# Internship report

# "Using Renewable Feedstock in Dual Transition Metal Photoredox Catalysis"

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2nd YEAR CHEMISTRY AND BIOTECHNOLOGY STUDENT

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# Acknowledgement

# List of Abbreviations

**ACN: Acetonitrile**

**DCM: Dichloromethane**

**d: doublet**

**DMF: Dimethylformamide**

**EtOAC: Ethyl acetate**

**GC-FID: Gas Chromatography-Flame Ionization Detection**

**GC-MS: Gas chromatography-mass spectrometry**

**m: multiplet**

**q: quartet**

**Std: Standard**

**t: triplet**

**TLC: Thin layer chromatography**

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# I-Introduction

For thousands of years, agriculture has been able to sustain the constantly growing population on earth. However, each year a significant amount of waste is generates from this agriculture. While one part of this waste can be used for composting the other is sometimes burnt by farmers resulting in green houses emissions like carbon dioxide.[1]In the aim of developing a more sustainable chemistry, the waste deriving from crop cultivation or biomass can be used in chemistry as they contain diverse useful molecules.

Aspergus or Agaricus Bisporus for example has a smell that come from asparagusinic acid which has anti-bacterial properties. The byproduct roots of this Aspergus plant contained molecules like polysaccharides, free amino acids and phenolic acids.[2]The seeds and leaves of plants like Blueberries, Nettle or Strawberies also contains a large amount of ferulic or phenolic acids.[3]These phenolic acids can be isolated from blueberries for instance by a simple treatment with HCl following by a liquid-liquid extraction with hexane/water first to remove the lipids and then with ethyl acetate/water to extract the compounds of interest. (Claudio reference, not given)

To remain with the ideology of 'green chemistry' these phenolic acids can be converted into polyfunctional monomers[4], [5] by using isocyanides based multicomponent reactions (MCRs) (figure1). MCRs are one-pot reactions involving at least three reactants. They are convergent one step reactions with high efficiency and atom economy. One of the most common types of MCRS are Isocyanides based MCRs like the Ugi or Passerini reactions.
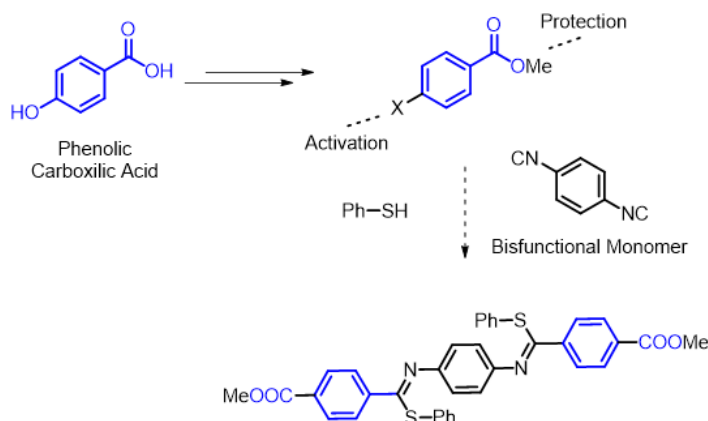


**Figure 1**: Transformation of phenolic carboxylic acid into a monomer using MCR

Isocyanides have a similar property compared to carbenes or carbon monoxide as they all can react as nucleophile or electrophile. The alone pair on the carbon atom allow them to act as ligand in transition metal-catalyzed reactions and thus allowing different type of reactivity.[6]Indeed, over the past years the interest of Isocyanide based MCRs catalyzed by transition metals have emerged.

In this report, the focus will be on MCRs involving isocyanides and dual metal-photoredox catalysis.

Previous studies have shown that isocyanides can be inserted in a Pd-carbon bond and allow the synthesis of molecules like amidines [7]. This type of transition-metal reactions where an isocyanide is inserted into a sigma bond are referred as 'isocyanide insertion'. Despite its well-

known reactivity Pd is a rare and expensive metal. The used of cheap base metal catalyst is underexplored in this type of reaction.

In 2022, Indrajit et al. published [8]in Nature a new type of adjustive cross coupling reactions using homogeneous catalysis with Ni and an organophotocatalyst under visible light.
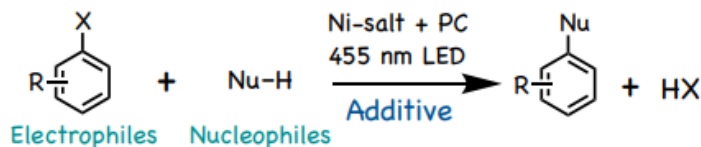


**Figure 2:** General adaptive catalytic homogeneous reactions

This adaptive system was the basis of the main reaction of this project:
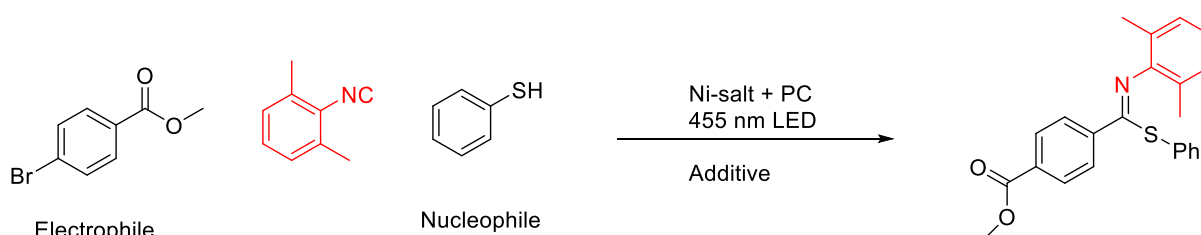


**Figure 3**: General scheme of the main reaction

In contrary of the adaptive system mentioned previously, there is an isocyanide that is present, and the aryl bromide can be derived from the phenolic acid previously mentioned.

The main objective of this project was to optimize the reaction to avoid the sides products and thus increase the yield of the desired product. To do so, different bases, photocatalysts, ligands and reagents were tested and each of them impacted more or less of one the keys steps of the reaction. The mechanism of the Ni (II)-Photocatalyst isocyanide insertion is not elucidated yet. However, a general mechanism can be proposed in 3 steps: Oxidative addition, 1,1 migratory insertion and reductive elimination.
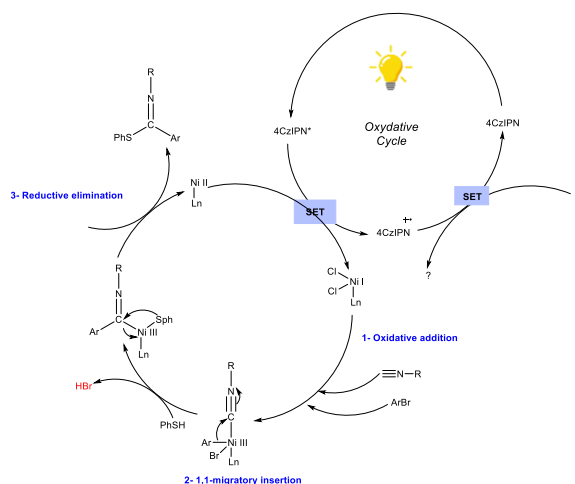


**Figure 4** : General mechanism of the reaction

# II-Institute overview

AMIBM or Aachen-Maastricht Institute for Biobased Materials, is a Dutch research institute founded in 2016 through a collaboration between Maastricht, RTWH Aachen universities, Fraunhofer IME and DWI Leibniz Institute for Interactive Materials.

It is located on the Brightlands Chemelot Campus in the province of Limburg near Belgium, with a branch office in Germany.

It focuses on innovative fundamental, applied and translational research in biobased material. AMIBM's work involves designing, creating, and translating biobased molecules into practical applications that excel in both functionality and sustainability.

The institute include transdisciplinary research groups in molecular and applied biotechnology, biobased organic chemistry and Sustainable polymer synthesis.

The Biobased organic chemistry team focused on alternative peptide synthesis, sustainable cultivation and isocyanides synthesis using photoflow reactors.

