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Development of Synthetic Concepts for C1-Homologative Events and Activation of Molecular Rearrangements

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Development of Synthetic Concepts for C1-Homologative Events and Activation of Molecular Rearrangements

The transfer of a reactive nucleophilic CH_2X unit into an electrophile enables the introduction of a methylene fragment featuring a precise degree of functionalization through a single synthetic operation. The substituted carbon-centered functionality, installed within a starting molecular array through the introduction of a methylene unit into a preformed bond, is susceptible to further manipulation to access a more complex molecular architecture at a later stage.

Within this thesis we disclose the preparation and the synthetic exploitation of α -substituted organolithium reagents of type LiCH_2X (X = halogen, CN, OR, SR, SeR) towards electrophilic platforms such as Weinreb amides, imines and isothiocyanates, to install directly a methylene moiety presenting the desired degree of substitution on the recipient substrate. We also describe sequential homologation events taking place in one synthetic operation allowing a consecutive methylene insertion into a starting heterocumulene-type compound. Additionally, we demonstrate the versatility of fluoroiodomethane as an electrophilic monofluoromethylating agent for heteroatom-centered nucleophiles.

The instability of metallated α -organometallic species often poses serious questions on the practicability of using this conceptually intuitive and simple approach to form C-C and C-heteroatom bonds. The preparation of these unstable species requires carefully controlled techniques and by the proper management and tuning of the reaction conditions chemocontrolled strategies can be designed. The understanding of the mechanism ruling the formation and the decomposition of these organometallic reagents, contributes to expand their versatile synthetic potential. The excellent chemoselectivity and enantioselectivity, the mild reaction conditions, and the short reaction times featured by procedures involving these organometallic species, make them powerful reagents in organic synthesis. The development of these highly efficient methods should increasingly become a crucial tool in modern synthetic chemistry for rapidly accessing structures of pharmaceutical interest.



Graphical Abstract. Introducing a functionalized CH_2X fragment *via* a single synthetic operation.

Entwicklung einer Synthesestrategie zur C-1 Homologisierung und Aktivierung von Umlagerungsreaktionen

Der Transfer eines reaktiven CH_2X -Fragments in ein Elektrophil gestattet die Einführung einer Methylen-Einheit und damit eine genau definierte Funktionalisierung in einem einzigen Syntheseschritt. Die dadurch neu formierte C-Funktionalität kann als Ausgangspunkt für weitere Syntheseschritte hin zu komplexeren molekularen Strukturen dienen.

Im Rahmen der vorliegenden Dissertation wird sowohl die Herstellung als auch das synthetische Potential von α -substituierten Organolithium-Reagentien vom Typ LiCH_2X (mit X = Halogen, CN, OR, SR, SeR) hinsichtlich Reaktionen mit elektrophilen Substraten wie Weinreb-Amiden, Iminen und Isothiocyanaten beschrieben. Weiters werden sequentielle Homologisierungen an Heterocumulenverbindungen im Verlauf einer einzigen synthetischen Operation beschrieben. Die Demonstration des großen synthetischen Potentials von Fluorjodmethan als elektrophiles Monofluormethylierungsreagenz für Heteroatom-zentrierte Nukleophile stellt einen weiteren, wichtigen Teil der vorliegenden Arbeit dar.

Die vorgestellten Synthesen zur Ausbildung von C-C bzw. C-Heteroatom Bindungen erscheinen zwar konzeptuell einfach, stellen jedoch aufgrund der Instabilität der eingesetzten organometallischen Spezies hohe Anforderung hinsichtlich der Kontrolle der jeweiligen Reaktionsbedingungen. Daher bilden Untersuchungen zum ‚Feintuning‘ der Reaktionen und zur Erlangung vollständiger Chemokontrolle einen wichtigen Punkt der vorliegenden Untersuchungen, ebenso wie solche zum tieferen Verständnis jener Mechanismen, welche der Bildung bzw. dem Zerfall der relevanten Organometall-Reagentien zugrunde liegen.

Die exzellente Chemo- und Enantioselektivität, die milden Reaktionsbedingungen und kurzen Reaktionszeiten machen die vorgestellten Reaktionen zu nützlichen Werkzeugen in der organischen Synthese. Die Weiterentwicklung dieser hocheffizienten Methoden stellt einen wertvollen Beitrag für einen schnellen Zugang zu Strukturen von pharmazeutisch-chemischen Interesse dar.

Abbreviations List

2-MeTHF	2-Methyltetrahydrofuran
B ₂ mpd ₂	Bis(hexylene glycolato)diboron
Bn	Benzyl
Boc	<i>tert</i> -Butyloxycarbonyl
B ₂ pin ₂	Bis(pinacolato)diboron
Bu	Butyl
DMAc	Dimethylacetamide
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DTBB	Di- <i>tert</i> -butylbiphenyl
EDG	Electron donating group
EWG	Electron withdrawing group
HRMS	High Resolution Mass Spectrometry
LDA	Lithium diisopropylamide
LiHMDS	Lithium bis(trimethylsilyl)amide
LNCy ₂	Lithium dicyclohexylamide
LTMP	Lithium tetramethylpiperidide
Me	Methyl
MeCN	Acetonitrile
NMR	Nuclear Magnetic Resonance
PG	Protecting group
Ph	Phenyl
Pin	Pinacol
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMS	Trimethylsilyl
Ts	Tosyl

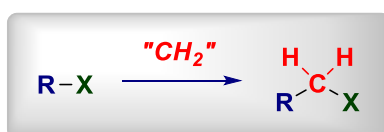
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- Publication 1** **Senatore, R.**; Ielo, L.; Monticelli, S.; Castoldi L.; Pace, V.*
Weinreb Amides as Privileged Acylating agents for Accessing α -Substituted Ketones.
Synthesis, **2019**, 51(14), 2792.
- Publication 2** **Senatore, R.**; Ielo, L.; Urban, E.; Holzer, W.; Pace, V.*
Substituted α -Sulfur Methyl Carbanions: Effective Homologating Agents for the Chemoselective Preparation of β -Oxo Thioethers from Weinreb Amides.
Eur. J. Org. Chem. **2018**, 2018, 2466.
- Publication 3** **Senatore, R.**; Castoldi, L.; Ielo, L.; Urban, E.; Holzer, W.; Pace, V.*
Expedition and Chemoselective Synthesis of α -Aryl and α -Alkyl Selenomethylketones via Homologation Chemistry.
Org. Lett. **2018**, 20, 2685 - Highlighted in *Synfacts* **2018**, 14, 769.
- Publication 4** **Senatore, R.**; Malik, M.; Touqeer, R.; Listro, R.; Collina, S.; Holzer, W.; Pace, V.*
Straightforward and Direct Access to β -seleno-amines and sulfonylamides via the controlled addition of phenylselenomethyl lithium (LiCH_2SePh) to imines.
Tetrahedron, **2020**, 76, 51, 131220.
- Publication 5** De la Vega-Hernandez, K.; **Senatore, R.**; Miele, M.; Urban, E.; Holzer, W.; Pace, V.*
Chemoselective reduction of isothiocyanates to thioformamides mediated by the Schwartz reagent.
Org. Biomol. Chem. **2019**, 17, 1970.
- Publication 6** **Senatore, R.**; Malik, M.; Langer, T.; Holzer, W.; Pace, V.*
Consecutive and Selective Double Methylene Insertion of Lithium Carbenoids to Isothiocyanates: A Direct Assembly of Four-membered Sulfur-Containing Cycles.
Provisionally accepted in Angew. Chem. **2021** (manuscript ID: 202106258).
- Publication 7** **Senatore, R.**; Malik, M.; Spreitzer, M.; Holzer, W.; Pace, V.*
Direct and Chemoselective Electrophilic Monofluoromethylation of Heteroatoms (O-, S-, N-, P-, Se-) with Fluoroiodomethane.
Org. Lett. **2020**, 22, 4, 1345.
- Publication 8** **Senatore, R.**;* Malik, M.; Urban, E.; Holzer, W.; Pace, V.*
Synthesis of stable α -fluoromethyl putative carbanions via a chemoselective reduction-monofluoromethylation sequence of diselenides under sustainable conditions.
Tetrahedron, **2021**, 85, 131921.
- Appendix** *Supporting information for Publication n. 6*
Consecutive and Selective Double Methylene Insertion of Lithium Carbenoids to Isothiocyanates: A Direct Assembly of Four-membered Sulfur-Containing Cycles.

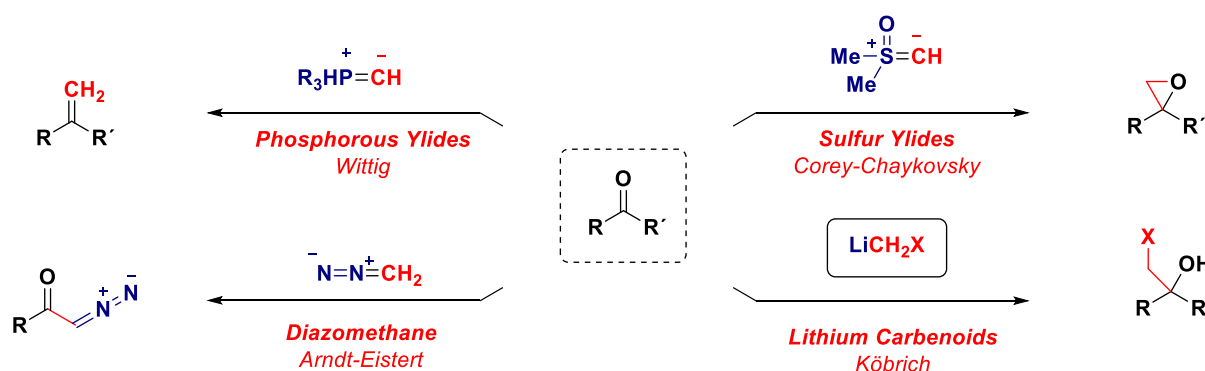
1. Introduction

Homologation reactions, defined as transformations converting a reactant into the next member of the homologous series by insertion of a methylene group,¹ constitute established and highly versatile synthetic operations whose importance in chemical sciences is showcased – *inter alia* – by the alteration of the pharmacological profile of various biologically active substances² or by simplification of the synthetic route to reach a target structure of medicinal interest.³ Carbon chains extension or the ring expansion of carbonyl compounds represent classical examples of homologation processes.⁴



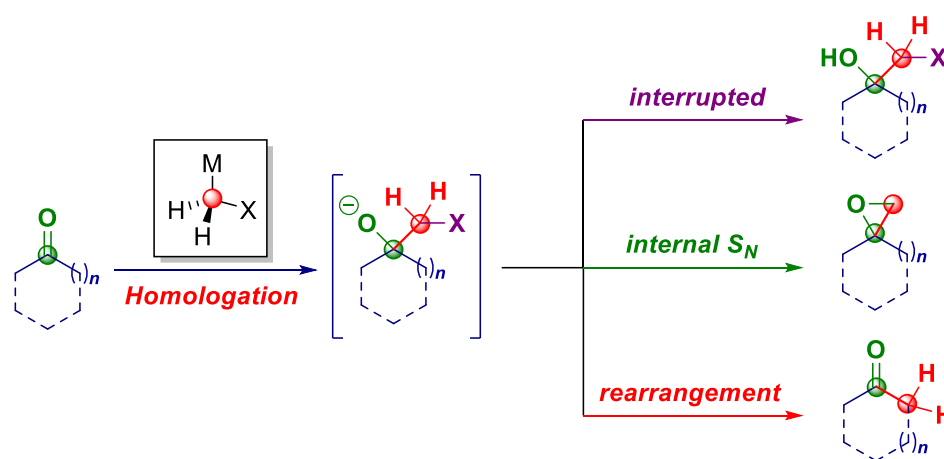
Scheme 1. Methylene insertion in homologation processes.

Classical methylenic reagents, allowing the formal insertion of a methylene unit into a preformed bond, are the Wittig-type phosphorous ylides,⁵ the Corey-Chaykovsky sulphur ylides,⁶ diazomethane^{1c,7} and the Köbrich lithium carbenoids.⁸ The extremely pronounced reactivity of the latter species renders them particularly attractive and highly versatile C1-building blocks in organometallic chemistry. Moreover, considering the well-known safety issues related to the employment of diazomethane, metal carbenoids are considered valuable alternatives in homologation chemistry.



Scheme 2. Classic homologating reagents.

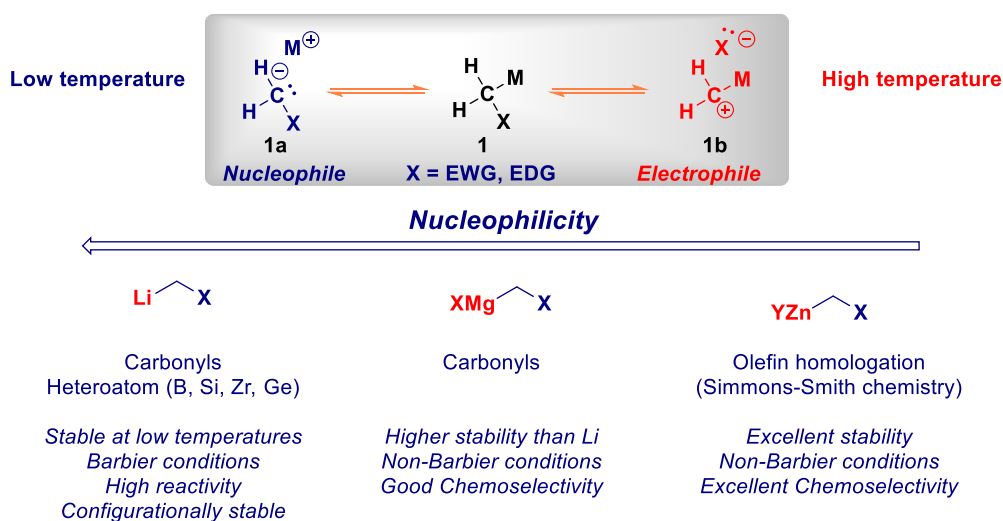
Depending on the outcome of the reaction, homologative transformations can be categorized as follow, considering the reactivity behaviour of the intermediate formed and the obtained molecular architecture: 1) *interrupted* homologations in which the resulting structure embodies the halogen or the functionalization transferred with the reagent of type $M-CH_2-X$; 2) *ring-closure* events occurring through an intramolecular nucleophilic displacement within the intermediate formed upon the addition of $M-CH_2-X$; 3) *pure* homologations in which the displacement of the halogen leads to chain elongation or ring enlargement events.



Scheme 3. Different outcomes for homologations of a carbonyl compound with MCH_2X reagents.

2. General features and properties of carbenoids

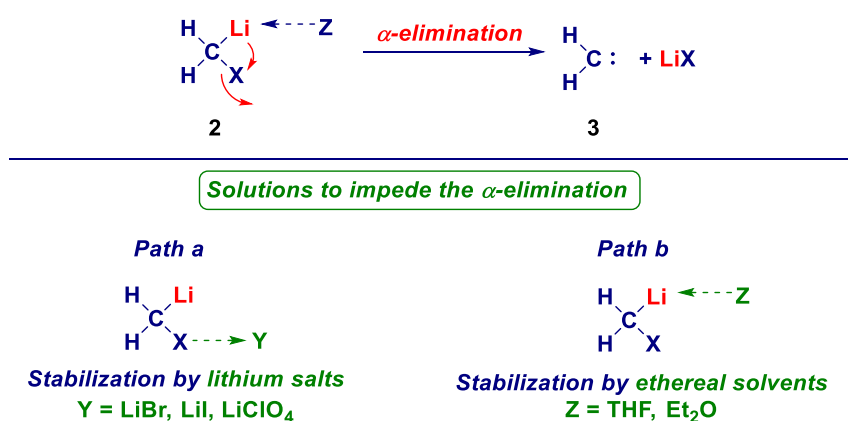
The classical definition by Closs⁹ and Moss¹⁰ describes carbenoids as “species presenting reactions qualitatively analogous to those of carbenes without being free divalent carbene species”. These organometallic species present a metal (*e.g.* Li, Mg) and an electronegative element (*e.g.* halogen, CN, OR) at the same carbon atom.¹¹ The simultaneous presence of an electron-donating and an electron-withdrawing substituent at the carbon center leads to ambiphilicity.¹⁰⁻¹² Therefore, the same chemical entity can display different behaviors according to the different experimental set up employed.¹³ The proper selection of the reaction conditions allows to direct the carbenoids intrinsic ambiphilicity towards their nucleophilic character. It is generally accepted that at low temperature, nucleophilic properties are observed (in analogy to classical organometallic species), while at higher temperatures the electrophilic behavior comes into play. Because of their excellent nucleophilicity, lithium and magnesium carbenoids react mainly as carbanions,^{8b} while a preferential electrophilic behavior is displayed by zinc and rhodium carbenoids.¹⁴



Scheme 4. Ambiphilicity of metal carbenoids.

The synthetic potential and versatility of carbenoids was in the past limited by their pronounced thermal instability. Among the metal carbenoids, lithium species can be regarded as the less stable ones, when compared to magnesium or zinc analogues. The coexistence of C-Li and C-halogen bonds on the same carbon atom promotes the high tendency to induce Kirmse's α -elimination degradation phenomenon, triggered by the strong Li-X internal coordination, leading to a lithium halide salt and a free carbene **3**.^{8a,15} Anyhow, careful and fine tuning of the reaction conditions employed could overcome this intrinsic instability:

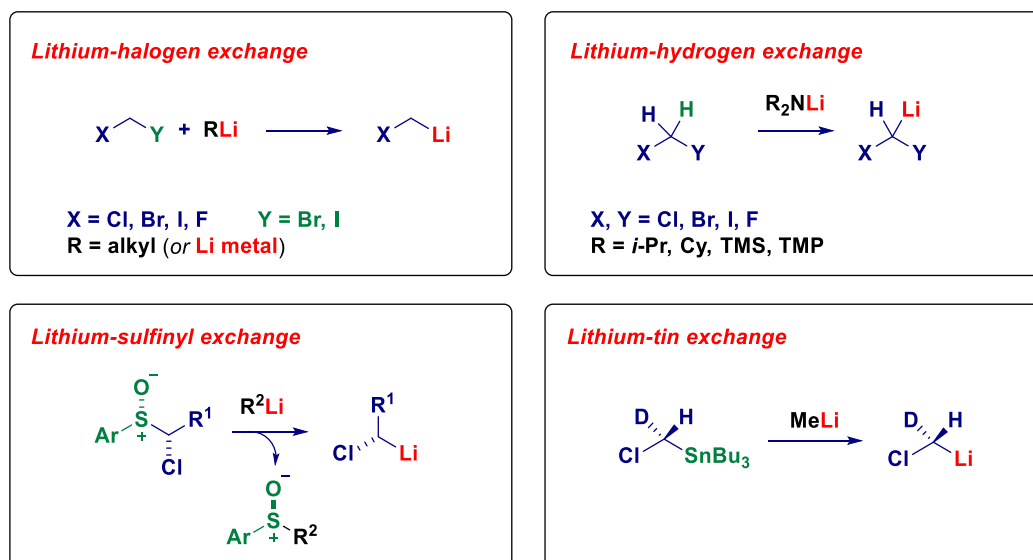
- 1) The generation of the carbenoid from a given precursor (dihalomethane, sulfoxide, stannane, as in detail described in the next section) must be conducted in the presence of the electrophile in the reaction medium (Barbier-type conditions), to ensure that no degradation takes place. Initial studies by Köbrich, generating chloromethyl lithium from bromochloromethane and *n*-BuLi at -110 °C, pointed out how the synthetic efficiency under non-Barbier conditions was quite limited as indicated by the extremely low yield (4%) observed in the carboxylation of LiCH₂Cl. A partial solution to this limitation was provided by Cainelli,¹⁶ who showed that lithium halocarbenoids could be efficiently generated at -78 °C carrying out the experiment under Barbier-type conditions: the generation of the carbenoid resulted faster than the direct addition of the organolithium employed to the electrophile.
- 2) The use of Lewis basic ethereal-type solvents, such as THF or Et₂O, coordinating the metal atom of the carbenoid, thus disrupting the internal Li-X coordination, and the presence of lithium halide salts contribute to tame (if not eliminate) the Krimse's α-elimination to a free carbene and a LiX species. Additionally, the use of this kind of solvents contributes to disaggregate organolithium species.¹⁷ Moreover, according to Matteson,¹⁸ the presence of LiBr also avoids the competing attack of MeLi to the electrophile under Barbier-type conditions.



Scheme 5. Decomposition pathway of lithium carbenoids.

3. Generation of lithium carbenoids

Lithium halocarbenoids can be generated by one of the following approaches: a) lithium-halogen exchange; b) lithium hydrogen exchange; c) lithium-sulfoxide exchange; d) lithium-tin exchange.^{17,19}



Scheme 6. Preparation of lithium halocarbenoids.

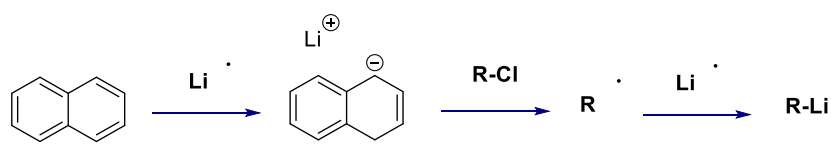
- The lithium-halogen exchange run on a given dihalomethane precursor is undoubtedly the most common method for preparing halocarbenoids for synthetic purposes.²⁰ Accordingly, an alkyl or aryl- lithium reagent promotes the exchange on $\text{XCH}_2\text{I}(\text{Br})$ furnishing the corresponding Li carbenoid. Villieras indicated *n*-BuLi as lithiated agents and the Trapp mixture (THF-Et₂O-*n*-pentane 75:15:10 v/v) as the solvent at -115 °C.²¹ Despite nowadays MeLi or PhLi are considered more suitable for lithium-halogen exchange, the commercially available MeLi-LiBr complex in Et₂O is the reagent of choice to generate lithium carbenoids as reported in the last years by Matteson¹⁸ and Pace.²² The presence of the LiBr stabilizes the carbenoid and limits the attack of MeLi to the electrophile, increasing also the electrophilicity acting as a Lewis acid.
- Because of the acidity of dihalomethanes conferred by the electron-withdrawing halogens, the proton abstraction is easily achieved with a lithium amide base such as LDA, LNCy₂, LTMP, LiHMDS leading to the formation of lithium dihalomethyl carbenoids. Deprotonation with highly basic *s*-BuLi does not occur even at -115°, being lithium-halogen exchange the

main event. Molinski deprotonated chloroform with *n*-BuLi at -100 °C to give trichloromethylithium.²³

The choice of a specific lithium amide base can only in some case affect the chemocontrol and the success of the reaction: using isocyanates as substrates, the employment of a high sterically hindered base (*e.g.* LTMP) is required to avoid the attack of the base to the heterocumulene.²⁴

- c) Blackemore²⁵ and coworkers described the generation of lithium carbenoids by lithium-sulfinyl exchange, starting from a halogenated aryl sulfoxides (*e.g.* *p*-tolyl). The lithium reagent attacks the electrophilic sulfur, releasing a thioether and the carbenoid. Inversion of configuration at sulfur center is observed. This strategy paved the way for the synthesis of optically active carbenoids by metalation of diastereopure sulfoxides.
- d) Hammerschmidt reported the generation of a chiral deuterated carbenoid from homochiral [*D*₁]-chloromethyl-tri-(*n*-butyl)-stannane precursor, synthesized from tributylstannyl-*[D*₁]-methanol, affording configurationally stable chloromethylithium (LiCHDCl) upon lithium halogen exchange with MeLi, which was trapped with benzaldehyde at -95 °C.²⁶ Similar experiments have been performed with iodomethylithium and fluoromethylithium analogues. Despite their chemical instability, these studies pointed out configurational stability of halomethylithium species at very low temperature.²⁷

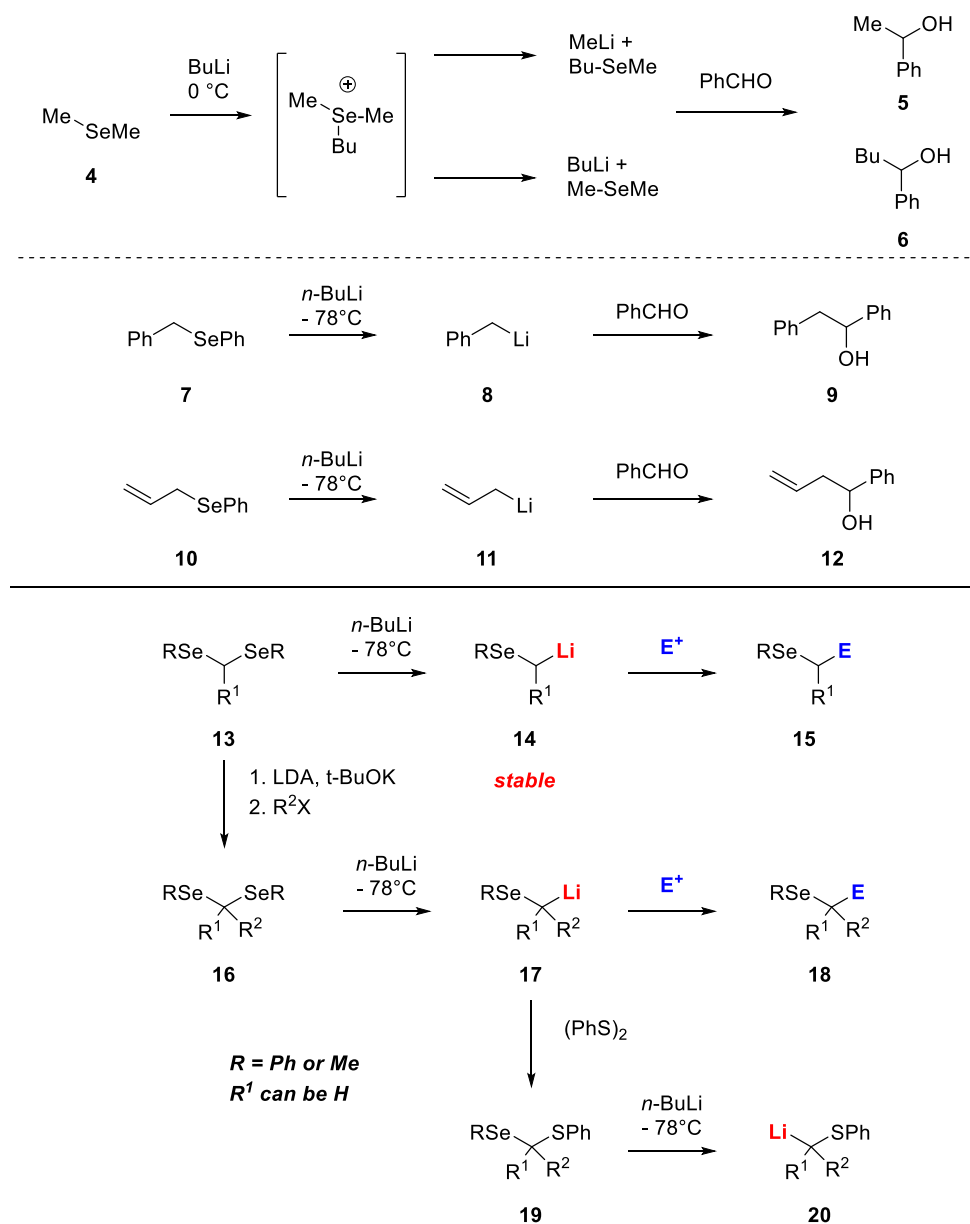
The aforescribed lithium-halogen exchange can also be realized through the so-called arene-catalyzed reductive lithiation with metallic lithium, using 4,4'-di-*tert*-butylbiphenyl (DTBB) or naphthalene in catalytic or stoichiometric amounts. Industrial preparation of commercially available organolithiums is usually achieved by following this approach. However, several reports in the literature showed how the reductive lithiation of alkyl or aryl halide can conveniently be used for preparative purposes. In addition to organic halides, other classes of substrates (*e.g.* sulfides, alcohols) can be suitable for generation of organolithiums *via* the arene-catalyzed reductive lithiation.^{17,28}



Scheme 7. Arene-catalyzed reductive lithiation for lithium-halogen exchange.

4. Selenium-lithium exchange

First reports from Gilman in 1949 indicates how butyllithiums displaces phenyllithium from phenylselenides. As indicated by Krief, reacting a dialkylselenide with *n*-BuLi, selenium-lithium exchange occurs in THF at 0 °C. When the starting selenide carries a benzyl or allyl group, the reaction allows the generation of benzylolithiums or allyllithiums, not accessible by lithium-halogen exchange. As reported by Seebach selenoacetals undergo selenium-lithium exchange at -78 °C with *i*-BuLi, *s*-BuLi and *n*-BuLi in THF. The generated selenium stabilized organolithiums are stable entities at -78 °C for hours and do not undergo rearrangement to more stable methylolithium or phenyllithium. Use of less nucleophilic reagents such as LDA-*t*-BuOK leads to deprotonation.

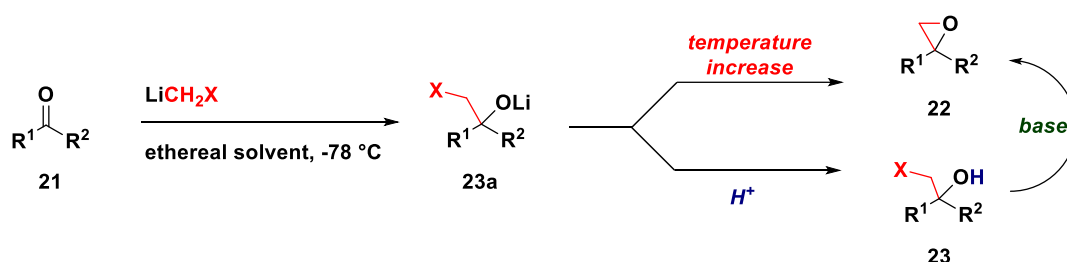


Scheme 8. Overview of the selenium-lithium exchange.

5. Electrophilic partners for lithium carbenoids

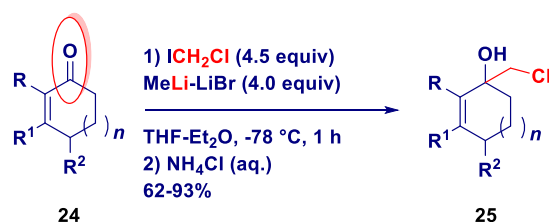
5.1 Carbonyl compounds

Earlier reports by Cainelli,^{16,29} Villieras,³⁰ and Matteson,¹⁸ and more recent contributions by Barluenga, Concellòn^{5b,31} and Lautens³² showed how carbonyl compounds can be employed as electrophilic counterparts in reaction with nucleophilic lithium carbenoids. The addition of a carbenoid to an aldehyde or a ketone gives, upon acidic quenching, an isolable β -halohydrin. A subsequent epoxide ring closure occurs by increasing the temperature or by means of a base-assisted process on the halohydrin formed after hydrolysis.



Scheme 9. Addition of lithium carbenoids to carbonyl compounds.

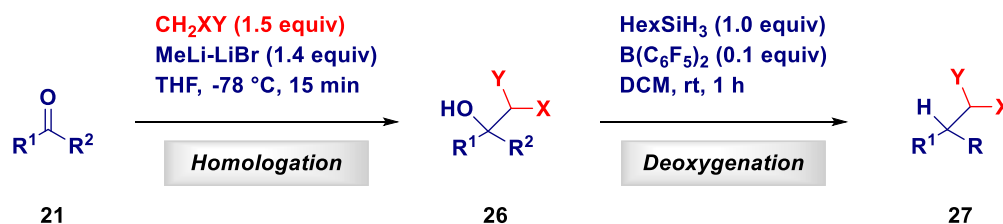
α,β -Unsaturated cyclic ketones undergo a highly chemoselective homologation with chloromethyl lithium to give chloromethyl allylic alcohols through a 1,2-addition, as reported by Pace and coworkers.³³ Beside the already discussed stabilization effect on the carbenoid, LiBr enhances the electrophilicity of the carbonyl-carbon, leading to a 1,2-chemoselectivity, considering that a 1,4-addition on cyclic enones could in principle occur as documented by Phillips³⁴ and Hernandez-Galan.³⁵



Scheme 10. Chemoselective addition of chloromethyl lithium to cyclic enones.

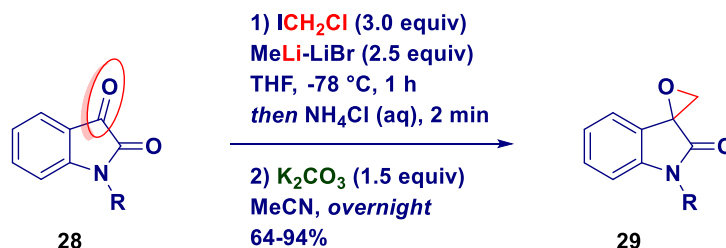
Two sequential distinct processes, namely homologation and silane-mediated deoxygenation, allowed the installation of a halomethyl fragment into a carbonyl compound to form a halohydrin and subsequent removal of the hydroxy group: the addition of two nucleophiles, a halocarbenoid and a hydride, to the carbonyl carbon of aldehydes and ketones affords an halomethyl alkyl

derivative.³⁶ Diverse carbanion-like species can also act as nucleophile and can be employed in the sequence to accomplish a different functionalization of the starting compound.



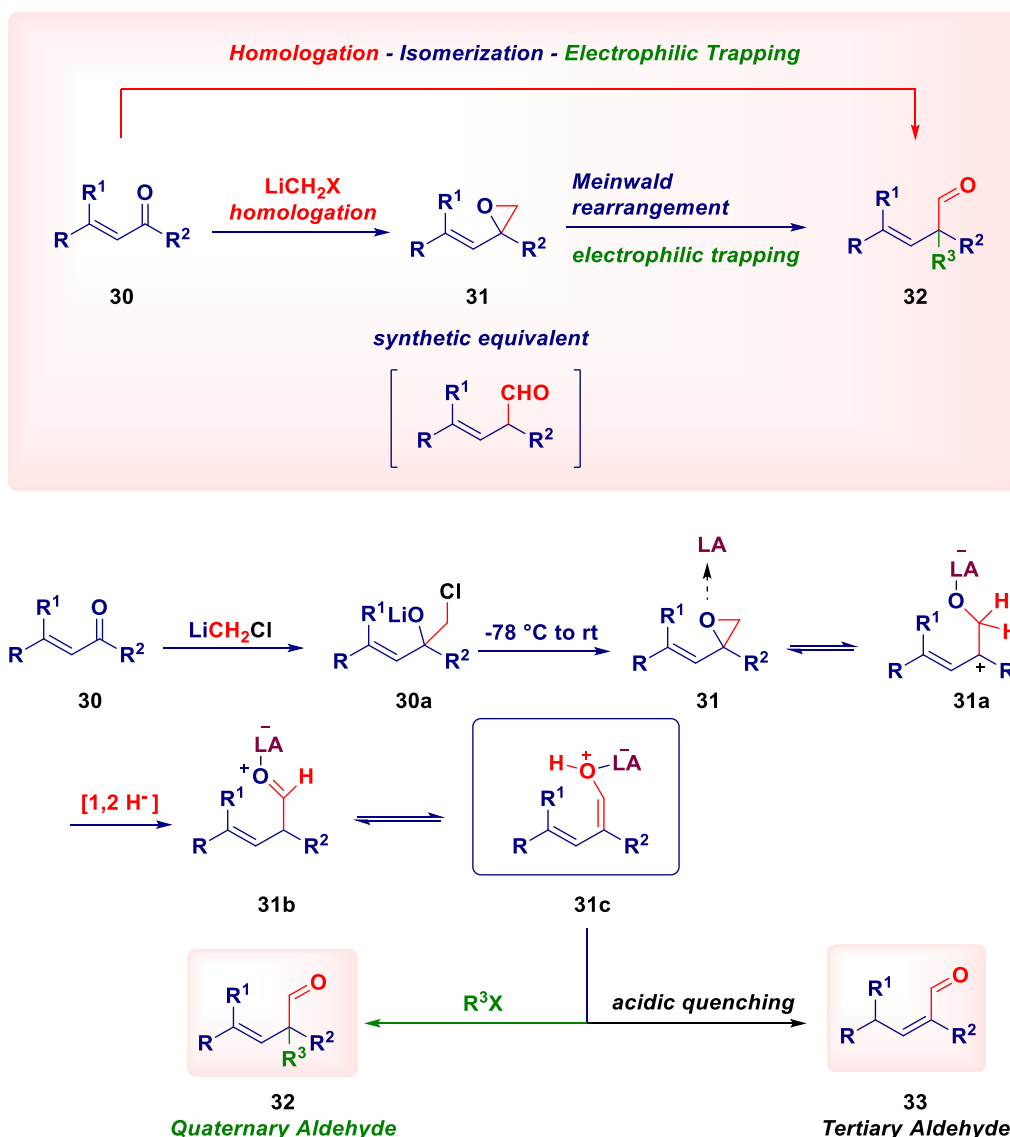
Scheme 11. Homologation-deoxygenation to convert carbonyls into halomethyl alkanes.

An efficient chemoselective access to rare spiro-epoxyoxindoles has been reported through the nucleophilic addition of chloromethyl lithium to the high electrophilic C3 carbon of N-functionalized isatines, followed by base-triggered ring closure of the so-formed halohydrine.³⁷ The excellent electrophilicity of the C3 carbon of the isatin, due to the presence of the electron-withdrawing lactam, allows the chemoselective addition of the halocarbenoid at this level, even in the presence of functionalities known to be placeholders for halomethylating reagents.



Scheme 12. Pace's synthesis of spiro-epoxyoxindoles.

The homologation of α,β -unsaturated acyclic and cyclic ketones with lithium carbenoids affords – upon increasing of the temperature – all-carbon quaternary and tertiary α -aldehydes in a single synthetic operation consisting of three different transformations: 1) C1-homologation of a vinyl ketone; 2) epoxide-aldehyde Lewis acid mediated isomerization (Meinwald rearrangement); 3) electrophilic trapping for α -derivatization of an aldehyde enolate, crucial intermediate whose intervention was confirmed by labeling experiments. The attack of the nucleophilic LiCH_2Cl to the carbonyl compound **30** produces the O-lithiated halohydrin **30a**, which undergo cyclization to the vinyl epoxide **31**. LiBr, acting as Lewis acid, triggers the ring opening – favored by the formation of the allylic carbocation **31a** – to finally give the enolate **31c** through 1,2-hydride shift and tautomeric equilibrium, which can react with an electrophile to yield the quaternary aldehyde **32** or, upon acidic quenching and tautomerization, the tertiary aldehyde **33**.



Scheme 13. Access to quaternary and tertiary aldehydes from α,β -unsaturated ketones.

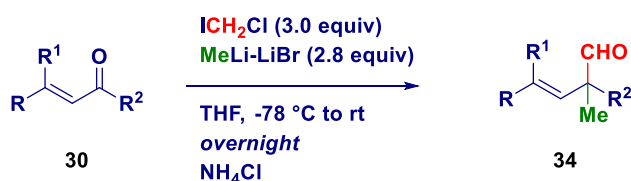
Modulating the different conditions for the homologating carbenoid formation event was found to be critical for the chemoselectivity and the outcome of the transformation. Generating the lithium carbenoid with MeLi-LiBr from chloriodomethane, electrophilic methyl iodide arises from lithium halogen-exchange, thus being the source for the methyl unit in the quaternary α -methyl aldehyde **34**. Switching to TMSCH₂Li-LiBr as the lithiating agent to generate chloromethyl lithium carbenoid, a non electrophilic TMSCH₂I is generated, giving the possibility for a functionalization with an additional electrophile. Indeed, by adding 3 equiv of an electrophile, after generating the LiCH₂Cl carbenoid with TMSCH₂Li-LiBr, it was possible to access in high yields all-carbon quaternary α -functionalized aldehydes **32** chemoselectively. On the other hand, when no additional electrophile

was added to the reaction mixture β,γ -unsaturated α -tertiary aldehydes **33** were obtained after acidic quenching through a one-step homologation-isomerization process. Significantly, the β,γ -unsaturated aldehydes spontaneously isomerized during the work-up and purification procedures to the more stable α,β -unsaturated ones **35**. Reaction with deuterium labelled carbenoids and/or methyllithium were crucial in order to ascertain the enolate-type reaction mechanism.³⁸

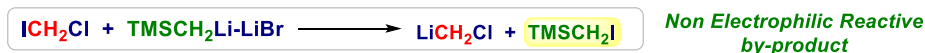
Carbenoid generation event



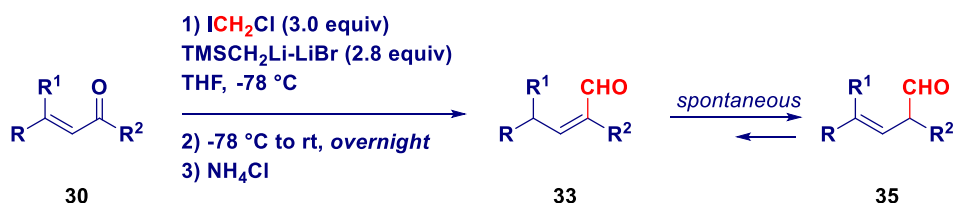
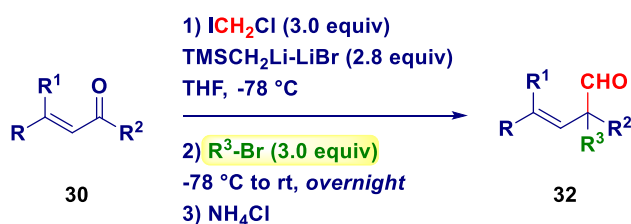
Homologation / α -Derivatization



Carbenoid generation event



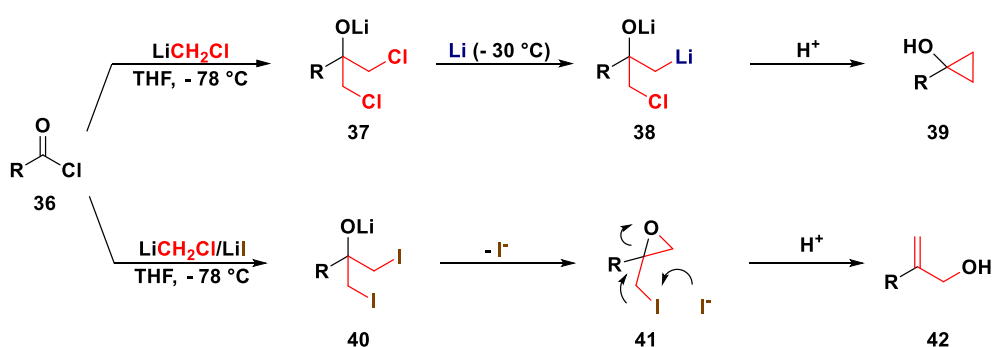
Homologation with or without α -Derivatization



Scheme 14. Synthesis of quaternary and tertiary aldehydes from α,β -unsaturated ketones.

5.2 Carboxylic acid chlorides

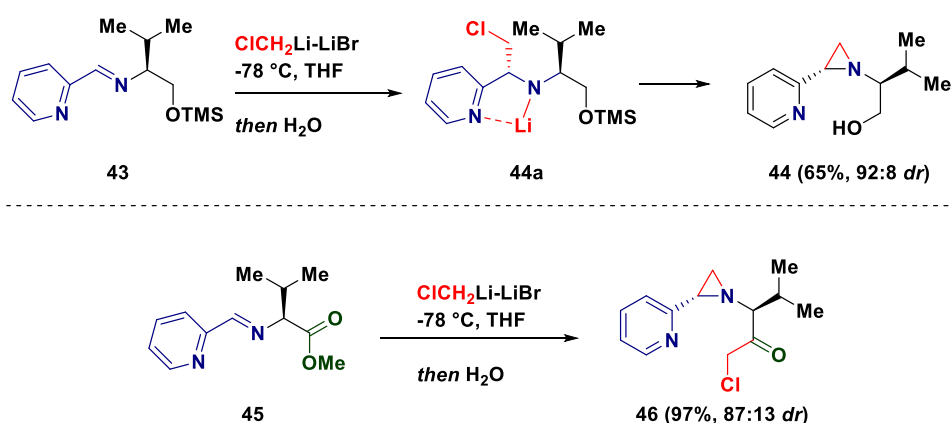
Barluenga and coworkers³⁹ reported the homologations of acyl chlorides **36** with chloromethylithium for the preparation of cyclopropanols **39** and allylic alcohols **42**. Double addition of chloromethylithium to the highly reactive carbonyl of the acyl chloride furnishes an intermediate alkoxide **37**, which by treatment with Li metal yields the dilithiated species **38**. Acidic quenching gives directly the cyclopropanol **39**. In the presence of lithium iodide, the corresponding iodinated intermediate **40** is formed. The attack of the halide anion on the resulting intermediate epihalohydrine **41**, finally furnishes the allylic alcohol **42**.



Scheme 15. Lithium carbenoid-mediated access to cyclopropanols and allylic alcohols.

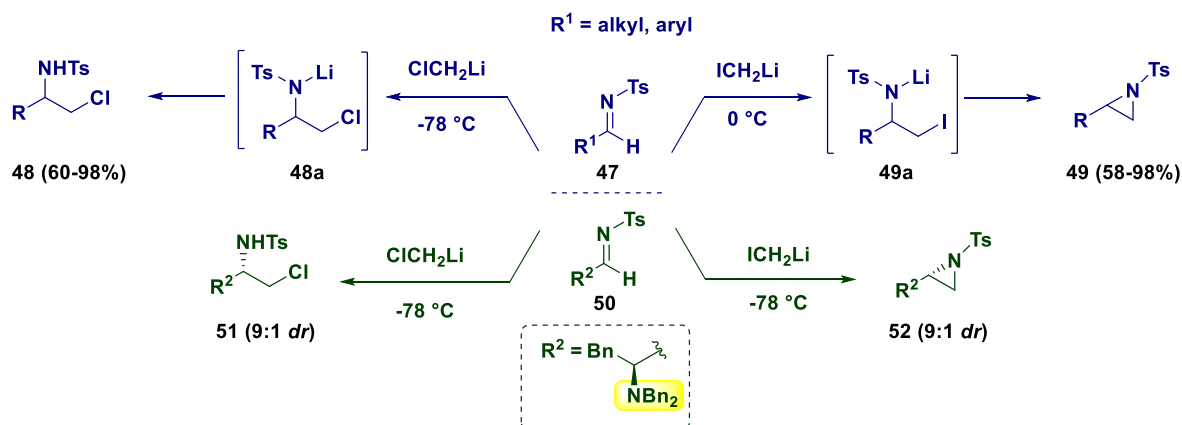
5.3 Imines and their surrogates

Different methylene transfer protocols have been established for the synthesis of aziridines from imines by employing diazomethane, sulfur ylides, dihalomethanes and diethylzinc.⁴⁰ Imines represent good placeholders for the addition of halocarbenoids to access β -haloamines or aziridines. In 2006, Savoia and coworkers described the addition of chloromethylithium to poorly electrophilic imine **43**, derived from 2-pyridinecarboxaldehyde and (*S*)-valinol, to access diastereopure aziridine **44**.⁴¹ The formed β -haloamine **44a** spontaneously cyclized to form the aziridine **43** upon raising of temperature. The presence of the 2-pyridinyl moiety, which chelate the incipient carbenoid and enhances its nucleophilic character, thus allowing the attack to the poorly electrophilic imine carbon, resulted essential to accomplish the transformation. Less nucleophilic zinc carbenoid proved to be unreactive, while the employment of iodomethylithium resulted in complex mixtures. In the presence of an ester functionality as in compound **45** lack of chemoselectivity was observed and the homologation occurred on both electrophilic sites.



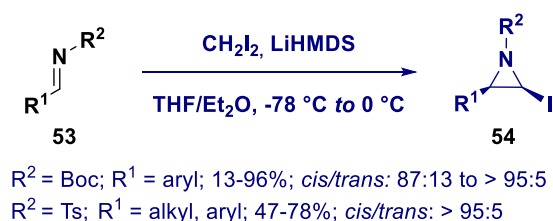
Scheme 16. Savoia's carbenoid-mediated 2-aziridination of 2-pyridinimines.

Concellòn and coworkers⁴² showed how the electrophilicity of the azomethinic carbon is enhanced by the presence of an electron-withdrawing group on the imine nitrogen. *N*-tosylaziridines **49** were rapidly prepared in one pot *via* the addition of iodomethyl lithium to sulfonyl-protected imines **47** at 0 °C. Switching to chloromethyl lithium, β -chloroamines **48** were obtained at -78 °C upon acidic quenching. The divergent synthesis of *N*-tosylaziridines with LiCH₂I and β -chloroamines with LiCH₂Cl can be explained by the different tendency of the resulting iodinated or chlorinated lithium amide to undergo a spontaneous heterocyclization. The presence of a sterically hindered *N,N*-dibenzylamino group at the α position to the imine carbon (imines **50**) allows the divergent access to the two corresponding products with stereocontrol.



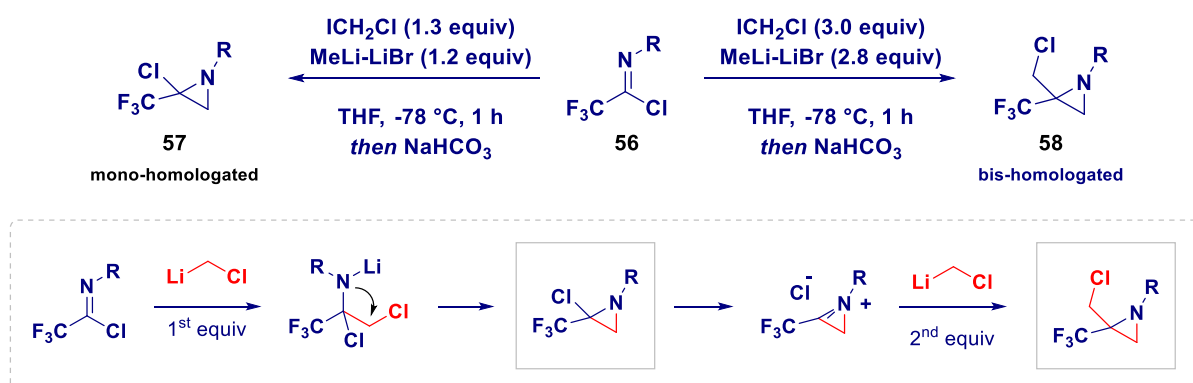
Scheme 17. Divergent access to aziridines or β -chloroamines *via* carbenoid addition to imines.

In 2012, Bull⁴³ described the preparation of *N*-Boc and *N*-tosyl protected α -iodoaziridines **54**, by adding diiodomethylithium, generated via deprotonation of diiodomethane with LiHMDS at $-78\text{ }^{\circ}\text{C}$, to protected imines **53**. The one pot transformation proceeds with high *cis*-selectivity.



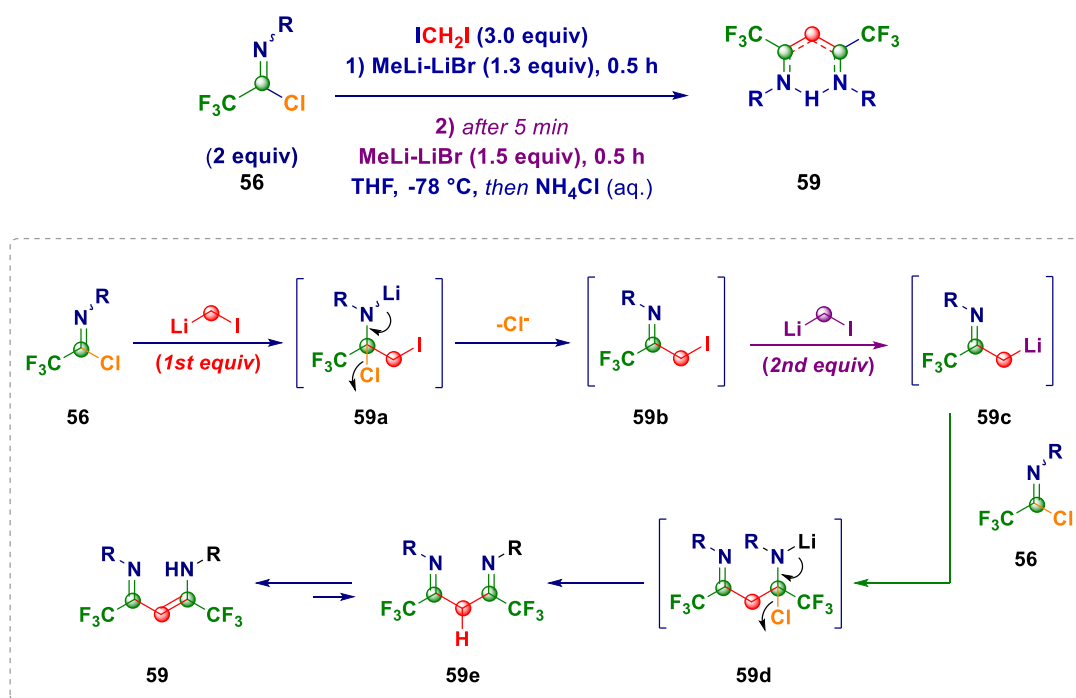
Scheme 18. Synthesis of iodoaziridines with diiodomethylithium.

Pace's group reported an assembly of unprecedented quaternary all-substituted α -halo- α -trifluoromethylaziridines **57** and α -halomethyl- α -trifluoromethylaziridines **58**, starting from trifluoroacetimidoyl chlorides (TFAICs) **56**.⁴⁴ Through a single synthetic operation, a lithium-halocarbenoid-mediated mono- or bis-homologation of trifluoroacetimidoyl chlorides **56** could be accomplished under full chemocontrol, by tuning the reaction stoichiometry: α -chloroaziridines **57** were obtained as the sole reaction product when using 1.2 equivalents of LiCH_2Cl under standard homologations conditions. The increase of the lithium halocarbenoid loading to 2.8 equivalents allowed two simultaneous functionalizations to the bis-homologated product, α -halomethyl- α -trifluoromethylaziridines **58**: following the generation of the tetrahedral intermediate formed upon the addition of the first equivalent of the lithium halocarbenoids, an internal nucleophilic displacement takes place leading to the formation of the mono-homologated chloroaziridine, susceptible of a second functionalization event to give an α -halomethylaziridine in the presence of an excess of the homologating agent if no quenching is realized.



Scheme 19. mono- and bis-homologation of trifluoroacetimidoyl chlorides.

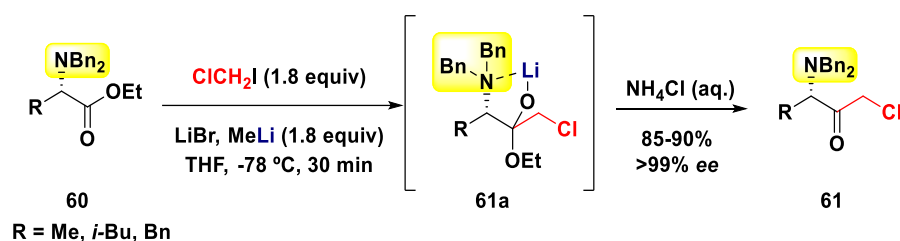
Generating iodomethyl lithium carbenoid from diiodomethane via lithium-halogen exchange with MeLi-LiBr it was possible to achieve a formal insertion of a carbon atom bridging two TFAICs, resulting in the one-step assembly of bis-trifluoromethylated- β -diketiminates **59**.⁴⁵ Mechanistically, the nucleophilic addition of LiCH₂I to TFAIC, leads to the formation of the tetrahedral intermediate **59a**, which collapse to a not isolable α -iodomethylimine **59b**, metalated through subsequent addition of organolithium reagent to give α -iminomethyl lithium **59c** which reacts with the second TFAIC finally yielding the homologated product **59**, presenting two trifluoromethyl-containing imine moieties connected to the inserted carbon. Iodomethyl lithium carbenoid displayed a dual role, acting as the delivery agent the C1-synthon (homologation) to TFAIC and as the lithiating agent for the iodomethylimine to give the reactive α -iminomethyl lithium.



Scheme 20. Assembly of bis-Trifluoromethyl- β -diketiminates from trifluoroacetoimidoyl chlorides with LiCH₂I.

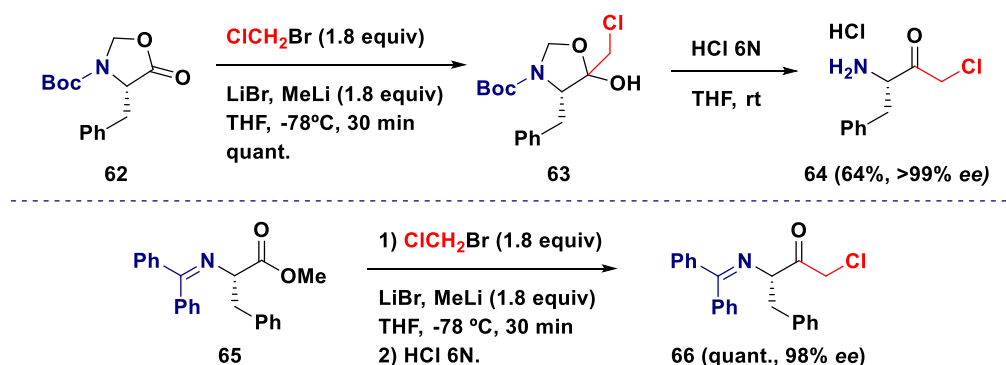
5.4 Esters

Regardless the organometallic reagent is employed in excess or not, a tertiary alcohol is obtained from an ester via a double addition of the carbenoid. As documented by Barluenga^{31,46} in the early 1990's, the presence of a disubstituted α -amino group guarantees high chemocontrol, enabling an internal coordination of the lithium alkoxide with the electron-rich nitrogen within the resulting tetrahedral intermediate, which prevents the elimination of the alkoxide group, thus avoiding the double addition of the carbenoid. The tetrahedral intermediate **61a** formed upon the addition of carbenoid to ester **60** is stable under the reaction conditions, giving, after acidic quenching, the corresponding α -haloketone **61** even when the organometallic species is used in excess.



Scheme 21. Use of α -*N*-dibenzyl esters to access α -haloketones.

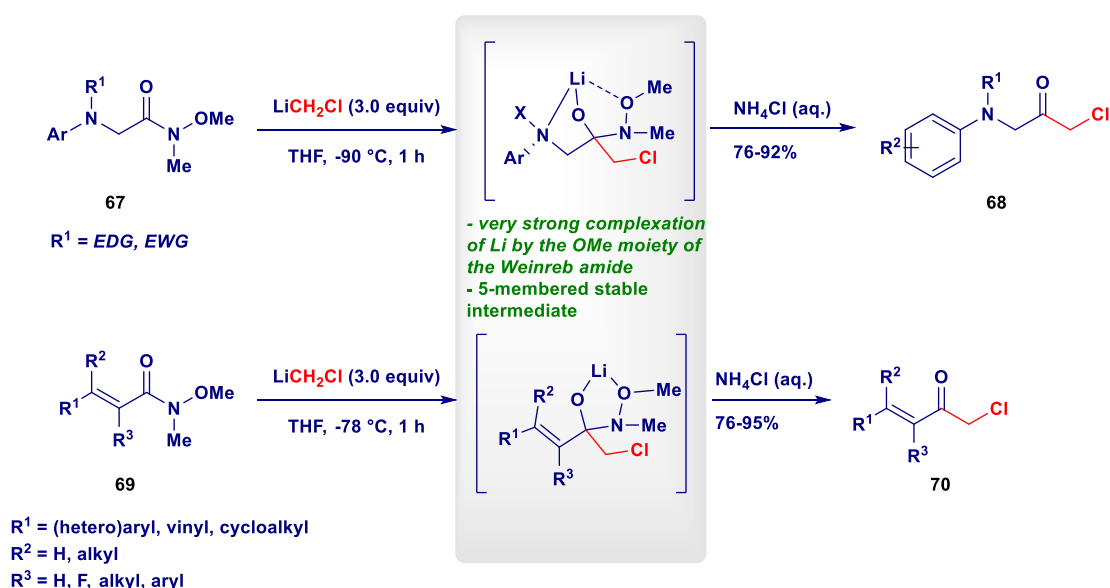
On the other hand, as shown by the group of Izawa, the presence of a non fully substituted amino or amido group inhibits the homologation reaction, because the basic carbenoid abstracts the hydrogen rather than attacking the ester functionality. The employment of *N*-protected 3-oxazolidin-5-ones **62** represented a solution to overcome this limitation, since this species can be easily chloromethylated to give the intermediate **63**, being converted into the desired chloroketone **64** after deprotection by acidic treatment. The same group reported the chemoselective chloromethylation of *N*-imine protected amino acids esters **65** to give compound **66**.



Scheme 22. Izawa's homologation of esters to access α -amino- α' -chloroketones.

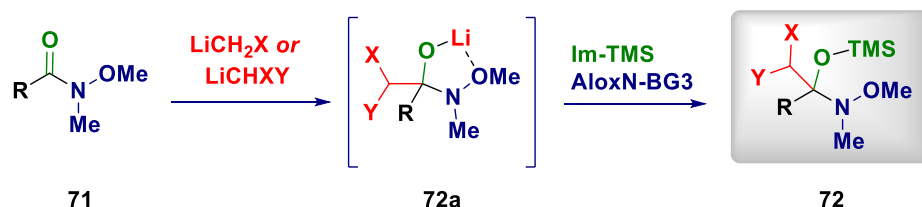
5.5 Weinreb Amides

Since seminal work by Weinreb, *N*-methoxy-*N*-methyl amides, now called Weinreb amides, emerged and gained wide importance as effective acylating manifolds for various organometallic reagents.⁴⁷ Even when using a large excess of organometallic species, these substrates yield cleanly and exclusively ketones and no overaddition occurs. The effective chelation of metal ion between carbonyl oxygen and OMe group provides a 5-membered stable intermediate which collapse after aqueous acidic work up, leading to the formation of the new C-C bond. The *N*-alkoxy group enhances the electrophilicity of the amide carbonyl C-atom and increase the stability of the intermediate, being an additional coordination site. In recent years Pace and coworkers reported the homologation of Weinreb amides with lithium carbenoids to give synthetically versatile α -haloketones including α -amino (**68**)²² and α,β -unsaturated (**70**)⁴⁸ ones. The stability of the tetrahedral intermediate prevents the second addition of the nucleophilic organometallic species and full chemocontrol is observed in the case of unsaturated substrates **69**. The vinyl fragment conjugated with the carbonyl group represents an additional electrophilic site, being a Michael acceptor. Remarkably, cyclopropanation which is known to be accomplished by using lithium carbenoids under Corey-Chaykovsky conditions, did not occur and, thus, the double bond remained untouched during the process. Moreover, the reaction of lithium halocarbenoids with Weinreb amides presenting further sensitive functionalities, such as esters or potentially exchangeable aromatic iodide, afforded only the target α -haloketones. The protocol is also not dependent on the employment of different halomethyl fragment (CH_2X , X = Cl, Br or I).



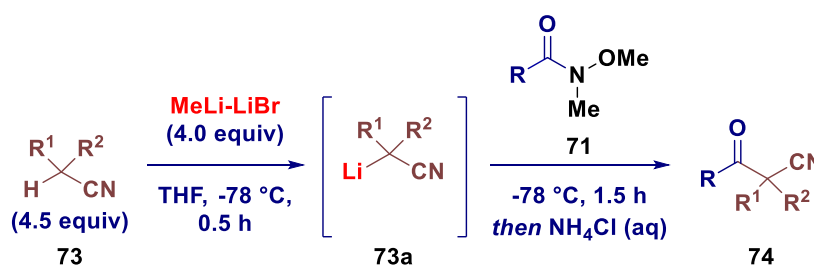
Scheme 23. Weinreb amides for preparing α -haloketones.

The stability of the tetrahedral intermediates **72a** formed upon the addition of lithium (di)halocarbenoids to Weinreb amides **71** was demonstrated by their isolation as *O*-TMS protected hemiaminals **72**.⁴⁹ The commercially available *N*-TMS-imidazole, presenting remarkable oxophilicity and sufficient stability to avoid the elimination of the *N*-methyl-*N*-methoxy fragment, was found to be the ideal silylating trapping agent. The isolation and full characterization of this labile species required particular work-up and purification techniques. Basic aqueous treatment (NaHCO₃ 5%) and extraction with Et₂O followed by purification on Brockmann III grade neutral alumina allowed the isolation of the silyl protected intermediate. Recording the NMR spectra in CDCl₃ the product was transformed into the corresponding ketone, presumably because of the acidity of this deuterated solvent. Remarkably, C₆D₆ solutions of these intermediates showed an excellent stability up to 6 months at -20 °C.



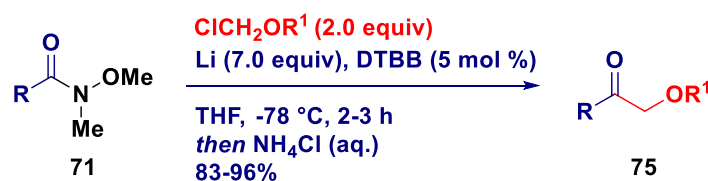
Scheme 24. Mechanism and isolation of the tetrahedral intermediate as *O*-TMS protected hemiaminals.

Given the excellent nucleophilicity of nitrile-type carbanions, Pace's group documented how Weinreb amides **71** are acylating agents also for lithiated acetonitriles species **73a**. The employed cyanomethylolithiums **73a** shows higher intrinsic stability when compared to halocarbenoids and so the use of Barbier-type conditions is not required. Thus, the generation of lithiated acetonitriles followed by the trapping with variously functionalized Weinreb amides affords α -cyanomethylketones (β -oxonitriles) **74**. Furthermore, by simply selecting the proper R¹R²LiCN carbanion **73a** it is possible to access multisubstituted cyanomethylketones.



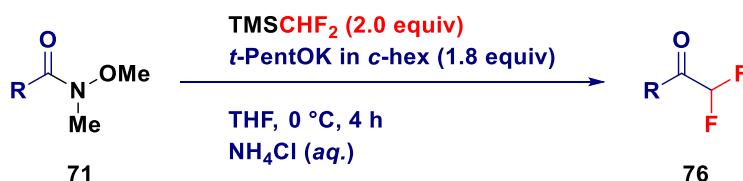
Scheme 25. Synthesis of α -cyanoketones from Weinreb amides and cyanomethylolithium.

Pace's investigation in this area continued with the preparation of α -oxygenated ketones **75**. The Yus'arene catalyzed reductive lithiation of α -chloromethyl alkyl ethers^{28a,50} generates α -oxygenated methyllithium species (LiCH_2OR), which can be employed in a direct homologation process towards Weinreb amides for the synthesis of α -oxyketones **75**.⁵¹ The process showed broad scope in terms of Weinreb amides as acylating agents and carbanions used: both aromatic and heteroaromatic Weinreb amides, as well as aliphatic and α,β -unsaturated ones underwent nucleophilic addition of this oxygenated organolithium species; enantiopure Weinreb amides could be employed as starting material without any loss of optical purity; the generation of LiCH_2OMe and its homologue LiCH_2OEt allowed to assemble α -alkoxymethyl ketones in very good yield; the scope of the methodology could be expanded employing non alkyl type chloromethyl ethers for the synthesis of α -phenoxyethyl ketones; both the enantiomeric forms of (+)- and (-)-chloromethyl menthyl ethers could be employed in order to generate optically active α -oxygenated lithium species that smoothly and cleanly added to the Weinreb amide with full transfer of the stereochemical information.



Scheme 26. Synthesis of α -oxyethylketones from Weinreb amides.

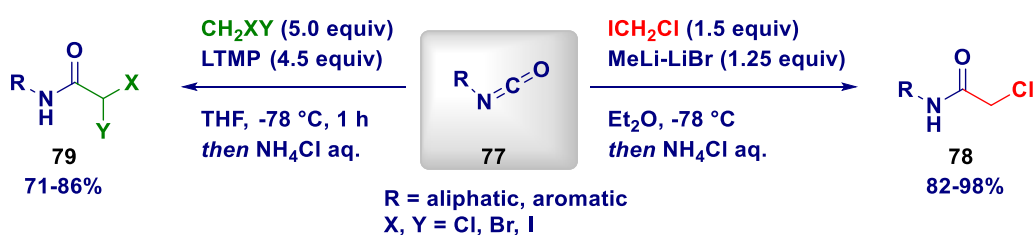
A one-step homologation of widely substituted Weinreb amides into α,α -difluoromethylketones **76** with nucleophilic difluoromethyl carbanion, generated from the commercially available and easy to manipulate (difluoromethyl)trimethylsilane (TMSCHF_2) upon proper activation with potassium *tert*-amylate in THF at 0°C , was reported by Pace's group.⁵² Excellent tolerance of sensitive functionalities and complete retention of the stereochemical information contained in enantioenriched Weinreb amides were observed.



Scheme 27. Synthesis of α,α -difluoromethylketones from Weinreb amides.

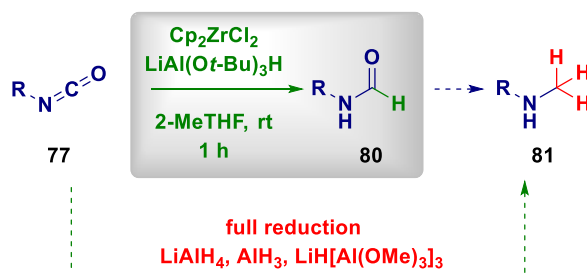
5.6 Heterocumulenes

The nucleophilic addition of functionalized organometallic reagents to iso(thio)cyanates represents an attractive tool for the preparation of amide-type compounds not always efficiently reachable *via* classical chemistry. In recent years, seminal studies by Gilman⁵³ and Worrall⁵⁴ in the 1920s dealing with the reaction of organometallic reagents to heterocumulenes (*e.g.* isocyanates or isothiocyanates), experienced a renewed interest for the construction of the (thio)amide linkage, as indicated in reports by the groups of Bode,⁵⁵ Molander,⁵⁶ Kerr⁵⁷ and Pace.⁵⁸ In particular, the excellent electrophilicity of the heterocumulene's *sp* carbon, as also recognized in recent work by Martin on metal-catalyzed amidations,⁵⁹ together with the minimal (if not absent) electronic and sterical influence displayed by the substituent on nitrogen, make them superb placeholders for (thio)amides. Significantly, nowadays extensive series of both isocyanates and isothiocyanates are available from common chemical suppliers or, alternatively can be prepared through standard methods. Pace's group reported a high yielding chemoselective preparation of *N*-substituted α -haloacetamides **78**⁶⁰ and α,α -dihaloacetamides **79**²⁴ through the addition of halo- and dihalocarbenoids to isocyanates **77**, respectively. The stereochemical information embodied in the starting isocyanates is fully transferred to the products. Dihalomethyl lithium carbenoids were generated via deprotonation of dihalomethanes with LTMP under Barbier conditions, with the exception of diiodomethyl lithium, generated with LiHMDS according to the Bull's protocol.



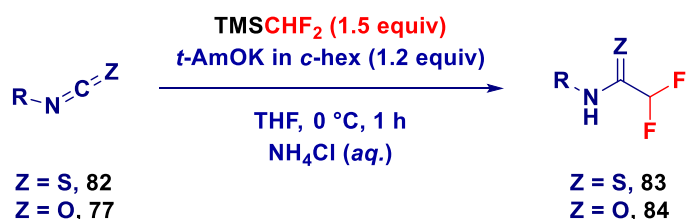
Scheme 28. Synthesis of α -haloamides from isocyanates and lithium carbenoids.

In 2016, by switching to a hydride nucleophile, the group also documented the highly chemoselective partial reduction of isocyanates **77** to the corresponding formamides **80** realized under mild reaction conditions⁶¹ in the presence of the Schwartz reagent generated *in situ* according to the Snieckus' procedure.⁶² Despite the method does not involve a lithium carbenoid it is worth to mention here this transformation realized on the same class of electrophiles, considering also the further developments and results obtained employing analogous isothiocyanates presented during the course of this thesis.



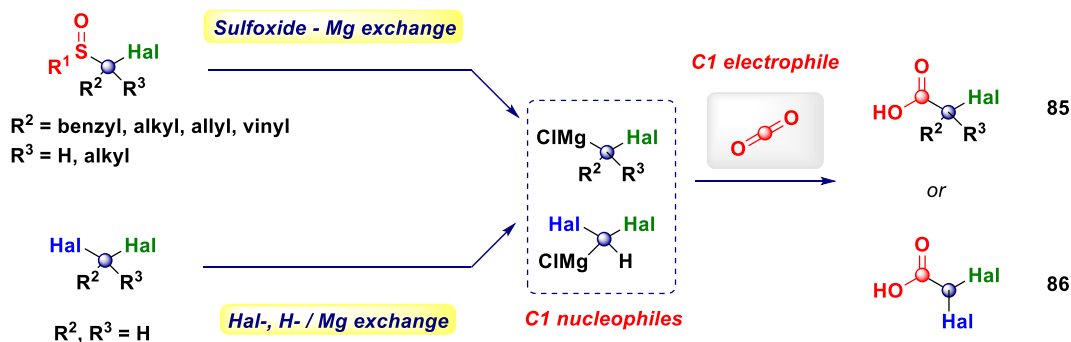
Scheme 29. Schwartz reagent-mediated partial reduction of isocyanate to formamides.

Employing the same conditions described for the synthesis of α,α -difluoromethylketones from Weinreb amides, Pace and coworkers reported the generation of difluoromethyl carbanion from TMSCHF_2 in the presence of potassium *tert*-amylate for the straightforward preparation of α,α -difluoromethyl thio- **83** and oxoamides **84** from isothiocyanates and isocyanates, respectively.⁶³



Scheme 30. Difluoromethylative homologation of iso(thio)cyanates to access α,α -difluoro(thio)amides.

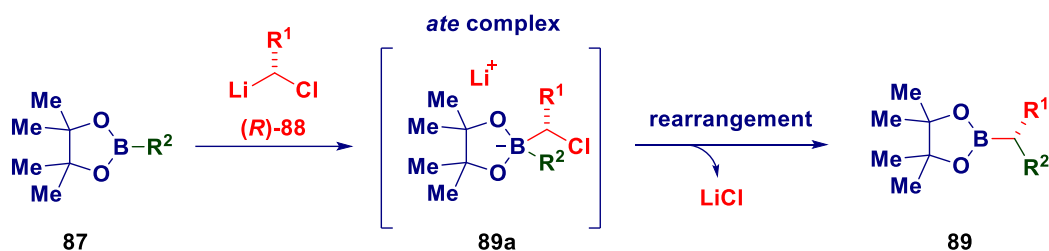
A straightforward access to α -halo and α,α -dihalo carboxylic acids **85** and **86** through the homologation of carbon dioxide with stable magnesium carbenoids, generated *via* magnesium-sulfoxide exchange was reported by the same group in 2018.⁶⁴ The use of more stable – but less nucleophilic – magnesium carbenoids allowed to overcome the limitations pointed out in early studies by Köbrich with lithium carbenoids. When using enantiopure magnesium carbenoids inversion of configuration at the carbon atom was noticed.



Scheme 31. Homologation of carbon dioxide with magnesium carbenoids.

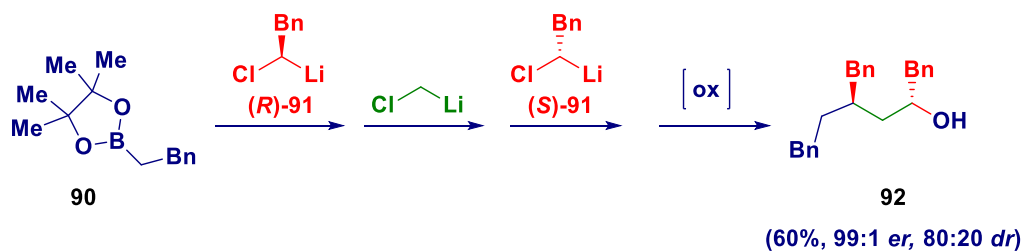
5.7 Boron electrophiles

In 1980, Matteson reported the first homologation of boronic esters **87** with lithium carbenoids.⁶⁵ The homologation of boronic esters featuring a chiral diol consists in a two steps sequence: 1) addition of the LiCH_2Cl carbenoid to give an (α -haloalkyl)boronic ester; 2) Reaction with a Grignard reagent. These processes proceeded with high level of stereocontrol. In 2013, Blackmore exploited the Matteson homologation to accomplish a stereocontrolled homologation of boronic esters.^{25a,25b,66} The enantioenriched α -chloroalkyllithium carbenoids **88** are generated *in situ* via lithium-sulfoxide exchange starting from a diastereopure α -chloroalkyl sulfoxide.⁶⁷ The addition of the carbenoid to the boron atom leads to the formation of an ate complex **89a**, which rearranges into the homologated structure **89** by raising the temperature.



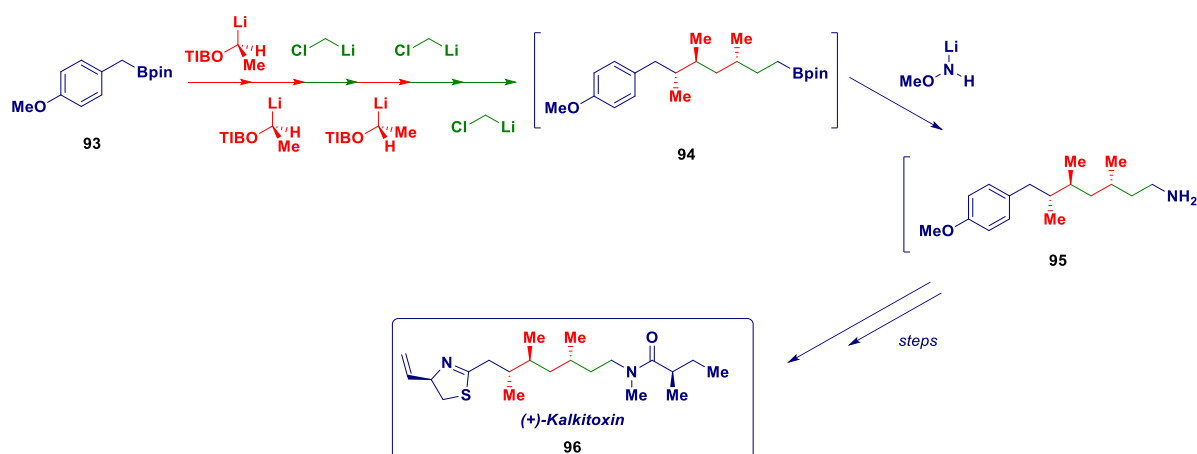
Scheme 32. Blakemore's stereocontrolled homologation of boronic esters.

The concept of the Matteson homologation could be applied in iterative homologation processes. The insertion of the enantioenriched chiral carbenoid into organoboron substrates (in particular, pinacol boronates) gives homologated products susceptible of further cycles of stereospecific reagent controlled homologation (StReCH), allowing the programmed assembly of polysubstituted alkyl moieties.^{25b} Additionally, enantiopure alcohols can be finally obtained after oxidation of the C-B bond.



Scheme 33. Blakemore's iterative stereospecific reagent controlled homologation (StReCH).

Aggarwal reported the iterative homologation processes for the efficient stereocontrolled synthesis of the two natural products (+)-Kalkitoxin **96** and (+)-Hydroxyphthioceranic acid, using chiral lithiated benzoate esters and chloromethyl lithium.⁶⁸ In the case of (+)-Kalkitoxin, six iterative homologations were performed on the commercially available boronic ester **93**, before transforming the C-B bond into the desired C-N bonds of compound **95**, without any purification of the intermediate required.



Scheme 34. Aggarwal's assembly-line synthesis of (+)-kalkitoxin.

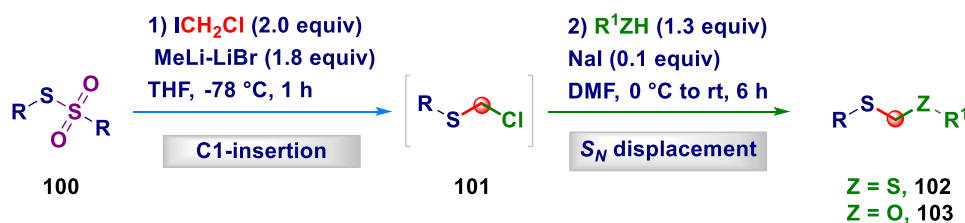
5.8 Heteroatom electrophiles

Pace employed an efficient chemoselective bromomethyl lithium-mediated homologation of disulfides **97** and diselenides **98** to access dithioacetals and diselenoacetals **99**.⁶⁹ The procedure could be employed for the homologation of an asymmetric disulfide and diselenide. The addition of the halomethyl unit yields a stable α -halomethyl thiosulfide intermediate which undergoes to nucleophilic displacement (promoted by the addition of TMSCl) by the mercapto anion (RS⁻) released during the first homologation step. Recalling the Matteson homologation of boronic esters or the epoxidation of carbonyl compounds, the halogen of the carbenoid is present only at the intermediate level, but not in the final products.



Scheme 35. Homologation of disulfides and diselenides with bromomethyl lithium carbenoid.

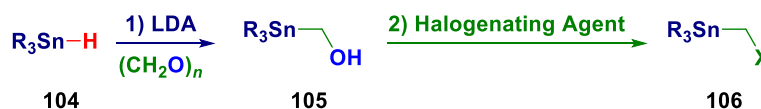
Recently, Pace and coworkers reported a sequential C1-homologation – nucleophilic substitution to synthesize unsymmetrical dithioacetals **102**⁷⁰ and oxothioacetals **103**⁷¹ starting from thiosulfonates **100**. The rational use of these electrophilic sources for the (isolable) intermediate α -halothioether **101**, generated upon addition of the homologating lithium carbenoid, allowed the functionalization with an externally added thiols or phenol to give dithioacetals and *O,S*-oxothioacetals, respectively. The homologation of thiosulfonates furnishes a sulfonate group ($-\text{SO}_2\text{R}$) presenting a tamed nucleophilic character when compared with the RS^- anion generated from disulfide as just described above and therefore a reduced tendency to undergo nucleophilic displacement of the formed α -chlorothioether, allowing to realize the substitution with a second nucleophile added to the reaction mixture at a later stage.



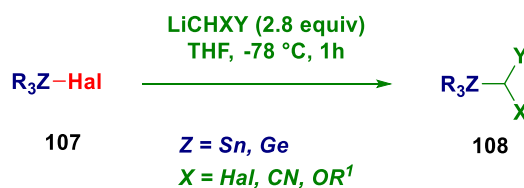
Scheme 36. sequential C1-homologation – nucleophilic substitution of thiosulfonates.

In 2018 Pace's group reported a direct nucleophilic substitution of halostannanes and halogermanes **107** with lithium carbenoids to obtain in a single operation α - and α,α -disubstituted methyl derivatives **108**.⁷² This homologative transformation shows a higher level of efficiency when compared to the commonly used Appel-type protocol starting from a tin hydride **104**⁷³ or low efficient homologation strategies dealing with the use of diazomethane or zinc carbenoid.⁷⁴

1. Two-Steps Appel-type Approach

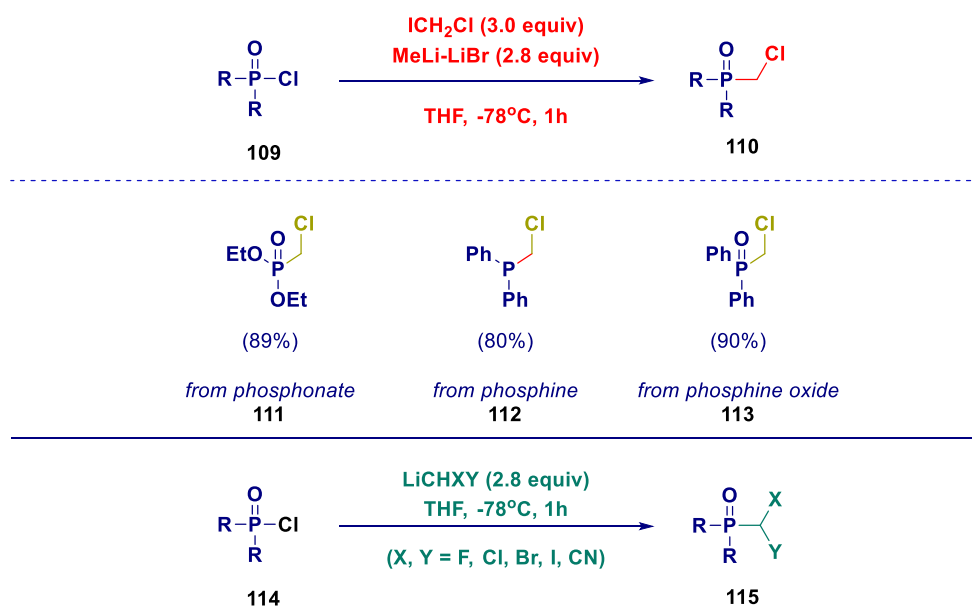


2. One-step Homologation Approach



Scheme 37. Homologation of halostannanes and halogermanes.

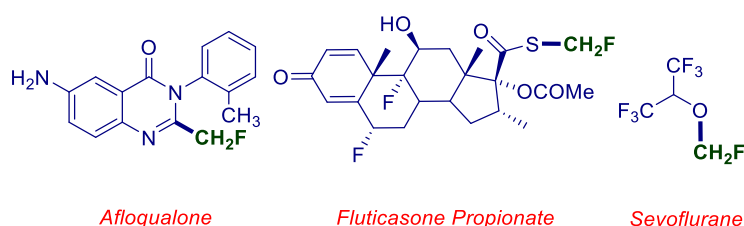
The direct transfer of different α -substituted methyllithium reagents (especially halocarbenoids) to chlorinated phosphorous electrophiles **109** in various oxidation state (phosphonates **111**, phosphines **112** and phosphine oxides **113**) *via* nucleophilic substitution on the P-Cl linkage was recently described by Pace's group to access geminal P-containing methanes **110** and **115**.⁷⁵



Scheme 38. Homologation of phosphorous electrophiles.

6. Fluoroiodomethane: versatile reagent for transferring the CH₂F unit

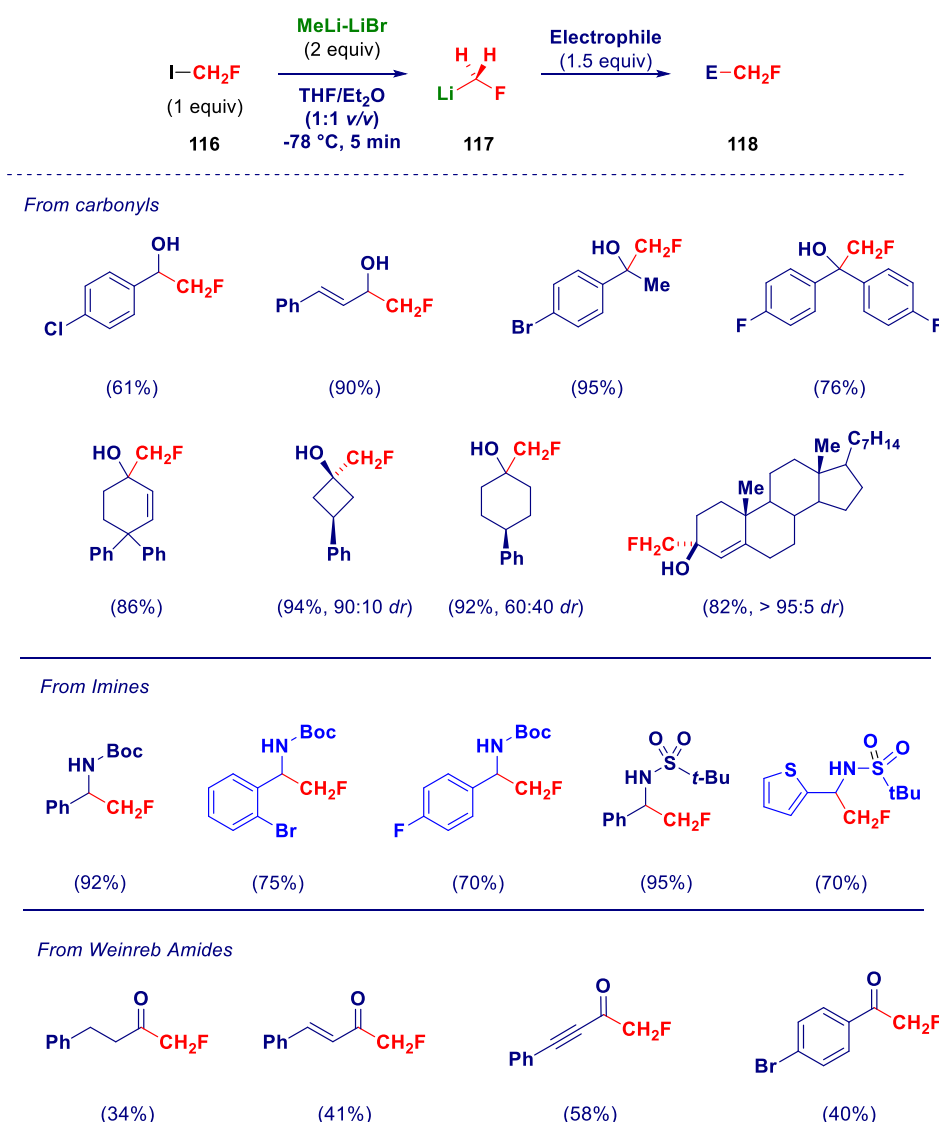
The introduction of fluorine containing motifs into organic arrays to modulate their physicochemical parameters represents an established tool in modern synthetic medicinal chemistry. Due to the isosterism existing between hydrogen and fluorine, the installation of this halogen could lead to beneficial effect in terms of metabolic stability, acute toxicity, bioactivity.⁷⁶ About 25% of approved drugs and agrochemicals feature a fluorine atom in their organic skeleton.^{76a,77} In this context, in the last years fluoroiodomethane (FIM) emerged as a highly versatile and valuable reagents to accomplish several transformations to finally deliver the monofluoromethyl unit.⁷⁸ Its relatively high boiling point (52 °C) and its commercial availability render it highly manipulable and attractive for the synthetic purpose. The development of monofluoromethylation strategies (in nucleophilic or electrophilic regime or in transition metal-catalyzed processes) with FIM overcomes the requirement of monofluoromethylating agents with no immediate access, whose employment is often associated with a nonoptimal atom economy.



Scheme 39. Approved drugs featuring a -CH₂F motif.

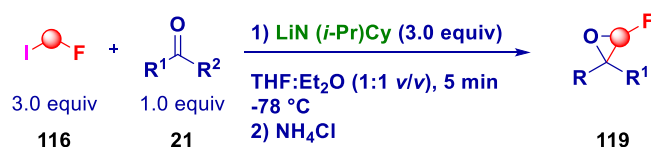
6.1 Fluoroiodomethane as precursor of fluorinated carbenoids

Cognizant of the well-established applicability of dihalomethanes as carbenoid precursors, Pace and Luisi identified precise reaction conditions for the generation and synthetic exploitation of a “fleeting” lithium fluorocarbenoid **117** from fluoroiodomethane **116** *via* a fast iodine-lithium exchange – under Barbier conditions - carried out with MeLi-LiBr in a 1:1 mixture of THF:Et₂O at -78 °C. The employment of such a labile fluoromethyl lithium species allowed an unprecedented one-pot direct and straightforward nucleophilic fluoromethylation of a plethora of carbon electrophiles, including carbonyls, imines and Weinreb amides. The protocol proved to be chemoselective in the presence of sensitive functionalities. Moreover, good stereocontrol was observed. The versatility of the method is showcased by more than 50 examples encompassing fluorinated alcohols, β-fluoroamines and α-fluoroketones, obtained in good to excellent yields in a single synthetic operation.⁷⁹



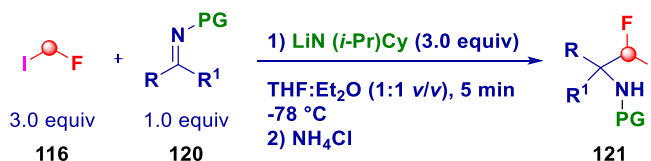
Scheme 40. Direct nucleophilic fluoromethylation with fluoromethyl lithium.

Switching the carbenoid formation event to a deprotonation process of fluoroiodomethane **116** with a lithium amide base, Pace and Luisi reported the formation of a bivalent fluoroiodomethyl carbanion, suitable for introducing the CHIF fragment into an electrophile.⁸⁰ The different reactivity of the C-I and C-F bonds allowed to design a concerted homologation/ring closure reaction leading to α -fluorinated three-membered rings, starting from widely available carbonyl-like precursors and fluoroiodomethyl lithium under internal quenching conditions. After extensive optimization study lithium *i*-propyl-cyclohexyl amide was found to be optimal for the purpose, giving the desired α -fluoroepoxides **119** chemoselectively in excellent yields and moderate to very good diastereoselectivity, starting from diaryl- and alkyl-aryl ketones **21**. Additionally, a biologically relevant steroidal analogue was amenable for the transformation.

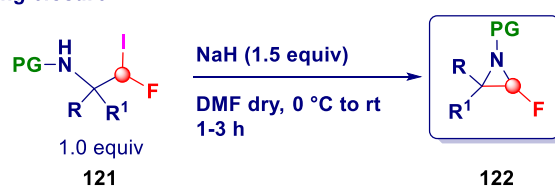


Scheme 41. Synthesis of α -fluoroepoxides *via* homologation/ring closure of ketones.

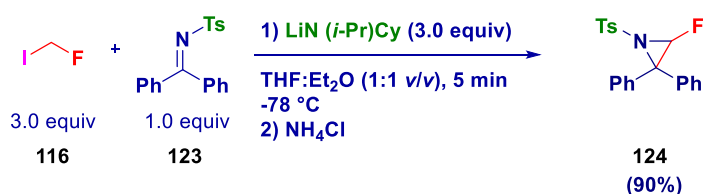
Given the reactivity analogy between ketones and imines, the tactic was extended towards the synthesis of α -fluoroaziridines **122**, accessible *via* a two steps process, because of the lower propensity of lithiated fluoroiodoamides to undergo intramolecular cyclization. *N*-activated imines **120** (including aldimines) were susceptible to the chemoselective attack of the fluoroiodomethyl lithium species, giving the corresponding β -fluoroiodoamine **121** in very high to excellent yields. The ring closure could be then triggered in the presence of NaH in DMF, affording the desired α -fluoroaziridines **122** with high efficiency. It is worth mentioning that an *N*-Sulfonyl-protected ketimine **123** underwent a smooth homologation ring-closure sequence, giving the final α -fluoroaziridines **124** in 90% yield.



Base-mediated ring closure

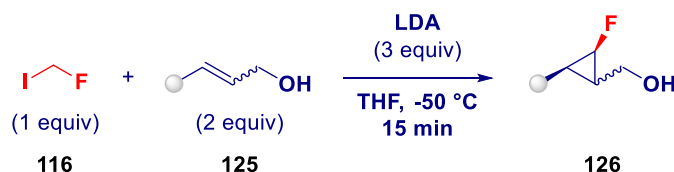


Direct homologation-ring closure



Scheme 42. Synthesis of α -fluoroiodoamines from protected imines with fluoroiodomethyl lithium and subsequent ring closure *en route* to α -fluoroaziridines.

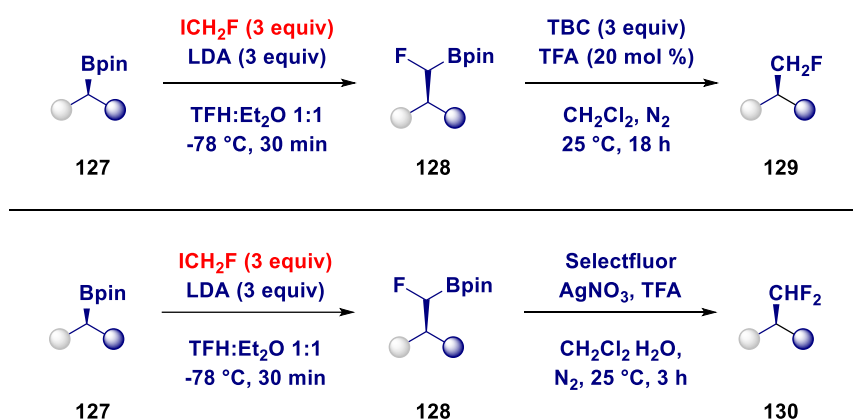
Exploiting an unprecedented electrophilic behavior of the same fluoroiodomethyl lithium carbenoid, by properly tuning the reaction conditions, Luisi reported an efficient direct chemo- and stereoselective fluorocyclopropanation of allylic alcohols **125**.⁸¹ The process occurs with absolute preservation of the enantiopurity of the starting material. Electron-donating groups and halogens, as substituents of the aromatic ring, were tolerated. In contrast to that, the presence of electron-withdrawing groups affected the cyclopropanation process: no reaction was observed in the presence of a NO₂-substituent while a CF₃-group was tolerated giving the product in a modest 15% yield although as a single diastereoisomer. The use of conjugated allylic alcohols resulted in a high chemo- and stereoselective reaction. Cyclic allylic alcohol led to the desired product in reasonable yield although with different stereocontrol. The reaction with allylic ethers resulted to be unfruitful, as well as the one with cinnamic acid, cinnamyl alcohol, homoallylic alcohols, propargylic alcohol and styrenes, ruling out the involvement of a carbolithiation sequence. Moreover, despite an alcohol would be expected to be incompatible with organolithium species, the hydroxyl group at the allylic position is an essential structural requirement for the process.



Scheme 43. Stereoselective fluorocyclopropanation of allylic alcohols with fluoroiodomethyl lithium.

Recently, Aggarwal reported the divergent and stereospecific reaction of fluoroiodomethyl lithium towards boronic esters **127** to give α -fluoro-boronic esters **128**, readily transformed into the corresponding mono- or difluoromethylated derivatives **129** and **130**, via proto- or fluorodeboration, respectively. Enantioenriched boronic esters were transformed into a CH₂F group by a stereospecific Matteson-type homologation (via 1,2-migration) with a monofluorinated carbenoid precursor, followed by removal of the boron functionality.⁸² It was found that using TFA and 4-tBu-cathecyl (TBC) in dichloromethane, the corresponding alkyl fluoride was obtained in high yields, in agreement with a previous work by Renaud, showing how pinacol boronic esters undergo radical-mediated protodeboration by acid catalysed transesterification to a catechol boronic ester followed by oxidation and hydrogen atom transfer. Fluorodeboration of α -fluoro boronic esters with selectfluor and AgNO₃ gives access to a CHF₂ functionality. The homologation-protodeboration and

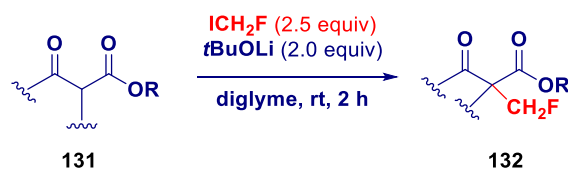
homologation-fluorodeboration sequences, without purification of the intermediate α -fluoro-boronic esters (one being the unique example of an isolated alkyl α -fluoroboronic ester), proved to be general in scope: the process tolerates primary boronic esters bearing different electron-donating and electron-withdrawing elements on the aromatic ring, with no competing addition to potentially sensitive functionalities. In case of enantioenriched secondary or cyclic boronic ester, the reactions were fully stereospecific.



Scheme 44. Stereospecific mono- and difluoromethylation of boronic esters.

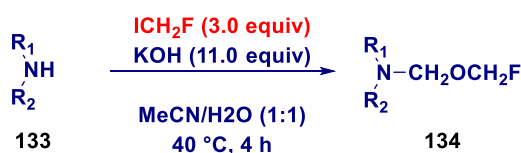
6.2 Electrophilic monofluoromethylation with fluoroiodomethane

In 2019 Yi reported the first example of highly carbon-selective monofluoromethylation of a broad range of β -ketoesters **131** with fluoroiodomethane under mild basic conditions.⁸³ The employment of lithium *tert*-butoxide as a base and diglyme as the solvent was found to be optimal for providing the reported high C/O regioselectivity. A broad range of both tetralone carboxylates and indanone carboxylates reacted with fluoromethyl iodide to afford the corresponding Csp³-CH₂F products in good yields and with high C/O regioselectivities. The reaction was also applied to heterocycled-ketoesters. For the β -ketoesters with a seven-membered ring a decrease in yield and regioselectivity was observed. The less reactive acyclic aryl β -ketoesters were not compatible, affording the C-selective monofluoromethylated products in <10% yield. Further applications of fluoromethyl iodide in the C-monofluoromethylation of malonates were also evaluated and the corresponding products were obtained in high yields and regioselectivities when using Cs₂CO₃ as a base and DMF as the solvent.



Scheme 45. C-Selective monofluoromethylation of β -ketoesters with ICH_2F .

The same group described a fluoromethoxymethylation of indoles, 1*H*-indazoles and other nitrogen heterocyclic compounds **133** with ICH_2F .⁸⁴ A variety of fluoromethoxymethylated nitrogen heterocyclic compounds **134** including indoles, carbazoles, and 1*H*-indazoles were formed. The screening of the reaction conditions indicated as optimal the use of KOH as the base and MeCN/ H_2O (1:1) as the solvent. The protocol showed broad applicability with indoles bearing either electron-donating or electron-withdrawing substituent to form fluoromethoxymethylated products in good yields. Additionally, carbazole derivatives underwent this transformation to afford the corresponding products in good yields. The reaction was then extended to different 1*H*-indazoles derivatives smoothly converted to form *N*-1 fluoromethoxymethylated products in moderate yields with the generation of *N*-2 monofluoromethylated by-product. Mechanism study indicated that this reaction consists of electrophilic monofluoromethylation, rapid hydrolysis and another electrophilic monofluoromethylation.



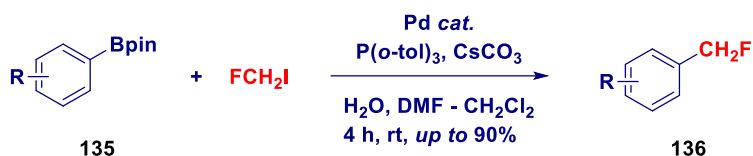
Scheme 46. Fluoromethoxymethylation of nitrogen heterocycles with ICH_2F .

