> substituent (**42a-42d**), the corresponding products selectively resulted from a 6-*endo*-cyclization (**43a-43d**). Otherwise, when the R<sup>1</sup> substituent was a hydrogen or an alkyl group, the olefins underwent a 5-*exo*-cyclization and the transformation led to the final product in good to excellent yields (**44a-44i**). The length of the alkyl chain did not impact the outcome of the reaction (**44b-44e**). However, when an alkene with a bulkier R<sup>1</sup> substituent was used (*tert*-butyl group, **43f**), the yield dropped to 51%. Note that the reaction also worked well with a derivative having a cyclohexyl group (**42g**). Finally, when the protecting group was changed from nosyl to mesyl (**42h**) or tosyl (**42i**), the transformation proceeded smoothly, albeit in slightly lower yields. The authors proposed the following mechanism (Scheme 17): activation of the *N*-thiocyanatosaccharin **VI** with BF<sub>3</sub>·Et<sub>2</sub>O, followed by a reaction with the diphenyl selenide would afford the intermediate **A**. Then, the species **B** would be obtained and after reaction with **42**, would lead to the corresponding iranium ion species **C**. Depending on the nature of the R<sup>1</sup> substituent, the cyclization would then proceed either *via* a 6-*exo*- or a 5-*endo*-cyclization providing hence the expected products **43** or **44** and would regenerate the catalyst.

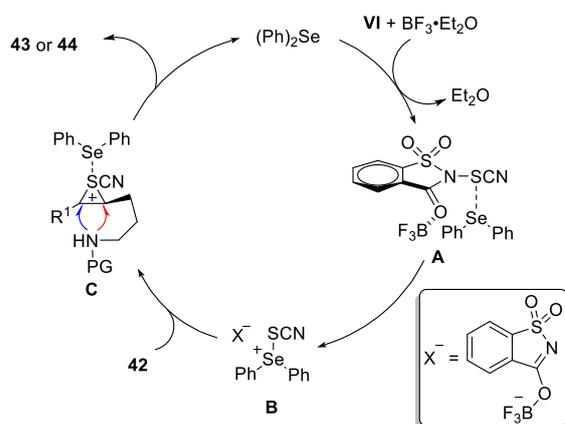
Zhao *et al.*



Selected examples



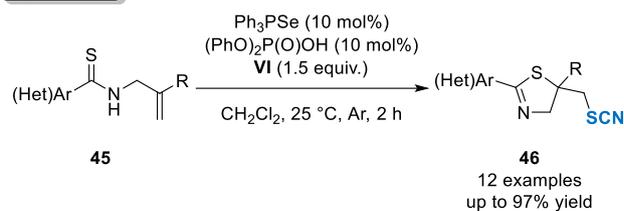
Proposed mechanism



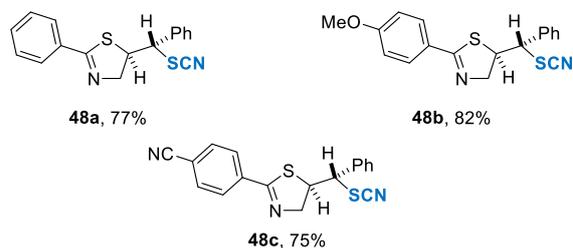
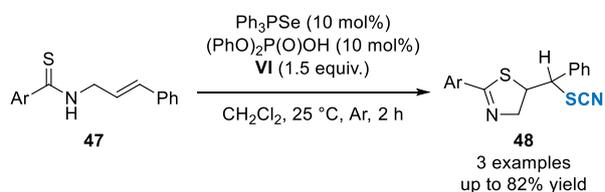
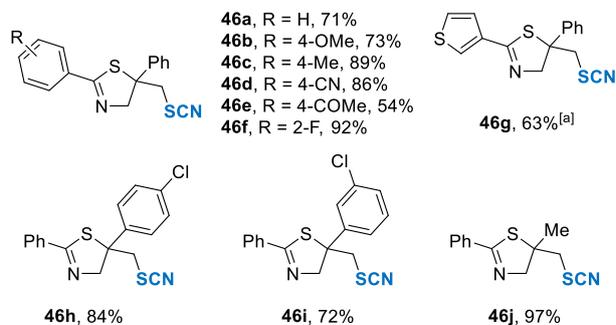
**Scheme 17.** Scope and mechanism of the regio- and diastereoselective thiocyanation of alkenes with the reagent **VI**. [a] Toluene was used as the solvent instead of DCE. All diastereoselectivities are > 19:1. DCE = 1,2-dichloroethane, Ns = Nosyl, Ms = Mesyl, Ts = Tosyl.

