Raül Lleberia Gómez

MECHANISTIC STUDY OF C–H AMIDATION WITH A Cp*Rh(III) CATALYST

UNDERGRADUATE THESIS

Directed by Mónica Pérez-Temprano

Chemistry Degree

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Table of Contents

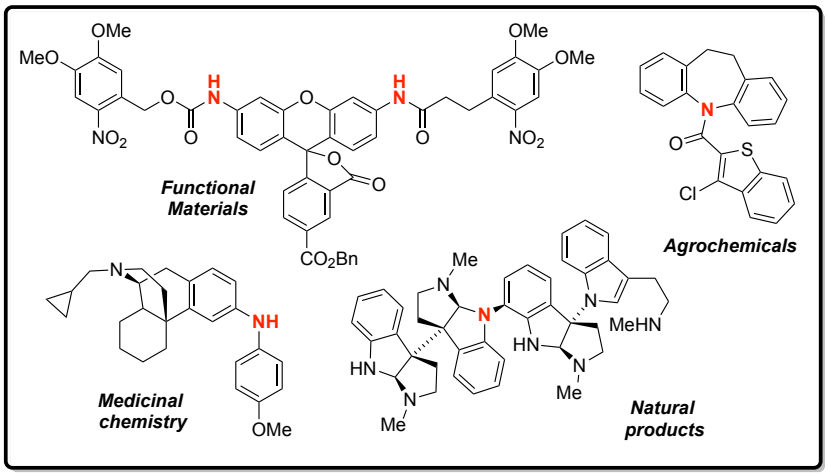
1. Abstract

Cp*Rh(III) catalysts have emerged as a very attractive alternative to other noble transition metals for the direct C–H bond amidation. Despite this, studies on this reactivity has been limited to certain amidating reagents with dearth of experimental data to confirm the computational mechanistic proposal. Here in, an experimental mechanistic study of Cp*Rh(II)-catalysed direct C–H amidation with sulphonamides in presence of an external oxidant is reported. This work aims at gaining further inside into the possible reaction intermediates highlighting the most likely mechanistic pathway this reaction may undergo.

2. Introduction

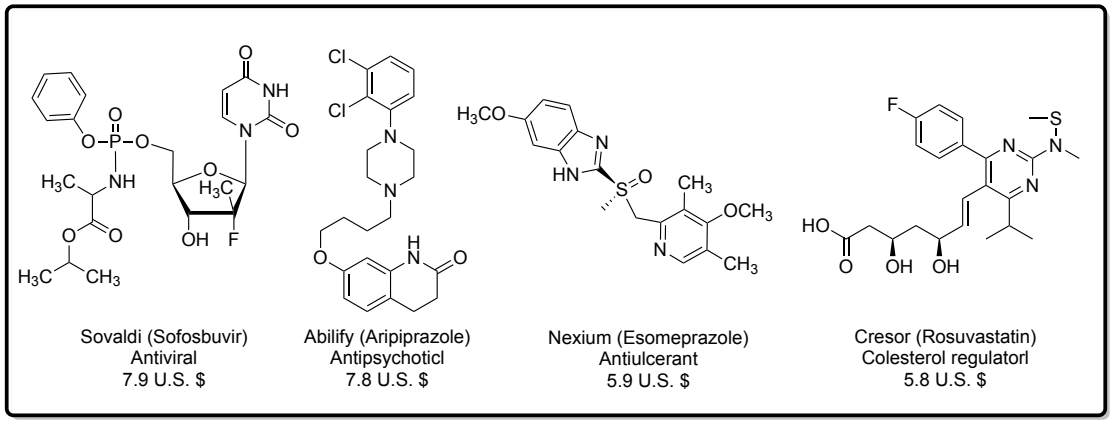
2.1. Precedents on C–N functionalisation

Nitrogen-containing moieties constitute one of the basic structures in functional materials, agrochemicals, natural products and pharmaceutically active species (**Scheme 1**).[1]



Scheme 1. Fields wherein nitrogen-containing structures are important.[2]

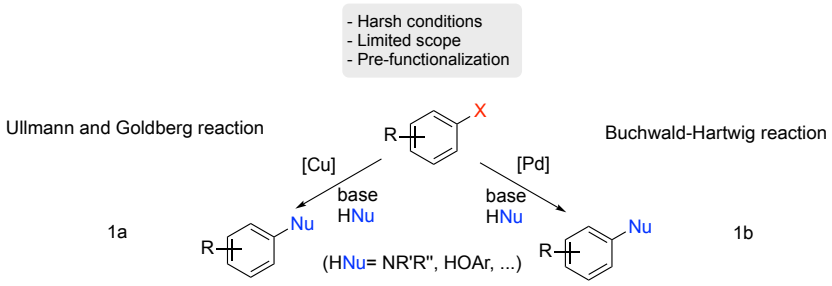
The economic transcendence of this type of structures can be highlighted in the case of the prescribed oncologic drugs Tasigna® and Gleevec® manufactured by the multinational pharmaceutical company Novartis. These two drugs alone accounted for more than a billion U.S. dollars on net sales during the first quarter of 2016.[3] From a wider point of view, the U.S. reported in 2014 almost 35 billion dollars sales from which an 80% of financial benefit came from the top 5 prescription drugs containing nitrogen heterocyclic structures (**Scheme 2**).[4] Due to this economic influence, research and development of new and more efficient reactivity involved in C–N bond formation is still ongoing.



Scheme 2. Top 4 selling small molecule drugs in the U.S. as of 2014.[4]

[1] Chiba, S.; Narasaka, K. In *Amino Group Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA: 2008, p 1.
[2] Ruiz-Castillo, P.; Buchwald, S. L. *Chem. Rev.* **2016**, *116*, 12564.
[3] Novartis. https://www.novartis.com/investors/financial-data/quarterly-results#ui-id-1=4 (consulted on June 12th 2017). Part of Novartis Quarterly Financial Results.
[4] Martins, P.; Jesus, J.; Santos, S.; Raposo, L.; Roma-Rodrigues, C.; Baptista, P.; Fernandes, A. *Molecules* **2015**, *20*, 16852.

Among the different strategies developed to synthesise these organic scaffolds, metal-catalysed C–N bond reactions have become a transcendent and versatile tool to achieve this reactivity. Representative procedures of this approach include copper-catalysed amination proposed by Ullmann and Goldberg[5] (**Scheme 3**, **1a**) and palladium-catalysed N-arylation of pre-halogenated arenes also known as Buchwald-Hartwig reaction (**Scheme 3**, **1b**).[6]

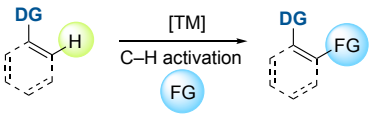


Scheme 3. Ullmann and Goldberg, and Buchwald-Hartwig reactions.

Despite the benefits of using metallic catalysts for C–N functionalisation, copper-/palladium-mediated reactivity depends on a pre-functionalisation of the substrate. This is one of the reason why much effort has been put into developing alternative routes that avoid pre-functionalisation to achieve the same reactivity.

2.2. Direct C–H activation

Recently, direct C–H amination has become a target of metallic-catalyst dependant reaction, in order to overcome the substrate pre-functionalization step in the overall process. This major advantage confronts with minor problems when recurring to this reactivity.



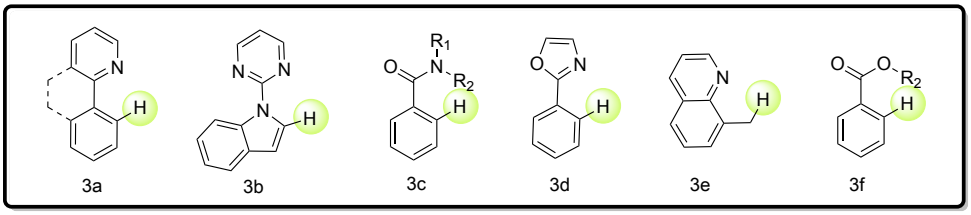
Scheme 4. Chelation-assisted direct C–H activation through a directing group (DG).

The most challenging aspect to be considered is to overcome the differentiation among the multitude of C–H bonds that constitutes any organic molecule.[7] Murai and co-workers tackled this problem in 1993 and proposed the use of directing groups as a possible solution (**Scheme 4**).[8] This pioneering work supposed the beginning of a brand-new reactivity dominated by noble metals. Over the last decades, Rh has become one of the most utilized metals in this field granting the access to systems wherein sp^2 and sp^3 C–H functionalization can take place.[9]

Despite this advances, intermolecular C–H amination is still limited to specific substrates. This can be seen in **Scheme 5,** where common structures of substrates are represented.

[5] Monnier, F.; Taillefer, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 6954.
[6] (a) Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901. (b) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969.
[7] Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res.* **2012**, *45*, 936.
[8] Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529.
[9] For selected examples of Rh(III)-catalyzed C–H activation, see: (a) Huang, X.; You, J. *Chem. Lett.* **2015**, *44*, 1685. (b) Wippich, J.; Truchan, N.; Bach, T. *Adv. Synth. Catal.* **2016**, *358*, 2083. (c) Zhou, B.; Yang, Y.; Shi, J.; Feng, H.; Li, Y. *Chem. Eur. J.* **2013**, *19*, 10511. (d) Mishra, N. K.; Oh, Y.; Jeon, M.; Han, S.; Sharma, S.; Han, S. H.; Um, S. H.; Kim, I. S. *Eur. J. Org. Chem.* **2016**, *2016*, 4976.

Major structures focus on C(sp^2)–H bond functionalisation (**3a**, **3b**, **3c, 3d** and **3f**), albeit C(sp^3)–H bond-activating substrates are also described (**3e**).[10]

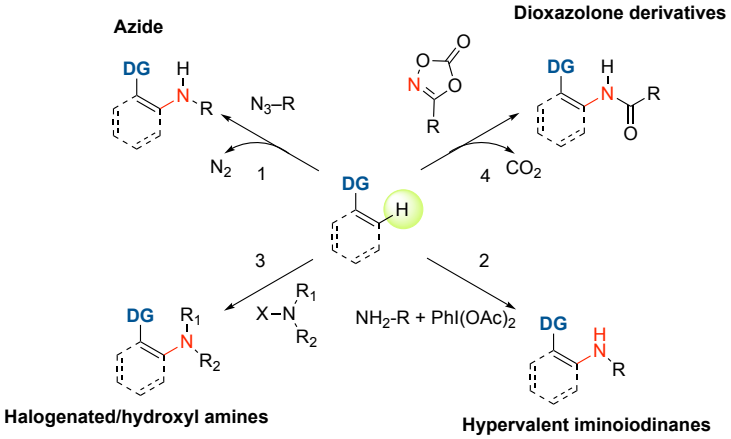


Scheme 5. Common structures for direct C–H activation.

2.3. Rhodium catalysis in direct C–H amidation

The use of Cp*Rh(III) as a catalyst for C–H amidation functionalisation has become more prominent as it usually displays a high catalytic activity and excellent functional group tolerance.[11] Azides (**1**), dioxazolones derivatives (**2**), hypervalent iminoiodinanes (in situ generated from hypervalent iodine reagent) (**3**), hydroxylamines or halogenated amines/sulphonamides (**4**) have been reported as nitrogen sources for this type of transformations (**Scheme 6**).

Even though there is an extensive work on Cp*Rh catalysed C–H amidation, most of experimental and theoretical works have been focused on the use of azide and oxazolone derivatives[12], whilst the others have received less interest. In particular, we turned our attention towards the C–H amidation reactions using sulphonamides as the nitrogen source in the presence of a hypervalent iodide reagent.

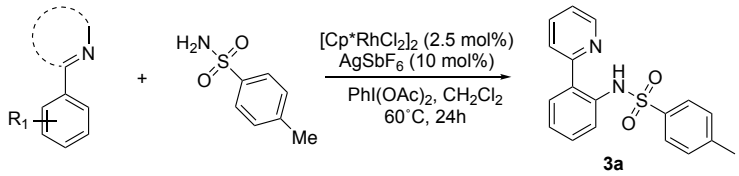


Scheme 6. List of amino precursors used in C–N bond formation through direct C(sp^2)–H activation with Cp*Rh(III) catalysts.