# III-Materials and methods

## 1) Synthesis of some starting materials

### a) Synthesis of the 2,6-Dimethylphenyl isocyanide[9]
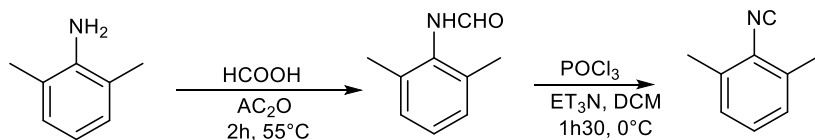


**Figure 5**: 2,6-Dimethylphenyl isocyanide reaction scheme

Formic acid (1equiv, 80 mmol, 4.5 ml) was added to acetic anhydride (1.1equiv, 88 mmol, 3.3 ml) and the mixture was stirred for 2h at 55°C. After 2h this mixture was added dropwise at 0°C to stirred solution of 2,6-dimethylaniline (1equiv, 20 mmol, 2.5 mL) in 40 mL of THF and stirred during 2h at rt. The reaction was monitored by TLC with Heptane/EtOAc (8:1). Formamides were obtained as solids after under pressure evaporation of the solvent.

The obtained formamides were putted in 20 mL of CH2CL2 and cooled down at 0°C were then dehydrated by adding dropwise POcl3 (1.2 equiv, 24 mmol, 2.2 mL). After the reaction was completed, a saturated solution of Na2CO3 was added at 0°C to quench the reaction. The workup was done by extracting the resulting mixture with CH2CL2. The residue was finally purified by Chromatography with the solvent mixture: Heptane/EtOAc (3:1) to obtain white solid 2,6-Dimethylphenyl isocyanide.

Analysis:

White smelly solid, yield = 23 %

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.21 – 7.07 (m, 3H), 2.42 (s, 6H). (Appendix 1)

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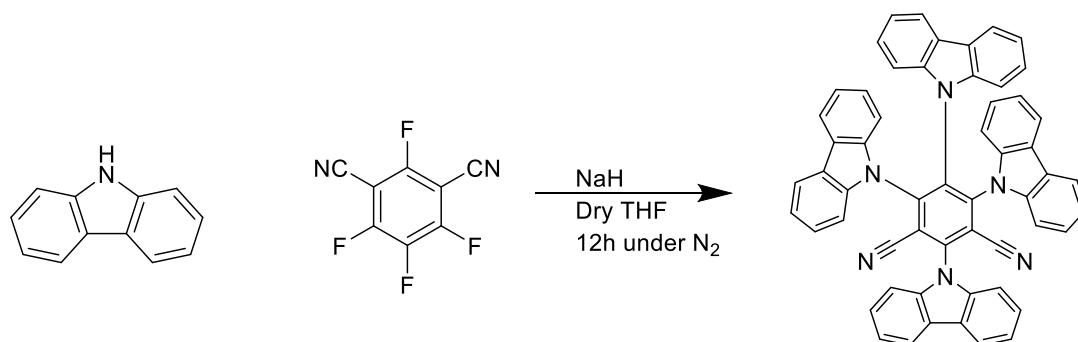
**Figure 6:** 4-CZIPN reaction scheme

To a stirred solution of carbazole ((8 equiv, 16 mmol, 2.68 g) in dry THF under nitrogen was added slowly sodium hydride in 60% suspension in mineral oil (5eq, 10 mmol, 240 mg)) at rt. 2,4,5,6- tetrafluoroisophthalonitrile (1 equiv, 2 mmol, 400 mg) was then added after 30 min and the stirring mixture was let for 12h at rt. After 12h, TLC was done with Heptane/EtOAc (8:1) and 4 mL of water was added to quench the excess of NaH.

The crude was purified by column chromatrograhy on silica gel using first Heptane:EtOAc (9:1) and then DCM:heptane (1:1).

Analysis:

Yellow powder, yield = 78 %

^{1}H NMR (300 MHz, CDCl$_3$) δ 8.22 (d, *J* = 7.7 Hz, 2H), 7.74 – 7.65 (m, 8H), 7.49 (ddd, *J* = 8.0, 6.4, 1.9 Hz, 2H), 7.33 (d, *J* = 7.2 Hz, 2H), 7.24 – 7.19 (m, 4H), 7.13 – 7.03 (m, 8H), 6.82 (t, *J* = 7.4 Hz, 4H), 6.66 – 6.59 (m, 2H) (Appendix 2).

## 2) Target product synthesis[8]
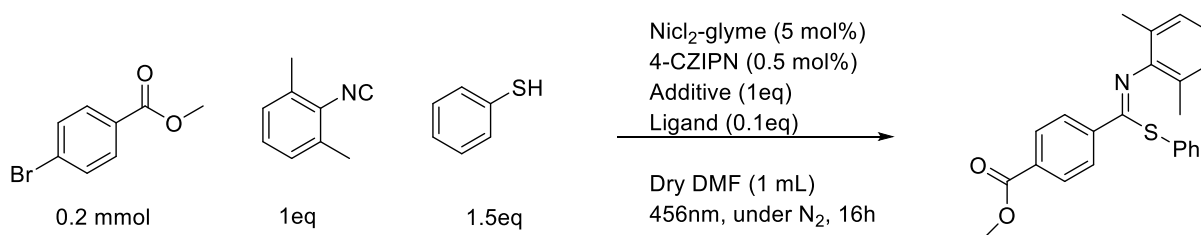


**Figure 7:** Target product reaction scheme

In a microvial were put the arylbromide (0.2 mmol, 43 mg), NiCl2-glyme (0.05 equiv, 2.4 mg) 4-CZIPN (0.005 equiv, 0.8 mg), ligand (0.1 equiv, 5.4mg) isocyanide and thiophenol (1.5 equiv, 30 ul). The microvial was sealed, the dry solvent was added, and the mixture was freezed under nitrogen, put under vacuum and melted under nitrogen, this same process was repeated 3 times before putting it at 456 nm at rt for 16h.

After 16h, a TLC was done with Heptane/EtOAC (8:1) and depending on the conditions, the crude was either, analyze by GC-FID or GC-MS with acetonitrile as solvent or by ^{1}H NMR.

The purification of the target product was done by auto column chromatrography using ECOFLEX Silica 12 g Column and Hexane/EtOAC (0-100% of EtOAC) as solvent mixture with 2% stepwise gradient elution (Appendix 3).

This is a general procedure but throughout the project, the conditions of the reactions were changed (adding additives, changing the limited reagent, metal catalyst, ligand, etc) but the procedure remained the same.

Analysis

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.89 (d, $J$ = 8.3 Hz, 2H), 7.63 (d, $J$ = 8.2 Hz, 2H), 7.21 – 6.93 (m, 9H), 3.89 (s, 3H), 2.24 (s, 6H). (Appendix 4)

CG-MS (ESI+): m/z= 375.1 (Appendix 5) for target product derived from 4-methylbromobenzoate

CG-MS (ESI+): m/z= 218 (Appendix 6) for target product derived from 4-iodobenzotrifluoride

# 3) Calibration curve of the target product by GC-FID

5 solutions at different concentrations of the pure target product were prepared by using acetonitrile as solvent and adding 60 µL of mesitylene (final concentration of 0.28 M).

The peak area ratio between the internal standard and the target product was measured by GC-FID (**Appendix 7**) to obtain to below table and drawn the external calibration curve.

|  | std 1 | std 2 | std 3 | std 4 | std 5 |
|---|---|---|---|---|---|
| $C_{P\,(M)}$ | 0.254 | 0.127 | 0.063 | 0.032 | 0.010 |
| $C_P/C_{IS}$ | 0.937 | 0.460 | 0.230 | 0.120 | 0.036 |
| $A_P/A_{IS}$ | 0.735 | 0.193 | 0.096 | 0.046 | 0.019 |

**Table 1**: Data of the different standards solutions of the pur target product.

# IV- Main Results

Due to their high cost, some starting reagents like the 2,6 dimethylphenylisocyanide and the photocatalyst 4-CZIPN were first synthetized. The photocatalyst was obtained pure with a good yield (78%), the isocyanide yield was less than that (23%) because the second step of the reaction was performed at 0°C following the general procedure and, in the literature, it is mentioned that for certain type of isocyanide it is important to be at least at – 78°C.