In 2020, Tripathi and co-workers reported the thiocyanation of unsaturated thioamides with the *N*-thiocyanatosaccharin **VI** via a Lewis base and a Brønsted acid co-catalyzed reaction (Scheme 18).<sup>[25]</sup> Using triphenylphosphine selenide and diphenyl phosphite as co-catalysts, an efficient access to thiocyanated thiazoline derivatives **46** was developed (up to 97% yield). The thiocyanation of the  $\beta,\gamma$ -unsaturated thioamides **45** was effective with both electron-rich and electron-poor arenes (**46a-46f**). The transformation was also tolerant to cyano (**45d**) and ketone (**45e**) groups along with thiophene (**45g**), albeit in the last two cases the corresponding products were obtained in only 54% yield and 63% yield, respectively. The transformation also proceeded smoothly when the phenyl group on the olefin was replaced by a chlorinated arene (**45h** and **45i**) or a methyl group (**45j**). This methodology was also applied to the functionalization of 1,2-disubstituted olefins **47** providing the expected compounds **48** in good yields regardless of the substituents on the aromatic ring via a 5-*exo-trig* cyclization process. It is worth mentioning that by switching the reagent **VI** to the *N*-thiocyanatophthalimide **V**, the thiocyanation of  $\beta,\gamma$ -unsaturated amides was also efficiently achieved.

Tripathi *et. al.*



Selected examples

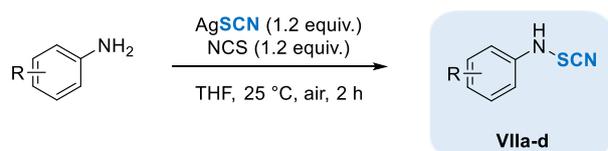


**Scheme 18.** Lewis base/brønsted acid catalyzed thiocyanation of thioamide derivatives with the reagent VI. [a] 4 h of reaction instead of 2 h.

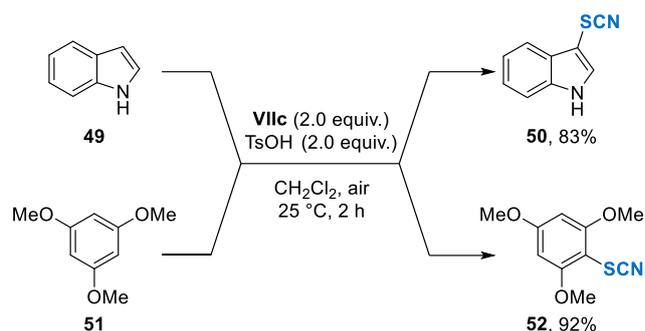
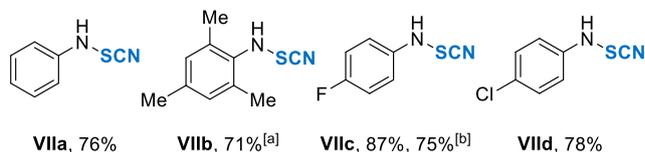
### 3.3.c The *N*-(Cyanosulfonyl)aniline Reagents

In 2016, Besset and co-workers developed the thiocyanation of aniline derivatives with silver thiocyanate. Several functionalized *N*-(cyanosulfonyl)anilines (**VIIa-VIIId**) were prepared in up to 85% yield (Scheme 19).<sup>[26]</sup> Note that when using NaSCN instead of AgSCN, the thiocyanation of the 4-fluoroaniline led to the corresponding thiocyanated aniline **VIIc** in a similar yield.<sup>[26],[27]</sup> The reagent **VIIc** was then used in a Friedel-Crafts type reaction with the indole **49** and the 1,3,5-trimethoxybenzene **51**, leading to the corresponding products **50** and **52**, respectively, in high yields (Scheme 19).

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4 examples  
up to 87% yield

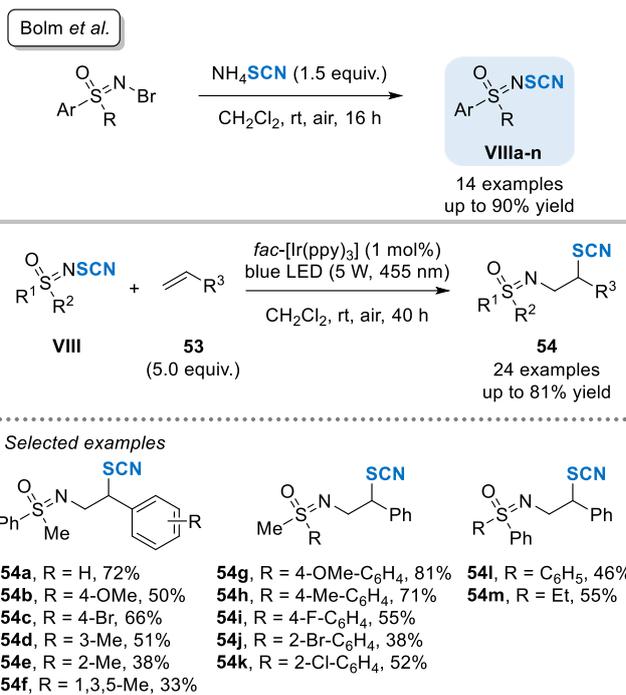


**Scheme 19.** Synthesis of the *N*-(cyanosulfonyl)aniline **VII** derivatives and the electrophilic thiocyanation of the indole **49** and the 1,3,5-trimethoxybenzene **51** using the reagent **VIIc**. [a] 18 h. [b] NaSCN instead of AgSCN.

