UNIVERSITY OF LIVERPOOL

Palladium-catalysed synthesis of sulfoxonium ylides

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor in Philosophy by:

Christopher Janot

September 2019

I travelled a lot…

Copyright statement

The research outlined herein was performed under the supervision of Dr. Christophe Aïssa and Dr. James Muir between October 2017 and September 2019 during the third year onwards of the PhD at the University of Liverpool. The majority of the second chapter of this thesis has been previously published in a peer-reviewed journal:

"Palladium-Catalyzed Synthesis of Bis-Substituted Sulfoxonium Ylides" – Janot C., Palamini P., Dobson B. C., Muir J., Aïssa C., *Org. Lett.* **2019**, *21*, 296–299.

Work on another project involving sulfoxonium ylides chemistry has also been carried out and published in a peer-reviewed journal but will not be discussed in this thesis.

"Cross-Coupling of α-Carbonyl Sulfoxonium Ylides with C−H Bonds" - Barday M., Janot C., Halcovitch N. R., Muir J., Aïssa C., *Angew. Chem. Int. Ed.* **2017**, *56*, 13117–13121.

I confirm that the work carried out within this thesis was conducted solely by me unless clearly stated. The work presented within this publication is copyrighted and no material should be published or quoted without prior consent.

Christopher Janot, September 2019

Acknowledgments

I would like to begin by thanking my advisor, Dr. Christophe Aïssa, for giving me the opportunity to carry out my PhD under his supervision. His passion for chemistry and his support allowed me to thrive as a scientist. I would also like to thank Dr. James Muir for his help, especially during my placement at AstraZeneca.

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Un grand merci à mes parents et à ma petite sœur sans qui je n'aurais jamais pu réussir ce projet. Merci pour votre soutient et vos encouragements durant ces 27 années.

Abstract

The chemistry of stabilised sulfoxonium ylides in the presence of transition metals has gained in interest over the past few years because of their improved safety profile as compared to their diazo counterparts. However, no general method is available to access α-aryl disubstituted derivatives, limiting the scope of those reactions. This thesis highlights the work done towards the palladium-catalysed synthesis of α-aryl-α-carbonyl sulfoxonium ylides. It includes a thorough review of the literature related to the metal-catalysed reactions with stabilised sulfoxonium ylide in Chapter 1. Chapters 2 and 3 describe the arylation of α-ester and α-keto sulfoxonium ylides, respectively, as well as their use for the formation of C–N and C–S bonds. An experimental study of the mechanism for the reactions with the α-keto derivatives is also detailed demonstrating a different mechanism as compared to when the reaction is carried out with the diazo equivalents.

Abbreviations

p-ABSA: 4-Acetamidobenzenesulfonyl azide

Ac: Acetate

API: Active Pharmaceutical Ingredient

Ar: Aryl

APT: Attached Proton Test

BINAP: 2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl

Bn: Benzyl

Boc: *tert*-Butoxycarbonyl

br: Broad

calcd: Calculated

cat.: Catalytic amount

CI: Chemical Ionisation

cod: 1,5-Cyclooctadiene

Cp*: 1,2,3,4,5-Pentamethylcyclopentadiene

dba: Dibenzylideneacetone

DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene

DCC: N,N'-Dicyclohexylcarbodiimide

1,2-DCE: 1,2-Dichloroethane

DCM: Dichloromethane

DFT: Density Functional Theory

DMAP: 4-Dimethylaminopyridine

DMF: Dimethylformamide

DMBQ: 2,6-Dimethoxybenzoquinone

DMSO: Dimethylsulfoxide

DSC: Differential Scanning Calorimetry

e: Even (NMR)

EDA: Ethyl diazoacetate

Elem. Anal.: Elemental analysis

equiv: Equivalent

ESI: Electrospray Ionisation

Het: Hetero-

HFIP: 1,1,1,3,3,3-Hexafluoroisopropanol

HMBC: Heteronuclear Multiple Bond Correlation

HMDS: Hexamethyldisilazane

HPLC: High-Performance Liquid Chromatography

HRMS: High-Resolution Mass Spectroscopy

HSQC: Heteronuclear Single Quantum Correlation

IR: Infrared spectroscopy

k_{obs}: Observed rate constant

k_{rel}: Relative rate constant

L: Ligand

m: Medium (IR)

m: Multiplet (NMR)

*m*CPBA: *meta*-Chloroperoxybenzoic acid

m.p.: Melting point

MS: Molecular sieves

Ms: Mesyl

MSDS: Material Safety Data Sheet

μW: Micro-wave

NHC: N–Heterocyclic Carbene

NMR: Nuclear Magnetic Resonance

o: Odd (NMR)

o/n: Overnight

Ph: Phenyl

PivOH: Pivalic acid

ppm: Parts per million

p-TSA: *para*-Toluenesulfonic acid

q: Quartet (NMR)

quint.: Quintet (NMR)

RDZone: Rate Determining Zone

rt: Room temperature

RSM: Recovered Starting Material

s: Strong (IR)

s: Singlet (NMR)

sat.: Saturated

sept.: Septet (NMR)

t: Triplet (NMR)

t-AmOH: *tert*-Amyl alcohol

TBS: *tert*-Butyldimethylsilyl

TCE: 2,2,2-Trichloroethyl

TDI: Turnover Frequency Determining Intermediate

TDTS: Turnover Frequency Determining Transition State

Tf: Triflate

TFE: 2,2,2-Trifluoroethanol

THF: Tetrahydrofuran

TLC: Thin Layer Chromatography

TMG: 1,1,3,3-Tetramethylguanidine

TMS: Trimethylsilyl

Tol: Tolyl

Ts: Tosyl

w: Weak (IR)

w/w: Weight per weight

Experimental and analysis statement

Analytical thin layer chromatography (TLC) was performed on Whatman F254 precoated silica gel plates (250 μM thickness). Visualisation was accomplished with UV light and/or appropriate stain. Flash column chromatography was performed using Merck silica gel 60 (230-400 mesh). Solvent for extraction and flash column chromatography were technical grade. Reported solvent mixture for flash column chromatography are volume/volume mixtures.

^{1}H, $^{13}C\{^{1}H\}$, $^{31}P\{^{1}H$, $^{13}C\}$, (^{1}H,^{13}C)-HSQC and (^{1}H,^{13}C)-HMBC spectra were recorded on a Bruker DRX 500 in the indicated deuterated solvents. $^{19}F\{^{1}H\}$ spectra were recorded on a Bruker Avance 400 spectrometer. The solvent signals were used as references and the chemical shifts converted to the TMS scale (for $CDCl_3$: δC = 77.0 ppm; residual $CHCl_3$ in $CDCl_3$: δH = 7.26 ppm). Data are reported in the following order: chemical shifts (δ) in ppm (apparent multiplicity designated using the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), quint. (quintet), sept. (septet), m (multiplet), br (broad), and the appropriate combinations, if applicable, coupling constants (*J*, Hz), integration). In ^{13}C NMR, Attached Proton Test (APT) sequence was used to separate methylene groups and quaternary carbons (e, even) from methine and methyl groups (o, odd). If, due to relaxation issues, quaternary carbons could not be observed, an HSQC and/or HMBC was carried out and the carbon was then noted (hsqc) or (hmbc), respectively.

Infrared spectra (IR) were obtained using PerkinElmer Spectrum 100 FT-IR spectrometer. The wavenumbers are reported in cm^{-1}, using the intensities broad (br), strong (s), medium (m) and weak (w). High Resolution Mass Spectrometry (HRMS) were determined at the University of Liverpool on Agilent 6540A Accurate-Mass Q-

ToF MS with Agilent Jetstream Source (ESI) or Agilent 7200 Series GC-ToF (solid probe) (CI). Melting points: Griffin melting point apparatus (not corrected). Elemental analyses were performed by the University of Liverpool Analytical Service.

Unless otherwise indicated, all reactions were carried out in flame-dried round-bottomed flask under dry nitrogen atmosphere. Solvents were either used after passage through Innovative Technology PureSolv MD system or from anhydrous bottles purchased from Acros unless otherwise noted. All starting material were purchased from Fluorochem, Sigma Aldrich, Alfa Aesar, TCI, Strem or Apollo Scientific and used without further purifications otherwise noted.

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Chapter 1:

Metal-catalysed reactions with stabilised sulfoxonium ylides

Chapter 1: Metal-catalysed reactions with stabilised sulfoxonium ylides

1 Introduction

The discovery of sulfoxonium ylides was first made by Corey and Chaykovsky in 1964. They hypothesised that dimethylsulfoxonium methylide could react in a manner comparable to diazomethane and could then be used for the homologation of cyclic ketones or that it could react similarly as Wittig reagent.[1] Instead, they discovered the now famous "Corey-Chaykovsky" reaction to form epoxides, aziridines or cyclopropanes.[2,3] That chemistry is well developed even with asymmetric versions of the reaction.[4–6] The stability of sulfoxonium ylides can be improved by delocalisation of the negative charge with electron-withdrawing groups such as ketones, ester or amides. However, improving the stability of the sulfoxonium ylide will ultimately give rise to a less reactive species.[2]

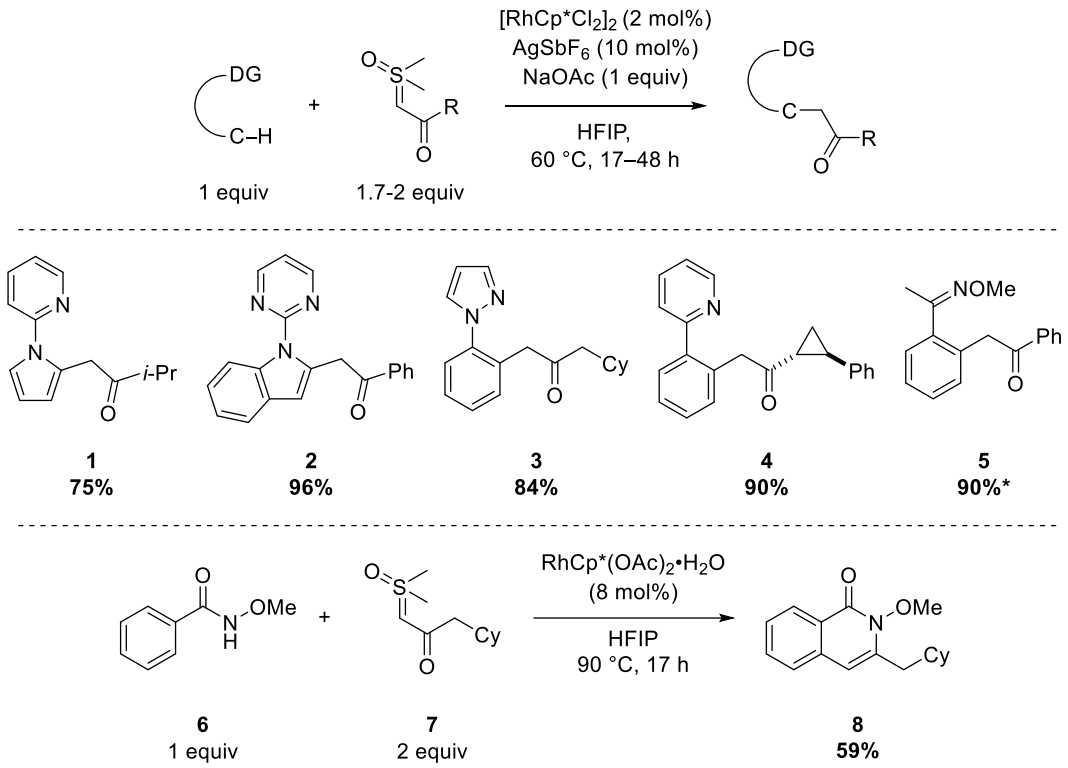
In contrast, the study into the reactivity of sulfoxonium ylides in metal-catalysed reactions has remained dormant for a long period since 1993.[7] Recently, this area has been revived and thus these reactions will be thoroughly reviewed hereafter. This will be discussed in two main sections: the reactions involving C–H activation and those involving heteroatom–H insertion (X–H insertion). The palladium-catalysed chemistry of sulfoxonium ylides will then be presented.

2 Reactions involving C–H activation

2.1 Reactions using rhodium

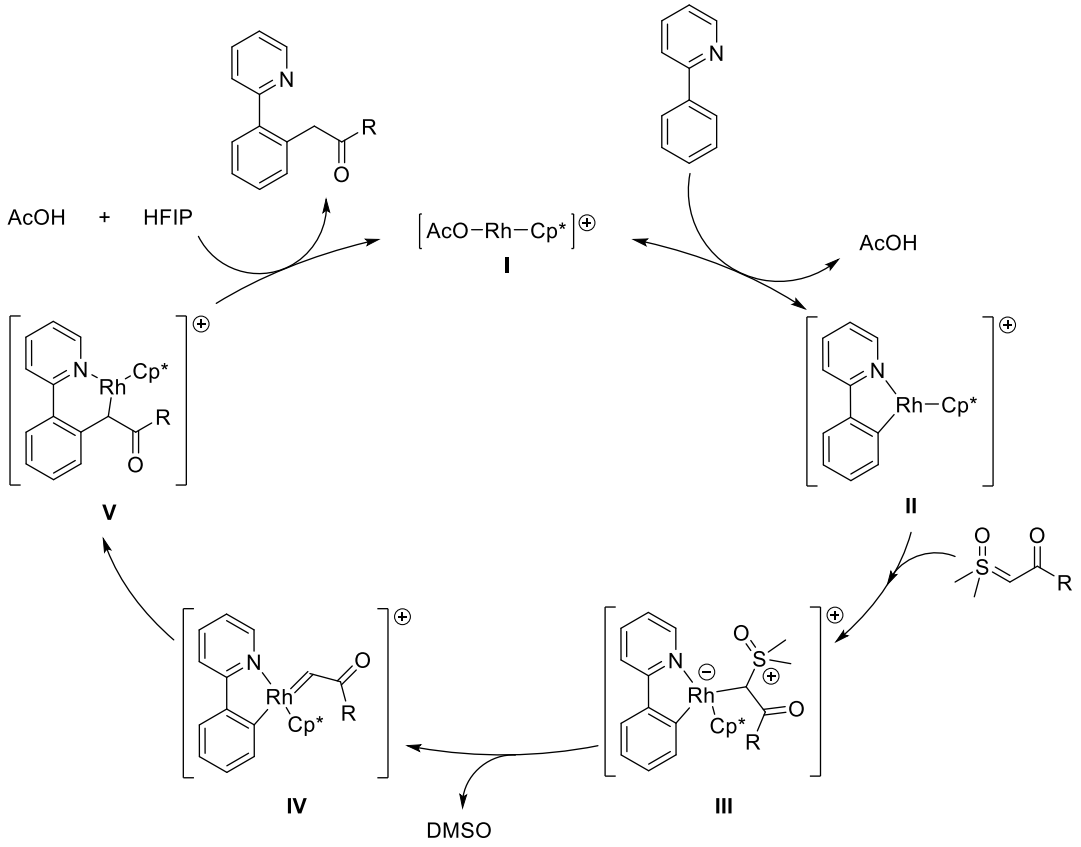
2.1.1 Pioneering work

The first C–H bond functionalisation with α-carbonyl sulfoxonium ylides was accomplished within the Aïssa group, in 2017, with $[RhCp^*Cl_2]_2$ used as a catalyst.[8] Pyridine was the main directing group used for the reaction although examples with pyrimidine, pyrazole, quinoline and methyl oximes were also described (Scheme 1). The reaction afforded good to excellent yield with an array of functional groups on the sulfoxonium ylide. HFIP (1,1,1,3,3,3-hexafluoroisopropanol), used as a solvent and proton source proved to be essential for the reaction to occur. It was also demonstrated the possibility of synthesising 3-*N*-methoxylactam **8** *in situ* with a slight change of conditions.



*Scheme 1: Aïssa's group pioneering work on the C–H bond functionalisation with sulfoxonium ylides. *At 90 °C, $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (8 mol%) was used as rhodium catalyst without $AgSbF_6$.*

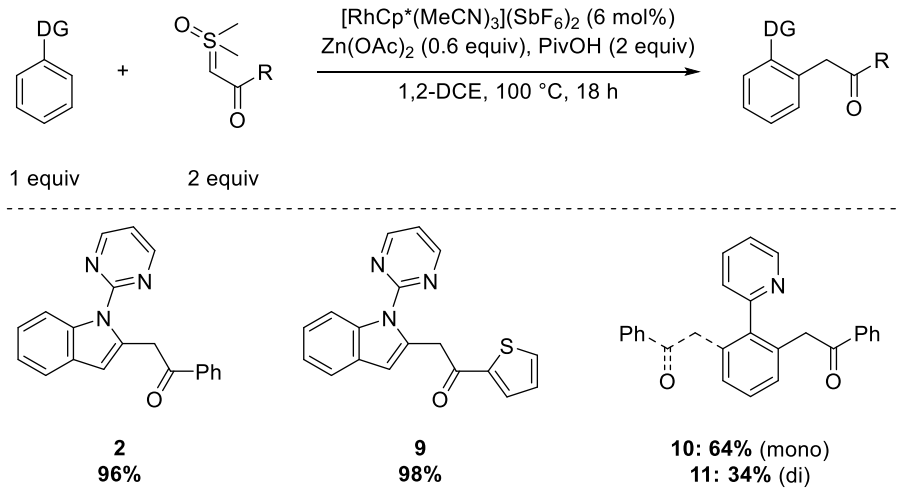
The study of the mechanism suggested that the reaction proceeded as shown in Scheme 2. The cationic active catalyst species **I** formed *in situ* in the presence of sodium acetate and silver hexafluoroantimonate would perform C–H activation with phenylpyridine generating **II**.[9] Nucleophilic attack of the sulfoxonium ylide would lead to **III**. Loss of DMSO would generate the rhodium carbene **IV** which would undergo migratory insertion to obtain **V**. Protonolysis would regenerate the active catalyst species and liberate the desired product.



Scheme 2: Suggested mechanism for the C–H functionalisation with sulfoxonium ylides.

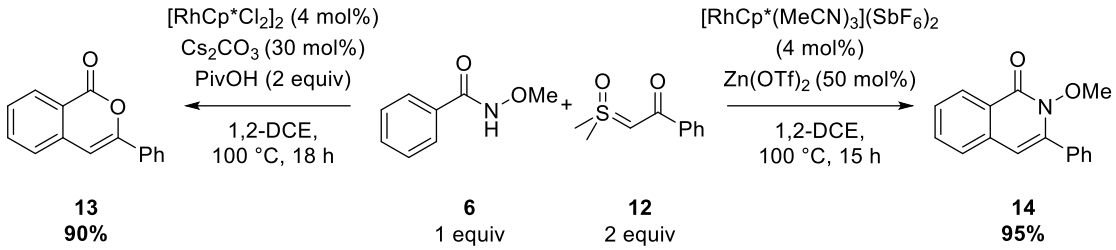
Independently, Li's group published a very similar reaction with another Rh(III) cationic catalyst (Scheme 3).[10] The reaction conditions differed from those described by Aïssa and co-workers and rely on the combination of a Lewis acid ($Zn(OAc)_2$) and pivalic acid as a sacrificial proton source. The method allowed a wide variety of

couplings on the C-2 position of indoles using pyrimidine as the main directing group in very good yield. However, when the directing group was changed to pyridine and the indole was replaced by a phenyl ring, the reaction afforded a mixture of mono- and disubstituted products **10** and **11** that was not observed in Aïssa's group.



Scheme 3: Li and co-workers' work on C–H bond functionalisation of sulfoxonium ylides.

The conditions could be further tuned for the selective synthesis of isoquinolones and isocoumarins (Scheme 4).[11] When using $[RhCp^*Cl_2]_2$, the combination of a base and pivalic acid led to the formation of **13** in 90% yield, whereas using the cationic rhodium catalyst $[RhCp^*(MeCN)_3](SbF_6)_2$ and a hard Lewis acid such as $Zn(OTf)_2$ led to the formation of **14** in 95% yield. The formation of the carbon–heteroatom bond in compound **13** and **14** was not promoted by the rhodium catalyst.

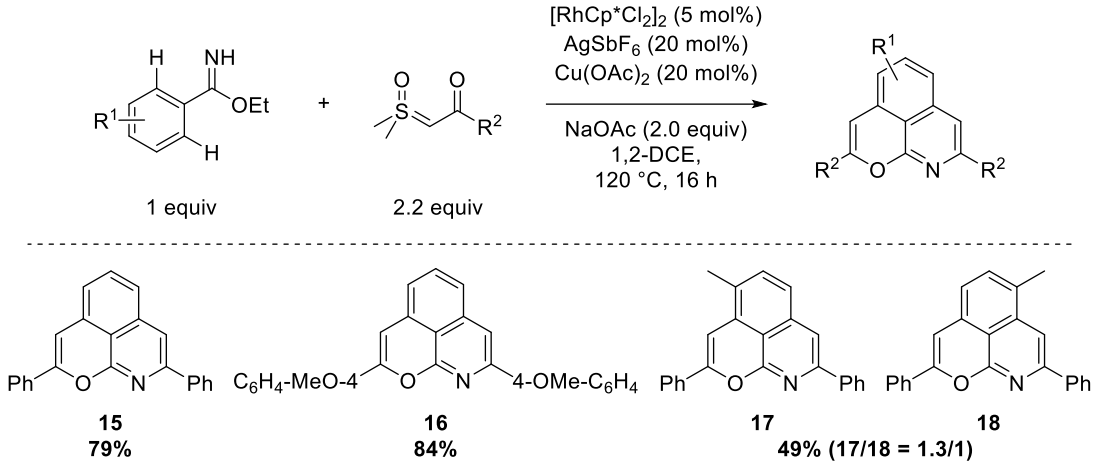


Scheme 4: Selective formation of isoquinolones or isocoumarins.

2.1.2 Exploration of the new reactivity

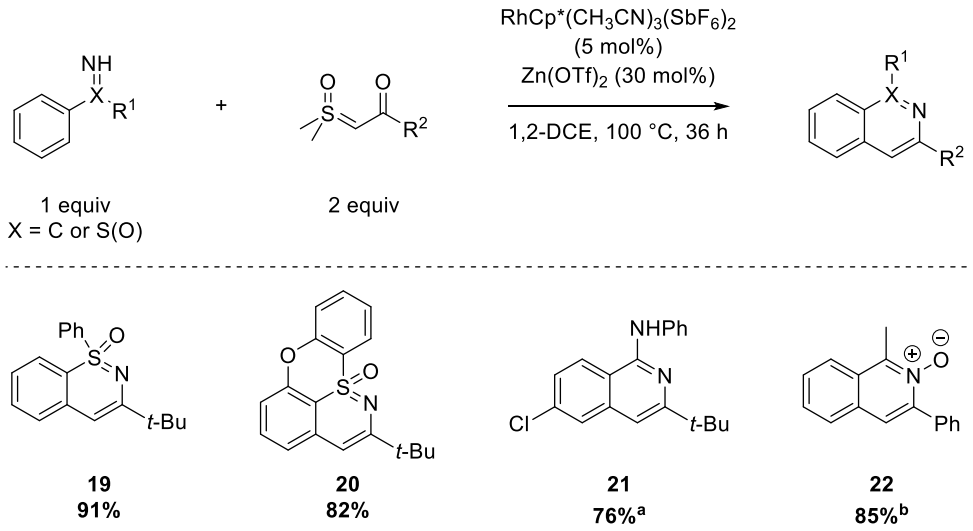
The reaction design demonstrated by Aïssa and Li was extended to many directing groups for the synthesis of heterocycles.

Cheng and co-workers described the synthesis of pyrano[4,3,2-*ij*]isoquinoline derivatives.[12] By reacting an excess of sulfoxonium ylide with alkyl benzimidate in the presence of $[RhCp^*Cl_2]_2$, $AgSbF_6$, $Cu(OAc)_2$ and NaOAc, the authors could trigger a di-annulation on both sides of the directing group as shown in Scheme 5. Good yields were obtained when the phenyl ring was substituted on the *para*-position and the reaction worked with a variety of electron deficient and electron rich arylsulfoxonium ylides. An inseparable 1: 1 mixture of isomers was obtained with methyl substituted aryl rings in *meta*-position. The optoelectronic properties of the compounds were tested and showed large Stokes shifts (up to 141 nm) which is an important property for bioimaging.[13]



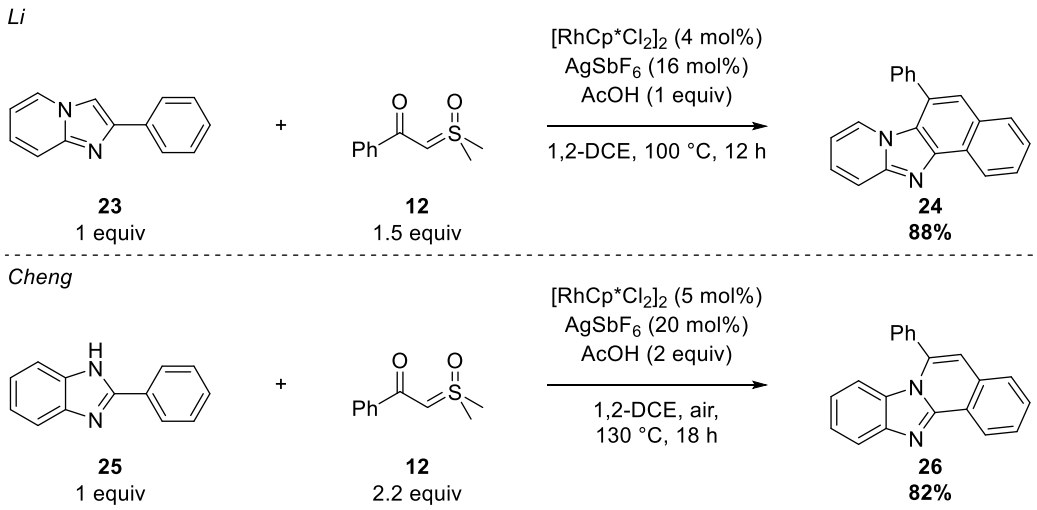
Scheme 5: Synthesis of pyrano[4,3,2-ij]isoquinoline derivatives.

Using sulfoximines and benzamidines, Li and co-workers have successfully synthesised benzothiazines and isoquinoline derivatives (Scheme 6).[14] Similar reaction conditions were used for both classes of substrate, the only difference being the addition of sodium acetate for the synthesis of isoquinolines. An example of reaction with cyclic diarylsulfoximine was shown and gave **20** in a good 82% yield. The quinoline N-oxide **22** was also synthesised in very good yield starting from acetophenone oxime using different conditions.



*Scheme 6: Synthesis of benzothiazines and isoquinoline derivatives. [a]NaOAc (1 equiv) was added. [b] From acetophenone oxime, conditions: [RhCp*Cl2]2 (4 mol%), Zn(OTf)2 (50 mol%), AcOH (2 equiv), TFE, 100 °C, 12 h.*

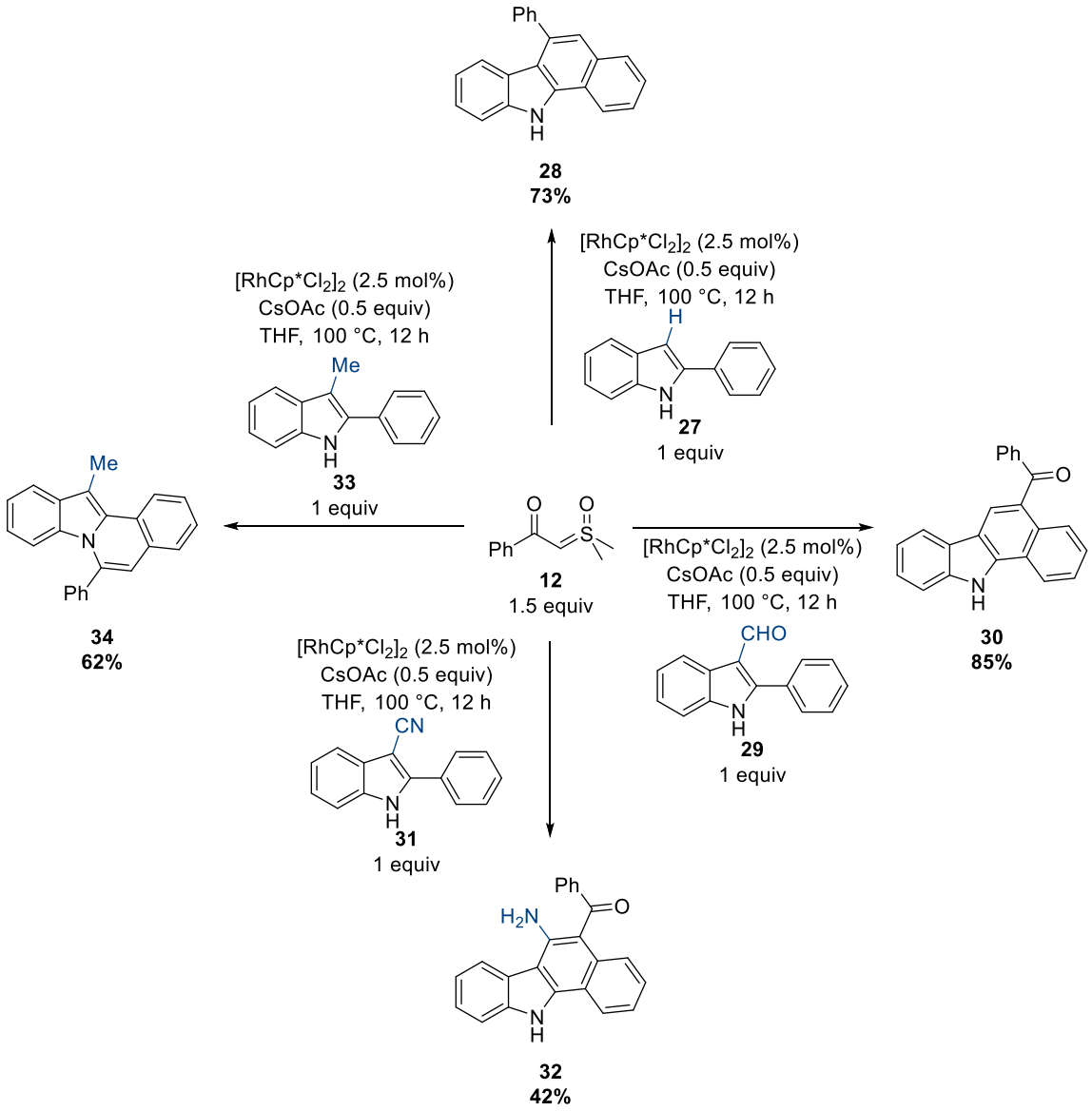
In the same publication, the authors also described the synthesis of 2-arylimidazo[1,2-*a*]pyridines using exclusively the sulfoxonium ylide **12** as shown in Scheme 7. Applying very similar conditions, Cheng and co-workers synthesised a variety of comparable 5-arylimidazo[2,1-*a*]isoquinolines such as **26** shortly after Li's publication. In their case, the reaction could be carried out under air but required higher temperature. Only (hetero)aryl sulfoxonium ylides were used for this coupling.



Scheme 7: Synthesis of 2-arylimidazo[1,2-a]pyridines and 5-arylimidazo[2,1-a]isoquinolines.

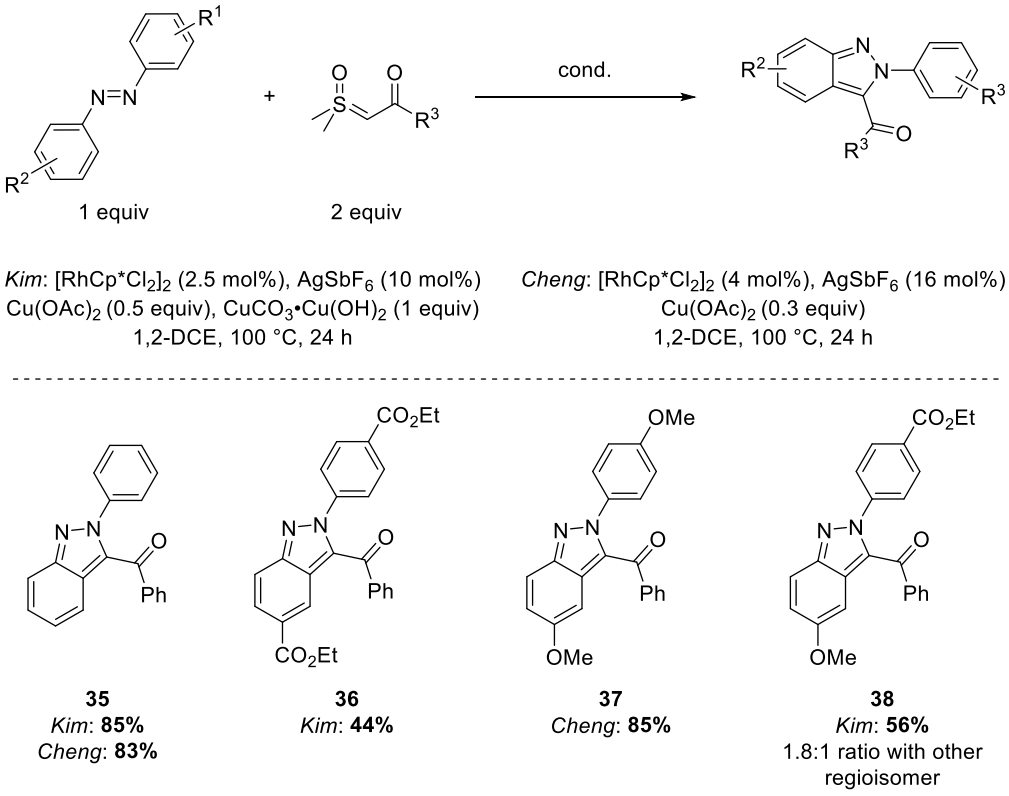
In a similar fashion, Fan *et al*. published a highly chemo- and regioselective synthesis of benzo[*α*]carbazoles and indolo[2,1-*α*]-isoquinolines (Scheme 8).[15] Using the same set of conditions but with different substituents on the position 3 of the indole starting material, the authors could access different products *via* four types of cyclisations. Using **27**, attack on the indole in position 3 followed by dehydration led to the formation of **28** in 73% yield. If **29** was used, the presence of an aldehyde in the position 3 prevented this cyclisation. Interestingly, it still did not trigger the N-1 cyclisation. Instead, aldolisation and crotonisation occurred on the aldehyde and provided the 11*H*-benzo[*α*]carbazole **30** substituted on the position 5 with the keto-group from the sulfoxonium ylide in 85% yield. The same strategy was applied by

replacing the aldehyde with a nitrile group. In that case, the carbazole obtained was substituted by an amine in the 6-position and the ketone from the sulfoxonium ylide on the position 5. Compound **32** could then be obtained in 42% yield. Finally, blocking the position 3 with an unreactive methyl group triggered the N-1 cyclisation to obtain **34**. It is noteworthy that mostly arylsulfoxonium ylides were used for those cross-coupling reactions.



Scheme 8: Chemo- and regioselective synthesis of benzo[α]carbazoles and indolo[2,1-α]-isoquinolines.

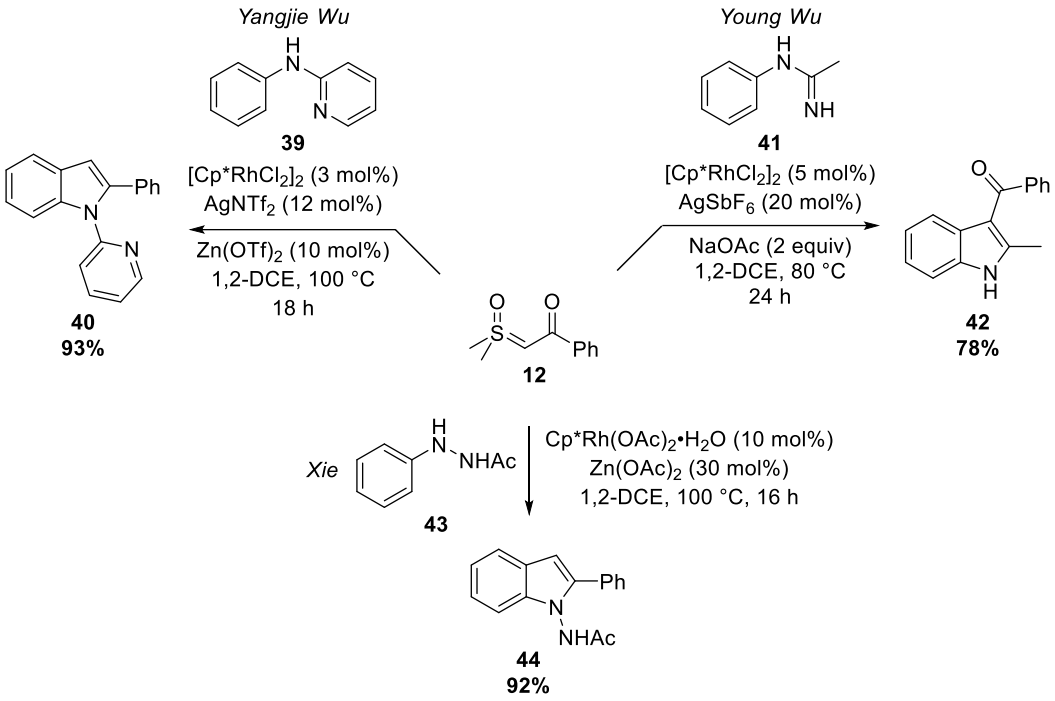
Kim and Cheng reported independently the annulation reaction of azobenzenes with sulfoxonium ylides using very similar conditions (Scheme 9).[16,17] Indeed, the main difference, despite the stoichiometry of reagents, was the use of $CuCO_3 \cdot Cu(OH)_2$ which improved the yield of the reactions in Kim's conditions. However, alkyl-sulfoxonium ylides were better tolerated in Cheng's case. The reaction was more efficient with electron-rich azobenzenes (compound **36** and **37**) and in case of unsymmetrical ones, the reaction occurred predominantly on the richer aromatic ring, although with poor selectivity (compound **38**).



Scheme 9: Reaction with azobenzene derivatives.

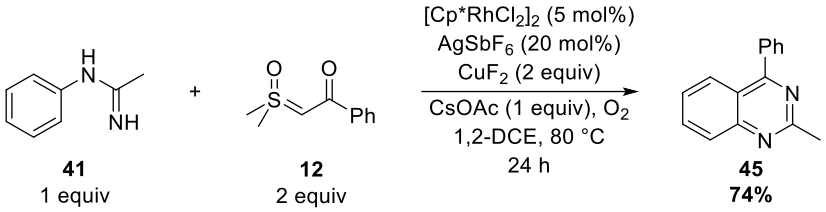
In early 2019, three strategies have been reported using sulfoxonium ylides towards the synthesis of indoles with different substitution patterns (Scheme 10). Wu and co-workers obtained the indole **40** in excellent yield and good regioselectivity when treating the aniline **39**, containing a pyridine as a directing group, with the

sulfoxonium ylide **12**.[18] Xie and co-workers treated sulfoxonium ylides with 1-acetyl-2-phenylhydrazine derivatives to obtain indoles with an acetamide group on the nitrogen which can be deprotected to the secondary amine under acidic conditions.[19] Good regioselectivity was also observed for the cyclisation but the reaction was very sensitive to steric hindrance and *ortho*-substitution of **43** only provided traces of products. Finally Wu and co-workers proposed a synthesis of 3-acyl substituted indoles such as **42** starting from N-arylamidines **41**.[20] In that case, the nitrogen of the indole remained free at the end of the reaction, facilitating further functionalisation.



Scheme 10: Strategies towards the synthesis of indoles.

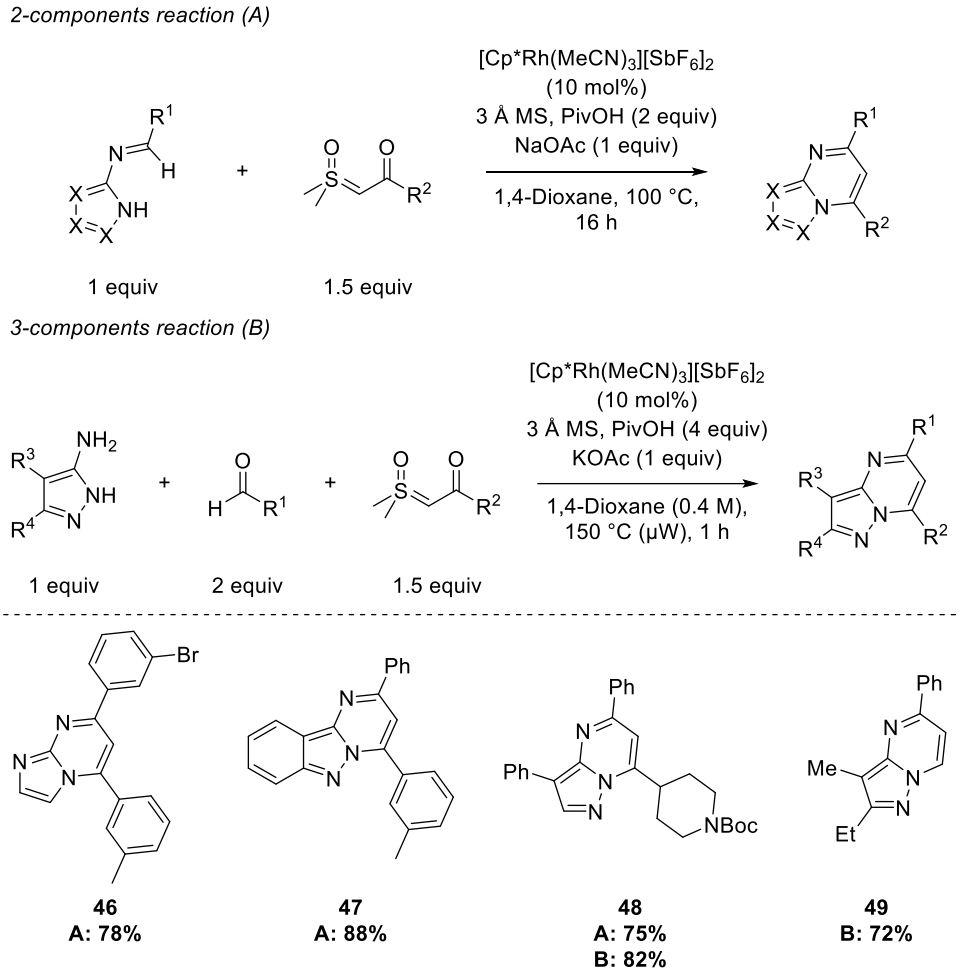
Interestingly, in this last case, replacing the NaOAc with CuF_2 and CsOAc oxygen atmosphere favoured the formation of the quinazolines (Scheme 11).



Scheme 11: Quinazolines synthesis.

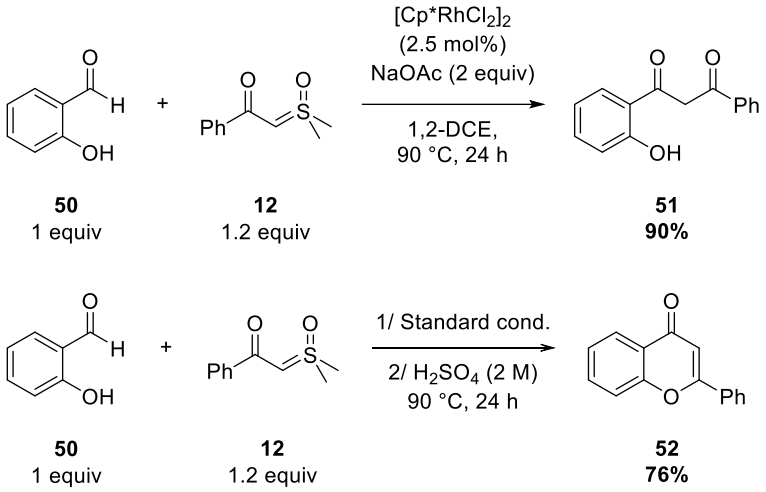
In order to get access to fused [5,6]-bicyclic bridgehead nitrogen heterocycles, Ellman's group developed a reaction between azoloaldimines and sulfoxonium ylides (Scheme 12).[21] The authors could obtain the imidazopyrimidine **46** in good yields and several pyrazolopyrimidines such as **47** and **48**. Their reactions were carried out in a glovebox but they also had one example of a 1 mmol scale reaction set up on the benchtop which proved to be as efficient.

Later, the same group re-designed this reaction in a 3-component fashion.[22] The aldimine was formed *in situ* from the primary amine and the corresponding aldehyde. However, the reaction had to be carried out at 150 °C in a microwave reactor to obtain similar results as for their two components reaction. Compound **48** was then obtained in 82% yield in that case. In addition, the publication described the first chemical transformation using the formyl sulfoxonium ylide (R^2 = H) affording **49** in 72% yield.



Scheme 12: Synthesis of fused [5,6]-bicyclic bridgehead nitrogen heterocycles through 2- or 3-component reactions.

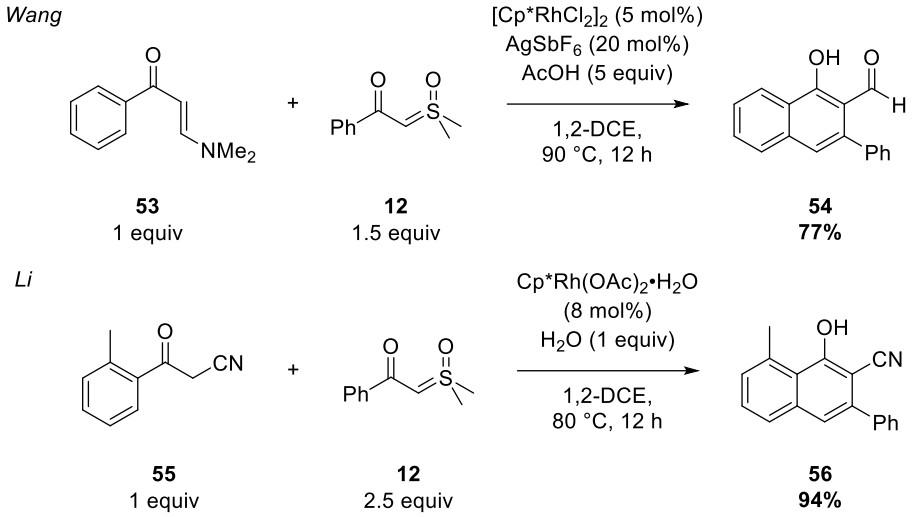
The reactivity of salicylaldehydes with sulfoxonium ylides has been reported by Huang and co-workers (Scheme 13).[23] The alcohol was used as the directing group for the C–H activation of the aldehyde. The 1,3-diketones **51** could be converted *in situ* into the corresponding chromone **52** by addition of sulfuric acid at the end of the reaction. Those compounds have the flavonoid backbone which is known for anti-oxidative, anti-inflammatory, anti-mutagenic and anti-carcinogenic properties, which makes them desirable building blocks.[24]



Scheme 13: C–H functionalisation of aldehydes and in situ *cyclisation.*

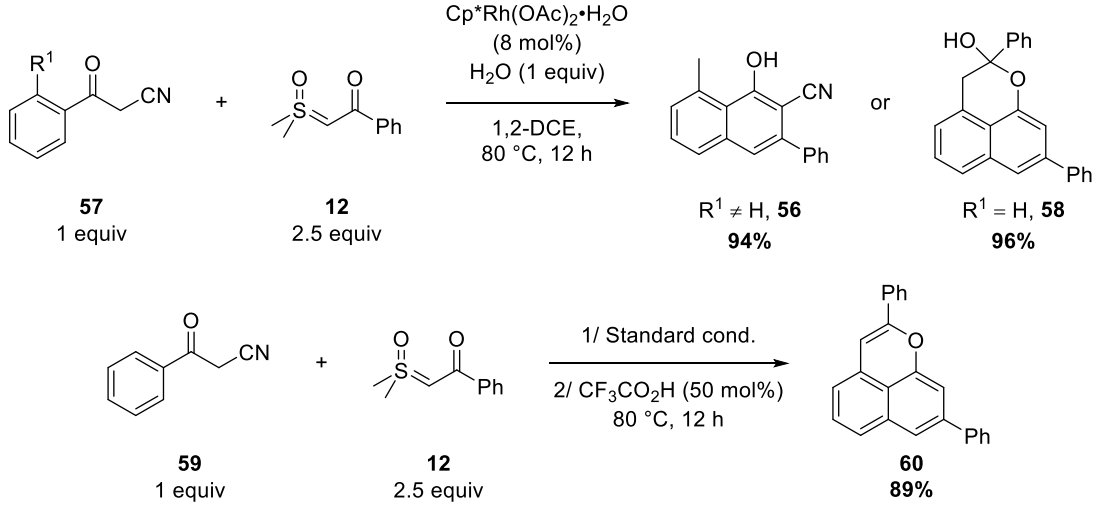
Naphthols have also been synthesised using sulfoxonium ylides.[25] Wang's group converted the unsaturated ketone **53** to the corresponding naphthol **54** bearing an aldehyde moiety in 77% yield (Scheme 14, top). The latter originated from the *in situ* hydrolysis of the imine.

Li and co-workers used another strategy towards the synthesis of nitrile substituted naphthols, in position 2, using the benzoylacetonitriles.[26] Only few examples were described in that case and the *ortho*-position of the benzoylacetonitrile had to be substituted to prevent overreaction (Scheme 14, bottom). Compound **56** was obtained in excellent yield from the corresponding 2-toluoylacetonitrile.



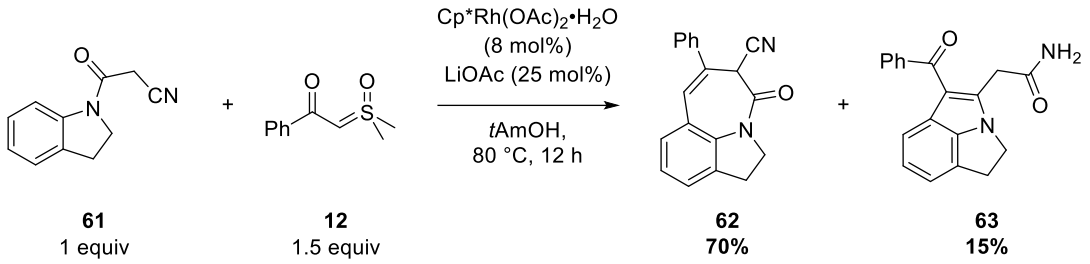
Scheme 14: Methodologies towards the formation of naphthols.

However, when R^1 from the benzoylacetonitriles was left unsubstituted, a second equivalent of the sulfoxonium ylide could react leading to the formation of the tricyclic compound **58** (Scheme 15). The authors described a wide scope of both benzoylacetonitriles and sulfoxonium ylides suitable for this reaction. Interestingly, the addition of triflic acid at the end of the reaction triggered the elimination of water, thus forming naphthopyrans in one pot as seen for compound **60**.



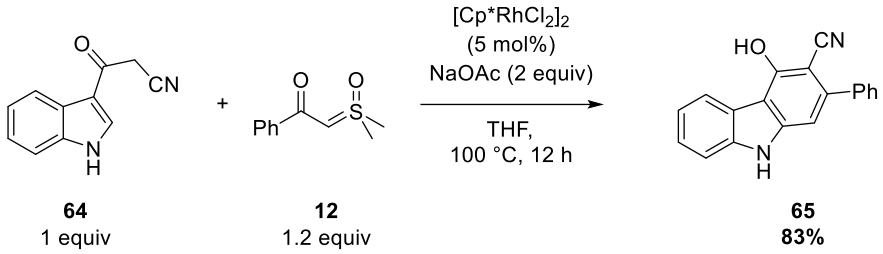
Scheme 15: Use of 3-aryl-3-oxopropanenitriles.

They used similar strategy for the synthesis of the azepinoindole **62**, although obtaining pyrroloindole **63** as minor products (Scheme 16).[27]



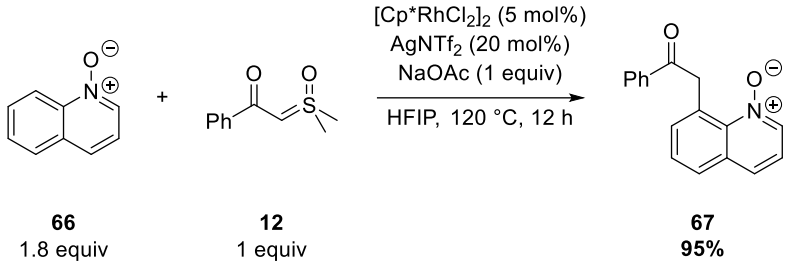
Scheme 16: Use of 3-indoline-3-oxopropanenitriles.

Finally, 3-oxopropanenitriles derivatives were also used on the position 3 of indoles by Cheng's and co-worker to access polysubstituted carbazoles (Scheme 17).[28] As expected, the formation of the aromatic 6-membered ring was favoured and no annulation occurred on the 4-position of the indole.



Scheme 17: Use of 3-indole-3-oxopropanenitriles.

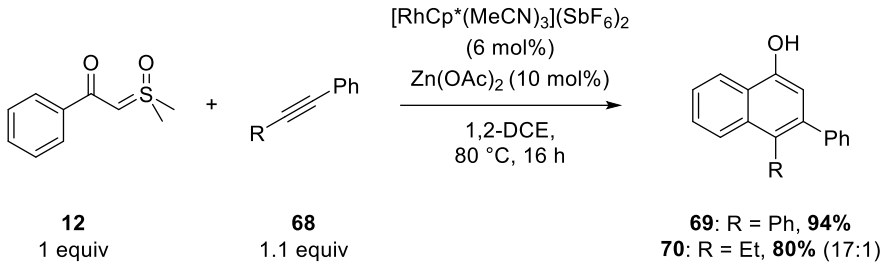
Cui and co-workers functionalised quinoline **66**, using the *N*-oxide as directing group to give **67** in excellent yield (Scheme 18).[29] Only the coupling with aryl sulfoxonium ylides was described. It is one of the rare reported case were the yields were better when the sulfoxonium ylide was used as limiting reagent.



Scheme 18: Functionalisation of quinoline N-oxide derivatives.

2.1.3 C–H activation of α-arylketone sulfoxonium ylides

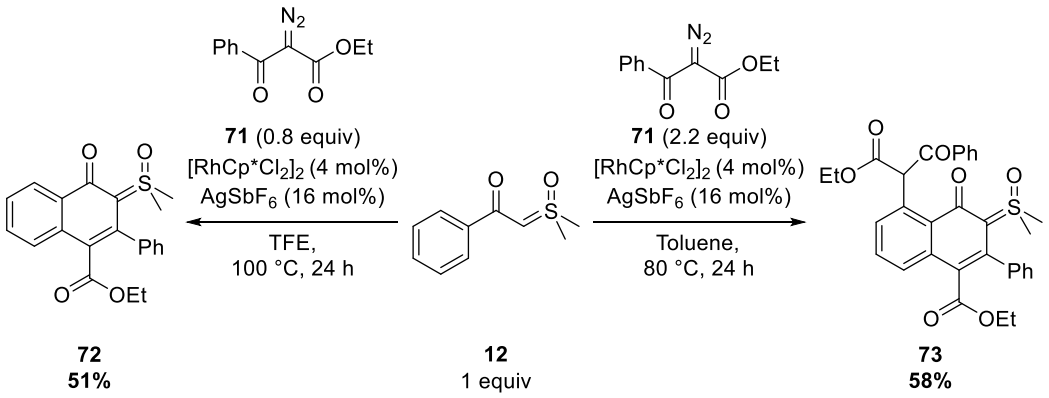
Li and co-workers demonstrated that sulfoxonium ylides can be coupled with alkynes to obtain naphthols (Scheme 19).[30] The mechanism for that reaction is quite different as compared to what was previously discussed as, in that case, the C–H activation occurs on the aryl sulfoxonium ylide derivative. The authors proposed that the ketone act as the directing group for that step. They showed very good results with symmetrical aryl alkynes such as **68** to obtain **69** in 94% yield. They also described a few examples with unsymmetrical alkyl−aryl alkynes with good regioselectivity.



Scheme 19: Coupling of sulfoxonium ylides with alkynes. Ratio of regioisomers in parenthesis.

As compared to their diazo equivalents, sulfoxonium ylides are known to have higher nucleophilicity but undergo metal decomposition to form metal carbenes at a slower rate.[2] Fan and co-workers used those different properties and described a cross-coupling of sulfoxonium ylides with diazo compounds (Scheme 20).[31] In that case, the sulfoxonium ylide remained on the product and offered a handle for further

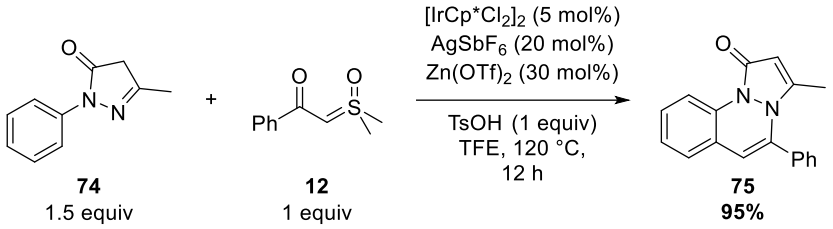
functionalisation. Depending on the solvent, temperature and quantity of diazo compound introduced in the reaction, two different products could be obtained, usually in moderate yields. If a slight excess of sulfoxonium ylide was used in TFE at 100 °C, the cyclised product **72** was obtained in 51% yield. On the other hand, with 2.2 equivalents of diazo compound **71** in toluene at 80 °C, **73** was obtained after a second addition of the diazo compound onto the aromatic ring of the intermediate **72**. Wang and co-workers reported a very similar work a few months after this publication.[32]



Scheme 20: Functionalisation of sulfoxonium ylides with diazo compounds.

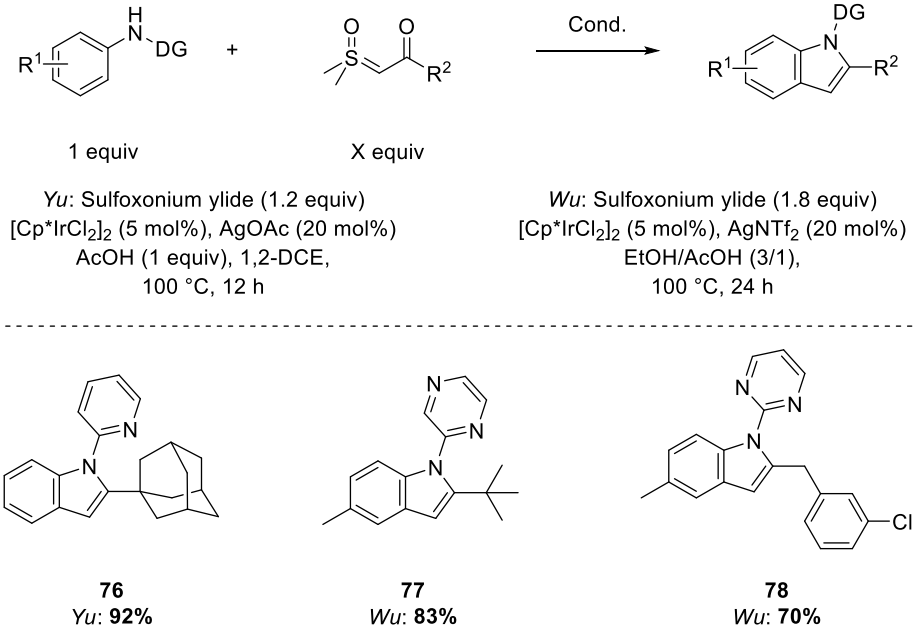
2.2 Using iridium

The first example of the use of iridium for C–H activation and coupling with sulfoxonium ylides was from Dong and co-workers (Scheme 21).[33] Pyrazolones were used as directing groups. After the coupling of the sulfoxonium ylide **12**, keto−enol tautomerism and cyclisation formed compound **75**. The reaction gave good to excellent yield with electron-rich and electron-poor substituents for both the electrophile and the nucleophile, but substitution on the *ortho*-position of the aryl-pyrazolone ring was not tolerated.



Scheme 21: Functionalisation of pyrazolones.

Indoles were also synthesised using iridium catalysts. Yu and Wu's groups simultaneously reported two similar methodologies in 2019 (Scheme 22).[34,35] In Yu's publication, only pyridine was used as a directing group but very good tolerance of steric hindrance was observed in the coupling of an adamantane derivative to afford **76** in 92% yield. In contrast, both pyrazines and pyrimidines were tolerated in Wu's case to afford **77** and **78** in good yields.



Scheme 22: Methodologies towards the formation of indoles.

