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Emergent Strategies for Catalytic Enantioselective Direct Thiocyanation and Selenocyanation Reactions

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Organothiocyanates and selenocyanates stood out over the last two decades as high-profile targets in synthetic organic chemistry. These classes of molecules, which have been known since the 1930s, have been the object of a recent revival of interest, especially regarding their synthesis.[1] The SCN and SeCN moieties are indeed of notable importance. In addition to be found in several bioactive natural products, which exhibit interesting anticancer and antibacterial activities for most of them, they are important synthetic linchpin to access other biorelevant sulfur- and selenium-containing functional groups. In this context, and even though the formation of C(sp^3)–SCN and C(sp^3)–SeCN bonds has been well documented, a simple observation strikes: enantioselective thiocyanation and selenocyanation reactions, *i.e.*, the direct introduction of the SCN or SeCN moieties on a carbon center in an enantioselective fashion, have long remained a challenge to be overcome. Several examples have been reported to access chiral organic thiocyanates for natural products synthesis endeavors, *via* S_N2 nucleophilic substitutions with SCN nucleophiles on already chiral nonracemic substrates.[2] Along with these developments, an early report from Falck and co-workers describes the diastereoselective α-thiocyanation of chiral *N*-acyl oxazolidinones using Evan's protocol.[3]

This spotlight highlights the first works recently reported in the field of direct enantioselective catalytic thiocyanations and selenocyanations and aims at stressing out the potential of these new approaches for the future development of original tools towards the asymmetric synthesis of thio- and selenocyanated derivatives.

Floris Buttard (left) received his PhD in organic chemistry at Orléans University in 2018 under the supervision of Prof. Franck Suzenet and Dr. Jean-François Brière. He joined in 2019 the group of Dr. Pier Alexandre Champagne at the New Jersey Institute of Technology and then moved back to France in 2021 to work at ICSN (UPR 2301) with Dr. Xavier Guinchard. In 2022, he joined the team of Dr. Tatiana Besset at the laboratory COBRA (UMR 6014, Rouen, France) as a WINNINGNormandy (H2020 MSCA COFUND) postdoctoral fellow to develop new thiocyanation approaches.

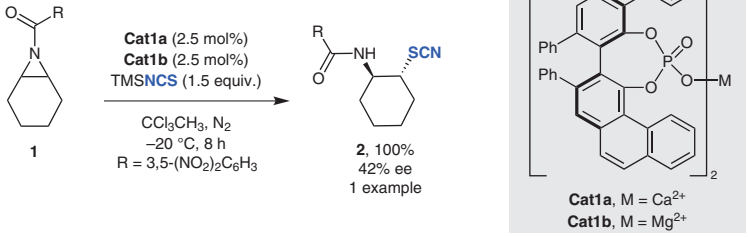
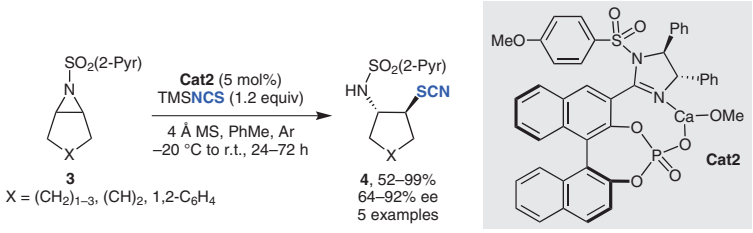
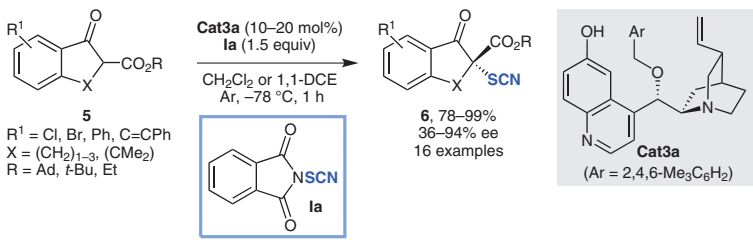
Tatiana Besset (right) obtained her PhD in organic chemistry (2009) at Grenoble University with Dr. Greene. She then moved to the WWU Münster as a postdoctoral fellow in the group of Prof. Glorius. In 2011, she joined the group of Prof. Reek at Amsterdam University as an industrial postdoctoral fellow (Eastman company). Since 2012, she is a CNRS Researcher in the 'Fluorinated Biomolecules Synthesis' group at the laboratory COBRA (UMR 6014, Rouen, France). Her research involves the design of new transformations involving transition-metal catalysis (C–H bond functionalization) and the development of new strategies in organofluorine chemistry.