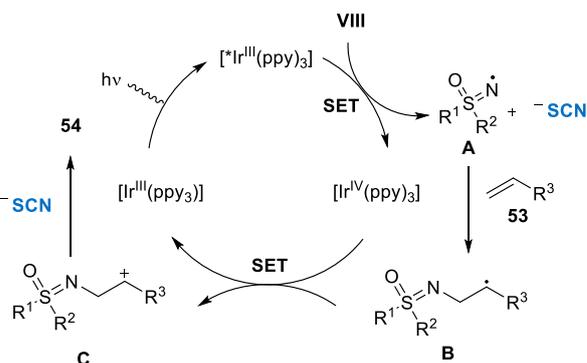
### 3.3.d The *N*-Thiocyanatosulfoximine Source

In 2018, the group of Bolm studied the synthesis of the *N*-thiocyanato sulfoximine derivatives as new electrophilic thiocyanating reagents (Scheme 20).<sup>[28]</sup> Indeed, prepared from *N*-bromo sulfoximines and ammonium thiocyanate, the *N*-thiocyanato sulfoximine derivatives **VIII** were obtained in good to high yields (up to 90% yield). In the presence of these electrophilic reagents and using the *fac*-[Ir(ppy)<sub>3</sub>] complex as a photocatalyst, the concomitant difunctionalization of styrene derivatives was achieved under blue light irradiation. With the *N*-thiocyanato sulfoximine, a panel of styrene derivatives was efficiently functionalized leading to the corresponding *para*- and *meta*-substituted products (**54b-54d**) in good yields, although *ortho*-substituted ones (**54e** and **54f**) were obtained in lower yields. Pleasingly, various *N*-thiocyanato sulfoximine derivatives with different substitution patterns and electronic properties on the aromatic ring were reacted with styrene leading to the corresponding compounds (**54g-54k**). Note that even the *S,S*-diphenyl sulfoximine **54l** and the *S*-ethyl *S*-phenyl sulfoximine **54m** were suitable on this reaction.

The authors suggested the following mechanism to explain the transformation: after excitation of the photocatalyst *fac*-[Ir<sup>III</sup>(ppy)<sub>3</sub>] under fluorescent light irradiation into the complex *fac*-[\*Ir<sup>III</sup>(ppy)<sub>3</sub>], a single electron transfer to the *N*-thiocyanato sulfoximine **VIII** would lead to the generation of a *fac*-[Ir<sup>IV</sup>(ppy)<sub>3</sub>] species along with a SCN<sup>-</sup> anion and a sulfoximidoyl radical **A**. This latter would react with the styrene **53** to afford the intermediate **B**, which would undergo a SET to give the intermediate **C** and after a final reaction with the thiocyanate anion, the desired product **54** would be obtained.



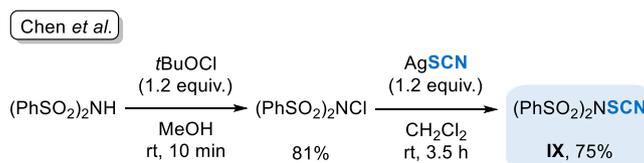
*Proposed mechanism*



**Scheme 20.** Photocatalyzed difunctionalization of styrene derivatives with the *N*-thiocyanato sulfoximine reagents **VIII**.

### 3.3.e The *N*-Thiocyanato-dibzenzenesulfonimide Reagent

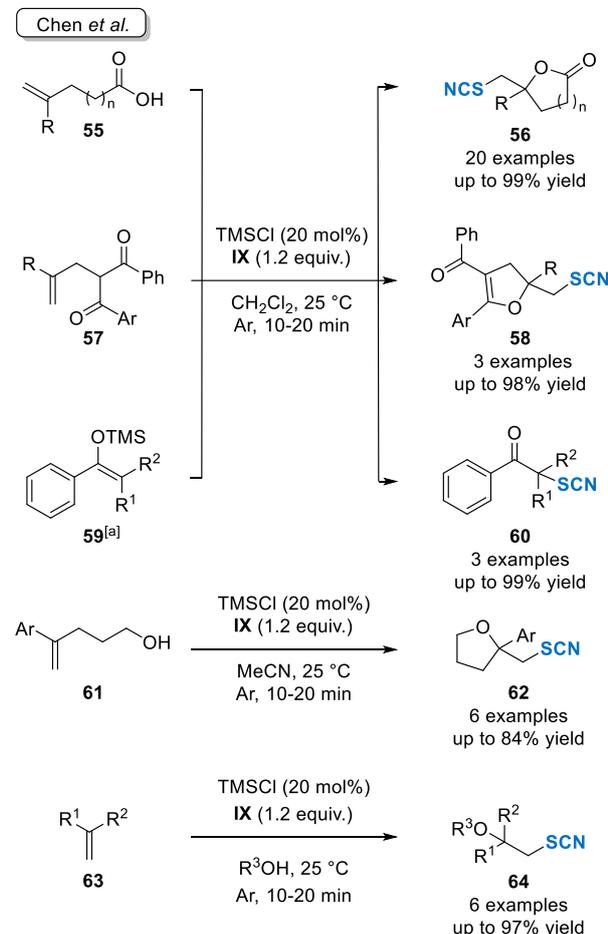
In 2019, Chen and co-workers described the first synthesis of the *N*-thiocyanato-dibzenzenesulfonimide reagent **IX** and studied its application in various thiocyanation reactions (Scheme 21).<sup>[29]</sup> The *N*-thiocyanato-dibzenzenesulfonimide **IX** was prepared in two steps. Starting from the dibzenzenesulfonimide in the presence of *tert*-BuOCl, the corresponding chlorinated product was isolated in a 81% yield. Then, this latter was engaged with AgSCN to furnish the reagent **IX** in a 75% yield. Note that this reagent was slightly sensitive to light.