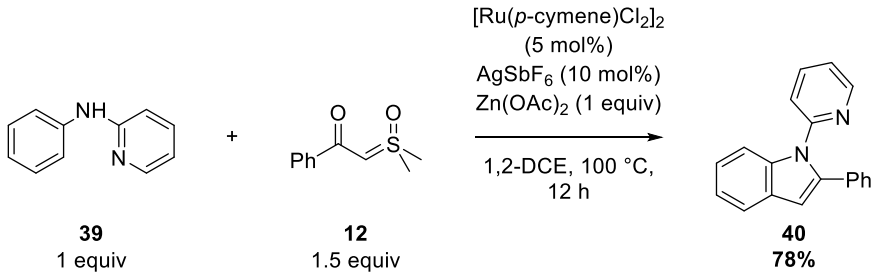
2.3 Using ruthenium

More recently, ruthenium has been used in C–H functionalisation with sulfoxonium ylides. We can separate those publications in two categories between

those that mimic the reactivity previously observed with rhodium or iridium leading to the same products and those leading to new products.

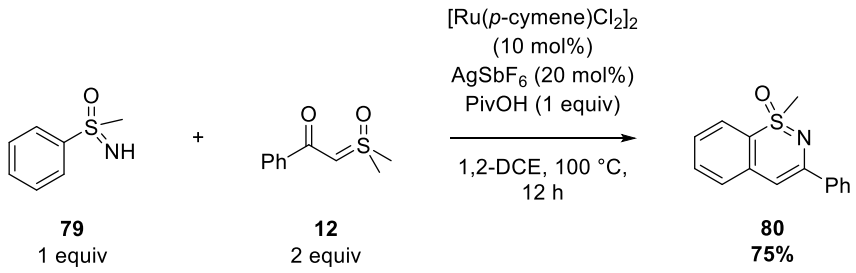
2.3.1 Similar reactivity to rhodium and iridium chemistry

Similarly to Yu[34] and Wu's[35] work with iridium, Huang and co-workers developed the ruthenium catalysed synthesis of pyridine-substituted indoles (Scheme 23).[36] Compound **40** was obtained in good yields from **39** with [Ru(*p*-cymene)Cl_2]$_2$ as a cheaper catalyst than iridium.



Scheme 23: Ruthenium-catalysed synthesis of indoles.

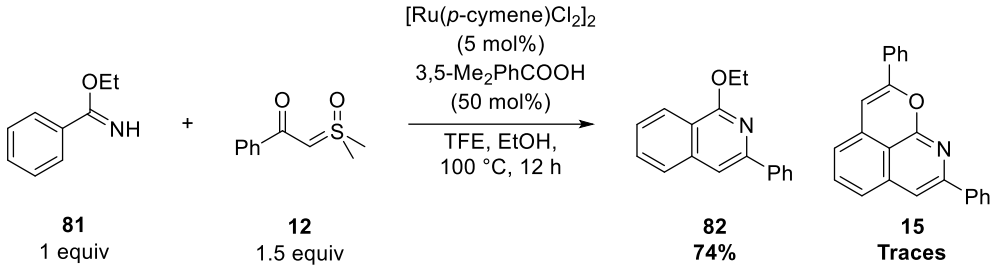
The 1,2-benzothiazine **80** has also been synthesised using the same catalyst by Zeng and co-workers (Scheme 24).[37] This reactivity is similar to what was published in 2018 by Li and co-workers using a rhodium catalyst.[14]



Scheme 24: Ruthenium catalysed synthesis of 1,2-benzothiazines.

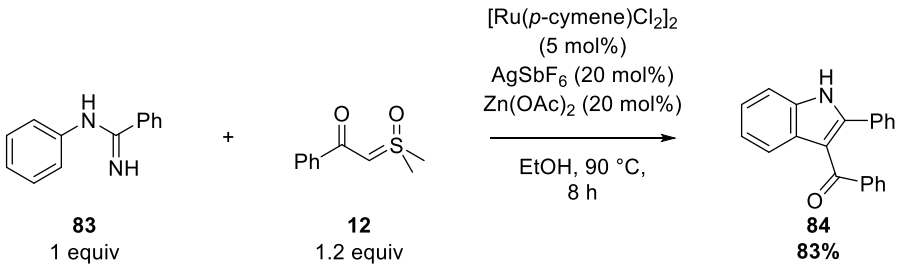
Wang and co-workers used the same catalyst to synthesise the isoquinolines **82** in good yield from the benzimidate **81** (Scheme 25).[38] The coupling partners that

were used here were the same as those used by Cheng previously.[12] However, they mainly obtained the mono substituted product **82** with only traces of the bis C–H activation product **15** observed under their optimised conditions.



Scheme 25: Ruthenium catalysed synthesis of 1-ethoxy-isoquinolines.

Finally, Liu and co-workers used arylamidines for the formation of indoles (Scheme 26).[39] As seen previously, those compounds have been used by Wu's group with rhodium catalysts.[20]

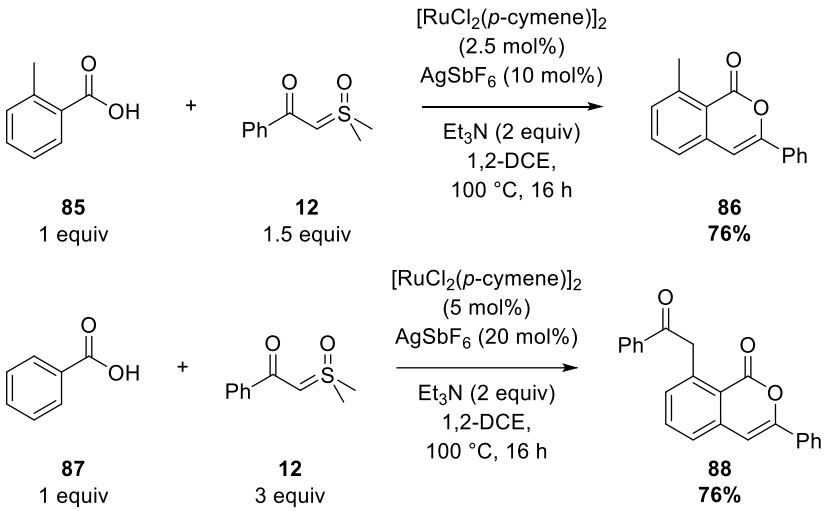


Scheme 26: Synthesis of 3-ketoindoles.

2.3.2 Formation of new products

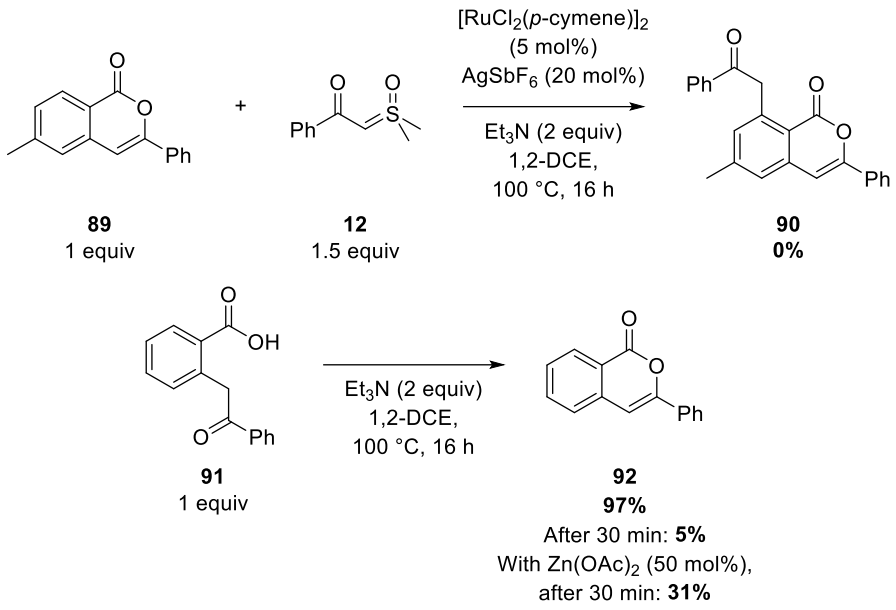
Ackermann and co-workers reported an interesting synthesis of the isocoumarin **86** from the corresponding benzoic acids **85** (Scheme 27).[40] The weak O–coordination with ruthenium was used to direct the C–H activation. By changing the number of equivalents of sulfoxonium ylides as well as catalyst loading and leaving the *ortho*-position free of substituents, the authors could trigger a second C–H

activation to obtain the 8-substituted isocoumarin **88**. When only the cyclisation was desired, addition of $Zn(OAc)_2$ was sometimes necessary to obtain good yields.



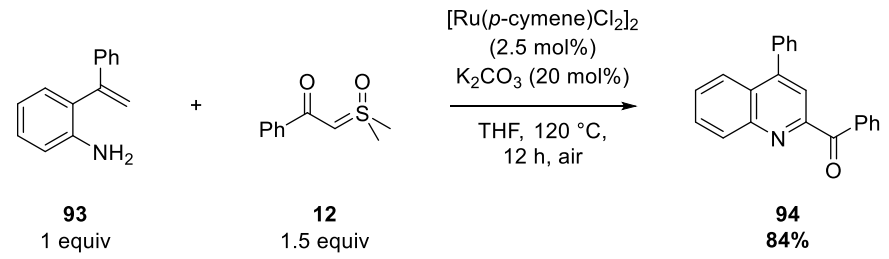
Scheme 27: Isocoumarin synthesis.

The authors conducted control experiments that showed that when the coupling on the isolated isocoumarin **89** was attempted, no compound **90** was observed (Scheme 28). This indicated that the carboxylic acid was essential for the second cyclisation to occur. Also, the cyclisation alone was done on the isolated carboxylic acid **91**, without the ruthenium catalyst nor the silver salt, to give **92** in 97% yield, proving that that step is not metal-catalysed. Secondly, the yield of that reaction after 30 minutes was increased significantly when $Zn(OAc)_2$ was added to the reaction.



Scheme 28: Isocoumarin synthesis: control experiments.

The first synthesis of quinoline derivatives with sulfoxonium ylides was proposed by Ma *et al* (Scheme 29).[41] Also using the inexpensive [Ru(*p*-cymene)Cl_2]$_2$ catalyst, they could promote the C–H activation of alkenes using primary amines as a directing group to undergo [5+1] annulation leading to the formation of **94** in excellent yield. Interestingly, air was used as a source of oxidant and the yield was greatly decreased when the reaction was carried out under a N_2 atmosphere.

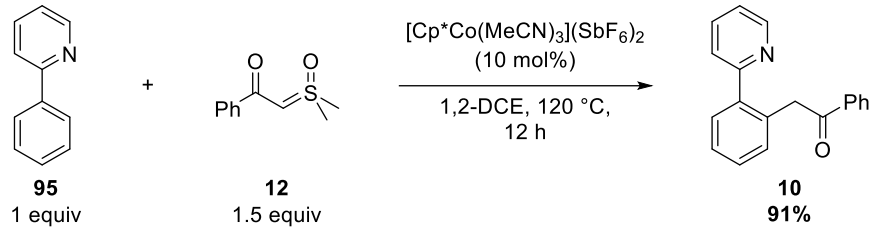


Scheme 29: Synthesis of quinolines.

2.4 Using cobalt

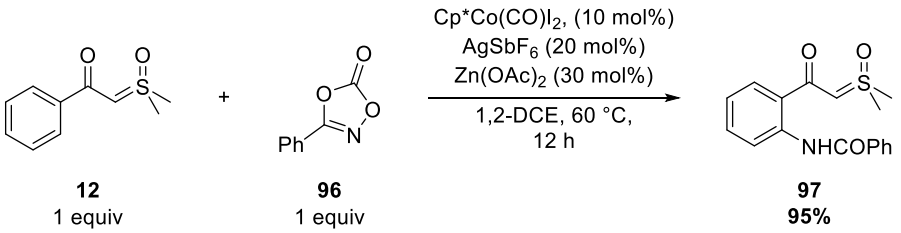
Two reactions have been developed using cobalt as a catalyst. The first one was the same pioneering cross-coupling that was done by Aïssa's group and Li's

group but using $[Cp^*Co(CH_3CN)_3](SbF_6)_2$ as the catalyst (Scheme 30).[42] The products were usually obtained in good yields when aryl-sulfoxonium ylides were used. Pyridine, pyrazole and pyrimidine could be used as the directing group but amide, ketone, oxime, azobenzene, imine and 2-phenyl imidazole were not tolerated. It is noteworthy that the reaction was done without any need of extra additives such as silver salts, Lewis acids or bases as it is usually the case when it was demonstrated with rhodium.



Scheme 30: C–H acylmethylation of arenes using cobalt catalyst.

The second report described a chemistry that has not been done previously with rhodium and was reported by Li and co-workers (Scheme 31).[43] Similarly to their previous work with rhodium (part 2.1.3),[43] the C–H activation was done directly on the aryl group of the α-arylketone sulfoxonium ylides but that moiety was still conserved in the product of the reaction. The reaction allowed the α-amidation of keto sulfoxonium ylides and **97** could be obtained in 95% yield.

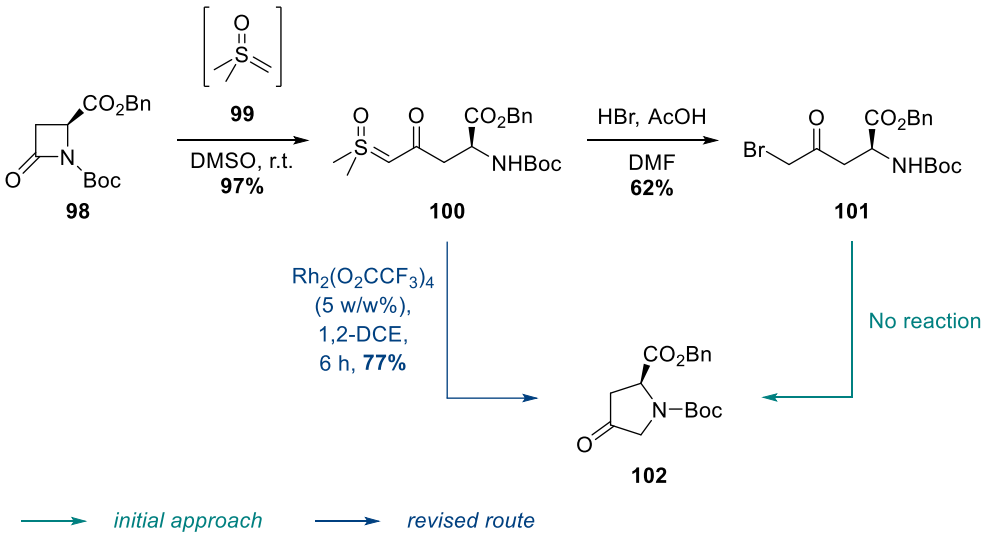


Scheme 31: α-amidation of sulfoxonium ylides.

3 X–H insertion

3.1 Using rhodium

The first example of N–H insertion was reported in 1993 by Baldwin and co-workers (Scheme 32).[7,44] In order to access the 2-pyrrolidinones **102**, the authors converted the *β*-lactam **98** into the sulfoxonium ylide **100** in quantitative yield. The latter was then converted to the corresponding α-bromoketone **101** which was reluctant to the cyclisation yielding **102**. In contrast, attempting the cyclisation directly on the sufoxonium ylide **100** *via* the formation of a rhodium carbene afforded **102** in 77% yield. A slow addition of **100** was necessary to obtain good yields.

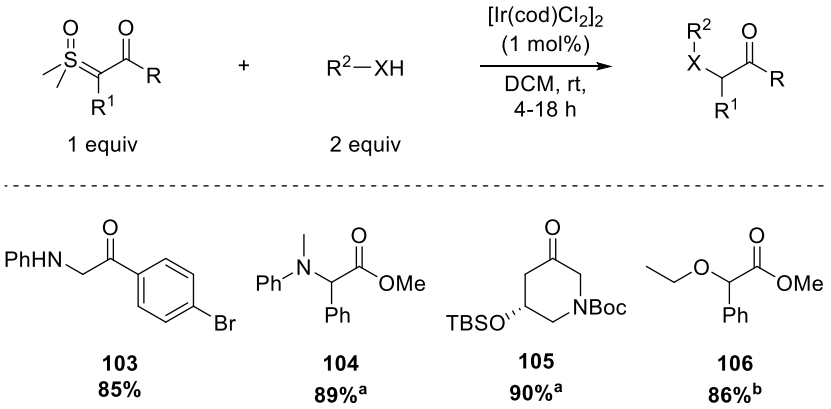


Scheme 32: First N–H insertion by Baldwin.

3.2 Using iridium

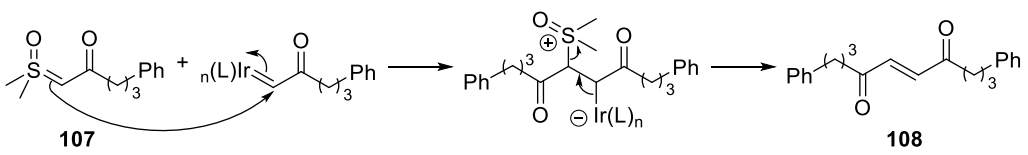
Further development of this reactivity was reported in 2009 by Mangion and co-workers from the process research department of Merck (Scheme 33).[45] The authors proved that the DMSO generated from the reaction was poisoning the rhodium catalyst, limiting the conversion of the starting material. Changing from a

rhodium catalyst to the more robust $[Ir(cod)Cl]_2$ improved the yield significantly. Very good yields were then obtained when the reaction was performed intermolecularly with primary or secondary anilines (compound **103** and **104**) or intramolecularly (compound **105**). C–O bond formation could also be achieved as shown for compound **106** but the starting alcohol had to be used as solvent.



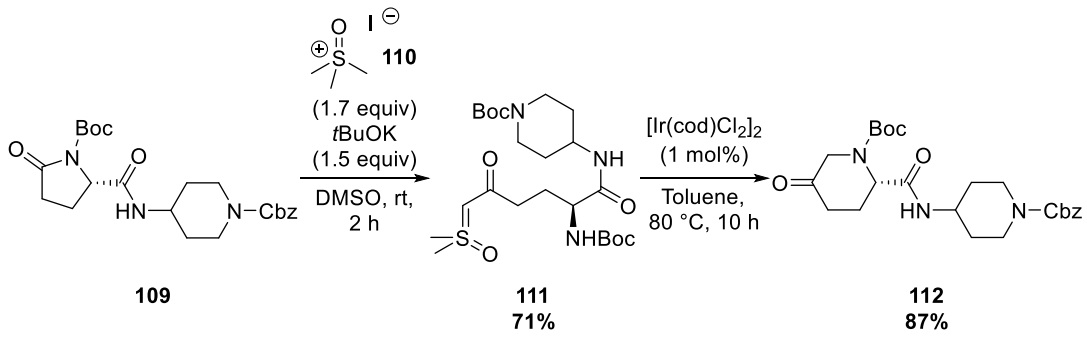
Scheme 33: Mangion's improvement of the N–H and O–H insertion. [a] at 70 °C in 1,2-DCE [b] Ethanol used as solvent.

C–H insertion on a benzylic position could not be achieved using those conditions and only the dimerization of the sulfoxonium ylide leading to the formation of the alkene **108** could be isolated (Scheme 34). In contrast, this phenomenon is not usually observed for the diazo equivalents. It could be explained by the higher nucleophilicity of the sulfoxonium ylides favouriting the attack onto the iridium carbene.



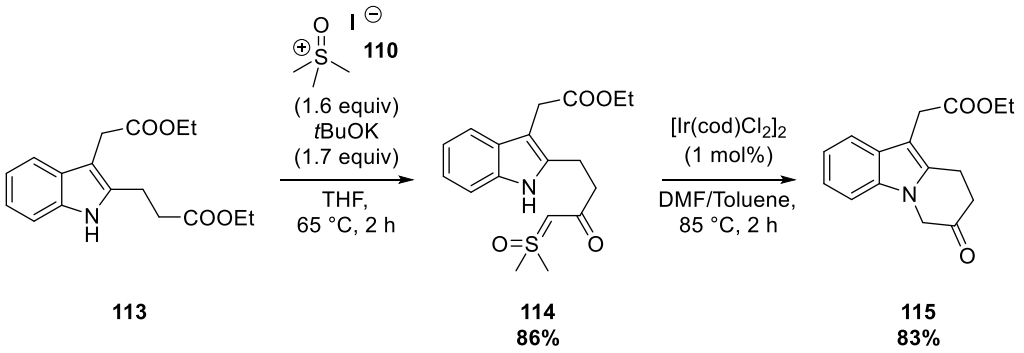
Scheme 34: Proposed mechanism for the dimerization.

The same group later used that methodology for the synthesis of MK-7655, a β-lactamase inhibitor (Scheme 35).[46] One of the key steps was a ring expansion of the L-pyroglutamic acid derivative **109** to obtain the cyclic α-amino acid **112**. The group was looking for a scalable synthesis, bearing in mind that the route could be adapted for manufacture. In this context, the option of ring opening with diazomethane followed by rhodium-catalysed intramolecular cyclisation was discarded due to potential safety hazards. Instead, the sulfoxonium ylide **111** was formed *via* the ring opening with trimethylsulfoxonium methylide formed *in situ* followed by iridium catalysed intramolecular cyclisation with 71% and 87% yield, respectively. That sequence was then used for the multikilogram scale synthesis of the target.



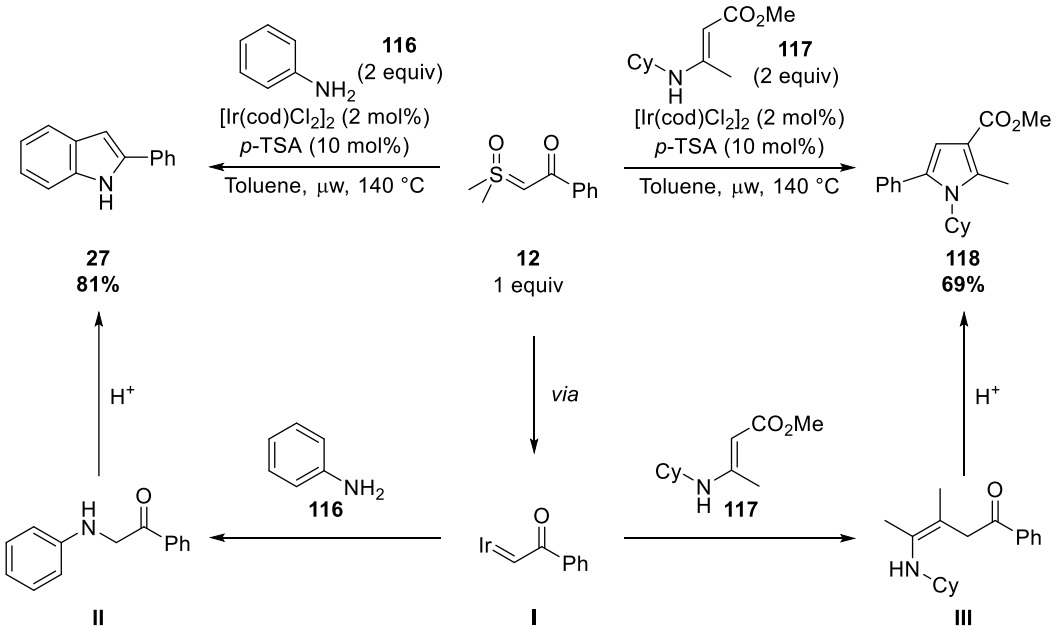
Scheme 35: Key steps toward the large scale synthesis of MK-7655.

O'Shea and co-workers, also from Merck, used a similar strategy for the synthesis of MK-7246 (Scheme 36).[47] The sulfoxonium ylide **114** was formed selectively from the indole **113** in 86% yield. The iridium catalysed cyclisation afforded **115** in 83% yield. This sequence was also used in multikilogram scale.



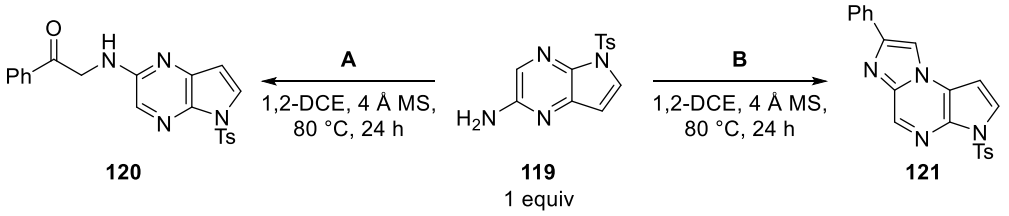
Scheme 36: Key steps toward the large scale synthesis of MK-7246.

Vaitla and co-workers exploited the formation of the iridium carbene with sulfoxonium ylide to form indoles and pyrroles from anilines and 3-aminoacrylates, respectively (Scheme 37).[48] The products were formed according to two different pathways. In the case of the indoles, the iridium carbene **I** was trapped by the amine **116** through C–N bond formation followed by acid-catalysed cyclisation to give indole **27** in very good yield. On the other hand, the iridium carbene **I** was trapped by the nucleophilic 3-aminoacrylate **117** forming the C–C bond leading to **III** before undergoing cyclisation to yield the desired pyrrole **118** in good yield .

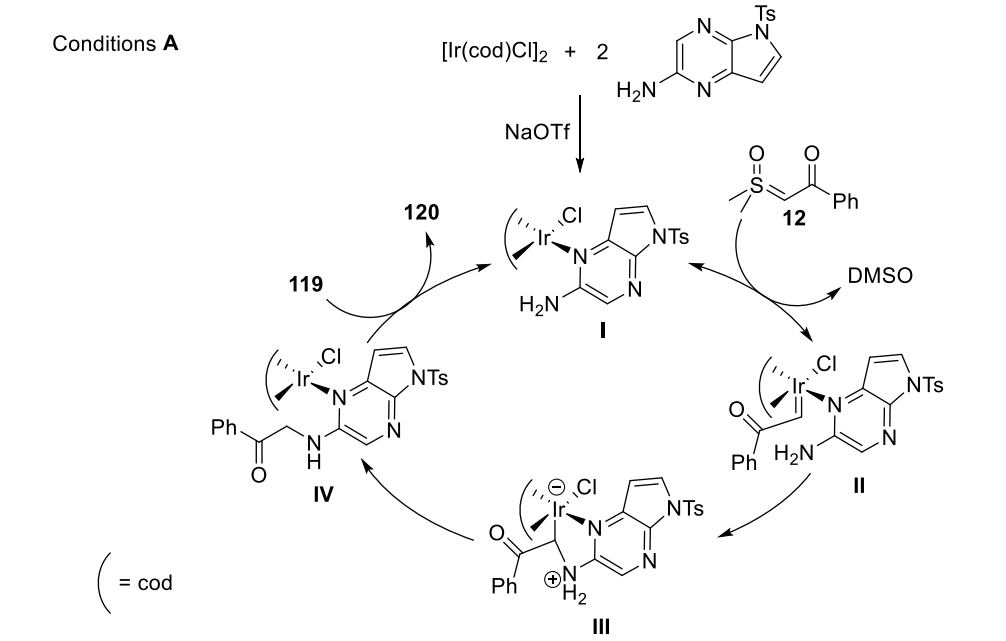


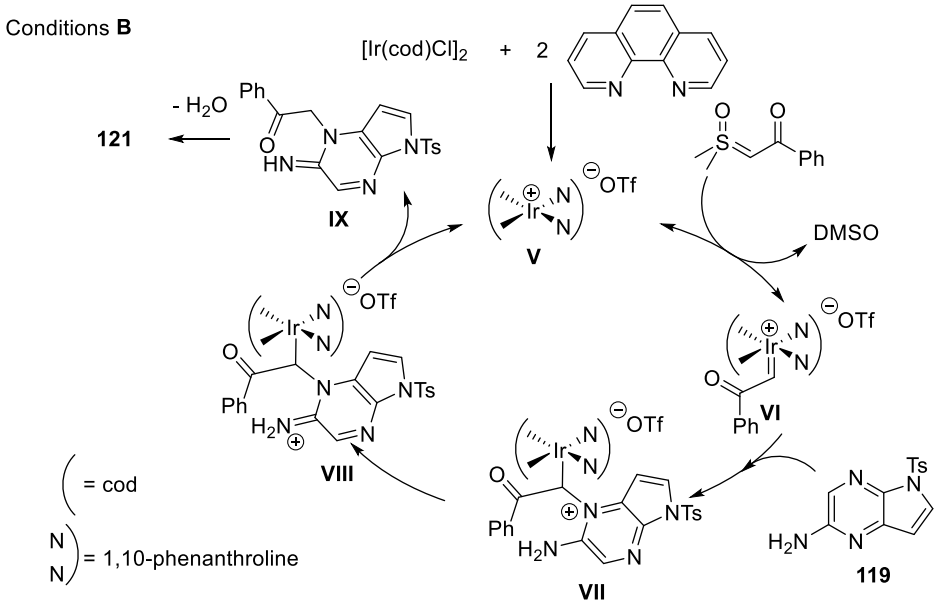
Scheme 37: Synthesis of indoles and pyrroles.

The iridium catalysed C–N bond formation has also been used by Shekhar and co-workers in 2016 (Scheme 38).[49] Interestingly, the addition of a ligand had a significant effect not only on the reactivity, but also on the mechanism of the reaction. Indeed, when $[Ir(cod)Cl]_2$ was used without ligand, it was proposed that the first step of the reaction is the coordination of **119** to the iridium, followed by the attack of the sulfoxonium ylide leading to the formation of the iridium ylide **II**. The latter could then be attacked by the amino group and form **III**, which would undergo protonolysis generating **IV** . Finally ligand exchange would liberate the product **120** and regenerate **I**. On the other hand, addition of 5 mol% of 1,10-phenantroline and NaOTf would generate the cationic iridium complex **V**. This complex would react directly with the sulfoxonium ylide to form the iridium carbene **VI** which would then be attacked by **119** to generate **VII**. After delocalisation of the charge, this complex would then undergo proton shift, cyclisation and dehydration to form compound **121**.



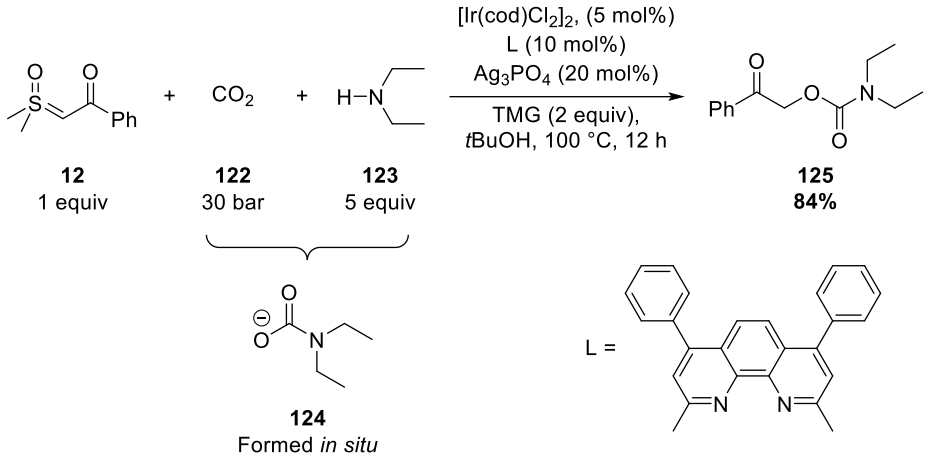
A: $[Ir(cod)Cl]_2$ (2.5 mol%), **12** (1.5 equiv)
B: $[Ir(cod)Cl]_2$ (2.5 mol%), **12** (1.5 equiv), 1,10-phenanthroline (5 mol%), NaOTf (5 mol%)





*Scheme 38: Ligand effect on the reactivity of **119** with sulfoxonium ylides.*

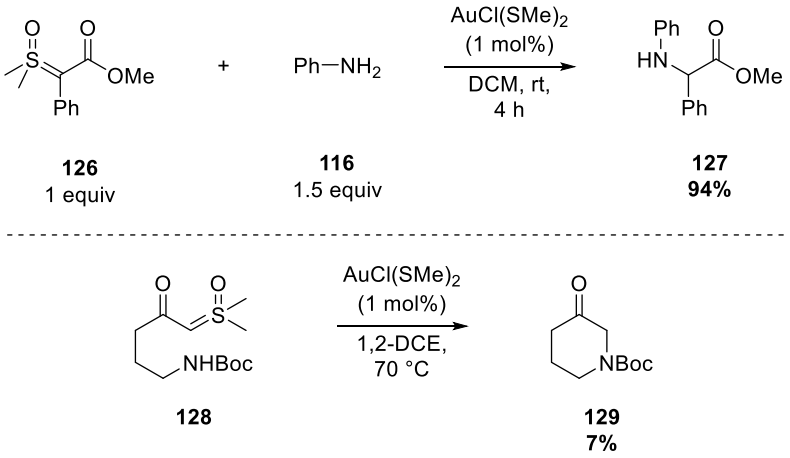
A similar cationic iridium complex was used by Jiang and co-workers for the three component coupling of carbon dioxide, amines, and sulfoxonium ylides for the synthesis of carbamates **125** in very good yield (Scheme 39).[50] The *in situ* formation of a carbamate anion that can react with the iridium carbene allowed the formation of carbamates without using phosgene or other toxic derivatives. The main limitation of this method is the necessity to use a secondary amine as the reaction did not work with primary ones.



Scheme 39: Three component reaction for the synthesis of O-β-oxoalkyl carbamates. TMG = 1,1,3,3-tetramethylguanidine.

3.3 Using gold

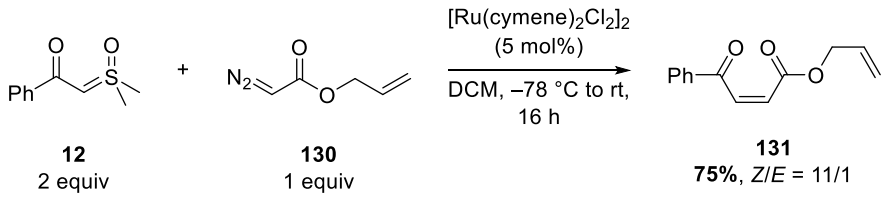
In 2010, Mangion and co-workers also used a gold catalyst to perform N–H and O–H insertion reactions (Scheme 40).[51] The reactivity was similar to what they published previously with iridium.[45] Notably, in that case, the reaction was carried out with a few amino acid sulfoxonium derivatives without any loss of stereochemical integrity. However, the intramolecular reaction was not successful with that catalyst and compound **129** was only obtained in 7% yield.



Scheme 40: Gold-catalysed N–H and O–H insertion.

4 Other metal-catalysed reaction

In 2018, Maulide and co-workers reported a ruthenium-catalysed cross-coupling of sulfoxonium ylides that allowed the formation of the alkene **131** in 75% yield (Scheme 41).[52] The *Z* isomer was favoured in those conditions but the *E* isomer could be obtained by addition of a catalytic amount of triphenylphosphine into the reaction. This strategy reduced significantly the risk of dimerization encountered during the cross dimerization of diazo compounds.

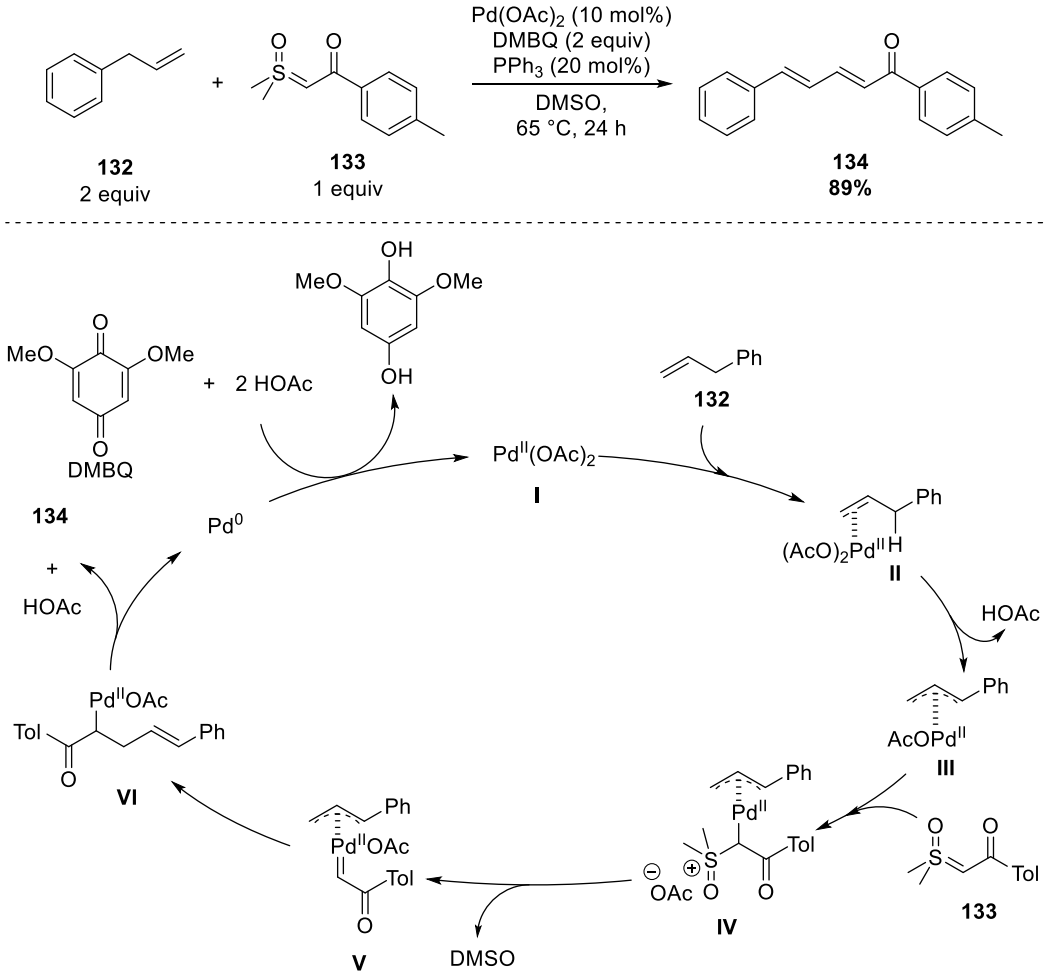


Scheme 41: Cross-olefination of diazo compounds with sulfoxonium ylides.

5 Chemistry of sulfoxonium ylides with palladium

As seen previously, the chemistry of sulfoxonium ylides is being widely explored mainly with rhodium, ruthenium, and iridium. However the use of sulfoxonium ylides as reagents with palladium catalysts remains underdeveloped.

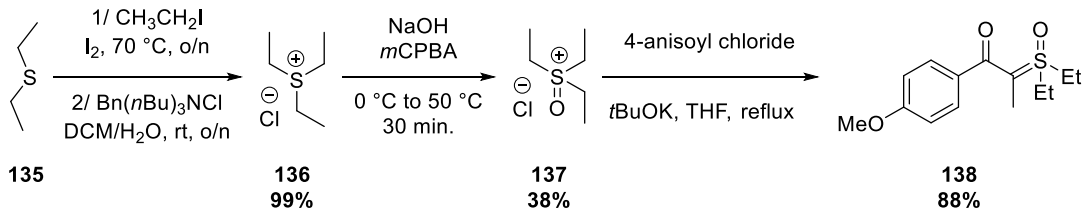
The only example was reported in 2019 by Jiang and co-workers (Scheme 42).[53] The authors developed the synthesis of conjugated dienones *via* the oxidative allylation of sulfoxonium ylides, which is an alternative to aldol condensation or Wittig reaction. The reaction has previously been developed using diazo compounds[54] and the suggested mechanism is depicted in Scheme 42. The Pd^{II} species **I** would first coordinate to the allyl moiety of **132** and would undergo allylic C–H activation to obtain **III**. Nucleophilic attack of the sulfoxonium ylide **133** would generate **IV** which would lead to the formation of the palladium carbene **V** upon loss of DMSO. Migratory insertion would give **VI**. β-hydride elimination would yield the product **134** and liberate the palladium centre which would be oxidised to regenerate the active catalyst.



Scheme 42: Oxidative allylation of sulfoxonium ylides – proposed catalytic cycle. Ligands omitted for clarity.

6 Conclusion

The breadth of the chemistry of sulfoxonium ylides enabled by transition metal catalysts has grown significantly in the past few years. However, clear limitations can already be observed. Indeed, exclusively α-keto sulfoxonium ylides have been used in C–H bond functionalisation reactions and very rare examples of α-ester sulfoxonium ylides were described for the C–N and C–S bond formation. Moreover, the α-keto sulfoxonium ylides that were used, most of the time, were bearing aryl groups on the α-position of the ketone. Fewer examples were demonstrated with sulfoxonium ylides containing alkyl groups, heteroaryl groups or more complex molecules such as active pharmaceutical ingredients. Finally, only one example of use of disubstituted sulfoxonium ylides has been reported for C–H bond functionalisation.[8] The methodology for the synthesis of the starting sulfoxonium ylide **138** that was used in the reaction was tedious, only allowed the introduction of a methyl group on the α-position of the sulfoxonium ylides and changed the two methyl groups of the sulfoxonium ylides to ethyl groups, thus increasing the bulk of that reagent (Scheme 43).



Scheme 43: Synthesis of the disubstituted sulfoxonium ylides used for C–H bond functionalisation.

The limitations that are observed might be explained by the lack of efficient methods to obtain disubstituted sulfoxonium ylides, thus decreasing significantly the scope of the reactions developed using sulfoxonium ylides.

We will see in the next chapter that although some methodologies towards the synthesis of disubstituted sulfoxonium ylides have been developed recently, they usually contain several drawbacks which includes: synthesis from the degradation of a potentially explosive diazo derivative, scope limited to sulfoxonium ylides containing two electron withdrawing groups and lack of regioselectivity or convenience of the synthesis. It then appears necessary to develop a general and flexible access to bis-substituted sulfoxonium ylides. Chapter 2 will be dedicated to the study of α-ester sulfoxonium ylides whereas the synthesis of α-aryl-α-ketone sulfoxonium ylides will be discuss in Chapter 3. In the latter will also be discussed the study of the reaction mechanism.

Chapter 2:

Synthesis of (hetero)aryl substituted α-ester sulfoxonium ylides

Chapter 2: Synthesis of (hetero)aryl substituted α-ester sulfoxonium ylides

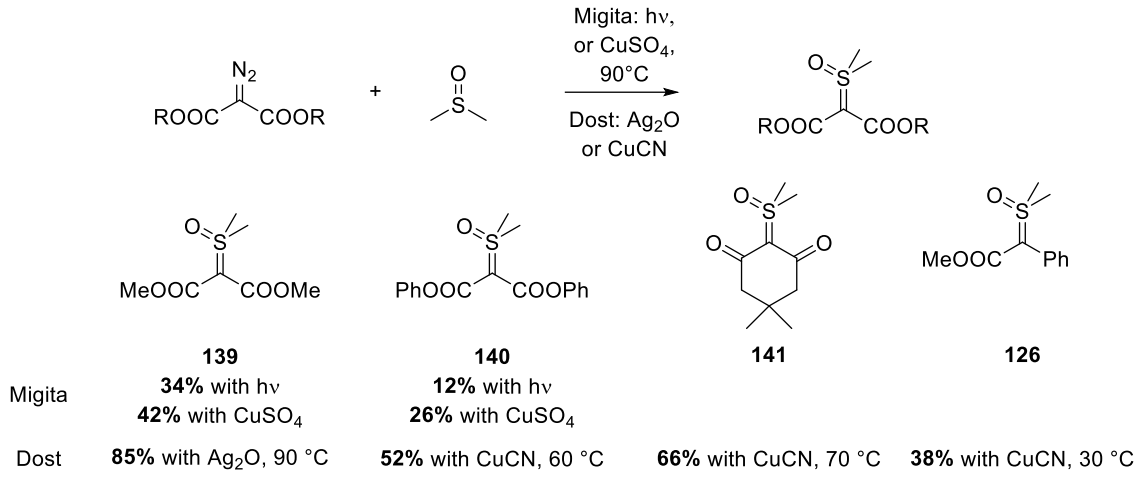
1 Disubstituted sulfoxonium ylides

1.1 Known syntheses in the literature

1.1.1 Synthesis using the diazo compounds

The first example of disubstituted sulfoxonium ylide was reported by Migita in 1969 (Scheme 44).[55] They carried out the photochemical decomposition of diazomalonates in DMSO using a mercury lamp and obtained the sulfoxonium ylide equivalent **139** in 34% yield. Slightly better results were obtained when they used $CuSO_4$ to generate the carbene instead of the photochemical degradation and the desired product **139** was obtained in 42% yield. The reaction was less efficient for the diphenyl sulfoxonium ylide **140** with 12% yield for the photochemical decomposition and 26% using the $CuSO_4$ method.

A year later, Dost and Gosselck used a similar strategy, this time using Ag_2O and CuCN for the carbene generation.[56] The reaction was more efficient and they could obtain **139** in 85% yield when using Ag_2O at 90 °C and **140** in 52% yield. They also reported the first example of cyclic sulfoxonium ylide **141** that they obtained in 66% yield. Finally the reaction was still efficient when they replaced one electron-withdrawing group by a phenyl ring (compound **126**) albeit in a lower yield of 38%.



Scheme 44: Synthesis of disubstituted sulfoxonium ylides from the diazo equivalents.

1.1.2 Drawbacks of the diazo compounds

The chemistry of α-diazocarbonyl compounds and their synthesis is now well known.[57,58] In contrast with them, the chemistry of sulfoxonium ylides remains underdeveloped. However, they have a major advantage: their improved safety profile. This statement has not been verified in the past so we compared the Differential Scanning Calorimetry (DSC) data of the diazo compound **142** with its sulfoxonium ylide equivalent **126** (Figure 1).[i] A significant difference was observed with a thermal potential energy of 706 J/g for **142** as compared to 435 J/g for compound **126**. We can also notice that the onset temperature is only at 115 °C for **142** whereas it occurs at 172 °C for **126**. This means that not only the sulfoxonium ylides are less explosive as they release less energy upon thermal degradation, but also that they will release that energy only at a significantly higher temperature. This is essential data for the use of those reagents for process scale reactions. An empirical rule is sometime used for the determination of "safe" temperature called the "100 K rule".[59] It consists on the subtraction of 100 °C from the onset temperature to

[i] DSC realised by Ben Dobson

choose the maximum operating temperature of a reaction for the secondary reaction not to happen. In the case of the compound **142**, it means a limit of 15 °C which is not operationally convenient. On the other hand, that temperature could be increased to 72 °C for its sulfoxonium ylide equivalent.

142
High thermal potential energy (706 J/g)
Decomposition occurs at 115 °C

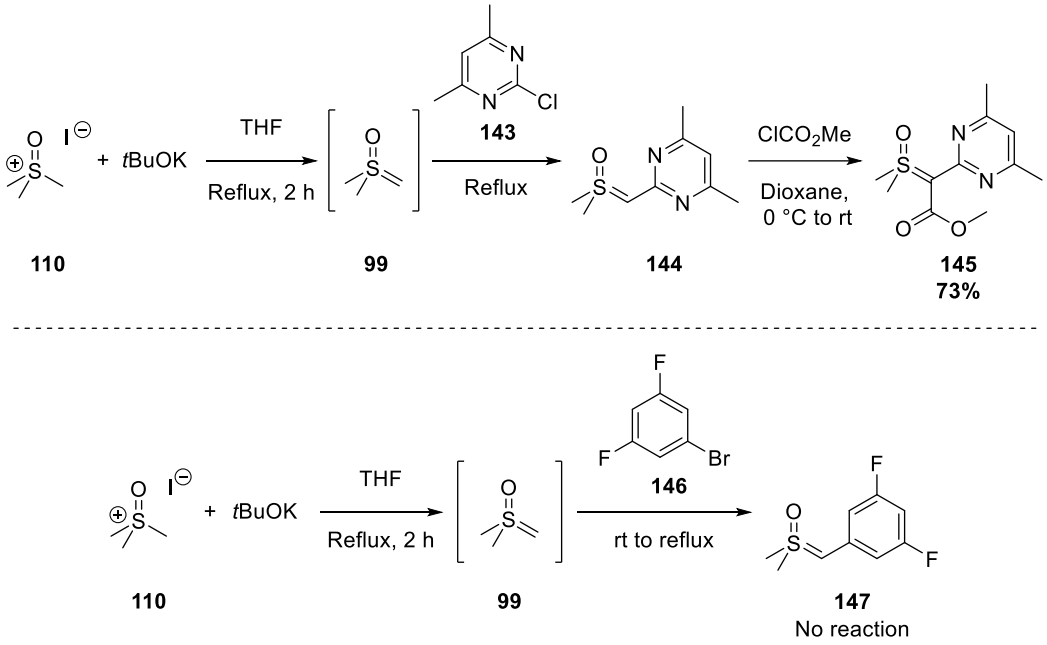
126
Lower thermal potential energy (435 J/g)
Decomposition occurs at 172 °C

*Figure 1: DSC comparison between the diazo compound **142** and its sulfoxonium ylide equivalent **126**.*

Moreover, upon reaction, diazo compounds will generate 1 molecule of N_2 per molecule of substrate reacting. This can lead to pressure build-up if not well controlled and can potentially lead to explosions which could have dramatic effects on plant scale.[60] On the other hand sulfoxonium ylides would only produce DMSO, a non-toxic liquid easily removed with an aqueous work up.[61]

1.1.3 Synthesis using heteroarylation of dimethylsulfoxonium methylide and nucleophilic substitution onto chloroformates

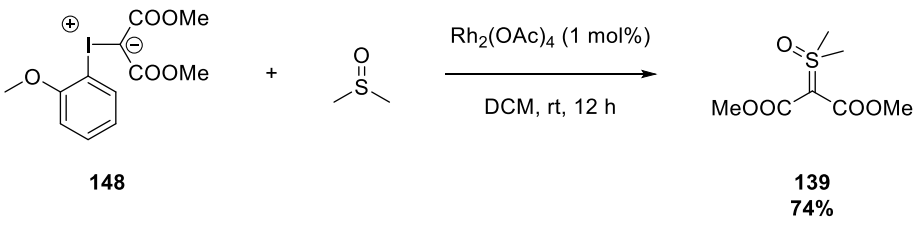
Disubstituted sulfoxonium ylides have also been synthesised by Gilchrist, Noji and co-workers in 1970 *via* direct nucleophilic aromatic substitution of dimethylsulfoxonium methylide **99** (formed *in situ* from trimethylsulfoxonium iodide **110** in presence of potassium *tert*-butoxide) onto **143** followed by nucleophilic substitution of methyl chloroformate to obtain **145** in 73% yield (Scheme 45, top).[62,63] However, this method was only applicable to reactive heterocycles and no reaction was observed when **146** was treated with **99** (Scheme 45, bottom).



Scheme 45: Heteroarylation of dimethylsulfoxonium methylide.

1.1.4 Synthesis using iodonium ylides

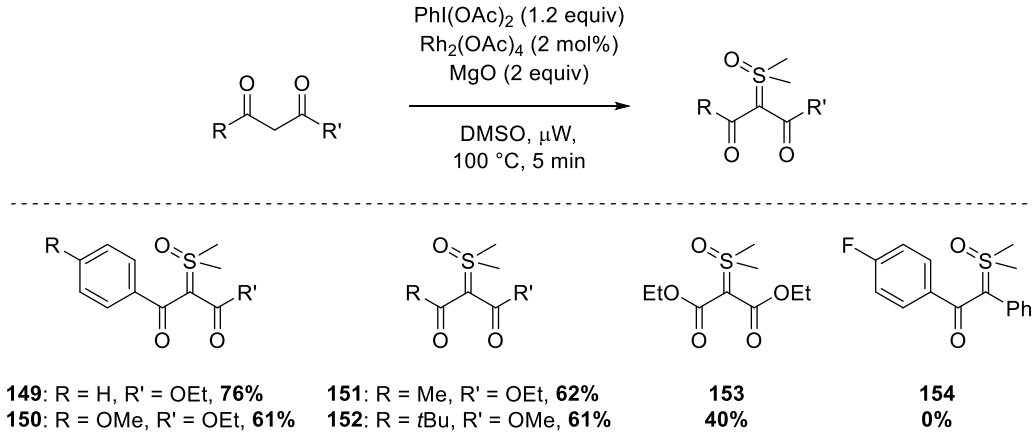
In 2012, Zhdankin also proposed a synthesis of **139** using a transylidation strategy.[64] They first synthesised the stable 2-substituted phenyliodinium ylide **148** which can be reacted with DMSO in presence of a rhodium (II) catalyst to obtain **139** in 74% yield (Scheme 46). Although the yield was slightly lower than with Dost's method, this strategy does not rely on the use of a diazo compound. It was however the only example of formation of sulfoxonium ylides in that paper.



Scheme 46: Synthesis of disubstituted sulfoxonium ylides using iodonium ylides.

Vaitla's group improved this methodology in 2017 by generating the iodonium ylide *in situ* (Scheme 47).[65] The reaction was very quick (usually 5 min) but had to be

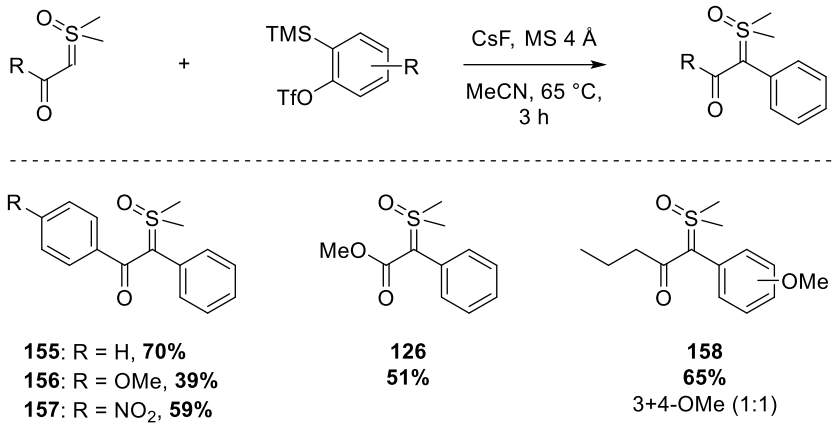
done in a microwave reactor at 100 °C. A large scope of malonate and β-keto ester sulfoxonium ylide derivatives was obtained (selected examples **149**-**153**). However, this method did not work when one of the electron withdrawing groups was replaced by a aryl ring, as for **154**. Then, it did not provide an alternative to the diazo strategy for that type of compound.



Scheme 47: Synthesis of disubstituted sulfoxonium ylides using in situ *generated iodonium ylides.*

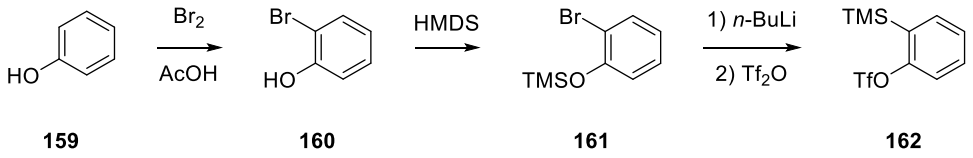
1.1.5 Synthesis using arynes

In 2018, Burtoloso's group published the first diazo-free method allowing the synthesis of arylated sulfoxonium ylides from the mono-substituted derivatives using benzyne chemistry (Scheme 48).[66] The reaction gave moderate to good yields for keto sulfoxonium ylides (selected examples **155**-**157**) and moderate yields for the ester derivatives (compound **126**).



Scheme 48: Synthesis of disubstituted sulfoxonium ylides using arynes.

Although this method employs cheap reagents, it has several drawbacks due to the use of benzyne chemistry. Indeed, asymmetrical arynes are well known to give mixtures of regioisomers and this problem can notably be observed for compound **158**.[67, 68] The second important drawback is the multistep synthesis of the aryne precursor which is not only inconvenient but also not always possible (Scheme 49).[69]

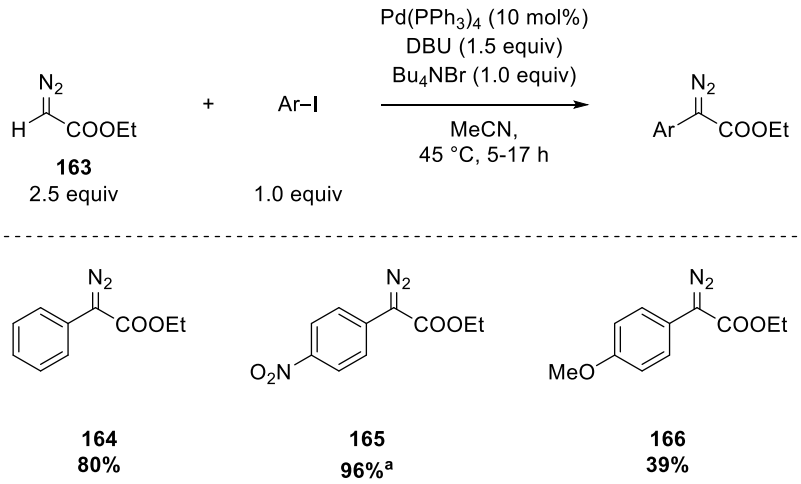


Scheme 49: General method for the synthesis of arynes.

1.2 Synthesis of disubstituted diazo compounds *via* palladium catalysed cross-coupling with aryl halides

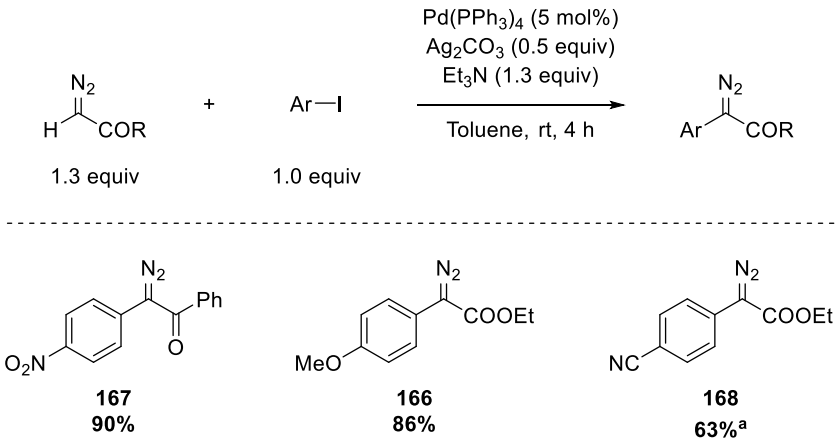
The first report of palladium catalysed synthesis of disubstituted diazo compound was done by Wang's group in 2007 (Scheme 50).[70] The coupling was carried out exclusively between ethyl diazoacetate **163** (EDA) and aryl iodides. Electron-neutral aryl iodide such as iodobenzene provided **164** in good yield and electron-poor ones such as 4-bromo-1-nitrobenzene yielded **165** in 96% yield. It is

noteworthy that, in that case, the catalyst loading could be halved. However, electron-rich electrophiles were not as efficient and **166** was only obtained in 39% yield. Moreover, substitution of the aryl iodide for the bromide only provided traces of products.



Scheme 50: Wang's first generation of conditions for the palladium-catalysed synthesis of disubstituted diazo compounds. [a] 5 mol% of $Pd(PPh_3)_4$ was used.

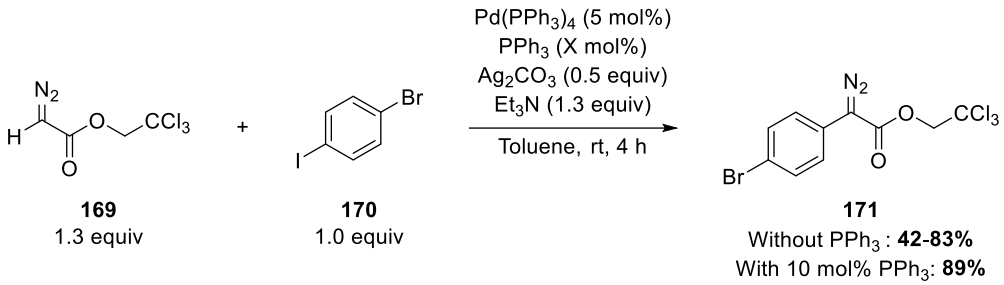
In 2015, the same group re-optimised the reaction conditions (Scheme 51).[71] They found that using the combination of triethylamine and silver carbonate in toluene was more efficient than using DBU and tetrabutylammonium bromide in acetonitrile. They could then decrease the catalyst loading to 5 mol%, the excess of diazo compound to 1.3 equivalents and perform the reaction at room temperature in 4 hours with a wider variety of diazo compounds, including α-keto derivatives as for **167**. The reaction now had a better tolerance for electron rich substituents which gave compound **166** in 86% yield. They also provided some examples of coupling with aryl bromides but the yields were average (compound **168** was obtained in 63%) and electron-withdrawing substituents were necessary.