In 2013, Della Sala described the very first enantioselective thiocyanation through the desymmetrization of the *meso*-aziridine **1** in the presence of TMSNCS and an equimolar mixture of two phosphate salts **Cat1a** and **Cat1b** (Table 1A).[4] Albeit a quantitative yield, the only example of chiral thiocyanate product **2** is obtained with a moderate 42% enantiomeric excess. Nakamura *et al.* later reported a similar approach on *N*-(sulfonyl)aziridines **3**, using the chiral calcium imidazoline–phosphate complex **Cat2** as a catalyst (Table 1B).[5] The pyridinyl moiety on the sulfonyl group plays a critical role in the stereoselectivity of the reaction by coordinating to the Ca^{2+} cation and allows for the formation of cyclic thiocyanates **4** with good to excellent enantioselec-

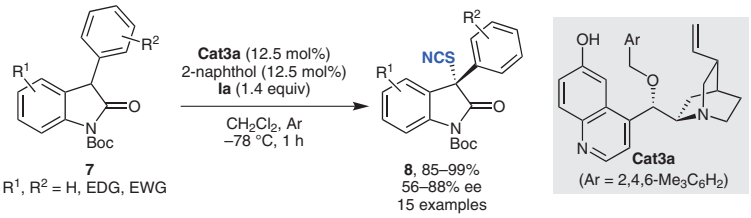
tivities. To the best of our knowledge, these two previous approaches are the only asymmetric nucleophilic thiocyanations reported so far, despite SCN nucleophiles being widely used for the synthesis of organothiocyanates.[1] After these pioneer works, the group of Chen demonstrated that *N*-thiocyanatoimide reagents could be successfully used for the organocatalyzed enantioselective thiocyanation of enolates. In 2018, they developed the synthesis of α-thiocyanato-β-keto esters **6** employing the quinidine derivative **Cat3a** as the catalyst in the presence of *N*-thiocyanatophthalimide **Ia**[6] (Table 1C).[7] The reaction furnishes the products with high yields and moderate to excellent enantioselectivities (36–94% ee) and represents the first enantioselective electrophilic thiocyanation. This approach has then been successfully extended to the α-thiocyanation of other enolates derived from oxindoles **7** (Table 1D) and alkylidene β-keto esters **9** (Table 1E).[8–10] In line with these developments, the first enantioselective selenocyanation was described in 2020.[11] In the presence of a Ni(II)-bisoxazoline complex and the selenocyanating reagent **II** derived from saccharin (Table 1F), the enantioenriched organoselenocyanate products **12** are obtained in good yields and overall satisfactory enantioselectivities (70–92% ee). While these last strategies used enolate nucleophiles to react with the electrophilic *N*-SCN and *N*-SeCN partners, the group of Zhao designed in 2019 the thiocyanating cyclization of alkenes in the presence of a selenide catalyst, a Lewis acid and *N*-thiocyanatosaccharin **Ic**.[12,13] Two examples are described with the chiral selenide **Cat4**, affording the chiral thiocyanates **15** and **16** with high yields, but low to moderate enantioselectivities.

In summary, the last years have witnessed the emergence of unprecedented synthetic strategies for enantioselective thiocyanation and selenocyanation reactions. A key aspect of these breakthroughs has been the design of original electrophilic reagents well suited for organo- and Lewis acid catalyzed transformations, although limited, as of now, to the reaction with enolate nucleophiles to achieve high enantioselectivities. Therefore, these recent advances will undoubtedly spark in the next few years the development of new approaches for enantioselective thiocyanation and selenocyanation transformations.

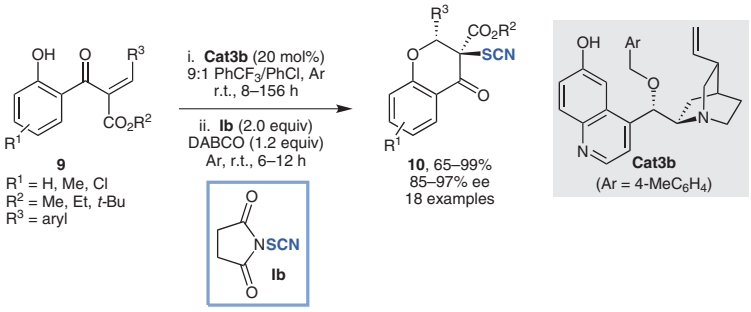
Table 1 Overview of the Reported Asymmetric Thio- and Selenocyanation Approaches