## 1) Reaction with Methyl 4-bromobenzoate as limiting reagent

The work done previously on this reaction (Figure 8), shown that the conditions below were giving the best yield (20%) and some control experiments confirmed the necessity of for example the use of the light or the metal catalyst (Appendix 8).
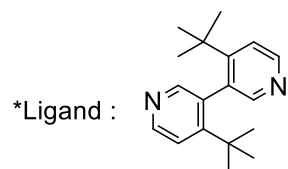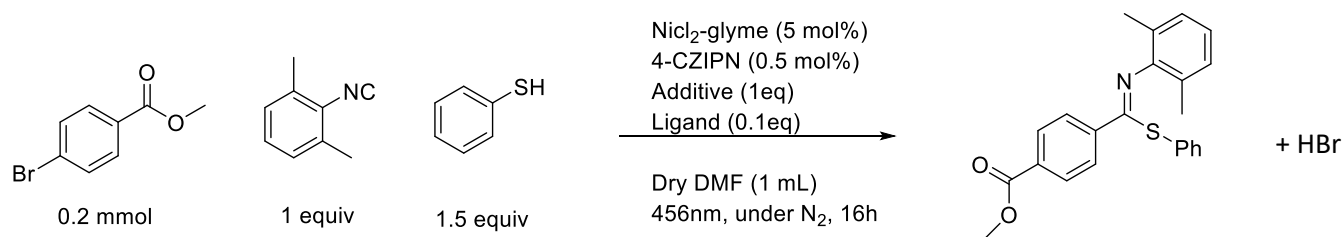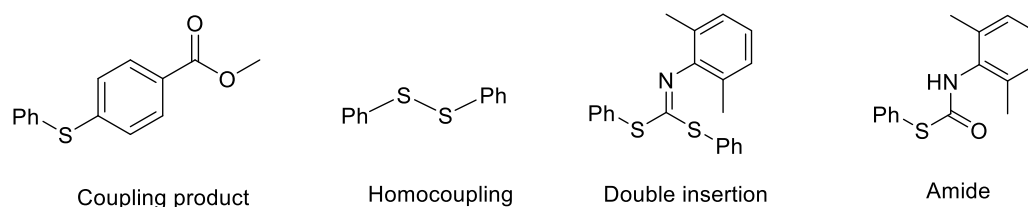
**Figure 8:** Reaction scheme with the main side products

Sides products identified by GC-MS (Appendix 6) like the coupling product and the homocoupling of the thiophenol have an impact on this yield.

The previous optimization done to obtain this 20% yield were only based on GC-MS yield and the $^1$H NMR spectra of the crude of the reaction was quite complex, it wasn't easy to distinguish the target product among the overlapping signals from other products like the double insertion.

So, to have another method of quantification, a calibration curve was done by using mesitylene as internal standard.

**Figure 9:** Calibration curve of the pure target product with mesitylene as internal standard

Ap: Area of target product, Ais : Area of internal standard, Cp : Concentration of target product, Cis: Concentration of internal standard

(std 1 was removed because, it wasn't in the curve's linear range)

Based on this calibration curve, the optimization began by adding different bases to neutralize the hydrobromic acid formed, (Figure 8) and it is known that isocyanides are quite sensitive to acidic conditions. (source)

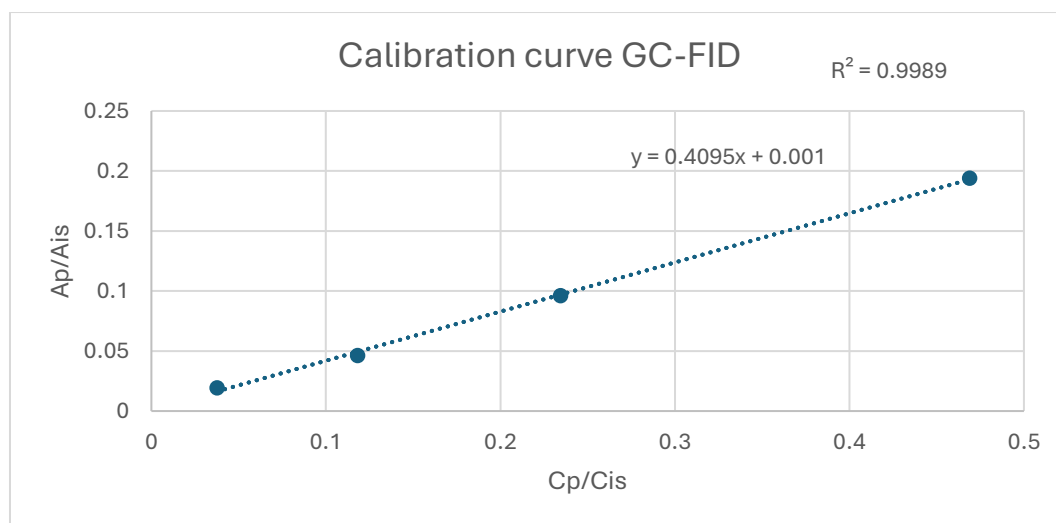| Entry | Solvent | Additive (1equiv) | GC-FID yield (%) | Isolated yield (%) |
|---|---|---|---|---|
| **Influence of a Base** | | | | |
| 1a | DMF | - | - | 20 |
| 2a | DMF | $CsCO_3$ | 12 | |
| 3a | DMF | $K_3PO_4$ | 32 | - |
| 4a | DMF | 2,6-Lutidine | 31 | - |
| 5a | DMF | $K_2CO_3$ | 78 | 11 |
| 6a | DMF | Pyridine | (209) | - |
| 7a | DMF | BTMG | (86) | 8 |
| 8a | DMF | Cyclohexylamine | (19) | 29 |
| 9a | DMF | $K_2CO_3$ + 1% water | (129) | 32 |
| 10a | DMF | $K_2CO_3$ + 5% water | (219) | 23 |
| 11a | DMF | $K_2CO_3$ + 8% water | (320) | 13 |
| 12a | DMF | $K_2CO_3$ + 10% water | (46) | - |
| 13a | DMF | $K_2CO_3$ + 30% water | (3) | - |
| **Influence of the solvent** | | | | |
| 14a | ACN | $K_2CO_3$ + 1% water | (73) | 34 |
| 15a | DCM | $K_2CO_3$ + 1% water | (50) | - |
| 16a | Toluene | $K_2CO_3$ + 1% water | (28) | - |
| 17a | THF | $K_2CO_3$ + 1% water | (34) | - |
| 18a | Methanol | $K_2CO_3$ + 1% water | (8) | - |

**Table 2:** Optimization results with different bases and solvent

Various bases were screened, the best yield was achieved with $K_2CO_3$ (5a) using the calibration curve. However, the isolated yield (11 %) of the target product was less than expected (78 %).

The solvent used was DMF, an organic solvent and $K_2CO_3$ being polar is not soluble in it. According to that, different reactions were performed by adding different amount of water with $K_2CO_3$. Interestingly, by adding 1% of water the yield increased by 10%, whereas adding more than 1% seems contrary to have a reducing effect on this yield.

Unfortunately, due to a technical issue with the GC-FID,the measurement of peak area in some conditions (in bracket) were measured with GC-MS to have an idea of the Ap/Ais ratio (Table 1). The results weren't making sense because GC-MS detector was different from the one of GC-FID.

The conditions with the presumed best yield were isolated, condition 9a gave the best yield and then some polar, non-polar and protic solvents were screened. The use of acetonitrile as solvent increased the yield from 32 to 34%.