Scheme 51: Wang's second generation of conditions for the palladium-catalysed synthesis of disubstituted diazo compounds. [a] The aryl bromide was used.

Those reaction conditions were nonetheless not very efficient for the functionalisation of 2,2,2-trichloroethyl (TCE) diazoacetates as the yields were not reliable (Scheme 52, yields varying between 42% and 83% for compound **171**).[72] However, that class of diazo compounds has gained popularity for their improved robustness, higher enantio- and site-selectivity and higher yields notably for the enantioselective C−H functionalisation of methyl ethers and electron-deficient methyl groups.[73,74]

Davies' group investigated that yield inconsistency and found that it was due to the rapid product decomposition under the reaction conditions. This was circumvented by the addition of an extra 10 mol% of triphenylphosphine. The reaction was then consistent, giving **171** in 89% yield. They did not propose any explanation for that phenomenon.



Scheme 52: Davies' improvement for the coupling with 2,2,2-TCE diazoacetates.

Because of their similarities of properties, we expected sulfoxonium ylides to react in a similar fashion as diazo compounds. As seen in the first part of this chapter, palladium cross-couplings between mono-substituted diazo compound and aryl halides have been developed. We envisioned that if that strategy could be applied to sulfoxonium ylides, it could solve the drawbacks from the current methods. We initiated our study with α-ester sulfoxonium ylides as their synthesis appeared more challenging and underdeveloped as compared to the α-keto derivatives.

2 Synthesis of the mono-substituted α-ester sulfoxonium ylides

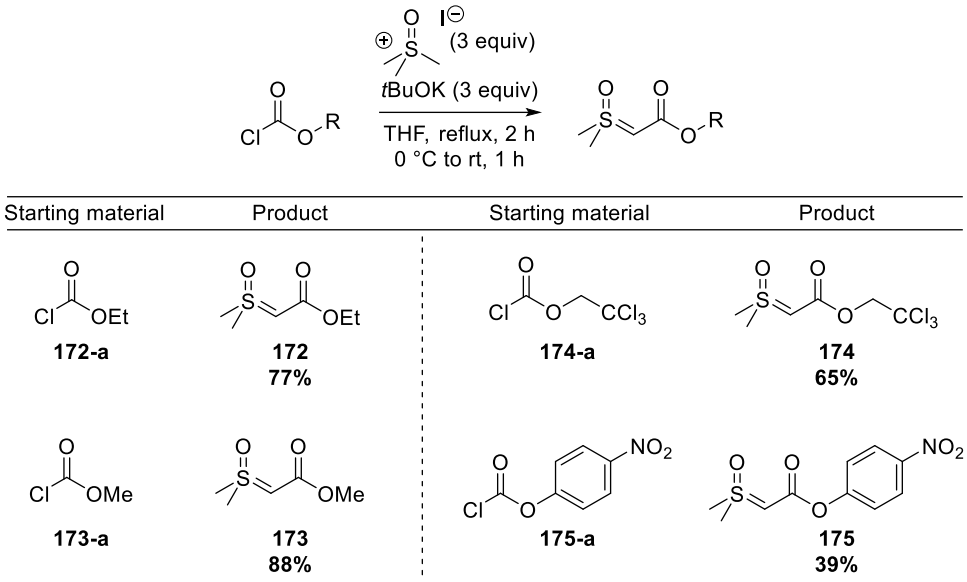
A placement student (Pierre Palamini) contributed to the synthesis of some mono-substituted sulfoxonium ylides derivatives. His results will be presented alongside those obtained by the author of this thesis.

2.1 Synthesis from the chloroformates

Mono-substituted sulfoxonium ylides can be synthesised in several manners. The most step-efficient method is using chloroformate derivatives of the desired sulfoxonium ylide. Moreover, chloroformate derivatives are often cheap and commercially available. Four sulfoxonium ylides have been synthesised using that method.

The first step was the generation of trimethylsulfoxonium methylide from trimethylsulfoxonium iodide using potassium *tert*-butoxide. Dropwise addition of the chloroformate onto the methylide generated the desired sulfoxonium ylides.

This method gave good yield for the sulfoxonium ylide **172** which will be used for most of the study (Scheme 53). Methyl chloroformate gave the best result and **173** was obtained in 88% yield. Compound **174** was obtained in only 65% yield due to difficult purification. Finally, compound **175** was obtained in 39% yield. This low yield was attributed to the decomposition of either the product or the starting material under the reaction conditions as 4-nitrophenol was observed by crude ^{1}H NMR.



Scheme 53: Synthesis of mono-substituted sulfoxonium ylides using chloroformates derivatives.

2-L Jacketed vessels were available during a placement in AstraZenecca (Macclesfield). The synthesis of **172** could conveniently be scaled up to over 100 g scale. This provided 19.3 g of **172** in 65% yield.

Although convenient, this strategy could only be applicable to commercially available chloroformates and another route had to be used for the synthesis of other sulfoxonium ylides.

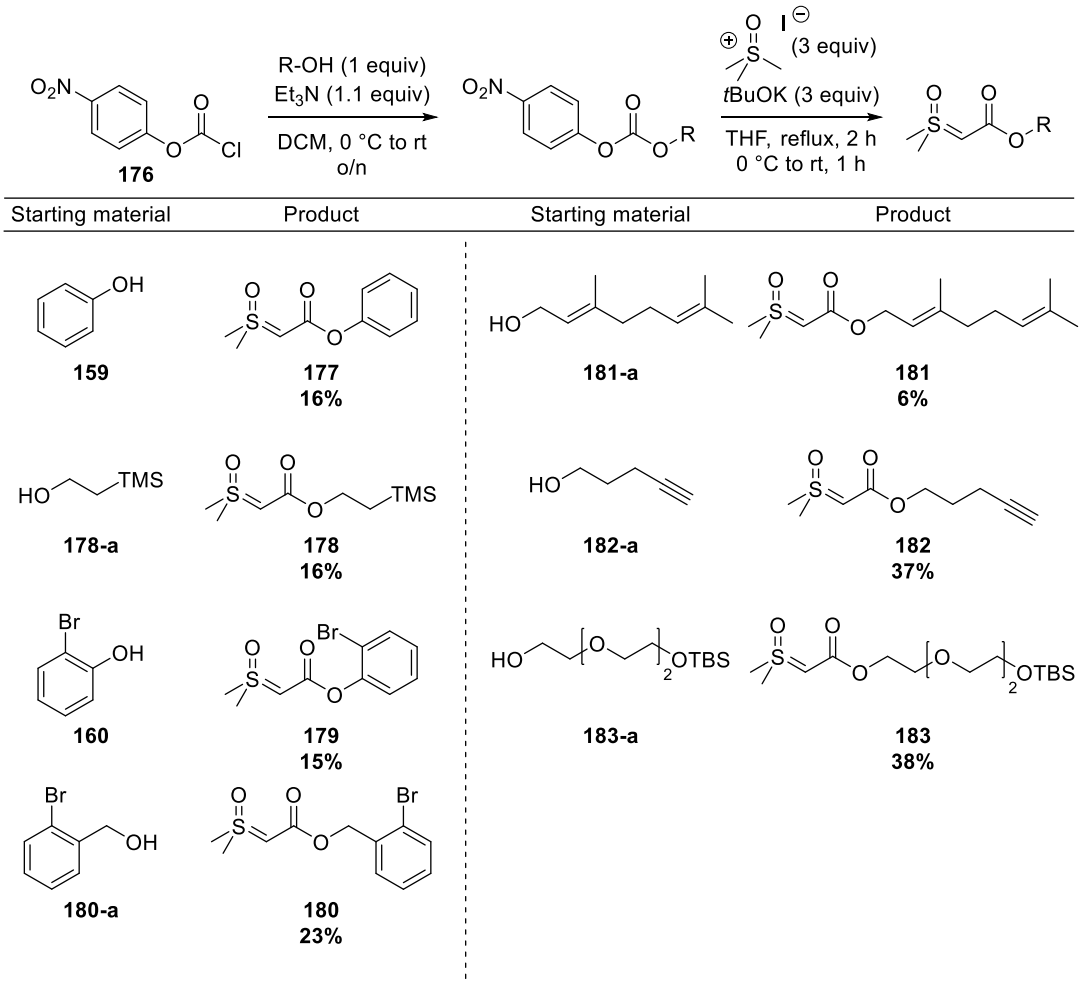
2.2 Synthesis from 4-nitrophenyl chloroformate

If the chloroformate was not available, the starting sulfoxonium ylide was synthesised in two steps from the corresponding alcohol (Scheme 54). It was first reacted with 4-nitrophenyl chloroformate **176** in presence of triethylamine in order to obtain the corresponding carbonate. The second step could then be carried out using the same method as for chloroformates.

Compounds **177**-**181** were obtained in less than 25% yield over two steps and **182** and **183** were obtained in better yields, 37% and 38%, respectively.

The low yields over the two steps of the reactions are mainly due to the poor selectivity of the first step of the synthesis leading to difficult purifications. However, those yields were not a problem in view of the inexpensive starting materials. Therefore, that step was not optimised any further. The reactions were then usually done on over a gram scale to ensure that a good amount of product was obtained.

This method, although longer, provided a good alternative for the synthesis of sulfoxonium ylides without commercially available chloroformates.



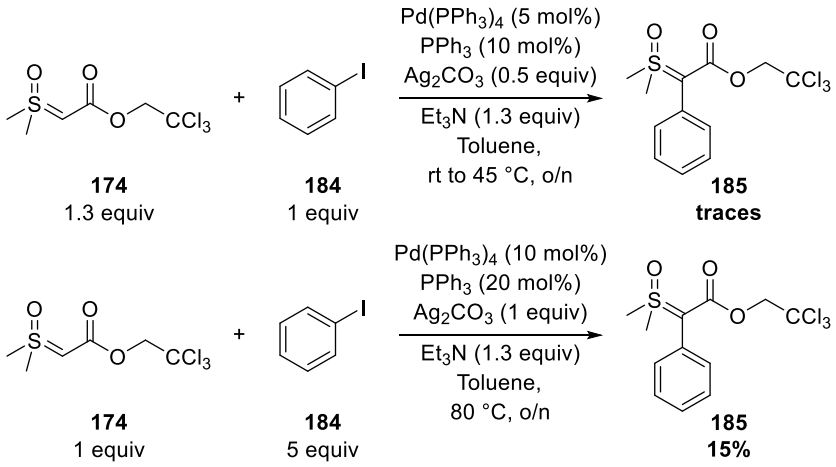
Scheme 54: Synthesis of mono-substituted sulfoxonium ylides from the 4-nitrophenyl chloroformate. Yields are given over two steps.

3 Palladium-catalysed C–H functionalisation of sulfoxonium ylides

3.1 First generation of conditions

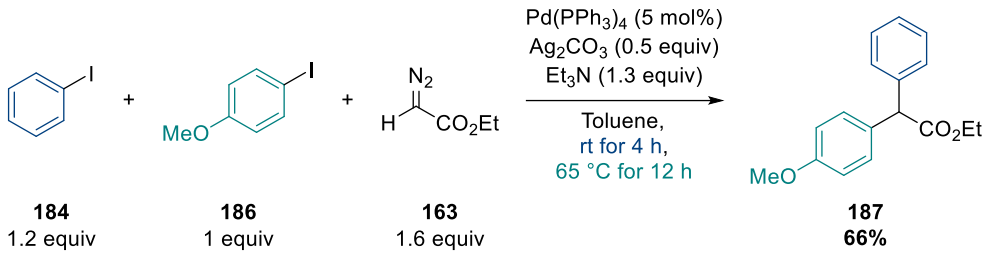
3.1.1 Initial result

With those sulfoxonium ylides in hand, we could begin our study of their reactivity in the palladium catalysed coupling. An initial coupling was attempted using the conditions that Davies and co-workers optimised for the diazo as a starting point (Scheme 55). Gratifyingly, traces of the desired product **185** could be observed. Increasing the amount of catalyst along with the phosphine, the base and the temperature led to an increase of yield and gave **185** in 15% yield.



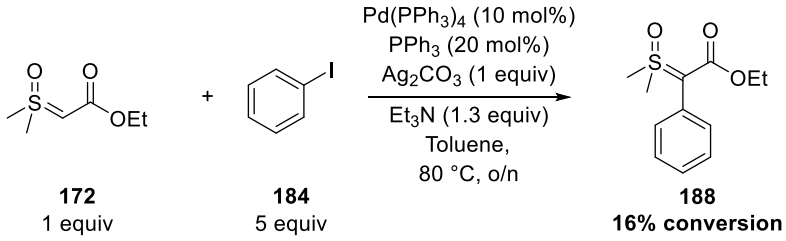
Scheme 55: Initial results for the palladium-catalysed coupling.

It is interesting to note that, as compared to diazo compound, increasing the temperature did not promote the formation of the carbene as for Wang's reaction (Scheme 56).[71]



*Scheme 56: Trapping of the carbene with **186** at higher temperature.*

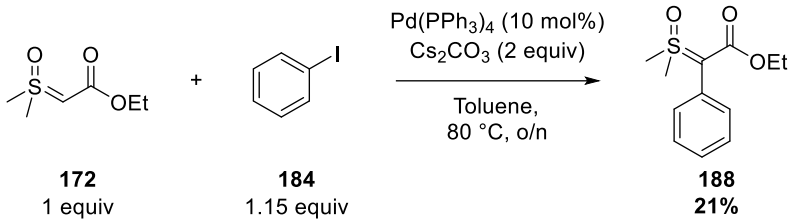
Although this result was encouraging, the poor relaxation by ^{1}H NMR for both the starting material **174** and the product **185**, as well as their low solubility made them inconvenient for proper screening of conditions and characterisation. It was then decided to use the ethyl ester derivative **172** which could be observed more easily by NMR and had higher solubility. The reactivity could still be observed by crude ^{1}H NMR with 16% conversion towards **188** (Scheme 57).



*Scheme 57: Initial result with sulfoxonium ylide **188**.*

3.1.2 Optimisation of the reaction conditions

In order to simplify the screening of conditions, the reaction was carried out without the excess of additives. Interestingly, removing the triphenylphosphine and silver carbonate as well as replacing the triethylamine with cesium carbonate afforded **188** in 21% yield after column chromatography and recrystallisation (Scheme 58). Although that yield was still low, it allowed us to have enough material to develop an HPLC method to increase the pace of the screening of conditions. The reactions were also stopped after 3 hours to be able to carry out more reactions per day.

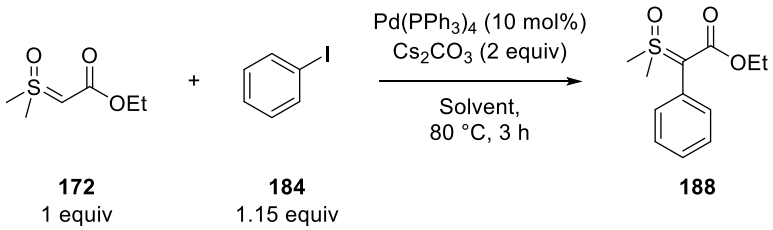


Scheme 58: Conditions used to obtain the material to develop the HPLC method.

3.1.2.1 Screening of solvents

The effect of the solvent was first investigated. At first sight, it can be noticed that the solvent had a limited effect on the outcome of the reaction. THF, 1,4-dioxane, and DMF (Table 1, entry 2, 3 and 5) performed almost as well as toluene (Table 1, entry 1) with 24%, 25%, and 22% yield, respectively. Slightly lower yield was observed for 1,2-DCE (Table 1, entry 4), and the worst result was obtained for EtOH with 14% yield (Table 1, entry 6). On the other hand, the yield increased to 45% when acetonitrile was used (Table 1, entry 7). The latter was then selected for the screening of bases.

Table 1: Screening of solvents.

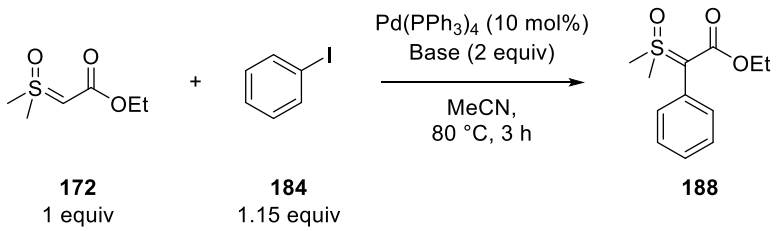


Entry	Solvent	HPLC Yield
1	Toluene	29%
2	THF	24%
3	1,4-Dioxane	25%
4	1,2-DCE	18%
5	DMF	22%
6	EtOH	14%
7	MeCN	45%

3.1.2.2 Screening of bases

As opposed to the solvent, the base seemed to have a critical impact on the reactivity. Indeed using organic bases such as DBU, Et_3N, and 1,6-lutidine completely shut down the reactivity and gave only traces of the product **188** with acetonitrile as solvent (Table 2, entry 1-3). Replacing cesium carbonate by the potassium and lithium equivalents were also unsuccessful, probably due to their lower solubility (Table 2, entry 5 and 6). Finally, using a stronger inorganic base such as potassium *tert*-butoxide was also inefficient (Table 2, entry 7). Cesium carbonate was then kept as a base for the reaction.

Table 2: Screening of bases.



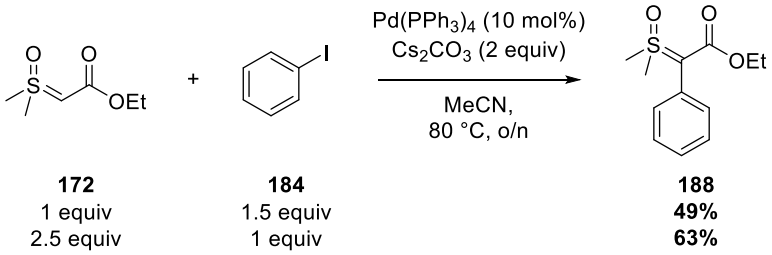
172 1 equiv | **184** 1.15 equiv | **188**

Entry	Base	HPLC Yield
1	DBU	Traces
2	Et_3N	Traces
3	1,6-Lutidine	Traces
4	Cs_2CO_3	45%
5	K_2CO_3	Traces
6	Li_2CO_3	Traces
7	*t*BuOK	Traces

3.1.2.3 Effect of the stoichiometry

The reaction was first left to stir overnight which only slightly increased the yield to 49%. However having an excess of sulfoxonium ylide instead of an excess of iodobenzene significantly increased the yield to 63% (Scheme 59). This was not an

issue thanks to the availability of the starting sulfoxonium ylides. It is noteworthy that 2.5 equivalents of ethyl diazoacetate was also used in Wang's palladium catalysed cross-coupling.[70]



Scheme 59: Effect of the stoichiometry.

3.1.2.4 Effect of the leaving group

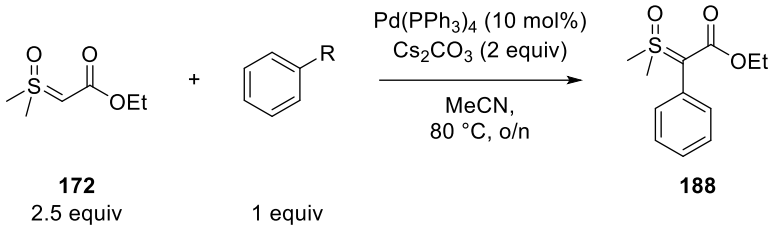
We then decided to see whether the reaction was compatible with leaving groups other than iodine. To our delight, using bromobenzene as opposed to iodobenzene increased the yield to 80% (Table 3, entry 2). This was a very good result as aryl bromides are usually less expensive than aryl iodides.[ii] Interestingly, triflate derivatives were tolerated and led to the formation of **188** in 87% yield (Table 3, entry 3). Unfortunately phenyl methanesulfonate and chlorobenzene did not afford any of the desired product (Table 3, entry 4 and 5).

Although the aryl triflate gave better results as compared to the aryl bromide, the wide commercial availability of aryl bromides made them more convenient for further studies.

[ii] Price for 500 mL of bromobenzene from Sigma-Aldrich (consulted 25/06/19): £33.20

Price for 500 g (c.a. 274 mL) of iodobenzene from Sigma-Aldrich (consulted 25/06/19): £117.00

Table 3: Effect of the leaving group.



172
2.5 equiv

1 equiv

188

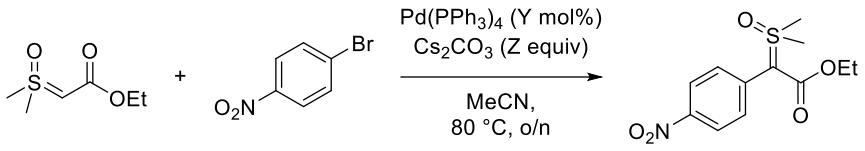
Entry	R group	Yield
1	I	63%
2	Br	80%
3	OTf	87%
4	OMs	No reaction
5	Cl	No reaction

3.1.2.5 Final optimisation

Our final goal was to try to decrease the excess of reagents in the reaction as much as possible. To do so, 1-bromo-4-nitrobenzene was used as a model substrate as it gave an excellent 94% yield under the current reaction conditions (Table 4, entry 1).

Decreasing the quantity of sulfoxonium ylides to 1.5 equivalents (Table 4, entry 2) had a significant impact on the yield and only 73% of **190** could then be obtained. However having 1.1 or 2 equivalents of cesium carbonate did not change the yield (Table 4, entry 3). Finally, lowering the amount of the catalyst had a critical impact on the yield with 68% and 27% of **190** obtained for 5% and 2 mol% of $Pd(PPh_3)_4$, respectively (Table 4, entry 4 and 5).

Table 4: Final optimisation of the reaction conditions.



172
X equiv

189
1 equiv

190

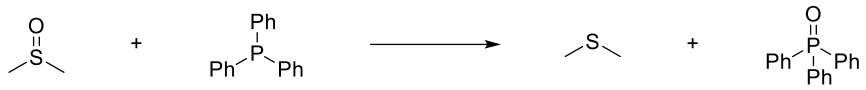
Entry	**172** (X equiv)	$Pd(PPh_3)_4$ (Y mol%)	Cs_2CO_3 (Z equiv)	Yield
1	2.5	10	2	94%
2	1.5	10	2	72%
3	2.5	10	1.1	94%
4	2.5	5	2	68%
5	2.5	2	2	27%

The conditions to assess the scope of the reaction will then be: 2.5 equivalents of sulfoxonium ylide, 1 equivalent of aryl bromide, 10 mol% of $(PdPPh_3)_4$, 1.1 equivalent of Cs_2CO_3 in 0.1 M of acetonitrile, at 80 °C for 14 to 15 hours.

3.1.3 Triphenylphosphine oxide issue

One significant issue of the reaction was the contamination of the desired product with between 5% and 10% of triphenylphosphine oxide. It was however possible to remove it by recrystallisation of the final compounds with ethyl acetate and pentane at the cost of an extra purification step and a slight yield loss.

It was proposed that this impurity came from the release of DMSO, upon decomposition of the starting material or the desired product, which can oxidise a free phosphine coming from the palladium to yield dimethyl sulfoxide and triphenylphosphine oxide. This is a known reaction which has been described in 1962 by Smith's group (Scheme 60).[75]



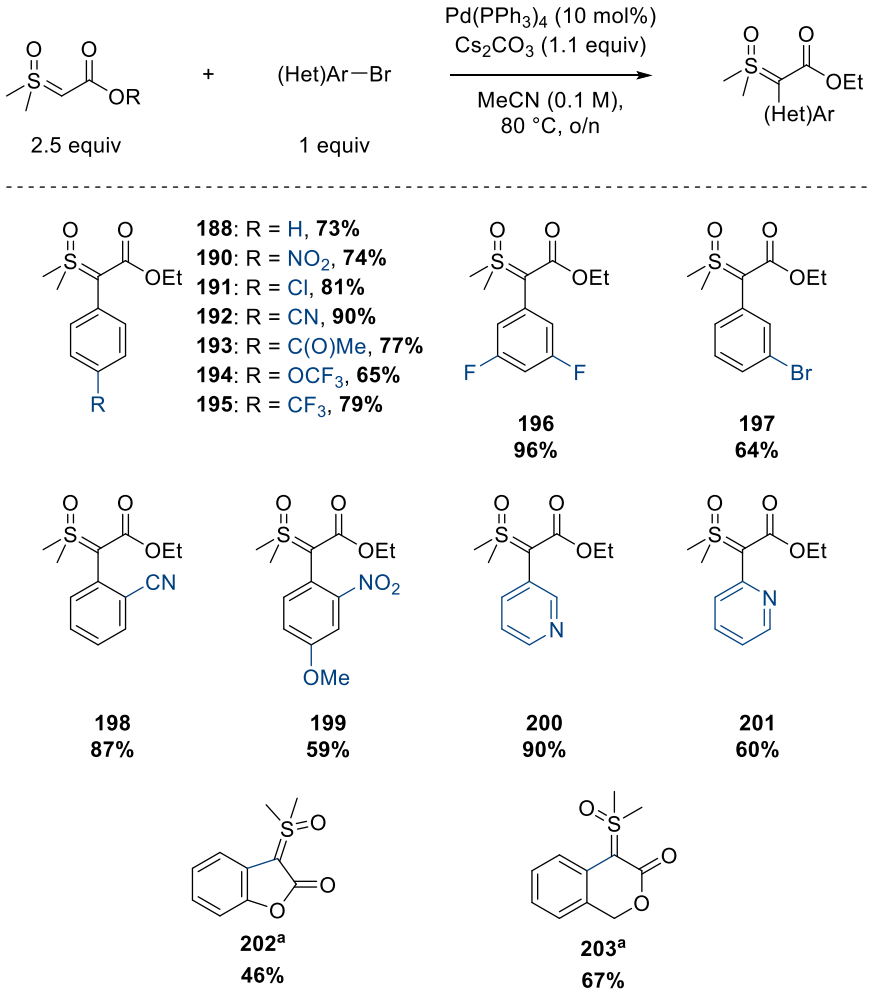
Scheme 60: Oxidation of free phosphine by DMSO described by Smith and co-workers.

The similar high polarity of the sulfoxonium ylides and triphenylphosphine oxide explains the difficulty of separation by flash chromatography.

To circumvent that problem, dropwise addition of the sulfoxonium ylide was attempted *via* a syringe pump over 4 hours to minimise the effect of the decomposition of sulfoxonium ylide. Unfortunately, this was detrimental to the reaction and led to a yield loss.

3.1.4 Scope

With our optimised conditions in hand, we decided to quickly evaluate the scope (Scheme 61). Although good yields were obtained for **188** and **190**, 73% and 74%, respectively, a significant loss of material was observed during the extra recrystallisation step. Indeed, the recalculated yields of compound containing small amounts of triphenylphosphine oxide were 80% and 94%, respectively. However, compounds **192**, **196**, **198** and **200** could be obtained in excellent yield without any need for recrystallisation due to their different polarities. Good yields could also be obtained for compounds **191** and **193**-**195** even with the necessity of the recrystallisation. Interestingly, 1,3-dibromobenzene only afforded compound **197** without any traces of the disubstituted product. Compounds **198** and **199** provided two examples of successful *ortho*-substitution even if **199** was obtained in a moderate yield. Two pyridines substituted in the positions 3 and 2, compound **200** and **201**, were obtained in 90% and 60% yield, respectively. Finally, the reaction could be conducted in an intramolecular fashion to form 5-membered ring **202** and the six-membered ring **203** in 46% and 67% yield, respectively.

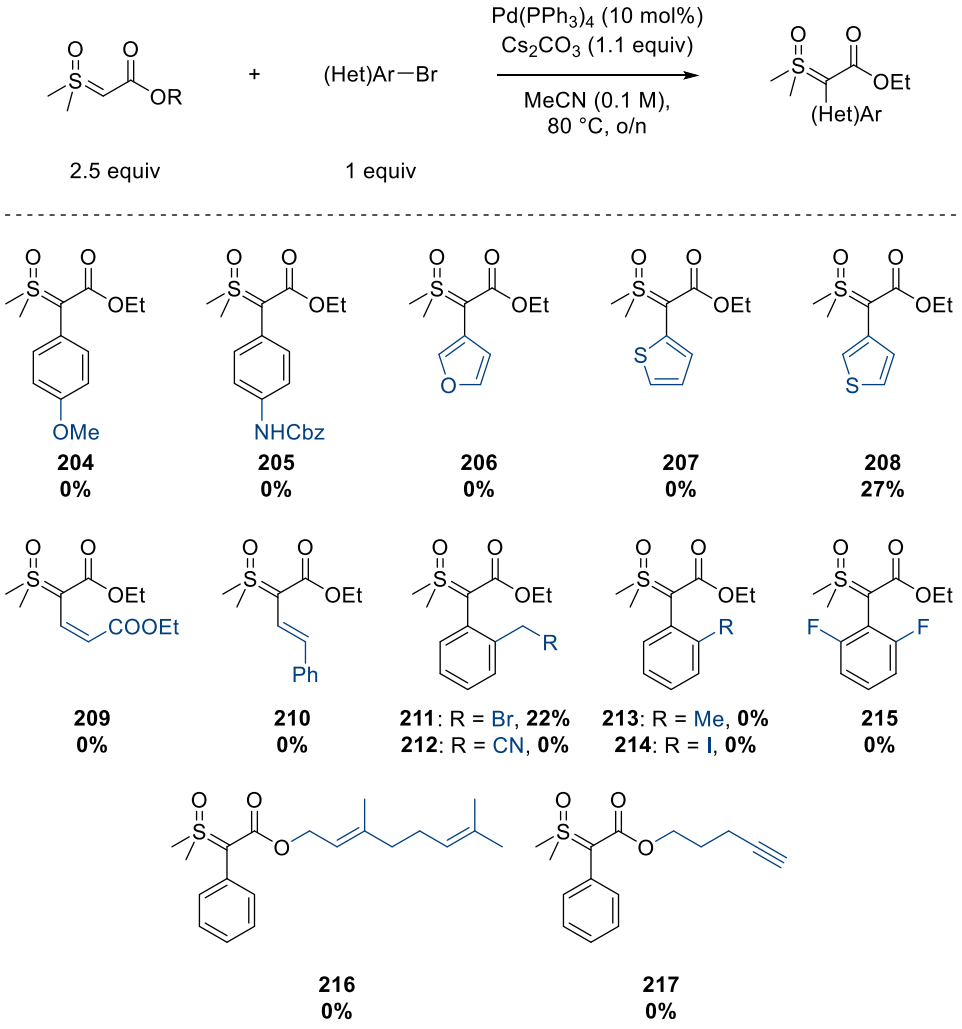


Scheme 61: Scope of the first generation of conditions. [a] Intramolecular reaction.

3.1.5 Limitations

Although a good range of functional groups was tolerated, these conditions still presented several drawbacks. The first one was the need of an extra recrystallisation step necessary for more than 75% of the substrates. Secondly, the aryl bromides that were tested in the previous part were mostly electron-poor. When electron-rich aryl bromides were used, no traces of compound **204** or **205** were observed (Scheme 62). The same outcome was observed when rich heteroaryl groups were used as neither the 3-furyl **206** nor the 2-thiophenyl **207** were obtained. The 3-thiophenyl **208** was synthesised, though in poor yield and low purity. Moreover,

bromoalkenes were not tolerated and neither **209** nor **210** were obtained. Only a nitrile or nitro group was tolerated in the *ortho*-position (see Scheme 55, compound **198** and **199**). Poor reactivity or no reaction was observed in cases when bromomethyl-, cyanomethyl-, methyl-, iodo-, and difluoro- substituents were on the *ortho*-position of the aryl ring (compounds **211**-**215**). Finally, attempts to vary the ester chain failed and neither **216** nor **217** could be isolated using those conditions. Those results encouraged us to re-evaluate our catalytic system with the main goal to remove the need for extra recrystallisation and hopefully expand the scope.



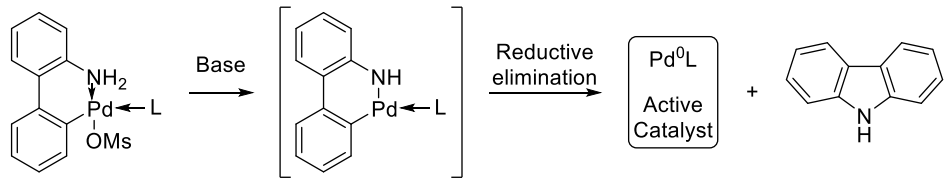
Scheme 62: Limitations of the first generation of conditions.

3.2 Second generation of conditions

3.2.1 Buchwald G3 pre-catalysts

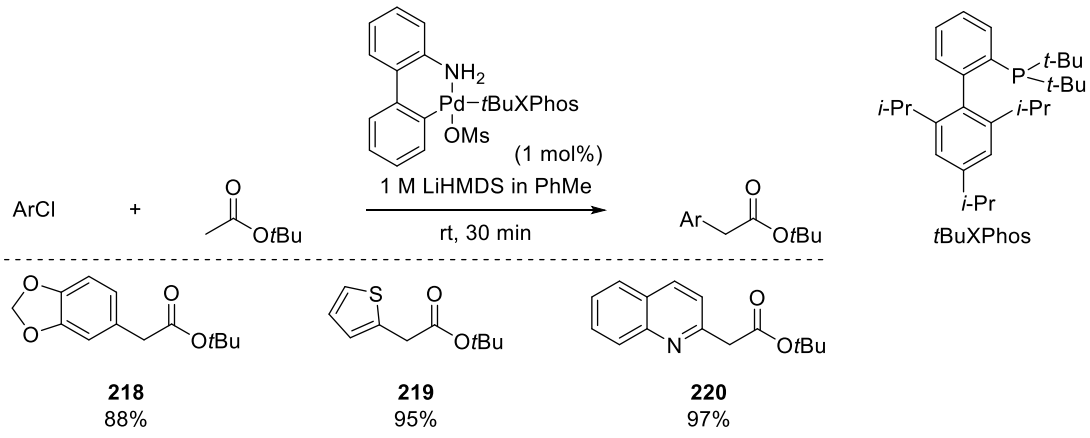
3.2.1.1 Generalities

Buchwald's G3 catalysts are air-, moisture-, and temperature-stable compounds that are able to generate carbazole and an active catalyst *in situ* after reductive elimination in presence of a base (Scheme 63).[76]



Scheme 63: Generation of the active catalyst species with Buchwald G3 pre-catalyst.

They have been used for a variety of cross-coupling reaction for the formation of C–C, C–N, and C–O bonds.[75–77] But what caught our attention was their efficiency for the α-arylation of enolates with aryl chlorides (Scheme 64).[78] The Pd-G3 catalyst with *t*BuXPhos as a ligand afforded compounds **218**-**220** in excellent yield, at room temperature, in 30 min.



Scheme 64: α-arylation of enolates using Pd-G3-tBuXPhos.

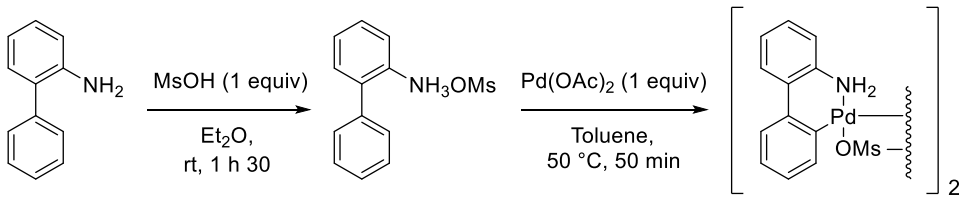
It appeared to us that similarities can be observed between enolates and our sulfoxonium ylides (Figure 2). Notably, the C=O stretch of mono-substituted ester sulfoxonium ylides usually appears around 1620-1630 cm^{-1} which is very low for the carbonyl group of an ester and is closer to what is observed for enols.[79]

Figure 2: Structural comparison between lithium enolate and sulfoxonium ylides.

Thus it was then decided to investigate the reactivity of the palladium G3 catalyst in our reaction to see if it could overcome the limitations observed in the first generation of conditions.

3.2.1.2 Synthesis of the pre-catalyst

Although they are commercially available, the synthesis of Pd-G3 complexes is well described in the literature in a 2-steps synthesis (Scheme 65), starting with the formation of the ammonium salt **222** in excellent yield. Reaction of the latter with $Pd(OAc)_2$ quickly afforded the dimer **223** in 87% yield.



221 **222** **89%** **223** **87%**

Scheme 65: Synthesis of the Pd-G3 complexes precursor.

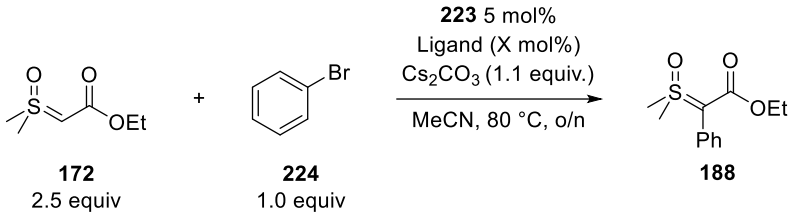
3.2.1.3 Ligand screening

For efficiency purposes, the active catalyst containing the ligand was generated *in situ* from the stable palladium dimer **223** previously synthesised. Interestingly, triphenylphosphine, which was the ligand for the first generation of conditions, did not give any reaction with 10 mol% and only traces of the desired product were observed with 20 mol% (Table 5, entry 1and 2). A variety of monodentate phosphines were screened but remained unsuccessful (Table 5, entry 5-8). The bulky *tert*-butyl phosphine gave the best result among them with 31% isolated yield with 10 mol% and 62% of pure isolated product with 20 mol% of phosphine (Table 5, entry 3 and 4).

A selection of Buchwald phosphines were then screened and a 49% isolated yield could be obtained using 20 mol% of XPhos (Table 5, entry 10). SPhos and BrettPhos also gave descent conversions but the product **188** contained unidentified impurities after simply column chromatography (Table 5, entry 12 and 13). The other phosphines showed poor reactivities (Table 5, entry 11 and 14-16).

Finally, bidentate ligands appeared to not be suitable for the reaction (Table 5, entry 16-21).

Table 5: In situ *ligand screening with Pd-G3 catalyst.*



Entry	Ligand	Conversion (isolated yield)
1	PPh_3 (10 mol%)	0%
2	PPh_3 (20 mol%)	Traces
3	P*t*Bu_3 (10%)	32% (31%)
4	P*t*Bu_3 (20%)	68% (62%)
5	P(2-furyl)$_3$ (20%)	0%
6	PCy_3 (20%)	0%
7	P(3,5-CF_3-phenyl)$_3$ (20%)	0%
8	P(3,5-Me-phenyl)$_3$ (20%)	Traces
9	Xphos (10%)	30%
10	Xphos (20%)	50% (49%)
11	JohnPhos (20%)	0%
12	Sphos (20%)	32%*
13	BrettPhos (20%)	37%*
14	DavePhos (20%)	10%*
15	*t*BuXPhos (20%)	0%
16	XantPhos (20%)	Traces
17	DPPF (20%)	0%
18	DPPB (20%)	0%
19	BINAP (10%)	0%
20	DTBPF (10%)	Traces
21	DPPE (20%)	0%

**Pure product could not be obtained after simple column chromatography.*

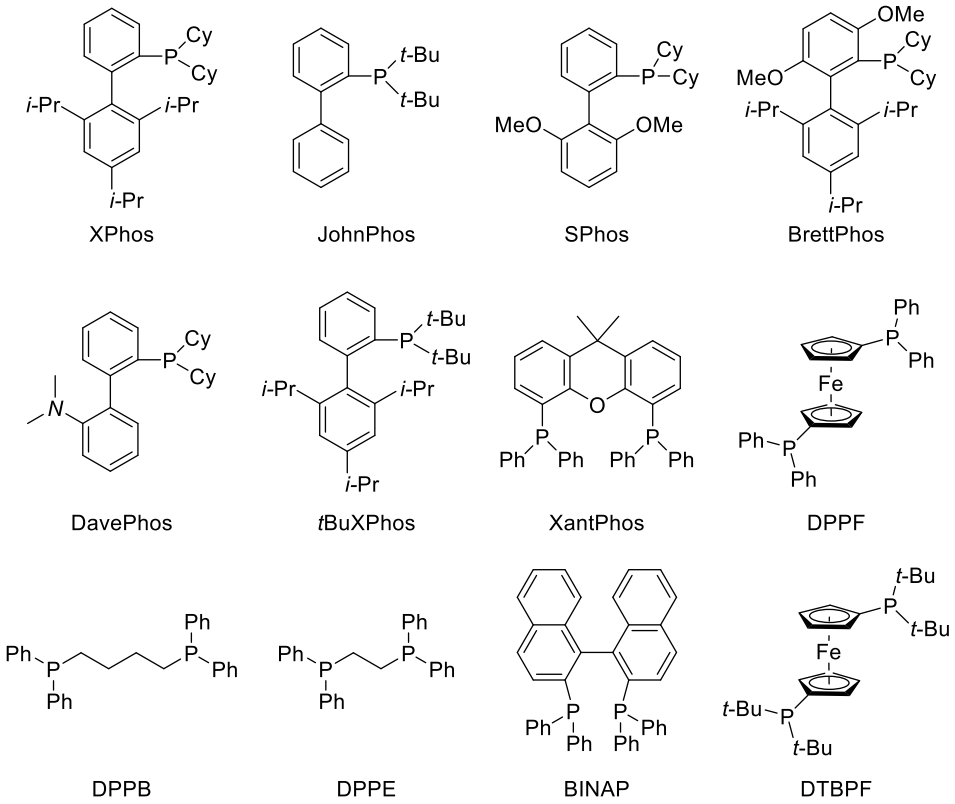
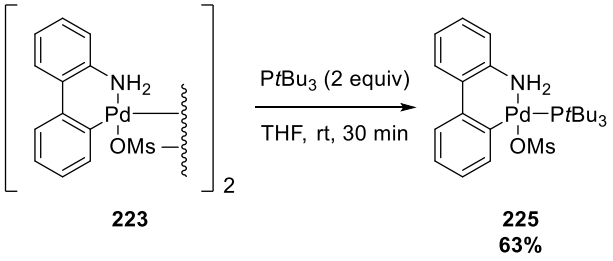


Figure 3: Structures of the ligands used for the ligand screening with Pd-G3 catalyst.

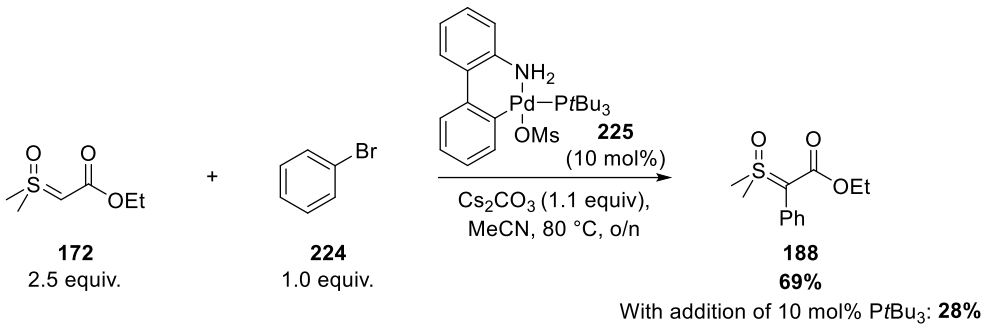
As P*t*Bu$_3$ was giving the best result for the reaction, the corresponding Buchwald pre-catalyst was prepared (Scheme 66). The reaction very quickly afforded the desired complex **225** in 63% yield.



*Scheme 66: Synthesis of complex **225**.*

Unfortunately, the reaction only performed slightly better when that catalyst was used as compared to when it was made *in situ* from **188** with a yield going from

62% to 69% (Scheme 67). Unexpectedly, addition of another 10 mol% of P*t*Bu$_3$ to mimic the conditions of Table 5 entry 4 decreased the yield to 28%.



*Scheme 67: Test reaction using complex **225** as palladium source.*

3.2.2 Nova and Hazari's catalyst

3.2.2.1 Uses of the catalyst

Nova and Hazari's pre-catalyst **227** was developed slightly later than Buchwald's G3 complexes and also appears as a bench stable palladium dimer (Figure 4).[80] It has been developed as an alternative to the Nolan-type pre-catalysts **226** and can tolerate NHC ligands. It can either be used in the form of the dimer with a ligand in the reaction mixture or as an isolated monomer containing the ligand.

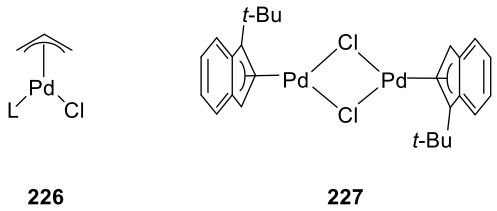
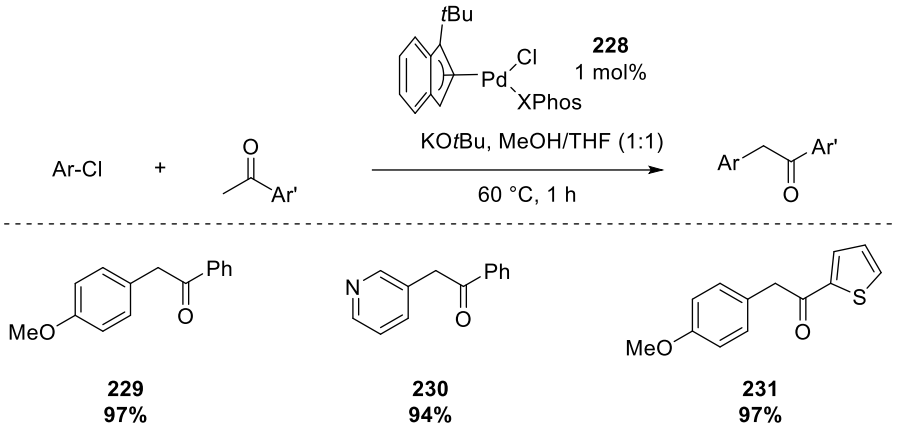


*Figure 4: Nolan catalyst (**226**) and Nova and Hazari's catalyst (**227**).*

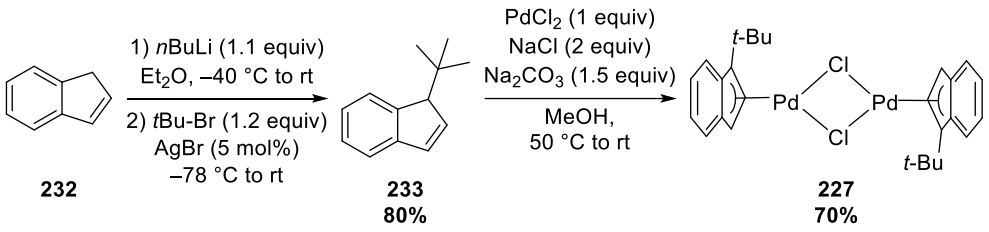
This type of catalyst has also shown very good reactivity for the α-arylation of enolates but required slightly higher reaction temperature (Scheme 68).



Scheme 68: α-arylation of enolates using Nova and Hazari's catalyst.

3.2.2.2 Synthesis of the catalyst

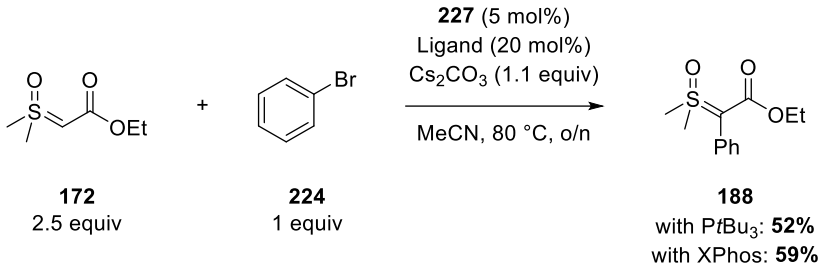
The synthesis of **227** was done in two steps. The first step is the alkylation of indene **232** to obtain **223**. It is then followed by the C–H activation using $PdCl_2$ yielding the desired dimer **227** in 70% yield (Scheme 69).



*Scheme 69: Synthesis of the pre-catalyst **227**.*

3.2.2.3 Results of the palladium coupling using the catalyst

No full screening of ligands was done with that new catalyst. Instead, P*t*Bu_3 and XPhos were selected as ligands for the test reactions as they gave the best results with Buchwald's G3 catalyst. However only 52% of **188** could be obtained with P*t*Bu_3 and 59% with XPhos (Scheme 70).



*Scheme 70: Test reactions using pre-catalyst **277**.*

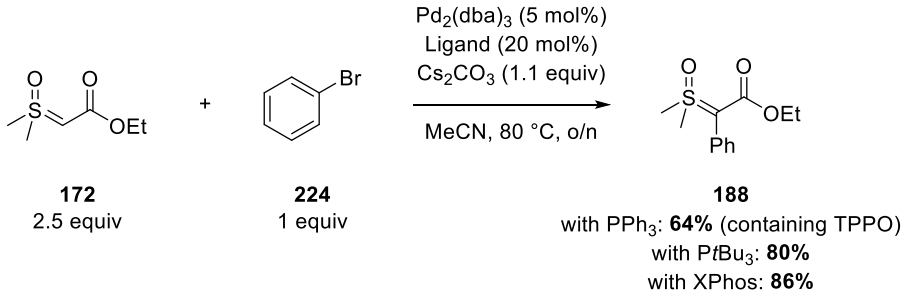
3.2.3 Conclusions

Although those two pre-catalysts afforded the desired compound in high purity, when P*t*Bu$_3$ and XPhos were used, after simple flash chromatography, without any need for recrystallisation, the yields were not as good as for the first generation of conditions.

3.3 Third generation of conditions

3.3.1 Optimisation

It was then desired to find a way to avoid the recrystallisation by decreasing the amount of triphenylphosphine in the reaction by generating the active catalyst *in situ* instead of using Pd(PPh$_3$)$_4$. It would significantly increase the isolated yield of the reaction. Pd$_2$(dba)$_3$ was first tried with two equivalents of PPh$_3$ but **188** could only be obtained in 64% corrected yield as it still contained 8% of triphenylphosphine oxide (Scheme 71). However, Pd$_2$(dba)$_3$ proved to be an excellent pre-catalyst when P*t*Bu$_3$ and XPhos were used as ligands with 80% and 86% yield towards the formation of **188**, respectively. Also, the product was then obtained pure without any need for recrystallisation. This was a good improvement of the yield as compared to the first generation of conditions where 73% of **188** could be obtained after an extra recrystallisation step.



Scheme 71: Test reactions using $Pd_2(dba)_3$ as pre-catalyst.

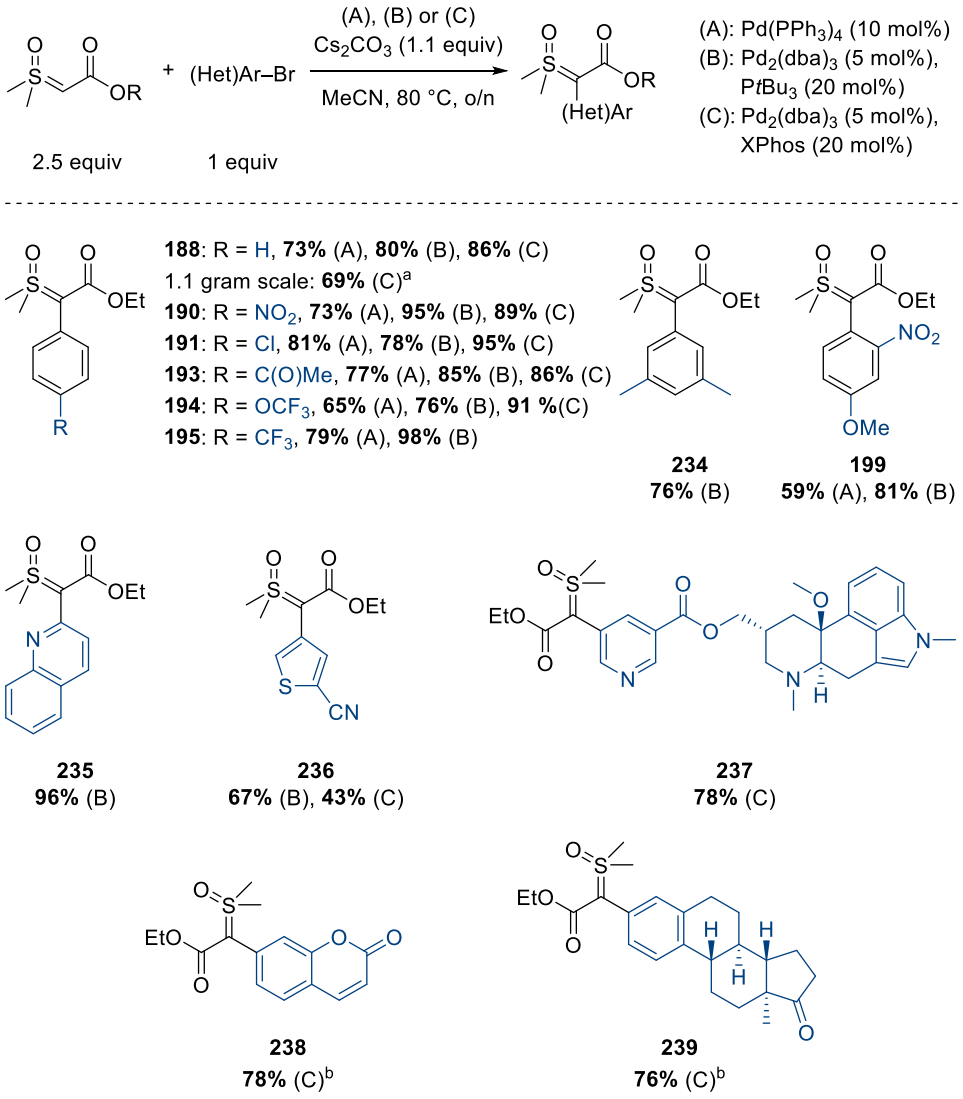
3.3.2 Scope

3.3.2.1 Scope of electrophiles

The scope of the reaction with the new conditions was then assessed (Scheme 72). The compounds that were tested for that reaction were usually the one that gave poor results with the first generation of conditions (condition A). The general trend observed was that the yields were usually higher when XPhos is used as a ligand (conditions C). As previously, electron withdrawing groups in *para*-positions gave good results with yields up to 98% (compounds **190**, **191** and **193**-**195**). Inductive donor methyl groups were well tolerated in *meta* position and the compound **234** was obtained in 76% yield with conditions B. The yield for compound **199** increased from 59% with conditions A to 81% with conditions B. Quinoline was added to the heteroaryl scope and **235** was obtained with an excellent yield. Compound **236** was obtained in higher quantity with condition B as compared to conditions C with 67% yield. In that case, the bromothiophenyl electrophile was made more electron deficient by addition of a CN group in the position 2 to increase the electrophilic character. The cross-coupling was also done on Active Pharamaceutical Ingredients (API) such as the Nicergoline to afford **237** in 78% yield. Estrone could also be coupled and gave a good 76% yield of **239**. It should be noted that in that case, it was the triflate of the estrone that was used as an electrophile which was prepared in one

step from the API. Finally, the coumarin derivative **238** was also prepared from the triflate in 78% yield.

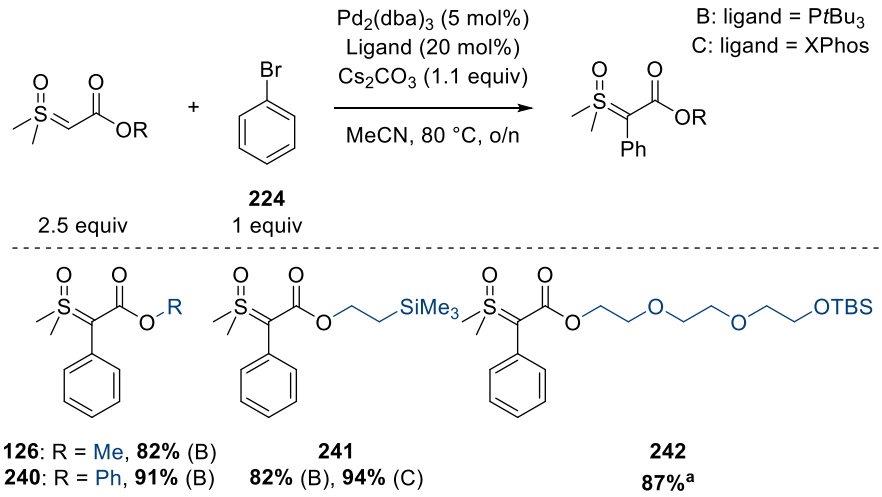
The reaction has also been done on 1.1 g scale of bromobenzene with conditions C. Compound **188** was obtained in 69% yield with both the amount of palladium and phosphine halved.



Scheme 72: Scope of electrophiles using the 3rd generation of conditions. [a] 2.5% of $Pd_2(dba)_3$ and 10% of XPhos were used. [b] Triflate used instead of the aryl bromide.

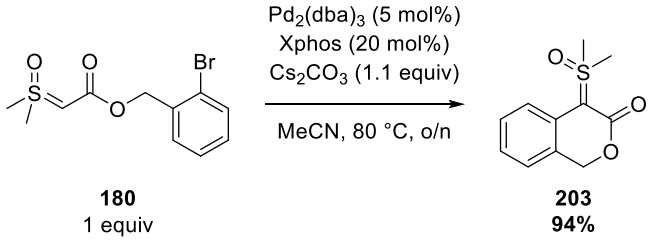
3.3.2.2 Scope of sulfoxonium ylides

Four of the sulfoxonium ylides synthesised previously where successful with the new reaction conditions (Scheme 73). Replacing the ethyl group by a methyl or a phenyl group had no significant impact on the yield and afforded **126** and **240** in 82% and 91% yield, respectively, with conditions B. The alkyl chain can be extended with a TMS and afforded **241** with yields up to 94% with conditions C. Finally, the TBS protected triethylene glycol derivative **242** also performed very well using Pd(P*t*Bu$_3$)$_2$ as catalyst in that case.



Scheme 73: Scope of sulfoxonium ylides using the 3rd generation of conditions. [a] Pd(PtBu$_3$)$_2$ (10 mol%) was used as catalyst.

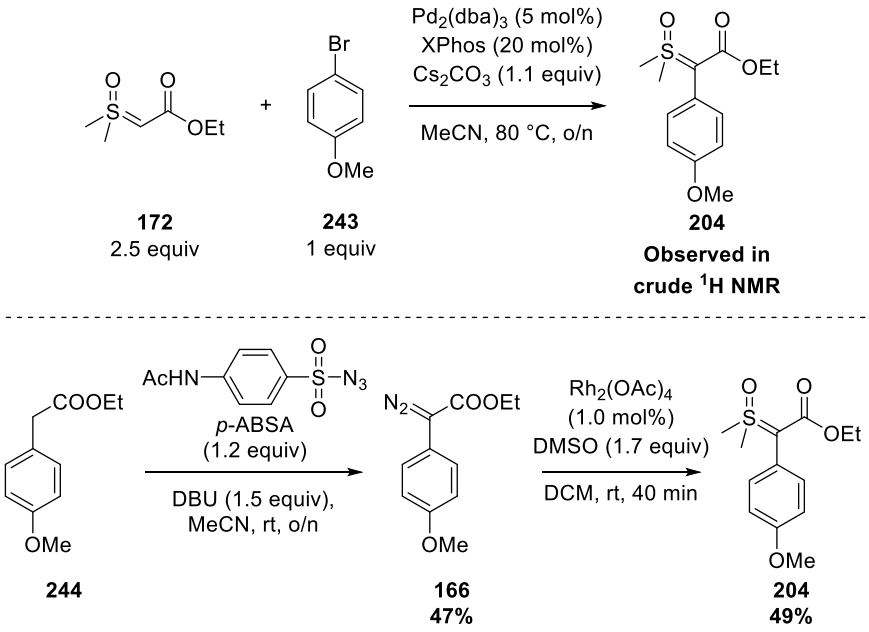
As with the first generation of conditions, the reaction can be done in an intramolecular fashion to obtain **203** in 94% yield (Scheme 74).



Scheme 74: Intramolecular reaction using the 3rd generation of conditions.

3.3.2.3 The 4-bromoanisole case

For those 3rd generation of conditions, the work-up of the reaction was changed from a rather acidic silica plug filtration to a neutral celite plug filtration. We then noticed that the product of **172** and 4-bromoanisole **243** could be observed in the crude ^{1}H NMR (Scheme 75). However, no trace of product could be observed by TLC. It was hypothesised that the product was formed but was unstable on silica. To verify that hypothesis, **204** was synthesised using another method. The first step was the known synthesis of the diazo equivalent **166** from ethyl 2-(4-methoxyphenyl)acetate using *p*-ABSA in presence of DBU.[81] This compound could be purified by column chromatography and was obtained in 47% yield. Rhodium catalysed carbene transfer with DMSO could then be carried out and **204** could be isolated in 49% yield after purification by recrystallisation.

