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Homogeneous catalytic reductive carbonylation of organic nitro compounds: bidentate nitrogen ligands as a key point

PhD Thesis of:

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Chapter 1

General Introduction

1.1 Introduction

Catalysis is a central technology in most of the industrial syntheses of both bulk and fine chemicals. Currently more than 90 % of chemical products derive from processes that involve, in one or more synthetic steps, the use of a catalyst. Although the majority of the catalytic reactions applied in industry take place in the heterogeneous phase, the number of homogeneously catalyzed processes has been raising in the last thirty years.

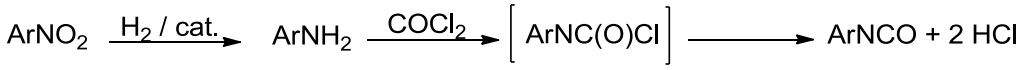
Among the industrial processes that employ homogeneous catalysts, those based on the use of carbon monoxide are a substantial part. In particular, the most important reactions in bulk chemicals production are carbonylation of methanol to acetic acid, methyl acetate to acetic anhydride, olefins to aldehydes and oxo alcohols, propyne to methyl methacrylate and benzyl chloride to phenyl acetic acid while in fine chemicals the Boots, Hoechst-Celanese process for the synthesis of Ibuprofen is the most outstanding example.[1, 2]

In the last fifty years, the reductive carbonylation of organic nitro compounds has been the subject of intense research due to the fact that industrially important chemicals can be obtained in a single step. Among these, the most relevant are isocyanates, ureas and carbamates but also a number of heterocycles and other non-cyclic compounds.

Isocyanates are commodity chemicals mostly employed in polyurethane synthesis but also intermediates in the production of carbamates and ureas. Polyurethanes are widely applied in almost every part of modern life in the form of plastic foams, coatings, adhesives, sealants and elastomers and binders.[3] Moreover carbamates and urea are important final products themselves in agrochemical and pharmaceutical industry. The annual world production of these chemicals is several millions metric tons and it is steadily increasing. Among the chemicals cited above, the most widely employed are aromatic isocyanates, especially toluenediisocyanate (TDI) and 4,4'-methylene diphenyl diisocyanate (MDI) that account for more than seven million metric tons per year. The industrial interest for these two compounds is evident from the recent investment on new plants by the major producers both in Europe and in Asia.

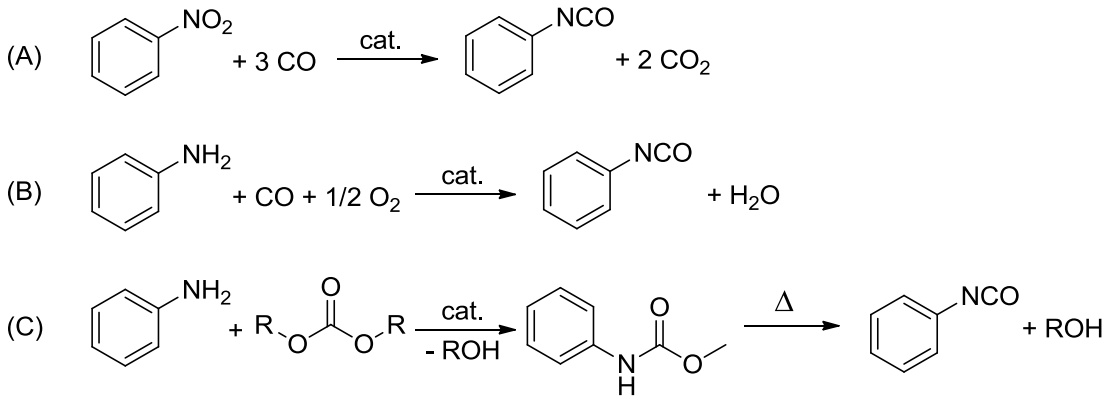
1.2 Isocyanate synthesis: the industrial approach

Currently the industrial synthesis of aromatic isocyanates is carried out in two steps from the nitro compounds with very high yields and selectivities. The nitroarene is initially reduced to the corresponding aniline by hydrogenation over a heterogeneous catalyst based on a transition metal, most likely Cu, Pd or Fe, and subsequently the amine is reacted with phosgene to give arylcarbamic chloride that readily lose an HCl molecule at the reaction temperature (65 – 80 °C). The reaction is then completed in a subsequent reactor by rising the temperature above 160 °C and venting the excess hydrogen chloride and phosgene (eq. 1).[4]



(1)

Although relatively high temperatures are required, from an economical point of view, the phosgene-based route seems to be the most effective strategy and the well-established phosgene technology appears to be difficult to replace. On the other hand phosgene is very toxic and corrosive, since it is an hydrolysable compound, it is produced by reaction of carbon monoxide with chlorine that is an extremely energy-intensive material.[5] Moreover phosgene is listed as a potential chemical weapon by the Chemical Weapon Convention that implies limits to stockpiling and restrictive controls for producers. This means that any process design incorporating phosgene will incur extra costs to ensure a safe environment. On August 2006, in Italy, a large plant employing phosgene in toluenediisocyanate production, was shut down mainly because investors were frightened by the local population concerns and the opposition by the authorities over the use of phosgene close to a populated area. Thus a more environmentally acceptable but still economically competitive phosgene-free route to isocyanates is required. Among the alternative ways to prepare isocyanates three have been sufficiently developed and are still economically feasible to have the potential for an industrial application (Scheme 1): the reductive carbonylation of nitroarenes (A), the oxidative carbonylation of amines (B) and the reaction of amines with organic carbonates (C). Industries interested in the production of both aromatic and aliphatic isocyanates may prefer to develop a process applicable to both and so could be more interested in the synthetic strategies that starts from the amine. Nevertheless the synthesis of anilines involves an hydrogenation of the corresponding nitro compound over a different catalyst in a different reactor. Thus for the production of TDI and MDI the direct reaction of nitro compounds with carbon monoxide to give isocyanates is the most attractive strategy.



Scheme 1.

1.3 Synthesis of carbamate and ureas

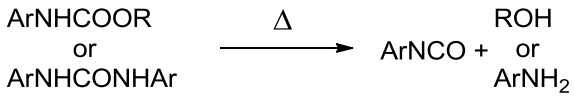
The reductive carbonylation of nitro compounds is the shortest and the potentially most economical pathway to aromatic isocyanates. Nevertheless the direct carbonylation of the nitroarene to isocyanate (A, Scheme 1) is a difficult process mainly due to the high reactivity of the formed isocyanate. Indeed, over a certain concentration the in-situ generated isocyanate self-reacts yielding oligomers and polymers leading mainly to tar formation when temperature is above 200 °C.[6, 7]

Alternatives to the direct carbonylation reaction are the so called "indirect" synthesis. These are very similar to the direct one since the nitroarene is intermediately reduced and then carbonylated, but the in-situ formed isocyanates reacts with a nucleophilic compound such as an alcohol (eq. 2) or an amine (eq. 3) affording respectively carbamates or ureas and avoiding self-condensation of the isocyanate.

$$ArNO_2 + ROH + 3\ CO \xrightarrow{cat.} ArNHCOOR + 2\ CO_2 \quad (2)$$

$$ArNO_2 + ArNH_2 + 3\ CO \xrightarrow{cat.} ArNHC(O)NHAr + 2\ CO_2 \quad (3)$$

Both ureas[8, 9] and carbamates[10-14] can be thermally or catalytically decomposed to isocyanates (eq. 4). However, thermolysis of ureas has several problems. The two main ones are the fast recombination of the products and the difficulty in separating the isocyanate and the amine due to their similar boiling points. Whereas carbamates thermolysis occurs at lower temperatures and allow to overcome the problem of product recombination by alcohol distillation. Is not surprising that much effort, in particular in the last decades, was devoted to developing indirect method and especially that involving alcohols as solvents.



(4)

Although the reaction of carbon monoxide with aromatic nitro compound is a thermodynamically favorable process, carbonylation to isocyanate does not occur if a catalyst is not present.[6] In the last fifty years several elements and transition metal were tested as catalysts.

Among the non-transition catalysts, sulfur, selenium and tellurium were reported, mainly in the patent literature, to be good catalysts for the carbonylation of nitroarenes to carbamates and ureas. In particular selenium gave the best results and raised industrial interest. However the toxicity of these elements and the difficulties encountered in catalyst removal from the product led the industries to leave the development of these catalytic systems.[6] Transition metal catalysts were tested both in direct and indirect synthesis of isocyanates but the best results were obtained in the latter. Heterogeneous catalysts based on the use of metals deposited on a solid support as well as polymeric precursors such as Rh and Pd chlorides were employed in combination with a ligand and a Lewis acid as poorly active catalytic systems.[6, 7] Carbonyl clusters of Rh[15] and Ru[16] showed higher activities as catalyst precursor in particular in combination with chelating ligands.[17] Only few studies are present in the literature on the use of Pt, Ni, Cu and Fe complexes for the synthesis of alkyl arylcarbamates and diarylureas, some of which report very good results in term of selectivity however the activities are usually low and low ArNO/catalyst ratios are employed.[6] Most of the studies conducted in the last three decades by both industrial and academic research groups involve the use of palladium complexes as catalysts, specifically those with phosphines[18-23] or bidentate N-N[19, 24-38] and P-N ligands.[23, 39]

Among the systems cited above, those based on palladium and 1,10-phenanthroline ligands showed the highest activity and are the best catalytic systems to date, in particular when a non-coordinating acid is used as co-catalyst. A little insight into mechanistic aspects will be given in Chapter 2.

Indeed the mechanism of this reaction was extensively studied by our research group and these studies allowed us to further improve the catalytic system. In particular by tailoring the electronic properties of the phenanthroline ligand we were able to further improve the activity of more than 50 %.[40] In this thesis we further extended the study by synthesizing and testing in catalysis other nitrogen ligands mostly based on the phenanthroline moiety (Chapter 2).

Since very high TON and TOF have been reached with the systems based on palladium and phenanthroline, one of the main obstacles to industrial application is the recycle of the catalyst. In this thesis we dealt with the problem studying the application of thermomorphic catalytic systems to

the synthesis of carbamates, definition of these systems and experimental details will be discussed in Chapter 3.

1.4 Synthesis of heterocycles

If the reductive catalytic carbonylation of nitroarenes to carbamates, ureas and isocyanates is still not competitive with respect to the currently employed phosgene route, it is mainly because of the cost of the precious metal catalyst and the big initial investment needed to develop world-scale industrial plants based on a new technology. Anyhow, the development of "greener" processes and technologies is still one of the main concern in the development and research politics of post-industrial economies. Thus there has been a growing interest in the study of possible application of catalytic carbonylation of organic nitro compounds to the synthesis of high-value products containing heterocyclic rings.

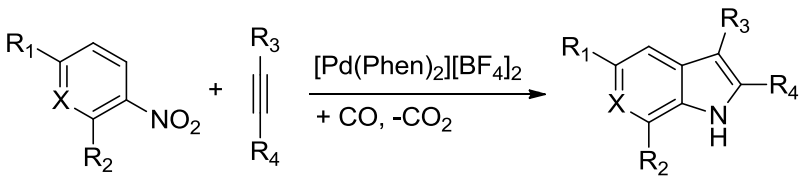
The subject was extensively reviewed in 1996[6, 41] and later in 2006[42] reporting the last updates. The synthesis of carbazoles, indoles, benzimidazoles, indazoles, triazoles, quinazolinones, pyridines and other compounds containing a pyridinic ring was successfully achieved by reductive cyclization of nitroarenes bearing an opportune functional group in *ortho* employing transition metal catalysts.

The catalytic performances strongly depend on the starting material and the type of heterocyclic ring synthesized, thus it is difficult to establish the superiority of a certain catalytic system over another.

The first report on deoxigenative cyclization of nitroarenes was reported by Cadogan and coworkers in 1962,[43] they found that carbazole can be synthesized by heating triethyl phosphite with *o*-nitrobyphenyl. This stoichiometric reaction was then further studied by Sundberg applying it to the synthesis of indoles.[44] Few years later Alper *et al.* reported the first transition metal mediated cyclization of an *o*-nitroarene in a stoichiometric reaction[45] and subsequently Cenini and coworkers in a catalytic reaction, employing CO as a reductant.[40] $M_x(CO)_y$ (M = Fe, Rh, Ru) were found to be good catalysts in many different heterocyclization reactions even though quite harsh conditions were required (usually T > 200 and P_{co} > 50 bar), whereas milder condition could be used when the catalysts were Pd/phosphines or Pd/phenanthrolines. Among these palladium based systems, that employing phenanthrolines as ligands gave better results, concerning stability of the catalytic system. Indeed also the use of phosphines gave good yields in heterocyclic products, however it has long been known that phosphines can directly deoxygenate the $–NO_2$ group, being transformed into phosphinoxide and leading to catalyst deactivation.

The most investigated class of heterocyclic compounds have been the indoles, due to their pharmaceutical importance. Most of the syntheses reported in the literature involve the

intramolecular cyclization of an *ortho*-substituted nitro compound; however indole could also be obtained by intermolecular cyclization between a nitro compound and alkyne (Scheme 2).



Scheme 2.

One of the main drawbacks of these syntheses is the commercial availability of the starting materials. Even if the problem could be overcome by preparing the required *ortho*-substituted nitroarene or the alkyne, the syntheses often proceed with low yields. In this thesis we report our study on a third synthetic strategy that involves the reductive cyclization of β-nitrostyrenes, easily obtainable from commercial benzaldehydes and nitroalkanes by nitro-aldol reaction (Chapter 5).

1.5 Nitroarenes catalytic reduction to anilines by carbon monoxide

The formation of anilines from nitroarenes is an important industrial transformation. The hydrogenation of non-functionalized nitroarenes is generally carried out in the gas phase over heterogeneous catalysts of copper or palladium. However these procedures are often not selective for the nitro group reduction when other reducible groups are present.

Functionalized anilines are important intermediates in for production of agrochemicals, pharmaceuticals, dyes and pigments thus developing selective catalytic method for their production is very important.

Nitroarenes catalytic reduction to anilines by CO/H_2O is a very promising reaction because of its high selectivity towards the nitro group also in the presence of other reducible moiety as cyano, keto, ester, halide (aromatic), and olefinic.[46] This reaction is promoted by several different transition metals carbonyls, however in some cases the reaction is only stoichiometric. The best results were obtained employing ruthenium catalysts. In particular the most active system was based on the use of $Ru_3(CO)_{12}$ as catalyst precursor and Ar-BIAN (bis(arylimino)acenaphthene) as the ligand.[47, 48]

As for many other homogeneously catalyzed reactions, one of the main problems is the recovery of the catalyst after the end of the reaction. For this reaction the recycle of the catalyst is even more challenging due to the instability of the active species $[Ru(Ar\text{-}BIAN)(CO)_3]$ in the presence of air.

Very recently in our group the immobilization of the catalytic system on a polymeric membrane was successfully performed and this allowed an easy separation of the catalyst from the products in an inert atmosphere, preventing catalyst decomposition.[49] Although good results were obtained, the synthesis and stability of polymeric membrane is not always obvious, thus in this thesis we explored another alternative for the immobilization of the catalyst by synthesizing an oligomeric ligand of the Ar-BIAN family (Chapter 6).

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Chapter 2

Nitrogen ligands effects in the palladium catalyzed synthesis of methyl *N*-phenylcarbamate

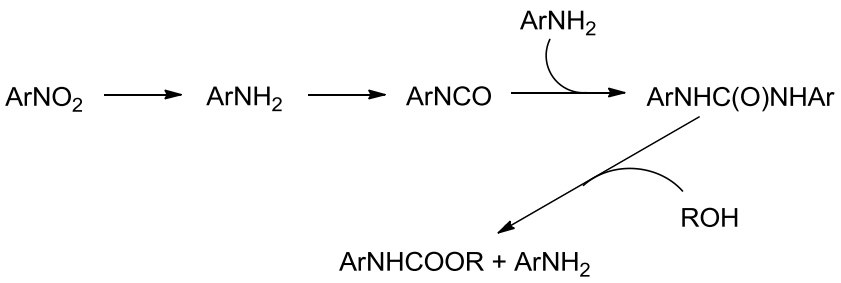
2.1 Introduction

We already mentioned in the introduction that one of the most developed phosgene-free route to isocyanate is the palladium catalyzed reductive carbonylation of nitroarenes. If this reaction is conducted in the presence of an alcohol, carbamates can be obtained (eq. 1):

$$ArNO_2 + ROH + 3\ CO \xrightarrow{cat.} ArNHCOOR + 2\ CO_2 \qquad (1)$$

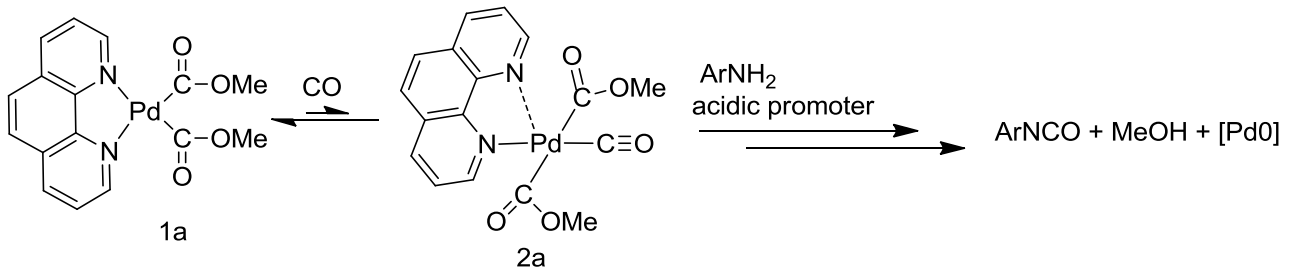
Carbamates are important final product and synthetic intermediates for the pharmaceutical[1, 2] and agrochemical[3] industries. Moreover they can be thermally[4-7] or catalytically[6] decomposed to give isocyanates (eq. 2). The synthesis of methyl *N*-phenylcarbamate (MPC) in particular was used as model reaction in many studies on the phosgene-free synthesis of isocyanates, furthermore MPC itself is an intermediate in the synthesis of dimethyl 4,4'-methylenebis(4,1-phenylene)dicarbamate that is a precursor of MDI.[8-11]

At the end of the last century, it was found that the most active catalysts for the reductive carbonylation of nitroarenes are those based on palladium and chelating nitrogen ligands,[12] especially Pd/phenanthroline complexes. The catalytic system was found to be more active if a Brønsted acid was added as a co-catalyst. However, it was observed that the promoting efficiency was not correlated with the acidity of the acid employed.[13] This suggested to our group that a bifunctional effect of the co-catalyst was involved and permitting us to further improve the catalytic performance by introducing the use as promoters of phosphorus acids, known to have good bifunctional properties.[14-16]



Scheme 1

Mechanistic aspect of the catalytic system were recently discussed in both a paper[17] and a review[18]. Even if the validity of the proposed mechanistic scheme has recently been questioned,[19, 20] the reasons adduced for criticism are in our opinion too weak with respect to the evidence in its support. Nevertheless there is evidence that several mechanisms can operate in competition with each other, with the predominating of one with respect to another depending on the reaction conditions. The mechanism reported by our group is the major under the optimized experimental conditions that were those employed also in the study conducted in this thesis. The most relevant features of the catalytic reaction are the following:



Scheme 2.

(1) During the catalytic cycle an intermediate reduction of the nitroarene to aniline take place, followed by carbonylation of the amine to arylisocyanate. This reacts with an aniline molecule to form diphenylurea that at high temperature is alcoholized by methanol, employed as solvent (Scheme 1).

(2) A phenanthroline-palladium bis-alkoxycarbonyl complex (**1a** in Scheme 2) is the catalytic active species. The reaction with carbon monoxide proceeds by the initial formation of a CO adduct, **2a**, which is then attacked by an arylamine on the coordinated CO. At last an acid-assisted proton transfer results in isocyanate production and formation of a palladium (0) complex that can reenter the catalytic cycle or decompose to metallic palladium when no nitroarene is present.

(3) Formation of **2a** could only be inferred by kinetic data, but an analogous complex (**2b**), bearing two chlorine instead of carbomethoxy groups and neocuproine (Neoc, 2,9-Me_2Phen) as nitrogen ligand, was characterized by X-ray diffraction.[17] The complex displayed a distorted square-planar coordination instead of the expected pentacoordination, indeed one of the two nitrogen atom detaches from the metal (Figure 1).