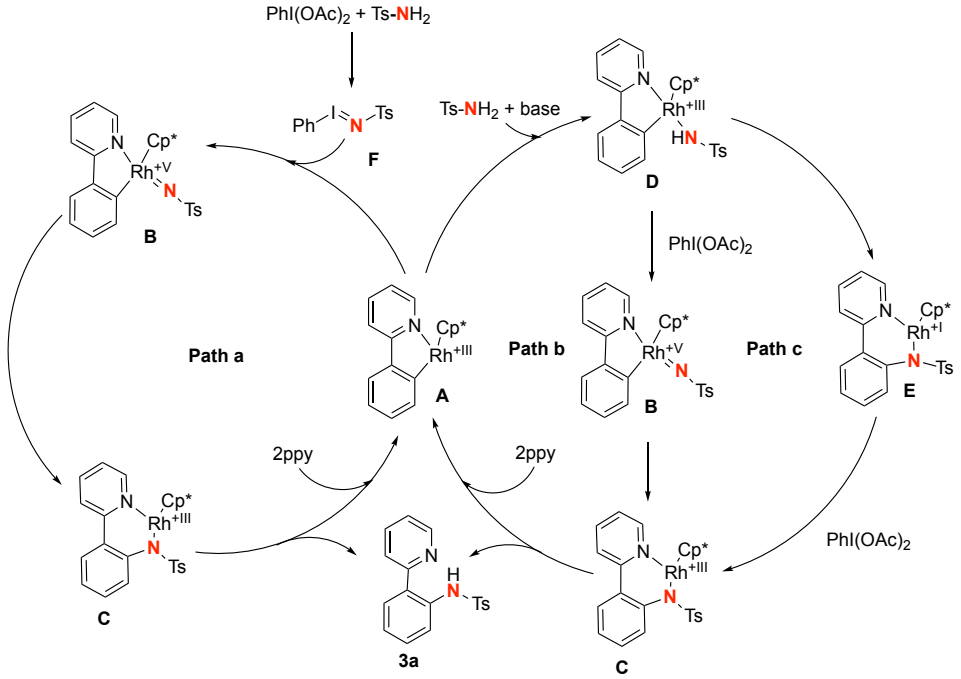
2.3.1. Mechanistic pathways

Su and co-workers reported in 2013 the C–H sulphonamidation of 2-phenylpyridine derivatives (**Scheme 7**), The authors proposed three possible mechanisms for this reaction (**Scheme 8**).[11] All the pathways have a common intermediate, a cationic 2-phenylpiridine-derived cyclometalated Cp*Rh^{III} complex, complex **A**, formed by through a C–H activation step from which the C–N bond-forming reaction can take place as represented in **Scheme 8**.

[10] Huang, X.; You, J. *Chem. Lett.* **2015**, *44*, 1685.
[11] Zhao, H.; Shang, Y.; Su, W. *Org. Lett.* **2013**, *15*, 5106. Examples can be found in references (10) and (11).
[12] Park, Y.; Heo, J.; Baik, M.-H.; Chang, S. *J. Am. Chem. Soc.* **2016**, *138*, 14020.



Scheme 7. Reaction studied by Su and co-workers.



Scheme 8. Mechanistic pathways suggested by Su and co-workers.

Path a is proposed to be the result of a first interaction between the sulphonamide Ts-NH_2 and the hyper valent iodine specie. The nitrene precursor formed in situ (**G**) would cause the oxidation of Rh(III) to Rh(V) at the same time a nitrenoid (**B**) specie is formed.

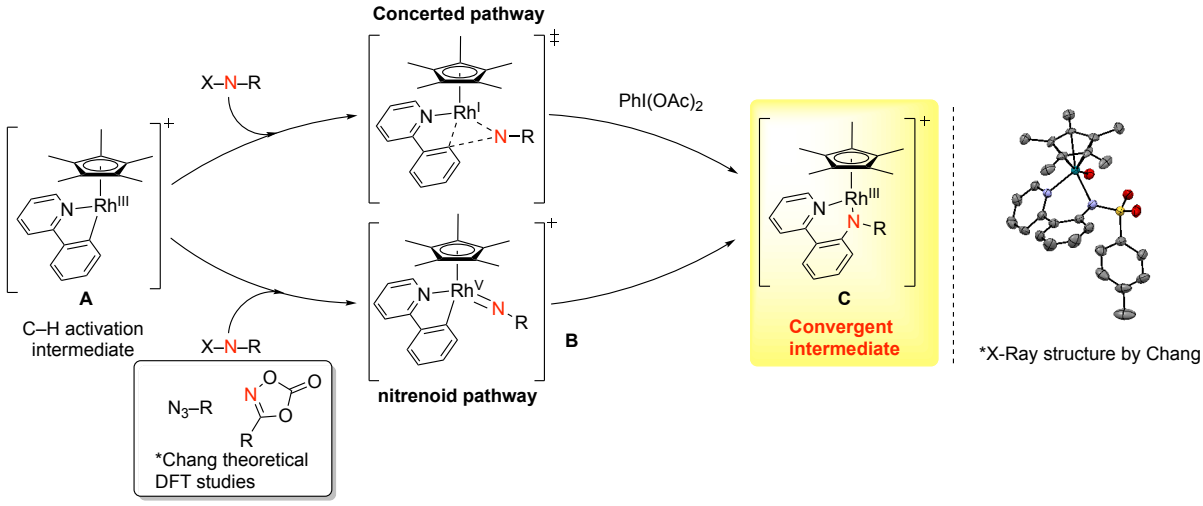
Path b starts from intermediate **D** to undergo an oxidation of Rh(III) metallic centre for the formation of a nitrenoid specie (**B**). Eventually, C–N formation would take place to form specie **C**. **Pathways a** and **b** are based on nitrenoid transfer from metal centre to activated C–H bond as seen on **Scheme 8**.

Path c involves sulphonamide activation via deprotonation in presence of acetates, for a subsequent coordination to 2ppy-rhodacycle (**A**) metallic centre in order to give (**D**). The new formed intermediate (**D**) would undergo a reductive elimination of Rh(III) to Rh(I) for C–N bond formation. Finally, Rh(I) intermediate (**E**) would suffer an oxidation to obtain specie (**C**). This mechanism goes through a concerted intermediate.

Protonation and release of the product **3a** is the last step of the catalytic cycle allowing the regeneration of the active specie and restarting the direct C–H activation by **2ppy** introduction.

2.3.2. Precedents

The concerted **pathway c** is considered to be less likely to take place taking into account several theoretical DFT studies by Chang and co-workers that specifies the fact that the nitrenoid is a much more energetically stabilised specie with respect to the TS of the concerted mechanism (**Scheme 9**).[13] As reported by Chang et al., azide and dioxazolones would undergo Rh(V) nitrenoid pathway.[12,14] Whilst hydroxilamines, or halogenated amines/sulphonamides have been suggested to proceed via low-valent Rh species (concerted route) even though no further studies have been performed.[15,16]



Scheme 9. The two possible intermediates suggested by literature. Azide and dioxazoline compounds are the only amidating reagents for which a DFT study has been undergone so far.

The main issue with these theoretical studies is the dearth of experimental information to confirm the computational proposals. All preliminary mechanistic studies made by Su et al. on Rh(III) N-chelator-direct C(sp^2)–H amidation with sulphonamides were not conclusive.[11]

To this date, a single intermediate on a Rh-catalysed direct C–H amidation has been isolated. This specie corresponds to the C–N coupled product chelate-coordinated to a Rh(III) centre (complex **C** in **Scheme 9**).[17] However, this product can be considered as the convergent intermediate of the three routes **a**, **b** and **c** (**Scheme 8**). Because of this, no conclusive information regarding the mechanism can be extracted.

In view of the lack of detailed mechanistic information and having recognized the importance of such knowledge for the further development of the direct C–H functionalization reactions catalysed by Rh complexes, it is our main goal to gather key information in an attempt to elucidate the operative catalytic cycle.

3. Objectives

Considering the system presented before, this undergraduate thesis aims at studying the Rhodium(III)-catalysed intermolecular N-chelator-directed aromatic C(sp^2)–H amidation with sulphonamides in the presence of an external oxidant.

[13] Park, S. H.; Kwak, J.; Shin, K.; Ryu, J.; Park, Y.; Chang, S. *J. Am. Chem. Soc.* **2014**, *136*, 2492.
[14] Park, Y.; Park, K. T.; Kim, J. G.; Chang, S. *J. Am. Chem. Soc.* **2015**, *137*, 4534.
[15] Tang, R.-J.; Luo, C.-P.; Yang, L.; Li, C.-J. *Adv. Synth. Catal.* **2013**, *355*, 869.
[16] Grohmann, C.; Wang, H.; Glorius, F. *Org. Lett.* **2012**, *14*, 656.
[17] Shin, K.; Kim, H.; Chang, S. *Acc. Chem. Res.* **2015**, *48*, 1040.

To achieve this goal, the following objectives are proposed:

1) To perform a preliminary study on the synthesis of the desired products for data compilation, solvent testing and optimization of reaction conditions to ease the subsequent mechanistic study.

2) To perform a systematic study on direct C–H activation of 2-phenylpyridine in order to gain further insight on the feasible mechanistic pathways the reaction may undergo and aiming at unravelling the key intermediates involved in the catalytic cycle. All these, taking into account previous works on the matter and an exhaustive NMR spectra analysis.

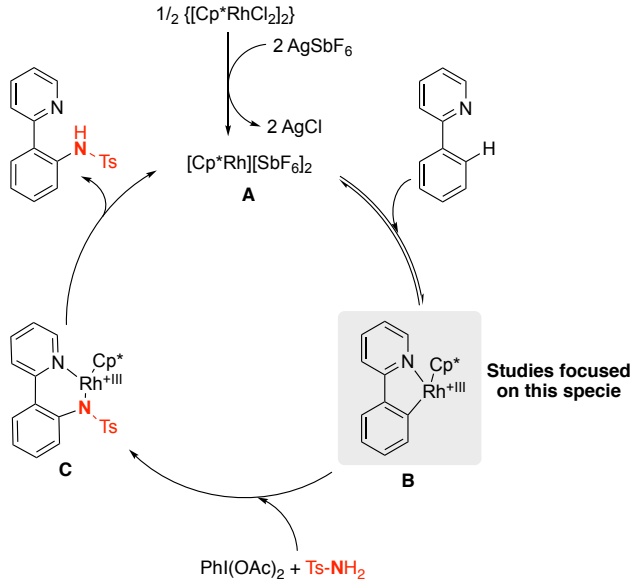
3) To explore the sulphonamidation of 2-phenylpyridine within this system trying a small scope of sulphonamides others than 4-methylbenzenesulphonamide.

4. Results and discussion

The results presented in this section are focused on a comparative study between catalytic and stoichiometric reactions in order to gain further insight into Rh-catalysed C–H amidation using sulphonamides and an external oxidant.

4.1. Catalytic reactions

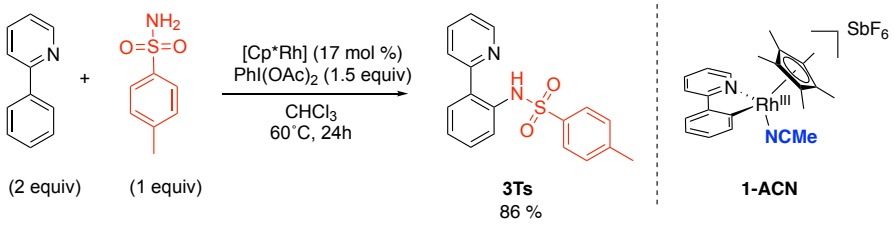
In 2013, Su and co-workers reported the Rh-catalysed C–H amidation reactions using sulphonamide as nitrogen sources in the presence of an external oxidant,[11] but no further mechanistic features of these transformations were studied (**Scheme 10**). Intrigued by the peculiarities of this reactivity, we decided to gain mechanistic insights into these transformations using a combination of experimental studies. Although Su and co-workers used $[Cp^*RhCl_2]_2$ as pre-catalyst, we decided to use cyclometalated rhodium complexes, such as **B** shown in **Scheme 10**. Different literature precedents have shown the potential of these rhodium species for not only catalysing this transformation but also allowing the elucidation of mechanistic details.



Scheme 10. Known species in catalytic C–H amidation with Rh using sulphonamides and an external oxidant.

The exact structure of the selected Cp*Rh complex, analogous to **B**, it is in **Scheme 10**. **1-ACN** has been chosen not just because it contains a stabilizing acetonitrile ligand that can

facilitate the access to previously elusive reaction intermediates,[18] but also because it simplifies the catalysis conditions since no $AgSbF_6$ is needed to abstract the halide from the commonly used $[Cp^*RhCl_2]_2$, affording a totally homogeneous reaction.



Scheme 10. Catalyst used in studied catalytic reaction.

If we compare the yields between the reaction performed by Su and co-workers and the one presented in **Scheme 10**, higher yield is obtained in the conditions shown up above. Though catalyst loading is 14.5 mol % greater and chloroform was used instead of reported DCM. Further experiments should be performed in order to confirm this increase in yield.

The catalytic reaction with **1-ACN** afforded the desired product **3a** as shown in **Figure 1**. Three important regions can be identified in the ^{1}H NMR spectra. The **region A** belongs to the aromatic region of the ^{1}H NMR spectra, and within it formation of the product can be observed. The aliphatic **region B** shows that with temperature and time, the sulphonamide and $PhI(OAc)_2$ disappear while product **3a** and acetic acid are formed. This may indicate interaction between both reagents. Finally, **region C** shows the disappearance of the Cp* signal belonging to **1-ACN** and the observation of a new Cp*Rh species what could mean the formation of an intermediate in catalysis.