6.3 Transition metal-catalyzed monofluoromethylation with fluoroiodomethane

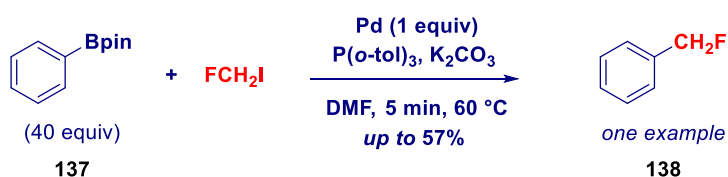
In 2015 Hu described the synthesis of monofluoromethyl arenes **136** by a straightforward and direct palladium-catalyzed monofluoromethylation of arylboronic esters **135** using fluoroiodomethane as the $-\text{CH}_2\text{F}$ donor unit.⁸⁵ The mild reaction conditions and the good functional group tolerance, further showcased in the late-stage monofluoromethylation of a biologically active estrone, make the protocol particularly attractive. The procedure can be considered an improvement of the previous work by Suzuki dealing with the preparation of benzyl fluoride **138** by reacting fluoromethyl

iodide with a large excess of pinacol phenylboronate **137** in the presence of stoichiometric palladium.⁸⁶

Hu (2015)



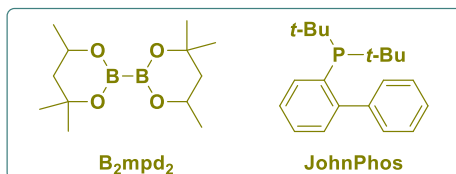
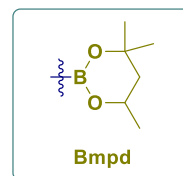
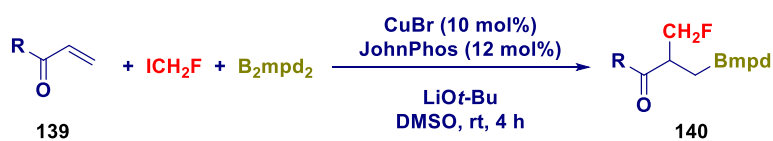
Suzuki (2009)



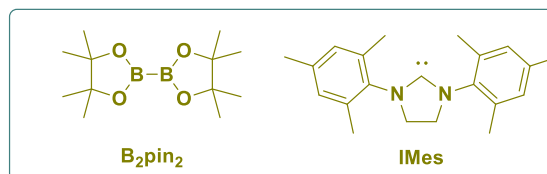
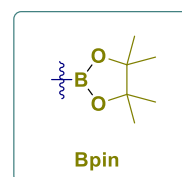
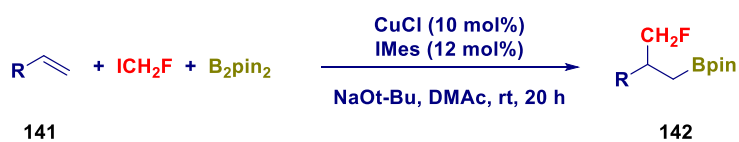
Scheme 47. Palladium-catalyzed monofluoromethylation of arylboronic esters.

A copper-catalyzed borylfluoromethylation of alkenes with fluoromethyl iodide and diboron reagents was reported by Qing in 2019.⁸⁷ This protocol afforded the previously unknown and synthetically useful borylfluoromethylated alkanes in good yields and excellent regioselectivity. Its synthetic potential was illustrated through the derivatization of organoboron products and preparation of a monofluorinated analogue of ibuprofen. A variety of α -fluoromethyl- β -boryl carbonyl compounds **140** were obtained from acrylamides **139** in moderate to high yields as mixture of diastereomers. The use of JohnPhos as a ligand and LiOtBu as base in DMSO showed the best results. After further investigation of the diboron reagents and copper salts, the yield was finally maximized when B_2mpd_2 and CuBr were used as the boron reagent and catalyst, respectively. The borofluoromethylation of styrenes **141** with ICH_2F occurred efficiently using B_2pin as the boron reagent, CuCl as the catalyst, IMes as the ligand, NaOtBu as the base and DMAc as the solvent. Under these optimized conditions, styrenes bearing different substituents were conveniently converted to borylfluoromethylated products **142**.

Borylfluoromethylation of Acrylamides



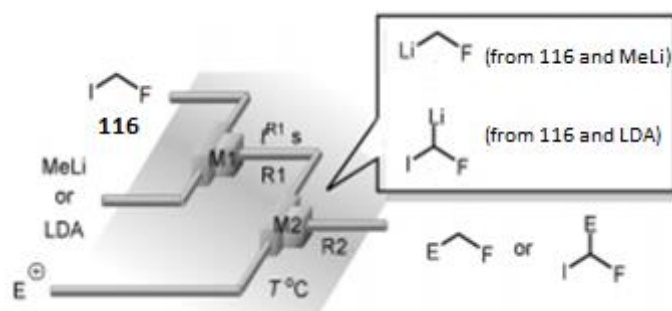
Borylfluoromethylation of Styrenes



Scheme 48. Cu-catalyzed borylfluoromethylation of alkenes.

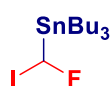
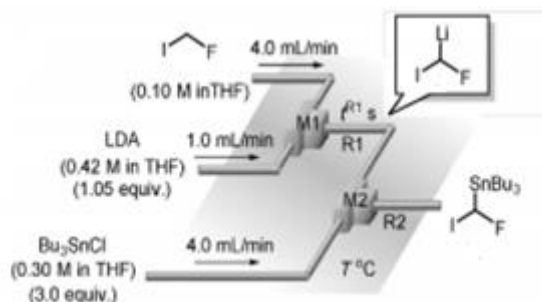
7. Microfluidic techniques in carbenoid chemistry

Flow methodologies became attractive tools in carbenoids chemistry in order to minimize the α -elimination degradation pathway. These strategies allow the effective *external* trapping of the labile short-lived lithiated species formed prior to the addition of the electrophile (non-Barbier conditions). Luisi and coworkers demonstrated how microfluidic systems are effective in the generation of the thermolabile LiCH_2Cl , followed by the trapping with electrophiles at high temperatures (up to $-20\text{ }^\circ\text{C}$).⁸⁸ The methodology – works with different electrophiles from carbonyl compounds, imines, Weinreb amides and isocyanates thus, paralleling the substrate scope observed under classical Barbier-type conditions. Analogously, an external quenching method based on flow microreactors allowed the generation of short-lived fluoro-substituted methyllithium, such as fluoromethyllithium, fluoroiodomethyllithium, and fluorostannylmethyllithium, in the absence of the electrophile and reacted before decomposition.⁸⁹ The described fine tuning of the reaction condition could not be realized in a batch reactor, where the carbenoidic species must be generated in the presence of the electrophile (internal quenching). In all cases examined and described the yields of fluoroketones, obtained through the addition of fluoromethyllithium to Weinreb amides were significantly improved by using the external quenching method in flow microreactors, in contrast to the low yields observed under internal quenching condition in batch. Excellent chemoselectivity was observed in the case of polyfunctional electrophiles. The reaction at a ketone functionality appears to be favored with respect to the Weinreb amide group. Similarly, the lithiation of fluoroiodomethane with LDA to generate fluoroiodomethyllithium under flow conditions was optimized and in all the cases the yields of fluoroepoxides were increased with a remarkable chemoselectivity profile, giving fluoroepoxides bearing an untouched additional electrophilic functionality.

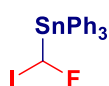


Scheme 49. Flow microreactor system for the generation of fluoromethyllithium or fluoroiodomethyllithium from fluoroiodomethane and subsequent external quenching with an electrophile.

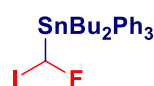
The generation of Fluoriodomethyl lithium in flow microreactors and subsequent trapping with chlorotributylstannane furnishes fluoriodomethylstannane **143**. This underwent a subsequent lithiation with LDA to generate a rare and very unstable intermediate **146** bearing F, I, Li and Sn atoms at the same carbon center. Effective subsequent trapping with electrophiles afforded in “one flow” tetrasubstituted epoxides and tetrasubstituted aziridines **147**, starting from ketones and imines, respectively.



143
(99%)

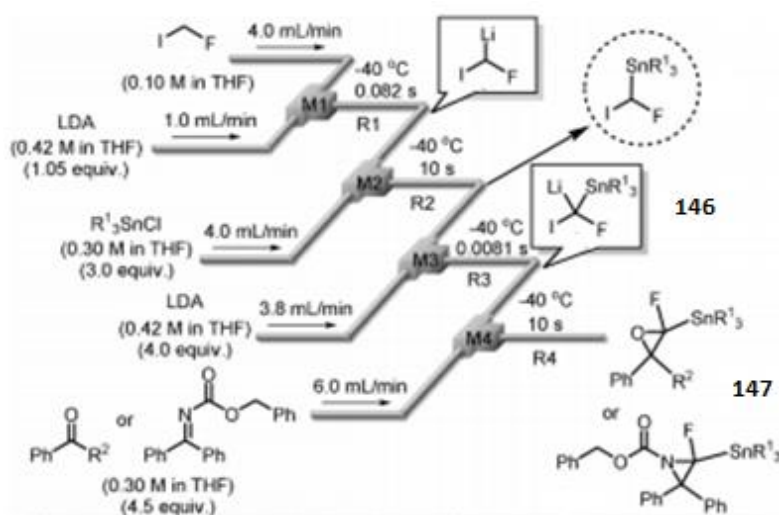


144
(95%)



145
(65%)

Scheme 50. Trapping reaction of fluoriodomethyl lithium with chlorotrialkylstannanes to give fluoriodomethylstannanes.



Scheme 51. Flow microreactor system for a one-flow three component lithiation/trapping sequence en route to tetrasubstituted epoxides and aziridines bearing a stannyl functionality.

8. References

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9. Results and discussion

In this section the results obtained during the realization of this doctoral thesis – published or submitted for publication - are presented. The reactivity of α -substituted organolithium reagents, including halocarbenoids, towards several different electrophiles encompassing Weinreb amides, imines and isothiocyanates is described. Particular attention was paid to the generation of the reactive organometallic species and the reaction conditions were carefully optimized in order to develop high-yielding and chemoselective strategies that can be exploited in synthetic medicinal chemistry or more generally can be of paramount interest for synthetic purposes.

The first publication provides an overview about the well-established applicability of Weinreb amides for accessing α -substituted ketones, presenting recent reports from our own and other groups (*Publication 1*). The proper generation of α -thiomethyl lithium reagents *via* reductive lithiation of chloromethyl methyl ether or deprotonation of thioanisole derivatives with *n*-BuLi followed by reaction with a broad scope of Weinreb amides to access β -oxo thioethers is described (*Publication 2*). The approach was feasible for preparing α -aryl- and α -alkyl selenomethyl ketones: it was demonstrated how Weinreb amides are suitable acylating agents for selenomethyl lithium carbanions (LiCH_2SeR), generated *via* selenium-lithium exchange from diselenoacetals, which were considered by-product in the previously reported Cu-catalyzed diazomethane homologation of selenoesters *en route* to α -selenoketones (*Publication 3*). Inspired by these results and having in hand the optimized reaction conditions to generate phenylselenomethyl lithium reagent, we disclosed the transfer of the same selenofunctionalized methylene fragment from selenium-centered carbanions to *N*-aryl and *N*-sulfonyl imines to synthesize β -selenoamines (*Publication 4*).

Due to our interest in using heterocumulenes as electrophilic partners for halocarbenoids or hydrides sources and encouraged by previous findings involving isocyanates reported in the last years by our group, we considered the analogous sulfur-containing iso(thio)cyanates to achieve similar transformations. In detail, we disclosed how the *in situ* generated Schwartz reagent could partially reduce isothiocyanates to the corresponding thioformamides (*Publication 5*).

We recently reported a formal $\text{CH}_2\text{-CH}_2$ homologation of isothiocyanates conducted with bromomethyl lithium carbenoid to obtain a four-membered cycle. The consecutive delivery of single methylene units to the competent electrophile results in the assembling of an unprecedented iminothietane cluster chemoselectively in a single synthetic operation (*Publication 6*).

Because of the outstanding importance of fluorine containing scaffolds in medicinal chemistry, we exploited the high manipulability of the commercially available fluoroiodomethane to introduce a monofluoromethyl fragment into a series of heteroatom (O-, S-, Se-, N-, P-) nucleophiles. The method was also used to accomplish the late-stage functionalization of a variety of drugs currently on the market (*Publication 7*).

With the aim to broaden the access to α -fluoromethylselenoethers by the installation of the fluoromethyl substituent on selenium-centered nucleophiles - in addition to the already employed phenylselenol - we generated recipients R-Se⁻ anion through a chemoselective reduction of easily accessible or commercially available symmetric diselenides with sodium borohydride, followed by electrophilic monofluoromethylation with fluoroiodomethane (*Publication 8*).

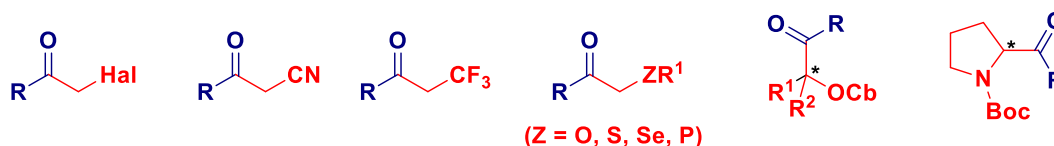
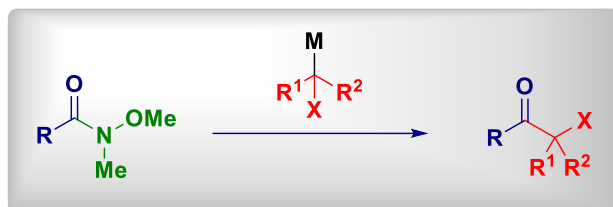
Publication n. 1

Raffaele Senatore, Laura Ielo, Serena Monticelli, Laura Castoldi and Vittorio Pace*

Weinreb Amides as Privileged Acylating agents for Accessing α -Substituted Ketones.

Synthesis, **2019**, 51(14), 2792.

Weinreb amides are excellent acylating manifolds for a wide series of α -substituted carbanion-type reagents, including carbenoids. The recent developments in the use of these electrophilic placeholders with a wide scope of highly functionalized and unstable nucleophilic organometallic species highlight their synthetic potential and versatility for preparing directly α -substituted ketones through high yielding homologative operations. The accessible level of substitution at the alpha position of the carbonyl center is remarkably flexible. No undesired phenomena such as overaddition of the organometallic species – which are common towards other acylating agents such as esters or acid chlorides - are observed. High levels of chemocontrol and full retention of the stereochemical information (embodied in both Weinreb amides and carbanions) are uniformly manifested.



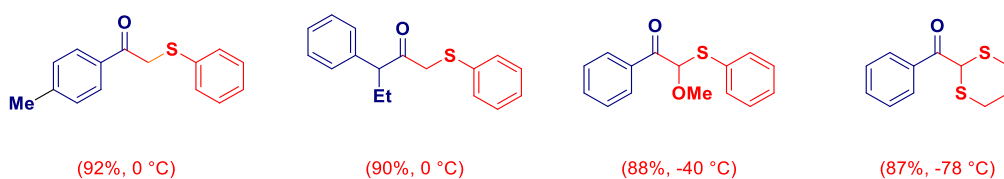
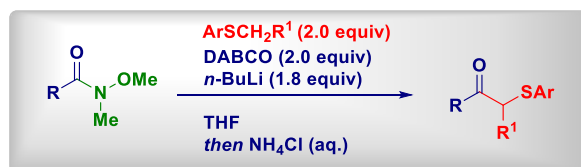
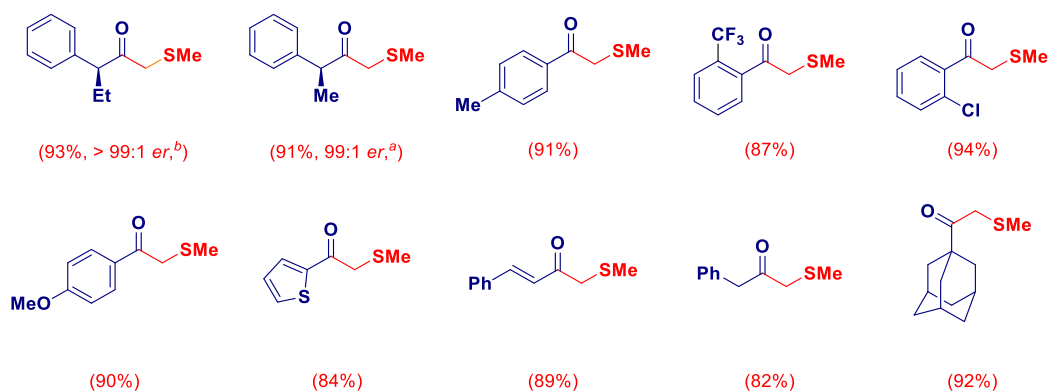
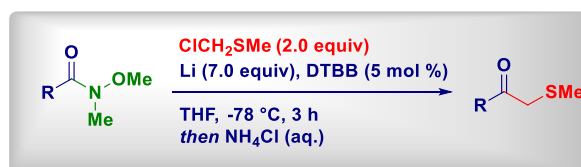
Publication n. 2

Raffaele Senatore, Laura Ielo, Ernst Urban, Wolfgang Holzer and Vittorio Pace*

Substituted α -Sulfur Methyl Carbanions: Effective Homologating Agents for the Chemoselective Preparation of β -Oxo Thioethers from Weinreb Amides.

Eur. J. Org. Chem. **2018**, 2018, 2466.

Reductive lithiation of chloromethyl thiomethyl ether or deprotonation of thioanisole derivatives generates α -thiomethyl lithium reagents, which react with variously functionalized Weinreb amides to give α -thiomethyl ketones (β -oxothioethers) in high yields. Aromatic Weinreb amides featuring different substitution patterns on the aryl ring, as well as heteroaromatic, α,β -unsaturated and aliphatic ones reacted effectively. The optical purity of the starting materials could be preserved.



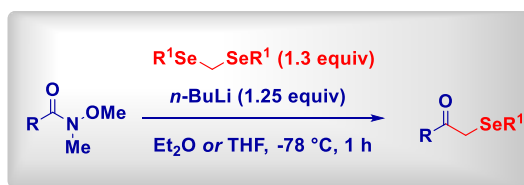
Publication n. 3

Raffaele Senatore, Laura Castoldi, Laura Ielo, Ernst Urban, Wolfgang Holzer and Vittorio Pace*

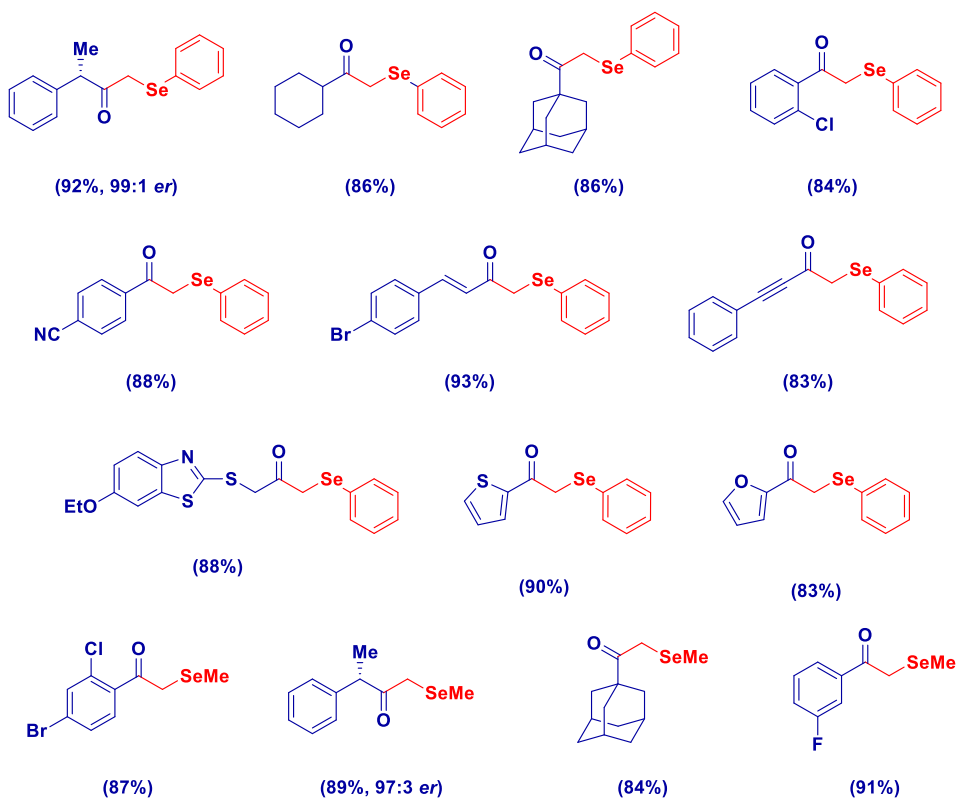
Expeditious and Chemoselective Synthesis of α -Aryl and α -Alkyl Selenomethylketones via Homologation Chemistry.

Org. Lett. **2018**, 20, 2685 - Highlighted in *Synfacts* **2018**, 14, 769.

The generation *via* selenium lithium exchange of a selenomethyl lithium carbanion (LiCH_2SeR) from diselenoacetal allows the transfer of α -selenosubstituted methylene unit to Weinreb amides to give a series of α -aryl and α -alkylselenomethyl ketones. The transformation occurs with full retention of the stereochemical information employing optically pure starting materials. Excellent chemoselectivity is observed in the presence of functionalities sensitive to lithium organometallics.



Selected examples



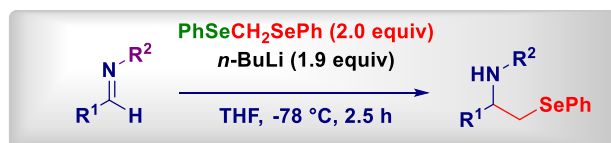
Publication n. 4

Raffaele Senatore, Monika Malik, Saad Touqeer, Roberta Listro, Simona Collina, Wolfgang Holzer and Vittorio Pace*

Straightforward and Direct Access to β -seleno-amines and sulfonylamides via the controlled addition of phenylselenomethyl lithium (LiCH_2SePh) to imines.

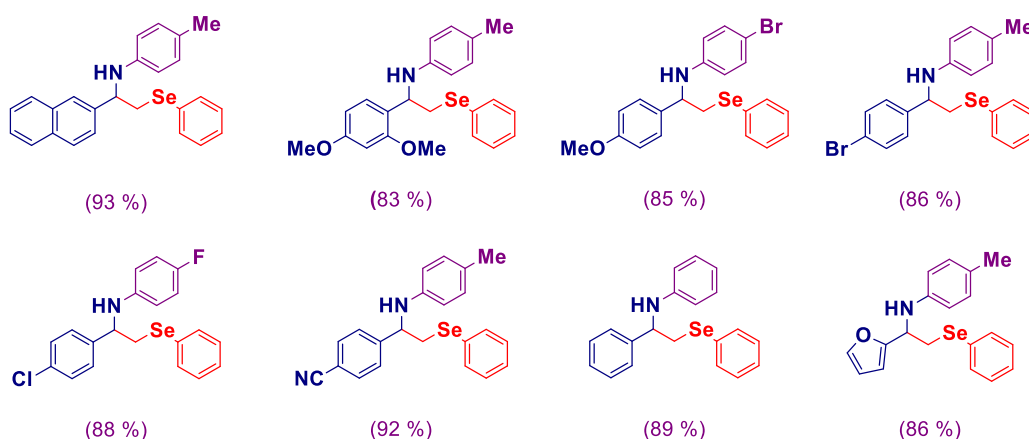
Tetrahedron, **2020**, 76, 51, 131220.

Selenium centered methyllithium carbanion were effectively transferred to variously functionalized *N*-aryl and *N*-sulfonyl imines to access β -seleno-amines. Phenylselenomethyl lithium (LiCH_2SePh), generated from diselenoacetals with *n*-BuLi attacks the azomethinic center of the electrophile chemoselectively, without affecting the chemical integrity of starting imines. This one step-process constitutes a direct and straightforward strategy to install the selenium functionalized methylene fragment in this (aza)-carbonyl-type electrophile.



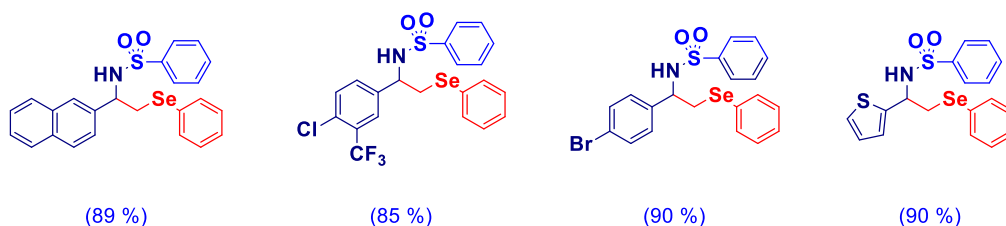
N-Aryl Imines

Selected examples



N-Sulfonyl Imines

Selected examples



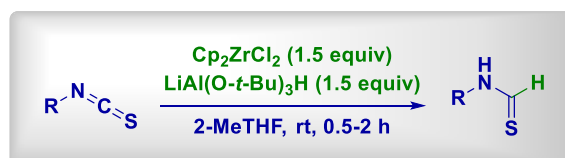
Publication n. 5

Karen De la Vega-Hernandez, **Raffaele Senatore**, Margherita Miele, Ernst Urban, Wolfgang Holzer and Vittorio Pace*

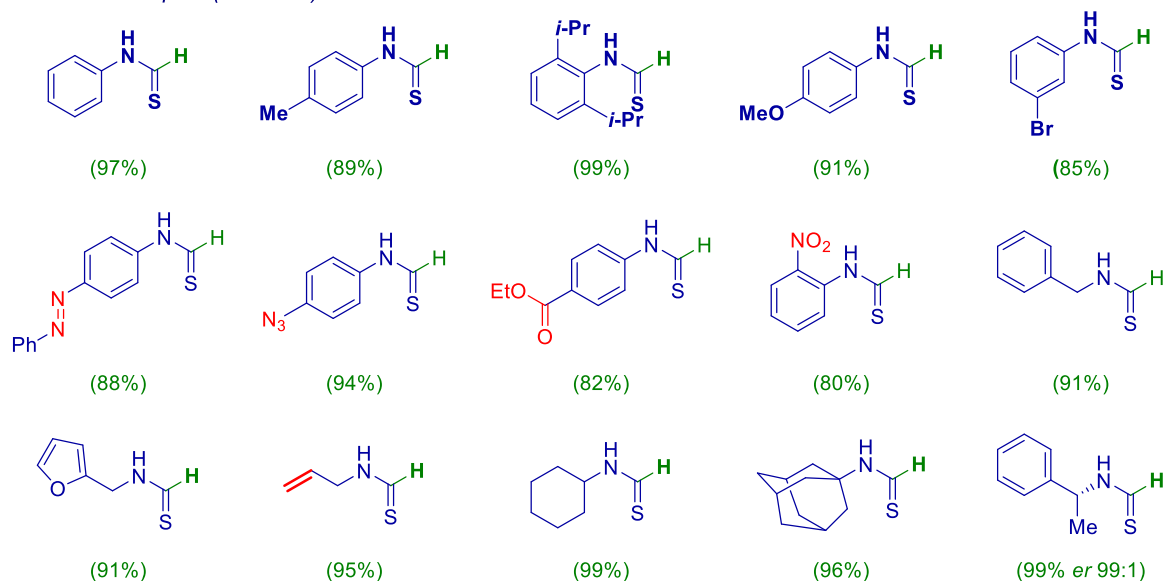
Chemoselective reduction of isothiocyanates to thioformamides mediated by the Schwartz reagent.

Org. Biomol. Chem. **2019**, 17, 1970.

Commercially available isothiocyanates can be partially reduced to the thioformamide level *via* hydride transfer from the *in situ* generated Schwartz reagent. This protocol allowed the synthesis of diverse *N*-substituted thioformamides in high yields under mild reaction conditions. The transformation occurs with full retention of the stereochemical information contained in the starting material and with a highly remarkable chemoselective profile. Several functionalities that could undergo concomitant reduction such as nitro, ester, alkene, azo, azide, and keto groups were well-tolerated and remained untouched during the overall transformation.



Selected examples (out of 27)



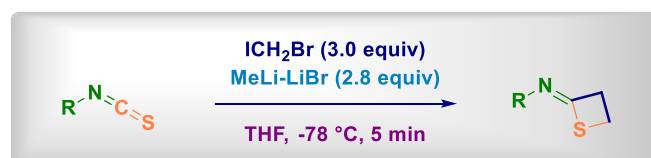
Publication n. 6

Raffaele Senatore, Monika Malik, Thierry Langer, Wolfgang Holzer and Vittorio Pace*

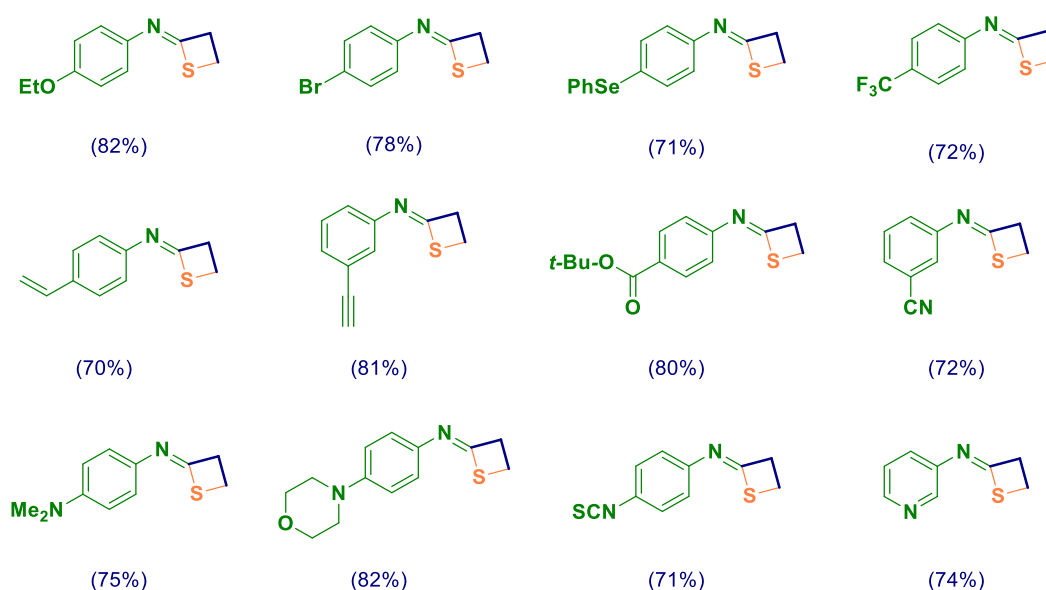
Consecutive and Selective Double Methylene Insertion of Lithium Carbenoids to Isothiocyanates: A Direct Assembly of Four-membered Sulfur-Containing Cycles.

Provisionally accepted in *Angew. Chem.* **2021** (manuscript ID: 202106258).

We have documented the installation of two methylene units consecutively onto isothiocyanates with bromomethyl lithium carbenoid to yield unprecedented four-membered iminothietane rings in a single synthetic operation. The overall strategies, being a formal C-2 homologation, relies on two sequential events: the initial formation of a thioimide anion is followed by an intramolecular cyclization to an iminothirane, which undergoes a second homologation giving a γ -halothioimide, direct precursor of the final compound upon a second ring closure. Experiments involving deuterated iodomethyl lithium proved how the reactive carbenoid represents the nucleophilic source of the two carbons inserted within the ethylene unit featured by the obtained products. A ring-opening hydride-mediated reduction of the synthesized moieties leading to γ -aminopropylthiols is also presented.



Selected examples (out of 33)



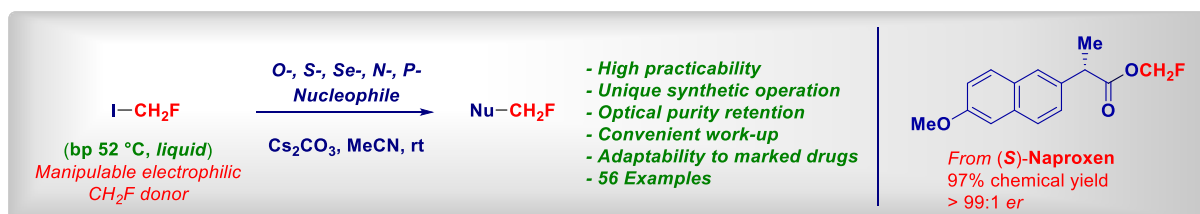
Publication n. 7

Raffaele Senatore, Monika Malik, Markus Spreitzer, Wolfgang Holzer and Vittorio Pace*

Direct and Chemoselective Electrophilic Monofluoromethylation of Heteroatoms (O-, S-, N-, P-, Se-) with Fluoroiodomethane.

Org. Lett. 2020, 22, 4, 1345.

We reported a direct transfer of the fluoromethyl fragment from fluoroiodomethane to a series of recipient heteroatom-centered nucleophiles under mild basic conditions. By means of an intuitive nucleophilic substitution, aromatic (thio and seleno)alcohols, (thio)carboxylic acids, heteroaromatic nitrogen compound and di-*n*-butylphosphine oxide, were transformed into the corresponding fluoromethylated derivatives. Full preservation of the optical purity was observed in the cases of α -substituted phenylacetic acid derivatives, including the nonsteroidal anti-inflammatory agent Naproxene. Pyrazol-5-ones were also employed for preparing fluomethylethers, including the analogue deriving from the anti-amyotrophic lateral sclerosis (ALS) agent edavarone. The robust tolerance of functional groups is showcased in 56 examples, encompassing fluoromethyl analogues of marked drugs. The development of electrophilic monofluoromethylation with ICH_2F overcomes the requirement of monofluoromethylating agents with no immediate access, whose employment is often associated with a nonoptimal atom economy.



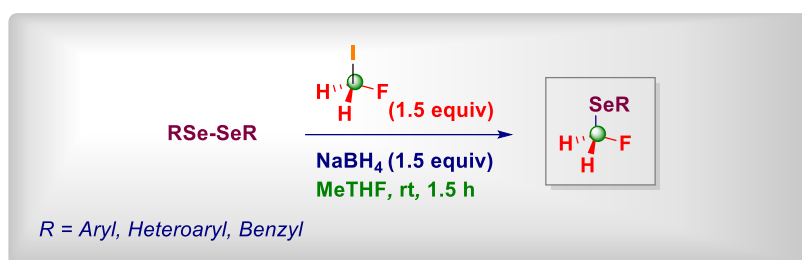
Publication n. 8

Raffaele Senatore,* Monika Malik, Ernst Urban, Wolfgang Holzer and Vittorio Pace*

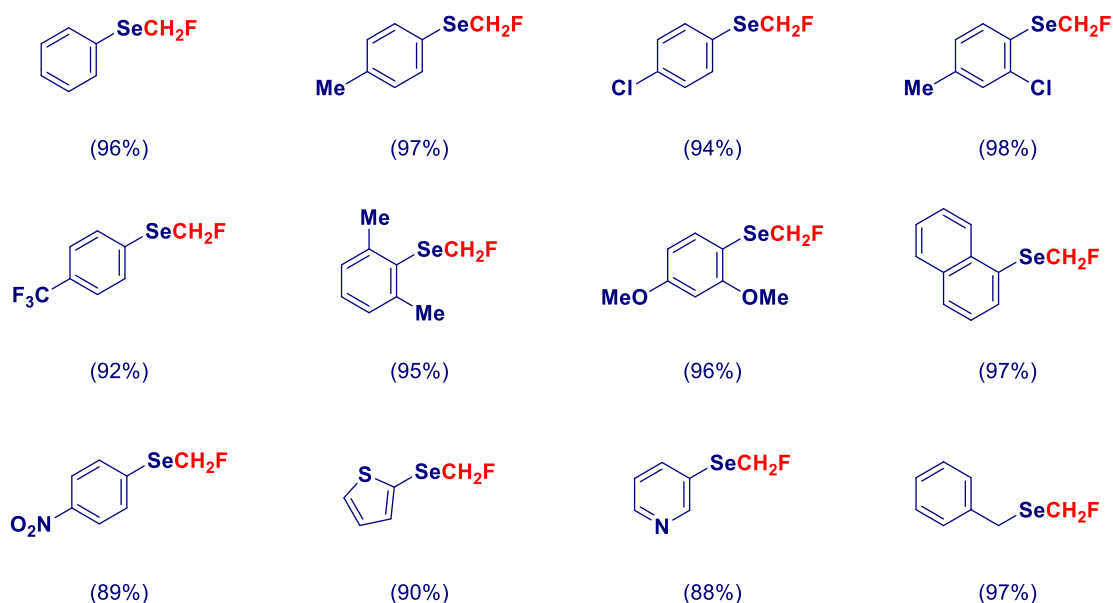
Synthesis of stable α -fluoromethyl putative carbanions via a chemoselective reduction-monofluoromethylation sequence of diselenides under sustainable conditions.

Tetrahedron, **2021**, 85, 131921.

In order to expand the possibility to access α -fluoromethylselenoethers we have developed a convenient one-pot diselenides reduction-monofluoromethylation sequence. A NaBH_4 -mediated reduction generates the desired nucleophilic selenium anion, immediately captured with fluoroiodomethane. The transformation occurred in environmentally friendly solvent 2-MeTHF, giving the desired α -fluoromethylselenoethers in excellent yields, without any purification needed in nearly all cases. Chemoselectivity was observed in the presence of a sensitive nitro functionality, which remained untouched during the transformation.



Selected examples (out of 15)



10. Conclusions

We successfully aimed at developing innovative synthetic strategies to achieve transformations with high level of chemo- and enantioselectivity by means of functionalized organolithiums. The synthetic potential of these reagents to form carbon-carbon and carbon-heteroatom bonds definitely overtakes the severe limitations related to their instability pointed out in the past, which can anyway be minimized by the fine tuning of the reaction conditions and by understanding the processes regulating the generation of these nucleophiles.

The transfer of the precisely substituted CH₂ fragment can be envisaged as the initial step of a synthetic sequence leading to more complex molecular architectures. Alternatively, a certain level of molecular complexity can be introduced on a given starting compound *via* a fast and controlled single synthetic operation rather than a multistep sequence.

We confirmed the synthetic versatility and flexibility of Weinreb amides to access α -substituted ketones, with focus on the functionalization with chalcogens (S and Se) containing fragments.

Overall, the compounds obtained through the different discussed tactics could be usually synthesized alternatively only employing less straightforward protocols. For instance, the presented partial reduction of isothiocyanates to the corresponding thioformamides by means of the Schwartz reagent results undoubtedly convenient when compared to the already reported methodologies to obtain the same class of compounds.

Two of the reported protocols occurred in an eco-friendly reaction medium, such as the biomass derived solvent 2-MeTHF, pointing out the sustainability profile of the developed synthetic procedures.

Publication n. 1

Weinreb Amides as Priviledge Acylating agents for Accessing α -Substituted Ketones.

Raffaele Senatore, Laura Ielo, Serena Monticelli, Laura Castoldi and Vittorio Pace*

Synthesis, **2019**, 51(14), 2792 (DOI: 10.1055/s-0037-1611549)

Weinreb Amides as Privileged Acylating Agents for Accessing α -Substituted Ketones

Raffaele Senatore

Laura Ielo

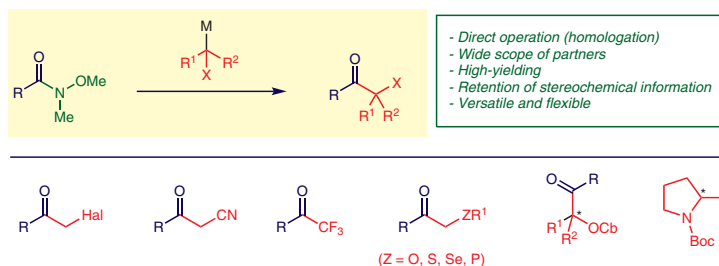
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Abstract The acylation of α -substituted carbanion-type reagents ($\text{MCR}^1\text{R}^2\text{X}$; X = halogen, OR, SR, NR^3R^4 , SeR, etc.) with Weinreb amides constitutes a highly versatile and flexible approach for accessing α -functionalized ketones. In this short review we will present a series of transformations—from our own and the work of others—documenting the general applicability of the methodology. Chemoselectivity is uniformly manifested including for critical substrates featuring additional electrophilic functionalities or sterically demanding elements. Importantly, the stereochemical information contained in the Weinreb amides can be fully transferred to the targeted ketones without affecting the optical purity. The protocol is also applicable to chiral carbanions generated through sparteine-mediated asymmetric deprotonation: the careful design of the experimental procedure allows recycling of the sparteine and the Weinreb ‘amine’ (*N,O*-dimethylhydroxylamine), thus improving the sustainability perspective of the processes.

1 Introduction

1.1 The Problem of the Synthesis of α -Substituted Ketones

1.2 Weinreb Amides: General Features and Preparation

2 Synthesis of α -Substituted Ketones

2.1 α -Haloketones

2.2 Synthesis of α -Cyanoketones

2.3 Synthesis of α -Oxyketones

2.4 Synthesis of β -Oxo Thioethers (α -Thioketones)

2.5 Synthesis of Chiral α -Oxy and α -Nitrogen Ketones via the Sparteine-Mediated Generation of Optically Active Organolithiums

2.6 Synthesis of α -Selenomethyl Ketones

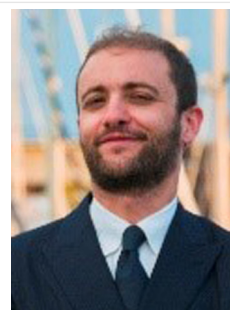
2.7 Reactivity of α -Phosphorus Carbanions with Weinreb Amides

2.8 Modification of the Weinreb Amide Core: The CLAMP Reagent

3 Competing Attack of Nucleophiles at More Reactive Electrophilic Sites than Weinreb Amides

4 Conclusions

Key words ketones, homologation, carbenoids, chemoselectivity, additions

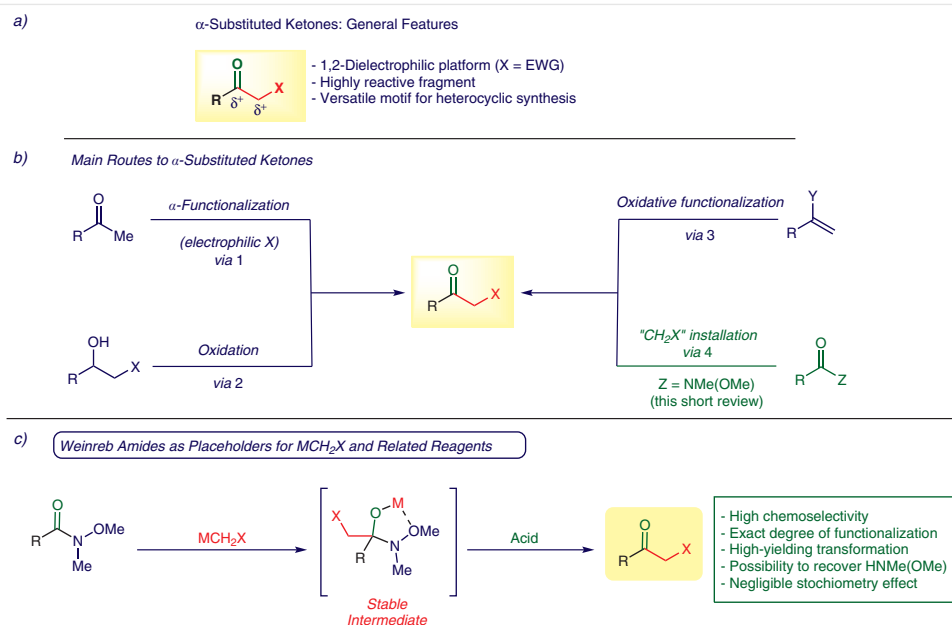


Vittorio Pace received his Ph.D. in Chemical Sciences *cum laude* from the Complutense University of Madrid in 2010 working with Prof. Alcántara and Prof. Sinisterra. After postdoctoral training at Vienna (Prof. Holzer), Manchester (Prof. Procter) and Stockholm (Prof. Olofsson), he obtained a group leader position at the University of Vienna and a tenure track in 2018. In 2016 he received his Habilitation in Pharmaceutical Chemistry from the University of Vienna and, in 2017, Habilitation as a Full Professor of Organic Chemistry. He has received several awards including the Ciamician Medal of the Italian Chemical Society (2015), the Caglioti Prize of the Accademia Nazionale dei Lincei (2015), the Young Investigator Award of the Faculty of Life Sciences at Vienna (2015), the Hoffmann-La Roche Award (2017) and a JSP Bürgenstock Grant (2018). His research interests are represented by the design and development of new transformations with functionalized organolithiums.

1 Introduction

1.1 The Problem of the Synthesis of α -Substituted Ketones

α -Substituted ketones represent versatile scaffolds across the chemical sciences as a consequence of the vicinal position of two highly reactive sites: the carbonyl and the adjacent methylene unit.¹ In particular, installing therein an electron-withdrawing group (EWG) results in the formation of a 1,2-di-electrophilic platform suitable for further elaboration en route to heterocyclic motifs (Scheme 1a).²



Scheme 1 α -Substituted ketones: General context and rationale for using Weinreb amides

Such a relevance in the synthetic panorama—not restricted to the pharmacological or natural products audiences—is crystallized in the continuous search for tactics enabling the conjugation of efficiency and selectivity.³ Four main tactics have appeared dominant in this scenario: 1) the α -functionalization of a ketone (or derivative thereof) mainly conducted in nucleophilic regime with an adequate electrophilic partner,⁴ 2) the oxidation of a β -substituted alcohol,⁵ 3) the oxidative functionalization of a naked protected ketone,⁶ and 4) the direct installation of a CH_2X fragment into an electrophilic placeholder according to a general addition–elimination pathway (Scheme 1b).⁷ Although there are some advantages offered by the first three techniques, the emergence of selectivity issues or the limitation of the scope to particular classes of substrates has stimulated the search for suitable alternatives of wide applicability and flexibility. In this context, the conceptual simplicity of transferring a nucleophile, featuring the exact degree of derivatization, into an electrophilic carbonyl-like linchpin appears to be an ideal solution, allowing direct access to the targeted compound and thus circumventing potential limitations. Assuming that the reacting nucleophile would be delivered as a metal carbanion (MCH_2X), the selection of the carbonyl platform becomes crucial to make the strategy productive.^{7c,8} Accordingly, Weinreb amides (*N,O*-dimethylhydroxyl amides), introduced in 1981, emerged as excellent placeholders for acylating α -substituted methyl carbanion species, thus establishing a series of robust protocols enabling the preparation of α -substituted ketones through a single synthetic operation.⁹ We anticipate that excellent levels of chemocontrol, chemical yields and preservation of

the optical information—contained in both the amide and the reactive nucleophile—will be uniformly observed regardless of the nature of the attacking carbon nucleophile.

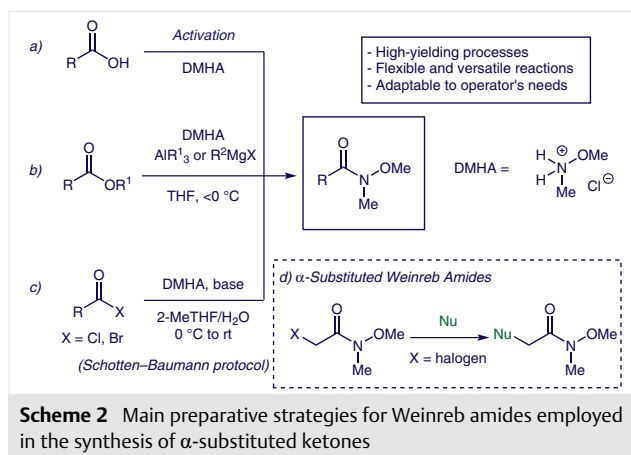
1.2 Weinreb Amides: General Features and Preparation

The well-known reluctance of carboxylic derivatives such as halides, esters or anhydrides to undergo the chemoselective mono-addition of carbon nucleophiles represents a significant drawback for preparing ketones.¹⁰ With the aim to circumvent the undesired formation of tertiary alcohols—originating from two consecutive additions of the nucleophiles—the simple tuning of the reaction conditions (stoichiometry, temperature or mode of the addition) were not general and did not suffice for this purpose.¹¹ For this reason, the quest for valuable acylating alternatives indicated amides as possible substrates for accomplishing the targeted transformation.

The mesomeric effect and the constituent poor electrophilicity characterizing the amidic linkage have been regarded as the main limiting factors for the routine employment of these ubiquitous materials in acyl nucleophilic substitutions.¹² However, non-generalized examples of direct additions of organometallic reagents to amides were known since pioneering studies conducted at the beginning of the 20th century by Bouveault,¹³ which were subsequently confirmed in later investigations.^{12a,14} Before the advent of robust tools for activating the poorly reactive carbonyl amide with electrophilic reagents (e.g., triflic anhydride)¹⁵ or with transition-metal-catalyzed strategies,¹⁶ the structural modification of the amidic functionality was

considered the method of choice for enabling the reluctant nucleophilic addition event.^{12a,c,17} In this context, the aforementioned Weinreb amides occupy a prominent position due to the following reasons: a) the constitutive presence of the methoxy group highly stabilizes the tetrahedral intermediate formed upon the addition of the organometallic unit to the carbonyl carbon, b) the formation of the five-membered chelate enabled by the coordination of the alkoxide metal cation and the methoxy group provides excellent stability to the intermediate during the whole process, thus resulting in its collapse to deliver the ketone only upon acidic quenching, c) the methoxy group increases the electrophilicity of the carbonyl carbon, thus making it more prone to nucleophilic attack (Scheme 1c).^{9,18} It is evident that the superb stability of the tetrahedral intermediate accounts for the excellent levels of chemocontrol in favor of the selective formation of ketones, thus eliminating *de facto* overaddition phenomena—even in the presence of excess of nucleophiles—observed with different acylating agents.

Weinreb amides can be easily prepared according to established high-yielding protocols starting from carboxylic derivatives such as acids, esters or halides. As a common characteristic these operations represent trivial amidation procedures with *N,O*-dimethylhydroxylamine hydrochloride (DMHA), the free base of which is obtained upon alkaline treatment. Evidently, the direct conversion of acids into Weinreb amides requires appropriate activation (Scheme 2a),¹⁸ which can be conveniently avoided by employing esters according to Weinreb's seminal report (in the presence of organoaluminium reagents)⁹ or modifications thereof (with Grignard reagents, Scheme 2b).¹⁹ The use of *per se* activated acid halides under Schotten–Baumann conditions is particularly convenient for the simplicity of the experimental aspects (Scheme 2c):²⁰ almost quantitative yields are uniformly observed in short reaction times without requiring tedious chromatographic purifications. Finally, nucleophilic substitution on an appropriate α -halomethyl Weinreb amide furnishes α -substituted analogues amenable for further derivatization at the carbonyl site (Scheme 2d).²¹ In general, the use of activated forms of carboxylic acids, as Weinreb amides are, is considered non optimal from a sustainable perspective for two main reasons: 1) the transformation of the acid into the Weinreb amide undoubtedly enlarges the synthetic sequence, often necessitating highly reactive agents to activate the carboxy group, and 2) upon completing the targeted carbanion acylation, the (expensive) amine (*N,O*-dimethylhydroxylamine) is eliminated during the work-up process. We anticipate that upon careful setting of the experimental procedure, this amine can be conveniently recycled (together with additional precious reagents),²² thus allowing adherence of the technique to the strict principles of green chemistry.²³



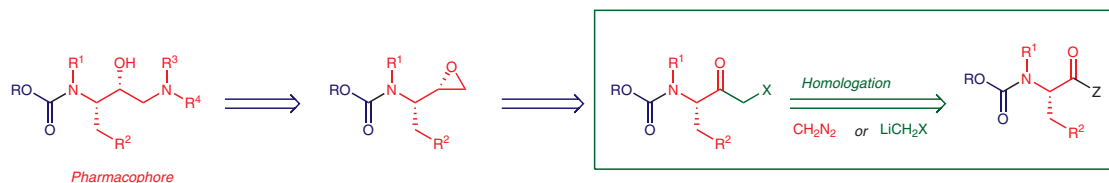
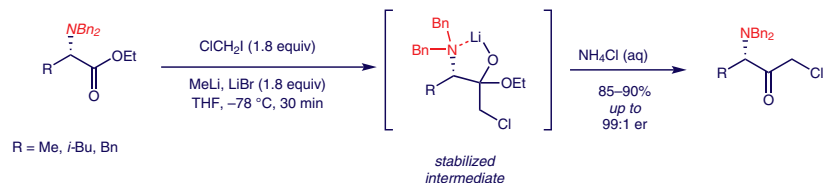
2 Synthesis of α -Substituted Ketones

2.1 α -Haloketones

The recognition that α -haloketones play a key role in the assembly of HIV protease inhibitors^{3a,24} motivated extensive investigations aimed at furnishing these scaffolds in an efficient and safe manner. In particular, the well-known risks associated with the initial employment of diazomethane, principally on pilot scale,²⁵ spurred the search for less hazardous techniques, culminating in a series of carbenoid-mediated homologation procedures of carboxylic derivatives (esters) introduced by Barluenga,²⁶ and quickly adapted for different necessities.²⁷ Although for a long time esters remained the substrates of choice for accomplishing such homologations, severe difficulties were evident for achieving a unified strategy en route to α,α' -disubstituted acetones starting from these carboxylic agents.^{21a} In particular, the success of the Barluenga's α -amino ester homologation protocol was highly dependent on the substitution pattern of the aminic group.²⁶ Accordingly, electron-donating groups (EDG) at that level, i.e., benzyl, enable the homologation event stabilizing the putative tetrahedral intermediate through coordination of the lithium cation with the electron-rich nitrogen (Scheme 3).

In an attempt to adapt Barluenga's homologation protocol to related α -arylamino esters, we noticed a dramatic effect of the aminic nitrogen substituents on the outcome of the transformation.^{21a} Although EDG-substituted α -arylamino esters undergo the homologation (Scheme 4a), EWG-substituted analogues did not (Scheme 4b). Evidently, decreasing the electronic density on the amine—through the installation of electron-withdrawing functionalities—results in the formation of a highly unstable intermediate that does not evolve into the desired α -haloketone. This substrate-depending limitation is efficiently circumvented by switching to Weinreb amides as the acylating agents.

Retrosynthetic Analysis of HIV Protease Inhibitors

Barluenga's Homologation of *N,N*-Dibenzylamino Esters**Scheme 3** Significance of α -haloketones in pharmaceutical chemistry and Barluenga's homologation of α -amino esters

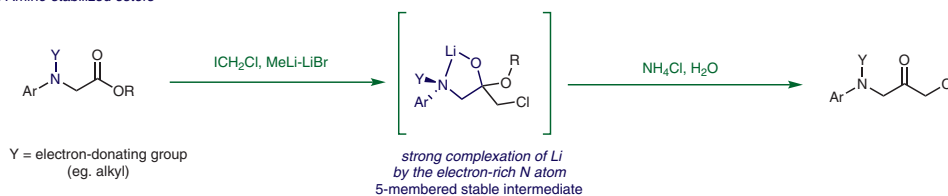
The presence of the *N*-methoxy group supplies the required coordinating element for the intermediate, thus rendering negligible the effect of substituents on the aminic functionality (Scheme 4c).^{21a}

The full chemoselective homologation of Weinreb amides features a formidable versatility as documented in a series of differently substituted *N*-arylglycine derivatives embodying both EWG and EDG elements (Scheme 5a). However, the presence of an acidic proton (i.e., secondary amine) was detrimental for the reaction, with it being abstracted by the basic organometallic species. Remarkably, this strat-

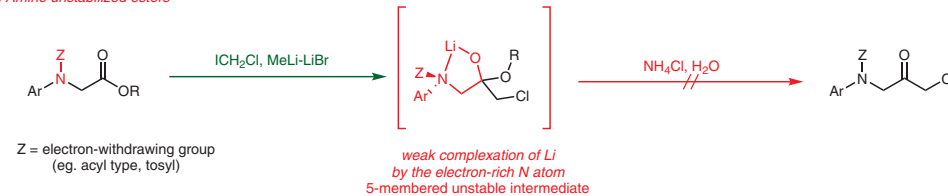
egy was amenable for the stereocontrolled synthesis of a key fragment for the preparation of nelfinavir (Scheme 5b).²⁸ The biocatalytic reduction of this haloketone afforded the *erythro* chlorohydrin, which was transformed into the drug through a trivial sequence of synthetic operations. Notably, in this particular case, the homologation event of the starting Weinreb amide is compatible with the presence of an acidic carbamate proton.

The success of halolithium-mediated homologations of Weinreb amides is further showcased for more complex targets such as α,β -unsaturated α' -haloketones (Scheme

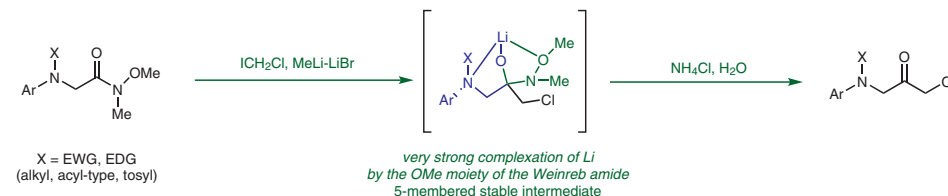
a) Amino-stabilized esters

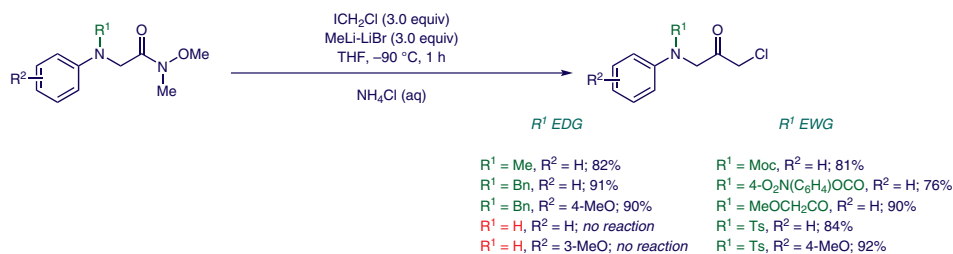


b) Amino unstabilized esters

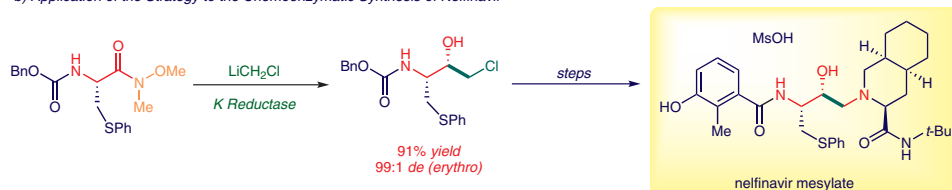


c) Per se stabilized Weinreb amides

**Scheme 4** Substitution-depending homologation of α -amino esters and α -amino Weinreb amides with halolithium carbenoids

a) Homologation of α -Arylamino-Substituted Weinreb Amides

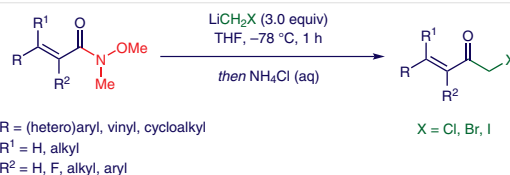
b) Application of the Strategy to the Chemoenzymatic Synthesis of Nelfinavir



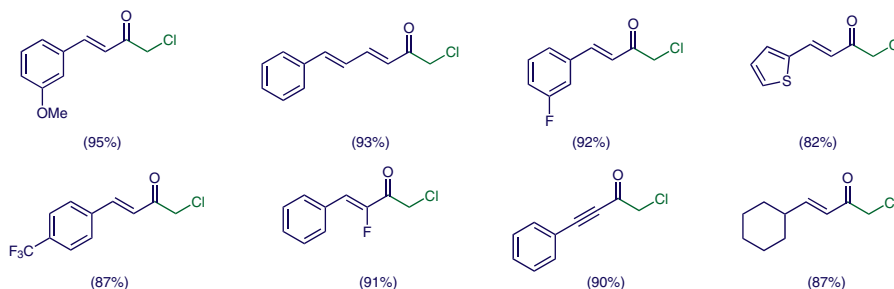
Scheme 5 Halolithium-mediated homologation of α -amino Weinreb amides en route to α -haloketones and application to the synthesis of nelfinavir

6).²⁹ In principle, the Michael acceptor tendency of cinnamoyl-type acylating agents could activate β -attack phenomena. However, Weinreb amides cleanly undergo a highly selective 1,2-addition of the carbenoids, thus providing the desired compounds in excellent yield regardless of the nature of the halogen and the substitution pattern on both the vinyl unit and the aromatic nucleus. The extension to β -cycloalkyl groups or alkynyl derivatives is permitted, thus establishing a valuable technique for synthesizing these challenging entities through a single operation. The remarkable stabilizing effect offered by Weinreb amides is deduced by comparing with the aptitude of analogous esters to undergo double addition of these nucleophiles, which could be only partially avoided by keeping the temperature at -115°C .

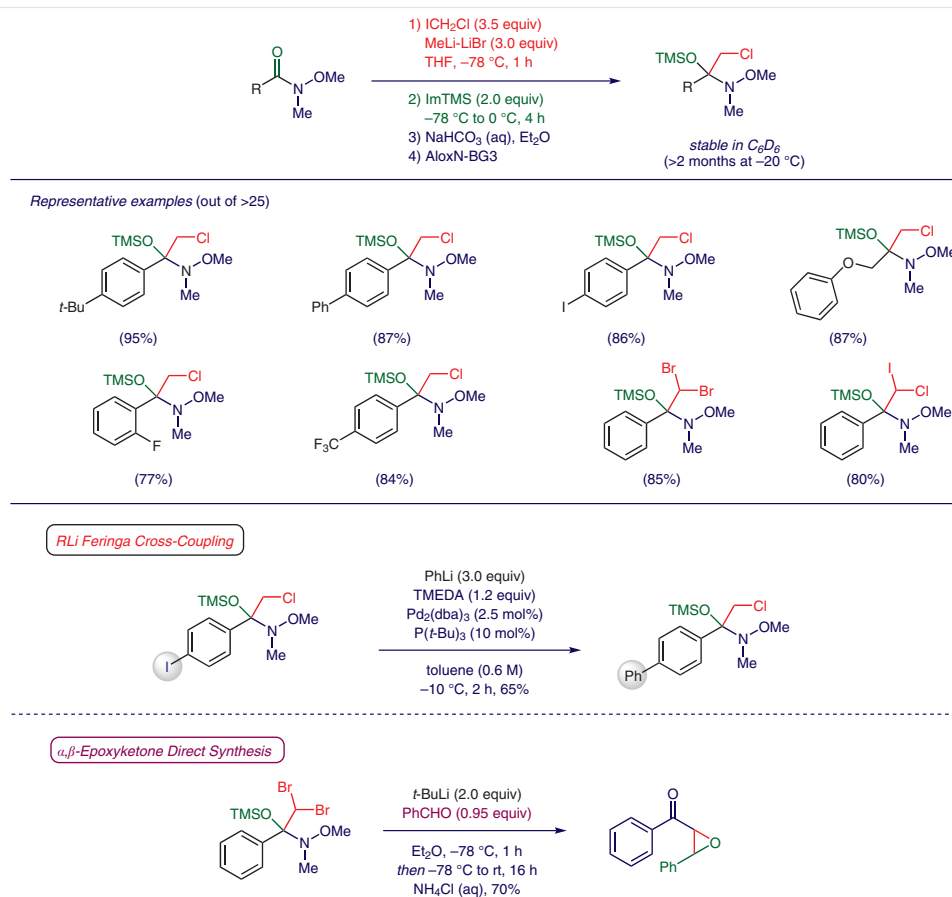
Pace and co-workers documented the isolation of an *O*-TMS hemiaminal tetrahedral intermediate generated upon the addition of a carbenoid reagent (mono- or dihalo-methylolithium) to Weinreb amides (Scheme 7).³⁰ Pivotal for the successful isolation and spectroscopic characterization were: 1) the use of TMS-imidazole (ImTMS) as the silylating agent, and 2) chromatographic purification on deactivated neutral alumina (Brockmann grade 3, Alox-BG3). No relevant difference was observed on switching from monohalo- to dihalo-methylolithiums. Although controlled conditions were required to ensure the chemical integrity, their synthetic potential could be advantageously recognized in straightforward transformations such as in Feringa's organolithium cross-coupling³¹ and the one-step formation of an



Representative examples (out of >25)



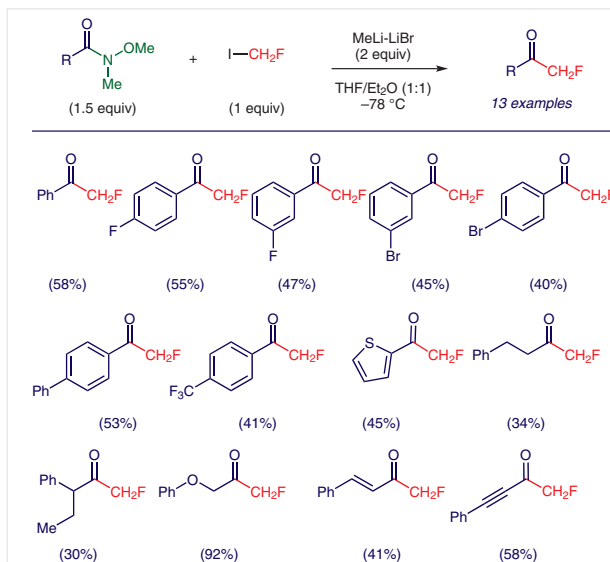
Scheme 6 Halolithium-mediated homologation for preparing α,β -unsaturated- α' -haloketones



Scheme 7 Evidence and isolation of hemiaminal tetrahedral intermediates derived from Weinreb amides and (di)-halomethylolithiums

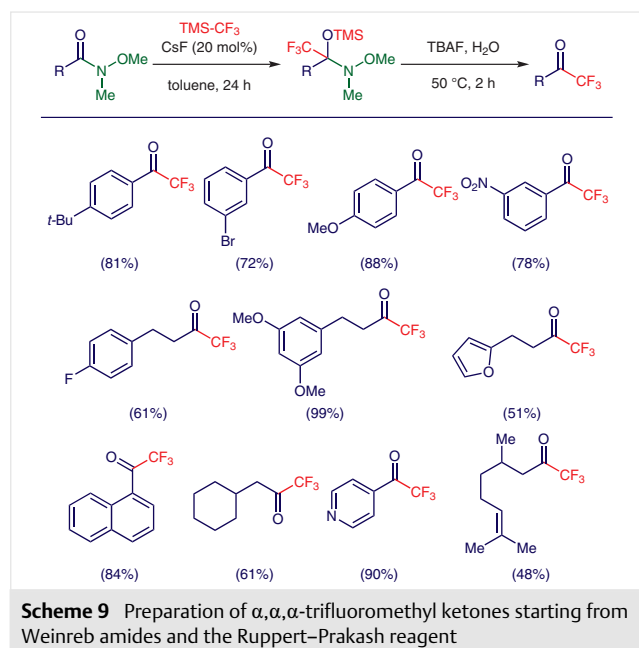
α,β -epoxyketone. The protocol for isolating tetrahedral Weinreb amide intermediates is completely adaptable for analogous hemiaminals derived from *N*-acyl pyrroles.³²

In 2017, Pace and Luisi introduced the preparative use of the highly unstable carbenoid fluoromethylolithium (LiCH_2F) generated under Barbier-type conditions via an expeditious iodine–lithium exchange³³ conducted on commercially available fluoroiodomethane (bp 52°C).³⁴ Among the plethora of electrophiles amenable for this straightforward and unprecedented nucleophilic fluoromethylation, Weinreb amides occupy a prominent role, as indicated in a series of examples ranging from (hetero)aromatic to aliphatic species (Scheme 8). Full chemocontrol, even in the presence of potentially exchangeable functionality (bromine), and good to excellent yields are homogeneously observed and not affected by specific structural characteristics of the starting materials. The unique behavior of this fluorinated carbenoid is further illustrated in the preparation of unsaturated (alkenyl and alkynyl) analogues.



Scheme 8 Synthesis of α -fluoromethyl ketones from Weinreb amides and the highly unstable carbenoid LiCH_2F

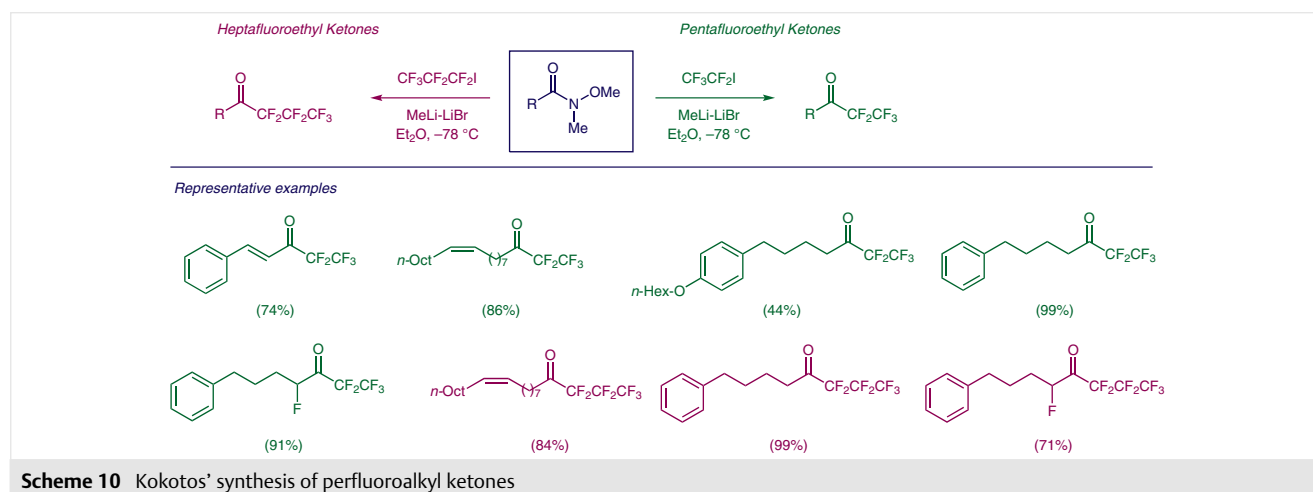
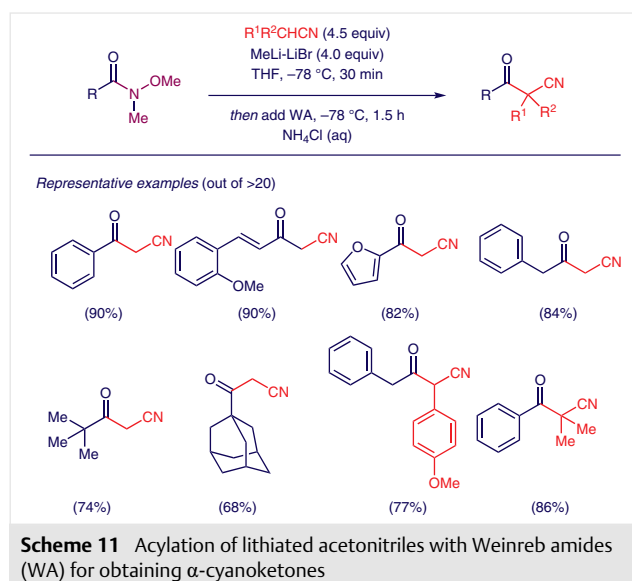
In 2012, Leadbeater and co-workers disclosed a method to access trifluoromethyl ketones (TFMKs) from Weinreb amides and CF_3 -type carbanions generated starting from the Ruppert–Prakash reagent (TMS-CF_3) and cesium fluoride as the initiator (Scheme 9).³⁵ By running the reaction in toluene, a silylated intermediate was formed and subsequently converted into the desired TFMK by elimination of the amino substituent with TBAF (tetrabutylammonium fluoride). Similarly, Kuhakarn's group reported the synthesis of difluoromethyl ketones via the installation of a difluoro(phenylsulfanyl)methyl moiety through the fluoride-induced nucleophilic addition of $\text{PhSCF}_2\text{SiMe}_3$ to Weinreb amides, followed by the reductive cleavage of the phenylsulfanyl group.³⁶



It is interesting to note that perfluoroalkyllithium carbanions have also been successfully added to Weinreb amides, as documented in previous work by Peet³⁷ and Kokotos (Scheme 10).³⁸ These significant precedents established the basis for accessing polyfluoroketones of biological relevance through short and effective sequences. Notably, the work of Kokotos highlights the effective performance of morpholino amides which could be employed in place of Weinreb amides.

2.2 Synthesis of α -Cyanoketones

Given the excellent nucleophilicity of nitrile-containing carbanions,³⁹ the Pace group documented the homologation of Weinreb amides for preparing related β -oxonitriles (i.e., α -cyanoketones) (Scheme 11).⁴⁰ The higher stability of cyanomethylolithiums (compared to halomethyl analogues) accounts for not requiring Barbier-type conditions during

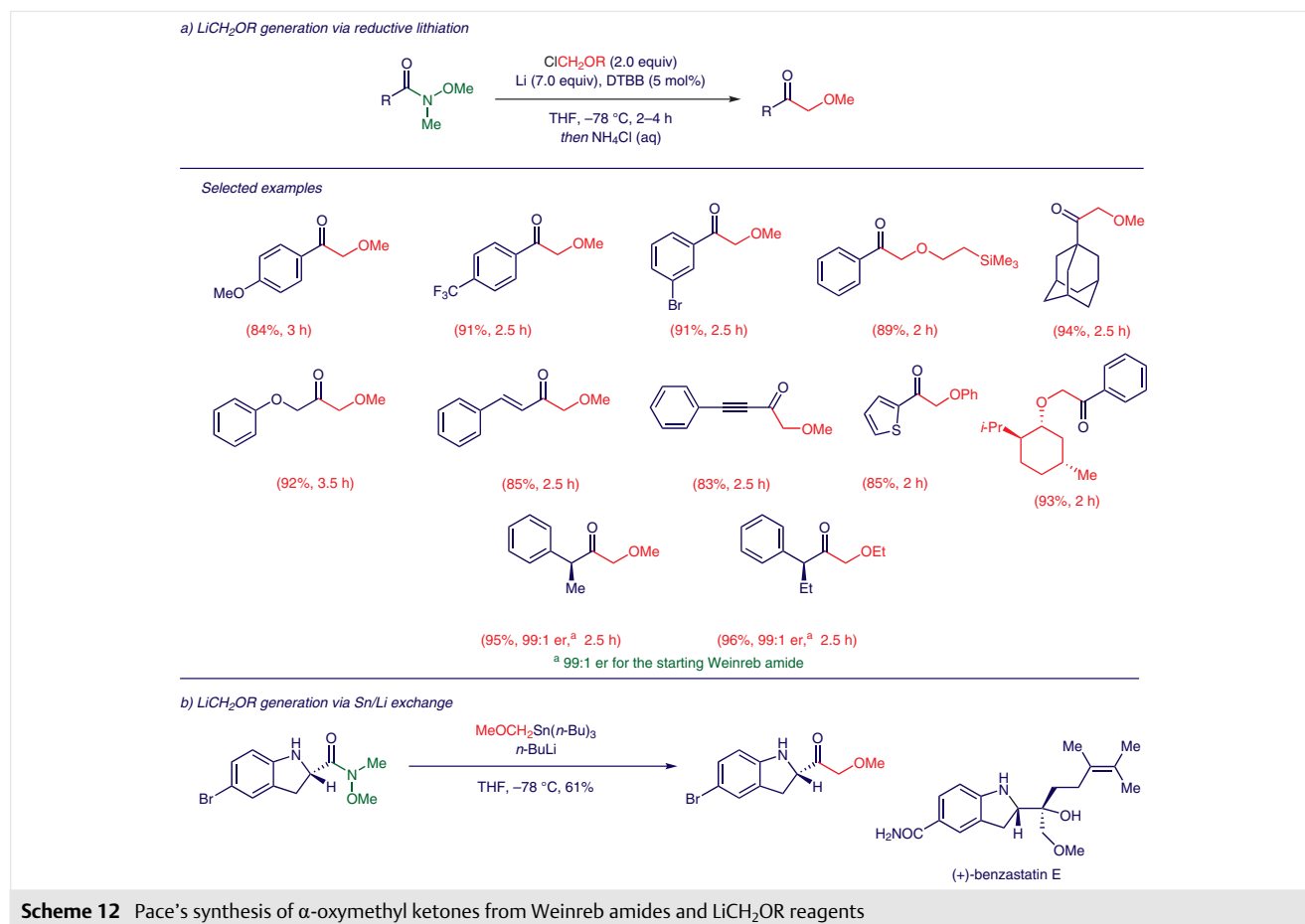


the carbanion formation event–homologation sequence. The targeted products were obtained in high yields under full chemocontrol, employing both differently substituted acetonitriles and/or Weinreb amides. Of particular relevance is the possibility to introduce tertiary and quaternary metalated acetonitriles, thus enabling a versatile one-pot access to α -mono- and α,α -disubstituted cyanoketones.

2.3 Synthesis of α -Oxyketones

The Yus arene-catalyzed reductive lithiation of α -chloromethyl alkyl ethers, in the presence of a catalyst such as DTBB (4,4'-di-*tert*-butylbiphenyl), generates α -oxygenated methyl lithium species (LiCH_2OR),⁴¹ which can directly homologate Weinreb amides to afford valuable α -oxyketones.⁴² The process showed broad scope in terms of Weinreb amides and carbanions: both aromatic, heteroaromatic and unsaturated Weinreb amides, as well as aliphatic and α,β -unsaturated examples underwent nucleophilic addition

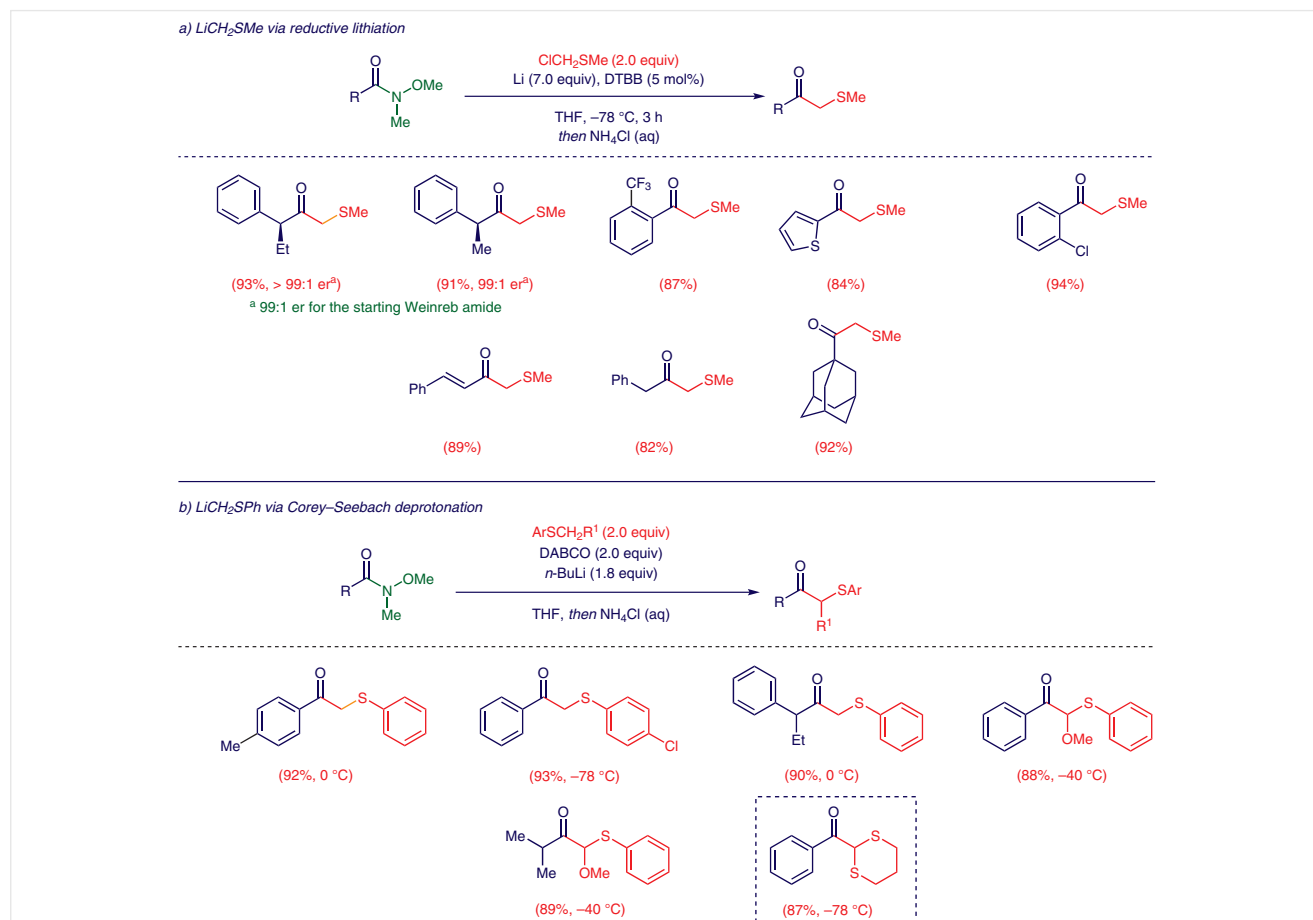
of this oxygenated organolithium species; the generation of LiCH_2OR (R = alkyl) nucleophiles allowed α -alkoxymethyl ketones to be assembled in very good yields and chemoselectivity (Scheme 12). The scope of the methodology could be expanded by employing non-alkyl-type chloromethyl ethers for the synthesis of α -phenoxymethyl ketones. Despite the highly basic nature of these organolithium reagents, full preservation of the stereochemical information embodied in enantiopure Weinreb amides was evidenced. Accordingly, no loss of the optical purity was evident during the homologation process and, as a consequence, non-racemic α -oxyketones could be prepared through a simple and convenient procedure. The reductive lithiation–Weinreb amide homologation procedure could be realized with optically active α -oxygenated lithium species, as indicated in the case of enantiomerically pure menthyl ethers. It is worth noting that α -oxymethyl lithium reagents can also be obtained via tin/lithium exchange, as demonstrated during the synthesis of (+)-benzastatin E.⁴³



2.4 Synthesis of β -Oxo Thioethers (α -Thioketones)

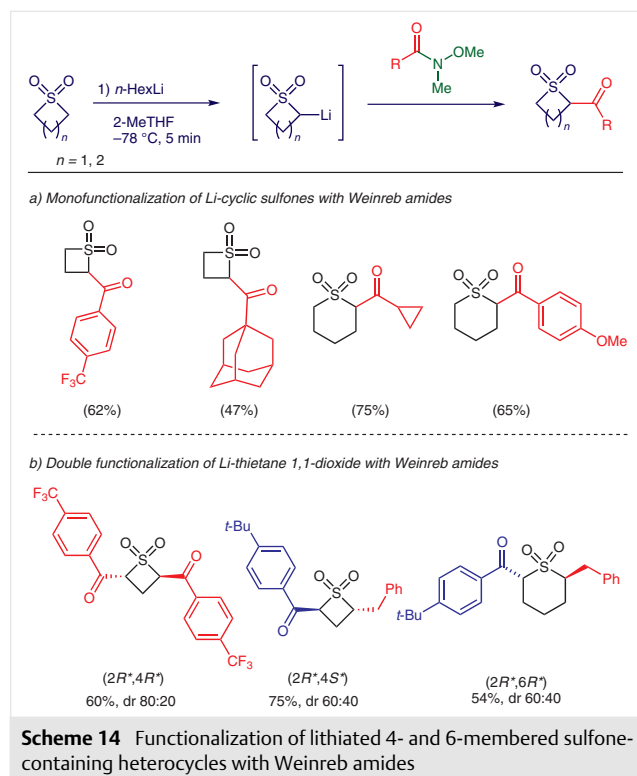
Pace and co-workers adapted the Yus reductive lithiation method to the preparation of thio-analogues:⁴⁴ the simple switching to chloromethyl thioethers, *ceteris paribus*, leads to the formation of LiCH_2SR -type reagents which could be effectively acylated with Weinreb amides for synthesizing β -oxo thioethers in high yields (Scheme 13). The methodology is effective for (hetero)aromatic, α,β -unsaturated and aliphatic Weinreb amides, including when steric factors may in principle be problematic. The process showed excellent stereofidelity when employing enantiopure Weinreb amides (in analogy to the above-presented α -oxymethyl ketones), with complete transfer of the stereochemical information contained in the starting material during the homologation step. The application of the Corey–Seebach deprotonation strategy⁴⁵ with thioanisole derivatives extended the tactic to the synthesis of similar α -arylthiomethyl ketones, again for both aromatic and aliphatic Weinreb amides. This procedure is also amenable for preparing β -oxo thioacetals via the generation of methoxy(phenylthio)methylolithiums and α,α -dithioketones by the lithiation of 1,3-dithiane.

Pace and collaborators investigated the reactivity of four- and six-membered cyclic sulfones in lithiation/electrophilic-trapping sequences (Scheme 14).⁴⁶ The regio- and stereoselective metalation of thietane 1,1-dioxide and its six-membered homologue, tetrahydro-2H-thiopyran 1,1-dioxide, was studied after trapping the lithiated species with various carbonyl-type electrophiles. When Weinreb amides were employed, ketones bearing an endocyclic sulfur at the α -position were obtained. In the case of thietane 1,1-dioxide, the cyclic α -sulfonyl carbanion could be generated by using the relatively less hazardous *n*-hexyllithium as base. A preliminary screening of the lithiation reaction conditions indicated 1.1 equivalents and 2.5 equivalents of *n*-HexLi as the optimal ratio to guarantee mono- and difunctionalization of thietane 1,1-dioxide, respectively. Moreover, the use of the green solvent 2-MeTHF⁴⁷ gave a more selective reaction leading to the desired C2 mono- or C2, C4 di-substituted derivatives in good yields as a single products, thus rendering the whole process eco-compatible. Regarding the double functionalization, a *trans* stereochemical propensity in the lithiation of thietane sulfones was observed. When the six-membered heterocycle tetrahydro-2H-thiopyran 1,1-dioxide was used as the carbanion



Scheme 13 Synthesis of α -thiomethyl ketones from Weinreb amides and α -thiomethyl carbanions

source, a mixture of mono- and disubstituted derivatives was obtained in all cases. Nevertheless, the use of 1.1 equivalents of *n*-HexLi in 2-MeTHF was found to be the best choice for the C2-monofunctionalization. However, a selective C2, C4 double functionalization was not possible due to a competing double H-abstraction, even when using 2.5 equivalents of *n*-HexLi for prolonged times.



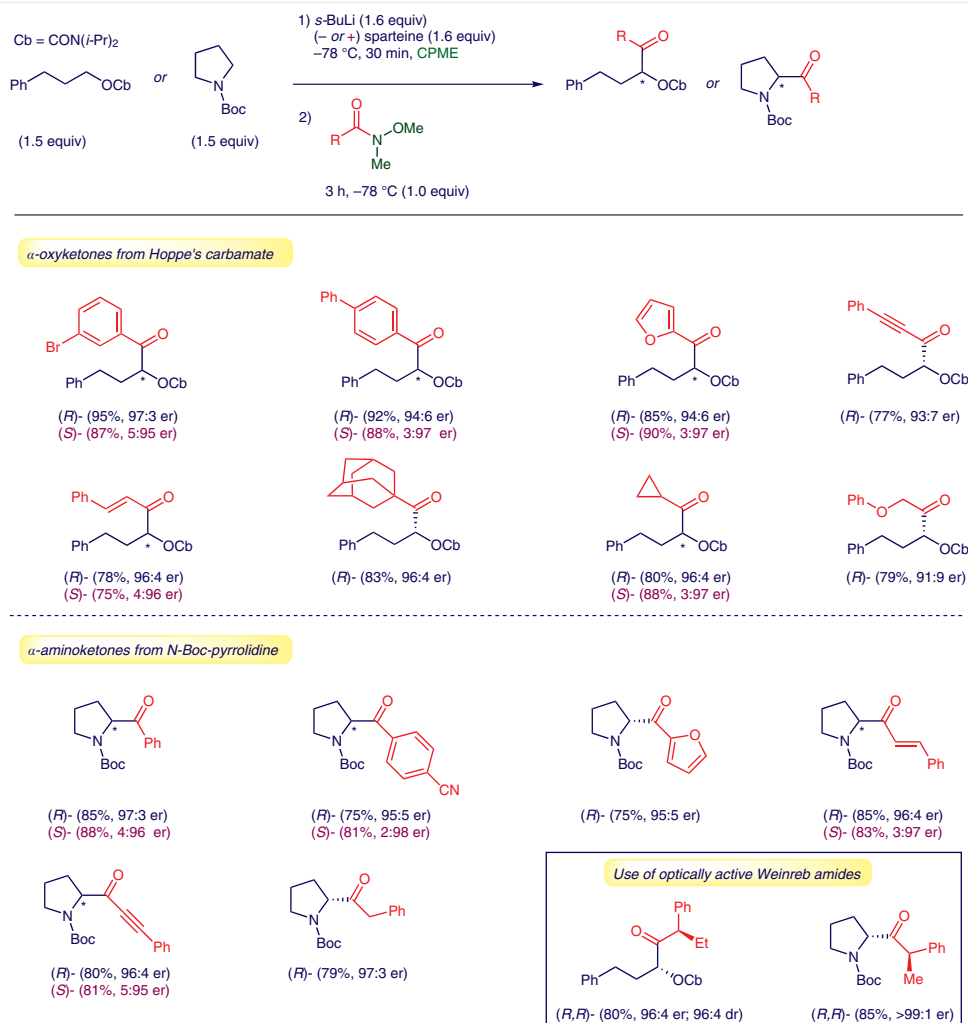
2.5 Synthesis of Chiral α -Oxy and α -Nitrogen Ketones via the Sparteine-Mediated Generation of Optically Active Organolithiums

The examples discussed above deal with the use of starting materials (enantioenriched Weinreb amides and/or α -substituted organolithiums) featuring well-defined stereochemical information. It is evident that inducing stereochemistry within the same process would make the overall strategy more flexible and versatile. Cognizant of the well-established Hoppe–Beak chemistry for furnishing optically active organolithiums through asymmetric deprotonation processes,⁴⁸ the Pace group reported very recently the preparation of enantiopure substituted ketones upon quenching of these carbanions with Weinreb amides (Scheme 15).²² Among the different acylating agents screened, Weinreb amides emerged as ideal for accomplishing this challenging goal under full chemo- and stereocontrol. The unprecedented use of such an approach for preparing chiral ketones is also particularly convenient from a sustainable perspective. The methodology shows an excellent

substrate scope, being completely adaptable to the synthesis of α -amino-type ketones (derived from the asymmetric deprotonation of *N*-Boc-pyrrolidine). Uniformly high yields and excellent *er* values were observed, and by simply switching from one enantioform of sparteine to the other, both enantiomers of a given ketone were prepared in comparable yield and optical purity. The scope of the methodology was extensive allowing modification of the Weinreb amide core at wish. In particular, sensitive functionalities such as halogens, electrophilic nitriles, sterically demanding groups and unsaturated substituents did not impact on the excellent chemoselective profile. The use of enantiopure Weinreb amides permits access to diastereopure ketones in which no erosion of optical purity was observed; remarkably, the subsequent manipulation of these scaffolds provides a valuable entry to important building blocks such as chiral diols. In analogy to tetrahedral intermediates originating from halolithiums,³⁰ the first evidence of these chiral species is provided with an enantiopure lithiated carbamate.

Furthermore, enantioenriched α -oxy- α -methylbenzyl-lithium reagents, generated in the absence of sparteine starting from optically active carbamates, are suitable partners for the reaction with variously functionalized Weinreb amides (Scheme 16). Significantly, in the case of a propargylic system, inversion of the configuration occurred at the quaternary lithiated carbon. In agreement with Hoppe's seminal studies⁴⁹ on the stereochemical outcome of analogous nucleophilic substitution processes, 1,4-addition of the carbanions was noticed. Such a Michael-type addition of organolithium reagents to α,β -unsaturated Weinreb amides represents a notable exception to the generally observed phenomenon of genuine 1,2-additions. The stereochemical outcome of the process is determined by the ability of the expelled leaving group to coordinate the lithium cation, and/or by the LUMO involved.⁴⁹ Taking into account that NMe(OMe) efficiently coordinates Li, similarly to a general RO group of an ester, it is possible to suppose that Weinreb amides prefer suprafacial attack with retention of configuration.

As indicated, cyclopentyl methyl ether (CPME)⁵⁰ constituted the best solvent for running the sparteine-mediated process. In particular, asymmetric deprotonation with both enantioforms of sparteine conducted in CPME⁵¹ are extremely fast (30 min)—compared to normally used diethyl ether—and allows the optical purity to be preserved within the whole process. The substantial immiscibility of this solvent with water guarantees extremely easy work-up procedures, often limited to simple recrystallization. Considering the scarcity⁵² and the high cost of sparteine at commercial level, careful optimization of the work-up procedure permits recovery of up to 80% of the sparteine used for generating the chiral organolithiums (Scheme 17).⁵³ Upon acidic quenching of the reaction mixture and water/organic phase separation, both the protonated sparteine and the Weinreb

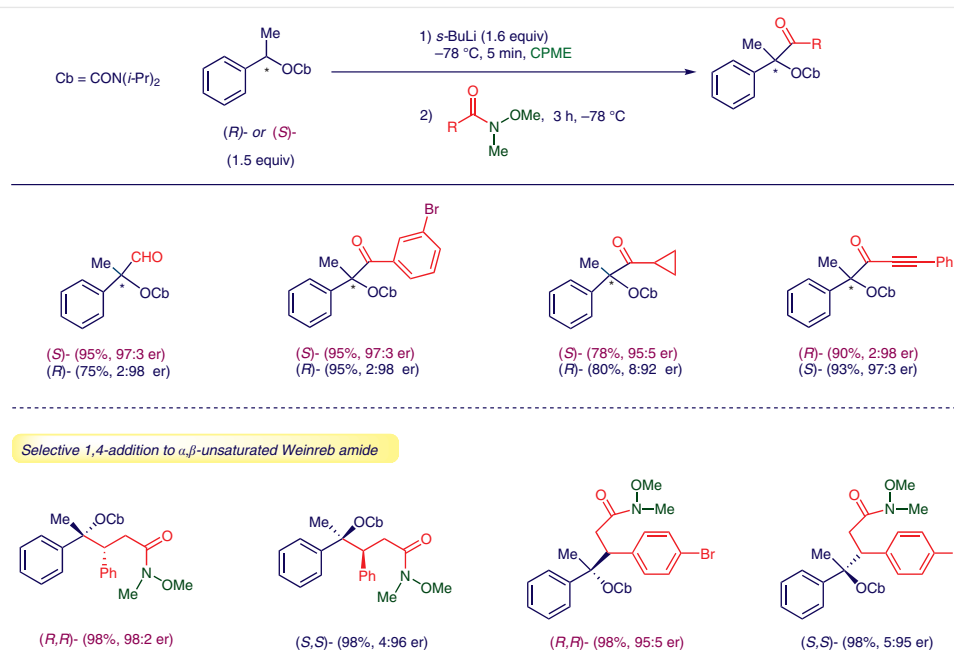
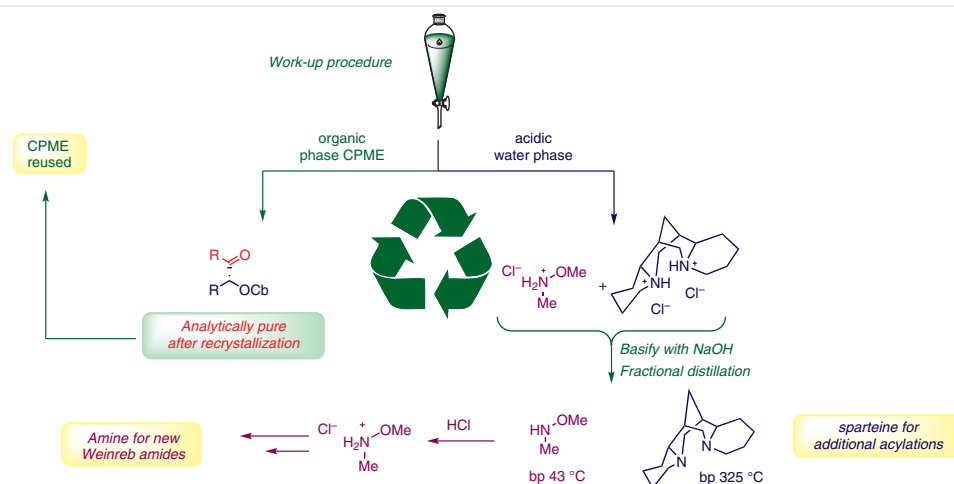


Scheme 15 Synthesis of chiral α -oxy- and α -amino ketones from Weinreb amides and lithiated Hoppe carbamates or *N*-Boc-pyrrolidine in the presence of (–)- and (+)-sparteine

‘amine’ [$\text{HNCH}_3(\text{OCH}_3)$] remained in the water phase. Through standard NaOH basification followed by fractional distillation, the two pure free aminic compounds could be separated and recycled for additional processes without affecting the efficiency. Evidently, the substantial difference between the boiling points of the Weinreb ‘amine’ (43°C) and sparteine (325°C) is the crucial factor enabling the success of the operation. As anticipated, having found a reliable technique to recycle the Weinreb ‘amine’ fragment (together with the expensive sparteine and CPME), it is hoped to contribute to further adhere classical polar organometallic chemistry to the demanding principles of green chemistry.²³

2.6 Synthesis of α -Selenomethyl Ketones

The Cu-catalyzed diazomethane homologation of selenoesters, first documented by Back in 1982, represents one of the few synthetic strategies en route to α -selenoketones.⁵⁴ With this methodology, diselenoacetals were obtained as reaction by-products in considerable amounts together with methyl ketones, while the desired α -substituted selenomethyl ketones were formed in only limited yields. Pace and co-workers realized that these diselenoacetals, obtainable in high yields via the bromomethyl lithium homologation of diselenides,⁵⁵ could serve as suitable precursors for the generation of lithium-substituted α -methylselenocarbanions through a convenient selenium/lithium exchange (Scheme 18).⁵⁶ Accordingly, upon formation under non-Barbier-type conditions of a series of aryl- and alkyl-selenomethyl lithium reagents (LiCH_2SeR), subsequent

Scheme 16 Reactivity of α -oxy- α -methylbenzylithium with Weinreb amides

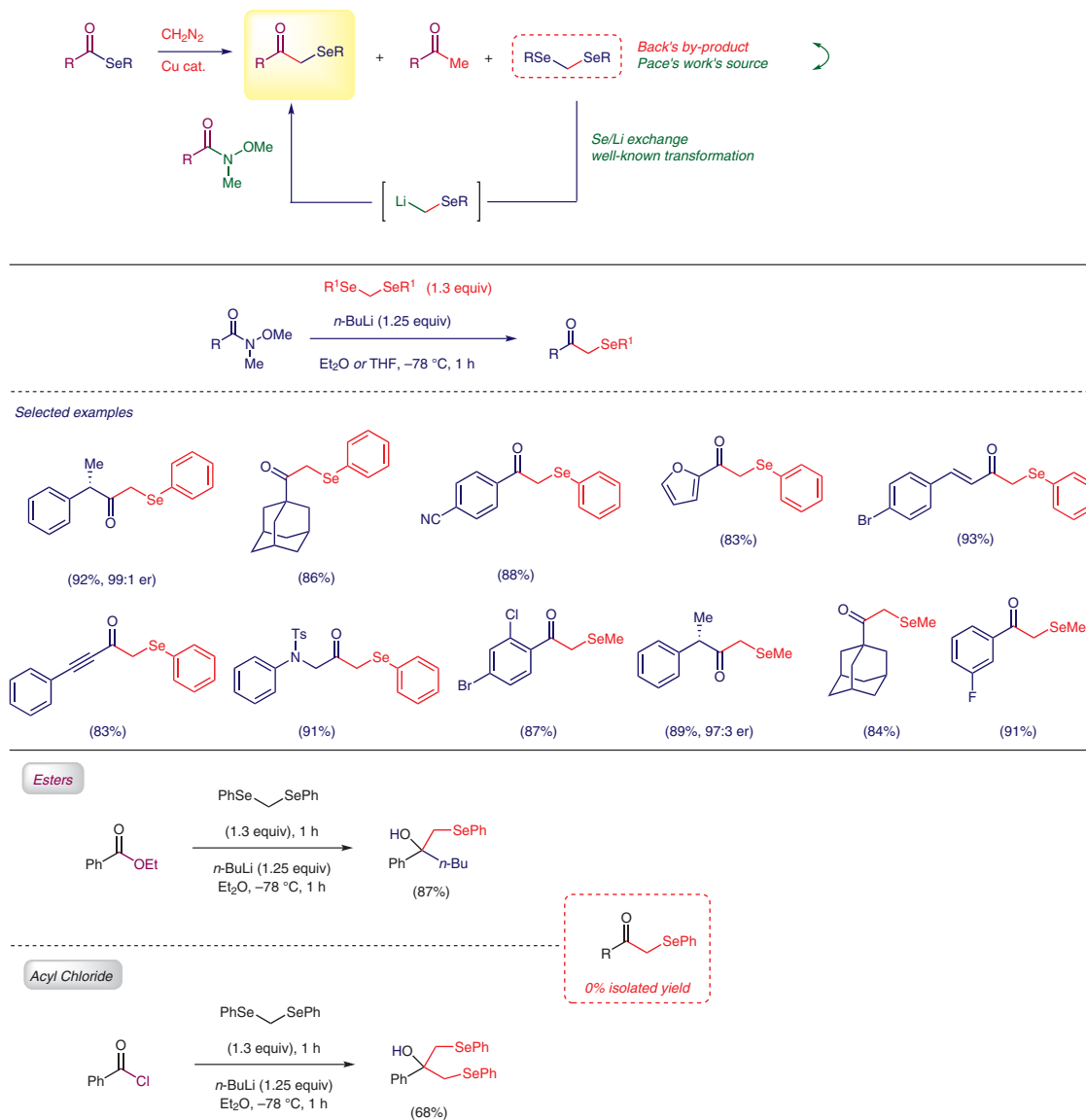
Scheme 17 A recycling system for sparteine, the Weinreb 'amine' and CPME analytically

trapping with variously substituted Weinreb amides offered a versatile strategy to reach α -selenomethyl ketones in good to excellent yields. Slight excesses of diselenoacetals (1.3 equiv) and $n\text{-BuLi}$ (1.25 equiv) in diethyl ether or THF (depending on the nature of the selenating agent) were found to be optimal for the genesis of the substituted carbanion, which could be added to a series of widely functionalized Weinreb amides. Again, sensitive groups (halogens, thioethers, unsaturated motifs, sterically demanding elements, nitriles, α -heteroatoms) were perfectly tolerated

during the standard nucleophilic acylation. As evidenced in the case of α -oxy and α -amino carbanions, the stereofidelity was preserved during the homologation sequence. It is important to highlight the unique capability of Weinreb amides in conferring the chemoselectivity. Control experiments conducted on an ester resulted in the formation of a carbinol, presumably obtained through the intervention of a Se-ate complex, while the analogue acid chlorides undergo the common double addition of the nucleophile leading to a diseleno-carbinol.