**Scheme 21.** Synthesis of the *N*-thiocyanato-dibzenzenesulfonimide **IX**.

The electrophilic reagent **IX** was used for the difunctionalization of olefins (Scheme 22).<sup>[29]</sup> Indeed, the group of Chen reported the synthesis of SCN-containing lactones **56** starting from alkenes bearing a carboxylic acid group **55** in presence of a catalytic amount of TMSCl. Other olefinic derivatives were also studied such as olefinic 1,3-diketones **57**, silyl enol

ethers **59** or alkene alcohols **61** leading to the corresponding thiocyanated dihydrofurans **58**, ketones **60** and tetrahydrofurans **62**, respectively. Finally, 1,1-disubstituted alkenes **63** were functionalized, the solvent ( $R^3OH$ ) playing the role of the nucleophile.



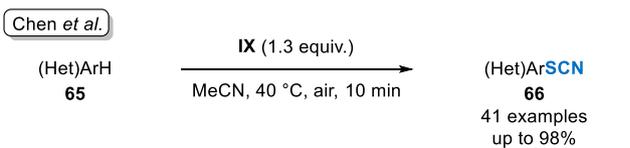
**Scheme 22.** Applications of *N*-thiocyanato-dibenzenesulfonimide **IX**. [a] No TMSCI was used in case of silyl enol ethers **59**.

The same year, the group of Chen independently investigated the thiocyanation of several classes of compounds using the reagent **IX** (Scheme 23).<sup>[30]</sup> First, the thiocyanation of indole derivatives was selectively achieved at the C3 position leading to the corresponding thiocyanated products (**66a-66h**) in good to excellent yields (up to 98% yield). The transformation was tolerant to halogens (**65c**, **65f** and **65g**) and to the cyano group (**65d**). A *N*-protected indole, a benzothiophene, a benzofuran and an 7-azaindole were also suitable substrates (**65e-65h**). Then, the methodology was extended to the selective *para*-thiocyanation of aniline derivatives (**66i-65l**) in good yields. In contrast, when *para*-halogenated anilines (**65m-65o**) were used, only the *N*-thiocyanation occurred. Interestingly, the thiocyanation was also possible on heteroaromatic derivatives such as the 8-aminoquinoline (**65p**). A series of phenol derivatives (**65q-65t**) was also functionalized along with the 2-methyl-anisole (**65u**) and the naphthol (**65v**). In the presence of TfOH, the thiocyanation of arenes was possible as shown with compounds **66w-66z**.

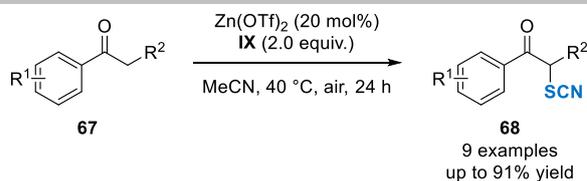
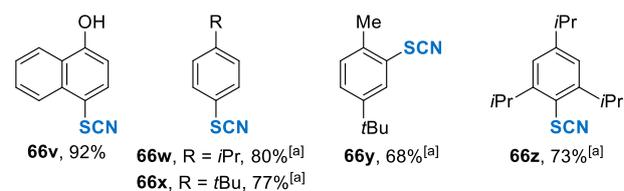
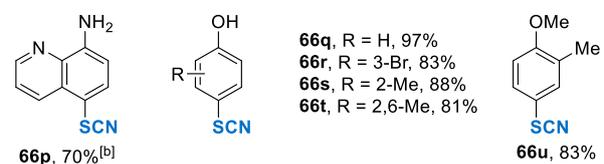
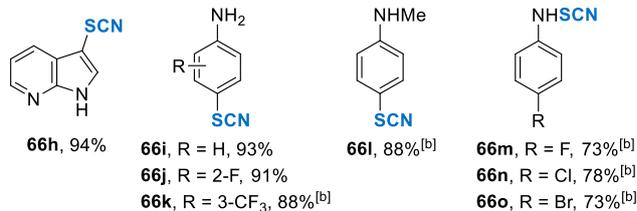
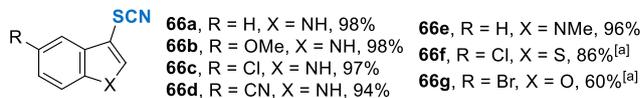
In presence of  $\text{Zn}(\text{OTf})_2$  as a Lewis acid, the thiocyanation of 1-indanone derivatives (**67a-67d**), the tetralone **67e** and the propiophenone **67f** was achieved. Finally, the difunctionalization of styrene derivatives was also studied and the corresponding amino thiocyanato products (**70a-70b**) were obtained in good yields. The methodology was also applied to cyclic alkenes such as the cyclopentene **69c** and the cyclohexene **69d**. However, in the case of the 1,1-diphenylethylene **69e**, only the thiocyanated product was obtained.