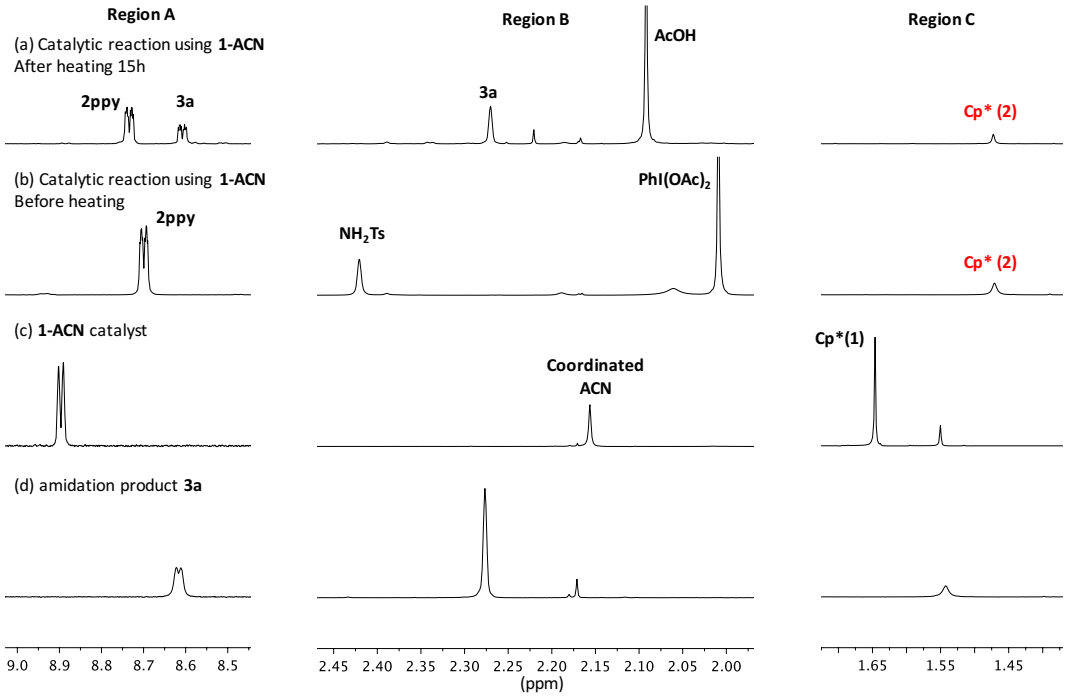
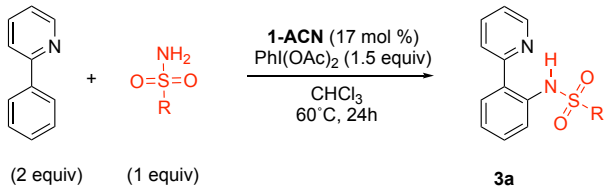


Figure 1. Spectra comparison between monitored catalytic reactions and product showing 3 important regions.

[18] Sanjosé-Orduna, J.; Gallego, D.; Garcia-Roca, A.; Martin, E.; Benet-Buchholz, J.; Perez-Temprano, M. H. *Angew. Chem. Int.* **2017**. DOI: 10.1002/anie.201704744

We explored the reactivity of this transformation using different sulphonamides sources (**Scheme 11**). As it can be seen in **Table 1**, though there is a big difference in the pKa values of the three sulphonamides, the yields can be compared, especially since no optimization was performed, and seem not to follow the acidity trend. Although not conclusive, this result indicates that the acidity and nucleophilicity of the sulphonamide is not a critical factor. In this regard, the nitrene pathway may be an explanation of this small difference.



Scheme 11. Catalytic reaction with different substrates.

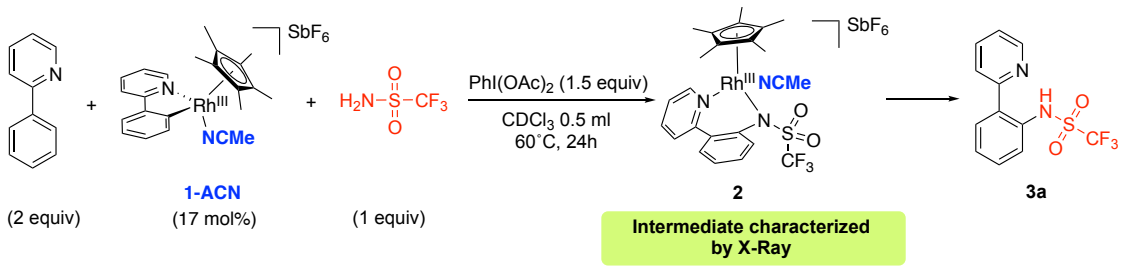
Table 1. Substrate scope for **1-ACN** catalyst

Entry	**Sulphonamide**	pKa	Yield (%)
1	NH_2Ts	10.26[19]	86
2	$NH_2SO_2PhCF_3$	9.68[c]	98
3	$NH_2SO_2CF_3$	6.37[19]	64

[a] Quantification of product was made through 1,3,5-trimethoxybenzene as internal standard. [b] Temperature and reaction time was 60ºC and 24 hours, respectively, for all the reactions.[c] Calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02 (© 1994-2017 ACD/Labs).

Gratifyingly, yellowish crystals were obtained using $TfNH_2$ as the nitrogen source (**Scheme 12**). As expected, further X-Ray diffraction analyses identified the crystal as the chelate-coordinated product (**Figure 2**) in agreement with previous reported results.[17]

This results lead to the idea that signal Cp*(2) may belong to an analogous intermediate containing the 4-methylbenzenesulphonamide ligand. However, the limits of solubility of these species in chloroform at *room temperature*[20] limit our ability to unambiguously characterize the intermediate observed under catalytic conditions.



Scheme 12. Catalytic reaction where crystals where observed to be formed. Stoichiometric reactions gave the same coordinated product.

[19] Pendleton, I. M.; Pérez-Temprano, M. H.; Sanford, M. S.; Zimmerman, P. M. *J. Am. Chem. Soc.* **2016**, *138*, 6049.
[20] Even though catalytic reaction conditions involve heating the reaction mixture to 60 ºC for up to 24 hours NMR measurements were performed at room temperature.

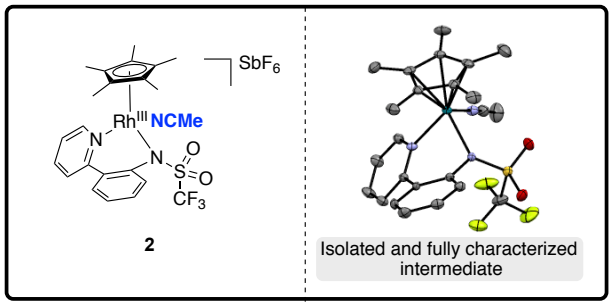
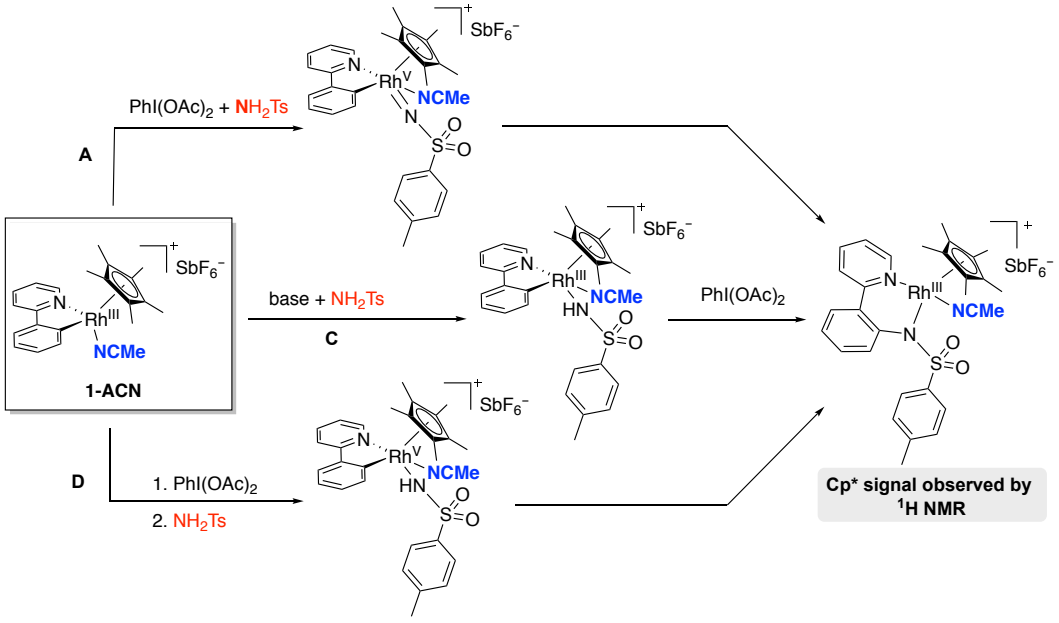


Figure 2. Crystallographic structure of specie 2. Hydrogen atoms and counterion are not included for simplicity.

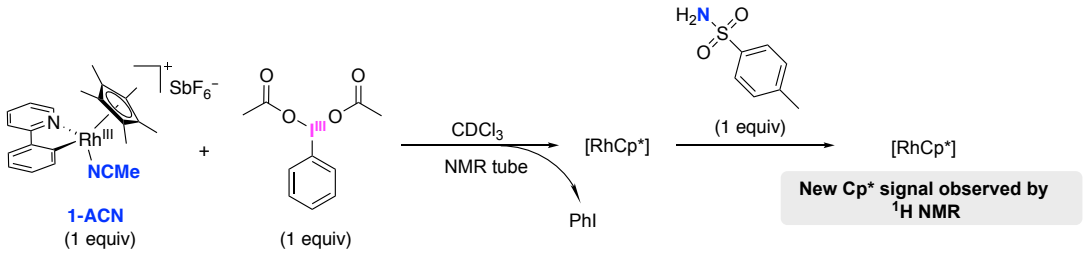
4.2. Stoichiometric reactions

In order to gain further insights into the mechanism of these transformations (**Scheme 13**) and determine how complex **2** is formed under the reaction conditions we performed a series of stoichiometric studies. Our working hypothesis was that there are different mechanistic pathways that could potentially lead to the formation of intermediate **2** (**Scheme 13**). The first possibility (Mechanism A) would involve the formation of a nitrene intermediate. Mechanism C would involve the coordination and insertion of the nitrogen source. Because of the limited time available, it was not possible to explore mechanism B shown in **Scheme 8**, however an additional mechanism D was explored, which involves the oxidation of complex **1-ACN** followed by the coordination of the nitrogen source to give a Rh^{V} intermediate from which the C–N reductive elimination takes place. Further studies on all three mechanisms and in special mechanism C are planned to be performed.



Scheme 13. Selected reactions performed in an attempt to elucidate the operative reaction pathway.

4.2.1. Reaction between **1-ACN** and oxidant and subsequent addition of sulphonamide



Scheme 14. Stoichiometric reaction where crystals from the dimeric specie 7 were obtained.

We first studied the viability of mechanism D. As PhI was observed from the very beginning in ^{1}H NMR in the catalytic experiments, we hypothesized that the reduction of the hypervalent iodine specie could suggest the oxidation of Rh^{III} to Rh^{V} as first step. However, reaction of **1-ACN** and $PhI(OAc)_2$ led to a complicated reaction mixture from which only one of the formed Rh compounds could be partially characterized (**Figure 3**). The X-ray analysis of **7** reveals the formation of a dimeric Cp*Rh species which had already described by Jones and co-workers under oxidant conditions.[21] The Cp* signals observed by ^{1}H NMR for this reaction do not coincide with the one above under catalytic conditions. Posterior addition of sulphonamide did not lead to the desired intermediate either, ruling out this pathway.

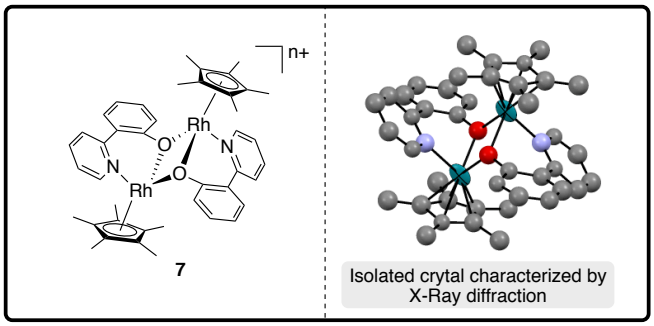
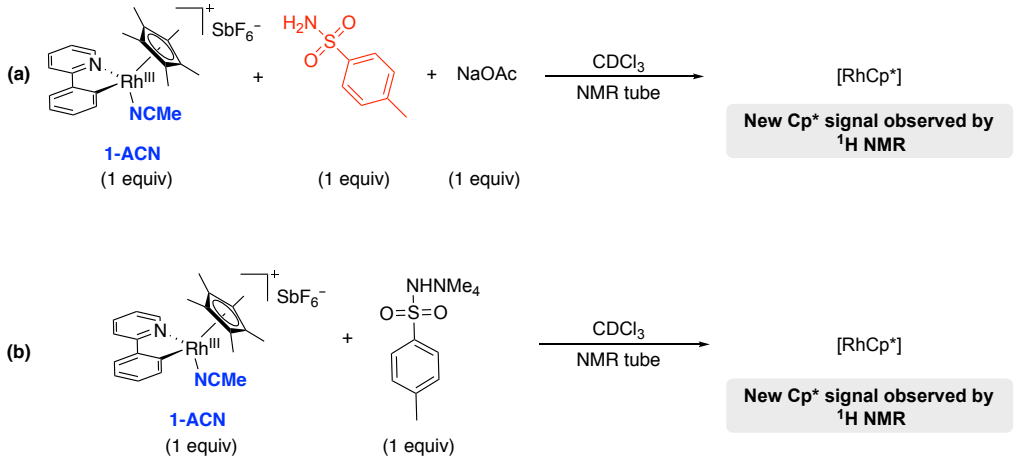


Figure 3. Crystallographic structure of dimeric specie 7. Hydrogen atoms and counterion are not included for simplification.