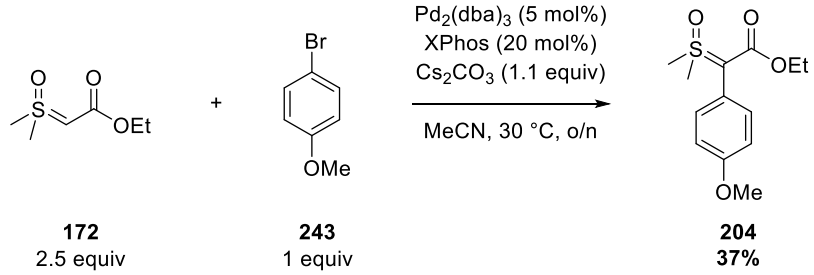


Scheme 75: Study of the coupling with 4-bromoanisole.

With **204** to hand, test reactions were carried out to understand its stability. It was first spotted on a TLC plate and eluted straight away. Only decomposition could

be observed at that stage except if the silica was deactivated using triethylamine confirming the acid sensitivity of the compound. The thermal stability was also evaluated. Compound **204** was dissolved in acetonitrile and heated to 80 °C to mimic the reaction conditions. Complete decomposition was observed by ^{1}H NMR after 40 min. When the same test was carried out at 60 °C, less than 25% of product was observed after 1 hour and 40 minutes. This also confirms the lack of thermal stability of **204**.

Our cross-coupling was then conducted using conditions C but at 30 °C to avoid *in situ* decomposition of the product. Compound **204** could then be obtained after purification on basic silica in 37% yield (Scheme 76).

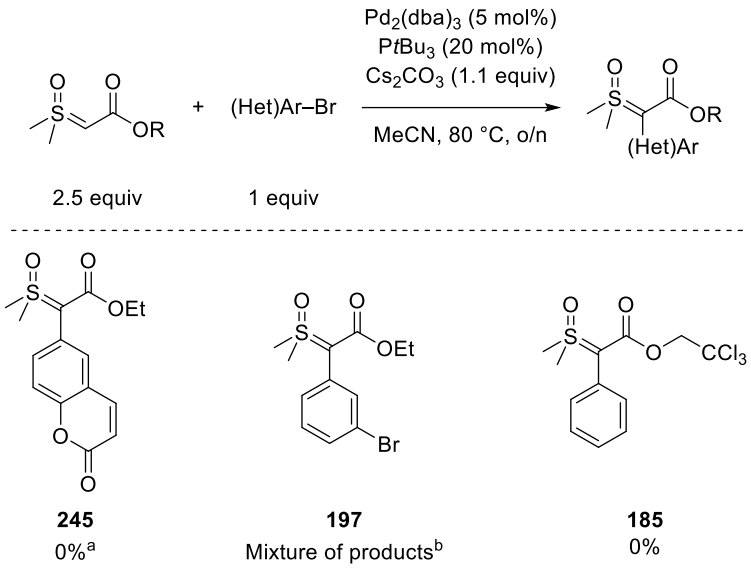


*Scheme 76: Modified conditions for the synthesis of **204**.*

3.3.2.4 Limitations of the reaction

Even if those new conditions solved the problem of the phosphine oxide in the final products and expanded the scope, several limitations remained (Scheme 77). Notably, the reaction with electron rich electrophiles was still giving either low yield or no reaction as for the reaction with 4-bromoanisole. Interestingly, the 6-substituted coumarin did not yield any product **245** whereas, as seen previously, the 7-subtituted one was obtained in 78% yield (Scheme 72, compound **238**). Also, **197** was only obtained as an inseparable mixture of mono- and bis-functionalized products with

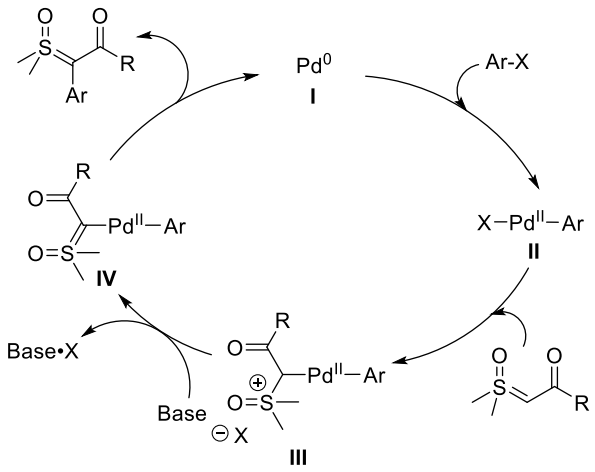
method B, even if 1.1 equivalent of sulfoxonium ylide was used. Finally, sulfoxonium **177** did not yield any product **185**.



Scheme 77: Limitations for the 3rd generation of conditions. [a] Triflate used instead of the aryl bromide. [b] 1.1 equiv of sulfoxonium ylide used.

3.4 Mechanism of the reaction

No thorough mechanistic study has been carried out on the reaction. However, based on the reactivity of diazo compound in similar cross-coupling, it can be suggested that the reaction would proceed through the oxidative addition of the palladium(0) into the C–Br bond to give intermediate **II** (Scheme 78).[70,71] Then, attack of the mono-substituted sulfoxonium ylide would occur to give intermediate **III** which could be deprotonated to generate **IV**. Reductive elimination would release the desired product as well as the palladium catalyst **I**.



Scheme 78: Potential catalytic cycle.

Fitton and Rick demonstrated in 1971 that, with the same reaction conditions, iodobenzene performed oxidative addition more rapidly with $Pd(PPh_3)_4$ than bromobenzene.[82] However, in our case, as seen during the optimisation of the reaction conditions, bromobenzene afforded greater yields than iodobenzene. This suggests that oxidative addition is not the rate limiting step of the reaction that we studied, as the coupling with iodobenzene should perform better otherwise.

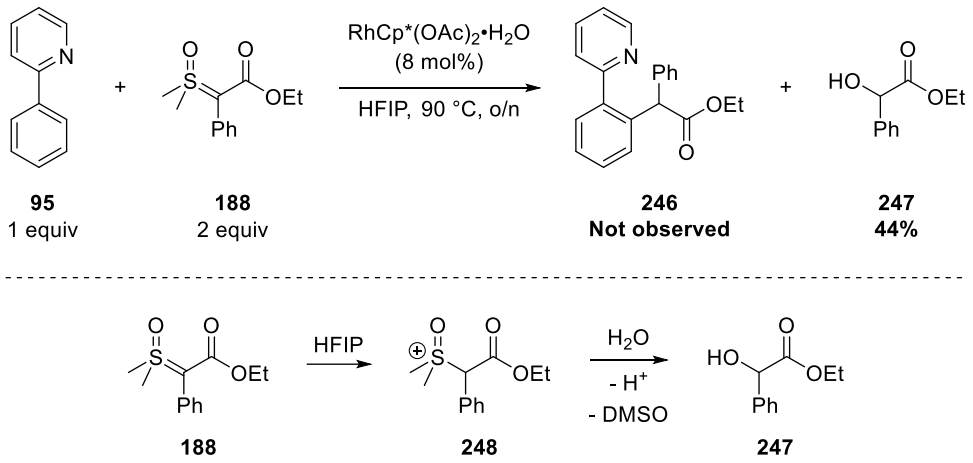
The higher performances of the bulky ligands P*t*Bu$_3$ and XPhos could suggest a slow reductive elimination as those ligand would improve the efficiency of this step.[83]

3.5 Post-functionalisation

3.5.1 C–C bond formation

Initially, C–C bond formation was attempted using the cross-coupling reaction developed within the Aïssa group in 2017.[8] It was an interesting test as that type of disubstituted sulfoxonium ylide was not available at the time of the development of the methodology. However, the desired reaction did not occur and **246** was not obtained (Scheme 79). Instead 44% of the hydrolysed compound **247** was isolated.

Its formation can be explained by the protonation of the sulfoxonium ylide by HFIP before it can coordinate to the Rh(III) catalyst. The intermediate **248** then formed can be attacked by the water contained in the HFIP (which was not purchased dry and not distilled).

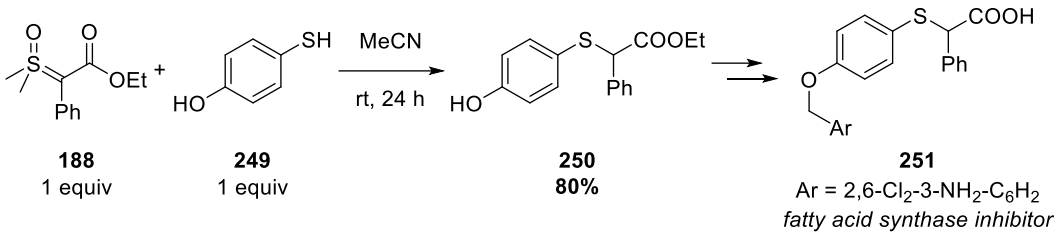


Scheme 79: Attempt of C–H bond functionalisation.

3.5.2 C–S bond formation

C–S bond formation can be done in a very efficient manner using sulfoxonium ylides.[84] Using Burtoloso's conditions, compound **250** could be synthesised in a good 80% yield by simply mixing **188** and 4-mercaptophenol **249** in acetonitrile under mild conditions with only DMSO as a side product (Scheme 80). Compound **250** is rather interesting as it is a precursor of compound **251** which is a fatty acid synthase inhibitor.[85]

With the possibility to synthesise **250** efficiently, without the need to use diazo compounds, this route to access **251** shows some good viability.



Scheme 80: C–S bond formation.

3.5.3 C–N bond formation

Mangion's methodology to form C–N bonds has been applied with the new disubstituted sulfoxonium ylides. Compound **253** was obtained in 69% yields. Once again, the only side product of the reaction was DMSO (Scheme 81).

Scheme 81: C–N bond formation.

The possibility of efficiently synthesising disubstituted sulfoxonium ylide without the use of diazo derivatives could allow the development of enantioselective version of that C–N bond formation using chiral ligands.

4 Conclusion

We have developed a convenient methodology for the formation of disubstituted α-ester-α-arylsulfoxonium ylides. Three different catalyst systems were used. Our first generation of conditions, referred as method A, were using the very common tetrakis(triphenylphosphine)palladium as a catalyst. The wide availability of this catalyst makes it convenient for a quick test reaction, which could be interesting in a medicinal chemistry context. The reaction had a good functional group tolerance notably with the possibility of mono substitution on 1,3-dibromobenzene. It could also be done in an intramolecular fashion. However, compounds often contained small quantity of triphenylphosphine oxide, supposedly coming from the decomposition of the starting material and reaction with triphenylphosphine. This impurity could be removed by recrystallisation.

This problem was solved in our latest conditions B and C using either tris-*tert*-butylphosphine or XPhos as ligand and tris(dibenzylideneacetone)dipalladium as a pre-catalyst. The yields were also generally increased with those methods and the need of the glovebox was completely eliminated when XPhos was used.

The main limitations for all three methods were the lack of reactivity with electron-rich electrophiles as well as the rather high catalyst loading.

The products could be further functionalised though catalyst-free C–S bond formation, or an iridium-catalysed C–N bond formation. Those reactions should be expanded to the asymmetric version in order to reach their full potential.

Chapter 3:

Synthesis of (hetero)aryl substituted α-keto sulfoxonium ylides

Chapter 3: Synthesis of (hetero)aryl substituted α-keto sulfoxonium ylides

1 Introduction

After exploring the reactivity of α-ester sulfoxonium ylides, it was the next natural progression to explore the reactivity of α-keto sulfoxonium ylide derivatives. Indeed, as seen in the first chapter, that class of sulfoxonium ylides was the most used for C–H and X–H functionalisation and, therefore, would probably benefit the most from a wider availability of disubstituted derivatives.

However, we will see that, when the coupling was attempted using the conditions from the second chapter, it appeared that the remaining excess of starting material could not be distinguished by TLC, thus preventing purification by flash chromatography, as opposed to the ester derivatives. The conditions previously developed were then not applicable directly for the synthesis disubstituted α-keto sulfoxonium ylides and had to be refined. The findings of the study of the mechanism and how they were applied to improve these conditions for larger scale reactions and coupling with valuable active pharmaceutical ingredients will also be discussed.

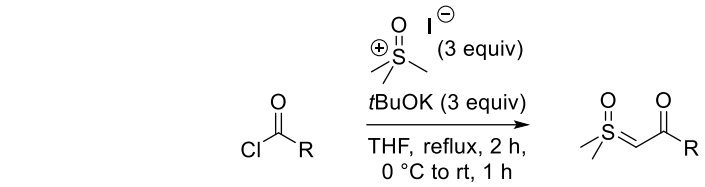
A placement student (Jean-Baptiste Chagnoleau) contributed to the study of the mechanism. His results will be presented alongside those obtained by the author of this thesis (see Chapter 4 for details).

2 Synthesis of the mono-substituted α-keto sulfoxonium ylides

2.1 Synthesis from the acyl chlorides

2.1.1 Synthesis from the commercially available acyl chlorides

As chloroformate compounds were the easiest option to synthesise the monosubstituted ester derivatives, using acyl chlorides also appeared as the most step-efficient option to synthesise the ketone derivatives in view of their wide commercial availability (Scheme 82). Thus, using trimethyl sulfoxonium iodide and potassium *tert*-butoxide in presence of the desired acyl chlorides precursors, primary alkyl group such as compounds **7** and **254** were obtained in 86% and 72%, respectively. Three aryl derivatives were synthesised using that method. Electron-poor aryl **255** was obtained in 79% yield and electron-rich aryl **256** was synthesised in 86% yield. Electron-neutral derivative **12** was obtained in excellent yield. The hetero-aryl derivatives **257** and **258**, previously synthesised in our laboratory by Manuel Barday, were obtained in 80% and 38% yield, respectively. Steric hindrance was well-tolerated as the bulky adamantane derivative **259** was obtained in 75% yield.

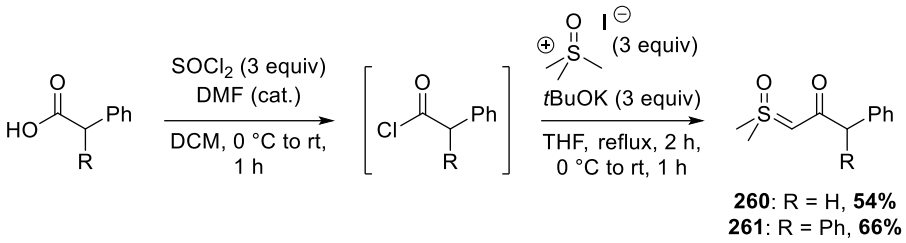


Starting material	Product	Starting material	Product
7-a	**7** **86%**	**256-a**	**256** **56%**
254-a	**254** **72%**	**257-a**	**257** **80%**
255-a	**255** **79%**	**258-a**	**258** **38%**
12-a	**12** **95%**	**259-a**	**259** **75%**

Scheme 82: Synthesis of mono-substituted sulfoxonium ylides using commercially available acyl chloride derivatives.

2.1.2 Synthesis from acyl chlorides formed *in situ*

When the desired acyl chloride derivatives were not commercially available, they could sometimes be made from the corresponding acids and used directly in the next step after removal of the volatiles and solvent exchange (Scheme 83). The primary alkyl derivative **260** was obtained in 54% yield using this method and the secondary alkyl **261** could be obtained in 66% yield.

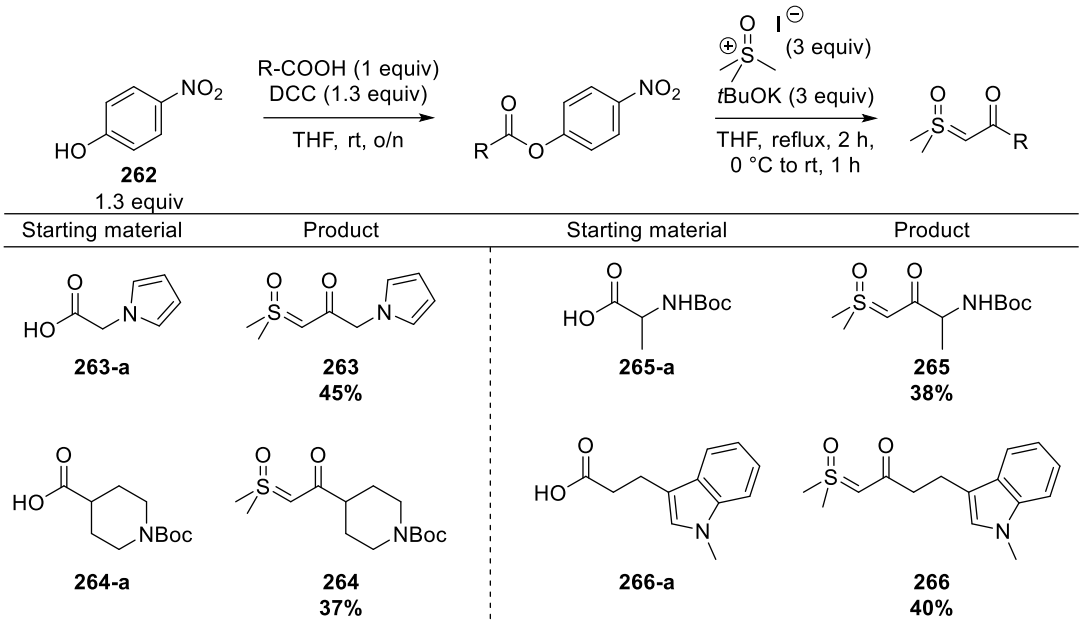


Scheme 83: Synthesis of mono-substituted sulfoxonium ylides using acyl chloride derivatives made in situ.

2.2 Synthesis from 4-nitrophenol

If the *in situ* formation of the acyl chloride was unsuccessful, the monosubstituted sulfoxonium ylides were synthesised from the 4-nitrophenol ester derivatives in a two step fashion (Scheme 84). The latter could be obtained through DCC-mediated coupling of the desired acid with 4-nitrophenol **262** to obtain the ester which were subjected to the classical conditions to form the corresponding sulfoxonium ylides.

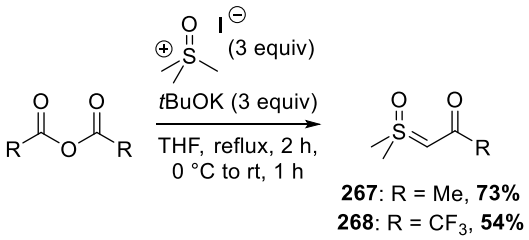
It is noteworthy that the yields were usually higher as compared to when this strategy was used for the ester derivatives to form the carbonates. Indeed, the indole derivative **263** was obtained in 45% yield over 2 steps and the piperidine derivative **264** was synthesised in 37% yield. The (±)-alanine afforded **265** in 38% yield and the two step sequence was also successful for the synthesis of the indole derivative **266** in 40% yield. Both **265** and **266** were previously synthesised in our laboratory by Manuel Barday and Daniel Clare.



Scheme 84: Synthesis of mono-substituted sulfoxonium ylides from the 4-nitrophenol esters. Yields are given over two steps.

2.3 Synthesis from the anhydrides

Monosubstituted α-keto sulfoxonium ylides can also be synthesised from anhydride derivatives as demonstrated in Scheme 85. Acetic anhydride afforded compound **267** in a good 73% yield. A lower 54% yield was obtained for the trifluoroacetic derivative **268**.

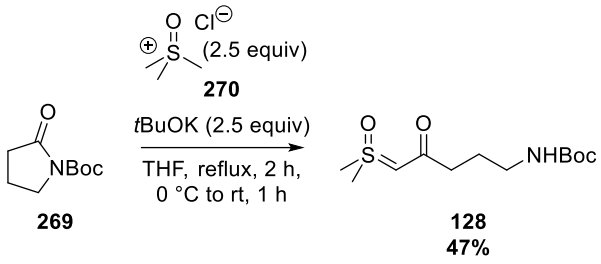


Scheme 85: Synthesis of mono-substituted sulfoxonium ylides using anhydride derivatives.

2.4 Other methods of synthesis

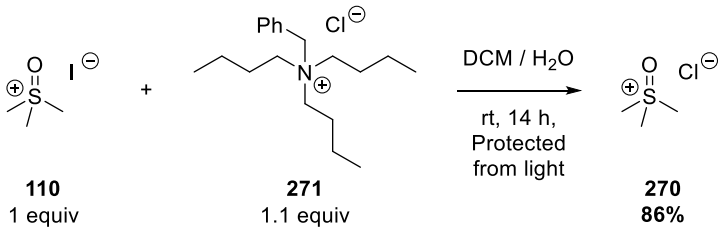
2.4.1 Synthesis by ring opening of lactams

Sulfoxonium **128** has previously been synthesised by Mangion and co-workers *via* the ring opening of boc-protected 2-pyrrolidone **269** using trimethylsulfoxonium chloride **270**.[45] However, when attempted in our laboratory, the method reported presented some reproducibility issues. Indeed, the amide salt formed *in situ* had to be quenched by water at the end of the reaction which dissolved the desired product **128** as well**.** Using small amounts of brine for the quench, as well as using a large amount of organic solvent, allowed the recovery of **128** in average yield (Scheme 86).



*Scheme 86: Synthesis of the sulfoxonium ylide **128**.*

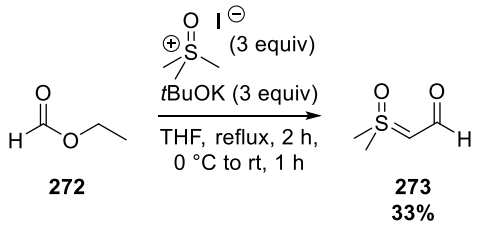
The trimethylsulfoxonium chloride **270** used for that reaction, although commercially available, can easily be prepared in 86% yield from trimethylsulfoxonium iodide **110** through an ion exchange with benzyltributylammonium chloride **271** as shown in Scheme 87.



*Scheme 87: Synthesis of trimethylsulfoxonium chloride **270**.*

2.4.2 Synthesis from ethyl formate

The formyl sulfoxonium ylide **273** was synthesised from ethyl formate in 33% yield using the method reported by Ellman (Scheme 88).[22] The yield was usually low due to the obtention of a complex mixture resulting in difficult purification.



*Scheme 88: Synthesis of the sulfoxonium ylide **273**.*

3 Palladium-catalysed C–H functionalisation of sulfoxonium ylides

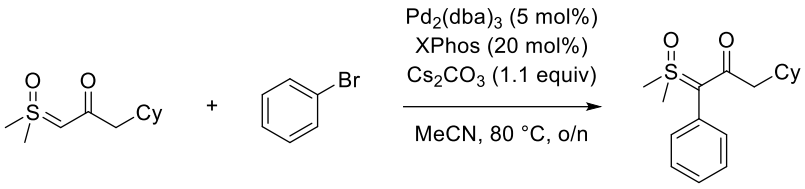
3.1 Optimisation of the reaction conditions

The conditions developed for the α-ester sulfonium ylides appeared to be unsuitable for the α-keto derivatives. Although good conversions were observed by ^{1}H NMR of the crude, the excess of starting material which was necessary to obtain good yields for the coupling of the α-ester derivatives could not be separated from the product by flash chromatography.

Compound **274** was then obtained in 92% yield but as a 1.6 to 1 mixture of starting material **7** and product **274** (Table 6, entry 1). Changing the stoichiometry to 2.5 equivalents of the electrophile partially solved the issue and 47% of the clean product could be obtained as well as 34% of a 5:1 mixture of **274** and **7** (entry 2). Further increasing the amount of electrophile to 3 equivalents did not allow full conversion to be reached and significant part of the desired product was still obtained as a mixture with starting material (entry 3).

However, increasing the concentration from 0.1 M to 0.5 M allowed the full consumption of the starting material and **274** was then obtained in 83% yield after purification by flash chromatography (entry 4).

Table 6: Optimisation of the reaction conditions



7 X equiv + **224** Y equiv → **274**

Entry	Ratio X:Y	Concentration	Yield
1	1:2.5	0.1 M	92%[a]
2	2.5:1	0.1 M	47%[d] + 34%[b]
3	3:1	0.1 M	62%[d] + 23%[c]
4	2.5:1	0.5 M	83%[d]

*[a] Obtained as a 1.6:1 mixture of **7**:**274** (corrected yield). [b] Obtained as a 5:1 mixture of **274**:**7** (corrected yield). [C] Obtained as a 3:1 mixture of **274**:**7** (corrected yield). [d] Isolated yield of pure product.*

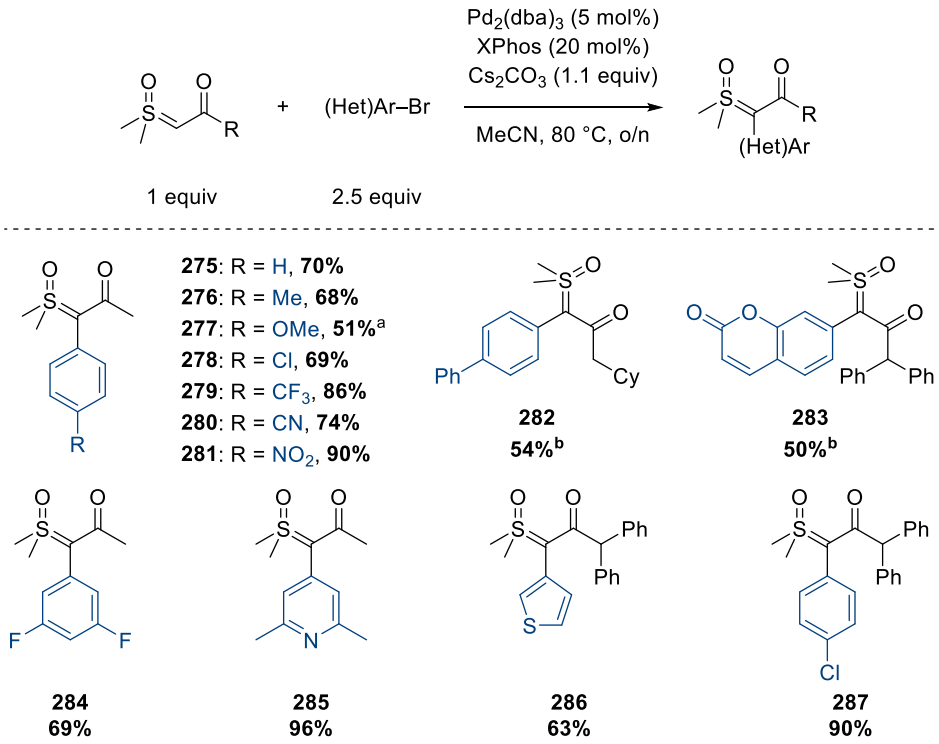
3.2 Evaluation of the scope

3.2.1 Scope of electrophiles

Although the reaction conditions were not fully optimised, we decided to evaluate the generality of the method. The scope of electrophiles was first assessed (Scheme 89).

Similarly to what was observed in Chapter 2 for the coupling with ester derivatives, electron poor aryl bromides such as compounds **278**-**281** gave good to excellent yields. The inductively electron rich electrophile 4-bromotoluene afforded **276** in 68% yield. The coupling with the more electron rich 4-bromoanisole afforded **277** in 51% NMR yields. In that case, the reaction had to be stopped after 2 hours as product decomposition in the reaction mixture was occurring after that time. After purification through a short pad of silica, the product could only be obtained in 26% yield with traces of starting material **268** and DMSO, demonstrating an instability of the compound on silica. The coupling could also be carried out with triflate derivatives

and provided compounds **282** and **283** in average yields, 54% and 50%, respectively. In contrast with the coupling with ester derivatives, the use of triflates was not as well tolerated which could suggest a different mechanism for the reaction. Compound **284** provided an example of *meta* substitution and was obtained in 69% yield. Pyridine derivative and thiophenyl were also evaluated and compound **285** and **286** were obtained in 96% and 63% yield, respectively. Another example of coupling with 4-bromo-1-chlorobenzene was synthesised affording **287** in 90% yield.



Scheme 89: Scope of electrophiles. [a] ^{1}H NMR yield, reaction stopped after 2 hours. [b] Triflate used instead of the aryl bromide. [c] Reaction done at 0.2 M instead of 0.5 M.

3.2.2 Scope of sulfoxonium ylides

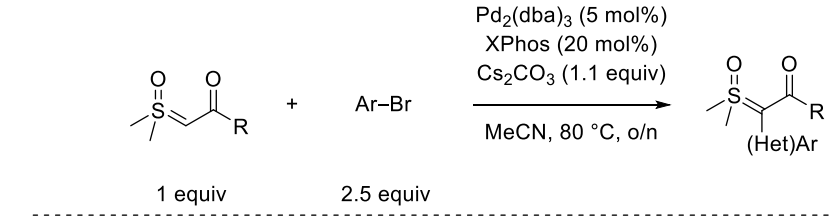
The scope of sulfoxonium ylides was then evaluated (Scheme 90). A very good functional group tolerance can be observed. Three examples of primary alkyl sulfoxonium ylides were synthesised. The indole derivative **288** was obtained in

excellent yield and compound **289** and **290** were obtained in 79% and 80% yield, respectively.

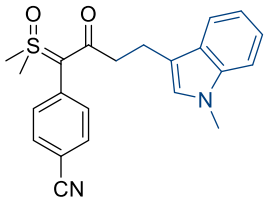
Three more examples of secondary alkyl sulfoxonium ylides were also evaluated. Interestingly the coupling with the Boc-protected alanine derivative **265** afforded compound **291** in very good yield so as the Boc-protected piperidine **292** which was isolated in 85% yield. Compound **293** was also obtained in 92% yield.

Aryl groups directly attached to the ketone were also well tolerated regardless of the electron density. Both the electron-poor aryl **294** or electron rich **295** were obtained in excellent yields. Compound **296** was obtained in a very good 90% yield. Heteroaryl groups such as thiophenyl and isoxazole provided compound **297** and **298** in 79% and 83% yield, respectively.

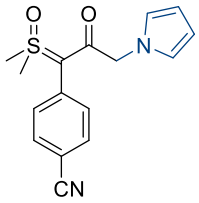
Finally, the formyl sufoxonium derivative **299** was obtained in 83% yield and the *ortho*-substituted equivalent **300** was obtained in 85% yield. These last two sulfoxonium ylides had to be purified on basic silica as partial decomposition was observed on the untreated silica.



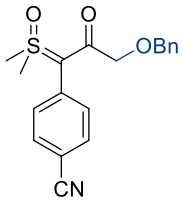
Primary alkyl groups



288
89%

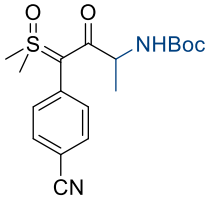


289
79%

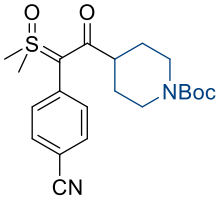


290
80%

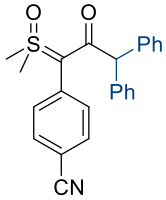
Secondary alkyl groups



291
87%

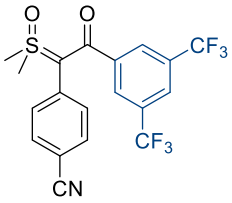


292
85%

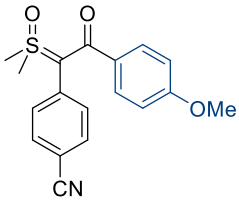


293
92%

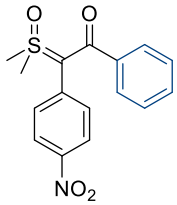
Aryl groups



294
82%

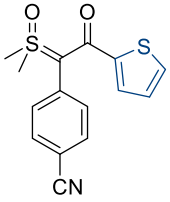


295
80%

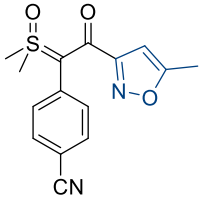


296
90%

Heteroaryl groups

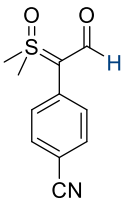


297
79%

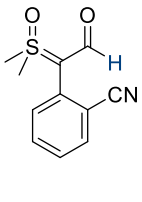


298
83%

Aldo sulfoxonium ylide



299
83%



300
85%

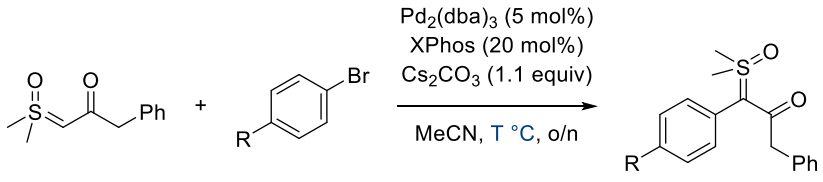
Scheme 90: Scope of sulfoxonium ylides.

3.2.3 Special cases

*3.2.3.1 Coupling of the benzylic sulfoxonium ylide **260***

Surprisingly, the coupling of the sulfoxonium ylide **260** with 4-bromobenzonitrile or 1-bromo-4-nitrobenzene under the classical conditions led either to low yield (27%, not pure for compound **301**) or no product at all as for compound **302** (Table 7, entry 1). However, full conversion of the sulfoxonium ylide **260** was observed by TLC and crude ^{1}H NMR. No side product could be isolated. Lowering the temperature of the reaction to 60 °C afforded 71% of compound **301** and 68% of compound **302** (Table 7, entry 2). Compound **260** was again completely consumed suggesting that the lower yield could be explained by the decomposition of the products **301** and **302** under the reaction conditions. The reaction was then carried out at 40 °C (Table 7, entry 3). A better mass balance was then obtained as some starting material could be recovered but lower yields of product were then obtained, confirming the sensitivity of the products towards heat.

*Table 7: Coupling with the sulfoxonium ylide **260**.*



260
1 equiv

2.5 equiv

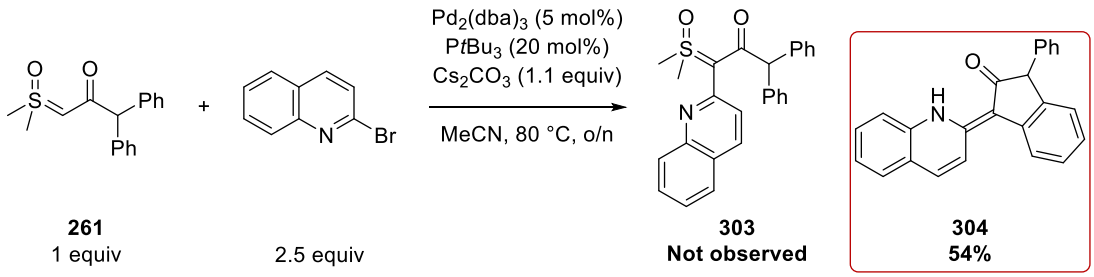
301: R = CN
302: R = NO_2

Entry	T	Yield **301**	Yield **302**
1	80 °C	<27%	0%
2	60 °C	71% (no RSM)	68% (no RSM)
3	40 °C	62% + 21% RSM	60% + 30% RSM

RSM = Recovered Starting Material.

3.2.3.2 Coupling with 2-bromoquinoline

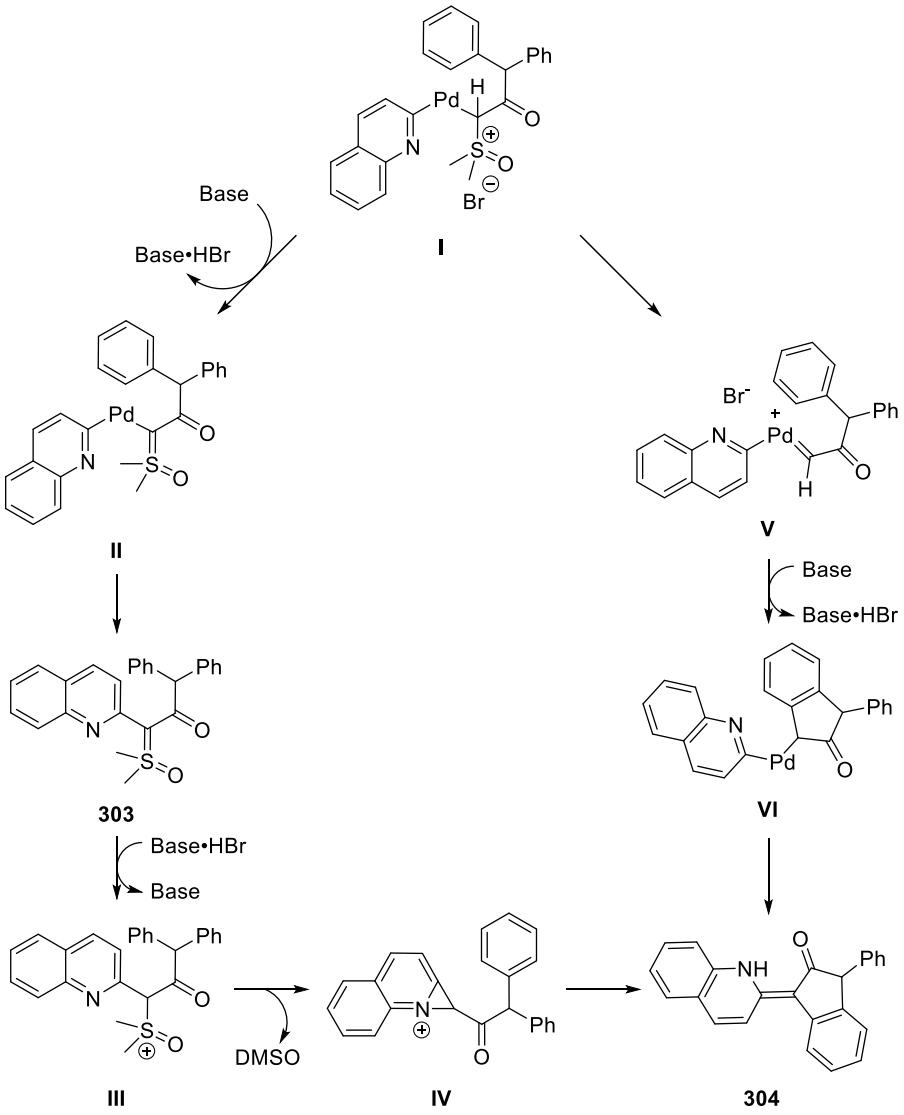
The coupling of compound **261** with 2-bromoquinoline using P*t*Bu$_3$ as a ligand also lead to an unexpected result. Full conversion was observed by TLC with a significant amount of decomposition without any trace of the desired coupling product **303** (Scheme 91). However, compound **304** could be isolated in 54% yield as a deep red solid.



*Scheme 91: Coupling of sulfoxonium **261** with 2-bromoquinoline.*

A rationale for the mechanism leading to compound **304** suggests that it could be formed through two different pathways from the suspected transmetalation intermediate **I** (Scheme 92). In the first case, deprotonation would occur forming the intermediate **II** which could undergo reductive elimination leading to the expected product **303**. The latter could be protonated to form intermediate **III**. The nitrogen atom could then attack the carbon bearing the sulfur, releasing DMSO and forming the ammonium **IV** which could undergo electrophilic aromatic substitution with one of the phenyl rings to form **304**.

In the second case, the intermediate **I** could form the palladium carbene **V** by DMSO extrusion. Intramolecular electrophilic aromatic substitution would then form the complex **VI** releasing **304** after reductive elimination.



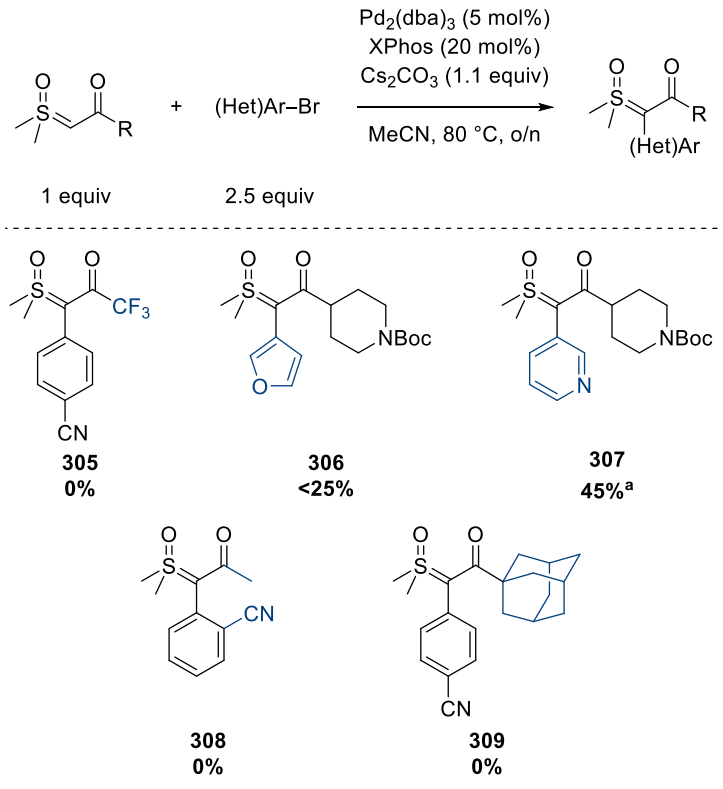
*Scheme 92: Proposed mechanism for the formation of compound **304**.*

3.3 Limitations

The coupling of the keto-sulfoxonium ylides appeared to have slightly better tolerance with electron rich electrophiles as compared to their ester equivalents as shown by the successful coupling with the naked thiophenyl **285** (Scheme 89). However, electronic effects still have a significant impact with some substrates (Scheme 93). For example, compound **305** could not be obtained with that methodology and compound **306** was only obtained in low yield and could not be obtained pure.

Also, in some cases, if full conversion of the starting sulfoxonium ylide could not be obtained, the product and the remaining starting material could not be separated as for compound **307** which was only observed in the crude ^{1}H NMR in 45% yield but could not be isolated.

Finally, except in the case of the formyl sufoxonium ylide **299** (Scheme 90), the reaction was very sensitive to steric hindrance and *ortho*-substitution on the bromoaryl derivative was not tolerated. Even a small methyl group on the sulfoxonium ylide inhibited the reaction and compound **308** could not be obtained. Tertiary alkyl groups were also not tolerated and the adamantane derivative **309** could not be synthesised.



Scheme 93: Limitations of the method. [a] ^{1}H NMR yield.

4 Study of the mechanism

It was then decided to study the mechanism of the reaction as it could potentially explain some of the limitations that were observed and allow us to improve the reaction conditions. We expected the reaction to react through a classical oxidative addition, transmetalation, deprotonation, reductive elimination mechanism as previously described in the literature by Wang for diazo compounds and depicted for the ester derivatives in Chapter 2, Scheme 78.[71]

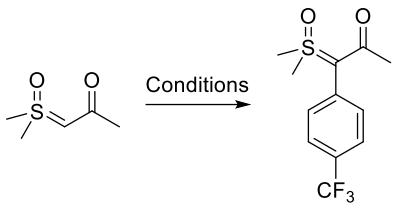
4.1 Evidence for product inhibition

α-Keto sulfonium ylides have previously been used as ligand for palladium catalysts, notably for the Suzuki-Miyaura and the Heck cross-coupling reactions.[86–89] Although sulfoxonium ylides are less reactive as compared to their sulfonium equivalents, we wanted to verify the potential impact of the catalyst on the product.

The cross-coupling leading to the formation of **278** was then carried out under the standard conditions but was stopped after 20 min (Table 8, entry 1). A conversion of 41% could then be observed. A second experiment was carried out with the same reaction conditions but with one equivalent of compound **278** added after 10 min of reaction (to ensure that the active catalyst was formed) (Table 8, entry 2). A significantly lower conversion of 25% was then observed indicating a product inhibition of the catalyst.[90–92]

This result indicates that only initial rates of the reaction had to be used for further study of the mechanism to minimize the inhibitory effect of the product.

Table 8: Evidence for product inhibition.



267 **278**

Entry	Conditions	Conversion
1	*p*-$CF_3C_6H_4Br$ (2.5 equiv) standard conditions, 20 min	41%
2	1) *p*-$CF_3C_6H_4Br$ (2.5 equiv) standard conditions, 10 min 2) **278** (1 equiv), 10 min	25%

4.2 Hammett plot

The study of the mechanism was initiated by the undergraduate student Jean-Baptiste Chagnoleau who realised a Hammett plot of the reactions leading to compounds **274**-**280** to understand the impact of the electronic effects on rate of the reaction (Figure 5). A very good correlation was observed using σ_p values ($R^2 = 0.99$) for electron withdrawing groups giving $\rho = 0.81$. However, these substituent parameters gave a poor correlation with electron-donating substituents ($R^2 = 0.91$). The modified parameters ρ^+ were then used and gave $\rho = -0.30$ with a good correlation ($R^2 = 0.99$). A V-shaped Hammett plot was then obtained with a stronger influence of the electron-withdrawing substituents as compare to the electron-donating ones. The negative ρ value for the electron-donating substituents indicates a build-up of positive charges, whereas the positive ρ value for the electron-withdrawing substituents indicates a build-up of negative one.

This could be obtained in 3 cases: a change of mechanism, a change of "rate-determining step" or change in the nature of the transition states depending on the electronic nature of the substituent.[93]

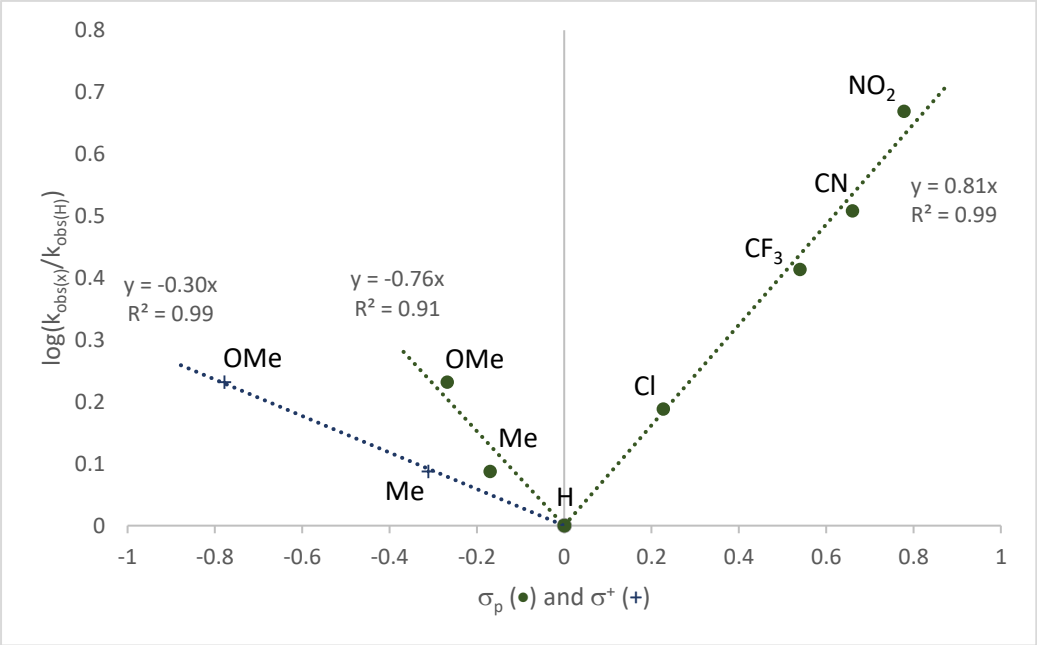


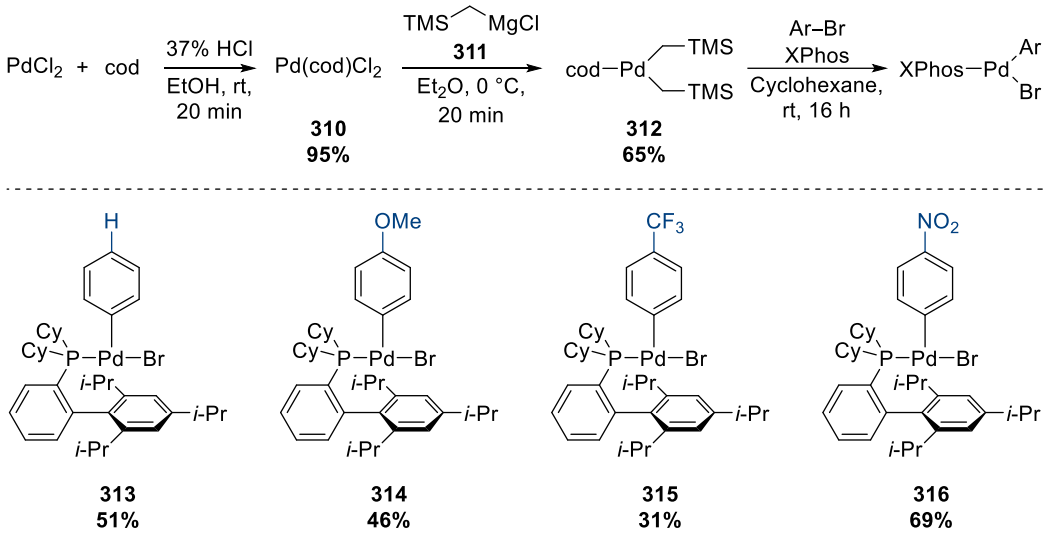
*Figure 5: Hammett plot obtained of the reactions leading to products **21**-**26**. Data from duplicate experiments.*

4.3 Control experiment with oxidative addition intermediates

In order to gain a better understanding of the electronic effects on the reaction, stoichiometric experiments were carried out from the isolated oxidative addition complexes.

4.3.1 Synthesis of the complexes

The synthesis of complexes **313**-**316** is described in Scheme 94. Pd(cod)Cl_2 was synthesised from $PdCl_2$ and 1,5-cyclooctadiene in 95% yield. Nucleophilic attack of the Grignard reagent **311** then provided the temperature sensitive compound **312** in 65% yield. The latter could then be reacted with XPhos and the desired aryl bromide to obtain the complexes **313**-**316** in yields ranging from 31% to 69%.



Scheme 94: Synthesis of the oxidative addition complexes.

Complexes **313** and **314** were described in the literature but complexes **315** and **316** were not. Therefore, these two complexes were characterised by single crystal X-Ray analysis. Interestingly, the two complexes appeared to be dimers bridged by the bromine atoms (Figure 6 and Figure 7).

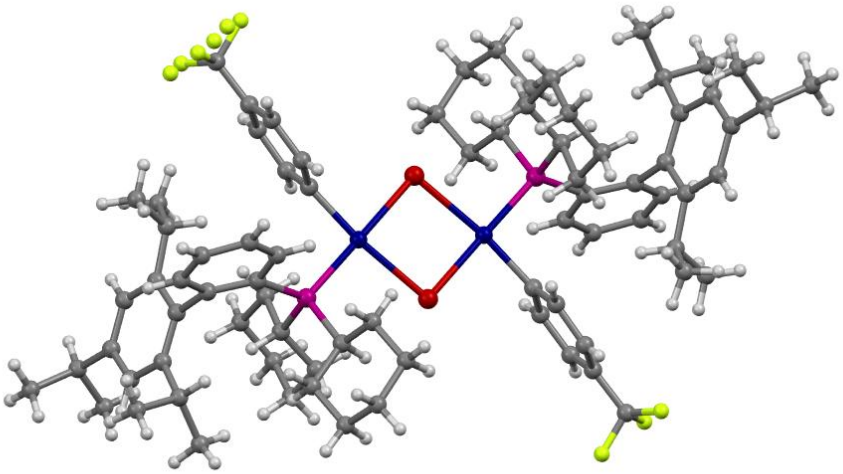


*Figure 6: X-Ray analysis of compound **315**.*

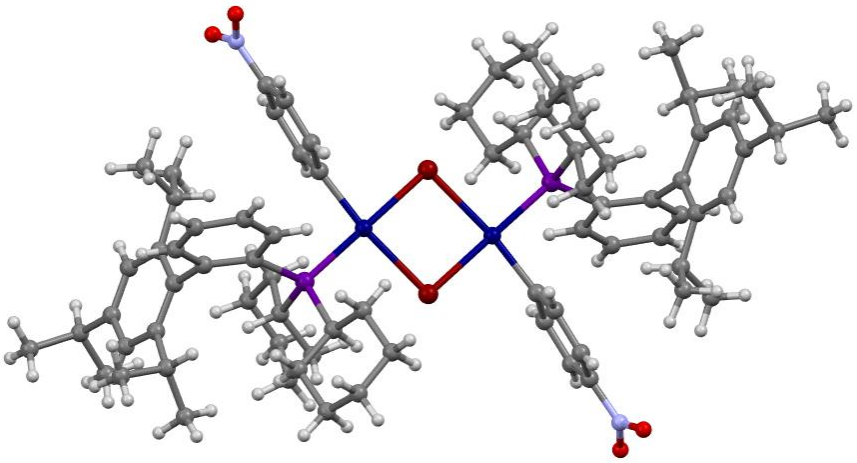


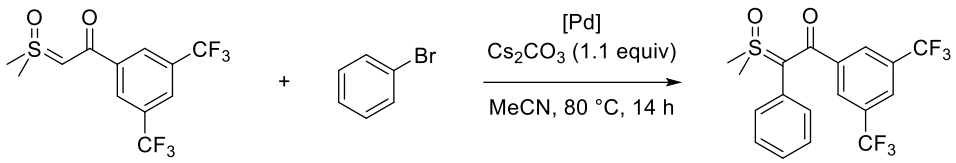
*Figure 7: X-Ray analysis of compound **316**.*

4.3.2 Catalytic and kinetic competency of the complexes

In order to verify that the synthesised complexes were actually reaction intermediates, their kinetic and catalytic competency were studied.

To do so, sulfoxonium ylide **255** was reacted with bromobenzene using the classical conditions in first instance and then replacing the catalyst by the complex **313** (Table 9). It was observed that the yield with the latter was actually slightly higher as compared to when $Pd_2(dba)_3$ was used as a pre-catalyst, proving the catalytic competency of the complex. A control experiment was also realised by repeating the reaction with complex **313** but with addition of 30 mol% of dba. Compound **317** was obtained in 85% yield showing that dba has no impact on the reactivity.

*Table 9: Study of the catalytic competency with the complex **313**.*

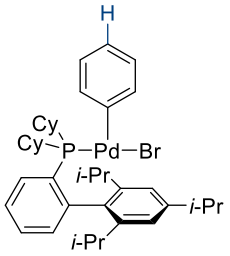


255
1 equiv

224
2.5 equiv

317

Entry	[Pd]	^{1}H NMR yield
1	$Pd_2(dba)_3$ (5 mol%) XPhos (20 mol%)	**73%**
2	**313** (10 mol%) XPhos (10 mol%)	**89%**



313

To determine the kinetic competency, the initial rates of the these two reactions were studied. As it can be observed in Figure 8, these initial rates were identical. That result established the kinetic competency of the complex **313**, confirming that those oxidative addition complexes were reaction intermediates. Importantly, it also suggested that the differences due to the electronic effects that were observed in the Hammett plot were not due to the oxidative addition as a difference of initial rates would have been observed otherwise.

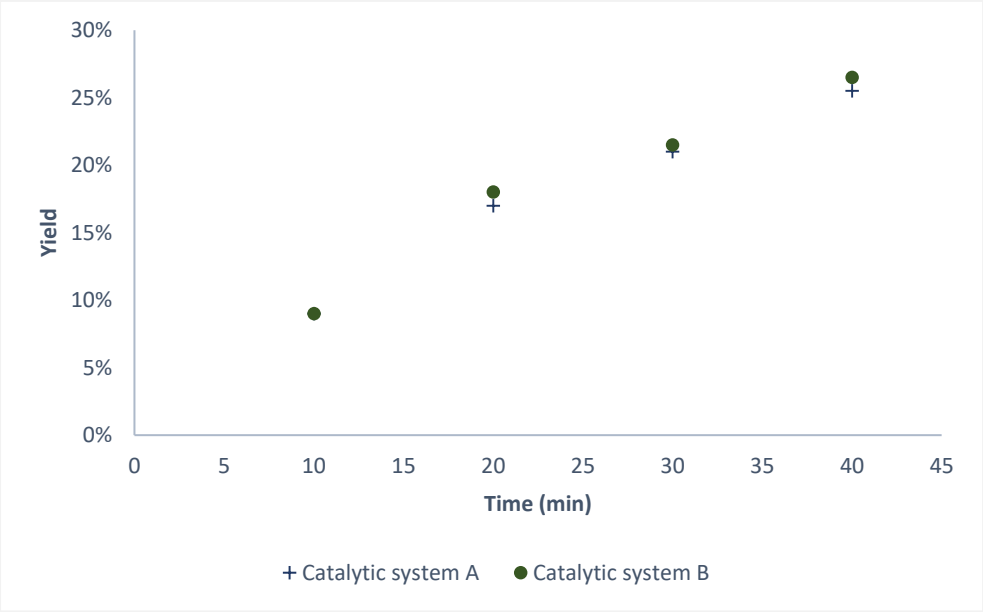
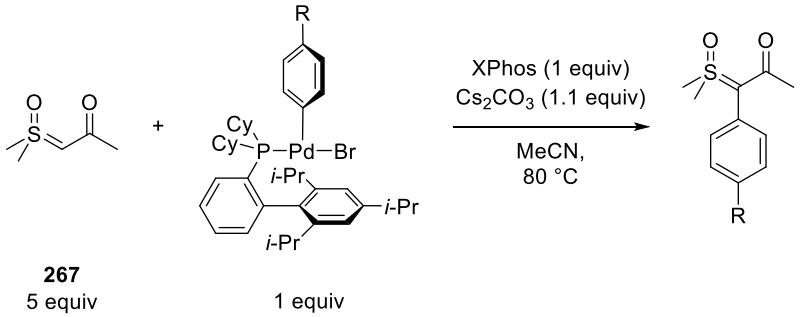


*Figure 8: Study of the kinetic competency of the reaction. Catalytic system A: $Pd_2(dba)_3$ (5 mol%), XPhos (20 mol%); Catalytic system B: Complex **313** (10 mol%), XPhos (10 mol%), dba (30 mol%). Data from duplicate experiments.*

4.3.3 Relative initial rates

The complexes **313**, **314** and **315** were then used in stoichiometric experiments and the initial rates of reaction were recorded (Figure 9). An excess of sulfoxonium ylide was used to mimic the real conditions at the beginning of the reaction and an extra equivalent of XPhos was also added to also reproduce the two equivalents of phosphine per atom of palladium.



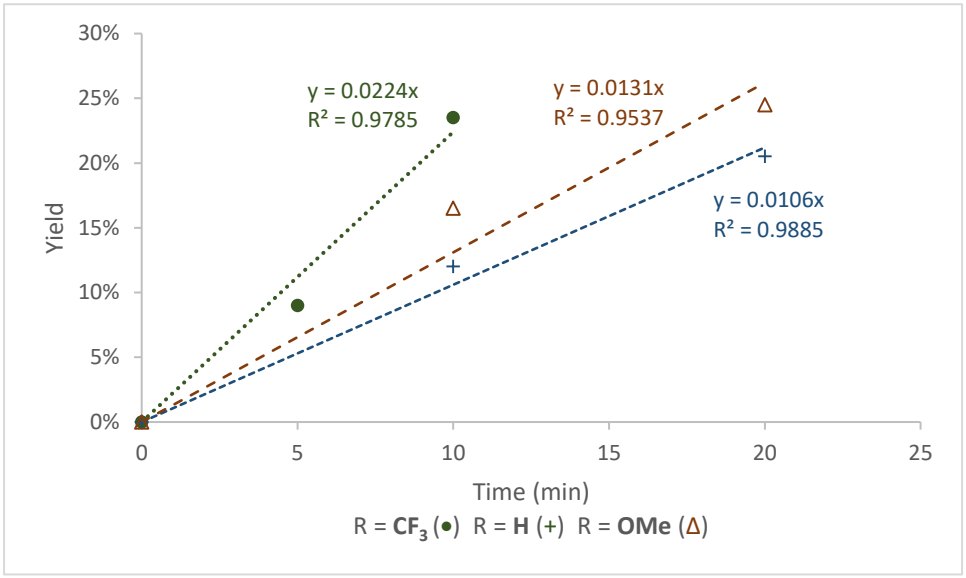


*Figure 9: Study of the initial reaction rates for complexes **313**-**315**. Data from duplicate experiments.*

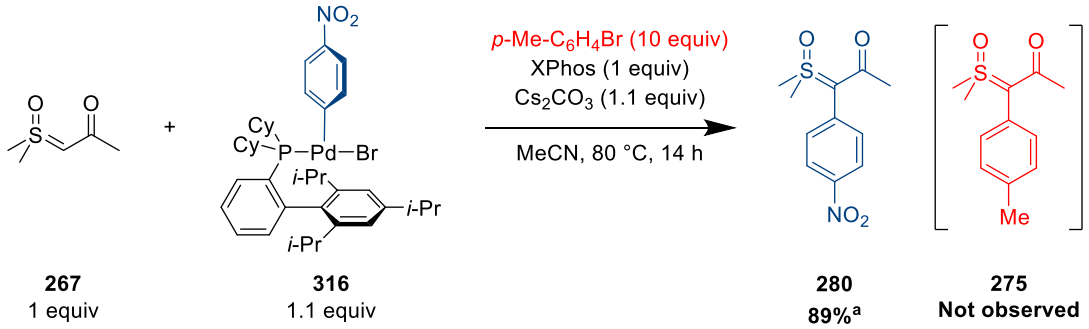
The K_{obs} obtained from this graph were then used to establish the relative rates (K_{rel}) as compared to the rate of the reaction for complex **313**. It could be observed that the K_{rel} were in the same ranking order as compared to what was observed in the Hammett plot with rate increasing in the order X = H < OMe < CF_3 (Table 10). This also suggested that the differences due to the electronic effects that were observed in the Hammett plot were not due to the oxidative addition.