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## 2) Reaction with 4-iodobenzotrifluoride as limiting reagent

The starting material or limiting reagent was changed (Figure 9) to be able to perform decoupling $^{19}$F NMR **(**Figure 10) where the peaks are easily recognizable. The reaction below was done with the optimal conditions found using the 4-methylbromobenzoate.
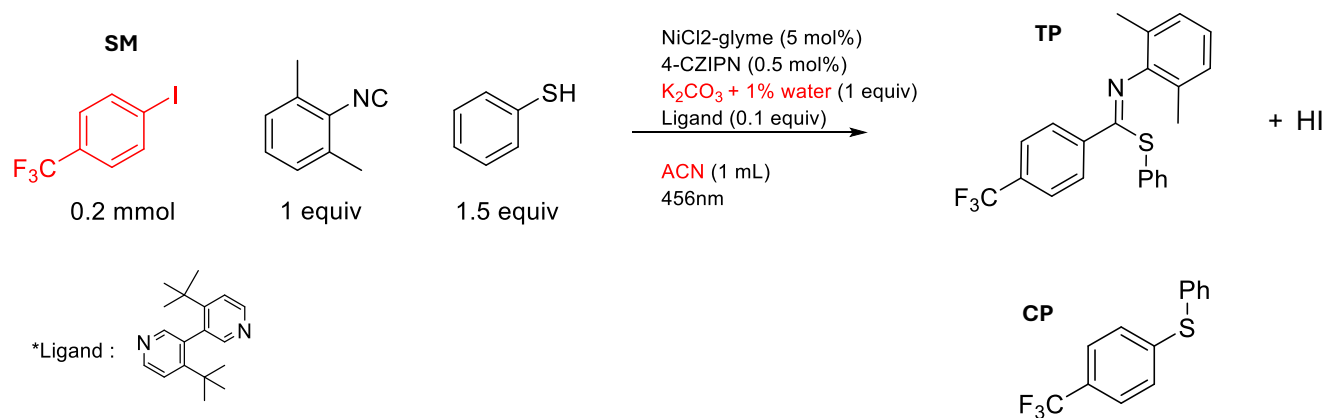


**Figure 9:** Reaction scheme with 4-iodobenzotrifluoride
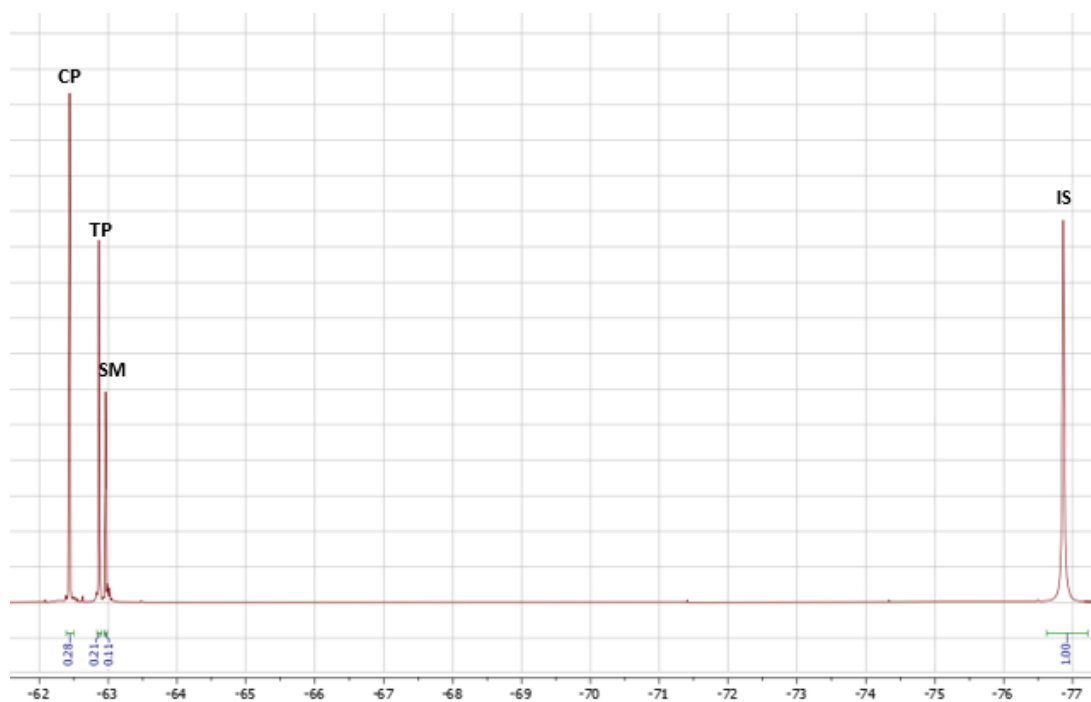


**Figure 10:** $^{19}$F NMR (300 MHz, CdCl$_3$) of the reaction crude.

CP: Coupling product SM: Starting material, TP: Target product, IS: internal standard or *2,2,2 trifluoroethanol*

The optimization then continued by screening different photocatalysts, Ni (II) and Cu (II) sources. When varying the Ni (II) sources any improvement on the yield was observed and by using Cu (II) instead of Ni (II), the yield of the target product decreased considerably (6b-9b).

| # | ArX | R-NC | Nu | Solvent | PC | Metal catalyst | Ligand | Additive | $^{19}F$-NMR yield (%) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | SM | TP | CP |
| **Reference** | | | | | | | | | | | |
| 1b | F3C-Ph-I | 2,6-Me-Ph-NC | PhSH | ACN | 4-CzIPN | NiCl2-glyme | L1 | K2CO3 + 1% water | 32 | 30 | 31 |
| **Influence of the Metal source** | | | | | | | | | | | |
| 2b | F3C-Ph-I | 2,6-Me-Ph-NC | PhSH | ACN | 4-CzIPN | NiCl2 | L1 | K2CO3 + 1% water | 11 | 21 | 28 |
| 3b | F3C-Ph-I | 2,6-Me-Ph-NC | PhSH | ACN | 4-CzIPN | NiOAc | L1 | K2CO3 + 1% water | 22 | 16 | 17 |
| 4b | F3C-Ph-I | 2,6-Me-Ph-NC | PhSH | ACN | 4-CzIPN | NiBr2 | L1 | K2CO3 + 1% water | 5 | 17 | 22 |
| 5b | F3C-Ph-I | 2,6-Me-Ph-NC | PhSH | ACN | 4-CzIPN | Ni(COD)(DQ) | L1 | K2CO3 + 1% water | 2 | 28 | 36 |
| 6b | F3C-Ph-I | 2,6-Me-Ph-NC | PhSH | ACN | 4-CzIPN | CuBr2 | L1 | K2CO3 + 1% water | 15 | 7 | 47 |
| 7b | F3C-Ph-I | 2,6-Me-Ph-NC | PhSH | ACN | 4-CzIPN | CuCl2 | L1 | K2CO3 + 1% water | 10 | 10 | 51 |
| 8b | F3C-Ph-I | 2,6-Me-Ph-NC | PhSH | ACN | 4-CzIPN | Cu(OTF)2 | L1 | K2CO3 + 1% water | 3 | 2 | 31 |
| 9b | F3C-Ph-I | 2,6-Me-Ph-NC | PhSH | ACN | 4-CzIPN | CuOAC | L1 | K2CO3 + 1% water | 26 | 3 | 37 |

**Table 3:** Optimization results with Ni (II) or Cu(II) salts

By screening different photocatalyst, it was observed that the coupling product was much more favored while using a derivative of 4-CZIPN, Tert-butyl 4-CZIPN the yield of the desired product increased.

| **Influence of the photocatalyst** | | | | | | | | | SM | TP | CP |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 10 b | F3C-Ph-I | 2,6-Me-Ph-NC | PhSH | ACN | 5-CzIPN | NiCl2-glyme | L1 | K2CO3 + 1% water | 2 | 26 | 47 |
| 11b | F3C-Ph-I | 2,6-Me-Ph-NC | PhSH | ACN | Tert-butyl 4-CzIPN | NiCl2-glyme | L1 | K2CO3 + 1% water | 10 | 36 | 57 |
| 12b | F3C-Ph-I | 2,6-Me-Ph-NC | PhSH | ACN | 3DPA-IPN | NiCl2-glyme | L1 | K2CO3 + 1% water | 13 | 21 | 34 |
| 13b | F3C-Ph-I | 2,6-Me-Ph-NC | PhSH | ACN | 4DPA-IPN | NiCl2-glyme | L1 | K2CO3 + 1% water | 8 | 21 | 52 |
| 14b | F3C-Ph-I | 2,6-Me-Ph-NC | PhSH | ACN | IBP-DI | NiCl2-glyme | L1 | K2CO3 + 1% water | 6 | 16 | 58 |