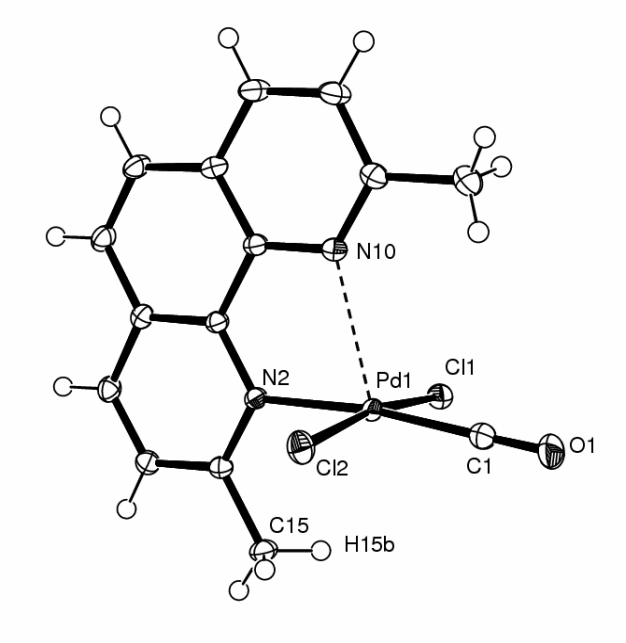


Figure 1. ORTEP projection of complex **2b** with selected labeling

Although the detachment of one of the two nitrogen atoms of the phenanthroline was detected in the solid state, it is very likely that the same could occur also in solution during the catalytic cycle. Thus this non-symmetric arrangement of the phenanthroline suggested us that hemilable ligands could be more effective than symmetrical ones for the catalytic reductive carbonylation reaction of nitroarenes. We verified this hypothesis in a previous work by testing in catalytic reactions several mostly new non-symmetric phenanthrolines and both their symmetrical counterparts.[21] It turned out that electronically non-symmetric phenanthroline are able to improve the performance of the catalytic system, whereas when a steric hindrance on the ligand is present, it has a severe negative effect on catalyst activity. In particular, donating substituent in the *para* position of one of the two pyridinic rings and an electron-withdrawing or no substituent on the *para* position of the other pyridinic ring gave the best increases in activity. The absolute order of maximum activity (highest TOF/h^{-1} in parentheses) was 4-methoxyphenanthroline (5710) > 4-carbomethoxy-7-methylphenanthroline (5409) > 4-methylphenanthroline (5326) > 3,4,7,8-tetramethylphenanthroline (5010) > 4,7-dimethylphenanthroline (4911) > 3-ethylphenanthroline (4810) ≈ phenanthroline (4803) > 4,7-dimethoxyphenanthroline (4754) > 3-tert-butylphenanthroline (3969) >> 2-methylphenanthroline (571) > neocuproine (≈ 0). An improvement in rate of 19 % with respect to the best value obtainable with phenanthroline was achieved at 60 bars with 4-methoxyphenantrholine. The spread between the obtained TOF for these two ligands increases with the increase of pressure, (57 % at 100 bar) attaining the highest turnover frequency ever reported for this kind of reactions. In this thesis the study of the influence on the activity of the system of non-

symmetric ligand substituted with stronger donor group is presented. Moreover the influence of substituents, different from methyl, in *ortho* position with respect to the pyridinic nitrogen atom is explored. Two phenanthroline ligands with an extended π system were also tested.

2.2 Results and discussion

2.2.1 Synthesis of the ligands

The second best ligand in order of improvement of the catalytic system activity was 4-carbomethoxy-7-methylphenanthroline, thus some attempts were made to synthetize 4-carbomethoxy-7-methoxyphenanthroline. However the separate formation and functionalization of one of the two pyridine cycles is not compatible with the functional group present on the other heterocyclic ring and the attempts of double functionalization starting from the symmetrical 4,7-dichlorophenanthroline only afforded mixtures of inseparable products.

Among donor substituents, dialkylamino and arylamino groups were not considered in our previous work due to their basicity, that in the presence of an excess of acidic promoter may result in their partial protonation, thus inverting their polarity. In this work we explore their influence on the catalytic system. The choice of the substituent was made considering the Hammett constants (σ) of various amine fragments.[22, 23] Piperidyl- and anilino- fragments were considered suitable for the synthesis of the phenanthroline ligands because of their σ values (respectively -0.41 and -0.56), intermediate between the lesser donating methoxy group (σ = -0.27) and the highly donating dimethyl amino group (σ = -0.83). The much lower basicity of the piperidino substituted ligand with respect to other alkyl substituted phenanthrolines was previously reported by Katritzky and coworker and it was explained by a twisting of the piperidino group out of the molecular plane due to steric effects.[24] In our previous work 3,4-dimethylphenanthroline (3,4-DMPhen) was not tested while we tried in catalysis the commercial symmetrical 3,4,7,8-dimethylphenanthroline, here we conclude the comparison among the methyl substituted phenanthrolines series.

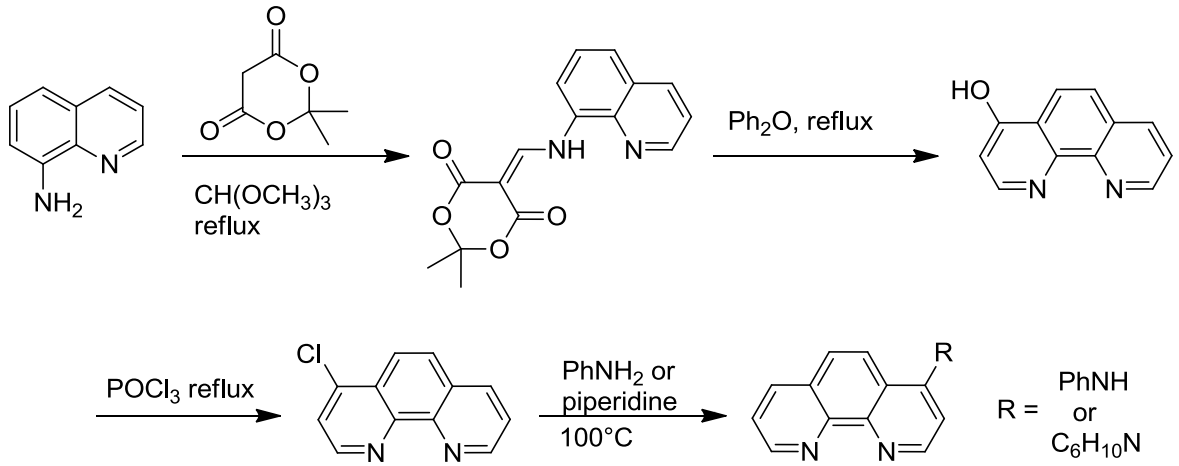
In addition, the almost complete inhibition of the catalytic activity exerted by *o*-methyl groups is quite surprising. To verify if it could be caused by a cyclopalladation reaction of the methyl, we tested the symmetrical 2,9-methoxyphenanthroline (2,9-$(MeO)_2$Phen) and non-symmetrical 2-methoxyphenanthroline (2-MeOPhen). Indeed the methoxy group is known to be less prone to metallation.

The last non-symmetric ligand that was tested is a guanidine-quinoline hybrid ligand: *N*-(1,3-dimethylimidazolidin-2-ylidene)quinolin-8-amine (DMEGqu). Guanidine are among the strongest

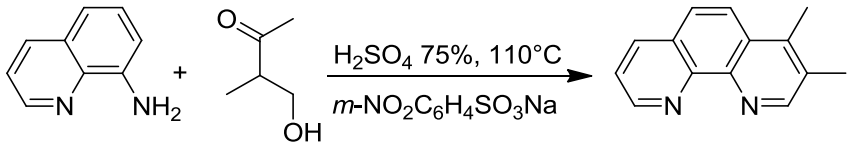
neutral organic bases due to their ability to stabilize positive charges.[25, 26] The hybrid ligands guanidine-quinoline, combines the excellent donor properties of guanidines while leaving the possibility to the pyridinic nitrogen atom to detach.

The dipyridil[3,2-*a*:2',3'-*c*]phenazine (DPPZ) and 2-phenylimidazo[4,5-*f*][1,10]phenanthroline (PIPhen) were also considered in this study because they have low energy π*orbitals, due to their extended aromatic systems. This feature make them better acceptors than phenanthroline moiety itself and could stabilizes the metal d_π orbital by $d_\pi - \pi^*$ back bonding interactions while maintaining the σ donor capability and rigidity of phenanthrolines.

All the ligands employed were not commercially available and they were prepared according to literature procedures or adapting and combining reactions previously reported.



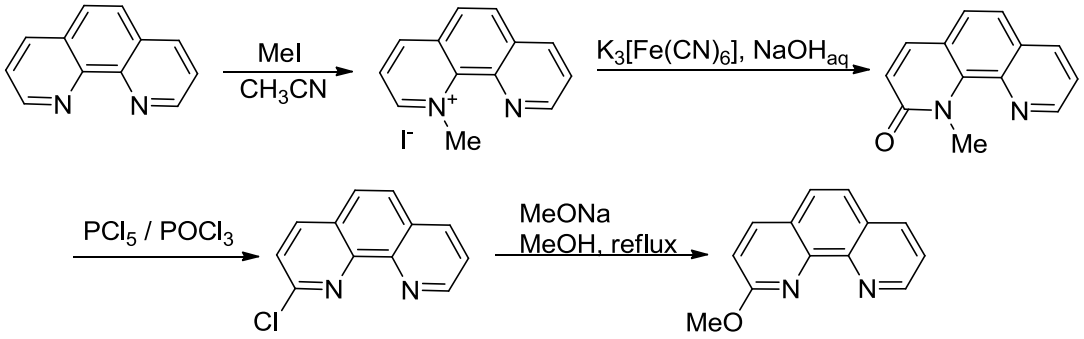
Scheme 3



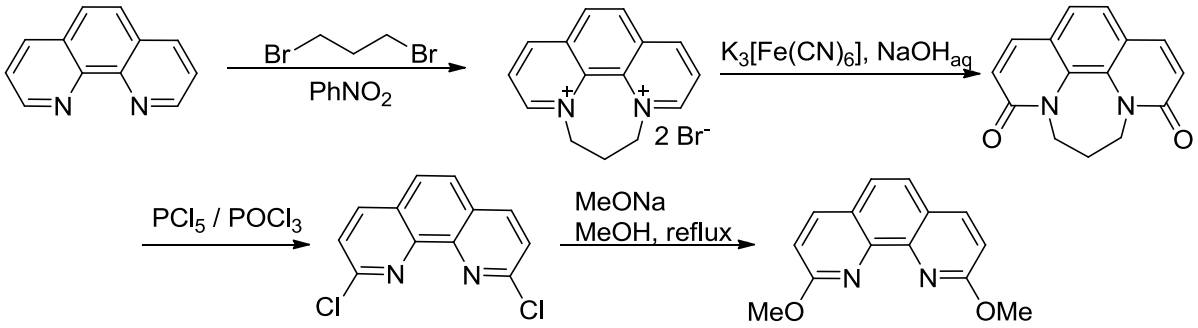
Scheme 4

The syntheses of the two amino substituted phenanthrolines[24] and 3,4-DMPhen[27] were previously reported in the literature however some modification were introduced (Scheme 3-4). Phenanthrolines bearing an amino group were prepared by a nucleophilic substitution of chloride on 4-chlorophenanthroline. Although Katritzky and coworkers stated that severe conditions cause extensive decomposition and mild conditions result in no chloride displacement,[24] we performed the reaction under a nitrogen atmosphere at 100 °C obtaining a quite pure product. 4-Chlorophenanthroline itself was prepared as previously reported by our group[21] employing a

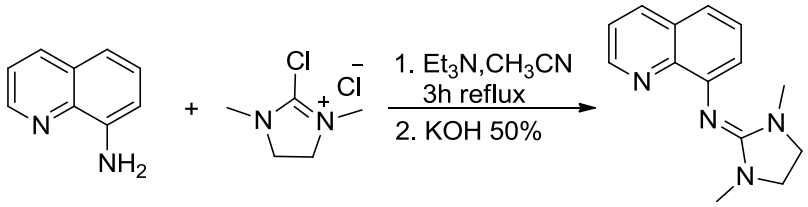
synthetic strategy previously devised for the symmetrical 4,7-chlorophenanthroline.[28] 3,4-DMPhen was synthesized from 8-aminoquinoline and 4-hydroxy-3-methyl-2-butanone employing a modified Skraup reaction. The reaction was performed in 75% H_2SO_4 employing a stoichiometric amount of sodium 3-nitrobenzenesulfonate as the oxidant (Scheme 4). The use of this salt is known to afford better yields and an higher degree of purity of the product than other oxidizing agents.[29]



Scheme 5



Scheme 6

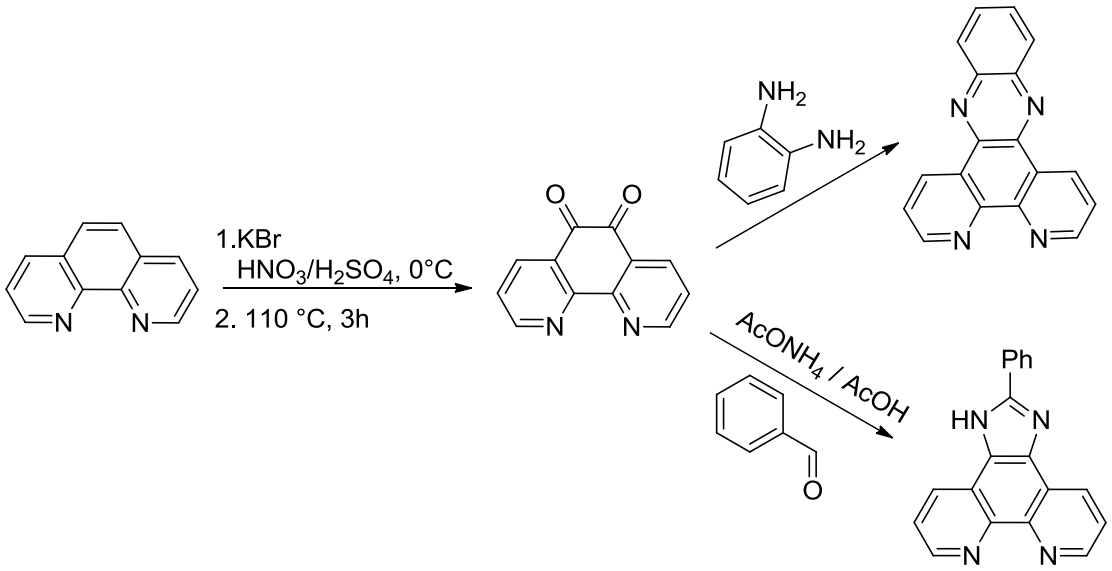


Scheme 7

The two *ortho* methoxy substituted phenanthrolines were synthesized as previously reported in the literature.[30] 2-MeOPhen was prepared by methylation of one nitrogen of 1,10-phenantroline with MeI, oxidation with $K_3[Fe(CN)_6]$ to 1-methyl-1,10-phenanthroline-2-one followed by chlorination of the ketone with a mixture of $POCl_3/PCl_5$ and nucleophilic substitution of chloride by

sodium methylate (Scheme 5). With an analogous procedure, 2,9-MeOPhen was synthesized from the *N,N'*-propane-bridged bis(quaternary salt) of 1,10-phenanthroline (Scheme 6).

The guanidine-quinoline hybrid ligand, DMEGqu, was synthesized by condensation of 8-aminoquinoline with N,N'-dimethylethylenechloroformamidinium chloride as previously reported (Scheme 7).[31] The chloroformamidiunium salt itself was prepared by the reaction of 1,3-dimethyl-2-imidazolidinone with oxalyl chloride,[32] instead of employing the highly toxic phosgene as reported in previously published accounts. Even though the ^{1}H NMR analysis of 3,4-DMPhen and DMEGqu showed a quite pure product, some minor very colored byproduct were present. Thus we applied a non-chromatographic purification procedure developed in our laboratory for phenanthroline ligands. It consists in the complexation of the chelating ligand with $ZnCl_2$ and crystallization of the so obtained little soluble complex in high polar solvents. The free ligand is then obtained by decomplexation with concentrated NH_3.



Scheme 8

DPPZ and PIPhen were both synthesized starting from 1,10-phenanthrolin-5,6-dione (Scheme 8). The last compound was previously reported to be easily obtainable from 1,10-phenanthroline oxidation by sulfonitric acid mixture and an excess of KBr. However the most recent procedures are imprecise and a big amount of a non-completely oxidized byproduct containing bromide was obtained. A more detailed synthetic method was reported by Yamada, which suggest more careful addition of the reagents to avoid side-products formation. The dione is then reacted with 1,2-phenylenediamine in methanol to yield DPPZ or with ammonium acetate and benzaldehyde in acetic acid to yield PIPhen.

2.2.2 Comparison of catalytic activities

The reaction of carbonylation of nitroarenes to carbamates is generally conducted at relatively high pressures (> 60 bar) and temperatures. Under these forcing conditions it is known that the detachment of the nitrogen chelating ligands from the metal center is very easy. To ensure a fast re-coordination to the catalyst and avoid decomposition, an excess free ligand should be used. Indeed we observed that in the catalytic system employed in this study the best molar excess varies widely (from a few mol% to a 500-fold molar excess or even more) with the experimental conditions but in particular with the identity of the ligand.[21] To have a reliable comparison different ligand/metal ratio should be employed, thus we determined individual ligand ratio/activity curves for each ligand and compared their maxima.

A series of carbonylation reactions of nitrobenzene have been performed employing methanol as solvent, resulting in methyl MPC as the main product. We choose to work at the very high catalytic ratio of 15200 (or 6.58×10^{-3} mol %) in order to avoid approaching complete conversion even with the more active systems. All catalytic tests have been performed employing the reaction conditions reported in our previous work,[21] to allow a comparison among the new obtained data and the old ones. Except for the ligand identity and ligand/palladium ratio, all the other reaction parameters were kept constant. Temperature (170 °C), identity of the acidic promoter (H_3PO_4 85 %), its concentration and the concentration of the other reagents, except for the ligand and the catalyst, are those previously optimized for 1,10-phenanthroline.[15] A small amount of initially added aniline (ca. 2.6 mol % with respect to nitrobenzene) was employed to avoid induction time of the reaction.[17, 33, 34] Dimethoxypropane was also added as an internal drying agent, as its positive effect on the selectivity was previously reported.[14, 15, 35, 36] The employed carbon monoxide pressure was for technical reasons fixed at 60 bars, even though better results could be obtained at higher pressures.[15, 21, 33] As in our previous study, $[Pd(Phen)_2][BF_4]_2$ was employed as catalyst. Although this means that two equivalents of the unsubstituted ligand are always present, the ideal ligand/Pd ratios are in the range 50-200, making the small amount of unsubstituted ligand negligible with respect to the much larger amount of substituted one. Ligand exchange is surely not a problem, since it occurs easily even at room temperature and is surely very fast at the reaction temperature.

Results of the catalytic test are reported in Appendix in Table A2.1, as a comparison also the data relative to the unsubstituted phenanthroline, the best performing 4-methoxyphenanthroline (4-MeOPhen) and 3,4,7,8-tetramethylphenanthroline (TMPhen) are reported. To permit an easier comparison among the ligands a graphical representation of ligand ratio/activity curves are reported in Figure 2. The activity of the system is represented by the turnover frequency (TOF) values calculated over all the reaction time for nitrobenzene conversion. These are a good index of the

reaction rate since the kinetics are zero-order in nitrobenzene and the addition of aniline at the beginning of the reaction eliminates the induction time of the catalytic cycle, as previously demonstrated.[17, 33, 34]

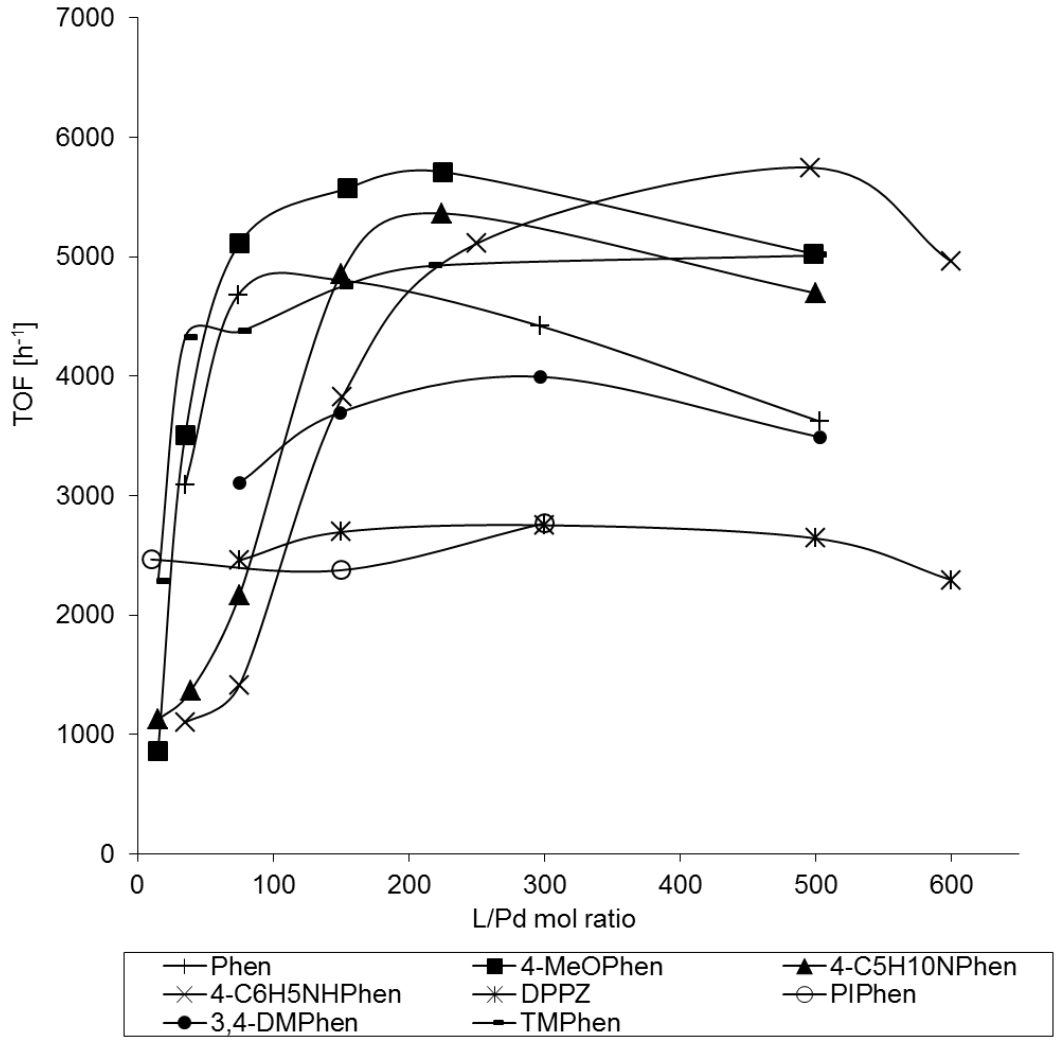


Figure 2. Nitrobenzene conversion for catalytic tests using different phenanthrolines as ligands.