- Diazomethane insertion into selenoesters (Back, 1982)

- Nucleophilic addition of α -selenomethyl lithium to Weinreb amides (Pace, 2018)

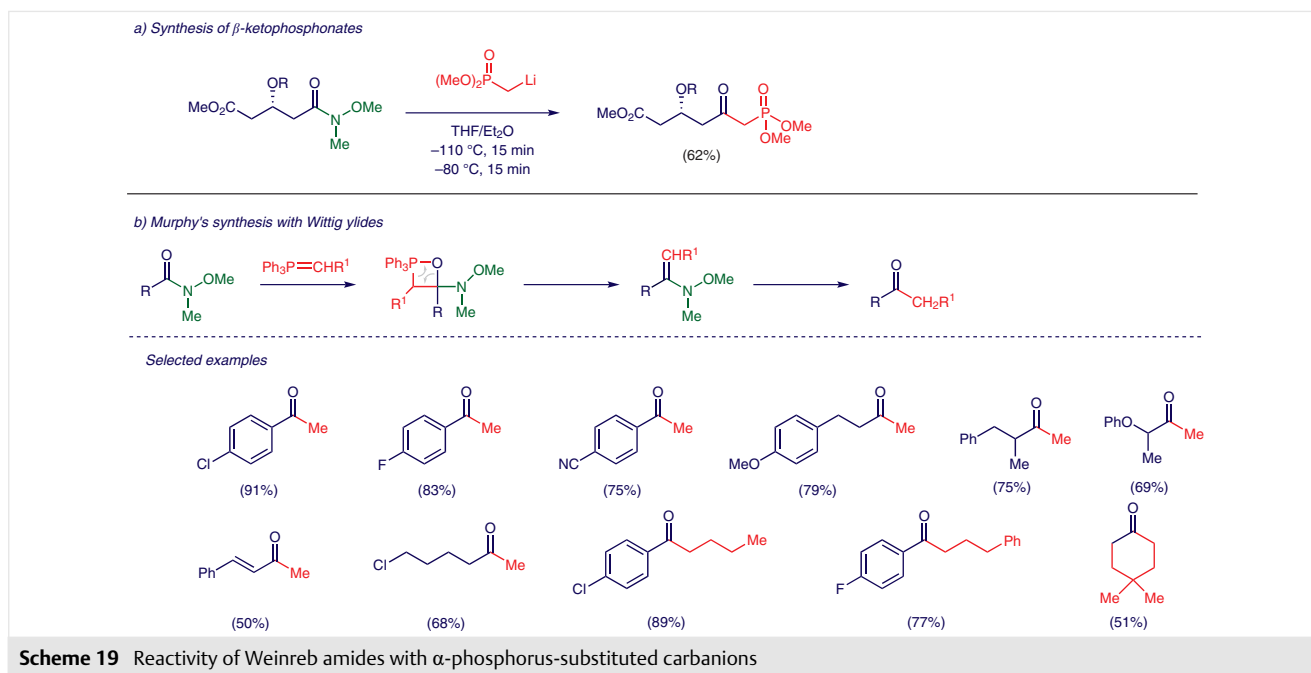


Scheme 18 The use of Weinreb amides for the preparation of α -selenomethyl ketones

2.7 Reactivity of α -Phosphorus Carbanions with Weinreb Amides

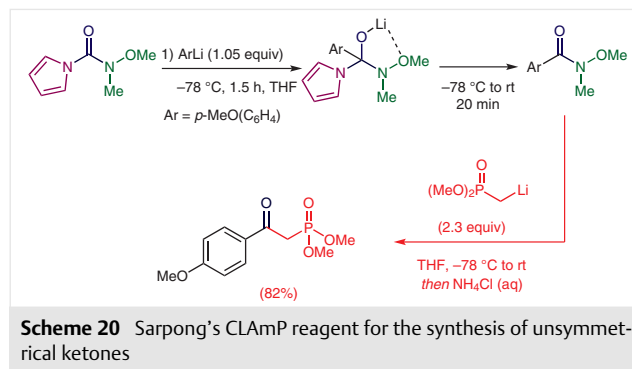
The addition of a phosphonate lithium anion to Weinreb amides is a versatile protocol used in total synthesis to form α -ketophosphonate precursors of Wadsworth–Emmons reagents.⁵⁷ Despite the strongly nucleophilic nature of lithium phosphonates, genuine chemoselectivity was evidenced in systems presenting contemporaneously a Weinreb amide and an ester (Scheme 19a).⁵⁸ Accordingly, at low temperatures, exclusive attack on the Weinreb amide was observed. In line with their unique reactivity, Wittig phosphorus

ylides interact with Weinreb amides furnishing ketones. As introduced by Murphy, the formation of an oxaphosphetane is followed by a cycloreversion—extruding triphenylphosphine oxide—which leads to a putative enamine, the hydrolysis of which furnishes the methyl ketone (Scheme 19b).⁵⁹ By properly selecting the Wittig reagent, it is possible to access variously functionalized ketones, including via triggering of intramolecular processes which result in the formation of cyclic motifs. Considering the mild conditions required, the protocol represents a valid entry to multifunctionalized ketones, which in principle could be problematic with classical carbanionic reagents.

Scheme 19 Reactivity of Weinreb amides with α -phosphorus-substituted carbanions

2.8 Modification of the Weinreb Amide Core: The CLAMP Reagent

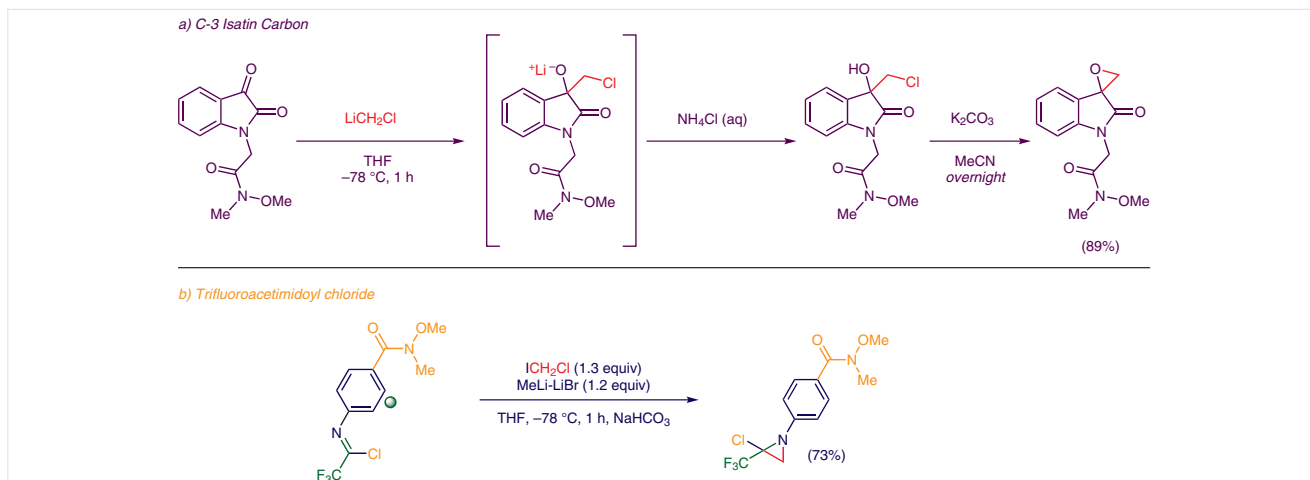
In 2015, Sarpong disclosed a one-pot procedure for the synthesis of unsymmetrical ketones by introducing an electrophilic carbonyl linchpin reagent, *N*-methoxy-*N*-methyl-1*H*-pyrrole-1-carboxamide (CLAMP), acting as a dication synthetic equivalent (Scheme 20).⁶⁰ This species features and combines two leaving groups, each of which generate differently stable tetrahedral intermediates upon sequential addition of two organometallic nucleophiles. The controlled collapse of the first tetrahedral intermediate generates a new carbonyl electrophile, i.e., a Weinreb amide, which can then react with a second organometallic reagent, finally furnishing the disubstituted ketone. While studying the wide scope of the method, lithium phosphonates were used in the second addition step to form unsymmetrical ketones bearing a phosphorus atom at the α -position to the carbonyl group. The ketone oxidation state is preserved by the persistence of the tetrahedral intermediate derived from the second addition, which prevents overalkylation at the electrophilic carbon.



Scheme 20 Sarpong's CLAMP reagent for the synthesis of unsymmetrical ketones

3 Competing Attack of Nucleophiles at More Reactive Electrophilic Sites than Weinreb Amides

Weinreb amides represent excellent acylating agents for α -substituted organometallic reagents and the concomitant presence of additional reactive sites usually does not impede selective transformations, thus targeting the nucleophile towards the amide (Scheme 21). However, highly electrophilic functionalities such as the ketones of isatins⁶¹ or trifluoroacetimidoyl chlorides⁶² alter this behavior and, accordingly, halomethylolithiums react exclusively at those positions generating interesting structures such as spiro-epoxyoxyindoles or a quaternary trifluoromethyl-aziridine decorated with a pendant Weinreb amide. As a consequence, late manipulations of this fragment offer the possibility to further increase the final molecular complexity.



Scheme 21 The non-reactivity of Weinreb amides towards halolithiums in the presence of higher order electrophiles

4 Conclusions

The unique reactivity of α -substituted methyl carbanions can be conveniently employed for preparing valuable α -functionalized ketones through their acylation with Weinreb amides. The use of these electrophiles enables researchers to usually confer high chemocontrol and, in this context, no undesired phenomena such as overaddition, which are rather common with different acylating agents such as esters or acid chlorides, are observed. Importantly, the use of reaction partners (both Weinreb amide and carbanion) embodying stereochemical information enables a conceptually intuitive and extremely easy access to enantiopure α -substituted ketones. Additionally, the economic aspects of the acylation can be advantageously improved by designing a valid protocol for recycling the expensive Weinreb 'amine' [$\text{HNCH}_3(\text{OCH}_3)$], which otherwise would be treated as waste. The fine-tuning of the work-up procedure enables not only the recovery of this amine, but also of the solvent, and more importantly, of the precious, highly expensive, ligand sparteine in up to 80% loading. In summary, the recent developments in the use of Weinreb amides with highly functionalized and potentially unstable α -substituted carbanions further strengthens their prominent position as safe, selective and highly versatile agents in acylation processes of interest for academic and industrial audiences.

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Publication n. 2

Substituted α -Sulfur Methyl Carbanions: Effective Homologating Agents for the Chemoselective Preparation of β -Oxo Thioethers from Weinreb Amides.

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Details on experimental procedures, characterization data and copies of NMR spectra of all compounds are reported.



Thioethers

Substituted α -Sulfur Methyl Carbanions: Effective Homologating Agents for the Chemoselective Preparation of β -Oxo Thioethers from Weinreb AmidesRaffaele Senatore,^[a] Laura Ielo,^[a,b] Ernst Urban,^[a] Wolfgang Holzer,^[a] and Vittorio Pace^{*[a]}

Dedicated to Professor Lucio Pellacani on the occasion of his retirement

Abstract: The proper generation of α -thiomethyl lithium reagents via reductive lithiation or deprotonation followed by reaction with variously functionalized Weinreb amides represents an excellent method to access β -oxo thioethers. The procedure is adaptable to alkyl- or aryl- thiomethyl lithium conjugates. It

has the advantages of conceptual simplicity and versatility of the addition of organometallics to Weinreb amides with the possibility to fully preserve the optical information contained in the starting materials.

Introduction

The β -oxo thioether motif constitutes an interesting organic framework widely present in biologically active or agrochemical relevant substances.^[1] From a synthetic perspective its versatility stems on the application as precursors of heterocycles^[2] or important intermediates as the Julia's sulfur ylides.^[3] Moreover, the presence of a sulfur-containing substituent at the α position of the ketone accounts for a significant stabilization of the corresponding enolate.^[4] As a consequence of this relevance, several strategies have been designed to address the preparation of such targets (Scheme 1). The nucleophilic substitution on reactive α -haloketones with mercaptans is conceptually the simplest approach (*path a*).^[5] However, the inherent high reactivity and the low safety profile of haloketones together with regiochemical issues make this strategy not ideal. Indeed, the base-triggered enolization of simple ketones followed by the quenching with electrophilic sulfur-analogues introduced by Trost in the 1970s (*path b*)^[4,6] does represent a versatile alternative which put the bases for developing catalytic asymmetric sulfenylation processes as recently documented by Denmark.^[7] Similar electrophilic sulfur agents (e.g. disulfides) can be conveniently employed in the Bolm's Cu-mediated sulfenylation of β -oxocarbonyls (*path c*).^[8] Metal-catalyzed S–H insertion into diazocarbonyls are not preferred options as a consequence of the somewhat limited selectivity and efficiency (*path d*).^[9] Novel

synthetic tools include the catalyst-free insertion of Corey–Chaykovsky type ylides into aryl thiols introduced by Burtoloso (*path e*)^[10] and Samec's Pd/Au catalyzed click-type chemistry (*path f*).^[11] Inter alia.^[12]

In recent years, our group documented the effectiveness of using Weinreb amides^[13] as privileged acylating agents in reactions involving α -functionalized methyl lithium reagents (LiCH_2X)^[14] for the straightforward preparation of α -substituted ketones.^[15] The high stability of (isolable) tetrahedral intermediates generated upon the reaction of the Weinreb amides with such carbenoid nucleophiles accounts for excellent chemocontrol and synthetic efficiency.^[16] The tactic is highly versatile, wide in scope and is not influenced by the nature of the two reactions partners (nucleophile and electrophile^[17]). Accordingly, halomethyl lithium compounds (LiCH_2Hal , $\text{Hal} = \text{Cl}, \text{Br}, \text{I}, \text{F}$)^[18] functionalized lithiated acetonitriles (LiCRR^1CN)^[19] or α -oxy or α -selenomethyl analogues (LiCH_2ZR , $\text{Z} = \text{O}, \text{Z} = \text{Se}$)^[20] can be added to Weinreb amides in a single synthetic operation, finally providing valuable α -substituted ketones. Pivotal for the success of the method was finding the optimal conditions enabling the safe employment of relatively unstable α -methyl lithium reagents: as such, the proper choice of the lithiation conditions (Barbier or non-Barbier type)^[21] represented the key parameter to be tuned case by case.

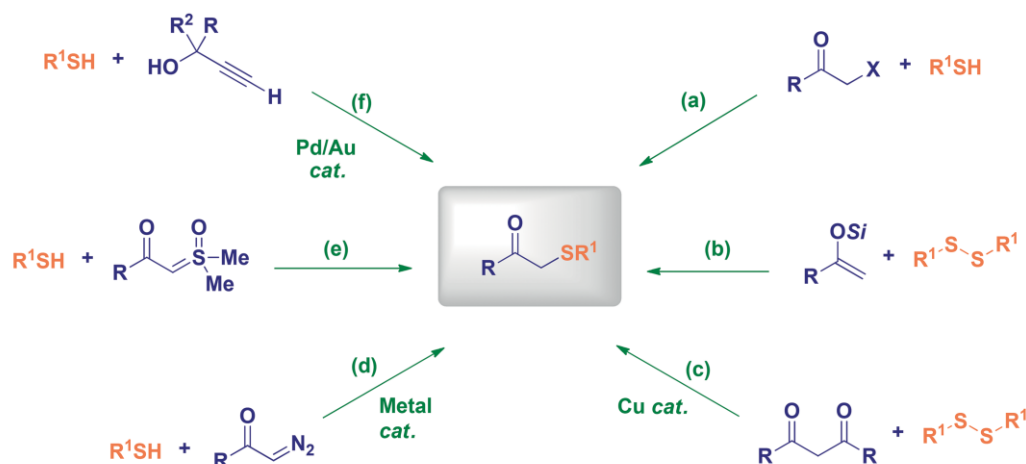
Should the tactic be extended to α -thiomethyl lithium reagents a direct and straightforward access to α -sulfur substituted ketones could be envisaged and, herein we introduce its feasibility. We anticipate the methodology enables the preparation of both S-alkyl and S-aryl type β -thiomethyl ketones thus, overcoming common difficulties in finding suitable procedures adaptable to both targets. Moreover, the formal introduction of the CH_2SR carbanion with the precise degree of functionalization and in the required (sulfur) oxidation state guarantees a high level of chemocontrol to the process.

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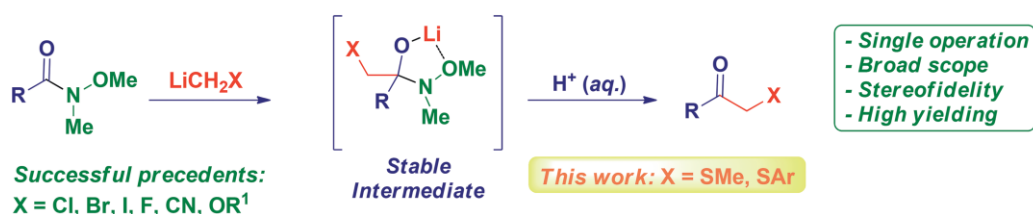
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Known Strategies



Homologation of Weinreb Amides en route to α -Substituted Methylketones



Scheme 1. General context of the presented work.

Results and Discussion

The reaction between the enantiopure Weinreb amide **1** (99:1 *er*) and LiCH₂SMe was individuated as the model transformation to assess both the synthetic efficiency and the preservation of the optical purity during the C–C bond formation event (Table 1). By lithiating dimethylsulfide with *n*BuLi-TMEDA,^[22] the expected ketone **2** was obtained in 71 % yield with significant loss of stereochemical information (78:22 *er*, entry 1). Analogously, generating the carbanion in the presence of DABCO (1,4-diazabicyclo[2.2.2]octane)^[23] resulted in a similar negative outcome (74:26 *er*, entry 2). Preparing the nucleophile via a Sn–Li exchange on (*n*-Bu)₃SnCH₂SMe with *n*BuLi in THF as introduced by Peterson in 1971^[24] allowed to prepare the desired target with better chemical yield and enantiopurity (82 %, 87:13 *er*, entry 3). Notably, by switching to more apolar reaction media (toluene or diethyl ether) resulted in slightly increase of stereocontrol (entries 4–5) and comparable yield. A significant improvement was observed by generating LiCH₂SMe through the arene (DTBB, 4,4'-di-*tert*-butylbiphenyl) catalyzed Yus' reductive lithiation^[25] of the commercially available chloromethyl thiomethyl ether ClCH₂SMe under non-Barbier conditions. Effectively, by adapting such an approach previously exploited for generating the oxo-analogue LiCH₂OMe,^[20] ketone **2** was synthesized in an excellent 93 % isolated yield and superb stereofidelity (> 99:1 *er*, entry 6). Attempts to decrease the amount of

Li metal (even with higher catalyst loading, entry 7) or switching to different ethereal solvents (2-MeTHF^[26] or CPME,^[27] entries 8–9) had a detrimental effect on the yield, although in the absence of noticeable racemization.

Having established the optimal conditions, we then studied the scope of the method (Scheme 2). Again, excellent yield and optical purity was found in the case of a different chiral Weinreb amide, thus opening the access to previously unknown enantiopure α -thioketone **3**. Aromatic Weinreb amides featuring a different substitution pattern on the aryl ring proved to be ideal starting materials for the corresponding β -oxo thioethers **4–10**; neither significant variation was noticed starting from an heteroaromatic Weinreb amide (**11**). Moreover, α,β -unsaturated systems could be conveniently employed for the protocol giving ketones **12** and **13** in high yield. The methodology preserves its effectiveness also in the case of aliphatic Weinreb amides (**14–16**): variously functionalized α -thioketones including the α -methylthiomethyl- α' -phenoxy analogue **15** or the high sterically demanding adamantyl derivative **16** could be smoothly prepared.

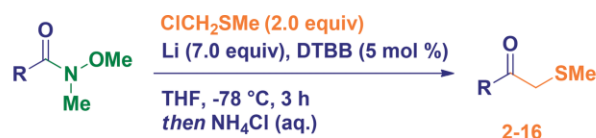
By applying the Corey–Seebach deprotonation strategy (*n*BuLi-DABCO, 0 °C, THF)^[28] of thioanisole derivatives (PhSMe) it was possible to extend the tactic to the synthesis of α -arylthiomethyl ketones **17–22** starting from aromatic or aliphatic Weinreb amides. The additional presence of a halogen on the

Table 1. Optimization of the method.^[a]

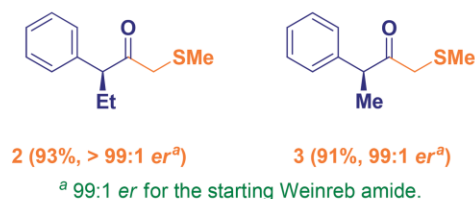
1 2

Entry	[CH ₂ SMe] source (equiv.)	Lithiating reagent (equiv.)	Additive (equiv.)	Yield of 2 ^[b] [%], <i>er</i>
1	MeSMe (2.0)	<i>n</i> BuLi (2.0)	TMEDA (2.0)	71, 78:22
2	MeSMe (2.0)	<i>n</i> BuLi (2.0)	DABCO (2.0)	68, 74:26
3	(<i>n</i> -Bu) ₃ SnCH ₂ SMe (1.6)	<i>n</i> BuLi (1.6)	–	82, 87:13
4 ^[c]	(<i>n</i> -Bu) ₃ SnCH ₂ SMe (1.6)	<i>n</i> BuLi (1.6)	–	80, 90:10
5 ^[d]	(<i>n</i> -Bu) ₃ SnCH ₂ SMe (1.6)	<i>n</i> BuLi (1.6)	–	77, 91:9
6	ClCH ₂ SMe (2.0)	Li (7.0)	DTBB (0.05)	93, 99:1
7	ClCH ₂ SMe (2.0)	Li (5.0)	DTBB (0.10)	75, 99:1
8 ^[e]	ClCH ₂ SMe (2.0)	Li (7.0)	DTBB (0.05)	84, 97:3
9 ^[f]	ClCH ₂ SMe (2.0)	Li (7.0)	DTBB (0.05)	80, 98:2

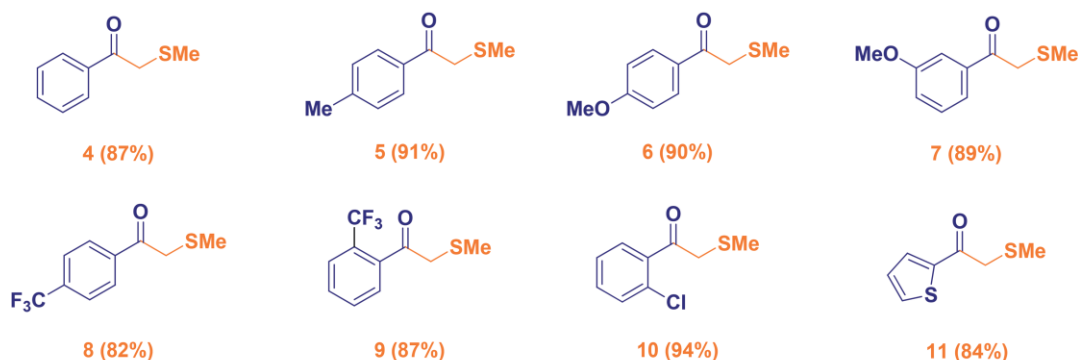
[a] Otherwise stated reactions were run in anhydrous THF. [b] Isolated yield. [c] Toluene as the solvent. [d] Et₂O as the solvent. [e] 2-MeTHF as the solvent. [f] CPME as the solvent.



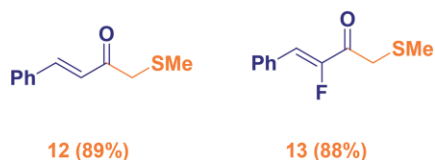
Optically Active Weinreb Amides



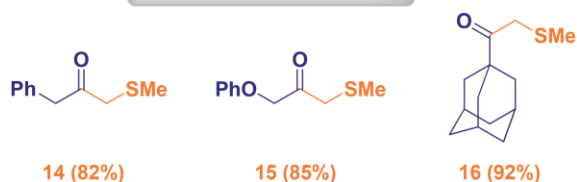
Aromatic Weinreb Amides



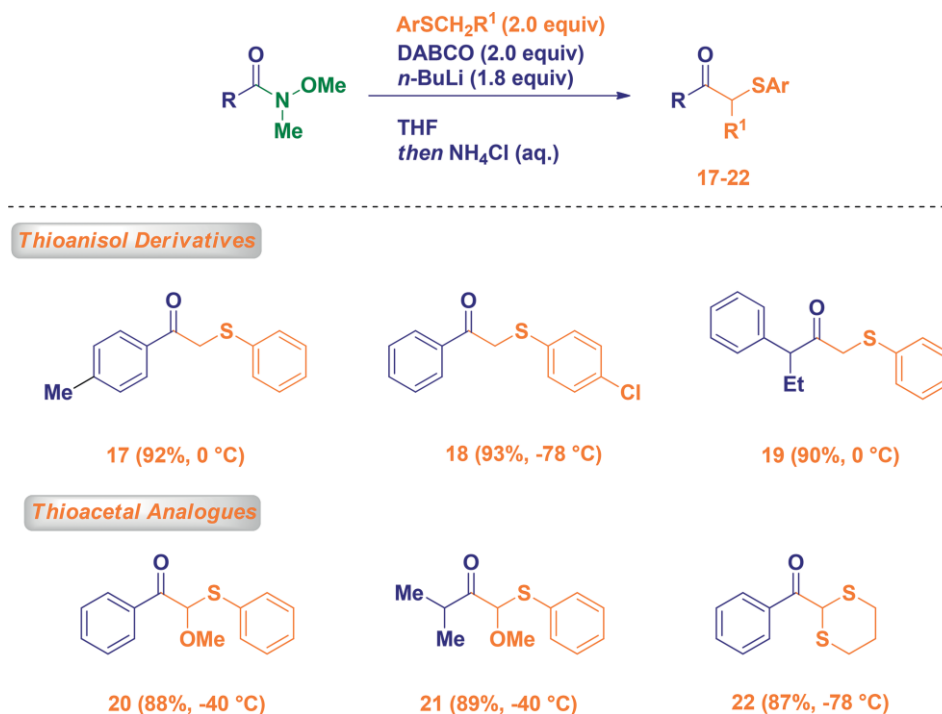
α,β-unsaturated Weinreb Amides



Aliphatic Weinreb Amides



Scheme 2. Scope of the LiCH₂SMe addition to Weinreb amides.



Scheme 3. Synthesis of α -arylthiomethyl ketones and α -thioacetal-like methyl ketones.

thioanisole core did not alter the outcome (**18**). Running the reaction at higher temperatures (-40 or 0 °C) would suggest a considerably increased stability of those α -sulfur substituted methylolithiums. The procedure is also amenable for furnishing interesting scaffolds such as β -oxo thioacetals **20–21** via the formation of methoxy(phenylthio)methylolithium.^[29] Finally, 1,3-dithiane underwent the lithiation and Weinreb amide trapping sequence, thus yielding the cyclic α,α -dithioketone **22** (Scheme 3).

Conclusions

In summary, we have disclosed a reliable and direct access to variously substituted β -thiomethyl ketones through the addition of α -sulfur methylolithium reagents to Weinreb amides. By properly selecting the conditions for forming the carbanions (the arene-catalyzed Li-metal mediated lithiation of Yus or the organolithium-mediated deprotonation), it is possible to chemoselectively modulate the access to the targets. Uniformly high yields and the full transfer of stereochemical information from the starting Weinreb amide to the final compounds make this simple tactic particularly suitable for further applications in organic synthesis.

Experimental Section

General Procedure for the Lithiation with Li Metal: Lithium metal (7.0 equiv., 25 % dispersion in mineral oil) was placed in a Schlenk tube under Argon, washed with dry THF for 3 times and suspended in the same solvent (1 M concentration). DTBB (5 mol-%) was added and, the mixture was stirred until the appearance of the dark green color. This suspension was cooled down to -78 °C and then,

$\text{ClCH}_2\text{SCH}_3$ (2.0 equiv.) was added dropwise. A 1.0 M solution of the Weinreb amide (1.0 equiv.) in dry THF was introduced and, the mixture was kept whilst stirring at -78 °C for 3 h and then, quenched with aqueous NH_4Cl . Subsequently, the reaction mixture was allowed to reach room temp. and extracted three times with Et_2O , washed with brine, and the organic phase was dried with Na_2SO_4 and concentrated in vacuo. The resulting crude compounds were purified through flash column chromatography.

General Procedure for the Lithiation via Deprotonation: The thioether derivative (2.0 equiv.) was added to a solution of DABCO (2 equiv.) at 0 °C (or, alternatively at -78 °C for compounds **18**, **20** and **21**) in THF (1 M concentration) under Argon atmosphere. Then *n*-butyllithium (1.8 equiv.) was added dropwise and, the mixture stirred for 1.5 h at the same temperature (-40 °C for compounds **20** and **21**). A 0.5 M solution of the Weinreb amide (1.0 equiv.) in dry THF was added and, the mixture was stirred at 0 °C for 1.5 h (-78 °C for 6 h and then room temp. for 12 h for compounds **20** and **21**). After quenching with aqueous NH_4Cl , the reaction mixture was allowed to reach room temp. Extraction with Et_2O ($\times 3$), washing with brine and drying the organic phase over Na_2SO_4 afforded a crude (previous concentration in vacuo) which was purified through flash column chromatography.

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Keywords: Homologation · Lithiation · Weinreb amides · Sulfur · Ketones

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Expeditious and Chemoselective Synthesis of α -Aryl and α -Alkyl Selenomethylketones via Homologation Chemistry.

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Details on experimental procedures, characterization data and copies of NMR spectra of all compounds are reported.

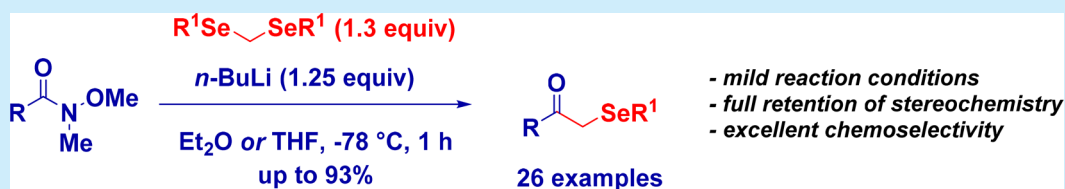
Expeditious and Chemoselective Synthesis of α -Aryl and α -Alkyl Selenomethylketones via Homologation Chemistry

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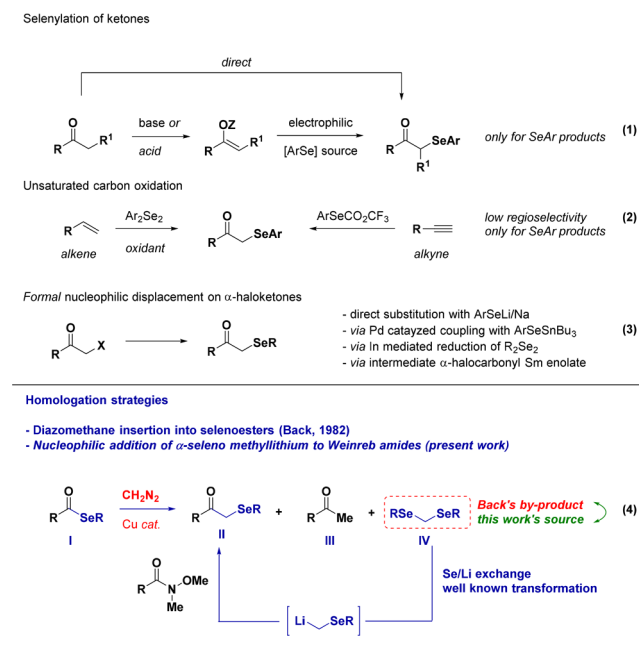
S Supporting Information



ABSTRACT: Diselenoacetals, previously considered byproducts in homologation tactics en route to α -selenoketones, are herein found to be excellent starting materials for this purpose. The easy selenium/lithium exchange they undergo affords seleno carbanions which are smoothly added to Weinreb amides to chemoselectively prepare α -aryl- and α -alkyl seleno methylketones through a single chemical operation. No racemization events are observed in the presence of optically pure starting materials.

The unique physical–chemical properties of selenium make the corresponding organometallic compounds formidable intermediates in modern chemistry.¹ The ideal balance between reactivity and selectivity observed through their judicious employment accounts for a prominent position in the design of chemo-, regio-, and stereocontrolled reactions.² In this context, the introduction of selenium (via electrophilic, nucleophilic, or radical chemistry) into organic arrays becomes crucial in order to exploit this synthetic potential.³ Within the broad variety of organoselenium compounds, substituted α -seleno methylketones^{1a,4} represent particularly versatile manifolds as documented in the seminal studies by Sharpless,⁵ Reich,⁶ and Clive.⁷ In fact, the extremely mild *syn* elimination of selenoxides they undergo constitutes currently an established tool for obtaining α,β -unsaturated carbonyls of particular interest, *inter alia*, for natural products synthesis.^{2a–d,8} From a conceptual point of view, the available preparative strategies can be included into the following main categories (Scheme 1): (1) electrophilic selenylation of ketones direct or via the corresponding enolates and enols (Scheme 1, eq 1);^{5b,6a,9} (2) oxidation of olefins¹⁰ or acetylenes¹¹ in the presence of electrophilic selenium sources (Scheme 1, eq 2); (3) formal substitution on α -haloketones with nucleophilic selenium species such as RSeLi/Na ^{6b} or generated via Pd-,¹² Sm-,¹³ and In-mediated¹⁴ processes (Scheme 1, eq 3). Although they represent useful platforms toward *cyclic* α -seleno ketones, the preparation of *acyclic* analogues and the synthesis of α -alkyl seleno ketones have been only partially addressed. Additionally, low regioselectivities, nonoptimal chemical yields, and a well-defined requirement for the nature of the selenylating reagent further narrow the applicability of these methods. In this context, the homologation of seleno esters¹⁵ **I** with diazomethane, via its insertion into the acyl-selenium linkage under

Scheme 1. α -Selenomethyl Ketones: State-of-the-Art



Cu catalysis, first documented by Back in 1982, constitutes one of the very few syntheses of α -substituted seleno methylketones **II** adaptable to both *alkyl* and *aryl* functionalities (Scheme 1, eq 4).¹⁶ However, such an advantage was counterbalanced by rather limited chemical yields and by the formation of

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byproducts, consisting of methylketone **III** and selenoacetal **IV**, in considerable amounts. In particular, the generation of the diselenoacetal, for instance, obtainable in high yield through simpler techniques,¹⁷ was quite intriguing for us, as, in principle, it could act as a convenient source of a lithium substituted α -methyl seleno carbanion (LiCH_2SeR) via the well-suited selenium–lithium exchange.¹⁸ Moreover, our previous experience in preparing α -substituted ketones through the acyl nucleophilic displacement of α -functionalized methyl-lithium derivatives¹⁹ to Weinreb amides²⁰ further spurred us to undertake the study, and herein we report a straightforward and versatile method to synthesize α -arylseleno- and α -alkylseleno-methylketones through a single synthetic operation. We anticipate the byproduct diselenoacetal formed under Back's condition represents the manifold for the crucial α -seleno methyl carbanion required in our tactic.

Our investigations commenced by selecting the enantiopure Weinreb amide **1** as a valuable acylating agent and the aromatic diselenoacetal **2** as the putative precursor for the key α -seleno methyl lithium carbanion (Table 1). According to the accepted

Table 1. Model Reaction: Optimization^a

entry	solvent	Lithiation time (min)	ratio 3/4	yield of 3 (%) ^a	er of 3
1	THF	10	97:3	78	96:4
2	THF	5	14:86	— ^b	—
3 ^c	THF	10	27:73	—	—
4	Et ₂ O	5	93:7	86	98:2
5	Et ₂ O	10	95:5	88	98:2
6	Et ₂ O	30	97:3	89	99:1
7	Et ₂ O	60	>99:1	92	99:1
8	MTHF	60	94:6	84	95:5
9	toluene	60	92:8	81	99:1
10 ^d	Et ₂ O	60	26:74	17	—
11 ^e	Et ₂ O	60	21:79	13	—

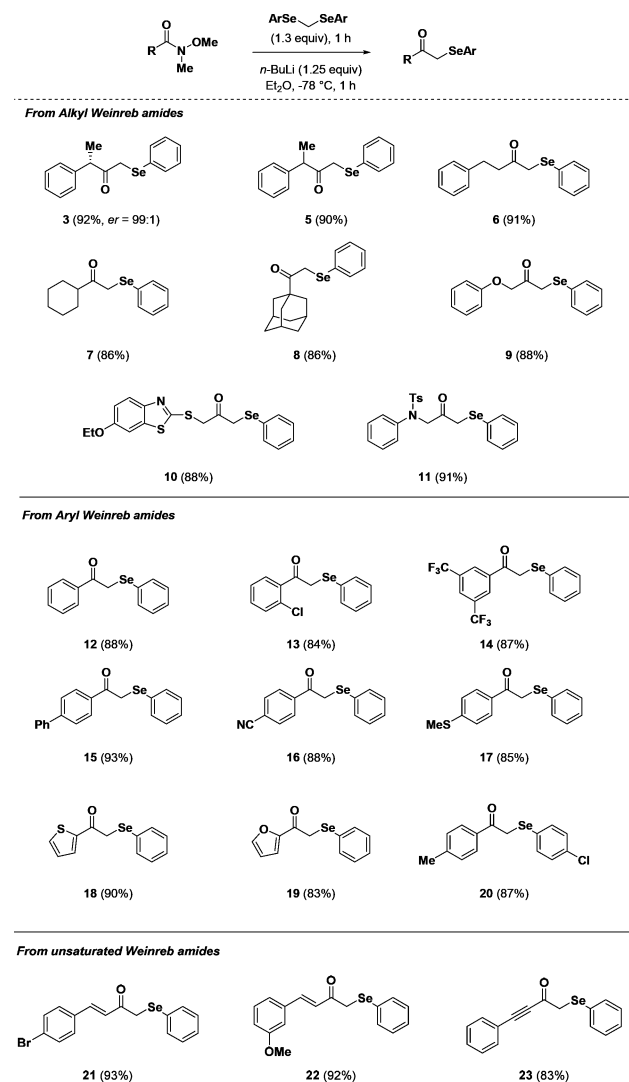
^aUnless otherwise stated *n*-BuLi (1.6 M in hexanes) was used as a lithiating agent, and yields refer to isolated ones. ^bCompound **4** was obtained in 61% isolated yield. ^cTMEDA (1.25 equiv) was added. An overall conversion of 22% was observed by ¹H NMR. ^d*s*-BuLi (1.25 equiv) was used: **4** (61% isolated yield). ^e*t*-BuLi (1.25 equiv) was used: **4** (67% isolated yield).

mechanism for the Se/Li exchange,^{18c} the formation of the carbanion would deliver 1 equiv of selenoether PhSeR, thus allowing the estimation of the exchange rate. Generating the nucleophile with *n*-BuLi in THF cleanly provided the desired α -selenomethyl ketone **3** after a lithiation time of 10 min with good enantiopurity (Table 1, entry 1). Some points merit a mention: (a) decreasing the lithiation time to 5 min dramatically affects the yield of **3**, the bis-seleno ketone **4**, originated from the simple deprotonation of **2**, being the major product (Table 1, entry 2); (b) analogously, the addition of TMEDA favors the deprotonation rather than the desired Se/Li exchange (Table 1, entry 3). By using Et₂O as the solvent, chemoselectivity was fully shifted toward our goal (Table 1, entries 4–6), and after a lithiation time of 60 min, it was practically complete and enantiopure (*er* > 99:1) (Table 1,

entry 7). It is worth mentioning that the full transfer of the stereochemical information of the Weinreb amide during the process indicated almost no racemization takes place despite the strong basicity of the medium. Attempts to employ different solvents [2-methyltetrahydrofuran (MTHF) or toluene] (Table 1, entries 8–9) diminished both the chemical yield and optical purity of **3**. More sterically hindered *s*-BuLi and *t*-BuLi acted almost exclusively as a base, thus resulting in the prevalent formation of the deprotonation derived product **4** (Table 1, entries 10–11). The absence of noticeable enolization phenomena under our reaction conditions should be highlighted, despite the use of strongly basic α -phenylseleno methyl lithium.

With the optimized conditions in hand, we then explored the scope of the reaction (Scheme 2). Alkyl Weinreb amides are

Scheme 2. Scope of the Reaction: Synthesis of α -Arylseleno Methyl Ketones

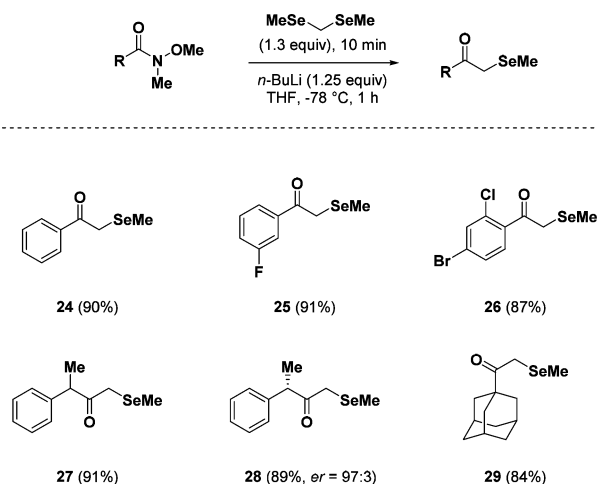


excellent substrates for the transformation, providing the corresponding α -phenylseleno methylketones **3–11** in average yields of >86%. Notably, the protocol is not influenced by the steric hindrance of the acyclic moiety as deduced in the case of the adamantyl derivative **8**. Interestingly, starting from α' -heteroatom substituted Weinreb amides, it is possible to prepare previously unknown α' -oxo-, α' -thio-, and α' -amino- α -

phenylseleno acetones **9–11** through a unique operation. The protocol works well also in the case of aryl Weinreb amides **12–20**. Accordingly, substitution across the aryl nuclei is permitted at the *ortho*, *meta*, and *para* position with different functionalities such as chloro **13**, trifluoromethyl **14**, and thioether **17** as well as the use of heteroaromatic acylating agents **18–19**. The formed carbanion displays excellent chemoselectivity toward the Weinreb amide even in the case of the simultaneous presence of an additional electrophilic group as a nitrile **16**. The technique is amenable for introducing a functionalized arylseleno (*p*-ClC₆H₄Se, **20**) methyl carbanion, thus expanding the versatility of the method. Sensitive substrates such as α,β -unsaturated Weinreb amides react with excellent 1,2-selectivity, thus giving the corresponding phenylseleno ketones **21–22** in high yields. These results clearly highlight the potentiality of our method because of the observed Michael-type addition on similar α,β -unsaturated analogues.^{18a} Notably, a potentially exchangeable bromine, which in analogous systems could interfere with the selenium–lithium exchange,^{4b} did not affect the chemoselectivity (**21**). Moreover, an alkyne Weinreb amide undergoes the transformation with unchanged efficiency (**23**).

With the aim to develop a versatile method suitable also for α -alkyl seleno methylketones and cognizant of the more difficult Se/Li exchange on bis(alkylseleno)acetals,^{4a,18a} we were not surprised to observe only traces of the desired compound **24** by applying the above established conditions [(RSe)₂CH₂ (1.3 equiv), *n*-BuLi (1.25 equiv), Et₂O, –78 °C]. Pleasingly, the simple switching to THF, *coeteris paribus*, allowed 95% conversion to be obtained (as evidenced by ¹H NMR on the reaction crude), which finally resulted in an excellent 90% isolated yield (Scheme 3). The reaction shows a

Scheme 3. Synthesis of α -Methylseleno Methyl Ketones

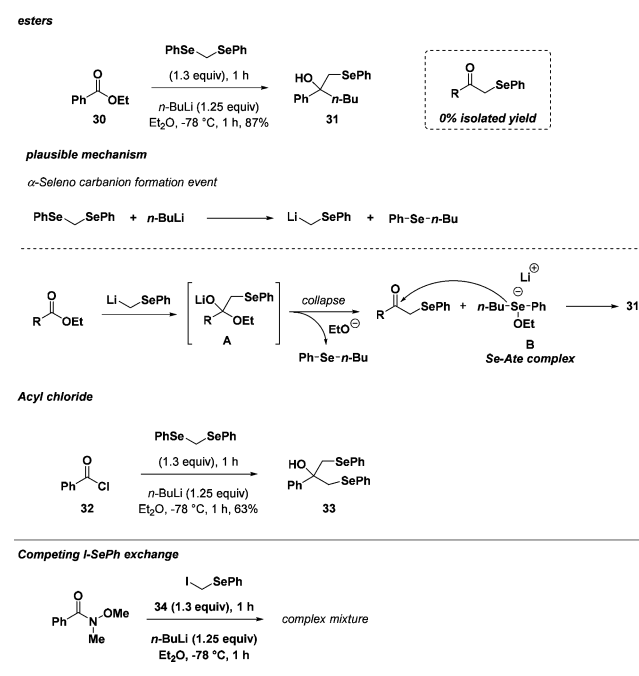


similar broad scope, thus enabling the addition–elimination sequence of the methylseleno methyl lithium carbanion to Weinreb amides, finally leading to the targeted seleno methylketones **24–29**. The stereochemical information featured in the starting material could be fully transferred to the final compound **28**. Again, the presence of an exchangeable halogen (**26**) or a bulky substituent (adamantyl, **29**) is irrelevant in determining both selectivity and efficiency.

In order to acquire full insights into the transformation and because of the limited studies available on the acylation, via nucleophilic substitution, of α -seleno carbanions,^{4a,18c} the

reactivity of different acylating agents (ester and chloride) was separately investigated (Scheme 4). Accordingly, by

Scheme 4. Use of Different Acylating Agents or Seleno Sources



reacting ester **30** under the classical conditions, carbinol **31** surprisingly resulted as the unique reaction product in 87% yield. Presumably, the collapse of the tetrahedral intermediate **A** generated upon the addition of LiCH₂SePh to the ester delivers an alkoxy residue²¹ which is intercepted by PhSe-*n*-Bu (byproduct of the seleno carbanion formation event), giving a selenium–ate complex **B**. Subsequently, the latter acts as a latent source of *n*-Bu carbanion, which in turn attacks the putative α -selenoketone, finally giving **31**. The use of a chloride **32** as the acylating agent yielded the diseleno-carbinol **33**, in agreement with the commonly accepted overaddition of organometallics to these electrophiles. On the other hand, attempting the generation of LiCH₂SePh via iodine/lithium exchange on iodomethyl phenylselenoether **34** gave a complex reaction mixture, further indicating the Se/Li exchange on diselenoacetal as the ideal method to prepare such a carbanion. These experiments confirm the usefulness of the combination of Weinreb amides and diselenoacetals for preparing α -selenoketones under lithiation conditions.

In conclusion, we have developed an expeditious access to aryl and alkyl selenomethyl ketones via the highly chemoselective nucleophilic addition of α -selenomethyl lithium carbanions to variously functionalized Weinreb amides. The present method documents the effectiveness of generating the requested nucleophilic seleno carbanion from a diselenoacetal which in the previously reported diazomethane homologation strategy was considered a byproduct of the reaction. Key features of the transformation are (1) uniformly high yields and full retention of the sterical information contained in the starting materials for both processes (α -arylsele and α -alkylsele) and (2) excellent chemoselectivity in the presence of functionalities sensitive to lithium organometallics including halogen, α,β -unsaturated systems.

■ ASSOCIATED CONTENT

■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.8b00896](https://doi.org/10.1021/acs.orglett.8b00896).

Experimental procedure, NMR spectra, HPLC traces and analytical data for all the compounds (PDF)

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Notes

The authors declare no competing financial interest.

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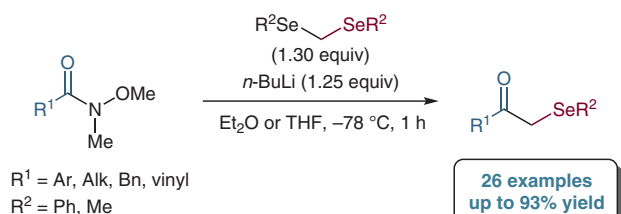
The authors thank the University of Vienna for financial support. L.C. acknowledges the Austrian Academy of Sciences for a postdoctoral L'OREAL grant. We thank D. Dobusch (University of Vienna) for HRMS measurements.

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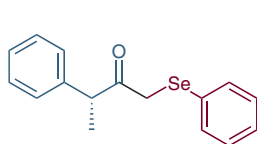
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R. SENATORE, L. CASTOLDI, L. IELO, W. HOLZER, V. PACE* (UNIVERSITY OF VIENNA, AUSTRIA AND UNIVERSITY OF MESSINA, ITALY)
 Expeditious and Chemoselective Synthesis of α -Aryl and -Alkyl Selenomethylketones via Homologation Chemistry
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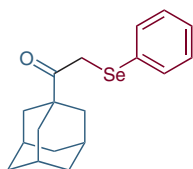
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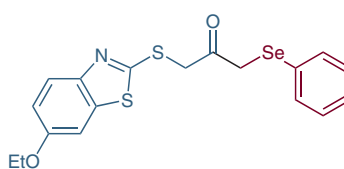
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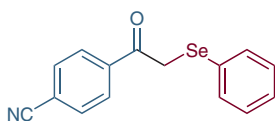
92% yield



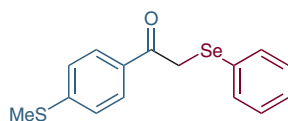
86% yield



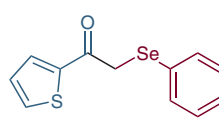
88% yield



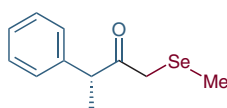
88% yield



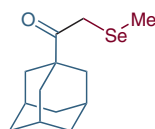
85% yield



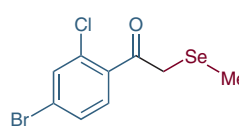
90% yield



89% yield



84% yield



87% yield

Significance: The authors report an easy and mild preparation of α -aryl and α -alkyl selenomethylketones via a selenium/lithium exchange and subsequent addition to Weinreb amides.

Comment: The transformation occurs under full retention of the stereochemistry and shows excellent chemoselectivity.

Publication n. 4

Straightforward and Direct Access to β -seleno-amines and sulfonylamides via the controlled addition of phenylselenomethylithium (LiCH_2SePh) to imines.

Raffaele Senatore, Monika Malik, Saad Touqeer, Roberta Listro, Simona Collina, Wolfgang Holzer and Vittorio Pace*

Tetrahedron, **2020**, 76, 51, 131220 (DOI: 10.1016/j.tet.2020.131220)

The Supporting information is available on the website at:

<https://ars.els-cdn.com/content/image/1-s2.0-S0040402020303550-mmc1.pdf>

Details on experimental procedures, characterization data and copies of NMR spectra of all compounds are reported.



Straightforward and direct access to β -seleno- amines and sulfonylamides *via* the controlled addition of phenylselenomethyl lithium (LiCH_2SePh) to imines

Raffaele Senatore ^a, Monika Malik ^a, Saad Touqeer ^a, Roberta Listro ^b, Simona Collina ^b, Wolfgang Holzer ^a, Vittorio Pace ^{a, c, *}

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Dedicated to Prof. Dr. Nuno Maulide for his outstanding contributions to the art of Synthesis.

ABSTRACT

The transfer of a α -methyl phenylseleno carbanion to variously functionalized *N*-aryl and *N*-sulfonyl imines is reported. The fast selenium-lithium exchange conducted on a diselenoacetal with *n*-BuLi enables the generation of the attacking homologative nucleophile under chemoselective conditions preserving concomitant potentially sensitive functionalities to the lithiating conditions. Uniformly high yields were observed, thus establishing a valuable and conceptually simple approach to the title compounds.

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1. Introduction

Embodying selenium containing groups into an organic skeleton profoundly influences the physical-chemical features of the resulting scaffold, thus complementing the reach and well-established portfolio of (stereoselective) transformations these organometallics offer [1]. Indeed, there is a continuous and growing interest towards the biological properties displayed by organoselenium analogues whose structures are frequently encountered in enzymes governing important metabolic cascades (e.g. selenoprotein P, glutathione peroxidase, *inter alia*) [2]. Additionally, recent uses of selenium-based pharmacologically active substances emerged as valuable tools for treating important diseases, as exemplified by ebiselen, thus further increasing the potential of such a chalcogen-containing motifs [3]. Evidently, the simultaneous derivatization of organoselenium species with additional functionalities expands the chemical space and the overall versatility of the so obtained materials. In this sense, including a nitrogen-centered group in a relevant position may represent an effective

strategy for tuning pivotal molecular properties (e.g. solubility, cell permeability, metabolic parameters *etc.*) or, by focusing on pure synthetic aspects, it enables selective chemistries *en route* to more complex architectures [4]. In fact, the proper activation of these β -seleno amine-type manifolds results in a versatile technique for assembling different aza-cycles such as aziridines [5a, 5b, 5c] or diastereomerically enriched 2,4-disubstituted pyrrolidines [6]. This applicative significance merged with the potential exhibited in different areas including material science and drug design, [7a, 7b] motivated the development of variously oriented tactics for the construction of the motif. In recent years, the amino- or amido-selenation of olefins – *i.e.* the simultaneous installation into the sp^2 -hybridized C–C bond of both the selenium atom and the nitrogenated moiety – emerged as an attractive and practical solution. Mechanistically, the electrophilic organoselenium agent generates a seleniranium ion susceptible of nucleophilic attack by the *N*-containing partner. The protocol manifests strong dependence on the nature and level of substitution of the competent olefin, as well as, on the nucleophilicity of the attacking amine or amide groups. As a consequence, the adequate modulation – *via* ionic [8], electrochemical [9] or radical [10] pathway – of these events becomes critical for the successful outcome of the targeted strategy. A logically distinct approach involves the ring opening of an aziridine with an *in situ* generated selenium anion [11]. It

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appears conceivable that using these highly valuable synthons may pose severe limitations in terms of costs. Alternatively, Outurquin proposed a two-steps methodology paved on forming highly unstable and difficult to purify α -selenoimines (from the corresponding ketones) followed by the controlled reduction to the desired compounds [5a,12] (see Scheme 1)

Inspired by our work on homologation of carbon electrophiles with α -substituted methyllithiums (LiCH_2XY) [13,14], in 2018 we reported a general approach for introducing substituted selenomethyl fragments – i.e. RSeCH_2 – onto Weinreb amides [13k,14a]. The strategy paved on the generation of the carbanion from a diselenoacetal [15] by adapting seminal Reich's studies [16],

Relevance of Organoseleniums in Med Chem

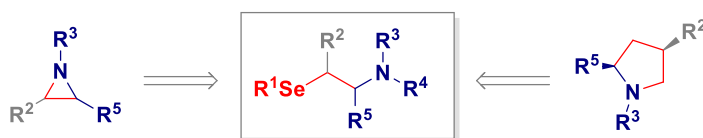


Ebselen

Prototypal Se-containing drug

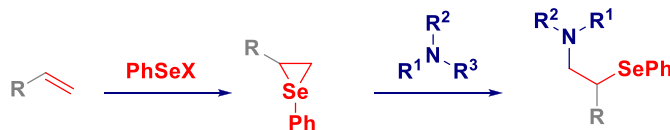
- Cytoprotective
- Anti-inflammatory
- Anti-oxidant

Versatility of β -Seleno Nitrogenated Motifs

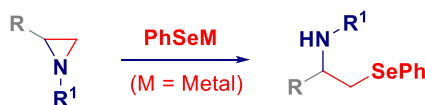


The Assembly of β -Seleno Nitrogenated Motifs

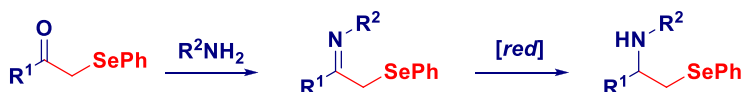
a) Oxidative Difunctionalization of Olefins



b) Ring Opening of Aziridines

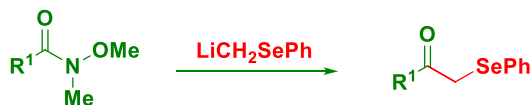


c) Construction-Reduction of α -Selenoimines

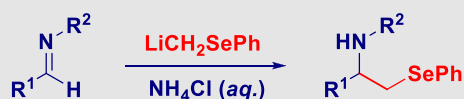


The Direct Transfer of LiCH_2SePh to C-Electrophiles

Weinreb Amides (Pace, 2018)



This work: Addition to Imines



- One-pot process
- High yielding
- Chemoselective
- 19 Examples

Scheme 1. General context of the presented work.

documented high versatility and chemoselectivity. We reasoned that delivering this Se-centered carbanion [17] to a given imine would produce the β -seleno nitrogenated adduct through a conceptually intuitive and novel approach. To the best of our knowledge, the employment of C–C bond forming operations for producing the title compounds is still unprecedented and, herein we disclose our findings.

2. Results and discussion

We selected the naphthyl-substituted imine **1** as the model compound for accomplishing the formal homologation with the lithiated α -methyl seleno carbanion (LiCH_2SePh). As anticipated, a convenient source of this species was individuated in the diselenoacetal [15a] ($\text{PhSeCH}_2\text{SePh}$) which undergoes an extremely fast selenium-lithium exchange upon treatment with *n*-BuLi. Evidently, the genesis of the requested carbanion is accompanied by the formation of the interconversion product – the selenoether *n*-BuSePh (**2b**) – which guarantees a quantitative estimation of the process. The optimization study revealed the adaptability of the conditions established for preparing α -selenoketones starting from Weinreb amides:^{14a} $\text{PhSeCH}_2\text{SePh}$ (1.3 equiv), *n*-BuLi (1.25 equiv) in Et_2O at -78°C under non-Barbier type conditions (Table 1). Although the initial experiment showed the formation of the expected β -selenoamine **2** in a reasonably good 70% yield, a noticeable amount of the aminic compound **2a** generated by the direct attack of *n*-BuLi to the azomethinic carbon was detected (entry 1). With the aim of improving the yield of **2**, we briefly screened the effect of additional parameters: i) the simple switching to THF as the reaction medium did not alter significantly the **2**:**2a** ratio (entry 2); ii) decreasing the lithiation time was detrimental in agreement with our previous study on Weinreb amides (entries 3–4); iii) the use of alternative ethereal-type solvents such as 2-MeTHF [18a, 18b, 18c] and CPME [19] significantly decreased the efficiency (entries 5–6); iv) pleasingly, the progressive increase of the loading of Se-carbanion enables to maximize the yield up to 93%, being practically undetectable the formation of the side product **2a** (entries 7–8); v) using a smaller excess of diselenoacetal (2.0 equiv) compared to the lithiating agent (1.90 equiv) guarantees the full generation of LiCH_2SePh and, thus to skip the concomitant,

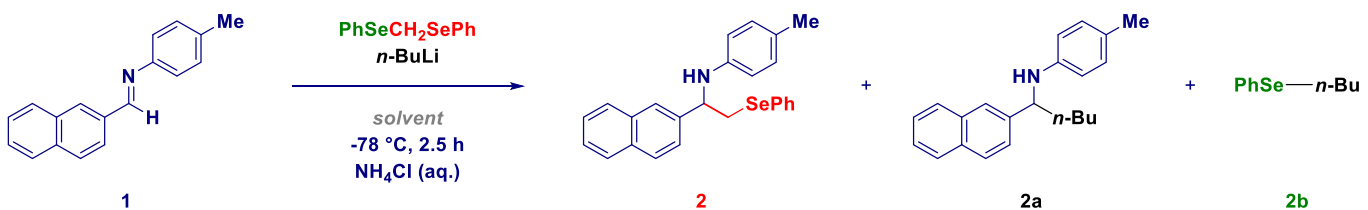
undesired attack of *n*-BuLi to **1**.

With the optimal conditions in hand, we then explored the scope of the transformation (Scheme 2). A series of variously functionalized *N*-aryl imines easily undergoes the transformation giving the expected β -phenylseleno adducts in high yields. The substitution on the aromatic ring of the starting *N*-phenyl-type aldimines was perfectly tolerated: the presence of electron-donating functionalities such as methoxy at different positions did not alter the efficiency of the methodology. Analogously, potentially sensitive halogens – including the reactive bromo-derivatives (**5** and **8**) – could be introduced on the nucleus yielding the corresponding seleno-amines. The chemoselectivity of the approach is further illustrated in the case of the nitrile-bearing compound **10**, in which this electrophilic group was preserved by the nucleophilic attack. Switching to heteroaromatic aldimines was also possible, as documented by the 2-furyl (**12**) derivative. The nature of the *N*-imine group can be conveniently shifted to a sulfonyl-analogue in order to prepare β -seleno sulfonyl imides (**13**–**19**). Interestingly, our approach constitutes an effective solution for accessing **14** whose previous synthesis through the ring-opening of an aziridine was affected by limited regiocontrol.[11] A comparable chemoselective profile was observed: halogen-containing groups – such as chlorine, fluoro, trifluoromethyl and bromo – maintain unaltered the productivity of the homologative technique. Similarly, poly- (naphthyl, **13**) or heteroaromatic (2-furyl, **18** – 2-thienyl, **19**) benzenesulfonylimines acted as competent starting materials without affecting the chemical integrity of these systems.

3. Conclusions

In conclusion, we have developed a straightforward and versatile methodology for the transfer of a selenium-centered methyl-lithium carbanion to variously functionalized imines. The selective lithiation of a diselenoacetal ($\text{PhSeCH}_2\text{SePh}$) smoothly provides the homologating agent (LiCH_2SePh) which can be easily released to the electrophilic azomethinic partners. The high degree of chemoselectivity, as well as the very good to excellent yields observed, make this conceptually intuitive strategy of wide and general applicability.

Table 1
Model Reaction: Optimization.

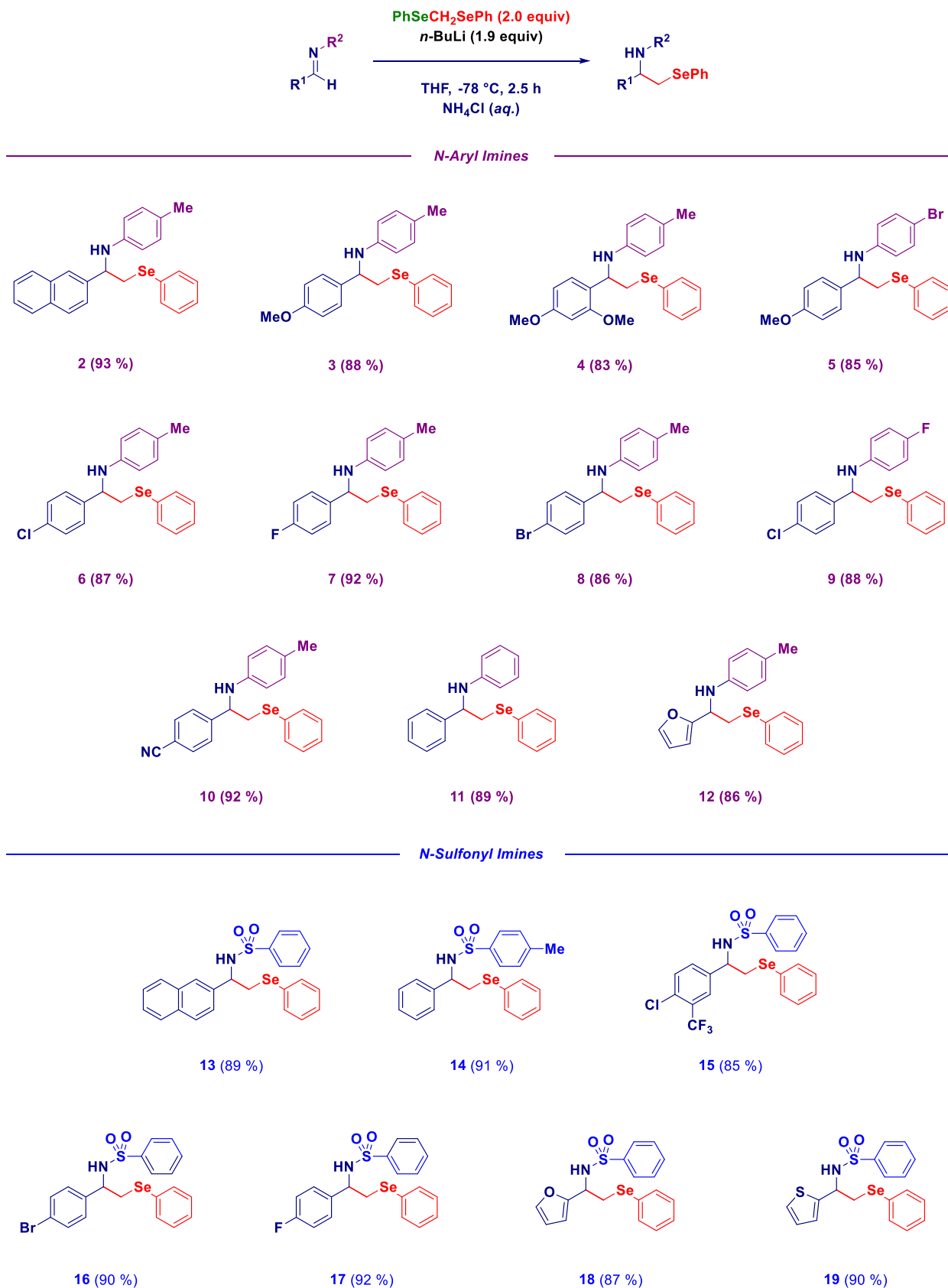


Entry	Solvent	LiCH_2SePh (equiv)	Lithiation time (min)	Ratio 2 : 2a	Yield of 2 (%) ^a
1 ^b	Et_2O	1.25	60	76:24	70
2	THF	1.25	60	78:22	73
3	THF	1.25	45	75:25	68
4	THF	1.25	30	77:23	64
5	2-MeTHF	1.25	60	65:45	50
6	CPME	1.25	60	71:29	58
7	THF	1.60	60	93:7	84
8	THF	1.90	60	>99:1	93
9 ^c	THF	1.90	60	95:5	90

^a Isolated yield.

^b **2a** was isolated in 19% yield.

^c $\text{PhSeCH}_2\text{SePh}$ (1.90 equiv) and *n*-BuLi (1.90 equiv) were used.



Scheme 2. Scope of the protocol.

3.1. Experimental Part

3.1.1. Instrumentation and general analytical methods

Melting points were determined on a Reichert–Kofler hot-stage microscope and are uncorrected. Mass spectra were obtained on a Shimadzu QP 1000 instrument (EI, 70 eV) and on a Bruker maXis 4G instrument (ESI-TOF, HRMS). ^1H , ^{13}C , ^{19}F , ^{15}N and ^{77}Se NMR spectra were recorded with a Bruker Avance III 400 spectrometer (400 MHz for ^1H , 100 MHz for ^{13}C , 376 MHz for ^{19}F , 40 MHz for ^{15}N and 76 MHz for ^{77}Se) at 297 K using a directly detecting broadband observe (BBFO) probe. The center of the (residual) solvent signal was used as an internal standard which was related to TMS with δ 7.26 ppm (^1H in CDCl_3), δ 77.0 ppm (^{13}C in CDCl_3). ^{19}F NMR spectra were referenced via the Ξ ratio (absolute referencing). ^{15}N NMR spectra (gs-HMBC, gs-HSQC) were referenced against neat, external nitromethane. ^{77}Se spectra were referenced against diphenyldiselenane (δ Ph_2Se_2 463 ppm). Spin-spin coupling constants (J) are given in Hz.

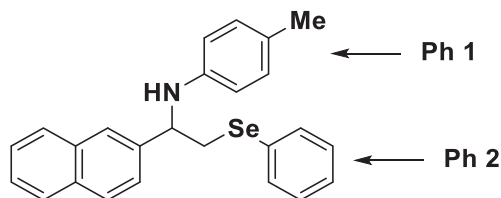
In nearly all cases, full and unambiguous assignment of all resonances was performed by combined application of standard NMR techniques, such as APT, HSQC, HMBC, HSQCTOCSY, COSY and NOESY experiments.

THF was distilled over Na/benzophenone. Chemicals were purchased from SigmaAldrich, Acros, Alfa Aesar and TCI Europe. Solutions were evaporated under reduced pressure with a rotary evaporator. TLC was carried out on aluminium sheets precoated with silica gel 60F254 (Merck) (Merck-Nagel, Merk); the spots were visualised under UV light ($\lambda = 254$ nm) and/or KMnO_4 (aq.) was used as revealing system.

3.1.2. General procedure

To a solution of 1,1'-(methylenediselanyl)dibenzene (2.0 equiv) in dry THF (2 mL) a 2.5 M solution of *n*-BuLi in hexanes (1.9 equiv) was added dropwise at -78°C under argon and the reaction mixture was stirred at -78°C for 1 h. Then, a solution of the starting imine (1.0 equiv) in dry THF (1 mL) was added and the mixture was stirred at -78°C for 2.5 h before quenching with sat. aqueous NH_4Cl . The mixture was exhaustively extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The product was obtained after purification by column chromatography on silica gel (*n*-hexane:EtOAc).

3.1.3. 4-methyl-N-[1-(2-naphthyl)-2-(phenylselanyl)ethyl]aniline (2)



By Following the general procedure, starting from 1,1'-(methylenediselanyl)dibenzene (0.652 g, 2.0 mmol, 2.0 equiv) in dry THF (2 mL), *n*-BuLi (2.5 M, 0.76 mL, 1.9 mmol, 1.9 equiv) and 4-methyl-N-(naphthalen-2-ylmethylene)aniline (0.245 g, 1.0 mmol, 1.0 equiv) in dry THF (1 mL), compound **2** was obtained in 93% yield (0.387 g) as colourless oil after purification by column chromatography on silica gel (*n*-hexane:EtOAc 99:1).

^1H NMR (400 MHz, CDCl_3): δ 7.81 (m, 1H, Naph H-1), 7.80 (m,

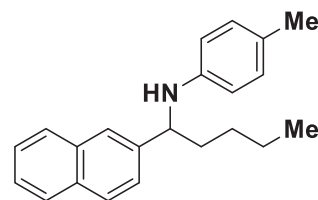
2H, Naph), 7.78 (m, 1H, Naph), 7.54 (m, 2H, Ph 2 H-2,6), 7.47 (m, 1H, Naph H-3), 7.46 (m, 1H, Naph), 7.45 (m, 1H, Naph), 7.27 (m, 1H, Ph 2 H-4), 7.26 (m, 2H, Ph 2 H-2,6), 6.87 (m, 2H, Ph 1 H-3,5), 6.43 (m, 2H, Ph 1 H-2,6), 4.59 (dd, $^3J = 8.9$ Hz, $^3J = 4.6$ Hz, 1H, CH), 4.5 (brs, 1H, NH), 3.44 (dd, $^2J = 12.6$ Hz, $^3J = 4.6$ Hz, 1H, CH_2), 3.28 (dd, $^2J = 12.6$ Hz, $^3J = 8.9$ Hz, 1H, CH_2), 2.18 (s, 3H, CH_3).

^{13}C NMR (100 MHz, CDCl_3): δ 144.7 (Ph 1 C-1), 140.3 (Naph C-2), 133.55 (Ph 2 C-2,6), 133.51 (Naph 8a), 133.0 (Naph 4a), 129.6 (Ph 1 C-3,5), 129.3 (Ph 2 C-1), 129.2 (Ph 2 C-3,5), 128.6 (Naph), 127.9 (Naph), 127.7 (Naph), 127.5 (Ph 2 C-4), 127.1 (Ph 1 C-4), 126.1 (Naph), 125.7 (Naph), 125.2 (Naph C-1), 124.4 (Naph C-3), 114.0 (Ph 1 C-2,6), 58.4 (CH), 36.4 (CH_2), 20.3 (CH_3).

^{77}Se NMR (76 MHz, CDCl_3): δ 267.3 (m).

HRMS (ESI), m/z [$\text{M} + \text{H}$] $^+$ calcd. for $\text{C}_{25}\text{H}_{24}\text{NSe}$: 418.1068; found: 418.1057.

3.1.4. 4-methyl-N-[1-(2-naphthyl)pentyl]aniline (2a)



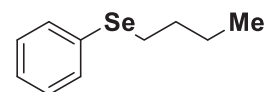
^1H NMR (400 MHz, CDCl_3): δ 7.82 (m, 3H, Naph H-4,5,8), 7.81 (s, 1H, Naph H-1), 7.50 (m, 1H, Naph H-3), 7.47 (m, 1H, Naph H-6), 7.45 (m, 1H, Naph H-7), 6.89 (m, 2H, Ph H-3,5), 6.50 (m, 2H, Ph H-2,6), 4.44 (m, 1H, CH), 3.9–4.4 (brs, 1H, NH), 2.18 (s, 3H, CH_3), 1.88 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.37 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.36 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 0.90 (t, $^3J = 7.0$ Hz, 3H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$).

^{13}C NMR (100 MHz, CDCl_3): δ 145.2 (Ph C-1), 142.0 (Naph C-2), 133.5 (Naph C-8a), 132.8 (Naph C-4a), 129.6 (Ph C-3,5), 128.3 (Naph), 127.8 (Naph), 127.6 (Naph), 126.4 (Ph C-4), 125.9 (Naph C-6), 125.4 (Naph C-7), 125.1 (Naph C-1), 124.8 (Naph C-3), 113.5 (Ph C-2,6), 58.8 (CH), 38.6 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 28.5 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 22.6 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 20.3 (CH_3), 14.0 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$).

^{15}N NMR (40 MHz, CDCl_3): δ -305.4.

HRMS (ESI), m/z [$\text{M} + \text{H}$] $^+$ calcd. for $\text{C}_{22}\text{H}_{26}\text{N}$: 304.2060; found: 304.2057.

3.1.5. Butyl phenyl selenide (2b)14a



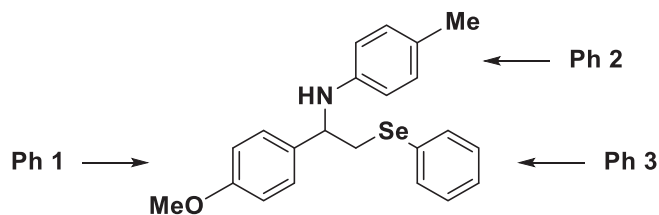
^1H NMR (400 MHz, CDCl_3): δ 7.48 (m, 2H, Ph H-2,6), 7.25 (m, 2H, Ph H-3,5), 7.23 (m, 1H, Ph H-4), 2.92 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.69 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.43 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 0.91 (t, $^3J = 7.4$ Hz, 3H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$).

^{13}C NMR (100 MHz, CDCl_3): δ 132.3 (Ph C-2,6), 130.7 (Ph C-1), 129.0 (Ph C-3,5), 126.6 (Ph C-4), 32.2 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 27.6 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 22.9 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 13.5 ($\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$).

^{77}Se NMR (76 MHz, CDCl_3): δ 290.5

HRMS (ESI), m/z [$\text{M} + \text{H}$] $^+$ calcd. for $\text{C}_{10}\text{H}_{15}\text{Se}$: 215.0333; found: 215.0336.

3.1.6. *N*-[1-(4-methoxyphenyl)-2-(phenylselanyl)ethyl]-4-methylaniline (3)



By Following the general procedure, starting from 1,1'-(methylenediselanyl)dibenzene (0.652 g, 2.0 mmol, 2.0 equiv) in dry THF (2 mL), *n*-BuLi (2.5 M, 0.76 mL, 1.9 mmol, 1.9 equiv) and *N*-(4-methoxybenzylidene)-4-methylaniline (0.225 g, 1.0 mmol, 1.0 equiv) in dry THF (1 mL), compound **3** was obtained in 88% yield (0.348 g) as colourless oil after purification by column chromatography on silica gel (*n*-hexane:EtOAc 9:1).

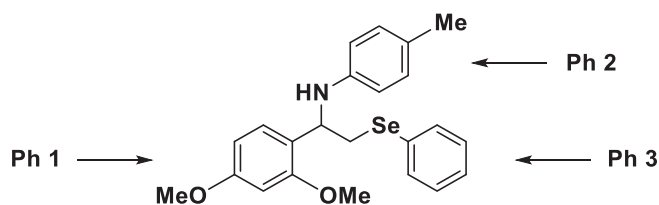
¹H NMR (400 MHz, CDCl₃): δ 7.50 (m, 2H, Ph 3 H-2,6), 7.26 (m, 3H, Ph 3 H-3,4,5), 7.25 (m, 2H, Ph 1 H-2,6), 6.88 (m, 2H, Ph 2 H-3,5), 6.83 (m, 2H, Ph 1 H-3,5), 6.40 (m, 2H, Ph 2 H-2,6), 4.39 (dd, ³*J* = 8.4 Hz, ³*J* = 5.1 Hz, 1H, CH), 4.0–4.8 (brs, 1H, NH), 3.78 (s, 3H, OCH₃), 3.33 (dd, ²*J* = 12.5 Hz, ³*J* = 5.1 Hz, 1H, CH₂), 3.22 (m, 1H, CH₂), 2.18 (s, 3H, CH₃).

¹³C NMR (100 MHz, CDCl₃): δ 158.9 (Ph 1 C-4), 144.9 (Ph 2 C-1), 134.6 (Ph 1 C-1), 133.4 (Ph 3 C-2,6), 129.5 (Ph 2 C-3,5), 129.4 (Ph 3 C-1), 129.2 (Ph 3 C-3,5), 127.5 (Ph 1 C-2,6), 127.4 (Ph 3 C-4), 127.2 (Ph 2 C-4), 114.1 (Ph 1 C-3,5, Ph 2 C-2,6), 57.7 (CH), 55.2 (OCH₃), 36.4 (CH₂), 20.4 (CH₃).

⁷⁷Se NMR (76 MHz, CDCl₃): δ 265.0 (m).

HRMS (ESI), *m/z* [M + H]⁺ calcd. for C₂₂H₂₄NOSe: 398.1018; found: 398.1016.

3.1.7. *N*-[1-(2,4-dimethoxyphenyl)-2-(phenylselanyl)ethyl]-4-methylaniline (4)



By Following the general procedure, starting from 1,1'-(methylenediselanyl)dibenzene (0.652 g, 2.0 mmol, 2.0 equiv) in dry THF (2 mL), *n*-BuLi (2.5 M, 0.76 mL, 1.9 mmol, 1.9 equiv) and *N*-(2,4-dimethoxybenzylidene)-4-methylaniline (0.255 g, 1.0 mmol, 1.0 equiv) in dry THF (1 mL), compound **4** was obtained in 83% yield (0.354 g) as brown oil after purification by column chromatography on silica gel (*n*-hexane:EtOAc 99:1).

¹H NMR (400 MHz, CDCl₃): δ 7.51 (m, 2H, Ph 3 H-2,6), 7.24 (m, 3H, Ph 3 H-3,4,5), 7.21 (d, ³*J* = 8.4 Hz, 1H, Ph 1 H-6), 6.89 (m, 2H, Ph 2 H-3,5), 6.43 (d, ⁴*J* = 2.4 Hz, 1H, Ph 1 H-3), 6.39 (m, 3H, Ph 1 H-5, Ph 2 H-2,6), 4.78 (dd, ³*J* = 8.3 Hz, ³*J* = 4.8 Hz, 1H, CH), 4.38 (brs, 1H, NH), 3.82 (s, 3H, 2-OCH₃), 3.77 (s, 3H, 4-OCH₃), 3.45 (dd, ²*J* = 12.4 Hz, ³*J* = 4.8 Hz, 1H, CH₂), 3.22 (dd, ²*J* = 12.4 Hz, ³*J* = 8.3 Hz, 1H, CH₂), 2.19 (s, 3H, CH₃).

¹³C NMR (100 MHz, CDCl₃): δ 160.0 (Ph 1 C-4), 157.6 (Ph 1 C-2), 144.8 (Ph 2 C-1), 132.9 (Ph 3 C-2,6), 130.2 (Ph 3 C-1), 129.5 (Ph 2 C-3,5), 128.9 (Ph 3 C-3,5), 128.0 (Ph 1 C-6), 126.9 (Ph 3 C-4), 126.6 (Ph 2 C-4), 122.2 (Ph 1 C-1), 113.8 (Ph 2 C-2,6), 104.1 (Ph 1 C-5), 98.7 (Ph 1

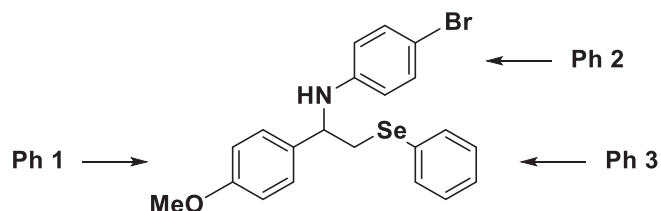
C-3), 55.3 (4-OCH₃), 55.2 (2-OCH₃), 53.0 (CH), 34.2 (CH₂), 20.3 (CH₃).

⁷⁷Se NMR (76 MHz, CDCl₃): δ 263.3 (m).

¹⁵N NMR (40 MHz, CDCl₃): δ -308.0.

HRMS (ESI), *m/z* [M + H]⁺ calcd. for C₂₃H₂₆NO₂Se: 428.1123; found: 428.1120.

4-bromo-*N*-[1-(4-methoxyphenyl)-2-(phenylselanyl)ethyl]aniline (5)



By Following the general procedure, starting from 1,1'-(methylenediselanyl)dibenzene (0.652 g, 2.0 mmol, 2.0 equiv) in dry THF (2 mL), *n*-BuLi (2.5 M, 0.76 mL, 1.9 mmol, 1.9 equiv) and 4-bromo-*N*-(4-methoxybenzylidene)aniline (0.290 g, 1.0 mmol, 1.0 equiv) in dry THF (1 mL), compound **5** was obtained in 85% yield (0.392 g) as yellow oil after purification by column chromatography on silica gel (*n*-hexane:EtOAc 98:2).

¹H NMR (400 MHz, CDCl₃): δ 7.51 (m, 2H, Ph 3 H-2,6), 7.28 (m, 1H, Ph 3 H-4), 7.27 (m, 2H, Ph 3 H-3,5), 7.22 (m, 2H, Ph 1 H-2,6), 7.13 (m, 2H, Ph 2 H-3,5), 6.84 (m, 2H, Ph 1 H-3,5), 6.30 (m, 2H, Ph 2 H-2,6), 4.34 (dd, ³*J* = 8.8 Hz, ³*J* = 4.6 Hz, 1H, CH), 3.8–5.0 (brs, 1H, NH), 3.78 (s, 3H, OCH₃), 3.32 (dd, ²*J* = 12.6 Hz, ³*J* = 4.6 Hz, 1H, CH₂), 3.15 (dd, ²*J* = 12.6 Hz, ³*J* = 8.8 Hz, 1H, CH₂).

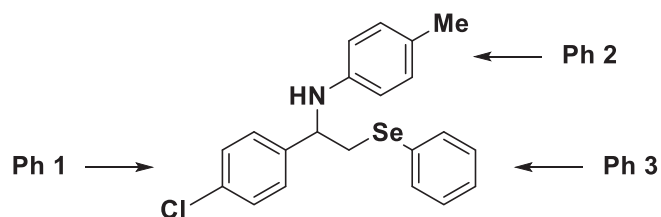
¹³C NMR (100 MHz, CDCl₃): δ 159.1 (Ph 1 C-4), 146.0 (Ph 2 C-1), 134.0 (Ph 1 C-1), 133.6 (Ph 3 C-2,6), 131.7 (Ph 2 C-3,5), 129.3 (Ph 3 C-3,5), 129.0 (Ph 3 C-1), 127.6 (Ph 3 C-4), 127.3 (Ph 1 C-2,6), 115.3 (Ph 2 C-2,6), 114.2 (Ph 1 C-3,5), 109.5 (Ph 2 C-4), 57.2 (CH), 55.2 (OCH₃), 36.4 (CH₂).

⁷⁷Se NMR (76 MHz, CDCl₃): δ 265.9 (m).

¹⁵N NMR (40 MHz, CDCl₃): δ -303.9.

HRMS (ESI), *m/z* [M + Na]⁺ calcd. for C₂₁H₂₀BrNNaOSe: 483.9786; found: 483.9785.

3.1.8. *N*-[1-(4-chlorophenyl)-2-(phenylselanyl)ethyl]-4-methylaniline (6)



By Following the general procedure, starting from 1,1'-(methylenediselanyl)dibenzene (0.652 g, 2.0 mmol, 2.0 equiv) in dry THF (2 mL), *n*-BuLi (2.5 M, 0.76 mL, 1.9 mmol, 1.9 equiv) and *N*-(4-chlorobenzylidene)-4-methylaniline (0.229 g, 1.0 mmol, 1.0 equiv) in dry THF (1 mL), compound **6** was obtained in 87% yield (0.349 g) as brown oil after purification by column chromatography on silica gel (*n*-hexane:EtOAc 99:1).

¹H NMR (400 MHz, CDCl₃): δ 7.51 (m, 2H, Ph 3 H-2,6), 7.27 (m, 7H, Ph 1 H-2,3,5,6, Ph 3 H-3,4,5), 6.90 (m, 2H, Ph 2 H-3,5), 6.35 (m, 2H, Ph 2 H-2,6), 4.40 (dd, ³*J* = 8.8 Hz, ³*J* = 4.6 Hz, 1H, CH), 4.36 (brs, 1H, NH), 3.32 (dd, ²*J* = 12.6 Hz, ³*J* = 4.5 Hz, 1H, CH₂), 3.16 (dd, ²*J* = 12.6 Hz, ³*J* = 8.8 Hz, 1H, CH₂), 2.20 (s, 3H, CH₃).

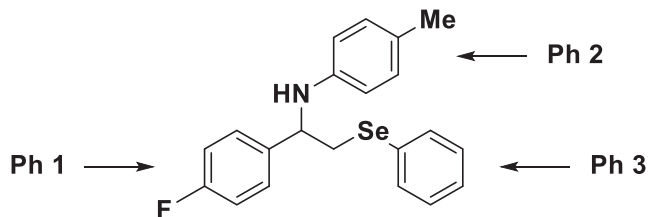
¹³C NMR (100 MHz, CDCl₃): δ 144.4 (Ph 2 C-1), 141.3 (Ph 1 C-1), 133.6 (Ph 3 C-2,6), 133.0 (Ph 1 C-4), 129.6 (Ph 2 C-3,5), 129.3 (Ph 3 C-3,5), 129.0 (Ph 3 C-1), 128.9 (Ph 1 C-3,5), 127.7 (Ph 1 C-2,6), 127.6 (Ph 3 C-4), 127.3 (Ph 2 C-4), 113.9 (Ph 2 C-2,6), 57.4 (CH), 36.4 (CH₂), 20.3 (CH₃).

⁷⁷Se NMR (76 MHz, CDCl₃): δ 266.0 (m).

¹⁵N NMR (40 MHz, CDCl₃): δ -307.1.

HRMS (ESI), *m/z* [M + H]⁺ calcd. for C₂₁H₂₁ClNSe: 402.0522; found: 402.0523.

3.1.9. *N*-[1-(4-fluorophenyl)-2-(phenylselanyl)ethyl]-4-methylaniline (7)



By Following the general procedure, starting from 1,1'-(methylenediselanyl)dibenzene (0.652 g, 2.0 mmol, 2.0 equiv) in dry THF (2 mL), *n*-BuLi (2.5 M, 0.76 mL, 1.9 mmol, 1.9 equiv) and *N*-(4-fluorobenzylidene)-4-methylaniline (0.213 g, 1.0 mmol, 1.0 equiv) in dry THF (1 mL), compound **7** was obtained in 92% yield (0.353 g) as yellow oil after purification by column chromatography on silica gel (*n*-hexane:EtOAc 99:1).

¹H NMR (400 MHz, CDCl₃): δ 7.50 (m, 2H, Ph 3 H-2,6), 7.30 (m, 2H, Ph 1 H-2,6), 7.27 (m, 1H, Ph 3 H-4), 7.26 (m, 2H, Ph 3 H-3,5), 6.98 (m, 2H, Ph 1 H-3,5), 6.89 (m, 2H, Ph 2 H-3,5), 6.36 (m, 2H, Ph 2 H-2,6), 4.41 (dd, ³*J* = 8.7 Hz, ³*J* = 4.8 Hz, 1H, CH), 4.35 (brs, 1H, NH), 3.32 (dd, ²*J* = 12.6 Hz, ³*J* = 4.8 Hz, 1H, CH₂), 3.18 (dd, ²*J* = 12.6 Hz, ³*J* = 8.7 Hz, 1H, CH₂), 2.19 (s, 3H, CH₃).

¹³C NMR (100 MHz, CDCl₃): δ 162.1 (d, ¹*J*_{CF} = 245.5 Hz, Ph 1 C-4), 144.4 (Ph 2 C-1), 138.3 (d, ⁴*J*_{CF} = 3.1 Hz, Ph 1 C-1), 133.5 (Ph 3 C-2,6), 129.6 (Ph 2 C-3,5), 129.3 (Ph 3 C-3,5), 129.1 (Ph 3 C-1), 127.9 (d, ³*J*_{CF} = 8.0 Hz, Ph 1 C-2,6), 127.5 (Ph 3 C-4), 127.4 (Ph 2 C-4), 115.6 (d, ²*J*_{CF} = 21.4 Hz, Ph 1 C-3,5), 114.0 (Ph 2 C-2,6), 57.5 (CH), 36.5 (CH₂), 20.3 (CH₃).

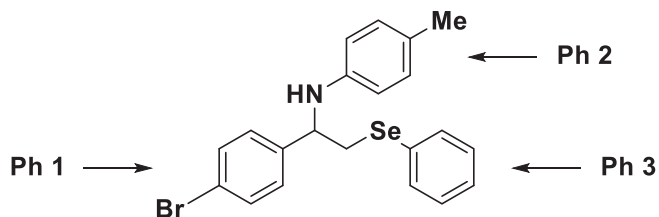
⁷⁷Se NMR (76 MHz, CDCl₃): δ 265.6 (m).

¹⁹F NMR (376 MHz, CDCl₃): δ -115.2 (m).

¹⁵N NMR (40 MHz, CDCl₃): δ -312.9.

HRMS (ESI), *m/z* [M + H]⁺ calcd. for C₂₁H₂₁FNSe: 386.0818; found: 386.0812.

3.1.10. *N*-[1-(4-bromophenyl)-2-(phenylselanyl)ethyl]-4-methylaniline (8)



By Following the general procedure, starting from 1,1'-(methylenediselanyl)dibenzene (0.652 g, 2.0 mmol, 2.0 equiv) in dry THF (2 mL), *n*-BuLi (2.5 M, 0.76 mL, 1.9 mmol, 1.9 equiv) and *N*-(4-bromobenzylidene)-4-methylaniline (0.274 g, 1.0 mmol, 1.0 equiv)

in dry THF (1 mL), compound **8** was obtained in 86% yield (0.383 g) as yellowish oil after purification by column chromatography on silica gel (*n*-hexane:EtOAc 98:2).

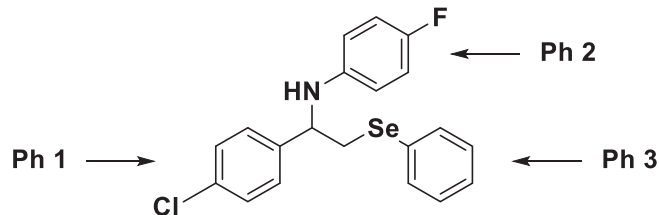
¹H NMR (400 MHz, CDCl₃): δ 7.49 (m, 2H, Ph 3 H-2,6), 7.40 (m, 2H, Ph 1 H-3,5), 7.27 (m, 1H, Ph 3 H-4), 7.26 (m, 2H, Ph 3 H-3,5), 7.21 (m, 2H, Ph 1 H-2,6), 6.89 (m, 2H, Ph 2 H-3,5), 6.36 (m, 2H, Ph 2 H-2,6), 4.37 (dd, ³*J* = 8.6 Hz, ³*J* = 4.8 Hz, 1H, CH), 4.0–5.0 (brs, 1H, NH), 3.32 (dd, ²*J* = 12.6 Hz, ³*J* = 4.8 Hz, 1H, CH₂), 3.18 (dd, ²*J* = 12.6 Hz, ³*J* = 8.6 Hz, 1H, CH₂), 2.19 (s, 3H, CH₃).

¹³C NMR (100 MHz, CDCl₃): 144.0 (Ph 2 C-1), 141.6 (Ph 1 C-1), 133.6 (Ph 3 C-2,6), 131.8 (Ph 1 C-3,5), 129.6 (Ph 2 C-3,5), 129.3 (Ph 3 C-3,5), 129.0 (Ph 3 C-1), 128.2 (Ph 1 C-2,6), 127.6 (Ph 2 C-4, Ph 3 C-4), 121.2 (Ph 1 C-4), 114.2 (Ph 2 C-2,6), 57.8 (CH), 36.1 (CH₂), 20.4 (CH₃).

⁷⁷Se NMR (76 MHz, CDCl₃): δ 266.5 (m).

HRMS (ESI), *m/z* [M + H]⁺ calcd. for C₂₁H₂₁BrNSe: 446.0017; found: 446.0021.

3.1.11. *N*-[1-(4-chlorophenyl)-2-(phenylselanyl)ethyl]-4-fluoroaniline (9)



By Following the general procedure, starting from 1,1'-(methylenediselanyl)dibenzene (0.652 g, 2.0 mmol, 2.0 equiv) in dry THF (2 mL), *n*-BuLi (2.5 M, 0.76 mL, 1.9 mmol, 1.9 equiv) and *N*-(4-chlorobenzylidene)-4-fluoroaniline (0.233 g, 1.0 mmol, 1.0 equiv) in dry THF (1 mL), compound **9** was obtained in 88% yield (0.356 g) as yellowish oil after purification by column chromatography on silica gel (*n*-hexane:EtOAc 98:2).

¹H NMR (400 MHz, CDCl₃): δ 7.50 (m, 2H, Ph 3 H-2,6), 7.27 (m, 7H, Ph 1 H-2,3,5,6, Ph 3 H-3,4,5), 6.78 (m, 2H, Ph 2 H-3,5), 6.35 (m, 2H, Ph 2 H-2,6), 4.31 (dd, ³*J* = 8.9 Hz, ³*J* = 4.5 Hz, 1H, CH), 4.0–4.9 (brs, 1H, NH), 3.32 (dd, ²*J* = 12.7 Hz, ³*J* = 4.5 Hz, 1H, CH₂), 3.14 (dd, ²*J* = 12.7 Hz, ³*J* = 8.9 Hz, 1H, CH₂).

¹³C NMR (100 MHz, CDCl₃): δ 156.2 (d, ¹*J*_{CF} = 235.9 Hz, Ph 2 C-4), 142.9 (Ph 2 C-1), 140.8 (Ph 1 C-1), 133.7 (Ph 3 C-2,6), 133.3 (Ph 1 C-4), 129.3 (Ph 3 C-3,5), 129.0 (Ph 1 C-3,5), 128.7 (Ph 3 C-1), 127.7 (Ph 1 C-2,6, Ph 3 C-4), 115.6 (d, ²*J*_{CF} = 22.4 Hz, Ph 2 C-3,5), 114.8 (m, Ph 2 C-2,6), 58.0 (CH), 36.2 (CH₂).

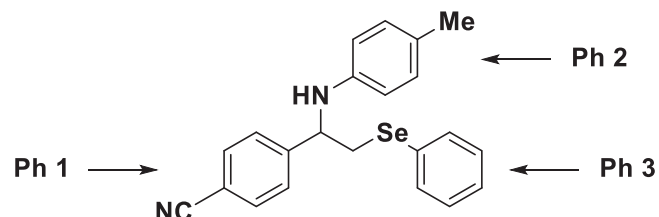
⁷⁷Se NMR (76 MHz, CDCl₃): δ 266.6 (m).

¹⁹F NMR (376 MHz, CDCl₃): δ -127.0 (m).

¹⁵N NMR (40 MHz, CDCl₃): δ -307.9.

HRMS (ESI), *m/z* [M + H]⁺ calcd. for C₂₀H₁₈ClFNSe: 406.0272; found: 406.0270.

3.1.12. 4-{1-[(4-methylphenyl)amino]-2-(phenylselanyl)ethyl}benzonitrile (10)



By Following the general procedure, starting from 1,1'-(methylenediselanyl)dibenzene (0.652 g, 2.0 mmol, 2.0 equiv) in dry THF (2 mL), *n*-BuLi (2.5 M, 0.76 mL, 1.9 mmol, 1.9 equiv) and 4-((*p*-tolylimino)methyl)benzotrile (0.220 g, 1.0 mmol, 1.0 equiv) in dry THF (1 mL), compound **10** was obtained in 92% yield (0.360 g) as yellowish oil after purification by column chromatography on silica gel (*n*-hexane:EtOAc 99:1).

¹H NMR (400 MHz, CDCl₃): δ 7.57 (m, 2H, Ph 1 H-2,6), 7.49 (m, 2H, Ph 3 H-2,6), 7.45 (m, 2H, Ph 1 H-3,5), 7.28 (m, 1H, Ph 3 H-4), 7.26 (m, 2H, Ph 3 H-3,5), 6.89 (m, 2H, Ph 2 H-3,5), 6.32 (m, 2H, Ph 2 H-2,6), 4.44 (dd, ³*J* = 8.7 Hz, ³*J* = 4.5 Hz, 1H, CH), 4.1–4.9 (brs, 1H, NH), 3.32 (dd, ²*J* = 12.8 Hz, ³*J* = 4.5 Hz, 1H, CH₂), 3.16 (dd, ²*J* = 12.8 Hz, ³*J* = 8.7 Hz, 1H, CH₂), 2.19 (s, 3H, CH₃).

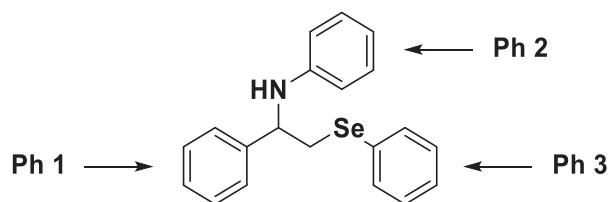
¹³C NMR (100 MHz, CDCl₃): δ 148.3 (Ph 1 C-4), 143.9 (Ph 2 C-1), 133.7 (Ph 3 C-2,6), 132.6 (Ph 1 C-2,6), 129.7 (Ph 2 C-3,5), 129.3 (Ph 3 C-3,5), 128.6 (Ph 3 C-1), 127.8 (Ph 2 C-4, Ph 3 C-4), 127.3 (Ph 1 C-3,5), 118.7 (C≡N), 114.0 (Ph 2 C-2,6), 111.3 (Ph 1 C-1), 57.9 (CH), 35.9 (CH₂), 20.3 (CH₃).

⁷⁷Se NMR (76 MHz, CDCl₃): δ 267.8.

¹⁵N NMR (40 MHz, CDCl₃): δ -308.3.

HRMS (ESI), *m/z* [M + H]⁺ calcd. for C₂₂H₂₁N₂Se: 393.0864; found: 393.0866.

3.1.13. *N*-[1-phenyl-2-(phenylselanyl)ethyl]aniline (**11**)



By Following the general procedure, starting from 1,1'-(methylenediselanyl)dibenzene (0.652 g, 2.0 mmol, 2.0 equiv) in dry THF (2 mL), *n*-BuLi (2.5 M, 0.76 mL, 1.9 mmol, 1.9 equiv) and *N*-benzylideneaniline (0.181 g, 1.0 mmol, 1.0 equiv) in dry THF (1 mL), compound **11** was obtained in 89% yield (0.313 g) as yellow solid after purification by column chromatography on silica gel (*n*-hexane:EtOAc 99:1).

mp: 125–127 °C.

¹H NMR (400 MHz, CDCl₃): δ 7.52 (m, 2H, Ph 3 H-2,6), 7.35 (m, 2H, Ph 1 H-2,6), 7.31 (m, 2H, Ph 1 H-3,5), 7.27 (m, 3H, Ph 3 H-3,4,5), 7.25 (m, 1H, Ph 1 H-4), 7.07 (m, 2H, Ph 2 H-3,5), 6.67 (m, 1H, Ph 2 H-4), 6.45 (m, 2H, Ph 2 H-2,6), 4.46 (dd, ³*J* = 8.8 Hz, ³*J* = 4.7 Hz, 1H, CH), 4.3–4.7 (brs, 1H, NH), 3.37 (dd, ²*J* = 12.6 Hz, ³*J* = 4.7 Hz, 1H, CH₂), 3.22 (dd, ²*J* = 12.6 Hz, ³*J* = 8.8 Hz, 1H, CH₂).

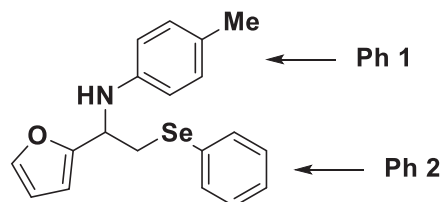
¹³C NMR (100 MHz, CDCl₃): δ 147.0 (Ph 2 C-1), 142.6 (Ph 1 C-1), 133.5 (Ph 3 C-2,6), 129.3 (Ph 3 C-1), 129.2 (Ph 3 C-3,5), 129.0 (Ph 2 C-3,5), 128.8 (Ph 1 C-3,5), 127.53 (Ph 3 C-4), 127.49 (Ph 1 C-4), 126.3 (Ph 1 C-2,6), 117.8 (Ph 2 C-4), 113.8 (Ph 2 C-2,6), 57.9 (CH), 36.4 (CH₂).

⁷⁷Se NMR (76 MHz, CDCl₃): δ 266.7 (m).

¹⁵N NMR (40 MHz, CDCl₃): δ -305.1.

HRMS (ESI), *m/z* [M + H]⁺ calcd. for C₂₀H₂₀NSe: 354.0755; found: 354.0751.

3.1.14. *N*-[1-(2-furyl)-2-(phenylselanyl)ethyl]-4-methylaniline (**12**)



By Following the general procedure, starting from 1,1'-(methylenediselanyl)dibenzene (0.652 g, 2.0 mmol, 2.0 equiv) in dry THF (2 mL), *n*-BuLi (2.5 M, 0.76 mL, 1.9 mmol, 1.9 equiv) and *N*-(furan-2-ylmethylene)-4-methylaniline (0.185 g, 1.0 mmol, 1.0 equiv) in dry THF (1 mL), compound **12** was obtained in 86% yield (0.306 g) as yellow oil after purification by column chromatography on silica gel (*n*-hexane:EtOAc 99:1).

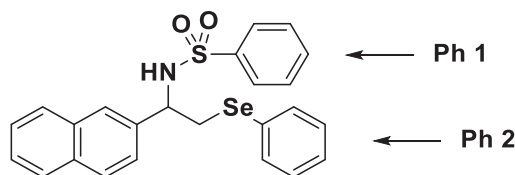
¹H NMR (400 MHz, CDCl₃): δ 7.49 (m, 2H, Ph 2 H-2,6), 7.30 (dd, ³*J* = 1.8 Hz, ⁴*J* = 0.9 Hz, 1H, Furyl H-5), 7.25 (m, 3H, Ph 2 H-3,4,5), 6.93 (m, 2H, Ph 1 H-3,5), 6.45 (m, 2H, Ph 1 H-2,6), 6.27 (dd, ³*J* = 3.2 Hz, ³*J* = 1.8 Hz, 1H, Furyl H-4), 6.19 (m, 1H, Furyl H-3), 4.68 (m, 1H, CH), 4.03–4.30 (brs, 1H, NH), 3.40 (dd, ²*J* = 12.5 Hz, ³*J* = 6.5 Hz, 1H, CH₂), 3.36 (dd, ²*J* = 12.5 Hz, ³*J* = 6.3 Hz, 1H, CH₂), 2.21 (s, 3H, CH₃).