Table 10: Relative initial reaction rates obtained from the K_{obs}.

Product	K_{rel}
274 (X = H)	1
276 (X = OMe)	1.24
278 (X = CF_3)	2.04

4.3.4 Crossover experiment

The reversibility of the oxidative addition was then assessed. A crossover experiment was carried out (Scheme 95). A slight excess of compound **316** was reacted with the sulfoxonium ylide **267** in presence of a large excess of 4-bromotoluene (10 equivalents). Although, according to the Hammett plot, the rate of the reaction with 4-bromonitrobenzene is faster than with 4-bromotoluene, the large excess of the latter would promote the formation of **275** in case of a reversible oxidative addition. However, no traces of compound **275** was observed and only compound **280**, sulfoxonium ylide **267** and DMSO could be observed in the ^{1}H crude NMR confirming that the oxidative addition is not reversible under the reaction conditions.



*Scheme 95: Crossover experiment between complex **316** and 4-bromotoluene. [a] Yield based on the remaining sulfoxonium ylide **267** (6%) and DMSO (5%) observed in the crude ^{1}H NMR.*

In summary, the stoichiometric experiments realised in part 4.3 suggest that:

- The isolated oxidative addition complexes are indeed those formed in the reaction mixture under the reaction conditions.
- The oxidative addition is not reversible.
- These complexes react at the same initial rate as compared to the initial reaction conditions, therefore, this step is fast.

Thus, the electronic effects observed in the Hammett plot are not related to the oxidative addition and this step is therefore not part of the rate determining zone (RDZone) of the reaction. The latter being the section between the turnover frequency determining intermediate (TDI) and the turnover frequency determining transition state (TDTS).[94] To further support this conclusion, the rate law of the reaction was determined.

4.4 Determination of the rate law

The work presented in this section was done by the undergraduate student Jean-Baptiste Chagnoleau. The rate law of the reaction was determined for each side of the Hammett plot using the sulfoxonium ylide **267** and 4-bromobenzotrifluoride for the electron-deficient electrophiles, and 4-bromoanisole for the electron rich ones. The concentrations in sulfoxonium ylides **267**, aryl bromides, Cs_2CO_3, $Pd_2(dba)_3$ and XPhos were varied for this study.

The initial rates ($rate_i$) that he obtained could be expressed by the following equations: $rate_i = k_{obs}[\mathbf{267}]^{0.6}[Cs_2CO_3]^{0.3}[Pd_{tot}]^{0.5}$ for the reaction with 4-bromobenzotrifluoride and $rate_i = k_{obs}[\mathbf{267}]^{0.5}[Cs_2CO_3]^{0.4}[Pd_{tot}]^{0.4}$ for the reaction with 4-bromoanisole, where $[Pd_{tot}]$ is the total concentration of palladium. The rate law is therefore the same for the electron-rich and the electron-poor electrophiles (within experimental errors).

A zeroth order was observed for the aryl bromides which is in accordance with what was previously demonstrated in the part 4.3 and reinforced the theory that the aryl bromide is not in the RDZone of the reaction.

A zeroth order was also observed in XPhos as long as there was at least one equivalent of XPhos per palladium. This suggest that two equivalents of ligand per palladium should not be necessary for the reaction to proceed.

However, partial orders were observed for both the base and the sulfoxonium ylides meaning that they are both involved in the RDZone and also indicating a complicated mechanism.[95,96] Moreover, the different values obtained for the linear regression of the Lineweaver-Burk plots for the sulfoxonium ylide and the base indicated that these two steps were not concerted (Figure 10 and Figure 11).

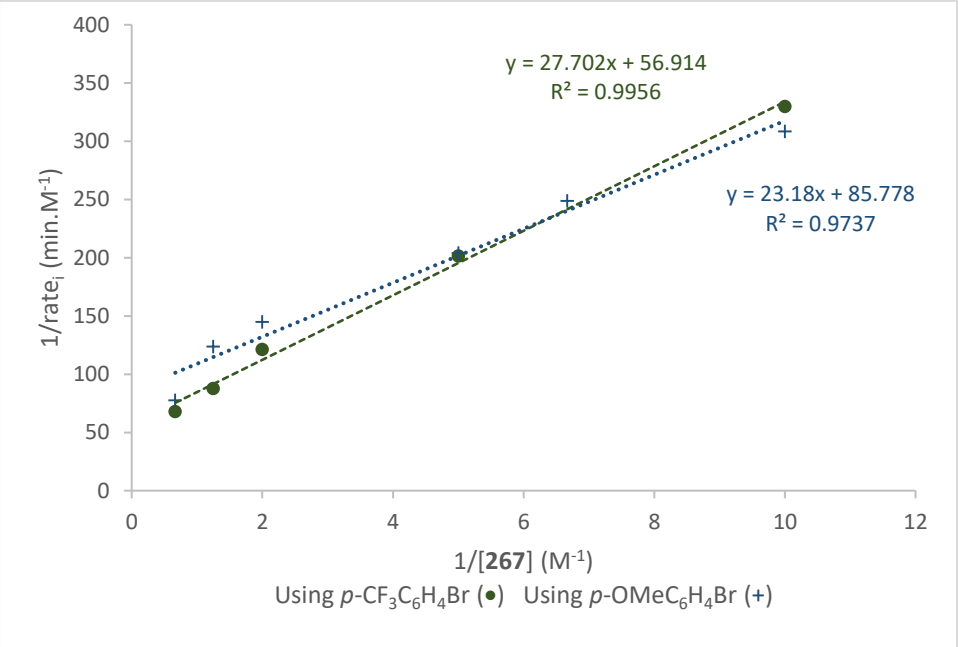


*Figure 10: Lineweaver-Burk plot for sulfoxonium ylide **267**.*

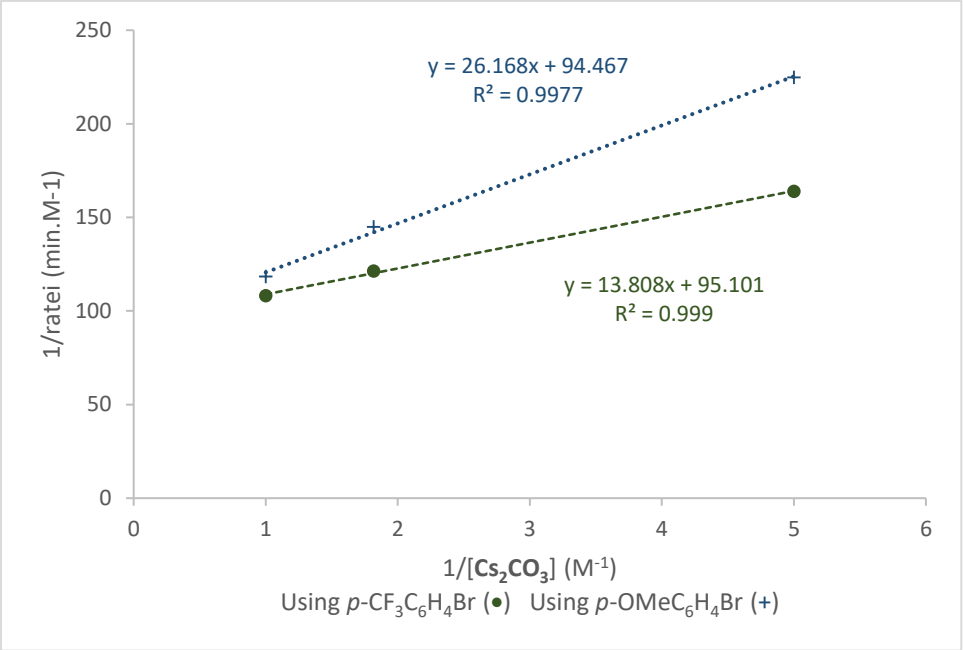


Figure 11: Lineweaver-Burk plot for Cs_2CO_3.

Finally, a half-order in palladium suggests an equilibrium between a monomeric active catalyst species and an inactive dimer as previously demonstrated by van Leeuwen and co-workers experimentally or by Blackmond and co-workers *via* kinetic modeling for the study of a Heck reaction.[97,98] This order, being closer to 0.5 than to 1, indicates that a major percentage of the catalyst is present as the inactive dimer.[99] This equilibrium could be attributed to the formation of the active catalyst from $Pd_2(dba)_3$ and XPhos as shown in (1).

$$Pd_2(dba)_3 + 2\,[XPhos] \rightleftharpoons 2\,[XPhosPd(dba)] + dba \quad (1)$$

However, it would lead to different initial rates for the reactions conducted under classical conditions and those conducted using oxidative addition complexes as source of catalytically active species, which was not the case as demonstrated in part 4.3.2. The equilibrium between a monomer and a dimer of palladium occurred at another step of the catalytic cycle.

4.5 *In situ* observation of the reaction intermediates

In order to gain more insight on the result obtained during the study of the rate law, some *in situ* analyses of the reaction were then carried out.

4.5.1 By ^{31}P NMR

Using NMR seemed to be the easiest method. However, the low solubility of the complexes in acetonitrile at room temperature complicated the analysis as shimming issues were often encountered and therefore no information could be obtained by ^{1}H and ^{13}C NMR.

However, with long acquisition time and sufficient relaxation delay, it was possible to obtain interpretable information from the ^{31}P NMRs, even though peaks were often broad.

Hii and co-workers demonstrated that the complex [(SPhos)PhPdCl], similar to our oxidative addition complexes [(XPhos)ArPdBr], could be observed by ^{31}P NMR as mixture of solvates or dimers depending on the solvent that was used for the NMR.[97] The ^{31}P NMR of the oxidative addition complex **315** showed a broad resonance around 27.7 ppm at 25 °C (Figure 12). This signal sharpened at lower temperature (–20 °C) into two peaks observed at 28.1 and 29.7 ppm in a 1: 0.1 ratio (Figure 13).

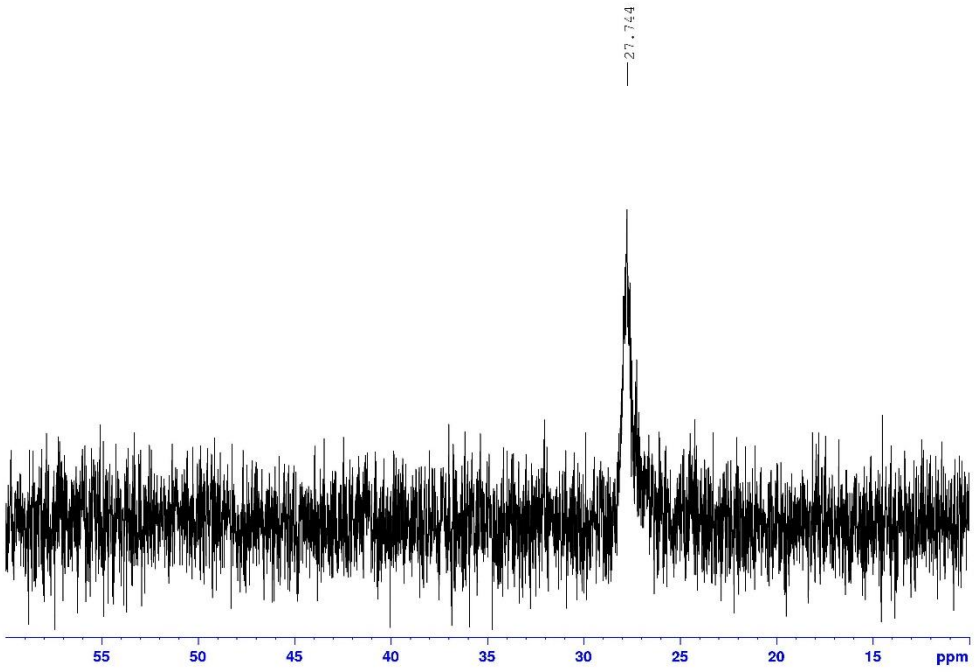


*Figure 12: ^{31}P NMR of complex **315** in CD_3CN at 25 °C.*

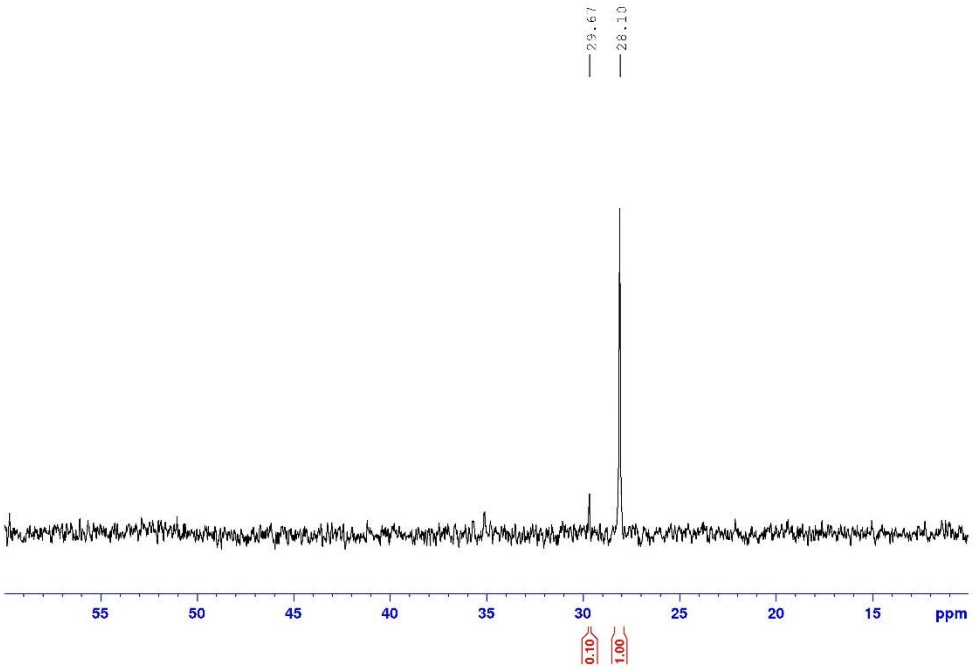


*Figure 13: ^{31}P NMR of complex **315** in CD_3CN at –20 °C.*

In agreement with the previous work reported by Hii and co-workers, these two peaks were attributed as being the *cis* and *trans* isomers of an acetonitrile solvate of complex **315**, the dimer being too insoluble to be observed (Figure 14). On the other hand, the dimer was soluble in $CDCl_3$ and was observed at 57.6 ppm in addition to the two solvates in the following ratio: dimer/*cis*/*trans* = 0.26: 0.02: 1 (Figure 15).

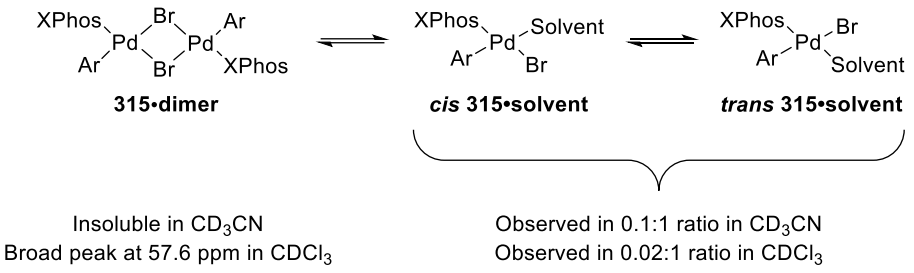


Figure 14: Proposed explanation for the ^{31}P NMR experiments. Ar = 4-CF_3-C_6H_4.

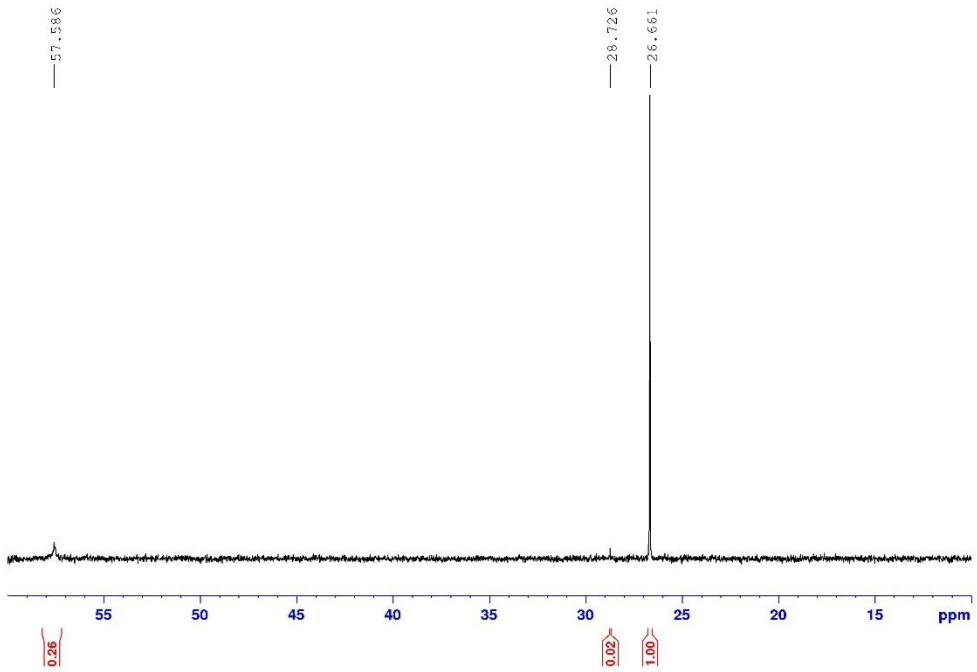


*Figure 15: ^{31}P NMR of complex **315** in $CDCl_3$ at 25 °C.*

The reaction towards the formation of **274** was also carried out in a J-Young NMR tube in CD_3CN under dilute conditions to improve solubilisation of species and

obtain better shimming. After 3 hours, two broad peaks at 27.2 ppm and 55.6 ppm were observed by ^{31}P NMR in a 1: 0.8 ratio which we attributed to the dimer of complex **313** and the solvate **313•MeCN**, respectively (Figure 16 and Scheme 96). Alongside, two other sharper peaks were observed corresponding to the excess of ligand XPhos (-12.3 ppm) and its oxide (43.8 ppm).

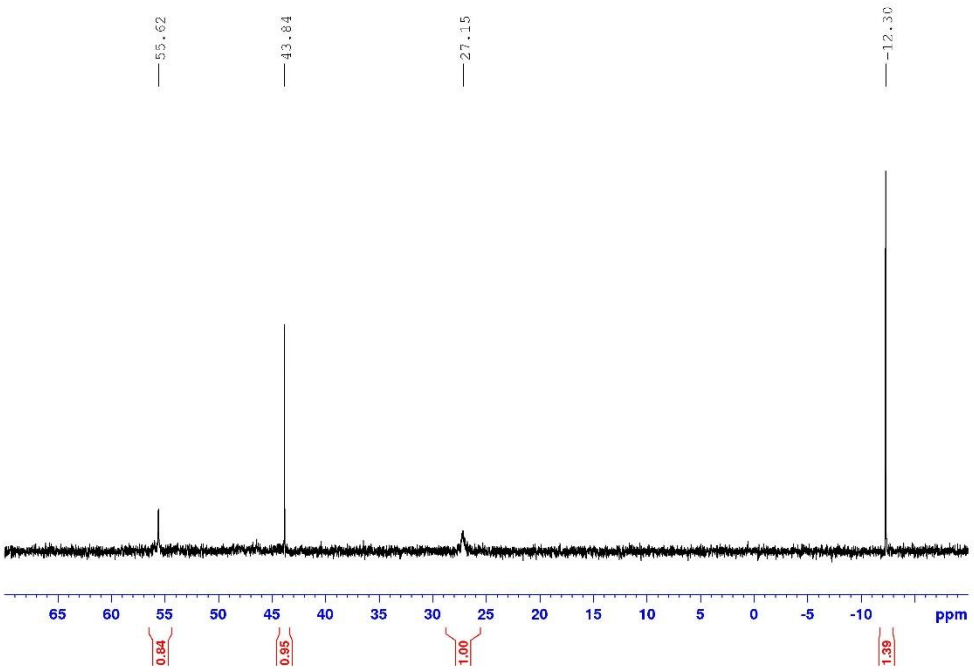
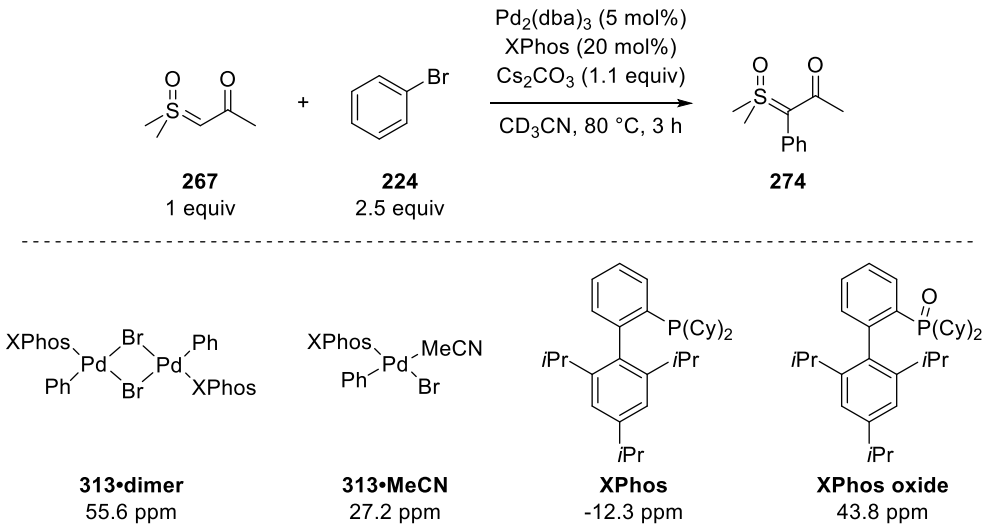


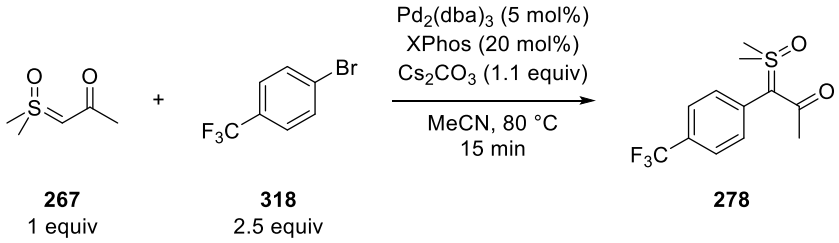
Figure 16: In situ ^{31}*P NMR of the reaction towards the formation of* ***274*** *at 25 °C.*



Scheme 96: Species observed by ^{31}P NMR in situ *monitoring of the reaction leading to **274**.*

4.5.2 By mass spectrometry

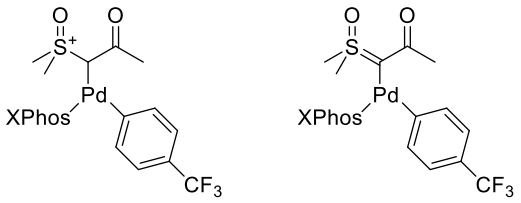
Attempts of isolation of the transmetalation intermediate were unfortunately unsuccessful. The supernatant of the reaction depicted in Scheme 97 was then subjected to mass spectrometry (ESI, direct injection). Due to extensive fragmentation and ligands scrambling in the instrument, not all the mass ions could be assigned.[97]



Scheme 97: Reaction studied by mass spectrometry.

Alongside the expected masses corresponding to the product **278** (279 m/z), XPhos (477 m/z) and XPhos oxide (493 m/z), the mass corresponding to the oxidative addition complex [**315** – Br]$^+$ (727 m/z) was obtained with the expected isotope distribution (Figure 18). More importantly, a mass corresponding to compound [**319**]$^+$

or compound [**320** + H]$^+$ was detected which could correspond either to the transmetalation intermediate or the ion of the intermediate post-deprotonation with the expected isotope distribution (Figure 17). This was an important result as neither of these two complexes could be isolated.



319 **320**

Figure 17: Possible structure for the transmetalation or deprotonation intermediates detected by mass spectrometry.

The result obtained in this part reinforced the hypothesis of an equilibrium between an active catalyst and its inactive dimer, notably with our observations by ^{31}P NMR. The accumulation of this oxidative addition complex observed by ^{31}P NMR in the catalytic experiment suggested that this complex was the turnover frequency determining intermediate (TDI) of the reaction. Finally, although the transmetalation intermediate could not be isolated, it has been detected by mass spectrometry.

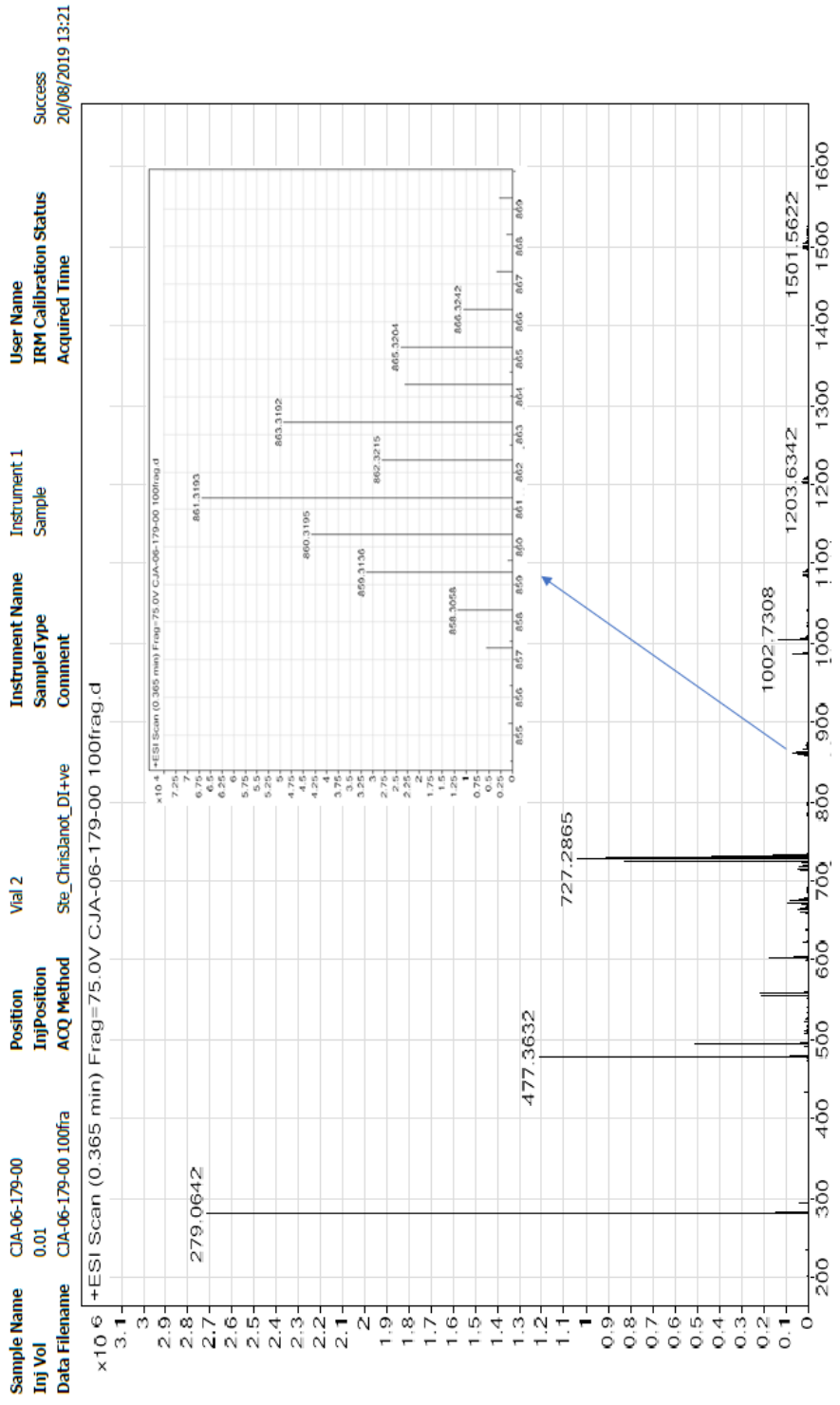
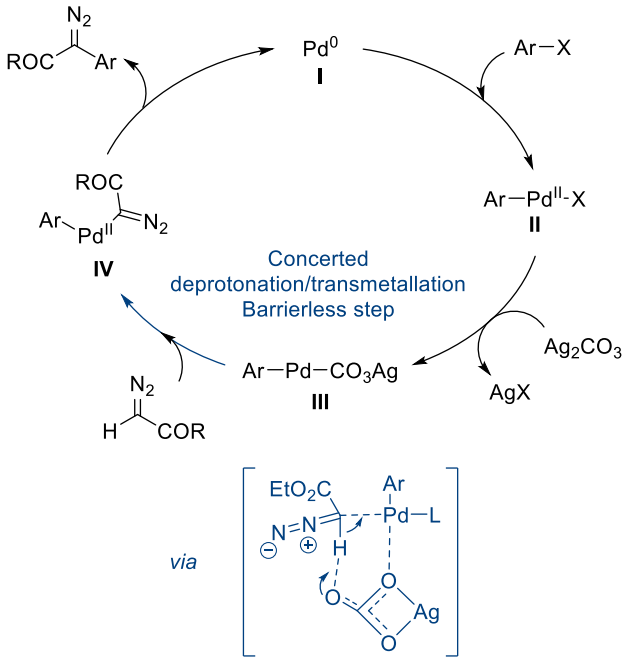


*Figure 18: Mass spectrum of the reaction leading to the formation of compound **278**.*

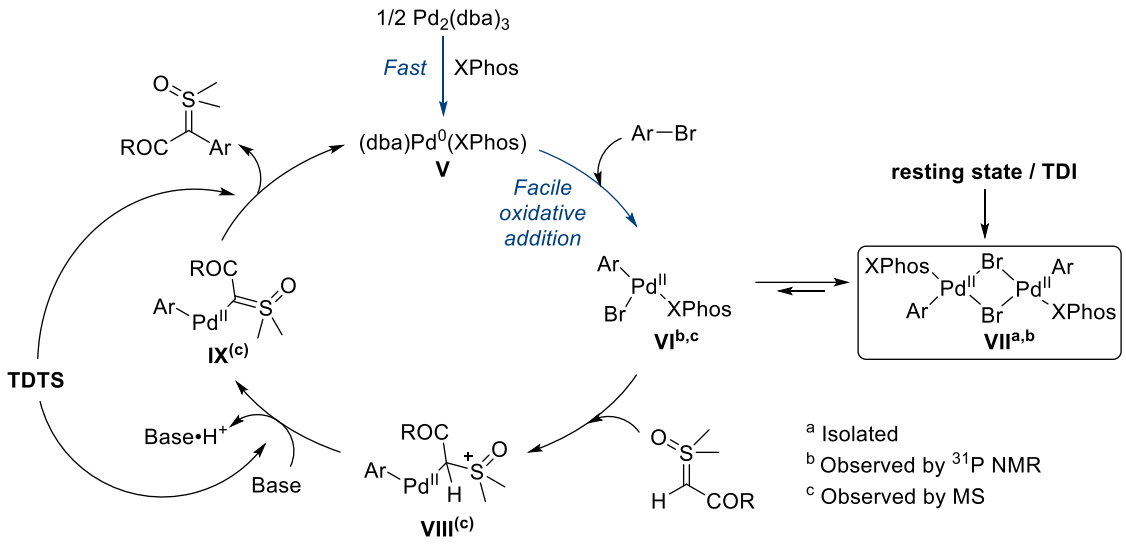
4.6 Conclusions on the study of the mechanism and plausible mechanism

In this section 4, data on the mechanism of the reaction has been gathered and present significant differences as compared to when this reaction is carried out with diazo compounds.[71] Indeed, DFT studies carried out by Wang and co-workers showed that the cross coupling of diazo compounds with aryl halides occurs *via* oxidative addition on the palladium complex **I** to generate the palladium intermediate **II** which would then react with Ag_2CO_3 generating the intermediate **III** (Scheme 98). Upon reaction with the diazo compound, the later would undergo concerted transmetalation/deprotonation with a virtually non-existent energy barrier (0.2 kcal/mol) to obtain the intermediate **IV** which would produce the desired cross-coupling product and regenerate the active catalyst species after reductive elimination.



Scheme 98: Reaction mechanism for the coupling of aryl halides with diazo compounds. Ligands omitted for clarity.

In contrast, it appeared that the coupling with sulfoxonium ylides occurred *via* the fast generation of the active species **V** from $Pd_2(dba)_3$ and XPhos (Scheme 99). A facile oxidative addition, generating **VI**, would follow as it has notably been shown by the zeroth order in aryl bromide. This active intermediate would be in equilibrium with its inactive dimer **VII** that has been characterised by single crystal X-ray diffraction. These two complexes have been observed in the reaction mixture by ^{31}P NMR and the half order in catalyst indicated that the equilibrium is strongly displaced toward the dimer **VII**. This intermediate would be the turnover frequency determining intermediate (TDI) as the accumulation of that complex is observed notably by ^{31}P NMR. Complex **VI** would then undergo transmetalation followed by deprotonation to form **VIII** and **IX**, respectively. Those two steps would occur in a non-concerted fashion as shown by the different values obtained for the slopes of the linear regression of the Lineweather-Burk plots for the concentration of sulfoxonium ylides and base. The presence of these intermediates has been proven by mass spectrometry but it cannot be determined whether **VIII** or **IX** was observed because of their identical mass after ionisation. The partial orders in sulfoxonium ylides and base suggest that these two complexes are in the rate determining zone of the reaction. It still remains unclear whether the turnover frequency determining transition state (TDTS) is before or after the reductive elimination.



Scheme 99: Reaction mechanism for the coupling of aryl halides with sulfoxonium ylides.

The V-shaped Hammett plot could be due to different transition states for the transmetalation or deprotonation depending on the electronegativity of the substituent on the aryl bromide as the two steps are in the rate determining zone of the reaction.

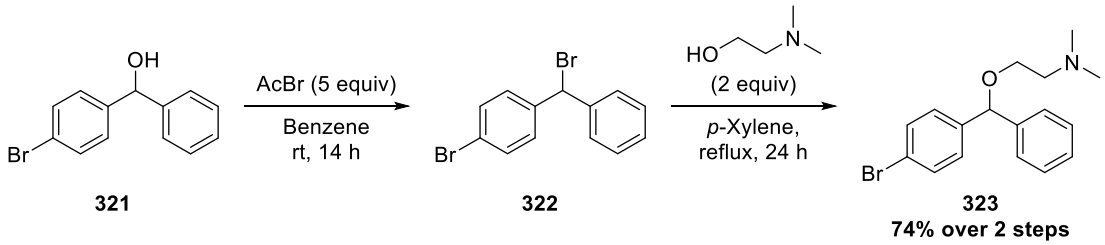
4.7 Refinement of the conditions

The zeroth order in XPhos and aryl bromides observed during the study of the mechanism indicated that the excess of these reagents used for the study of the scope should not be necessary for the reaction to proceed. Although these excesses can appear insignificant on small scale reactions with cheap, commercially available starting material, they become more important on larger scale with active pharmaceutical ingredients.

5 Post-functionalisation

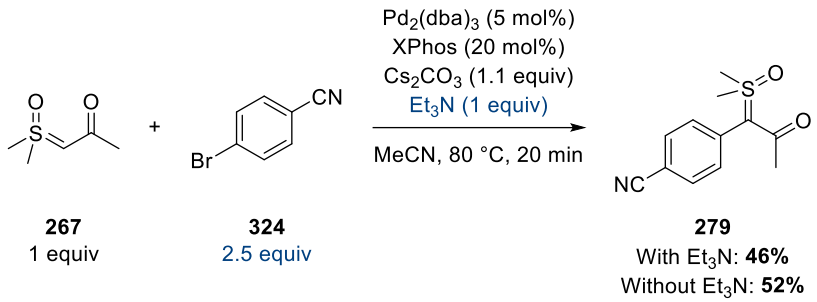
5.1 Late stage functionalisation of bromazine

Bromazine is an antihistamine drug that can be synthesised in two steps from 4-bromobenzhydrol **321**.[100] The first step is a bromination of the carbon bearing the alcohol providing **322** which can be used as a crude for the nucleophilic substitution with 2-dimethylaminoethanol affording the bromazine **323** in 74% yield other the two steps (Scheme 100).



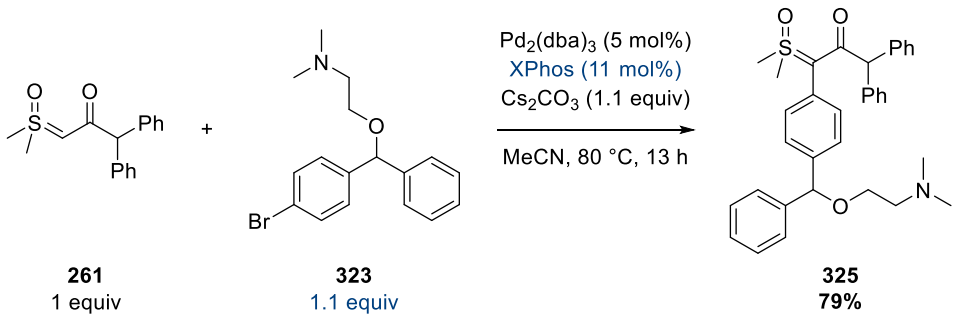
Scheme 100: Synthesis of bromazine.

Although, as seen during the study of the scope, the coupling reaction appeared to be tolerant with protected amines in the sulfoxonium ylide moiety, the tolerance towards non-bulky tertiary amine on the electrophile as the one from bromazine has not been tested. A quick test reaction was then realised by adding triethylamine to the reaction between **267** and 4-bromobenzonitrile to ensure that the reactivity was maintained before doing the reaction with the more valuable bromazine (Scheme 101). Yields of **46%** and **52%** were obtained after 20 minutes for the reactions with and without triethylamine, respectively, indicating that the amine should not prevent the reactivity.



Scheme 101: Test reaction with and without an equivalent of triethylamine. ^{1}H NMR yield using 1,3,5-trimethoxybenzene as internal standard.

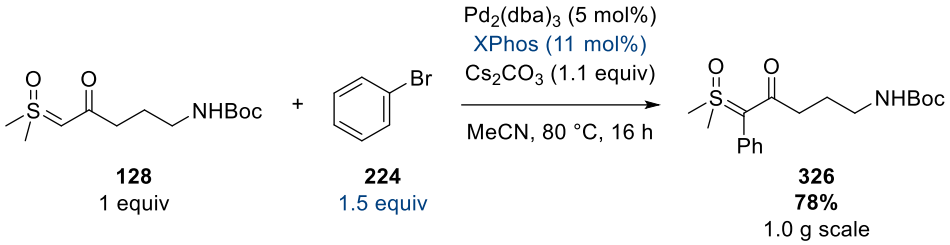
The bromazine **323** was then coupled to the sulfoxonium ylide **261** affording **325** in 79% yield using 1.1 equivalents of **323** and 11% of XPhos.



Scheme 102: Palladium catalysed coupling with bromazine using refined conditions.

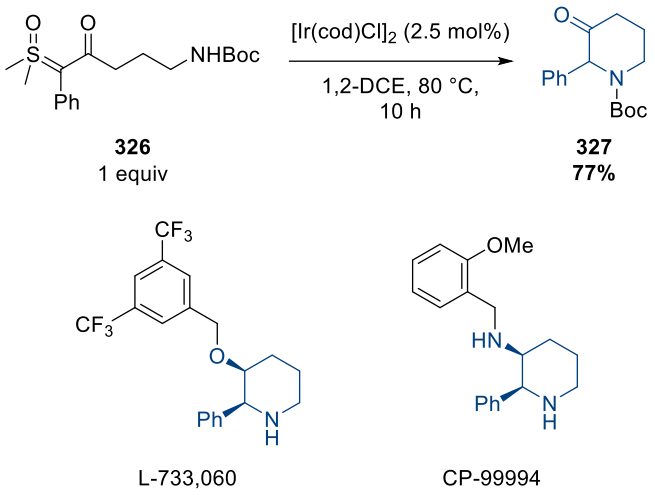
5.2 Gram-scale synthesis of a drug precursor

To demonstrate the scalability of the reaction, compound **326** was synthesised from the coupling of **128** and bromobenzene on a gram scale (Scheme 103). A yield of 78% could be obtained using 1.5 equivalents of bromobenzene. Using less than 1.5 equivalents resulted in lower conversion and separation issues between the starting material **128** and the product. This suggested that more demanding reaction still required a slight excess of reagent to reach full conversion.



*Scheme 103: Gram scale synthesis of compound **326**.*

The compound was then subjected to iridium catalysed intramolecular N–H insertion providing the pyrrolidinone **327** in 77% yield (Scheme 104). This compound is a common precursor of L-733,060 and CP-99994, two NK1-receptor antagonist with applications for the regulation of immune response, blocking of pain transmission and inhibition of neurogenic inflammation.[101]



Scheme 104: Iridium-catalysed intramolecular N–H insertion and structure of two NK1 receptor antagonists.

6 Conclusion

The palladium catalysed cross-coupling of α-ester sulfoxonium ylides with aryl halide has been expanded to the α-keto derivatives by means of a slight change of reaction conditions. The coupling was successful with an array of sulfoxonium ylides including primary and secondary alkyl derivatives as well as electron-poor and electron-rich (hetero-)aryl derivatives. The α-formyl sulfoxonium ylide also gave very good yields. α-keto sulfoxonium ylides appeared to be more tolerant than the α-ester derivatives towards electron-rich electrophiles although lower yields as compared to the electron neutral or electron poor electrophiles were still obtained. Good functional group tolerance was still observed for electron poor electrophiles and two examples of coupling with triflates were successfully demonstrated.

Several limitations remained. Notably, the coupling of the bulky adamantyl and very electron-poor sulfoxonium ylides were unsuccessful. Moreover, heteroaryl electrophiles were not as well tolerated as for the α-ester derivatives. The same was true for the *ortho*-substituted electrophiles when not coupled with the α-formyl sulfoxonium ylide.

The study of the mechanism taught us that the reaction was proceeding through a fast oxidative addition leading to the turnover frequency determining intermediate. This complex was in equilibrium with an inactive dimer that was characterised by single X-Ray diffraction. The active monomer could then undergo transmetalation with the sulfoxonium ylide followed by deprotonation. It was demonstrated that these last two steps were part of the rate determining zone of the reaction notably *via* the study of the rate law. Reductive elimination would then follow, liberating the desired product and regenerating the active catalyst species. It remains

unclear whether this last step is part of the rate determining zone. This could be answered with DFT calculations.

Using the information obtained from the study of the mechanism, refined reaction conditions could be obtained decreasing the excess of electrophile and ligands used in the reaction. These conditions were used in the late-stage functionalisation of the API bromazine. Gram scale reaction was also carried out using a decreased amount of ligand and electrophiles in good yield. The product of that reaction could undergo iridium-catalysed cyclisation yielding a common precursor to 733,060 and CP-99994, two NK1-receptor antagonists.

Conclusion and future work

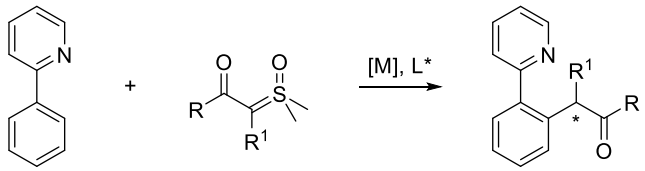
Conclusion and future work

Much work has been achieved recently towards the use of stabilised sulfoxonium ylides has safer carbene precursors, notably for the formation and functionalisation of a variety of heterocycles. However, very little work has been done using the disubstituted sulfoxonium ylides which could be explained by the lack of general method to access these reagents. Furthermore, the chemistry of stabilised sulfoxonium ylides with palladium catalysts remains underexplored, with only one report by Jiang and co-workers. Inspired by the palladium chemistry with diazo compound, the coupling of aryl halide with sulfoxonium ylides was developed.

Chapter 2 highlighted the development of the C–H functionalisation of α-ester sulfoxonium ylides. After several screenings of conditions including the modification of the catalyst system, base, solvent and modification of the stoichiometry, three different catalytic systems could be obtained. The first one used the very common tetrakis(triphenylphosphine)palladium which proved to be efficient but often required an extra purification step due to the presence of triphenylphosphine oxide that was produced *in situ* from the decomposition of the starting material. This issue was then solved by the use of the commercially available $Pd_2(dba)_3$ in combination with either tri-*tert*-butylphosphine or XPhos. The methods provided disubstituted α-ester sulfoxonium ylides in good to excellent yields with a good array of functional groups on the aryl halide, including active pharmaceutical ingredients. Several leaving groups could also be used as iodine, bromine and triflates. Limitations remained as electron-rich electrophiles and steric hindrance were not well tolerated. The products obtained were further functionalised by carrying out C–N and C–S bond formation to access amino-esters and thioethers.

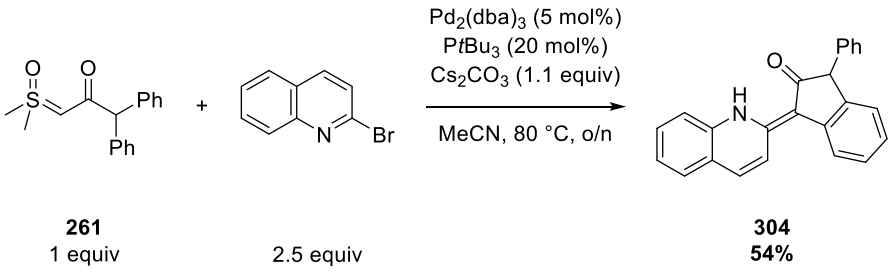
In Chapter 3, the scope was extended to α-keto sulfoxonium ylides after slight modification of the reaction conditions which proved to be essential to ensure facile purification. The reactivity of these compounds appeared to be different as compared to what was observed for the α-ester derivatives. Indeed, electron-rich electrophiles gave better yields in this case but lower reactivity toward heteroaryls and triflates was observed. The reaction was more sensitive to steric hindrance, both on the sulfoxonium ylide and the aryl halide. The study of the mechanism confirmed that the reaction proceeded through an oxidative addition, transmetalation, deprotonation, reductive elimination pathways. The facile oxidative addition leads to a complex in equilibrium with its inactive dimer of which the structure was confirmed by single crystal X-Ray analysis. The non-concerted transmetalation and deprotonation proved to be part of the rate determining zone of the reaction which is in great contrast with the facile, concerted, deprotonation/transmetalation step described in the literature for reaction with the diazo equivalents by Wang and co-workers. Refined conditions were developed using the insights obtained from the study of the mechanism and were used for the coupling with more valuable active pharmaceutical ingredients and gram-scale synthesis.

The future work would include DFT studies to confirm what was observed experimentally and know whether the reductive elimination is part of the rate determining zone or not. It would also be interesting to see how these disubstituted sulfoxonium ylides react in the C–H functionalisation reactions that are described in Chapter 1 (Scheme 105).



Scheme 105: Potential use of sulfoxonium ylides in known C–H bond functionalisation reactions.

Finally, further development of the tandem reaction observed in Chapter 3 (part 3.2.3.2) would be attractive as it leads to the formation of two C-C bonds in one step to build complex molecules (Scheme 106).



*Scheme 106: Tandem reaction leading to compound **304**.*

Chapter 4:

Experimental section

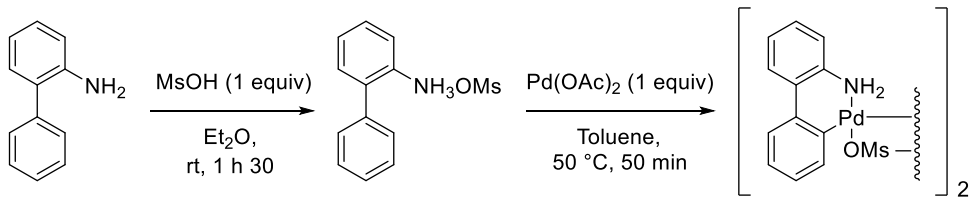
Chapter 4: Experimental section

1 Experimental data for Chapter 2

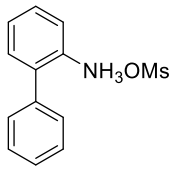
Compound **SI7**, **177**, **SI8**, **178**, **SI10**, **180**, **SI11**, **181** and **202** were synthesised and characterised by Pierre Palamini. He also carried out the reaction leading to **203** with method A.

1.1 Synthesis of catalysts

1.1.1 Buchwald G3 pre-catalyst for *in situ* screening



221 **222** **89%** **223** **87%**

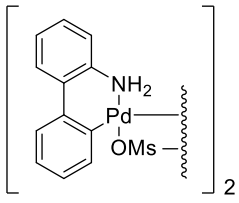


222

Following the literature's procedure,[102] to a round-bottomed flask, under argon atmosphere, 2-aminobiphenyl (2.54 g, 15 mmol, 1 equiv) was dissolved in diethyl ether (50 mL). A solution of methanesulfonic acid (0.97 mL, 15 mmol, 1 equiv) in diethyl ether (7.5 mL) was then added dropwise at room temperature. The reaction was left to stir at room temperature for 1 h 30 min. The residue formed was then filtered, washed with diethyl ether (3×8 mL) and dried under high vacuum to provide

compound **222** which was used in the next step without further purification (3.54 g, 89%, white solid).

^{1}H NMR (500 MHz, CD_3OD): δ 7.64-7.40 (m, 9H), 4.93 (s, 2H), 2.68 (s, 3H) in agreement with previously reported data.[102]

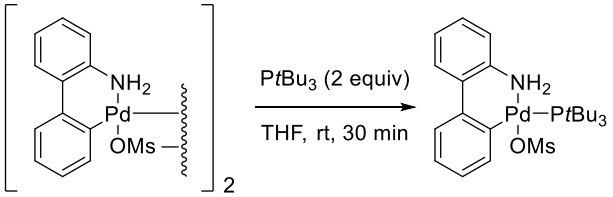


223

To a flame dried J-Young Schlenk tube under argon atmosphere was added palladium acetate (112 mg, 0.5 mmol, 1 equiv) and compound **222** (133 mg, 0.5 mmol, 1 equiv). Three vacuum-nitrogen cycles were performed and toluene (2 mL) was added. The Schlenk tube was sealed, placed in a pre-heated oil bath set at 50 °C and stirred for 50 min. The residue formed was then filtered, washed with toluene (2 mL) and diethyl ether (3×2 mL) and dried under high vacuum to provide compound **223** which was used without further purification (161 mg, 89%, off-white solid).

^{1}H NMR (500 MHz, CD_3CN): δ 7.63-7.61 (m, 1H), 7.49 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.38 (d, *J* = 8.8 Hz, 1H), 7.35-7.26 (m, 2H), 7.24-7.17 (m, 2H), 7.08 (td, *J* = 7.5, 1.6 Hz, 1H), 6.49 (br s, 2H), 2.56 (s, 3H) in agreement with previously reported data.[102]

1.1.2 Buchwald G3 pre-catalyst with P(*t*Bu)$_3$

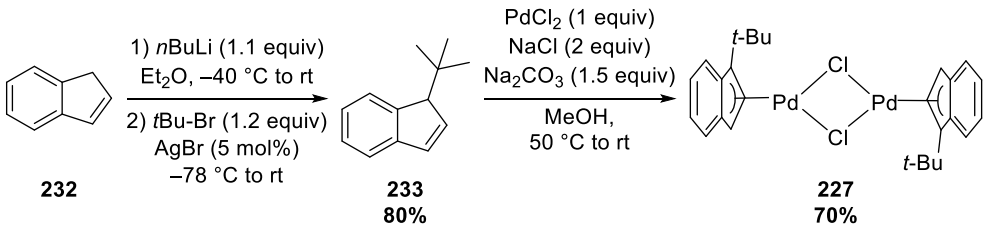


223 **225**
63%

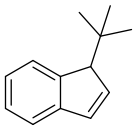
Following the literature's procedure,[102] in an argon-filled glovebox, to a flame dried J-Young Schlenk tube under argon atmosphere was added compound **223** (104 mg, 0.14 mmol, 1 equiv) and tri-*tert*-butylphosphine (57 mg, 0.28 mmol, 2 equiv). The tube was taken out of the glovebox, fitted with a rubber septum, three vacuum-nitrogen cycles were performed and THF (1.5 mL) was added. The reaction was allowed to stir at room temperature for 30 min. About 90% of the THF was removed under vacuum and the crude product was triturated with pentane, filtered and dried under high vacuum to provide compound **225** which was used without further purification (101 mg, 63%, brown solid).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57-7.46 (m, 1H), 7.44-7.39 (m, 2H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.24 (td, *J* = 7.6, 1.4 Hz, 1H), 7.20-7.13 (m, 2H), 7.04 (td, *J* = 7.3, 0.9 Hz, 1H), 6.96 (td, *J* = 7.5, 1.6 Hz, 1H), 4.01-3.94 (m, 1H), 2.82 (s, 3H), 1.29 (d, *J* = 12.5 Hz, 27H) in agreement with previously reported data.[102]

1.1.3 Nova and Hazari's catalyst synthesis



232 **233** **80%** **227** **70%**

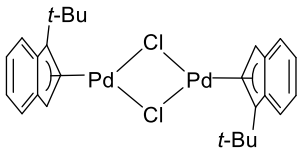


233

Following the literature's procedures,[103,104] to a flame dried J-Young Schlenk tube under N_2 atmosphere was added diethyl ether (20 mL) and the Schlenk tube was cooled to –40 °C (acetonitrile bath with dry ice) and *n*Buli (9.2 mL, 22 mmol, 1.1

equiv, 2.4 M in pentane) was added. Indene (2.3 mL, 20 mmol, 1 equiv) in diethyl ether (5 mL) was then added dropwise at −40 °C *via* a syringe. The reaction was left to stir at −40 °C for 10 min and was then allowed to stir at room temperature for 1 hour. Silver bromide (188 mg, 1 mmol, 0.05 equiv) was then added, the mixture was cooled down to −78 °C and 2-bromo-2-methylpropane (2.7 mL, 24 mmol, 1.2 equiv) was then added dropwise. The reaction was allowed to warm to room temperature and was left to stir for 18 hours. The reaction mixture was then opened to air and the product was extracted with ethyl acetate (40 mL) and washed with a saturated aqueous solution of ammonium chloride. The organic phase was dried with magnesium sulfate and filtered. Evaporation of the volatiles and purification by flash chromatography (100% hexane) afforded **233** (2.56 g, 74%, light yellow oil).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54 (d, *J* = 7.5 Hz, 1H), 7.32 (d, *J* = 7.4 Hz, 1H), 7.24 (t, *J* = 7.5 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 6.82 (dt, *J* = 5.7, 1.5 Hz, 1H), 6.55 (dd, *J* = 6.7, 1.8 Hz, 1H), 3.28 (s, 1H), 1.03 (s, 9H) in agreement with previously reported data.[105]



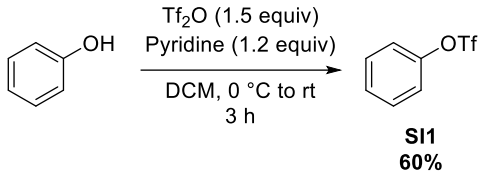
227

Following the literature's procedure,[103] to a flame dried J-Young Schlenk tube under N_2 atmosphere was added palladium dichloride (106 mg, 0.6 mmol, 1 equiv), sodium chloride (70 mg, 1.2 mmol, 2 equiv) and methanol (10 mL). The Schlenk tube was sealed, placed in a pre-heated oil bath set at 50 °C and the reaction was allowed to stir for 30 min. **233** (103 mg, 0.6 mmol, 1 equiv) dissolved in methanol (2 mL) was then added followed by sodium hydrogen carbonate (95 mg, 0.9 mmol, 1.5 equiv). The reaction was allowed to stir at room temperature for 2 hours and was then filtered.

The residue was washed with water and diethyl ether and dried under high vacuum to provide compound **227** which was used without further purification (133 mg, 70%, brown solid).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.17-7.10 (m, 2H), 6.90-6.60 (m, 8H), 5.52 (d, *J* = 2.5 Hz, 2H), 1.32 (s, 18H), in agreement with previously reported data.[103]

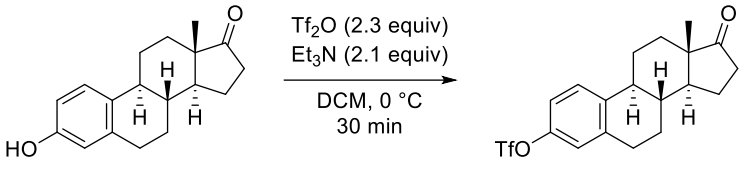
1.2 Synthesis of triflates



SI1
60%

Following the literature's procedure,[106] to a flame-dried round-bottomed flask under N_2 atmosphere was added phenol (1.41 g, 15 mmol, 1 equiv), dichloromethane (50 mL) and pyridine (1.4 mL, 18 mmol, 1.2 equiv). The reaction was cooled to 0 °C and triflic anhydride (3.8 mL, 22.5 mmol, 1.5 equiv) was added over 1 min. The reaction was then allowed to stir at room temperature for 3 hours. Diethyl ether (15 mL) was then added followed by HCl (20 mL, 1 M in water). The phases were separated and the organic layer was washed with a saturated aqueous solution of $NaHCO_3$, dried with magnesium sulfate and filtered. After evaporation of all volatiles, purification by flash chromatography (100% petroleum ether) gave **SI1** (2.04 g, 60**%**, white solid).

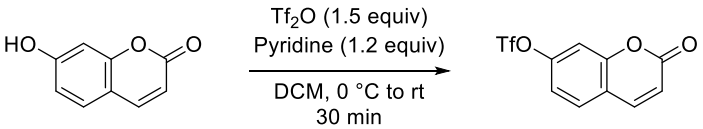
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50-7.43 (m, 2H), 7.42-7.36 (m, 1H), 7.31-7.26 (m, 2H), in agreement with previously reported data.[106]



SI2
71%

Following the literature's procedure,[107] to a flame-dried round-bottomed flask under N_2 atmosphere was added estrone (1.08 g, 4 mmol, 1 equiv) and dichloromethane (40 mL). The reaction was cooled to 0 °C and triethylamine (1.2 mL, 8.4 mmol, 2.1 equiv) was added followed by a dropwise addition of triflic anhydride (1.5 mL, 9.2 mmol, 2.3 equiv). The reaction was then allowed to stir at 0 °C for 30 min. Water (40 mL) was added and the phases were separated. The aqueous layer was extracted with DCM (2×40 mL). The combined organic layers were washed with brine, dried with magnesium sulfate and filtered. After evaporation of all volatiles, purification by flash chromatography (petroleum ether/diethyl ether: 80/20) gave **SI2** (1.14 g, 71**%**, white solid).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (d, *J* = 8.8 Hz, 1H), 7.04 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.00 (d, *J* = 2.7, 1H), 2.94 (dd, *J* = 8.9, 4.2 Hz, 2H), 2.52 (dd, *J* = 19.1, 9.2 Hz, 1H), 2.45-2.36 (m, 1H), 2.30 (td, *J* = 10.6, 4.1 Hz, 1H), 2.22-1.94 (m, 4H), 1.71-1.44 (m, 6H), 0.92 (s, 3H), in agreement with previously reported data.[108]

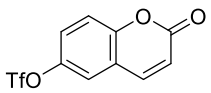


SI3
86%

Following the literature's procedure,[109] to a flame-dried round-bottomed flask under N_2 atmosphere was added 7-hydroxycoumarin (973 mg, 6 mmol, 1 equiv), dichloromethane (15 mL) and pyridine (1.0 mL, 12 mmol, 2 equiv). The reaction was cooled to 0 °C and triflic anhydride (1.2 mL, 7.2 mmol, 1.2 equiv) diluted in

dichloromethane (3 mL) was added dropwise. The reaction was then allowed to warm up to room temperature over 30 min before being quenched with HCl (20 mL, 1 M in water). The phases were separated and the organic layer was washed successively with, water and brine, dried with magnesium sulfate and filtered. After evaporation of all volatiles, purification by flash chromatography (petroleum ether/ethyl acetate: 85/15 to 75/25) gave **SI3** (1.53 g, 86**%**, white solid).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, *J* = 9.5 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.29-7.19 (m, 2H), 6.49 (d, *J* = 9.6 Hz, 1H), in agreement with previously reported data.[110]



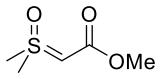
SI4

This compound was obtained from 6-hydroxycoumarin (324 mg, 2 mmol, 1 equiv), following the procedure described for the preparation of **SI3**, after purification by flash chromatography (petroleum ether/ethyl acetate: 90/10 to 80/20) (539 mg, 92%, white solid).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (d, *J* = 9.6 Hz, 1H), 7.46-7.41 (m, 3H), 6.55 (d, J = 9.6 Hz, 1H). *This compound was not fully characterised due to poor results obtained in the palladium-catalysed coupling with aryl halides*.