The *N*-thiocyanato-dibenzenesulfonimide **IX** was also used for the synthesis of  $\beta$ -thiocyanato carbonyl derivatives by means of a Lewis acid mediated thiocyanato semipinacol rearrangement of allylic alcohols (Scheme 24).<sup>[31]</sup> A panel of 1,1-disubstituted alkene alcohols **71** was functionalized and the corresponding rearranged 2-thiocyanatomethylcyclopentanone derivatives **72** were obtained in good to excellent yields. Note that various aromatic derivatives (**71a-71h**) with different substitution patterns and electronic properties as well as the aliphatic compound **71i**

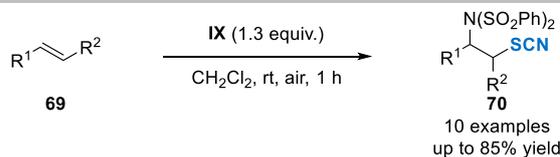
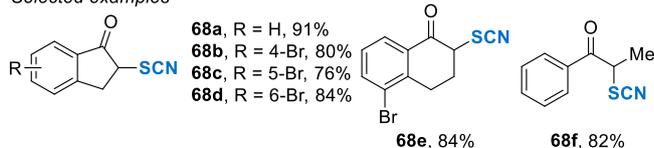
was suitable in this transformation. The approach was extended to other tertiary alcohols such as the molecule derived from the cyclopentanol **73a** and the acyclic tertiary alcohol **73b**. Even secondary alcohols were tolerated leading to the corresponding  $\alpha$ -quaternary center  $\beta$ -thiocyanato aldehydes **74c** and **74d**. In addition, the methodology was also successfully applied to the functionalization of trisubstituted alkenes (**75a-75e**) and the SCN-containing compounds (6 examples), bearing indanone, 1,2-dihydronaphthalene and chromene scaffolds for instance, were obtained in up to 86% yield with a good diastereoselectivity.