It should be noted from the results reported in Table A2.1 that the mass balance of the phenyl containing compounds is not complete. This is mainly caused by the formation of diphenylurea, which cannot be detected by gas chromatography, that is intermediately formed and later alcoholyzed to MPC and aniline (Scheme 1). Thus for short reaction times, such as those employed in this study, the carbamate selectivity values could be misleading as an indicator of the actual selectivity of the reaction, due to a non-complete urea alcoholysis. The main side products that do not reenter the cycle or do not evolve to carbamate in short times, are azo-, azoxybenzene and

methyl *N*-(*p*-methoxy)phenylcarbamate (*p*-MeO-MPC). Thus the amount of these compounds is the only indirect quantitative measure of the selectivity of the reaction.

In our previous work we reported that, in most cases, the activity of the system shows a sharp increase with the increase in ligand concentration, up to an optimal value, followed by a much slower decrease when this value is exceeded.[21] However for the two amino substituted phenanthroline we noticed an initially more gradual increase of activity. This behavior recalls the ligand ratio/activity curves obtained for 4,7-dimethoxyphenanthroline and TMPhen, in which a small plateau was present at intermediate ligand/Pd ratios, followed by a further rate increase. For those ligands we explained the different pattern recalling that those were the most basic ligands employed in that study and that the partial protonation of the pyridinic nitrogen could occur. Indeed it should be recalled that an acid is present in the reaction mixture, and it was previously shown by our group that the protonation equilibrium is not completely shifted toward the reagents even when diphenylphosphinic acid and phenanthroline are used.[17] Phosphoric acid is stronger than diphenylphosphinic acid, and in the case of the most basic ligands it is possible that protonation becomes more important, altering all the equilibria in the system.

Although in this study comparison with the corresponding diaminosubstituted symmetric ligands was not effected, the maxima of activity obtained with the two amino ligands were compared with those of phenanthroline and 4-MeOPhen. In both cases the maximum was higher than that of commercial ligand and in the case of 4-anilinophenanthroline it was almost indistinguishable from that of the 4-methoxy substituted ligand, although shifted at an higher ligand/Pd ratio. There is no direct correlation between the activity and the donor capability of the substituent since protonation equilibria are involved, however among the two amino substituted ligands the less basic ligand, 4-piperidinylphenanthroline, gave a lower activity maximum. The main drawback in the use of this highly basic ligands is the increase in azoxybenzene selectivity. Indeed it is known that the addition of acids to the reaction mixture reduce the azoxybenzene formation. [13-16, 37, 38]Thus the azoxybenzene selectivity increase with the basicity of the ligand in accord with a partial neutralization of the acid by excess ligand.

3,4-DMPhen gave only poor results with respect to phenanthroline. This was not expected since the symmetric TMPhen gave a maximum of activity higher than phenanthroline itself. From the previous work we noticed that the presence of an alkyl group in *meta* position had not an highly positive effect, probably due to steric hindrance. It should be remembered that the reaction mechanism requires the formation and interaction with aniline and acid co-catalyst of the highly crowded pentacoordinated adduct of bis-alkoxycarbonyl complex with CO. Thus also a low steric

hindrance could be detrimental and overcome the beneficial electronic effect. This is not evident for TMPhen because the electronic effect is stronger.

DPPZ and PIPhen gave much lower activity maxima with respect to that obtained with phenanthroline. This result is a bit surprising since no negative effect should arise from an extended π system, thus an activity at least similar to that of phenanthroline was expected. However in DPPZ the extended planar π-system enhance the π-stacking interactions among the ligands, reducing their solubility even when non-coordinated.[39] This phenomenon is less marked for PIPhen, that is more soluble in the free form, though the imidazole ring act as an hydrogen bond donor/acceptor enhancing the number of interactions among molecules.[40, 41] The formation of supramolecular aggregates could explain a reduced reactivity of the complexes.

The strong inhibiting effect exerted by *ortho*-methyl groups on the phenanthroline ligand, was present also when *ortho* methoxy substituents are employed. At all concentrations, the catalytic tests showed an almost complete deactivation of the system permitting us to conclude that the negative effect is likely of steric nature. Another example of this is represented by DMEGqu. The sterical crowd near the palladium center with this ligand is sufficient to completely deactivate the system.

2.2.3 Influence of phosphorus acids promoters

From a previous study of our group on the effect of different phosphorus acids as promoters,[15, 33, 42] it emerged that diphenylphosphinic acid and phenyl phosphonic acid were very effective in promoting the catalytic reaction. They gave slightly lower activities than 85 % H_3PO_4, however the selectivities in carbamates were higher. Their acid strength could be more adequate when the highly basic amino substituted ligands are employed, since it is lower than that of phosphoric acid.

Catalytic tests were performed maintaining the promoter/catalyst molar ratio unvaried while changing the promoter identity. In the case of the amino substituted ligands two tests with a doubled concentration of H_3PO_4 were performed. The two amino substituted phenanthroline were employed as ligands as well as 4-MeOPhen and phenanthroline itself. Selected catalytic results relative to the maxima of activity are reported in Table 1 (the complete data are in Appendix in Table A2.2): only azoxybenzene selectivities are reported as an index of the amounts of formed byproducts. The turnover frequencies for nitrobenzene conversion are reported graphically in Figure 3-4.

Table 1. Nitrobenzene carbonylation reactions catalyzed by $[Pd(Phen)_2][BF_4]_2$ and differently substituted phenanthrolines, in the presence of different acidic promoters.[a]

Entry	Ligand	L/Pd mol ratio	Acidic promoter	$PhNO_2$ conv.[%][b]	MPC sel.[%][c]	Azoxy sel.[%][c]	TOF [h^{-1}][d]
1	Phen	150	H_3PO_4	47.6	74.9	2.9	4803
2	Phen	150	$Ph_2P(O)OH$	33.9	83.1	2.6	3444
3	Phen	75	$PhP(O)(OH)_2$	43.2	75.0	2.5	4363
4	4-MeOPhen	225	H_3PO_4	56.1	71.1	5.8	5710
5	4-MeOPhen	150	$Ph_2P(O)OH$	49.0	87.5	3.4	4982
6	4-MeOPhen	300	$PhP(O)(OH)_2$	50.1	72.9	3.9	5060
7	4-C_5H_{10}NPhen	225	H_3PO_4	52.7	66.7	9.3	5363
8	4-C_5H_{10}NPhen	500	H_3PO_4[e]	51.4	52.6	17.7	5229
9	4-C_5H_{10}NPhen	150	$Ph_2P(O)OH$	38.7	75.4	4.7	3939
10	4-C_5H_{10}NPhen	225	$PhP(O)(OH)_2$	40.3	66.2	6.1	4071
11	4-C_6H_5NHPhen	500	H_3PO_4	56.5	70.7	12.1	5746
12	4-C_6H_5NHPhen	500	H_3PO_4[e]	59.1	54.4	17.4	6013
13	4-C_6H_5NHPhen	250	$Ph_2P(O)OH$	43.5	64.6	5.0	4394
14	4-C_6H_5NHPhen	500	$PhP(O)(OH)_2$	44.2	73.5	7.4	4460

[a] Experimental conditions: molar ratios $PhNO_2/PhNH_2/Acid/[Pd(Phen)_2][BF_4]_2$ = 15200:400:1400:1, $[Pd(Phen)_2][BF_4]_2 = 7.1 \times 10^{-5}$ mmol , in MeOH (1 mL) + 2,2-dimethoxypropane (34 μL), P_{CO} = 100 bar, at 170 °C for 1.5 h. $PhNH_2$, azobenzene and *p*-MeO-MPC were also found at the end of the reaction but are omitted in this table. [b] Calculated with respect to the initial $PhNO_2$ amount. [c]Calculated with respect to the sum of the reacted $PhNO_2$ and $PhNH_2$ amounts. [d] TOF = turnover frequency = mol $PhNO_2$ reacted/(mol Pd × h). [e]The amount of the acid promoter was doubled, molar ratio $Acid/[Pd(Phen)_2][BF_4]_2$ = 2800:1

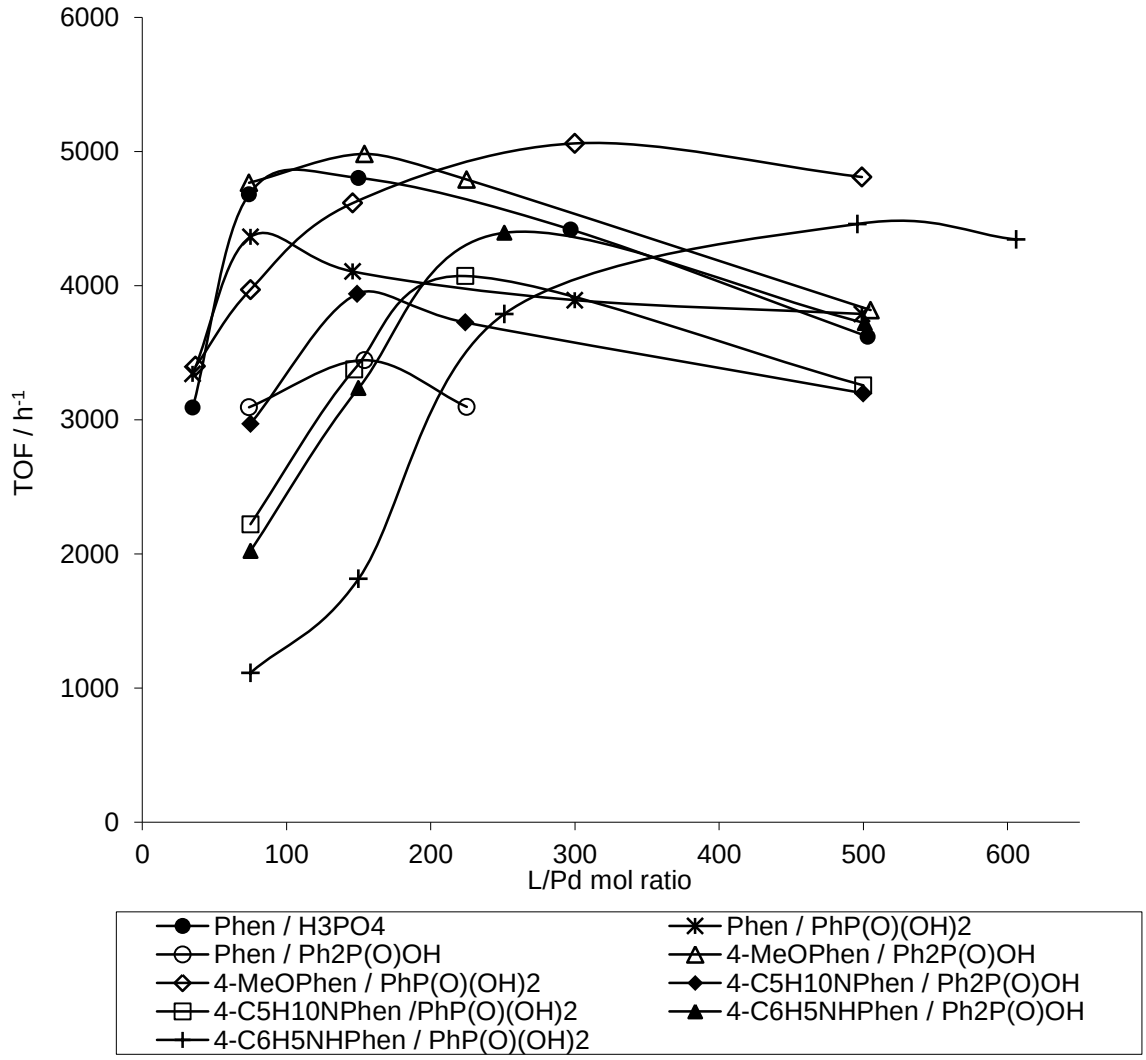


Figure 3. Nitrobenzene conversion for catalytic tests using different acid promoters and substituted phenanthrolines as ligands.

In all cases, when the two organic acids are employed, the maxima of catalytic activity were found to be lower with respect to that obtained with the same ligand with H_3PO_4, however the selectivities in azoxybenzene decreased. 4-MeOPhen gave the best results with both organic phosphorus acids even when compared with the best performance obtained with the commercial phenanthroline and H_3PO_4. The maximum of activity was higher and at the same time the selectivity in side-products is reduced by a third. Comparing with the results obtained with phosphoric acid, azoxybenze formation is reduced of about 30% also when $PhP(O)(OH)_2$ is employed together with the two amino ligands and is halved when $Ph_2P(O)OH$ is the promoter. The maxima of activity are lower than that obtained with phenanthroline, however it should be

remembered that the optimal amount of acidic promoter varies both with promoter and ligand identity, thus the molar ratio employed in this study could be far from the optimal value.

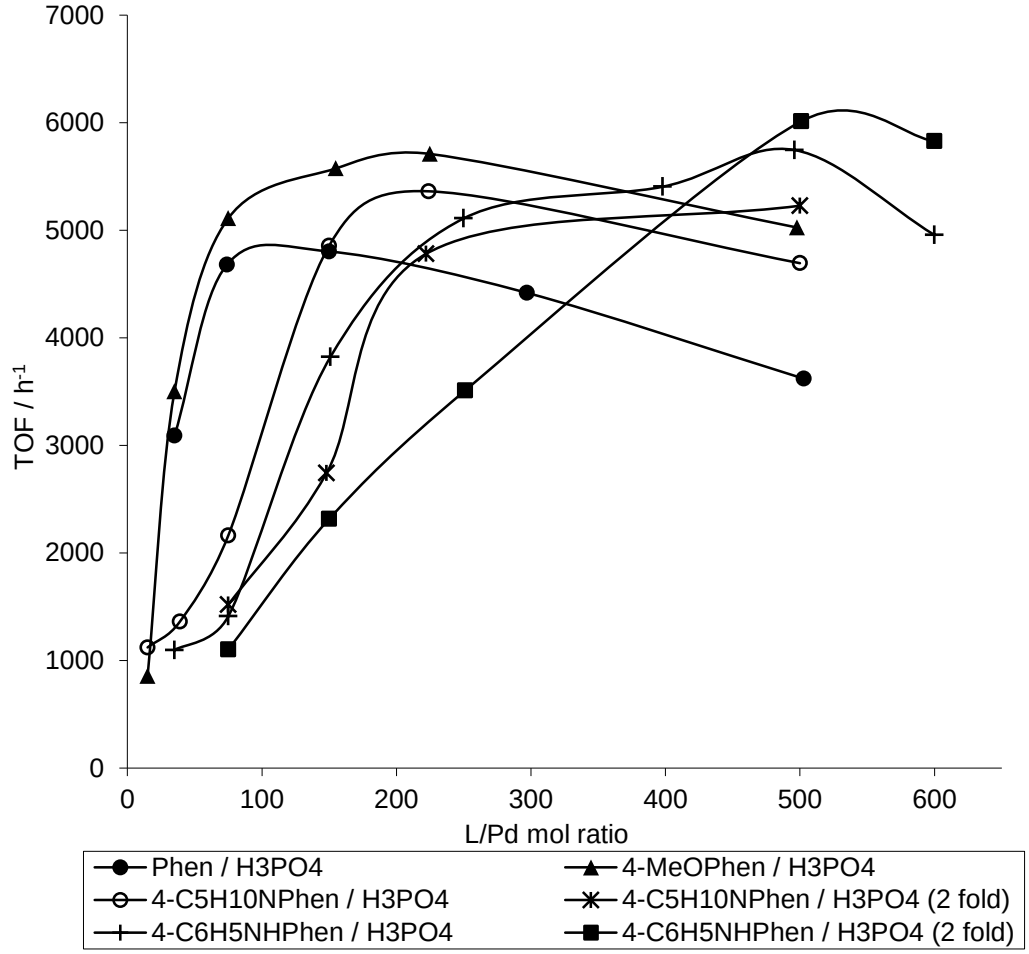


Figure 4. Nitrobenzene conversion for catalytic tests using different phosphoric acid concentrations and substituted phenanthrolines as ligands.

An inverse behavior was observed when the amount of phosphoric acid was increased two fold with respect to the standard conditions. Employing the two amino phenanthrolines, the maximum activity of the system is slightly enhanced (Figure 4) while there is an increase in azoxybenzene selectivity. The maximum of anilinophenanthroline is the highest obtained at this pressure, even though with a 17.4 % of azoxybenzene selectivity. However it should be remembered that 85 % H_3PO_4 was employed and that the presence of water lead to higher azoxybenzene selectivities. Thus a fine optimization of the amount of dehydrating agent at every H_3PO_4 concentration could lead to better results, though it was out of the scope of this study .

From the result is evident that the acidity of the promoter influence widely the protonation equilibria in solution when highly basic phenanthrolines are employed, the influence is marked

especially on the azoxybenzene selectivity on which a positive effect could be detected when the acidity of the promoter is lower.

2.3 Conclusions

On the basis of previously obtained results, different non-symmetric ligands were tested. We observed that good results are obtainable even with amino substituted phenanthrolines, however the nature of the amino fragment strongly influences the ligand performance. Steric crowd around the metal center hinders the substrate approach thus inhibiting the system. Planar ligands with extended π system are very poor ligands in the reaction conditions employed.

Amino substituted phenanthrolines gave higher byproduct formation due to the extensive deprotonation of the acidic promoter. A positive effect was noted when a less acid promoter was employed although with an activity decrease.

2.4 Experimental section

2.4.1 Materials and general procedures

All manipulations of the reagents involved in the catalytic reactions were conducted under a dinitrogen atmosphere. All solvents used in the catalytic reactions were dried by standard procedures and distilled under dinitrogen immediately before use. All glassware and magnetic stirring bars used in catalytic reactions were kept in an oven at 120 °C for at least two hours and allowed to cool under vacuum before use. 1,10-Phenanthroline (Phen) was purchased as hydrate. It was dried by dissolving it in CH_2Cl_2, drying the resulting solution with Na_2SO_4, and evaporating in vacuo the filtered solution. It was then stored under dinitrogen. It can be weighed in the air without problems, but must be stored in an inert atmosphere if water uptake is to be avoided. The same procedure was applied to all the synthesized ligands employed in catalytic reactions. Nitrobenzene and aniline were distilled and stored under dinitrogen before use. Triethylamine was distilled over CaH_2 and kept under a dinitrogen atmosphere. 4-Chlorophenanthroline,[21] 4-hydroxy-3-methyl-2-butanone,[43] $[Pd(Phen)_2][BF_4]_2$ were prepared and characterized according to the procedures reported in the literature.[44] All other chemicals were purchased from Aldrich or Alfa Aesar. NMRspectra were recorded on a Bruker AC300 FT or on an Avance Bruker DPX300 spectrometer. Elemental analyses were recorded on a PerkinElmer 2400 CHN elemental analyzer.

2.4.2 Catalytic reactions

For a typical catalytic reaction, stock solutions of the catalyst, $PhNH_2$, and DMOP (2,2-dimethoxypropane) in nitrobenzene and of the ligand and H_3PO_4 (85% in water) in methanol were prepared under dinitrogen, and the reagent amounts measured by volume to avoid errors in weighing very small amounts of materials. Reagent amounts are reported in the tables or in their footnotes, but in all cases the catalyst concentration was 6.20×10^{-2} mM and $[PhNO_2] = 0.942$ M (all reagent volumes are included in the concentration calculation, as they are not negligible). The reactions were conducted in parallel in three 10 mm wide × 40 mm high test tubes, each having a magnetic stirring bar, which were located in the holes of an aluminum block designed to fit a 200mLstainless steel autoclave. The block and the test tubes were placed inside a Schlenk tube with a wide mouth and the reagents added under dinitrogen. Each tube was closed with a screw cap with a glass wool-filled open mouth that allows gaseous reagents to exchange, and the block was rapidly transferred to the autoclave. The autoclave was purged from air, charging CO at 60 bar and discharging to 2 bar one time before performing the reaction. CO was then charged at room temperature at the required pressure, and the autoclave was immersed in an oil bath preheated at 170 °C. Other experimental conditions are reported in the captions to the tables. At the end of the reaction the autoclave was quickly cooled with an ice bath and vented, and the products were analyzed by gas chromatography (Dani 8620 gas chromatograph, equipped with a Supelco SLB-5 ms column; naphthalene as an internal standard; CH_2Cl_2, 1 mL, was added to the solution before taking a sample for the GC analysis to dissolve naphthalene, which is hardly soluble in methanol).