1.3 Synthesis of the mono-substituted α-ester sulfoxonium ylides

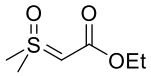
1.3.1 Synthesis from the chloroformates



173

Representative procedure with compound **173**. Under N_2, trimethylsulfoxonium iodide (13.21 g, 60.0 mmol, 3 equiv) was suspended in dry THF (120 mL) in a flame-dried round-bottomed flask that was protected from light with aluminium foil. Potassium *tert*-butoxide (6.73 g, 60.0 mmol, 3 equiv) was added and the mixture was stirred at reflux for 2 hours. After cooling to 0 °C, methyl chloroformate (1.54 mL, 20.0 mmol, 1 equiv) in THF (40 mL) was added dropwise to the mixture *via* a dropping funnel. After stirring at room temperature for 1 hour, the mixture was filtered through a plug of celite (elution dichloromethane). After evaporation of all volatiles, purification by flash chromatography (100% ethyl acetate) gave **173** (2.63 g, 88%, white solid).

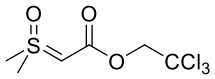
m.p.: 99-102 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 3.93 (s, 1H), 3.58 (s, 3H), 3.35 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 167.5 (hmbc), 55.2 (o), 49.8 (o), 41.8 (o, 2C); **IR** (neat): ν = 3089 (w), 3012 (w), 2926 (w), 1623 (s), 1435 (m), 1344 (m), 1315 (m), 1174 (m), 1137 (s), 1030 (s), 998 (m), 967 (w), 916 (w), 870 (s), 764 (s), 702 (m), 689 (w) cm^{-1}; **HRMS** (ESI) calcd for $(C_5H_{10}O_3S + H)^+$: 151.0423; found: 151.0427.



172

This compound was obtained from ethyl chloroformate (4.8 mL, 50.0 mmol, 1 equiv) following the general procedure described for the preparation of **173** (6.30 g, 77%, white solid) after purification by flash chromatography (100% ethyl acetate).

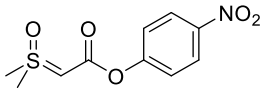
m.p.: 40-43 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.08-3.93 (m, 2H), 3.93-3.77 (m, 1H), 3.31 (s, 6H), 1.15 (t, *J* = 6.4 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 167.3 (hmbc), 58.5 (o), 55.5 (hsqc), 42.1 (o, 2C), 14.7 (o); **IR** (neat): ν = 3020 (w), 2977 (w), 2926 (w), 1618 (s), 1530 (w), 1485 (w), 1454 (w), 1374 (m), 1320 (s), 1300 (s), 1177 (m), 1130 (s), 1060 (w), 1026 (s), 994 (s), 950 (m), 877 (m), 861 (m), 761 (s), 722 (w), 686 (w) cm^{-1}; **HRMS** (ESI) calcd for $(C_6H_{12}O_3S + H)^+$: 165.0580; found: 165.0584.



174

This compound was obtained from 2,2,2-trichloroethyl chloroformate (1.4 mL, 10.0 mmol, 1 equiv) following the general procedure described for the preparation of **173** (1.74 g, 65%, white solid) after purification by recrystallisation (methanol/diethyl ether).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.92-4.62 (m, 2H), 4.18 (s, 1H), 3.43 (s, 6H). *This compound was not fully characterised due to poor results obtained in the palladium-catalysed coupling with aryl halides*.

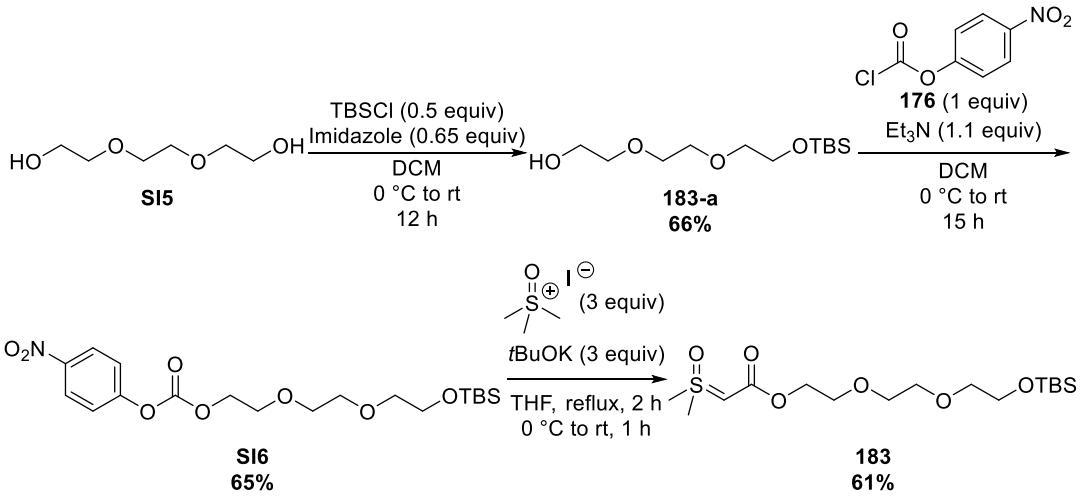


175

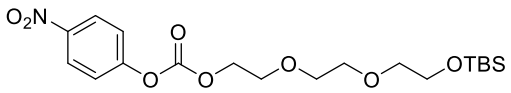
This compound was obtained from 4-nitrophenyl chloroformate (1.86 g, 10.0 mmol, 1 equiv) following the general procedure described for the preparation of **173** (584 mg, 23%, white solid) after purification by flash chromatography (petroleum ether/ethyl acetate: 80/20 to 100% ethyl acetate) and recrystallisation (ethyl acetate/pentane).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.23 (d, *J* = 9.0 Hz, 2H), 7.28 (d, *J* = 9.0 Hz, 2H), 4.24 (s, 1H), 3.46 (s, 6H). *This compound was not fully characterised due to poor results obtained in the palladium-catalysed coupling with aryl halides*.

1.3.2 Synthesis using 4-nitrophenol chloroformate



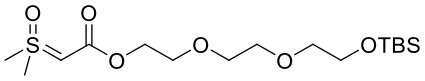
183-a was synthesised following the procedure from Kim et al.[111]



SI6

Representative procedure for the synthesis of **SI6**: Under N_2, 4-nitrophenyl chloroformate (2.02 g, 10.0 mmol, 1 equiv) was dissolved in dichloromethane (30 mL) and triethylamine (1.5 mL, 11 mmol, 1.1 equiv) was added. The reaction mixture was cooled to 0 °C and **183-a** (2.64 g, 10 mmol, 1 equiv) was added dropwise in dichloromethane (10 mL). The reaction was allowed to stir at room temperature overnight. Water was then added and the aqueous layer was extracted twice with dichloromethane. The organic layers were gathered and washed with water and brine and then dried with magnesium sulfate. After filtration, all the volatiles were removed under reduced pressure. Purification by flash chromatography (petroleum ether/ethyl acetate: 95/5 to 80/20) afforded **SI6** with traces of 4-nitrophenol which were removed in the next step (2.78 g, 65%, yellow oil).

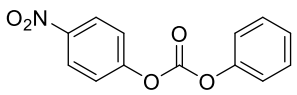
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.28 (dt, *J* = 9.2, 2.1 Hz, 2H), 7.39 (dt, *J* = 9.2, 2.1 Hz, 2H), 4.44 (t, *J* = 4.6 Hz, 1H), 4.44 (dd, J = 6.3, 3.1 Hz, 1H), 3.82 (t, *J* = 4.6 Hz, 1H), 3.82 (dd, *J* = 6.3, 3.1 Hz, 1H), 3.78 (t, *J* = 5.3 Hz, 2H), 3.69 (s, 4H), 3.58 (t, J = 5.3 Hz, 2H), 0.89 (s, 9H), 0.07 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 155.5 (e), 152.5 (e), 145.3 (e), 125.3 (o, 2C), 121.8 (o, 2C), 72.8 (e), 70.8 (e, 2C), 68.7 (e), 68.3 (e), 62.7 (e), 25.9 (o, 3C), 18.4(e), -5.3 (o, 2C); **IR** (neat): ν = 3118 (w), 2928 (w), 2857 (w), 1767 (s), 1616 (w), 1594 (w), 1525 (m), 1493 (w), 1463 (w), 1348 (m), 1339 (m), 1290 (w), 1255 (s), 1214 (s), 1164 (w), 1108 (s), 1066 (m), 1011 (w), 940 (w), 859 (m), 835 (s), 777 (m), 754 (w), 727 (w), 681 (w), 663 cm^{-1}; **HRMS** (ESI) calcd for $(C_{19}H_{31}NO_8Si + Na)^+$: 452.1711; found: 452.1716.



183

Representative procedure for the synthesis of **183**: Under N_2, trimethylsulfoxonium iodide (3.31 g, 15.0 mmol, 3 equiv) was suspended in dry THF (30 mL) in a flame-dried round-bottomed flask that was protected from light with aluminium foil. Potassium *tert*-butoxide (1.68 g, 15 mmol, 3 equiv) was added and the mixture was stirred at reflux for 2 hours. After cooling to 0 °C, **SI6** (2.15 g, 5 mmol, 1 equiv) in THF (10 mL) was added dropwise to the mixture *via* a dropping funnel. After stirring at room temperature for 1 hour, the mixture was filtered through a plug of celite (elution dichloromethane). After evaporation of all volatiles, purification by flash chromatography (dichloromethane/methanol: 98/2 to 95/5) gave **183** (1.13 g, 59%, thick oil).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.21-4.06 (m, 2H), 4.02-3.87 (m, 1H), 3.69 (t, *J* = 5.3 Hz, 2H), 3.65-3.53 (m, 6H), 3.48 (t, *J* = 5.5 Hz, 2H), 3.32 (s, 6H), 0.83 (s, 9H), 0.00 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 72.6 (e), 70.7 (e), 70.4 (e), 69.7 (e), 62.7 (e), 61.8 (e), 55.9 (hmbc), 42.2 (o, 2C), 25.9 (o, 3C), 18.3 (e), -5.3 (o, 2C). The C=O from the ester was not observed, even by HMBC; **IR** (neat): ν = 2928 (m), 2857 (m), 1637 (s), 1462 (w), 1387 (m), 1330 (s), 1251 (m), 1180 (m), 1106 (s), 1029 (s), 940 (m), 835 (s), 777 (m), 759 (m), 723 (w) cm^{-1}; **HRMS** (ESI) calcd for $(C_{16}H_{34}O_6SSi + H)^+$: 383.1928; found: 383.1918.

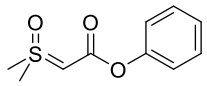


SI7

This compound was obtained from phenol (2.51 g, 39.1 mmol, 1 equiv) following the general procedure described for the preparation of **SI6** (3.38 g, 48%,

white solid) after purification by flash chromatography (petroleum ether/dichloromethane: 50/50).

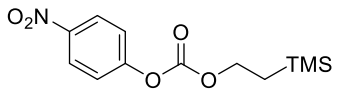
m.p: 127-128 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.28 (d, *J* = 9.0 Hz, 2H), 7.47 (d, *J* = 9.0 Hz, 2H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.33-7.25 (m, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 155.3 (e), 151.1 (e), 150.7 (e), 145.6 (e), 129.8 (o, 2C), 126.8 (o), 125.4 (o, 2C), 121.8 (o, 2C), 120.8 (o, 2C), in agreement with previously reported data.[112]



177

This compound was obtained from **SI7** (2.00 g, 7.7 mmol, 1 equiv) following the general procedure described for the preparation of **183** (569 mg, 34%, pale pink solid) after purification by flash chromatography (petroleum ether/ethyl acetate: 20/80) and recrystallisation (ethyl acetate/pentane).

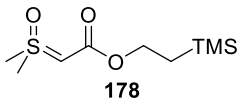
m.p.: 107-109 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.32 (t, *J* = 7.7 Hz, 2H), 7.14 (t, *J* = 7.1 Hz, 1H), 7.08 (d, *J* = 7.5 Hz, 2H), 4.18 (s, 1H), 3.32 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 165.6 (e), 151.4 (e), 129.1 (o, 2C), 124.8 (o), 122.2 (o, 2C), 56.4 (o), 41.8 (o, 2C); **IR** (neat): ν = 3121 (w), 3086 (w), 2449 (w), 2238 (w), 1947 (w), 1765 (s), 1751 (vs), 1656 (w), 1617 (m), 1595 (m), 1522 (vs), 1492 (m), 1460 (m), 1419 (w), 1345 (s), 1257 (vs), 1219 (vs), 1163 (m), 1106 (m), 1096 (m), 1045 (m), 1003 (m), 984 (m), 947 (m), 927 (m), 919 (m), 905 (m), 856 (s), 839 (m), 810 (m), 768 (m), 728 (m), 721 (m), 679 (m), 667 (m) cm^{-1}; **HRMS** (ESI) calcd for $(C_{10}H_{12}O_3S + H)^+$: 213.0588; found: 213.0580.



SI8

This compound was obtained from 2-(trimethylsilyl)ethan-1-ol (3.0 mL, 20.9 mmol, 1 equiv) following the general procedure described for the preparation of **SI6** (3.92 g, 66%, white solid) after purification by flash chromatography (petroleum ether/ethyl acetate: 95/5).

m.p: 37-38 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.27-8.23 (m, 2H), 7.38-34 (m, 2H), 4.37 (m, 2H), 1.14 (m, 2H), 0.07 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 155.7 (e), 152.5 (e), 145.4 (e), 125.3 (o, 2C), 121.9 (o, 2C), 68.3 (e), 17.6 (e), -1.5 (o, 3C); IR (neat): ν = 2958 (w), 1759 (s), 1616 (w), 1595 (w), 1524 (m), 1492 (m), 1469 (w), 1427 (w), 1377 (w), 1347 (m), 1246 (s), 1214 (s), 1177 (m), 1103 (m), 1065 (m), 1009 (w), 932 (m), 835 (vs), 757 9m), 727 9m), 696 (m), 674 (w), 665 (m) cm^{-1}; **Elem. Anal.** Calcd for $C_{12}H_{17}NO_5Si$: C 50.87, H 6.05, N 4.94; found: C 50.86, H 5.97, N 4.86.

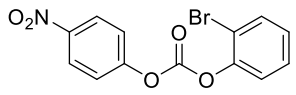


178

This compound was obtained from **SI8** (3.0 mL, 20.9 mmol, 1 equiv) following the general procedure described for the preparation of **183** (500 mg, 24%, white solid).

m.p.: 94-96 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 4.04 (t, *J* = 7.8 Hz, 2H), 3.87 (s, 1H), 3.31 (s, 6H), 0.89 (t, *J* = 7.3 Hz, 2H), -0.05 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 167.5 (hmbc), 60.6 (e), 55.4 (hsqc), 42.2 (o, 2C), 17.7 (e), -1.5 (o, 3C); **IR** (neat): ν = 3022 (w), 2953 (w), 2895 (w), 1626 (s), 1520 (w), 1473 (w), 1411 9w), 1382 (m), 1324 (vs), 1303 (m), 1248 (m), 1178 (m), 1127 (vs), 1045 (m), 1020 (vs), 995 (m),

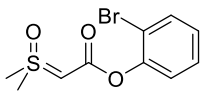
969 (w), 945 (m), 855 (s), 830 (vs), 757 (s), 691 (s) cm^{-1}; **Elem. Anal.** Calcd for $C_9H_{20}O_3SSi$: C 45.85, H 8.68, S 13.78; found: C 45.84, H 8.68, S 13.78.



SI9

This compound was obtained from 2-bromophenol (0.64 mL, 6.0 mmol, 1 equiv) following the general procedure described for the preparation of **SI6** (985 mg, 49%, white solid) after purification by flash chromatography (petroleum ether/ethyl acetate: 95/5 to 92/8).

m.p.: 107-109 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.33 (dt, *J* = 9.2 Hz, 2.1 Hz, 2H), 7.67 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.51 (dt, *J* = 9.2, 2.1 Hz, 2H), 7.41 (td, *J* = 8.2, 1.6 Hz, 1H), 7.33 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.22 (td, *J* = 8.0, 1.6 Hz, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 155.2 (e), 150.1 (e), 147.9 (e), 145.7 (e), 133.7 (o), 128.9 (o), 128.3 (o), 125.4 (o, 2C), 123.0 (o), 121.7 (o, 2C), 115.7 (e); **IR** (neat): ν = 3118 (w), 3080 (w), 2860 (w), 2226 (w), 1922 (w), 1767 (s), 1615 (w), 1615 (w), 1515 (s), 1495 (m), 1475 (m), 1446 (w), 1357 (m), 1325 (w), 1305 (w), 1253 (s), 1243 (s), 1193 (s), 1164 (s), 1110 (m), 1049 (m), 1028 (m), 1006 (m), 941 (w), 891 (m), 855 (s), 842 (m), 796 (w), 777 (w), 757 (w), 746 (s), 728 (w), 697 (m), 676 (m) cm^{-1}; **HRMS** (CI) calcd for $(C_{13}H_8BrNO_5 + H)^+$: 337.9659; found: 337.9667.

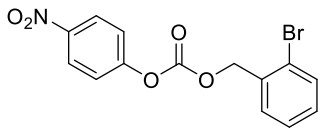


179

This compound was obtained from **SI9** (439 mg, 1.3 mmol, 1 equiv) following the general procedure described for the preparation of **183** (118 mg, 31%, white solid)

after purification by flash chromatography (1st column: dichloromethane/methanol: 98/2 to 95/5; 2nd column: 100% ethyl acetate).

m.p.: 106-108 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.58 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.30 (t, *J* = 7.1 Hz, 1H), 7.18 (d, *J* = 7.8 Hz, 1H), 7.06 (t, *J* = 7.1 Hz, 1H), 4.24 (br s, 1H), 3.44 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 164.5 (e), 148.8 (e), 133.0 (o), 128.2 (o), 126.4 (o), 124.6 (o), 117.1 (e) 55.5 (o), 42.3 (o, 2C); **IR** (neat): ν = 3110 (w), 3076 (w), 3019 (w), 2923 (w), 1651 (s), 1582 (w), 1470 (m), 1447 (w), 1427 (w)m 1408 (w), 1398 (w), 1348 (s), 1257 (m), 1224 (m), 1175 (s), 1112 (s), 1045 (m), 1026 (m), 979 (s), 943 (m), 875 (m)m 852 (m), 821 (w), 781 (w), 753 (m), 740 (m), 729 (m), 686 (m), 653 (w) cm^{-1}; **HRMS** (ESI) calcd for $(C_{10}H_{11}BrO_3S + H)^+$: 290.9685; found: 290.8687.

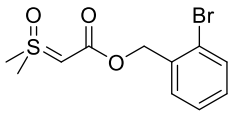


SI10

This compound was obtained from (2-bromophenyl)methanol (1.81 g, 8.1 mmol, 1 equiv) following the general procedure described for the preparation of **SI6** (1.01 g, 39%, white solid) after purification by flash chromatography (petroleum ether/ethyl acetate: 90/10).

m.p.: 93-96 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.28-8.23 (m, 2H), 7.61 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.50 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.42-7.38 (m, 2H), 7.36 (td, *J* = 7.7, 1.1 Hz, 1H), 7.25 (td, *J* = 7.6, 1.5 Hz, 1H), 5.40 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 155.5 (e), 152.3 (e), 145.5 (e), 133.7 (e), 133.1 (o), 130.6 (o), 130.4 (o), 127.8 (o), 125.4 (o, 2C), 123.8 (e), 121.8 (o, 2C), 70.3 (e); **IR** (neat): ν = 3116 (w), 3085 (w), 1752 (s), 1614 (w), 1591 (m), 1517 (s), 1491 (m), 1474 (m), 1454 (m), 1438 (m), 1386 (m), 1343 (s), 1253 (s), 1209 (s), 1167 (s), 1110 (m), 1049 (m), 1031 (m), 974 (m), 955 (m), 944 (m), 861 (vs), 847 (m), 813 (w), 776 (m), 751 (s), 733 (s), 713 (m), 680

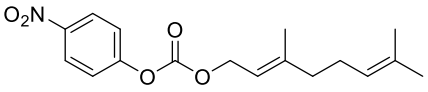
(w), 666 (w), 857 (w) cm^{-1}; **Elem. Anal.** Calcd for $C_{14}H_{10}BrNO_5$: C 47.75, H 2.86; found: C 47.77, H 2.77.



180

This compound was obtained from **SI10** (1.00 g, 8.5 mmol, 1 equiv) following the general procedure described for the preparation of **183** (526 mg, 60%, white solid) after purification by flash chromatography (dichloromethane/methanol: 98/2) and recrystallisation (ethyl acetate/pentane).

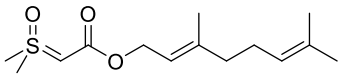
m.p.: 65-68 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.52 (d, *J* = 7.9 Hz, 1H), 7.41 (br s, 1H), 7.28 (t, *J* = 7.3 Hz, 1H), 7.13 (t, *J* = 7.4 Hz, 1H), 5.14 (s, 2H), 4.12 (s, 1H), 3.35 (s, 6 H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 166.8 (e), 136.7 (e), 132.5 (o), 129.1 (o, 2C), 127.4 (o), 122.7 (e), 63.8 (e), 55.7 (o), 41.9 (o, 2C); **IR** (neat): ν = 3095 (w), 3009 (m), 2924 (w), 1632 (s), 1617 (s), 1474 (w), 1439 (w), 1387 (s), 1330 (vs), 1277 (m), 1206 (w), 1172)s), 1134 (s), 1027 (s), 986 (s), 879 (s), 757 (s), 741 (vs), 706 (w), 689 (m), 658 (w) cm^{-1}; **HRMS** (ESI) calcd for $(C_{11}H_{13}BrO_3S + H)^+$: 304.9842; found: 304.9841.



SI11

This compound was obtained from geraniol (4.0 mL, 23.1 mmol, 1 equiv) following the general procedure described for the preparation of **SI6** (4.78 g, 65%, white solid) after purification by flash chromatography (ethyl acetate/methanol: 100/0 to 99/1).

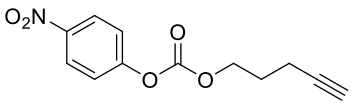
m.p: 36-38 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.26-8.21 (m, 2H), 7.38-7.34 (m, 2H), 5.43 (td, *J* = 7.3, 1.2 Hz, 1H), 5.06 (tt, *J* = 6.7, 1.3 Hz, 1H), 4.78 (d, *J* = 7.4 Hz, 2H), 2.14-2.04 (m, 4H), 1.75 (s, 3H), 1.66 (s, 3H), 1.58 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 155.7 (e), 152.5 (e), 145.3 (e), 144.7 (e), 132.0 (e), 125.3 (o, 2C), 123.6 (o, 2C), 121.8 (o), 116.8 (o), 66.1 (e), 39.6 (e), 26.2 (e), 25.7 (o), 17.7 (o), 16.6 (o); **IR** (neat): ν = 3120 (w), 2971 (w), 2911 (w), 2824 (w), 1750 (vs), 1677 (w), 1616 (w), 1597 (w), 1522 (vs), 1492 (m), 1456 (w), 1440 (w), 1398 (w), 1378 (m), 1348 (m), 1315 (m), 1263 (s), 1221 (vs), 1164 (m), 1120 (m), 1107 (m), 1053 (m), 1037 (m), 1010 (w), 988 (m), 967 (m), 941 (s), 859 (s), 848 (s), 813 (m), 789 (m), 774 (s), 720 (m), 678 (m), 668 (m) cm^{-1}; *This compound was not fully characterised due to poor results obtained in the palladium-catalysed coupling with aryl halides*.



181

This compound was obtained from **SI11** (2.00 g, 6.3 mmol, 1 equiv) following the general procedure described for the preparation of **183** (429 mg, 24%, white solid) after purification by flash chromatography (ethyl acetate/petroleum ether: 90/10) and recrystallisation (ethyl acetate/pentane).

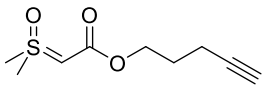
m.p: 46-48 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 5.27 (br s, 1H), 5.01 (t, *J* = 6.0 Hz, 1H), 4.48 (s, 2H), 3.93 (br s, 1H), 3.31 (s, 6H), 2.06-1.99 (m, 2H), 1.99-1.92 (m, 2H), 1.61 (d, *J* = 7.5 Hz, 6H), 1.52 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 167.2 (hmbc), 140.8 (e), 131.5 (e), 123.8 (o), 119.4 (o), 59.5 (e), 55.4 (o), 42.0 (o, 2C), 39.5 (e), 26.2 (o), 25.6 (o), 17.6 (o), 16.3 (o) **IR** (neat): ν = 3090 (w), 3010 (m), 2968 (w), 2922 (m), 1631 (vs), 1523 (w), 1394 (s), 1349 (s), 1312 (vs), 1172 (s), 1140 (vs), 1023 (vs), 976 (m), 875 (vs), 760 (s), 721 (m), 689 (m) cm^{-1}; **HRMS** (ESI) calcd for $(C_{14}H_{24}O_3S + H)^+$: 273.1519; found: 273.1519.



SI12

This compound was obtained from pent-4-yn-1-ol (0.93 mL, 10.0 mmol, 1 equiv) following the general procedure described for the preparation of **SI6** (1.19 g, 48%, pale yellow solid) after purification by flash chromatography (petroleum ether/ethyl acetate: 95/5 to 85/15).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.29 (dt, *J* = 9.2, 2.1 Hz, 2H), 7.39 (dt, *J* = 9.2, 2.1 Hz, 2H), 4.42 (t, *J* = 6.3 Hz, 2H), 2.39 (td, *J* = 6.9, 2.7 Hz, 2H), 2.02 (t, *J* = 2.7 Hz, 1H), 1.99 (quint., *J* = 6.7 Hz, 2H); *This compound was not fully characterised due to poor results obtained in the palladium-catalysed coupling with aryl halides*.

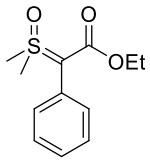


182

This compound was obtained from **SI12** (1.00 g, 4.0 mmol, 1 equiv) following the general procedure described for the preparation of **183** (630 mg, 78%, white solid) after purification by flash chromatography (ethyl acetate/methanol: 100/0 to 99/1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.11 (br s, 2H), 3.93 (br s, 1H), 3.37 (s, 6H), 2.03 (td, *J* = 7.1, 2.5 Hz, 2H), 1.95 (t, *J* = 2.7 Hz, 1H), 1.83 (quint., *J* = 6.6 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 83.5 (e), 68.7 (e), 61.2 (e), 55.0 (HSQC), 42.4 (o, 2C), 28.1 (e), 15.3 (e). The C=O from the ester was not observed, even by HMBC; **HRMS** (ESI) calcd for $(C_9H_{14}O_3S + H)^+$: 203.0741; found: 203.0736. *This compound was not fully characterised due to poor results obtained in the palladium-catalysed coupling with aryl halides*.

1.4 Cross coupling products



188

Method A: Representative procedure with compound **188** (liquid aryl halide): In an argon filled glovebox, a J-Young Schlenk tube was charged with $Pd(PPh_3)_4$ (23 mg, 0.02 mmol, 0.1 equiv) and Cs_2CO_3 (72 mg, 0.22 mmol, 1.1 equiv). The tube was then sealed and taken out of the glovebox. Under N_2, the tube was then charged with **172** (82 mg, 0.50 mmol, 2.5 equiv). Three vacuum-nitrogen cycles were performed and acetonitrile (1 mL) was then added to the reaction mixture. Bromobenzene (21 µL, 0.20 mmol, 1 equiv) was then added and the inner wall of the Schlenk tube was rinsed with acetonitrile (1 mL). The Schlenk tube was sealed, placed in a pre-heated oil bath set at 80 °C and stirred for 15 hours. The crude was then filtered over a plug of silica using a dichloromethane/methanol (85/15) mixture to transfer all the material and for rinsing. After evaporation of all volatiles, purification by flash chromatography (hexane/ethyl acetate: 40/60 to 20/80) and recrystallisation (ethyl acetate/pentane) gave **188** (35 mg, 73%, white solid).

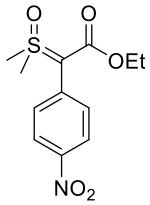
m.p.: 136-138 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.34-7.21 (m, 5H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.42 (s, 6H), 1.19 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 166.3 (e), 133.6 (o, 2C), 132.6 (e), 128.3 (o, 2C), 126.9 (o), 70.3 (e), 58.9 (e), 43.3 (o, 2C), 14.8 (o); **IR** (neat): ν = 3019 (w), 2989 (w), 2918 (w), 1615 (s), 1592 (m), 1492 (w), 1483 (w), 1443 (w), 1392 (w), 1373 (m), 1337 (m), 1323 (m), 1206 (m), 1168 (s), 1116 (w), 1089 (m), 1071 (m), 1044 (s), 1021 (s), 1000 (m), 971 (w), 950 (w), 937

(m), 857 (w), 793 (m), 756 (m), 707 (s), 688 (m), 636 (m) cm^{-1}; **HRMS** (ESI) calcd for $(C_{12}H_{16}O_3S + Na)^+$: 263.0712; found: 263.0710.

This compound can also be obtained using the same starting materials according to **Methods B** and **C** described below.

Method B: In an argon filled glovebox, a J-Young Schlenk tube was charged with P*t*Bu$_3$ (8 mg, 0.04 mmol, 0.2 equiv), Pd_2dba_3 (9 mg, 0.01 mmol, 0.05 equiv) and Cs_2CO_3 (72 mg, 0.22 mmol, 1.1 equiv). The tube was then sealed and taken out of the glovebox. Under N_2, acetonitrile (1 mL) was then added and the mixture was stirred at room temperature for 10 min. Then, bromobenzene (21 µL, 0.20 mmol, 1 equiv) was added followed by **172** (82 mg, 0.50 mmol, 2.5 equiv). The inner wall of the Schlenk tube was rinsed with acetonitrile (1 mL) and the tube was then sealed, placed in a pre-heated oil bath set at 80 °C and stirred for 15 hours. The crude was then filtered over a plug of celite using a dichloromethane/methanol (85/15) mixture to transfer all the material and for rinsing. After evaporation of all volatiles, purification by flash chromatography (hexane/ethyl acetate: 40/60 to 20/80) gave **188** (38 mg, 80%, white solid).

Method C: This method is identical to Method B, except that P(*t*Bu$_3$)$_2$ was replaced with XPhos (19 mg, 0.04 mmol, 0.2 equiv) and that all operations were performed out of the glove box under N_2 by using standard Schlenk technique. This method afforded **188** as white solid (44 mg, 92%).



190

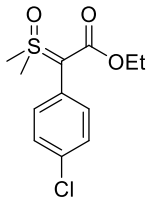
Method A: Representative procedure with compound **190** (solid aryl halide): In an argon filled glovebox, a J-Young Schlenk tube was charged with $Pd(PPh_3)_4$ (23 mg, 0.02 mmol, 0.1 equiv) and Cs_2CO_3 (72 mg, 0.22 mmol, 1.1 equiv). The tube was then sealed and taken out of the glovebox. Under N_2, the tube was then charged with **172** (82 mg, 0.50 mmol, 2.5 equiv) and 1-bromo-4-nitrobenzene (40 mg, 0.2 mmol, 1 equiv). Three vacuum-nitrogen cycles were performed and acetonitrile was then added to the reaction mixture (2 mL). The Schlenk tube was then sealed, placed in a pre-heated oil bath set at 80 °C and stirred for 15 hours. The crude was then filtered over a plug of silica at room temperature using a dichloromethane/methanol (85/15) mixture to transfer all the material and for rinsing. After evaporation of all volatiles, purification by flash chromatography (hexane/ethyl acetate: 40/60 to 20/80) and recrystallisation with the minimal amount of hot ethyl acetate/pentane gave **190** (42 mg, 74%, yellowish green solid).

m.p.: 160-161 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.12 (dt, *J* = 9.0, 2.0 Hz, 2H), 7.47 (dt, *J* = 9.0, 2.1 Hz, 2H), 4.15 (q, *J* = 7.0 Hz, 2H), 3.54 (s, 6H), 1.25 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 165.3 (e), 144.9 (e), 140.2 (e), 131.6 (o, 2C), 123.0 (o, 2C), 68.5 (e), 59.4 (e), 44.2 (o, 2C), 14.6 (o); **IR** (neat): ν = 3031 (w), 3000 (w), 2924 (w), 1617 (s), 1586 (s), 1508 (s), 1492 (m), 1483 (m), 1396 (w), 1372 (m), 1336 (s), 1326 (s), 1215 (s), 1168 (s), 1106 (m), 1084 (s), 1039 (s), 1011 (m), 971 (w), 950 (w), 935 (m), 860 (m), 848 (m), 838 (m), 789 (w), 756 (m), 704 (s), 683 (m), 629 (w) cm^{-1}; **HRMS** (ESI) calcd for $(C_{12}H_{15}NO_5S + Na)^+$: 308.0563; found: 308.0568.

This compound can also be obtained using the same starting materials according to Methods B and C described for compound **188**.

Method B. afforded **190** (54 mg, 95%, yellowish green solid) after purification by flash chromatography (hexane/ethyl acetate: 40/60 to 20/80).

Method C. afforded **190** (51 mg, 89%, yellowish green solid) after purification by flash chromatography (hexane/ethyl acetate: 40/60 to 20/80).



191

This compound was obtained from **172** (82 mg, 0.5 mmol, 2.5 equiv) and 1-bromo-4-chlorobenzene (38 mg, 0.2 mmol, 1 equiv) following:

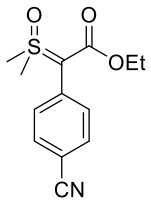
Method A for the preparation of **190** (45 mg, 81%, beige solid) after purification by flash chromatography (hexane/ethyl acetate: 40/60 to 20/80).

Method B (43 mg, 78%, beige solid) after purification by flash chromatography (hexane/ethyl acetate: 50/50 to 20/80).

Method C (52 mg, 95%, beige solid) after purification by flash chromatography (hexane/ethyl acetate: 50/50 to 20/80).

m.p.: 136-139 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.30-7.21 (m, 4H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.43 (s, 6H), 1.19 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 166.1 (hmbc), 134.6 (o, 2C), 132.6 (e), 131.0 (e), 128.4 (o, 2C), 68.6 (hmbc), 59.0 (e), 43.4 (o, 2C), 14.8 (o); **IR** (neat): ν = 3024 (w), 2995 (w), 2921 (w), 1613 (s), 1587 (m), 1494 (m), 1478 (m), 1456 (w), 1393 (w), 1373 (m), 1339 (m), 1326 (m), 1305 (w),

1208 (m), 1182 (m), 1166 (s), 1083 (s), 1060 (m), 1040 (s), 1012 (m), 970 (m), 952 (w), 934 (m), 839 (s), 815 (w), 785 (w), 755 (m), 720 (m), 687 (m) cm^{-1}; **HRMS** (ESI) calcd for $(C_{12}H_{15}ClO_3S + Na)^+$: 297.0323; found: 297.0323.

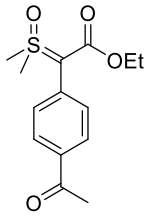


192

This compound was obtained from **172** (82 mg, 0.2 mmol, 2.5 equiv) and 4-bromobenzonitrile (36 mg, 0.2 mmol, 1 equiv) following:

Method A for the preparation of **190** (48 mg, 90%, white solid) after purification by flash chromatography (hexane/ethyl acetate: 50/50 to 20/80).

m.p.: 143-145 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.54 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.3 Hz, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 3.50 (s, 6H), 1.22 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 165.3 (e), 137.8 (e), 132.2 (o, 2C), 131.4 (o, 2C), 119.3 (e), 108.5 (e), 68.4 (hmbc), 59.2 (e), 44.0 (o, 2C), 14.6 (o); **IR** (neat): ν = 2980 (m), 2926 (m), 2219 (m), 1620 (s), 1595 (s), 1501 (m), 1483 (w), 1436 (w), 1395 (m), 1368 (s), 1338 (s), 1326 (m), 1303 (w), 1214 (s), 1181 (s), 1164 (s), 1110 (w), 1082 (s), 1040 (s), 968 (w), 632 (m), 842 (s), 795 (w), 755 (m), 725 (m), 688 (m) cm^{-1}. **HRMS** (ESI) calcd for $(C_{13}H_{15}NO_3S + Na)^+$: 288.0665; found: 288.0670.



193

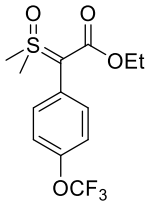
This compound was obtained from **172** (82 mg, 0.5 mmol, 2.5 equiv) and 4'-bromoacetophenone (40 mg, 0.2 mmol, 1 equiv) following:

Method A for the preparation of **190** (44 mg, 77%, white solid) after purification by flash chromatography (hexane/ethyl acetate: 30/70 to 20/80) and recrystallisation (ethyl acetate/pentane).

Method B (48 mg, 85%, white solid) after purification by flash chromatography (hexane/ethyl acetate: 50/50 to 20/80).

Method C (49 mg, 86%, white solid) after purification by flash chromatography (hexane/ethyl acetate: 50/50 to 20/80).

m.p.: 98-102 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.1 Hz, 2H), 7.41 (d, *J* = 8.2 Hz, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.49 (s, 6H), 2.58 (s, 3H), 1.21 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 197.7 (e), 165.7 (e), 138.2 (e), 134.5 (e), 132.2 (o, 2C), 128.1 (o, 2C), 69.4 (HMBC), 59.1 (e), 43.8 (e, 2C), 26.5 (e), 14.7 (e); **IR** (neat): ν = 2997 (w), 2920 (w), 1675 (m), 1615 (s), 1592 (s), 1556 (w), 1513 (w), 1479 (w), 1431 (w), 1395 (w), 1373 (m), 1338 (m), 1324 (m), 1264 (m), 1213 (s), 1169 (s), 1086 (s), 1075 (m), 1040 (s), 1022 (m), 962 (m), 934 (m), 853 (w), 834 (m), 789 (w), 756 (m), 735 (m), 715 (m), 686 (s), 634 (w) cm^{-1}; **HRMS** (ESI) calcd for $(C_{14}H_{18}O_4S + Na)^+$: 305.0818; found: 305.0825.



194

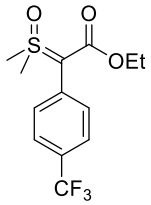
This compound was obtained from **172** (82 mg, 0.5 mmol, 2.5 equiv) and 1-bromo-4-(trifluoromethoxy)benzene (30 μL, 0.2 mmol, 1 equiv) following:

Method A for the preparation of **188** (42 mg, 65%, white solid) after purification by flash chromatography (hexane/ethyl acetate: 50/50 to 20/80) and recrystallisation (ethyl acetate/pentane).

Method B (49 mg, 76%, white solid) after purification by flash chromatography (hexane/ethyl acetate: 35/65 to 25/75).

Method C (59 mg, 91% white solid) after purification by flash chromatography (hexane/ethyl acetate: 50/50 to 25/75).

m.p.: 135-136 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.34-7.29 (m, 2H), 7.13 (d, *J* = 8.1 Hz, 2H), 4.10 (q, *J* = 7.0 Hz, 2H), 3.42 (s, 6H), 1.19 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): 166.0 (e), 147.8 (e), 134.6 (o, 2C), 131.2 (e), 120.5 (e, q, *J* = 257.0 Hz), 120.5 (o, 2C), 68.4 (e), 59.0 (e), 43.5 (o, 2C), 14.7 (o); **^{19}F** (376.5 MHz, $CDCl_3$): δ -57.7; **IR** (neat): ν = 3031 (w), 3000 (w), 2925 (w), 1615 (s), 1598 (m), 1498 (m), 1483 (w), 1398 (w), 1374 (m), 1339 (w), 1327 (w), 1306 (w), 1255 (m), 1201 (s), 1174 (s), 1148 (s), 1086 (s), 1042 (s), 1016 (m), 973 (m), 938 (m), 920 (w), 958 (m), 836 (w) 813 (w), 777 (w), 757 (w), 735 (w) 691 (s), 642 cm^{-1}; **HRMS** (ESI) calcd for $(C_{13}H_{15}F_3O_4S + H)^+$: 325.0716; found: 325.0722.



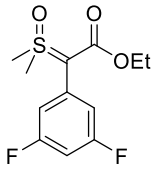
195

This compound was obtained from **172** (82 mg, 0.5 mmol, 2.5 equiv) and 4-bromobenzotrifluoride (28 µL, 0.2 mmol, 1 equiv) following:

Method A for the preparation of **188** (49 mg, 79%, off-white solid) after purification by flash chromatography (hexane/ethyl acetate: 50/50 to 20/80) and recrystallisation (ethyl acetate/pentane).

Method B (61 mg, 98%, off-white solid) after purification by flash chromatography (hexane/ethyl acetate: 50/50 to 20/80).

m.p.: 124-126 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.53 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 8.0 Hz 2H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.46 (s, 6H), 1.20 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 165.6 (e), 136.5 (e), 132.7 (o, 2C), 127.8 (e, q, *J* = 32.1 Hz), 124.8 (o, q, *J* = 3.6 Hz, 2C), 124.3 (e, q, *J* = 271.5 Hz), 68.8 (e), 59.0 (e), 43.6 (o, 2C), 14.6 (o); **^{19}F** (376.5 MHz, $CDCl_3$): δ -62.3; **IR** (neat): ν = 2999 (w), 2924 (w), 1621 (s), 1603 (s), 1515 (w), 1483 (w), 1375 (m), 1340 (m), 1320 (s), 1214 (m), 1192 (m), 1172 (s), 1118 (s), 1088 (s), 1065 (s), 1040 (s), 972 (m), 952 (m), 936 (m), 850 (m), 794 (w), 757 (m), 736 (m), 692 (m), 666 (m), 635 (w), 608 (m) cm^{-1}; **HRMS** (ESI) calcd for $(C_{13}H_{15}F_3O_3S + H)^+$: 309.0767; found: 309.0774.

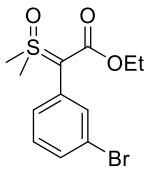


196

This compound was obtained from **172** (82 mg, 0.5 mmol, 2.5 equiv) and 1-bromo-3,5-difluorobenzene (23 μL, 0.2 mmol, 1 equiv) following:

Method A for the preparation of **188** (53 mg, 96%, white solid) after purification by flash chromatography (hexane/ethyl acetate: 50/50 to 20/80).

m.p.: 97-99 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.88-6.81 (m, 2H), 6.64 (td, *J* = 9.0, 2.2, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.46 (s, 6H), 1.21 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 165.5 (e), 163.3 (e, d, *J* = 14.2 Hz,), 161.3 (e, d, *J* = 13.9 Hz), 135.6 (e, t, *J* = 10.8 Hz), 115.3 (o, d, *J* = 5.6 Hz), 115.1 (o, d, *J* = 5.6 Hz), 101.6 (o, t, *J* = 25.4 Hz), 68.5 (hmbc), 59.1 (e), 43.6 (o, 2C), 14.6 (o); **^{19}F** (376.5 MHz, $CDCl_3$): δ -111.4; **IR** (neat): ν = 3071 (w), 3019 (w), 2983 (w), 2934 (w), 1631 (s), 1615 (s), 1587 (s), 1472 (w), 1457 (w), 1426 (m), 1406 (m), 1372 (m), 1347 (w), 1330 (w), 1267 (s), 1215 (w), 1184 (s), 1153 (s), 1120 (s), 1093 (s), 1056 (m), 1024 (s), 981 (m), 930 (s), 859 (w), 829 (w), 759 (m), 727 (w), 694 (s), 678 (s) cm^{-1}. **HRMS** (ESI) calcd for $(C_{12}H_{14}F_2O_3S + H)^+$: 277.0704; found: 277.0713.

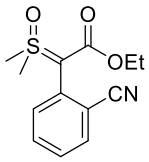


197

This compound was obtained from **172** (82 mg, 0.5 mmol, 2.5 equiv) and 1,3-dibromobenzene (24 μL, 0.2 mmol, 1 equiv) following:

Method A for the preparation of **188** (38 mg, 60%, white solid) after purification by flash chromatography (hexane/ethyl acetate: 40/60 to 20/80) and recrystallisation with ethyl acetate/pentane.

m.p.: 42-45 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.48-7.45 (m, 1H), 7.37-7.32 (m, 1H), 7.23 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.16 (t, *J* = 7.8 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.42 (s, 6H), 1.19 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): 165.9 (e), 136.1 (o), 134.7 (e), 131.8 (o), 129.6 (o), 129.5 (o), 121.9 (e), 69.0 (e), 59.0 (e), 43.5 (o, 2C), 14.7 (o); **IR** (neat): ν = 3029 (w), 2998 (w), 2975 (w), 2924 (w), 2899 (w), 1614 (s), 1584 (m), 1554 (w), 1473 (m), 1404 (w), 1393 (w), 1367 (m), 1337 (m), 1322 (m), 1305 (w), 1293 (w), 1255 (w), 1205 (m), 1177 (s), 1160 (s), 1113 (w), 1095 (m), 1080 (m), 1070 (m), 1041 (s), 994 (w), 979 (w), 941 (m), 909 (w), 861 (w), 798 (m), 781 (m), 755 (m), 705 (s), 680 (m) cm^{-1}; **HRMS** (ESI) calcd for $(C_{12}H_{15}BrO_3S + H)^+$: 318.9998; found: 319.0002.



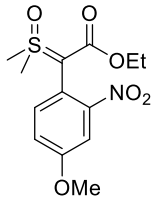
198

This compound was obtained from **172** (82 mg, 0.5 mmol, 2.5 equiv) and 2-bromobenzonitrile (36 mg, 0.2 mmol, 1 equiv) following:

Method A for the preparation of **190** (46 mg, 87%, light yellow thick oil) after purification by flash chromatography (hexane/ethyl acetate: 40/60 to 20/80).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.51 (td, *J* = 7.7, 1.0 Hz, 1H), 7.43 (d, *J* = 7.5Hz, 1H) 7.32 (td, *J* = 7.7, 0.7, 1H), 4.32-3.91 (m, 2H), 3.64 (s, 3H), 3.39 (s, 3H), 1.33-0.98 (m, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 165.7 (e),

136.1 (e), 135.7 (o), 132.7 (o), 132.3 (o), 127.4 (o), 119.4 (e), 117.9 (e), 65.2 (hmbc), 59.1 (e), 44.1 (o), 42.8 (o), 14.7 (o); **IR** (neat): ν = 2981 (w), 2929 (w), 2223 (m), 1619 (s), 1590 (m), 1480 (m), 1444 (m), 1393 (w), 1368 (m), 1327 (m), 1229 (s), 1205 (s), 1185 (s), 1082 (m), 1021 (s), 979 (m), 939 (m), 857 (w), 759 (m), 733 (m), 687 (m), 645 (w) cm^{-1}; **HRMS** (ESI) calcd for $(C_{13}H_{15}NO_3S + H)^+$: 266.0845; found: 266.0844.



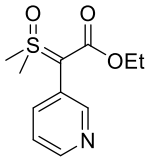
199

This compound was obtained from **172** (82 mg, 0.5 mmol, 2.5 equiv) and 5-bromo-2-nitroanisole (46 mg, 0.2 mmol, 1 equiv) following:

Method A for the preparation of **190** (37 mg, 59%, orange amorphous solid) after purification by flash chromatography (hexane/ethyl acetate: 35/65 to 20/80).

Method B (51 mg, 81%, orange amorphous solid) after purification by flash chromatography (hexane/ethyl acetate: 50/50 to 30/70).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (d, *J* = 8.5 Hz, 1H), 7.30 (d, *J* = 2.8 Hz, 1H), 7.04 (dd, *J* = 8.5, 2.8 Hz, 1H), 4.08-3.98 (m, 1H), 3.94-3.86 (m, 1H), 3.84 (s, 3H), 3.66 (s, 3H), 3.26 (s, 3H), 1.07 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 165.6 (e), 159.1 (e), 152.5 (e), 138.0 (o), 118.0 (o), 117.9 (e), 109.5 (o), 62.2 (e), 58.9 (e), 55.8 (o), 43.6 (o), 40.8 (o), 14.3 (o). **IR** (neat): ν = 2983 (w), 1615 (s), 1561 (w), 1521 (s), 1409 (w), 1366 (s), 1332 (m), 1311 (m), 1291 (m), 1241 (s), 1229 (s), 1200 (s), 1146 (w), 1085 (m), 1020 (s), 976 (s), 943 (m), 858 (m), 804 (m), 759 (m), 729 (w), 688 (m), 670 (w), 642 (w) cm^{-1}; **HRMS** (ESI) calcd for $(C_{13}H_{17}NO_6S + H)^+$: 316.0849; found: 316.0851.

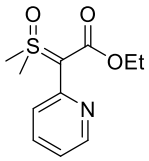


200

This compound was obtained from **172** (82 mg, 0.5 mmol, 2.5 equiv) and 3-bromopyridine (19 μL, 0.2 mmol, 1 equiv) following:

Method A for the preparation of **188** (43 mg, 90%, off-white solid) after purification by flash chromatography (100% ethyl acetate to ethyl acetate/methanol: 90/10).

m.p.: 111-114 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.49 (d, *J* = 1.4 Hz, 1H), 8.38 (dd, *J* = 4.6, 1.0 Hz, 1H), 7.58 (td, *J* = 7.8, 1.9 Hz, 1H), 7.19 (dd, *J* = 7.8, 4.8 Hz, 1H), 4.06 (q, *J* = 7.1 Hz, 2H), 3.43 (s, 6H), 1.15 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 165.9 (e), 153.7 (o), 147.1 (o), 140.1 (o), 128.8 (e), 122.9 (o), 65.8 (e), 59.0 (e), 43.6 (o, 2C), 14.7 (o); **IR** (neat): ν = 3021 (w), 2993 (w), 2920 (w), 1611 (s), 1580 (w), 1515 (w), 1475 (w), 1400 (w), 1369 (m), 1338 (m), 1322 (m), 1215 (m), 1169 (s), 1118 (w), 1088 (s), 1050 (s), 1031 (s), 1022 (s), 972 (m), 935 (m), 823 (w), 782 (w), 756 (m), 719 (s), 691 (m), 666 (w), 616 (w) cm^{-1}; **HRMS** (ESI) calcd for $(C_{11}H_{15}NO_3S + H)^+$: 242.0845; found: 242.0839.

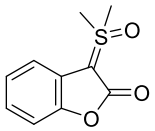


201

This compound was obtained from **172** (82 mg, 0.5 mmol, 2.5 equiv) and 2-bromopyridine (19 μL, 0.2 mmol, 1 equiv) following:

Method A for the preparation of **188** (29 mg, 60%, amorphous solid) after purification by flash chromatography (ethyl acetate/methanol: 97/3 to 93/7).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.47-8.37 (m, 1H), 7.57-7.48 (m, 2H), 6.95-6.90 (m, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.63 (s, 6H), 1.25 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 165.4 (e), 154.8 (e), 147.6 (o), 135.7 (o), 125.1 (o), 118.9 (o), 68.1 (e), 59.2 (e), 44.2 (o, 2c), 14.7 (o); **IR** (neat): ν = 2978 (w), 2926 (w), 1726 (w), 1625 (s), 1585 (s), 1558 (w), 1468 (m), 1430 (w), 1368 (m), 1325 (m), 1286 (w), 1246 (s), 1150 (s), 110 (m), 1077 (m), 1050 (m), 1027 (s), 992 (m), 859 (w), 804 (w), 784 (w), 746 (s), 688 (m), 675 (m), 623 (w) cm^{-1}; **HRMS** (ESI) calcd for $(C_{11}H_{15}NO_3S + Na)^+$: 264.0665; found: 264.0670.



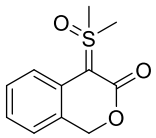
202

This compound was obtained from **179** (58 mg, 0.2 mmol, 1 equiv) following:

Method A but without adding any aryl bromide (19 mg, 46%, off-white solid) after purification by flash chromatography (ethyl acetate/hexane: 80/20) and recrystallisation with ethyl acetate/pentane.

m.p: 129-135 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.23 (d, *J* = 7.1 Hz, 1H), 7.09-6.98 (m, 3H), 3.66 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 163.9 (e), 147.0 (e), 126.1 (e), 123.0 (o), 121.9 (o), 114.8 (o), 109.8 (o), 65.6 (e), 42.0 (o, 2C); **IR** (neat): ν = 3024 (m), 3004 (m), 2918 (m), 1884 (w), 1812 (w), 1694 (s), 1606 (m), 1585 (m), 1468 (m), 1457 (m), 1415 (m), 1394 (m), 1359 (m), 1332 (w), 1293 (vs), 1245 (s), 1199 (s), 1172 (vs), 1096 (w), 1035 (m), 1015 (m), 985 (w), 942 (s), 921 (m), 908 (s), 857 (m),

763 (m), 748 (s), 729 (m), 709 (m), 681 (m) cm^{-1}; **HRMS** (ESI) calcd for $(C_{10}H_{10}O_3S + H)^+$: 233.0243; found: 233.0243.



203

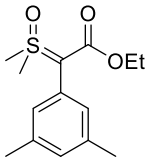
This compound was obtained from **180** (122 mg, 0.4 mmol, 1 equiv) following:

Method A but without adding any aryl bromide (58 mg, 64%, off-white solid) after purification by flash chromatography (ethyl acetate/hexane: 80/20) and recrystallisation with ethyl acetate/pentane.

This compound was obtained from **180** (61 mg, 0.2 mmol, 1 equiv) following:

Method C but without adding any aryl bromide (42 mg, 93%, white solid) after purification by flash chromatography (hexane/ethyl acetate: 30/70 to 0/1).

m.p: 127-134 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.42 (d, *J* = 7.9 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.06 (d, *J* = 7.2 Hz, 1H), 6.94 (t, *J* = 7.3 Hz, 1H), 5.00 (s, 2H), 3.62 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 166.2 (e), 132.4 (e), 128.2 (o), 125.7 (e), 124.6 (o), 122.0 (o), 118.2 (o), 69.1 (e, 2C), 67.3 (e), 43.3 (o); **IR** (neat): ν = 3002 (m), 2921 (w), 1747 (w), 1621 (s), 1598 (s), 1483 (m), 1459 (m), 1411 (m), 1381 (m), 1324 (m), 1309 (m), 1294 (m), 1268 (w), 1248 (m), 1231 (s), 1200 (s), 1121 (m), 1044 (m), 1018 (s), 984 (s), 948 (s), 936 (s), 828 (m), 764 (s), 750 (s), 704 (m), 683 (s) cm^{-1}; **HRMS** (ESI) calcd for $(C_{11}H_{12}O_3S + H)^+$: 247.0399; found: 247.0405.

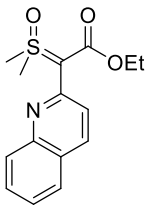


234

This compound was obtained from **172** (82 mg, 0.5 mmol, 2.5 equiv) and 1-bromo-3,5-dimethylbenzene (27 μL, 0.2 mmol, 1 equiv) following:

Method B (41 mg, 76%, amorphous yellow solid) after purification by flash chromatography (hexane/ethyl acetate: 50/50 to 20/80).

^{1}H NMR (500 MHz, $CDCl_3$): δ 6.92 (s, 2H), 6.88 (s, 1H), 4.11 (q, *J* = 7.0 Hz, 2H), 3.38 (s, 6H), 2.29 (s, 6H), 1.20 (t, *J* = 7.1 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 166.4 (e), 137.6 (e, 2C), 132.2 (e), 131.4 (o, 2C), 128.9 (o), 70.5 (e), 58.8 (e), 43.1 (o, 2C), 21.2 (o, 2C), 14.8 (o); **IR** (neat): ν = 2980 (w), 2928 (w), 1736 (w), 1625 (m), 1608 (s), 1596 (s), 1516 (w), 1454 (w), 1420 (w), 1395 (w), 1367 (m), 1336 (w), 1266 (s), 1254 (s), 1184 (s), 1154 (s), 1090 (m), 1072 (m), 1020 (s), 947 (w), 932 (w), 848 (m), 822 (w), 796 (w), 757 (m), 726 (w), 701 (s) cm^{-1}; **HRMS** (ESI) calcd for $(C_{14}H_{20}O_3S + H)^+$: 269.1216; found: 269.1206.

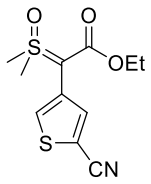


235

This compound was obtained from **172** (82 mg, 0.5 mmol, 2.5 equiv) and 2-bromoquinoline (42 mg, 0.2 mmol, 1 equiv) following:

Method B (55 mg, 95%, amorphous yellow solid) after purification by flash chromatography (hexane/ethyl acetate: 50/50 to 20/80).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.8 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.74 (d, *J* = 8.6 Hz, 1H), 7.69 (d, *J* = 8.1 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 4.22 (q, *J* = 7.0 Hz, 2H), 3.71 (s, 6H), 1.28 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 165.3 (e), 155.5 (e), 146.6 (e), 134.8 (o), 128.9 (o), 127.9 (o), 127.2 (o), 125.2 (e), 124.9 (o), 123.5 (o), 79.3 (e), 59.2 (e), 44.3 (o, 2C), 14.6 (o); **IR** (neat): ν = 2978 (w), 2931 (w), 2246 (w), 1634 (s), 1614 (s), 1594 (s), 1552 (m), 1497 (m), 1459 (m), 1389 (w), 1366 (m), 1342 (m), 1299 (s), 1259 (s), 1236 (s), 1174 (s), 1122 (w), 1075 (s), 1030 (s), 921 (w), 851 (w), 829 (m), 786 (w), 749 (s), 730 (s), 691 (m), 646 (w), 622 (w) cm^{-1}; **HRMS** (ESI) calcd for $(C_{15}H_{17}NO_3S + H)^+$: 292.1002; found: 292.1010.



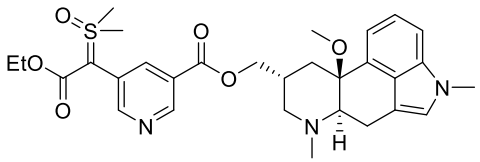
236

This compound was obtained from **172** (82 mg, 0.5 mmol, 2.5 equiv) and 4-bromothiophene-2-carbonitrile (38 mg, 0.2 mmol, 1 equiv) following:

Method B (36 mg, 67%, amorphous brown solid) after purification by flash chromatography (hexane/ethyl acetate: 40/60 to 20/80).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 (s, 1H), 7.35 (s, 1H), 4.11 (q, *J* = 7.2 Hz, 2H), 3.46 (s, 6H), 1.23 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 165.3 (hmbc), 141.1 (o), 132.3 (e), 129.3 (o), 114.6 (e), 108.1 (e), 62.5 (hmbc), 59.3 (e), 43.6 (o, 2C) 14.7 (o); **IR** (neat): ν = 3085 (w), 3025 (w), 3012 (w), 2953 (w), 2930 (w), 2215 (m), 2735 (w), 1630 (s), 1520 (w), 1462 (w), 1420 (w), 1367 (m), 1344 (w), 1326 (w), 1309 (w), 1285 (s), 1192 (s), 1157 (s), 1129 (s), 1095 (m), 1073 (w), 1035 (s), 1020

(s), 987 (m), 879 (m), 852 (w), 829 (m), 799 (w), 757 (m), 730 (w), 690 (s) cm^{-1}; **HRMS** (ESI) calcd for $(C_{11}H_{13}NO_3S_2 + H)^+$: 272.0410; found: 272.0413.