**Table 4:** Optimization results with different photocatalysts

As the yield stayed around 35 %, the number of equivalents of the starting materials has been changed to see the effect (table 4).

| **Influence of the number of equivalent** | | | | | | | | | SM | TP | CP |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 15b | F3C-Ph-I | 2,6-Me-Ph-NC | PhSH (0 eq) | ACN | Tert-butyl 4-CzIPN | NiCl2-glyme | L1 | K2CO3 + 1% water | 0 | 0 | 100 |
| 16b | F3C-Ph-I | 2,6-Me-Ph-NC | PhSH (0.75 eq) | ACN | Tert-butyl 4-CzIPN | NiCl2-glyme | L1 | K2CO3 + 1% water | 28 | 21 | 39 |
| 17b | F3C-Ph-I | 2,6-Me-Ph-NC | PhSH (3 eq) | ACN | Tert-butyl 4-CzIPN | NiCl2-glyme | L1 | K2CO3 + 1% water | 1 | 19 | 58 |
| 18b | F3C-Ph-I | 2,6-Me-Ph-NC (0 eq) | PhSH | ACN | Tert-butyl 4-CzIPN | NiCl2-glyme | L1 | K2CO3 + 1% water | 100 | 0 | 0 |
| 19b | F3C-Ph-I | 2,6-Me-Ph-NC (0.5 eq) | PhSH | ACN | Tert-butyl 4-CzIPN | NiCl2-glyme | L1 | K2CO3 + 1% water | 0 | 16 | 37 |
| 20b | F3C-Ph-I | 2,6-Me-Ph-NC (2 eq) | PhSH | ACN | Tert-butyl 4-CzIPN | NiCl2-glyme | L1 | K2CO3 + 1% water | 52 | 21 | 47 |

**Table 5:** Optimization results after changing of the number of equivalents of thiophenol and isocyanide

As expected without thiophenol, the main product is the coupling product. Interestingly without the isocyanide (18b) there was no conversion at all.

| # | ArX | R-NC | Nu | Solvent | PC | Metal catalyst | Ligand | Additive | $^{19}F$-NMR yield (%) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | SM | TP | CP |
| **Reference** | | | | | | | | | | | |
| 11b | F3C-Ph-I (0.2mmol) | 2,6-Me-Ph-NC (1 eq) | PhSH (1.5 eq) | ACN | Tert-butyl 4-CzIPN (0.005 eq) | NiCl2-glyme (0.05 eq) | L1 (0.1 eq) | K2CO3 + 1% water (1 eq) | 10 | 36 | 57 |
| **Influence of the the ligand** | | | | | | | | | | | |
| 27b | F3C-Ph-I | 2,6-Me-Ph-NC | PhSH | ACN | Tert-butyl 4-CzIPN | NiCl2-glyme | L2 | K2CO3 + 1% water | 0 | 40 | 64 |
| 28b | F3C-Ph-I | 2,6-Me-Ph-NC | PhSH | ACN | Tert-butyl 4-CzIPN | NiCl2-glyme | L3 | K2CO3 + 1% water | 19 | 37 | 48 |
| 29b | F3C-Ph-I | 2,6-Me-Ph-NC | PhSH | ACN | Tert-butyl 4-CzIPN | NiCl2-glyme | L4 | K2CO3 + 1% water | 3 | 22 | 59 |
| 30b | F3C-Ph-I | 2,6-Me-Ph-NC | PhSH | ACN | Tert-butyl 4-CzIPN | NiCl2-glyme | L6 | K2CO3 + 1% water | 10 | 15 | 26 |
| 31b | F3C-Ph-I | 2,6-Me-Ph-NC | PhSH | ACN | Tert-butyl 4-CzIPN | NiCl2-glyme | L7 | K2CO3 + 1% water | 60 | 21 | 29 |
| 32b | F3C-Ph-I | 2,6-Me-Ph-NC | PhSH | ACN | Tert-butyl 4-CzIPN | NiCl2-glyme | L8 | K2CO3 + 1% water | 63 | 29 | 46 |
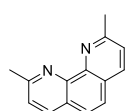


L2: Néocuproïne
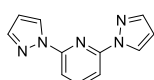
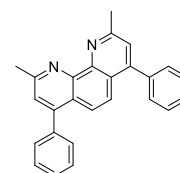L3 : 2,6-Di(1-pyrazolyl)pyridine
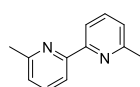
L4 : 6,6'-Dimethyl-2,2'-dipyridyl
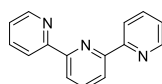
L6 : 2,2':6',2''-Terpyridine
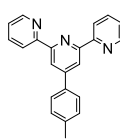
L7: 4'-(4-Methylphenyl)-2,2':6',2''-terpyridine

L8 : Bathocuproine

**Table 6:** Optimization results after changing the ligand

Changing the ligand, has also an effect on the yield, as it is involved in the activation of the nickel. Overall, the ligands tried, gave a target product yield around 30% with a slight increase at 40% when using néocuproine (27b), the ligand 2.

Increasing the steric hindrance, adding an electron withdrawing or donating group on the thiophenol decreased considerably the yield to around 10%. Same things happen, with reducing the steric hindrance or adding an electron donating group to the isocyanide.

| # | ArX | R-NC | Nu | Solvent | PC | Metal catalyst | Ligand | Additive | $^{19}F$-NMR yield (%) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | SM | TP | CP |
| **Reference** | | | | | | | | | | | |
| 11b | F3C-Ph-I | 2,6-Me-Ph-NC (1 eq) | PhSH (1.5 eq) | ACN | Tert-butyl 4-CzIPN (0.005 eq) | NiCl2-glyme (0.05 eq) | L1 (0.1 eq) | K2CO3 + 1% water (1 eq) | 10 | 36 | 57 |
| **Screening reagents** | | | | | | | | | | | |
| 36b | F3C-Ph-I | 2,6-Me-Ph-NC | (Me)₂PhSH | ACN | Tert-butyl 4-CzIPN | NiCl2-glyme | L1 | K2CO3 + 1% water | 52 | 4 | 16 |
| 37b | F3C-Ph-I | 2,6-Me-Ph-NC | BrPhSH | ACN | Tert-butyl 4-CzIPN | NiCl2-glyme | L1 | K2CO3 + 1% water | 28 | 6 (6) | 23 |
| 38b | F3C-Ph-I | 2,6-Me-Ph-NC | MeoPhSH | ACN | Tert-butyl 4-CzIPN | NiCl2-glyme | L1 | K2CO3 + 1% water | 11 | 10 | 32 |
| 39b | F3C-Ph-I | MeoPhNC | PhSH | ACN | Tert-butyl 4-CzIPN | NiCl2-glyme | L2 | K2CO3 + 1% water | 44 | 11 | 27 |
| 40b | F3C-Ph-I | PhNC | PhSH | ACN | Tert-butyl 4-CzIPN | NiCl2-glyme | L2 | K2CO3 + 1% water | 25 | 6 | 25 |
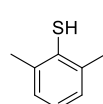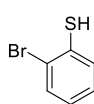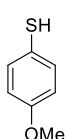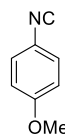


36b   37b   38b   39b   40b

**Table 6:** Optimization results of reagents screening

# V-Discussion and Conclusion

At the beginning of the project, the target product yield was initially 20% and thanks to a series of optimizations, the yield doubled to 40%. This increase was achieved by using $K_2CO_3$ and water, using tert-butyl 4CZIPN as a photocatalyst, and neocuproine as a ligand and CAN as solvent.