2.4.3 Ligand syntheses

The detailed procedures for the ligand and intermediate compounds synthesis are reported below, some of which have been modified with respect to the previously published accounts.

4-Aminophenanthroline. General procedure. A Schlenk flask was charged with 4-chlorophenanthroline (450 mg, 2.10 mmol) and the amine (42 mmol) under a dinitrogen atmosphere. The mixture was heated at 100 °C under magnetic stirring for 6 h and then allowed to cool. At room temperature the mixture was solid or semi-solid depending on the amine, due to the formation of the product and quaternary ammonium salts. The mixture was suspended in 1M NaOH (40 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were dried over Na_2SO_4 and the solvent evaporated in vacuo. The obtained product was recrystallized from Et_2O and then dried over P_2O_5 at 90 °C under vacuum.

4-Anilinophenanthroline. Off-white solid (90 % yield). ^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ = 9.19 (dd, $^{3}J_{H,H}$ = 4.3 Hz, $^{4}J_{H,H}$ = 1.7 Hz, 1H, H9), 8.84 (d, $^{3}J_{H,H}$ = 5.4 Hz, 1 H, H2), 8.25 (dd, $^{3}J_{H,H}$ = 8.1 Hz, $^{4}J_{H,H}$ = 1.7 Hz, 1H, H7), 7.99 (d, $^{3}J_{H,H}$ = 9.1 Hz, 1 H, H5), 7.78 (d, $^{3}J_{H,H}$ = 9.1 Hz, 1 H, H6), 7.63 (dd, $^{3}J_{H,H}$ = 8.1 Hz, $^{3}J_{H,H}$ = 4.3 Hz, 1H, H8), 7.45 (t, $^{3}J_{H,H}$ = 7.3 Hz, 2 H, H3' e H5'), 7.34 (d, $^{3}J_{H,H}$ = 7.3 Hz, 2 H, H2' e H6'), 7.25 (d, $^{3}J_{H,H}$ = 5.4 Hz, 1 H, H3), overlapped with 7.22 (t, $^{3}J_{H,H}$ = 7.3 Hz, 1 H, H4') ppm ^{13}C NMR (75 MHz, $CDCl_3$, 300 K): δ = 150.8 (C9 e C2), 148.2 (C10b), 147.5 (C4), 146.9 (C10a), 140.5 (C1'), 136.2 (C7), 130.2 (C3' e C5'), 128.7 (C6a), 125.3 (C6), 125.0 (C4'), 123.3 (C8), 122.8 (C2' e C6'), 119.2 (C4a), 119.1 (C5), 106.0 (C3) ppm. Anal. Calcd. for $C_{18}H_{13}N_3$: C, 79.68; H, 4.83; N, 15.49 Found: C, 79.29; H, 4.90; N.15.27

4-Piperidylphenanthroline. Pale yellow solid. (65 % yield). ^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ = 9.16 (dd, $^{3}J_{H,H}$ = 4.3 Hz, $^{4}J_{H,H}$ = 1.8 Hz, 1H, H9), 8.98 (d, $^{3}J_{H,H}$ = 5.1 Hz, 1 H, H2), 8.21 (dd, $^{3}J_{H,H}$ = 8.1 Hz, $^{4}J_{H,H}$ = 1.8 Hz, 1H, H7), 8.03 (d, $^{3}J_{H,H}$ = 9.1 Hz, 1 H, H5), 7.72 (d, $^{3}J_{H,H}$ = 9.1 Hz, 1 H, H6), 7.59 (dd, $^{3}J_{H,H}$ = 8.1 Hz, $^{3}J_{H,H}$ = 4.3 Hz, 1H, H8), 7.09 (d, $^{3}J_{H,H}$ = 5.1 Hz, 1 H, H2), 3.27 (t, $^{3}J_{H,H}$ = 5.3 Hz, H2 and H6 piperidine, 4 H), 1.87 (m, H3 and H5 piperidine, 4H), 1.74 (m, H4 piperidine, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 300 K): δ = 158.6 (*C*), 151.1 (C9), 150.4 (C2), 147.9 (*C*), 147.2 (*C*), 136.0 (C7), 128.6 (*C*), 124.8 (C6), 123.9 (*C*), 123.1 (C8 and C5), 111.7 (C3), 54.2 (C2 and C6, piperidine), 26.5 (C3 and C5, piperidine), 24.7 (C4 piperidine) ppm. Anal. Calcd. for $C_{17}H_{17}N_3$: C, 77.54; H, 6.51; N, 15.96 Found: C, 77.19; H, 6.52; N15.78.

3,4-Dimethylphenanthroline. In a two neck round bottom flask, 8-aminoquinoline (2.02 g, 14.0 mmol) and sodium 3-nitrobenzenesulfonate (3.44 g, 15.3 mmol) were dissolved in 75% H_2SO_4 (10 mL, 126 mmol), heating at 90 °C to allow the complete dissolution of the solids. The flask was equipped with a dropping funnel and 4-hydroxy-3-methyl-2-butanone (2.88 g, 28.2 mmol) was added over 5 h at 110 °C, maintaining vigorous magnetic stirring. After a further hour at 110 °C the dark reaction mixture was allowed to cool at room temperature and slowly poured into ice water (30 mL). The mixture was carefully brought to basic pH by the addition of 28 wt. % NH_3 (40 mL) and then extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were retroextracted with 37% HCl (3 × 20 mL). The acidic solution was neutralized by the addition of concentrated NaOH solution and extracted with CH_2Cl_2 (3 × 100 mL). The organic layers were combined and the solvent evaporated in vacuo. The solvent was evaporated yielding 2.68 g of a dark solid.

3,4-Dimethylphenanthroline purification by complexation with zinc chloride. The crude product was dissolved in ethylene glycol (5 mL) and a solution of $ZnCl_2$ (2.64 g, 19.37 mmol) in

ethylene glycol (5mL) was added. A light brown precipitate formed immediately, however the mixture was heated at 100 °C while stirring for one hour to ensure a complete complexation of the ligand. The mixture was then heated at 100 °C while stirring for one hour. The suspension was allowed to cool to room temperature and methanol (10 mL) was added to decrease viscosity of the solvent. The brown precipitate that formed was filtered on a Buchner funnel, washed with 5 mL of methanol and dried in vacuo affording 3.28 g (9.52 mmol) of $ZnCl_2$(3,4-DMPhen). The complex was recrystallized two times from ethylene glycol (4.5 mL per gram of compound). After cooling to room temperature, the resulting light-brown solid was collected by vacuum filtration, washed with a small amount of diethyl ether and dried in vacuo. CH_2Cl_2 (19 mL) and 28% NH_3 (19 mL) were added and the mixture stirred overnight. The two layers were separated and the aqueous solution was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic layers were filtered through a Celite pad on a frit and dried over Na_2SO_4. The solvent was evaporated affording 1.51g of a light brown solid (7.25 mmol, 52 % yield based on the initial aminoquinoline). ^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ 9.20 (dd, $^3J_{H,H}$ = 4.2 Hz and $^4J_{H,H}$ = 1.5 Hz, 1 H, H9), 9.01 (s, 1 H, H2), 8.25 (dd, $^3J_{H,H}$ = 8.0 Hz and $^4J_{H,H}$ = 1.5 Hz, 1 H, H7), 8.07 (d, $^3J_{H,H}$ = 9.1 Hz, 1 H, H5), 7.82 (d, $^3J_{H,H}$ = 9.1 Hz, 1 H, H6), 7.62 (dd, $^3J_{H,H}$ = 8.0 Hz and $^4J_{H,H}$ = 4.3 Hz,1 H, H8), 2.72 (s, 3 H, CH_3), 2.57 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 300 K): δ = 151.4(*C*H), 149.9 (*C*H), 146.5 (*C*), 144.3 (*C*), 141.3 (*C*), 135.4 (*C*H), 130.8 (*C*), 127.5 (*C*), 127.3 (*C*), 125.6 (*C*H), 122.3 (two isochronous *C*H), 17.31 (CH_3), 14.3 (CH_3) ppm. Anal. Calcd. for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.25; H, 5.86; N, 13.31.

1-methyl-1,10-phenanthrolin-1-ium iodide.[45] The 1,10-phenanthroline (1.0 g, 5.5 mmol) was dissolved in acetonitrile (5ml). Methyl iodide (1.0 mL, 16.1 mmol) was added and the mixture heated to reflux for 1 h 30'. The solution was allowed to cool and the yellow precipitate that formed was collected by filtration (1.64 g, 5.09 mmol, 91 % yield).

1-methyl-1,10-phenanthrolin-2(1*H*)-one.[46] Potassium ferricyanide (4.27 g, 12.97 mmol) was dissolved in water (30 mL) and NaOH (5.90 g, 147 mmol in 30 mL of water) was gradually added under stirring. The flask was then placed in an ice/water bath and a solution of 1-methyl-1,10-phenanthrolin-1-ium iodide (1.64 g, 5.09 mmol) in water (60 mL, dissolution is complete only by heating at 50°) was added dropwise over a period of 30'. The mixture was stirred for an additional hour while keeping the flask cooled and then filtered and washed abundantly with water. The obtained yellow solid was dissolved in the minimum amount of CH_2Cl_2 and dried over Na_2SO_4.

Evaporation of the solvent afforded the product as a straw yellow solid (0.97 g, 4.63 mmol, 90 % yield). The product was employed in the subsequent synthetic step without further purification.

2-Chloro-1,10-phenanthroline.[46] In an oven-dried Schlenk flask, 1-methyl-1,10-phenanthrolin-2(1*H*)-one (0.97 g, 4.63 mmol) and PCl_5 (1.23 g, 5.91 mmol) were suspended in $POCl_3$ (8 ml) under a dinitrogen atmosphere. The flask was fitted with an oven-dried reflux condenser and the mixture was refluxed for 8 h. The excess $POCl_3$ was removed under reduced pressure while heating at 50 °C. Cold water (20 mL) was then added to the residual solid and the mixture was brought to pH 10 with NaOH pellets. The obtained suspension was extracted with CH_2Cl_2 (4 × 30 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated in vacuo affording a tan solid (0.91 g, 4.26 mmol, 92 % yield). The product was employed in the subsequent synthetic step without further purification.

2-Methoxy-1,10-phenanthroline.[30] In an oven-dried Schlenk flask 2-chloro-1,10-phenanthroline (0.91 g, 4.26 mmol) and sodium methoxide (1.28 g, 23.8 mmol) were dissolved in anhydrous methanol (40 mL) under a dinitrogen atmosphere. The solution was heated to reflux while stirring for 14 h. After cooling to room temperature, the solvent was evaporated, water (50 mL) was added and the product was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over Na_2SO_4 and the solvent evporated in vacuo affording an oily product that solidify after several hours under vacuum yielding a light brown solid (0.78 g, 3.71 mmol, 87 % yield). ^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ 9.15 (dd, $^3J_{H,H}$ = 4.3 Hz and $^4J_{H,H}$ = 1.5 Hz, 1 H, H9), 8.22 (dd, $^3J_{H,H}$ = 8.1 Hz and $^4J_{H,H}$ = 2.2 Hz, 1 H, H7), 8.10 (d, $^3J_{H,H}$ = 8.8 Hz, 1 H, H4), 7.74 (d, $^3J_{H,H}$ = 8.8 Hz, 1 H, H5), 7.65 (d, $^3J_{H,H}$ = 8.8 Hz, 1 H, H6), 7.58 (dd, $^3J_{H,H}$ = 8.1 Hz and $^4J_{H,H}$ = 4.3 Hz,1 H, H8), 7.12 (d, $^3J_{H,H}$ = 8.8 Hz, 1 H, H3), 4.31 (s, 3H) ppm. Anal. Calcd. for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79; N, 13.33. Found: C, 73.91; H, 4.96; N, 12.97.

6,7-dihydro-5*H*-[1,4]diazepino[1,2,3,4-*lmn*][1,10]phenanthroline-4,8-diium bromide.[47] 1,3-dibromopropane (5.2 mL, 51 mmol) was added to a solution of 1,10-phenanthroline monohydrate (2.00 g, 10.1 mmol) in nitrobenzene (16 mL), under magnetic stirring. The solution was heated to 120 °C for 4 h. During the reaction, a yellow solid precipitated from the reaction mixture. The mixture was then allowed to cool to room temperature, the solid was collected by filtration and washed with diethyl ether. Although the product contained some nitrobenzene it was used in the subsequent synthetic step without further purifications.

6,7-dihydro-3*H*-[1,4]diazepino[1,2,3,4-*lmn*][1,10]phenanthroline-3,9(5*H*)-dione.[47] Potassium ferricyanide (29.5 g, 89.6 mmol) was dissolved in water (50 mL) and solid NaOH (13.4 g, 336mmol) was gradually added under stirring. The flask was then placed in an ice/water bath and a solution of phenanthrolinium dibromide (3.76 g, 9.83 mmol) in water (20 mL, dissolution is complete only by heating at 50°) was added dropwise over a period of 30'. The mixture was stirred for additional two hours while keeping the flask cooled, filtered and washed abundantly with water. Since the product is only little soluble in organic solvents, the solid was placed on a fritted extractor and extracted with CH_2Cl_2 (3 × 40 mL). The organic layers were combined and dried over Na_2SO. Evaporation of the solvent afforded the product as a light brown solid (0.70 g, 2.77 mmol, 27.3 % yield). ^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ 7.72 (d, $^3J_{H,H}$ = 9.6 Hz, 2H, H4 and H7), 7.36 (s, 2H, H5 and H6), 6.80 (d, $^3J_{H,H}$ = 9.6 Hz, 2H, H3 and H8), 4.32 (t, $^3J_{H,H}$ = 6.3 Hz, 4H, H-a), 2.46 (q, $^3J_{H,H}$ = 6.3 Hz, 2H, H-b) ppm.

2,9-Dichloro-1,10-phenanthroline.[46] The synthesis was performed analogously to what reported for the corresponding monosubstituted ligand. The product was purified filtration on a silica gel pad (CH_2Cl_2). Yellow solid (83% yield). ^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ 8.22 (d, $^3J_{H,H}$ = 8.8 Hz, 2H, H4 and H7), 7.84 (s, 2H, H5 and H6), 7.66 (d, $^3J_{H,H}$ = 8.8 Hz, 2H, H3 and H8) ppm.

2,9-Dimethoxy-1,10-phenanthroline.[46] The synthesis was performed analogously to what reported for the corresponding monosubstituted ligand. Light brown solid (97 % yield). ^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ 8.12 (d, $^3J_{H,H}$ = 8.7 Hz, 2H, H4 and H7), 7.64 (s, 2H, H5 and H6), 7.11 (d, $^3J_{H,H}$ = 8.7 Hz, 2H, H3 and H8), 4.31 (s, 6H, CH_3) ppm. Anal. Calcd. for: $C_{14}H_{12}N_2O_2$ C, 69.99; H, 5.03; N, 11.66 found: C, 69.72; H, 5.20; N, 11.31.

N-(1,3-dimethylimidazolidin-2-ylidene)quinolin-8-amine (DMEGqu).[31] In an oven dried Schenk flask, oxalyl chloride was added dropwise (0.50 mL, 5.8 mmol) at room temperature to a solution of 1,3-dimethyl-2-imidazolidinone (0.50 mL, 4.6 mmol) and dry DMF (0.04 mL, 0.52 mmol) in CH_2Cl_2 (4.6 mL). The solution was stirred for 1 h at room temperature and then refluxed for 4 h. The solvent was evaporated under vacuum, and the resulting yellow solid was stirred two times with CH_2Cl_2 (2 mL) and followed by evaporation of the organics after each treatment to favor excess oxalyl chloride removal. The obtained chloroformamidinium chloride was then dissolved in dry MeCN (5 mL) and added dropwise under vigorous stirring to an ice-cooled solution of aminoquinoline (0.66 g, 4.6 mmol) and triethylamine (0.64 mL, 4.6 mmol) in dry MeCN (5 mL). At the end of the addition, the solution was heated to reflux for 3h. The reaction was quenched with a

solution of KOH (258 mg, 4.6 mmol in 5mL) and the solvent and NEt_3 evaporated under vacuum. 50 wt.% KOH in water (5 mL) was added in order to deprotonate the guanidine hydrochloride and then the product was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4. Evaporation of the solvent afforded the product as a greenish solid (0.94 g). Although the product was quite pure, a purification by complexation with $ZnCl_2$ as reported for 3,4-dimethylphenanthroline was performed.

DMEGqu purification by complexation with zinc chloride. The product was dissolved in methanol (4 mL) and a solution of $ZnCl_2$ (0.94 g, 6.8 mmol) in methanol (4 mL) was added. A yellow precipitate immediately formed, however the mixture was heated at 100 °C while stirring for one hour to ensure a complete complexation of the ligand. The suspension was allowed to cool to room temperature and filtered on a Buchner funnel and washed with 2 mL of methanol. The brown color of the mother liquor indicates that a purification had occurred. The product was dried in vacuo affording 1.32 g (3.50 mmol) of $ZnCl_2$(DMEGqu). CH_2Cl_2 (15 mL) and 28% NH_3 (15 mL) were added and the mixture stirred overnight. The two layers were separated and the aqueous solution was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated affording 0.83 g of a yellow solid (3.45 mmol, 75 % yield based on the initial aminoquinoline). ^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ = 8.92 (dd, $^3J_{H,H}$ = 4.1 Hz, $^4J_{H,H}$ = 1.8 Hz, 1H, CH),.8.09 (dd, $^3J_{H,H}$ = 8.1 Hz, $^4J_{H,H}$ = 1.8 Hz, 1H, CH),7.40 (pseudo triplet, ^3J = 8.0 Hz, $^3J_{H,H}$ = 7.4 Hz, 1H, CH),7.33 (m, 2H, CH),7.19 (dd, $^3J_{H,H}$ = 7.4 Hz, $^4J_{H,H}$ = 1.2 Hz, 1 H, CH), 3.40 (s, 4H, CH_2), 2.68 (s, 6H,CH_3) ppm. Anal. Calcd. for: C, 69.87; H, 6.71; N, 23.32 found: C, 69.47; H, 6.64; N, 23.58.

1,10-phenanthroline-5,6-dione.[48] 1,10-Phenanthroline hydrate (0.500 g, 2.52 mmol) and KBr (3.32 g, 27.9 mmol) were placed in a round bottom flask placed in an ice bath. Concentrated sulfuric acid (8 mL) was added in small portions, and then 65 % HNO_3 (4 mL). The resulting solution was then heated at 80 °C for 2h (there is evolution of red Br_2 vapors) and then allowed to cool. The reaction mixture was then poured into ice water (250 mL) and neutralized with Na_2CO_3. The neutralization should be made carefully since at basic pH decarbonylation of the product to 4,5-diazafluoren-9-one occurs.[49] The suspension was extracted with CH_2Cl_2 (3 × 200 mL). Evaporation of the solvent afforded the product as yellow powder (0.51 g, 2.43 mmol, 87 % yield). ^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ = 9.13 (dd, $^3J_{H,H}$ = 4.7 Hz, $^4J_{H,H}$ = 1.8 Hz, 2H, H2 and H9), 8.51 (dd, $^3J_{H,H}$ = 7.7 Hz, $^4J_{H,H}$ = 1.8 Hz, 2H, H4 and H7), 7.61 (dd, $^3J_{H,H}$ = 7.7 Hz and 4.7 Hz, 2H, H3 and H8) ppm.

Dipyridil[3,2-*a*:2',3'-*c*]phenazine.[50] 1,10-phenanthroline-5,6-dione (0.51 g, 2.43 mmol) and 1,2-phenylenediamine (0.40 g, 3.70 mmol) were dissolved in methanol (20 mL) and refluxed for 1 h 30'. After cooling to room temperature a light brown precipitate was formed. The mixture was filtered and the solid washed abundantly with methanol. After recrystallization from methanol the product was obtained as a light yellow solid (0.66 g, 2.33 mmol, 96 % yield). ^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ = 9.65 (dd, $^{3}J_{H,H}$ = 8.1 Hz, $^{4}J_{H,H}$ = 1.7 Hz, 2H), 9.29 (dd, $^{3}J_{H,H}$ = 4.4 Hz, $^{4}J_{H,H}$ = 1.7 Hz, 2H), 8.36 (dd, $^{3}J_{H,H}$ = 6.5 Hz and 3.5 Hz, 2H), 7.94 (dd, $^{3}J_{H,H}$ = 6.6 and 3.4 Hz, 2H), 7.81 (dd, $^{3}J_{H,H}$ = 8.1 and 4.4 Hz, 2H) ppm.