4.2.2. Reaction between **1-ACN** and sulphonamide with a base presence and posterior heating

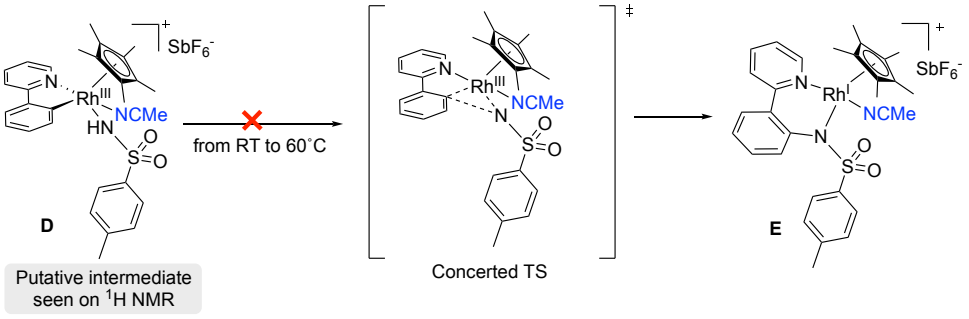
We next investigated pathway C. At room temperature, the stoichiometric reaction between **1-ACN** and sulphonamide in presence of a base gave a new and different intermediate signal if compared to the catalysis (**Scheme 15**). This signal may belong to $Cp^{*}Rh^{III}$ bound to the corresponding sulphonamide (**D**)**.**

[21] Turlington, C. R.; Morris, J.; White, P. S.; Brennessel, W. W.; Jones, W. D.; Brookhart, M.; Templeton, J. L. *Organometallics* **2014**, *33*, 4442.



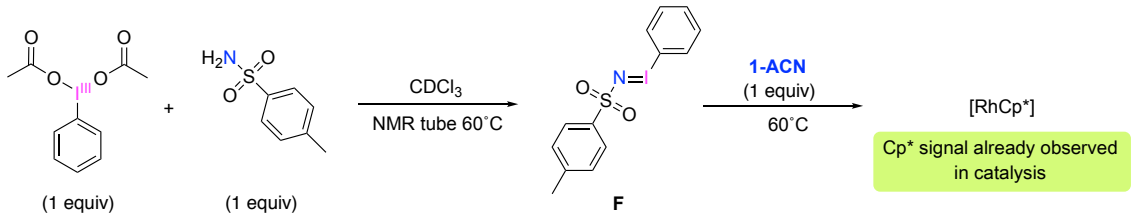
Scheme 15. Stoichiometric reactions without presence of oxidant. Both reactions (a) and (b) displayed the signals for a distinct Cp*Rh specie.

The same result was obtained when we used NMe_4NHTs instead of the combination sulphonamide/base. When heating the reaction mixture, no significant change was observed. Results obtained from this experience are a clear evidence for the dismissal of concerted pathway (**Scheme 16**), since there is no sign of reductive elimination after giving the conditions that favours this step.



Scheme 16. Suggested intermediate for reaction in Scheme 15. As no change in signal is observed, concerted pathway is dismissed.

4.2.3. Reaction between sulphonamide and $PhI(OAc)_2$ and subsequent **1-ACN** addition

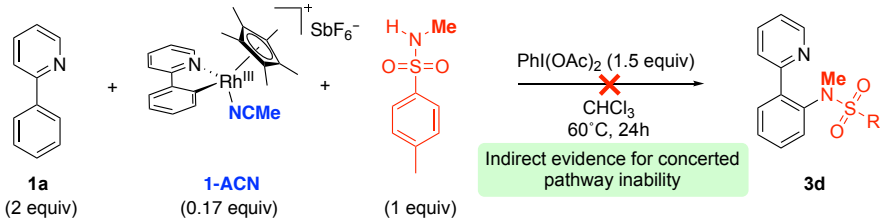


Scheme 17. Consecutive reactions where intermediate seen in catalytic reaction is also observed.

Finally, to test mechanism A, oxidant and sulphonamide were reacted in the conditions described in **Scheme 17**. The ^1H NMR signals for this solution are not clarifying, but when adding **1-ACN** to this same mixture, signals corresponding to the intermediate described in the catalytic reaction were seen. This suggests the feasibility of needing a prior interaction between sulphonamide and oxidant, presumably forming nitrene precursor **F**, and a subsequent reaction between this specie and the rhodacycle intermediate (**1-ACN** analogue) once C–H activation has taken place. These results support a nitrene pathway.

4.2.4. Pathway confirmation

In order to contrast that nitrenoid pathway is the more likely to take place, catalysis with N,4-dimethylbenzenesulphonamide was performed. The basis of the use of this sulphonamide rely on the incapability for this substrate to form the nitrene precursor.[22] Since reaction between this sulphonamide and $PhI(OAc)_2$ does not proceed, the obtention of product would mean that there is an explicit concerted mechanism taking place.



Scheme 18. Catalytic reaction where N,4-mehtylbenzenesulphonamide was tested.

Results confirmed that no reaction took place and no product could be observed, so nitrenoid pathway was highlighted again.

[22] According to IUPAC's gold-book a nitrene or aminylene is "The neutral compound HN: having univalent nitrogen, and its derivatives RN". Therefore, substitution at nitrogen blocks formation of such species. McNaught A. D.; Wilkinson A.; IUPAC. Compendium of Chemical Terminology, 2nd ed. (the "Gold Book"). Compiled by. Blackwell Scientific Publications, Oxford (1997). XML on-line corrected version: (2006-) created by Nic M., Jirat J., Kosata B.; updates compiled by Jenkins A. ISBN 0-9678550-9-8. https://doi.org/10.1351/goldbook.N04145.

5. Conclusions

The mechanism of rhodium(III)-catalysed intermolecular N-chelator-direct aromatic C(sp^2)–H amidation with sulphonamides in the presence of an external oxidant has been studied.

Initial experimentation on the catalytic system allowed the optimization of reaction conditions for the mechanistic study, avoiding the use of $AgSbF_6$ as a non-homogeneous reaction compound by the use of **1-ACN** as catalyst, and the use of chloroform instead of CH_2Cl_2 as solvent.

Through a systematic study, it has been possible to unravel some important features of direct amidation of 2-phenylpyridine with a Cp*Rh catalyst. Stoichiometric reactions strategically planned were used in order to gain an insight on the putative mechanism of the catalytic reaction. Three different mechanistic pathways were suggested, from which a concerted mechanism has been dismissed because of the experimental results. The gathered evidence continuously favours the nitrene pathway as the more likely operative mechanism.

An important intermediate of reaction has been isolated and fully characterized. Even though this type of intermediate has been previously reported for 4-methylbenzenesulphonamide, and it has been described within this work as a non-conclusive specie, thanks to it the extensive mechanistic study through NMR techniques has been possible.

Apart from stoichiometric reactions, some other sulphonamides have been tried under catalytic conditions obtaining high to moderate yields. Further studies must be performed to clarify if there is an influence of yield on nucleophilicity.

Before the interesting possibility of a complete unravelling of a mechanism involving a Rh^V nitrenoid intermediate, a more detailed study will be performed

6. Experimental section

6.1. Materials and Methods

Commercially available reagents 2-phenylpyridine, $PhI(OAc)_2$, acetonitrile, 4-methylbenzenesulphonamide, trifluoromethanesulphonamide, 4-(trilfluoromethyl)-benzenesulphonamide, 4-amino-N-methylbenzenesulphonamide, $AgSbF_6$, NMe_4OH, methanol, hexane, ethyl ether, ethyl acetate and acetone were used without further purification directly as received from the commercial supplier, and stored under inert gas and/or low temperature when required.

If necessary, the solvents (Hexanes, Et_2O, CH_3CN, Pentane) were used from a solvent purification system pure-solv (SPS-400, Innovative Technology) and stored under argon with activated molecular sieves.

Solvents were degassed (when necessary) by bubbling an argon stream at 0 ºC for at least 2 h. Deuterated solvents ($CDCl_3$, CD_3CN) were stored under argon with activated molecular sieves 4 Å. $CDCl_3$ was covered in aluminium foil to avoid photochemical decomposition.

Compounds **1-Cl, 1-ACN,** and **2-Ts** were synthesized according to previous literature procedures with some modifications.

6.2. Most used reagents

Table 2. More representative reagents

Reactive	Purity	Toxicological information
Acetonitrile	99.9+%	
Chloroform	98%	
Chloroform-d_3	"100%", 99.96 atom % D, contains 0.03 % (v/v) TMS	
2-phenylpyridine	98%	
Trifluoromethanesulphonamide	99%	
4-methylbenzenesulphonamide	95%	
4-(trilfluoromethyl)benzenesulphonamide	98%	
4-amino-N-methylbenzenesulphonamide	98%	
Iodobenzene diacetate	>97%	

Preventive measures for a safe handling:

. **Acetonitrile**. Avoid eye and skin contact, as well as vapour and mist inhalation. Keep away from all flame or sparkle source. No smoking**.** Take measures to avoid electrostatic charges build-up.

. **Chloroform**. Avoid eye and skin contact, as well as vapour and mist inhalation.

. **2-phenylpyridine**. Handle in fume hood. Wash hands immediately after contamination. P264: Wash hands thoroughly after handling.

. **All sulphonamides (Trifluoromethanesulphonamide, 4-methylbenzenesulphonamide, 4-(trilfluoromethyl)benzenesulphonamide, 4-amino-N-methylbenzenesulphonamide)**. Handle in fume hood. Wash hands immediately after contamination. P264: Wash hands thoroughly after handling.

. **Iodobenzene diacetate**. Handling is performed in a well-ventilated place. Wear suitable protective equipment. Be careful not to cause leakage, overflow, or dispersion. Steam should not be generated unnecessarily. Keep away from heat/sparks/open flame/hot surfaces. No smoking. Take measures to prevent the build-up of electrostatic charge. Avoid shock and friction. Wash hands and face before breaks and immediately after handling the product. Use a local exhaust if dust or aerosol will be generated. Avoid contact with skin, eyes and clothing.

6.3. General Procedures

Most experiments were conducted without the need of an inert atmosphere, only those involving silver salts and sulphonamide salts were performed under an argon-filled glove box (mBraun Unilab 4420) with concentrations of O_2 and $H_2O < 0.1$ ppm or using Schlenk techniques under argon atmosphere or capped vials. NMR-tube scale stoichiometric reactions were performed the same way that is described up above, adjusting the methodology to fit NMR quantities and requirements.

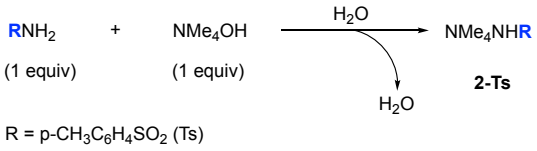
All the glassware was oven-dried at 100 ºC overnight and cooled under vacuum prior use.

NMR spectra were obtained on a Bruker 400 MHz or a 500 MHz cryoprobe spectrometers. ^{1}H, ^{13}C and ^{19}F NMR chemical shifts are reported in parts per million (ppm), relative to tetramethylsylane (TMS) for ^{1}H and ^{13}C with the residual solvent peak used as an internal reference, and relative to $CFCl_3$ (Freon) for ^{19}F. Multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), doublet of doublet of doublets (ddd) triplet of doublets (td), triplet (t) and multiplet (m).

Quantification of product in ^{1}H NMR spectra was made through 1,3,5-trimethoxybenzene as internal standard.

6.4. Modified Procedures

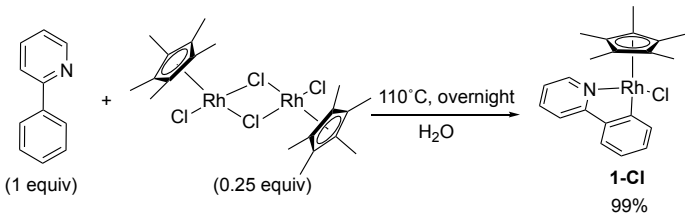
6.4.1. Synthesis of **2-Ts**.[23]



A 20-ml vial was charged with RNH_2 (2.5 mmol) and H_2O (5 ml). NMe_4OH (2.5 ml, 2.5 mmol) was then added and the mixture was stirred for 10 min at room temperature- H_2O was removed under reduced pressure heating at 80ºC. The white product was dried under reduced pressure at 90 ºC overnight.

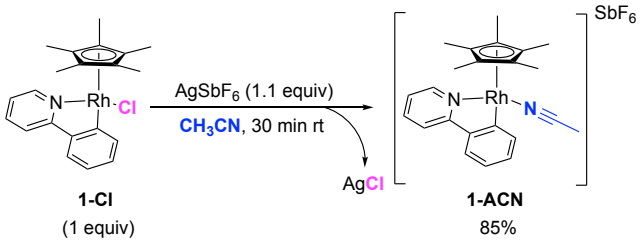
Product **2-Ts** was obtained by this procedure as a white powder and stored inside the globe.