The most notable improvement occurred when $K_2CO_3$ with 1% water was added, $K_2CO_3$ not only neutralized the hydrobromic or hydroiodic acid formed but also can act as a ligand due to the lone pair on the carbonate group. Interestingly, increasing the amount of $K_2CO_3$ led to a drop in yield, which can be explained by the fact that, in the presence of water, isocyanide can convert back to formamide.

The oxidative addition step (figure 4) appears to be a determinant step, as modifying the isocyanide by adding an electron-donating group or reducing steric hindrance significantly lowered the yield. For thiophenol, it seems to coordinate with Ni (II) during oxidative addition or after the 1,1-migratory insertion of isocyanide. In all cases, adding steric hindrance, electron-donating, or electron-withdrawing groups to thiophenol led to reduced yields.

Further research screening of different isocyanides and thiophenols with various substituents need to be done. It's worth noting that the current yield measurements are based on 19F NMR analysis, and further work is required to isolate the product to confirm these results. Attempts to purify the product showed impurities in the ^{19}F NMR spectra, despite TLC and chromatogram data indicating good separation from side products (Appendix 10). In most conditions tested, the coupling product was predominant, and the incomplete conversion suggests that the coupling product could potentially act as an intermediate in forming the target product. It would be great to isolate the coupling product and test whether it can produce the target compound under the same reaction conditions. If so, optimizing the reaction to favor this pathway would be a logical next step. Additionally, exploring conditions that avoid the formation of the coupling product might provide further insights.

In conclusion, the optimizations performed successfully doubled the yield from 20% to 40%. This project has largely relied on a trial-and-error approach. Looking ahead, it would be good to focus first on improving the purification of the target product, as 19F NMR yields are not fully reliable, and isolated yields provide a more accurate assessment. Repeating the reactions to confirm the reproducibility of the 19F NMR will also be great and tried to find an organic base instead of potassium carbonate, which is not soluble in ACN it will facilitate the NMR analysis and will be more convenient if in the future photoflow reactors are used for the optimization.

Instead of focusing solely on optimizing the reaction that uses the phenolic acid, it's crucial to first determine whether the extraction method aligns with sustainable principles.When considering sustainability, it's important to evaluate whether it's more sustainable to extract phenolic acid from seeds or to synthesize or just buy it.

# VI-References

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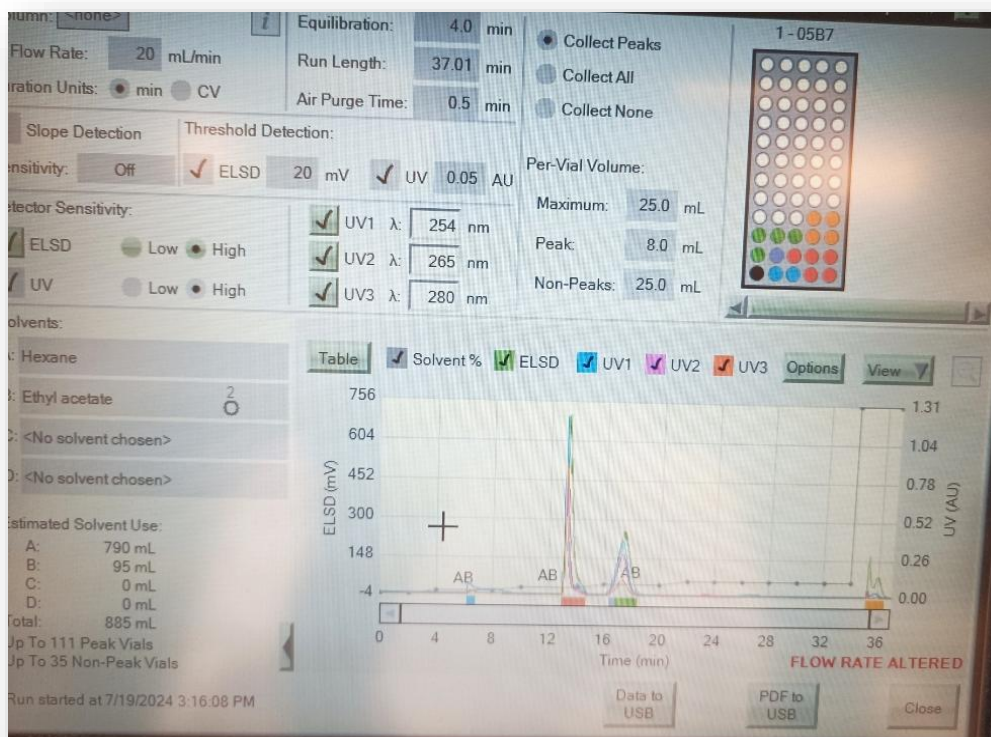
# VII-Appendices