2-phenylimidazo[4,5-*f*][1,10]phenanthroline.[51] A mixture of 1,10-phenanthroline-5,6-dione (410 mg, 1.95 mmol), ammonium acetate (3.00 g, 38.9 mmol) and benzaldehyde (258 μL, 2.54 mmol) in acetic acid (4 mL) was heated to reflux for 3 h. After cooling to room temperature water was added (10 mL) and the mixture neutralized with aqueous 28 % NH_3. The formed solid was filtered and washed with H_2O (10 mL). The obtained solid was recrystallized from a mixture MeOH/H_2O (3:1). The obtained solid was dissolved in CH_2Cl_2 and dried over Na_2SO_4 affording the pure product as a pale yellow powder. (394 mg, 1.33 mmol, 68 % yield). ^{1}H NMR (300 MHz, DMSO-d_6, 300 K): δ = 13.78 (bs, 1H, NH), 9.05 (dd, $^{3}J_{H,H}$ = 4.3 Hz, $^{4}J_{H,H}$ = 1.7 Hz, 2H), 8.95 (dd, $^{3}J_{H,H}$ = 8.1 Hz $^{4}J_{H,H}$ = 1.5 Hz, 2H), 8.31 (dd, $^{3}J_{H,H}$ = 7.2 Hz, $^{4}J_{H,H}$ = 1.3 Hz, 2H), 7.85 (m, $^{3}J_{H,H}$ = 8.1 and 4.3 Hz, 2H), 7.63 (t, $^{3}J_{H,H}$ = 7.4 and 4.5 Hz, 2H), 7.50 (tt, $^{3}J_{H,H}$ = 7.3 Hz and$^{4}J_{H,H}$ = 1.3 Hz Hz, 2H) ppm.

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Chapter 3

Catalyst recycling in the palladium catalyzed synthesis of methyl *N*-phenylcarbamate

3.1 Introduction

Homogeneous catalysis by metal complexes is a powerful tool both for the chemical industry and for the academic chemist. The main advantages over heterogeneous catalysis are the higher activities and selectivities. However, despite the big effort in studying and developing new homogeneous catalysts in the last decades, the commercialized industrial processes are rather limited. One of the main problems is the difficulty in recovering the catalyst in an active form at the end of the reaction and the contamination of the product with metal residues. One of the most employed strategies to overcome these problems is the heterogenization of the catalyst on solid supports. However, generally, poor catalyst productivities, irreproducible activities and selectivities, degradation of the support or metal leaching are the main reasons for a non commercialization of the heterogenized catalyst. The most important alternative from an industrial point of view is surely that based on the use of liquid-liquid biphasic catalysis. It found a large scale application in the hydroformylation of propene and butene (Ruhrchemie/Rhône-Poulenc process, RCH/RP). However the mass transfer problems render it not suitable for higher olefines and most of the organic transformations.

The development of the palladium catalyzed carbonylation of nitroarenes has achieved very important results with high TOF (turnover frequency)[1] and high TON (turnover number)[2, 3] however one of the main hindrance to its commercialization is the loss of the metal at the end of the reaction. Several attempts have been made to develop heterogeneous catalysts with well-defined mononuclear active sites on organic or inorganic supports for this kind of reaction.[4-9] The application of an aqueous/organic biphasic system would not be possible mainly for the side reaction of the intermediately formed isocyanate with water.

An alternative to the “classical” immobilization of the catalyst that overcome these problems is represented by thermomorphic systems. Their main feature is that they allow to run the reaction in an homogeneous environment and subsequently recover the catalyst in a separate phase as a consequence of a temperature change.[10] In this thesis we considered two kind of thermomorphic systems: those in which the catalyst separates as a solid, leaving products in solution; and those in which the catalyst and product separates into different liquid phases after the reaction. A large part

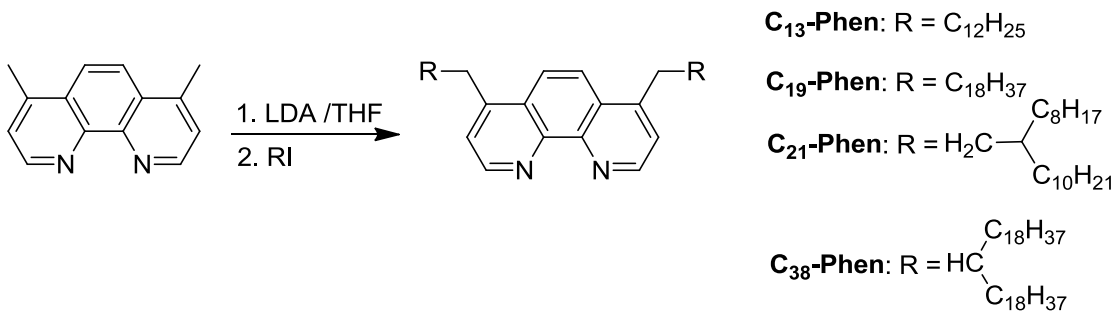
of the literature on thermomorphic systems concerns the use of perfluorinated compounds,[11] however they are not suitable for a large scale application, as would be isocyanate production from nitroarenes, because of their high cost and environmental persistence. Good alternatives to fluorous compounds are catalysts anchored to soluble organic polymer[10, 12] as well as ligands substituted with well-defined polyethylene oligomers.[13, 14] In this thesis we report the application of long alkyl chain substituted phenanthrolines as thermomorphic ligands for the palladium catalyzed reductive carbonylation of nitrobenzene.

3.2 Results and discussion

3.2.1 Synthesis

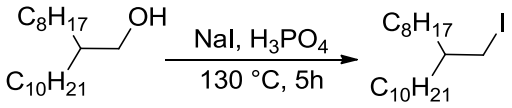
As underlined recently by Gladysz "what is always being recycled is the catalyst resting state".[15] Thus, to design a good ligand for a catalyst recovery strategy, the researcher must be sure which is the nature of the resting state. In the case of carbonylation of nitroarenes, as previously mentioned, the catalyst resting state is a phenanthroline-palladium bis-alkoxycarbonyl complex which forms the carbonylated active species only under a CO atmosphere. This complex is neutral and thus recyclable in a non-polar phase if tagged with the opportune phase selector.

Taking into account the results previously obtained with non-symmetric phenanthrolines,[1] the ligand of choice for a recovery strategy should be a 4-alkoxy substituted phenanthroline. However the exchange of the alkoxy moiety in aryl ether is easy under the catalytic reaction conditions (170 °C in methanol in the presence of a phosphorus acid) and only one long alkyl chain could not be sufficient to render the catalyst insoluble in methanol or selectively soluble in a non-polar phase. Thus we synthesized four different phenanthrolines substituted symmetrically with long alkyl chains in 4 and 7 positions. Among the synthesized ligands only the two substituted with linear alkyl chains were previously reported in the literature.[16, 17]

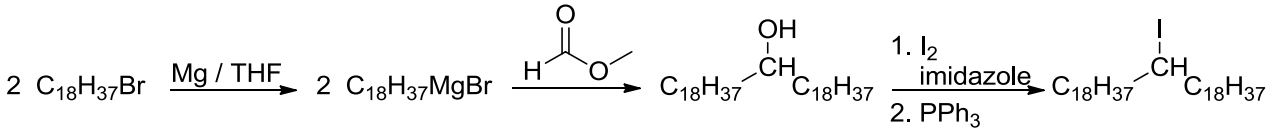


Scheme 1

The syntheses were performed following a previously reported procedure.[18] The commercial 4,7-dimethylphenanthroline was lithiated using lithium diisopropylamide in tetrahydrofuran and then reacted with a iodoalkane (Scheme 1). 4,7-ditridecylphenathroline (C_{13}-Phen), 4,7-dinonadecylphenanthroline (C_{19}-Phen), 4,7-bis(3-octyltridecyl)phenanthroline (C_{21}-Phen) and 4,7-bis(2-octadecylicosyl)phenanthroline (C_{38}-Phen) were obtained respectively from 1-iodododecane, 1-iodooctadecane, 9-(iodomethyl)nonadecane and 19-iodoheptatriacontane. While the first two linear iodoalkanes are commercial the two latter were synthesized from the corresponding alcohols (Scheme 2-3).



Scheme 2



Scheme 3

The synthetized ligands show a good solubility in non-polar solvents and they are insoluble or very little soluble in polar protic solvents as methanol, thus we could employ both a liquid/solid and a liquid/liquid separation strategy. The only exception is C_{21}Phen that is an oil at room temperature then recoverable only with a liquid/liquid separation.

3.2.2 Catalysis

One of the main methodological error present in many papers dealing with catalyst recovery, is to report total or very high conversions of reagents and taking them as a good index of the system recyclability. In this way many information are lost and a non-recyclable system could be misleadingly considered a recyclable one. Thus all the reaction were conducted avoiding to reach conversion higher than 80 %.

In our studies on the carbonylation of nitroarenes we usually employ $[Pd(Phen)_2][BF_4]_2$ as catalyst precursor, however the presence of two equivalent of phenanthroline, competing with the thermomorphic ligands to metal coordination, its use could result in catalyst loss after the first recycle. Several attempts were done to synthesize an analogous catalyst precursor with the long chain substituted ligands, either starting from palladium acetate[19] or by ligand exchange with

$[Pd(Bipy)_2][BF_4]_2$ (Bipy = bipyridine). However the obtained complexes were in a gummy form and they resulted inseparable from the excess ligand. Thus the active complexes were generated in situ by ligand exchange with $[Pd(Bipy)_2][BF_4]_2$. Bipyridine is a much weaker ligand with respect to phenanthroline thus it would not take away palladium during the first recycle. An high catalytic ratio was employed (4000 for liquid/solid systems and 2000 for liquid/liquid systems) to avoid complete conversions. 85% H_3PO_4 was used as acidic promoter as previously reported.[2, 3] Dimethoxypropane was added as internal drying agent and an small amount of aniline was initially added to avoid induction time of the reaction.[2, 3, 20] Concentrations of the ligands were unoptimized and the optimal ligand/ratio previously identified for 4,7-dimethylphenanthroline was employed.[1] In general, the reagent concentrations are those previously optimized in our group. The reactions were conducted at 170 °C, temperature at which the system is homogeneous under thermomorphic mode. After separation of the methanol phase, by centrifugation or decantation depending on the kind of system, all the reagents with the obvious exclusion of the ligand and the catalyst were refilled to the reactor for the subsequent run.

Turnover frequencies (TOF) calculated over all the reaction time for nitrobenzene conversion were chosen as an index of catalytic system activity since the kinetic of the reaction is zero-order in nitrobenzene and no induction time is present when a small amount of aniline is initially added as demonstrated in a previous work.[20] Selectivities in azo-, azoxybenzene and methyl *p*-methoxyphenylcarbamate are good index of the total selectivity of the system since these are the only side product that are only very slowly converted to the desired product.

At first, a liquid/solid separation strategy was studied. In order to assess the solubility of the ligands, they were suspended in methanol, separated by centrifugation and then the solvent evaporated. The results evidenced that C_{13}Phen was too soluble even at ambient temperature thus it was not used in catalytic tests involving liquid/solid separation. C_{18}Phen And C_{38}Phen were both completely soluble when the temperature was raised and precipitated when the solution was cooled at room temperature.

Although the ligands are almost insoluble in pure methanol, the solubility increases in the reaction mixture due to the presence of the other reactants. Good recyclability was obtained over the first tree cycles for the linear C_{19}Phen with a sudden drop at the fourth, while a more gradual decrease is noted for C_{38}Phen (Table 1). The activity of the system is decreased with respect to 4,7-dimethylphenanthroline, however it should be remembered that the ligand/Pd molar ratio is unoptimized and moreover aggregation phenomena could occur in solution thus reducing the total activity.

Table 1. Nitrobenzene carbonylation under thermomorphic conditions: liquid/solid separation.[a]

Cycle no.	TOF [h^{-1}][b]	
	C_{19}Phen	C_{38}Phen
1	778	817
2	753	622
3	688	456
4	503	386

[a] Experimental conditions: molar ratios $PhNO_2/PhNH_2/H_3PO_4/[Pd(Bipy)_2][BF_4]_2$ = 4000:200:750:1, $[Pd(Bipy)_2][BF_4]_2 = 1.3 \times 10^{-3}$ mmol , in MeOH (10 mL) + 2,2-dimethoxypropane (0.5 mL), P_{CO} = 60 bar, at 170 °C for 3 h. [b] TOF = turnover frequency = mol $PhNO_2$ reacted/(mol Pd × h).

The application of thermomorphic liquid/liquid separation strategy was more challenging for the choice of the non-polar co-solvent. Indeed hexane, heptane and cyclohexane are too miscible with methanol while higher linear alkanes are too expensive. Moreover it should be borne in mind that also the addition of water to favor the separation should be avoided in an hypothetical industrial process. Decalin was chosen at first because of its low miscibility and relatively low cost. Nevertheless the recyclability of the catalyst was low. This due to an enhancement of the solubility of the ligands in the polar phase caused by the little, but still non-negligible, miscibility of decalin with methanol.

Among the other potential solvents, we identified mineral oil as a possible choice due to: 1) its almost complete immiscibility with methanol at room temperature. 2) Its partial or complete, depending on the ratio with methanol, miscibility at the reaction temperature. 3) Its low cost. However it should be remembered that mineral oil is not always the same mixture of hydrocarbons thus its density and miscibility varies with the composition.[21]

A decrease of more than 50 % in activity was obtained with C_{13}Phen and C_{21}Phen employing decalin as co-solvent, and the drop was even more evident when mineral oil was used.

Catalytic results for C_{19}Phen and C_{38}Phen in liquid/liquid thermomorphic systems are reported in Table 2. Decalin/methanol system (1:1 in volume) gave appreciable results with C_{19}Phen, however at every recycle the non-polar decalin phase visibly diminished. Thus it cannot be considered as a suitable solvent mixture and C_{38}Phen was not tested in it. Employing a biphasic system mineral oil/methanol 2:5 in volume both C_{19}Phen and C_{38}Phen systems showed a good recyclability.

Table 2. Nitrobenzene carbonylation under thermomorphic conditions: liquid/liquid separation.

Cycle no.	TOF [h^{-1}][b]			
	C_{19}Phen/dec.[c]	C_{19}Phen/oil[d]	C_{19}Phen/oil[d,e]	C_{38}Phen/oil[d,f]
1	978	311	224	633
2	793	340	382	460
3	548	396	316	337
4	319	400	51	283
5	238	431		164
6		197		113

[a] Experimental conditions: molar ratios $PhNO_2/PhNH_2/H_3PO_4$/Ligand/$[Pd(Bipy)_2][BF_4]_2$ = 2000:100:375:1, $[Pd(Bipy)_2][BF_4]_2$ = 2.7 × 10^{-3} mmol, in MeOH (10 mL) + 2,2-dimethoxypropane (0.5 mL), P_{CO} = 60 bar, at 170 °C for 3 h. [b] TOF = turnover frequency = mol $PhNO_2$ reacted/(mol Pd × h). [c] Decalin/methanol volume ratio = 1:1, the amount of catalyst was halved while maintaining unvaried the concentrations of the other reagents [d] Mineral oil/methanol volume ratio = 2:5 [e] Octadecylphosphonic acid was added instead of H_3PO_4. The addition was done only at the first cycle. [f]The reaction was stopped at 2h 20' to avoid complete conversion.

However while for C_{19}Phen there is no loss of activity during the first five cycles and a sudden drop at the sixth, with C_{38}Phen the loss is more gradual. It is generally accepted that the systems based on the use of nitrogen ligands give the best results when an excess of the ligand is used, however the optimal amount could vary widely depending on the reaction conditions and ligand identity.[1] We suppose that during the recycle a "natural" optimization of the ligand concentration occurred. With C_{19}Phen there is a progressive loss of the free ligand up to the optimal concentration in run 5 followed by a sudden drop when the ligand amount is no more sufficient . On the other hand with C_{38}Phen the loss of activity is more gradual meaning that both catalyst and free ligand are lost during the cycles. This hypothesis is supported also by the different activities of the two systems. Indeed, although it seems that at the reaction temperature only one phase is present, it is possible that the more complex hydrophilic aggregates form during the reaction resulting in different activities depending on the partition coefficient of the ligand/catalyst.

One of the main reasons for free ligand loss is its partial salification caused by the acidic promoter. To overcome this problem we run a reaction employing octadecylphosphonic acid as a promoter hoping in the formation of a species more soluble in the mineral oil phase. However the

formed salt was found to have a metastable solubility in methanol and precipitate only after several hours thus raising the extent of ligand loss.

Although TOF is a good index of recyclability also the selectivity of the system should be taken into account. As stated above we took azoxybenzene selectivity as an index. We noted that when the system is recycled successfully, the selectivity values are almost unvaried however an increase was detected when the activity begins to drop (Table A3.1-A3.2 in Appendix).

3.3 Conclusions

In conclusion we applied for the first time a thermomorphic system to the reaction of carbonylation of nitroarenes. The results indicate that the catalyst recycle is possible by recovering the catalyst either as a solid or in solution. The most promising system is that employing mineral oil as co-solvent, however further optimization of the reaction conditions are needed. The substitution with long alkyl branched chains on the phenanthroline ligands seems to increase the solubility in methanol and thus to be detrimental for recycling.

Moreover, to the best of our knowledge this is the first time that mineral oil is employed as a solvent in catalytic reactions. Due to its non-toxicity, thermomorphic catalysts recovery based on its use could find application in pharmaceutical synthesis.

3.4 Experimental section

3.4.1 General procedures

Unless otherwise stated all manipulations and reactions were conducted under a dinitrogen atmosphere. All solvents were dried by standard procedures and distilled under dinitrogen immediately before use. All glassware and magnetic stirring bars used in catalytic reactions were kept in an oven at 120 °C for at least two hours and allowed to cool under vacuum before use. 1,10-Phenanthroline (Phen) was purchased as hydrates. It was dried by dissolving it in CH_2Cl_2, drying the resulting solution with Na_2SO_4, and evaporating in vacuo the filtered solution. It was then stored under dinitrogen. It can be weighed in the air without problems, but must be stored in an inert atmosphere if water uptake is to be avoided. The same procedure was applied to all the synthesized ligands employed in catalytic reactions. Nitrobenzene and aniline were distilled and stored under dinitrogen before use. Triethylamine was distilled over CaH_2 and kept under a dinitrogen atmosphere. $[Pd(Bipy)_2][BF_4]_2$ were prepared and characterized according to the procedures reported in the literature.[19] The mineral oil employed in catalytic reactions was “Sigma-Aldrich ®-(M3516) Mineral oil for infrared spectroscopy (light oil)”, d = 0.84 g/mL; immediately before use it

was degassed in vacuum for ten minutes under stirring. All other chemicals were purchased from Aldrich, Acros or Alfa Aesar. NMR spectra were recorded on a Bruker AC300 FT or on an Avance Bruker DPX300 spectrometer. Elemental analyses were recorded on a PerkinElmer 2400 CHN elemental analyzer.

3.4.2 Catalytic reactions

Liquid/solid separation. In a typical catalytic reaction, alkyl substituted ligand, $PhNO_2$, $PhNH_2$ and 85 wt.% H_3PO_4 were weighed in a 30 mL centrifuge tube and a solution of the catalyst in methanol was added by volume in order to avoid large errors in weighing small amounts of catalyst. The tube was placed inside a Schlenk tube with a wide mouth under dinitrogen and was frozen with liquid N_2. After the solvent was also frozen it was evacuated and filled with dinitrogen. Then the liner was closed with a screw cap having a glass wool-filled open mouth which allows gaseous reagents to exchange and rapidly transferred to a 200-mL stainless steel autoclave with magnetic stirring. The autoclave was then evacuated and filled with dinitrogen three times. CO was then charged at room temperature at 60 bar and the autoclave was immersed in an oil bath preheated at 170 °C. Other experimental conditions are reported in the captions to the tables and figures. At the end of the reaction the autoclave was cooled with an ice bath, vented, and the glass tube rapidly transferred to a Schlenk tube with a wide mouth under dinitrogen. It was then closed with a screw cap and centrifuged for 10' at 2750 rpm. The liquid phase was separated and the solid washed two times with methanol under a dinitrogen atmosphere. The mother liquor and the two washings were combined and the products were analyzed by gas chromatography (Dani 8620 gas chromatograph, equipped with a Supelco SLB™-5ms column; naphthalene as an internal standard). 2,2-dimethoxypropane, $PhNH_2$, $PhNO_2$, H_3PO_4 and methanol were added and the procedure repeated for the subsequent cycles.

Liquid/liquid separation. The procedure for the preparation of the reaction was identical to that used for liquid/solid separation except that a non-polar solvent was also added. At the end of the reaction the autoclave was cooled with an ice bath, vented, and the glass tube rapidly transferred to a Schlenk tube with a wide mouth under dinitrogen. Then, when mineral oil was employed, it was necessary to stir the reaction mixture for some minutes to allow liberation of the dissolved CO. Although the separation of the two phases occurs rapidly in most of the cycles, sometimes it was necessary to centrifuge the tube for 1' at 2750 rpm to favor the separation. The methanol upper phase was separated and washed two times with methanol stirring for five minutes every time under

a dinitrogen atmosphere. The mother liquor and the two washings were combined and the products were analyzed by gas chromatography (Dani 8620 gas chromatograph, equipped with a Supelco SLB™-5ms column; naphthalene as an internal standard). 2,2-dimethoxypropane, $PhNH_2$, $PhNO_2$, H_3PO_4 and methanol were added and the procedure repeated for the subsequent cycles.