¹³C NMR (100 MHz, CDCl₃): δ 154.6 (Furyl C-2), 144.1 (Ph 1 C-1), 141.8 (Furyl C-5), 133.4 (Ph 2 C-2,6), 129.7 (Ph 1 C-3,5), 129.5 (Ph 2 C-1), 129.1 (Ph 2 C-3,5), 127.6 (Ph 1 C-4), 127.3 (Ph 2 C-4), 114.0 (Ph 1 C-2,6), 110.3 (Furyl C-4), 106.8 (Furyl C-3), 52.4 (CH), 32.9 (CH₂), 20.4 (CH₃).

⁷⁷Se NMR (76 MHz, CDCl₃): δ 262.2 (m).

HRMS (ESI), *m/z* [M + H]⁺ calcd. for C₁₉H₂₀NSe: 358.0705; found: 358.0707.

3.1.15. *N*-(1-(naphthalen-2-yl)-2-(phenylselanyl)ethyl)benzenesulfonamide (**13**)



By Following the general procedure, starting from 1,1'-(methylenediselanyl)dibenzene (0.652 g, 2.0 mmol, 2.0 equiv) in dry THF (2 mL), *n*-BuLi (2.5 M, 0.76 mL, 1.9 mmol, 1.9 equiv) and *N*-(naphthalen-2-ylmethylene)benzenesulfonamide (0.295 g, 1.0 mmol, 1.0 equiv) in dry THF (1 mL), compound **13** was obtained in 89% yield (0.414 g) as colourless oil after purification by column chromatography on silica gel (*n*-hexane:EtOAc 9:1).

¹H NMR (400 MHz, CDCl₃): δ 7.74 (m, 1H, Naph H-5), 7.67 (m, 1H, Naph H-8), 7.63 (m, 1H, Naph H-4), 7.61 (m, 2H, Ph 1 H-2,6), 7.46 (m, 1H, Naph H-1), 7.45 (m, 2H, Naph H-6, Naph H-7), 7.38 (m, 1H, Ph 1 H-4), 7.37 (m, 2H, Ph 2 H-2,6), 7.24 (m, 3H, Ph 1 H-3,5, Ph 2 H-4), 7.22 (m, 2H, Ph 2 H-3,5), 7.14 (m, 1H, Naph H-3), 5.43 (d, ³*J* = 5.5 Hz, 1H, NH), 4.58 (m, 1H, CH), 3.32 (dd, ²*J* = 12.8 Hz, ³*J* = 7.3 Hz, 1H, CH₂), 3.25 (dd, ²*J* = 12.8 Hz, ³*J* = 6.4 Hz, 1H, CH₂).

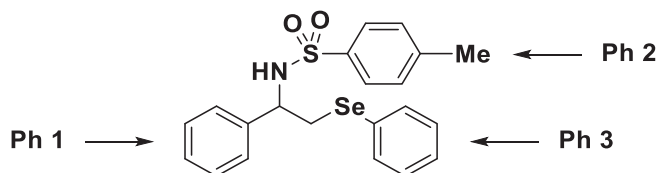
¹³C NMR (100 MHz, CDCl₃): δ 139.9 (Ph 1 C-1), 136.4 (Naph C-2), 133.3 (Ph 2 C-2,6), 132.96 (Naph C-8a), 132.94 (Naph C-4a), 132.4 (Ph 1 C-4), 129.3 (Ph 2 C-3,5), 128.7 (Ph 1 C-3,5), 128.52 (Naph C-4), 128.51 (Ph 2 C-1), 127.9 (Naph C-8), 127.59 (Ph 2 C-4), 127.77 (Naph C-5), 127.1 (Ph 1 C-2,6), 126.3 (Naph C-7), 126.2 (Naph C-6), 126.1 (Naph C-1), 124.0 (Naph C-3), 57.3 (CH), 35.0 (CH₂).

⁷⁷Se NMR (76 MHz, CDCl₃): δ 257.8 (m).

¹⁵N NMR (40 MHz, CDCl₃): δ -271.7.

HRMS (ESI), m/z [M + H]⁺ calcd. for C₂₄H₂₂NO₂SSe: 468.0531; found: 468.0532.

3.1.16. 4-methyl-N-[1-phenyl-2-(phenylselanyl)ethyl]benzenesulfonamide (**14**)¹¹



By Following the general procedure, starting from 1,1'-(methylenediselanyl)dibenzene (0.652 g, 2.0 mmol, 2.0 equiv) in dry THF (2 mL), *n*-BuLi (2.5 M, 0.76 mL, 1.9 mmol, 1.9 equiv) and *N*-benzylidene-4-methylbenzenesulfonamide (0.261 g, 1.0 mmol, 1.0 equiv) in dry THF (1 mL), compound **14** was obtained in 91% yield (0.391 g) as white solid after purification by column chromatography on silica gel (*n*-hexane:EtOAc 99:1).

mp: 92–93 °C (lit. 92–93 °C).

¹H NMR (400 MHz, CDCl₃): δ 7.51 (m, 2H, Ph 2 H-2,6), 7.34 (m, 2H, Ph 3 H-2,6), 7.26 (m, 1H, Ph 3 H-4), 7.22 (m, 2H, Ph 3 H-3,5), 7.20 (m, 2H, Ph 1 H-3,5), 7.19 (m, 1H, Ph 1 H-4), 7.12 (m, 2H, Ph 2 H-3,5), 7.06 (m, 2H, Ph 1 H-2,6), 5.27 (m, 1H, NH), 4.37 (m, 1H, CH), 3.24 (dd, ²*J* = 12.8 Hz, ³*J* = 7.2 Hz, 1H, CH₂), 3.16 (dd, ²*J* = 12.8 Hz, ³*J* = 6.4 Hz, 1H, CH₂), 2.37 (s, 3H, CH₃).

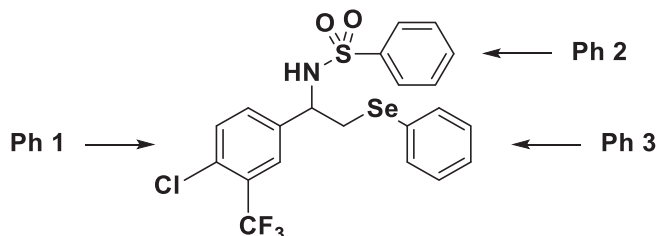
¹³C NMR (100 MHz, CDCl₃): δ 143.2 (Ph 2 C-4), 139.5 (Ph 1 C-1), 136.9 (Ph 2 C-1), 133.2 (Ph 3 C-2,6), 129.4 (Ph 2 C-3,5), 129.2 (Ph 3 C-3,5), 128.7 (Ph 3 C-1), 128.5 (Ph 1 C-3,5), 128.0 (Ph 1 C-4), 127.5 (Ph 3 C-4), 127.2 (Ph 2 C-2,6), 126.6 (Ph 1 C-2,6), 57.1 (CH), 35.1 (CH₂), 21.5 (CH₃).

⁷⁷Se NMR (76 MHz, CDCl₃): δ 256.8 (m)

¹⁵N NMR (40 MHz, CDCl₃): δ -271.4.

HRMS (ESI), m/z [M + Na]⁺ calcd. for C₂₁H₂₁NNaO₂SSe: 454.0350; found: 454.0342.

3.1.17. *N*-[1-[4-chloro-3-(trifluoromethyl)phenyl]-2-(phenylselanyl)ethyl] benzenesulfonamide (**15**)



By Following the general procedure, starting from 1,1'-(methylenediselanyl)dibenzene (0.652 g, 2.0 mmol, 2.0 equiv) in dry THF (2 mL), *n*-BuLi (2.5 M, 0.76 mL, 1.9 mmol, 1.9 equiv) and *N*-(4-chloro-3-(trifluoromethyl)benzylidene)benzenesulfonamide (0.347 g, 1.0 mmol, 1.0 equiv) in dry THF (1 mL), compound **15** was obtained in 85% yield (0.440 g) as yellow solid after purification by column chromatography on silica gel (*n*-hexane:EtOAc 99:1).

mp: 125–126 °C.

¹H NMR (400 MHz, CDCl₃): δ 7.59 (m, 2H, Ph 2 H-2,6), 7.50 (m, 1H, Ph 2 H-4), 7.35 (m, 2H, Ph 2 H-3,5), 7.32 (m, 2H, Ph 3 H-2,6), 7.28 (m, 1H, Ph 3 H-4), 7.25 (m, 1H, Ph 1 H-5), 7.23 (m, 1H, Ph 1 H-2), 7.22

(m, 2H, Ph 3 H-3,5), 7.18 (m, 1H, Ph 1 H-6), 5.43 (d, ³*J* = 5.0 Hz, 1H, NH), 4.45 (m, 1H, CH), 3.11 (d, ³*J* = 6.6 Hz, 2H, CH₂).

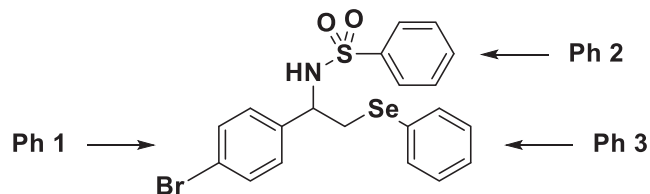
¹³C NMR (100 MHz, CDCl₃): δ 139.7 (Ph 2 C-1), 138.5 (Ph 1 C-1), 133.7 (Ph 3 C-2,6), 132.9 (Ph 2 C-4), 131.8 (q, ³*J*_{CF} = 1.9 Hz, Ph 1 C-4), 131.4 (Ph 1 C-5), 131.3 (Ph 1 C-6), 129.4 (Ph 3 C-3,5), 128.9 (Ph 2 C-3,5), 128.3 (q, ²*J*_{CF} = 31.5 Hz, Ph 1 C-3), 128.1 (Ph 3 C-4), 127.6 (Ph 3 C-1), 127.1 (Ph 2 C-2,6), 125.9 (q, ³*J*_{CF} = 5.4 Hz, Ph 1 C-2), 122.4 (q, ¹*J*_{CF} = 273.7 Hz, CF₃), 56.2 (CH), 34.9 (CH₂).

¹⁹F NMR (376 MHz, CDCl₃): δ -62.7 (s, CF₃).

¹⁵N NMR (40 MHz, CDCl₃): δ -272.8.

HRMS (ESI), m/z [M + Na]⁺ calcd. for C₂₁H₁₇ClF₃NNaO₂SSe: 541.9678; found: 541.9691.

3.1.18. *N*-[1-(4-bromophenyl)-2-(phenylselanyl)ethyl] benzenesulfonamide (**16**)



By Following the general procedure, starting from 1,1'-(methylenediselanyl)dibenzene (0.652 g, 2.0 mmol, 2.0 equiv) in dry THF (2 mL), *n*-BuLi (2.5 M, 0.76 mL, 1.9 mmol, 1.9 equiv) and *N*-(4-bromobenzylidene)benzenesulfonamide (0.324 g, 1.0 mmol, 1.0 equiv) in dry THF (1 mL), compound **16** was obtained in 90% yield (0.445 g) as white solid after purification by column chromatography on silica gel (*n*-hexane:EtOAc 99:1).

mp: 124–125 °C.

¹H NMR (400 MHz, CDCl₃): δ 7.61 (m, 2H, Ph 2 H-2,6), 7.50 (m, 1H, Ph 2 H-4), 7.35 (m, 2H, Ph 2 H-3,5), 7.33 (m, 2H, Ph 3 H-2,6), 7.27 (m, 1H, Ph 3 H-4), 7.27 (m, 2H, Ph 1 H-3,5), 7.22 (m, 2H, Ph 3 H-3,5), 6.91 (m, 2H, Ph 1 H-2,6), 5.37 (d, ³*J* = 5.5 Hz, 1H, NH), 4.35 (m, 1H, CH), 3.16 (dd, ²*J* = 12.9 Hz, ³*J* = 7.4 Hz, 1H, CH₂), 3.11 (dd, ²*J* = 12.9 Hz, ³*J* = 6.2 Hz, 1H, CH₂).

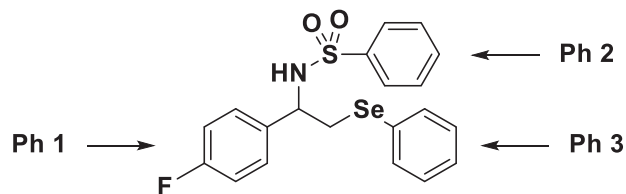
¹³C NMR (100 MHz, CDCl₃): δ 139.8 (Ph 2 C-1), 138.4 (Ph 1 C-1), 133.4 (Ph 3 C-2,6), 132.6 (Ph 2 C-4), 131.6 (Ph 1 C-3,5), 129.4 (Ph 3 C-3,5), 128.9 (Ph 2 C-3,5), 128.4 (Ph 1 C-2,6), 128.2 (Ph 3 C-1), 127.8 (Ph 3 C-4), 127.1 (Ph 2 C-2,6), 122.0 (Ph 1 C-4), 56.6 (CH), 34.9 (CH₂).

⁷⁷Se NMR (76 MHz, CDCl₃): δ 257.9 (m).

¹⁵N NMR (40 MHz, CDCl₃): δ -272.2.

HRMS (ESI), m/z [M + H]⁺ calcd. for C₂₀H₁₉BrNO₂SSe: 495.9480; found: 495.9476.

3.1.19. *N*-[1-(4-fluorophenyl)-2-(phenylselanyl)ethyl] benzenesulfonamide [**17**]



By Following the general procedure, starting from 1,1'-(methylenediselanyl)dibenzene (0.652 g, 2.0 mmol, 2.0 equiv) in dry THF (2 mL), *n*-BuLi (2.5 M, 0.76 mL, 1.9 mmol, 1.9 equiv) and *N*-(4-fluorobenzylidene)benzenesulfonamide (0.263 g, 1.0 mmol, 1.0 equiv) in dry THF (1 mL), compound **17** was obtained in 92% yield

(0.399 g) as yellowish solid after purification by column chromatography on silica gel (*n*-hexane:EtOAc 98:2).

mp: 99–102 °C.

¹H NMR (400 MHz, CDCl₃): δ 7.61 (m, 2H, Ph 2 H-2,6), 7.48 (m, 1H, Ph 2 H-4), 7.35 (m, 2H, Ph 3 H-2,6), 7.34 (m, 2H, Ph 2 H-3,5), 7.27 (m, 1H, Ph 3 H-4), 7.23 (m, 2H, Ph 3 H-3,5), 7.00 (m, 2H, Ph 1 H-2,6), 6.83 (m, 2H, Ph 1 H-3,5), 5.38 (d, 1H, ³*J* = 5.4 Hz, 1H, NH), 4.38 (m, 1H, CH), 3.18 (dd, ²*J* = 12.9 Hz, ³*J* = 7.4 Hz, 1H, CH₂), 3.12 (dd, ²*J* = 12.9 Hz, ³*J* = 6.3 Hz, 1H, CH₂).

¹³C NMR (100 MHz, CDCl₃): δ 162.3 (d, ¹*J*_{CF} = 247.0 Hz, Ph 1 C-4), 139.9 (Ph 2 C-1), 135.1 (d, ⁴*J*_{CF} = 3.2 Hz, Ph 1 C-1), 133.4 (Ph 3 C-2,6), 132.6 (Ph 2 C-4), 129.3 (Ph 3 C-3,5), 128.8 (Ph 2 C-3,5), 128.4 (d, ³*J*_{CF} = 8.3 Hz, Ph 1 C-2,6), 128.3 (Ph 3 C-1), 127.7 (Ph 3 C-4), 127.1 (Ph 2 C-2,6), 115.4 (d, ²*J*_{CF} = 21.6 Hz, Ph 1 C-3,5), 56.5 (CH), 35.1 (CH₂).

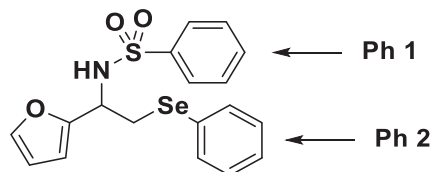
⁷⁷Se NMR (76 MHz, CDCl₃): δ 258.0 (m).

¹⁹F NMR (376 MHz, CDCl₃): δ –113.9 (m).

¹⁵N NMR (40 MHz, CDCl₃): δ –271.6.

HRMS (ESI), *m/z* [M + Na]⁺ calcd. for C₂₀H₁₈FNNaO₂SSe: 458.0100; found: 458.0108.

3.1.20. *N*-[1-(2-furyl)-2-(phenylselanyl)ethyl]benzenesulfonamide (18)



By Following the general procedure, starting from 1,1'-(methylenediselanyl)dibenzene (0.652 g, 2.0 mmol, 2.0 equiv) in dry THF (2 mL), *n*-BuLi (2.5 M, 0.76 mL, 1.9 mmol, 1.9 equiv) and *N*-(furan-2-ylmethylene)benzenesulfonamide (0.235 g, 1.0 mmol, 1.0 equiv) in dry THF (1 mL), compound **18** was obtained in 87% yield (0.353 g) as yellowish oil after purification by column chromatography on silica gel (*n*-hexane:EtOAc 9:1).

¹H NMR (400 MHz, CDCl₃): δ 7.70 (m, 2H, Ph 1 H-2,6), 7.50 (m, 1H, Ph 1 H-4), 7.39 (m, 2H, Ph 1 H-3,5), 7.39 (m, 2H, Ph 2 H-2,6), 7.25 (m, 1H, Ph 2 H-4), 7.24 (m, 2H, Ph 2 H-3,5), 7.11 (dd, ³*J* = 1.8 Hz, ⁴*J* = 0.8 Hz, 1H, Furyl H-5), 6.12 (dd, ³*J* = 3.3 Hz, ³*J* = 1.8 Hz, 1H, Furyl H-4), 5.99 (m, 1H, Furyl H-3), 5.30 (d, ³*J* = 8.0 Hz, 1H, NH), 4.63 (m, 1H, CH), 3.36 (dd, ²*J* = 12.7 Hz, ³*J* = 5.7 Hz, 1H, CH₂), 3.17 (dd, ²*J* = 12.7 Hz, ³*J* = 7.3 Hz, 1H, CH₂).

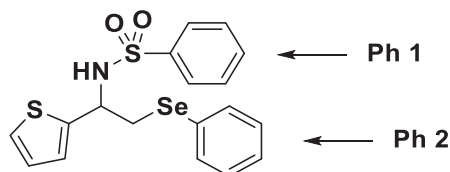
¹³C NMR (100 MHz, CDCl₃): δ 151.2 (Furyl C-2), 142.2 (Furyl C-5), 140.2 (Ph 1 C-1), 133.2 (Ph 2 C-2,6), 132.5 (Ph 1 C-4), 129.2 (Ph 2 C-3,5), 128.9 (Ph 1 C-3,5), 128.8 (Ph 2 C-1), 127.4 (Ph 2 C-4), 127.0 (Ph 1 C-2,6), 110.2 (Furyl C-4), 108.0 (Furyl C-3), 51.4 (CH), 32.5 (CH₂).

⁷⁷Se NMR (76 MHz, CDCl₃): δ 260.3 (m).

¹⁵N NMR (40 MHz, CDCl₃): δ –274.5.

HRMS (ESI), *m/z* [M + Na]⁺ calcd. for C₁₈H₁₇NNaO₃SSe: 429.9987; found: 429.9987.

3.1.21. *N*-[2-(phenylselanyl)-1-(2-thienyl)ethyl]benzenesulfonamide (19)



By Following the general procedure, starting from 1,1'-(methylenediselanyl)dibenzene (0.652 g, 2.0 mmol, 2.0 equiv) in dry THF (2 mL), *n*-BuLi (2.5 M, 0.76 mL, 1.9 mmol, 1.9 equiv) and *N*-(thiophen-2-ylmethylene)benzenesulfonamide (0.251 g, 1.0 mmol, 1.0 equiv) in dry THF (1 mL), compound **19** was obtained in 90% yield (0.379 g) as yellowish oil after purification by column chromatography on silica gel (*n*-hexane:EtOAc 9:1).

¹H NMR (400 MHz, CDCl₃): δ 7.68 (m, 2H, Ph 1 H-2,6), 7.50 (m, 1H, Ph 1 H-4), 7.42 (m, 2H, Ph 2 H-2,6), 7.37 (m, 2H, Ph 1 H-3,5), 7.27 (m, 1H, Ph 2 H-4), 7.26 (m, 2H, Ph 2 H-3,5), 7.12 (dd, ³*J* = 5.1 Hz, ⁴*J* = 1.2 Hz, 1H, Th H-5), 6.81 (dd, ³*J* = 5.1 Hz, ³*J* = 3.5 Hz, 1H, Th H-4), 6.74 (m, 1H, Th H-3), 5.31 (d, ³*J* = 6.8 Hz, 1H, NH), 4.79 (m, 1H, CH), 3.40 (dd, ²*J* = 12.8 Hz, ³*J* = 6.0 Hz, 1H, CH₂), 3.20 (dd, ²*J* = 12.8 Hz, ³*J* = 6.7 Hz, 1H, CH₂).

¹³C NMR (100 MHz, CDCl₃): δ 143.1 (Th C-2), 140.0 (Ph 1 C-1), 133.3 (Ph 2 C-2,6), 132.6 (Ph 1 C-4), 129.3 (Ph 2 C-3,5), 128.9 (Ph 1 C-3,5), 128.8 (Ph 2 C-1), 127.6 (Ph 2 C-4), 127.1 (Ph 1 C-2,6), 126.7 (Th C-4), 125.5 (Th C-3), 125.4 (Th C-5), 53.1 (CH), 35.7 (CH₂).

⁷⁷Se NMR (76 MHz, CDCl₃): δ 259.0 (m).

¹⁵N NMR (40 MHz, CDCl₃): δ –268.8.

HRMS (ESI), *m/z* [M + H]⁺ calcd. for C₁₈H₁₈NO₂S₂Se: 423.9939; found: 423.9936.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.tet.2020.131220>.

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Publication n. 5

Chemoselective reduction of isothiocyanates to thioformamides mediated by the Schwartz reagent.

Karen De la Vega-Hernandez, Raffaele Senatore, Margherita Miele, Ernst Urban, Wolfgang Holzer and Vittorio Pace*

Org. Biomol. Chem. **2019**, 17, 1970 (DOI: 10.1039/C8OB02312C)

The Supporting information is available on the website at:

<https://www.rsc.org/suppdata/c8/ob/c8ob02312c/c8ob02312c1.pdf>

Details on experimental procedures, characterization data and copies of NMR spectra of all compounds are reported.

PAPER



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Chemoselective reduction of isothiocyanates to thioformamides mediated by the Schwartz reagent†

Karen de la Vega-Hernández,‡ Raffaele Senatore, Margherita Miele, Ernst Urban, Wolfgang Holzer and Vittorio Pace *

Thioformamides are easily prepared – under full chemocontrol – through the partial reduction of isothiocyanates with the *in situ* generated Schwartz reagent. The high electrophilicity of the starting materials enables the straightforward addition of the hydride ion, thus constituting a reliable and high-yielding method for obtaining variously functionalized thioformamides. Sensitive chemical groups to the reduction conditions such as nitro, ester, alkene, azo, azide and keto groups do not interfere with the chemoselectivity of the process. Moreover, the stereochemical information embodied in the starting material is fully retained in the final products. The synthetic potential of the selected thioformamide template is also briefly discussed.

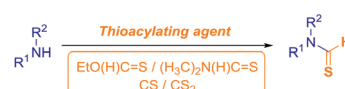
Introduction

Within the class of amide-type compounds, a prominent position is covered by thioamide-analogues.¹ The simple replacement of oxygen with sulfur accounts for dramatic modifications of the reactivity pattern, often associated with positive effects on physico-chemical properties such as stability or crystallizability.² Also after the advent of reliable techniques for activating the poorly electrophilic oxo-amide linkage, thioamides are still considered first-choice agents which enable the nucleophilic addition of organometallic and reducing agents to the carbonyl-type carbon atom.³ A particular category of thioamides is constituted by thioformamides which are versatile scaffolds in organic synthesis acting as pivotal intermediates for the construction of biologically significant sulfur-containing heterocycles,⁴ secondary thiocarbamoylsilanes⁵ and amidines.⁶ Despite the wide availability of methods to access thioamides^{1a,2b,7} surprisingly, strategies to access simpler thioformamides are rather limited, having attracted considerably minor interest within the synthetic community. Accordingly, it is possible to categorize them as follows (Scheme 1): (a) thioacylation of amines with agents such as

thioformates,⁸ dimethyl thioformamide,⁹ and carbon mono-¹⁰ or disulfide (path a)¹¹ and (b) formal oxygen–sulfur replacement on oxoamides in the presence of thionating agents

I. Previous Strategies for the Synthesis of Thioformamides

a) Thioacylation of Amines



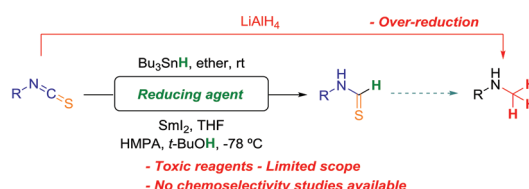
Common disadvantages

- Toxic reagents
- Unpleasant smelling
- Unstable reagents
- Harsh reaction conditions
- Tedious work-up

b) Thionation of Oxoamides



c) Reaction of Isothiocyanates with Reducing Agents



Schwartz Reagent mediated Reduction of Iso(thio)cyanates to (Thio)Formamides



X = O (Pace, 2016)

X = S (This work)

- High yields - Wide scope - Versatile
- Chemoselective - Mild conditions
- Full transfer of stereochemistry

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†Electronic supplementary information (ESI) available. See DOI: 10.1039/c8ob02312c

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Scheme 1 General context of the work.

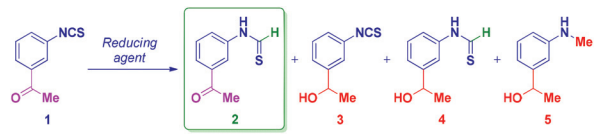
including the Lawesson reagent,¹² phosphorus pentasulfide^{2b} or elemental sulfur (path b).¹³ The inherent drawbacks associated with the employment of thionating-type procedures (toxicity, unpleasant odor, harsh conditions) pose serious limitations to their applicability, thus making the quest for alternative routes an important task for chemists. In recent years, seminal studies by Gilman¹⁴ and Worrall¹⁵ in the 1920s dealing with the addition of organometallic reagents to heterocumulenes (*e.g.* isocyanates or isothiocyanates) have experienced renewed interest for the construction of the (thio)amide linkage, as indicated in reports by the groups of Bode,¹⁶ Martin,¹⁷ Molander,¹⁸ Kerr¹⁹ and our own.²⁰ In particular, the excellent electrophilicity of the heterocumulene's carbon together with the minimal (if not absent) electronic and steric influence displayed by the substituent on nitrogen makes them superb placeholders for (thio)amides.²¹

In 2016 we documented the chemoselective partial reduction of isocyanates to the corresponding formamides realized under mild conditions²² in the presence of the Schwartz reagent generated *in situ* according to the Snieckus' procedure (path c).²³ Would this tactic be applicable to analogous isothiocyanates, a modular and chemoselective preparation of thioformamides, – overcoming difficulties highlighted in previous reports consisting of the *full* reduction of the isothiocyanate to a methyl amine²⁴ – could be envisaged. In this context, the partial reduction of isothiocyanates has been previously investigated on very simple, non-functionalized materials, evidencing the possibility to perform the process with a tedious hydride source (Bu_3SnH)²⁵ or under radical conditions (SmI_2) in the presence of the highly toxic HMPA (path c).²⁶ However, the very limited scope presented and the absence of insights into the chemoselectivity further spurred us to undertake the study of this transformation, and, herein we present the results of our investigations. We anticipate that the methodology is suitable for preparing the title compounds under more benign environmental conditions due to the absence of unpleasant thionating agents (*e.g.* Lawesson reagent) during the process.

Results and discussion

The challenging isothiocyanate **1** – featuring a potentially interfering (*i.e.* reductable) ketone functionality – was selected as the model substrate. As indicated in Table 1, four possible products could be obtained during the reduction process, namely: (i) the targeted thioformamide adduct presenting the ketone carbonyl group untouched (**2**), (ii) the isothiocyanate resulting from the exclusive reduction of the carbonyl to the corresponding alcohol (**3**), (iii) the unselectively reduced product arising from the simultaneous reduction of the isothiocyanate and keto groups (**4**) and finally (iv) the amino-alcohol (**5**) originated from the further over-reduction of the isothiocyanate to the corresponding amine and the keto reduction. LiAlH_4 realized both the partial and over-reduction of the isothiocyanate moiety along with the reduction of the

Table 1 Optimization of the reaction conditions



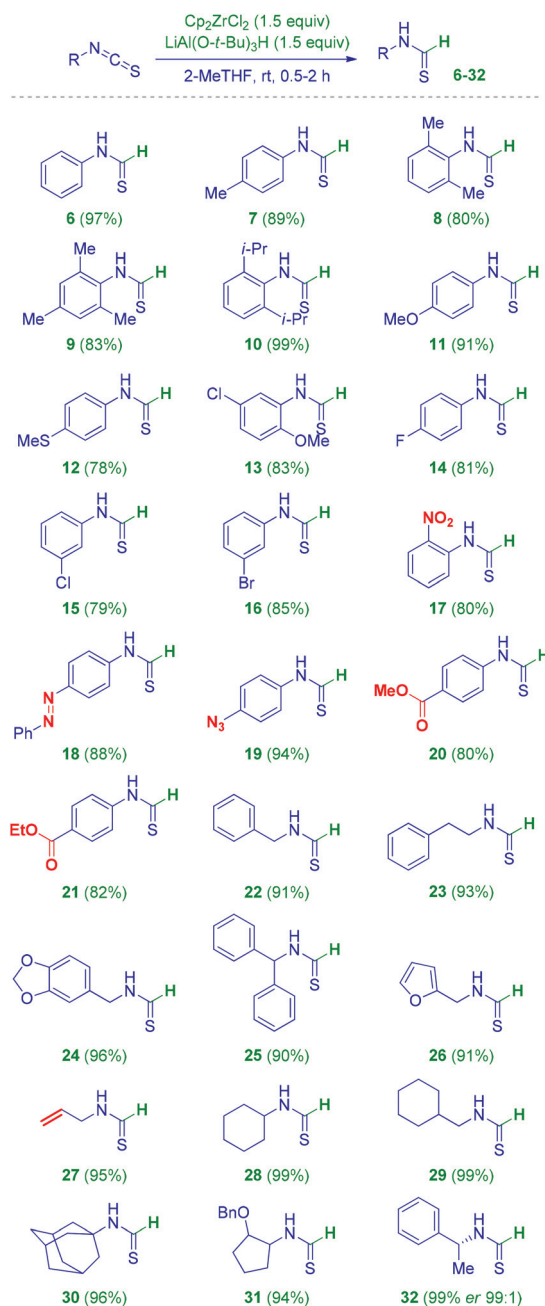
Entry	Reducing agent (equiv.)	Solvent	T (°C)/time (h)	2/3/4/5 ratio	Yield of 2 ^a (%)
1	LiAlH_4 (1.5)	THF	0/0.5	0 : 0 : 27 : 61	—
2	LiAlH_4 (0.3)	THF	0/0.5	0 : 74 : 0 : 0	—
3	LiBH_4 (0.3)	THF	0/0.5	0 : 38 : 12 : 34	—
4	NaBH_4 (0.3)	THF	0/0.5	24 : 27 : 28 : 0	18
5	DIBAL-H (1.0)	THF	0/0.5	0 : 82 : 0 : 0	—
6	$\text{LiAl}(\text{O}-t\text{-Bu})_3\text{H}$ (1.5)	THF	0/0.5	37 : 16 : 0 : 0	31
7	Cp_2ZrHCl (1.2) ^b	THF	0/1	69 : 9 : 4 : 0	64
8	Cp_2ZrHCl (1.5) ^b	THF	0/0.5	78 : 5 : 10 : 0	72
9	Cp_2ZrHCl (1.5) ^b	THF	−20/6	52 : 3 : 4 : 0	45
10	Cp_2ZrHCl (2.0) ^b	THF	−20/3	60 : 2 : 8 : 0	53
11	Cp_2ZrHCl (1.2) ^b	THF	rt/0.5	83 : 4 : 9 : 0	76
12	Cp_2ZrHCl (1.2) ^{b,c}	THF	rt/0.5	88 : 3 : 6 : 0	82
13	Cp_2ZrHCl (1.2) ^{b,c}	MeTHF	rt/0.5	91 : 2 : 4 : 0	84
14	Cp_2ZrHCl (1.2) ^d	MeTHF	rt/0.5	75 : 2 : 6 : 0	68

^a Isolated yield. ^b Cp_2ZrHCl was prepared according to the procedure of Snieckus (ref. 23). ^c $\text{LiAl}(\text{O}-t\text{-Bu})_3\text{H}$ (1 M in THF) was added to Cp_2ZrCl_2 at 0 °C. ^d Commercially available.

keto group (compounds **4** and **5**, entry 1). By lowering the load of this reducing agent to 0.3 equiv. compound **3** was formed as the unique product (entry 2), hence burying the possibility of chemoselectivity with LiAlH_4 towards the NCS functionality. When we switched to LiBH_4 , a complex mixture of products **3**, **4** and **5** was obtained (entry 3). A milder reducing agent such as NaBH_4 allowed us to detect for the first time the targeted product **2** (entry 4); however, the yield was low and the chemoselectivity was poor with concurrent formation of byproducts **3** and **4** in comparable yields to **2**. It is worth mentioning that no over-reduction of the isothiocyanate functionality to the corresponding amine was detected under this circumstance, in contrast to the above seen observations.^{24b} The use of DIBAL-H in equimolar ratio to the substrate afforded the undesired compound **3** in good yield as the unique product, thus making it a selective agent for this unknown transformation (entry 5). Switching to the milder $\text{LiAl}(\text{O}-t\text{-Bu})_3\text{H}$ slightly improved the ratio **2**:**3**, allowing to obtain the desired compound in 31% isolated yield (entry 6). In the pursuit of a more chemoselective reducing agent, we turned our attention to the Schwartz reagent²⁷ which demonstrated high versatility and synthetic potential in selective transformations with various functional groups.²⁸ However, we were cognizant of the difficulties in avoiding concomitant reduction of ketones, as reported by Georg,²⁹ Ganem³⁰ and Snieckus.^{23,31} Upon reaction of **1** with 1.2 equiv. of the *in situ* generated Schwartz reagent [from Cp_2ZrCl_2 and $\text{LiAl}(\text{O}-t\text{-Bu})_3\text{H}$],²³ we were delighted in observing the preferred reduction of the isothiocyanate, thus affording **2**:**3**:**4** in a very good 69 : 9 : 4 ratio (entry 7). By increasing the Schwartz reagent loading up to 1.5 equiv., it was possible to improve the ratio up to 78 : 5 : 10 (entry 8); notably, the ratio

between **3** and **4** was practically inverted, thus indicating that the slight excess of the hydride-releasing agent improved the reduction of the isothiocyanate. Cooling the system at $-20\text{ }^{\circ}\text{C}$ has a beneficial effect on the ratio **2**:**3**:**4** but, unfortunately even after considerably longer reaction time or, the use of an additional excess of reagent, reactions could not reach completion (entries 9 and 10). Lowering the hydride transfer agent to 1.2 equiv., while temperature was increased up to rt, resulted in a further improvement of the **2**:**3**:**4** ratio, allowing to isolate **2** in 76% yield (entry 11). An additional optimization was achieved by using the Schwartz reagent under *non*-Barbier conditions: $\text{LiAl}(\text{O}-t\text{-Bu})_3\text{H}$ was added to the THF solution of Cp_2ZrCl_2 at $0\text{ }^{\circ}\text{C}$ and then, the resulting mixture was slowly cannulated into the solution of isothiocyanate (entry 12). Finally, the switching to the environmentally benign MeTHF³² as the solvent for the reduction process benefited the overall transformation, maximizing the ratio to 91:2:4, thus allowing to isolate the desired product **2** in an excellent 84% yield (entry 13). The higher performance of the Schwartz reagent generated according to the Snieckus procedure²³ compared to the commercially available reagent (entry 14) is worth mentioning. The well-known drawbacks (air-, light-, and moisture-sensitivity) responsible for previously observed decreasing of the efficiency³³ could be easily circumvented by the preparation of the reagent immediately prior to its employment. Overall, the optimization study revealed the feasibility of a (preferential) chemoselective reduction of the isothiocyanate moiety in the concomitant presence of an easily reducible ketone.

We next focused on the scope of the reduction of widely available isothiocyanates with the Schwartz reagent to synthesize (almost) previously unknown thioformamides (Scheme 2). We were pleased to observe the successful, high-yielding – chemoselective – transformation of the isothiocyanate to the thioformamide level, regardless of the electronic nature [aromatic (**6**–**21**) and aliphatic (**22**–**32**)] of the starting materials. Decoration of aromatic rings with both electron-donating [alkyl, (thio)ether, **7**–**13**] and electron-withdrawing functionalities (halogens, nitro, azo, azide, *e.g.* **13**–**19**) is permitted without a noticeable difference in the particular (*ortho*-, *meta*-, and *para*-) position they occupy. Aliphatic isothiocyanates (eventually featuring heteroaromatic systems – **24**, **26**) reacted in slightly better efficiency than aromatic counterparts, as demonstrated by the (practically) quantitative yields of the corresponding thioformamides (**22**–**32**). Crowded substrates, both in the case of aromatic (**8**–**10**) and aliphatic (**25**, **30**) systems, performed extremely well, thus confirming the negligible effect of sterical factors in nucleophilic additions to heterocumulenes. Highly indicative confirmations on the chemoselectivity of the methodology were deduced by the exclusive reduction of the isothiocyanate moiety in the simultaneous presence of sensitive (to the reductive environment) functionalities, including ester (**20**–**21**) or olefin (**27**). Analogously, different nitrogen-containing groups such as nitro (**17**), azo (**18**) and azide (**19**) were perfectly tolerated and remained untouched during the transformation. The stereochemical

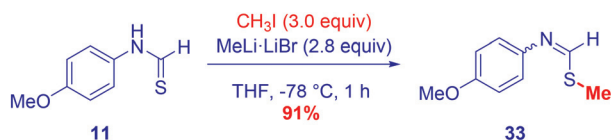


Scheme 2 Scope of the reaction.

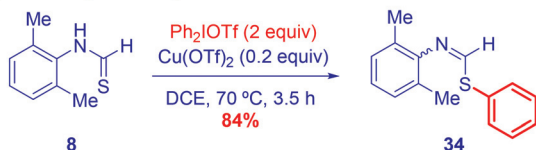
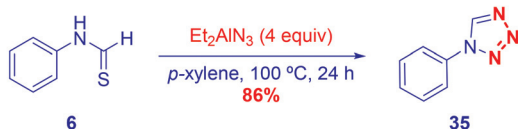
information is preserved during the reduction event, thus allowing the production of the enantiopure thioformamide (**32**) with a superb 99:1 er from the corresponding chiral isothiocyanate.

With the aim to expand the significance of the synthetic work and, considering the limited detailed studies on the chemical reactivity of thioformamides, we briefly investigated selective manipulations of this chemical functionality (Scheme 3). The deprotonation with an organolithium reagent (MeLi-LiBr) of the acidic NH proton, followed by electrophilic quenching with MeI , provided the corresponding *S*-methylated adduct **33**

a) Electrophilic Sulfur Alkylation



b) Cu-catalyzed S-Arylation

c) Tetrazole formation by cycloaddition with Et_2AlN_3 

Scheme 3 Synthetic potential of the thioformamide moiety.

(thioimide)³⁴ in excellent yield (*via* a). Arylation under copper catalyzed conditions in the presence of diphenyliodonium triflate proved to be an excellent method for realizing a selective sulfur arylation 34 (*via* b), thus providing modular, divergent access to aliphatic or aromatic thioimides³⁵ depending on the reaction conditions. Finally, the thioformamide functionality can act as a convenient placeholder for a monosubstituted tetrazole³⁶ upon reaction with an activated aluminium azide.³⁷

Conclusions

In summary, wide-ranging commercially available isothiocyanates can be partially reduced to the thioformamide level *via* hydride transfer from the *in situ* generated Schwartz reagent. This protocol allowed the synthesis of diverse *N*-substituted thioformamides in high yields under mild reaction conditions. The transformation occurs with full retention of the stereochemical information contained in the starting material and in a highly remarkable chemoselective fashion. Several functionalities that could undergo concomitant reduction such as nitro, ester, alkene, azo, azide, and keto groups were well-tolerated and remained untouched during the overall transformation.

Experimental

Reduction of 3-acetylphenyl isothiocyanate; general procedure 1

To a solution of 3-acetylphenyl isothiocyanate **1** (0.177 g, 1.0 mmol, 1.0 equiv.) in dry THF (5 mL) at the appropriate temperature, the corresponding reducing agents were added

dropwise (see conditions indicated in Table 1). After the appropriate time, the reaction mixtures were quenched with the following reagents: H_2O and 2.5 M NaOH (entries 1–3)/ H_2O (entry 4)/ NH_4Cl (entry 5)/ H_2O and 1 M HCl (entries 6–14), respectively. The aqueous layers were extracted with Et_2O (3 $\times$) and the organic phases were combined. The organic extracts were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude products were purified by flash SiO_2 column chromatography to yield the products indicated in Table 1.

Reduction of isothiocyanates to thioformamides with the *in situ* generated Schwartz reagent; general procedure 2

To an oven-dried and argon-flushed flask was added the isothiocyanate and Cp_2ZrCl_2 . The reagents were dissolved in anhydrous 2-MeTHF at rt and then the mixture was cooled at 0 $^\circ\text{C}$. $\text{LiAl(O-}t\text{-Bu)}_3\text{H}$ (1 M in THF) was added dropwise at 0 $^\circ\text{C}$ and then the cooling bath was removed, allowing the mixture to reach rt. After the appropriate time, the reaction mixture was quenched with H_2O (5 mL) and stirred for 1–2 min. Then, a solution of 1 M HCl (4 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (3 $\times$) and the organic layers were combined. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude mixtures were purified by flash SiO_2 column chromatography – whenever necessary – to yield the product, using *n*-hexane : EtOAc as the mobile phase.

N-(3-Acetylphenyl)thioformamide (2)

By following the General Procedure 2, to a solution of 3-acetylphenyl isothiocyanate (0.177 g, 1.0 mmol, 1.0 equiv.) and Cp_2ZrCl_2 (0.438 g, 1.5 mmol, 1.5 equiv.) in dry 2-MeTHF (5 mL) at 0 $^\circ\text{C}$, $\text{LiAl(O-}t\text{-Bu)}_3\text{H}$ (1.5 mL, 1.5 mmol, 1.5 equiv.) was added dropwise, and then, the reaction was allowed to warm to rt. Compound **2** was obtained in 84% yield (0.151 g) as a brown solid; mp 111–114 $^\circ\text{C}$, after purification by column chromatography on silica gel (eluent hexane : EtOAc 9 : 1).

s-trans : *s-cis* ~9 : 1.

s-trans rotamer:

^1H NMR (CDCl_3 , 400 MHz): δ = 9.90 (d, 3J = 14.5 Hz, 1H, HC=S), 9.59 (br d, 3J = 14.5 Hz, 1H, NH), 7.80 (ddd, 3J = 7.7 Hz, 4J = 1.5 Hz, 4J = 1.0 Hz, 1H, Ph H-4), 7.77 (m, 1H, Ph H-2), 7.51 (m, 1H, Ph H-5), 7.36 (ddd, 3J = 8.1 Hz, 4J = 2.4 Hz, 4J = 1.0 Hz, 1H, Ph H-6), 2.63 (s, 3H, CH_3).

^{13}C NMR (CDCl_3 , 100 MHz): δ = 196.8 (C=O), 187.7 (C=S), 139.0 (Ph C-1), 138.7 (Ph C-3), 130.4 (Ph C-5), 126.0 (Ph C-4), 121.6 (Ph C-6), 116.6 (Ph C-2), 26.7 (CH_3).

^{15}N NMR (CDCl_3 , 40 MHz): δ = -213.8 (NH).

s-cis rotamer:

^1H NMR (CDCl_3 , 400 MHz): δ = 9.74 (d, 3J = 6.6 Hz, 1H, HC=S), 9.31 (br s, 1H, NH), 7.94 (m, 1H, Ph H-2), 7.92 (m, 1H, Ph H-4), 7.58 (m, 2H, Ph H-5,6), 2.65 (s, 3H, CH_3).

^{13}C NMR (CDCl_3 , 100 MHz): δ = 196.7 (C=O), 187.5 (C=S), 138.8 (Ph C-3), 130.9 (Ph C-5), 128.0 (Ph C-4), 124.4 (Ph C-6), 117.5 (Ph C-2), 26.8 (CH_3).

^{15}N NMR (CDCl_3 , 40 MHz): δ = -215.6 (NH).

HRMS (ESI): m/z $[M + Na]^+$ calcd for C_9H_9NNaOS : 202.0297; found: 202.0302.

N-Mesitylthioformamide (9)

By following the General Procedure 2, to a solution of 2,4,6-trimethylphenyl isothiocyanate (0.177 g, 1.0 mmol, 1.0 equiv.) and Cp_2ZrCl_2 (0.438 g, 1.5 mmol, 1.5 equiv.) in dry 2-MeTHF (5 mL) at 0 °C, $LiAl(O-t-Bu)_3H$ (1.5 mL, 1.5 mmol, 1.5 equiv.) was added dropwise, and then, the reaction mixture was allowed to warm to rt. Compound **9** was obtained in 83% yield (0.149 g) as a white solid; mp 197–198 °C, after purification by chromatography on silica gel (eluent hexane : EtOAc 9 : 1).

s-trans : *s-cis* ~2.7 : 1.

s-trans rotamer:

1H NMR ($CDCl_3$, 400 MHz): δ = 9.25 (br d, 3J = 15.0 Hz, 1H, HC=S), 8.87 (br s, 1H, NH), 6.92 (s, 2H, Ph H-3,5), 2.29 (s, 3H, Ph-4-CH₃), 2.26 (s, 6H, Ph-2,6-CH₃).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 193.1 (C=S), 138.2 (Ph C-4), 134.4 (Ph C-1), 133.7 (Ph C-2,6), 129.5 (Ph C-3,5), 20.9 (Ph-4-CH₃), 18.4 (Ph-2,6-CH₃).

^{15}N NMR ($CDCl_3$, 40 MHz): δ = -219.6 (NH).

s-cis rotamer:

1H NMR ($CDCl_3$, 400 MHz): δ = 9.68 (d, 3J = 5.9 Hz, 1H, HC=S), 8.38 (br s, 1H, NH), 6.94 (s, 2H, Ph H-3,5), 2.29 (s, 3H, Ph-4-CH₃), 2.22 (s, 6H, Ph-2,6-CH₃).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 189.2 (C=S), 138.5 (Ph C-4), 134.9 (Ph C-2,6), 131.6 (Ph C-1), 129.2 (Ph C-3,5), 21.0 (Ph-4-CH₃), 18.1 (Ph-2,6-CH₃).

^{15}N NMR ($CDCl_3$, 40 MHz): δ = -221.7 (NH).

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{10}H_{14}NS$: 180.0841; found: 180.0843.

N-(2-Nitrophenyl)thioformamide (17)

By following the General Procedure 2, to a solution of 2-nitrophenyl isothiocyanate (0.180 g, 1.0 mmol, 1.0 equiv.) and Cp_2ZrCl_2 (0.438 g, 1.5 mmol, 1.5 equiv.) in dry 2-MeTHF (5 mL) at 0 °C, $LiAl(O-t-Bu)_3H$ (1.5 mL, 1.5 mmol, 1.5 equiv.) was added dropwise, and then, the reaction mixture was allowed to warm to rt. Compound **17** was obtained in 80% yield (0.146 g) as an orange solid; mp 98–101 °C, after purification by column chromatography on silica gel (eluent hexane : EtOAc 9 : 1).

1H NMR ($CDCl_3$, 400 MHz): δ = 11.51 (br s, 1H, NH), 10.08 (d, 3J = 13.6 Hz, 1H, HC=S), 8.27 (dd, 3J = 8.4 Hz, 4J = 1.5 Hz, 1H, Ph H-3), 7.71 (m, 1H, Ph H-5), 7.56 (m, 1H, Ph H-6), 7.35 (m, 1H, Ph H-4).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 188.8 (C=S), 136.1 (Ph C-5), 135.7 (Ph C-2), 134.5 (Ph C-1), 126.7 (Ph C-3), 125.2 (Ph C-4), 117.8 (Ph C-6).

^{15}N NMR ($CDCl_3$, 40 MHz): δ = -223.6 (NH), -13.2 (NO₂).

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_7H_7N_2O_2S$: 183.0223; found: 183.0221.

N-[4-(Phenyldiazenyl)phenyl]thioformamide (18)

By following the General Procedure 2, to a solution of 4-phenylazophenyl isothiocyanate (0.239 g, 1.0 mmol, 1.0 equiv.) and

Cp_2ZrCl_2 (0.438 g, 1.5 mmol, 1.5 equiv.) in dry 2-MeTHF (5 mL) at 0 °C, $LiAl(O-t-Bu)_3H$ (1.5 mL, 1.5 mmol, 1.5 equiv.) was added dropwise, and then, the reaction mixture was allowed to warm to rt. Compound **18** was obtained in 88% yield (0.212 g) as an orange solid; mp 157–160 °C, after purification by column chromatography on silica gel (eluent hexane : EtOAc 9 : 1).

1H NMR ($CDCl_3$, 400 MHz): δ = 10.07 (d, 3J = 14.2 Hz, 1H, HC=S), 9.58 (d, 3J = 14.2 Hz, 1H, NH), 7.98 (m, 2H, Ph H-3,5), 7.92 (m, 2H, Ph H-2',6'), 7.52 (m, 2H, Ph H-3',5'), 7.50 (m, 1H, Ph H-4'), 7.28 (m, 2H, Ph H-2,6).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 187.1 (C=S), 152.5 (Ph C-1'), 150.4 (Ph C-4), 140.1 (Ph C-1), 131.3 (Ph C-4'), 129.2 (Ph C-3',5'), 124.8 (Ph C-3,5), 122.9 (Ph C-2',6'), 117.5 (Ph C-2,6).

^{15}N NMR ($CDCl_3$, 40 MHz): δ = -212.2 (NH).

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{13}H_{11}N_3NaS$: 264.0566; found: 264.0566.

N-(4-Azidophenyl)thioformamide (19)

By following the General Procedure 2, to a solution of 4-azidophenyl isothiocyanate (0.176 g, 1.0 mmol, 1.0 equiv.) and Cp_2ZrCl_2 (0.438 g, 1.5 mmol, 1.5 equiv.) in dry 2-MeTHF (5 mL) at 0 °C, $LiAl(O-t-Bu)_3H$ (1.5 mL, 1.5 mmol, 1.5 equiv.) was added dropwise, and then, the reaction mixture was allowed to warm to rt. Compound **19** was obtained in 94% yield (0.168 g) as a yellow solid; mp 184 °C, after purification by column chromatography on silica gel (eluent hexane : EtOAc 9 : 1).

s-trans : *s-cis* ~6 : 1.

s-trans rotamer:

1H NMR ($DMSO-d_6$, 200 MHz): δ = 12.22 (d, 3J = 14.0 Hz, 1H, NH), 9.93 (d, 3J = 14.0 Hz, 1H, HC=S), 7.42 (m, 2H, Ph H-2,6), 7.10 (m, 2H, Ph H-3,5).

^{13}C NMR ($DMSO-d_6$, 100 MHz): δ = 188.4 (C=S), 136.8 (Ph C-1), 136.1 (Ph C-4), 120.2 (Ph C-3,5), 118.8 (Ph C-2,6).

^{15}N NMR ($DMSO-d_6$, 40 MHz): δ = -206.7 (NH).

s-cis rotamer:

1H NMR ($DMSO-d_6$, 200 MHz): δ = 12.07 (br d, 3J = 6.8 Hz, 1H, NH), 9.50 (d, 3J = 6.8 Hz, 1H, HC=S), 8.06 (m, 2H, Ph H-2,6), 7.15 (m, 2H, Ph H-3,5).

^{13}C NMR ($DMSO-d_6$, 100 MHz): δ = 186.5 (C=S), 136.3 (Ph C-4), 135.8 (Ph C-1), 123.2 (Ph C-2,6), 119.3 (Ph C-3,5).

^{15}N NMR ($DMSO-d_6$, 40 MHz): δ = -206.5 (NH).

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_7H_7N_4S$: 179.0386; found: 179.0387.

Methyl 4-(thioformylamino) benzoate (20)

By following the General Procedure 2, to a solution of 4-(methoxycarbonyl)phenyl isothiocyanate (0.193 g, 1.0 mmol, 1.0 equiv.) and Cp_2ZrCl_2 (0.438 g, 1.5 mmol, 1.5 equiv.) in dry 2-MeTHF (5 mL) at 0 °C, $LiAl(O-t-Bu)_3H$ (1.5 mL, 1.5 mmol, 1.5 equiv.) was added dropwise, and then, the reaction mixture was allowed to warm to rt. Compound **20** was obtained in 80% yield (0.156 g) as a yellow solid; mp 217–218 °C (lit.,³⁸ 215–219 °C), after purification by column chromatography on silica gel (eluent hexane : EtOAc 9 : 1).

s-trans : *s-cis* ~10 : 1.

s-trans rotamer:

^1H NMR (DMSO- d_6 , 400 MHz): δ = 12.39 (br d, 3J = 13.4 Hz, 1H, NH), 10.15 (d, 3J = 13.7 Hz, 1H, HC=S), 7.92 (m, 2H, Ph H-2,6), 7.51 (m, 2H, Ph H-3,5), 3.82 (s, 3H, OCH₃).

^{13}C NMR (DMSO- d_6 , 100 MHz): δ = 190.3 (C=S), 165.6 (OC=O), 143.2 (Ph C-4), 130.8 (Ph C-2,6), 125.8 (Ph C-1), 116.8 (Ph C-3,5), 52.06 (OCH₃).

^{15}N NMR (DMSO- d_6 , 40 MHz): δ = -205.7 (NH).

s-cis rotamer:

^1H NMR (DMSO- d_6 , 400 MHz): δ = 12.28 (br s, 1H, NH), 9.63 (s, 1H, HC=S), 8.20 (m, 2H, Ph H-3,5), 7.99 (m, 2H, Ph H-2,6), 3.83 (s, 3H, OCH₃).

^{13}C NMR (DMSO- d_6 , 100 MHz): δ = 188.3 (C=S), 165.5 (OC=O), 142.7 (Ph C-4), 130.0 (Ph C-2,6), 126.5 (Ph C-1), 121.1 (Ph C-3,5), 52.10 (OCH₃).

HRMS (ESI): m/z [M + Na]⁺ calcd for C₉H₉NNaO₂S: 218.0246; found: 218.0246.

Ethyl 4-(thioformylamino) benzoate (21)

By following the General Procedure 2, to a solution of 4-(ethoxycarbonyl)phenyl isothiocyanate (0.207 g, 1.0 mmol, 1.0 equiv.) and Cp₂ZrCl₂ (0.438 g, 1.5 mmol, 1.5 equiv.) in dry 2-MeTHF (5 mL) at 0 °C, LiAl(O-*t*-Bu)₃H (1.5 mL, 1.5 mmol, 1.5 equiv.) was added dropwise, and then, the reaction mixture was allowed to warm to rt. Compound **21** was obtained in 82% yield (0.172 g) as a brown solid; mp 109–112 °C, after purification by column chromatography on silica gel (eluent hexane : EtOAc 9 : 1).

^1H NMR (CDCl₃, 400 MHz): δ = 9.95 (br d, 3J = 14.1 Hz, 1H, HC=S), 9.34 (br d, 3J = 14.1 Hz, 1H, NH), 8.08 (m, 2H, Ph H-2,6), 7.18 (m, 2H, Ph H-3,5), 4.38 (q, 3J = 7.1 Hz, 2H, OCH₂), 1.40 (t, 3J = 7.1 Hz, 3H, CH₃).

^{13}C NMR (CDCl₃, 100 MHz): δ = 187.5 (C=S), 165.5 (OC=O), 141.7 (Ph C-4), 131.7 (Ph C-2,6), 128.0 (Ph C-1), 116.5 (Ph C-3,5), 61.2 (OCH₂), 14.3 (CH₃).

^{15}N NMR (CDCl₃, 40 MHz): δ = -213.3 (NH).

HRMS (ESI): m/z [M + Na]⁺ calcd for C₁₀H₁₁NNaO₂S: 232.0403; found: 232.0403.

N-Benzylthioformamide (22)

By following the General Procedure 2, to a solution of benzyl isothiocyanate (0.149 g, 1.0 mmol, 1.0 equiv.) and Cp₂ZrCl₂ (0.438 g, 1.5 mmol, 1.5 equiv.) in dry 2-MeTHF (5 mL) at 0 °C, LiAl(O-*t*-Bu)₃H (1.5 mL, 1.5 mmol, 1.5 equiv.) was added dropwise, and then, the reaction mixture was allowed to warm to rt. Compound **22** was obtained in 91% yield (0.138 g) as a brown solid; mp 62–64 °C (lit.,³⁹ 63–64 °C), after purification by column chromatography on silica gel (eluent hexane : EtOAc 8 : 2).

s-cis : *s-trans* ~4 : 1.

s-cis rotamer:

^1H NMR (CDCl₃, 400 MHz): δ = 9.49 (dt, 3J = 6.2 Hz, 4J = 1.1 Hz, 1H, HC=S), 7.57 (br s, 1H, NH), 7.42–7.23 (m, 5H, Ph H), 4.87 (d, 3J = 5.4 Hz, 2H, CH₂).

^{13}C NMR (CDCl₃, 100 MHz): δ = 188.8 (C=S), 135.6 (Ph C-1), 129.0 (Ph C-3,5), 128.3 (Ph C-2,6), 128.2 (Ph C-4), 47.6 (CH₂).

^{15}N NMR (CDCl₃, 40 MHz): δ = -219.4 (NH).

s-trans rotamer:

^1H NMR (CDCl₃, 400 MHz): δ = 9.26 (d, 3J = 15.0 Hz, 1H, HC=S), 7.89 (br s, 1H, NH), 7.42–7.23 (m, 5H, Ph H), 4.60 (d, 3J = 6.2 Hz, 2H, CH₂).

^{13}C NMR (CDCl₃, 100 MHz): δ = 191.6 (C=S), 137.9 (Ph C-1), 129.1 (Ph C-3,5), 127.5 (Ph C-2,6), 53.4 (CH₂); Ph C-4 not unambiguously assigned.

^{15}N NMR (CDCl₃, 40 MHz): δ = -223.3 (NH).

HRMS (ESI): m/z [M + Na]⁺ calcd for C₈H₉NNaS: 174.0348; found: 174.0347.

N-[(1*R*)-1-Phenylethyl]thioformamide (32)

By following the General Procedure 2, to a solution of (*R*)-(-)-1-phenylethyl isothiocyanate (0.163 g, 1.0 mmol, 1.0 equiv.) and Cp₂ZrCl₂ (0.438 g, 1.5 mmol, 1.5 equiv.) in dry 2-MeTHF (5 mL) at 0 °C, LiAl(O-*t*-Bu)₃H (1.5 mL, 1.5 mmol, 1.5 equiv.) was added dropwise, and then, the reaction mixture was allowed to warm to rt. Compound **32** was obtained in 99% yield (0.163 g) as a yellow solid; mp 50–52 °C, [α]_D²⁰ +158° (c 0.5, CHCl₃), without column chromatographic purification.

s-cis : *s-trans* ~1.8 : 1.

s-cis rotamer:

^1H NMR (CDCl₃, 400 MHz): δ = 9.31 (s, 1H, HC=S), 8.19 (br s, 1H, NH), 7.34 (m, 4H, Ph H-2,3,5,6), 7.29 (m, 1H, Ph H-4), 5.81 (q, 3J = 6.9 Hz, 1H, PhCH(CH₃)NH), 1.58 (d, 3J = 6.9 Hz, 3H, PhCH(CH₃)NH).

^{13}C NMR (CDCl₃, 100 MHz): δ = 187.4 (C=S), 140.7 (Ph C-1), 128.7 (Ph C-3,5), 127.7 (Ph C-4), 126.4 (Ph C-2,6), 51.8 (PhCH(CH₃)NH), 20.0 (PhCH(CH₃)NH).

^{15}N NMR (CDCl₃, 40 MHz): δ = -203.3 (NH).

s-trans rotamer:

^1H NMR (CDCl₃, 400 MHz): δ = 9.12 (s, 1H, HC=S), 8.66 (br s, 1H, NH), 7.36 (m, 2H, Ph H-3,5), 7.31 (m, 1H, Ph H-4), 7.25 (m, 2H, Ph H-2,6), 4.75 (q, 3J = 6.9 Hz, 1H, PhCH(CH₃)NH), 1.60 (d, 3J = 6.9 Hz, 3H, PhCH(CH₃)NH).

^{13}C NMR (CDCl₃, 100 MHz): δ = 190.0 (C=S), 140.5 (Ph C-1), 129.0 (Ph C-3,5), 128.2 (Ph C-4), 126.1 (Ph C-2,6), 59.1 (PhCH(CH₃)NH), 22.1 (PhCH(CH₃)NH).

^{15}N NMR (CDCl₃, 40 MHz): δ = -206.3 (NH).

HRMS (ESI): m/z [M + Na]⁺ calcd for C₉H₁₁NNaS: 188.0504; found: 188.0508.

HPLC Chiralpak® IG; λ = 220 nm; *n*-hexane/*i*-propanol 98/2; flow rate = 1.00 mL min⁻¹. Racemate: (starting from (*R,S*)-1-phenylethyl isothiocyanate: t_r = 21.048 min; t_r = 22.334 min; enantioenriched (compound **32**): t_r = 21.142 min. er > 99 : 1.

Methyl (4-methoxyphenyl)imidothioformate (33)

To a solution of thioformanilide **11** (0.167 g, 1.0 mmol, 1.0 equiv.) in dry THF (1 mL) at -78 °C was added MeI (0.19 mL, 3.0 mmol, 3.0 equiv.), followed by the dropwise addition of MeLi-LiBr (1.5 M, 1.87 mL, 2.8 mmol, 2.8 equiv.). After 1 h at -78 °C, a solution of 1 M HCl (4 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (3×) and washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure.

Compound **33** was obtained in 91% yield (0.165 g) as a yellow oil, after purification by column chromatography on silica gel (eluent hexane : EtOAc 95 : 5).

^1H NMR (CDCl_3 , 400 MHz): δ = 8.47 (s, HC=N), 7.01 (m, 2H, Ph H-2,6), 6.86 (m, 2H, Ph H-3,5), 3.80 (s, 3H, OCH_3), 2.51 (s, 3H, SCH_3).

^{13}C NMR (CDCl_3 , 100 MHz): δ = 157.5 (Ph C-4), 156.9 (HC=N, $^1J_{\text{C-H}}$ = 175.1 Hz), 144.8 (Ph C-1), 121.6 (Ph C-2,6), 114.3 (Ph C-3,5), 55.5 (OCH_3), 11.7 (SCH_3).

^{15}N NMR (CDCl_3 , 40 MHz): δ = -77.8 (C=N).

HRMS (ESI): m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_9\text{H}_{11}\text{NOS}$: 182.0634; found: 182.0636.

Phenyl (2,6-dimethylphenyl)imidothioformate (**34**)

To a solution of thioformanilide **8** (0.165 g, 1.0 mmol, 1.0 equiv.) in 1,2-dichloroethane (DCE) (5.0 mL) were added Ph_2IOTf (0.860 g, 2.0 mmol, 2.0 equiv.) and $\text{Cu}(\text{OTf})_2$ (72 mg, 0.2 mmol, 0.2 equiv.). The reaction mixture was then heated at 70 °C for 3.5 h. Afterward, the mixture was diluted with CH_2Cl_2 (50 mL) and washed with a saturated sodium bicarbonate solution (50 mL). The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers were dried over anhydrous Na_2SO_4 , and concentrated to dryness. Compound **34** was obtained in 84% yield (0.206 g) as a yellow liquid, after purification by column chromatography on silica gel (eluent hexane : EtOAc 95 : 5).

^1H NMR (CDCl_3 , 400 MHz): δ = 8.56 (s, HC=N), 7.50 (m, 2H, Ph H-8,12), 7.42 (m, 2H, Ph H-9,11), 7.41 (m, 1H, Ph H-10), 7.11 (d, 3J = 7.5 Hz, 2H, Ph H-3,5), 7.02 (t, 3J = 7.5 Hz, 1H, Ph H-4), 2.23 (s, 6H, CH_3).

^{13}C NMR (CDCl_3 , 100 MHz): δ = 159.7 (C=N), 147.9 (Ph C-1), 132.8 (Ph C-8,12), 131.2 (Ph C-7), 129.5 (Ph C-9,11), 128.9 (Ph C-10), 128.1 (Ph C-3,5), 126.0 (Ph C-2,6), 124.2 (Ph C-4), 17.6 (CH_3).

^{15}N NMR (CDCl_3 , 40 MHz): δ = -56.8 (C=N).

HRMS (ESI): m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_{15}\text{H}_{16}\text{NS}$: 242.0998; found: 242.1001.

1-Phenyl-1H-tetrazole (**35**)

To a solution of thioformanilide **6** (0.137 g, 1.0 mmol, 1.0 equiv.) in xylene (2 mL) was added Et_2AlN_3 (0.508 g, 4.0 mmol, 4.0 equiv.). The reaction mixture was heated at 100 °C for 24 h and then, when TLC analysis showed complete conversion, it was cooled to 0 °C and a solution of 15% aq NaOH (13.0 equiv.) containing sodium nitrite (13.0 equiv., solution pH 13.5) was added. The pH value was then adjusted to 1.5 with 6N HCl and the mixture was exhaustively extracted with ethyl acetate (2 $\times$). The solvents were removed under reduced pressure to afford the crude product, which was re-dissolved in ethyl acetate and extracted with aq K_2CO_3 (10%) to the aqueous phase (pH 11). The combined basic aq. phases were cooled to 0 °C and carefully treated with 6N HCl to adjust the pH value to 2.5. The product was then extracted with AcOEt, the combined organic phases were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. Compound **35** was obtained in 86% yield (0.125 g) as a brown

solid; mp 64 °C (lit.,⁴⁰ 64–66 °C), after purification by column chromatography on silica gel (eluent hexane : EtOAc 8 : 2).

^1H NMR (CDCl_3 , 400 MHz): δ = 8.99 (s, tetrazole-H), 7.72 (m, 2H, Ph H-2,6), 7.60 (m, 2H, Ph H-3,5), 7.55 (m, 1H, Ph H-4).

^{13}C NMR (CDCl_3 , 100 MHz): δ = 140.4 (tetrazole-C), 133.9 (Ph C-1), 130.2 (Ph C-3,5), 130.1 (Ph C-4), 121.3 (Ph C-2,6).

HRMS (ESI): m/z [$\text{M} + \text{H}$] $^+$ calcd for $\text{C}_7\text{H}_7\text{N}_4$: 147.0665; found: 147.0669.

Conflicts of interest

There are no conflicts to declare.

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Publication n. 6

Consecutive and Selective Double Methylene Insertion of Lithium Carbenoids to Isothiocyanates: A Direct Assembly of Four-membered Sulfur-Containing Cycles.

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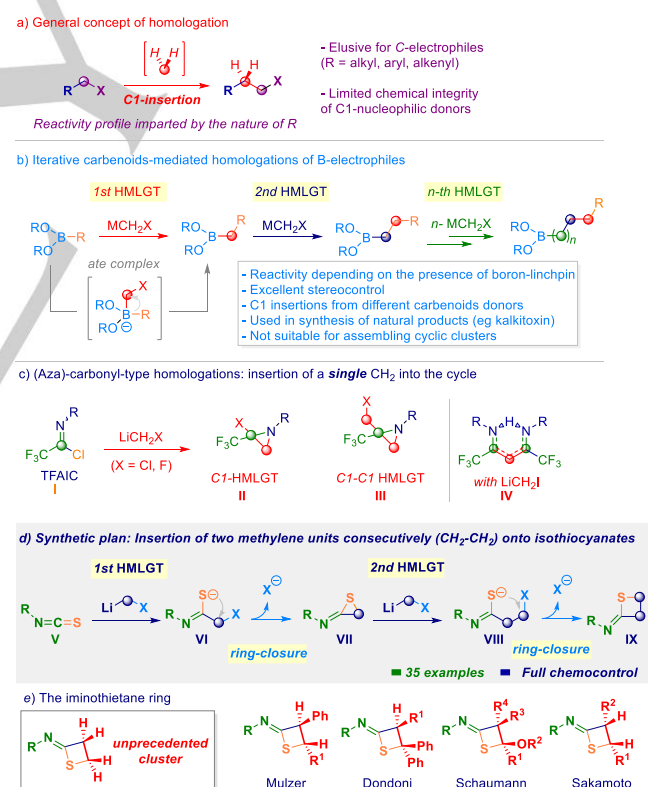
Consecutive and Selective Double Methylene Insertion of Lithium Carbenoids to Isothiocyanates: A Direct Assembly of Four-membered Sulfur-Containing Cycles

Raffaele Senatore,^a Monika Malik,^a Thierry Langer,^a Wolfgang Holzer^a and Vittorio Pace^{a,b,*}

Abstract: A formal CH₂-CH₂ homologation conducted with C1 carbenoids on a carbon electrophile for the obtainment of a four-membered cycle is reported. The logic proposes the consecutive delivery of two single nucleophilic CH₂ units to an isothiocyanate – as competent electrophilic partner – resulting in the assembling of a rare imino-thietane cluster. The single synthetic operation procedure documents genuine chemocontrol, as indicated by the tolerance to various reactive elements decorating the starting materials. Significantly, the double homologation protocol is accomplished directly on a carbon electrophile, thus not requiring the installation of heteroatom-centered manifolds (e.g. boron).

The progressive formal insertion of a constant methylene (CH₂) unit into an organic array is known as homologation and, ultimately enables the modular assembly of complex skeletons,^[1] thus mimicking fundamental biosynthetic pathways.^[2] Regardless the essence of the adopted regime (nucleophilic, electrophilic or radical), the carbon skeleton elongation is limited to one methylene unit *per* homologation cycle, thus making multiple-homologations highly elusive processes in synthesis (Scheme 1 – *path a*).^[3] Although the intrinsic limited instability of reagents used for the purpose – e.g. metal carbenoids^[4] – may account for this reluctant behaviour, the installation of valuable linchpins on the chain results an effective solution to the problem. In this sense, the introduction by Matteson of boronic esters (I) as privileged electrophilic manifolds to conduct homologation with lithium carbenoids,^[5] underpinned the elaboration of the elegant concept of iterative homologations illustrated more recently by Aggarwal^[6] and Blakemore (Scheme 1 – *path b*).^[7] Notably, this logic features remarkable flexibility and robust stereocontrol thus, enabling the use of (different) various C1-units as competent donors, as documented in the elaboration of acyclic complex natural products.^[8] Notwithstanding, analogous elongations directly conducted on *carbon*-centered manifolds remain underdeveloped and of limited preparative significance, regardless the hybridization of the competent carbon (*sp*³ and *sp*²).^[9] In recent years, our group developed modular homologations of C-electrophiles with reactive lithium carbenoids (LiCH₂X) enabling the assembly of sophisticated structures, as a consequence of molecular rearrangements triggered by the fine tuning of reaction conditions.^[3, 10] In this context, we documented the halogen-driven selective homologations of trifluoroacetimidoyl chlorides (TFAIC, I) to *gem*-chloro-trifluoromethylaziridines (II) or *gem*-halomethyl-trifluoromethylaziridines (III)^[11] and bis-trifluoromethyl-β-diketiminates (IV)^[12] respectively, highlighting the critical role played by the reaction stoichiometry in discriminating between C1 and C1-C1 insertions (Scheme 1 – *path c*). Conceptually, these precedents could be ascribed to the well-established carbonyl-oxirane (and related imine-aziridine) homologative chemistry:^[13] this is, the cyclic cluster is constructed *via* the incorporation of a *single* C1 unit delivered by the carbenoid donor.^[14] We wondered if homologation tactics with C1 carbenoids could promote the

assembly of four-membered cycles^[15] through the consecutive release of *two* methylene fragments on a proper electrophile. Crucial for the successful reaction design was ensuring that the homologation sequence could reach completion within the short lifetime of the carbenoid used.^[16] To this end, we conceived to generate a *first* homologation reactive intermediate susceptible of rapid *second* CH₂-insertion, furnishing the targeted four-membered cycle.^[17] Ideally, an electrophilic platform fulfilling this criterion could be represented by an isothiocyanate (V): in fact, the formation of a nucleophilic thioamide anion (VI) – after the first homologative event – would induce a fast cyclization to a highly reactive thiiranimine (VII),^[18] which would then undergo the second homologation. Finally, the additional ring closure of the elongated thioamide (VIII) presenting the inserted CH₂-CH₂ motif would result in the thietane scaffold (IX) presenting the *exo* imine-appendix (Scheme 1 – *path d*).



Scheme 1. General context of the presented work (HMLGT = homologation).

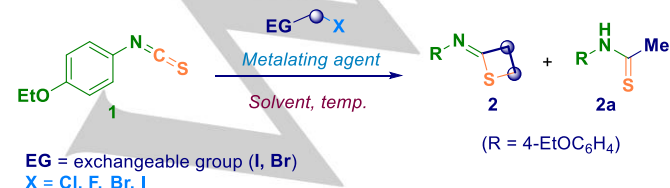
Collectively, our synthetic strategy would construct the rare imino-thietane skeleton through a conceptually intuitive logic starting from commercially available (or easily accessible) isothiocyanates. We anticipate the proposed direct approach conducts to the imino-thietane core presenting an integral CH₂-CH₂ linkage. To the best of our knowledge, such a structural

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characteristic is unprecedented among the scattered imino-thietanes previously described (Scheme 1 – *path e*). Indeed, uniformly – the recyclization of β -lactones (Mulzer),^[19] the cycloaddition of ketenimines to thioketones (Dondoni),^[20] the cycloaddition of vinyl ethers with sulfonyl isothiocyanates (Schaumann),^[21] and, the photochemical isomerization of *N*-monosubstituted α,β -unsaturated thioamides (Sakamoto)^[22] – afforded imino-thietanes variously substituted on the C-C linkage.^[23]

4-Ethoxyisothiocyanate **1** was selected as the model substrate for the reaction optimization (Table 1). Upon treatment with the carbenoid chloromethylithium (LiCH_2Cl), only a complex mixture was obtained, even at very short reaction times (entries 1–2).^[24] Because of the absence in the mixture of the product resulting from the attack of MeLi-LiBr to the electrophilic isothiocyanate (*i.e.* thioamide **3**), it could be assumed that the carbenoid was effectively generated. The switching to the highly unstable LiCH_2F ^[25] enabled to assemble the targeted four-membered cycle **2**, thus validating the initial working hypothesis (entry 3). It was essential to quench the reaction after only 5 min (from the end of the addition of MeLi-LiBr) to ensure a clean crude, thus confirming the high reactivity of intermediates conceived during the process design (entries 4–5). Notably, the overall transformation is in agreement with the observation by J. Hu on the suitability of $\text{CH}_2\text{-F}$ fragments as manifolds for nucleophilic substitutions.^[26] Additional improvement was achieved employing LiCH_2Br , which served as a competent C1 delivery agent for constructing the thietane backbone **2** (entries 6) in an excellent 82% isolated yield. Confirming the pattern observed with LiCH_2F (entries 4–5), also the reaction with the bromo carbenoid benefited from brief reaction time (entry 6 vs. 7), presumably because of avoiding the triggering of deleterious carbenoids decomposition events. Although presenting a better halogen leaving-group, the use of LiCH_2I resulted in slightly dwindled yield (entry 8) presumably due to its tendency to act also as metalating agent.^[12] Some additional points merit mention: a) in line with our previous investigations, the optimal LiCH_2Br precursor proved to be ICH_2Br which undergoes a rapid and efficient I/Li exchange,^[27] thus avoiding the detection of thioamide **3**,^[28] formed at significant extent in the presence of CH_2Br_2 (entry 9); b) conducting the process at higher temperature resulted in untractable mixtures because of compromised chemical integrity of carbenoids (entry 10); c) running the consecutive homologation in more apolar solvents (diethyl ether, toluene – entries 11–12), dramatically decreased reaction yields; d) considerable excess of nucleophile did not boost the transformation (entry 13), while using quasi-stoichiometric loading dropped the yield (entry 14); e) no reactivity was displayed by less nucleophilic magnesium carbenoids, even at higher temperatures (entries 15–16).^[29]

Table 1. Reaction optimization.



Entry	Carbenoid precursor (equiv) ^a	Metalating agent	Reaction time (min)	Isolated Yield of 2 (%)
1	ClCH_2I (3.0)	MeLi-LiBr (2.8)	5	Compl. mix.
2	ClCH_2I (3.0)	MeLi-LiBr (2.8)	60	Compl. mix.
3 ^b	FCH_2I (3.0)	MeLi-LiBr (2.8)	5	69
4 ^b	FCH_2I (3.0)	MeLi-LiBr (2.8)	15	45
5 ^b	FCH_2I (3.0)	MeLi-LiBr (2.8)	60	Compl. mix.
6	BrCH_2I (3.0)	MeLi-LiBr (2.8)	5	82
7	BrCH_2I (3.0)	MeLi-LiBr (2.8)	15	54
8	I_2CH_2 (3.0)	MeLi-LiBr (2.8)	5	71
9 ^c	Br_2CH_2 (3.0)	MeLi-LiBr (2.8)	5	65
10 ^d	BrCH_2I (3.0)	MeLi-LiBr (2.8)	5	Compl. mix.
11 ^e	BrCH_2I (3.0)	MeLi-LiBr (2.8)	5	9
12 ^f	BrCH_2I (3.0)	MeLi-LiBr (2.8)	5	Traces
13	BrCH_2I (6.0)	MeLi-LiBr (5.8)	5	80
14 ^g	BrCH_2I (1.3)	MeLi-LiBr (1.1)	5	27
15	BrCH_2I (2.8)	$i\text{-PrMgCl-LiCl}$	5	No reaction
16 ^d	BrCH_2I (2.8)	$i\text{-PrMgCl-LiCl}$	5	No reaction

^a LiCH_2X reagents were generated under Barbier conditions. ^b LiCH_2F was generated in a 1:1 v/v mixture of THF and Et_2O (ref. 25). ^c Thioamide **3** was also formed in 21% isolated yield. ^d Reaction run at -40°C . ^e Reaction run in Et_2O . ^f Reaction run in toluene. ^g No mono-homologated product (type **VII** – Scheme 1) was detected.

The unambiguous assignment of the imino-thietane backbone was ascertained via X-ray crystallographic analysis of compound **2** (Figure 1). The very small value of torsion angles C7-S1-C9-C8 (0.76°), C9-C8-C7-S1 (0.91°) and C1-N1-C7-S1 (1.86°) are diagnostic for the almost complete planarity of the ring, thus differentiating it from a classical non-planar thietane characterized by a puckering angle of 26° .^[30] The internal angles C9-C8-C7 (84.65°), S1-C9-C8 (87.65°), C7-S1-C9 (77.01°) alternating from the sp^3 geometry and, S1-C7-C7-C8 (95.27°) deviating from a canonical C-sp^2 confirm the formation of the thietane ring. The analysis of bond lengths indicates that the S1-C9 bond ($1.835\text{ \AA}$) is significantly longer than an average $\text{C}(sp^3)\text{-S}$ linkage ($1.817\text{ \AA}$),^[31] but slightly shorter than the C-S bond ($1.847\text{ \AA}$) of the unsubstituted thietane.^[30] The constructed C8-C9 bond ($1.541\text{ \AA}$) is in the average of the analogous $\text{CH}_2\text{-CH}_2$ linkage found in the simple thietane ($1.549\text{ \AA}$).^[30]

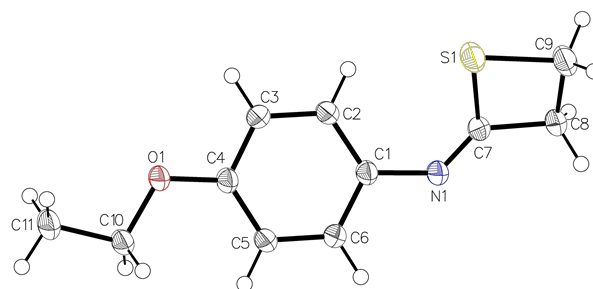
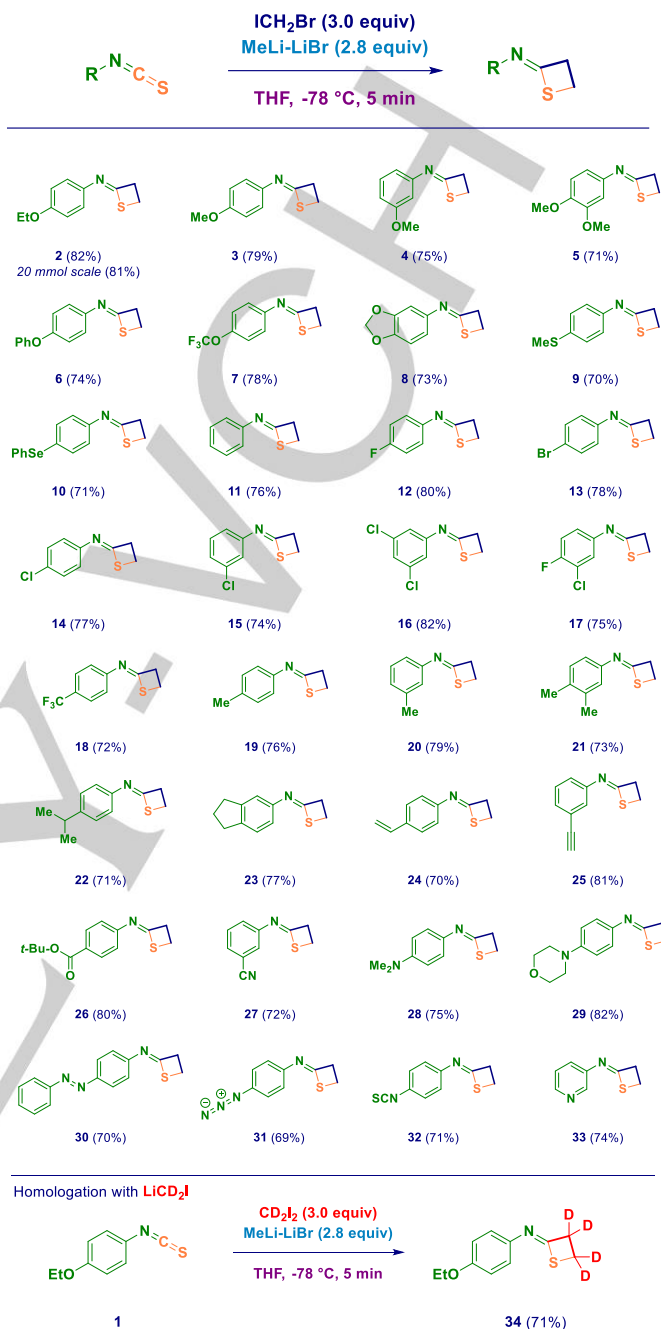


Figure 1. X-ray structural analysis of compound **2** (CCDC 2081745).

Having established the optimal conditions for the transformation, we next studied the scope of the consecutive double CH_2 insertion (Scheme 2). The presence of electron-donating groups – *i.e.*

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ethers - on the aromatic nucleus of the isothiocyanates is uniformly tolerated, furnishing the corresponding imino-thietanes (**2-5**) in very good yields, including when the ethereal oxygen presented phenyl- (**6**) or trifluoro- (**7**) functionalities. Running the protocol on bigger scale (20 mmol) resulted in comparable efficiency (**2**). An acetal-substituted isothiocyanate, as exemplified by the benzo[d][1,3]dioxole structure (**8**), is also amenable for the protocol. Chalcogens such as sulfur – embodied as a thioether (**9**) or, selenium – in the case of the selenoether (**10**), also act as productive starting materials. Notably, the adopted lithiation conditions for the carbenoid genesis do not activate a concomitant Se/Li exchange thus, leaving untouched this functionality. Aside of an unsubstituted phenyl ring (**11**), the incorporation of halogen such as fluorine (**12, 17, 18**), bromine (**13**), chlorine (**14-17**) at different positions of the ring are compatible with the methodology and, their presence could be advantageously exploited for further elaboration (*vide infra*). sp^3 -Hybridized hydrocarbons do not alter the efficiency of the technique (**19-21**), including when an *i*-propyl group (**22**) or the bicyclic indanyl system (**23**) were installed on the heterocumulene starting material. Preparing imino-thietanes with the proposed strategy proceeded with remarkable chemocontrol, as documented by isothiocyanates decorated with unsaturated residues: no concomitant carbenoid-mediated cyclopropanation^[32] took place on a vinyl-substituted analogue (**24**), neither deprotonation of a terminal alkyne (**25**) despite the basic conditions. Furthermore, the chemical integrity of electrophilic substituents potentially suffering the attack of nucleophilic carbenoids was preserved, as deduced by the ester (**26**) and the nitrile (**27**). The methodology showed that the presence of nitrogen-centered substituents – in principle able to invalidate the correct carbenoid formation – was not detrimental: accordingly, *N,N*-dimethylamino- (**28**), morpholino- (**29**), phenyldiazo- (**30**) and azido- (**31**) bearing isothiocyanates were consecutively homologated to afford the corresponding four-membered sulfur-ring. Intriguingly, 1,4-diisothiocyanatobenzene was subjected to selective assembly of the cycle on a single NCS appendix (**32**). This same pattern was confirmed also with a considerable excess of carbenoid (6.0 equiv). Finally, the flexibility to heteroaromatic systems was documented with the 3-pyridyl derivative, which furnished the desired motif in comparable good yield (**33**). The effective release of the two carbons backbone C-C from the carbenoid source was gathered conducting the experiment – *coeteris paribus* – with di-deuterated iodomethyl lithium ($LiCD_2I$) conveniently prepared from the commercially available CD_2I_2 .^[10] The evidence for the ethylene fragment in **34** featuring full deuteration – i.e. CD_2 - CD_2 – was evidently consistent with the envisaged rationale.



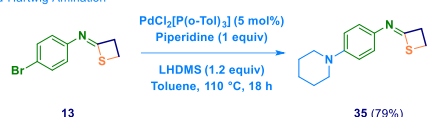
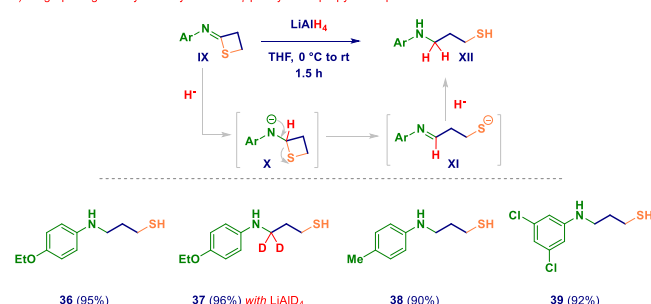
Scheme 2. Scope of the consecutive CH_2 - CH_2 consecutive homologation.

Eager to understand the reactivity of the assembled system, we conducted manipulations both on the aromatic ring (proceeding from the parent isothiocyanate) and on the four-membered cycle (Scheme 3). The Buchwald-Hartwig amination^[33] with piperidine on the bromo-analogue **13** clearly furnished the corresponding product **35** in which the thioimide system was preserved (*path a*). Cognizant of the ring strain of four-membered rings (e.g. thietane 80.3 kJ/mol),^[34] we devised the ring-opening with a nucleophile leveraging on the electrophilicity of the sp^2 -carbon (*path b*). Thus, *via* the addition of a reducing hydride – accomplished with $LiAlH_4$ – γ -amino-mercaptanes **XII** were formed in high yield,

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as demonstrated by the straightforward synthesis of different analogues (**36–39**). The transformation can be rationalized through the formation of a tetrahedral intermediate (**X**), whose collapse entails the breaking of the NC-S bond giving the γ -*N*-phenyliminopropyl mercapto anion (**XI**) amenable for a second hydride-reduction *en route* to the final, not previously accessible, structures (**XII**). The experiment with labelled LiAlD_4 (**37**) confirmed the attack of both nucleophiles at the initially thioimide carbon.

a) Buchwald-Hartwig Amination

b) Ring-opening with hydride: synthesis of γ -phenylaminopropylmercaptanes

Scheme 3. Synthetic manipulation of imino-thietanes.

In summary, we have documented the installation of the ethylene unit ($-\text{CH}_2-\text{CH}_2-$) – a formal C2-homologation – onto isothiocyanates through the consecutive delivery of two methylene fragments furnished by the carbenoid bromomethylithium (LiCH_2Br). The tactic enables the straightforward access to four-membered cyclic imino-thietanes through a single synthetic operation. The overall strategy relies on two sequential homologative events commenced on the electrophilic *sp*-carbon of a competent isothiocyanate, resulting in the formation – upon ring-closure – of a highly reactive imino-thirane which then undergoes a second homologation giving a γ -halothioimide direct precursor of the final imino-thietane. A remarkable degree of chemoselectivity was uniformly observed, as evidenced by running the reaction of isothiocyanates featuring additional sensitive functionalities such as halogens, seleno-, thio-ethers, amines or electrophilic groups susceptible of the attack of the nucleophilic carbenoid. The assembled four-membered imino-thioethane – whose structure was ascertained by X-ray analysis – may serve as a versatile platform for preparing γ -aminopropylthiols *via* hydride-mediated reduction. To the best of our knowledge this concept constitutes the first example of a controlled consecutive C1-homologation on carbon electrophiles with a carbenoid without the requirement of hetero-atom linchpins (e.g. boron).

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Keywords: Homologation • Isothiocyanates • Carbenoids • Thietanes • Chemoselectivity.

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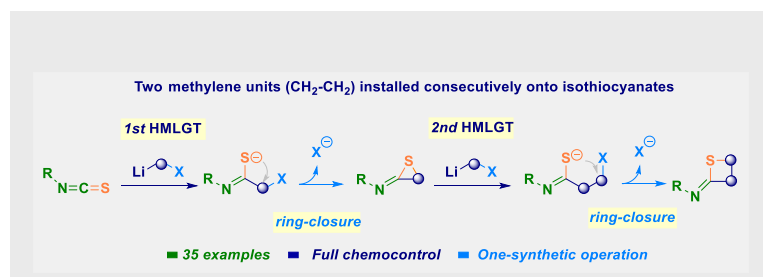
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*Raffaele Senatore, Monika Malik, Thierry Langer, Wolfgang Holzer and Vittorio Pace**

Consecutive and Selective Double Methylene Insertion of Lithium Carbenoids to Isothiocyanates: A Direct Assembly of Four-membered Cycles

Publication n. 7

Direct and Chemoselective Electrophilic Monofluoromethylation of Heteroatoms (O-, S-, N-, P-, Se-) with Fluoriodomethane.

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Details on experimental procedures, characterization data and copies of NMR spectra of all compounds are reported.

Direct and Chemoselective Electrophilic Monofluoromethylation of Heteroatoms (O-, S-, N-, P-, Se-) with Fluoroiodomethane

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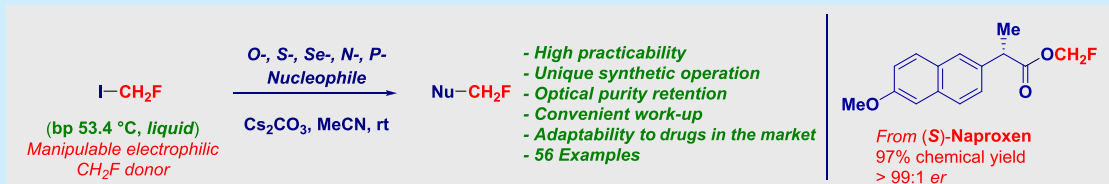
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ABSTRACT: The commercially available fluoroiodomethane represents a valuable and effective electrophilic source for transferring the CH₂F unit to a series of heteroatom-centered nucleophiles under mild basic conditions. The excellent manipulability offered by its liquid physical state (bp 53.4 °C) enables practical and straightforward one-step nucleophilic substitutions to retain the chiral information embodied, thus allowing it to overcome *de facto* the requirement for fluoromethylating agents with no immediate access. The high-yielding methodology was successfully applied to a variety of nucleophiles including a series of drugs currently in the market.

Modulating critical physicochemical parameters of organic arrays through the introduction of fluorine-containing motifs represents an established tool in modern chemistry.¹ Accordingly, significant fine-tuning of metabolic stability and lipophilicity within the drug optimization process, *inter alia*, is achieved by exploiting some of the unique properties offered by embodying fluorine such as its small van der Waals radius (1.47 Å)² and its high electronegativity.³ Evidently, depending on the desired degree of fluorination of a given carbon skeleton, a multitude of synthetic techniques can be devised.⁴ Although a plethora of methodologies have emerged for introducing polyfluorinated methyl fragments (–CF₃ and –CHF₂ groups),^{4a,5} protocols for formally transferring the monofluoromethyl (CH₂F) analogue—an isostere for CH₃ or CH₂OH groups—onto a valuable heteroatom remain still underdeveloped.⁶ This aspect is particularly elusive when compared to the widespread relevance of this motif in pharmaceuticals as illustrated in the cases of afloqualone, fluticasone, or sevoflurane *inter alia* (Scheme 1).^{3,7} From a retrosynthetic perspective, the delivery of the formal electrophilic CH₂F unit to the recipient nucleophile represents the conceptually simplest disconnection to achieve the goal.⁸ Indeed, recent advancements indicate the versatility of hypervalent sulfur species as valuable transfer agents working under an electrophilic regime. A breakthrough in the field was documented in 2008 by Prakash and Olah through the development of shelf-stable electrophilic fluoromethylated diarylsulfonium salts capable of releasing the CH₂F motif to various nucleophiles encompassing O-, S-, N-, and P- species (Scheme 1, path a),⁹ subsequently extended to the transfer of –CHFMe systems by Besset et al.¹⁰ Furthermore, Shibata

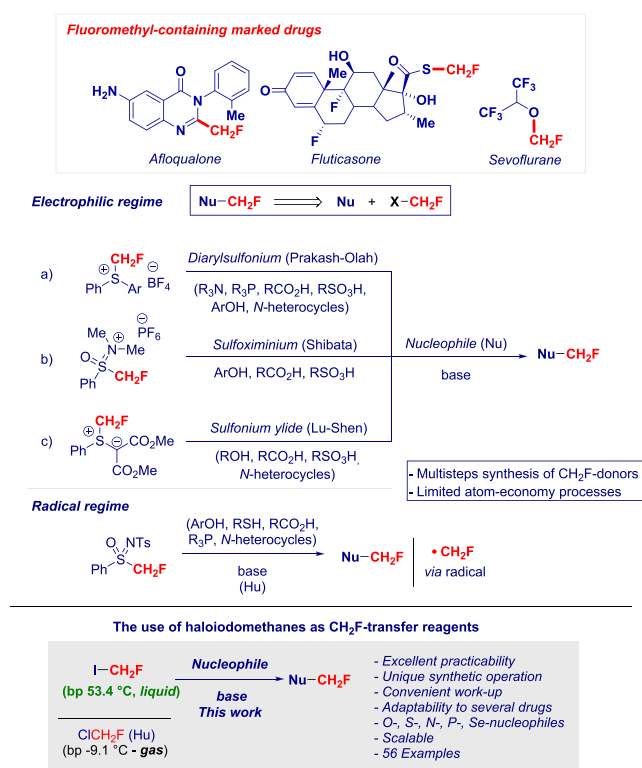
introduced in 2011 sulfoximinium salts for accessing fluoromethylated aromatic alcohols and carboxylic and sulfonic acids (among other nucleophiles, i.e., enolates) (Scheme 1, path b).¹¹ Additionally, Lu and Shen designed more versatile analogues (sulfonium ylides) manifesting broader substrate scope, thus allowing the use also of aliphatic alcohols as competent nucleophiles (Scheme 1, path c).¹² Stemming from a radical pathway, Hu and co-workers demonstrated that *N*-tosyl sulfoximines could transfer the CH₂F group to O-, S-, N-, and P-nucleophiles;¹³ importantly, they documented the accelerating effect displayed by the α-fluorine substituent toward nucleophilic substitutions.¹⁴ However, the multistep preparation of these fluoromethyl donor agents jointly with the nonoptimal atom economy associated with their employment tends to circumscribe the applicability to model systems of academic interest, thus making somehow difficult the routine access to fluoromethyl analogues of potential medicinal relevance. Remarkably, Hu proposed the gaseous reagent ClCH₂F—Freon 31 (bp –9.1 °C)—as an effective solution for installing the motif on a variety of heteroatom nucleophiles.¹⁵ Unfortunately, its physical state—gas—poses severe limitations for the experimental execution (e.g., impractical handling process and imprecise measurements of small quantities), which ultimately lead to the eclipse of the innate synthetic potential of such an approach. In this context, the simple

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Scheme 1. Heteroatom-Based Monofluoromethylation: State-of-the-Art



replacement of the leaving chlorine atom with the heavier iodine confers a dramatic enhancement of the manipulability of the resulting fluoroiodomethane (FIM, bp 53.4 °C).¹⁶ Aware of this practical advantage, our group conducted on it selective iodine/lithium or hydrogen/lithium exchanges en route to unprecedented nucleophilic fluoro-containing carbenoids for preparation, through a single synthetic operation, of α -fluoromethyl skeletons¹⁷ or three-membered fluorinated rings (epoxides and aziridines).¹⁸ Furthermore, recently the reagent is finding significant application in different areas of synthesis as showcased in transition-metal-catalyzed cross-couplings with boronic acids,¹⁹ in Cu-catalyzed borylfluoromethylation of olefins,²⁰ in fluorocyclopropanations,²¹ and in C-selective monofluoromethylation of β -ketoesters²² and fluoromethyl-phosphonium ylides.²³

Herein, we disclose a convenient direct and simple transfer of the fluoromethyl fragment from the commercially available FIM to a series of heteroatom-based nucleophiles [aromatic (thio and seleno)alcohols, (thio)carboxylic acids, heteroaromatic nitrogen, phosphorus] by means of an intuitive nucleophilic substitution (Scheme 1, bottom). We anticipate the complete adaptability of the methodology for transformations realized on currently employed drugs, thus enabling rapid molecular modifications for preparing pharmaceutical relevant fluoro-analogues.

Because of our interest toward chiral drugs²⁴ and cognizant of the different bioactivity displayed by the enantiomers of the nonsteroidal anti-inflammatory agent Naproxene (1), we selected the most active enantiomer—(S)-1 (>99:1 er)—as the model substrate for evaluating both the CH_2F transfer efficiency from FIM and the preservation of the stereochemical information. As indicated in Table 1, the use of a base was critical for accomplishing the transformation (entry 1). Polar

Table 1. Model Reaction: Optimization^a

entry	solvent	base	reaction time (h)	yield of (S)-2 (%) ^b	er of (S)-2
1	DMF	-	24	traces	-
2	DMF	NaH	6	71	95:5
3	THF	NaH	6	64	94:6
4	DMF	CsF	6	86	97:3
5	DMF	Cs ₂ CO ₃	6	90	97:3
6	DMF	KF-Celite	12	72	96:4
7	MeCN	CsF	6	91	98:2
8	MeCN	KF-Celite	8	78	97:3
9	MeCN	Cs ₂ CO ₃	6	97	>99:1
10 ^c	MeCN	Cs ₂ CO ₃	4	98	>99:1
11 ^d	MeCN	Cs ₂ CO ₃	6	95	>99:1
12	MeCN	DIPEA	12	61	98:2

^aUnless otherwise stated, a ratio of (S)-1:ICH₂F:base = 1:1.2:1.2 was employed. ^bIsolated yield. ^cICH₂F (2.4 equiv), Cs₂CO₃ (2.4 equiv).

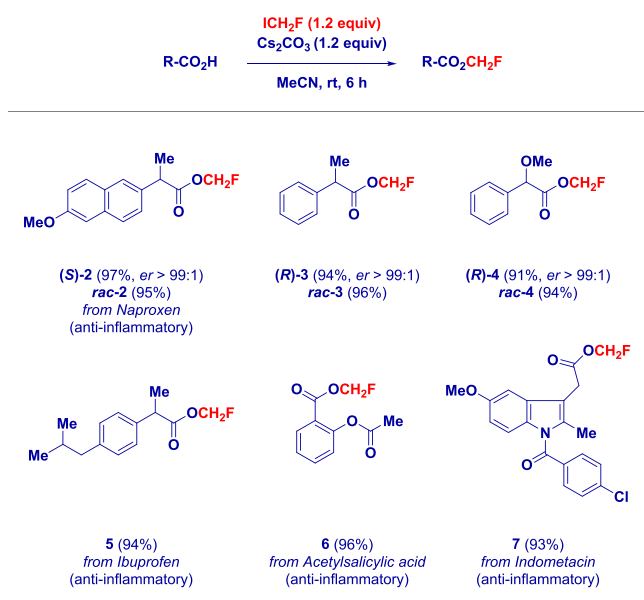
^dReaction run at 10 mmol scale.

aprotic solvents performed reasonably well under basic conditions, evidencing a noticeable role of the base in triggering epimerization. Accordingly, running reactions in the presence of NaH resulted in incomplete conversion and perceptible racemization regardless of the solvent used (DMF or THF, entries 2–3). Switching to cesium bases was beneficial in terms of yield and er (entries 4 and 5), while substantial reaction slowing was evidenced with the supported base KF-Celite²⁵ [entry 6 and entry 8 (in MeCN)]. Pleasingly, the combination of acetonitrile and cesium carbonate resulted in the ideal combination for optimizing the process, thus allowing it to reach completion within 6 h without any erosion of the optical purity (entry 9). Some additional points merit mention: (1) analytically pure compounds were recovered after simple extraction of the water phase with diethyl ether, thus advantageously allowing us to skip chromatographic purifications; (2) only a small excess of ICH₂F and Cs₂CO₃ was needed for completing the reaction, higher loading being unfavorable for cost effectiveness/reaction time ratio (entry 10); (3) performing the reaction in 10 mmol scale was possible without affecting both the yield and the er (entry 11); and (4) changing to an organic base such as DIPEA (*N,N*-di-*i*-propyl-*N*-ethylamine) was detrimental, thus confirming the gainful outcome with the cesium salt (entry 12).