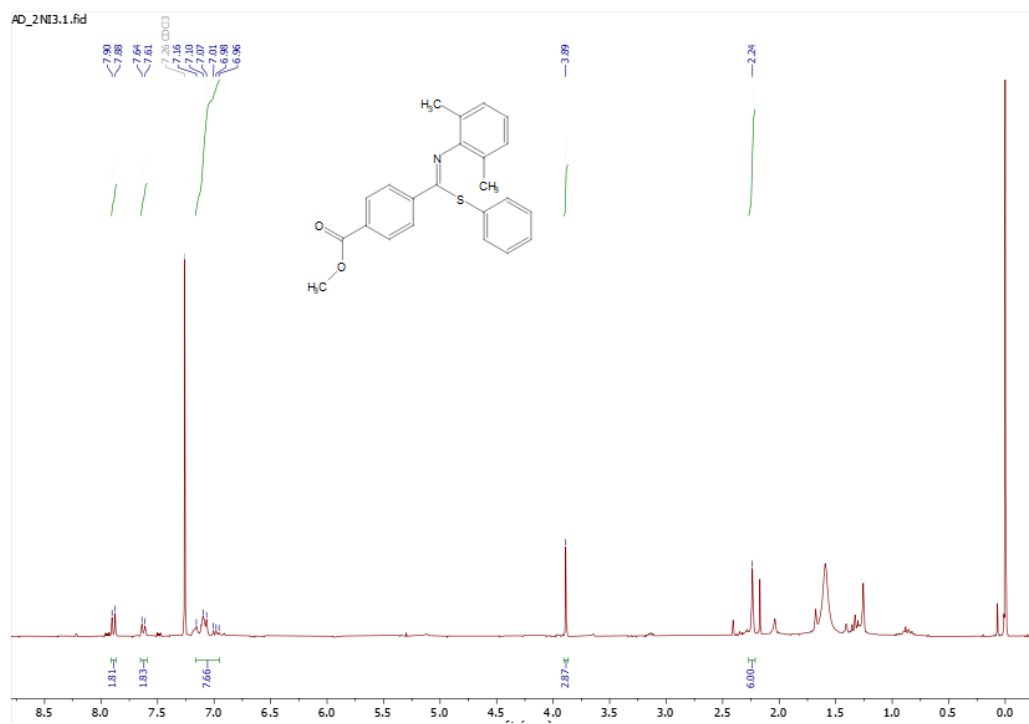**Appendix 1**: 2,6-dimethylphenyl isocyanide ^{1}H NMR spectra (300 MHz, CDCl3)
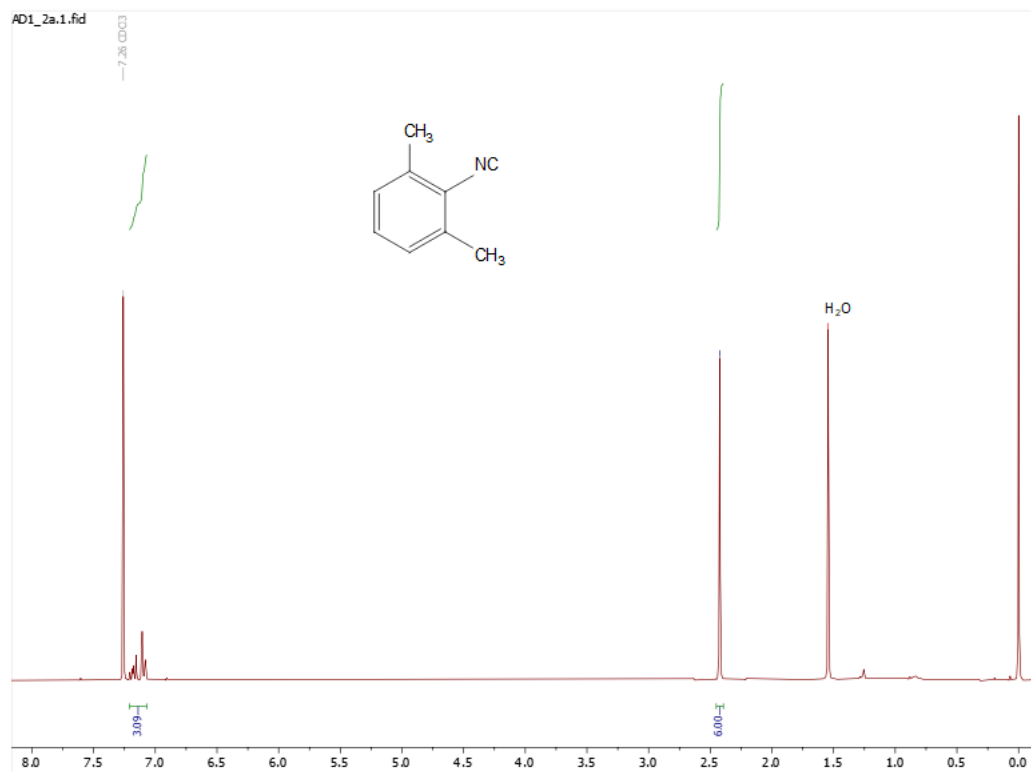
## Appendix 2: 4-CZIPN $^1$H NMR spectra (300 MHz, CDCl$_3$)
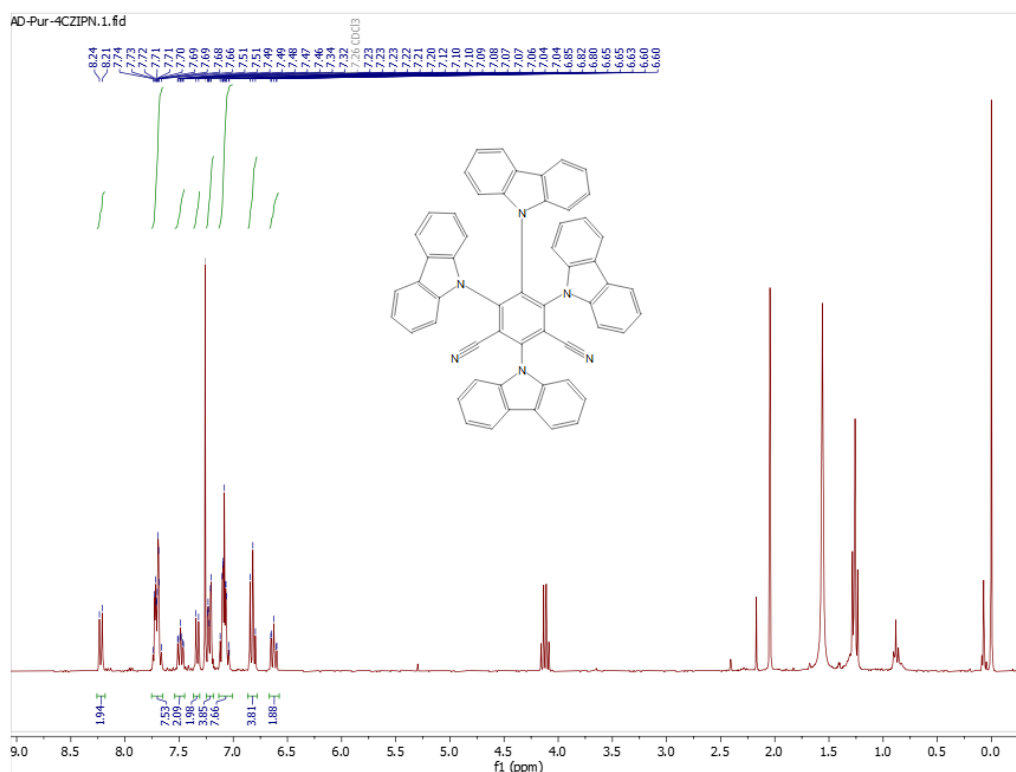


## Appendix 3: Parameters and Chromatogram of the autocoumn (the red pic or vials 9-13 correspond to the target product and the other to the side products)
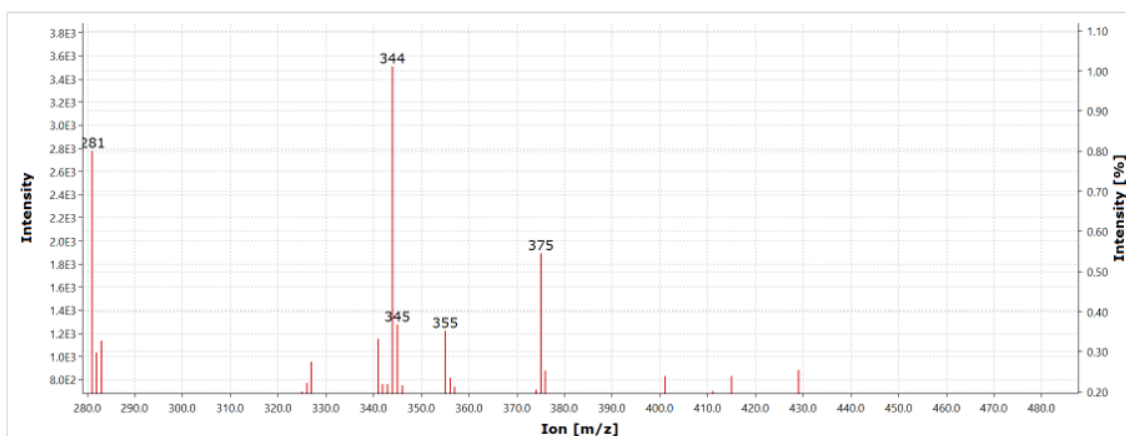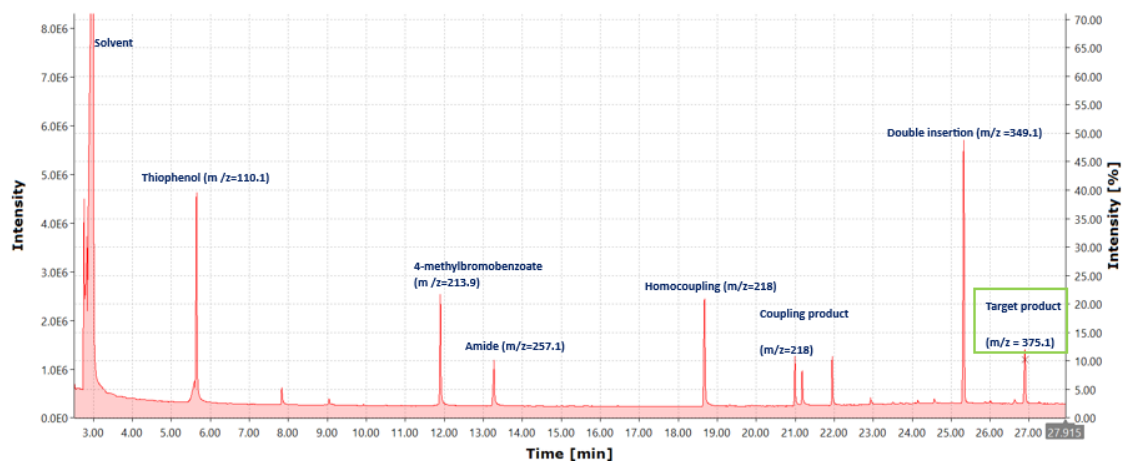
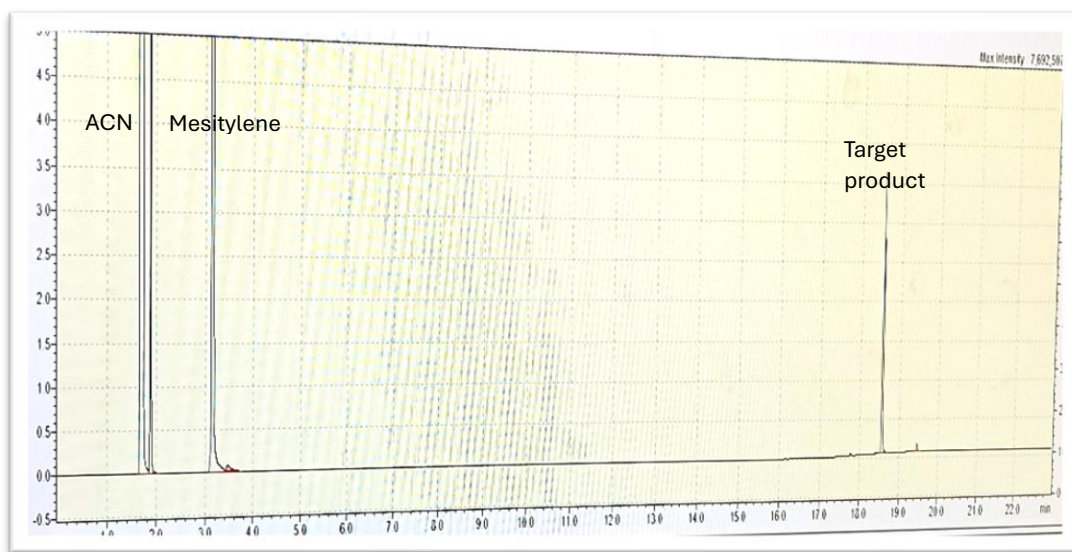**Appendix 4**: Target product $^1$H NMR spectra (300 MHz, CDCl$_3$)