6.4.2. Synthesis of **1-Cl**.[24]



Distilled water (20 ml) and 2-phenylpyridine (464 µl, 3.24 mmol) was added into a 100 ml Young-type flask with a magnetic stirring bar. $[RhCp^*Cl_2]_2$ (500 mg, 0.81 mmol) was then added to the mixture, the flask sealed and heted overnight to 110ºC with constant stirring. The mixture was extracted with dichloromethane (20 ml x 3) and organic layer then filtered through a plug of celite washing with dichloromethane (20 ml x 3). The solvents were removed under reduced pressure and then washed with hexane (20 ml x 4). The cyclometalated compound **1-Cl** was quantitatively obtained as a red-orange solid (170.19 mg). Obtained product was compared with literature for clarity on its obtention.[25]

6.4.3. Synthesis of **1-ACN**[26]



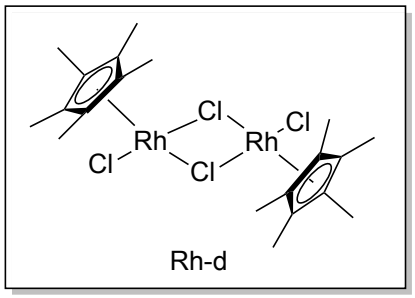
The synthesis was similar to the already reported procedure by Chang and co-workers however the procedure was modified. Under Ar atmosphere, to a Young-type flask containing a solution of rhodacycle **1-Cl** (200 mg, 0.468 mmol) in dry ACN (2.34 ml) was added dropwise a solution of $AgSbF_6$ (176.7 mg, 0.514 mmol) in dry ACN (7 ml) over 2 min at room temperature. The reaction mixture was allowed to stir at room temperature under Ar atmosphere for 30 min. Once

[23] Pérez-Temprano, M. H.; Racowski, J. M.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2014**, *136*, 4097.
[24] Ali, M. A.; Yao, X.; Li, G.; Lu, H. *Org. Lett.* **2016**, *18*, 1386.
[25] Hernandez, J. G.; Bolm, C. *Chem. Commun.* **2015**, *51*, 12582.
[26] Shin, K.; Ryu, J.; Chang, S. *Org. Lett.* **2014**, *16*, 2022.

reaction was finished, the reaction mixture was transferred into a Schlenk flask by cannula transfer under Ar, in order to get rid of solids, and solvent was removed under reduced pressure and a yellow oil formed. To this oil hexane was added (2 x 20 ml) and the flask was subjected to sonication until the oil became a suspension. Hexane was evaporated *in vacuo* and a yellow solid **1-ACN** obtained (265.5 mg, 85% yield).

6.5. Characterisation

6.5.1. Characterization of **Rh-d**

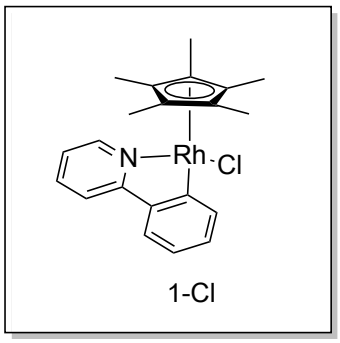


Rh-d

^{1}H NMR (500 MHz, Chloroform-*d*, 25ºC) δ 1.64 (s, 30H).

^{13}C NMR (126 MHz, Chloroform-*d*, 25ºC) δ 94.1 (d, J = 9.2 Hz), 9.4.

6.5.2. Characterization of **1-Cl**

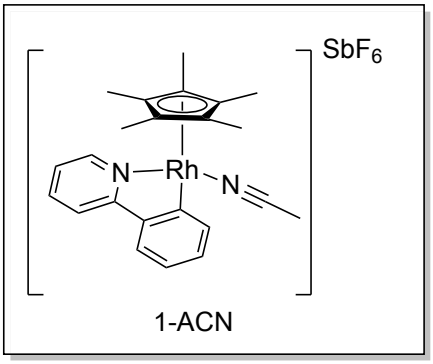


1-Cl

^{1}H NMR (500 MHz, Chloroform-*d*, 25ºC): δ 8.77 (ddt, *J* = 5.6, 1.3, 0.6 Hz, 1H), 7.84 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.79 (dt, *J* = 8.0, 1.1 Hz, 1H), 7.73 (ddd, *J* = 8.1, 7.4, 1.6 Hz, 1H), 7.63 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.29 – 7.23 (m, 1H), 7.15 (ddd, *J* = 7.2, 5.6, 1.5 Hz, 1H), 7.09 (td, *J* = 7.4, 1.2 Hz, 1H), 1.65 (s, 15H).

^{13}C NMR (126 MHz, Chloroform-*d*, 25ºC): δ 178.7 (d, *J* = 31.9 Hz), 165.5 (d, *J* = 1.8 Hz), 151.3, 143.7, 137.0 (d, *J* = 13.4 Hz), 130.5, 129.0 (d, *J* = 24.9 Hz), 126.9, 123.5, 122.8, 121.9, 119.0, 96.0 (d, *J* = 6.3 Hz), 94.1 (d, *J* = 9.2 Hz), 9.3 (d, *J* = 27.4 Hz).

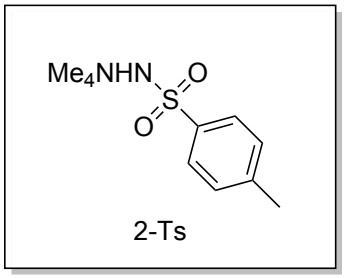
6.5.3. Characterization of **1-ACN**



^{1}H NMR (500 MHz, Chloroform-*d*, 25ºC): δ 8.90 (dt, *J* = 5.7, 1.0 Hz, 1H), 7.91 (ddd, *J* = 8.7, 7.3, 1.5 Hz, 1H), 7.89 – 7.84 (m, 1H), 7.76 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.69 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.44 (ddd, *J* = 7.3, 5.7, 1.5 Hz, 1H), 7.33 (td, *J* = 7.4, 1.4 Hz, 1H), 7.22 (td, *J* = 7.5, 1.2 Hz, 1H), 2.18 (s, 3H), 1.67 (s, 15H).

^{13}C NMR (126 MHz, Chloroform-d, 25ºC): δ 173.7 (d, J = 29.9 Hz), 164.9, 152.5, 144.4, 138.8, 136.4, 131.1, 124.5, 124.0 (d, J = 19.5 Hz), 122.6, 119.4, 100.0, 98.2 (d, J = 6.4 Hz), 9.1, 3.4.

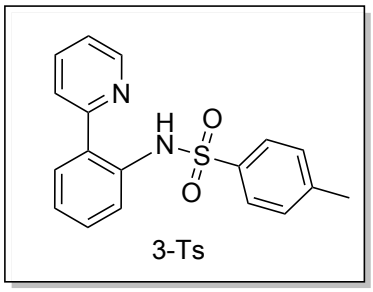
6.5.4. Characterization of **2-Ts**



^{1}H NMR (400 MHz, Acetonitrile-d_3, 25ºC): δ 7.72 – 7.67 (m, 2H), 7.20 (dt, *J* = 7.9, 0.7 Hz, 2H), 3.19 – 3.09 (m, 9H), 2.37 (d, *J* = 0.6 Hz, 3H).

^{13}C NMR (101 MHz, Acetonitrile-d_3, 25ºC): δ 147.5, 139.2, 128.5, 125.4, 117.3, 55.5 – 54.8 (m), 20.3, 0.3 (dp, *J* = 41.4, 20.8 Hz).

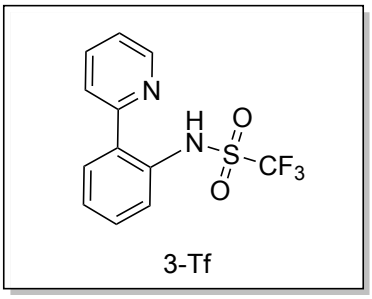
6.5.5. Characterization of **3-Ts**



^{1}H NMR (500 MHz, Chloroform-*d*, 25ºC): δ 12.16 (s, 1H), 8.64 (ddd, *J* = 4.9, 1.9, 0.9 Hz, 1H), 7.78 – 7.67 (m, 2H), 7.56 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.46 – 7.33 (m, 4H), 7.27 (ddd, *J* = 7.5, 5.0, 1.1 Hz, 1H), 7.18 (td, *J* = 7.6, 1.3 Hz, 1H), 7.02 – 6.97 (m, 2H), 2.30 (s, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*, 25ºC): δ 157.1, 147.4, 142.9, 137.4, 136.9, 136.5, 130.1, 129.1, 128.5, 127.4, 126.8, 124.6, 123.4, 122.2, 122.0, 29.7, 21.4.

6.5.6. Characterization of **3-Tf**

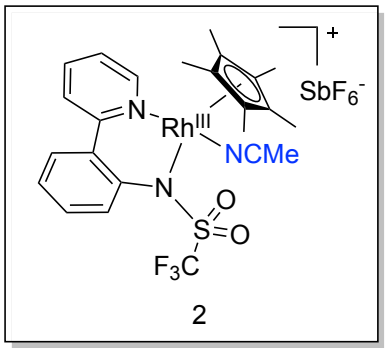


^{1}H NMR (400 MHz, Chloroform-*d,* 25ºC): δ 8.68 – 8.62 (m, 1H), 8.01 – 7.88 (m, 2H), 7.84 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.46 (ddd, *J* = 8.3, 7.4, 1.6 Hz, 1H), 7.38 (ddd, *J* = 6.3, 5.0, 2.3 Hz, 1H), 7.31 (ddd, *J* = 7.9, 7.4, 1.3 Hz, 1H), 1.28 (s, 1H).

^{13}C NMR (101 MHz, Chloroform-*d*, 25ºC): δ 156.4, 146.5, 138.5, 136.1, 130.8, 128.2, 125.3, 125.1, 122.7, 122.0, 121. 8, 29.7.

^{19}F NMR (376 MHz, Chloroform-*d*, 25ºC): δ -76.6.

6.5.7. Characterization of **intermediate 2**



2

^{1}H NMR (400 MHz, Chloroform-*d,* 25ºC): δ 8.73 (dd, *J* = 5.8, 1.6 Hz, 1H), 8.13 (td, *J* = 7.8, 1.6 Hz, 1H), 7.93 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.86 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.65 – 7.50 (m, 4H), 7.32 (td, *J* = 7.6, 1.2 Hz, 1H), 1.96 (s, 3H), 1.38 (s, 15H).

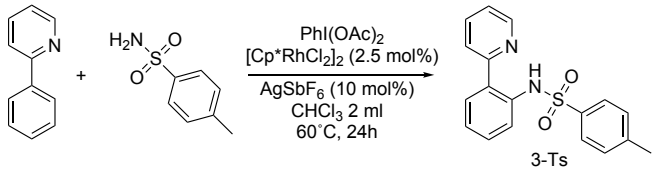
^{13}C NMR (101 MHz, Chloroform-*d*, 25ºC): δ 158.0, 154.0, 142.8, 141.4, 135.1, 132.7, 131.6, 128.9, 126.6, 126.3, 123.1, 120.5, 99.3 (d, *J* = 8.3 Hz), 8.7.

^{19}F NMR (376 MHz, Chloroform-*d*, 25ºC): δ -76.8.

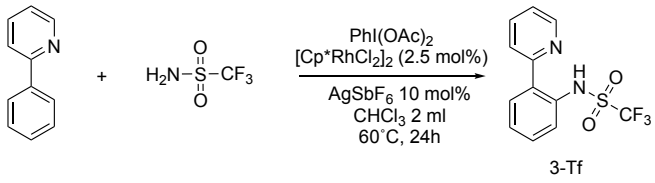
6.6. Catalytic reaction

6.6.1. General modified procedure

The synthesis of the sulphonamidated product was performed as the reported procedure by Chang et al.[11], with minor changes in the purification step. Once the product **3-Ts** was isolated, reaction was confirmed to be feasible in chloroform as well. From this point ahead, chloroform was used as solvent due to its availability in deuterated form for the testing of stoichiometric reactions.

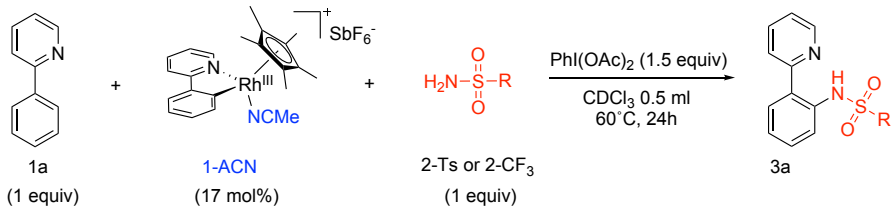


In a glove box, a capped vial equipped with a stirring bar and $[Cp^*RhCl_2]_2$ (3.1 mg, 2.5 mol%), $PhI(OAc)_2$ (96.9 mg, 0.3 mmol) and p-toluenesulfonamide (34.2 mg, 0.2 mmol) was charged with $AgSbF_6$ (6.9 mg, 10 mol%). Once all solids were weighted, the vial was crimped and taken out from the glove box. Then, 2-phenyl pyridine (57 µl, 0.4 mmol) was added through the rubber septum using a syringe. Finally, dry CH_2Cl_2 (2 ml) were added through the rubber septum. The reaction mixture was heated at 60ºC and allowed to stir for 24 h. Once reaction was finished, product was purified by silica gel column with AcOEt: hexane (1:10) as eluent. TLC in 1:10 proportion of AcOEt: hexane solution was performed on reaction crude to clarify if product was formed. ^{1}H NMR spectrum confirmed the obtention of the product.



For the obtention of **3-Tf** the same procedure was followed using **2-Tf** (29.82 mg, 0.2 mmol) as nitrogen source. Once reaction was finished, product was purified by silica gel column with AcOEt: hexane (20:80) as eluent. TLC in 20:80 proportion of AcOEt: hexane solution was performed on reaction crude, before final purification, to clarify if a new specie was formed. Synthesis of **3-Tf** was unprecedented.

6.6.2. Using **1-ACN** as catalyst



The use of **1-ACN** specie as catalyst intended to: (1) Confirm whether or not reaction take place through this specie, (2) Abstain from using $AgSbF_6$ easing the reaction conditions.