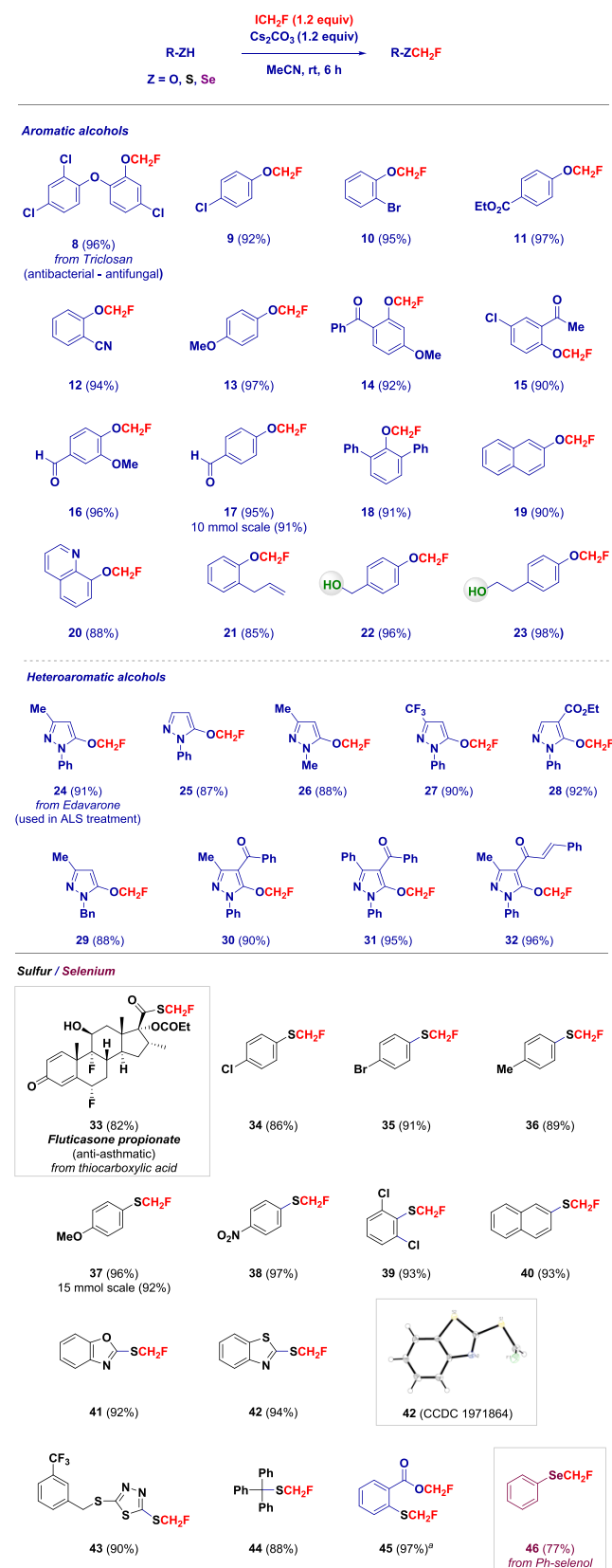
With the optimized conditions in hand, we then studied the scope of the fluoromethylation on additional carboxylic acids (Scheme 2). The full preservation of the optical purity was confirmed in the cases of α -substituted phenylacetic acid derivatives (3 and 4), and other common anti-inflammatory agents underwent the transformation very efficiently: ibuprofen (5), acetylsalicylic acid (aspirin, 6) and indomethacin (7). Remarkably, this approach compared favorably with reported protocols requiring sulfur-based CH₂F donors, nondirectly assembled.¹¹

Pleasingly, the technique could be applied to chemo-selectively fluoromethylate aromatic alcohols²⁶ in the presence of various decorating elements such as halogens (8–10), ester (11), nitrile (12), ethers 13, ketones (14–15), and aldehydes (16–17) (Scheme 3). Notably, sterically hindered (18) and

Scheme 2. Fluoromethylation of Carboxylic Acids



(hetero)polyaromatic systems (**19–20**) acted as competent partners for the reaction, as well as an allyl-presenting phenol (**21**). It is worth noting that the established conditions allow us to perfectly discriminate the reactivity of aromatic vs aliphatic alcohols which remained untouched (plausibly because of their inherent lower acidity) during the transformation (**22–23**). Unfortunately, attempts to realize the double fluoromethylation on both alcohol functionalities in the presence of harder bases (KH or NaH in DMF or THF) resulted in complex mixtures. Furthermore, 2-pyrazolin-5-ones—known to manifest complex prototropic tautomerization phenomena²⁷—could be similarly employed to exclusively afford the corresponding fluoromethyl ethers, including the analogue (**24**) derived from the anti-amyotrophic lateral sclerosis (ALS) agent edavarone. Substitution across the pyrazole nucleus was uniformly permitted (**25–32**), the ester- (**28**), ketone- (**30–31**), and cinnamoyl- (**32**) bearing systems being representative examples. Full flexibility of the reaction conditions was evidenced for sulfur-centered nucleophiles,²⁸ including a smooth access to the steroidal agent fluticasone (**33**) prepared starting from the parent thiocarboxylic acid. In analogy to the aromatic alcohols discussed above, various thiophenol derivatives (**34–37**) reacted with comparable efficiency, thus providing versatility to the protocol, as for example observed for nitro (**38**), 2,6-disubstituted phenyl (**39**), and heteroaromatic mercaptanes (**41–43**). It should be highlighted that this monofluoromethylthiolation process overcomes *de facto* the initial generation of thioate-type shuttles from the same FIM introduced by Lu and Shen [*S*-(fluoromethyl)-benzenesulfonothioate]²⁸ and Jiang and Yi [Bunte salt $\text{FCH}_2\text{SSO}_3\text{Na}$].²⁹ The higher acidity of a thiophenol (compared to an aliphatic alcohol) rendered feasible the transformation for the trityl derivative (**44**), whereas an excess of FIM and Cs_2CO_3 enabled the double functionalization on both oxygen and sulfur sites of thiosalicylic acid (**45**). The method proved to be modular as indicated by the synthesis of a selenium derivative (**46**), previously prepared through a complex sequence involving aniline diazotization—conversion into organoselenocyanate—formation of a diselenide, and finally transfer of a RSe^- anion to FIM.³⁰

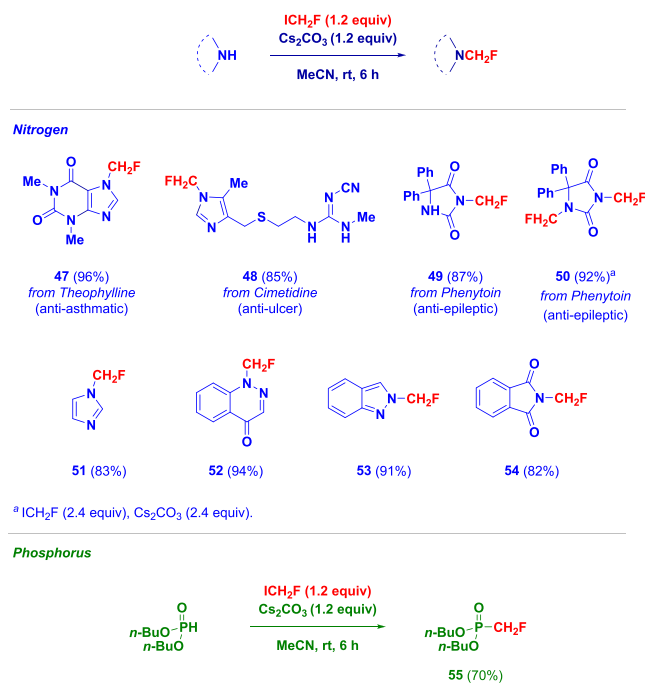
Scheme 3. Fluoromethylation of *O*-, *S*-, and *Se*-Nucleophiles^a

^a ICH_2F (2.4 equiv), Cs_2CO_3 (2.4 equiv).

To cover the range of nucleophilic groups amenable for the proposed functionalization, we then demonstrated the validity

of the technique for medicinally important nitrogenated heterocycles (Scheme 4). The purinic base stimulant drug

Scheme 4. Fluoromethylation of *N*- and *P*-Nucleophiles

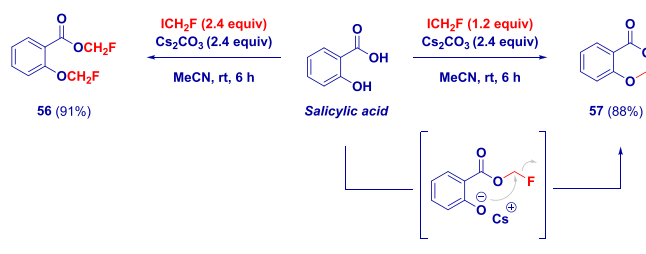


theophylline (47) or the prototypal histaminic-H₂ antagonist cimetidine was selectively fluoromethylated at positions 7 and 1 (the guanidine portion remaining unaffected), respectively. The anticonvulsant and class IB antiarrhythmic agent phenytoin underwent mono- (49) or bis-monofluoromethylation (50) on the hydantoinic nucleus depending on the reaction stoichiometry. Moreover, the nitrogen atoms of imidazole, 4(1*H*)-cinnolinone, indazole, and phthalimide represented excellent linchpins for introducing the CH₂F fragment (51–54). Much to our delight, also di-*n*-butylphosphine oxide was fluoromethylated upon deprotonation in very good yield (55), thus further expanding the scope of substrates suitable for this simple and convenient operation.

The fine-tuning of the stoichiometry of the process was crucial for synthesizing elaborated motifs by taking advantage of the aforementioned inherent reactivity of CH₂F groups toward nucleophilic displacements.¹⁴ Indeed, an excess of ICH₂F and Cs₂CO₃ allowed the bis-derivatization of salicylic acid, yielding 56 (in analogy to the thio compound 45 discussed above), thus formally constituting a homologation process. However, by employing only 1.2 equiv of ICH₂F and an excess of base, the bicyclic lactone 57 was obtained as the unique reaction product (Scheme 5). Presumably, the fluoromethylation occurs (almost) preferentially at the more nucleophilic carboxylate site, giving a reactive (not isolable) fluoromethyl ester which undergoes the internal substitution carried out by the cesium phenoxide.

In summary, we have reported a conceptually highly intuitive and convenient transfer of the fluoromethyl fragment to recipient heteroatom-centered nucleophiles starting from the commercially available and easy to manipulate fluoroiodomethane under mild basic conditions. This operationally simple and (often) chromatographic-free protocol is suitable for derivatizing a plethora of common chemical functionalities

Scheme 5. Stoichiometry-Controlled Fluorinative Homologation of Salicylic Acid



including marked and routinely used drugs. Significantly attractive features of this uniformly high-yielding and general methodology can be recapitulated as follows: (1) robust tolerance of sensitive groups (including challenging carbonyls, ester, guanidine, amide, nitro, nitrile groups, *inter alia*) and (2) complete retention of the stereochemical information contained in optically active drugs.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.9b04654>.

Experimental procedures, NMR spectra, HPLC traces, and analytical data for all the compounds (PDF)

Accession Codes

CCDC 1971864 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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Publication n. 8

Synthesis of stable α -fluoromethyl putative carbanions via a chemoselective reduction-monofluoromethylation sequence of diselenides under sustainable conditions.

Raffaele Senatore,* Monika Malik, Ernst Urban, Wolfgang Holzer and Vittorio Pace*

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Details on experimental procedures, characterization data and copies of NMR spectra of all compounds are reported.



Synthesis of stable α -fluoromethyl putative carbanions *via* a chemoselective reduction-monofluoromethylation sequence of diselenides under sustainable conditions

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ABSTRACT

α -Fluoromethyl selenoethers were prepared through a sequential one-pot diselenide reduction-fluoromethylation with the fluorinated, highly manipulable C1 source ICH₂F. The reaction benefited from the employment of the environmentally friendly solvent MeTHF (2-methyltetrahydrofuran) which enabled to maximize the efficiency of both steps of the technique. A series of variously functionalized analogues – featuring a remarkable degree of stability imparted by selenium – could be chemoselectively accessed in high yield and purity through an intuitive and experimentally simple protocol.

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1. Introduction

Organoselenium compounds play a central role in metal-mediated chemistry as a consequence of the positive modulating effect manifested by this chalcogen on key aspects of the chemical reactivity encompassing the stability and critical physical-chemical properties [1]. In particular, the installation of a selenium-residue into a fragment represents a solid tactic for implementing the constitutional chemical integrity of the resulting species [2]. This operation – being a formal transmetalation – gains a particular significance in cases of highly unstable entities characterized by pronounced disruptive phenomena. In this context, metalated α -fluorinated methyl carbanions (MCH₂F – usually referred as carbenoids) are intriguing synthons whose high tendency to undergo the Kirmse α -elimination [3] (to a free carbene and a metal halide) eclipsed for decades their use in preparative chemistry (Scheme 1 –

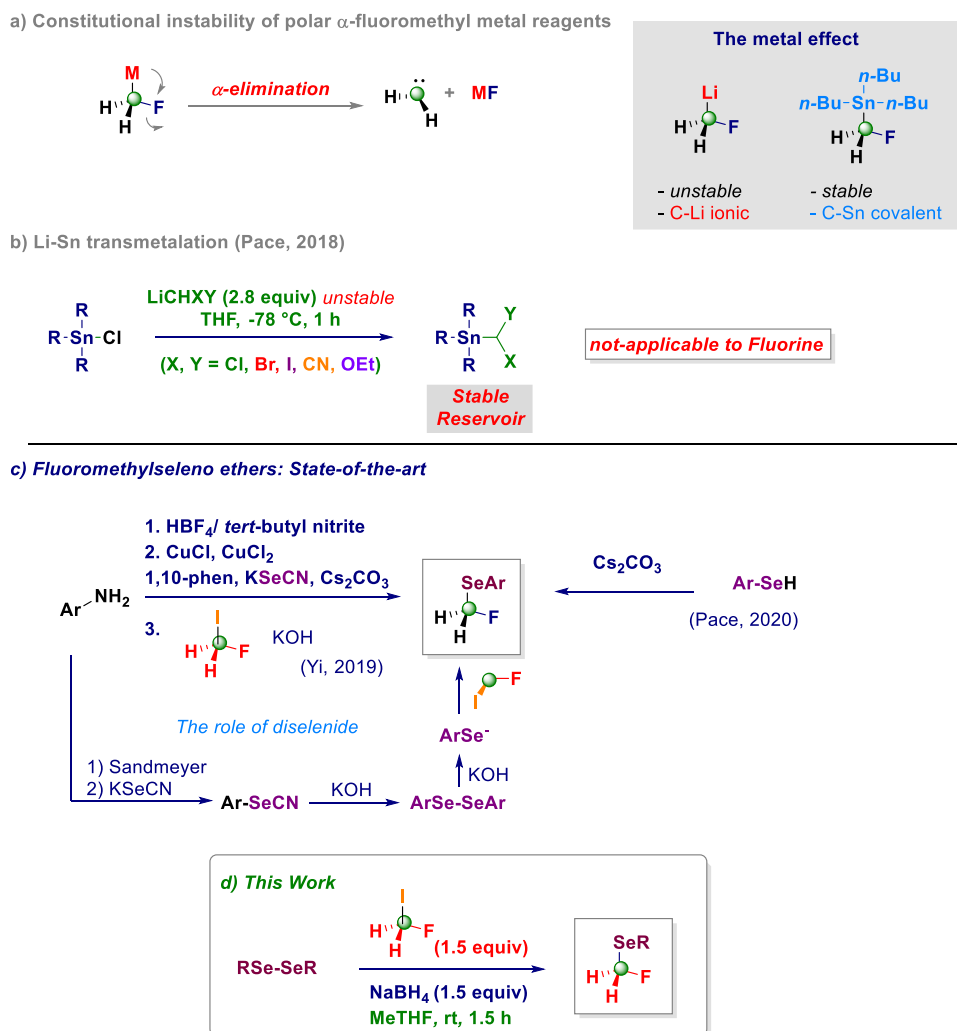
path a) [4]. A preliminary solution to this long-standing issue was disclosed by Hammerschmidt in 2014 documenting the positive stabilizing effect exerted by tin, thus enabling the preparation of the isolable (*n*-Bu)₃SnCH₂F reagent [5]. The covalency of the Sn–C bond – responsible for the excellent chemical stability of these species – was afterwards exploited by our group for accessing a plethora of shuttle-type tin-lithium organometallics generated under transmetalating conditions (Scheme 1 – path b) [6]. Remarkably, this concept could not be applied to the stannylation in batch conditions of the exceptionally unstable fluoromethyl lithium (LiCH₂F) which, as reported by us in 2017 [7], may be formed only through the direct lithiation of the commercially available liquid ICH₂F (bp 52 °C) [8], presumably as a consequence of the easier iodine-lithium exchange [9]. Accordingly, with the aim to evaluate the stability of differently metalated MCH₂F fragments and cognizant of the seminal work by Reich on Se-organometallics [10], we reasoned that selenium could effectively impart additional stability to the fluoromethyl carbanion-like unit. However, despite the structural simplicity the synthesis of RSeCH₂F reagents has only recently been reported in literature. Yi and coworkers reported in 2019 a convenient tactic dealing with the KOH-treatment of selenocyanates (RSeCN) furnishing diselenides (RSeSeR) acting as precursors of RSe[−] anions (*via* further KOH-activation) [11],

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Scheme 1. General context of the presented work.

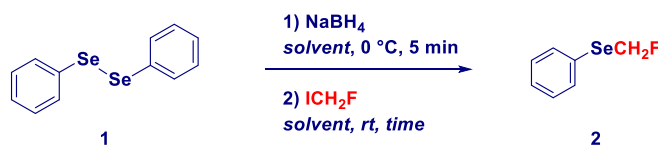
amenable for triggering a nucleophilic substitution on ICH_2F [12]. Unfortunately, the scarce availability of selenocyanates as competent starting materials required their previous preparation from alkyl bromides or, in the case of aromatic analogues, from anilines through a Sandmeyer-type chemistry (Scheme 1 – path c left). Moreover, in 2020 our group reported a single example of monofluorinated arylselenoether synthesized *via* the alkaline-mediated fluoromethylation – conducted on the same ICH_2F – of an aromatic selenol (Scheme 1 – path c right) [13]. Conceptually, both the Yi's and our own strategy rely on the CH_2F transfer to a convenient RSe^- nucleophile: evidently, remodulating the conditions for accessing the Se-containing anion [14] may offer an alternative and straightforward approach towards α -fluoromethyl selenoethers. Herein, we report an intuitive protocol levered on the generation of the nucleophilic element RSe^- through the reduction of widely available (or accessible) diselenides with NaBH_4 , followed by the immediate capture with ICH_2F acting as fluorinating source working in electrophilic regime. Ideally, the diselenide reduction-fluoroalkylation sequence necessitates that the two separate transformations proceed quantitatively to ensure high yields of the final products. In this sense, we anticipate the crucial role of the environmentally friendly solvent 2-MeTHF [15] which guarantees the high efficiency of the technique, limiting to the simple organic phase-water extraction the work-up procedure.

2. Results and discussion

We selected the commercially available diphenyl diselenide **1** as the model compound for realizing the one-pot two steps reductive fluoromethylation sequence (Table 1). In particular, the critical tuned generation of the PhSe^- nucleophile was performed at 0°C through the NaBH_4 treatment in agreement with previous reports, whereas our recent work on the fluoromethylation of heteroatom-based nucleophiles (including Se) motivated us to employ ICH_2F as the fluoromethyl-unit donor. To ensure the smooth reduction of the diselenide a supra-stoichiometric loading of the reductant (2.0 equiv) was employed: pleasingly, intercepting the so-formed nucleophile with ICH_2F (3.0 equiv) furnished the desired fluoromethyl selenoether **2** in an excellent 88% yield after only 60 min (entry 1). Notably, this preliminary experiment was conducted at rt in the polar aprotic solvent MeCN because of its positive effects displayed in the direct fluoromethylation of selenol reported by our group. Dwindling the stoichiometry of both reductant and ICH_2F enabled to observe a sensitive increase of the yield of **2**, though the process required additional time to reach completion (entry 2). The use of THF (entry 3) gave comparable results to MeCN, while further lowering the fluorinating agent resulted in a negative effect on the overall yield (entry 4). The amount of reducing agent was critical for the transformation: in fact, dropping it to only 1.0 equiv

Table 1

Model Reaction: Optimization.



Entry	Solvent	NaBH ₄ (equiv)	ICH ₂ F (equiv)	Reaction time (min)	Yield of 2 (%) ^a
1	MeCN	2.0	3.0	60	88
2	MeCN	1.5	1.5	90	91
3	THF	1.5	1.5	60	91
4	THF	1.5	1.0	90	86
5	THF	1.0	1.5	120	74
6	MeTHF	1.5	1.5	90	96
7 ^b	MeTHF	1.5	1.5	120	68
8 ^c	MeTHF	1.5	1.5	120	72
9 ^d	MeTHF	1.5	1.5	120	87
10	Et ₂ O	1.5	1.5	90	82
11	CPME	1.5	1.5	90	79
12	DMF	1.5	1.5	90	75

^a Isolated yield.^b NaBH₃CN (1.5 equiv) was used as the reducing agent.^c The treatment with NaBH₄ was realized at rt.^d The reaction with ICH₂F was run at 60 °C.

(while keeping ICH₂F at 1.5 equiv) caused a significant lowering of the efficiency, thus suggesting that the formation of the Se-anion is the limiting step of the sequence (entry 5). The switching to MeTHF enabled to maximize – *coeteris paribus* – the reaction yield up to 96% (entry 6). Some additional points merit mention: a) the replacement of NaBH₄ with the milder NaBH₃CN – although admissible – provokes a significant decrease of the yield of 2 (entry 7); b) the reducing step was benefited when run at 0 °C (compared to rt, entry 8); c) analogously, performing the nucleophilic substitution at 60 °C (entry 9) decreases the efficiency, possibly because of the volatility of ICH₂F; d) MeTHF afforded the best results when compared to other solvents such as Et₂O, CPME [16] and DMF (entries 10–12). The sustainable aspects of the sequential transformation conducted in the biomass derived (corncoobs or bagasse) MeTHF, and thus in agreement with the Anastas' Principles of Green Chemistry (IV, V, VII, X, XII) [17] are worth to note: i) its practically immiscibility with water (4 g/100 g) [15d] enables to avoid common solvents (e.g. halogenated, esters, ethers) for the extraction of the organic phase after finalizing the chemical process; ii) high-quality anhydrous solvent was obtained upon normal distillation (i.e. it forms an easily removable azeotrope with water), thus avoiding the use of dangerous drying agents (Na, etc.); iii) toxicological essays suggested the absence of genotoxicity related to the exposure to MeTHF [18].

With the optimal conditions in hand, we then explored the scope of the transformation (Scheme 2). A series of commercially available or smoothly assembled aromatic diselenides [19] were amenable substrates for the methodology, thus affording in high yield and purity the corresponding fluoromethyl selenoethers. The decoration of the aromatic nuclei with functional groups of distinct electronic behaviour was uniformly permitted. Simple alkyl groups could be placed not only in the non-critical *para* position (3) but also when they could induce critical hindrance elements during the nucleophilic substitution (2,6-dimethylphenyl, 7). Halogen-containing functionalities did not alter the efficiency of the method, thus allowing to prepare *p*-chloro- (4), *p*-trifluoromethyl- (5) and mixed 2-chloro-4-methyl- (6) analogues in excellent yields (>92%). The presence of electron-donating functionalities equally ensued the obtainment of the targeted fluorinated selenoethers as

documented in the cases of *p*-methoxy (8) and 2,4-dimethoxyphenyl (9). The additional presence of aromatic groups both as substituent (*p*-phenyl, 10) and fused system (naphthyl, 11) further diversify the accessible structures. Genuine chemo-selectivity during the reaction of a nitro-containing diselenide was achieved with our protocol which furnished derivative 12 featuring the NO₂-group untouched. The procedure was employed also for preparing analogue 13 presenting a nitrogen substituent at a lower oxidation state (primary amine). Heteroaromatic diselenides could be employed in the transformation with similar efficiency, as evidenced in the case of the 2-thienyl- (14) and 3-pyridyl- (15) monofluoroselenoethers. Finally, the flexibility to the preparation of non-(hetero)aromatic systems was deduced in the case of the benzyl derivative 16. Notably, all the synthesized motifs manifested a robust stability when stored at 0 °C for > 3 months, as evidenced by ¹H-, ¹³C- and ⁷⁷Se- NMR spectra.

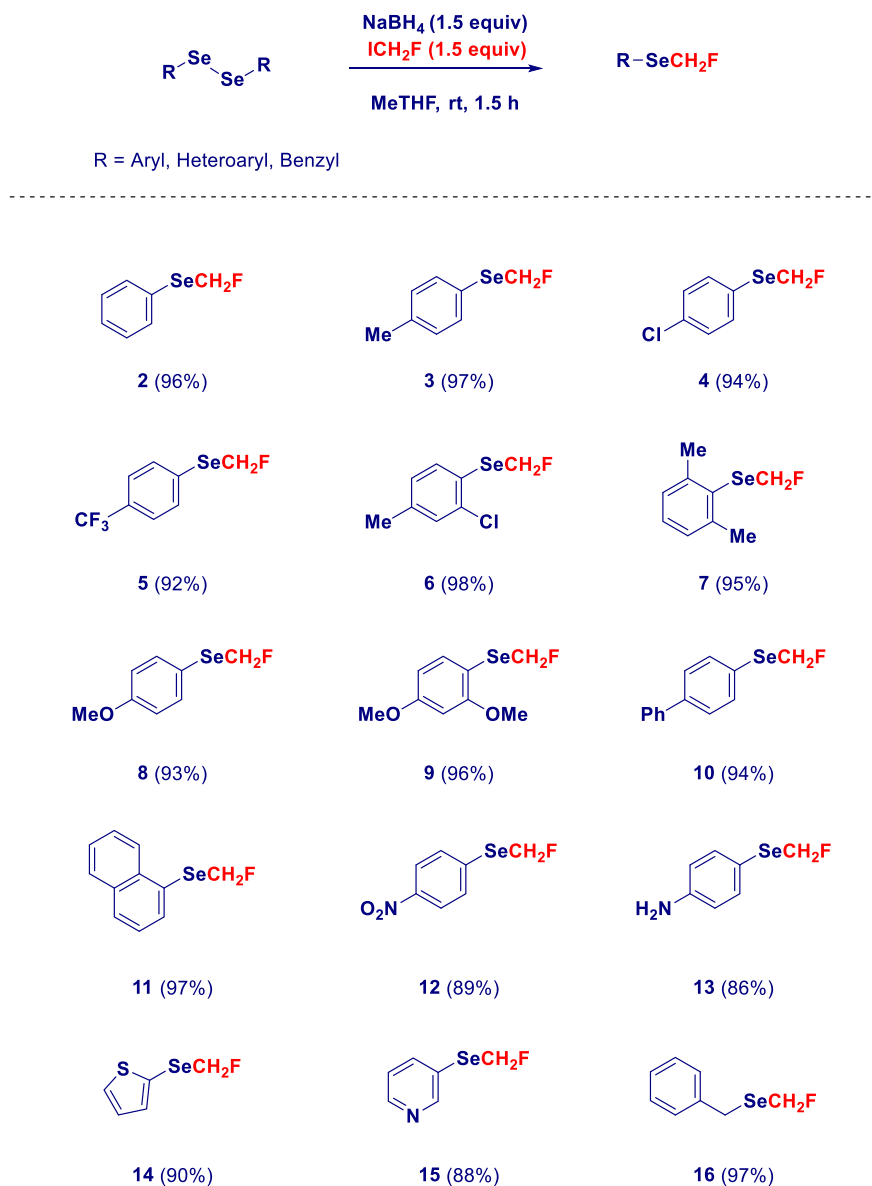
3. Conclusions

In summary a convenient, consequential diselenide reduction (with NaBH₄) – fluoroalkylation (with ICH₂F) is reported for the one-pot synthesis of α-fluoromethyl selenoethers. Crucial for the development of the strategy was identifying the biomass derived – and environmentally friendly – solvent 2-MeTHF as the optimal medium for carrying out the process. Accordingly, the wide available (from commercial sources or easily assembled) diselenides underwent the smooth transformation into the targeted compounds with remarkable chemocontrol, as documented in cases featuring additional sensitive functionalities. Uniformly high yields were obtained, thus furnishing α-fluoromethyl selenoethers of remarkable stability imparted by the embodying of selenium. Additional studies on the synthetic applicability of these motifs are currently undergoing in our group and the results will be reported in due course.

3.1. Experimental Part

3.1.1. Instrumentation and general analytical methods

Melting points were determined on a Reichert–Kofler hot-stage



Scheme 2. Scope of the protocol.

microscope and are uncorrected. Mass spectra were obtained on a Shimadzu QP 1000 instrument (EI, 70 eV) and on a Bruker maXis 4G instrument (ESI-TOF, HRMS). ^1H , ^{13}C , ^{19}F and ^{77}Se NMR spectra were recorded with a Bruker Avance III 400 spectrometer (400 MHz for ^1H , 100 MHz for ^{13}C , 376 MHz for ^{19}F and 76 MHz for ^{77}Se) at 297 K using a directly detecting broadband observe (BBFO) probe. The center of the (residual) solvent signal was used as an internal standard which was related to TMS with δ 7.26 ppm (^1H in CDCl_3), 7.16 ppm (^1H in C_6D_6) and δ 77.0 ppm (^{13}C in CDCl_3), 128.06 (^{13}C in C_6D_6). ^{19}F NMR spectra were referenced via the Ξ ratio (absolute referencing). ^{77}Se spectra were referenced against diphenyldiselenane (δ Ph_2Se_2 463 ppm). Spin-spin coupling constants (J) are given in Hz.

In nearly all cases, full and unambiguous assignment of all resonances was performed by combined application of standard NMR techniques, such as APT, HSQC, HMBC, HSQCTOCSY, COSY and NOESY experiments.

Starting diselenides were commercially available or prepared by

a reported procedure [19]. Fluoroiodomethane was purchased from ABCR Germany. Other chemicals were purchased from SigmaAldrich, Acros, Alfa Aesar, Fluorochem and TCI Europe. MeTHF was distilled under reduced pressure. Solutions were evaporated under reduced pressure with a rotary evaporator.

For column chromatography silica Gel 60 (0.04–0.063 mm) and RP-18 (0.04–0.063 mm) were used. TLC was carried out on aluminium sheets precoated with silica gel 60F254 (Merchery-Nagel, Merk); the spots were visualised under UV light ($\lambda = 254$ nm) and/or KMnO_4 (aq.) was used as revealing system.

3.1.2. General procedure

Under an inert atmosphere of argon, a solution of the starting diselenide (1.0 equiv) in dry MeTHF (5 mL) was added slowly to solid NaBH_4 (1.5 equiv) at 0°C and the reaction was stirred at the same temperature for 5 min. Then fluoroiodomethane (1.5 equiv) was added dropwise at 0°C . After the addition was complete, the reaction was stirred at room temperature for 1.5 h before being

quenched with water. The reaction mixture was directly extracted with the same solvent (3×10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 , and the solvent was removed under reduced pressure. The product was obtained in nearly quantitative yield without any further purification or after purification by column chromatography.

4. [(fluoromethyl)selanyl]benzene (2)^{13a}

By following the general procedure, starting from 1,2-diphenyldisilane (0.312 g, 1.0 mmol, 1.0 equiv), NaBH_4 (0.057 g, 1.5 mmol, 1.5 equiv) and fluoroiodomethane (0.240 g, 0.10 mL, 1.5 mmol, 1.5 equiv) in dry MeTHF (5 mL), compound **2** was obtained in 96% yield (0.182 g) as a colorless oil after purification by column chromatography on reverse phase silica gel (MeCN:H₂O; 8:2).

¹H NMR (400 MHz, C₆D₆): δ 7.45 (m, 2H, Ph H-2,6), 6.94 (m, 1H, Ph H-4), 6.93 (m, 2H, Ph H-3,5), 5.41 (d, $^2J_{\text{H,F}} = 52.0$ Hz, 2H, CH₂F).

¹³C NMR (100 MHz, C₆D₆): δ 133.3 (d, $^4J_{\text{C,F}} = 1.7$ Hz, Ph C-2,6), 130.1 (d, $^3J_{\text{C,F}} = 2.4$ Hz, Ph C-1), 129.5 (Ph C-3,5), 128.0 (Ph C-4), 83.6 (d, $^1J_{\text{C,F}} = 228.0$ Hz, CH₂F).

¹⁹F NMR (376 MHz, C₆D₆): δ -190.4 (t, $^2J_{\text{H,F}} = 52.0$ Hz, CH₂F).

⁷⁷Se NMR (76 MHz, C₆D₆): δ 408.1 (dt, d: $^2J_{\text{Se,F}} = 127.7$ Hz, t: $^2J_{\text{Se,H}} = 17.6$ Hz).

HRMS (ESI), m/z [M + H]⁺ calcd. for C₇H₈FSe: 190.9770; found: 190.9773.

5. 1-[(fluoromethyl)selanyl]-4-methylbenzene (3)¹²

By following the general procedure, starting from 1,2-di-*p*-tolylidisilane (0.340 g, 1.0 mmol, 1.0 equiv), NaBH_4 (0.057 g, 1.5 mmol, 1.5 equiv) and fluoroiodomethane (0.240 g, 0.10 mL, 1.5 mmol, 1.5 equiv) in dry MeTHF (5 mL), compound **3** was obtained in 97% yield (0.197 g) as a yellow oil.

¹H NMR (400 MHz, C₆D₆): δ 7.43 (m, 2H, Ph H-2,6), 6.78 (m, 2H, Ph H-3,5), 5.45 (d, $^2J_{\text{H,F}} = 52.1$ Hz, 2H, CH₂F), 1.98 (s, 3H, CH₃).

¹³C NMR (100 MHz, C₆D₆): δ 138.0 (Ph C-4), 133.8 (d, $^4J_{\text{C,F}} = 1.6$ Hz, Ph C-2,6), 130.3 (Ph C-3,5), 126.4 (d, $^3J_{\text{C,F}} = 2.2$ Hz, Ph C-1), 84.0 (d, $^1J_{\text{C,F}} = 227.9$ Hz, CH₂F), 20.9 (CH₃).

¹⁹F NMR (376 MHz, C₆D₆): δ -190.4 (t, $^2J_{\text{H,F}} = 52.1$ Hz, CH₂F).

⁷⁷Se NMR (76 MHz, C₆D₆): δ 400.8 (dt, d: $^2J_{\text{Se,F}} = 128.3$ Hz, t: $^2J_{\text{Se,H}} = 16.9$ Hz).

HRMS (ESI), m/z [M + H]⁺ calcd. for C₈H₁₀FSe: 204.9926; found: 204.9927.

6. 1-Chloro-4-[(fluoromethyl)selanyl]benzene (4)¹²

By following the general procedure, starting from 1,2-bis(4-chlorophenyl)disilane (0.381 g, 1.0 mmol, 1.0 equiv), NaBH_4 (0.057 g, 1.5 mmol, 1.5 equiv) and fluoroiodomethane (0.240 g, 0.10 mL, 1.5 mmol, 1.5 equiv) in dry MeTHF (5 mL), compound **4** was obtained in 94% yield (0.210 g) as a yellow oil after purification by column chromatography on silica gel (*n*-hexane).

¹H NMR (400 MHz, CDCl₃): δ 7.54 (m, 2H, Ph H-3,5), 7.29 (m, 2H, Ph H-2,6), 5.99 (d, $^2J_{\text{H,F}} = 51.9$ Hz, 2H, CH₂F).

¹³C NMR (100 MHz, CDCl₃): δ 134.5 (d, $^4J_{\text{C,F}} = 1.8$ Hz, Ph C-3,5), 134.4 (Ph C-1), 129.5 (Ph C-2,6), 127.4 (d, $^3J_{\text{C,F}} = 2.3$ Hz, Ph C-4), 83.8 (d, $^1J_{\text{C,F}} = 228.1$ Hz, CH₂F).

¹⁹F NMR (376 MHz, CDCl₃): δ -191.1 (t, $^2J_{\text{H,F}} = 51.9$ Hz, CH₂F).

⁷⁷Se NMR (76 MHz, CDCl₃): δ 406.0 (dt, d: $^2J_{\text{Se,F}} = 127.0$ Hz, t: $^2J_{\text{Se,H}} = 17.2$ Hz).

HRMS (ESI), m/z [M + H]⁺ calcd. for C₇H₇ClFSe: 224.9380; found: 224.9382.

7. 1-[(fluoromethyl)selanyl]-4-(trifluoromethyl)benzene (5)

By following the general procedure, starting from 1,2-bis(4-(trifluoromethyl)phenyl)disilane (0.448 g, 1.0 mmol, 1.0 equiv), NaBH_4 (0.057 g, 1.5 mmol, 1.5 equiv) and fluoroiodomethane (0.240 g, 0.10 mL, 1.5 mmol, 1.5 equiv) in dry MeTHF (5 mL), compound **5** was obtained in 92% yield (0.236 g) as a colorless oil after purification by column chromatography on silica gel (*n*-hexane).

¹H NMR (400 MHz, C₆D₆): δ 7.15 (m, 2H, Ph H-2,6), 7.07 (m, 2H, Ph H-3,5), 5.28 (d, $^2J_{\text{H,F}} = 51.8$ Hz, 2H, CH₂F).

¹³C NMR (100 MHz, C₆D₆): δ 135.0 (m, Ph C-1), 132.3 (d, $^4J_{\text{C,F}} = 1.8$ Hz, Ph C-2,6), 129.8 (q, $^2J_{\text{C,F}} = 32.5$ Hz, Ph C-4), 126.1 (q, $^3J_{\text{C,F}} = 3.8$ Hz, Ph C-3,5), 124.7 (q, $^1J_{\text{C,F}} = 272.0$ Hz, CF₃) 82.7 (d, $^1J_{\text{C,F}} = 229.0$ Hz, CH₂F).

¹⁹F NMR (376 MHz, C₆D₆): δ -191.1 (t, $^2J_{\text{H,F}} = 51.8$ Hz, CH₂F).

⁷⁷Se NMR (76 MHz, C₆D₆): δ 414.8 (dt, d: $^2J_{\text{Se,F}} = 127.7$ Hz, t: $^2J_{\text{Se,H}} = 17.6$ Hz).

HRMS (ESI), m/z [M + H]⁺ calcd. for C₈H₇F₄Se: 258.9644; found: 258.9646.

8. 2-Chloro-1-[(fluoromethyl)selanyl]-4-methylbenzene (6)

By following the general procedure, starting from 1,2-bis(2-chloro-4-methylphenyl)disilane (0.409 g, 1.0 mmol, 1.0 equiv), NaBH_4 (0.057 g, 1.5 mmol, 1.5 equiv) and fluoroiodomethane (0.240 g, 0.10 mL, 1.5 mmol, 1.5 equiv) in dry MeTHF (5 mL), compound **6** was obtained in 98% yield (0.233 g) as a colorless oil.

¹H NMR (400 MHz, C₆D₆): δ 7.35 (d, $^3J = 8.0$ Hz, 1H, Ph H-6), 6.91 (m, 1H, Ph H-3), 6.56 (m, 1H, Ph H-5), 5.40 (dd, $^2J_{\text{H,F}} = 51.9$ Hz, $^1J = 1.0$ Hz, 2H, CH₂F), 1.81 (s, 3H, CH₃).

¹³C NMR (100 MHz, C₆D₆): δ 139.1 (Ph C-4), 135.4 (d, $^4J_{\text{C,F}} = 2.0$ Hz, Ph C-2), 132.4 (Ph C-6), 130.5 (Ph C-3), 128.8 (Ph C-5), 127.2 (d, $^3J_{\text{C,F}} = 2.6$ Hz, Ph C-1), 81.9 (d, $^1J_{\text{C,F}} = 228.0$ Hz, CH₂F), 20.4 (CH₃).

¹⁹F NMR (376 MHz, C₆D₆): δ -193.0 (t, $^2J_{\text{H,F}} = 51.9$ Hz, CH₂F).

⁷⁷Se NMR (76 MHz, C₆D₆): δ 389.6 (dt, d: $^2J_{\text{Se,F}} = 125.7$ Hz, t: $^2J_{\text{Se,H}} = 18.8$ Hz).

HRMS (ESI), m/z [M + H]⁺ calcd. for C₈H₉ClFSe: 238.9537; found: 238.9538.

9. 2,6-Dimethylphenyl fluoromethyl selenide (7)

By following the general procedure, starting from 1,2-bis(2,6-dimethylphenyl)disilane (0.368 g, 1.0 mmol, 1.0 equiv), NaBH_4 (0.057 g, 1.5 mmol, 1.5 equiv) and fluoroiodomethane (0.240 g, 0.10 mL, 1.5 mmol, 1.5 equiv) in dry MeTHF (5 mL), compound **7** was obtained in 95% yield (0.206 g) as a yellowish oil after purification by column chromatography on reverse phase silica gel (MeCN).

¹H NMR (400 MHz, C₆D₆): δ 6.95 (m, 1H, Ph H-4), 6.93 (m, 2H, Ph H-3,5), 5.26 (d, $^2J_{\text{H,F}} = 51.8$ Hz, 2H, CH₂F), 2.45 (s, 6H, CH₃).

¹³C NMR (100 MHz, C₆D₆): δ 143.6 (d, $^4J_{\text{C,F}} = 1.4$ Hz, Ph C-2,6), 130.9 (d, $^3J_{\text{C,F}} = 1.6$ Hz, Ph C-1), 129.4 (Ph C-4), 128.2 (Ph C-3,5), 84.0 (d, $^1J_{\text{C,F}} = 228.9$ Hz, CH₂F), 25.1 (CH₃).

¹⁹F NMR (376 MHz, C₆D₆): δ -190.8 (t, $^2J_{\text{H,F}} = 51.9$ Hz, CH₂F).

⁷⁷Se NMR (76 MHz, C₆D₆): δ 281.1 (dt, d: $^2J_{\text{Se,F}} = 125.4$ Hz, t: $^2J_{\text{Se,H}} = 17.2$ Hz).

HRMS (ESI), m/z [M + H]⁺ calcd. for C₉H₁₂FSe: 219.0083; found: 219.0085.

10. 1-[(fluoromethyl)selanyl]-4-methoxybenzene (8)

By following the general procedure, starting from 1,2-bis(4-methoxyphenyl)disilane (0.327 g, 1.0 mmol, 1.0 equiv), NaBH_4 (0.057 g, 1.5 mmol, 1.5 equiv) and fluoroiodomethane (0.240 g, 0.10 mL, 1.5 mmol, 1.5 equiv) in dry MeTHF (5 mL), compound **8** was

obtained in 93% yield (0.204 g) as a colorless oil after purification by column chromatography on silica gel (*n*-hexane:Et₂O 99:1).

¹H NMR (400 MHz, C₆D₆): δ 7.45 (m, 2H, Ph H-2,6), 6.58 (m, 2H, Ph H-3,5), 4.93 (d, ²J_{H,F} = 52.1 Hz, 2H, CH₂F), 3.19 (s, 3H, OCH₃).

¹³C NMR (100 MHz, C₆D₆): δ 160.5 (Ph C-4), 136.1 (d, ⁴J_{C,F} = 1.6 Hz, Ph C-2,6), 119.8 (d, ³J_{C,F} = 2.1 Hz, Ph C-1), 115.3 (Ph C-3,5), 84.5 (d, ¹J_{C,F} = 227.9 Hz, CH₂F), 54.8 (OCH₃).

¹⁹F NMR (376 MHz, C₆D₆): δ -190.6 (t, ²J_{H,F} = 52.0 Hz, CH₂F).

⁷⁷Se NMR (76 MHz, C₆D₆): δ 396.3 (dt, d: ²J_{Se,F} = 126.9 Hz, t: ²J_{Se,H} = 16.9 Hz).

HRMS (ESI), *m/z* [M + H]⁺ calcd. for C₈H₁₀FOSe: 220.9875; found: 220.9878.

11. 1-[(fluoromethyl)selanyl]-2,4-dimethoxybenzene (9)

By following the general procedure, starting from 1,2-bis(2,4-dimethoxyphenyl)diselane (0.432 g, 1.0 mmol, 1.0 equiv), NaBH₄ (0.057 g, 1.5 mmol, 1.5 equiv) and fluoroiodomethane (0.240 g, 0.10 mL, 1.5 mmol, 1.5 equiv) in dry MeTHF (5 mL), compound **9** was obtained in 96% yield (0.239 g) as a yellowish oil.

¹H NMR (400 MHz, C₆D₆): δ 7.53 (d, ³J = 8.4 Hz, 1H, Ph H-6), 6.31 (d, ⁴J = 2.5 Hz, 1H, Ph H-3), 6.23 (dd, ³J = 8.4 Hz, ⁴J = 2.5 Hz, 1H, Ph H-5), 5.61 (d, ²J_{H,F} = 52.2 Hz, 2H, CH₂F), 3.28 (s, 3H, 4-OCH₃), 3.19 (s, 3H, 2-OCH₃).

¹³C NMR (100 MHz, C₆D₆): δ 161.8 (Ph C-4), 159.6 (d, ⁴J_{C,F} = 1.4 Hz, Ph C-2), 134.8 (Ph C-6), 109.6 (d, ³J_{C,F} = 2.3 Hz, Ph C-1), 105.8 (Ph C-5), 99.6 (Ph C-3), 82.2 (d, ¹J_{C,F} = 226.7 Hz, CH₂F), 55.3 (2-OCH₃), 55.0 (4-OCH₃).

¹⁹F NMR (376 MHz, C₆D₆): δ -192.3 (t, ²J_{H,F} = 52.3 Hz, CH₂F).

⁷⁷Se NMR (76 MHz, C₆D₆): δ 331.2 (dt, d: ²J_{Se,F} = 124.9 Hz, t: ²J_{Se,H} = 18.0 Hz).

HRMS (ESI), *m/z* [M + H]⁺ calcd. for C₉H₁₂FO₂Se: 250.9981; found: 250.9984.

12. 4-[(fluoromethyl)selanyl]biphenyl (10)

By following the general procedure, starting from 1,2-di([1,1'-biphenyl]-4-yl)diselane (0.464 g, 1.0 mmol, 1.0 equiv), NaBH₄ (0.057 g, 1.5 mmol, 1.5 equiv) and fluoroiodomethane (0.240 g, 0.10 mL, 1.5 mmol, 1.5 equiv) in dry MeTHF (5 mL), compound **10** was obtained in 94% yield (0.249 g) as a white solid (m.p. 51–52 °C) after purification by column chromatography on silica gel (*n*-hexane).

¹H NMR (400 MHz, C₆D₆): δ 7.51 (m, 2H, Ph 1 H-3,5), 7.36 (m, 2H, Ph 2 H-2,6), 7.24 (m, 2H, Ph 1 H-2,6), 7.20 (m, 2H, Ph 2 H-3,5), 7.13 (m, 1H, Ph 2 H-4), 5.46 (d, ²J_{H,F} = 52.0 Hz, 2H, CH₂F).

¹³C NMR (100 MHz, C₆D₆): δ 141.3 (Ph 1 C-1), 140.7 (Ph 2 C-1), 133.8 (d, ⁴J_{C,F} = 1.7 Hz, Ph 1 C-3,5), 129.1 (Ph 2 C-3,5), 129.0 (d, ³J_{C,F} = 2.4 Hz, Ph 1 C-4), 128.4 (Ph 1 C-2,6), 127.8 (Ph 2 C-4), 127.4 (Ph 2 C-2,6), 83.7 (d, ¹J_{C,F} = 228.2 Hz, CH₂F).

¹⁹F NMR (376 MHz, C₆D₆): δ -190.4 (t, ²J_{H,F} = 52.0 Hz, CH₂F).

⁷⁷Se NMR (76 MHz, C₆D₆): δ 402.5 (dt, d: ²J_{Se,F} = 128.3 Hz, t: ²J_{Se,H} = 17.1 Hz).

HRMS (ESI), *m/z* [M + H]⁺ calcd. for C₁₃H₁₂FSe: 267.0083; found: 267.0085.

13. 1-[(fluoromethyl)selanyl]naphthalene (11)

By following the general procedure, starting from 1,2-di(naphthalen-1-yl)diselane (0.412 g, 1.0 mmol, 1.0 equiv), NaBH₄ (0.057 g, 1.5 mmol, 1.5 equiv) and fluoroiodomethane (0.240 g, 0.10 mL, 1.5 mmol, 1.5 equiv) in dry MeTHF (5 mL), compound **11** was obtained in 97% yield (0.232 g) as a yellowish oil after purification by column chromatography on reverse phase silica gel (MeCN).

¹H NMR (400 MHz, C₆D₆): δ 8.42 (m, 1H, Naph H-8), 7.84 (dd, ³J = 7.2 Hz, ⁴J = 1.2 Hz, 1H, Naph H-2), 7.54 (m, 1H, Naph H-5), 7.50 (m, 1H, Naph H-4), 7.29 (m, 1H, Naph H-7), 7.21 (m, 1H, Naph H-6), 7.03 (dd, ³J = 8.2 Hz, ³J = 7.2 Hz, 1H, Naph H-3) 5.40 (d, ²J_{H,F} = 51.8 Hz, 2H, CH₂F).

¹³C NMR (100 MHz, C₆D₆): δ 134.8 (d [⁴J_{C,F} = 1.5 Hz, Naph C-8a), 134.5 (Naph C-4a), 133.8 (d [⁴J_{C,F} = 1.6 Hz, Naph C-2), 129.6 (Naph C-4), 129.3 (d [³J_{C,F} = 2.2 Hz, Naph C-1), 128.9 (Naph C-5), 128.1 (Naph C-8), 127.1 (Naph C-7), 126.6 (Naph C-6), 126.2 (Naph C-3), 83.5 (d, ¹J_{C,F} = 229.0 Hz, CH₂F).

¹⁹F NMR (376 MHz, C₆D₆): δ -190.3 (t, ²J_{H,F} = 51.8 Hz, CH₂F).

⁷⁷Se NMR (76 MHz, C₆D₆): δ 342.5 (dt, d: ²J_{Se,F} = 128.5 Hz, t: ²J_{Se,H} = 17.5 Hz).

HRMS (ESI), *m/z* [M + H]⁺ calcd. for C₁₁H₁₀FSe: 240.9926; found: 240.9927.

14. 1-[(fluoromethyl)selanyl]-4-nitrobenzene (12)¹²

By following the general procedure, starting from 1,2-bis(4-nitrophenyl)diselane (0.402 g, 1.0 mmol, 1.0 equiv), NaBH₄ (0.057 g, 1.5 mmol, 1.5 equiv) and fluoroiodomethane (0.240 g, 0.10 mL, 1.5 mmol, 1.5 equiv) in dry MeTHF (5 mL), compound **12** was obtained in 89% yield (0.208 g) as a yellow solid (m.p. 83–85 °C) after purification by column chromatography on silica gel (*n*-hexane:Et₂O 9:1).

¹H NMR (400 MHz, C₆D₆): δ 7.56 (m, 2H, Ph H-3,5), 6.92 (m, 2H, Ph H-2,6), 5.19 (d, ²J_{H,F} = 51.6 Hz, 2H, CH₂F).

¹³C NMR (100 MHz, C₆D₆): δ 147.4 (Ph C-4), 138.8 (d, ³J_{C,F} = 2.6 Hz, Ph C-1), 131.3 (d, ⁴J_{C,F} = 1.9 Hz, Ph C-2,6), 124.0 (Ph C-3,5), 82.1 (d, ¹J_{C,F} = 229.6 Hz, CH₂F).

¹⁹F NMR (376 MHz, C₆D₆): δ -191.9 (t, ²J_{H,F} = 51.6 Hz, CH₂F).

⁷⁷Se NMR (76 MHz, C₆D₆): δ 421.3 (dt, d: ²J_{Se,F} = 126.2 Hz, t: ²J_{Se,H} = 18.0 Hz).

HRMS (ESI), *m/z* [M + H]⁺ calcd. for C₇H₇FNO₂Se: 235.9621; found: 235.9624.

15. 4-[(fluoromethyl)selanyl]aniline (13)

By following the general procedure, starting from 4,4'-diselanediyldianiline (0.342 g, 1.0 mmol, 1.0 equiv), NaBH₄ (0.057 g, 1.5 mmol, 1.5 equiv) and fluoroiodomethane (0.240 g, 0.10 mL, 1.5 mmol, 1.5 equiv) in dry MeTHF (5 mL), compound **13** was obtained in 86% yield (0.176 g) as a yellow oil after purification by column chromatography on silica gel (*n*-hexane:Et₂O 6:4).

¹H NMR (400 MHz, C₆D₆): δ 7.41 (m, 2H, Ph H-3,5), 6.10 (m, 2H, Ph H-2,6), 5.45 (d, ²J_{H,F} = 52.2 Hz, 2H, CH₂F), 2.73 (br s, 2H, NH₂).

¹³C NMR (100 MHz, C₆D₆): δ 147.6 (Ph C-1), 136.4 (d, ⁴J_{C,F} = 1.6 Hz, Ph C-3,5), 116.2 (d, ³J_{C,F} = 2.1 Hz, Ph C-4), 115.7 (Ph C-2,6), 84.9 (d, ¹J_{C,F} = 227.4 Hz, CH₂F).

¹⁹F NMR (376 MHz, C₆D₆): δ -190.6 (t, ²J_{H,F} = 52.1 Hz, CH₂F).

⁷⁷Se NMR (76 MHz, C₆D₆): δ 393.9 (dt, d: ²J_{Se,F} = 126.9 Hz, t: ²J_{Se,H} = 16.7 Hz).

HRMS (ESI), *m/z* [M + H]⁺ calcd. for C₇H₉FNSe: 205.9879; found: 205.9882.

16. 2-[(fluoromethyl)selanyl]thiophene (14)

By following the general procedure, starting from 1,2-di(thiophen-2-yl)diselane (0.324 g, 1.0 mmol, 1.0 equiv), NaBH₄ (0.057 g, 1.5 mmol, 1.5 equiv) and fluoroiodomethane (0.240 g, 0.10 mL, 1.5 mmol, 1.5 equiv) in dry MeTHF (5 mL), compound **14** was obtained in 90% yield (0.176 g) as a red oil after purification by column chromatography on silica gel (*n*-hexane).

¹H NMR (400 MHz, C₆D₆): δ 7.07 (dd, ³J = 3.5 Hz, ⁴J = 1.2 Hz, 1H, Th H-3), 6.84 (dd, ³J = 5.3 Hz, ⁴J = 1.2 Hz, 1H, Th H-5), 6.56 (dd,

$^3J = 5.3$ Hz, $^3J = 3.5$ Hz, 1H, Th H-4), 5.16 (d, $^2J_{H,F} = 51.5$ Hz, 2H, CH₂F).

^{13}C NMR (100 MHz, C₆D₆): δ 136.5 (d, $^4J_{C,F} = 1.4$ Hz, Th C-3), 131.7 (Th C-5), 128.3 (Th C-4), 122.4 (d, $^3J_{C,F} = 2.4$ Hz, Th C-2), 85.3 (d, $^1J_{C,F} = 231.0$ Hz, CH₂F).

^{19}F NMR (376 MHz, C₆D₆): δ -190.3 (t, $^2J_{H,F} = 51.5$ Hz, CH₂F).

^{77}Se NMR (76 MHz, C₆D₆): δ 321.2 (dt, d: $^2J_{Se,F} = 121.5$ Hz, t: $^2J_{Se,H} = 18.3$ Hz).

HRMS (ESI), m/z [M + H]⁺ calcd. for C₅H₆FS₂: 196.9334; found: 196.9337.

17. 3-[(fluoromethyl)selenyl]pyridine (15)

By following the general procedure, starting from 1,2-di(pyridin-3-yl)diselane (0.314 g, 1.0 mmol, 1.0 equiv), NaBH₄ (0.057 g, 1.5 mmol, 1.5 equiv) and fluoroiodomethane (0.240 g, 0.10 mL, 1.5 mmol, 1.5 equiv) in dry MeTHF (5 mL), compound **15** was obtained in 88% yield (0.167 g) as colorless oil after purification by column chromatography on silica gel (*n*-hexane:Et₂O 6:4).

^1H NMR (400 MHz, C₆D₆): δ 8.84 (dd, $J = 4.8$ Hz, $J = 1.5$ Hz, 1H, Pyr H-6), 8.83 (d, $J = 1.9$ Hz, 1H, Pyr H-2), 7.40 (m, 1H, Pyr H-4), 6.48 (m, 1H, Pyr H-5), 5.18 (d, $^2J_{H,F} = 51.7$ Hz, 2H, CH₂F).

^{13}C NMR (100 MHz, C₆D₆): δ 153.6 (d, $^4J_{C,F} = 2.0$ Hz, Pyr C-2), 149.4 (Pyr C-6), 140.4 (d, $^4J_{C,F} = 1.3$ Hz, Pyr C-4), 126.7 (d, $^3J_{C,F} = 2.1$ Hz, Pyr C-3), 124.1 (Pyr C-5), 83.2 (d, $^1J_{C,F} = 229.4$ Hz, CH₂F).

^{19}F NMR (376 MHz, C₆D₆): δ -190.4 (t, $^2J_{H,F} = 51.7$ Hz, CH₂F).

^{77}Se NMR (76 MHz, C₆D₆): δ 379.4 (dt, d: $^2J_{Se,F} = 125.5$ Hz, t: $^2J_{Se,H} = 17.5$ Hz).

HRMS (ESI), m/z [M + H]⁺ calcd. for C₆H₇FNSe: 191.9722; found: 191.9725.

18. {[(fluoromethyl)selenyl]methyl} benzene (16)

By following the general procedure, starting from 1,2-dibenzylidiselane (0.340 g, 1.0 mmol, 1.0 equiv), NaBH₄ (0.057 g, 1.5 mmol, 1.5 equiv) and fluoroiodomethane (0.240 g, 0.10 mL, 1.5 mmol, 1.5 equiv) in dry MeTHF (5 mL), compound **16** was obtained in 97% yield (0.197 g) as a colorless oil.

^1H NMR (400 MHz, C₆D₆): δ 7.04 (m, 4H, Ph H-2,3,5,6), 6.99 (m, 1H, Ph H-4), 5.21 (d, $^2J_{H,F} = 52.2$ Hz, 2H, CH₂F), 3.54 (d, $^3J_{H,F} = 1.9$ Hz, 2H, CH₂).

^{13}C NMR (100 MHz, C₆D₆): δ 138.4 (Ph C-1), 129.4 (Ph C-2,6), 128.8 (Ph C-3,5), 127.2 (Ph C-4), 79.5 (d, $^1J_{C,F} = 224.9$ Hz, CH₂F), 27.3 (CH₂).

^{19}F NMR (376 MHz, C₆D₆): δ -195.7 (t, $^2J_{H,F} = 52.1$ Hz).

^{77}Se NMR (76 MHz, C₆D₆): δ 364.7 (m).

HRMS (ESI), m/z [M + H]⁺ calcd. for C₈H₁₀FS₂: 204.9926; found: 204.9928.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at

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Appendix

Supporting information for Publication n. 6

Consecutive and Selective Double Methylene Insertion of Lithium Carbenoids to Isothiocyanates: A Direct Assembly of Four-membered Sulfur-Containing Cycles.

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SUPPORTING INFORMATION

for

Consecutive and Selective Double Methylene Insertion of Lithium Carbenoids to Isothiocyanates: A Direct Assembly of Four-membered Sulfur-Containing Cycles

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Instrumentation and General Analytical Methods

Melting points were determined on a Reichert–Kofler hot-stage microscope and are uncorrected. Mass spectra were obtained on a Shimadzu QP 1000 instrument (EI, 70 eV) and on a Bruker maXis 4G instrument (ESI-TOF, HRMS). ^1H , ^{13}C , ^{15}N , ^{19}F and ^{77}Se NMR spectra were recorded with a Bruker Avance III 400 spectrometer (400 MHz for ^1H , 100 MHz for ^{13}C , 40 MHz for ^{15}N , 376 MHz for ^{19}F and 76 MHz for ^{77}Se) at 297 K using a directly detecting broadband observe (BBFO) probe. The center of the (residual) solvent signal was used as an internal standard which was related to TMS with δ 7.26 ppm (^1H in CDCl_3), 7.16 ppm (^1H in C_6D_6) and δ 77.0 ppm (^{13}C in CDCl_3), 128.06 (^{13}C in C_6D_6). ^{15}N NMR (gs-HMBC) spectra were referenced against neat, external nitromethane. ^{19}F NMR spectra were referenced via the Ξ ratio (absolute referencing). ^{77}Se spectra were referenced against diphenyldisilane (δ Ph_2Se_2 463 ppm). Spin-spin coupling constants (J) are given in Hz.

In nearly all cases, full and unambiguous assignment of all resonances was performed by combined application of standard NMR techniques, such as APT, HSQC, HMBC, HSQCTOCSY, COSY and NOESY experiments.

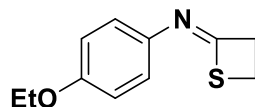
All reactions were performed under an inert atmosphere of argon using standard schlenk techniques. THF was distilled over Na/benzophenone. Starting isothiocyanates were commercially available or prepared as reported. Fluoroiodomethane was supplied from ABCR Germany. Other chemicals were purchased from SigmaAldrich, Acros, Alfa Aesar, Fluorochem and TCI Europe. Solutions were evaporated under reduced pressure with a rotary evaporator. For column chromatography, silica Gel 60 (0.04-0.063 mm) was used. TLC was carried out on aluminium sheets precoated with silica gel 60F254 (Merckery-Nagel, Merk); the spots were visualised under UV light ($\lambda = 254$ nm) and/or KMnO_4 (aq.) was used as revealing system.

General Procedure for the synthesis of four-membered imino-thietanes.

To a solution of the starting isothiocyanate (1.0 equiv) in dry THF (3 mL) bromoiodomethane (3.0 equiv) was added. Then, a solution of MeLi-LiBr (2.2 M in Et_2O , 2.8 equiv) was added dropwise at -78°C . After stirring for 5 min at -78°C , the reaction was quenched with sat. aqueous NH_4Cl . The reaction mixture was allowed to reach room temperature and exhaustively extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and the solvent was removed under reduced pressure. The final products were obtained after purification by column chromatography on silica gel.

Characterization and Spectral Data of the Compounds

4-ethoxy-*N*-[(2*Z*)-2-thietanylidene]aniline (**2**)



By following the general procedure, starting from 4-ethoxyphenyl isothiocyanate (0.179 g, 1.0 mmol, 1.0 equiv), bromiodomethane (0.662 g, 0.22 mL, 3.0 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M in Et₂O, 1.27 mL, 2.8 mmol, 2.8 equiv) in dry THF (3 mL), compound **2** was obtained in 82% yield (0.170 g) as a brown solid (mp: 62-65 °C) after purification by column chromatography on silica gel (*n*-hexane:EtOAc 8:2).

Scaling-up of the reaction (20 mmol) - By following the general procedure, starting from 4-ethoxyphenyl isothiocyanate (3.580 g, 20.0 mmol, 1.0 equiv), bromiodomethane (13.250 g, 4.52 mL, 60.0 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M in Et₂O, 25.45 mL, 56.0 mmol, 2.8 equiv) in dry THF (60 mL), compound **2** was obtained in 81% yield (3.358 g) as a brown solid after purification by column chromatography on silica gel (*n*-hexane:EtOAc 8:2). *Spectroscopic and spectrometric data match with those reported for the 1.0 mmol scale*

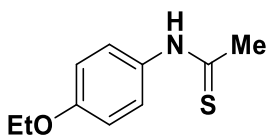
¹H NMR (400 MHz, C₆D₆) δ: 7.24 (m, 2H, Ph H-2,6), 6.81 (m, 2H, Ph H-3,5), 3.54 (q, ³*J* = 7.0 Hz, 2H, OCH₂), 3.33 (m, 2H, CH₂), 2.39 (m, 2H, SCH₂), 1.08 (t, ³*J* = 7.0 Hz, 3H, CH₃).

¹³C NMR (100 MHz, C₆D₆) δ: 158.0 (C=N), 157.1 (Ph C-4), 141.4 (Ph C-1), 122.7 (Ph C-2,6), 115.4 (Ph C-3,5), 63.4 (OCH₂), 47.1 (CH₂), 20.4 (SCH₂), 14.9 (CH₃).

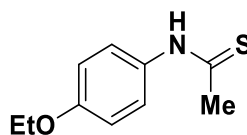
¹⁵N NMR (40 MHz, C₆D₆) δ: -82.5 (C=N).

HRMS (ESI), *m/z*: calcd. for C₁₁H₁₄NOS⁺: 208.0791 [M + H]⁺; found: 208.0792.

***N*-(4-ethoxyphenyl)ethanethioamide (2a)**



s-cis rotamer



s-trans rotamer

Obtained in 21% yield (0.041 g) as a yellowish solid (mp: 114 °C), as reported in Table 1 of the manuscript (Entry 9).

s-trans : *s-cis* ~ 1 : 1

s-cis rotamer:

¹H NMR (400 MHz, CDCl₃) δ: 8.59 (br s, 1H, NH), 7.50 (m, 2H, Ph H-2,6), 6.90 (m, 2H, Ph H-3,5), 4.03 (q, ³*J* = 7.0 Hz, 2H, OCH₂CH₃), 2.72 (s, 3H, CH₃), 1.41 (t, ³*J* = 7.0 Hz, 3H, OCH₂CH₃).

¹³C NMR (100 MHz, CDCl₃) δ: 200.3 (C=S), 157.7 (Ph C-4), 130.8 (Ph C-1), 125.7 (Ph C-2,6), 114.6 (Ph C-3,5), 63.7 (OCH₂CH₃), 35.8 (CH₃), 14.8 (OCH₂CH₃).

¹⁵N NMR (40 MHz, CDCl₃) δ: -219.5 (NH).

s-trans rotamer:

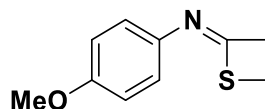
¹H NMR (400 MHz, CDCl₃) δ: 9.31 (br s, 1H, NH), 7.08 (m, 2H, Ph H-2,6), 6.90 (m, 2H, Ph H-3,5), 4.04 (q, ³*J* = 7.0 Hz, 2H, OCH₂CH₃), 2.45 (s, 3H, CH₃), 1.43 (t, ³*J* = 7.0 Hz, 3H, OCH₂CH₃).

¹³C NMR (100 MHz, CDCl₃) δ: 205.0 (C=S), 158.6 (Ph C-4), 131.5 (Ph C-1), 126.8 (Ph C-2,6), 115.2 (Ph C-3,5), 63.8 (OCH₂CH₃), 29.8 (CH₃), 14.7 (OCH₂CH₃).

¹⁵N NMR (40 MHz, CDCl₃) δ: -217.4 (NH).

HRMS (ESI), *m/z*: calcd. for C₁₀H₁₄NOS⁺: 196.0791 [M + H]⁺; found: 196.0792.

4-methoxy-*N*-[(2*Z*)-2-thietanylidene]aniline (3)



By following the general procedure, starting from 4-methoxyphenyl isothiocyanate (0.165 g, 1.0 mmol, 1.0 equiv), bromiodomethane (0.662 g, 0.22 mL, 3.0 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M in Et₂O, 1.27 mL, 2.8 mmol, 2.8 equiv) in dry THF (3 mL), compound **3** was obtained in 79% yield (0.152 g) as a brown oil after purification by column chromatography on silica gel (*n*-hexane:EtOAc 8:2).

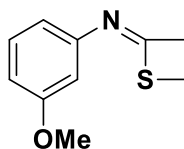
¹H NMR (400 MHz, C₆D₆) δ: 7.22 (m, 2H, Ph H-2,6), 6.77 (m, 2H, Ph H-3,5), 3.33 (m, 2H, CH₂), 3.26 (s, 3H, OCH₃) 2.39 (m, 2H, SCH₂).

¹³C NMR (100 MHz, C₆D₆) δ: 158.2 (C=N), 157.7 (Ph C-4), 141.6 (Ph C-1), 122.7 (Ph C-2,6), 114.9 (Ph C-3,5), 54.9 (OCH₃), 47.0 (CH₂), 20.4 (SCH₂).

¹⁵N NMR (40 MHz, C₆D₆) δ: -82.0 (C=N).

HRMS (ESI), *m/z*: calcd. for C₁₀H₁₂NOS⁺: 194.0634 [M + H]⁺; found: 194.0640.

3-methoxy-*N*-[(2*Z*)-2-thietanylidene]aniline (4**)**



By following the general procedure, starting from 3-methoxyphenyl isothiocyanate (0.165 g, 1.0 mmol, 1.0 equiv), bromiodomethane (0.662 g, 0.22 mL, 3.0 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M in Et₂O, 1.27 mL, 2.8 mmol, 2.8 equiv) in dry THF (3 mL), compound **4** was obtained in 75% yield (0.144 g) as a yellow oil after purification by column chromatography on silica gel (*n*-hexane:EtOAc 8:2).

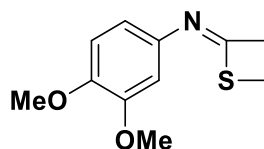
¹H NMR (400 MHz, C₆D₆) δ: 7.11 (m, 1H, Ph H-5), 6.91 (m, 1H, Ph H-2), 6.90 (m, 1H, Ph H-6), 6.62 (m, 1H, Ph H-4), 3.30 (s, 3H, OCH₃), 3.27 (m, 2H, CH₂), 2.33 (m, 2H, SCH₂).

¹³C NMR (100 MHz, C₆D₆) δ: 161.2 (Ph C-3), 160.7 (C=N), 150.0 (Ph C-1), 130.4 (Ph C-5), 113.4 (Ph C-6), 111.3 (Ph C-4), 107.1 (Ph C-2), 54.8 (OCH₃), 46.7 (CH₂), 20.1 (SCH₂).

¹⁵N NMR (40 MHz, C₆D₆) δ: -79.4 (C=N).

HRMS (ESI), *m/z*: calcd. for C₁₀H₁₂NOS⁺: 194.0634 [M + H]⁺; found: 194.0639.

3,4-dimethyl-*N*-[(2*Z*)-2-thietanylidene]aniline (5)



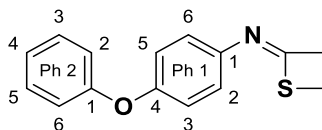
By following the general procedure, starting from 3,4-dimethoxyphenyl isothiocyanate (0.195 g, 1.0 mmol, 1.0 equiv), bromiodomethane (0.662 g, 0.22 mL, 3.0 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M in Et₂O, 1.27 mL, 2.8 mmol, 2.8 equiv) in dry THF (3 mL), compound **5** was obtained in 71% yield (0.158 g) as a brown oil after purification by column chromatography on silica gel (*n*-hexane:EtOAc 6:4).

¹H NMR (400 MHz, C₆D₆) δ: 6.88 (dd, ³*J* = 8.3 Hz, ⁴*J* = 2.3 Hz, 1H, Ph H-6), 6.85 (d, ⁴*J* = 2.3 Hz, 1H, Ph H-2), 6.59 (d, ³*J* = 8.3 Hz, 1H, Ph H-5), 3.40 (s, 3H, 3-OCH₃), 3.38 (s, 3H, 4-OCH₃), 3.37 (m, 2H, CH₂), 2.43 (m, 2H, SCH₂).

¹³C NMR (100 MHz, C₆D₆) δ: 158.3 (C=N), 150.8 (Ph C-3), 147.8 (Ph C-4), 142.0 (Ph C-1), 112.9 (Ph C-5), 112.8 (Ph C-6), 106.8 (Ph C-2), 55.8 (4-OCH₃), 55.4 (3-OCH₃), 47.0 (CH₂), 20.5 (SCH₂).

HRMS (ESI), *m/z*: calcd. for C₁₁H₁₄NO₂S⁺: 224.0740 [M + H]⁺; found: 224.0741.

4-phenoxy-*N*-[(2*Z*)-2-thietanylidene]aniline (**6**)



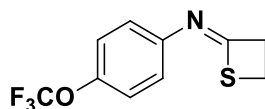
By following the general procedure, starting from 4-phenoxyphenyl isothiocyanate (0.227 g, 1.0 mmol, 1.0 equiv), bromiodomethane (0.662 g, 0.22 mL, 3.0 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M in Et₂O, 1.27 mL, 2.8 mmol, 2.8 equiv) in dry THF (3 mL), compound **6** was obtained in 74% yield (0.189 g) as a brown oil after purification by column chromatography on silica gel (*n*-hexane:EtOAc 8:2).

¹H NMR (400 MHz, C₆D₆) δ: 7.15 (m, 2H, Ph 1 H-2,6), 7.03 (m, 2H, Ph 2 H-3,5), 6.93 (m, 4H, Ph 1 H-3,5 and Ph 2 H-2,6), 6.84 (m, 1H, Ph 2 H-4) 3.27 (m, 2H, CH₂), 2.35 (m, 2H, SCH₂).

¹³C NMR (100 MHz, C₆D₆) δ: 159.7 (C=N), 158.1 (Ph 2 C-1), 155.0 (Ph 2 C-4), 143.9 (Ph 1 C-1), 130.0 (Ph 2 C-3,5), 123.3 (Ph 2 C-4), 122.8 (Ph 1 C-2,6), 120.1 (Ph 1 C-3,5), 119.1 (Ph 2 C-2,6), 46.9 (CH₂), 20.3 (SCH₂).

HRMS (ESI), *m/z*: calcd. for C₁₅H₁₄NOS⁺: 256.0791 [M + H]⁺; found: 256.0786.

***N*-[(2*Z*)-2-thietanylidene]-4-(trifluoromethoxy)aniline (**7**)**



By following the general procedure, starting from 4-(trifluoromethoxy)phenyl isothiocyanate (0.219 g, 1.0 mmol, 1.0 equiv), bromiodomethane (0.662 g, 0.22 mL, 3.0 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M in Et₂O, 1.27 mL, 2.8 mmol, 2.8 equiv) in dry THF (3 mL), compound **7** was obtained in 78% yield (0.192 g) as a brown oil after purification by column chromatography on silica gel (*n*-hexane:EtOAc 7:3).

¹H NMR (400 MHz, C₆D₆) δ: 6.96 (m, 2H, Ph H-2,6), 6.90 (m, 2H, Ph H-3,5), 3.20 (m, 2H, CH₂), 2.29 (m, 2H, SCH₂).

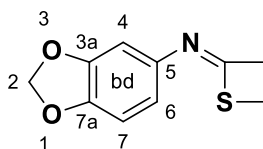
¹³C NMR (100 MHz, C₆D₆) δ: 161.9 (C=N), 147.0 (Ph C-1), 146.4 (q, ³*J*_{C,F} = 1.9 Hz, Ph C-4), 122.5 (Ph C-2,6), 122.3 (q, ⁴*J*_{C,F} = 0.9 Hz, Ph C-3,5), 121.3 (q, ¹*J*_{C,F} = 256.5 Hz, OCF₃), 46.7 (CH₂), 20.1 (SCH₂).

¹⁵N NMR (40 MHz, C₆D₆) δ: -83.5 (C=N).

¹⁹F NMR (376 MHz, C₆D₆) δ: -57.8 (s, OCF₃).

HRMS (ESI), *m/z*: calcd. for C₁₀H₉F₃NOS⁺: 248.0351 [M + H]⁺; found: 148.0350.

***N*-[(2*Z*)-2-thietanylidene]-1,3-benzodioxol-5-amine (**8**)**



By following the general procedure, starting from 3,4-methylenedioxyphenyl isothiocyanate (0.179 g, 1.0 mmol, 1.0 equiv), bromiodomethane (0.662 g, 0.22 mL, 3.0 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M in Et₂O, 1.27 mL, 2.8 mmol, 2.8 equiv) in dry THF (3 mL), compound **8** was obtained in 73% yield (0.151 g) as a yellow oil after purification by column chromatography on silica gel (*n*-hexane:EtOAc 8:2).

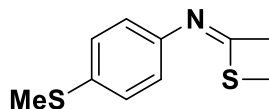
¹H NMR (400 MHz, C₆D₆) δ : 6.90 (d, ⁴*J* = 2.0 Hz, 1H, bd H-4), 6.70 (dd, ³*J* = 8.2 Hz, ⁴*J* = 2.0 Hz, 1H, bd H-6), 6.63 (d, ³*J* = 8.2 Hz, 1H, bd H-7), 5.25 (s, 2H, bd H-2), 3.24 (m, 2H, CH₂), 2.33 (m, 2H, SCH₂).

¹³C NMR (100 MHz, C₆D₆) δ : 159.2 (C=N), 148.9 (bd C-3a), 145.5 (bd C-7a), 143.0 (bd C-5), 114.4 (bd C-6), 108.8 (bd C-7), 103.0 (bd C-4), 101.2 (bd C-2), 46.8 (CH₂), 20.4 (SCH₂).

¹⁵N NMR (40 MHz, C₆D₆) δ : -81.4 (C=N).

HRMS (ESI), *m/z*: calcd. for C₁₀H₁₀NO₂S⁺: 208.0427 [M + H]⁺; found: 208.0431.

4-(methylsulfanyl)-*N*-[(2*Z*)-2-thietanylidene]aniline (9)



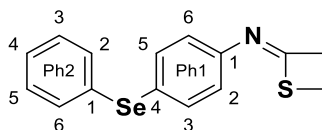
By following the general procedure, starting from 4-(methylthio)phenyl isothiocyanate (0.181 g, 1.0 mmol, 1.0 equiv), bromiodomethane (0.662 g, 0.22 mL, 3.0 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M in Et₂O, 1.27 mL, 2.8 mmol, 2.8 equiv) in dry THF (3 mL), compound **9** was obtained in 70% yield (0.147 g) as a brown oil after purification by column chromatography on silica gel (*n*-hexane:EtOAc 8:2).

¹H NMR (400 MHz, C₆D₆) δ: 7.12 (m, 2H, Ph H-3,5), 7.11 (m, 2H, Ph H-2,6), 3.27 (m, 2H, CH₂), 2.34 (m, 2H, SCH₂), 1.96 (s, 3H, SCH₃).

¹³C NMR (100 MHz, C₆D₆) δ: 160.1 (C=N), 145.8 (Ph C-1), 135.4 (Ph C-4), 128.4 (Ph C-3,5), 122.0 (Ph C-2,6), 46.9 (CH₂), 20.3 (SCH₂), 16.0 (SCH₃).

HRMS (ESI), *m/z*: calcd. for C₁₀H₁₂NS₂⁺: 210.0406 [M + H]⁺; found: 210.0405.

4-(phenylselanyl)-*N*-[(2*Z*)-2-thietanylidene]aniline (**10**)



Preparation of (4-isothiocyantophenyl)(phenyl)selane: 4-(Phenylselanyl)aniline (0.500 g, 2.0 mmol, 1.0 equiv) was dissolved in DCM (20 mL). Thiophosgene (0.463 g, 0.31 mL, 4.0 mmol, 2.0 equiv) was added dropwise at 0 °C. After the addition was complete the reaction was allowed to reach room temperature and stirred for 3 hours. The reaction mixture was diluted with DCM, washed with sat. aqueous NaHCO₃, brine and dried over Na₂SO₄. Evaporation of the solvent gave (4-isothiocyantophenyl)(phenyl)selane as an orange oil in 96% yield (0.557 g) which was used without any further purification. ¹H-NMR (200 MHz, CDCl₃) δ: 7.51 (m, 2H), 7.39-7.31 (m, 5H), 7.09 (m, 2H). ¹³C-NMR (50 MHz, CDCl₃) δ: 134.0, 133.2, 131.5, 130.2, 130.0, 129.7, 128.8, 126.6.

By following the general procedure, starting from (4-isothiocyantophenyl)(phenyl)selane (0.290 g, 1.0 mmol, 1.0 equiv), bromiodomethane (0.662 g, 0.22 mL, 3.0 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M in Et₂O, 1.27 mL, 2.8 mmol, 2.8 equiv) in dry THF (3 mL), compound **10** was obtained in 71% yield (0.226 g) as a yellow oil after purification by column chromatography on silica gel (*n*-hexane:EtOAc 8:2).

¹H NMR (400 MHz, C₆D₆) δ: 7.43 (m, 2H, Ph 1 H-3,5), 7.39 (m, 2H, Ph 2 H-2,6), 7.04 (m, 2H, Ph 1 H-2,6) 6.91 (m, 3H, Ph 2 H-3,4,5), 3.21 (m, 2H, CH₂), 2.29 (m, 2H, SCH₂).

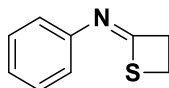
¹³C NMR (100 MHz, C₆D₆) δ: 161.2 (C=N), 148.0 (Ph 1 C-1), 135.0 (Ph 1 C-3,5), 132.8 (Ph 2 C-2,6), 132.4 (Ph 2 C-1), 129.6 (Ph 2 C-3,5), 127.2 (Ph 1 C-4, Ph 2 C-4), 122.4 (Ph 1 C-2,6), 46.8 (CH₂), 20.1 (SCH₂).

¹⁵N NMR (40 MHz, C₆D₆) δ: -81.7 (C=N).

⁷⁷Se NMR (76 MHz) δ: 410.5 (s).

HRMS (ESI), *m/z*: calcd. for C₁₅H₁₄NSSe⁺: 320.0007 [M + H]⁺; found: 320.0007.

***N*-[(2*Z*)-2-thietanylidene]aniline (**11**)**



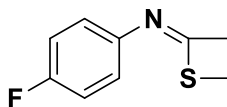
By following the general procedure, starting from phenyl isothiocyanate (0.135 g, 1.0 mmol, 1.0 equiv), bromiodomethane (0.662 g, 0.22 mL, 3.0 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M in Et₂O, 1.27 mL, 2.8 mmol, 2.8 equiv) in dry THF (3 mL), compound **11** was obtained in 76% yield (0.124 g) as a brown oil after purification by column chromatography on silica gel (*n*-hexane:EtOAc 8:2).

¹H NMR (400 MHz, C₆D₆) δ: 7.23 (m, 2H, Ph H-2,6), 7.17 (m, 2H, Ph H-3,5), 6.94 (m, 1H, Ph H-4), 3.26 (m, 2H, CH₂), 2.32 (m, 2H, SCH₂).

¹³C NMR (100 MHz, C₆D₆) δ: 160.4 (C=N), 148.6 (Ph C-1), 129.6 (Ph C-3,5), 125.3 (Ph C-4) 121.3 (Ph C-2,6), 46.8 (CH₂), 20.0 (SCH₂).

HRMS (ESI), *m/z*: calcd. for C₉H₁₀NS⁺: 164.0528 [M + H]⁺; found: 164.0530.

4-fluoro-*N*-[(2*Z*)-2-thietanylidene]aniline (12**)**



By following the general procedure, starting from 4-fluorophenyl isothiocyanate (0.153 g, 1.0 mmol, 1.0 equiv), bromiodomethane (0.662 g, 0.22 mL, 3.0 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M in Et₂O, 1.27 mL, 2.8 mmol, 2.8 equiv) in dry THF (3 mL), compound **12** was obtained in 80% yield (0.145 g) as a brown oil after purification by column chromatography on silica gel (*n*-hexane:EtOAc 8:2).

¹H NMR (400 MHz, C₆D₆) δ: 7.00 (m, 2H, Ph H-2,6), 6.78 (m, 2H, Ph H-3,5), 3.23 (m, 2H, CH₂), 2.32 (m, 2H, SCH₂).

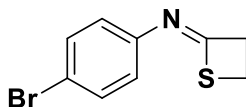
¹³C NMR (100 MHz, C₆D₆) δ: 160.6 (d, ⁶*J*_{C,F} = 1.8 Hz, C=N), 160.6 (d, ¹*J*_{C,F} = 243.4 Hz, Ph C-4), 122.8 (d, ³*J*_{C,F} = 8.1 Hz, Ph C-2,6), 116.2 (d, ²*J*_{C,F} = 22.5 Hz, Ph C-3,5), 46.8 (CH₂), 20.1 (SCH₂).

¹⁵N NMR (40 MHz, C₆D₆) δ: -82.5 (C=N).

¹⁹F NMR (376 MHz, C₆D₆) δ: -117.9 (m).

HRMS (ESI), *m/z*: calcd. for C₉H₉FNS⁺: 182.0434 [M + H]⁺; found: 182.0434.

4-bromo-*N*-[(2*Z*)-2-thietanylidene]aniline (13**)**



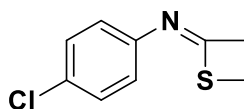
By following the general procedure, starting from 4-bromophenyl isothiocyanate (0.214 g, 1.0 mmol, 1.0 equiv), bromiodomethane (0.662 g, 0.22 mL, 3.0 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M in Et₂O, 1.27 mL, 2.8 mmol, 2.8 equiv) in dry THF (3 mL), compound **13** was obtained in 78% yield (0.189 g) as a brown oil after purification by column chromatography on silica gel (*n*-hexane:EtOAc 8:2).

¹H NMR (400 MHz, C₆D₆) δ: 7.22 (m, 2H, Ph H-3,5), 6.86 (m, 2H, Ph H-2,6), 3.19 (m, 2H, CH₂), 2.29 (m, 2H, SCH₂).

¹³C NMR (100 MHz, C₆D₆) δ: 161.6 (C=N), 147.4 (Ph C-1), 132.7 (Ph C-3,5), 123.0 (Ph C-2,6), 118.4 (Ph C-4), 46.7 (CH₂), 20.1 (SCH₂).

HRMS (ESI), *m/z*: calcd. for C₉H₉BrNS⁺: 241.9634 [M + H]⁺; found: 241.9632.

4-chloro-*N*-[(2*Z*)-2-thietanylidene]aniline (14**)**



By following the general procedure, starting from 4-chlorophenyl isothiocyanate (0.169 g, 1.0 mmol, 1.0 equiv), bromiodomethane (0.662 g, 0.22 mL, 3.0 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M in Et₂O, 1.27 mL, 2.8 mmol, 2.8 equiv) in dry THF (3 mL), compound **14** was obtained in 77% yield (0.152 g) as a brown oil after purification by column chromatography on silica gel (*n*-hexane:EtOAc 8:2).

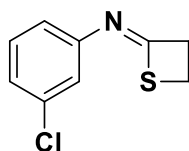
¹H NMR (400 MHz, C₆D₆) δ: 7.07 (m, 2H, Ph H-3,5), 6.93 (m, 2H, Ph H-2,6), 3.20 (m, 2H, CH₂), 2.29 (m, 2H, SCH₂).

¹³C NMR (100 MHz, C₆D₆) δ: 161.5 (C=N), 146.9 (Ph C-1), 130.6 (Ph C-4), 129.7 (Ph C-3,5), 122.6 (Ph C-2,6), 46.7 (CH₂), 20.1 (SCH₂).

¹⁵N NMR (40 MHz, C₆D₆) δ: -82.3 (C=N).

HRMS (ESI), *m/z*: calcd. for C₉H₉ClNS⁺: 198.0139 [M + H]⁺; found: 198.0139.

3-chloro-*N*-[(2*Z*)-2-thietanylidene]aniline (15**)**



By following the general procedure, starting from 3-chlorophenyl isothiocyanate (0.169 g, 1.0 mmol, 1.0 equiv), bromiodomethane (0.662 g, 0.22 mL, 3.0 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M in Et₂O, 1.27 mL, 2.8 mmol, 2.8 equiv) in dry THF (3 mL), compound **15** was obtained in 74% yield (0.146 g) as a brown oil after purification by column chromatography on silica gel (*n*-hexane:EtOAc 8:2).

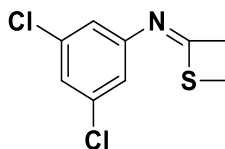
¹H NMR (400 MHz, C₆D₆) δ: 7.27 (t, *J* = 2.0 Hz, 1H, Ph H-2), 6.93 (m, 1H, Ph H-6), 6.90 (m, 1H, Ph H-4), 6.83 (m, 1H, Ph H-5), 3.16 (m, 2H, CH₂), 2.25 (m, 2H, SCH₂).

¹³C NMR (100 MHz, C₆D₆) δ: 162.7 (C=N), 149.9 (Ph C-1), 135.3 (Ph C-3), 130.7 (Ph C-5), 125.2 (Ph C-4), 121.5 (Ph C-2), 119.4 (Ph C-6), 46.5 (CH₂), 20.0 (SCH₂).

¹⁵N NMR (40 MHz, C₆D₆) δ: -81.7 (C=N).

HRMS (ESI), *m/z*: calcd. for C₉H₉ClNS⁺: 198.0139 [M + H]⁺; found: 198.0137.

3,5-dichloro-*N*-[(2*Z*)-2-thietanylidene]aniline (16**)**



By following the general procedure, starting from 3,5-dichlorophenyl isothiocyanate (0.204 g, 1.0 mmol, 1.0 equiv), bromiodomethane (0.662 g, 0.22 mL, 3.0 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M in Et₂O, 1.27 mL, 2.8 mmol, 2.8 equiv) in dry THF (3 mL), compound **16** was obtained in 82% yield (0.190 g) as a yellow solid (mp: 55-58 °C) after purification by column chromatography on silica gel (*n*-hexane:DCM 3:7).

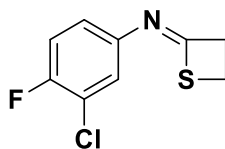
¹H NMR (400 MHz, C₆D₆) δ: 7.00 (d, ⁴*J* = 1.9 Hz, 2H, Ph H-2,6), 6.90 (t, ⁴*J* = 1.9 Hz, 1H, Ph H-4), 3.08 (m, 2H, CH₂), 2.19 (m, 2H, SCH₂).

¹³C NMR (100 MHz, C₆D₆) δ: 164.6 (C=N), 150.5 (Ph C-1), 135.9 (Ph C-3,5), 125.1 (Ph C-4), 119.8 (Ph C-2,6), 46.3 (CH₂), 20.0 (SCH₂).

¹⁵N NMR (40 MHz, C₆D₆) δ: -84.8 (C=N).

HRMS (ESI), *m/z*: calcd. for C₉H₈Cl₂NS⁺: 231.9749 [M + H]⁺; found: 231.9739.

3-chloro-4-fluoro-*N*-[(2*Z*)-2-thietanylidene]aniline (17**)**



By following the general procedure, starting from 3-chloro-4-fluorophenyl isothiocyanate (0.188 g, 1.0 mmol, 1.0 equiv), bromiodomethane (0.662 g, 0.22 mL, 3.0 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M in Et₂O, 1.27 mL, 2.8 mmol, 2.8 equiv) in dry THF (3 mL), compound **17** was obtained in 75% yield (0.162 g) as a brown oil after purification by column chromatography on silica gel (*n*-hexane:EtOAc 8:2).

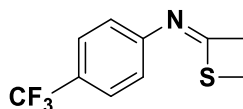
¹H NMR (400 MHz, C₆D₆) δ : 7.17 (m, 1H, Ph H-2), 6.73 (ddd, ³*J* = 8.7 Hz, ⁴*J* = 4.3 Hz, ⁴*J* = 2.6 Hz, 1H, Ph H-6), 6.61 (t, ³*J* = 8.7 Hz, 1H, Ph H-5) 3.16 (m, 2H, CH₂), 2.27 (m, 2H, SCH₂).

¹³C NMR (100 MHz, C₆D₆) δ : 162.6 (C=N), 155.9 (d, ¹*J*_{C,F} = 246.3 Hz, Ph C-4), 145.1 (d, ⁴*J*_{C,F} = 3.4 Hz, Ph C-1), 123.2 (Ph C-2), 121.8 (d, ²*J*_{C,F} = 18.7 Hz, Ph C-3), 120.9 (d, ³*J*_{C,F} = 6.9 Hz, Ph C-6), 117.3 (d, ²*J*_{C,F} = 22.0 Hz, Ph C-5), 46.6 (CH₂), 20.1 (SCH₂).

¹⁹F NMR (376 MHz, C₆D₆) δ : -120.3 (m).

HRMS (ESI), *m/z*: calcd. for C₉H₈ClFNS⁺: 216.0045 [M + H]⁺; found: 216.0046.

***N*-[(2*Z*)-2-thietanylidene]-4-(trifluoromethyl)aniline (**18**)**



By following the general procedure, starting from 4-trifluoromethylphenyl isothiocyanate (0.203 g, 1.0 mmol, 1.0 equiv), bromiodomethane (0.662 g, 0.22 mL, 3.0 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M in Et₂O, 1.27 mL, 2.8 mmol, 2.8 equiv) in dry THF (3 mL), compound **18** was obtained in 72% yield (0.166 g) as a brown oil after purification by column chromatography on silica gel (*n*-hexane:EtOAc 8:2).

¹H NMR (400 MHz, C₆D₆) δ : 7.31 (m, 2H, Ph H-3,5), 6.98 (m, 2H, Ph H-2,6), 3.18 (m, 2H, CH₂), 2.27 (m, 2H, SCH₂).

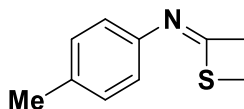
¹³C NMR (100 MHz, C₆D₆) δ : 163.2 (C=N), 151.5 (Ph C-1), 128.3 (Ph C-4), 126.9 (q, ³*J*_{C,F} = 3.8 Hz, Ph C-3,5), 125.1 (q, ¹*J*_{C,F} = 271.6 Hz, CF₃), 121.3 (Ph C-2,6), 46.6 (CH₂), 19.9 (SCH₂).

¹⁵N NMR (40 MHz, C₆D₆) δ : -81.8 (C=N).

¹⁹F NMR (376 MHz, C₆D₆) δ : -61.7 (s, CF₃).

HRMS (ESI), *m/z*: calcd. for C₁₀H₉F₃NS⁺: 232.0402 [M + H]⁺; found: 232.0407.

4-methyl-*N*-[(2Z)-2-thietanylidene]aniline (19**)**



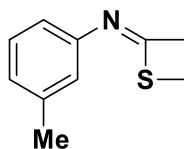
By following the general procedure, starting from *p*-tolyl isothiocyanate (0.149 g, 1.0 mmol, 1.0 equiv), bromiodomethane (0.662 g, 0.22 mL, 3.0 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M in Et₂O, 1.27 mL, 2.8 mmol, 2.8 equiv) in dry THF (3 mL), compound **19** was obtained in 76% yield (0.135 g) as a brown oil after purification by column chromatography on silica gel (*n*-hexane:EtOAc 8:2).

¹H NMR (400 MHz, C₆D₆) δ: 7.20 (m, 2H, Ph H-2,6), 6.99 (m, 2H, Ph H-3,5), 3.30 (m, 2H, CH₂), 2.35 (m, 2H, SCH₂), 2.07 (s, 3H, CH₃).

¹³C NMR (100 MHz, C₆D₆) δ: 159.4 (C=N), 146.1 (Ph C-1), 134.6 (Ph C-4), 130.2 (Ph C-3,5), 121.3 (Ph C-2,6), 46.9 (CH₂), 20.9 (CH₃), 20.2 (SCH₂).

HRMS (ESI), *m/z*: calcd. for C₁₀H₁₂NS⁺: 178.0685 [M + H]⁺; found: 178.0688.

3-methyl-*N*-[(2*Z*)-2-thietanylidene]aniline (20**)**



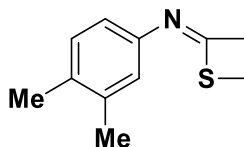
By following the general procedure, starting from 3-tolyl isothiocyanate (0.149 g, 1.0 mmol, 1.0 equiv), bromiodomethane (0.662 g, 0.22 mL, 3.0 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M in Et₂O, 1.27 mL, 2.8 mmol, 2.8 equiv) in dry THF (3 mL), compound **20** was obtained in 79% yield (0.140 g) as a brown oil after purification by column chromatography on silica gel (*n*-hexane:EtOAc 9:1).

¹H NMR (400 MHz, C₆D₆) δ: 7.13 (m, 1H, Ph H-5), 7.11 (m, 1H, Ph H-6), 7.08 (m, 1H, Ph H-2), 6.80 (m, 1H, Ph H-4), 3.30 (m, 2H, CH₂), 2.35 (m, 2H, SCH₂), 2.10 (s, 3H, CH₃).

¹³C NMR (100 MHz, C₆D₆) δ: 160.0 (C=N), 148.7 (Ph C-1), 139.3 (Ph C-3), 129.5 (Ph C-5), 126.1 (Ph C-4), 122.1 (Ph C-2), 118.2 (Ph C-6), 46.8 (CH₂), 21.4 (CH₃), 20.0 (SCH₂).

HRMS (ESI), *m/z*: calcd. for C₁₀H₁₂NS⁺: 178.0685 [M + H]⁺; found: 178.0692.

3,4-dimethyl-*N*-[(2*Z*)-2-thietanylidene]aniline (21**)**



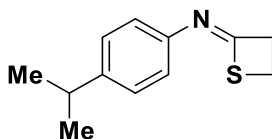
By following the general procedure, starting from 3,4-dimethylphenyl isothiocyanate (0.163 g, 1.0 mmol, 1.0 equiv), bromiodomethane (0.662 g, 0.22 mL, 3.0 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M in Et₂O, 1.27 mL, 2.8 mmol, 2.8 equiv) in dry THF (3 mL), compound **21** was obtained in 73% yield (0.140 g) as a brown oil after purification by column chromatography on silica gel (*n*-hexane:EtOAc 9:1).

¹H NMR (400 MHz, C₆D₆) δ: 7.11 (m, 1H, Ph H-2), 7.09 (m, 1H, Ph H-6), 7.00 (m, 1H, Ph H-5), 3.33 (m, 2H, CH₂) 2.38 (m, 2H, SCH₂) 2.00 (s, 3H, 3-CH₃), 1.97 (s, 3H, 4-CH₃).

¹³C NMR (100 MHz, C₆D₆) δ: 159.1 (C=N), 146.5 (Ph C-1), 137.6 (Ph C-3), 133.3 (Ph C-4), 130.7 (Ph C-5), 122.8 (Ph C-2), 118.6 (Ph C-6), 46.5 (CH₂), 20.2 (SCH₂), 19.9 (3-CH₃), 19.2 (4-CH₃).

HRMS (ESI), *m/z*: calcd. for C₁₁H₁₄NS⁺: 192.0841 [M + H]⁺; found: 192.0845.

4-isopropyl-*N*-[(2*Z*)-2-thietanylidene]aniline (**22**)



By following the general procedure, starting from 4-isopropylphenyl isothiocyanate (0.177 g, 1.0 mmol, 1.0 equiv), bromiodomethane (0.662 g, 0.22 mL, 3.0 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M in Et₂O, 1.27 mL, 2.8 mmol, 2.8 equiv) in dry THF (3 mL), compound **22** was obtained in 71% yield (0.146 g) as a brown oil after purification by column chromatography on silica gel (*n*-hexane:EtOAc 9:1).

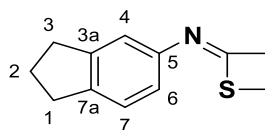
¹H NMR (400 MHz, C₆D₆) δ: 7.26 (m, 2H, Ph H-2,6), 7.09 (m, 2H, Ph H-3,5), 3.30 (m, 2H, CH₂), 2.67 (sept, ³*J* = 6.9 Hz, 1H, CH), 2.36 (m, 2H, SCH₂), 1.10 (d, ³*J* = 6.9 Hz, 6H, CH₃).

¹³C NMR (100 MHz, C₆D₆) δ: 159.3 (C=N), 146.4 (Ph C-1), 145.7 (Ph C-4), 127.6 (Ph C-3,5), 121.4 (Ph C-2,6), 46.9 (CH₂), 34.0 (CH), 24.2 (CH₃), 20.2 (SCH₂).

¹⁵N NMR (40 MHz, C₆D₆) δ: -80.1 (C=N).

HRMS (ESI), *m/z*: calcd. for C₁₂H₁₆NS⁺: 206.0998 [M + H]⁺; found: 206.1005.

***N*-[(2*Z*)-2-thietanylidene]-5-indanamine (**23**)**



By following the general procedure, starting from 5-indanyl isothiocyanate (0.175 g, 1.0 mmol, 1.0 equiv), bromiodomethane (0.662 g, 0.22 mL, 3.0 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M in Et₂O, 1.27 mL, 2.8 mmol, 2.8 equiv) in dry THF (3 mL), compound **23** was obtained in 77% yield (0.157 g) as a brown oil after purification by column chromatography on silica gel (*n*-hexane:EtOAc 9:1).

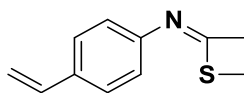
¹H NMR (400 MHz, C₆D₆) δ: 7.19 (s, 1H, indanyl H-4), 7.14 (m, 1H, indanyl H-6), 7.10 (m, 1H, indanyl H-7), 3.33 (m, 2H, CH₂), 2.66 (m, 2H, indanyl H-3), 2.63 (m, 2H, indanyl H-1), 2.38 (m, 2H, SCH₂), 1.76 (m, 2H, indanyl H-2).

¹³C NMR (100 MHz, C₆D₆) δ: 158.9 (C=N), 147.1 (indanyl C-5), 145.6 (indanyl C-3a), 141.0 (indanyl C-7a), 125.2 (indanyl C-7), 119.4 (indanyl C-6), 117.3 (indanyl C-4), 46.9 (CH₂), 33.2 (indanyl C-3), 32.7 (indanyl C-1), 25.9 (indanyl C-2), 20.2 (SCH₂).

¹⁵N NMR (40 MHz, C₆D₆) δ: -79.1 (C=N).

HRMS (ESI), *m/z*: calcd. for C₁₂H₁₄NS⁺: 204.0841 [M + H]⁺; found: 204.0845.

***N*-[(**2Z**)-2-thietanylidene]-4-vinylaniline (**24**)**



By following the general procedure, starting from 4-vinylphenyl isothiocyanate^[1] (0.161 g, 1.0 mmol, 1.0 equiv), bromiodomethane (0.662 g, 0.22 mL, 3.0 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M in Et₂O, 1.27 mL, 2.8 mmol, 2.8 equiv) in dry THF (3 mL), compound **24** was obtained in 70% yield (0.132 g) as a brown oil after purification by column chromatography on silica gel (*n*-hexane:EtOAc 8:2).

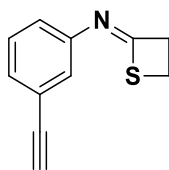
¹H NMR (400 MHz, C₆D₆) δ: 7.23 (m, 2H, Ph H-3,5), 7.17 (m, 2H, Ph H-2,6), 6.54 (dd, ³*J* = 17.6, 10.9 Hz, 1H, CH=CH₂), 5.54 (dd, ³*J* = 17.6 Hz, ²*J* = 1.0 Hz, 1H, CH=CH₂ trans), 5.04 (dd, ³*J* = 10.9 Hz, ²*J* = 1.0 Hz, 1H, CH=CH₂ cis), 3.28 (m, 2H, CH₂), 2.34 (m, 2H, SCH₂).

¹³C NMR (100 MHz, C₆D₆) δ: 160.5 (C=N), 148.0 (Ph C-1), 136.9 (CH=CH₂), 134.9 (Ph C-4), 127.7 (Ph C-3,5), 121.5 (Ph C-2,6), 113.0 (CH=CH₂), 46.8 (CH₂), 20.2 (SCH₂).

¹⁵N NMR (40 MHz, C₆D₆) δ: -80.6 (C=N).

HRMS (ESI), *m/z*: calcd. for C₁₁H₁₂NS⁺: 190.0685 [M + H]⁺; found: 190.0684.

3-ethynyl-*N*-[(2*Z*)-2-thietanylidene]aniline (25**)**



By following the general procedure, starting from 3-ethynylphenyl isothiocyanate^[2] (0.159 g, 1.0 mmol, 1.0 equiv), bromiodomethane (0.662 g, 0.22 mL, 3.0 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M in Et₂O, 1.27 mL, 2.8 mmol, 2.8 equiv) in dry THF (3 mL), compound **25** was obtained in 81% yield (0.152 g) as a yellow oil after purification by column chromatography on silica gel (*n*-hexane:DCM 3:7).

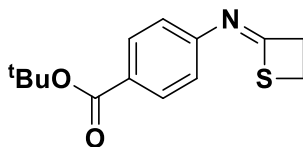
¹H NMR (400 MHz, C₆D₆) δ : 7.50 (m, 1H, Ph H-2), 7.20 (m, 1H, Ph H-4), 7.07 (m, 1H, Ph H-6), 6.93 (m, 1H, Ph H-5), 3.18 (m, 2H, CH₂), 2.70 (s, 1H, C $\equiv$ CH), 2.26 (m, 2H, SCH₂).