Selected examples



Selected examples

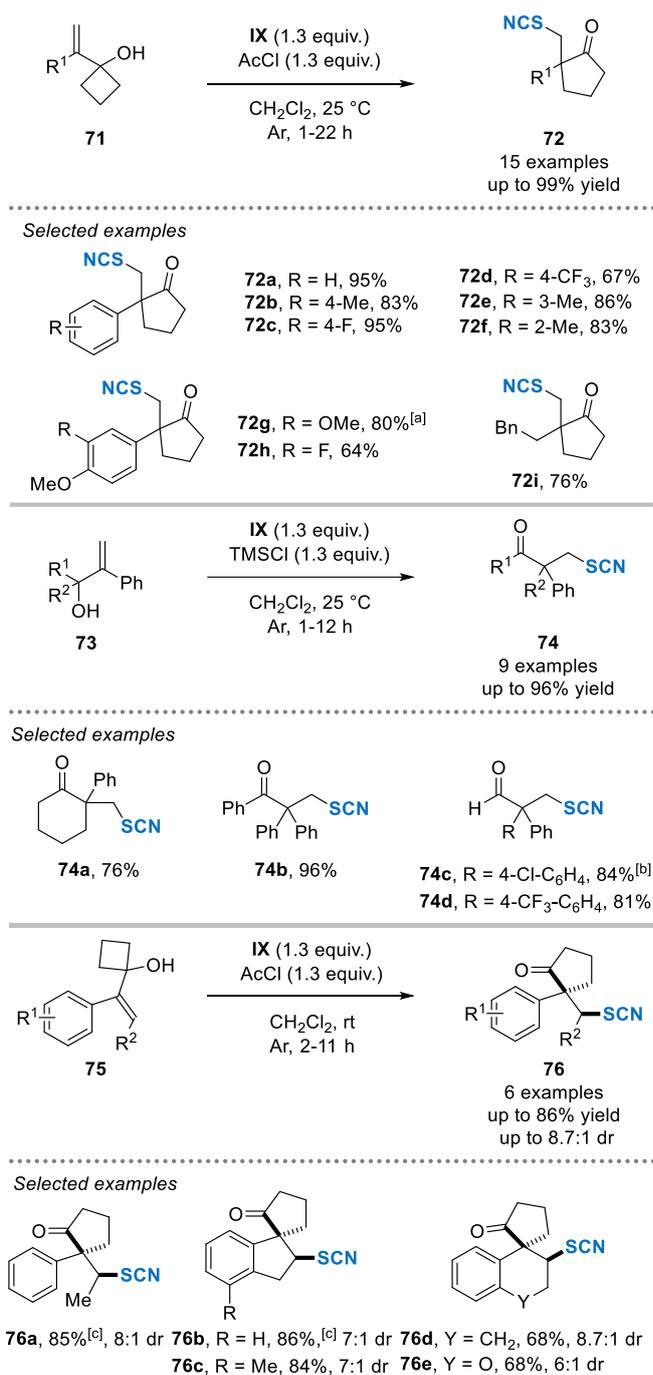


Selected examples



**Scheme 23.** First application of IX for the thiocyanation of (hetero)arenes,  $\alpha$ -ketones and alkene derivatives. [a] TfOH (1.0 equiv.), 60 °C, 12 h. [b] CH<sub>2</sub>Cl<sub>2</sub>, rt, 10 min.

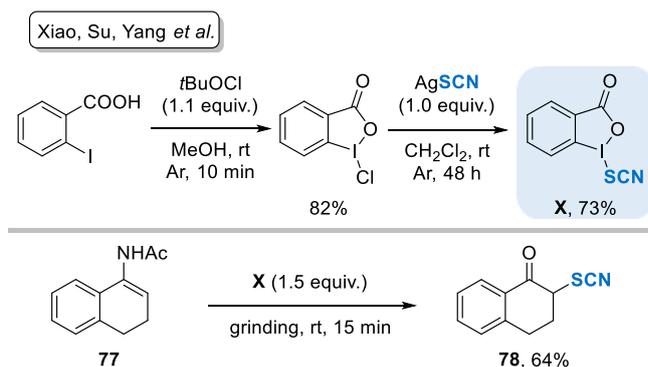
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**Scheme 24.** Synthesis of  $\beta$ -thiocarbonyl derivatives by means of a Lewis acid mediated thiocarbonyl semipinacol rearrangement of allylic alcohols using the reagent IX. [a] Reaction was performed at 0 °C. [b] AcCl was used. [c] TMSCl was used.

### 3.4 Electrophilic Hypervalent Iodine Reagent for the Thiocyanation Reaction

In 2019, in the course of their investigation regarding the design of an electrophilic selenocyanating reagent, the group of Xiao, Su, Yang synthesized the first thiocyanobenzenodioxolone **X** in two steps from the commercially available 2-iodobenzoic acid with a 60% overall yield (Scheme 25).<sup>[32]</sup> Under grinding conditions, the  $\alpha$ -thiocyanation of the *N*-acetyl- $\alpha$ -arylamines **77** was achieved leading to the corresponding tetralone **78** in 64% yield.



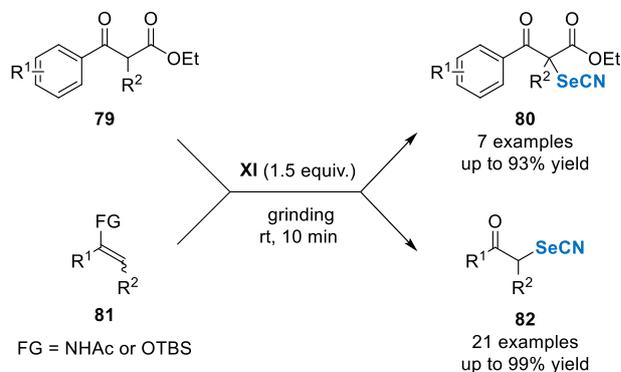
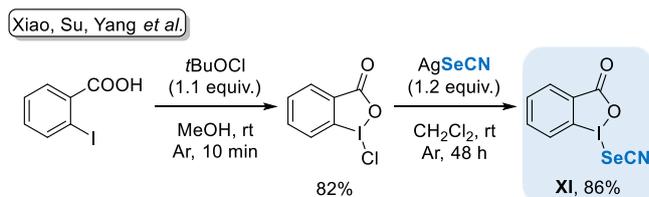
**Scheme 25.** Thiocyanation of the *N*-acetyl- $\alpha$ -arylenamine **77** with the reagent **X**.