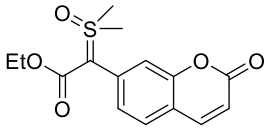


237

This compound was obtained from **172** (41 mg, 0.25 mmol, 2.5 equiv) and nicergoline (48 mg, 0.1 mmol, 1 equiv) following:

Method C (44 mg, 78%, white solid) after purification by flash chromatography (100% acetone to acetone/methanol: 85/15) followed by a second column (dichloromethane/methanol: 90/10).

m.p.: 78-80 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 9.01 (d, *J* = 2.0 Hz, 1H), 8.70 (d, *J* = 2.1 Hz, 1H), 8.21 (t, *J* = 2.1 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.20 (t, *J* = 7.0 Hz, 1H), 7.06 (d, *J* = 6.9 Hz, 1H), 6.80 (s, 1H), 4.38 (dd, *J* = 10.7, 5.0 Hz, 1H), 4.28 (dd, *J* = 10.9, 7.5 Hz, 1H), 4.11 (q, *J* = 7.0 Hz, 2H), 3.77 (s, 3H), 3.51 (s, 6H), 3.30-3.19 (m, 2H), 3.10-2.98 (m, 5H), 2.65 (br s, 1H), 2.56-2.34 (m, 4H), 2.23-2.06 (m, 1H), 1.40 (t, *J* = 13.4 Hz, 1H), 1.20 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$, CPD experiment): δ 165.3, 165.1, 156.6, 147.2, 140.1, 134.8, 129.2, 128.4, 125.9, 125.0, 123.0, 121.1, 114.7, 109.7, 108.7, 73.2, 69.6, 67.5, 63.7, 60.1, 58.9, 49.2, 43.6, 43.4 (2C), 32.5, 31.0, 29.8, 21.9, 14.3; **IR** (neat): ν = 2932 (w), 2781 (w), 2200 (w), 1719 (s), 1615 (s), 1465 (m), 1420 (w), 1367 (m), 1306 (m), 1269 (s), 1221 (s), 1203 (s), 1165 (m), 1102 (w), 1070 (m), 1024 (s), 971 (w), 935 (w), 907 (s), 811 (w), 723 (s), 680 (w) cm^{-1}; **HRMS** (ESI) calcd for $(C_{30}H_{37}N_3O_6S + H)^+$: 568.2476; found: 568.2485.

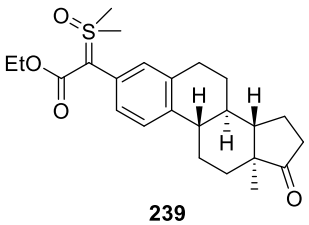


238

This compound was obtained from **172** (82 mg, 0.5 mmol, 2.5 equiv) and **SI3** (59 mg, 0.2 mmol, 1 equiv) following:

Method B (48 mg, 77%, yellowish solid) after purification by flash chromatography (hexane/ethyl acetate: 50/50 to 20/80).

m.p.: 144-147 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.64 (d, *J* = 9.4 Hz, 1H), 7.34 (d, *J* = 8.3 Hz, 1H), 7.28 (s, 1H), 7.23 (d, *J* = 8.2 Hz, 1H), 6.31 (d, *J* = 9.5 Hz, 1H), 4.11 (q, *J* = 7.2 Hz, 2H), 3.50 (s, 6H), 1.20 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 165.5 (e), 161.1 (e), 153.7 (e), 143.3 (o), 137.2 (e), 128.4 (o), 126.8 (o), 119.8 (o), 116.5 (e), 115.4 (o), 69.0 (e), 59.2 (e), 43.9 (o, 2C), 14.7 (o); **IR** (neat): ν = 3049 (w), 3013 (w), 2975 (w), 2928 (w), 1718 (m), 1626 (m), 1598 (s), 1540 (w), 1500 (w), 1461 (w), 1444 (w), 1399 (m), 1367 (w), 1340 (w), 1315 (w), 1293 (m), 1278 (s), 1256 (s), 1227 (m), 1216 (m), 1185 (s), 1164 (m), 1138 (m), 1094 (w), 1066 (m), 1021 (s), 991 (m), 970 (m), 933 (s), 880 (m), 832 (s), 812 (w), 756 (s), 779 (w), 734 (w), 689 (m), 628 (w), 610 (m) cm^{-1}; **HRMS** (ESI) calcd for $(C_{15}H_{16}O_5S + H)^+$: 309.0791; found: 309.0798.

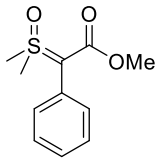


239

This compound was obtained from **172** (82 mg, 0.5 mmol, 2.5 equiv) and **SI2** (81 mg, 0.2 mmol, 1 equiv) following:

Method C (63 mg, 76%, white solid) after purification by flash chromatography (hexane/ethyl acetate: 20/80).

m.p.: 42-45 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.22 (d, *J* = 8.0 Hz, 1H), 7.07 (d, *J* = 7.9 Hz, 1H), 7.04 (s, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.42 (s, 3H), 3.40 (s, 3H), 2.92–2.86 (m, 2H), 2.50 (dd, *J* = 18.9, 9.0 Hz, 1H), 2.45-2.38 (m, 1H), 2.29 (td, *J* = 10.1, 3.7 Hz, 1H), 2.19-1.91 (m, 4H), 1.67-1.38 (m, 6H), 1.21 (t, *J* = 7.1 Hz, 3H), 0.91 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 220.9 (e), 166.4 (e), 138.4 (e), 136.3 (e), 134.0 (o), 131.0 (o), 129.7 (e), 125.3 (o), 69.6 (e), 58.8 (e), 50.6 (o), 48.0 (e), 44.4 (o) 43.4 (o), 43.4 (o), 38.1 (o), 35.9 (e), 31.6 (e), 29.3 (e), 26.6 (e), 25.6 (e), 21.6 (e), 14.9 (o), 13.9 (o); **IR** (neat): ν = 2928 (m), 1733 (s), 1625 (s), 1497 (w), 1453 (w), 1406 (w), 1367 (m), 1321 (m), 1228 (s), 1163 (s), 1082 (m), 1026 (s), 919 (w), 846 (w), 824 (w), 756 (w), 725 (s), 689 (m) cm^{-1}; **HRMS** (ESI) calcd for $(C_{24}H_{32}O_4S + H)^+$: 417.2094; found: 417.2101.

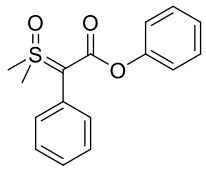


126

This compound was obtained from **173** (75 mg, 0.5 mmol, 2.5 equiv) and bromobenzene (21 μL, 0.2 mmol, 1 equiv) as a white solid following:

Method B after purification by flash chromatography (hexane/ethyl acetate: 35/65 to 20/80) (37 mg, 82%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.25 (m, 5H), 3.61 (s, 3H), 3.42 (s, 6H), in agreement with previously reported data.[45]

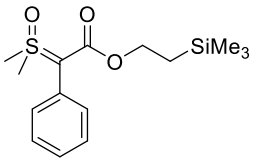


240

This compound was obtained from **177** (106 mg, 0.5 mmol, 2.5 equiv) and bromobenzene (21 µL, 0.2 mmol, 1 equiv) following:

Method B (53 mg, 91%, white solid) after purification by flash chromatography (hexane/ethyl acetate: 1/1 to 100% ethyl acetate).

m.p.: 148-149 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.45 (d, *J* = 7.5 Hz, 2H), 7.37 (t, *J* = 7.3 Hz, 2H), 7.34 – 7.27 (m, 3H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.08 (d, *J* = 7.5 Hz, 2H), 3.43 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 164.5 (e), 151.5 (e), 133.8 (o, 2C), 131.8 (e), 129.0 (o, 2C), 128.5 (o, 2C), 127.4 (o), 124.7 (o), 122.3 (o, 2C), 71.0 (e), 43.0 (o, 2C); **IR** (neat): ν = 3014 (w), 2937 (w), 1640 (s), 1593 (w), 1485 (m), 1455 (w), 1443 (w), 1416 (w), 1335 (m), 1304 (w), 1231 (m), 1189 (s), 1174 (s), 1161 (s), 1072 (w), 1041 (w), 1023 (m), 1006 (m), 991 (m), 924 (m), 915 (m), 796 (m), 762 (m), 752 (m), 737 (m), 702 (m), 693 (s), 655 (w) cm^{-1}; **HRMS** (ESI) calcd for $(C_{16}H_{16}O_3S + H)^+$: 289.0893; found: 289.0884.



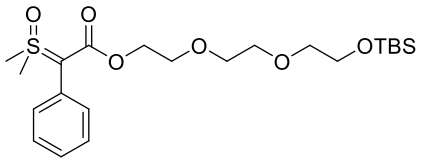
241

This compound was obtained from **178** (118 mg, 0.5 mmol, 2.5 equiv) and bromobenzene (21 µL mg, 0.2 mmol, 1 equiv) following:

Method B (51 mg, 82%, grey solid) after purification by flash chromatography (hexane/ethyl acetate: 50/50 to 20/80).

Method C (58 mg, 94%, grey solid) after purification by flash chromatography (hexane/ethyl acetate: 50/50 to 20/80).

m.p.: 80-82 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.34-7.20 (m, 5H), 4.14 (t, *J* = 8.4 Hz, 2H), 3.40 (s, 6H), 0.92 (t, *J* = 8.4 Hz, 2H), -0.06 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 166.6 (e), 133.8 (o, 2C), 132.6 (e), 128.3 (o, 2C), 127.0 (o), 70.4 (e), 61.0 (e), 43.2 (o, 2C), 17.7 (e), -1.52 (o, 3C); **IR** (neat): ν = 3029 (w), 3008 (w), 2949 (w), 2925 (w), 2895 (w), 1733 (w), 1611 (s), 1590 (m), 1490 (w), 1441 (w), 1388 (m), 1340 (m), 1326 (m), 1249 (m), 1211 (m), 1182 (s), 1167 (s), 1090 (m), 1061 (m), 1027 (m), 1005 (m), 977 (w), 954 (w), 934 (w), 914 (w), 852 (m), 832 (s), 793 (m), 756 (s), 706 (s), 689 (m), 641 (w), 604 (w) cm^{-1}; **HRMS** (ESI) calcd for $(C_{15}H_{24}O_3SSi + H)^+$: 313.1288; found: 313.1298.



242

This compound was obtained from **183** (191 mg, 0.5 mmol, 2.5 equiv) and bromobenzene (21 μL, 0.2 mmol, 1 equiv) following:

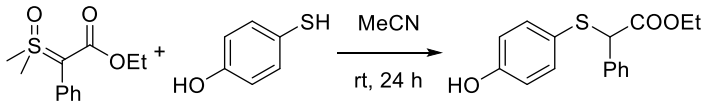
Method B but $PdP(tBu_3)_2$ (10 mg, 0.02 mmol, 0.1 equiv) was used instead of $Pd_2(dba)_3$ and $PtBu_3$), (80 mg, 87%, white amorphous solid) after purification by flash chromatography (hexane/ethyl acetate: 30/70 to 20/80).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33-7.18 (m, 5H), 4.23-4.13 (m, 2H), 3.72 (t, *J* = 5.50 Hz, 2H), 3.66-3.45 (m, 8H), 3.37 (s, 6H), 0.87 (s, 9H), 0.04 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 165.7 (e), 133.6 (o, 2C), 132.7 (e), 128.3 (o, 2C), 126.9 (o), 72.6 (e), 70.7 (e), 70.4 (hmbc), 70.5 (e), 69.5 (e), 62.7 (e), 62.3 (e), 43.4 (o, 2C), 26.0 (o,

3C), 18.4 (e), -5.23 (o, 2C); **IR** (neat): ν = 3002 (w), 2928 (m), 2855 (m), 1619 (s), 1593 (m), 1491 (w), 1471 (w), 1441 (w), 1406 (w), 1380 (m), 1338 (m), 1325 (m), 1248 (w), 1212 (m), 1168 (s), 1141 (m), 1091 (s), 1072 (m), 1062 (m), 1026 (w), 1003 (w), 970 (w), 938 (m), 912 (w), 831 (s), 813 (w), 776 (m), 756 (w), 706 (m), 690 (w), 661 (w) cm^{-1}; **HRMS** (ESI) calcd for $(C_{22}H_{38}O_6SSi + H)^+$: 459.2231; found: 459.2237.

1.5 Post-functionalisation

1.5.1 C–S bond formation



188 1 equiv | **249** 1 equiv | **250** **80%**

Following the literature's procedure:[84] Under N_2, to a round-bottomed flask was suspended **188** (48 mg, 0.2 mmol, 1 equiv) and 4-mercaptophenol (25 mg, 0.2 mmol, 1 equiv) in acetonitrile (0.2 mL). The reaction mixture was stirred for 24 hours at room temperature. The volatiles were removed under vacuum. Purification by flash chromatography (hexane/ethyl acetate: 90/10 to 80/20) afforded **250** (46 mg, 80%, white solid).

m.p.: 54-56 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.44-7.39 (m, 2H), 7.34-7.25 (m, 5H), 6.71 (d, *J* = 8.6 Hz, 2H), 5.84 (s, 1H), 4.78 (s, 1H), 4.19-4.07 (m, 2H), 1.19 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 171.2 (e), 156.6 (e), 136.4 (o, 2C), 135.6 (e), 128.6 (o, 4C), 128.3 (o), 123.5 (e), 116.1 (o, 2C), 61.9 (e), 57.5 (o), 14.0 (o); **IR** (neat): ν = 3444 (m), 3364 (br m), 2979 (w), 1710 (s), 1597 (m), 1579 (m), 1494 (m), 1465 (w), 1455 (w), 1427 (w), 1389 (w), 1368 (m), 1336 (m), 1304 (m), 1275 (s), 1210 (s), 1180 (s), 1152 (s), 1094 (m), 1076 (w), 1023 (s), 879 (w), 832 (s),

799 (w), 714 (m), 721 (m), 700 (m), 693 (m), 647 (w) cm^{-1}; **HRMS** (ESI) calcd for $(C_{16}H_{16}O_3S + Na)^+$: 311.0712; found: 311.0714.

1.5.2 C–N bond formation

Following the literature's procedure:[45] Compound **195** (62 mg, 0.2 mmol, 1 equiv) and $[Ir(cod)Cl]_2$ (3.4 mg, 0.005 mmol, 0.025 equiv) were added to a dry Schlenk tube under nitrogen. After 3 vacuum/nitrogen cycles dichloromethane (1 mL) was added followed by *p*-anisidine (37 mg, 0.3 mmol, 1.5 equiv). The mixture was stirred at room temperature for 4 hours before evaporation of the volatiles under vacuum. The residue thus obtained was purified by flash chromatography (heptane / ethyl acetate: 100/0 to 90/10) affording **253** (49 mg, 69%, light yellow oil).

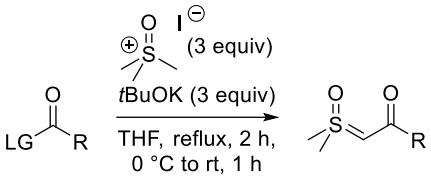
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68-7.58 (m, 4H), 6.75–6.69 (m, 2H), 6.53-6.46 (m, 2H), 5.05 (d, *J* = 5.6 Hz, 1H), 4.77 (d, *J* = 5.9 Hz, 1H), 4.29-4.09 (m, 2H), 3.70 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H), in agreement with previously reported data.[113]

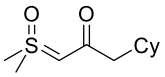
2 Experimental data for Chapter 3

Compound **277**-**282** and **295** were synthesised and characterised by Jean-Baptiste Chagnoleau.

2.1 Synthesis of the monosubstituted α-keto sulfoxonium ylides

2.1.1 Synthesis from the acyl chlorides

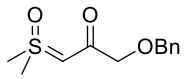




7

Representative procedure for the synthesis of compound **7**. Under N_2, trimethylsulfoxonium iodide (6.14 g, 27.9 mmol, 3 equiv) was suspended in dry THF (55 mL) in a flame-dried round-bottomed flask that was protected from light with aluminium foil. Potassium *tert*-butoxide (3.13 g, 27.9 mmol, 3 equiv) was added and the mixture was stirred at reflux for 2 hours. After cooling to 0 °C, 2-cyclohexylacetyl chloride (1.4 mL, 9.4 mmol, 1 equiv) in THF (18 mL) was added dropwise to the mixture *via* a dropping funnel. After stirring at room temperature for 1 hour, the mixture was filtered through a plug of celite (elution dichloromethane). After evaporation of all volatiles, purification by flash chromatography (dichloromethane/methanol: 98/2 to 94/6) afforded **7** (1.75 g, 86%, white solid).

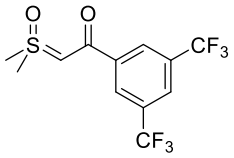
^{1}H NMR (500 MHz, $CDCl_3$): δ 4.34 (s, 1H), 3.39 (s, 6H), 2.04 (d, *J* = 6.8 Hz, 2H), 1.79-1.60 (m, 6H), 1.32-1.20 (m, 2H), 1.18-1.08 (m, 1H), 0.99-0.87 (m, 2H) in agreement with previously reported data.[8]



254

This compound was obtained from 2-(benzyloxy)acetyl chloride (1.3 mL, 8.0 mmol, 1 equiv) following the representative procedure for the synthesis of compound **7** (1.38 g, 72%, off-white solid) after purification by flash chromatography (ethyl acetate/methanol: 92/8 to 88/12), solubilisation in ethyl acetate (100 mL) and washing with brine (3X20 mL), drying the organic phase with magnesium sulfate, concentration and washing of the residue with hexane.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40-7.27 (m, 5H), 4.90 (s, 1H), 4.59 (s, 2H), 3.92 (s, 2H), 3.42 (s, 6H) in agreement with previously reported data.[114]

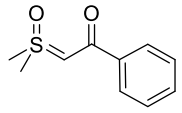


255

This compound was obtained from 3,5-bis(trifluoromethyl)benzoyl chloride (5.4 mL, 8.0 mmol, 1 equiv) following the representative procedure for the synthesis of compound **7** (7.86 g, 79%, white solid) after purification by flash chromatography (petroleum ether/ethyl acetate: 30/70 to 1/9) and recrystallisation from ethyl acetate/hexane.

m.p.: 152-154 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.23 (s, 2H), 7.93 (s, 1H), 5.06 (s, 1H), 3.85 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 178.2 (e), 140.9 (e), 131.6

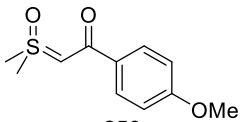
(e, q, *J* = 33.3 Hz, 2C), 126.8 (o), 126.8 (o), 124.0 (o, quint., *J* = 3.7 Hz), 123.2 (e, q, *J* = 271.3 Hz, 2C), 70.0 (o), 42.2 (o, 2C); **^{19}F NMR** (376 MHz, $CDCl_3$): δ -62.9; **IR** (neat): ν = 3103 (w), 3025 (w), 3005 (w), 2921 (w), 1627 (w), 1548 (m), 1451 (w), 1406 (w), 1354 (m), 1311 (m), 1278 (s), 1191 (m), 1166 (s), 1132 (s), 1106 (s), 1027 (s), 996 (m), 956 (m), 924 (w), 909 (m), 900 (m), 859 (m), 844 (m), 767 (w), 753 (w), 698 (w), 682 (w), 670 (w) cm^{-1}; **HRMS** (ESI) calcd for $(C_{12}H_{10}F_6O_2S + H)^+$: 333.0378; found: 333.0382.



12

This compound was obtained from benzoyl chloride (1.7 mL, 15.0 mmol, 1 equiv) following the representative procedure for the synthesis of compound **7** (2.8 g, 95%, white solid) after purification by flash chromatography (dichloromethane/methanol: 95/5 to 92/8).

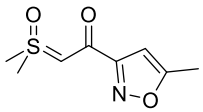
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82-7.78 (m, 2H), 7.46-7.37 (m, 3H), 4.97 (s, 1H), 3.52 (s, 6H) in agreement with previously reported data.[49]



256

This compound was obtained from 4-methoxybenzoyl chloride (1.6 mL, 11.7 mmol, 1 equiv) following the representative procedure for the synthesis of compound **7** (1.48 g, 56%, white solid) after purification by flash chromatography (ethyl acetate/methanol: 95/5 to 90/10).

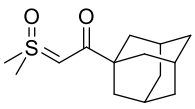
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (dt, *J* = 8.8 Hz, 2H), 6.87 (dt, *J* = 8.8Hz, 2H), 4.90 (s, 1H), 3.82 (s, 3H), 3.49 (s, 6H) in agreement with previously reported data.[115]



258

This compound was previously made by Manuel Barday but not characterised.

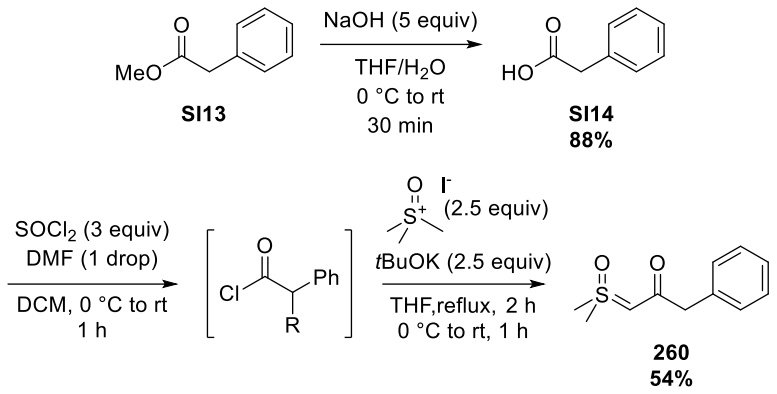
m.p.: 117-119 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.30 (q, *J* = 0.9 Hz, 1H), 5.33 (s, 1H), 3.50 (s, 6H), 2.43 (d, *J* = 0.9 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 173.4 (e), 170.0 (e), 163.1 (e), 100.3 (o), 70.7 (o), 42.1 (o, 2C), 12.3 (o); **IR** (neat): ν = 3140 (w), 3097 (w), 3009 (w), 2922 (w), 1599 (w), 1547 (s), 1465 (w), 1449 (s), 1344 (s), 1318 (w), 1295 (w), 1245 (w), 1182 (s), 1133 (w), 1073 (w), 1020 (s), 1008 (m), 996 (m), 979 (m), 941 (w), 901 (m), 848 (s), 827 (m), 813 (w), 768 (w), 753 (w), 689 (w), 658 (w) cm^{-1}; **HRMS** (ESI) calcd for $(C_8H_{11}NO_3S + H)^+$: 202.0532; found: 202.0530.



259

This compound was obtained from 1-adamantanecarbonyl chloride (1.39 g, 7.0 mmol, 1 equiv) following the the representative procedure for the synthesis of compound **7** (1.34 g, 75%, white solid) after purification by flash chromatography (ethyl acetate/methanol: 90/10).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.38 (s, 1H), 3.35 (s, 6H), 2.01-1.95(m, 3H), 1.78-1.74 (m, 6H), 1.72-1.62 (m, 6H) in agreement with previously reported data.[8]



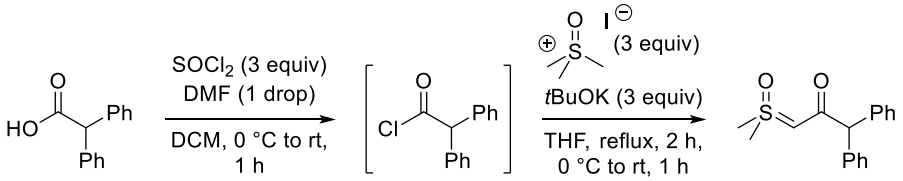
Under air, **SI13** (15.02 g, 100 mmol, 1 equiv) was suspended in a mixture THF (140 mL) and water (140 mL). The reaction was cooled to 0 °C and sodium hydroxide (20.00 g, 500 mmol, 5 equiv) was added in one portion. The reaction was allowed to stir at 0 °C for 30 min and was then allowed to warm up to room temperature. The reaction mixture was washed with dichloromethane (200 mL) and the aqueous layer was collected and carefully acidified to pH 1 using 12 M aqueous HCl. It was then extracted with dichloromethane (3×200 mL). The organic fractions were gathered and dried with $MgSO_4$. Filtration and evaporation of all the volatiles under reduced pressure afforded **SI14** (12.03 g, 88%, white solid) which was used in the next step without further purification.

Under N_2, **SI14** (6.81 g, 50 mmol, 1 equiv) was dissolved in dichloromethane (33 mL) and cooled to 0 °C. Thionyl chloride (11.0 mL, 150 mmol, 3 equiv) was added dropwise *via* a syringe at 0 °C followed by a drop of DMF. The reaction mixture was allowed to warm up to room temperature and was left to stir for 1 hour. The solvent was then removed under high vacuum and the crude acyl chloride was used in the next step without further purification.

Under N_2, trimethylsulfoxonium iodide (27.51 g, 125 mmol, 2.5 equiv) was suspended in dry THF (250 mL) in a flame-dried round-bottomed flask that was protected from light with aluminium foil. Potassium *tert*-butoxide (14.03 g, 125 mmol,

2.5 equiv) was added and the mixture was stirred at reflux for 2 hours. After cooling to 0 °C, the previously made crude acyl chloride in THF (50 mL) was added dropwise to the mixture *via* a dropping funnel. After stirring at room temperature for 1 hour, the mixture was filtered through a plug of celite (elution dichloromethane). After evaporation of all volatiles, purification by flash chromatography (ethyl acetate/methanol: 90/10) and recrystallisation from ethyl acetate/hexane afforded **260** (5.71 g, 54%, white needles).

m.p.: 76-79 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.35-7.22 (m, 5H), 4.30 (s, 1H), 3.50 (s, 2H), 3.36 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 188.3 (e), 137.0 (e), 129.3 (o, 2C), 128.6 (o, 2C), 126.2 (o), 69.8 (o), 48.0 (e), 41.9 (o, 2C) ppm; **IR** (neat): ν = 3083 (w), 3025 (m), 3003 (m), 2917 (w), 1583 (m), 1563 (s), 1492 (m), 1451 (w), 1415 (m), 1374 (s), 1323 (m), 1309 (w), 1272 (w), 1160 (s), 1105 (m), 1067 (w), 1032 (s), 994 (m), 973 (w), 956 (w), 938 (w), 910 (m), 847 (s), 766 (m), 753 (m), 720 (m), 694 (s) cm^{-1}; **HRMS** (ESI) calcd for $(C_{11}H_{14}O_2S + H)^+$: 211.0787; found: 211.0787.



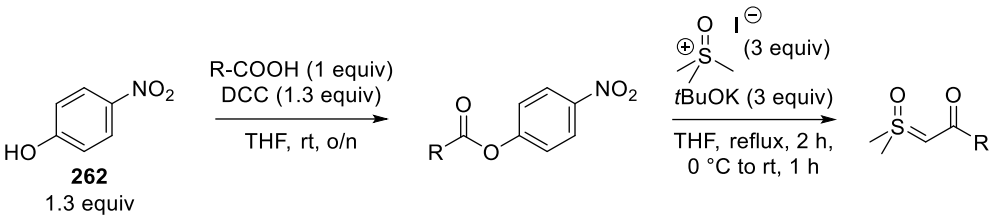
SI15 **261**

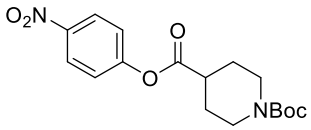
Under N_2, **SI15** (8.49 g, 40 mmol, 1 equiv) was dissolved in dichloromethane (27 mL) and cooled to 0 °C. Thionyl chloride (8.8 mL, 120 mmol, 3 equiv) was added dropwise *via* a syringe at 0 °C followed by a drop of DMF. The reaction mixture was allowed to warm up to room temperature and was left to stir for 1 hour. The solvent was then removed under high vacuum and the crude acyl chloride was used in the next step without further purification.

Under N_2, trimethylsulfoxonium iodide (26.41 g, 120 mmol, 3 equiv) was suspended in dry THF (240 mL) in a flame-dried round-bottomed flask that was protected from light with aluminium foil. Potassium *tert*-butoxide (13.46 g, 120 mmol, 3 equiv) was added and the mixture was stirred at reflux for 2 hours. After cooling to 0 °C, the previously made crude acyl chloride in THF (50 mL) was added dropwise to the mixture *via* a dropping funnel. After stirring at room temperature for 1 hour, the mixture was filtered through a plug of celite (elution dichloromethane). After evaporation of all volatiles, purification by flash chromatography (ethyl acetate to ethyl acetate/methanol: 80/20) and recrystallisation from ethyl acetate afforded **261** (6.26 g, 55%, white solid).

m.p.: 143-144 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.33-7.18 (m, 10H), 4.85 (s, 1H), 4.37 (s, 1H), 3.39 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 188.8 (e), 141.0 (e, 2C), 128.9 (o, 4C), 128.2 (o, 4C), 126.5 (o, 2C), 71.3 (o), 62.1 (o), 41.9 (o, 2C); **IR** (neat): ν = 3100 (w), 3083 (w), 3053 9w), 3005 (w), 2919 (w), 1596 (w), 1559 (s), 1493 (m), 1453 (w), 1443 (w), 1431 (w), 1374 (s), 1322 (w), 1300 9w), 1258 (w), 1241 (w), 1167 (s), 1119 (m), 1071 (w), 1030 (s), 989 (w), 948 (w), 929 (w), 909 (w), 862 (m), 818 (w), 789 (w), 757 (w), 743 (m), 724 (m), 695 (s) cm^{-1}; **HRMS** (ESI) calcd for $(C_{17}H_{18}O_2S + H)^+$: 287.1100; found: 287.1099.

2.1.2 Synthesis from the 4-nitrophenol

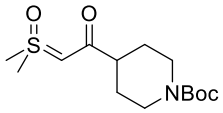




SI16

Representative procedure for the synthesis of **SI16**. Under N_2, 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid (11.24 g, 48 mmol, 2 equiv) was dissolved in THF (120 mL) then, 4-nitrophenol **262** (3.36 g, 24 mmol, 1 equiv) and DCC (9.89 g, 48 mmol, 2 equiv) were added. The reaction was allowed to stir at room temperature overnight. The reaction mixture was then filtered on celite (elution dichloromethane) and all the volatiles were removed under reduced pressure. Purification by flash chromatography (petroleum ether / ethyl acetate: 8 / 2) afforded **SI16**(6.34 g, 75%, white solid).

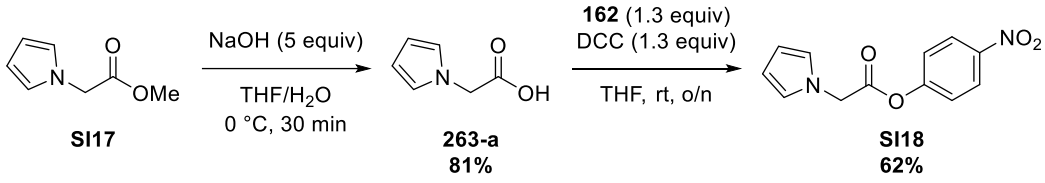
^{1}H NMR (500 MHz, $CDCl_3$): 8.24 (dt, *J* = 9.1, 2.0 Hz, 2H), 7.24 (dt, *J* = 9.1, 2.0 Hz, 2H), 4.08 (br s, 2H), 2.90 (t, *J* = 11.7 Hz, 2H), 2.74 (tt, *J* = 10.9, 3.8 Hz, 1H), 2.07-1.97 (m, 2H), 1.81-1.58 (m, 2H), 1.44 (s, 9H) in agreement with previously reported data.[116]



264

This compound was obtained from **SI16** (2.80 g, 8.0 mmol, 1 equiv) following the representative procedure for the synthesis of compound **7** (1.19 g, 49%, white solid) after purification by flash chromatography (ethyl acetate/methanol: 90/10 to 84/16) and purification by a second flash chromatography (dichloromethane/methanol: 96/4 to 94/6).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.36 (s, 1H), 4.12 (br s, 2H), 3.39 (s, 6H), 2.80-2.63 (m, 2H), 2.25-2.14 (tt, *J* = 12.0, 3.6 Hz, 1H), 1.84-1.72 (m, 2H), 1.58-1.40 (m, 11H) in agreement with previously reported data.[8]



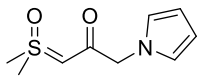
SI17 **263-a** **81%** **SI18** **62%**

Under air, **SI17** (6.00 g, 43 mmol, 1 equiv) was suspended in a mixture THF (60 mL) and water (60 mL). The reaction was cooled to 0 °C and sodium hydroxide (8.76 g, 219 mmol, 5 equiv) was added in one portion. The reaction was allowed to stir at 0 °C for 30 min and was then allowed to warm up to room temperature. The reaction mixture was washed with dichloromethane (80 mL) and the aqueous layer was collected and acidified to pH 1 using 12 M aqueous HCl (ca 20 mL). It was then extracted with dichloromethane (3X80 mL). The organic fractions were gathered and dried with magnesium sulfate. Filtration and evaporation of all the volatiles under reduced pressure afforded **263-a** which was used in the next step without further purification (4.43 g, 82%, white solid).

^{1}H NMR (500 MHz, $CDCl_3$): δ 11.3 (br s, 1H), 6.69 (t, *J* = 2.0 Hz, 2H), 6.27 (t, *J* = 2.0 Hz, 2H), 4.71 (s, 2H) in agreement with previously reported data.[117]

Under N_2, **263-a** (3.00 g, 24 mmol, 1 equiv) was dissolved in THF (120 mL) then, by 4-nitrophenol (4.37 g, 31.2 mmol, 1.3 equiv) and DCC (6.43 g, 31.2 mmol, 1.3 equiv) were added. The reaction was allowed to stir at room temperature overnight. The reaction mixture was then filtered on celite (elution dichloromethane) and all the volatiles were removed under reduced pressure. Purification by recrystallisation (diethyl ether, reflux to –30 °C) afforded **SI18** (3.68 g, 62%, off-white solid) with traces of DCC which could be removed in the next step.

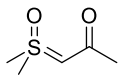
m.p.: 85-89 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.28 (dt, *J* = 9.2, 3.2 Hz, 2H), 7.32 (dt, *J* = 9.2, 3.2 Hz, 2H), 6.75 (t, *J* = 2.2 Hz, 2H), 6.26 (t, *J* = 2.2 Hz, 2H), 4.93 (s, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 166.4 (e), 154.7 (e), 125.2 (o, 2C), 122.0 (o, 2C), 121.8 (o, 2C), 109.6 (o, 2C), 50.6 (e, 2C); **IR** (neat): ν = 3122 (w), 3087 (w), 2933 (w), 2850 (w), 2075 (w), 1926 (w), 1774 (m), 1616 (m), 1592 (m), 1520 (s), 1489 (s), 1449 (w), 1409 (w), 1376 (w), 1345 (s), 1296 (s), 1242 (w), 1212 (s), 1151 (s), 1108 (s), 1093 (s), 1067 (s), 1067 (s), 1014 (w), 967 (w), 958 (w), 928 (m), 892 (w), 864 (m), 852 (s), 766 (m), 732 (s), 715 (s), 676 (w); **HRMS** (CI (NH_3)) calcd for $(C_{12}H_{10}N_2O_4 + H)^+$: 247.0713; found: 247.0716.



263

This compound was obtained from **SI18** (1.97 g, 8.0 mmol, 1 equiv) following the representative procedure for the synthesis of compound **7** (1.17 g, 73%, white solid) after purification by flash chromatography (dichloromethane/methanol: 97/3 to 95/5).

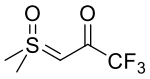
m.p.: 88-90 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.65 (t, *J* = 2.0 Hz, 2H), 6.17 (t, *J* = 2.0 Hz, 2H), 4.44 (s, 2H), 4.07 (s, 1H), 3.37 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 186.2 (e), 121.8 (o, 2C), 108.7 (o, 2C), 68.8 (o), 56.9 (e), 42.1 (o, 2C); **IR** (neat): ν = 3106 (w); 3068 (w); 3023 (w); 3006 (m); 2921 (w); 2240 (w); 1723 (w); 1548 (s); 1493 (w); 1424 (w); 1403 (w); 1375 (s); 1324 (m); 1308 (m); 1288 (m); 1174 (s); 1164 (s); 1089 (m); 1064 (m); 1028 (s); 991 (m); 974 (m); 964 (m); 916 (m); 859 (m); 816 (w); 762 (m); 726 (s); 701 (s) cm^{-1}; **HRMS** (ESI) calcd for $(C_9H_{13}NO_2S + H)^+$: 200.0740; found: 200.0742.



267

This compound was obtained from acetic anhydride (2.9 mL, 30 mmol, 1 equiv) following the representative procedure for the synthesis of compound **7** (2.97 g, 73%, white solid) after purification by flash chromatography (ethyl acetate/methanol: 90/10).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.34 (s, 1H), 3.36 (s, 6H), 1.92 (s, 3H), in agreement with previously reported data.[8]

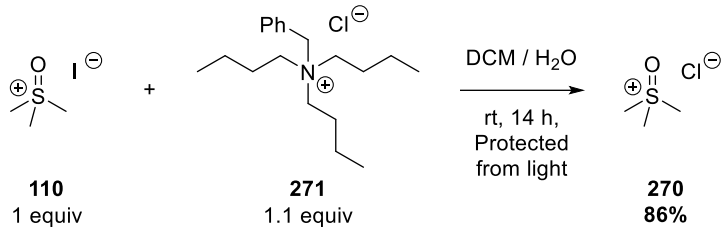


268

This compound was obtained from triflic anhydride (1.1 mL, 8 mmol, 1 equiv) following the representative procedure for the synthesis of compound **7** (808 mg, 54%, white solid) after purification by flash chromatography (hexane/ethyl acetate: 30/70 to 100% ethyl acetate).

^{1}H NMR (500 MHz, CD_3CN): 5.43 (s, 1H), 3.61 (s, 6H). *This compound was not fully characterised due to poor results obtained in the palladium-catalysed coupling with aryl halides*.

2.1.3 Synthesis by ring opening of lactams



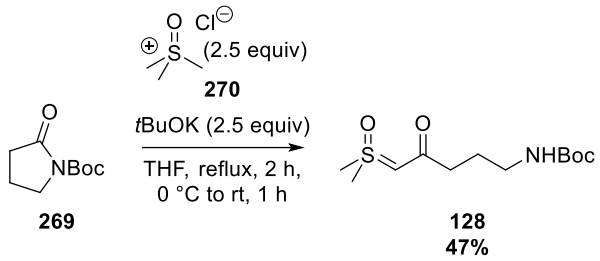
110
1 equiv

271
1.1 equiv

270
86%

Following the literature's procedure,[118] Under air, trimethylsulfoxonium iodide (22.01 g, 100 mmol, 1 equiv) was suspended in dichloromethane (170 mL) and water (230 mL) in a round-bottomed flask protected from light with aluminium foil. Benzyltributylammonium chloride (34.62 g, 111 mmol, 1.1 equiv) was then added and the reaction mixture was vigorously stirred at room temperature for 14 hours. The aqueous layer was separated, washed with dichloromethane (100 mL) and evaporated *in vacuo*. The residue obtained was recrystallised (methanol/toluene: 80/20) and dried in a desiccator under vacuum to provide trimethylsulfoxonium chloride (11.00 g, 86%, white solid).

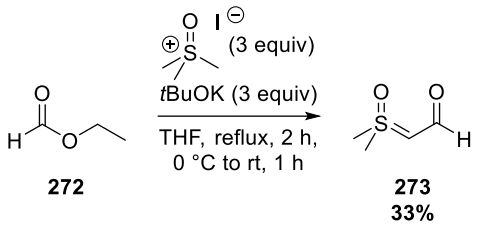
^{1}H NMR (500 MHz, DMSO-d_6): δ 3.89 (s), in agreement with previously reported data.[118]



Following the literature's procedure,[45] Under N_2, trimethylsulfoxonium chloride (2.08 g, 16.2 mmol, 3 equiv) was suspended in dry THF (26 mL) in a flame-dried round-bottomed flask protected from light with aluminium foil. Potassium *tert*-butoxide (1.82 g, 16.2 mmol, 3 equiv) was added and the mixture was stirred at reflux for 2 hours. After cooling to room temperature, **269** (0.92 mL, 5.4 mmol, 1 equiv) was added neat *via* a syringe. After stirring at room temperature for 1 hour, brine (20 mL) and ethyl acetate (100 mL) were added to the reaction mixture. The organic phase was collected and the aqueous phase was extracted with ethyl acetate (3×20 mL). The organic fractions were gathered and dried with magnesium sulfate. After evaporation of all the volatiles, purification by recrystallisation (ethyl acetate/hexane) afforded **128** (700 mg, 47%, white solid).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.80 (br s, 1H), 4.39 (s, 1H), 3.49 (s, 6H), 3.19-3.09 (m, 2H), 2.22 (t, *J* = 7.2 Hz, 2H), 1.77 (quint., *J* = 7.1 Hz, 2H), 1.43 (s, 9H) in agreement with previously reported data.[45]

2.1.4 Synthesis from ethyl formate

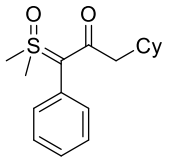


272 **273** **33%**

Following the literature's procedure,[119] Under N_2, trimethylsulfoxonium iodide (10.57 g, 48 mmol, 3 equiv) was suspended in dry THF (96 mL) in a flame-dried round-bottomed flask protected from light with aluminium foil. Potassium *tert*-butoxide (5.39 g, 48 mmol, 3 equiv) was added and the mixture was stirred at reflux for 2 hours. After cooling to 0 °C, ethyl formate (1.3 mL, 16 mmol, 1 equiv) in THF (32 mL) was added dropwise to the mixture *via* a dropping funnel. After stirring at room temperature for 1 hour, a solution of dichloromethane/methanol: 98/2 (100 mL) was added and the reaction was stirred for further 15 min. The mixture was filtered through a plug of celite (elution dichloromethane/methanol: 98/2). After evaporation of all volatiles, purification by flash chromatography (dichloromethane/methanol: 90/10 to 85/15) afforded **273** as a 97/3: *cis*/*trans* ratio of stereoisomers (635 mg, 33%, white solid).

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.08 (*trans*, d, *J* = 9.6 Hz, 0.04H), 8.61 (*cis*, d, *J* = 2.6 Hz, 1H), 4.63 (*trans*, d, *J* = 9.6 Hz, 0.04H), 4.35 (*cis*, d, *J* = 2.6 Hz, 1H), 3.41 (*cis*, s, 6H), 3.38 (*trans*, s, 0.24H), in agreement with previously reported data.[119]

2.2 Cross-coupling products

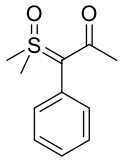


274

Representative procedure for the synthesis of compound **274**. Under N_2, a J-Young Schlenk tube was charged with XPhos (38 mg, 0.08 mmol, 0.2 equiv), Pd_2dba_3 (18 mg, 0.02 mmol, 0.05 equiv) and Cs_2CO_3 (143.4 mg, 0.44 mmol, 1.1 equiv). Acetonitrile (0.4 mL) was then added and the mixture was stirred at room temperature for 10 min. Then, 4-bromobenzonitrile (182 mg, 1.0 mmol, 2.5 equiv) was added followed by sulfoxonium ylide **7** (111 mg, 0.4 mmol, 1 equiv). The inner wall of the Schlenk tube was rinsed with acetonitrile (0.4 mL) and the tube was then sealed, placed in a pre-heated oil bath set at 80 °C and stirred for 15 hours. The crude was then filtered over celite at room temperature using dichloromethane to transfer all the material and for rinsing. After evaporation of all volatiles, purification by flash chromatography (ethyl acetate/methanol: 90/10) afforded compound **274** (135 mg, 89%, off-white solid).

m.p.: 109-112 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.36-7.27 (m, 3H), 7.25-7.21 (m, 2H), 3.47 (s, 6H), 2.01 (d, *J* = 7.3 Hz, 2H), 1.84-1.71 (m, 1H), 1.67-1.52 (m, 5H), 1.27-1.14 (m, 2H), 1.11-0.97 (m, 1H), 0.77 (q, *J* = 13.3 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 188.6 (e), 134.8 (o, 2C), 132.1 (e), 128.4 (o, 2C), 127.7 (o), 86.7 (e), 45.4 (e), 43.1 (o, 2C), 35.2 (o), 33.2 (e, 2C), 26.3 (e), 26.2 (e, 2C); **IR** (neat): ν = 3063 (w), 3014 (w), 2943 (w), 2916 (m), 2848 (w), 1534 (s), 1490 (w), 1439 (w), 1375 (s), 1312 (w), 1294 (w), 1272 (w), 1225 (m), 1182 (s), 1112 (w), 1073 (w), 1007 (m), 994 (m),

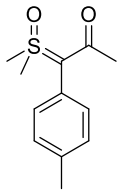
965 (m), 939 (m), 916 (w), 888 (w), 848 (w), 795 (w), 760 (w), 742 (m), 701 (s) cm^{-1}; **HRMS** (ESI) calcd for $(C_{17}H_{24}O_2S + H)^+$: 293.1570; found: 293.1578.



275

This compound was obtained from **267** (134 mg, 1.0 mmol, 1 equiv) and bromobenzene (160 μL, 1.5 mmol, 1.5 equiv) following the representative procedure for the synthesis of compound **274** (147 mg, 70%, amorphous solid) after purification by short and quick flash chromatography (ethyl acetate/methanol: 90/10 to 87/13).

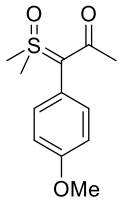
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42-7.25 (m, 5H), 3.49 (s, 6H), 1.90 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 186.4 (e), 134.3 (o, 2C), 132.5 (e), 128.4 (o, 2C), 127.7 (o), 85.8 (e), 42.9 (o, 2C), 26.5 (o); **IR** (neat): ν = 3393 (w), 3013 (m), 2921 (m), 1532 (s), 1489 (m), 1410 (w), 1366 (s), 1308 (w), 1234 (s), 1166 (s), 1023 (s), 1001 (s), 967 (m), 939 (w), 914 (w), 850 (w), 804 (w), 760 (m), 738 (w), 702 (s), 661 (w), 654 (w) cm^{-1}; **HRMS** (ESI) calcd for $(C_{11}H_{14}O_2S + H)^+$: 211.0787; found: 211.079.



276

This compound was obtained from **267** (54 mg, 0.4 mmol, 1 equiv) and 4-bromotoluene (123 μL, 1.0 mmol, 2.5 equiv) following the representative procedure for the synthesis of compound **274** (62 mg, 69%, amorphous solid) after purification by short and quick flash chromatography (ethyl acetate/methanol: 90/10 to 86/14).

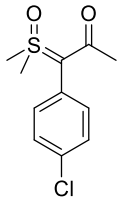
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14 (br s, 4H), 3.46 (s, 6H), 2.35 (s, 3H), 1.88 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 186.5 (e), 137.6 (e), 134.2(o, 2C), 129.4 (e), 129.3 (o, 2C), 85.4 (e), 42.8 (o, 2C), 26.5 (o), 21.1 (o); **IR** (neat): ν = 3350 (m), 3018 (m), 2920 (m), 2232 (w), 1536 (s), 1509 (m), 1406 (m), 1366 (s), 1306 (w), 1234 (s), 1165 (s), 1107 (w), 1024 (s), 970 (m), 940 (w), 923 (w), 814 (m), 794 (w), 722 (s), 695 (m) cm^{-1}; **HRMS** (ESI) calcd for $(C_{12}H_{16}O_2S + H)^+$: 225.0944; found: 225.0947.



277

This compound was obtained from **267** (54 mg, 0.4 mmol, 1 equiv) and 4-bromoanisole (125 µL, 1.0 mmol, 2.5 equiv) following the representative procedure for the synthesis of compound **274** as an inseparable mixture of starting material/DMSO/**277** in 5/1/94 ratio (23 mg, corrected yield: 26%, yellow solid) after addition of water to the crude (10 mL) and extraction with ethyl acetate (3X50 mL) followed by a silica plug (ethyl acetate/methanol: 80/20 to 50/50).

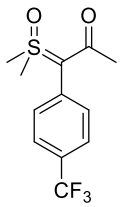
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.17 (dt, *J* = 8.7, 2.1 Hz, 2H), 6.88 (dt, *J* = 8.7, 2.1 Hz, 2H), 3.81 (s, 3H), 3.46 (s, 6H), 1.87 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 186.8 (e), 159.3 (e), 135.7 (o, 2C), 124.5 (e), 113.4 (o, 2C), 85.0 (e), 55.2 (o), 42.8 (o, 2C), 26.5 (o); **IR** (neat): ν = 2997 (w), 2919 (m), 2848 (w), 2523 (w), 2036 (w), 1904 (w), 1717 (w), 1660 (w), 1602 (m), 1566 (w), 1541 (s), 1508 (s), 1442 (m), 1414 (m), 1360 (s), 1339 (m), 1304 (w), 1278 (m), 1231 (s), 1193 (w), 1174 (w), 1161 (s), 1104 (m), 1025 (s), 978 (m), 949 (w), 923 (w), 906 (w), 831 (m), 793 (w), 759 (w), 731 (m), 702 (m) cm^{-1}.



278

This compound was obtained from **267** (54 mg, 0.4 mmol, 1 equiv) and 1-bromo-4-chlorobenzene (192 mg, 1.0 mmol, 2.5 equiv) following the representative procedure for the synthesis of compound **274** (68 mg, 69%, yellow solid) after purification by flash chromatography (ethyl acetate/methanol: 95/5 to 85/15).

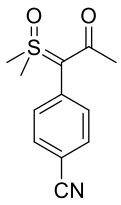
m.p.: 111-114 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.28 (dt, *J* = 8.5 and 2.5 Hz, 2H), 7.16 (dt, *J* = 8.6 and 2.1 Hz, 2H), 3.46 (s, 6H), 1.86 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 186.1 (e), 135.4 (o, 2C), 133.6 (e), 130.8 (e), 128.5 (o, 2C), 84.2 (e), 42.9 (o, 2C), 26.4 (o); **IR** (neat): ν = 3050 (w), 3030 (w), 3014 (m), 2998 (w), 2929 (m), 1587 (w), 1552 (s), 1488 (m), 1421 (w), 1395 (w), 1361 (s), 1343 (m), 1322 (w), 1259 (w), 1235 (s), 1177 (w), 1156 (s), 1101 (w), 1086 (m), 1057 (w), 1033 (s), 1012 (s), 989 (m), 979 (s), 924 (m), 911 (m), 842 (m), 818 (m), 752 (m), 730 (w), 718 (m), 689 (m) cm^{-1}; **HRMS** (ESI) calcd for $(C_{11}H_{13}ClO_2S + H)^+$: 245.0398; found: 245.0402.



279

This compound was obtained from **267** (54 mg, 0.4 mmol, 1 equiv) and 4-bromobenzotrifluoride (140 μL, 1.0 mmol, 2.5 equiv) following the representative procedure for the synthesis of compound **274** (96 mg, 86%, off-white solid) after purification by flash chromatography (ethyl acetate/methanol: 90/10).

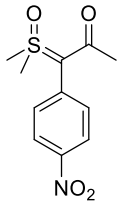
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 3.48 (s, 6H), 1.89 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 186.0 (e), 136.3 (e), 134.0 (o, 2C), 128.9 (e, q, *J* = 32.0 Hz), 125.0 (o, q, *J* = 3.5 Hz, 2C) 124.1 (e, q, *J* = 272.0 Hz), 84.5 (e), 43.1 (o, 2C), 26.4 (o); **^{19}F NMR** (376 MHz, $CDCl_3$): δ -62.4; **IR** (neat): ν = 3025 (w), 2925 (w), 1609 (w), 1538 (s), 1403 (w), 1376 (m), 1322 (s), 1241 (m), 1177 (s), 1110 (s), 1067 (s), 1019 (m), 1005 (m), 983 (w), 972 (w), 946 (w), 835 (s), 777 (w), 735 (m), 701 (m), 664 (w) cm^{-1}; **HRMS** (ESI) calcd for $(C_{12}H_{13}F_3O_2S + H)^+$: 279.0661; found: 279.0667.



280

This compound was obtained from **267** (54 mg, 0.4 mmol, 1 equiv) and 4-bromobenzonitrile (182 mg, 1.0 mmol, 2.5 equiv) following the representative procedure for the synthesis of compound **274** (70 mg, 74%, yellow solid) after purification by flash chromatography (ethyl acetate/methanol: 95/5 to 85/15).

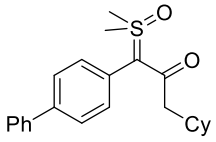
m.p.: 106-109 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 3.51 (s, 6H), 1.92 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 185.8 (e), 137.6 (e), 133.8 (o, 2C), 131.7 (o, 2C), 118.8 (e), 110.0 (e), 84.7 (e), 43.3 (o, 2C), 26.4 (o); **IR** (neat): ν = 3411 (w), 3054 (w), 3016 (m), 2995 (m), 2910 (m), 2227 (s), 1601 (m), 1521 (s), 1403 (w), 1376 (s), 1348 (w), 1310 (m), 1267 (w), 1242 (m), 1200 (s), 1114 (w), 1033 (s), 1011 (m), 985 (w), 968 (s), 949 (s), 917 (w), 865 (w), 850 (m), 840 (m), 777 (m), 732 (s), 685 (s) cm^{-1}; **HRMS** (ESI) calcd for $(C_{12}H_{13}NO_2S + H)^+$: 236.074; found: 236.0742.



281

This compound was obtained from **267** (54 mg, 0.4 mmol, 1 equiv) and 1-bromo-4-nitrobenzene (202 mg, 1.0 mmol, 2.5 equiv) following the representative procedure for the synthesis of compound **274** (92 mg, 90%, yellow solid) after purification by flash chromatography (ethyl acetate/methanol: 95/5 to 90/10).

m.p.: 135-140 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.13 (dt, *J* = 8.9, 2.1 Hz, 2H), 7.36 (dt, *J* = 8.9, 2.1 Hz, 2H), 3.56 (s, 6H), 1.98 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 186.0 (e), 146.0 (e), 139.8 (e) 133.5 (o, 2C), 123.1 (o, 2C), 84.6 (e), 43.5 (o, 2C), 26.5 (o); **IR** (neat): ν = 3066 (w), 3022 (w), 3000 (w), 2916 (m), 2436 (w), 1586 (m), 1526 (s), 1508 (s), 1437 (w), 1405 (w), 1363 (m), 1346 (m), 1324 (s), 1307 (m), 1245 (m), 1194 (s), 1108 (s) cm^{-1}; **HRMS** (ESI) calcd for $(C_{11}H_{13}NO_4S + H)^+$: 256.0638; found: 256.0644.

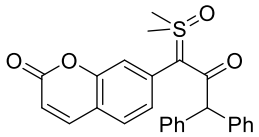


282

This compound was obtained from **7** (87 mg, 0.4 mmol, 1 equiv) and 4-phenylphenyl triflate (302 mg, 1.0 mmol, 2.5 equiv) following the representative procedure for the synthesis of compound **274** (79 mg, 54%, white solid) after purification by flash chromatography (ethyl acetate/methanol: 95/5 to 92/8).

m.p.: 126-128 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.62 (d, *J* = 7.3 Hz, 2H), 7.57 (d, *J* = 8.1 Hz, 2H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.29 (d, *J* = 8.3

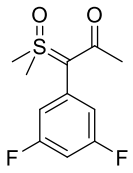
Hz, 2H), 3.49 (s, 6H), 2.08 (d, *J* = 7.1 Hz, 2H), 1.87-1.76 (m, 1H), 1.76-1.70 (m, 5H), 1.29-1.18 (m, 2H), 1.12-1.00 (m, 1H), 0.86-0.76 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 188.5 (e), 140.4 (e), 140.2 (e), 135.0 (o, 2C), 131.0 (e), 128.7 (o, 2C), 127.3 (o), 127.0 (o, 2C), 126.9 (o, 2C), 86.2 (e), 45.4 (e), 43.1 (o, 2C), 35.2 (o), 33.1 (e, 2C), 26.3 (e), 26.2 (e, 2C); **IR** (neat): ν = 3025 (w), 2918 (s), 2846 (m), 1550 (s), 1485 (m), 1446 (w), 1374 (m), 1321 (w), 1276 (w), 1254 (w), 1228 (m), 1177 (s), 1164 (s), 1112 (m), 1076 (w), 1066 (w), 1008 (m), 1019 (m), 969 (w), 937 (w), 889 (w), 836 (w), 796 (w), 765 (m), 730 (s), 693 (s) cm^{-1}; **HRMS** (ESI) calcd for $(C_{23}H_{28}O_2S + H)^+$: 369.1883; found: 369.1887.



This compound was obtained from **261** (115 mg, 0.4 mmol, 1 equiv) and **SI3** (294 mg, 1.0 mmol, 2.5 equiv) following the representative procedure for the synthesis of compound **274** but with 2 mL of acetonitrile (86 mg, 50%, coral solid) after purification by flash chromatography (hexane/ethyl acetate: 50/50 to 100% ethyl acetate) and washing with diethyl ether.

m.p.: 134-138 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.68 (d, *J* = 9.5 Hz, 1H), 7.38 (d, *J* = 7.9 Hz, 1H), 7.29-7.23 (m, 4H), 7.23-7.17 (m, 6H), 7.14 (d, *J* = 0.8 Hz, 1H), 7.04 (dd, *J* = 7.9, 1.5 Hz, 1H), 6.41 (d, *J* = 9.5 Hz, 1H), 5.07 (s, 1H), 3.53 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 186.1 (e), 160.5 (e), 153.6 (e), 142.9 (o), 140.7 (e, 2C), 135.7 (e), 130.6 (o), 128.8 (o, 4C), 128.3 (o, 4C),127.2 (o), 126.5 (o, 2C), 122.1 (o), 118.0 (e), 116.6 (o), 85.5 (e), 57.7 (o), 43.1 (o, 2C); **IR** (neat): ν = 3060 (w), 3025 (w), 3008 (m), 2924 (w), 1721 (s), 1610 (m), 1540 (s), 1493 (m), 1449 (w), 1402 (m), 1360 (m), 1308 (m), 1290 (w), 1278 (w), 1247 (m), 1227 (w), 1193 (s), 1152 (m), 1134 (m),

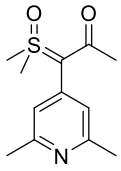
1103 (m), 1077 (w), 1024 (s), 1013 (m), 982 (m), 941 (m), 924 (m), 909 (w), 897 (w), 878 (w), 816 (w), 784 (w), 770 (w), 750 (m), 727 (m), 719 (s), 695 (s) cm^{-1}; **HRMS** (ESI) calcd for $(C_{26}H_{22}O_4S + Na)^+$: 453.1131; found: 453.1136.



284

This compound was obtained from **267** (54 mg, 0.4 mmol, 1 equiv) and 1-bromo-3,5-difluorobenzene (110 µL, 1.0 mmol, 2.5 equiv) following the representative procedure for the synthesis of compound **274** (68 mg, 69%, yellow solid) after purification by flash chromatography (ethyl acetate/methanol: 95/5 to 90/10).

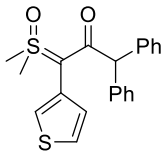
m.p.: 134-136 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.82-6.70 (m, 3H), 3.51 (s, 6H), 1.93 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 186.1 (e), 163.4 (e, d, *J* = 13.6 Hz, 2C), 161.5 (e, d, *J* = 13.6 Hz), 135.6 (e, t, *J* = 10.0 Hz), 116.7 (o, dd, *J* = 19.0 Hz, 5.8 Hz, 2C), 103.0 (o, t, *J* = 25.4 Hz), 43.2 (o, 2C), 26.5 (o); **^{19}F NMR** (125 MHz, $CDCl_3$): δ -110.6; **IR** (neat): ν = 3063 (w), 3014 (w), 2943 (w), 2916 (m), 2848 (w), 1534 (s), 1490 (w), 1439 (w), 1375 (s), 1312 (w), 1294 (w), 1272 (w), 1225 (m), 1182 (s), 1112 (w), 1073 (w), 1007 (m), 994 (m), 965 (m), 939 (m), 916 (w), 888 (w), 848 (w), 795 (w), 760 (w), 742 (m), 701 (s) cm^{-1}; **HRMS** (ESI) calcd for $(C_{11}H_{12}F_2O_2S + H)^+$: 247.0608; found: 247.0599.