3.4.3 Phenanthrolines synthesis

General procedure. The synthesis was adapted from a previously reported procedure.[18] In an oven-dried Schlenk flask, 4,7-dimethyl-1,10-phenanthroline (1.0 g, 4.8 mmol) was dissolved in 100 mL of dry THF. 2 M LDA solution in THF/heptane/ethylbenzene (6.0 mL) was slowly added at -78 °C while stirring. After 1h the alkyl iodide (12 mmol) , previously dissolved in dry THF (30 mL) was added and stirred for 5 h at -78 °C and overnight at room temperature. After evaporation of the solvent under vacuum, CH_2Cl_2 (100 mL) was added, washed with H_2O (3 × 25 mL) and then dried over Na_2SO_4. The solvent was evaporated, the crude product dissolved in the minimum amount of CH_2Cl_2 and filtered over an alumina pad (CH_2Cl_2 until excess iodoalkane was completely and then CH_2Cl_2 / 1 % MeOH to elute the phenantholine). Evaporation of the solvent afforded the product as a white solid.

C_{13}Phen. White powder.57 % yield, the ^{1}H NMR spectrum conforms to what previously reported in the literature.[16] ^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ 9.15 (d, $^3J_{H,H}$ = 4.5 Hz, 2H), 8.12 (s, 2H), 7.56 (d, $^3J_{H,H}$ = 4.5 Hz, 2H), 3.20 (t, $^3J_{H,H}$ = 7.5 Hz, 4H), 1.83 (tt, $^3J_{H,H}$ = 7.5 Hz, 4H), 1.54 – 1.28 (m, 36H), 0.89 (t, $^3J_{H,H}$ = 6.6 Hz, 6H) ppm. Anal. Calcd. for $C_{38}H_{60}N_2$: C, 83.76; H, 11.10; N, 5.14 Found: C, 83.56; H, 11.23; N.5.12.

C_{19}Phen. White powder. 61 % yield, ^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ 9.31 (d, $^3J_{H,H}$ = 4.5 Hz, 2H), 8.17 (s, 2H), 7.65 (d, $^3J_{H,H}$ = 4.5 Hz, 2H), 3.23 (t, $^3J_{H,H}$ = 7.6 Hz, 4H), 1.85 (tt, $^3J_{H,H}$ = 7.5 Hz, 4H), 1.54 – 1.28 (m, 64H), 0.90 (t, $^3J_{H,H}$ = 6.6 Hz, 6H) ppm. Anal. Calcd. for $C_{50}H_{84}N_2$: C, 84.20; H, 11.87; N, 3.93 Found: C, 84.10; H, 11.84; N, 3.79.

9-(Iodomethyl)nonadecane. The synthesis was adapted from a procedure previously reported in the literature for different primary alcohols.[22] 2-Octyldodecan-1-ol (5.0 mL, 14.0 mmol), hydroiodic acid (57% HI, 5.0 mL) and H_3PO_4 (85%, 5.0 mL) were added to a round bottom flask. The resulting biphasic mixture was vigorously stirred at 130°C. After 4 hours the reaction mixture was allowed to cool, poured into ice water (10 mL), extracted with CH_2Cl_2 (3 × 10 mL). The

combined organic layers were washed with a saturated solution of sodium thiosulfate (2 × 10 mL) and then again with water (10 mL). The organic phase was dried over $MgSO_4$ and the solvent evaporated affording a brown oil (5.22 g, 12.8 mmol, 91% yield).
^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ 3.27 (d, $^3J_{H,H}$ = 4.49 Hz, 4H), 1.35 – 1.00 (m, 64H), 0.88 (t, $^3J_{H,H}$ = 7.0 Hz, 6H) ppm. MS: m/e 281.3(M - I, $C_{20}H_{41}$, 4), 99.1 (9), 85.1 (28), 71.1 (54), 57.1 (100), 43.1 (63), 41.5 (40)

C_{21}Phen. Light brown oil. 42 % yield. ^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ 9.17 (d, $^3J_{H,H}$ = 4.5 Hz, 2H), 8.10 (s, 2H), 7.54 (d, $^3J_{H,H}$ = 4.5 Hz, 2H), 3.16 (t, $^3J_{H,H}$ = 8.2 Hz, 4H), 1.81-1.68 (m, 4H), 1.59 – 1.04 (m, 66H), 0.94-0.87 (m, 12H) ppm.

Heptatriacontan-19-ol. In an oven-dried Schlenk flask Mg turnings (0.74g, 30.4 mmol) were suspended in dry and deoxygenated THF (15 mL). A small crystal of iodine was added (obtaining a light yellow coloration) and the solution was heated until decoloration. 1-bromooctadecane (6.65 g, 19.9 mmol) was separately dissolved in THF (15 mL) and added dropwise, while stirring, in order to maintain warm the mixture. The suspension was left 1h at room temperature and a further hour at 40 °C. After cooling to room temperature dry methylformate (410 μL, 6.67 mmol) was added while cooling the flask with water (the reaction is very exothermic but ice cooling of the flask could result in Grignard reagent precipitation). The mixture was stirred overnight and then quenched with H_2O (50 mL) and 1M H_2SO_4 was added to consume the excess Mg. CH_2Cl_2 was added and most of the solid pass in the organic phase forming a suspension. The organic layer was washed with water (50 mL) and the solvent evaporated. The obtained solid was recrystallized from acetone (100 mL) obtaining a white product insoluble in all common solvents. (4.12 g, 7.67 mmol, 77 % yield). Due to its insolubility it was used in the subsequent step without further characterization except for elemental analysis. Anal. Calcd. for $C_{37}H_{76}O$: C, 82.76; H, 14.27; Found: C, 82.38; H, 14.34.

19-Iodoheptatriacontane. The synthesis was adapted from a procedure previously reported in the literature for the synthesis of bromides.[23] In a two-neck round bottom flask, imidazole (0.57 g, 8.47 mmol), PPh_3 (2.23 g, 8.48 mmol) and I_2 (2.22 g, 8.7 mmol) were added to 19-heptatriacontanol (4.12 g, 7.67 mmol) suspended in dry THF (150 mL). After 24 h, methanol (1.5 mL) was added and the solvent was removed under reduced pressure. Purification by filtration on a pad of silica gel with hexane as eluent afforded a white powder (4.61 g, 7.13 mmol, 93 %yield). ^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ 4.15 (m, 1H), 1.95 – 1.80 (m, 2H), 1.70 (m, 2H), 1.60 – 1.47 (m, 4H), 1.47 – 1.01 (m, 60H), 0.90 (t, $^3J_{H,H}$ =6.8 Hz, 6H). Anal. Calcd. for $C_{37}H_{75}I$: C, 68.70; H, 11.69; Found:

C, 71.0; H, 11.90. The slightly higher values obtained for C and H are due to the presence of hexane that remains in the product also after several hours in vacuo.

C_{38}Phen. Pure product was obtained by column chromatography (silica gel, hexane/ 3% triethylamine / 1% isopropanol). White powder (31 % yield), ^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ 9.07 (d, $^{3}J_{H,H}$ = 4.5 Hz, 2H), 8.05 (s, 2H), 7.42 (d, $^{3}J_{H,H}$ = 4.5 Hz, 2H), 3.06 (d, $^{3}J_{H,H}$ = 6.8 Hz, 4H), 1.88 (m, 2H), 1.47 – 1.06 (m, 136H), 0.90 (t, $^{3}J_{H,H}$ = 7.1 Hz, 12H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 300 K): δ 149.5 (*C*H), 147.8 (*C*), 147.0 (*C*), 127.5 (*C*), 124.2 (*C*H), 121.9 (*C*H), 39.2 (*C*H), 37.5 (CH_2), 33.5 (CH_2), 31.9 (CH_2), 30.0 (CH_2), 29.69 (CH_2), 29.65 (CH_2), 29.3 (CH_2), 26.5 (CH_2), 22.7 (CH_2), 14.1 (CH_3).

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[21] In this study the miscibility of two different mineral oils with methanol in proportion 2:5 in volume was tested in a pressure tube. a) Acros® - Mineral oil, pure (4150800): d = 0.88 g/mL, is only partially miscible at 170 °C. b) Sigma-Aldrich ®-(M3516) Mineral oil for infrared spectroscopy (light oil): d = 0.84 g/mL, is completely miscible over 160 °C.

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Chapter 4

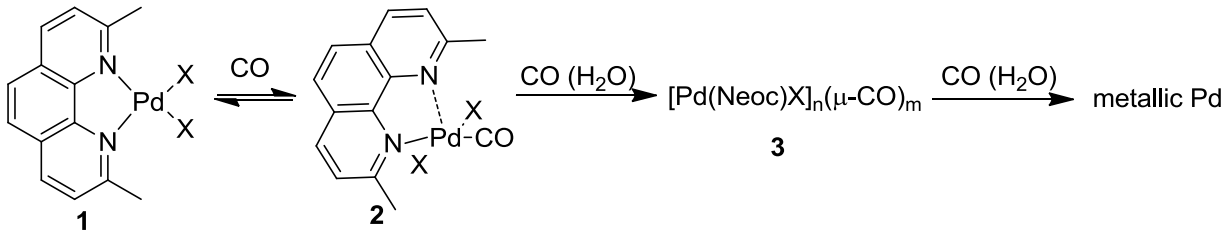
Studies on palladium complexes relevant to the reaction of carbonylation of nitroarenes

4.1 Introduction

In recent years, an enormous number of new applications of palladium-based homogeneous catalysts have been reported. However, palladium applications to carbonylation reactions have increased to a much slower pace. This is surely mostly due to the notorious easiness with which metallic palladium is generated from palladium(II) complexes under a CO atmosphere. Understanding the early stages of palladium reduction and aggregation is essential in designing more effective catalytic systems, but only in few cases intermediate complexes in the reduction process have been unequivocally characterized.

As mentioned in Chapter 2 we have recently reported that reversible coordination of CO to palladium complexes of the kind $Pd(RPhen)X_2$ (**1**, RPhen = 1,10-phenanthroline or a substituted phenanthroline, X = -COOMe, or a carboxy group) to initially give an adduct of composition $Pd(RPhen)X_2(CO)$ (**2**) is an essential step in the palladium/phenanthroline catalyzed carbonylation of nitroarenes to carbamates and ureas.[1] Although only kinetic evidence could be obtained for these adducts in several cases, use of 2,9-dimethylphenanthroline (neocuproine, Neoc) allowed the spectroscopic observation of these compounds and the isolation of single crystals of the chloride analogue $Pd(Neoc)Cl_2(CO)$ (**2a**), suitable for X-ray structure determination. None of the complexes of type **2** was indefinitely stable in solution and they generally evolved to metallic palladium in a timeframe ranging from less than one hour to a couple of days at room temperature. Only the chloride complex **2a** was stable enough to allow the growth of single crystals at low temperature. However, during the decomposition, a third type of complex (**3**) was observed in all cases. Type **3** complexes are characterized by an IR absorption in the range 1877-1884 cm^{-1}, typical of bridging CO groups, indicating they are dimers or higher aggregates. No IR absorption is observed in the region of terminal CO groups. Despite the fact that no complex of this class could be isolated or even observed alone in solution, a low temperature NMR study of the reaction of $Pd(Neoc)(TMB)_2$ (**1b**) (TMB = 2,4,6-trimethylbenzoate) with CO allowed the attribution of a set of signals to the corresponding **3b** complex. These signals indicate that it contains one neocuproine and one trimethylbenzoate group per palladium atom. The neocuproine ligand is in a symmetrical environment, although this may be due to fluxionality. Together, these information indicates that

complexes **3** are palladium(I) complexes of general composition $[Pd(Neoc)(X)]_n(\mu\text{-}CO)_m$, where n ≥ 2 and m ≥ 1, but nothing more than this can be said (Scheme 1).



Scheme 1

4.2 Results and discussion

Following the studies described in the introduction, we have made more attempts to unveil the nature of complexes **3**, with the idea that knowing the structure of an intermediate in an unwanted reaction may help avoiding it. Since the chloride complex **1a** has a lower tendency to evolve toward metallic palladium than all complexes having –COOMe or a carboxylate as the anionic ligand, we decided to investigate this complex and its bromide (**1c**) and iodide (**1d**) analogues in more details.[2]

It was previously reported by our group that by placing a suspension of **1a** in CH_2Cl_2 under a CO atmosphere at room temperature, the compound gradually dissolves and an absorption at 2133 cm^{-1} appears in the infrared spectrum of the solution, due to $Pd(Neoc)Cl_2(CO)$ (**2a**). At the same time, a weaker absorption at 1875 cm^{-1} also appeared. Moreover it was observed that, by prolonging the reaction time, that precipitation of a yellow solid starts after several hours. The IR spectrum of the solid, in nujol, showed a strong absorbance at 1875 cm^{-1}, coincident with the band observed in solution for **3a,** accompanied by a weak absorption at 1921 cm^{-1} and a very weak one at 1846 cm^{-1}. The precipitation is complete in about four days, after which the solution has become colorless and no more absorptions are observed in the carbonyl region of the IR spectrum. The precipitate at this stage showed the two aforementioned bands, but a weak band was also observed at 2143 cm^{-1}. If the suspension was left in a CO atmosphere for two weeks, two new bands at 1900 (m) and 1966 (vw) cm^{-1} also appeared, which were not observed for shorter reaction times. The 2143 cm^{-1} absorption is very close to that reported in the literature for $[NH_2Et_2][PdCl_3(CO)]$ (2146 cm^{-1}) [3-5] and may be attributed to the same anionic complex, whereas the last two bands and their relative intensity are consistent with those of $[Pd_2Cl_4(\mu\text{-}CO)_2]^{2-}$ (1906, 1966 cm^{-1} in CH_2Cl_2 solution, 1896 and 1903 cm^{-1} in nujol for two independent molecules in the crystals of the Bu_4N^+ salt).[6]

Once precipitated, **3a** was insoluble in most solvents and only little soluble in DMSO. An ^{1}H NMR spectrum of the residue in this solvent showed the presence of only one set of signals due to a neocuproine ligand in a symmetrical environment. As for **3b**, this may be due to fluxionality. Signals due to the minor complexes observed by IR could not be assigned because they are too weak.

Attempts to purify **3a** or to get crystals suitable for X-ray diffraction failed. Thus in a previous thesis we started investigating the corresponding bromide complexes. Carbonylation of $Pd(Neoc)Br_2$ (**1c**) proceeds analogously to that of **1a** and the initial $Pd(Neoc)Br_2(CO)$ **2c** adduct (ν_{CO} = 2124 cm^{-1}) was even more stable. Indeed, no peak in the bridging CO region is initially observable in the IR spectrum of the solution and only after several hours does a very weak peak at 1887 cm^{-1} appear, attributable to **3c**. This peak always remained very weak due to the very low solubility of **3c** in CH_2Cl_2, which precipitated as the reaction proceeded. The reaction was continued at RT for several days, after which the solution was colorless and no carbonyl absorption was observable by IR. The yellow residue obtained showed in the IR spectrum in nujol the same pattern as that observed for **3a**, that is an intense IR absorption at 1878 cm^{-1}, accompanied by a weak absorptions at 1922 cm^{-1} and a very weak one at 1846 cm^{-1}. The elemental analysis of the solid agrees with a composition of the $[Pd(Neoc)Br(CO)]_n$ type. Again this is consistent with a dimer of composition $[Pd(Neoc)Br]_2(\mu\text{-}CO)_2$, but higher aggregates cannot be excluded.

During the reaction, samples were withdrawn by time-to-time and layered with hexane. From these attempts, crystals of **2c**.

In this thesis, while repeating the experiment in order to synthesize the complex **3c**, trying to obtain good crystals for X-ray diffraction. It was possible to isolate and characterize by X-ray diffraction the complex $[PdBr_3(CO)][NeocH]$ (**4c**).

The structure of anionic part of **4c** (Figure 1) is very similar to that previously reported for the anionic part of $[PdBr_3(CO)][NBu_4]$[4] or $[PdCl_3(CO)][NBu_4]$[4] and not worth further discussion. However, this structural determination unambiguously show that compounds of composition $[PdX_3(CO)]^-$ are indeed formed under these conditions and supports the assignment of the 2143 cm^{-1} absorption observed in the case of the chloride complex to $[PdCl_3(CO)]^-$. Compound **4c** should be formed only in very small amounts because no IR absorption around 2120 cm^{-1} (as expected from the literature for a solution in CH_2Cl_2)[4] could be observed either in solution during the reaction or in the nujol mull of the precipitated product.

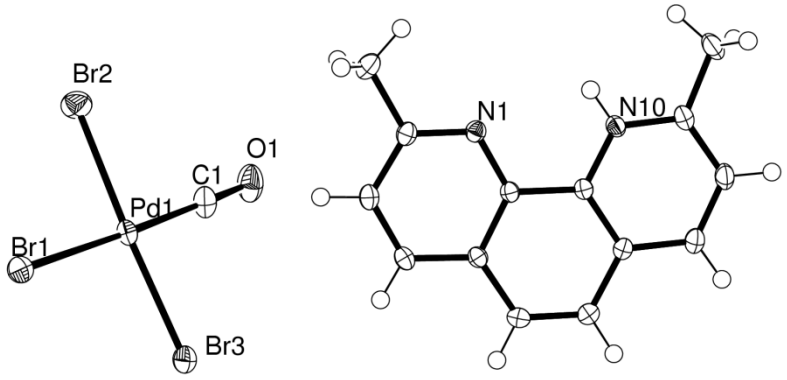


Figure 1 Ortep drawing of [$PdBr_3(CO)$][NeocH] (**4c**), ellipsoids draw at 30% probability level (H atoms are simple spheres)

The iodide complex $Pd(Neoc)I_2$ (**1d**) was also successfully carbonylated to $Pd(Neoc)I_2(CO)$ (**2d**) ($\nu_{(CO)}$ = 2101 cm^{-1} in CH_2Cl_2). Complex **2d** is the most stable in the series and only a very weak absorption at 1889 cm^{-1} attributable to **3d** was observable even after a several days standing in a CO atmosphere.

Although, during a previous master thesis, it was possible to grow good quality crystals of compounds **2a,c,d**, ^1H NMR characterization was not possible because the carbonylation reaction at atmospheric pressure proceed slowly and some starting material was still observable when formation of byproducts began especially in the case of **1a**. During this thesis in order to get clean spectra, a few milligrams of each of the starting palladium complexes was placed in a test tube with a stirring bar and treated with 1 mL of $CDCl_3$. The test tubes were placed inside an autoclave and stirred under 30 bar CO for 2 h at RT. The autoclave was then vented and the ^1H NMR spectrum of the three solutions immediately recorded. This procedure resulted in a fast enough carbonylation to avoid byproducts formation and clean spectra of the adducts **2a,c,d** were obtained. They all show signals attributable to a single neocuproine ligand in a symmetrical environment, evidencing that the compounds are fluxional at room temperature, as the two N-Pd distances are not equivalent in the solid state. After recording the ^1H NMR spectra (Appendix Figure A4.4, A4.6, A4.8), the three solutions were also analyzed by IR spectroscopy (Appendix Figure A4.5, A4.7, A4.9), to confirm that the compounds of which the NMR spectrum had been recorded are indeed **2a,c,d**. The IR spectra confirm the identity of the obtained compounds, although some decomposition is already evident in the spectrum of the chloride derivative.

It is worth evidencing the different chemical stability of the three CO adducts. The chloride adduct **2a** is only moderately stable and fully decomposes in solution at room temperature in several hours. Indeed, the single crystals of this compound employed in the previously published paper had

to be grown at -50 °C.[1] On the other hand, the bromide derivative **2c** is stable under a CO atmosphere at room temperature for several days. The iodide compound **2d** is the most stable. Its solutions can be evaporated in vacuo and the compound redissolved under a dinitrogen atmosphere without any evidence for CO loss. The higher stability of the iodide derivative may be important to further study the reactivity of this kind of compounds. It is worth mentioning that this stability order is opposite to that observed for several halocarbonyl derivatives of palladium (and even of platinum and gold) not containing other donating ligands.[4, 7, 8] The reasons for this reversal of stability may be multifold and cannot be discussed here, but this observation may be relevant to the catalytic behavior of complexes of this class.

In this thesis several attempts were done to grow single crystals of any compound of type **3**, but without success. However a single crystal of the corresponding complex with 6,6'-dimethyl-2,2'-bipyridine and X = I was previously obtained, allowing the confirmation of the dinuclear structure of the complex (Figure 2).