## 4. Design of New Electrophilic Selenocyanating Reagents: Synthesis and Applications

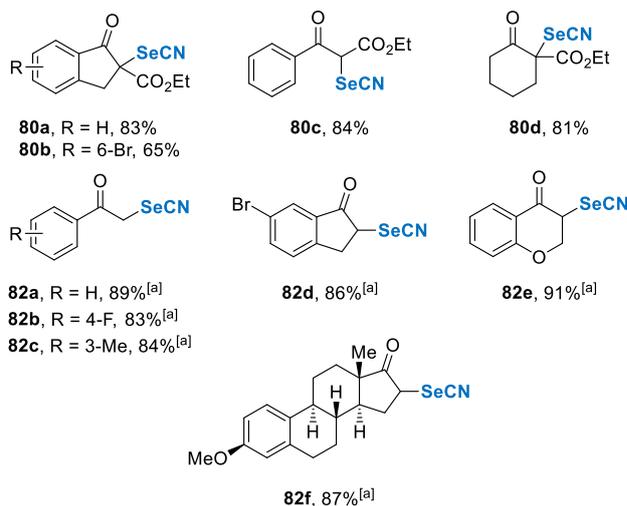
As numerous organoselenium compounds demonstrated biological activities such as the SeCN-aspirin analogue (Se-NSAID, Figure 1), a lot of attention was paid to the development of straightforward methodologies to synthesize them. Very recently, the use of electrophilic reagents has emerged although restricted so far to a handful of examples. In this section, the synthesis of the SeCN-containing sources and their applications will be depicted.

### 4.1 The Selenocyanobenziodoxolone Reagent

So far very few electrophilic sources have been designed and among them, the selenocyanobenziodoxolone reagent **XI** was studied.<sup>[33]</sup> In 2019, the group of Xiao, Su and Yang reported the synthesis of the selenocyanobenziodoxolone **XI** and its application as an electrophilic source (Scheme 26).<sup>[32]</sup> The reagent **XI** was prepared in two steps. Starting from the 2-iodobenzoic acid and in the presence of the *tert*-butyl hypochlorite, the 1-chloro-1,2-benziodoxol-3(*1H*)-one was synthesized. Then, this latter reacted with AgSeCN to afford the selenocyanobenziodoxolone **XI** in a 86% yield. This reagent was then applied to the functionalization of various nucleophiles under solvent-free conditions (grinding conditions). Various  $\beta$ -keto esters including indanone derivatives (**79a** and **79b**) and the acyclic  $\beta$ -ketoester **79c** were functionalized in good yields. The reaction was also efficient with the cyclohexanone derived  $\beta$ -ketoester **79d**, offering an access to the corresponding product **80d** in a 81% yield. The selenocyanation was also performed on aromatic enamines (**81a-81c**) with different substituents, providing the corresponding selenocyanated aromatic ketones (**82a-82c**) in good yields. When cyclic enamines (**81d-81e**) were reacted under these reaction conditions, the corresponding ketones were obtained in high yields. The methodology was then further applied to the functionalization of steroid derivatives, leading to the SeCN-containing product **82f** in a 87% yield.



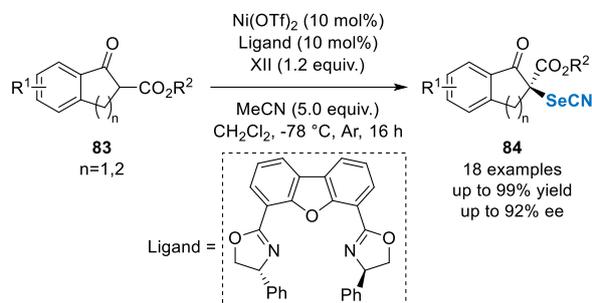
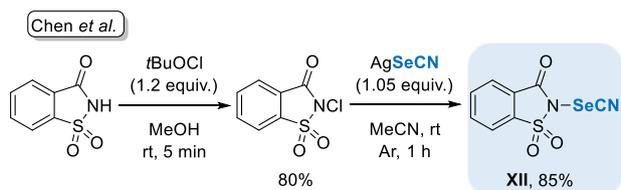
Selected examples



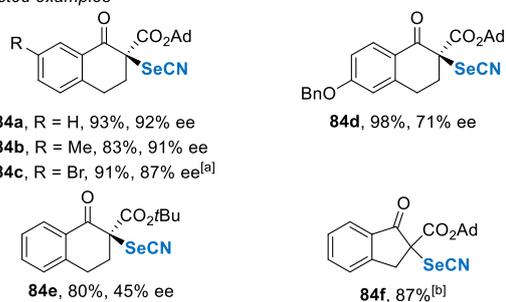
**Scheme 26.** The selenocyanobenzodioxolone reagent **XI**: synthesis and applications. [a] A final hydrolysis step was necessary to release the products **82**.

#### 4.2 The *N*-Selenocyanatosaccharin Reagent

Very recently, Chen's group developed a methodology for the asymmetric selenocyanation of  $\beta$ -ketoesters by means of a Lewis acid catalysis (Scheme 27).<sup>[34]</sup> To reach that goal, a new electrophilic reagent **XII** derived from saccharin was synthesized in two steps in an overall 68% yield. In the presence of the selenocyanatosaccharin **XII**, a nickel-catalyzed selenocyanation of various  $\beta$ -ketoesters was achieved in high yields (up to 99% yield) and a good control of the enantioselectivity (up to 92% ee). The reaction showed a good functional group tolerance regardless to the nature of the substituent on the aromatic part of the tetralone derivatives (**83a-83e**). Note that the nature of the ester did have an impact as the derivative **84e** was obtained in a 80% yield although with only 45% ee. However, when the indanone derivative **83f** was used as a substrate, the selenocyanated product **84f** was obtained in a high yield (87%) as a racemic mixture.