In a NMR tube with $PhI(OAc)_2$ (16.91 mg, 0.053 mmol), **1-ACN** (4.01 mg, 0.006 mmol) and 4-methylbenzenesulphonamide (6 mg, 0.0356 mmol) opened to air is added a solution of 2-phenylpyridine (10 µl, 0.07 mmol) in dry chloroform-d_3.

6.7. Single Crystal X-Ray Structure of 2 and 7

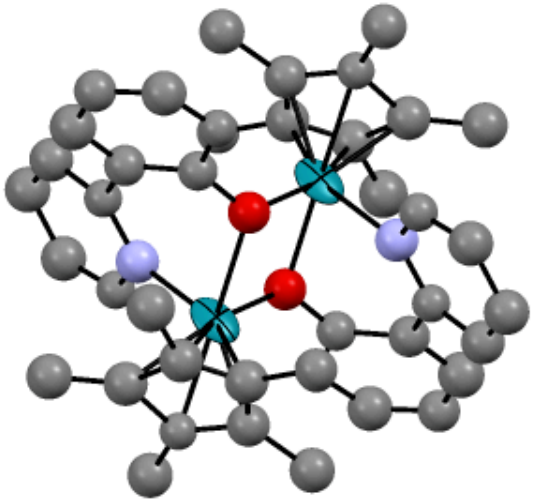


Figure S1. ORTEP representation of the structures of 7 from reaction in section 3.2.1. Hydrogen atoms and, solvent molecules or counterions have been omitted for clarity. Due to crystal quality, ORTEP representation is not optimum.

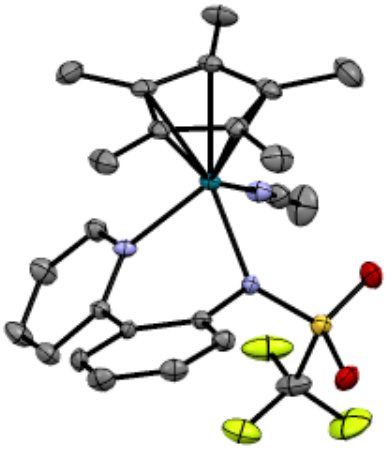


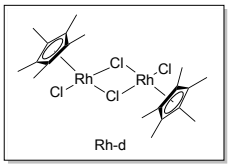
Figure S2. ORTEP representation of the structures of intermediate **2** from reaction in section 3.1. Hydrogen atoms and, solvent molecules or counterions have been omitted for clarity.

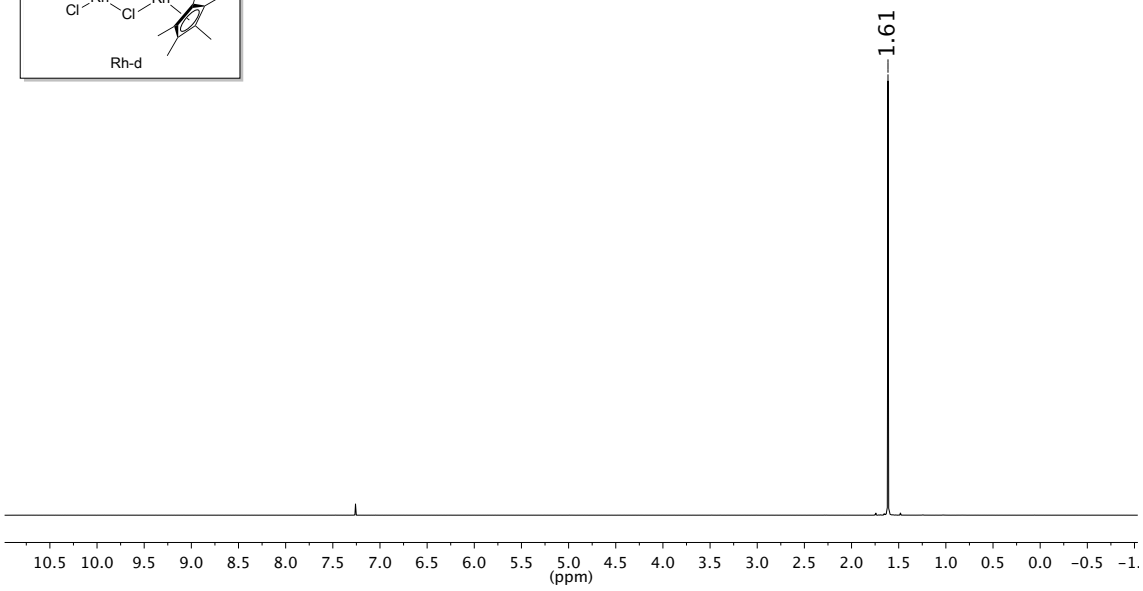
Crystal preparation: Crystals of intermediate **2** where obtained several times inside the NMR tube after monitoring stoichiometric and catalytic reactions at 50ºC. Crystals of compound **7** were grown by slow diffusion of Et_2O into solutions of acetone. The measured crystals were prepared without the need of using inert conditions and at -32 ºC.

6.8. NMR characterisation

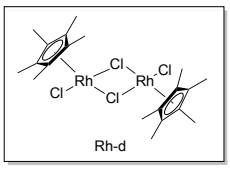
6.8.1. NMR characterization of complex **Rh-d**

^{1}H NMR spectrum of Rh-d at 25ºC ($CDCl_3$)



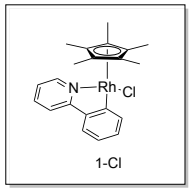


^{13}C NMR spectrum of Rh-d at 25ºC ($CDCl_3$)

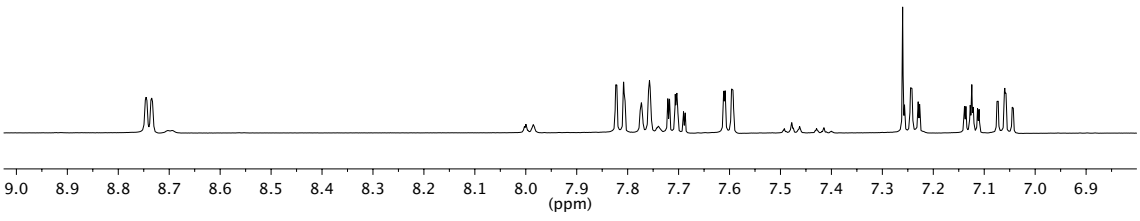


6.8.2. NMR characterization of complex **1-Cl**

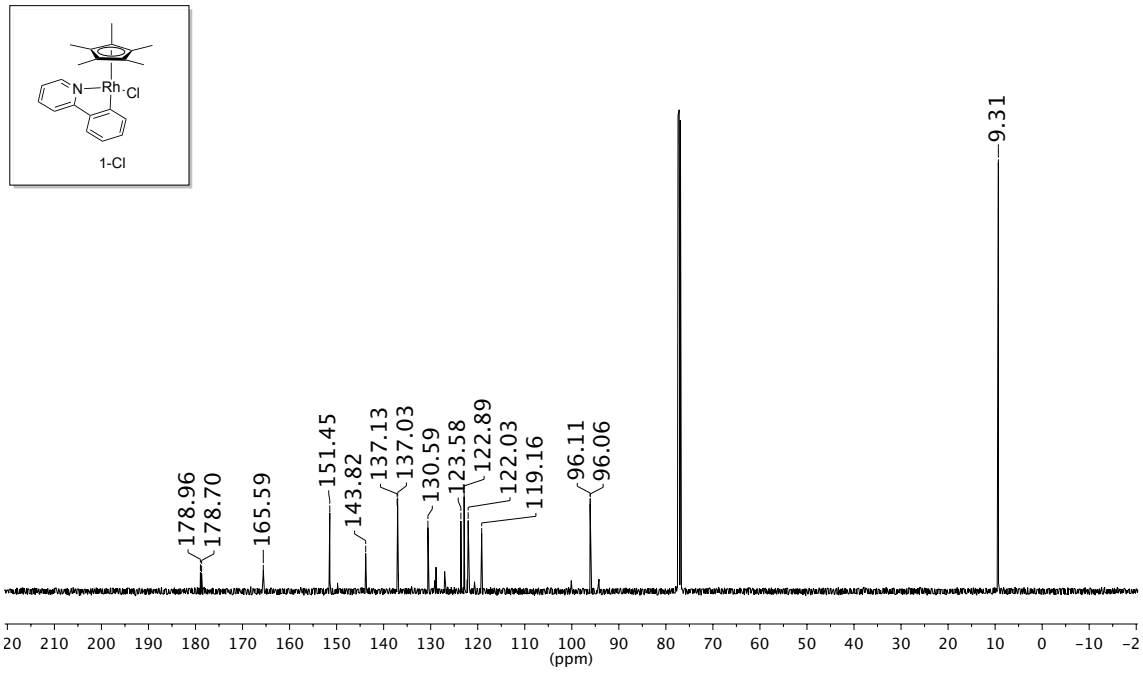
^{1}H NMR spectrum of 1-Cl at 25ºC ($CDCl_3$)

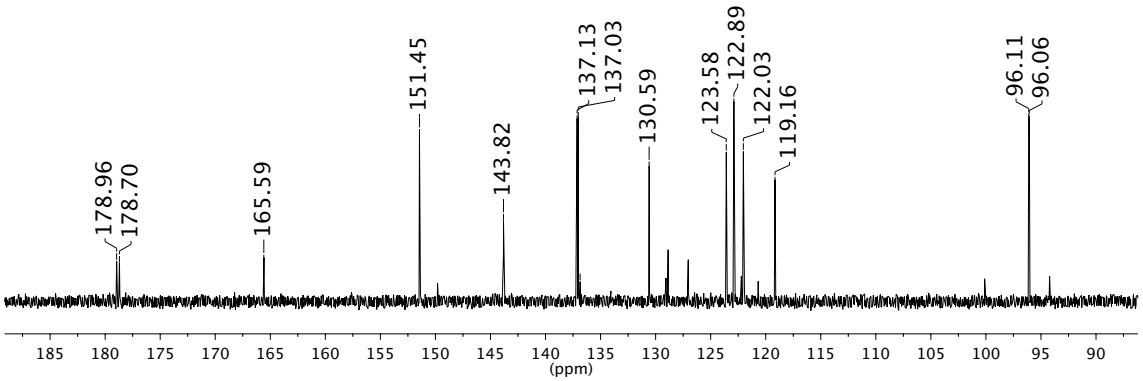


1-Cl



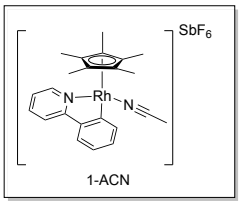
^{13}C NMR spectrum of 1-Cl at 25ºC ($CDCl_3$)

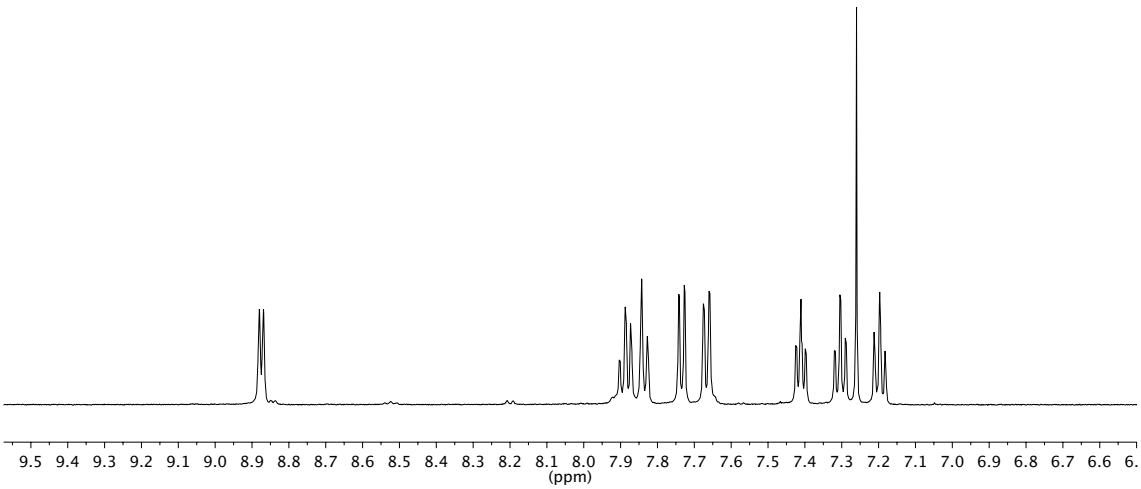




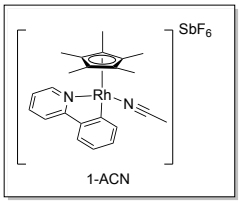
6.8.3. NMR characterization of complex **1-ACN**

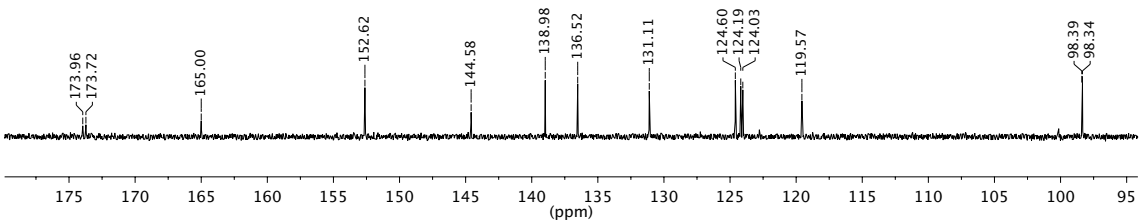
^{1}H NMR spectrum of 1-ACN at 25ºC ($CDCl_3$)