¹³C NMR (100 MHz, C₆D₆) δ : 162.0 (C=N), 148.7 (Ph C-1), 129.7 (Ph C-5), 129.0 (Ph C-4), 124.8 (Ph C-2), 123.9 (Ph C-3), 121.9 (Ph C-6), 83.7 (C $\equiv$ CH), 78.1 (C $\equiv$ CH), 46.6 (CH₂), 20.0 (SCH₂).

¹⁵N NMR (40 MHz, C₆D₆) δ : -81.8 (C=N).

HRMS (ESI), *m/z*: calcd. for C₁₁H₁₀NS⁺: 188.0528 [M + H]⁺; found: 188.0525.

2-methyl-2-propanyl-4-[(2Z)-2-thietanylideneamino]benzoate (26)



By following the general procedure, starting from *tert*-butyl 4-isothiocyanatobenzoate (0.235 g, 1.0 mmol, 1.0 equiv), bromiodomethane (0.662 g, 0.22 mL, 3.0 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M in Et₂O, 1.27 mL, 2.8 mmol, 2.8 equiv) in dry THF (3 mL), compound **26** was obtained in 80% yield (0.211 g) as a yellowish solid (mp: 52-55 °C) after purification by column chromatography on silica gel (*n*-hexane:EtOAc 6:4).

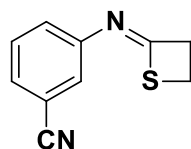
¹H NMR (400 MHz, C₆D₆) δ: 8.17 (m, 2H, Ph H-2,6), 7.12 (m, 2H, Ph H-3,5), 3.20 (m, 2H, CH₂), 2.27 (m, 2H, SCH₂), 1.47 (s, 9H, CCH₃).

¹³C NMR (100 MHz, C₆D₆) δ: 165.3 (C=O), 162.6 (C=N), 152.3 (Ph C-4), 131.5 (Ph C-2,6), 129.2 (Ph C-1), 120.8 (Ph C-3,5), 80.2 (CCH₃), 46.6 (CH₂), 28.2 (CCH₃), 19.9 (SCH₂).

¹⁵N NMR (40 MHz, C₆D₆) δ: -80.4 (C=N).

HRMS (ESI), *m/z*: calcd. for C₁₄H₁₇NNaO₂S⁺: 286.0872 [M + Na]⁺; found: 286.0868.

3-[(2Z)-2-thietanylideneamino]benzonitrile (**27**)



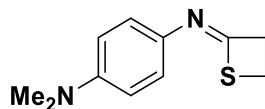
By following the general procedure, starting from 3-cyanophenyl isothiocyanate (0.160 g, 1.0 mmol, 1.0 equiv), bromiodomethane (0.662 g, 0.22 mL, 3.0 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M in Et₂O, 1.27 mL, 2.8 mmol, 2.8 equiv) in dry THF (3 mL), compound **27** was obtained in 72% yield (0.136 g) as a brown solid (mp: 122-125 °C) after purification by column chromatography on silica gel (*n*-hexane:EtOAc 7:3).

¹H NMR (400 MHz, C₆D₆) δ: 7.16 (m, 1H, Ph H-2), 6.97 (m, 1H, Ph H-6), 6.78 (m, 1H, Ph H-4), 6.67 (m, 1H, Ph H-5), 3.12 (m, 2H, CH₂), 2.23 (m, 2H, SCH₂).

¹³C NMR (100 MHz, C₆D₆) δ: 163.9 (C=N), 149.0 (Ph C-3), 130.2 (Ph C-5), 128.3 (Ph C-6), 125.0 (Ph C-4), 124.3 (Ph C-2), 118.6 (C≡N), 114.0 (Ph C-1), 46.4 (CH₂), 19.9 (SCH₂).

HRMS (ESI), *m/z*: calcd. for C₁₀H₉N₂S⁺: 189.0481 [M + H]⁺; found: 189.0478.

***N,N*-dimethyl-*N'*-[(2*Z*)-2-thietanylidene]-1,4-benzenediamine (**28**)**



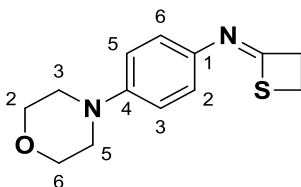
By following the general procedure, starting from 4-(*N,N*-dimethylamino)phenyl isothiocyanate (0.178 g, 1.0 mmol, 1.0 equiv), bromiodomethane (0.662 g, 0.22 mL, 3.0 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M in Et₂O, 1.27 mL, 2.8 mmol, 2.8 equiv) in dry THF (3 mL), compound **28** was obtained in 75% yield (0.155 g) as a brown solid (mp: 78-80 °C) after purification by column chromatography on silica gel (*n*-hexane:EtOAc 8:2).

¹H NMR (400 MHz, C₆D₆) δ: 7.35 (m, 2H, Ph H-3,5), 6.58 (m, 2H, Ph H-2,6), 3.40 (m, 2H, CH₂), 2.47 (s, 6H, CH₃), 2.45 (m, 2H, SCH₂).

¹³C NMR (100 MHz, C₆D₆) δ: 155.4 (C=N), 148.8 (Ph C-1), 138.1 (Ph C-4), 122.8 (Ph C-3,5), 113.6 (Ph C-2,6), 47.4 (CH₂), 40.4 (CH₃), 20.7 (SCH₂).

HRMS (ESI), *m/z*: calcd. for C₁₁H₁₅N₂S⁺: 207.0950 [M + H]⁺; found: 207.0953.

4-(4-morpholinyl)-*N*-[(2*Z*)-2-thietanylidene]aniline (29)



By following the general procedure, starting from 4-morpholinophenyl isothiocyanate (0.220 g, 1.0 mmol, 1.0 equiv), bromiodomethane (0.662 g, 0.22 mL, 3.0 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M in Et₂O, 1.27 mL, 2.8 mmol, 2.8 equiv) in dry THF (3 mL), compound **29** was obtained in 82% yield (0.195 g) as a yellowish solid (mp: 115-117 °C) after purification by column chromatography on silica gel (*n*-hexane:EtOAc 6:4).

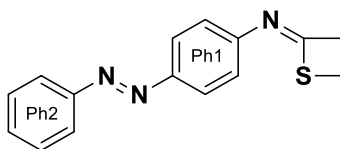
¹H NMR (400 MHz, C₆D₆) δ: 7.30 (m, 2H, Ph H-2,6), 6.66 (m, 2H, Ph H-3,5), 3.52 (m, 4H, morph H-2,6), 3.38 (m, 2H, CH₂), 2.69 (m, 4H, morph H-3,5), 2.43 (m, 2H, SCH₂).

¹³C NMR (100 MHz, C₆D₆) δ: 157.4 (C=N), 149.4 (Ph C-4), 140.8 (Ph C-1), 122.5 (Ph C-2,6), 116.7 (Ph C-3,5), 66.9 (morph C-2,6), 49.6 (morph C-3,5), 47.2 (CH₂), 20.5 (SCH₂).

¹⁵N NMR (40 MHz, C₆D₆) δ: -318.9 (morph), -81.9 (C=N).

HRMS (ESI), *m/z*: calcd. for C₁₃H₁₇N₂OS⁺: 249.1056 [M + H]⁺; found: 249.1064.

4-[(E)-phenyldiazenyl]-N-[(2Z)-2-thietanylidene]aniline (30)



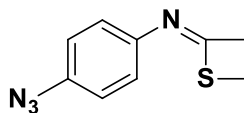
By following the general procedure, starting from 4-(phenylazo)phenyl isothiocyanate (0.239 g, 1.0 mmol, 1.0 equiv), bromiodomethane (0.662 g, 0.22 mL, 3.0 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M in Et₂O, 1.27 mL, 2.8 mmol, 2.8 equiv) in dry THF (3 mL), compound **30** was obtained in 70% yield (0.187 g) as an orange oil after purification by column chromatography on silica gel (*n*-hexane:EtOAc 8:2).

¹H NMR (400 MHz, C₆D₆) δ: 8.07 (m, 2H, Ph 1 H-3,5), 8.03 (m, 2H, Ph 2 H-2,6), 7.25 (m, 2H, Ph 1 H-2,6), 7.19 (m, 2H, Ph 2 H-3,5), 7.10 (m, 1H, Ph 2 H-4), 3.23 (m, 2H, CH₂), 2.30 (m, 2H, SCH₂).

¹³C NMR (100 MHz, C₆D₆) δ: 162.2 (C=N), 153.4 (Ph2 C-1), 151.0 (Ph 1 C-1), 150.6 (Ph 1 C-4), 130.9 (Ph2 C-4), 129.3 (Ph 2 C-3,5), 124.9 (Ph 1 C-3,5), 123.3 (Ph2 C-2,6), 121.9 (Ph 1 C-2,6), 46.7 (CH₂), 20.1 (SCH₂).

HRMS (ESI), *m/z*: calcd. for C₁₅H₁₄N₃S⁺: 268.0903 [M + H]⁺; found: 268.0902.

4-azido-*N*-[(2*Z*)-2-thietanylidene]aniline (31**)**



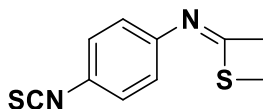
By following the general procedure, starting from 4-azidophenyl isothiocyanate (0.176 g, 1.0 mmol, 1.0 equiv), bromiodomethane (0.662 g, 0.22 mL, 3.0 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M in Et₂O, 1.27 mL, 2.8 mmol, 2.8 equiv) in dry THF (3 mL), compound **31** was obtained in 69% yield (0.141 g) as a brown oil after purification by column chromatography on silica gel (*n*-hexane:EtOAc 8:2).

¹H NMR (400 MHz, C₆D₆) δ: 7.02 (m, 2H, Ph H-2,6), 6.67 (m, 2H, Ph H-3,5), 3.25 (m, 2H, CH₂), 2.34 (m, 2H, SCH₂).

¹³C NMR (100 MHz, C₆D₆) δ: 160.6 (C=N), 145.3 (Ph C-1), 137.0 (Ph C-4), 122.8 (Ph C-2,6), 120.2 (Ph C-3,5), 46.8 (CH₂), 20.3 (SCH₂).

HRMS (ESI), *m/z*: calcd. for C₉H₉N₄S⁺: 205.0542 [M + H]⁺; found: 205.0541.

4-isothiocyanato-N-[(2Z)-2-thietanylidene]aniline (**32**)



By following the general procedure, starting from 1,4-phenylene diisothiocyanate (0.192 g, 1.0 mmol, 1.0 equiv), bromiodomethane (0.662 g, 0.22 mL, 3.0 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M in Et₂O, 1.27 mL, 2.8 mmol, 2.8 equiv) in dry THF (3 mL), compound **32** was obtained in 71% yield (0.156 g) as a white solid (mp: 102-104 °C) after purification by column chromatography on silica gel (*n*-hexane:EtOAc 9:1).

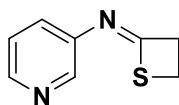
¹H NMR (400 MHz, C₆D₆) δ: 6.81 (m, 2H, Ph H-2,6), 6.55 (m, 2H, Ph H-3,5), 3.18 (m, 2H, CH₂), 2.29 (m, 2H, SCH₂).

¹³C NMR (100 MHz, C₆D₆) δ: 162.1 (C=N), 147.1 (Ph C-1), 127.9 (Ph C-4), 126.9 (Ph C-3,5), 122.1 (Ph C-2,6), 46.7 (CH₂), 20.1 (SCH₂).

¹⁵N NMR (40 MHz, C₆D₆) δ: -82.9 (C=N).

HRMS (ESI), *m/z*: calcd. for C₁₀H₉N₂S₂⁺: 221.0202 [M + H]⁺; found: 221.0198.

***N*-[(2*Z*)-2-thietanylidene]-3-pyridinamine (**33**)**



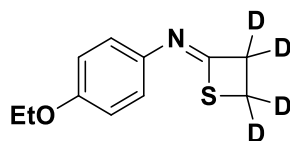
By following the general procedure, starting from pyridine-3-isothiocyanate (0.136 g, 1.0 mmol, 1.0 equiv), bromiodomethane (0.662 g, 0.22 mL, 3.0 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M in Et₂O, 1.27 mL, 2.8 mmol, 2.8 equiv) in dry THF (3 mL), compound **33** was obtained in 74% yield (0.122 g) as a brown oil after purification by column chromatography on silica gel (*n*-hexane:EtOAc 6:4).

¹H NMR (400 MHz, C₆D₆) δ : 8.76 (dd, ⁴*J* = 2.6 Hz, ⁵*J* = 0.8 Hz, 1H, Pyr H-2), 8.34 (dd, ³*J* = 4.7 Hz, ⁴*J* = 1.6 Hz, 1H, Pyr H-6), 7.18 (ddd, ³*J* = 8.1 Hz, ⁴*J* = 2.6 Hz, ⁴*J* = 1.6 Hz, 1H, Pyr H-4), 6.72 (dd, ³*J* = 8.1 Hz, ³*J* = 4.7 Hz, ⁵*J* = 0.8 Hz, 1H, Pyr H-5), 3.15 (m, 2H, CH₂), 2.24 (m, 2H, SCH₂).

¹³C NMR (100 MHz, C₆D₆) δ : 163.5 (C=N), 146.7 (Pyr C-6), 144.3 (Pyr C-3), 143.7 (Pyr C-2), 127.4 (Pyr C-4), 123.8 (Pyr C-5), 46.7 (CH₂), 19.9 (SCH₂).

HRMS (ESI), *m/z*: calcd. for C₈H₉N₂S⁺: 165.0481 [M + H]⁺; found: 165.0489.

4-ethoxy-*N*-[(2Z)-(2H₄)-2-thietanylidene]aniline (34**)**



By following the general procedure, starting from 4-ethoxyphenyl isothiocyanate (0.179 g, 1.0 mmol, 1.0 equiv), diiodomethane-*d*₂ (0.810 g, 0.24 mL, 3.0 mmol, 3.0 equiv) and MeLi-LiBr (2.2 M in Et₂O, 1.27 mL, 2.8 mmol, 2.8 equiv) in dry THF (3 mL), compound **34** was obtained in 71% yield (0.150 g) as a brown solid (mp: 64–66 °C) after purification by column chromatography on silica gel (*n*-hexane:EtOAc 8:2).

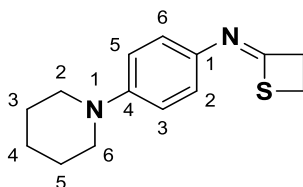
¹H NMR (400 MHz, C₆D₆) δ: 7.24 (m, 2H, Ph H-2,6), 6.81 (m, 2H, Ph H-3,5), 3.54 (q, ³*J* = 7.0 Hz, 2H, OCH₂), 1.09 (t, ³*J* = 7.0 Hz, 3H, CH₃).

¹³C NMR (100 MHz, C₆D₆) δ: 157.9 (C=N), 157.1 (Ph C-4), 141.5 (Ph C-1), 122.7 (Ph C-2,6), 115.4 (Ph C-3,5), 63.4 (OCH₂), 46.3 (quint, ¹*J*_{C,D} = 21.0 Hz, CH₂), 19.6 (quint, ¹*J*_{C,D} = 19.6 Hz, SCH₂), 14.9 (CH₃).

¹⁵N NMR (40 MHz, C₆D₆) δ: -81.4 (C=N).

HRMS (ESI), *m/z*: calcd. for C₁₁H₁₀D₄NOS⁺: 212.1042 [M + H]⁺; found: 212.1036.

4-(1-piperidiny)-*N*-[(*2Z*)-2-thietanylidene]aniline (**35**)



4-bromo-*N*-[(*2Z*)-2-thietanylidene]aniline (0.170 g, 0.7 mmol, 1.0 equiv), dichlorobis(tri-*o*-tolylphosphine)palladium(II) (0.028 g, 5 mol%), and piperidine (0.060 g, 0.07 mL, 0.7 mmol, 1.0 equiv) were dissolved in toluene. A solution of lithium bis(trimethylsilyl)amide (1 M in THF, 0.84 mL, 0.8 mmol, 1.2 equiv) was added and the mixture was heated at 110 °C for 18 hours. The reaction mixture was filtered on celite. The filtrate was washed two times with water, dried over Na₂SO₄ and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane:EtOAc 8:2) to give compound **35** in 79% yield (0.136 g) as a brown oil.

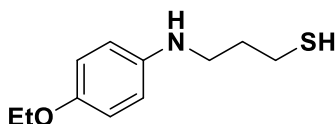
¹H NMR (400 MHz, C₆D₆) δ: 7.32 (m, 2H, Ph H-2,6), 6.80 (m, 2H, Ph H-3,5), 3.37 (m, 2H, CH₂), 2.86 (m, 4H, piperidine H-2,6), 2.43 (m, 2H, SCH₂), 1.43 (m, 4H, piperidine H-3,5), 1.28 (m, 2H, piperidine H-4).

¹³C NMR (100 MHz, C₆D₆) δ: 156.6 (C=N), 150.4 (Ph C-4), 140.2 (Ph C-1), 122.5 (Ph C-2,6), 117.6 (Ph C-3,5), 50.9 (piperidine C-2,6), 47.2 (CH₂), 26.1 (piperidine C-3,5), 24.6 (piperidine C-4), 20.5 (SCH₂).

¹⁵N NMR (40 MHz, C₆D₆) δ: -314.2 (piperidine), -81.6 (C=N).

HRMS (ESI), *m/z*: calcd. for C₁₄H₁₉N₂S⁺: 247.1263 [M + H]⁺; found: 247.1270.

3-[(4-ethoxyphenyl)amino]-1-propanethiol (**36**)



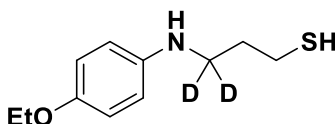
To a solution of 4-ethoxy-*N*-[(2*Z*)-2-thietanylidene]aniline (0.145 g, 0.7 mmol, 1.0 equiv) in dry THF (2 mL) a solution of LiAlH₄ (1M in THF, 0.7 mL, 0.7 mmol, 1.0 equiv) was added dropwise at 0 °C. The reaction mixture was allowed to reach room temperature and then stirred for 1.5 hours before being quenched with water. The reaction mixture was extracted exhaustively with Et₂O (3 x 10 mL). The combined organic extracts were washed with brine, dried over Na₂SO₄ and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane:EtOAc 8:2) to give compound **36** in 95% yield (0.140 g) as a yellow oil.

¹H NMR (400 MHz, C₆D₆) δ: 6.78 (m, 2H, Ph H-3,5), 6.59 (m, 2H, Ph H-2,6), 3.96 (q, ³*J* = 7.0 Hz, 2H, OCH₂CH₃), 3.22 (t, ³*J* = 6.9 Hz, 2H, CH₂CH₂CH₂SH), 2.65 (t, ³*J* = 7.0 Hz, 2H, CH₂CH₂CH₂SH), 1.91 (m, 2H, CH₂CH₂CH₂SH), 1.37 (t, ³*J* = 7.0 Hz, 3H, OCH₂CH₃).

¹³C NMR (100 MHz, C₆D₆) δ: 151.5 (Ph C-4), 142.2 (Ph C-1), 115.8 (Ph C-3,5), 114.2 (Ph C-2,6), 64.1 (OCH₂CH₃), 43.4 (CH₂CH₂CH₂SH), 33.5 (CH₂CH₂CH₂SH), 22.3 (CH₂CH₂CH₂SH), 15.0 (OCH₂CH₃).

HRMS (ESI), *m/z*: calcd. for C₁₁H₁₆NOS⁺: 212.1104 [M + H]⁺; found: 212.1109.

3-[(4-ethoxyphenyl)amino](3,3-²H₂)-1-propanethiol (**37**)



To a solution of 4-ethoxy-*N*-[(2*Z*)-2-thietanylidene]aniline (0.124 g, 0.6 mmol, 1.0 equiv) in dry THF (2 mL) solid LiAlH₄-*d*₄ (0.025 g, 0.6 mmol, 1.0 equiv) was added in one portion at 0 °C. The reaction mixture was allowed to reach room temperature and then stirred for 1.5 hours before being quenched with water. The reaction mixture was extracted exhaustively with Et₂O (3 x 10 mL). The combined organic extracts were washed with brine, dried over Na₂SO₄ and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane:EtOAc 9:1) to give compound **37** in 96% yield (0.123 g) as a yellow oil.

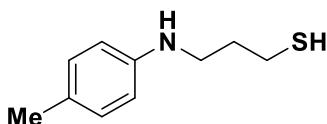
¹H NMR (400 MHz, C₆D₆) δ: 6.78 (m, 2H, Ph H-3,5), 6.58 (m, 2H, Ph H-2,6), 3.96 (q, ³*J* = 7.0 Hz, 2H, OCH₂CH₃), 2.65 (t, ³*J* = 7.0 Hz, 2H, CD₂CH₂CH₂SH), 1.90 (t, ³*J* = 7.0 Hz, 2H, CD₂CH₂CH₂SH), 1.37 (t, ³*J* = 7.0 Hz, 3H, OCH₂CH₃).

¹³C NMR (100 MHz, C₆D₆) δ: 151.4 (Ph C-4), 142.3 (Ph C-1), 115.8 (Ph C-3,5), 114.2 (Ph C-2,6), 64.1 (OCH₂CH₃), 42.6 (q, ¹*J*_{C,D} = 20.5 Hz, CD₂CH₂CH₂SH), 33.3 (CD₂CH₂CH₂SH), 22.2 (CD₂CH₂CH₂SH), 15.0 (OCH₂CH₃).

¹⁵N NMR (40 MHz, C₆D₆) δ: -320.9.

HRMS (ESI), *m/z*: calcd. for C₁₁H₁₄D₂NOS⁺: 214.1229 [M + H]⁺; found: 214.1231.

3-[(4-methylphenyl)amino]-1-propanethiol (**38**)



To a solution of 4-methyl-*N*-[(2*Z*)-2-thietanylidene]aniline (0.124 g, 0.7 mmol, 1.0 equiv) in dry THF (2 mL) a solution of LiAlH₄ (1M in THF, 0.7 mL, 0.7 mmol, 1.0 equiv) was added dropwise at 0 °C. The reaction mixture was allowed to reach room temperature and then stirred for 1.5 hours before being quenched with water. The reaction mixture was extracted exhaustively with Et₂O (3 x 10 mL). The combined organic extracts were washed with brine, dried over Na₂SO₄ and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane:EtOAc 8:2) to give compound **38** in 90% yield (0.114 g) as a yellow oil.

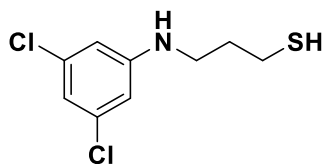
¹H NMR (400 MHz, C₆D₆) δ: 6.99 (m, 2H, Ph H-3,5), 6.55 (m, 2H, Ph H-2,6), 3.24 (t, ³*J* = 6.8 Hz, 2H, CH₂CH₂CH₂SH), 2.65 (m, 2H, CH₂CH₂CH₂SH), 2.24 (s, 3H, CH₃), 1.92 (q, ³*J* = 6.9 Hz, 2H, CH₂CH₂CH₂SH).

¹³C NMR (100 MHz, C₆D₆) δ: 145.8 (Ph C-1), 129.8 (Ph C-3,5), 126.7 (Ph C-4), 113.0 (Ph C-2,6), 42.7 (CH₂CH₂CH₂SH), 33.4 (CH₂CH₂CH₂SH), 22.2 (CH₂CH₂CH₂SH), 20.3 (CH₃).

¹⁵N NMR (40 MHz, C₆D₆) δ: -318.2.

HRMS (ESI), *m/z*: calcd. for C₁₀H₁₆NS⁺: 182.0998 [M + H]⁺; found: 182.0999.

3-[(3,5-dichlorophenyl)amino]-1-propanethiol (**39**)



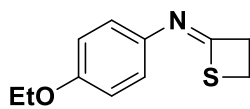
To a solution of 3,5-dichloro-*N*-[(2*Z*)-2-thietanylidene]aniline (0.162 g, 0.7 mmol, 1.0 equiv) in dry THF (2 mL) a solution of LiAlH₄ (1M in THF, 0.7 mL, 0.7 mmol, 1.0 equiv) was added dropwise at 0 °C. The reaction mixture was allowed to reach room temperature and then stirred for 1.5 hours before being quenched with water. The reaction mixture was extracted exhaustively with Et₂O (3 x 10 mL). The combined organic extracts were washed with brine, dried over Na₂SO₄ and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane:EtOAc 8:2) to give compound **39** in 92% yield (0.152 g) as a yellow oil.

¹H NMR (400 MHz, C₆D₆) δ: 6.66 (t, ⁴*J* = 1.8 Hz, 1H, Ph H-4), 6.46 (d, ⁴*J* = 1.8 Hz, 2H, Ph H-2,6), 3.89 (brs, 1H, NH), 3.24 (t, ³*J* = 6.8 Hz, 2H, CH₂CH₂CH₂SH), 2.64 (m, 2H, CH₂CH₂CH₂SH), 1.91 (q, ³*J* = 6.8 Hz, 2H, CH₂CH₂CH₂SH), 1.41 (t, ³*J* = 7.9 Hz, 1H, SH).

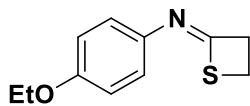
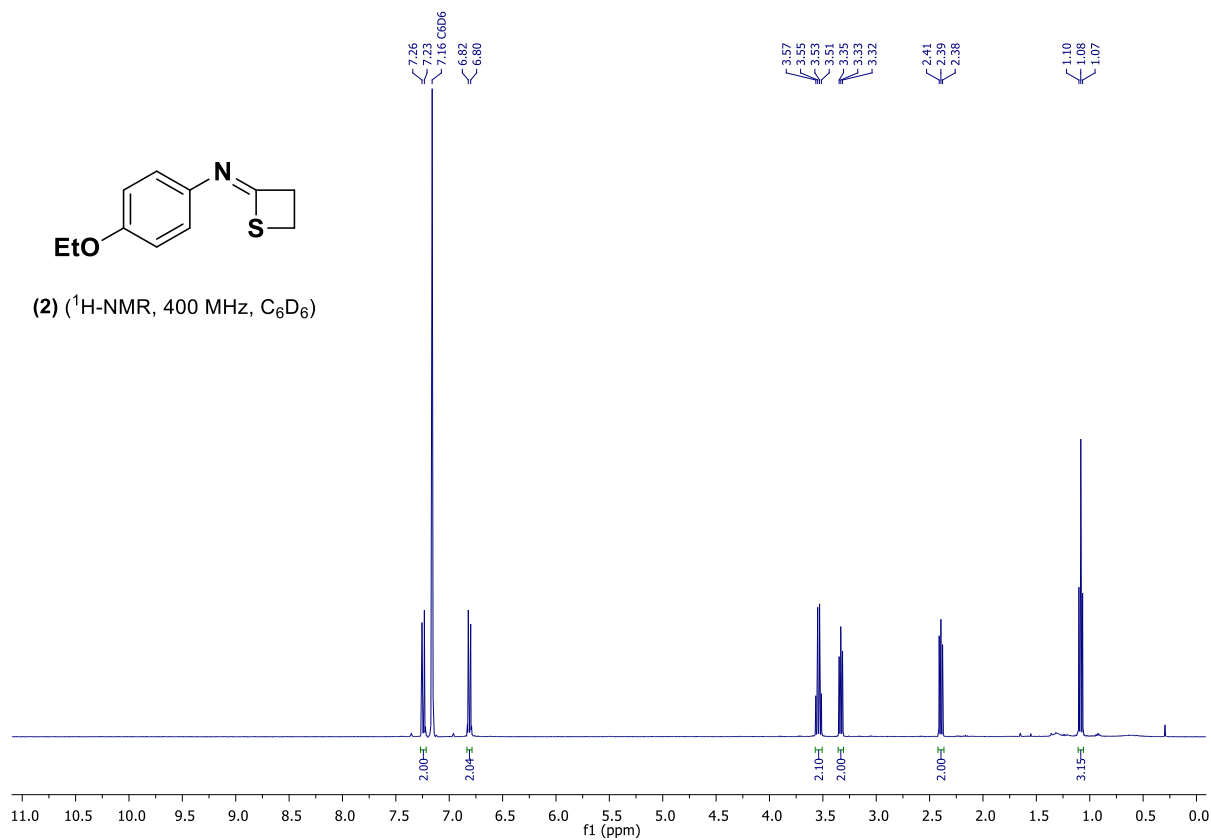
¹³C NMR (100 MHz, C₆D₆) δ: 149.6 (Ph C-1), 135.5 (Ph C-3,5), 117.1 (Ph C-4), 110.9 (Ph C-2,6), 42.0 (CH₂CH₂CH₂SH), 32.9 (CH₂CH₂CH₂SH), 22.0 (CH₂CH₂CH₂SH).

HRMS (ESI), *m/z*: calcd. for C₉H₁₂Cl₂NS⁺: 236.0062 [M + H]⁺; found: 236.0064.

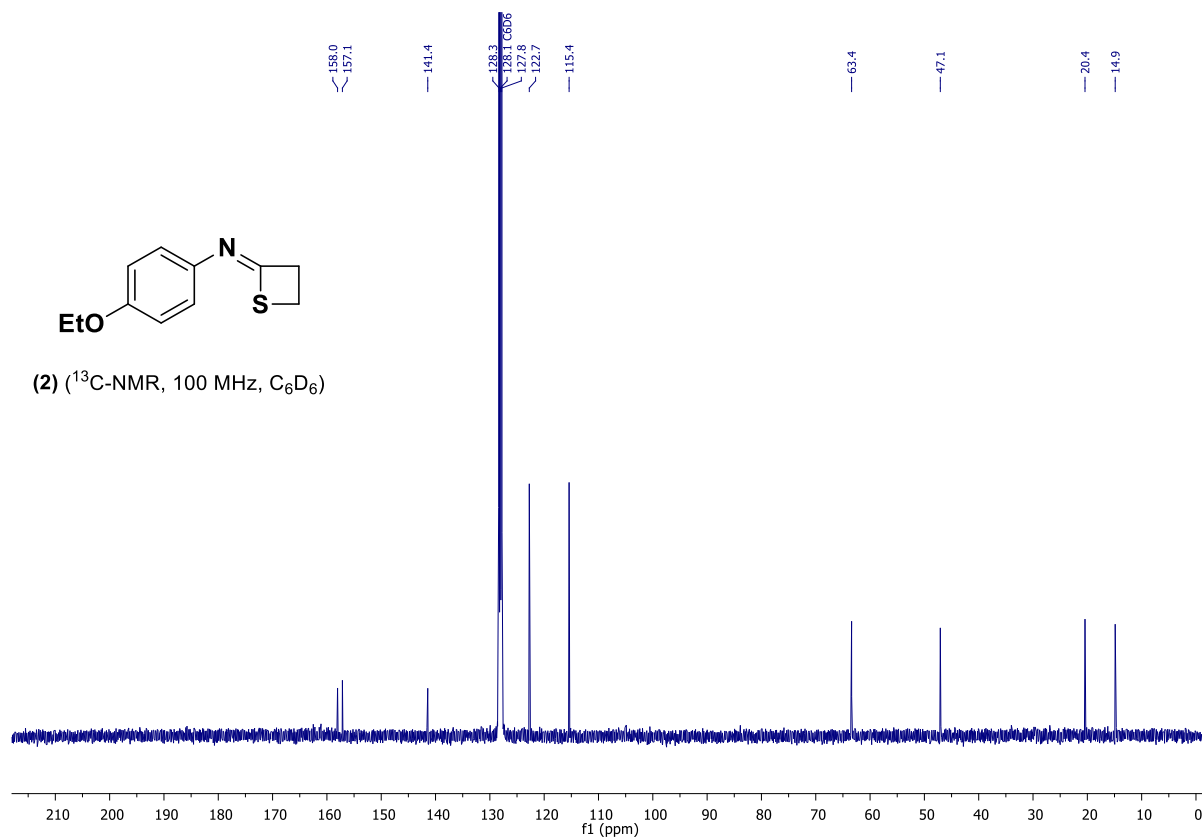
Copies of ^1H - and ^{13}C -NMR Spectra

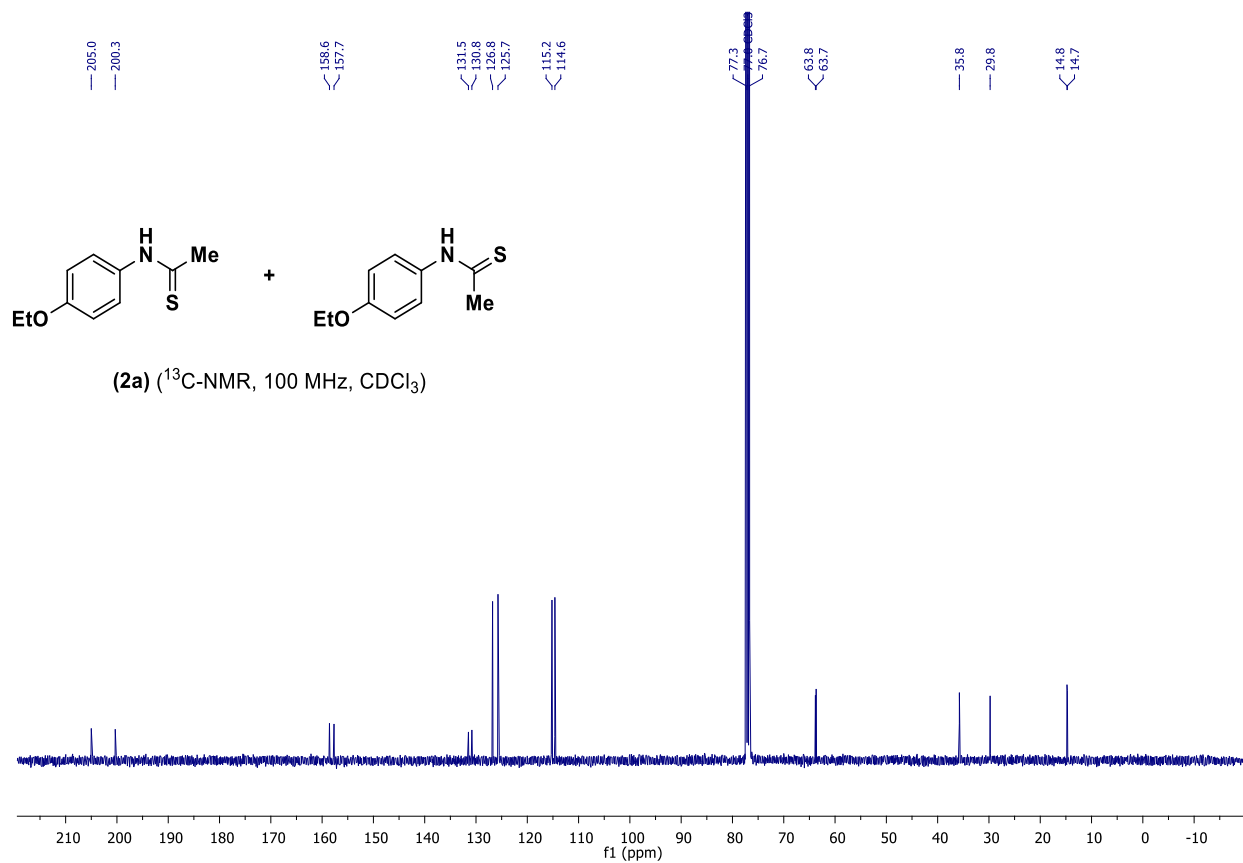
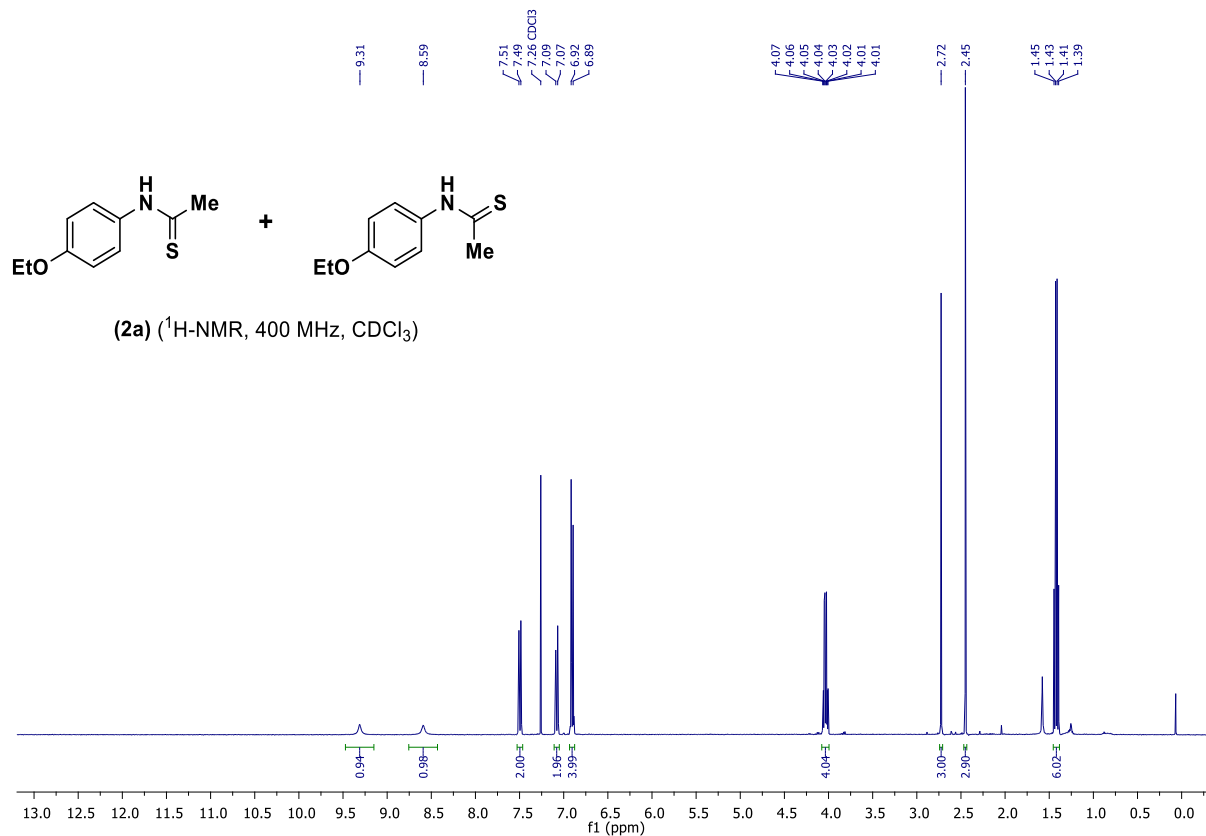


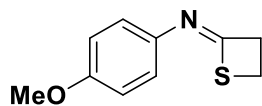
(2) (^1H -NMR, 400 MHz, C_6D_6)



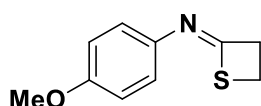
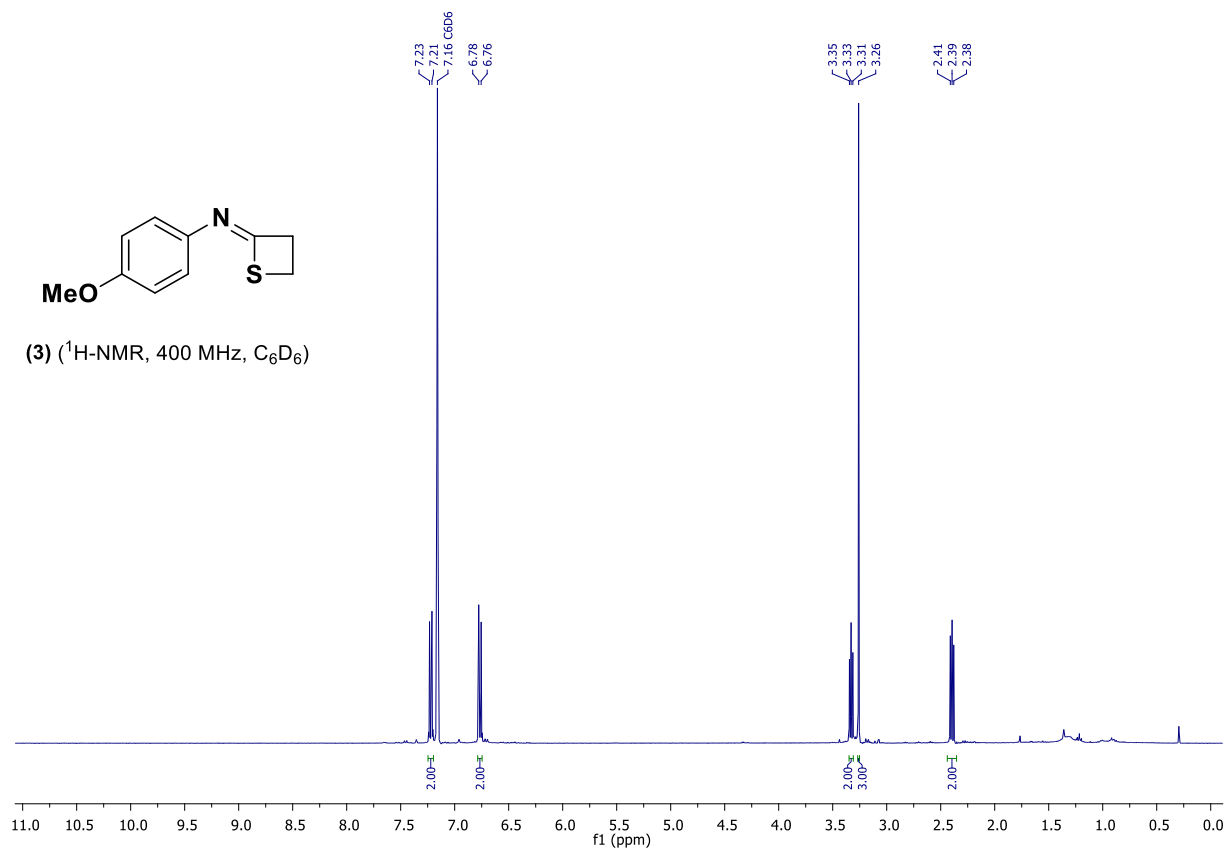
(2) (^{13}C -NMR, 100 MHz, C_6D_6)



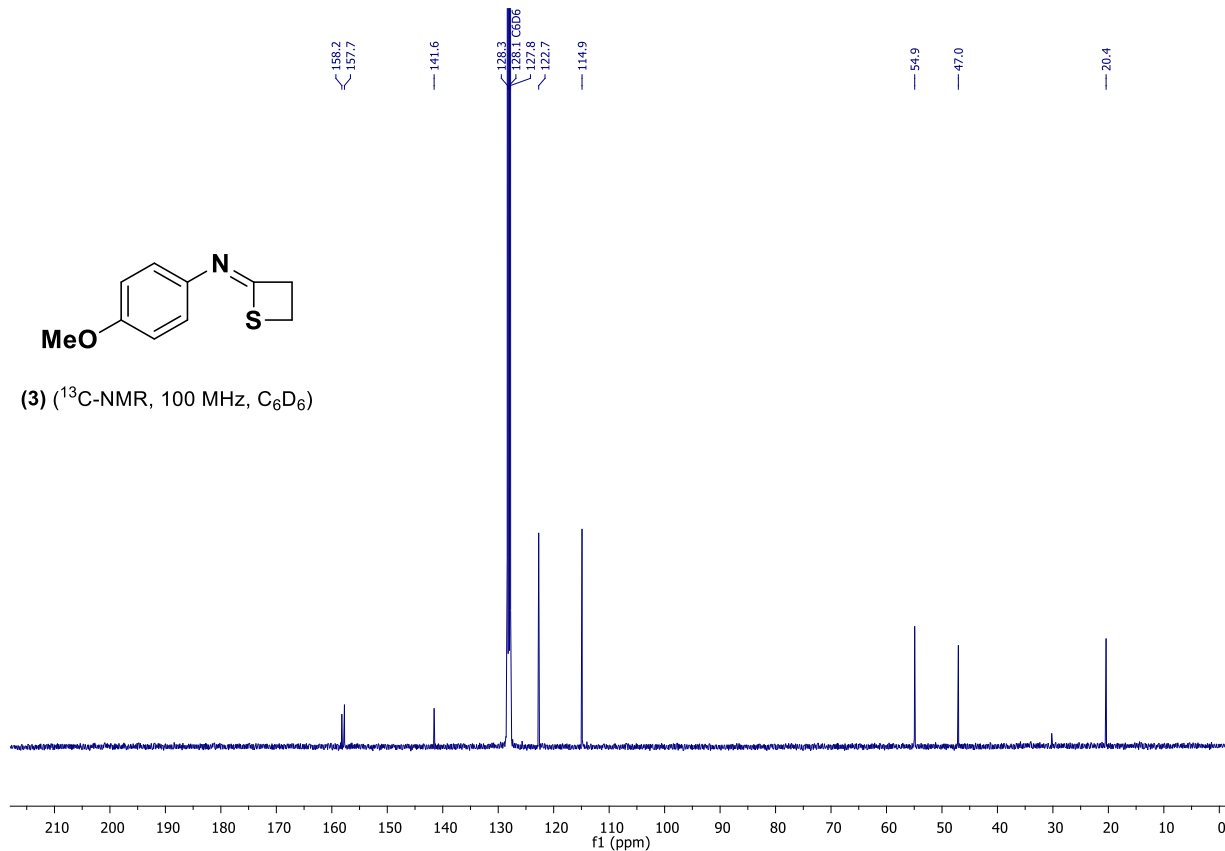


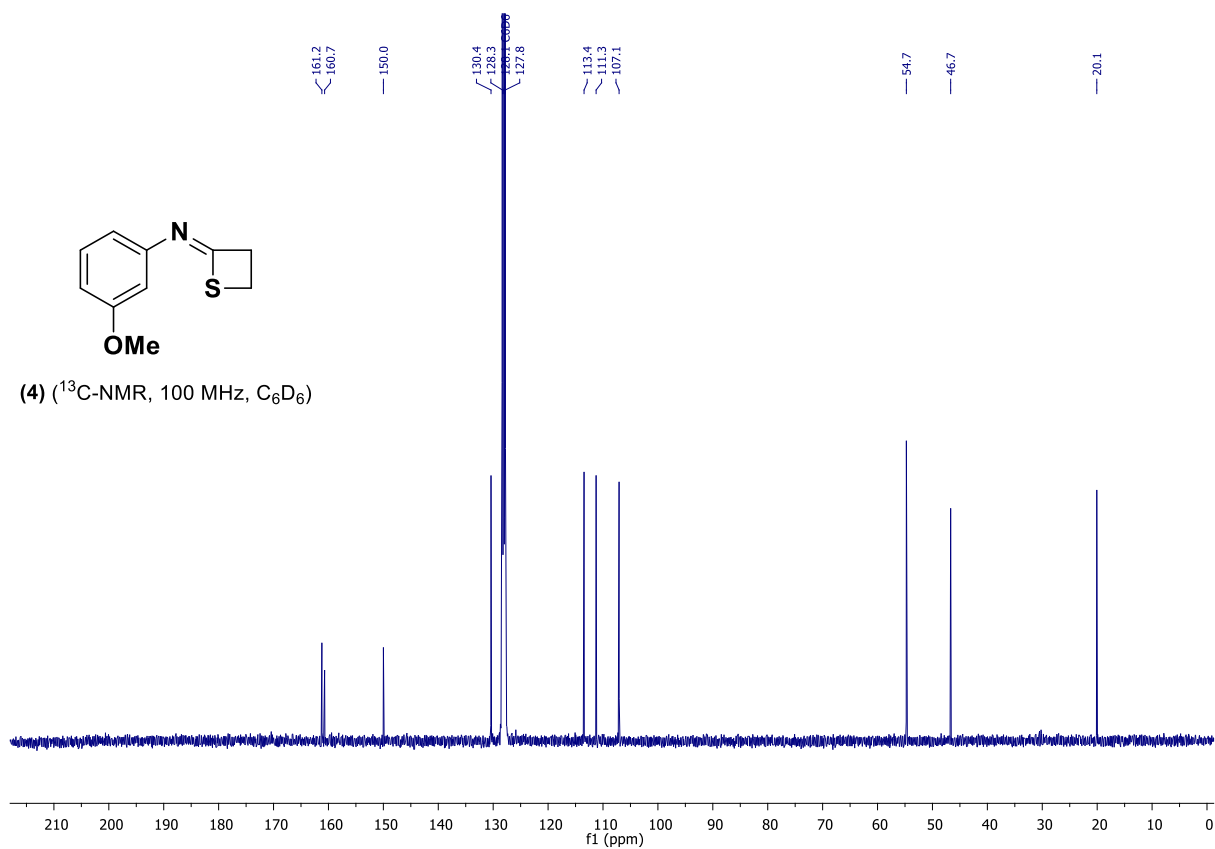
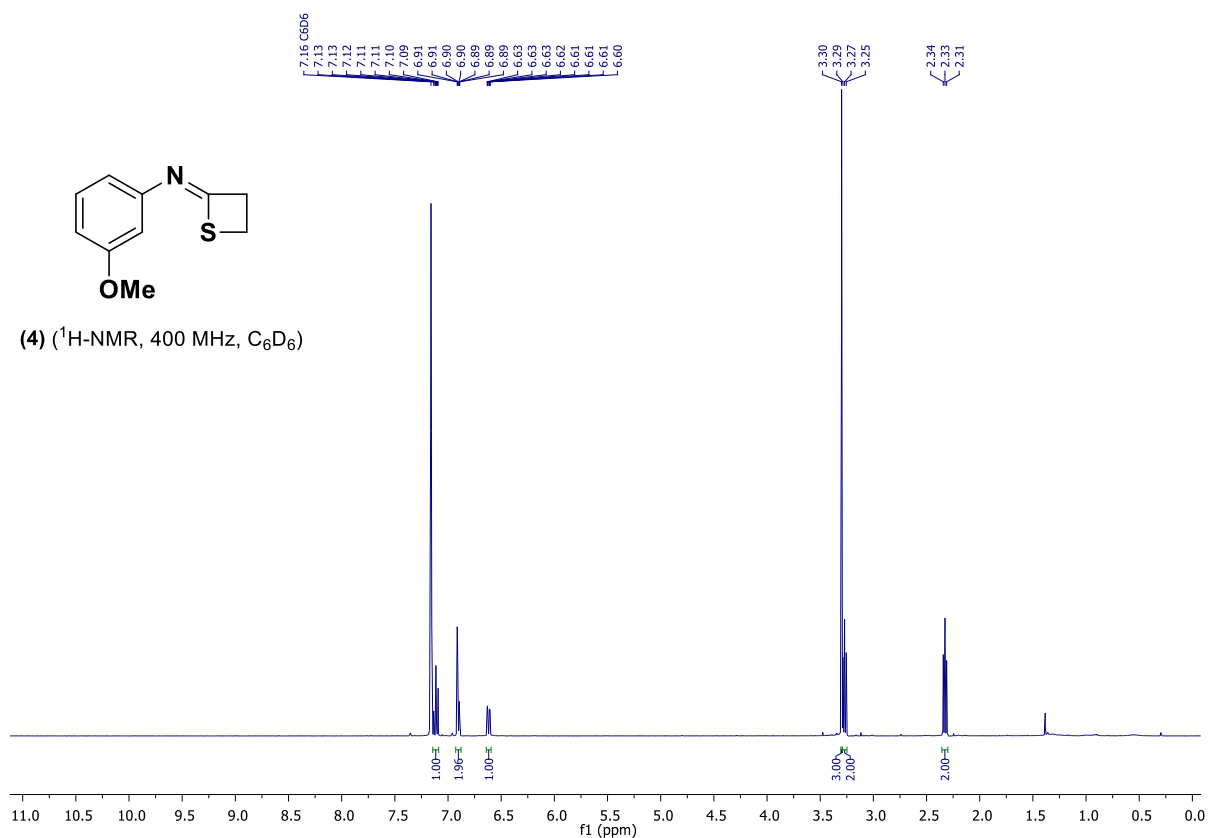


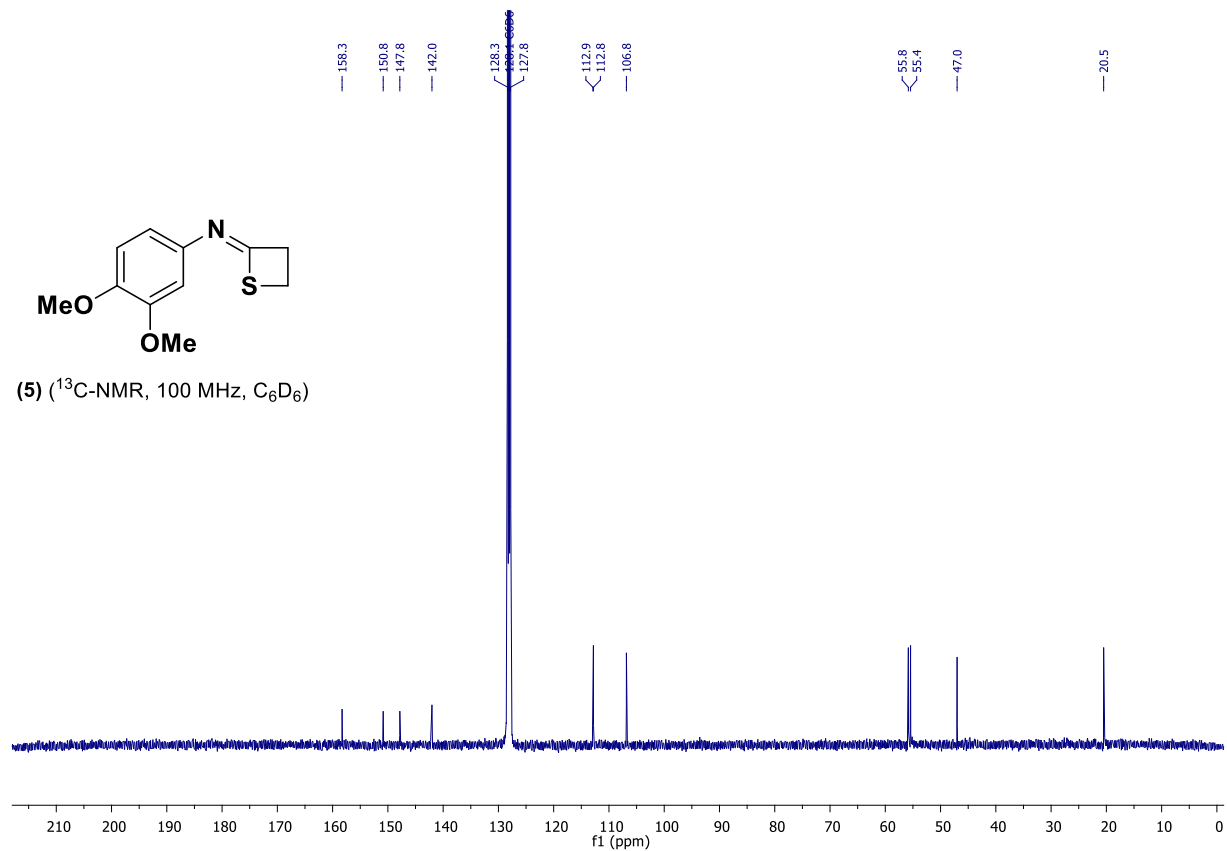
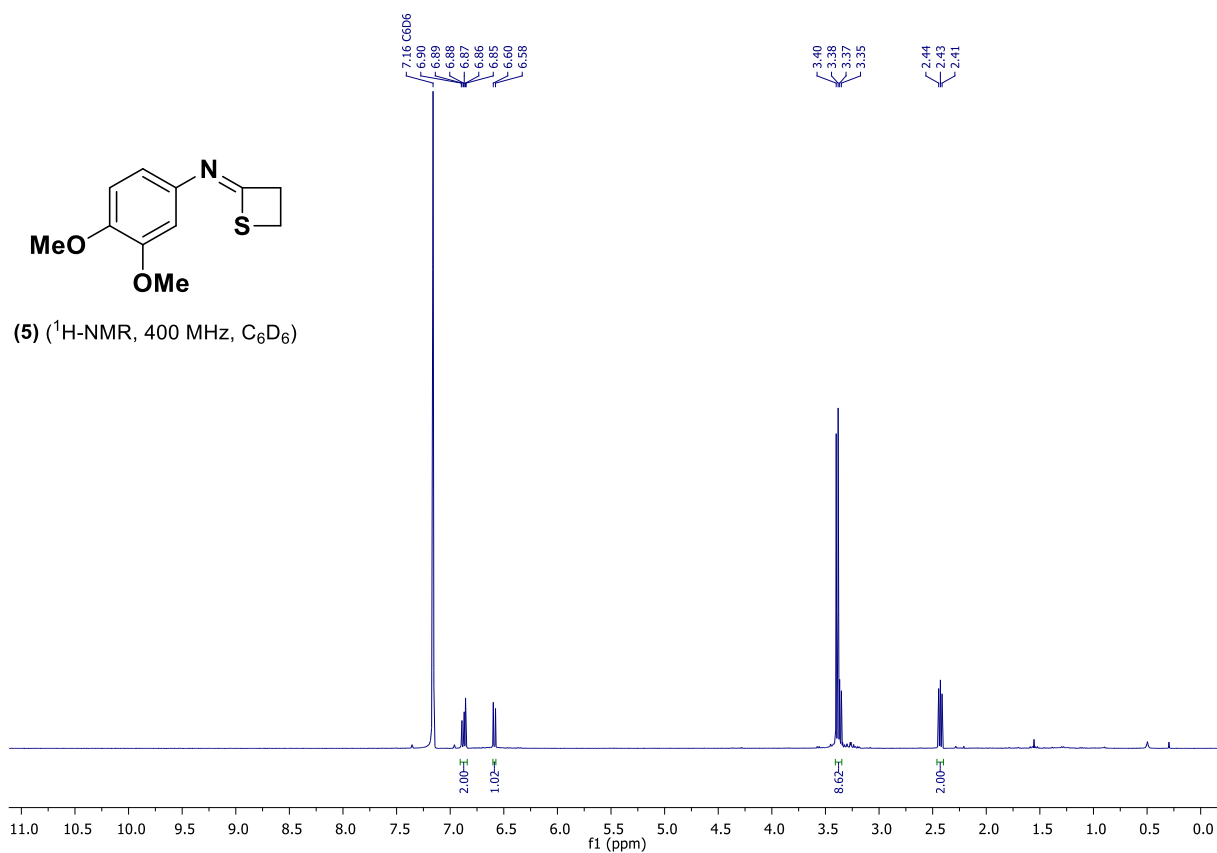
(3) (^1H -NMR, 400 MHz, C_6D_6)

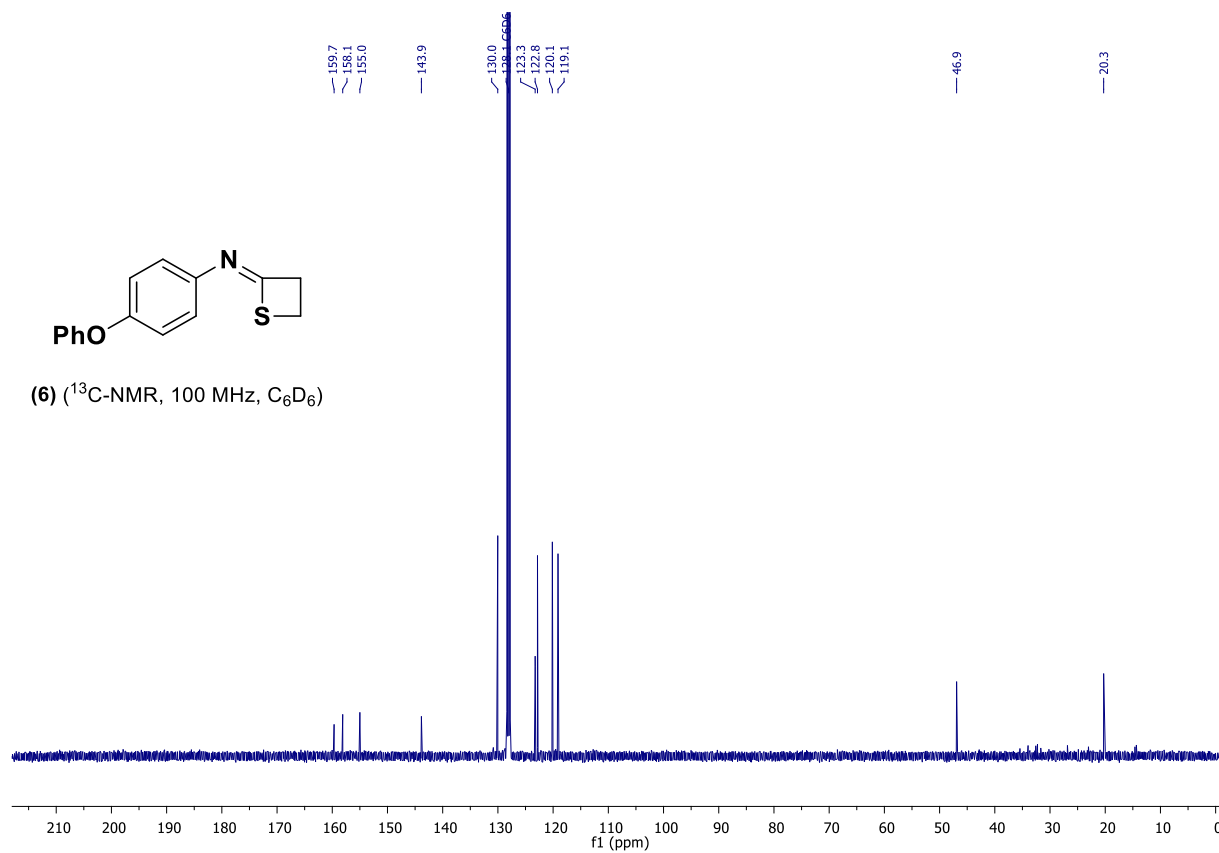
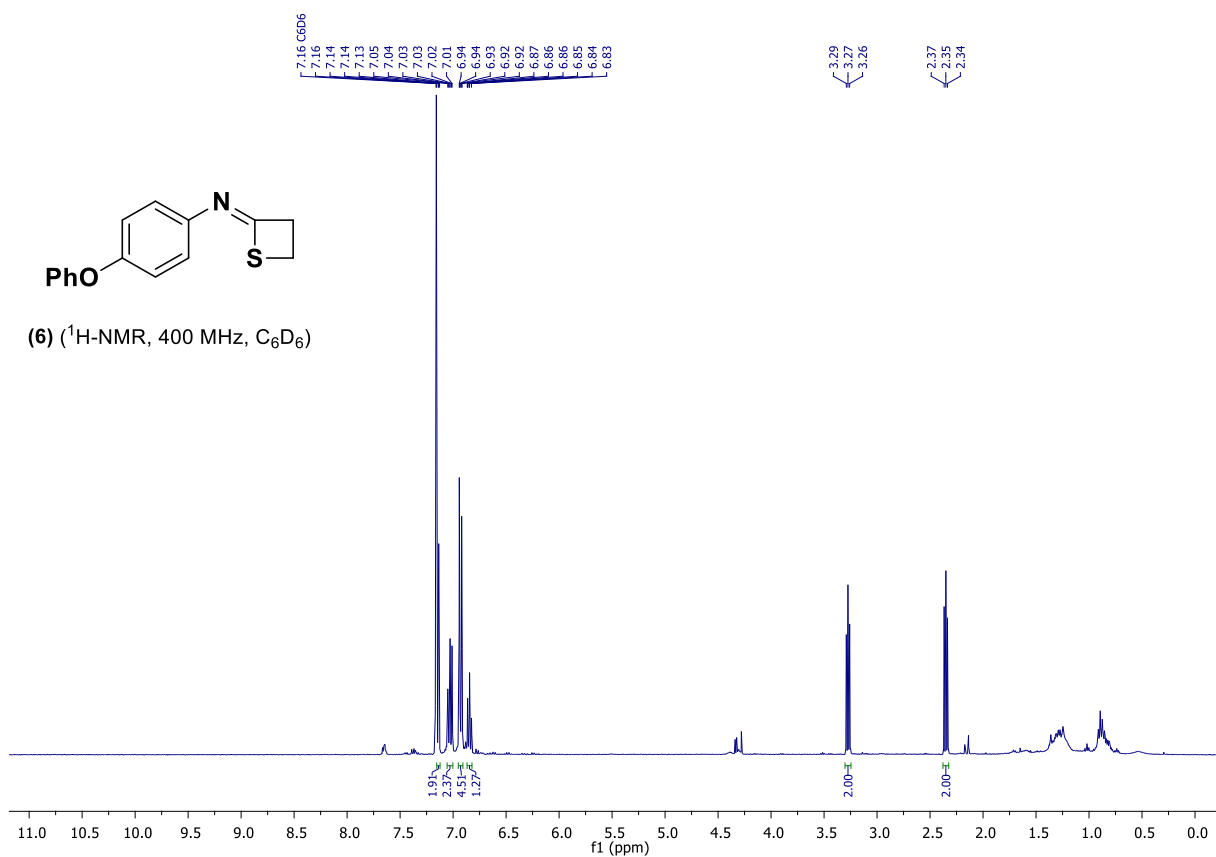


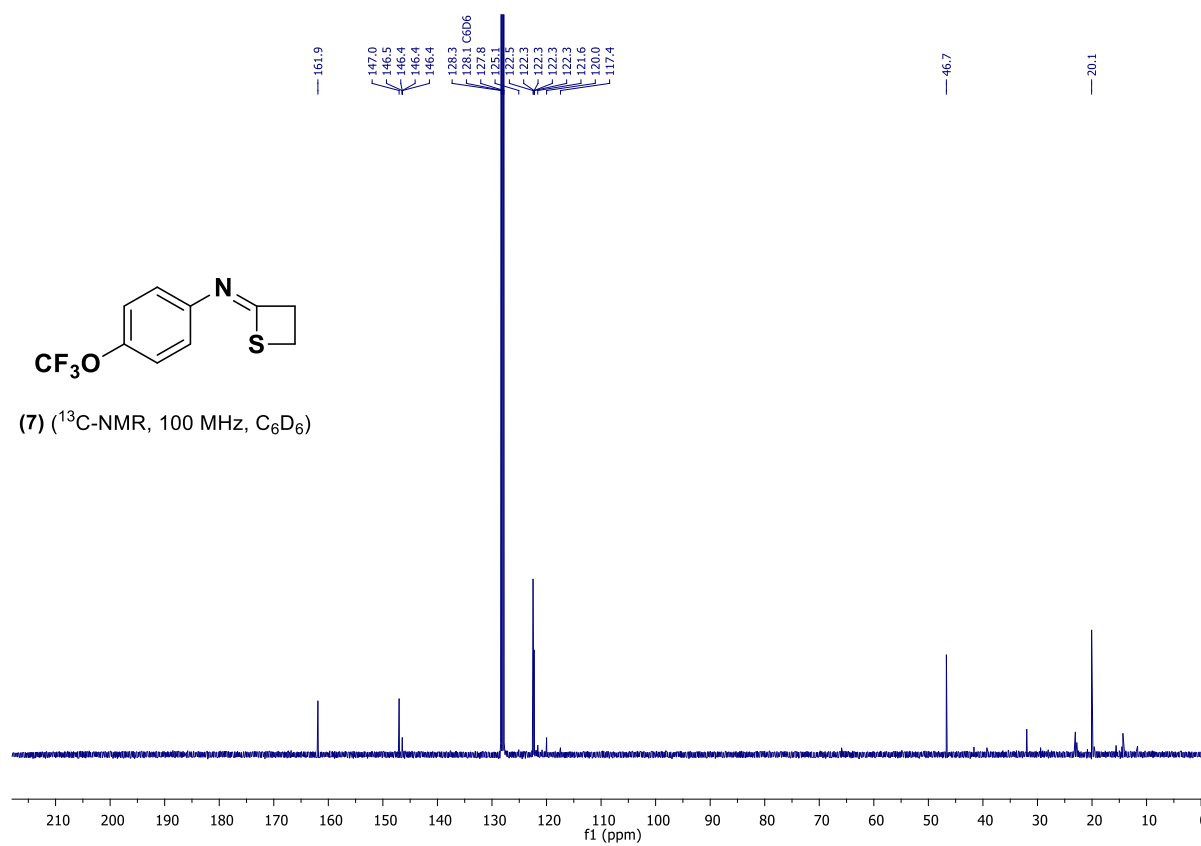
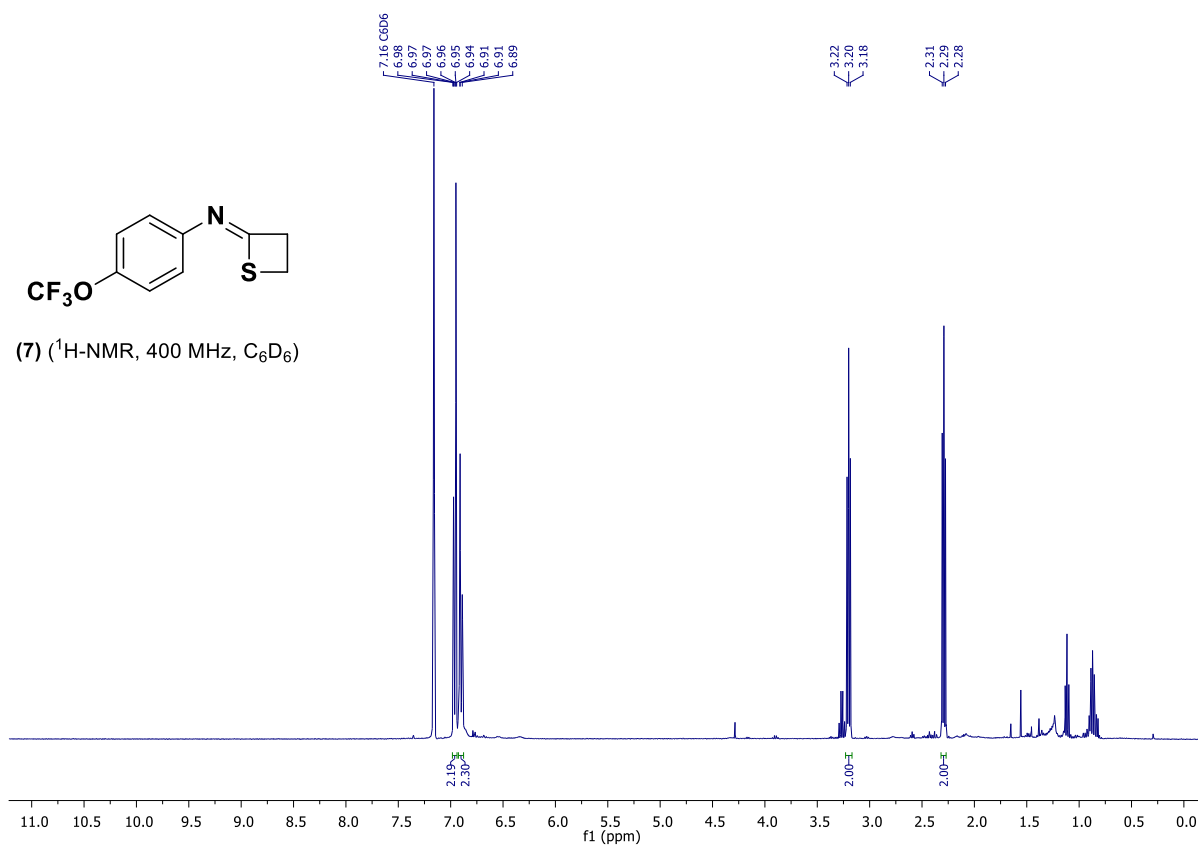
(3) (^{13}C -NMR, 100 MHz, C_6D_6)

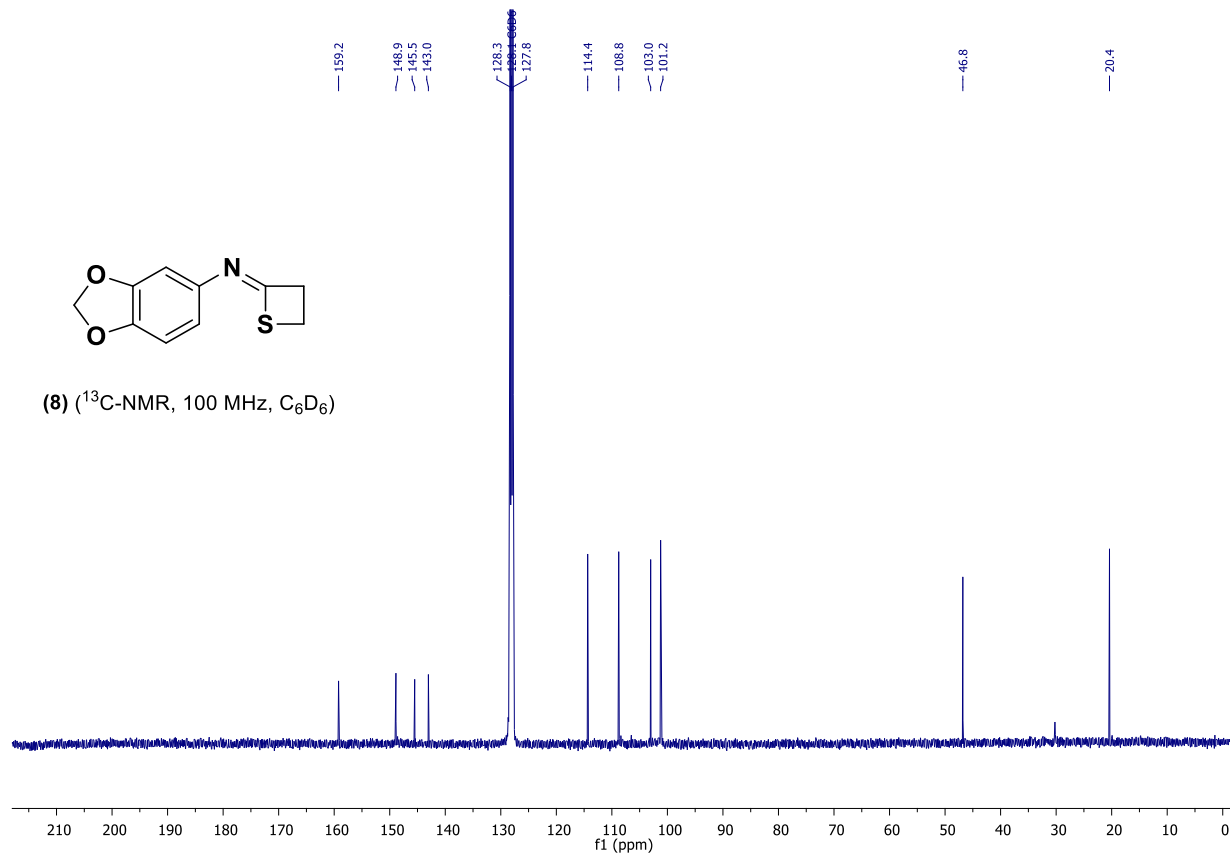
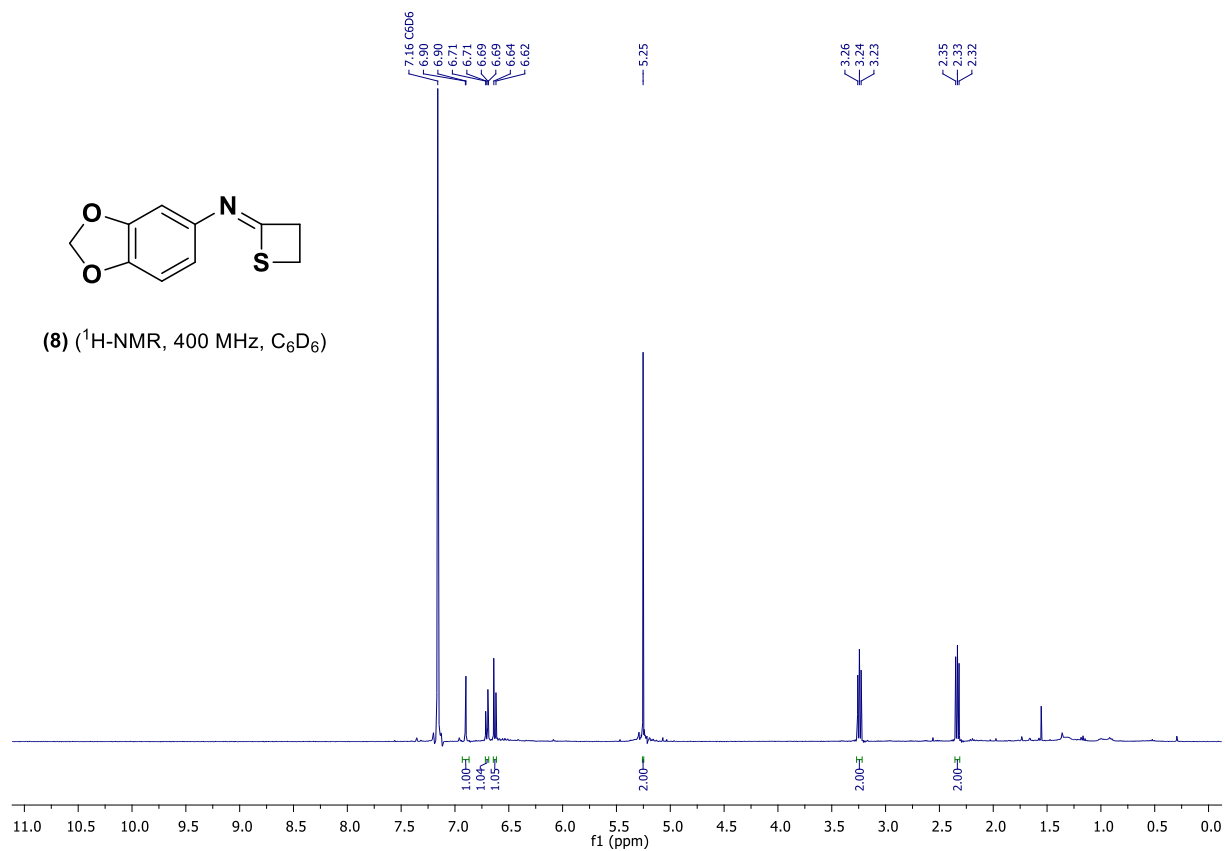


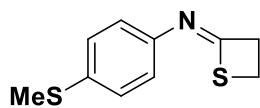




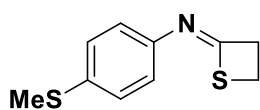
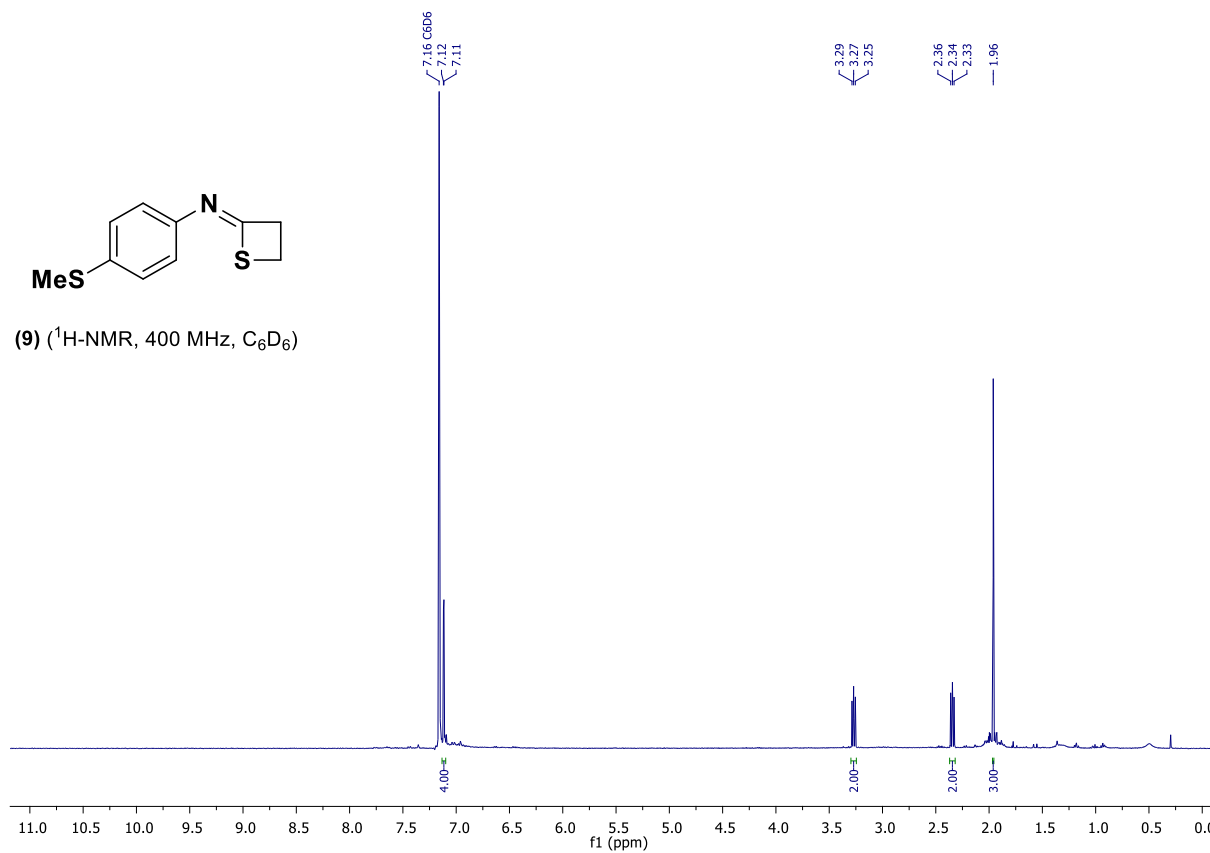




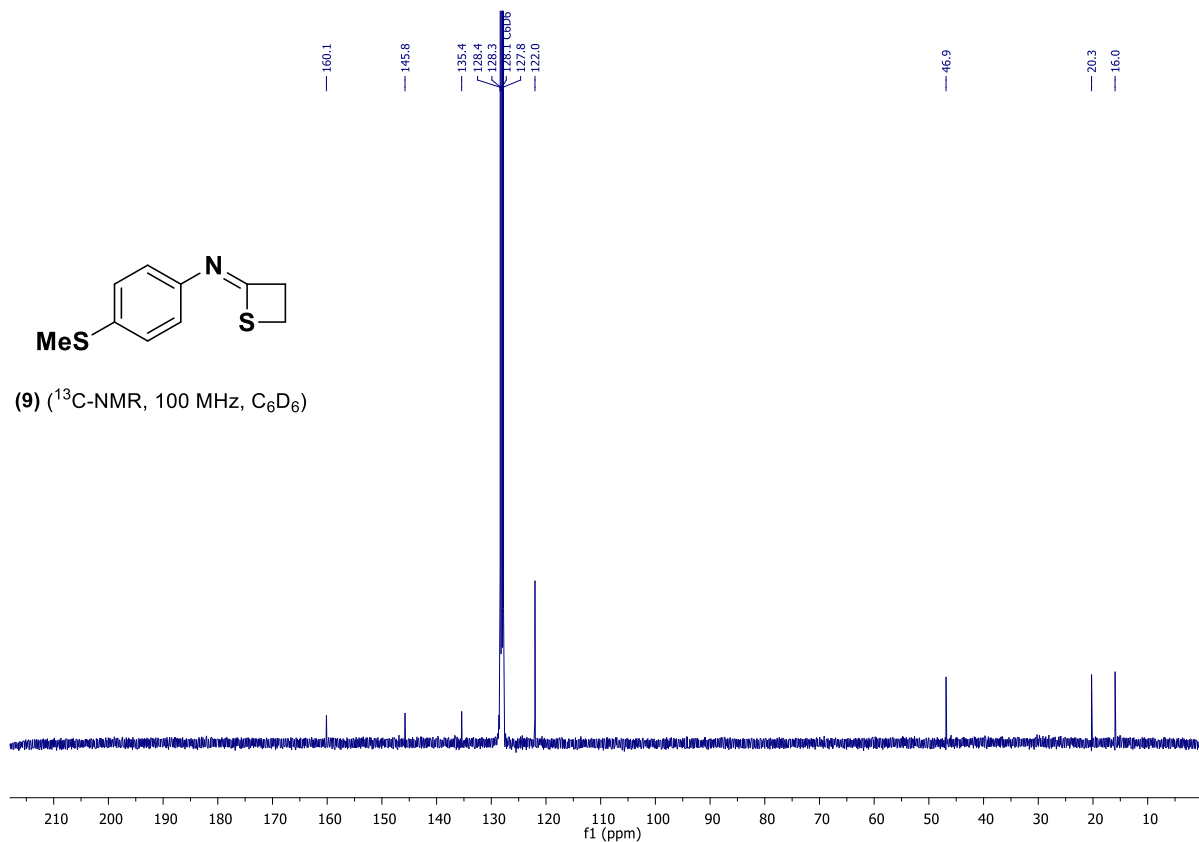


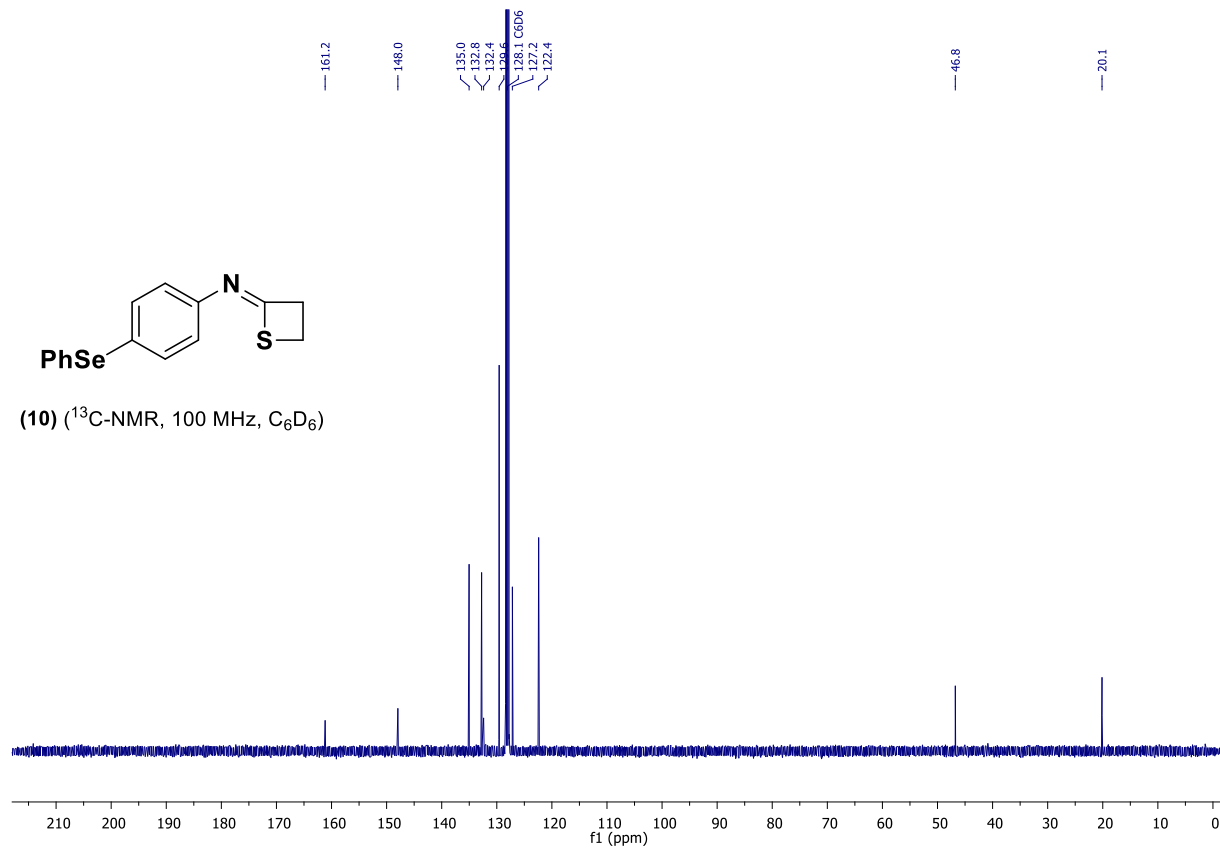
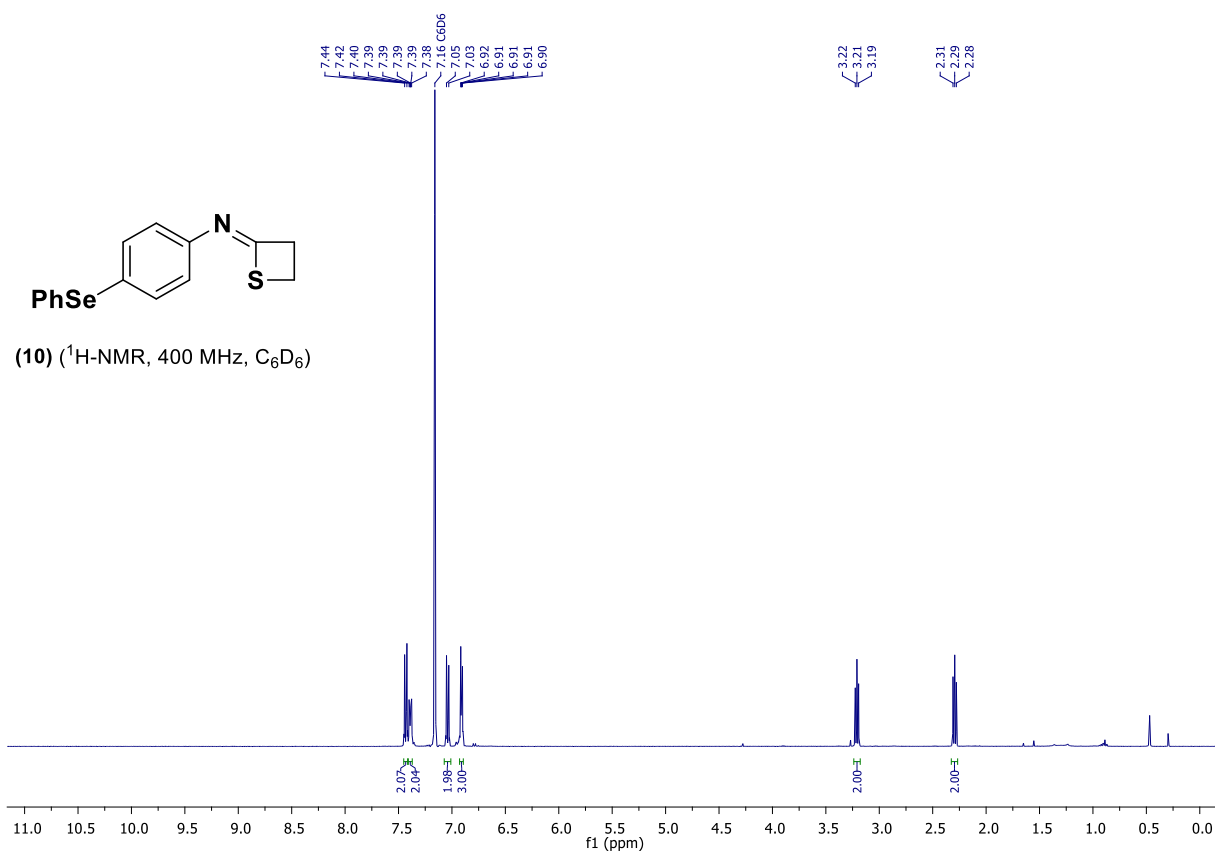


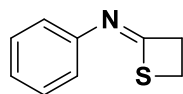
(9) (^1H -NMR, 400 MHz, C_6D_6)



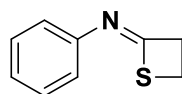
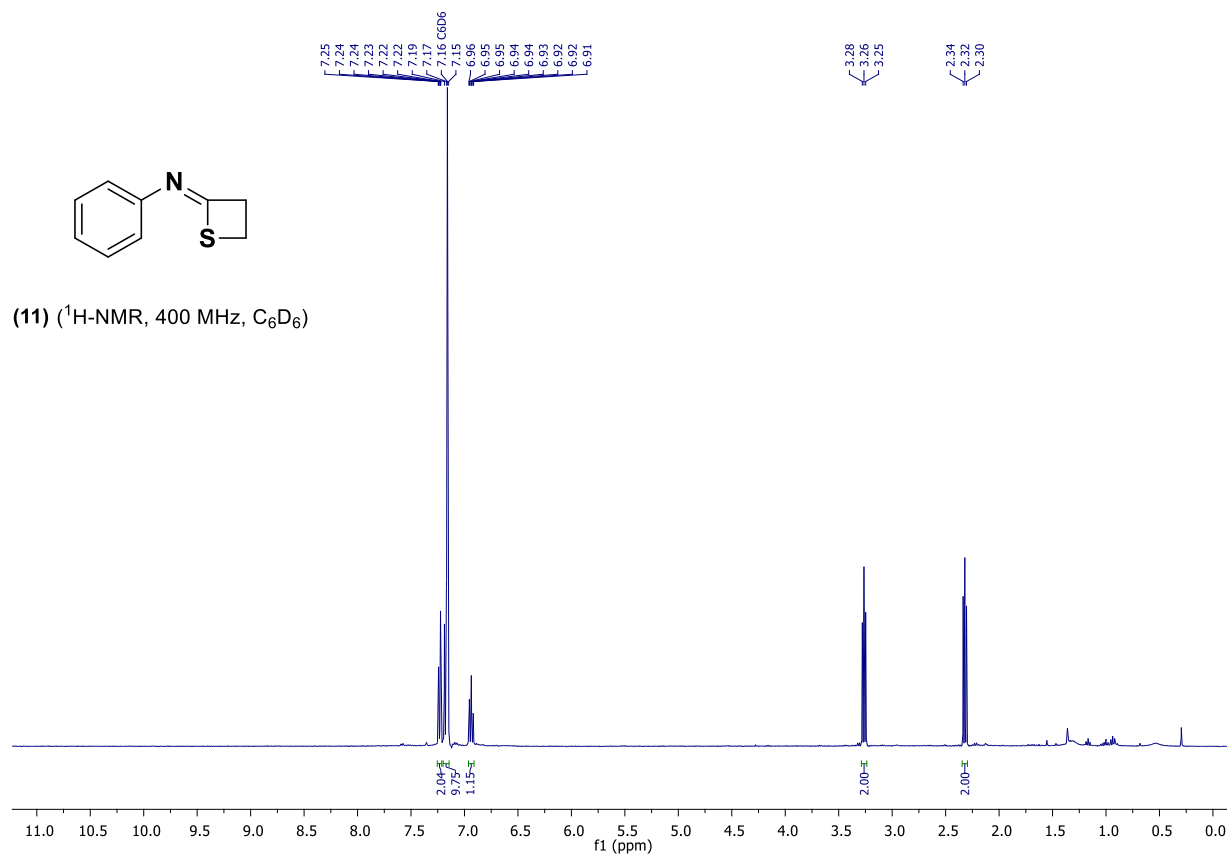
(9) (^{13}C -NMR, 100 MHz, C_6D_6)



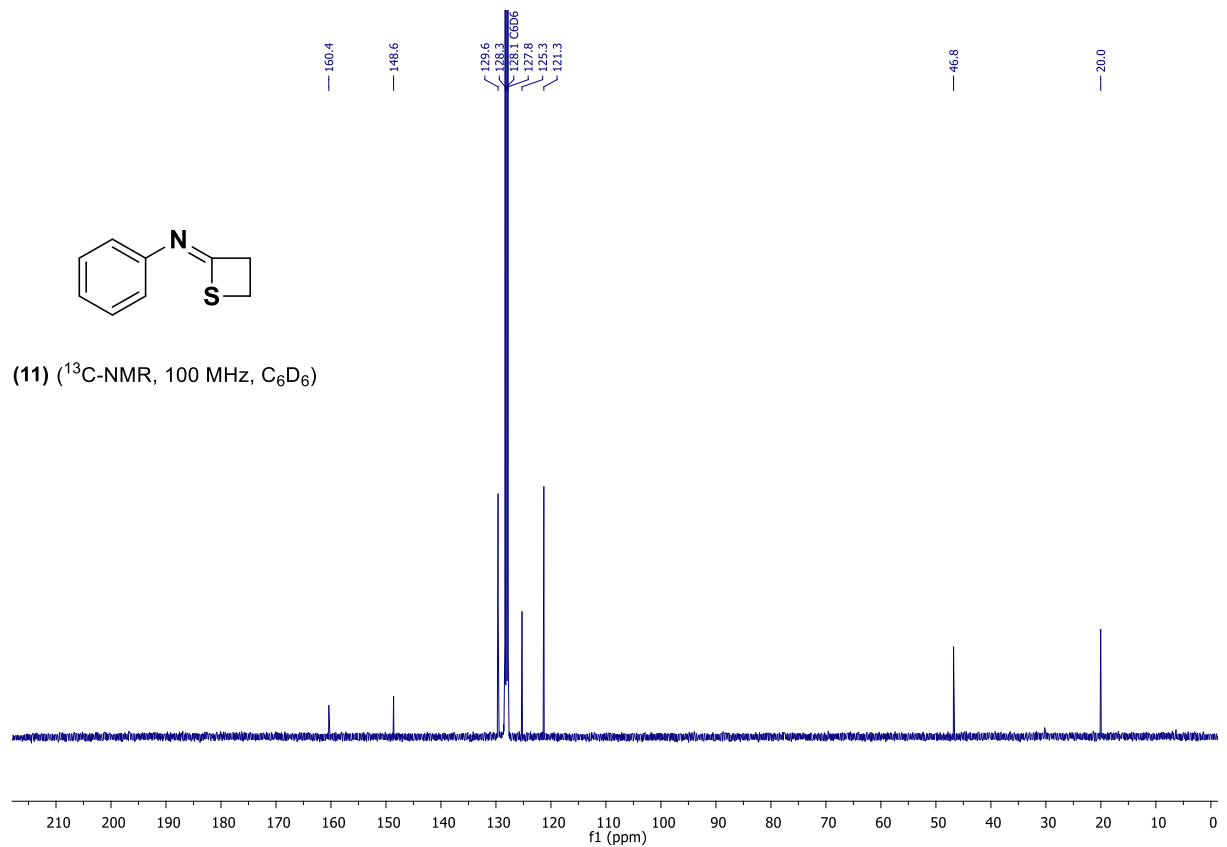


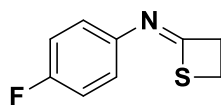


(11) (^1H -NMR, 400 MHz, C_6D_6)

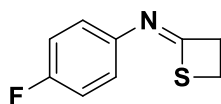
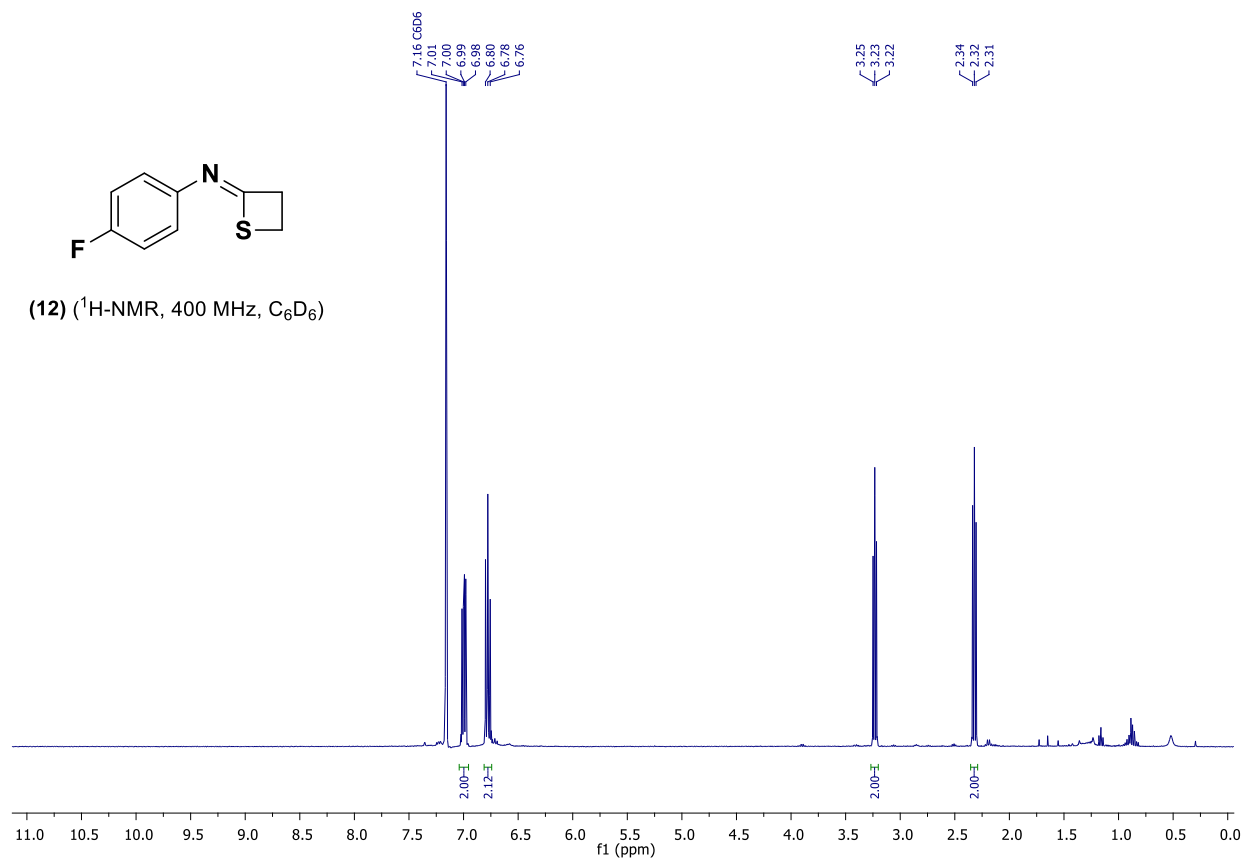


(11) (^{13}C -NMR, 100 MHz, C_6D_6)