285

This compound was obtained from **267** (54 mg, 0.4 mmol, 1 equiv) and 4-bromo-2,6-dimethylpyridine (186 mg, 1 mmol, 2.5 equiv) following the representative procedure for the synthesis of compound **274** (92 mg, 96%, yellow solid) after purification by flash chromatography (ethyl acetate/methanol: 85/15 to 80/20).

m.p.: 138-141 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.74 (s, 2H), 3.44 (s, 6H), 2.41 (s, 6H), 1.88 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 185.9 (e), 157.2 (e, 2C), 141.2 (e), 124.2 (o, 2C), 84.1 (e), 43.2 (o, 2C), 26.3 (o), 24.2 (o, 2C); **IR** (neat): ν = 3037 (w), 2977 (w), 2922 (w), 2904 (w), 1597 (m), 1567 (s), 1549 (s), 1397 (m), 1384 (m), 1356 (m), 1291 (s), 1221 (w), 1170 (s), 1063 (m), 1031 (s), 998 (m), 948 (w), 911 (w), 893 (w), 870 (w), 787 (w), 756 (w), 741 (m), 688 (m) cm^{-1}; **HRMS** (ESI) calcd for $(C_{12}H_{17}NO_2S + H)^+$: 240.1053; found: 240.1057.

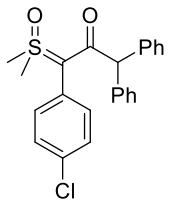


286

This compound was obtained from **261** (115 mg, 0.4 mmol, 1 equiv) and 3-bromothiophene (94 μL, 1.0 mmol, 2.5 equiv) following the representative procedure for the synthesis of compound **274** (92 mg, 63%, off-white solid) after purification by flash chromatography (hexane/ethyl acetate: 50/50 to 20/80).

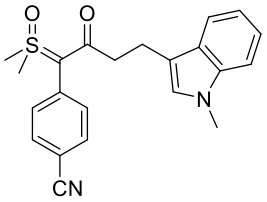
m.p.: 118-120 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.32-7.16 (m, 11H), 7.03 (dd, *J* = 2.9, 1.0 Hz, 1H), 6.83 (dd, *J* = 4.8, 0.9 Hz, 1H), 5.03 (s, 1H), 3.40 (s, 6H); **^{13}C**

NMR (125 MHz, $CDCl_3$): δ 187.0 (e), 141.3 (e, 2C), 132.5 (o), 131.0 (e), 129.3 (o), 129.0 (o, 4C), 128.3 (o, 4C), 126.4 (o, 2C), 125.2 (o), 80.6 (e), 57.9 (o), 42.5 (o, 2C); **IR** (neat): ν = 3081 (w), 3060 (w), 3026 (w), 2929 (w), 1753 (w), 1716 (w), 1656 (w), 1560 (s), 1492 (m), 1447 (w), 1392 (w), 1344 (m), 1315 (w), 1304 (w), 1248 (w), 1210 (w), 1168 (s) 1155 (s), 1076 (w), 1028 (s), 953 (w), 927 (w), 904 (w), 876 (w), 850 (m), 807 (m), 783 (w), 752 (w), 736 (m), 714 (s), 699 (s), 683 (s) cm^{-1}; **HRMS** (ESI) calcd for $(C_{21}H_{20}O_2S_2 + H)^+$: 369.0977; found: 369.0978.



This compound was obtained from **261** (115 mg, 0.4 mmol, 1 equiv) and 1-bromo-4-chlorobenzene (192 mg, 1.0 mmol, 2.5 equiv) following the representative procedure for the synthesis of compound **274** (142 mg, 90%, white solid) after purification by flash chromatography (hexane/ethyl acetate: 40/60 to 20/80).

m.p.: 122-125 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.34-7.47 (m, 12H), 7.08 (d, *J* = 8.3 Hz, 2H), 4.99 (s, 1H), 3.43 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 186.0 (e), 140.9 (e, 2C), 136.0 (o, 2C), 134.1 (e), 130.0 (o), 128.7 (o, 4C), 128.5 (o, 2C), 128.1 (o, 4C), 126.3 (o, 2C), 85.3 (e), 57.6 (o), 42.6 (o, 2C); **IR** (neat): ν = 2988 (w), 2925 (w), 1561 (s), 1489 (m), 1445 (w), 1400 (w), 1362 (m), 1325 (w), 1307 (w), 1267 (w), 1195 (m), 1165 (s), 1152 (m), 1088 (m), 1076 (w), 1057 (w), 1024 (s), 982 (w), 953 (w), 929 (m), 906 (w), 877 (w), 841 (w), 828 (w), 786 (w), 739 (m), 720 (w), 700 (s), 680 (m) cm^{-1}; **HRMS** (ESI) calcd for $(C_{23}H_{21}ClO_2S + H)^+$: 397.1023; found: 397.1024.



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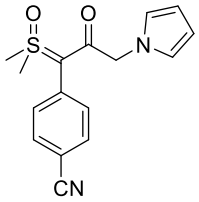
This compound was obtained from **266** (111 mg, 0.4 mmol, 1 equiv) and 4-bromobenzonitrile (182 mg, 1.0 mmol, 2.5 equiv) following the representative procedure for the synthesis of compound **274** (135 mg, 89%, off-white solid) after purification by flash chromatography (ethyl acetate/methanol: 97/3 to 93/7).

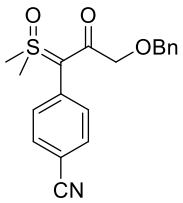
m.p.: 127-130 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.43 (dt, *J* = 8.3, 2.1 Hz, 2H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 8.2 Hz, 1H), 7.19 (dd, *J* = 6.9, 0.8 Hz, 1H), 7.05-7.00 (m, 3H), 6.70 (s, 1H), 3.68 (s, 3H), 3.44 (s, 6H), 3.02 (t, *J* = 7.4 Hz, 2H), 2.56 (t, *J* = 7.4 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 188.0 (e), 137.0 (e), 136.6 (e), 134.1 (o, 2C), 131.4 (o, 2C), 127.5 (e), 126.0 (o), 121.3 (o), 118.7 (o), 118.7 (e), 188.3 (o), 113.9 (e), 109.9 (e), 108.9 (o), 85.0 (e), 43.1 (o, 2C), 38.9 (e), 32.3 (o), 21.2 (e); **IR** (neat): ν = 3082 (w), 3038 (w), 3013 (w), 2967 (w), 2926 (w), 2855 (w), 2226 (m), 1600 (w), 1560 (s), 1497 (w), 1485 (w), 1474 (w), 1450 (w), 1434 (w), 1419 (w), 1395 (w), 1377 (w), 1343 (m), 1329 (m), 1321 (m), 1279 (w), 1264 (w), 1248 (w), 1223 (m), 1205 (m), 1172 (s), 1119 (w), 1065 (m), 1036 (m), 1008 (w), 976 (w), 934 (m), 915 (w), 847 (w), 800 (w), 748 (s), 735 (m), 697 (m), 656 (w) cm^{-1}; **HRMS** (ESI) calcd for $(C_{22}H_{22}N_2O_2S + H)^+$: 379.1475; found: 379.1479.



289

This compound was obtained from **263** (80 mg, 0.4 mmol, 1 equiv) and 4-bromobenzonitrile (182 mg, 1.0 mmol, 2.5 equiv)) following the representative procedure for the synthesis of compound **274** (95 mg, 79%, light brown solid) after purification by flash chromatography (ethyl acetate/methanol: 97/3 to 93/7).

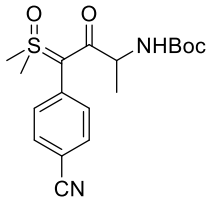
mp: 123-125 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.3 Hz, 2H), 6.52 (t, *J* = 2.1 Hz, 2H), 6.11 (t, *J* = 2.1 Hz, 2H), 4.46 (s, 2H), 3.51 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 180.9 (e), 135.6 (e), 134.4 (o, 2C), 132.1 (o, 2C), 121.4 (o, 2C), 118.5 (e), 111.2 (e), 108.3 (o, 2C), 83.9 (e), 54.2 (e), 42.9 (o, 2C); **IR** (neat): ν = 3094 (w), 3012 (w), 2915 (w), 2228 (m), 1603 (w), 1541 (s), 1500 (m), 1432 (w), 1391 (w), 1382 (w), 1329 (w), 1296 (w), 1280 (w), 1226 (w), 1195 (s), 1183 (s), 1116 (w), 1095 (w), 1070 (w), 1056 (w), 1013 (m), 986 (w), 969 (m), 955 (M), 932 (w), 908 (w), 888 (w), 847 (w), 836 (w), 807 (w), 774 (w), 731 (s), 738 (s), 688 (w), 654 (w) cm^{-1}; **HRMS** (ESI) calcd for $(C_{16}H_{16}N_2O_2S + Na)^+$: 323.0825; found: 323.0823.



290

This compound was obtained from **254** (96 mg, 0.4 mmol, 1 equiv) and 4-bromobenzonitrile (182 mg, 1.0 mmol, 2.5 equiv) following the representative procedure for the synthesis of compound **274** (112 mg, 82%, orange oil) after purification by flash chromatography (ethyl acetate/methanol: 90/10).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56 (dt, *J* = 8.4, 1.9 Hz, 2H), 7.35-7.21 (m, 7H), 4.52 (s, 2H), 4.00 (s, 2H), 3.57 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 183.2 (e), 137.4 (e), 135.8 (e), 133.8 (o, 2C), 131.6 (o, 2C), 128.1 (o, 2C), 127.7 (o, 2C), 127.5 (o), 118.6 (e), 110.4 (e), 84.1 (e), 73.1 (e), 71.8 (e), 42.9 (o, 2C); **IR** (neat): ν = 3006 (w), 2919 (w), 2858 (w), 2224 (m), 1542 (s), 1499 (m), 1454 (w), 1404 (m), 1328 (m), 1307 (m), 1198 (s), 1179 (s), 1104 (s), 1020 (s), 970 (m), 942 (w), 912 (w), 837 (w), 734 (s), 699 (m), 683 (w); **HRMS** (ESI) calcd for $(C_{19}H_{19}NO_3S + H)^+$: 342.1158; found: 342.1165.

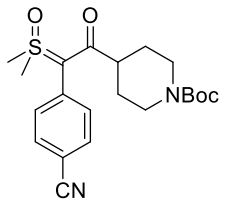


291

This compound was obtained from **265** (105 mg, 0.4 mmol, 1 equiv) and 4-bromobenzonitrile (182 mg, 1.0 mmol, 2.5 equiv) following the representative procedure for the synthesis of compound **274** (127 mg, 87%, fluffy yellow solid) after purification by flash chromatography (ethyl acetate/methanol: 95/5 to 92/8).

mp: 130-133 °C, **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.57 (d, *J* = 8.2 Hz, 2H), 7.39 (d, *J* = 7.9 Hz, 2H), 5.28 (d, *J* = 7.3 Hz, 1H), 4.29 (q, *J* = 7.3 Hz, 1H), 3.53 (s, 3H), 3.42 (s, 3H), 1.35 (s, 9H), 1.00 (d, *J* = 6.9 Hz, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 186.5 (e), 154.8 (e), 135.9 (e), 134.6 (o, 2C), 132.0 (o, 2C), 118.6 (e), 110.9 (e), 83.1 (e), 78.9 (e), 49.5 (o), 42.9 (o), 42.8 (o), 28.2 (o, 3C), 19.3 (o); **IR** (neat): ν = 3245 (m, br), 2934 (m), 2934 (w), 2227 (m), 1685 (s), 1603 (w), 1536 (s), 1452 (w), 1391 (m), 1365 (m), 1337 (w), 1311 (w), 1296 (m), 1280 (m), 1253 (m), 1213 (m), 1199 (s), 1165 (s), 1107 (m), 1058 (m), 1011 (s), 963 (m), 943 (m), 880 (w), 852 (w), 792 (w), 744

(m), 681 (m) cm^{-1}; **HRMS** (ESI) calcd for $(C_{18}H_{24}N_2O_4S + H)^+$: 365.1530; found: 365.1532.



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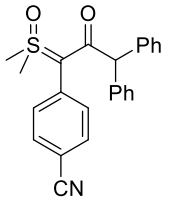
This compound was obtained from **264** (121 mg, 0.4 mmol, 1 equiv) and 4-bromobenzonitrile (182 mg, 1.0 mmol, 2.5 equiv) following the representative procedure for the synthesis of compound **274** (138 mg, 85%, off-white solid) after purification by flash chromatography (ethyl acetate/methanol: 95/5 to 92/8).

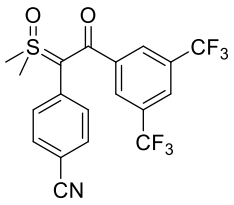
m.p.: 154-156 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.59 (d, *J* = 8.5 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 4.01 (br s, 2H), 3.49 (s, 6H), 2.57-2.36 (m, 3H), 1.60 (qd, *J* = 12.8, 4.4 Hz, 2H), 1.53-1.42 (m, 2H), 1.38 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 189.9 (e), 154.5 (e), 136.8 (e), 134.3 (o, 2C), 131.9 (o, 2C), 118.66 (e), 110.7 (e), 84.1 (e), 79.2 (e), 43.4 (o, 2C), 43.1 (2C, HSQC), 42.8 (o), 28.4 (e, 2C), 28.3 (o, 3C); **IR** (neat): ν = 3008 (w), 2976 (w), 2919 (w), 2855 (w), 2228 (m), 1673 (s), 1601 (w), 1571 (w), 1540 (s), 1499 (w), 1477 (w), 1466 (w), 1431 (m), 1388 (m), 1364 (w), 1349 (w), 1304 (w), 1273 (w), 1242 (w), 1192 (s), 1159 (s), 1125 (m), 1068 (w), 1031 (s), 989 (w), 965 (m), 945 (w), 928 (w), 865 (w), 845 (w), 812 (w), 756 (w), 727 (s), 680 (w) cm^{-1}; **HRMS** (ESI) calcd for $(C_{21}H_{28}N_2O_4S + H)^+$: 405.1843; found: 405.1849.



293

This compound was obtained from **261** (115 mg, 0.4 mmol, 1 equiv) and 4-bromobenzonitrile (182 mg, 1.0 mmol, 2.5 equiv) following the representative procedure for the synthesis of compound **274** (138 mg, 89%, salmon solid) after purification by flash chromatography (hexane/ethyl acetate: 20/80).

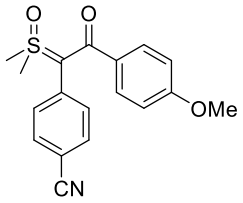
m.p.: 99-102 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.56 (d, *J* = 7.6 Hz, 2H), 7.30-7.16 (m, 12H), 5.01 (s, 1H), 3.49 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 185.9 (e), 140.5 (e, 2C), 136.7 (e), 134.7 (o, 2C), 131.7 (o, 2C), 128.6 (o, 4C), 128.2 (o, 4C), 126.4 (o, 2C), 118.6 (e), 110.8 (e), 85.5 (e), 57.7 (o), 43.0 (o, 2C); **IR** (neat): ν = 3083 (w), 3060 (w), 3029 (w), 3008 (w), 2913 (w), 2221 (m), 1755 (w), 1718 (w), 1673 (w), 1600 (m), 1539 (s), 1495 (m), 1448 (w), 1397 (w), 1371 (m), 1302 (m), 1272 (w), 1198 (s), 1180 (m), 1110 (w), 1077 (w), 10323 (w), 1014 (m), 970 (m), 957 (w), 935 (m), 877 (w), 836 (m), 782 (w), 734 (s), 704 (s), 681 (m) cm^{-1}; **HRMS** (ESI) calcd for $(C_{24}H_{21}NO_2S + H)^+$: 388.1366; found: 388.1363.



294

This compound was obtained from **255** (132 mg, 0.4 mmol, 1 equiv) and 4-bromobenzonitrile (182 mg, 1.0 mmol, 2.5 equiv) following the representative procedure for the synthesis of compound **274** (142 mg, 82%, fluffy yellow solid) after purification by flash chromatography (hexane/ethyl acetate: 60/40 to 30/70).

m.p.: 91-94 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.73 (s, 3H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 3.67 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 179.1 (e), 141.4 (e), 136.4 (e), 134.3 (o, 2C), 131.8 (o, 2C), 131.0 (e, q, *J* = 34.0 Hz, 2C), 128.9 (o, unresolved q, *J* = 2.6 Hz), 123.1 (o, sept., *J* = 3.7 Hz, 2C), 121.7 (e, q, *J* = 273.2 Hz, 2C), 118.5 (e), 110.6 (e), 86.8 (e), 42.8 (o, 2C); **^{19}F NMR** (376 MHz, $CDCl_3$): -63.2; **IR** (neat): ν = 3075 (w), 3004 (w), 2989 (w), 2918 (w), 2223 (m), 1624 (w), 1602 (w), 1538 (s), 1505 (m), 1444 (w), 1407 (w), 1389 (w), 1349 (m), 1275 (s), 1240 (m), 1211 (m), 1196 (m), 1169 (s), 1112 (s), 1027 (s), 991 (w), 968 (w), 944 (w), 922 (w), 891 (s), 844 (m), 835 (m), 754 (m), 729 (m), 698 (m), 678 (s) cm^{-1}; **HRMS** (ESI) calcd for $(C_{19}H_{13}F_6NO_2S + H)^+$: 434.0644; found: 434.0644.

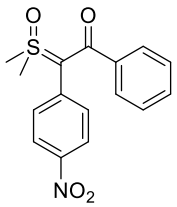


295

This compound was obtained from **256** (91 mg, 0.4 mmol, 1 equiv) and 4-bromobenzonitrile (182 mg, 1.0 mmol, 2.5 equiv) following the representative procedure for the synthesis of compound **274** (105 mg, 80%, yellow solid) after purification by flash chromatography (ethyl acetate/methanol: 95/5 to 90/10).

m.p.: 149-152 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.40 (d, *J* = 8.5 Hz, 2H), 7.24 (d, *J* = 8.7 Hz, 2H), 7.18 (d, *J* = 8.5 Hz, 2H), 6.65 (d, *J* = 8.8 Hz, 2H), 3.71 (s, 3H), 3.60 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 183.1 (e), 160.8 (e), 138.0 (e), 133.9 (o, 2C), 131.8 (e), 131.3 (o, 2C), 130.4 (o, 2C), 119.0 (e), 112.8 (o, 2C), 109.2 (e), 84.5 (e), 55.0 (o), 43.3 (o, 2C); **IR** (neat): ν = 2991 (w), 2914 (w), 2839 (w), 2228 (s), 1601 (m), 1579 (m), 1505 (s), 1494 (s), 1463 (w), 1374 (s), 1303 (m), 1250 (s), 1187 (s), 1171 (s), 1119 (w), 1016 (s), 984 (w), 967 (w), 954 (m), 942 (m), 861 (w), 844 (s), 818

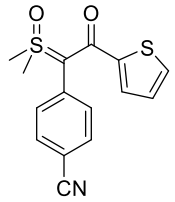
(m), 781 (w), 770 (w), 757 (s), 728 (m), 689 (w), 675 (w) cm^{-1}; **HRMS** (ESI) calcd for $(C_{18}H_{17}NO_3S + H)^+$: 328.1002; found: 328.1007.



296

This compound was obtained from **12** (79 mg, 0.4 mmol, 1 equiv) and 1-bromo-4-nitrobenzene (202 mg, 1.0 mmol, 2.5 equiv) following the representative procedure for the synthesis of compound **274** (114 mg, 90%, lime solid) after purification by flash chromatography (100% ethyl acetate to ethyl acetate/methanol: 97/3).

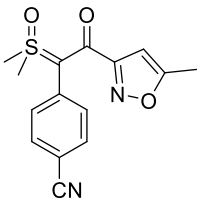
m.p.: 163-165 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.98 (dt, *J* = 8.9, 1.9 Hz, 2H), 7.34-7.25 (m, 3H), 7.22 (dt, *J* = 8.9, 2.0 Hz, 2H), 7.18 (t, *J* = 7.7 Hz, 2H), 3.68 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 184.3 (e), 145.6 (e), 140.0 (e), 139.5 (e), 133.6 (o, 2C), 130.0 (o), 128.5 (o, 2C), 127.8 (o, 2C), 122.9 (o, 2C), 85.2 (e), 43.4 (o, 2C); **IR** (neat): ν = 3075 (w), 3014 (w), 2989 (w), 2910 (w), 1581 (m), 1515 (s), 1406 (w), 1349 (s), 1304 (m), 1290 (w), 1247 (m), 1201 (s), 1157 (w), 1124 (w), 1111 (w), 1099 (w), 1074 (w), 1020 (m), 983 (m), 958 (m), 943 (m), 866 (w), 852 (m), 790 (m), 753 (w), 737 (m), 723 (m), 702 (s), 654 (w) cm^{-1}; **HRMS** (ESI) calcd for $(C_{16}H_{15}NO_4S + H)^+$: 318.0795; found: 318.0797.



297

This compound was obtained from **257** (81 mg, 0.4 mmol, 1 equiv) and 4-bromobenzonitrile (182 mg, 1.0 mmol, 2.5 equiv)) following the representative procedure for the synthesis of compound **274** (95 mg, 82%, off-white solid) after purification by flash chromatography (100% ethyl acetate to ethyl acetate/methanol: 95/5).

m.p.: 201-203 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.62-7.57 (m, 2H), 7.44-7.40 (m, 2H), 7.32 (dd, *J* = 5.0, 1.1 Hz, 1H), 6.81 (dd, *J* = 5.0, 3.8 Hz, 1H), 6.66 (dd, *J* = 3.8, 1.0 Hz, 1H), 3.65 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 174.4 (e), 144.8 (e), 136.7 (e), 135.5 (o, 2C), 132.0 (o, 2C), 129.6 (o), 129.3 (o), 127.1 (o), 118.8 (e), 111.3 (e), 83.9 (e), 43.6 (o, 2C); **IR** (neat): ν = 3112 (w), 3069 (w), 3023 (w), 2999 (m), 2914 (w), 2220 (m), 1601 (w), 1518 (m), 1504 (s), 1492 (s), 1415 (m), 1405 (m), 1380 (s), 1347 (w), 1306 (w), 1289 (w), 1251 (m), 1230 (w), 1191 (s), 1180 (s), 1108 (w), 1092 (m), 1071 (w), 1044 (w), 1020 (s), 980 (m), 962 (m), 947 (s), 868 (w), 846 (m), 831 (w), 763 (m), 741 (m), 718 (s), 674 (m), 664 (m) cm^{-1}; **HRMS** (ESI) calcd for $(C_{15}H_{13}NO_2S_2 + H)^+$: 304.0460; found: 304.0495.

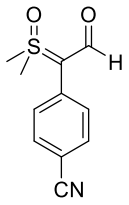


298

This compound was obtained from **258** (81 mg, 0.4 mmol, 1 equiv) and 4-bromobenzonitrile (182 mg, 1.0 mmol, 2.5 equiv) following the representative

procedure for the synthesis of compound **274** (100 mg, 83%, sand-like solid) after purification by flash chromatography (ethyl acetate/methanol: 95/5 to 92/8).

m.p.: 162-165 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.53 (dt, *J* = 8.5, 1.8 Hz, 2H), 7.32 (dt, *J* = 8.5, 1.8 Hz, 2H), 5.90 (s, 1H), 3.66 (s, 6H), 2.33 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 172.2 (e), 169.0 (e), 162.3 (e), 135.6 (e), 134.4 (o, 2C), 131.4 (o, 2C), 118.7 (e), 110.6 (e), 101.1 (o), 88.1 (e), 42.5 (o, 2C), 11.9 (o); **IR** (neat): ν = 3122 (w), 2995 (w), 2914 (w), 2227 (m), 1601 (m), 1526 (s), 1444 (m), 1406 (m), 1348 (m), 1308 (m), 1274 (w), 1260 (m), 1992 (s), 1108 (w), 1017 (s), 986 (w), 961 (m), 943 (s), 920 (w), 900 (m), 846 (m), 792 (w), 765 (m), 738 (w), 727 (w), 681 (m), 657 (w) cm^{-1}; **HRMS** (ESI) calcd for $(C_{15}H_{14}N_2O_3S + H)^+$: 325.0617; found: 325.0622.

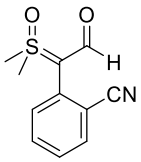


299

This compound was obtained from **273** (48 mg, 0.4 mmol, 1 equiv) and 4-bromobenzonitrile (182 mg, 1.0 mmol, 2.5 equiv) following the representative procedure for the synthesis of compound **274** (74 mg, 83%, beige solid) after purification by a short flash chromatography. The silica was pre-treated with an ethyl acetate/methanol/triethylamine (92/8/1) mixture, washed with ethyl acetate/methanol (92/8) and eluted with a quick gradient (ethyl acetate/methanol: 92/8 to 85/15).

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.92 (s, 1H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.6 Hz, 2H), 3.58 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 178.0 (o), 137.2 (e), 132.0 (o, 2C), 128.5 (o, 2C), 119.1 (e), 108.5 (e), 87.5 (e), 42.6 (o, 2C); **IR** (neat): ν = 3028 (w), 2989 (w), 2919 (w), 2903 (w), 2219 (m), 1577 (s), 1503 (m), 1415 (w), 1391 (m), 1313 (s), 1303 (s), 1275 (w), 1189 (s), 1175 (s), 1113 (w), 1076 (w), 1066 (w), 1056

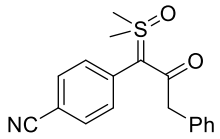
(w), 1025 (s), 984 (m), 959 (m), 946 (m), 919 (w), 835 (m), 819 (m), 770 (w), 739 (m), 724 (w), 703 (m), 656 (w) cm^{-1}; **HRMS** (ESI) calcd for $(C_{11}H_{11}NO_2S + H)^+$: 222.0583; found: 222.0585.



300

This compound was obtained from **273** (48 mg, 0.4 mmol, 1 equiv) and 2-bromobenzonitrile (182 mg, 1.0 mmol, 2.5 equiv) following the representative procedure for the synthesis of compound **274** (76 mg, 85%, amorphous solid) after purification by a short flash chromatography. The silica was pre-treated with an ethyl acetate/methanol/triethylamine (90/10/1) mixture, washed with ethyl acetate/methanol (90/10) and eluted with a quick gradient (ethyl acetate/methanol: 90/10 to 86/14).

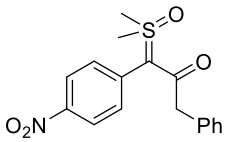
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.75 (s, 1H), 7.63 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.52 (td, *J* = 7.8, 1.5 Hz, 1H), 7.38-7.31 (m, 2H), 3.61 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 177.5 (o), 134.9 (e), 134.1 (o), 132.8 (o), 132.6 (o), 127.5 (o), 119.5 (e), 116.1 (e), 84.9 (e), 42.2 (o, 2C); **IR** (neat): ν = 3026 (w), 2995 (w), 2915 (w), 2854 (w), 2220 (m), 1554 (s), 1483 (m), 1450 (w), 1400 (m), 1358 (m), 1330 (w), 1314 (w), 1281 (w), 1261 (w), 1204 (s), 1163 (m), 1103 (w), 1004 (s), 994 (w), 949 (m), 939 (m), 877 (w), 788 (w), 763 (m), 952 (m), 742 (s), 701 (w), 686 (s) cm^{-1}; **HRMS** (ESI) calcd for $(C_{11}H_{11}NO_2S + H)^+$: 222.0583; found: 222.0583.



301

This compound was obtained from **260** (84 mg, 0.4 mmol, 1 equiv) and 4-bromobenzonitrile (182 mg, 1.0 mmol, 2.5 equiv) following the representative procedure for the synthesis of compound **274** but at 60 °C (89 mg, 71%, white solid) after purification by flash chromatography (ethyl acetate/methanol: 98/2 to 90/10).

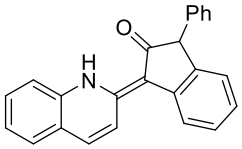
m.p.: 117-119 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.59 (dt, *J* = 8.4, 1.9 Hz, 2H), 7.31 (tt, *J* = 8.5, 1.7 Hz, 2H), 7.25-7.20 (m, 2H), 7.17 (tt, *J* = 7.4, 1.3 Hz, 1H), 7.10-7.05 (m, 2H), 3.51-3.49 (m, 8H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 185.8 (e), 137.0 (e), 136.6 (e), 134.6 (o, 2C), 131.8 (o, 2C), 128.8 (o, 2C), 128.2 (o, 2C), 126.2 (o), 118.7 (e), 110.6 (e), 84.8 (e), 44.8 (e), 43.2 (o, 2C); **IR** (neat): ν = 3086 (w), 3065 (w), 3021 (w), 2988 (w), 2917 (w), 2224 (m), 1599 (w), 1535 (s), 1502 (m), 1494 (m), 1452 (w), 1375 (s), 1306 (w), 1287 (w), 1224 (m), 1189 (s), 1147 (m), 1113 (w), 1072 (w), 1027 (s), 989 (w), 971 (m), 961 (m), 949 (m), 908 (w), 888 (w), 843 (m), 830 (m), 757 (w), 740 (w), 729 (m), 712 (m), 692 (m), 684 (m) cm^{-1}; **HRMS** (ESI) calcd for $(C_{18}H_{17}NO_2S + H)^+$: 312.1053; found: 312.1051.



302

This compound was obtained from **260** (84 mg, 0.4 mmol, 1 equiv) and 1-bromo-4-nitrobenzene (202 mg, 1.0 mmol, 2.5 equiv) following the representative procedure for the synthesis of compound **274** but at 60 °C (90 mg, 68%, orange solid) after purification by flash chromatography (ethyl acetate/methanol: 98/2 to 90/10).

m.p.: 138-140 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.8 Hz, 2H), 7.37 (dt, *J* = 8.8, 1.9 Hz, 2H), 7.24 (t, *J* = 7.1 Hz, 2H), 7.20-7.16 (m, 1H), 7.09 (d, *J* = 7.1 Hz, 2H), 3.55 (s, 2H), 3.54 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 185.9 (e), 146.4 (e), 139.2 (e), 136.6 (e), 134.3 (o, 2C), 128.9 (o, 2C), 128.3 (o, 2C), 126.3 (o), 123.2 (o, 2C), 84.7 (e), 44.8 (e), 43.3 (o, 2C); **IR** (neat): ν = 3032 (w), 3009 (w), 2923 (w), 1601 (w), 1587 (w), 1541 (s), 1508 (s), 1455 (w), 1401 (w), 1367 (m), 1334 (s), 1309 (m), 1295 (w), 1283 (w), 1232 (m), 1189 (s), 1139 (m), 1104 (m), 1074 (w), 1017 (m), 989 (w), 969 (m), 939 (m), 893 (w), 851 (m), 765 (w), 751 (w), 715 (s), 702 (m), 696 (s) cm^{-1}; **HRMS** (ESI) calcd for $(C_{17}H_{17}NO_4S + H)^+$: 332.0951; found: 332.0951.

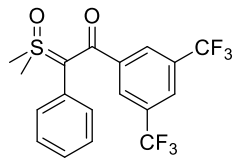


304

This compound was obtained from **261** (115 mg, 0.4 mmol, 1 equiv) and 2-bromoquinoline (208 mg, 1.0 mmol, 2.5 equiv) following the representative procedure for the synthesis of compound **274** but using P*t*Bu_3 as a ligand (73 mg, 54%, deep red solid) after purification by flash chromatography (petroleum ether/ethyl acetate: 90/10 to 80/20).

m.p.: 183-185 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 15.29 (br s, 1H), 7.82 (d, *J* = 9.6 Hz, 1H), 7.65 (d, *J* = 9.5 Hz, 1H), 7.60-7.47 (m, 3H), 7.41-7.30 (m, 4H), 7.30-7.27 (m, 1H), 7.27-7.21 (m, 3H), 7.19-7.18 (d, *J* = 7.3 Hz, 1H), 7.08 (t, *J* = 7.3 Hz, 1H), 4.56 (s, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 200.9 (e), 147.6 (e), 141.7 (e), 139.6 (e), 138.7 (e), 137.8 (o), 137.2 (e), 131.7 (o), 128.6 (o, 2C), 128.6 (o, 2C), 127.6 (o), 127.4 (o), 126.8 (o), 125.2 (o), 123.7 (o), 123.1 (o), 122.5 (e), 118.0 (o), 117.8 (o), 117.1 (o), 101.1 (e), 58.0 (o); **IR** (neat): ν = 3030 (w), 1630 (s), 1597 (s), 1580 (s), 1569 (s),

1537 (s), 1493 (m), 1469 (m), 1453 (m), 1410 (w), 1391 (s), 1334 (m), 1305 (w), 1292 (m), 1273 (s), 1211 (s), 1160 (w), 1143 (s), 1123 (w), 1097 (w), 1072 (w), 1025 (w), 987 (m), 966 (w), 948 (w), 921 (w), 875 (m), 857 (m), 837 (w), 804 (s), 782 (w), 763 (m), 764 (m), 743 (s), 720 (s), 694 (s), 674 (m) cm^{-1}; **HRMS** (ESI) calcd for $(C_{24}H_{17}NO + H)^+$: 336.1383; found: 336.1388.

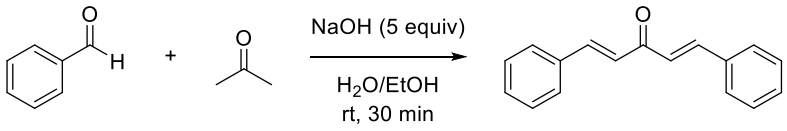


317

This compound was obtained from **255** (133 mg, 0.4 mmol, 1 equiv) and bromobenzene (107 μL, 1 mmol, 2.5 equiv) following the representative procedure for the synthesis of compound **274** (76 mg, 47%, white solid) after difficult purification by flash chromatography (petroleum ether/ethyl acetate: 50/50 to 30/70) that led to a moderate yield despite a yield of 73% determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard.

m.p.: 145-147 °C; **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.79 (s, 2H), 7.69 (s, 1H), 7.31-7.23 (m, 3H), 7.19-7.13 (m, 2H), 3.64 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 178.4 (e), 141.9 (e), 134.7 (o, 2C), 130.8 (e), 130.7 (e, q, *J* = 33.2 Hz, 2C), 129.0-128.8 (o, m, 2C), 128.7 (o, 2C), 128.2 (o), 123.0 (e, q, *J* = 271.1 Hz, 2C), 122.6 (o, quint., *J* = 3.7 Hz), 88.3 (e), 42.6 (o, 2C); **^{19}F NMR** (376 MHz, $CDCl_3$): -63.1; **IR** (neat): ν = 3083 (w), 3040 (w), 3023 (w), 2990 (w), 2914 (w), 1621 (w), 1523 (s), 1463 (w), 1436 (w), 1411 (m), 1348 (s), 1304 (w), 1283 (s), 1274 (s), 1232 (s), 1197 (s), 1187 (s), 1169 (s), 1159 (m), 1120 (s), 1109 (s), 1069 (w), 1012 (s), 984 (m), 961 (m), 935 (s), 905 (s), 876 (s), 843 (m), 773 (w), 753 (s), 699 (s), 681 (s), 672 (m) cm^{-1}; **HRMS** (ESI) calcd for $(C_{18}H_{14}F_6O_2S + H)^+$: 409.0691; found: 409.0690.

2.3 Synthesis of dba



SI19
2 equiv

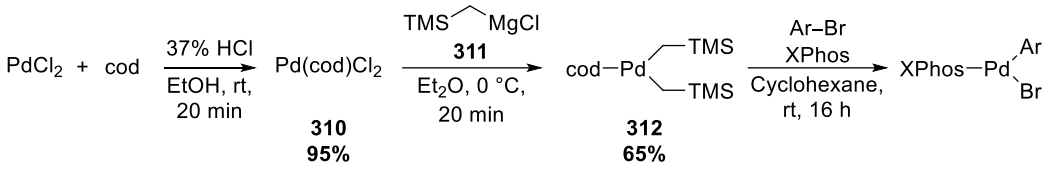
SI20
1 equiv

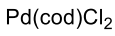
SI21
25%

Following the procedure described by Raju and co-workers,[100] under air, to a round-bottomed flask was dissolved sodium hydroxide (5.00 g, 125 mmol, 5 equiv) in water (25 mL) and the solution was allow to cool to room temperature. Ethanol (20 mL) was added followed by acetone (1.9 mL, 25 mmol, 1 equiv) and benzaldehyde (5.1 mL, 50 mmol, 2 equiv). The reaction was allowed to stir for 30 min at room temperature and the precipitate was filtered and wash thoroughly with cold water. The residue was dissolved in ethyl acetate and dried with magnesium sulfate. After filtration and removal of all the volatiles under vacuum, recrystallisation (ethyl acetate) afforded dibenzylideneacetone **SI21** (1.47 g, 25% yield, yellow solid).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, *J* = 16.0 Hz, 2H), 7.64-7.61 (m, 4H), 7.43-7.40 (m, 6H), 7.09 (d, *J* = 16.0 Hz, 2H), in agreement with previously reported data.[100]

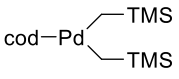
2.4 Synthesis of the oxidative addition complexes





310

Following the procedure described by Gómez-Ruiz and co-workers,[120] $PdCl_2$ (2.00 g, 11.3 mmol, 1 equiv) was dissolved in 37% HCl (12 mL) in a round-bottomed flask under air. The mixture was stirred until it cooled to room temperature and was then diluted with ethanol (226 mL) and filtered. The residue was washed with ethanol (2×10 mL). Then, 1,5-cyclooctadiene (3.3 mL, 27.1 mmol, 2.4 equiv) was added while stirring, which triggered the immediate formation of a yellow precipitate. The reaction was allowed to stir for another 20 minutes. The solid was then filtered, washed with diethyl ether (2×20 mL) and dried under high vacuum to afford dichloro(1,5-cyclooctadiene)palladium (3.07 g, 95%, yellow solid) which was used in the next step without further purification.

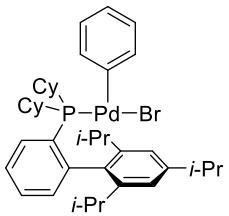


312

Following the procedure described by Skrydstrup and co-workers,[121] dichloro(1,5-cyclooctadiene)palladium (2.00 g, 7 mmol, 1 equiv) was suspended in diethyl ether (35 mL) in a flame-dried round-bottom flask under nitrogen. The reaction was cooled to 0 °C and (trimethylsilyl)methylmagnesium chloride (21 mL, 21.0 mmol, 3 equiv, 1 M in diethyl ether) was added dropwise over 10 minutes *via* syringe. The reaction was stirred at 0 °C for another 20 min. The reaction was quenched with

acetone (1 mL). All volatiles were removed under high vacuum at 0 °C. The flask was then open to air. The residue was triturated with pentane (70 mL) at 0 °C. After filtration on celite, the filtrate was recovered into an ice-cooled round-bottomed flask and all volatiles were removed under vacuum at 0 °C. The flask containing the desired product (1.77 g, white solid, 65%) was transferred into an argon-filled glovebox for storage at −30 °C. The compound can be handled briefly at room temperature and is air stable but decomposes quickly at room temperature (turns black). The compound can be stored for an extended period of time at 0 °C or below.

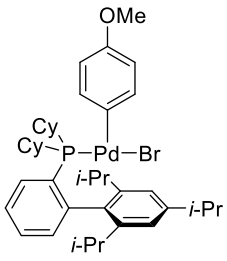
^{1}H NMR (400 MHz, C_6D_6): δ 5.15 (s, 4H), 2.03-1.83 (m, 8H), 0.77 (s, 4H), 0.34 (s, 18H), in agreement with previously reported data.[122]



313

Following a procedure reported by Iwasawa and co-workers that was modified.[123] Representative procedure for the synthesis of compound **313**. A J-Young Schlenk tube was charged with Pd(cod)(CH_2SiMe_3)$_2$ (389 mg, 1.0 mmol, 1 equiv) and XPhos (476.7 mg, 1.0 mmol, 1 equiv) in an argon-filled glovebox. The tube was sealed and taken out of the glovebox. Under N_2, distilled cyclohexane (20 mL) and bromobenzene (0.21 mL, 2 mmol, 2 equiv) were added. The tube was sealed and the mixture was stirred at room temperature for 16 hours. Pentane (20 mL) was then added to the reaction which was then stirred slowly (*ca* 100 rpm) at −30 °C for 1 hour. The precipitate thus formed was filtered, washed with pentane (2 × 20 mL), and dried under high vacuum to afford **313** (380 mg, 51%, white solid).

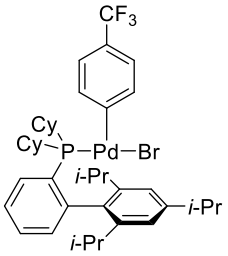
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67 (dt, *J* = 6.3, 3.2 Hz, 1H), 7.43-7.39 (m, 2H), 7.13 (s, 2H), 7.04 (d, *J* = 6.3 Hz, 2H), 6.93-6.85 (m, 3H), 6.80 (t, *J* = 7.0 Hz, 1H), 3.12 (sept., *J* = 6.9 Hz, 1H), 2.45 (sept., *J* = 6.7 Hz, 2H), 2.28-2.17 (m, 2 H), 2.00-1.89 (br s, 2H), 1.83-1.75 (m, 2H), 1.74-1.56 (m, 14H), 1.39 (d, *J* = 6.9 Hz, 6H), 1.29-1.07 (m, 6H), 0.90 (d, *J* = 6.6 Hz, 6H), 0.67-0.55 (m, 2H), in agreement with previously reported data.[13]



314

Compound **314** was obtained using 4-bromoanisole (0.25 mL, 2 mmol, 2 equiv) and $Pd(cod)(CH_2SiMe_3)_2$ (389 mg, 1 mmol, 1 equiv), following the general procedure described for the preparation of **313** (358 mg, 46%, white solid).

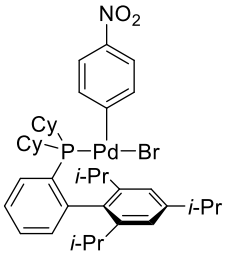
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 (dt, *J* = 6.3, 3.3 Hz, 1H), 7.44-7.35 (m, 2H), 7.11 (s, 2H), 6.92-6.84 (m, 3H), 6.60 (d, *J* = 8.3 Hz, 2H), 3.69 (s, 3H), 3.08 (sept., *J* = 6.9 Hz, 1H), 2.44 (sept., *J* = 6.7 Hz, 2H), 2.28-2.17 (m, 2H), 2.00-1.90 (m, 2 H), 1.83-1.76 (m, 2H), 1.74-1.55 (m, 14H), 1.39 (d, *J* = 6.9 Hz, 6H), 1.28-1.08 (m, 6 H), 0.89 (d, *J* = 6.6 Hz, 6H), 0.68 (qt, *J* = 12.9, 3.8 Hz, 2H), in agreement with previously reported data.[124]



315

In an argon-filled glovebox, a J-Young Schlenk tube was charged with Pd(cod)(CH_2SiMe_3)$_2$ (389 mg, 1.0 mmol, 1 equiv) and XPhos (477 mg, 1.0 mmol, 1 equiv). The tube was sealed and taken out of the glovebox. Under N_2, distilled cyclohexane (20 mL) and 4-bromobenzotrifluoride (0.14 mL, 1 mmol, 2 equiv) were added. The tube was sealed and the reaction was allowed to stir at room temperature for 48 hours. Pentane (20 mL) was then added to the reaction which was then stirred slowly (*ca* 100 rpm) at −40 °C for 24 hours. The precipitate which was formed was filtered, washed with pentane (2×20 mL), collected and dried under high vacuum to afford **315** (126 mg, 31%, white solid). Crystals suitable for X-ray were grown by slow evaporation over two weeks of a solution containing 10 mg of complex **315**, 1 mL of dichloromethane and 2 mL of hexane.

The **^{1}H NMR** reported here because of the complexity due to a slow equilibration between conformers; [125] **^{19}F NMR** (376 MHz, $CDCl_3$): -61.90 (s), -61.95 (br s), -62.8 (s); **^{31}P NMR** (202 MHz, $CDCl_3$): δ 57.6 (br), 28.7, 26.7; **HRMS** (ESI, MeCN): m/z calcd for $[C_{40}H_{53}F_3PPdBr - Br]^+$: 727.2872; found: 727.2878.



316

In an argon-filled glovebox, a J-Young Schlenk tube was charged with Pd(cod)(CH_2SiMe_3)$_2$ (389 mg, 1.0 mmol, 1 equiv) and XPhos (477 mg, 1.0 mmol, 1 equiv). The tube was sealed and taken out of the glovebox. Under N_2, distilled cyclohexane (20 mL) and 4-bromo-1-nitrobenzene (404 mg, 2 mmol, 2 equiv) were added. The tube was sealed and the reaction was allowed to stir at room temperature for 48 hours. Pentane (20 mL) was then added to the reaction which was then stirred slowly (*ca* 100 rpm) at −30 °C for 3 hours. The precipitate which was formed was filtered, washed with pentane (2×20 mL), collected and dried under high vacuum to afford **316** (545 mg, 69%, white solid). Crystals suitable for X-ray were grown by slow evaporation over two weeks of a solution containing 10 mg of complex **316**, 1 mL of dichloromethane and 2 mL of hexane. The **^{1}H NMR** is not reported here because of the complexity due to a slow equilibration between conformers;[125] **^{31}P NMR** (202 MHz, $CDCl_3$): δ 57.9 (br), 29.3, 27.1.

2.5 Control experiments with oxidative addition intermediates

2.5.1 Catalytic and kinetic competency of the complexes

Under nitrogen, a J-Young Schlenk tube was charged with XPhos (19 mg, 0.04 mmol, 0.1 equiv), complex **313** (30 mg, 0.04 mmol, 0.1 equiv), dba (28 mg, 0.12 mmol, 0.3 equiv) and Cs_2CO_3 (143 mg, 0.44 mmol, 1.1 equiv). Acetonitrile (0.4 mL) was then added and the mixture was stirred at room temperature for 10 minutes. Then, bromobenzene (107 µL, 1.0 mmol, 2.5 equiv) was added and the mixture was

stirred at room temperature for 3 minutes. Sulfoxonium ylide **255** (133 mg, 0.4 mmol, 1 equiv) was added, the inner wall of the Schlenk tube was rinsed with acetonitrile (0.4 mL). The tube was then sealed and placed in a pre-heated oil bath set at 80 °C, and the mixture was stirred for 10, 20, 30, and 40 minutes. The mixture was then filtered over celite using dichloromethane to transfer all the material and for rinsing. After evaporation of all volatiles, the crude was dissolved in $CDCl_3$ and analysed by ^1H NMR using 1,3,5-trimethoxybenzene as internal standard.

Similar measurements were performed for the coupling of bromobenzene and the ylide **255** when carried out under the standard conditions described for the preparation of compound **7**. No significant difference of conversion was observed, as shown in the table below.

Reaction using **313** as Pd source		Reaction using $Pd_2(dba)_3$ as Pd source	
time (min)	Product **317**	time (min)	Product **317**
10	9%	10	8%
10	9%	10	10%
20	17%	20	17%
20	19%	20	17%
30	21%	30	20%
30	22%	30	22%
40	25%	40	24%
40	28%	40	27%

After 14 hours, the conversion of the reaction using **313** as Pd source reached 85%; a control reaction with the same Pd source, but without added dba, reached 89% conversion after the same duration.

2.5.2 Relative initial rates

Under N_2, a J-Young Schlenk tube was charged with XPhos (0.1 mmol, 1 equiv), the relevant palladium complex (1 equiv), Cs_2CO_3 (1.1 equiv) and sulfoxonium ylide **267** (5 equiv). The tube was evacuated and refilled with nitrogen three times. Acetonitrile (2 mL) was added and the tube was then sealed, placed in a pre-heated oil bath set at 80 °C and stirred for 5, 10 or 20 minutes. The mixture was then allowed to cool to room temperature over 1 minute and the mixture was then filtered over celite using dichloromethane to transfer all the material and for rinsing. After evaporation of all volatiles, the conversion was measured by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard. Initial rates from the linear regressions were determined from the following data.

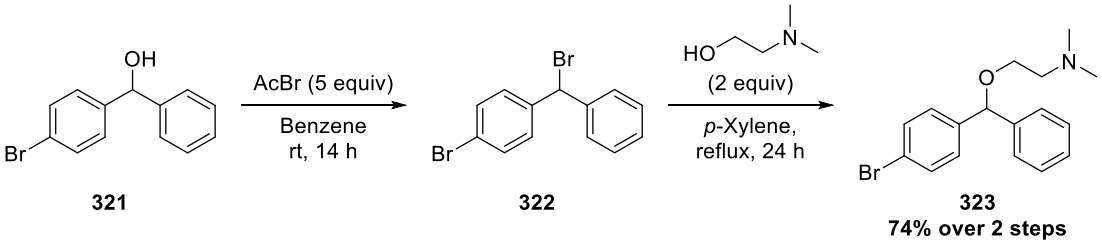
Reaction of complex **313**		Reaction of complex **314**		Reaction of complex **315**	
time (min)	Product **274**	time (min)	Product **276**	time (min)	Product **278**
10	12%	10	15%	5	10%
10	12%	10	18%	5	8%
20	19%	20	23%	10	23%
20	22%	20	26%	10	24%

2.5.3 Crossover experiment

Under nitrogen, a J-Young Schlenk tube was charged with XPhos (26 mg, 0.055 mmol, 1.1 equiv), complex **316** (43 mg, 0.055 mmol, 1.1 equiv), Cs_2CO_3 (17 mg, 0.05 mmol, 1.1 equiv) and sulfoxonium ylide **267** (7 mg, 0.05 mmol, 1 equiv). The tube was evacuated and refilled with nitrogen three times. Acetonitrile (0.5 mL) and *p*-bromotoluene (62 µL, 0.5 mmol, 10 equiv) were added, then the tube was sealed

and placed in a pre-heated oil bath set at 80 °C, and the mixture stirred for 14 h. The mixture was then filtered over celite using dichloromethane to transfer all the material and for rinsing. After evaporation of all volatiles, the crude was dissolved in $CDCl_3$ and analysed by ^1H NMR using 1,3,5-trimethoxybenzene as internal standard. A mixture of **280**/**267**/DMSO was observed in a 89/6/5 ratio. Cross-coupling product **275** was not detected.

2.6 Synthesis of bromazine



321 **322** **323**
74% over 2 steps

Following the modified procedure from Ahmadi *et al*,[126] Under N_2, **321** (2.63 g, 10 mmol, 1 equiv) was dissolved in distilled benzene (30 mL) in a flame-dried round-bottomed flask. Acetyl bromide (1.5 mL, 50 mmol, 5 equiv) was added over 1 min *via* syringe at room temperature. The reaction was stirred at room temperature for 14 hours. After evaporation of all volatiles, the residue was dissolved in 200 mL of diethyl ether and washed with a saturated aqueous solution of $NaHCO_3$ (2×50 mL) and brine (50 mL). The organic layer was dried with magnesium sulfate. Filtration and evaporation of the solvent *in vacuo* afforded **322** which was used in the next step without further purification (3.21 g, 98%, yellow oil).

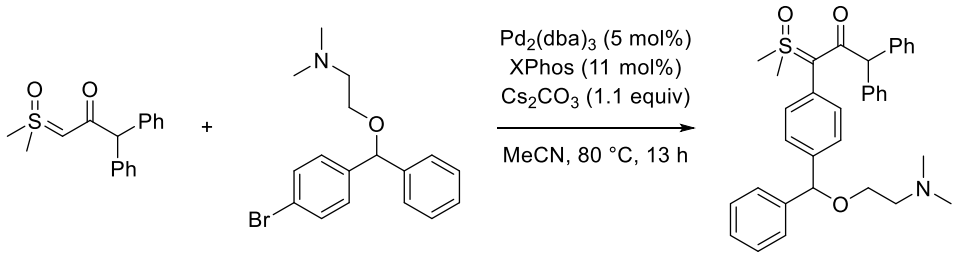
^1H NMR (500 MHz, $CDCl_3$): δ 7.49-7.40 (m, 4H), 7.37-7.24 (m, 5H), 6.22 (s, 1H).

Under N_2, 2-(dimethylamino)ethan-1-ol (1.6 mL, 16 mmol, 2 equiv) was dissolved in dry p-xylene (32 mL) in a flame-dried round-bottomed flask. **322** (2.61 g , 8 mmol, 1 equiv) was then added in solution in p-xylene (8 mL) and the mixture was heated at reflux for 24 h. The reaction mixture was then cooled to 0 °C and a saturated aqueous solution of Na_2CO_3 (50 mL) was carefully added. The aqueous layer was extracted with ethyl acetate (2×100 mL). The combined organic layers were washed with brine and dried with magnesium sulfate. After filtration and evaporation of the solvent *in vacuo*, the crude product was purified by flash chromatography on silica gel (dichloromethane/methanol: 90/10) to afford **323** (2.02 g, 76%, yellow oil).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.3 Hz, 2H), 7.32-7.29 (m, 4 H), 7.27-7.20 (m, 3H), 5.31 (s, 1H), 3.55 (t, *J* = 6.0 Hz, 2H), 2.60 (t, *J* = 6.0 Hz, 2H), 2.27 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 141.7 (e), 141.4 (e), 131.4 (o, 2C), 128.7 (o, 2C), 128.5 (o, 2C), 127.6 (o), 127.0 (o, 2C), 121.2 (e), 83.3 (o), 67.6 (e), 58.9 (e), 46.0 (o, 2C); **IR** (neat): ν = 3026 (w), 2940 (w), 2861 (w), 2817 (w), 2768 (w), 2449 (w), 1590 (w), 1485 (m), 1453 (m), 1397 (m), 1337 (w), 1295 (w), 1184 (w), 1103 (s), 1070 (s), 1035 (s), 1010 (s), 957 (w), 930 (w), 889 (w), 794 (s), 748 (m), 714 (m), 714 (w), 700 (s), 673 (w) cm-1; **HRMS** (ESI) calcd for $(C_{17}H_{20}BrNO + H)^+$: 334.0801; found: 334.0804.

2.7 Post-functionalisation

2.7.1 Coupling with bromazine



261
1 equiv

323
1.1 equiv

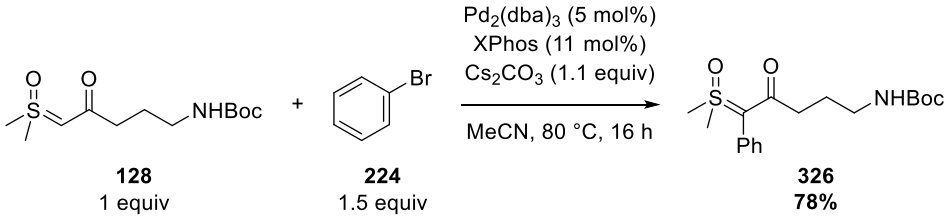
325
79%

Under N_2, a J-Young Schlenk tube was charged with XPhos (21 mg, 0.044 mmol, 0.11 equiv), Pd_2dba_3 (18 mg, 0.02 mmol, 0.05 equiv) and Cs_2CO_3 (143.4 mg, 0.44 mmol, 1.1 equiv). Acetonitrile (0.4 mL) was then added and the mixture was stirred at room temperature for 10 min. Then, bromazine **323** (147 mg, 0.44 mmol, 1.1 equiv) was added in solution in acetonitrile (0.4 mL) followed by sulfoxonium ylide **261** (115 mg, 0.4 mmol, 1 equiv). The tube was then sealed, placed in a pre-heated oil bath set at 80 °C and stirred for 13 hours. The crude was then filtered over celite using dichloromethane to transfer all the material and for rinsing. After evaporation of all volatiles, purification by flash chromatography (dichloromethane/methanol: 95/5 to 85/15) afforded compound **325** (170 mg, 79%, amorphous solid).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38-7.31 (m, 4H), 7.30-7.25 (m, 3H), 7.27-7.19 (m, 4H), 7.18-7.13 (m, 6H), 7.08 (d, *J* = 8.2 Hz, 2H), 5.38 (s, 1H), 4.98 (s, 1H), 3.62 (t, *J* = 5.7 Hz, 2H), 3.45 (s, 6H), 2.69 (t, *J* = 5.8 Hz, 2H), 2.34 (s, 6H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 186.2 (e), 141.8 (e), 141.6 (e), 141.0 (e, 2C), 134.7 (o, 2C), 130.6 (e), 128.8 (o, 4C), 128.2 (o, 2C), 127.9 (o, 4C), 127.4 (o), 126.9 (o, 2C), 126.8 (o, 2C), 126.0 (o, 2C), 86.6 (e), 83.5 (o), 66.8 (e), 58.5 (e), 57.4 (o), 45.5 (o, 2C), 42.5 (o, 2C); **IR** (neat): ν = 3416 (w), 3023 (w), 2971 (w), 2971 (w), 2923 (w), 2820 (w), 2771 (w),

1599 (w), 1546 (s), 1493 (m), 1451 (m), 1406 (w), 1362 (w), 1302 (w), 1266 (w), 1186 (s), 1165 (s), 1098 (m), 1073 (m), 1057 (m), 1021 (s), 971 (m), 935 (w), 853 (w), 811 (w), 784 (w), 737 (m), 697 (s) cm^{-1}; **HRMS** (ESI) calcd for $(C_{34}H_{37}NO_3S + H)^+$: 540.2567; found: 540.2570.

2.7.2 Gram scale reaction

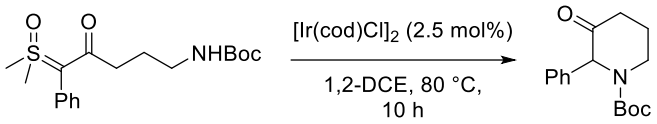


Under N_2, a J-Young Schlenk tube was charged with XPhos (189 mg, 0.396 mmol, 0.11 equiv), Pd_2dba_3 (165 mg, 0.18 mmol, 0.05 equiv) and Cs_2CO_3 (1.29 g, 3.96 mmol, 1.1 equiv). Acetonitrile (3.6 mL) was then added and the mixture was stirred at room temperature for 10 min. Then, bromobenzene (0.58 mL, 5.4 mmol, 1.5 equiv) was added followed by sulfoxonium ylide **128** (1.00 g, 3.6 mmol, 1 equiv) The inner wall of the Schlenk tube was rinsed with acetonitrile (3.6 mL) and the tube was then sealed, placed in a pre-heated oil bath set at 80 °C and stirred for 15 hours. The crude was then filtered over celite® at room temperature using dichloromethane to transfer all the material and for rinsing. After evaporation of all volatiles, purification by flash chromatography (ethyl acetate/methanol: 95/5 to 90/10) afforded compound **326** (1.00 g, 79%, off-white solid).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40-7.30 (m, 3H), 7.28-7.22 (m, 2H), 4.80 (br s, 1H), 3.49 (s, 6H), 3.14-2.96 (m, 2H), 2.19 (t, *J* = 6.6 Hz, 2H), 1.71 (q, *J* = 6.6 Hz, 2H), 1.41 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 188.2 (e), 155.9 (e), 134.6 (o, 2C), 131.8 (e), 128.6 (o, 2C), 128.0 (o), 82.2 (e), 78.7 (e), 43.0 (o, 2C), 40.4 (e), 35.5 (e), 28.4 (o, 3C), 25.3 (e); **IR** (neat): ν = 3373 (m), 3019 (w), 2999 (w), 2969 (w), 2949

(w), 2930 (w), 2867 (w), 1684 (s), 1557 (s), 1520 (s), 1489 (w), 1447 (w), 1439 (w), 1409 (w), 1365 (m), 1346 (m), 1321 (w), 1290 (w), 1267 m), 1246 (s), 1189 (s), 1151 (s), 1088 (w), 1063 (w), 1030 (s), 988 (s), 938 (w), 915 (w), 863 (w), 791 (w), 781 (w), 771 (w), 758 (w), 728 (w), 700 (m), 677 (w) cm^{-1}; **HRMS** (ESI) calcd for $(C_{18}H_{27}NO_4S + H)^+$: 354.1734; found: 354.174.

2.7.3 Iridium-catalysed cyclisation



326
1 equiv

327
77%

Under N_2, a J-Young Schlenk tube was charged with **326** (35 mg, 0.1 mmol, 1 equiv) and $[Ir(cod)Cl]_2$ (1.7 mg, 0.0025 mmol, 0.025 equiv). The tube was evacuated and refilled 3 times with N_2. 1,2-Dichloroethane (1.0 mL) was then added and the mixture was stirred at 80 °C overnight. After cooling down to room temperature, the reaction mixture was transferred into a round-bottomed flask using dichloromethane to transfer all the material and for rinsing. After evaporation of all volatiles, purification by flash chromatography (petroleum ether/ethyl acetate: 90/10 to 85/15) afforded compound **327** (19 mg, 69%, colourless oil).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (t, *J* = 7.4 Hz, 2H), 7.31-7.26 (m, 1H), 7.21 (d, *J* = 7.6 Hz, 2H), 5.64, (br s, 1H), 4.08 (br s, 1H),3.39-3.24 (m, 1H), 2.53-2.37 (m, 2H), 2.01-1.83 (m, 2H), 1.43 (s, 9H), in agreement with previously reported data.[127]

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