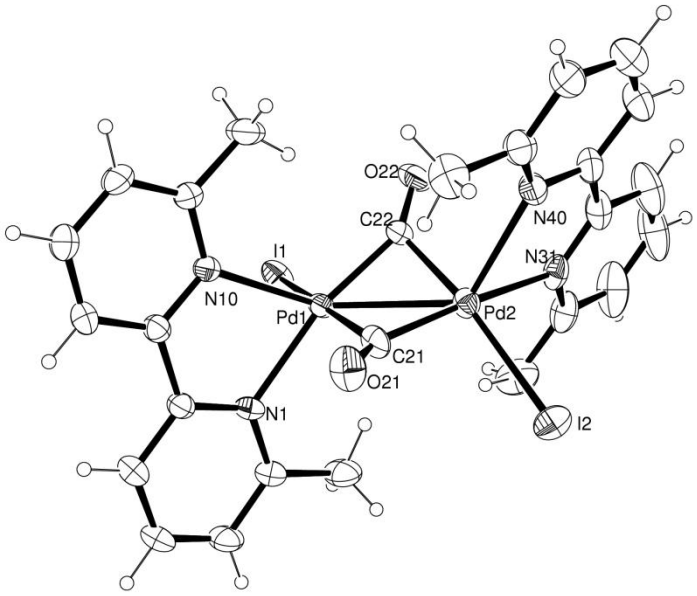


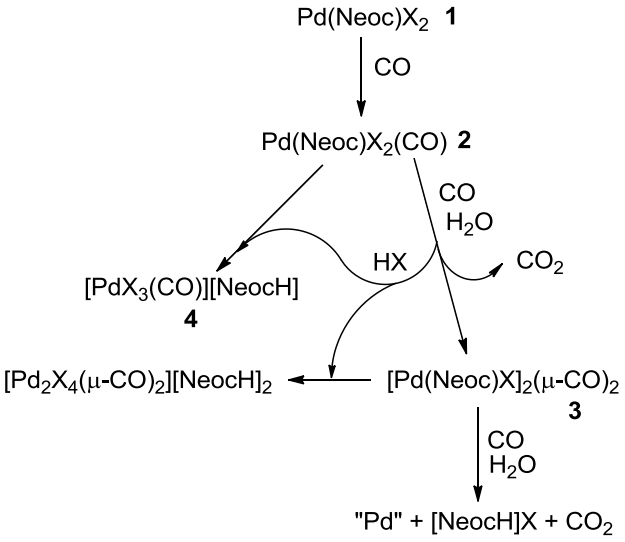
Figure 2 Ortep drawing of $[Pd(Me_2Bipy)I]_2(\mu\text{-}CO)_2$ (**3e**), ellipsoids are drawn at 30% probability level (H atoms are simple spheres)

Compounds **3e** and **3c** are too unsoluble to allow the recording of an NMR spectrum, but the ^1H NMR spectra of **3a** in DMSO and **3b** in $CDCl_3$[1] show that they are also diamagnetic.

It is important to recall that 6,6'-dimethyl-2,2'-bipyridine, neocuproine and its subtituted derivatives have shown to lead to higher catalytic activities with respect to phenanthroline when employed as ligands for several palladium catalyzed reactions, including the Heck reaction,[9] the

oxidative Heck arylation of olefins by boronic acids,[10-12] the production of hydrogen peroxide,[13, 14] and especially the alcohol oxidation by dioxygen.[15-19] The reason with general validity has not been unveiled for this higher reactivity, however the most frequent explanation is that the two ortho methyl groups inhibits or at least disfavor the formation of catalytically inactive complexes. However, the X-ray structure of **3e** demonstrates that such steric hindrance does not inhibit a dimerization Thus, a reduced tendency to dimerization cannot be the reason for better catalytic performances. This is also in agreement with the results by Tsuji and co-workers,[20, 21] who reported an enhanced stability for pyridine and bipyridine palladium complexes where the steric hindrance is due to much larger substituents.

Complexes **3** are clearly intermediates in the reduction by CO of palladium(II) complexes to metallic palladium, a very important process whose details are however little understood. In the case of the synthesis of $[Pd_2Cl_4(CO)_2]^{2-}$, it was proposed that the reduction of the initial palladium(II) complex is due to phosgene elimination,[22, 23] whereas when acetate is the counteranion, elimination of CO_2 and acetic anhydride have been observed.[24] On the other hand, reduction by CO/H_2O is a general pathway for the reduction of a variety of metals.



Scheme 2. General reaction scheme.

As far as the mechanism of formation of complexes **3** is concerned, we have no evidence for the formation of phosgene (IR absorption 1810 cm^{-1} in CH_2Cl_2 solution[25]) or its brominated analogue. Moreover no carboxylate is present in several cases and in the only case in which a carboxylate is present and the organic products of the reduction were identified, that is in the case of **3b** (2,4,6-trimethylbenzoate is the counteranion), the observed co-product was trimethylbenzoic acid and not the corresponding anhydride.[1] Since monoelectronic reduction of palladium is very unlikely under

the conditions of this study, we consider that the most likely route for the formation of **3** is that **2** is initially reduced to a palladium(0) complex by reaction with CO and trace amounts of water that cannot be completely removed from the system even if CO was passed through molecular sieves before reaching the reaction flask.

The so formed complex would be trapped by still unreacted **2** to afford the dimeric **3**. Formation of a small amount of CO_2 could indeed be observed by IR. The intentional addition of small amounts of water to the reaction solution also resulted in a strong acceleration of the reduction process, but in this case the reaction could not be stopped at the stage of the dimeric complexes and extensive formation of metallic palladium was observed.

Scheme 2 accounts for the formation of all observed products.

4.3 Conclusions

Identification of the possible species involved in catalytic reaction is a key point for understanding the mechanism of catalytic reactions. In this thesis we completed the characterization of the complexes Pd(Neoc)X_2(CO) (**2**), previously identified by X-ray diffraction. Although the preparation of crystals suitable for X-ray diffraction of complexes **3a,b,c** was not succeeded, during their synthesis a further species, [$PdBr_3$(CO)][NeocH], was identified. Such compound together with the Pd(I) dimer previously synthesized in our group, completes the picture of the reactivity of the complexes Pd(Neoc)X_2 in a CO atmosphere

4.4 Experimental section

4.4.1 General procedures.

Unless otherwise stated, all reactions and manipulations were conducted under a dinitrogen atmosphere. Carbon monoxide employed in the reaction at atmospheric pressure was passed though molecular sieves before reaching the reaction flask, but no purification could be done on the CO employed in the high-pressure reactions. All solvents were dried by standard procedures and distilled under dinitrogen immediately before use. All glassware and magnetic stirring bars used in catalytic reactions were kept in an oven at 120 °C for at least two hours and let to cool under vacuum before use. 2,9-dimethyl-1,10-phenanthroline was purchased as hydrate. It was dried by dissolving it in CH_2Cl_2, drying the resulting solution with Na_2SO_4, filtering the suspension under dinitrogen, and evaporating in vacuo the filtered solution. It was then stored under dinitrogen. It can be weighed in the air without problems, but must be stored in an inert atmosphere if water uptake is to be avoided. Pd(Neoc)Cl_2,[1, 26] Pd(Neoc)Br_2,[26] Pd(Neoc)I_2,[26] and Pd(dba)$_2$[27, 28] were prepared

and characterized according to the procedures reported in the literature. All other chemicals were purchased from Aldrich, Acros or Alfa Aesar and used as received. $CDCl_3$ was purified by passing through a short column of basic alumina that had been previously dried by heating in vacuo by a heating gun (to remove all acidic impurities and most of the water). The so purified solvent was degassed and stored over activated molecular sieves under dinitrogen and in the dark. d_6-DMSO was distilled over CaH_2, degassed and stored over activated molecular sieves under dinitrogen. NMR spectra were recorded on a Bruker AC300 FT or on an Avance Bruker DPX300 spectrometer. Unless otherwise noted, IR spectra were recorded on a Varian Scimitar FTS 1000 FT-IR spectrophotometer. Elemental analyses were recorded on a PerkinElmer 2400 CHN Elemental Analyzer.

4.4.2 Carbonylation reactions at atmospheric pressure

Pd(Neoc)Cl_2 (1a): The reaction has been performed several times, varying the sampling time and the total reaction time. A reaction aimed at isolating Pd(Neoc)Cl_2(CO) (**2a**) has been described in a previous paper.[1] In a typical preparation, Pd(Neoc)Cl_2 (13.9 mg, 3.60 10^{-2} mmol) was placed in a Schlenk tube under a CO atmosphere and suspended in CH_2Cl_2 (5 mL). The initially yellow suspension gradually turned into a yellow solution. Stirring was continued for 4 days, after which a pale yellow precipitate was separated by centrifugation from the colorless solution and washed twice with CH_2Cl_2. IR (nujol): 2143 (vw. The intensity of this band relative to the others is variable from one preparation to the other), 1921 (w), 1875 (s), 1846 (vw) cm^{-1} (see also Fig. A4.1, Appendix). Attempts to remove the impurity failed and the elemental analysis of the solid is out of range for [Pd(Neoc)Cl]$_2$(μ-CO)$_2$ (**3a**): Anal Cald. for $C_{30}H_{24}Cl_2N_4O_2Pd_2$: C, 47.64; H, 3.20; N, 7.41 %. Found: C, 46.31; H, 3.47; N, 7.18 %. The precipitate is insoluble in $CDCl_3$, but soluble enough in DMSO to allow recording of a ^{1}H NMR spectrum: ^{1}H NMR (d_6-DMSO, RT): δ 8.74 (d, 2H, H^4, H^7 or H^3, H^8, J = 8.26 Hz); 8,17 (s, 2H, H^5 and H^6); 8,02 (d, 2H, H^3, H^8 or H^4, H^7, J = 8.30 Hz); 3.22 (s, 6H, CH_3).

The reaction was also performed with the same amounts, but for 14 days instead of 4. The IR spectrum (nujol) of the formed precipitate showed, in addition to those mentioned above, two additional bands at 1900 (ms) and 1966 (w) cm^{-1} also appeared (see also Fig. A4.2, Appendix).

Pd(Neoc)Br_2 (1c): The reaction has been performed several times, varying the sampling time and the total reaction time. In a typical preparation, Pd(Neoc)Br_2 (**1c**, 41.0 mg, 8.64 10^{-2} mmol) was placed in a Schlenk tube under a CO atmosphere and suspended in CH_2Cl_2 (5 mL). An IR absorption immediately start to grow at 2120 cm^{-1} and the initially orange suspension gradually

turned into an orange solution. Stirring was continued for 5 days. During this time, samples of the solution were withdrawn and layered with hexane. From these attempts, in a previous thesis, single crystals suitable for X-ray diffraction analysis were obtained for Pd(Neoc)Br_2(CO) (**2c**,) and, in this thesis, [$PdBr_3$(CO)][NeocH] (**4c**). After the allotted time was finished, a yellow precipitate was separated by centrifugation from the almost colorless solution and washed twice with CH_2Cl_2. The solid was analytically pure [Pd(Neoc)Br]$_2$(μ-CO)$_2$ (**3c**): Anal Cald. for $C_{30}H_{24}Br_2N_4O_2Pd_2$: C, 42.63; H, 2.86; N, 6.63 %. Found: C, 42.75; H, 3.25; N, 6.43 %. IR (nujol): 1922 (w), 1877 (s), 1847 (vw) cm^{-1} (see also Fig. A4.3, Appendix).

4.4.3 Carbonylation reactions under high CO pressure.

The reactions were conducted in parallel in three 10 mm wide × 40 mm high test tubes, each having a magnetic stirring bar, which were located in the holes of an aluminum block designed to fit a 200 mL stainless steel autoclave. The block and the test tubes were placed inside a Schlenk tube with a wide mouth, compounds 1a,c,d (1.8 10^{-2} mmol each) and dry and degassed $CDCl_3$ (1 mL to each test tube) were added under dinitrogen. Each tube was closed with a screw cap with a glass wool-filled open mouth that allows gaseous reagents to exchange and the block was rapidly transferred to the autoclave. The autoclave was purged from air, charging CO at 30 bar and discharging to 2 bar one time before performing the reaction. CO (30 bar) was then charged at room temperature and stirring was continued for 2 h at RT. After this time, the autoclave was vented, the solutions were rapidly transferred to three NMR tubes under a CO atmosphere and the ^{1}H NMR spectra recorded immediately. After the NMR spectrum had been recorded, an IR spectrum of the same solution was also recorded, to confirm that the two spectra are attributed to the same species. In all cases, a single species was observable by ^{1}H NMR. The IR spectra of the carbonylated samples of 1c,d also showed the exclusive presence of 2c,d (the single band is only slightly shifted on passing from CH_2Cl_2 to $CDCl_3$ as solvent), although some decompositions is evident in the spectrum of the 2a. This must have occurred in the timeframe from the recording of the NMR and IR spectra, since the NMR spectrum is clearly due to a single species.

2a: ^{1}H NMR ($CDCl_3$, RT): δ 8.34 (d, 2H, H4, H7 or H3, H8, J = 8.4 Hz); 7.86 (s, 2H, H5 and H6); 7.55 (d, 2H, H3, H8 or H4, H7, J = 8.4 Hz); 3.27 (s, 6H, CH_3) (see also Fig. A4.4, Appendix). IR ($CDCl_3$) $\nu_{(CO)}$ = 2133 cm^{-1} (see also Fig. A4.5, Appendix).

2c: ^{1}H NMR ($CDCl_3$, RT): δ ^{1}H NMR ($CDCl_3$, RT): δ 8.29 (d, 2H, H4, H7 or H3, H8, J = 8.2 Hz); 7.83 (s, 2H, H5 and H6); 7.71 (d, 2H, H3, H8 or H4, H7, J = 8.2 Hz); 3.46 (s, 6H, CH_3) (see also Fig. A4.6, Appendix). IR ($CDCl_3$) $\nu_{(CO)}$ = 2124 cm^{-1} (see also Fig. A4.7, Appendix).

2d: ^{1}H NMR ($CDCl_3$, RT): δ 8.28 (d, 2H, H4, H7 or H3, H8, *J* = 8.2 Hz); 7.84 (s, 2H, H5 and H6); 7.69 (d, 2H, H3, H8 or H4, H^7, *J* = 8.2 Hz); 3.32 (s, 6H, C*H*$_3$) (see also Fig. A4.8, Appendix). IR ($CDCl_3$) $\nu_{(CO)}$ = 2105 cm^{-1} (see also Fig. A4.9, Appendix).

4.4.4 X-ray single crystal structure determination.

Crystal sample of **4c** was mounted in air on a glass fiber put on a goniometer head and then centered on the goniometer of a Bruker APEX II CCD diffractometer, equipped with Oxford Cryosystem 700+ cryostream, with generator operating at 50 kV and 30 mA. An extensive data collection at low temperature was carried out with the intent to map the electron density distribution in $NeocH^+$, but the quality of the crystal was not enough for a more detailed modeling.

The raw integrated intensities of all datasets were corrected for absorption and diffraction anisotropies using SADABS.[29] The structures were solved with direct methods using SIR97[30] and refined based on full-matrix least squares on F^2 with SHELX97[31] within the WINGX package.[32] Hydrogens were always modeled as riding on the corresponding carbon atoms, with a fixed isotropic thermal parameter. All other atoms were refined with anisotropic thermal parameters.

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[2] During the studies conducted in this thesis and in the previous works, we have found that complexes **1a**, **1c** and **1d** exist in two different bond isomeric forms.The identity of the employed isomer is not influential to the present discussion, since both yielded the same products Some preliminary studies on the precursor identity have been conducted during this work but full resultswere obtained in another thesis and described in: M. Rimoldi, F. Ragaini, E. Gallo, F. Ferretti, P. Macchi, N. Casati, *Dalton Trans.* **2012**, *41*, 3648-3658

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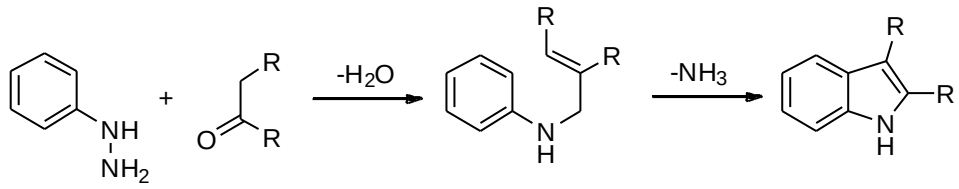
Chapter 5

Palladium-Catalyzed Synthesis of Indoles by Cyclization of β-Nitrostyrenes Using Carbon Monoxide as the Reductant

5.1 Introduction

The indole skeleton is central to many biological active pharmaceutical drugs and natural alkaloids due to its capability of binding to a number of receptors.[1] For this reason the indoles synthesis continues to attract the attention of many researchers.[2-7]

Indole was isolated for the first time by Adolf von Baeyer from the treatment of indigo dye with oleum. Its name is a combination of the words *indigo* and *oleum*. Its importance in pharmaceutical chemistry grew from 1950s, when several compounds containing the indole subunit were found to have significant biological activities. The synthesis and functionalization of indoles has been the object of research for over 100 years and a variety of well-established classical methods are available (*i.e.*: the Fisher indole synthesis, the Bischler-Mölau condensation of anilines and α-bromoacetophenone, the Madelung cyclization of *N*-acyl-*o*-toluidines, the Gassman synthesis of indoles, the palladium catalyzed Larock synthesis from *o*-nitroanilines and disubstituted alkynes, etc.). For almost one century the Fisher indole synthesis has remained one of the most used methodologies for the synthesis of indole derivatives. This approach consists in the condensation of an aromatic hydrazine with a ketone or an aldehyde employing an acid catalysis, followed by a [3,3]-sigmatropic rearrangement, ammonia elimination and aromatization (Scheme 1). One of the main advantage of the Fischer reaction is the tolerance to a wide range of functional groups on the aromatic ring.[2]



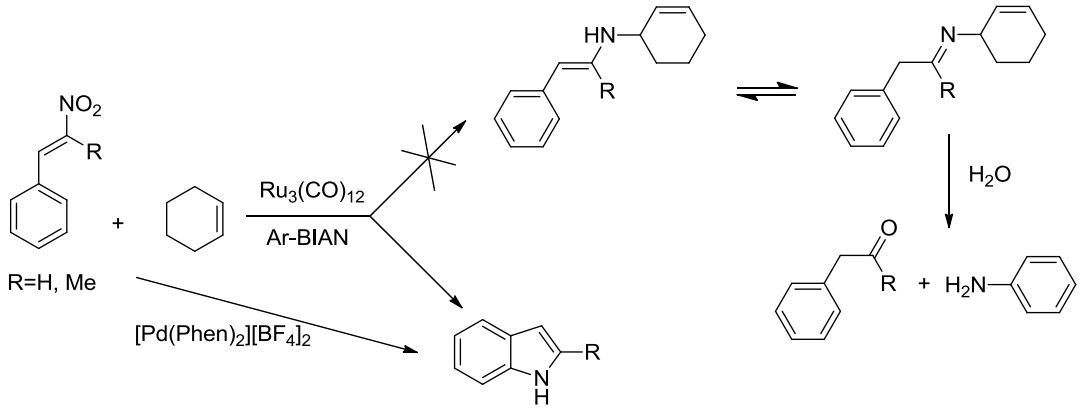
Scheme 1. Fischer indole synthesis

Beside the "classical" organic synthetic methodologies, many transition-metal catalyzed synthetic strategies were developed in the last fifty years. Palladium covered a central role in indole syntheses in particular due to the general tolerance to a wide range of functionality showed.[5, 6] Among the myriad of possible palladium-catalyzed reaction, reductive cyclization of nitro

compound by CO is one of the most interesting due to the general low cost and availability of substituted nitro compound.

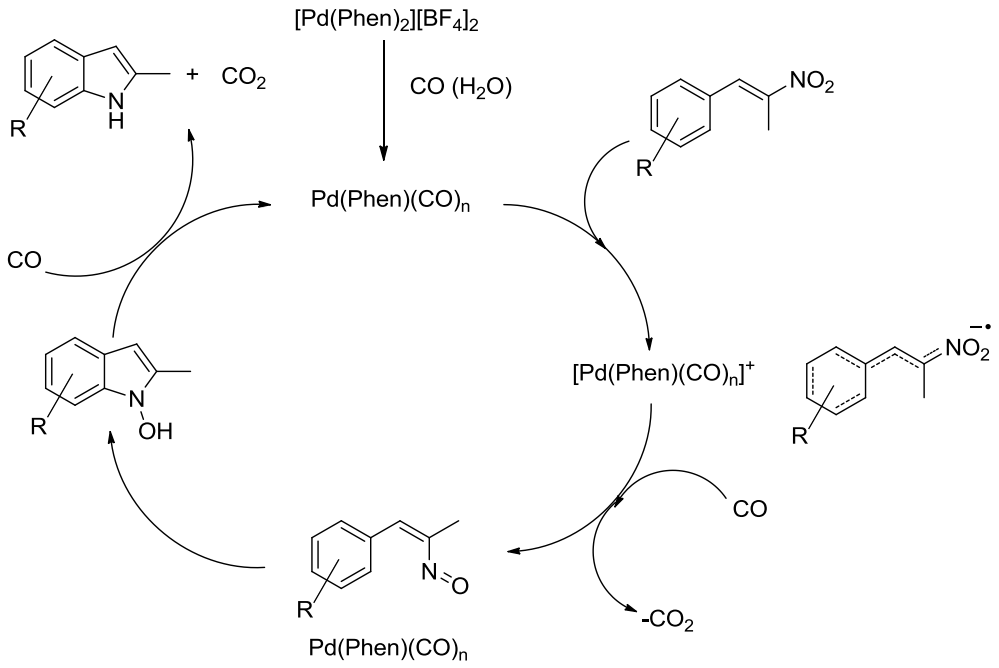
The reductive cyclization of nitrostyrenes have been known from 1965 when Sundberg inspired by a work of Cadogan on triethylphosphite reactivity,[8] developed a reductive cyclization reaction *o*-nitrostyrenes to indoles by trivalent phosphorus.[9] Years later Cenini and coworkers employing the same substrates obtained the catalytic deoxigenation of the nitro group using carbon monoxide and transition metal carbonyls in harsh conditions (220 °C under 80 bar of CO).[10] Milder conditions (100 °C under 20 bar of CO) were found to be possible by Watanabe and coworkers if $PdCl_2(PPh_3)_2/SnCl_2$ was employed.[11] Since then many studies were conducted on reductive cyclization of nitroarenes to indoles by CO both intramolecular (as for *o*-nitrostyrenes) and intermolecular (nitroarenes and olefins or alkynes).[12-14]

Several years ago, while investigating the possibility of using β-nitrostyrenes as aminating agents for olefins, employing a protocol, based on the use of a ruthenium catalyst, previously devised for nitroarenes,[15-17] we found that a cyclization reaction to give indoles occurs (Scheme 2). The strength of this reaction is the possibility of using β-nitrostyrenes as the substrate. In fact, in most cases, they can be easily prepared from an aldehyde and a nitroalkane by the Henry reaction (nitroaldol reaction).