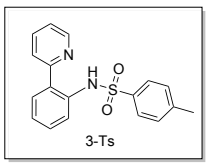
^{13}C NMR spectrum of 1-ACN at 25ºC ($CDCl_3$)

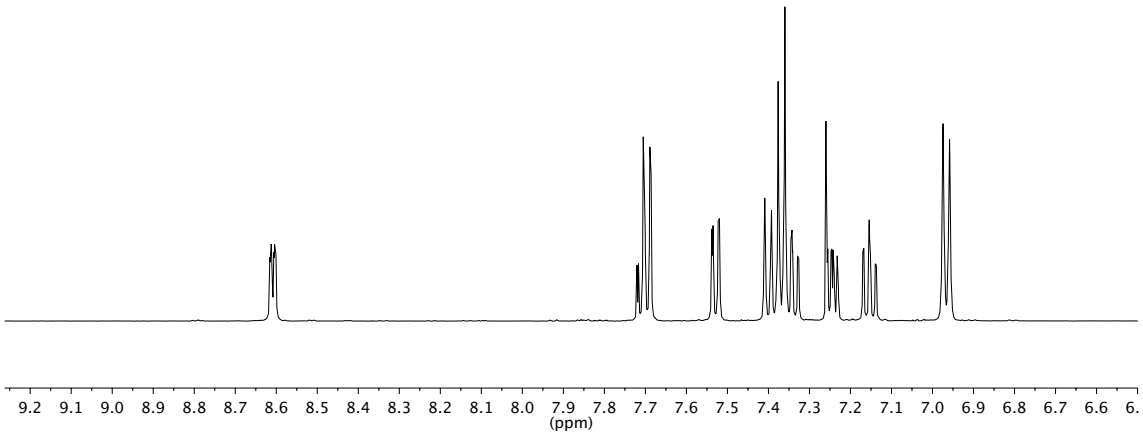




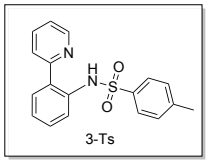
6.8.4. NMR characterization of product **3-Ts**

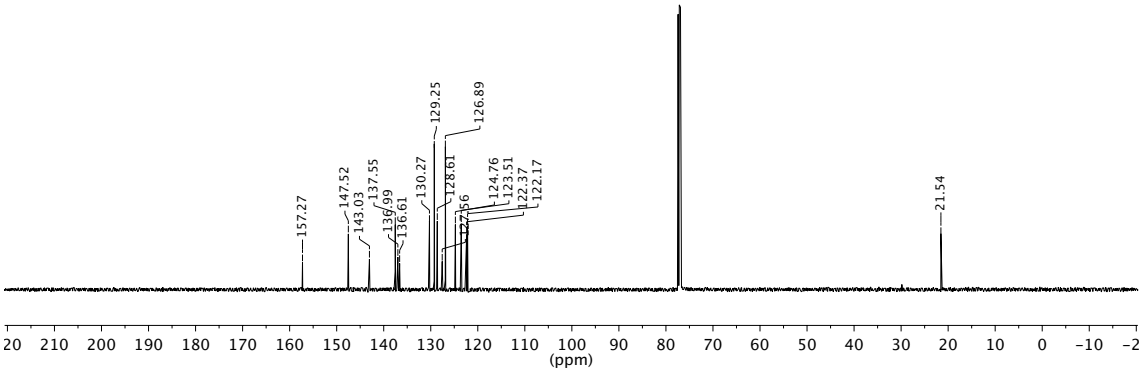
^{1}H NMR spectrum of 3-Ts at 25ºC ($CDCl_3$)

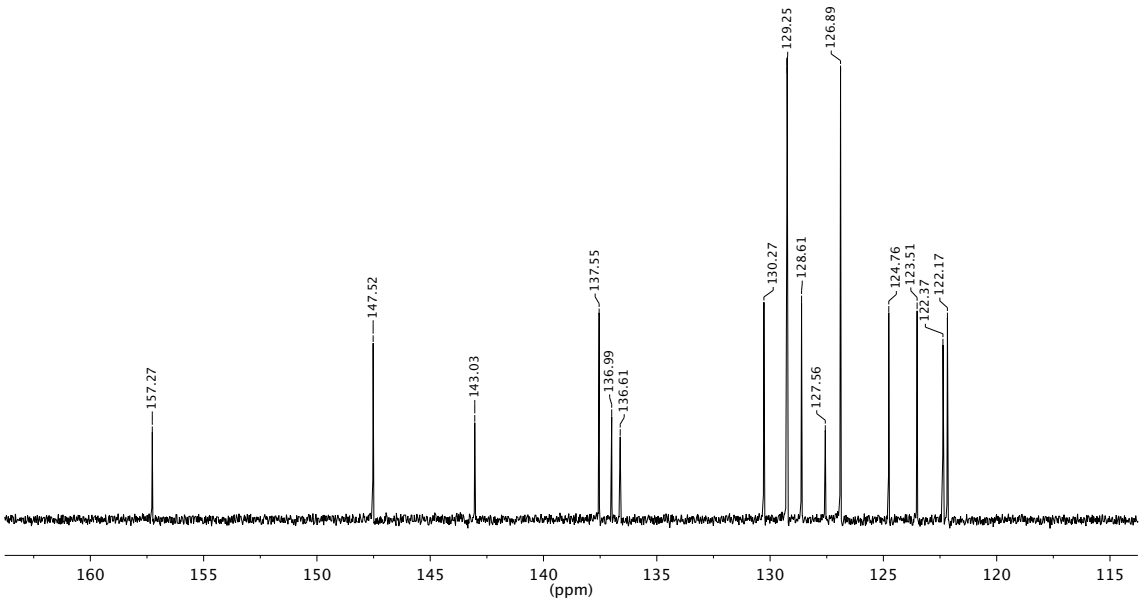




^{13}C NMR spectrum of 3-Ts at 25ºC ($CDCl_3$)

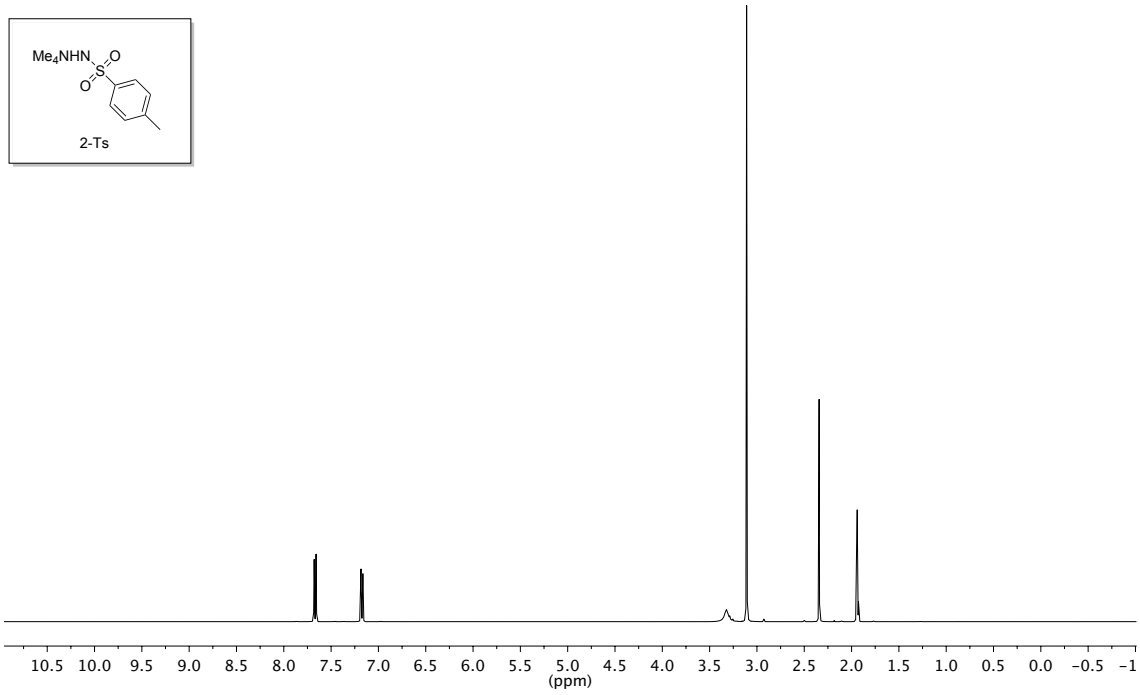




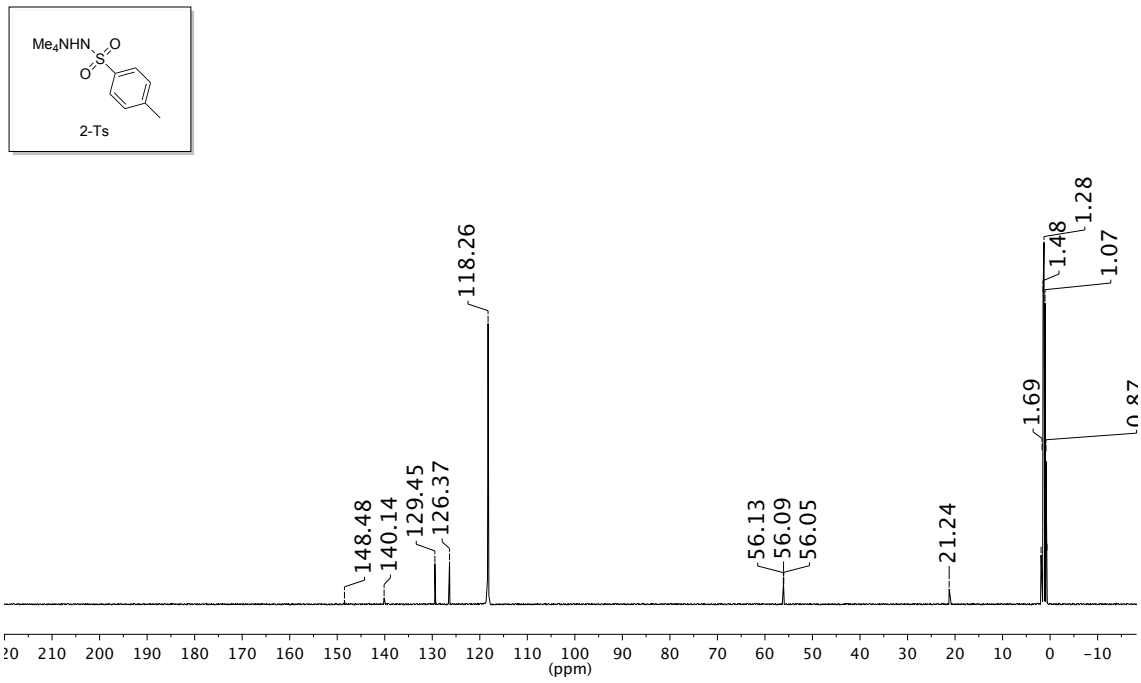


6.8.5. NMR characterization of susbtrate **2-Ts**

^{1}H NMR spectrum of 2-Ts at 25ºC (CD_3CN)

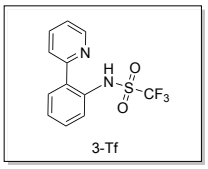


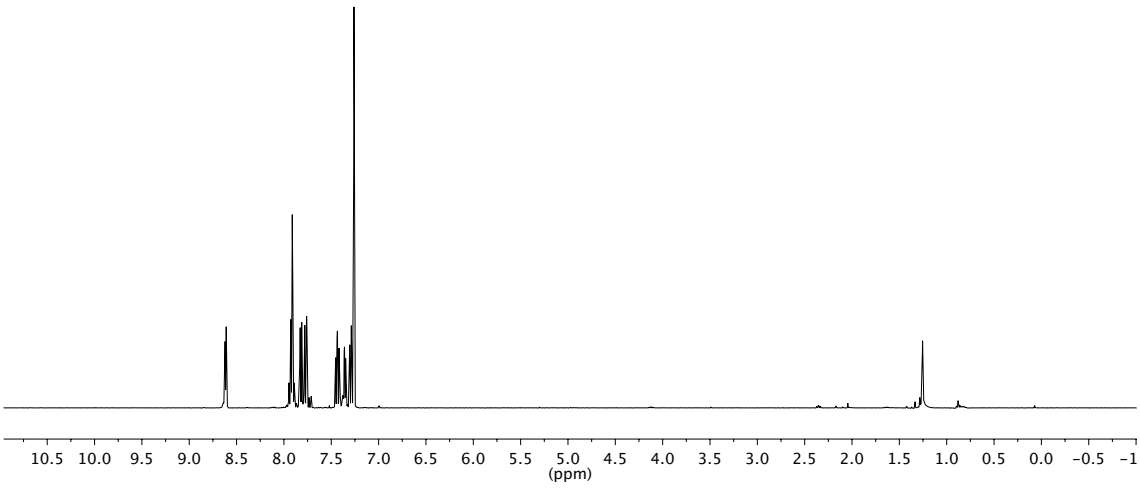
^{13}C NMR spectrum of 3-Ts at 25ºC (CD_3CN)