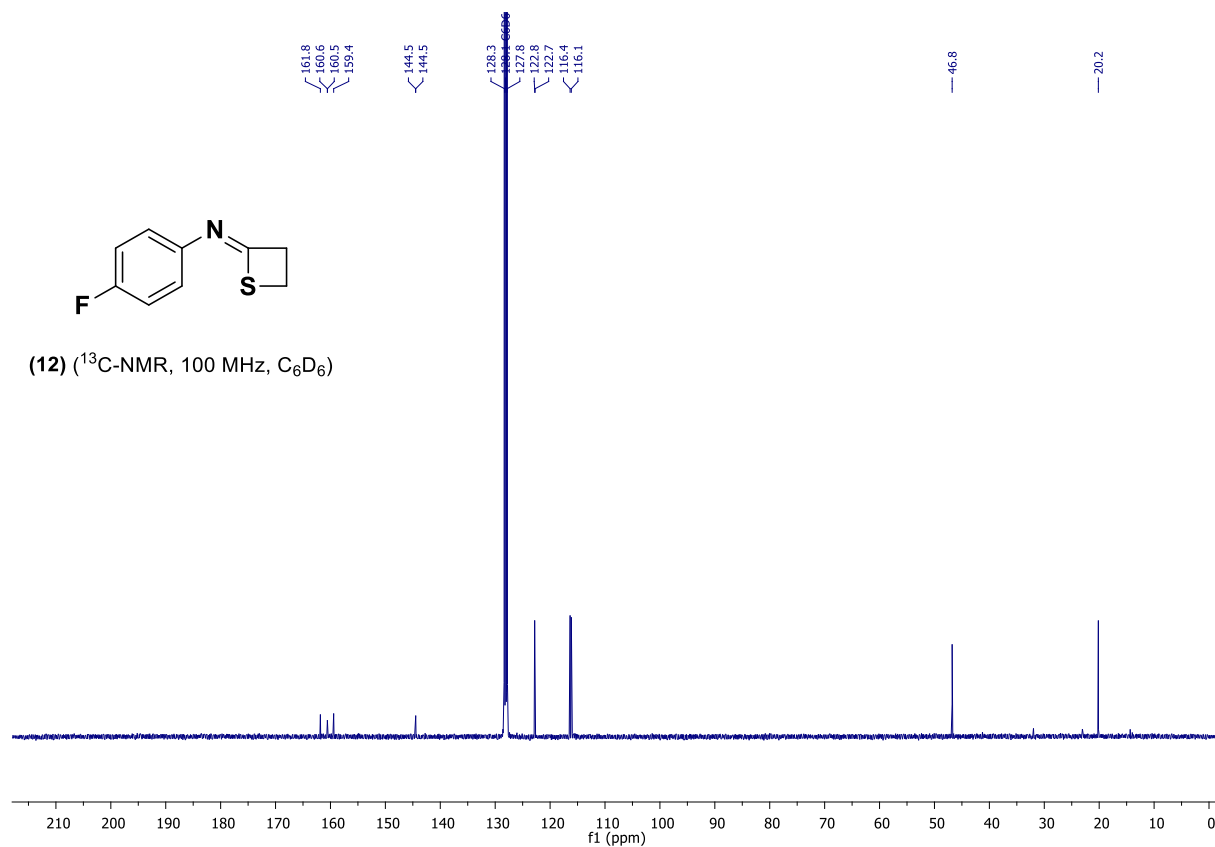


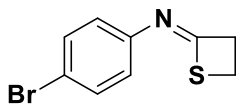


(12) (^1H -NMR, 400 MHz, C_6D_6)

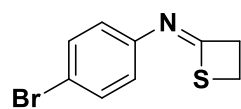
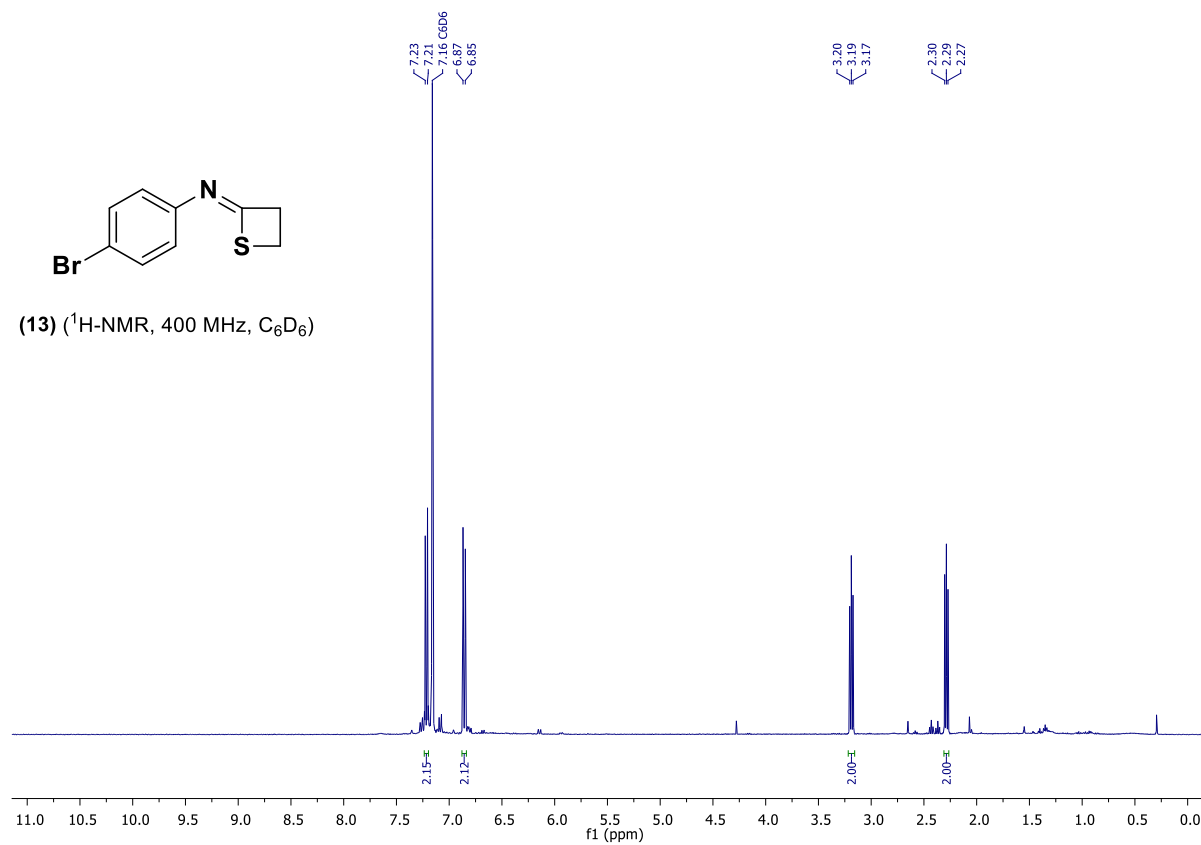


(12) (^{13}C -NMR, 100 MHz, C_6D_6)

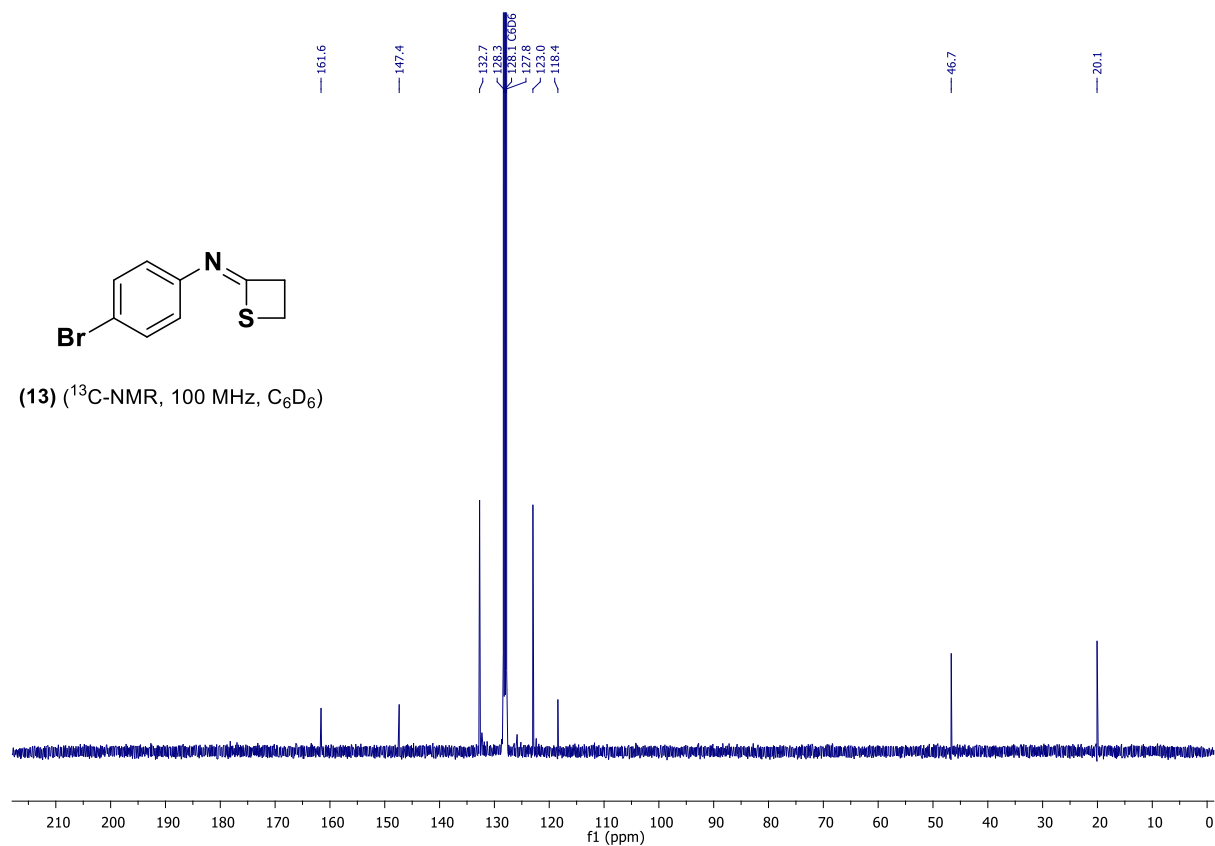


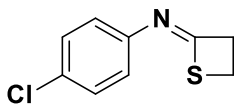


(13) (^1H -NMR, 400 MHz, C_6D_6)

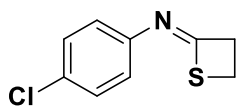
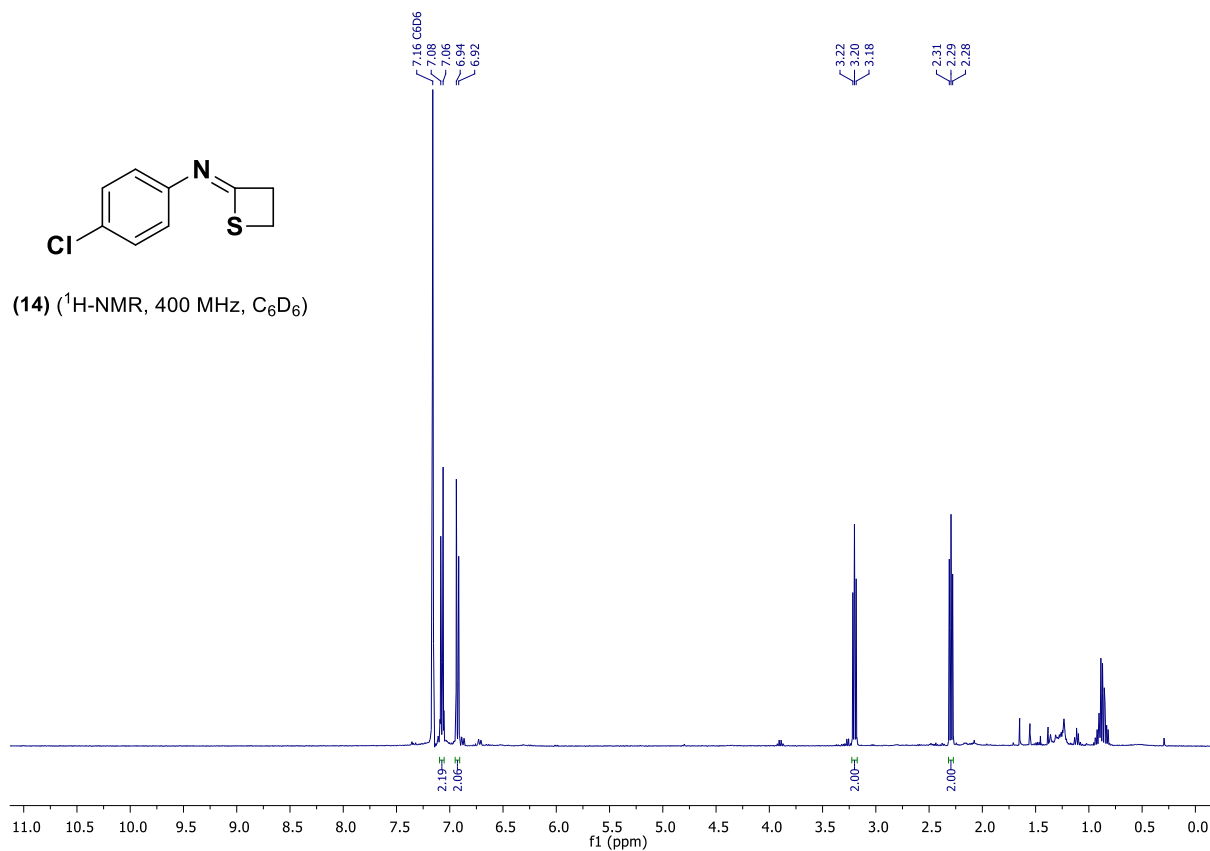


(13) (^{13}C -NMR, 100 MHz, C_6D_6)

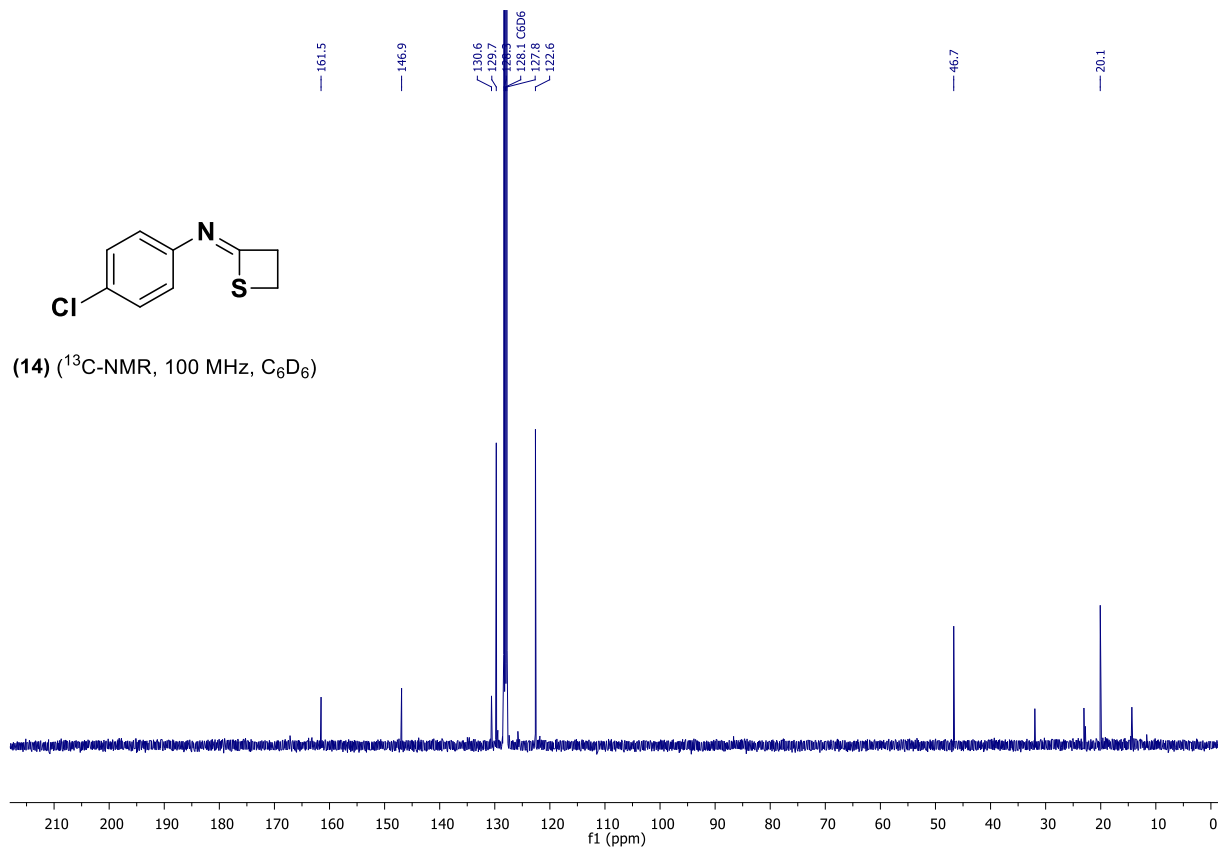


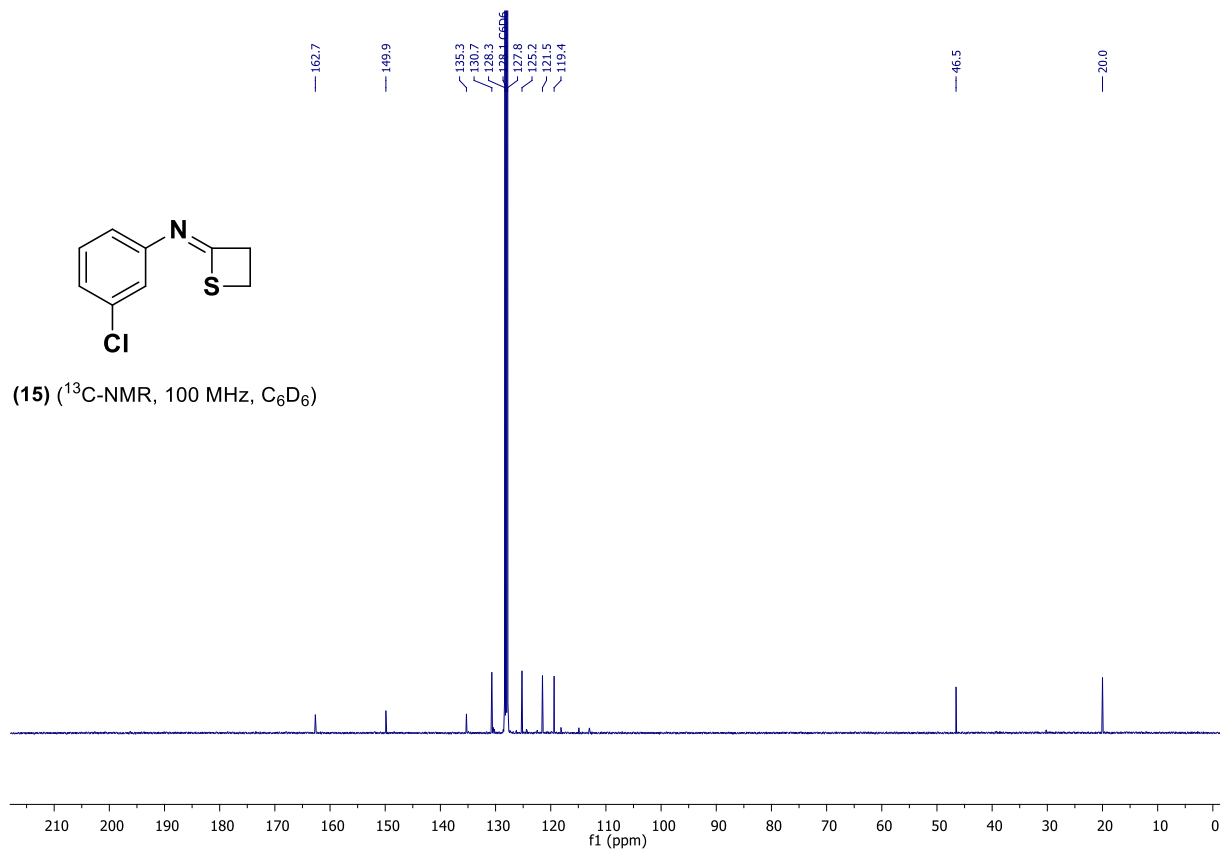
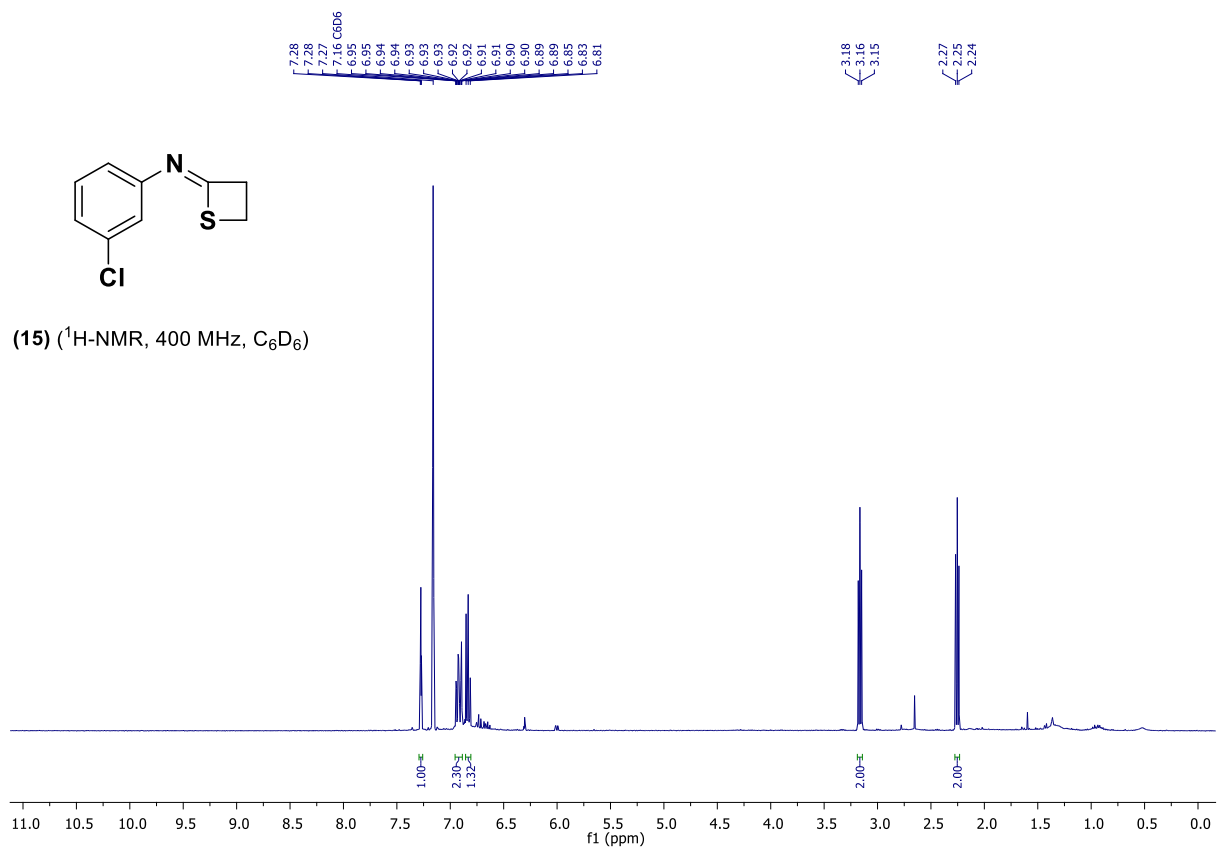


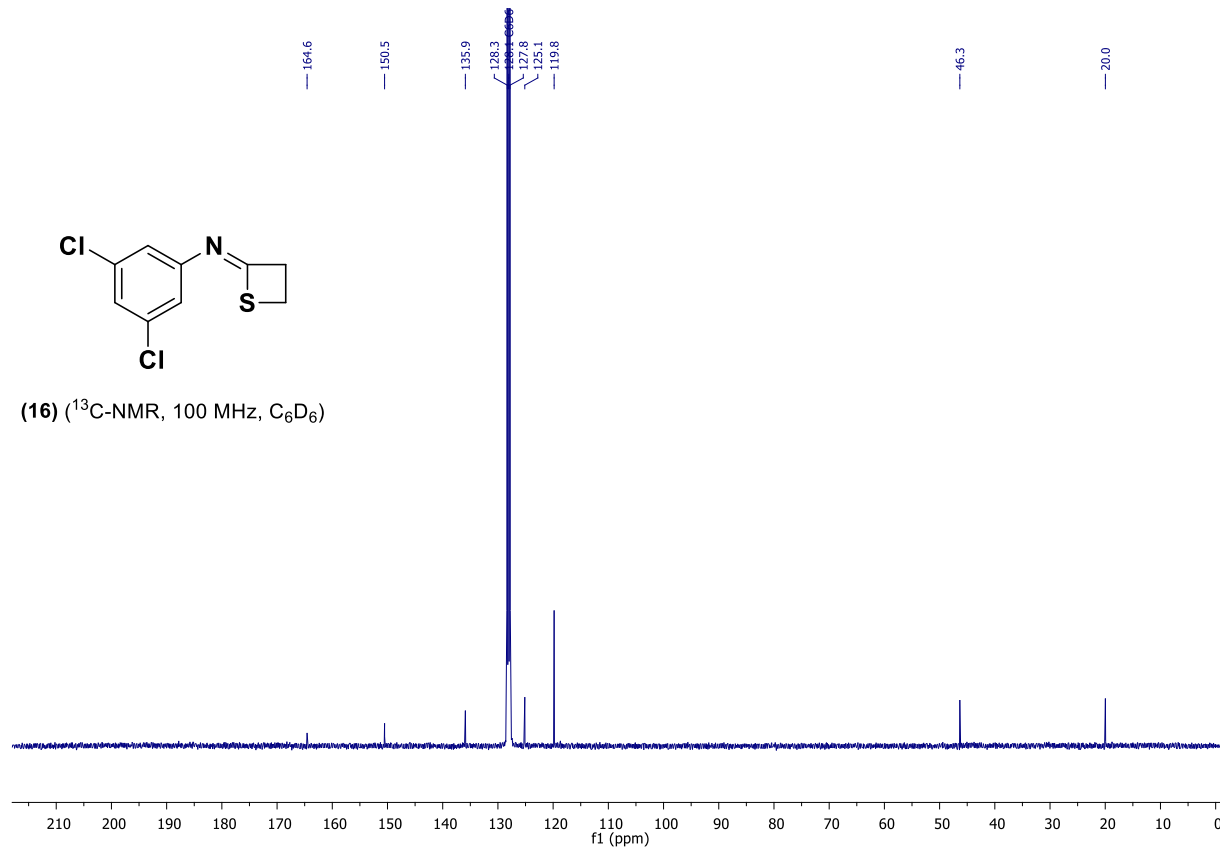
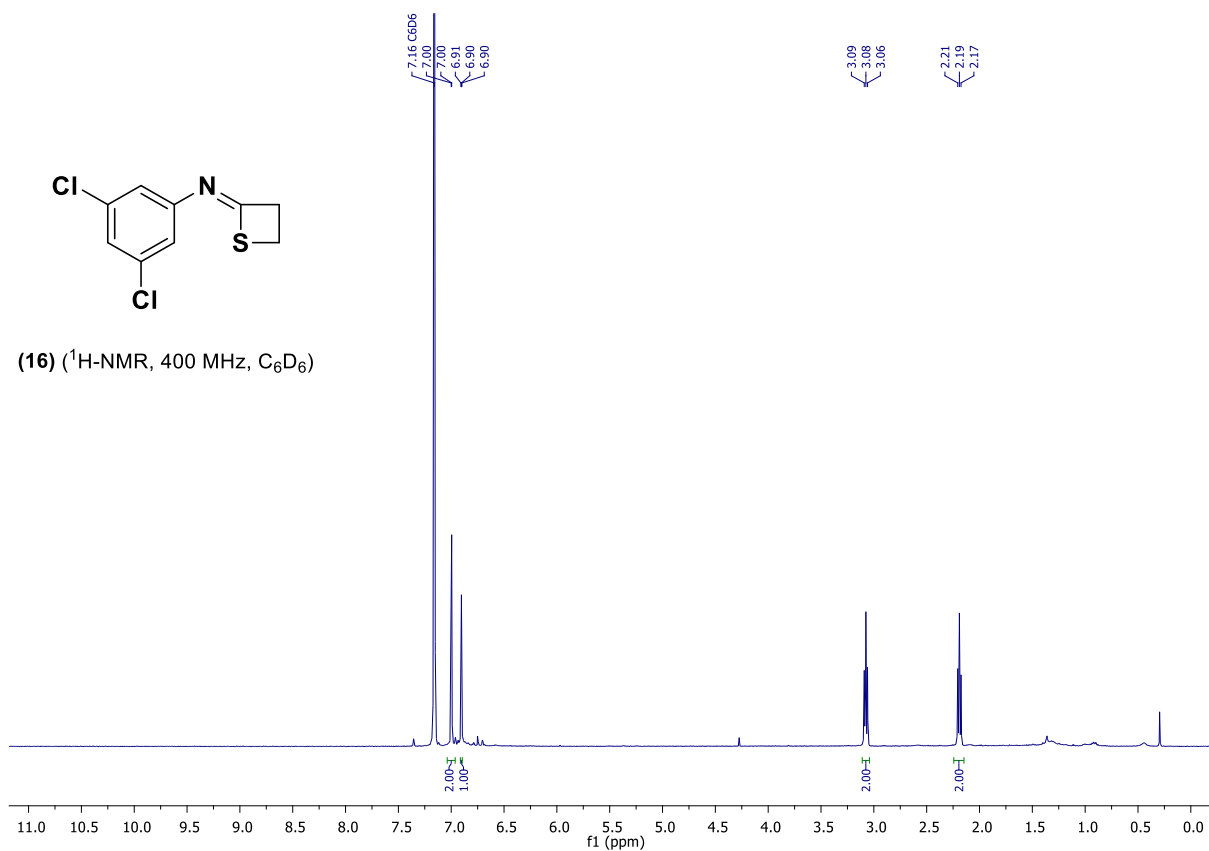
(14) (^1H -NMR, 400 MHz, C_6D_6)

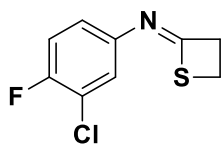


(14) (^{13}C -NMR, 100 MHz, C_6D_6)

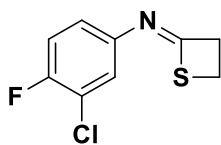
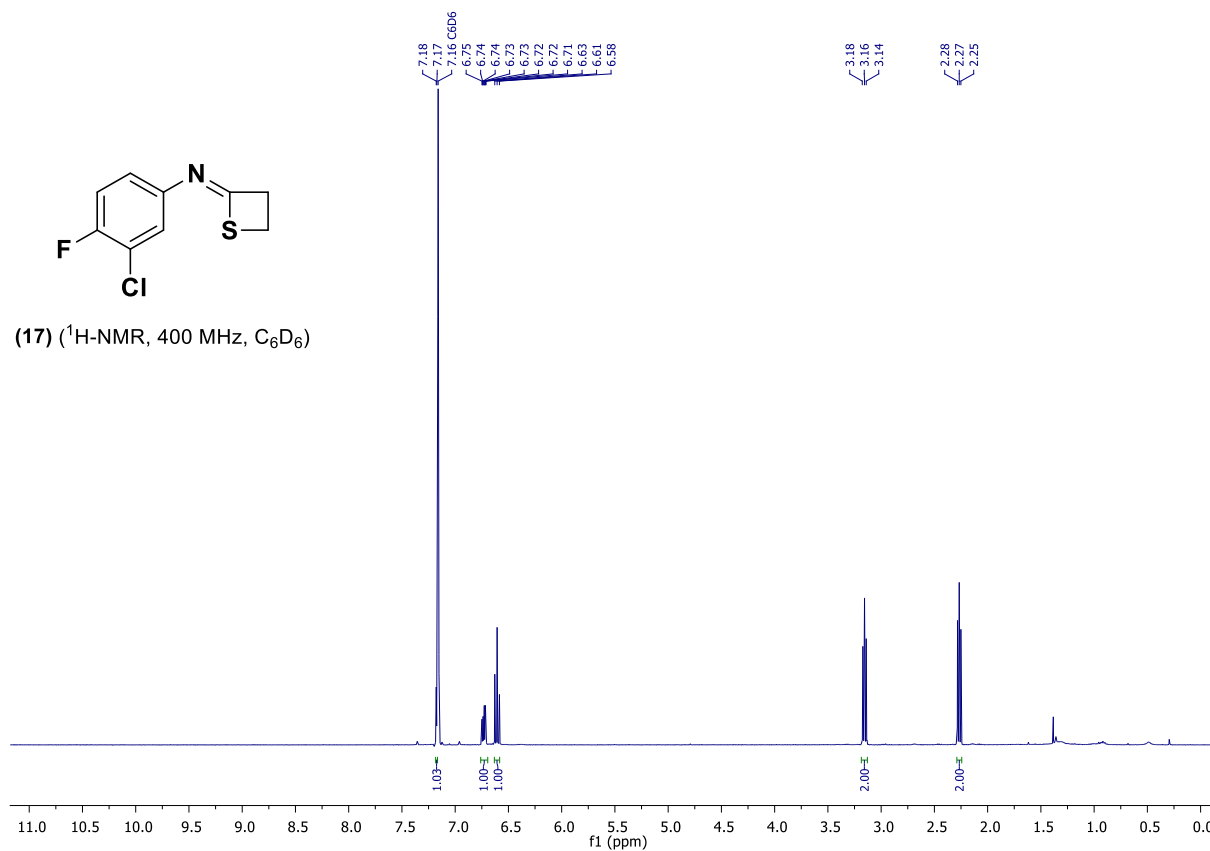




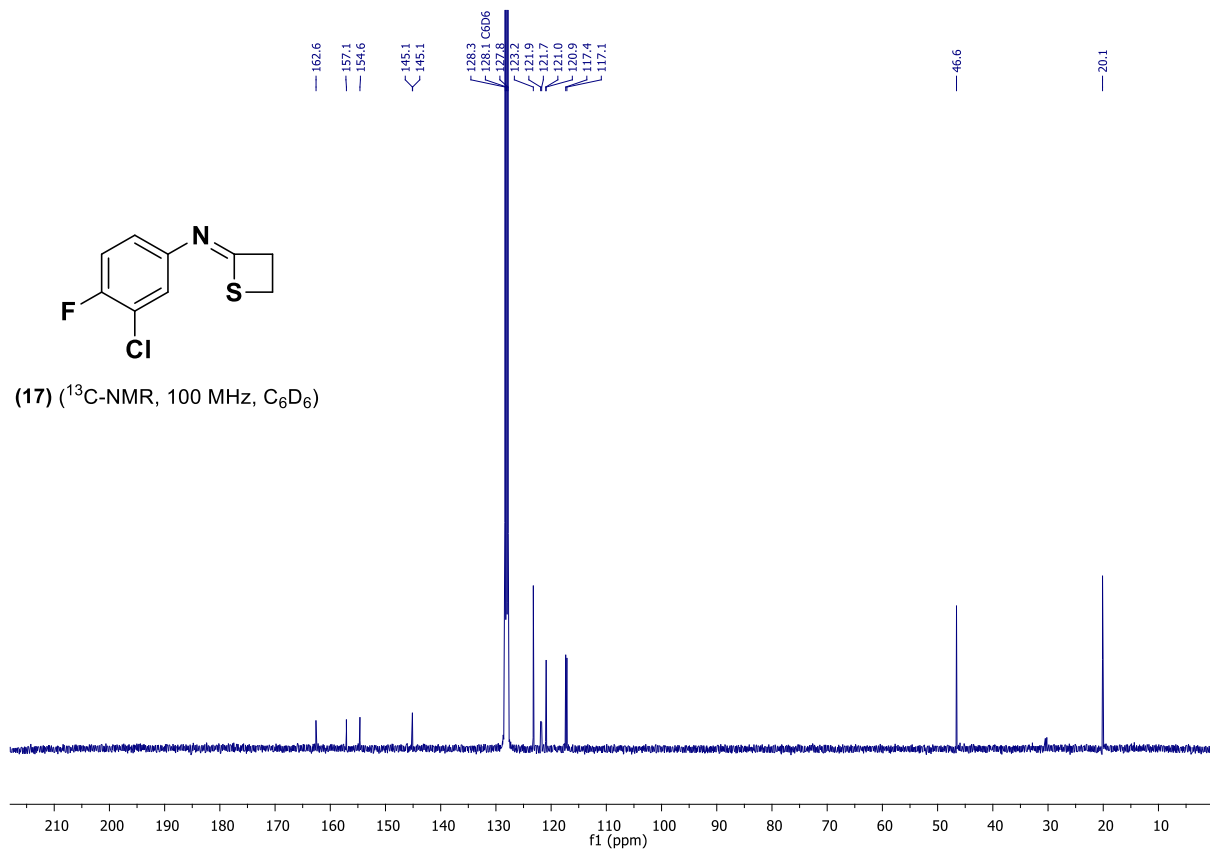


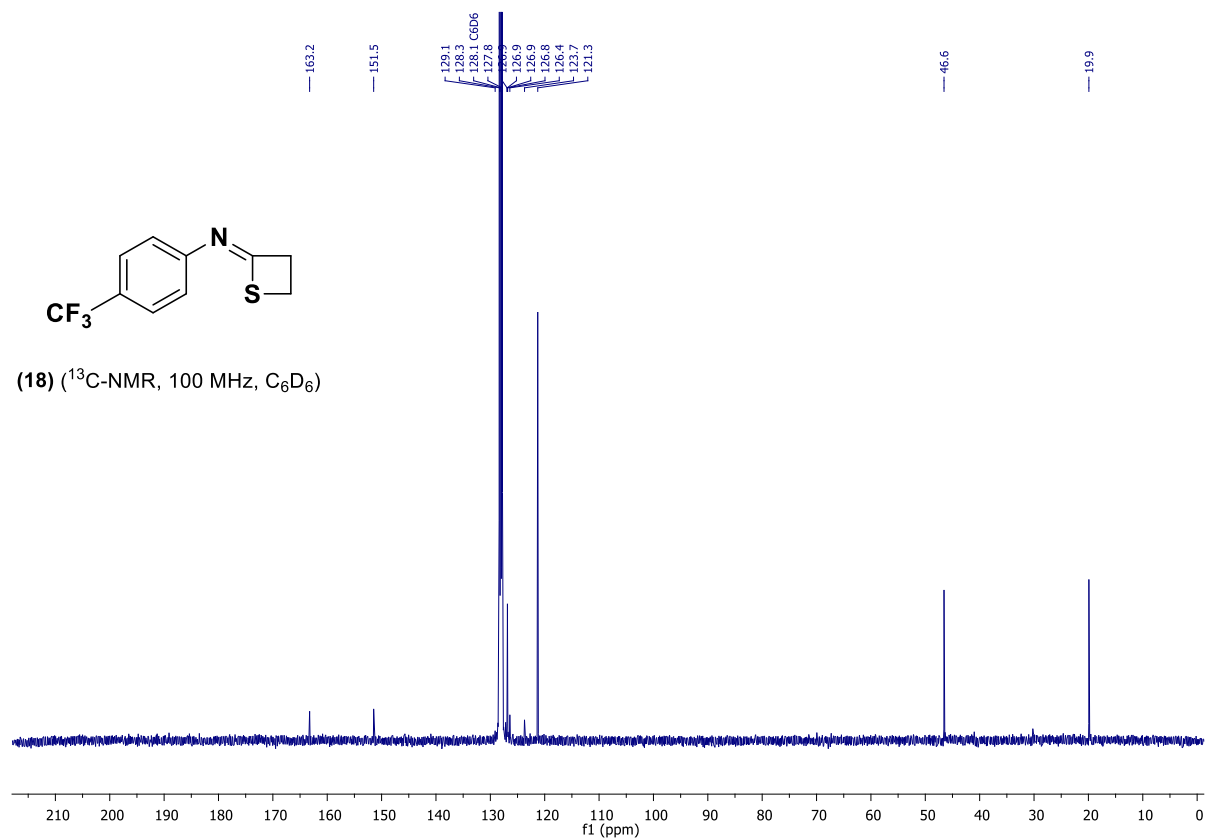
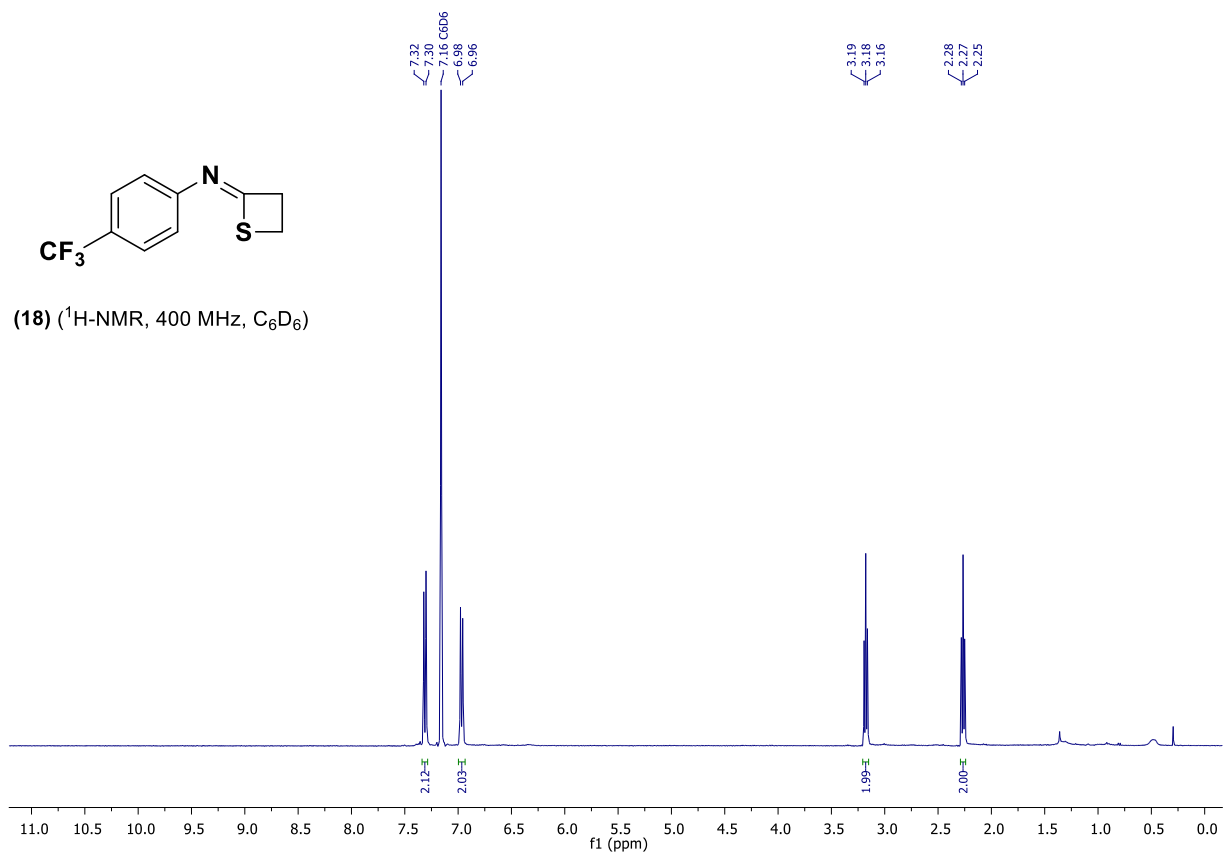


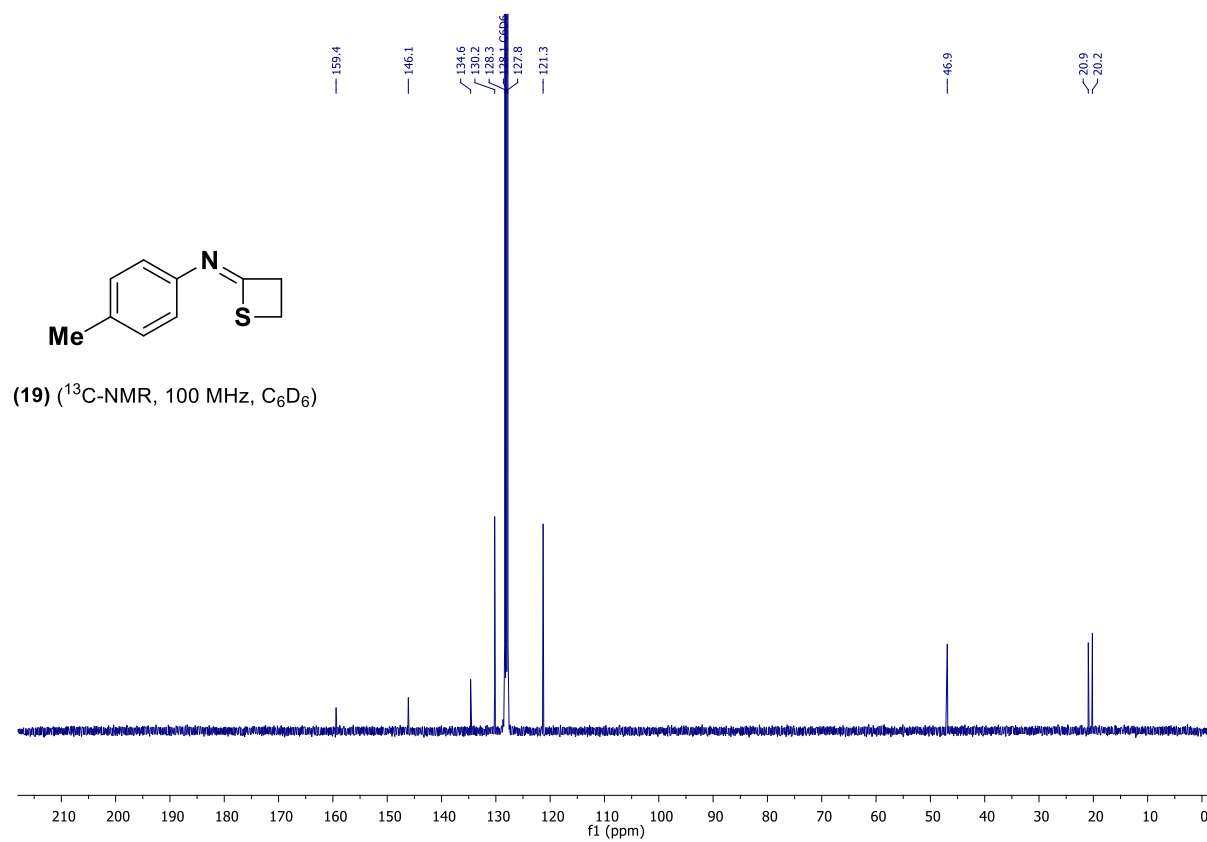
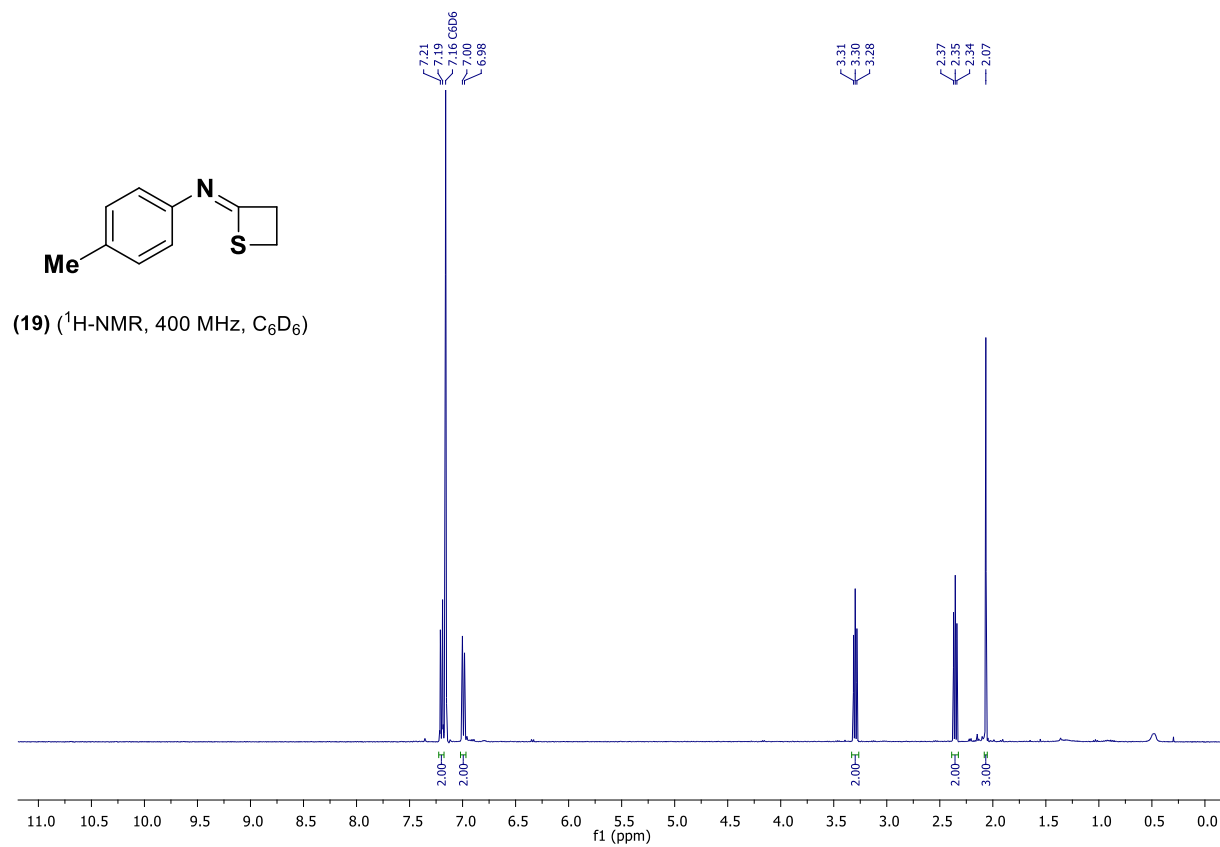
(17) (^1H -NMR, 400 MHz, C_6D_6)

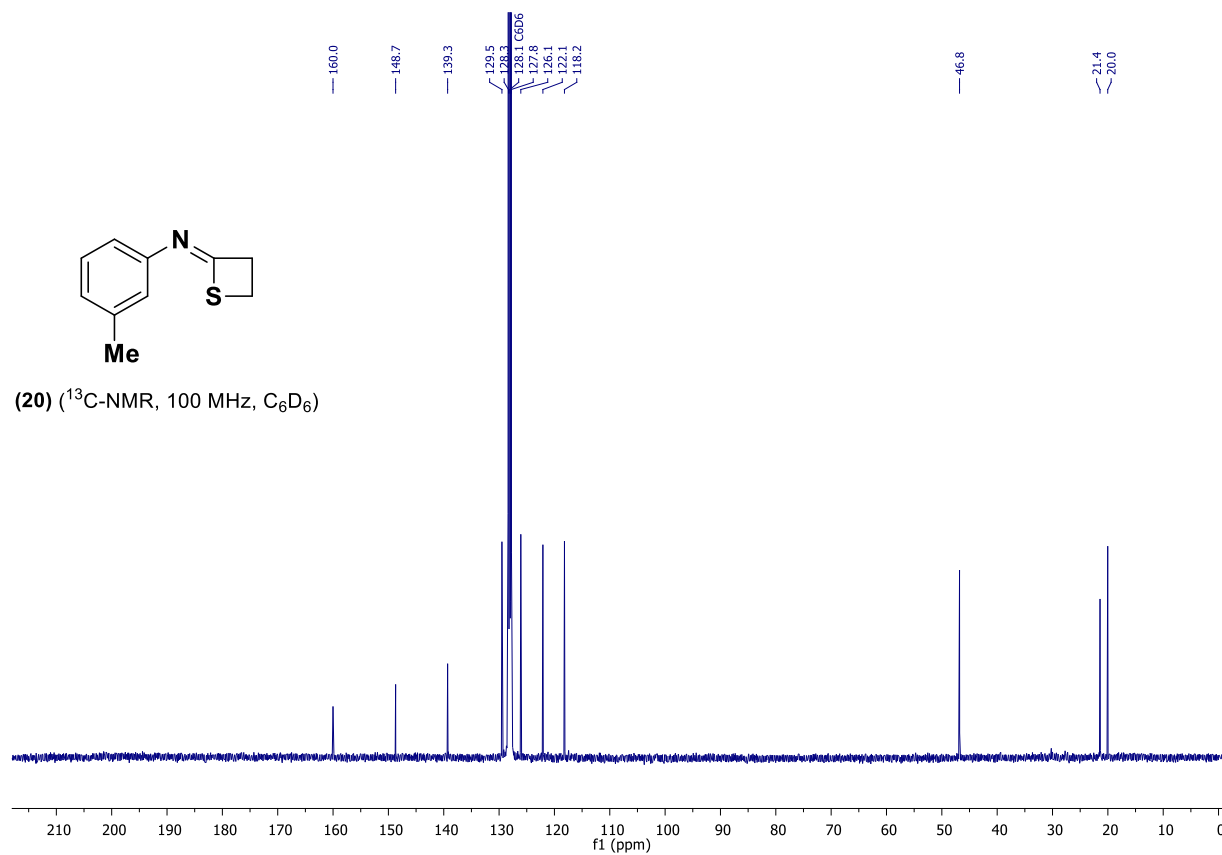
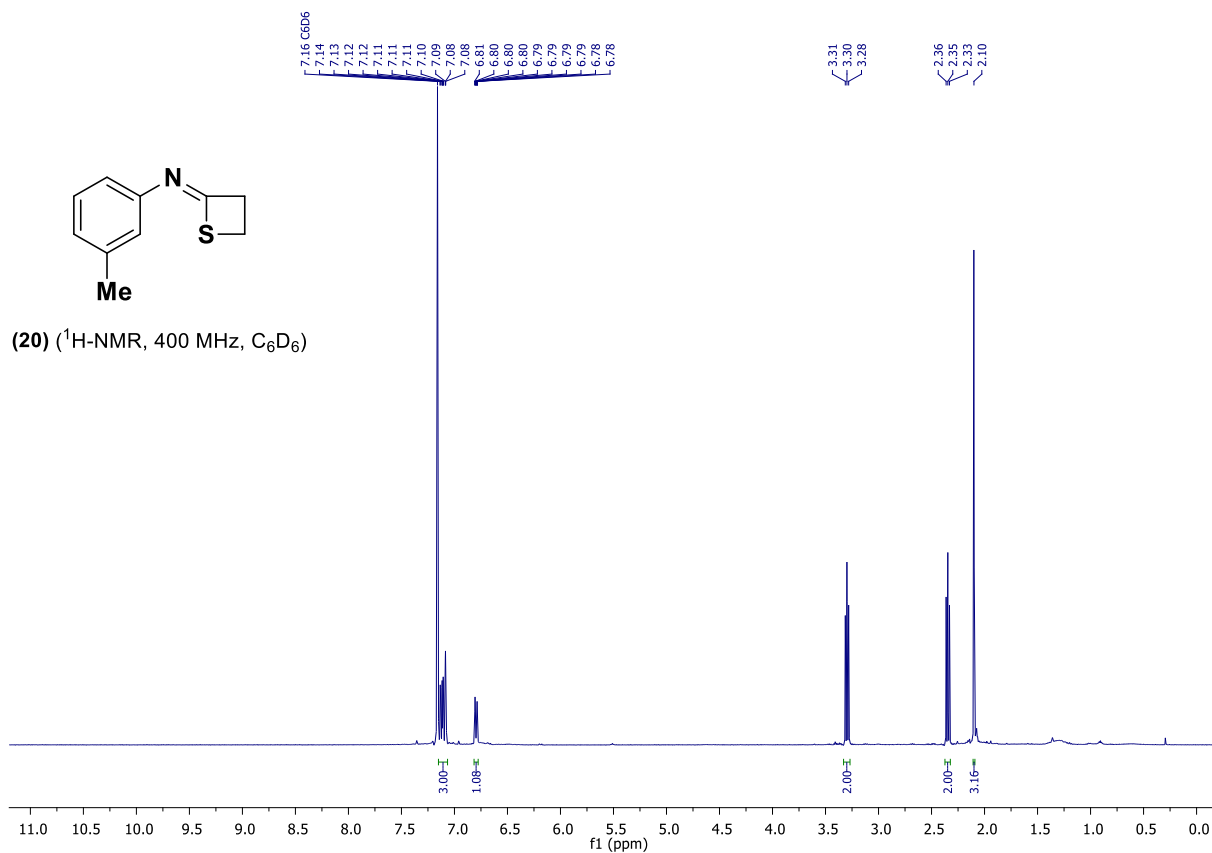


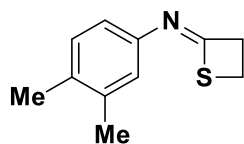
(17) (^{13}C -NMR, 100 MHz, C_6D_6)



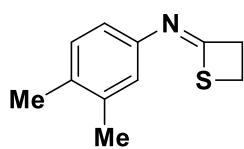
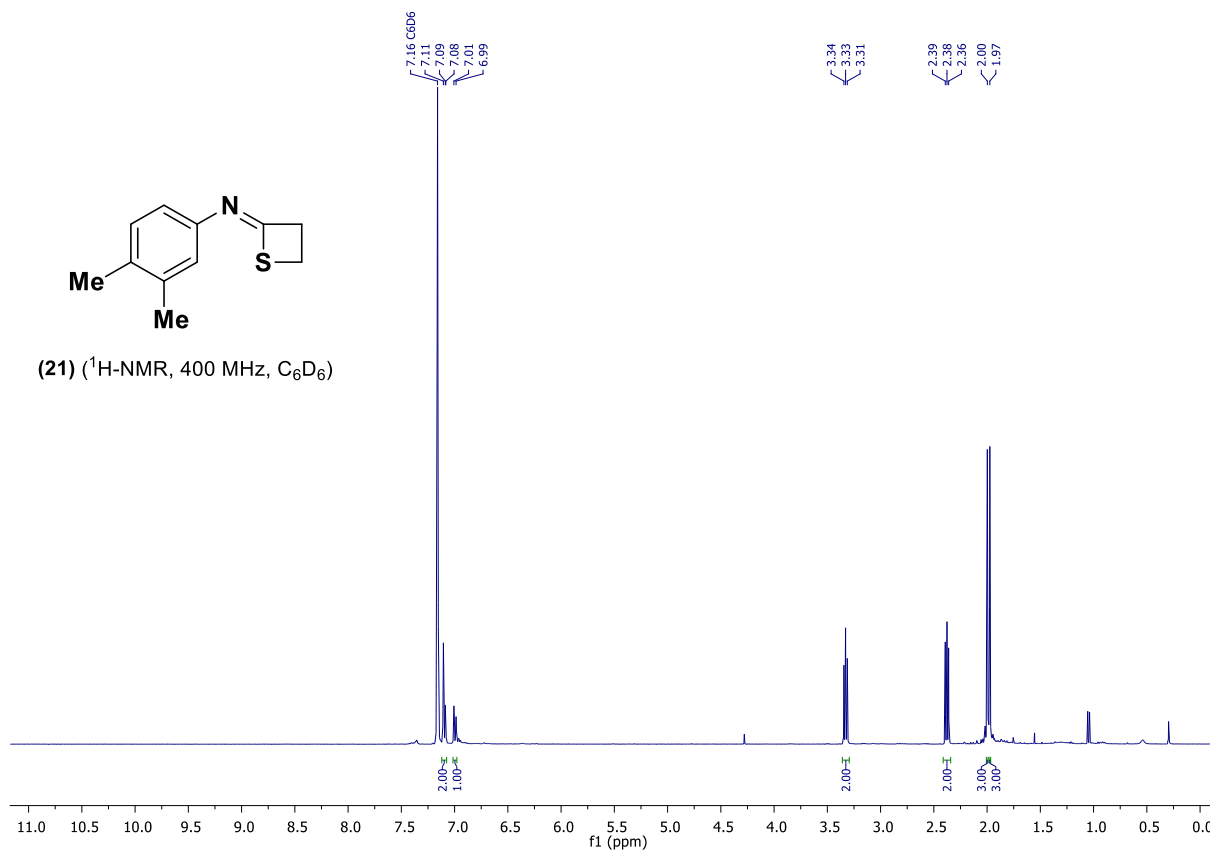




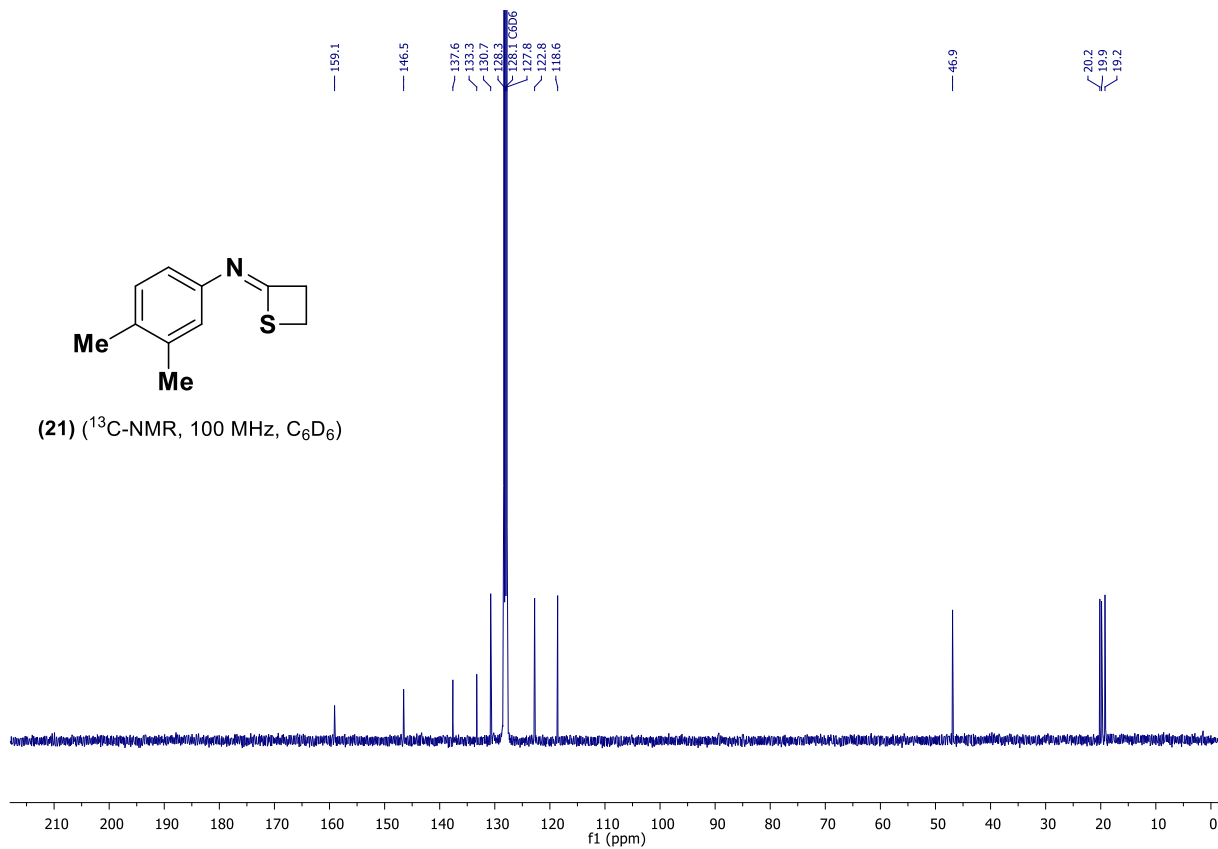


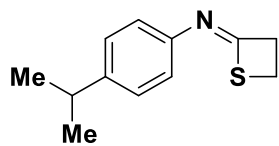


(21) (^1H -NMR, 400 MHz, C_6D_6)

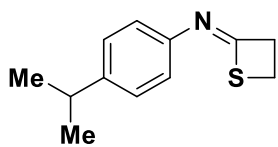
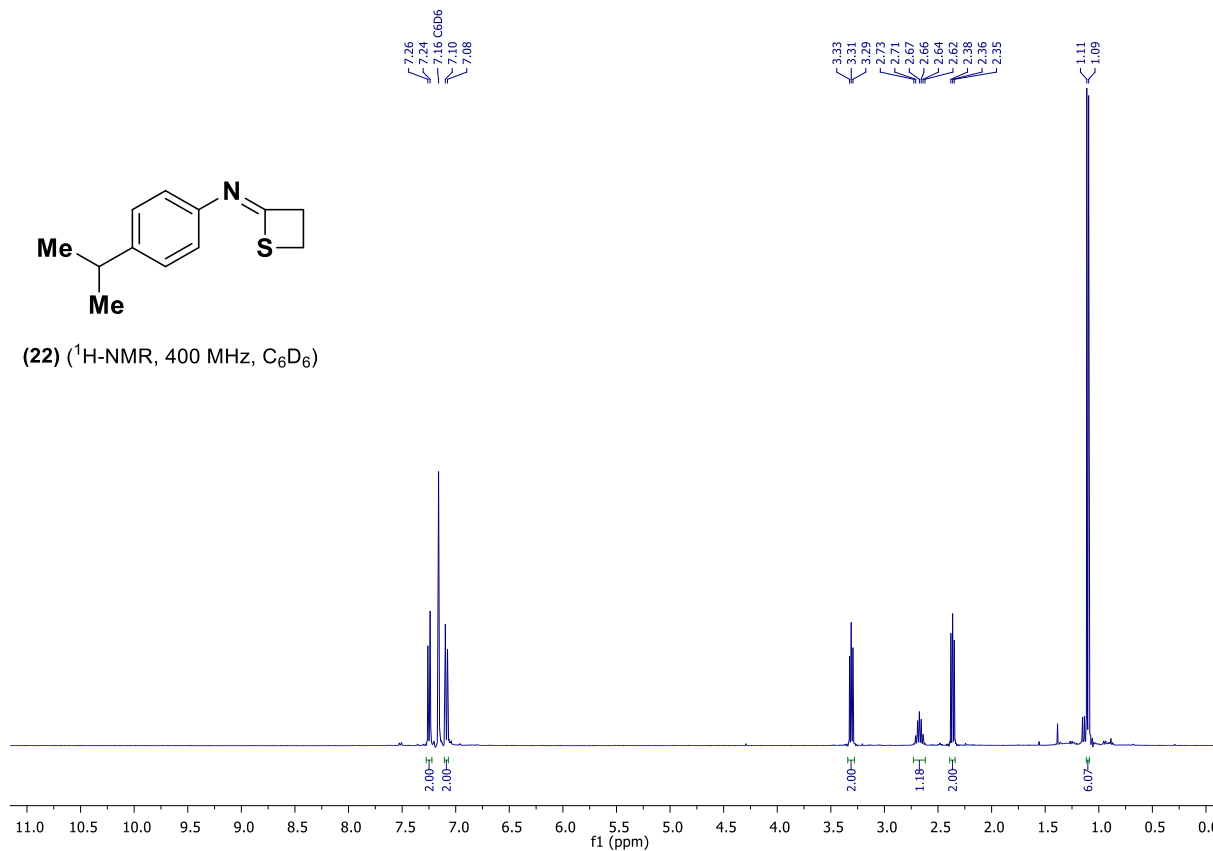


(21) (^{13}C -NMR, 100 MHz, C_6D_6)

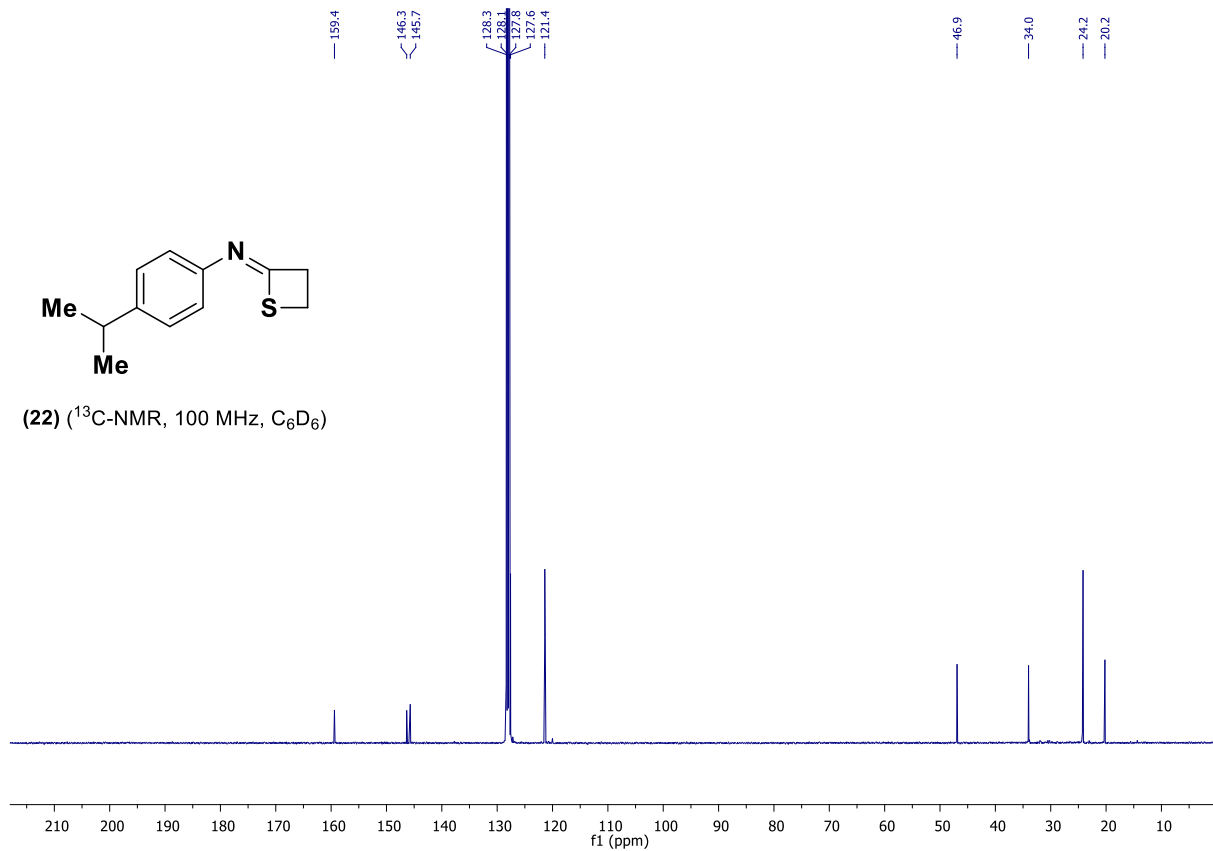


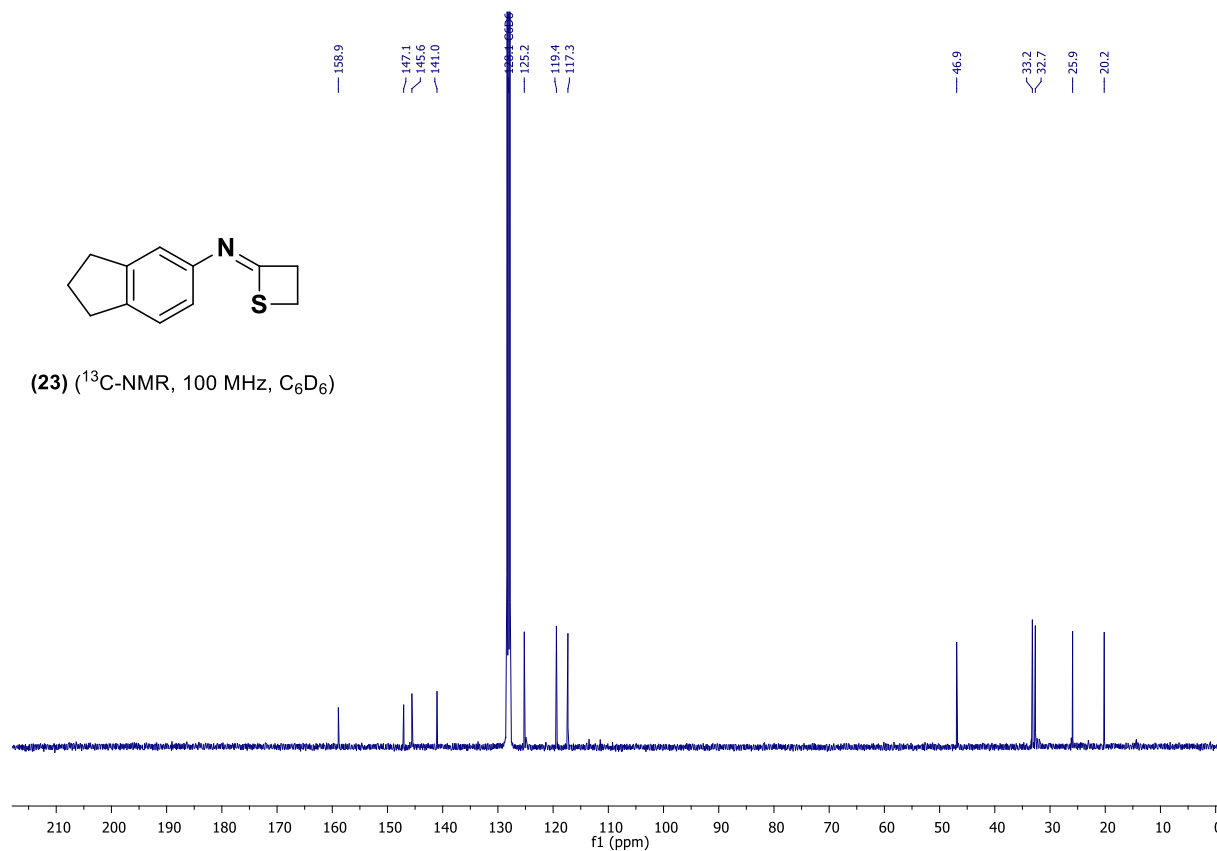
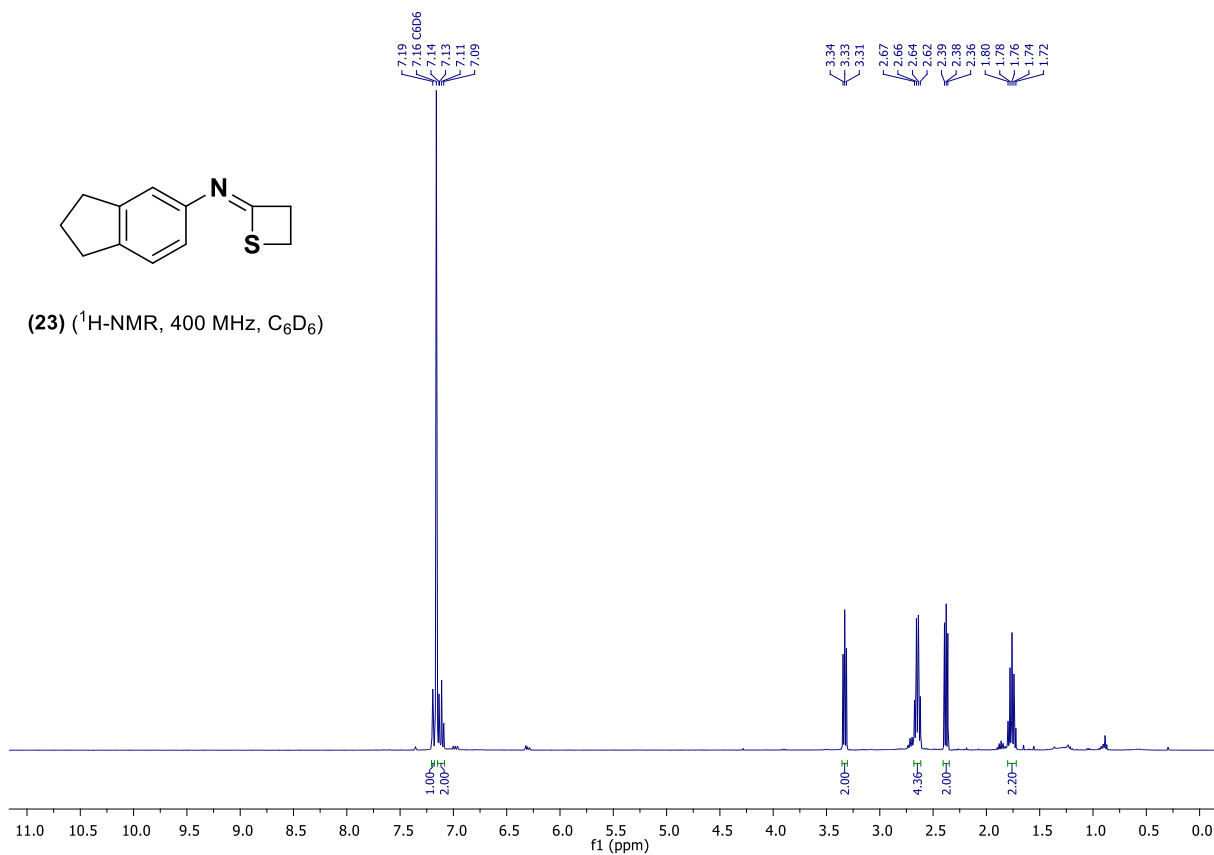


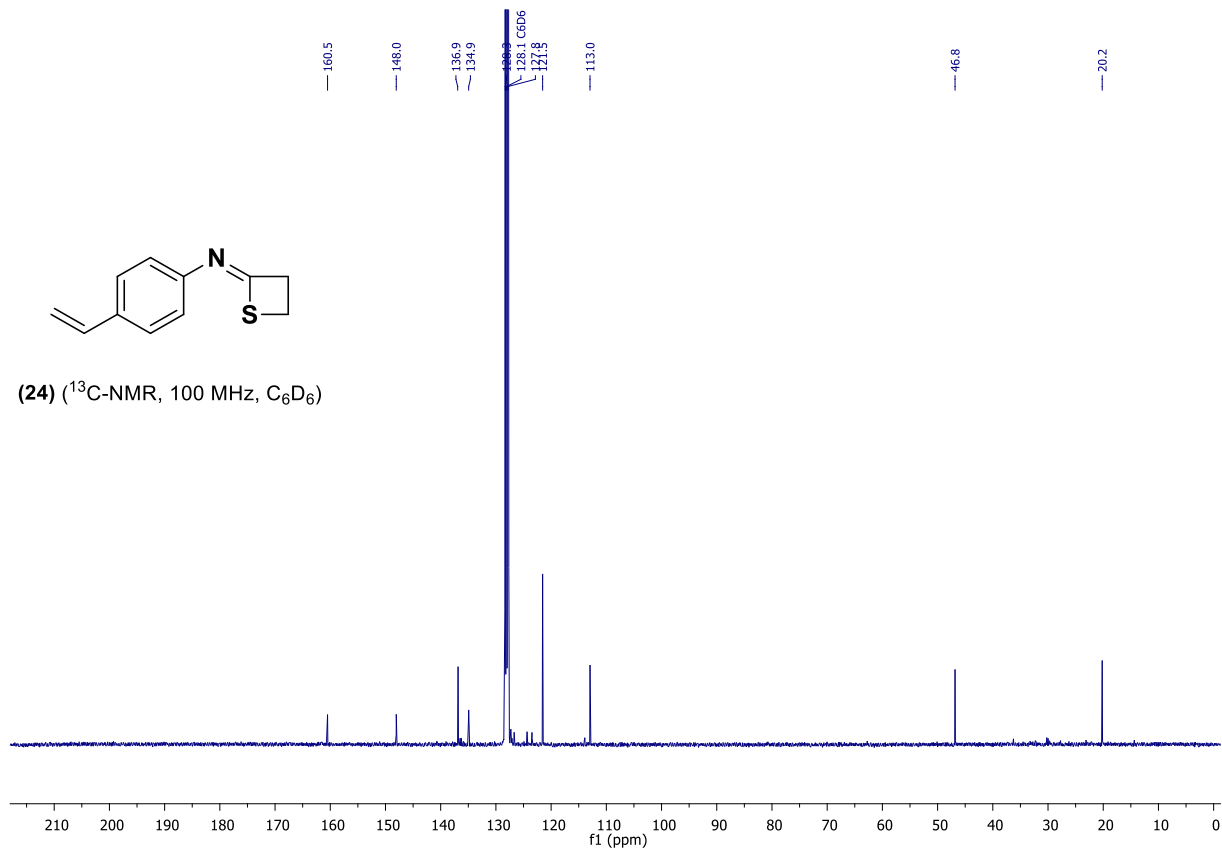
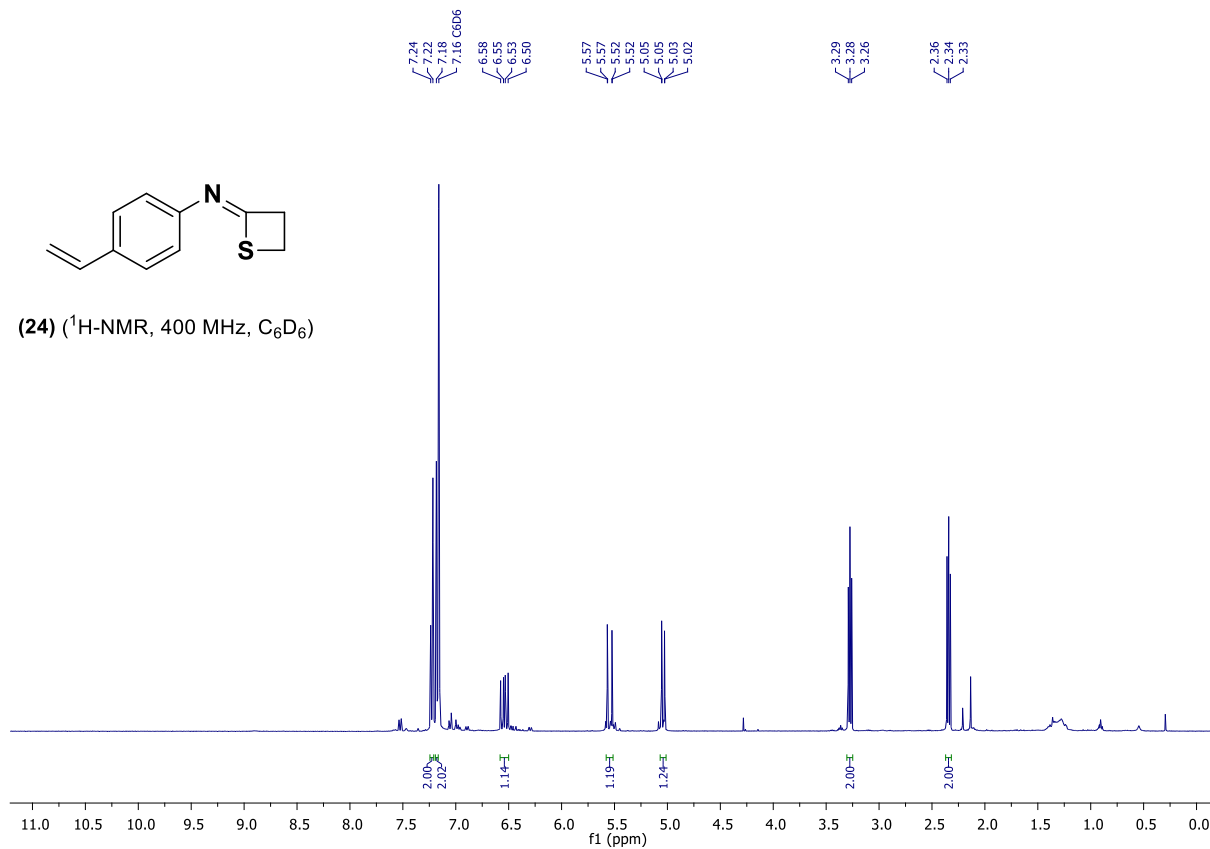
(22) (^1H -NMR, 400 MHz, C_6D_6)

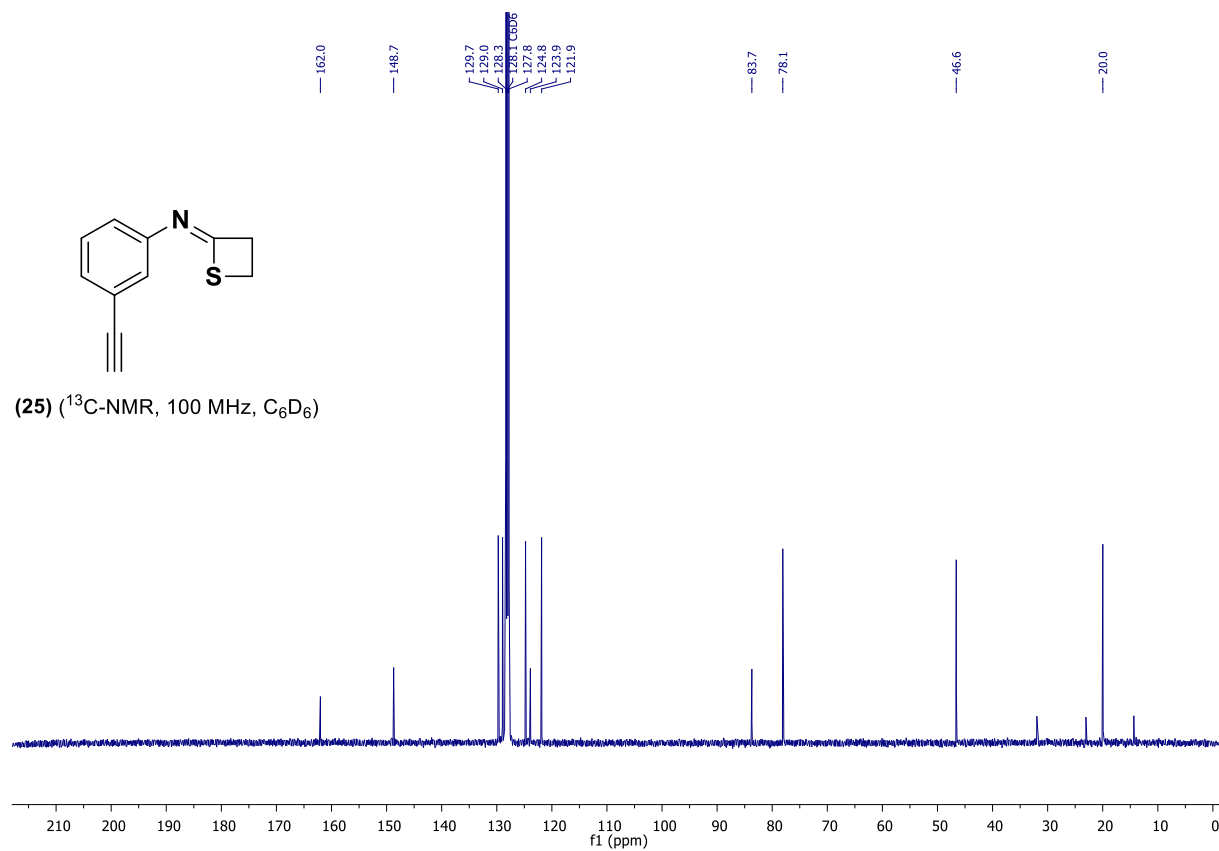
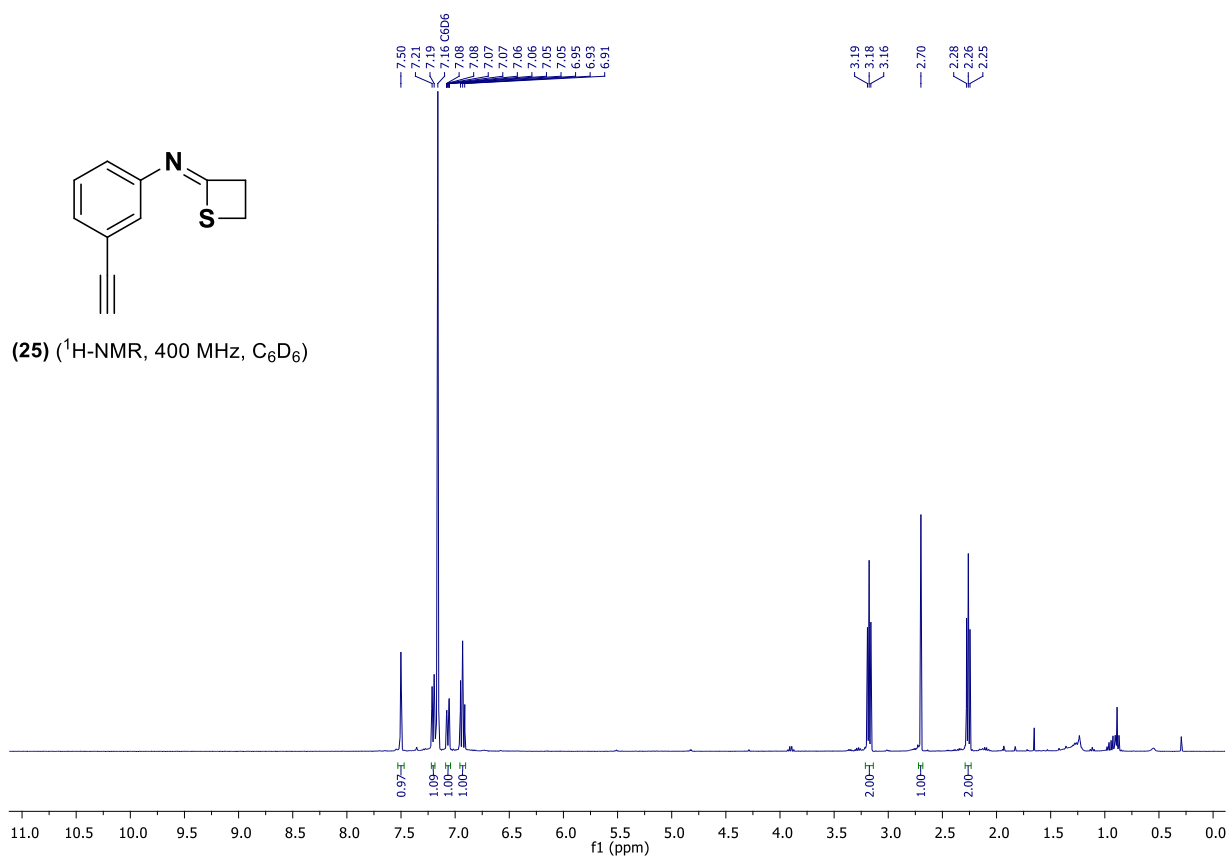


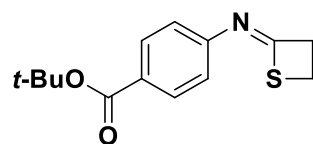
(22) (^{13}C -NMR, 100 MHz, C_6D_6)



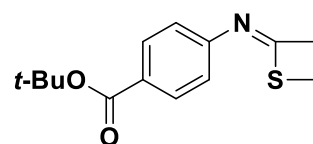
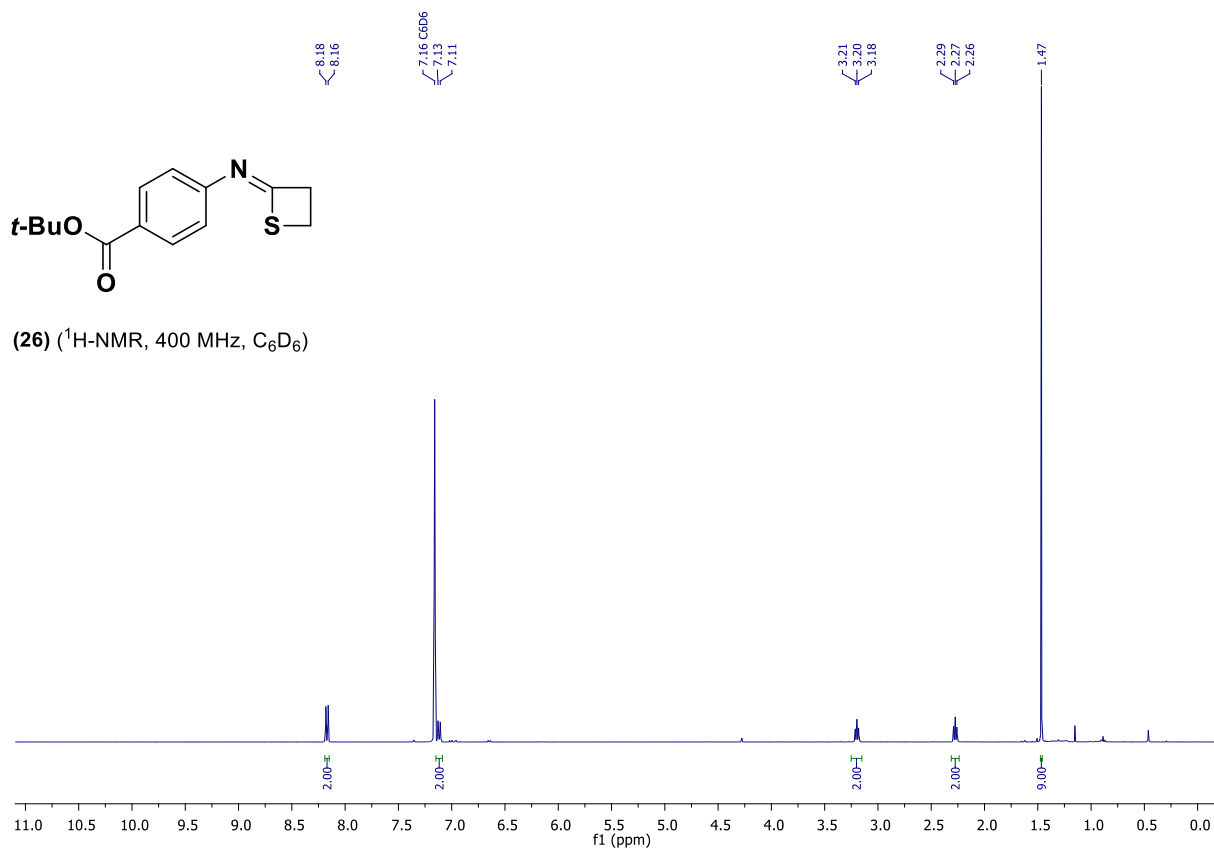




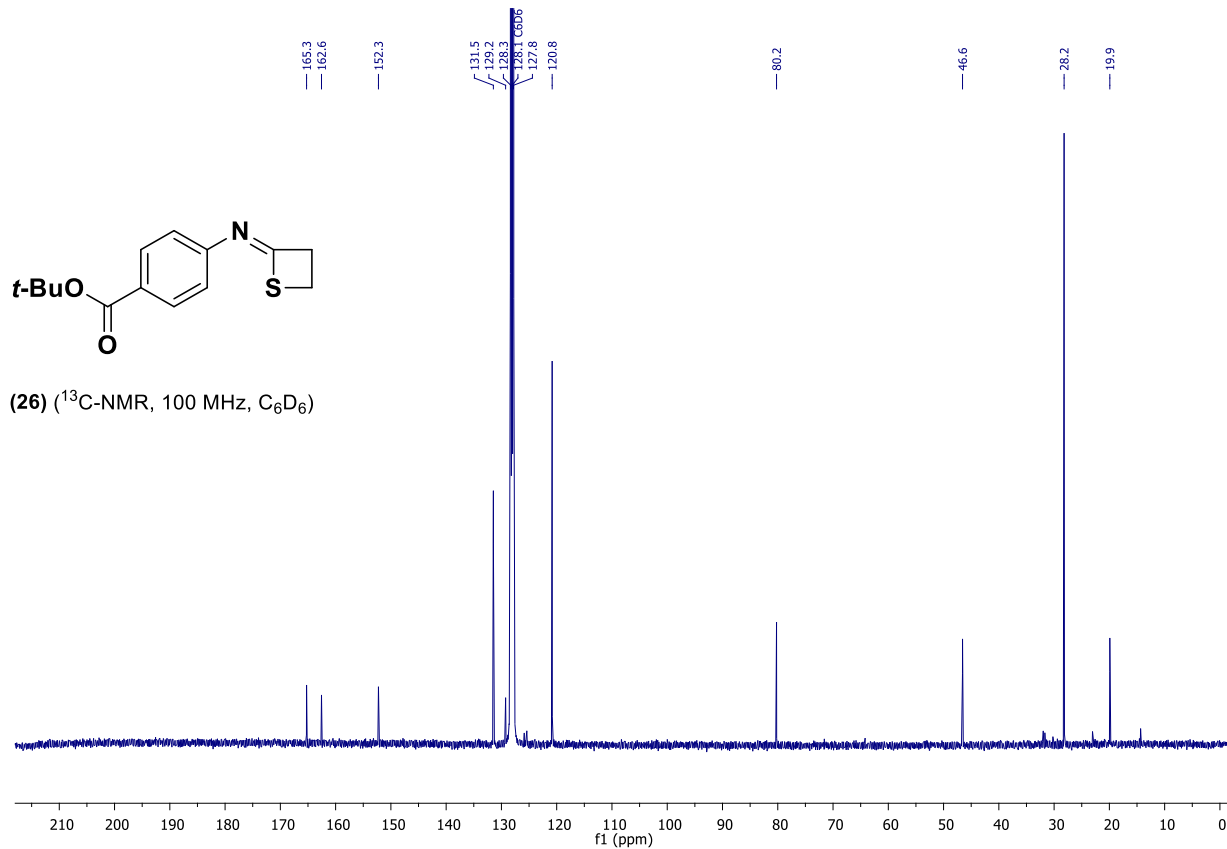


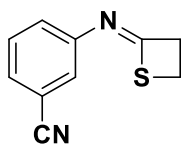


(26) (^1H -NMR, 400 MHz, C_6D_6)

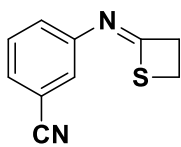
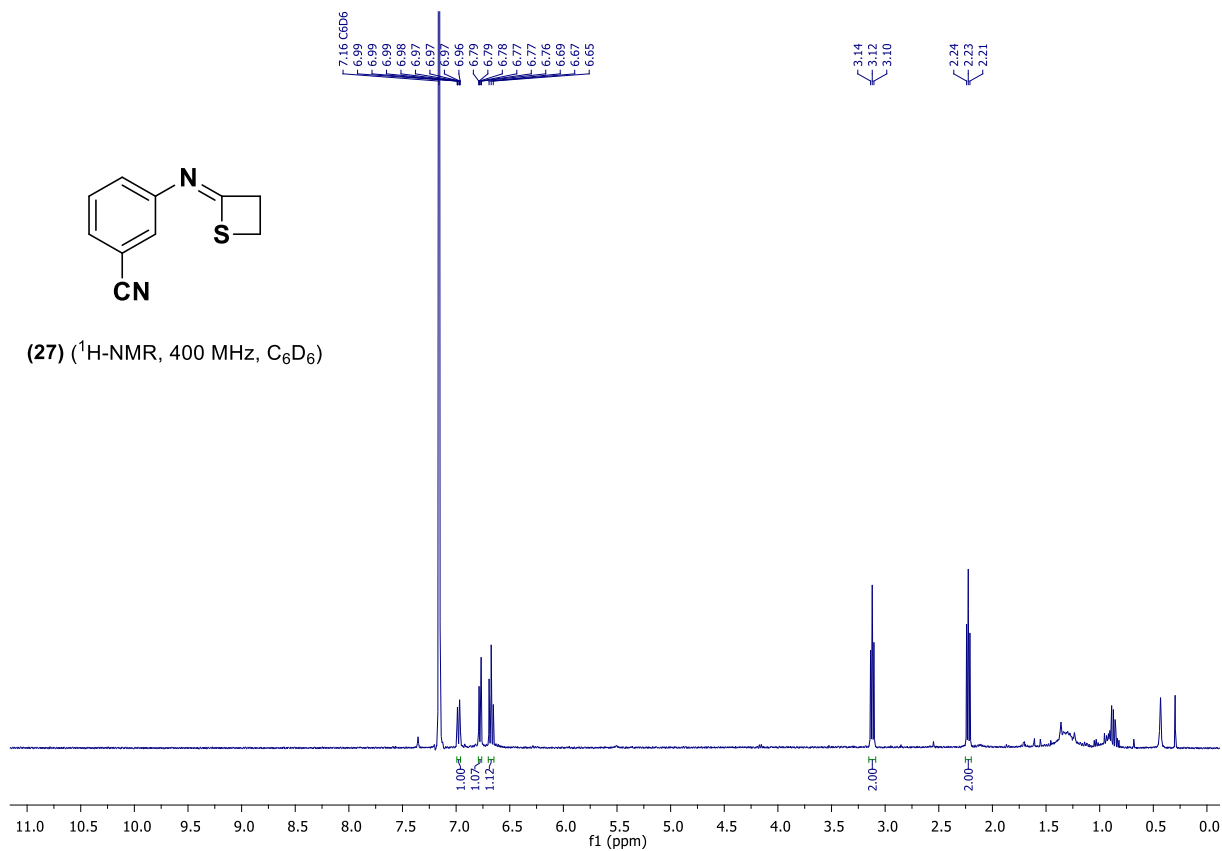


(26) (^{13}C -NMR, 100 MHz, C_6D_6)

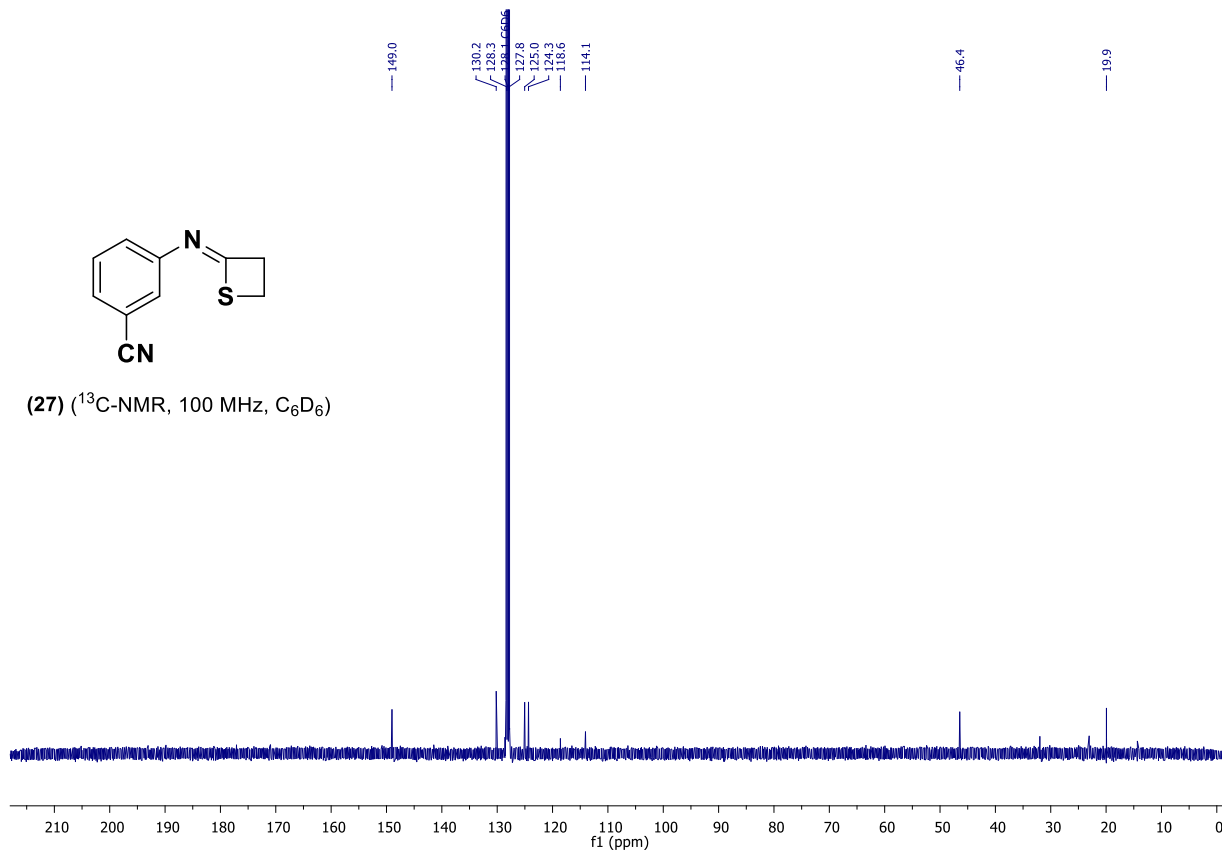


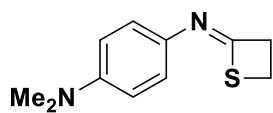


(27) (^1H -NMR, 400 MHz, C_6D_6)