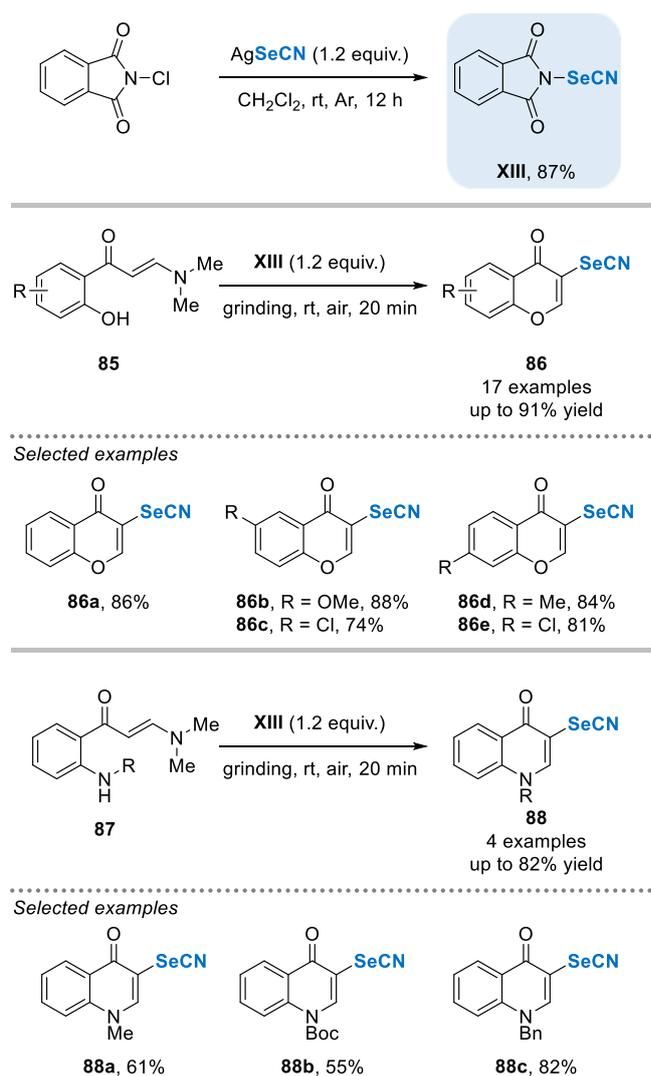
Selected examples



**Scheme 27.** Synthesis of the selenocyanatosaccharin **XII** and its use to functionalize various  $\beta$ -ketoesters. [a] Reaction on 1 mmole scale. [b] The product was obtained as a racemic mixture.

### 4.3 The *N*-Selenocyanatophthalimide Source

Very recently, Xiao, Ren, Huang and co-workers reported the synthesis of the electrophilic selenocyanate source **XIII**<sup>[35]</sup> from *N*-chlorophthalimide and silver selenocyanate in a 87% yield (Scheme 28).<sup>[36]</sup> The selenocyanatophthalimide reagent **XIII** was then applied to the selenocyanation of enaminone derivatives **85** or **87**, which after cyclization led to the corresponding 3-selenocyanato-substituted chromones **86** and quinolinones **88**.



**Scheme 28.** Synthesis of the *N*-selenocyanatophthalimide **XIII** and its applications to the functionalization of enaminone derivatives.

## 4. Conclusion

In summary, the selective introduction of SCN and SeCN groups onto molecules is of matter of importance in the organic chemistry field. Therefore, a growing attention was paid by the scientific community to the quest of efficient synthetic solutions. In this Minireview were discussed the major advances made over the last years to build up thiocyanated or selenocyanated molecules thanks to the design and use of a panel of electrophilic reagents with various backbones. These emergent reagents were able to react with various classes of nucleophiles, expanding further the chemical space of molecular complexity. By unlocking the door towards unprecedented thiocyanation or selenocyanation reactions, the newly-designed tools will definitely have a strong impact on the way to synthesize SCN- and SeCN-containing molecules and will offer new perspectives in the field of organic synthesis. Nevertheless, the use of these reagents in more challenging transformations is still a goal to be reached and major advances are expected in the coming-years.

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**Keywords:** thiocyanation reaction • electrophilic reagents • methodologies • synthetic transformations • selenocyanation reaction

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Over the years, SCN- and SeCN-containing molecules have received significant attention due to their importance in pharmaceuticals and agrochemicals as well as key intermediates in organic chemistry. Recently, original electrophilic reagents were designed, offering straightforward synthetic pathways to thiocyanated and selenocyanated molecules. This Minireview will highlight and discuss these recent advances.