**Appendix 5**: GC-MS spectra of the reaction crude with 4-methylbromobenzoate as starting material.
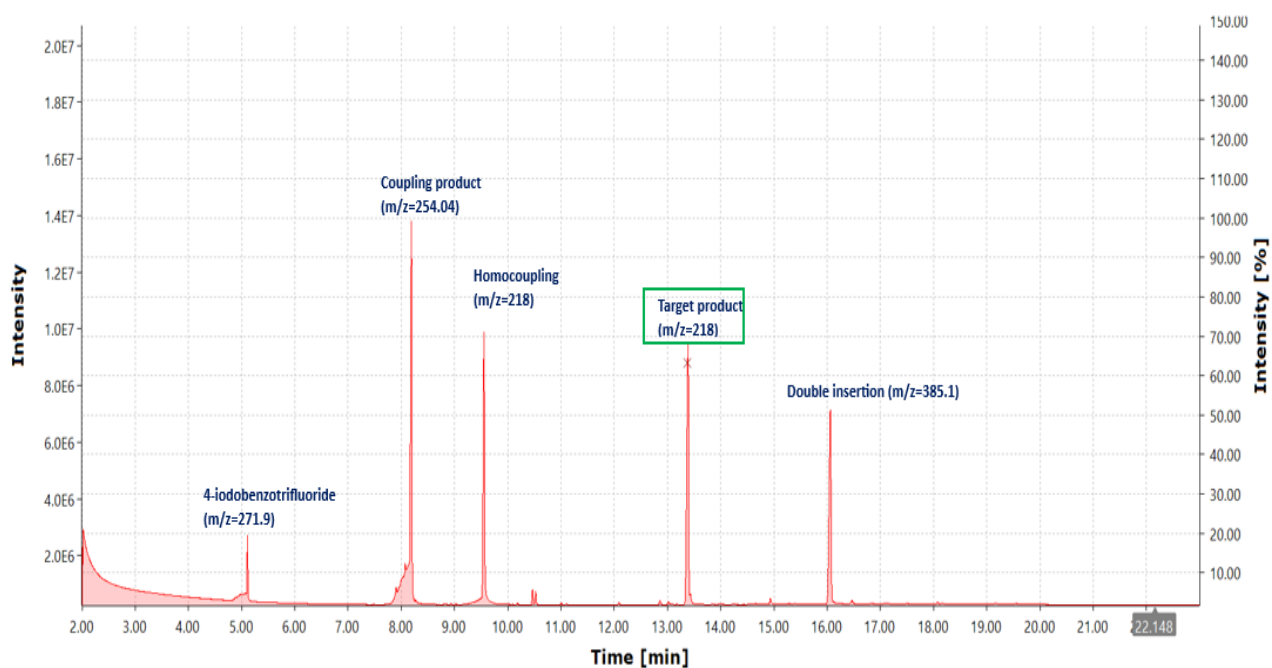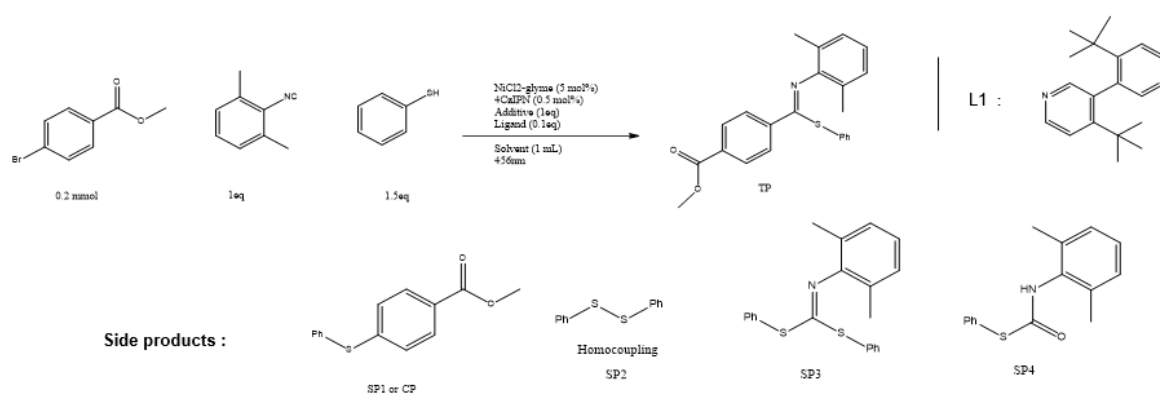
A: GC spectra and B: MS spectra of the target product

**Appendix 6**: Exemple GC-FID spectra of standard 2



**Appendix 7**: GC-MS spectra of the reaction crude with 4-iodobenzotrifluoride_as limiting reagent

# **Appendix 8:** Control experiments



| Entry | ArBr | Isocyanide | Thiophenol | NiCl2-glyme | Ligand | Photocatalyst | Light | Oxygen | Temperature | Products |
|-------|------|------------|------------|-------------|--------|---------------|-------|--------|-------------|----------|
| 17'a | X | X | X | X | X | X | X | X | RT | CP |
| 18a | X | X | X | X | X | - | - | - | RT | - |
| 19a | X | X | X | X | X | - | X | - | RT | TP,SP2 , SP3, SP4 |
| 20a | X | X | X | - | - | X | X | - | RT | - |
| 21a | X | X | X | - | X | X | X | - | RT | - |
| 22a | X | X | - | X | X | X | X | - | RT | - |
| 23a | X | - | X | X | X | X | X | - | RT | SP2 |
| 24a | X | X | X | X | X | X | X | - | 60°C | TP,CP, SP2,SP4 |

Conclusion :
- Need to be under nitrogen
- Photocatalyst is not obligatory for the reaction

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**Appendix 9:** $^1$H NMR ((300 MHz, CDCl3) spectra of the pure target product derived from 4-iodobenzotrifluoride as limiting reagent