(A) **Desymmetrization of *meso*-Aziridines in the Presence of Nucleophilic TMSNCS**[4] Della Sala, 2013: the first enantioselective thiocyanation strategy reported. • reaction in the presence of a calcium phosphate and a potassium phosphate (1:1 mixture) • complementary activity of the two salts: the calcium phosphate **Cat1a** enhances the reactivity, while the magnesium phosphate **Cat1b** is essential for the enantioinduction • one single example of chiral thiocyanate is reported, with a moderate enantioselectivity (42% *ee*)	
(B) **Desymmetrization of *meso*-*N*-(Sulfonyl)aziridines**[5] Nakamura *et al.*, 2014: highly enantioselective thiocyanation approach using a nucleophilic reagent. • calcium imidazoline-phosphate salt **Cat2** as a catalyst • 2-pyridinylsulfonyl moiety as stereocontrolling group *via* coordination to the Ca^{2+} cation • low *ee* with the phosphoric acid alone • other enantiomer accessible with the magnesium phosphate salt (Mg^{2+} instead of Ca^{2+} in **Cat2**, –72% *ee*)	
(C) **Organocatalyzed α-Thiocyanation of Cyclic β-Keto Esters**[7] Chen *at al.*, 2018: enantioselective thiocyanation using an electrophilic source. • new electrophilic reagent: *N*-thiocyanatophthalimide **Ia**[6] • bifunctional quinidine derivative **Cat3a** as catalyst • 6′-OH on catalyst turned out to be critical for enantioinduction, • lower enantioselectivity on substrates with a 6- or 7-membered ring	

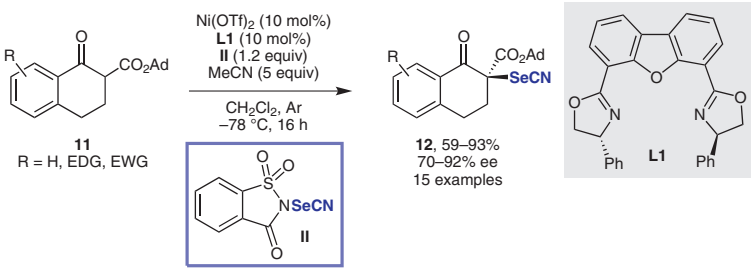
(D) **Organocatalyzed Thiocyanation of Oxindoles**[8]
Chen *at al.*, 2019: extension of their previously reported strategy to the thiocyanation of 3-aryl oxindoles **7**.
- *N*-thiocyanatophthalimide **Ia** as an electrophilic reagent
- 2-naphtol as a key additive for the enantioselectivity (self-assembly with catalyst *via* H-bonding)
- lower enantioselectivity (56–80% ee) with electron-withdrawing groups on either aryl moieties (R^1 or R^2)



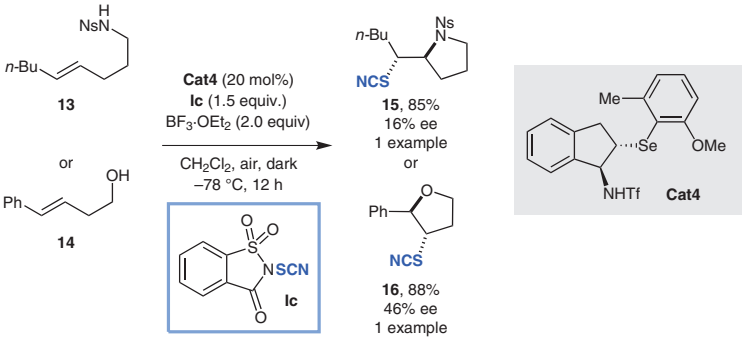
(E) **Organocatalyzed Tandem oxa-Michael/Thiocyanation Sequence on Alkylidene β-Keto Esters**[9]
Chen *et al.*, 2022: thiocyanation of oxa-Michael enolate intermediates en route to α-SCN flavanones.
- *N*-thiocyanatosuccinimide **Ib**[10] as SCN source
- 1 example of selenocyanation in the presence of *N*-selenocyanatosaccharin **II** (62% yield, 91% ee)



(F) **Nickel-Catalyzed α-Selenocyanation of β-Keto Esters**[11]
Chen *et al.*, 2020: first enantioselective selenocyanation reaction.
- new reagent: *N*-selenocyanatosaccharin **II**
- tridentate dibenzofuran bisoxazoline ligand **L1** for Ni(II) catalyst
- lower enantioselectivity with less bulky substituents on the ester (*t*-Bu 45% ee, Me 13% ee)
- 0% *ee* with 5-membered-ring substrates



(G) **Thiocyanocyclizations of alkenes**.[12]
Zhao *et al.*, 2019: only approach using nucleophilic partners other than enolates.
- chiral Lewis basic selenide **Cat4** as catalyst
- activation of *N*-thiocyanatosaccharin **Ic**[13] by Lewis acidic BF_3
- formation of a thiiranium ion intermediate from the alkene and subsequent cyclization
- two enantioselective examples, with low to moderate ees



Conflict of Interest

The authors declare no conflict of interest.

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