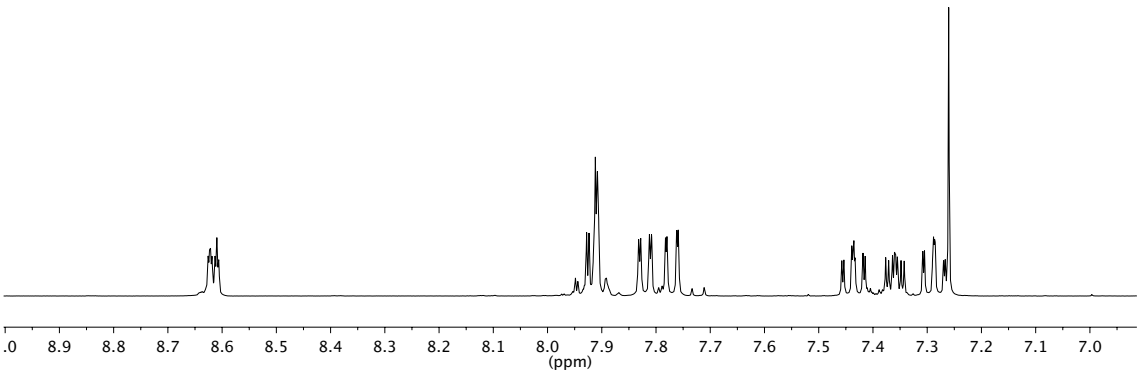


6.8.6. NMR characterization of product **3-Tf**

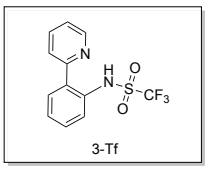
^{1}H NMR spectrum of 3-Tf at 25ºC ($CDCl_3$)

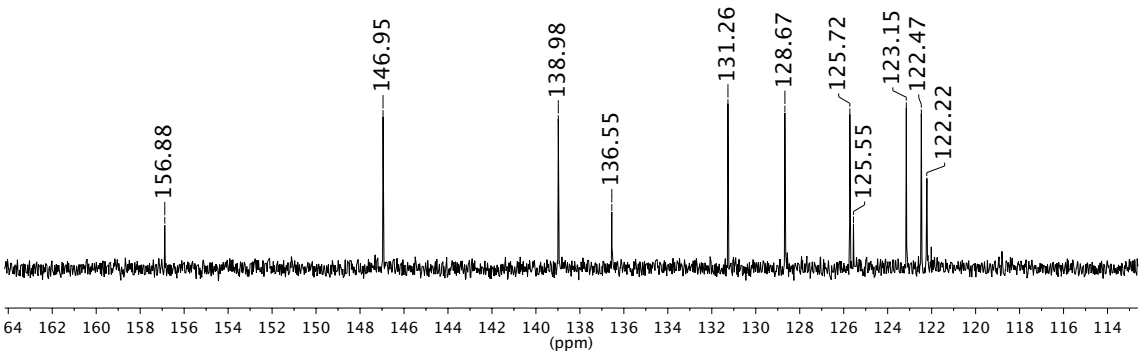




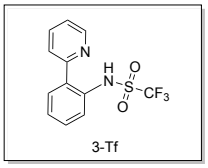


^{13}C NMR spectrum of **3-Tf** at 25ºC ($CDCl_3$)

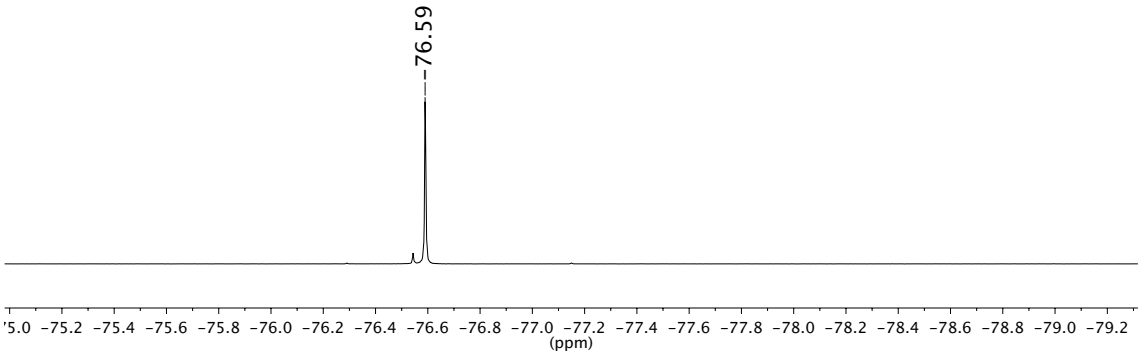




^{19}F NMR spectrum of **3**-Tf at 25ºC ($CDCl_3$)

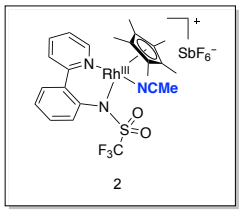


3-Tf

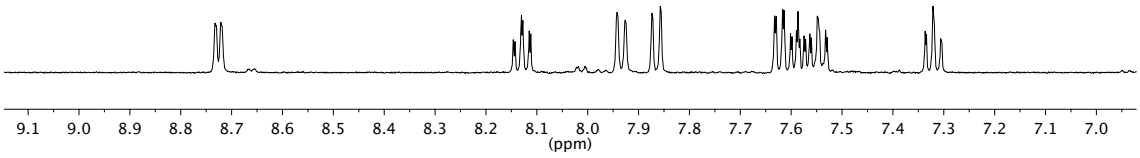


6.8.7. NMR characterization of intermediate **2**

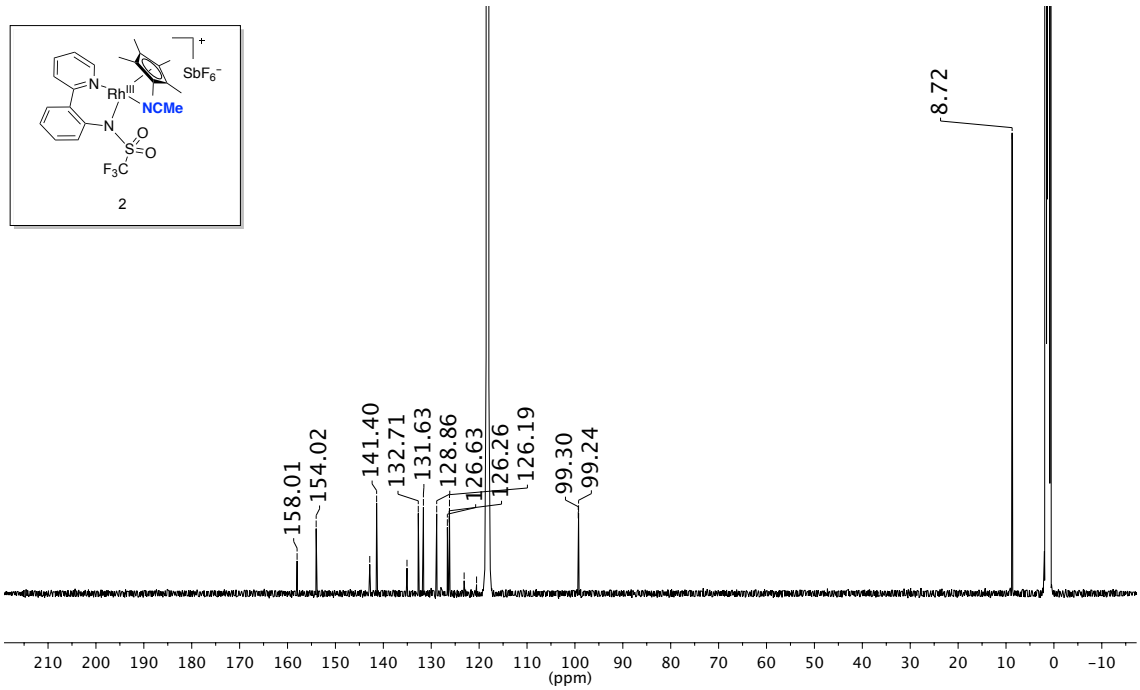
^{1}H NMR spectrum of intermediate **2** at 25ºC (CD_3CN)

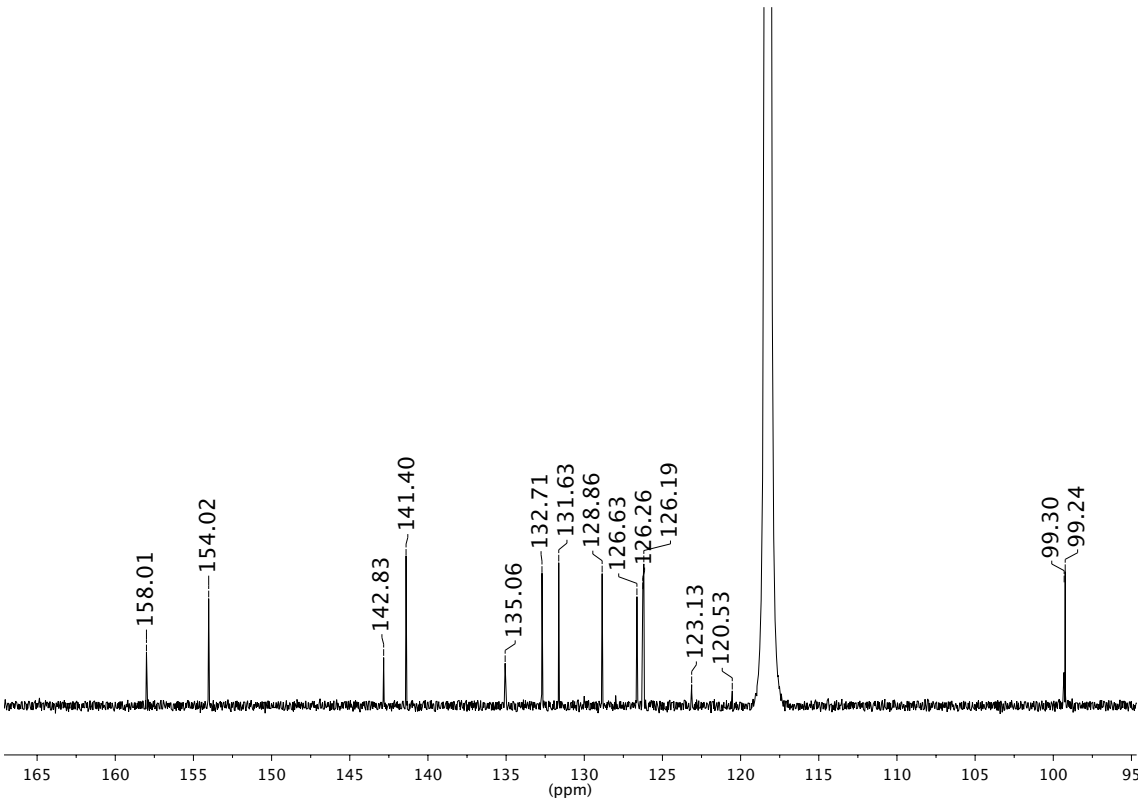


2

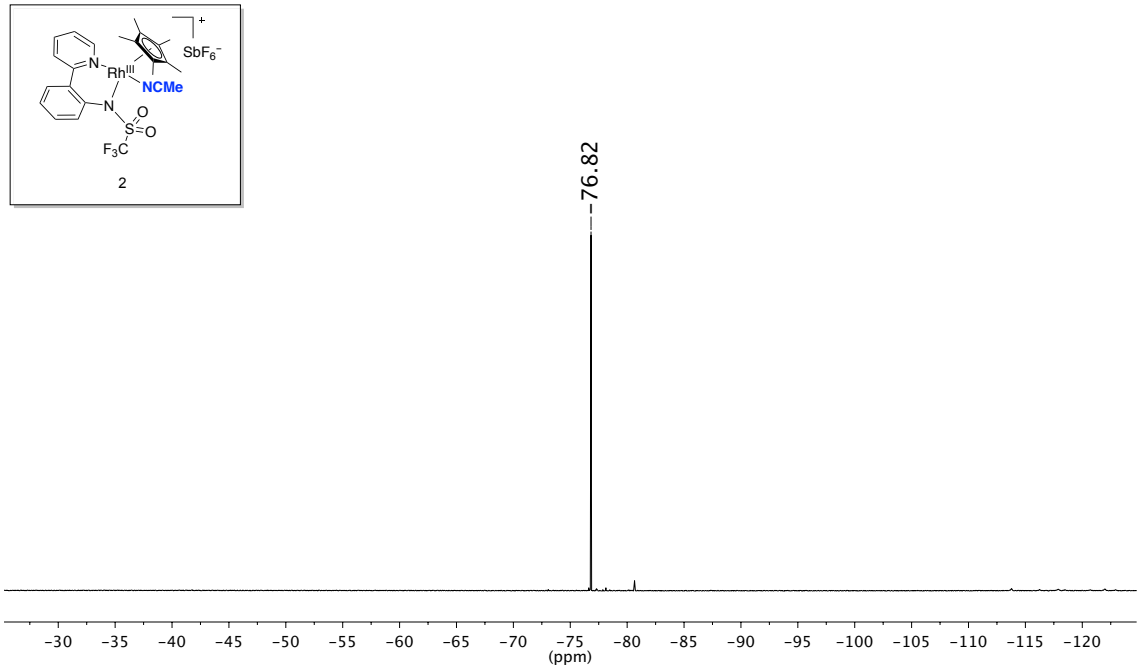


^{13}C NMR spectrum of intermediate 2 at 25ºC (CD_3CN)





^{19}F NMR spectrum of intermediate 2 at 25ºC (CD_3CN)



HSQC NMR spectrum of intermediate **2** at 25ºC (CD_3CN)