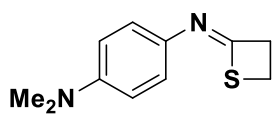
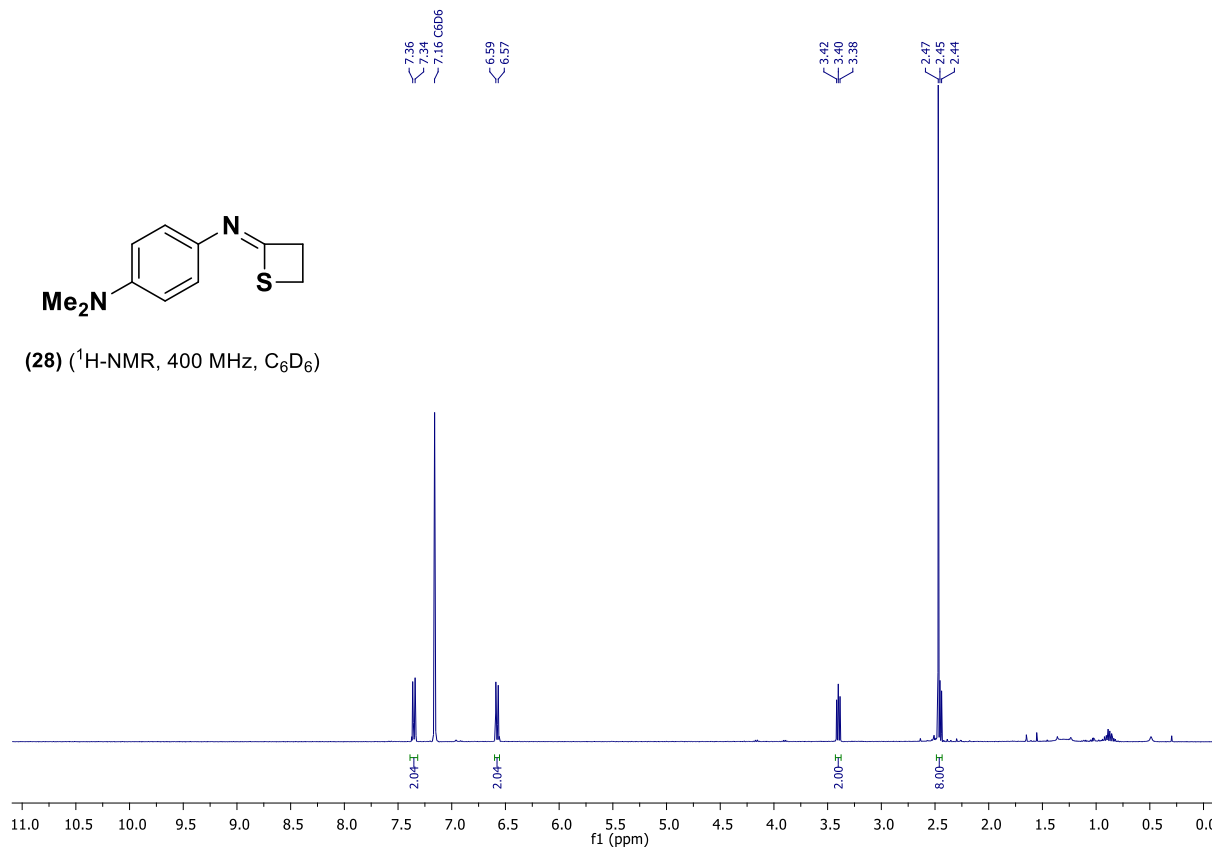


(27) (^{13}C -NMR, 100 MHz, C_6D_6)

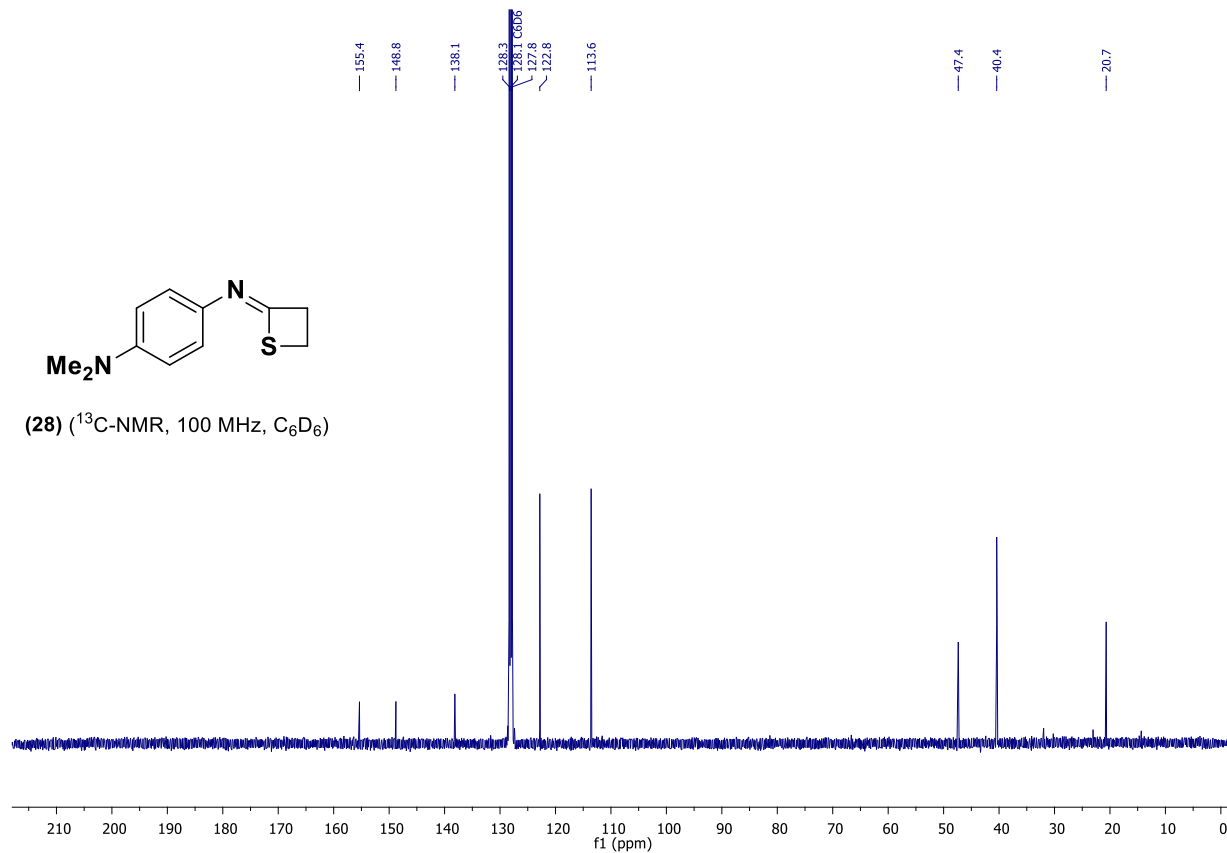


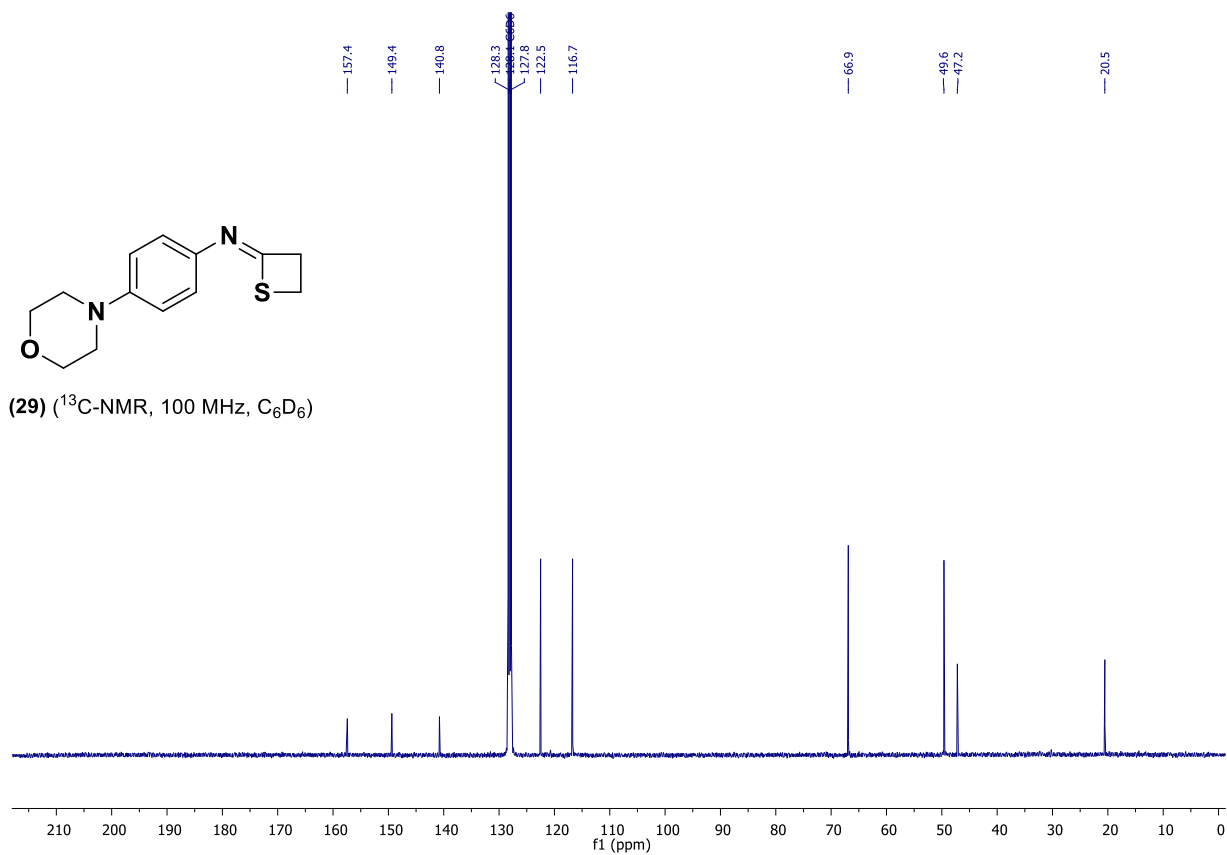
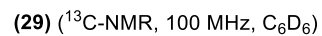
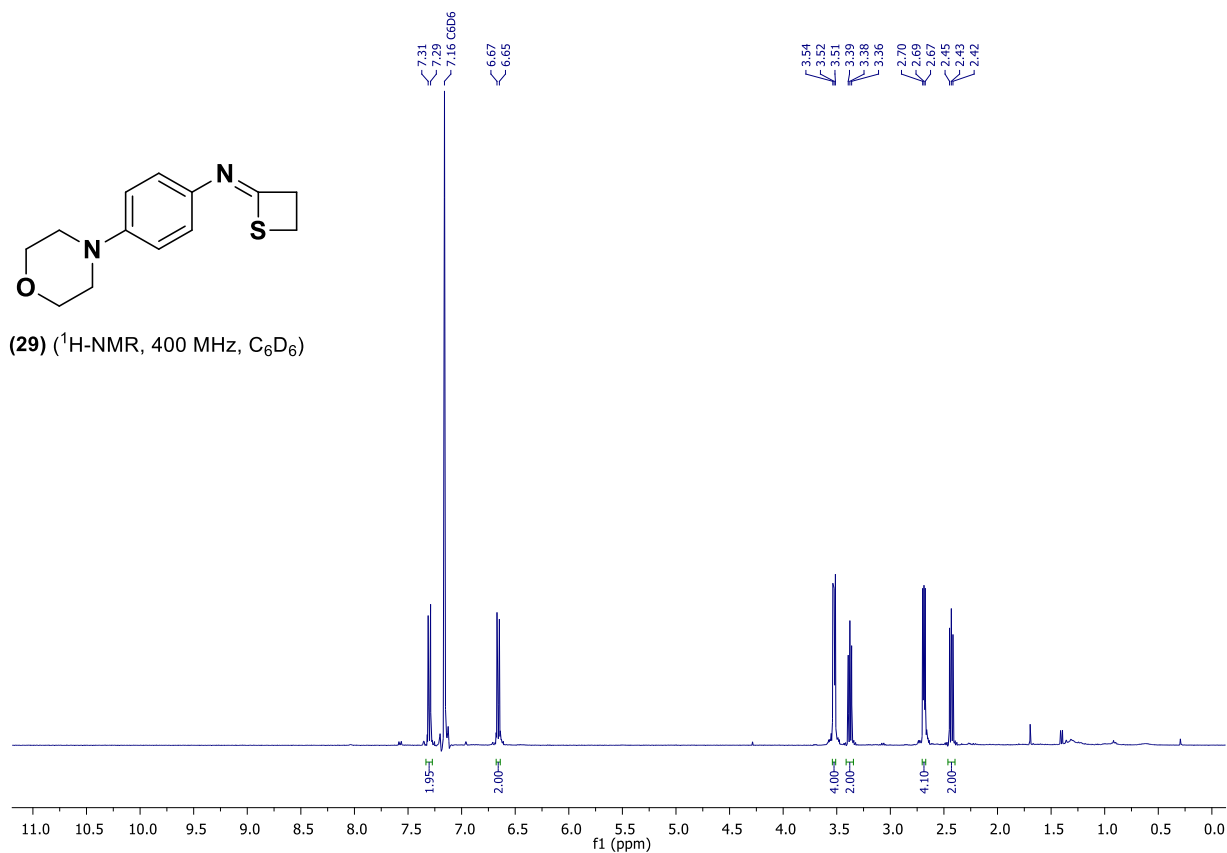
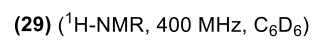


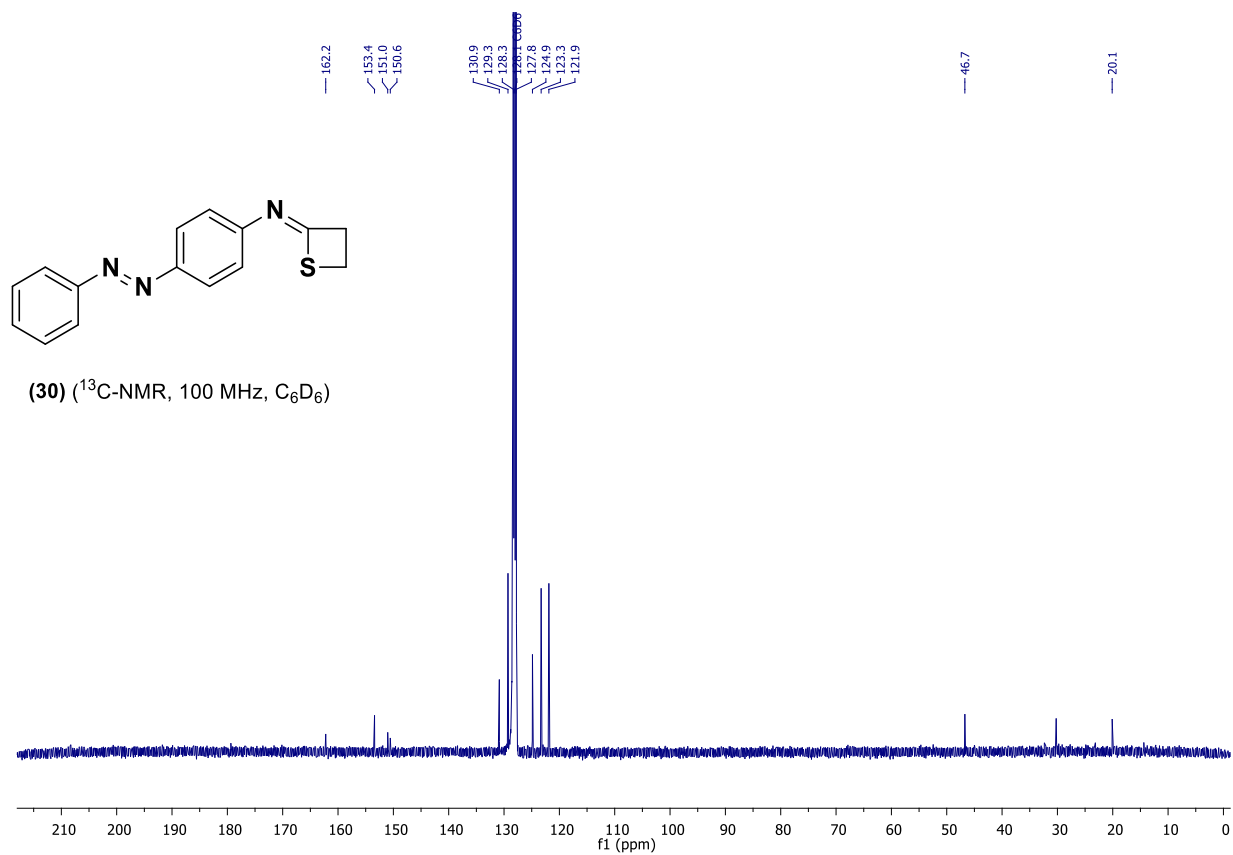
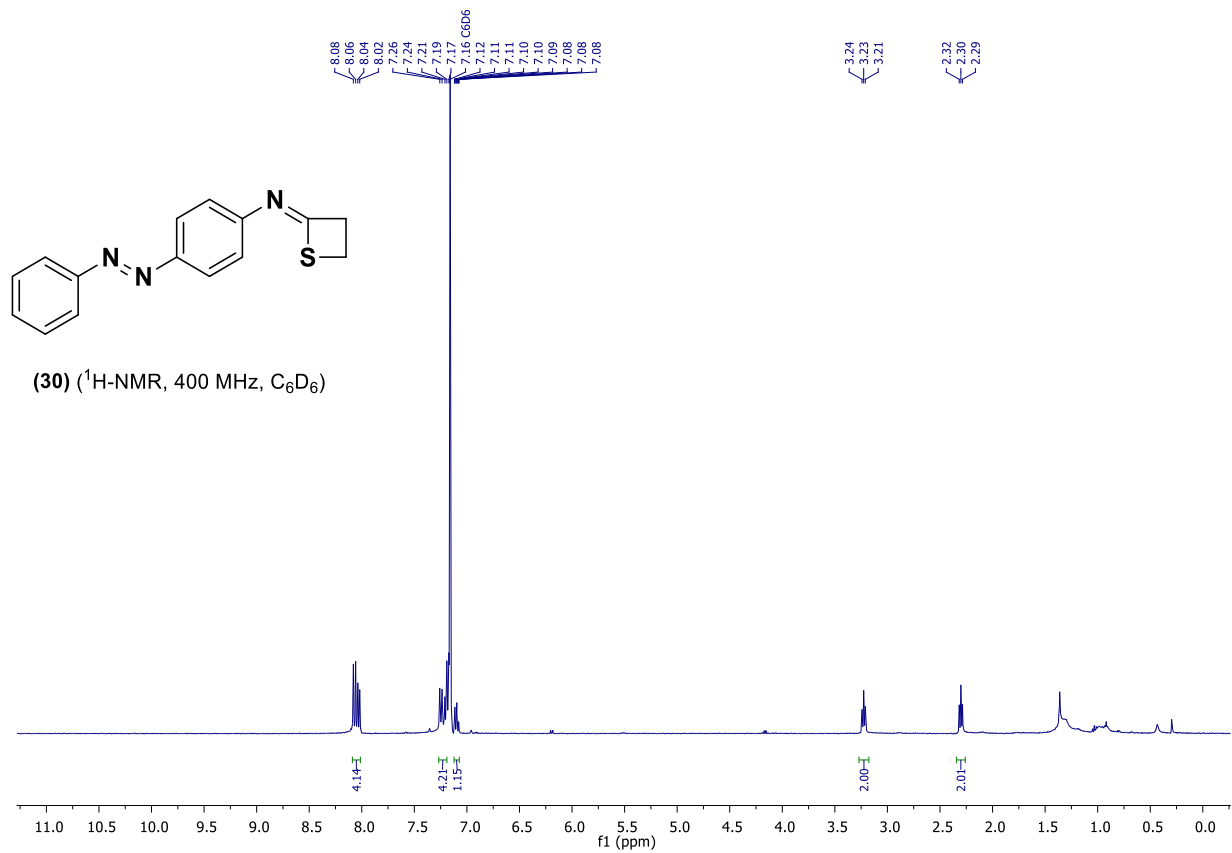
(28) (^1H -NMR, 400 MHz, C_6D_6)

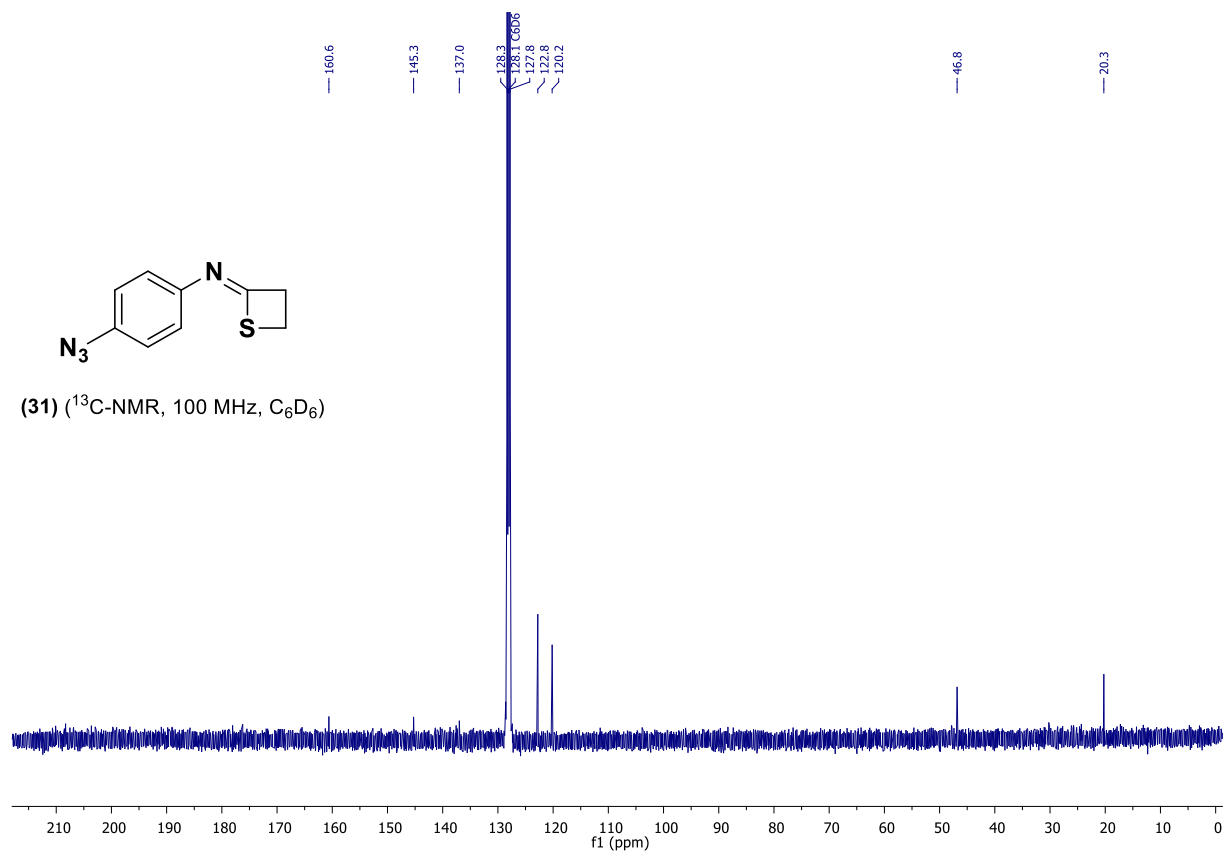
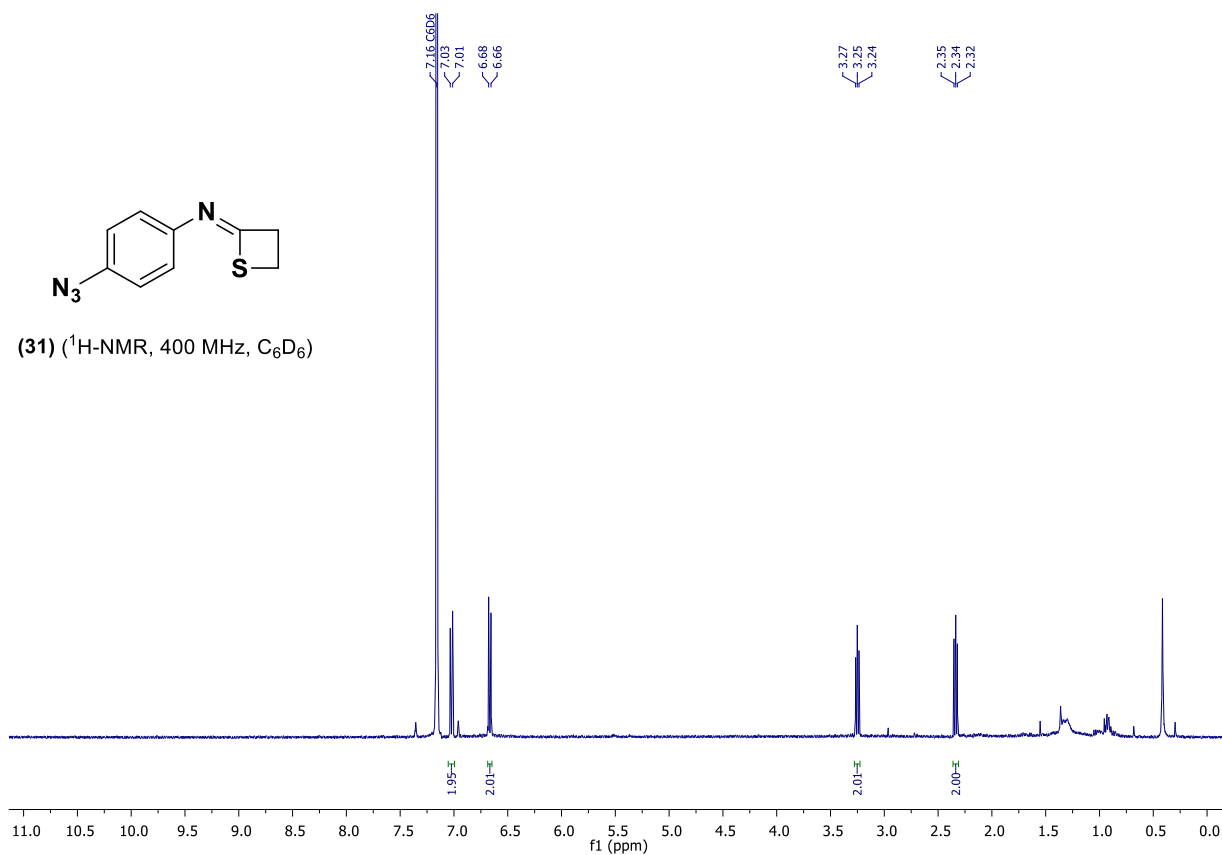


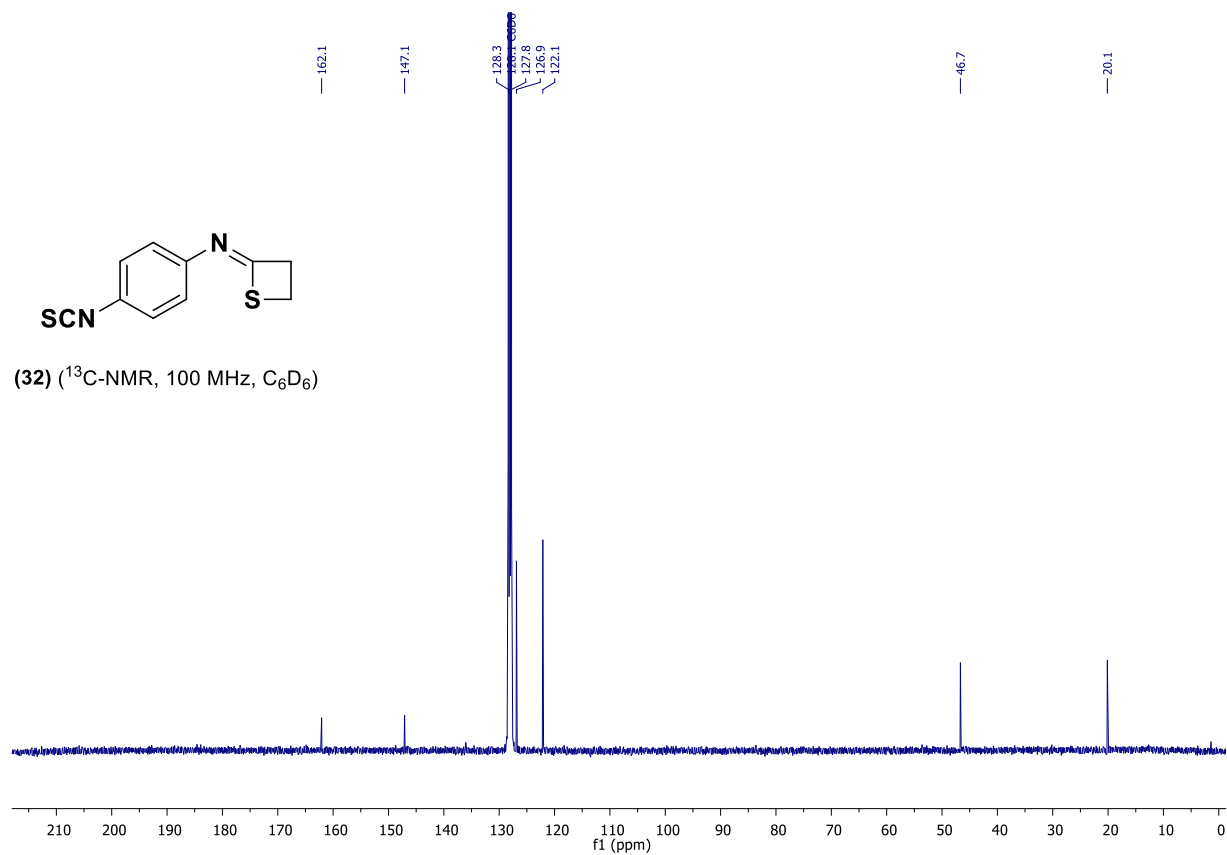
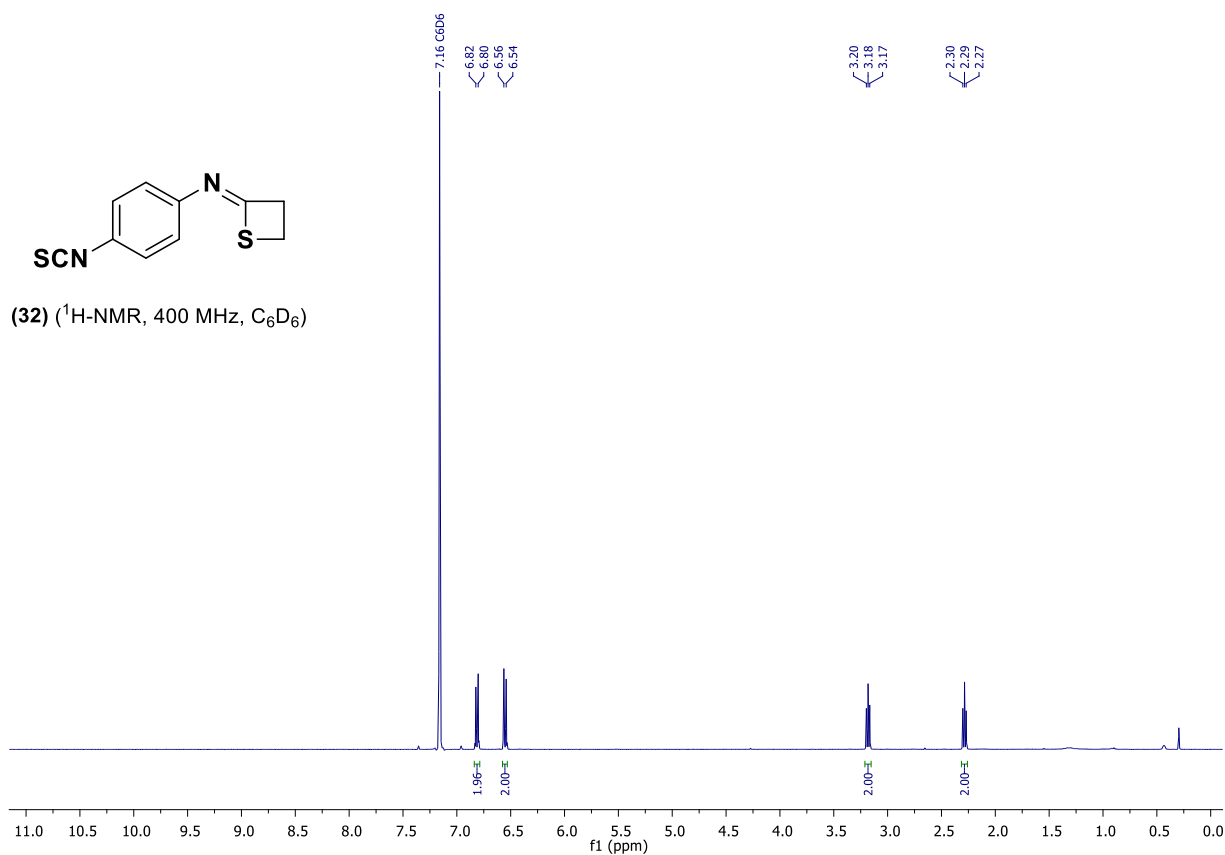
(28) (^{13}C -NMR, 100 MHz, C_6D_6)

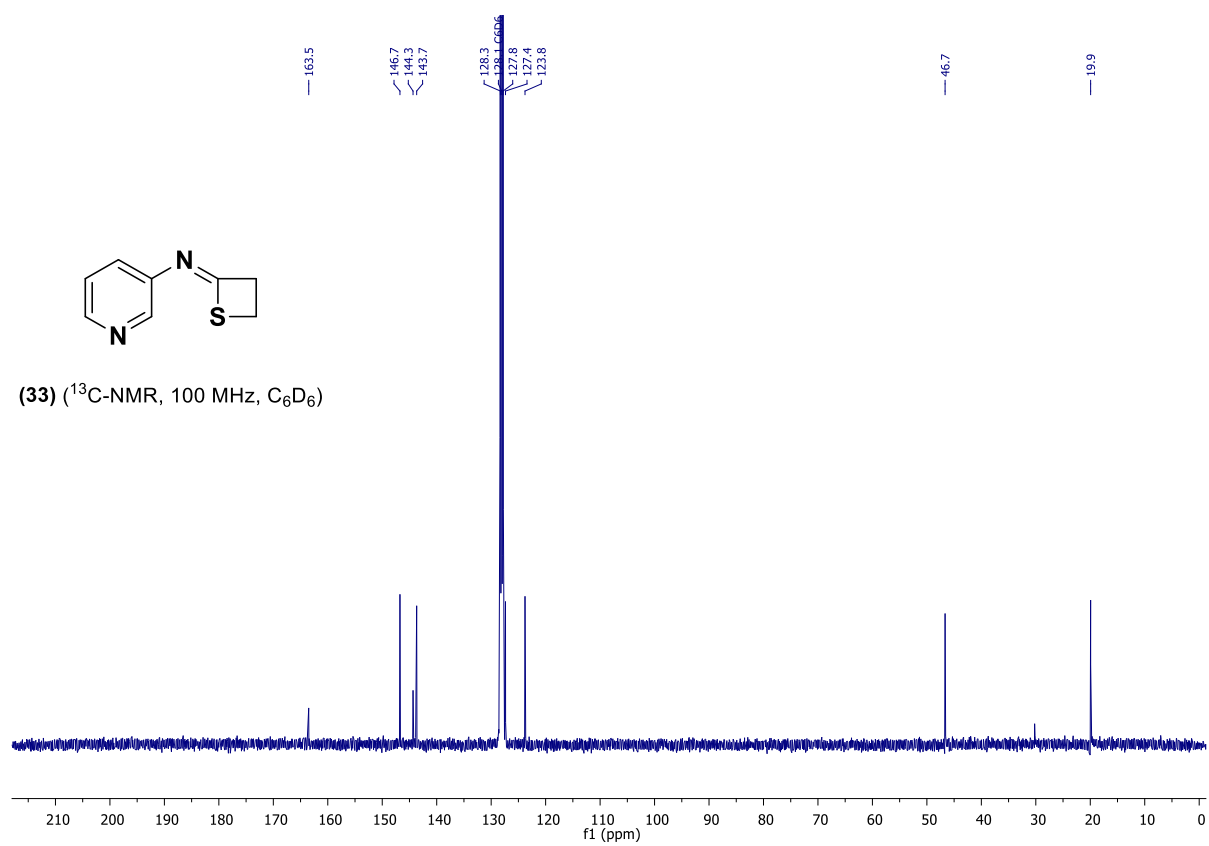
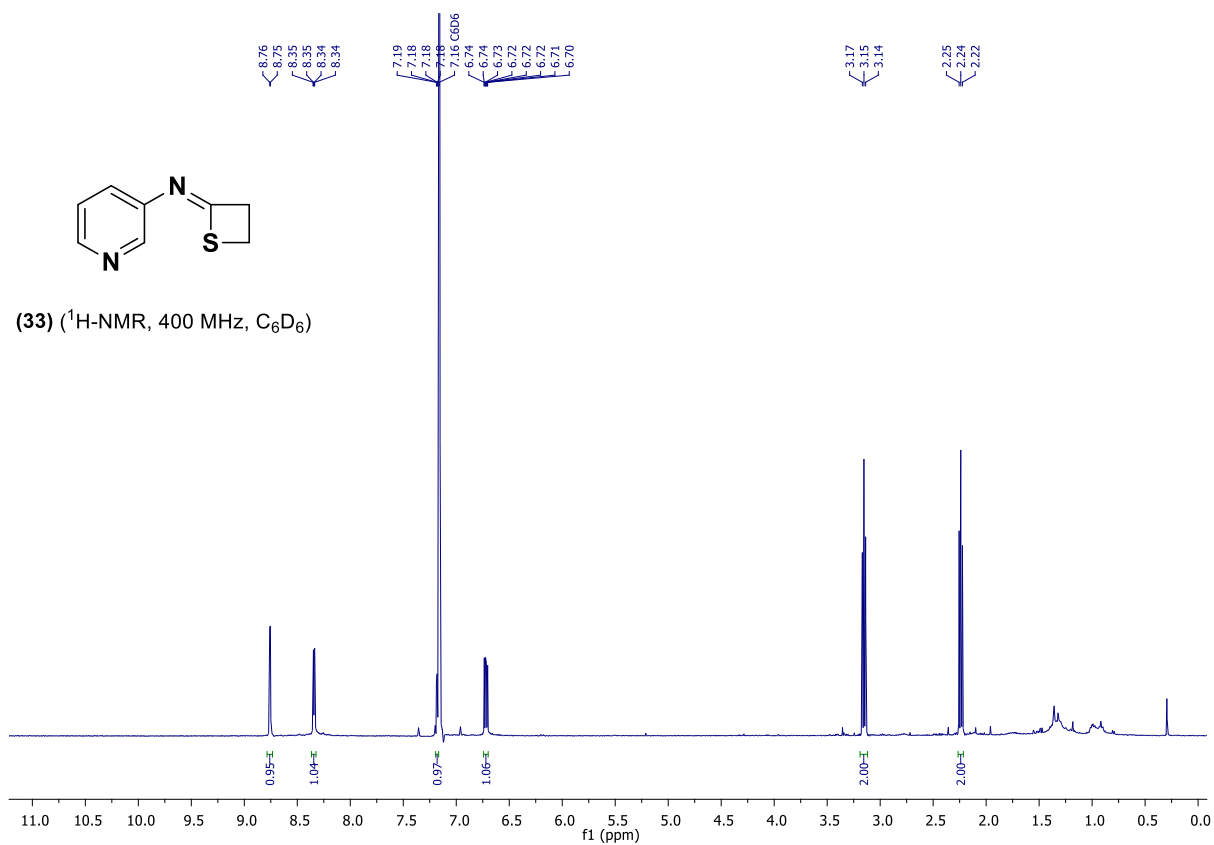


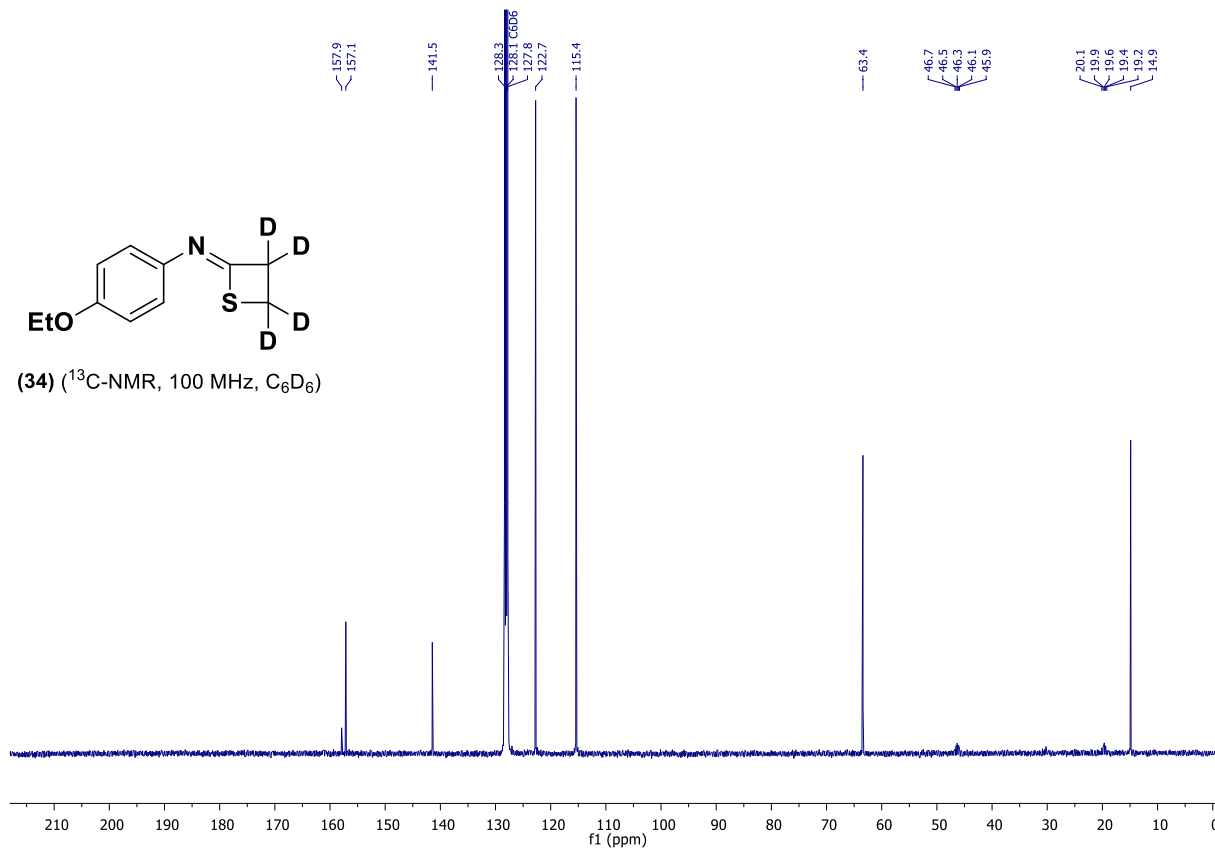
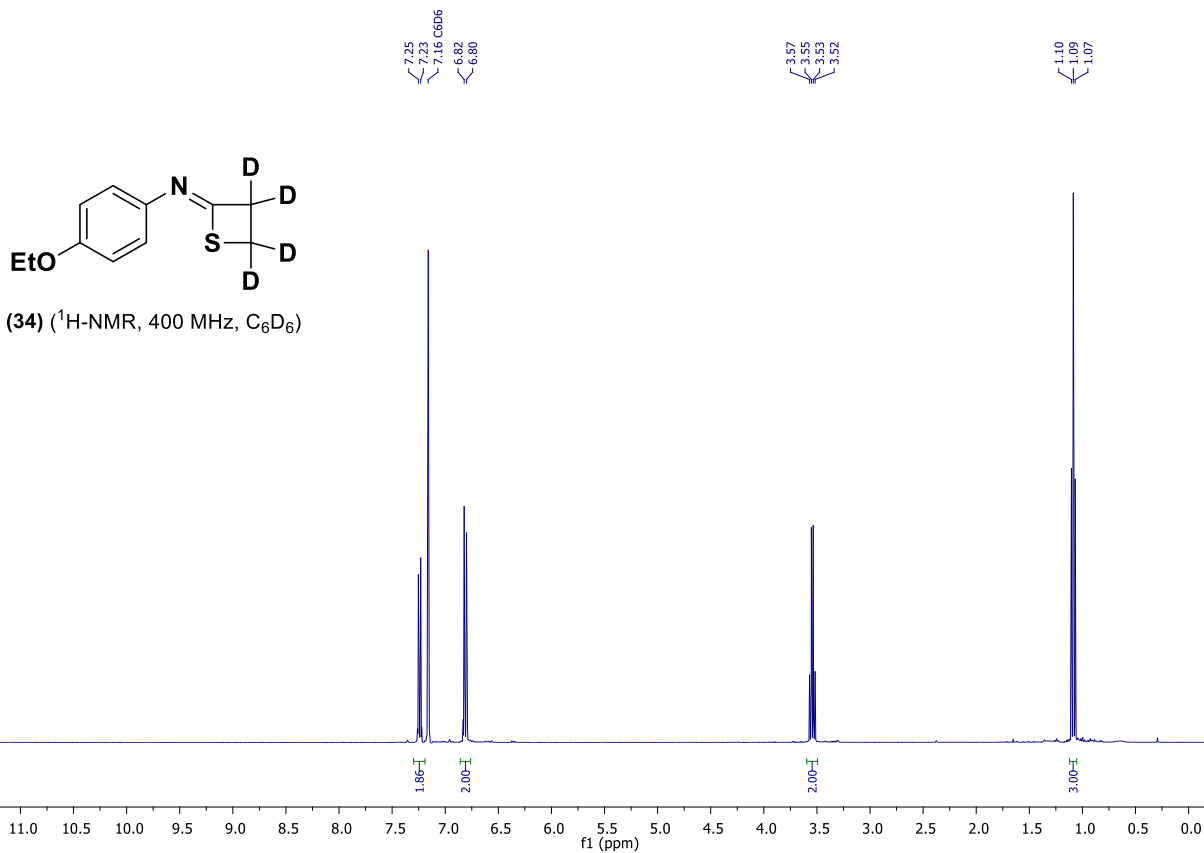


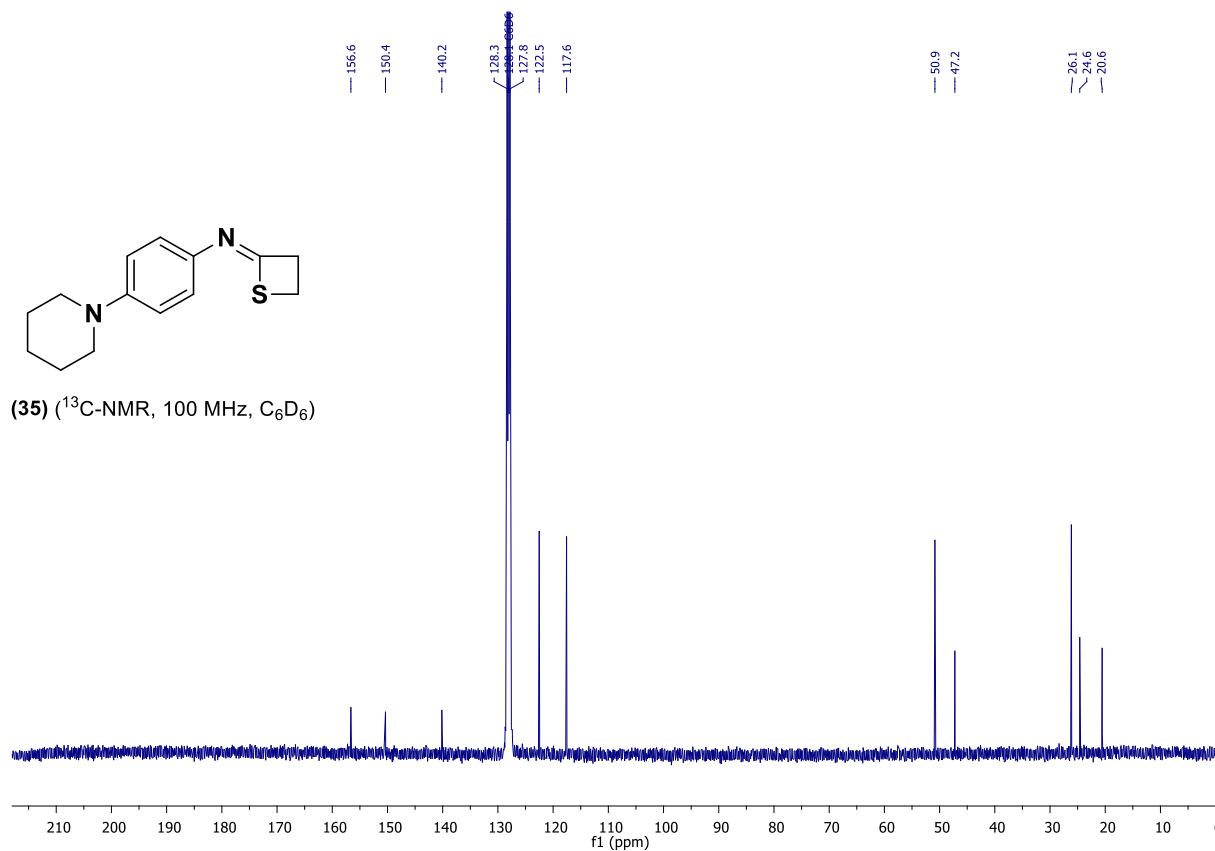
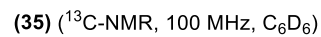
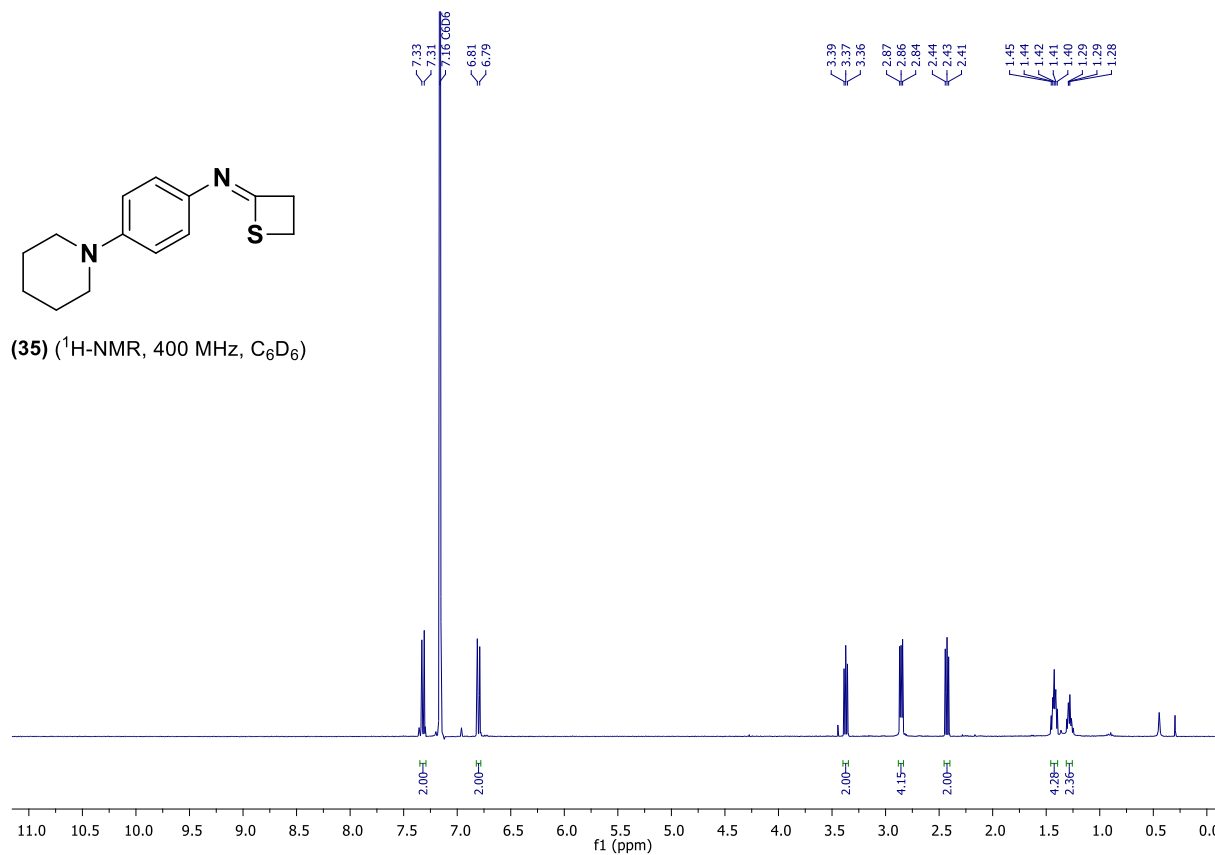
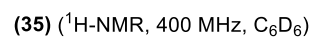


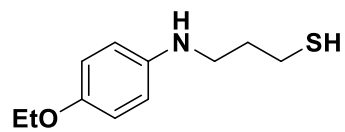




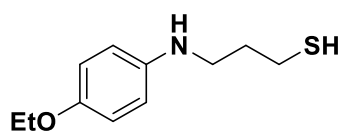
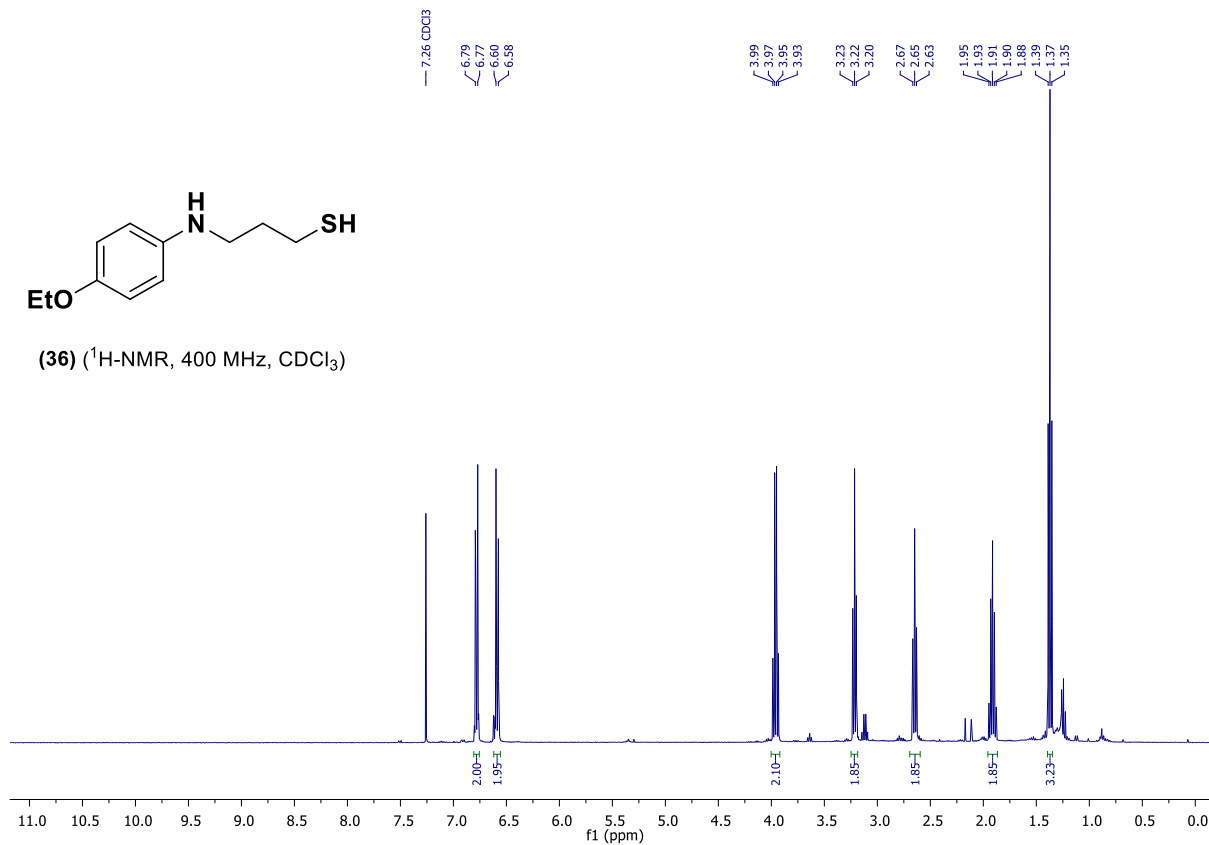




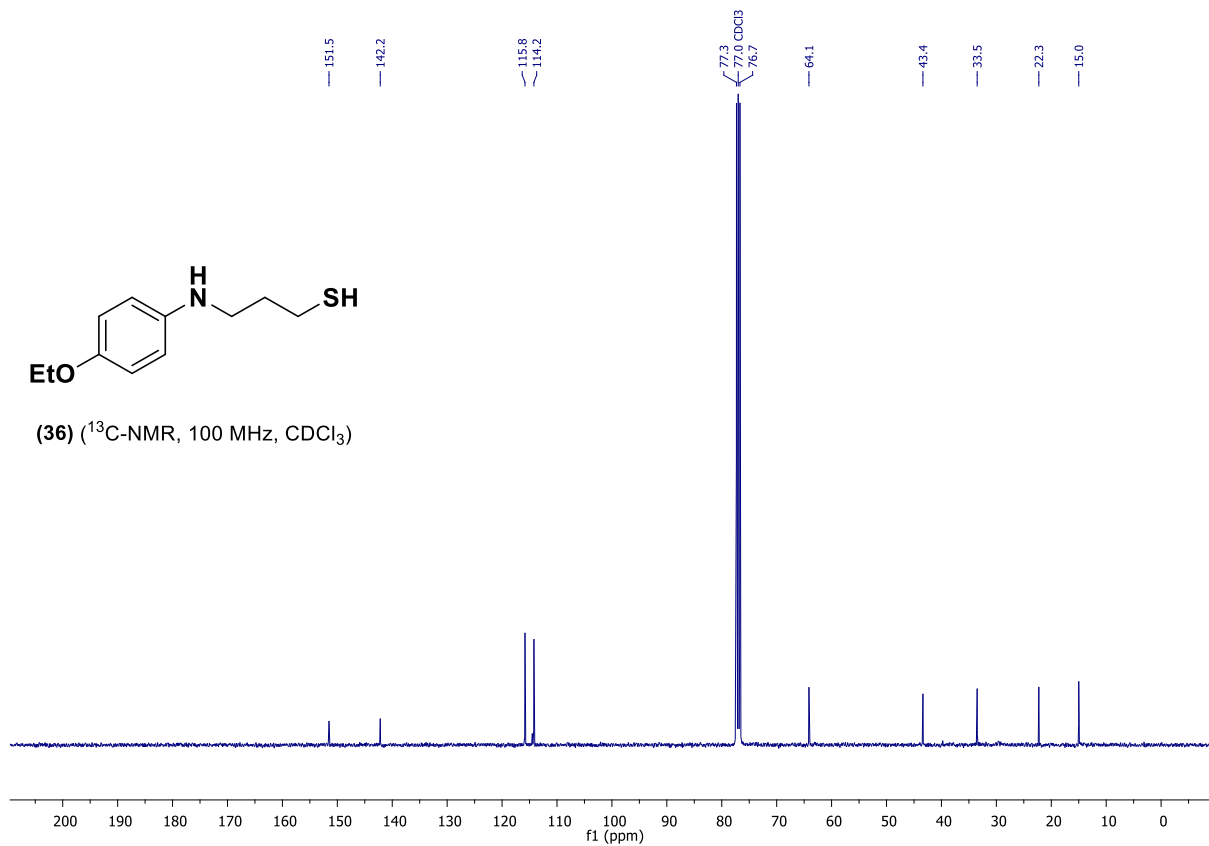


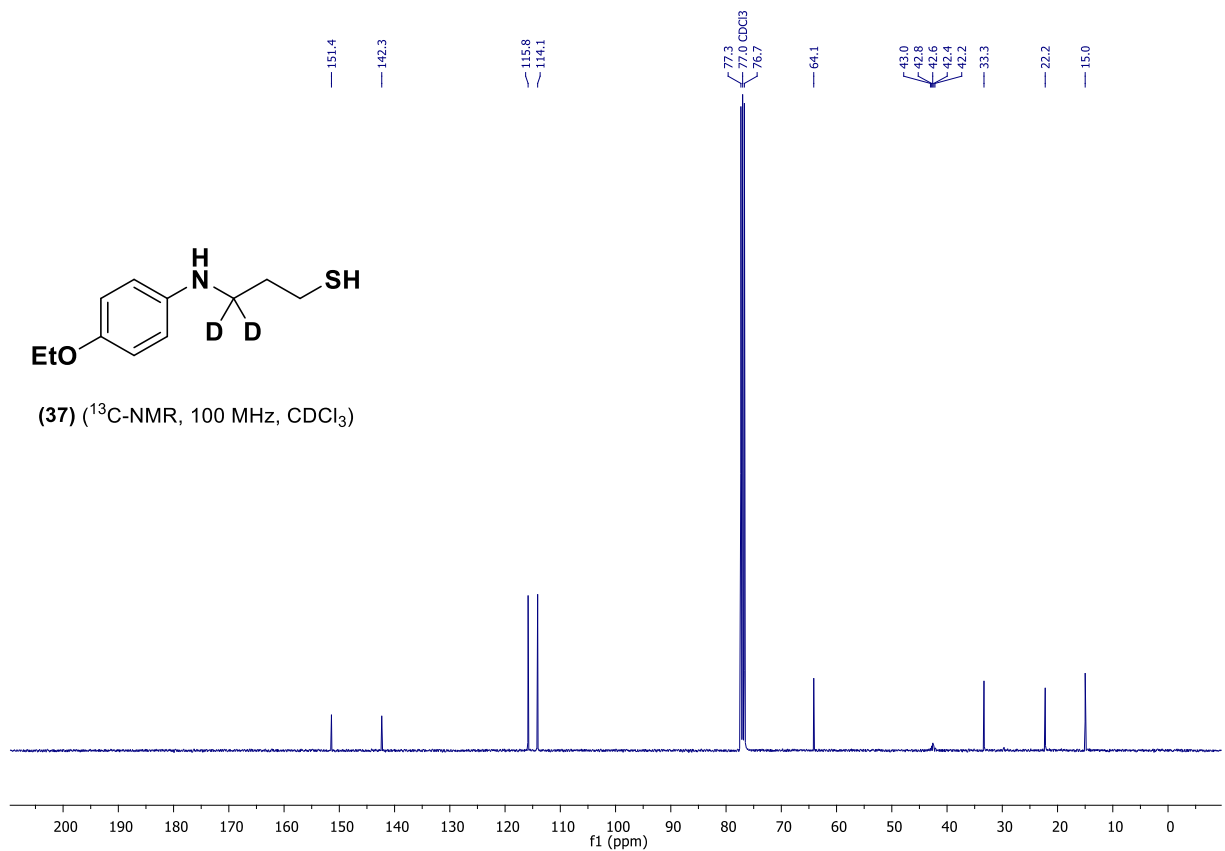
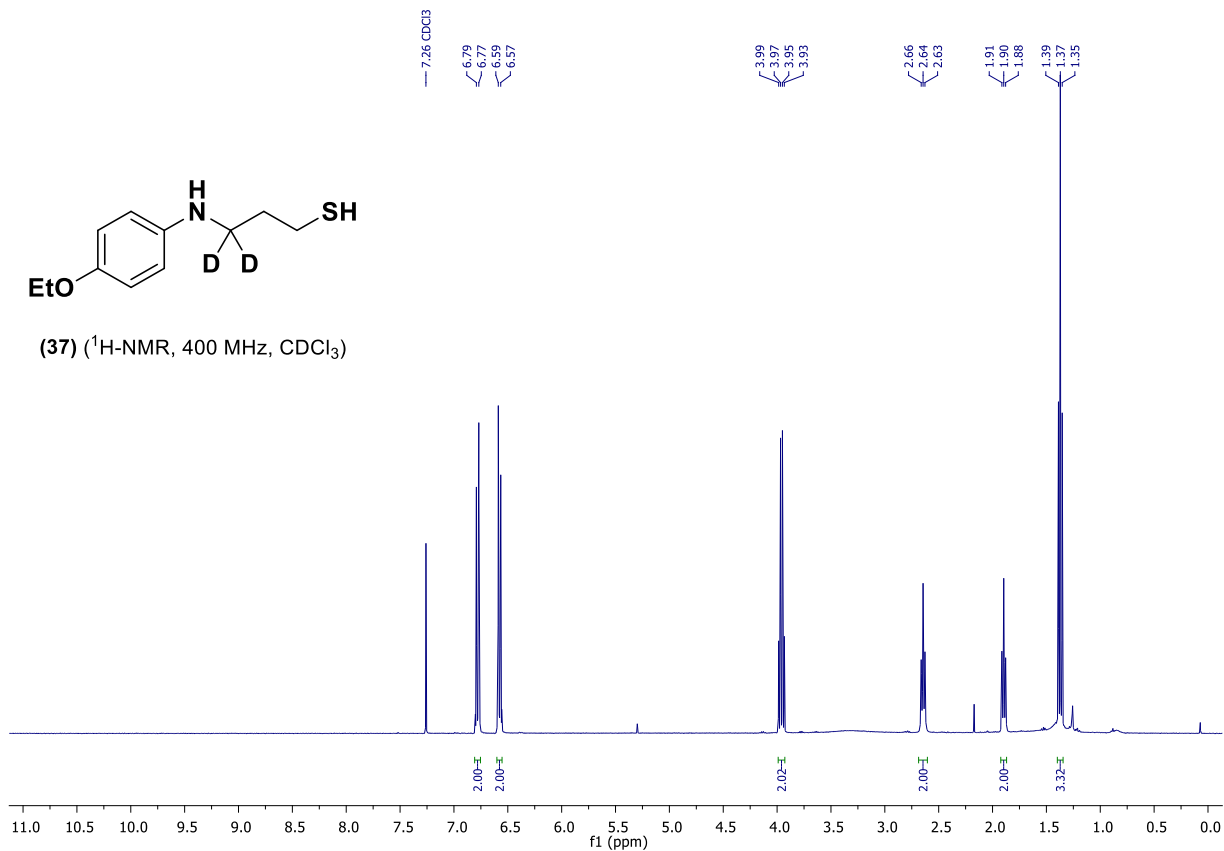


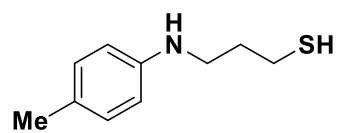
(36) (^1H -NMR, 400 MHz, CDCl_3)



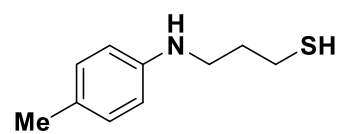
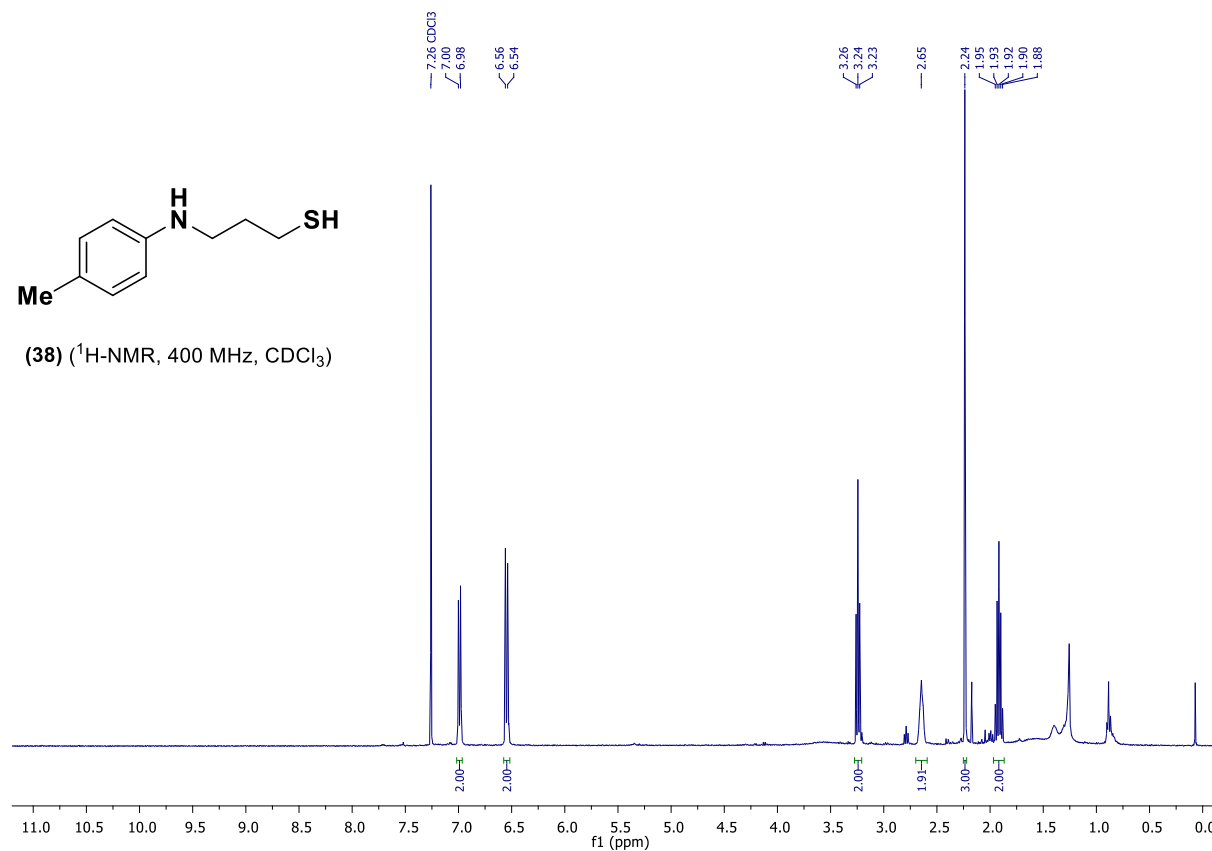
(36) (^{13}C -NMR, 100 MHz, CDCl_3)



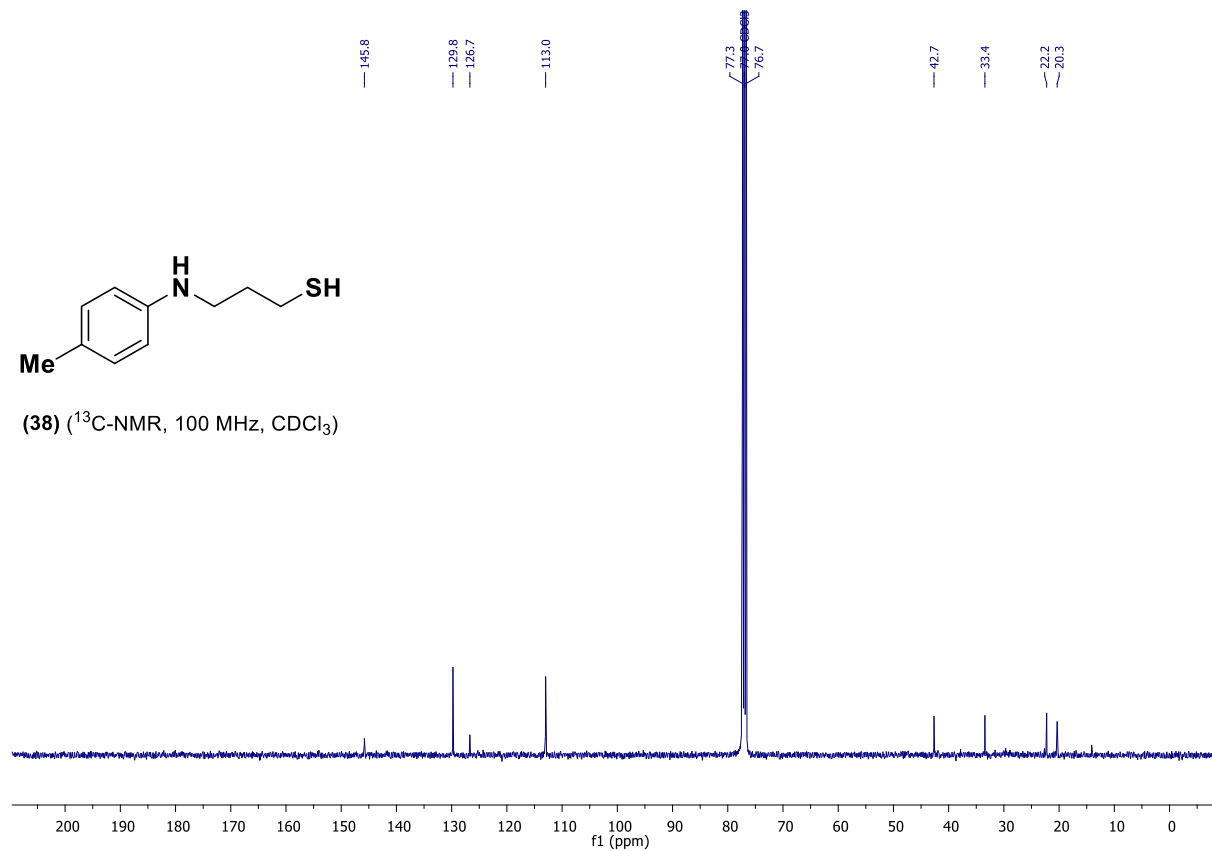


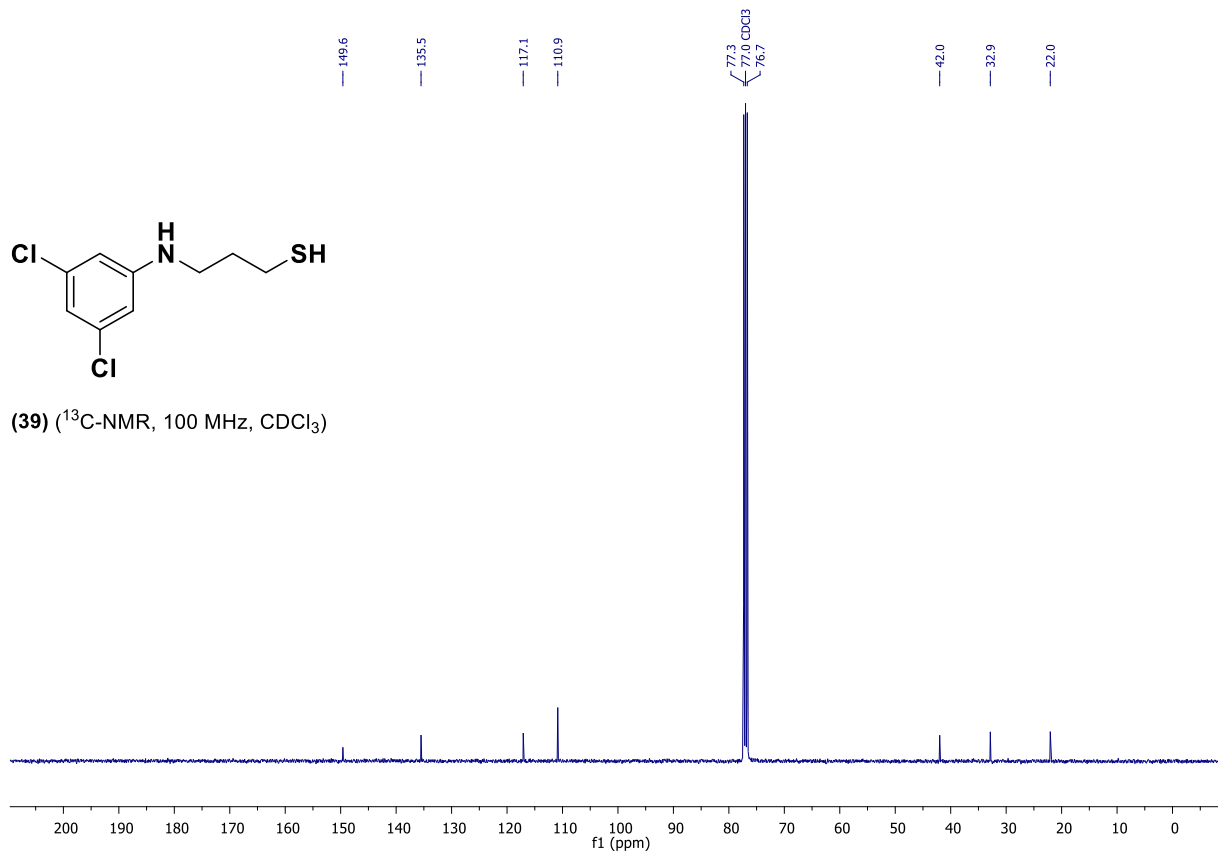
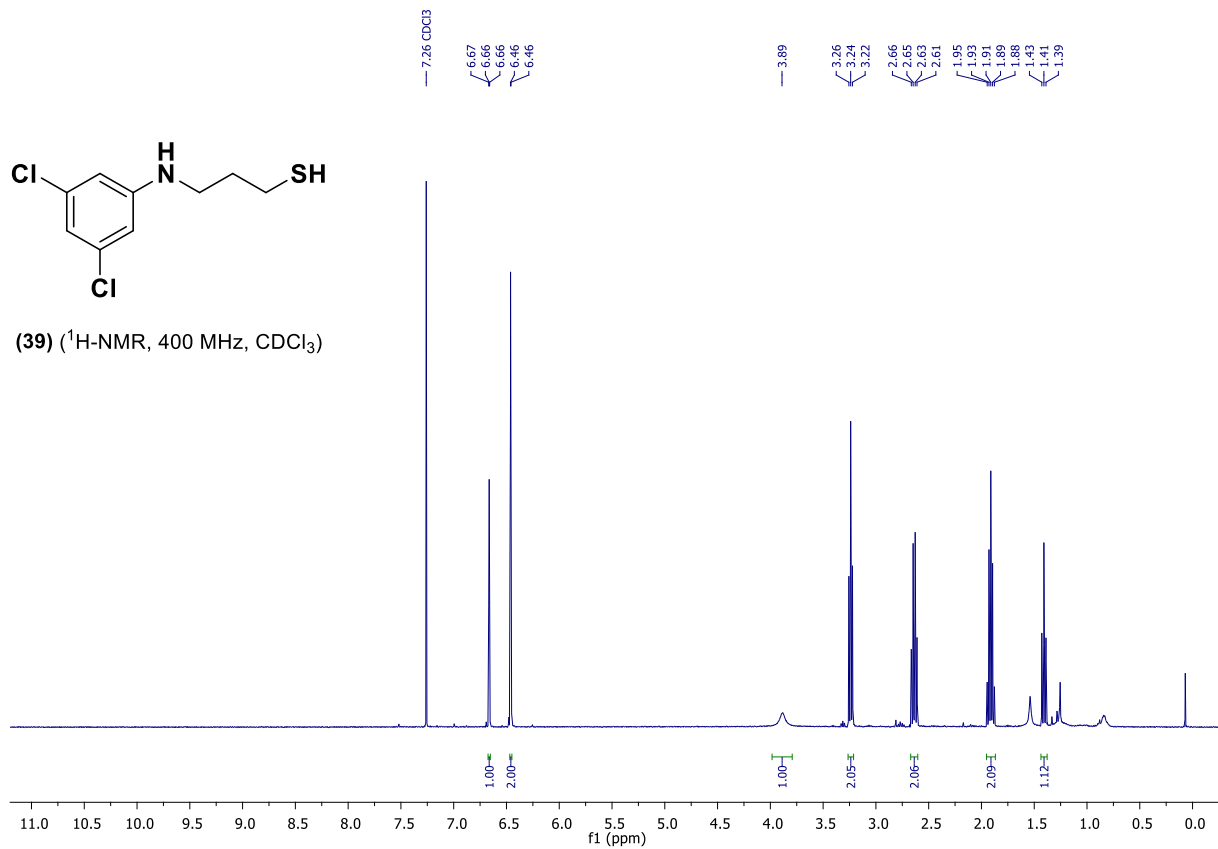


(38) ($^1\text{H-NMR}$, 400 MHz, CDCl_3)

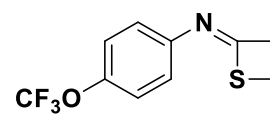


(38) ($^{13}\text{C-NMR}$, 100 MHz, CDCl_3)

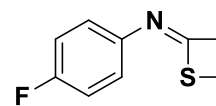
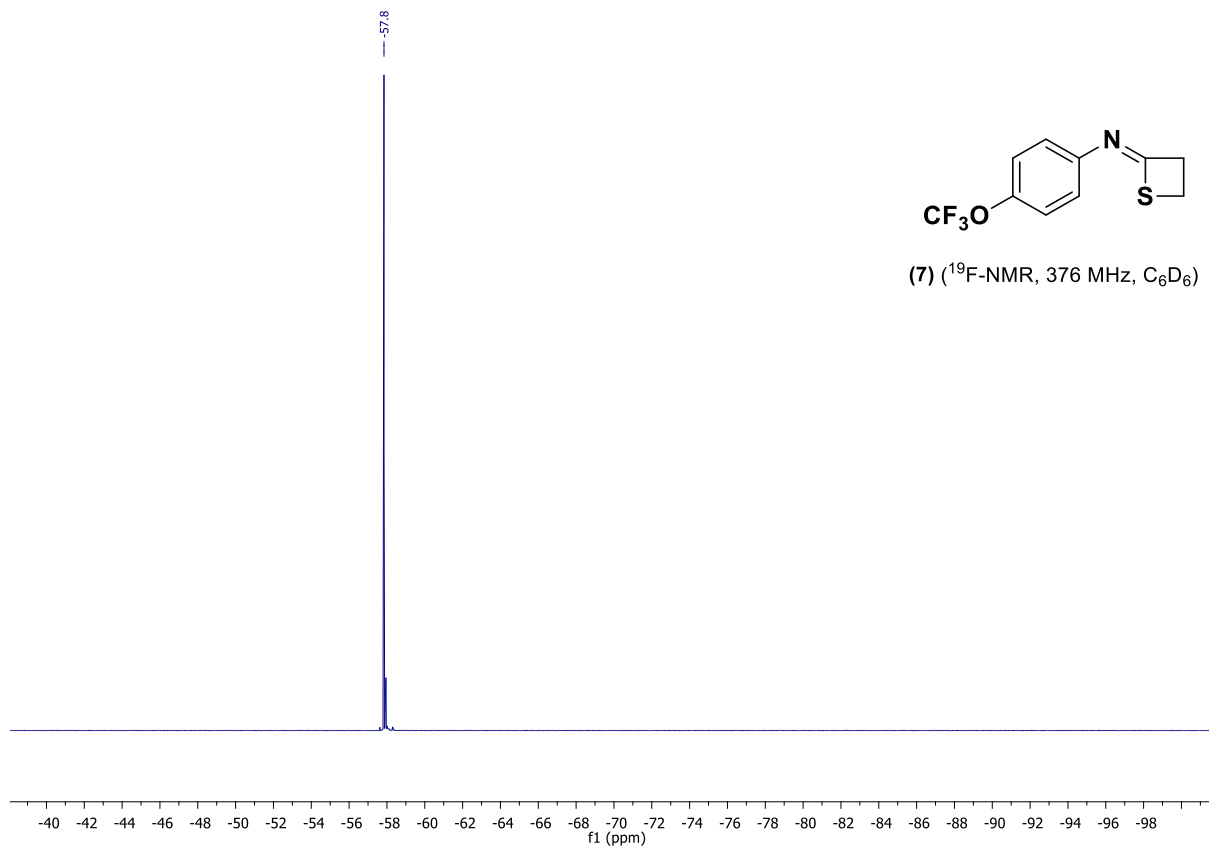




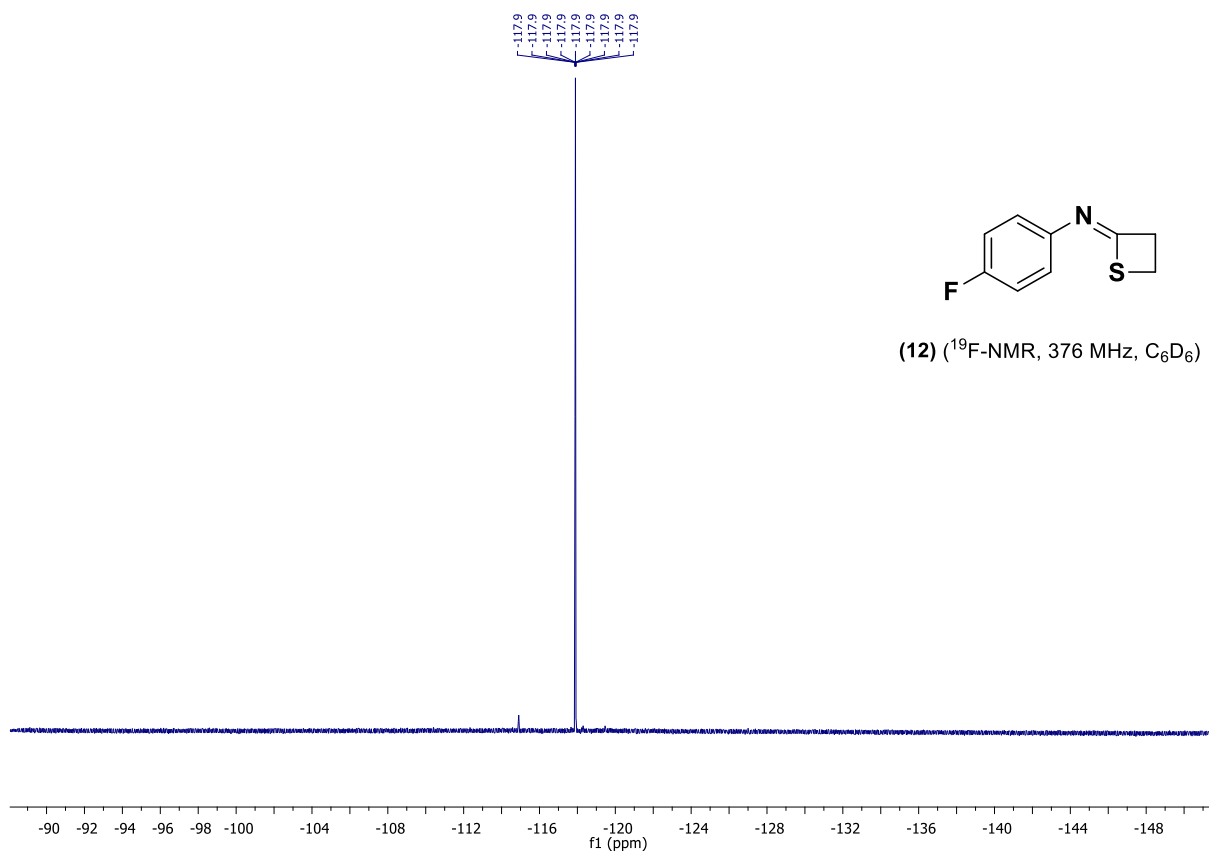
Copies of ^{19}F - and ^{77}Se -NMR Spectra

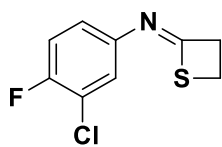


(7) (^{19}F -NMR, 376 MHz, C_6D_6)

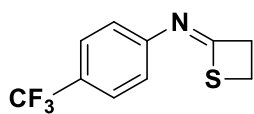
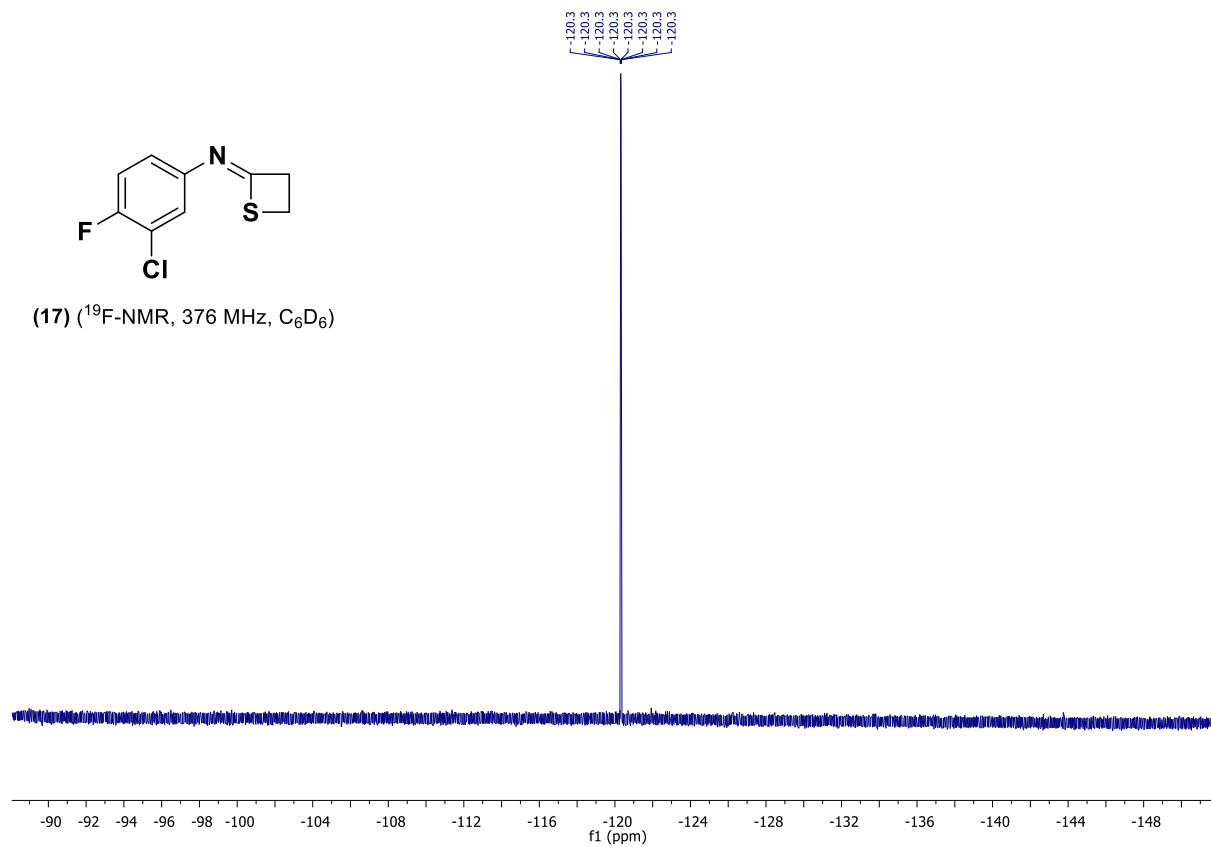


(12) (^{19}F -NMR, 376 MHz, C_6D_6)

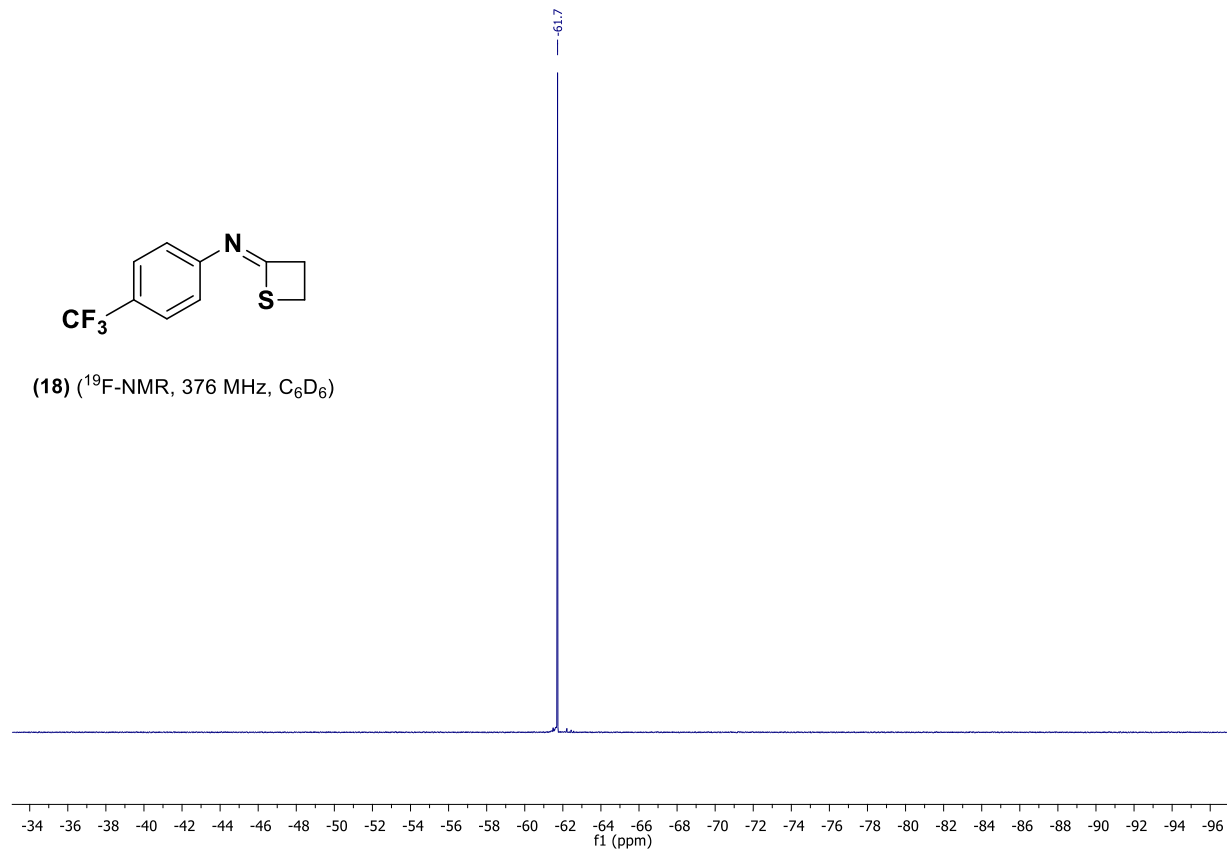


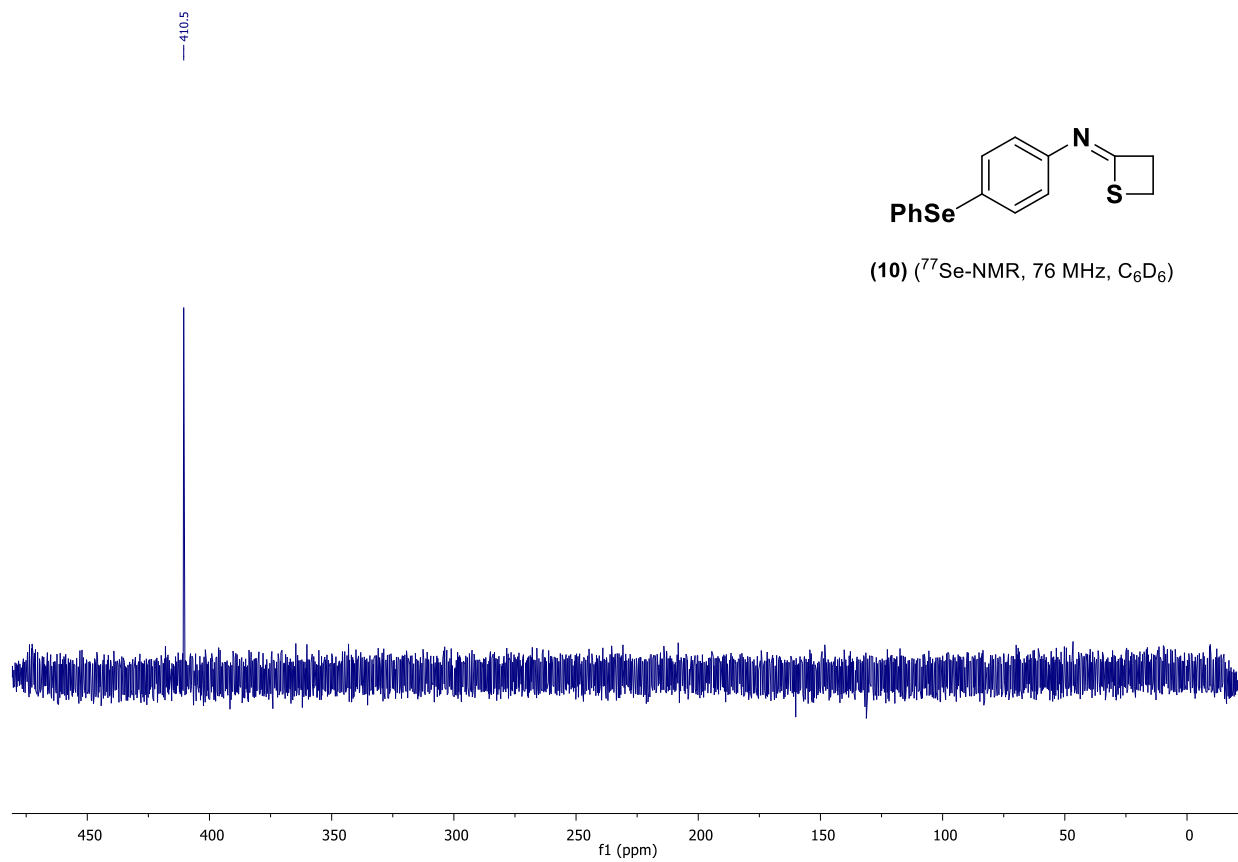


(17) (^{19}F -NMR, 376 MHz, C_6D_6)



(18) (^{19}F -NMR, 376 MHz, C_6D_6)





X-ray Analysis for Compound 2

The X-ray intensity data were measured on Bruker D8 Venture diffractometer equipped with multilayer monochromator, Mo K/ α INCOATEC micro focus sealed tube and Oxford cooling system. The structure was solved by *Direct Methods*. Non-hydrogen atoms were refined with *anisotropic displacement parameters*. Hydrogen atoms were inserted at calculated positions and refined with riding model. The following software was used: *Bruker SAINT software package*^[3] using a narrow-frame algorithm for frame integration, *SADABS*^[4] for absorption correction, *OLEX*^[5] for structure solution, refinement, molecular diagrams and graphical user-interface, *Shelxle*^[6] for refinement and graphical user-interface *SHELXS-2015*^[7] for structure solution, *SHELXL-2015*^[7] for refinement, *Platon*^[8] for symmetry check. Experimental data and CCDC-Codes Experimental data (Available online: <http://www.ccdc.cam.ac.uk/conts/retrieving.html>) can be found in Table 1. Crystal data, data collection parameters, and structure refinement details are given in Tables 2 to 3. Asymmetric Unit visualized in Figure 1.

Table 1 Experimental parameter and CCDC-Code.

Sample	Machine	Source	Temp.	Detector Distance	Time/ Frame	#Frames	Frame width	CCDC
	Bruker		[K]	[mm]	[s]		[°]	
Compound 2	D8	Mo	150	40	60	1511	0.500	2081745

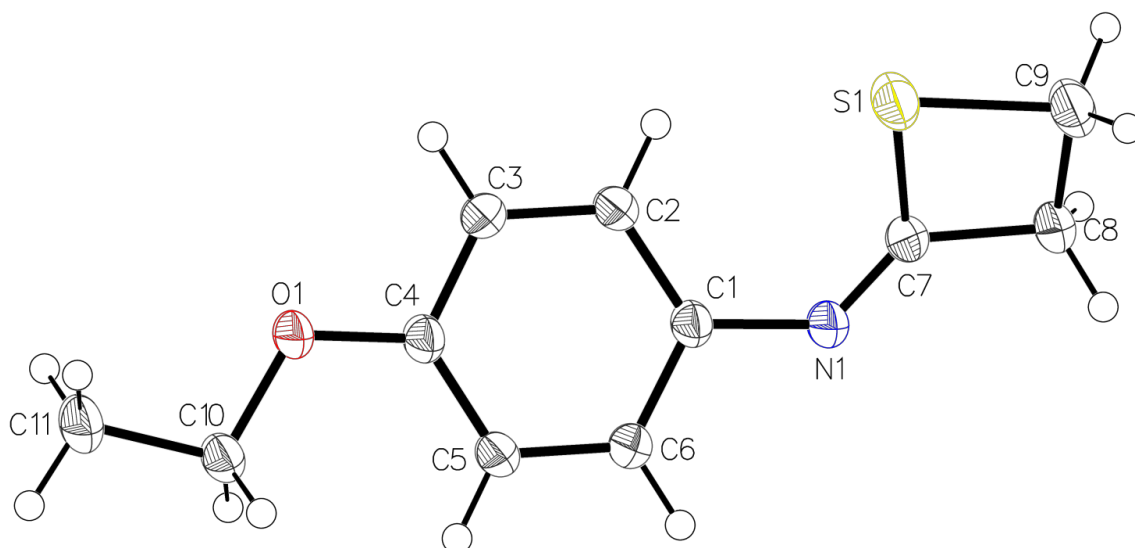


Figure 1 Crystal structure, drawn with 50% displacement ellipsoid. The bond precision for C-C single bonds is 0.0021Å.

Table 2 Sample and crystal data.

Radiation [Å]	MoK α (λ = 0.71073)	Z	2	Measurement method	\f and \w scans
Crystal habit	clear colourless block	a [Å]	6.7458(9)		
Crystal size [mm ³]	0.6 × 0.04 × 0.03	b [Å]	7.2758(10)	Abs. correction type	multiscan
Empirical formula	C ₁₁ H ₁₃ NOS	c [Å]	82.878(6)	Abs. correction Tmin	0.5985
Formula weight [g/mol]	207.28	α [°]	82.878(6)	Abs. correction Tmax	0.7460
Temperature [K]	150.0	β [°]	80.158(5)	Density (calculated) [g/cm ³]	1.344
Crystal system	Triclinic	γ [°]	78.337(6)	Absorption coefficient [mm ⁻¹]	0.281
Space group	P-1	Volume [Å ³]	512.30(12)	F (000) [e ⁻]	220.0

Table 3 Data collection and structure refinement.

2 θ range for data collection [°]	5.742 to 60.16	Index ranges		Goodness-of-fit on F ²	1.035
Reflections collected	12143	h	-9 ≤ h ≤ 9	Diff. peak and hole [e ⁻ Å ⁻³]	0.29/-0.26
Data / restraints / parameters	2868/0/128	k	-10 ≤ k ≤ 9		
Refinement method	Direct Methods	l	-15 ≤ l ≤ 15	Function minimized	$\sum w (F_o^2 - F_c^2)^2$
		all data	R1 = 0.0680, wR2 = 0.1038	Weighting scheme	where
		l > 2 σ (l)	R1 = 0.0437, wR2 = 0.0929	$w = 1 / [\sigma^2(F_o^2) + (0.0364P)^2 + 0.2642P]$	$P = (F_o^2 + 2F_c^2) / 3$

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