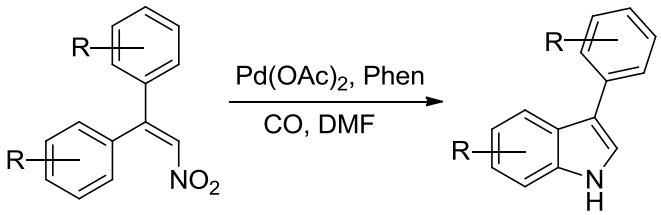
Scheme 2. Palladium and ruthenium catalyzed cyclization of β-methyl-β-nitrostyrene.

The reaction mechanism (Scheme 3), based on both experimental[18] and theoretical[19] studies for nitroarenes cyclization reactions, involves an initial activation of the nitro compound due to a single-electron transfer from the metal to the nitroalkene and following the formation of an intermediate nitrosoalkene, which is proposed to be the aminating species. Rotation of the double bond in the nitro radical anion intermediate explains why good selectivities are obtained even from *trans*-β-nitrostyrenes. Eventually the hydroxy indole, formed by amination, is reduced to indole by carbon monoxide.



Scheme 3. Palladium-catalyzed reductive cyclization of β-methyl-β-nitrostyrenes.

While we were studying this reaction, in 2009, the group of Dong reported the palladium catalyzed reductive cyclization of α-aryl-β-nitrostyrenes to 3-arylindoles under mild reaction conditions (Scheme 4) with very good yields.[20] The substrate used for the reaction optimization was 1,1-diphenyl-2-nitroethene and the best reaction conditions were found to be 110 °C, 2 bar of CO absolute pressure in dimethylformamide (DMF) for 3 h using $Pd(OAc)_2$ as the catalyst and phenanthroline (Phen) as the ligand. The molar ratio of catalyst/Phen/substrate was 1:2:50. In their study, they report the use of these reaction conditions only on diaryl-substituted nitroalkenes, that are non-commercial substrates and more difficult to prepare than β-alkyl-β-nitrostyrenes.



Scheme 4.

Reproducing the reaction conditions reported by Dong and coworkers, we confirmed that they work well for α-aryl-β-nitrostyrenes but they almost completely fail when an alkyl group is present

in β position, whereas the reaction condition optimized in this thesis work are suitable also in this case.

Here we report the details of the optimization of this reaction, using commercial β-methyl-β-nitrostyrene as the substrate. Under the new optimized conditions the reaction scope was extended to other substituted β-nitrostyrenes.

5.2 Results and discussion

5.2.1 Optimization of the catalytic reaction

Preliminary studies, reported in a Ph.D. thesis that was made in our research group,[21] showed that substrate/Phen/catalyst ratio 300:16:1, 60 bar of CO in acetonitrile at 170 °C, for 4 h were good reaction conditions to obtain total conversion and high selectivity in the indole (75%). However a year later we were not able to reproduce them. In this thesis we report a re-optimization of the reaction conditions.

However during this work we checked on the purity of reagents and catalyst and we identified carbon monoxide as the possible source of impurity in the previous optimization work. It is known from the literature and industrial knowledge that CO cylinders can contain $Fe(CO)_5$, as impurity.[22-24] In a previous master thesis we evidenced that the concentration of this impurity was so high that from a catalytic reaction of reductive carbonylation of nitrobenzene employing a similar catalytic system (catalyst = $[Pd(Phen)_2][BF_4]_2$, 60 bar of CO, 10 mL of methanol as solvent and excess phenanthroline as ligand) it was possible to isolate and characterize by X-ray a ferroin complex. The difference between CO purity in preliminary tests and in that reported in this thesis are due to a change in the cylinder material from carbon steel to an aluminium alloy performed by our supplier. Later tests that we will discuss below confirmed our doubt.

Therefore, in this thesis, we performed again an optimization study on the reaction conditions avoiding any contamination from iron sources.

$[Pd(Phen)_2][BF_4]_2$ was chosen as the catalyst for the optimization reactions. This complex showed to be the best choice in the reductive carbonylation of nitroarenes[25-27] and reductive intermolecular cyclization of alkynes and nitroarenes[28, 29] studied in our group due to the non-coordinating nature of BF_4^-. Although the reaction does not require a base to occur, the addition of a base influences positively both the system activity and the selectivity in indole. Triethylamine (TEA) was employed as the base due to its low cost and moderate basicity. In preliminary studies previously performed in the PhD thesis work (Dr. Hagar), the use of a stronger base as DABCO under unoptimized reaction condition was found to be detrimental for the selectivity. Moreover an

initial screening of polar solvents was performed by Dr. Hagar in his PhD thesis and acetonitrile was found to be the solvent of choice, even compared to DMF, usually used in this type of reactions.

We initially set catalyst/Phen/β-methyl-β-nitrostyrene molar ratio to 1:16:100. Some preliminary reactions were carried out both in a 35 mm wide × 100 mm high glass liner and in three 10 mm wide × 40 mm high test tubes used for parallel reactions. The results achieved were much different: the same reaction carried out under 60 bar of CO, at 170 °C for 4 h, employing the bigger liner as reactor led to a lower conversion (51%) than that obtained using the smaller test tubes (85%). Since the reaction produces two CO_2 molecules per molecule of substrate converted (Scheme 3), this behavior is probably due to a different exchange rate of the CO_2 inside the reactor with the CO of the autoclave. The exchange is hindered by the presence of a glass wool-filled screw cap used to avoid excessive solvent evaporation. The buildup of CO_2 in solution could be the cause of the reduced reactivity in the bigger reactor. Since the data collected in the previous PhD thesis were obtained from reaction conducted in 35mm of diameter liner, we decided to use it for the optimization.

The optimization of CO pressure, temperature, reaction time and solvent was performed. Results are reported in Table 1. Initially 60 bar of CO at 170 °C were employed. These parameters were found by us to be the best in the intramolecular reductive cyclization of nitroarenes and alkynes.[28, 29] With these conditions, running the reaction for 4 h, the conversion and the selectivity in 2-methyl-*1H*-indole were low. By decreasing the pressure to 40 bar both the conversion and the selectivity strongly increased (Table 1, Entry 2). A maximum of catalytic activity was reached at 20 bar of CO (Table 1, Entry 3) with complete conversion and good selectivity. A further reduction of pressure to 10 bar was detrimental for the indole selectivity.

Since the solubility of gases into solvents increases when lowering the temperature, we performed some tests at 140 °C to verify if a further reduction of the operating pressure was possible (Table 1, Entry 5-7). While the conversion remained high in all cases, the selectivity slightly decreased even at 20 bar. Additional tests performed employing temperature between 170 °C and 140 °C, showed us that the activity is not much sensitive to temperature lowering and the indole selectivity reaches a maximum at 150 °C (Table 1, Entry 10).

Since in most cases complete conversion was obtained after 4 hours we verified if reaction time could be reduced (Table 1, Entry 11-14). We were able to decrease it to 2.5 hours without affecting the conversion while the selectivity increased up to 88 %. A catalytic test was performed employing DMF as the solvent in the absence of TEA, not necessary due to the basicity of this solvent, but the

activity of the system decreased and the selectivity was very poor because of by-products formation (Table 1, Entry 16).

Table 1. Reductive cyclization of β-methyl-β-nitrostyrene to 2-methyl-*1H*-indole by CO, catalyzed by $[Pd(Phen)_2][BF_4]_2$: reaction condition optimization.

Entry	Et_3N (mL)	Solvent (mL)	T (°C)	P (bar)	Time (h)	conv (%)	sel (%)
1	0,356	CH_3CN (15)	170	60	4	51	15
2	0,356	CH_3CN (15)	170	40	4	97	63
3	0,356	CH_3CN (15)	170	20	4	100	71
4	0,356	CH_3CN (15)	170	10	4	100	56
5	0,356	CH_3CN (15)	140	20	4	100	67
6	0,356	CH_3CN (15)	140	10	4	100	66
7	0,356	CH_3CN (15)	140	5	4	90	56
8	0,356	CH_3CN (15)	160	20	4	100	75
9	0,356	CH_3CN (15)	155	20	4	100	73
10	0,356	CH_3CN (15)	150	20	4	100	75
11	0,356	CH_3CN (15)	150	20	3	100	73
12	0,356	CH_3CN (15)	150	20	2,5	100	88
13	0,356	CH_3CN (15)	150	20	2	96	83
14	0,356	CH_3CN (15)	150	20	1	92	82
15	0,178	CH_3CN (15)	150	20	2,5	90	87
16	0	DMF (15)	150	20	2,5	72	7.7

Experimental conditions: all results $[Pd(Phen)_2][BF_4]_2 = 11.0\times10^{-3}$ mmol; mol ratio Pd/Phen/styrene, 1:16:100.

By summing up the data, the best result were obtained at 150 °C, 20 bar of CO, for 2.5 h in acetonitrile (Table 1, Entry 12).

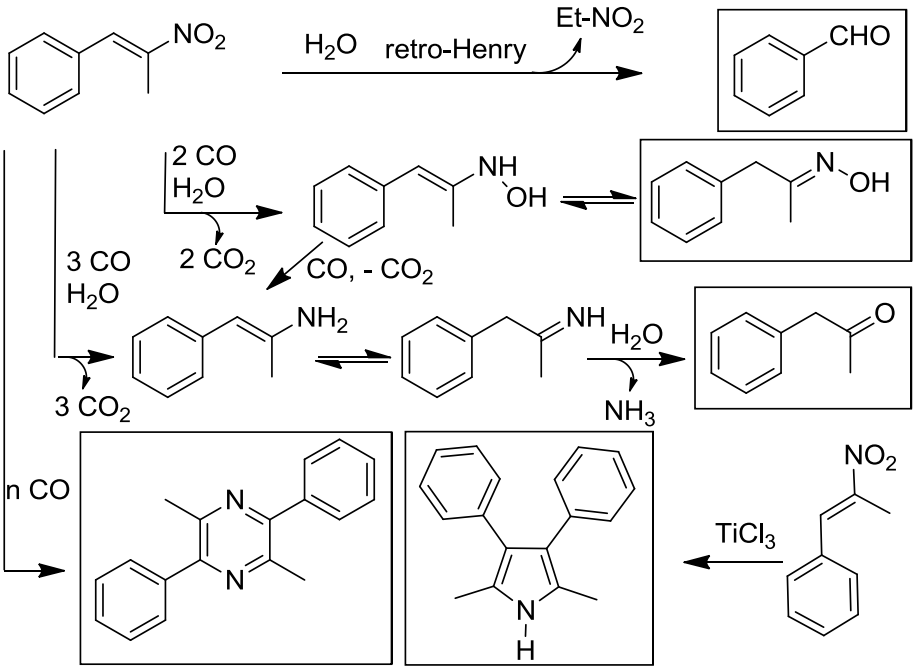
After the optimization of the reaction parameters, the effect of amount of TEA employed was investigated. Both reducing (Table 2, Entry 2-3) and increasing (Table 2, Entry 5) the amount of base from the arbitrary chosen value (0.356 mL) initially used in the optimization result the system lost in activity and selectivity. Moreover, the reduction of the Phen/Pd ratio led to system deactivation and palladium black formation before the substrate was completely converted (Table 2, Entry 6-7). Since the high amount of TEA used could lead to replacement of phenanthroline at the metal center resulting in partial catalyst decomposition, some tests were conducted reducing the ligand and the base amount at the same time (Table 2, Entry 8) but without positive effects. The base seems to give stability to the system, in fact, the increase of TEA at low ligand concentration (Table 2, Entry 11) gave better results than with the optimized amount of base (Table 2, Entry 7).

Table 2. Reductive cyclization of β-methyl-β-nitrostyrene to 2-methyl-1H-indole by CO, catalyzed by $[Pd(Phen)_2][BF_4]_2$: ligand and base concentration optimization.

Entry	Phen/Pd mol ratio	Et_3N/Pd mol ratio (mL)	Time (h)	conv. (%)	sel. (%)
1	16	232 (0.356)	2.5	100	87.8
2	16	116 (0.178)	2.5	90.3	87.4
3	16	58 (0.089)	2.5	89.7	74.6
4	16	232 (0.356)	1	92.0	82.0
5	16	350 (0.537)	1	85.7	59.6
6	8	232 (0.356)	2.5	90.3	79.5
7	4	232 (0.356)	2.5	60.7	42.7
8	4	116 (0.178)	2.5	36.6	12.9
9	8	232 (0.356)	4	99.2	80.2
10	4	232 (0.356)	4	58.7	19.5
11	4	350 (0.537)	2.5	88.8	66.4

Experimental conditions: $[Pd(Phen)_2][BF_4]_2 = 11.0\times10^{-3}$ mmol, mol ratio Pd/styrene = 1 : 100, P_{co} = 20 bar, at 150 °C in CH_3CN (15 mL)

During the optimization study, some by-products were identified by GC-MS analysis, although quantitative determination of their amount was not done. The benzaldehyde comes from a retro-nitroaldol reaction (retro-Henry); 1-phenyl-2-propanone forms from the enamine derived from $-NO_2$ reduction followed by hydrolysis of the tautomeric iminic form; 1-phenyl-2-propanone oxime, obtained by partial reduction of nitro group and oxygen protonation and 2,5-dimethyl-3,6-diphenylpyrazine formed by a coupling reaction of nitrostyrene (Scheme 5). In some of the reactions 2,5-dimethyl-3,4-diphenyl-1*H*-pyrrole was detected in small amount. The formation of this compound was previously reported in the literature to occur when □-nitrostyrenes are reduced with aqueous $TiCl_3$.[30, 31]



Scheme 5. Byproducts formation pathways for the reductive cyclization of β-methyl-β-nitrostyrene

As mentioned above, during the optimization work, Dong and co-workers published a study on the reaction of palladium-catalyzed reductive cyclization of diaryl-substituted nitroalkenes by carbon monoxide and optimized the reaction conditions using 1,1-diphenyl-2-nitroethene as model substrate.[20] $Pd(AcO)_2$ was used as catalyst, the molar ratio of cat/Phen/substrate was 1:2:50 and the reaction was carried in DMF, at 110 °C and 1 bar of CO for 3 h, obtaining excellent yields. Reproducing that reaction conditions we obtained a very similar result (82% of conversion and 92% of indole selectivity instead of 99% yield, Table 3, Entry 1) employing 1,1-diphenyl-2-nitroethene as the substrate. The slightly different result is due to the different nature of reactors employed. While in the system employed by Dong it is possible to feed CO during the reaction, with our autoclaves it was impossible and this could have an effect on the reaction at the low pressure used. However when β-methyl-β-nitrostyrene was employed as the substrate both conversion and selectivity were very poor (Table 3, Entry 3) Since the reaction involves an initial electron transfer from the metal to the alkene with formation of a radical (Scheme 3), we suggest that the difference in reactivity between the two substrates should be searched in the more extended π system in 1,1-diphenyl-2-nitroethene. This favors the radical delocalization and thus the formation and stabilization of nitroso compound. Moreover while in the reaction of *trans*-β-methyl-β-nitrostyrene the formed radical species must isomerize to *cis*-β-methyl-β-nitrosostyrene to cyclize to the indole (Scheme 3), the presence of the second phenyl group removes this necessity. This result in a faster reaction of the nitroso species that is known to be one of the main causes of by-product formation.

To further ensure that $Pd(AcO)_2$ is not the cause of an increased reactivity, it was employed as the precatalyst also in our optimized condition but it did not improve the catalytic performance.

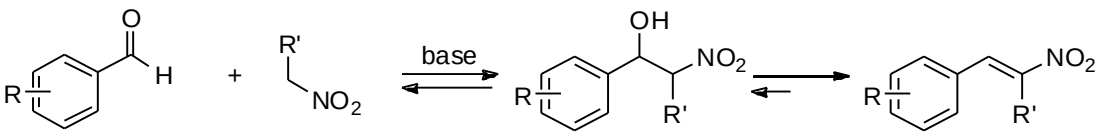
Table 3. Reductive cyclization of β-methyl-β-nitrostyrene and 1,1-diphenyl-2-nitroethene under Dong's and our optimized reactions**.**

Entry	nitrostyrene	cat/Phen/styrene mol ratio	Et_3N (ml)	solvent (ml)	T (°C)	P (bar)	Time (h)	conv (%)	sel (%)
1[a]	1,1-diphenyl-2-nitroethene	1:2:50	-	DMF (5)	110	1	3	81.6	91.6
2[b]	1,1-diphenyl-2-nitroethene	1:16:100	0.356	CH_3CN (15)	150	20	2,5	100	93.0
3[a]	β-methyl-β-nitrostyrene	1:2:50	-	DMF (5)	110	1	3	19.1	36.1
4[b]	β-methyl-β-nitrostyrene	1:16:100	0.356	CH_3CN (15)	150	20	2.5	100	87.8
5[c]	β-methyl-β-nitrostyrene	1:16:100	0.356	CH_3CN (15)	150	20	2.5	100	87.0

Experimental conditions: [a]$Pd(AcO)_2$ = 20.0×10^{-3} mmol; [b]$[Pd(Phen)_2][BF_4]_2$ = 11.0×10^{-3} mmol; [c]$Pd(AcO)_2$ = 11.0×10^{-3} mmol.

5.2.2 Scope of the reaction

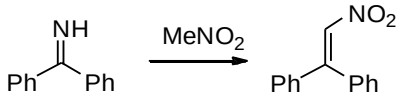
To explore the scope of the reaction, the optimized conditions were applied to some different substituted β-nitrostyrenes. The different substrates were synthesized by the nitro-aldol reaction (Henry reaction) that consists in a base catalyzed coupling reaction between an aldehyde or a ketone, and an alkyl nitrocompound bearing at least one α-hydrogen (Scheme 6).[32, 33] If acidic protons are available, the product tends to eliminate water to give nitroalkenes in particular when the formed double bond is conjugated to an aromatic ring.



Scheme 6

The Henry reaction is a classical name reaction known from more than one century. The extensive studies performed by organic chemists and commercial availability of the relatively low cost starting materials make it a versatile and widespread used reaction. Far from the idea of

exploring the extensive amount of literature on the subject we used one of the most simple and economical set of reaction conditions reported in the literature.[34] The substituted β-methyl-β-nitrostyrenes were synthesized by heating a mixture of the aldehyde and ammonium acetate in neat nitroethane. We obtained from fair to good yields. A different approach was needed for the synthesis of 1,1-diphenyl-2-nitroethene since the condensation of the ketone is more difficult. The strategy consists in the condensation of the commercial benzophenone imine with nitromethane (Scheme 7).[35]

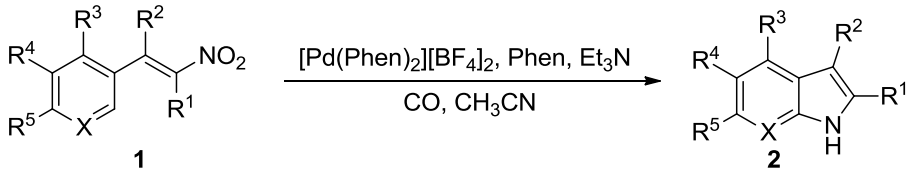


Scheme 7

The synthesiszed β-nitrostyrenes were employed as the substrate in the reductive cyclization reaction affording the corresponding indoles with good selectivities (Table 4).

The best results were obtained for 1,1'-diphenyl-nitroethene (**1i**) cyclization due to the activating effect of the α-aryl group, as mentioned above. For the other substrates, the presence of a methyl group at the β-position was found to be fundamental for the indole formation and its absence gave low reactivity (64.5% conversion in 3h, with palladium black formation) and very low indole selectivity (Table 4, Entry 8). The main byproduct, identified by GC-MS analysis, was diphenylpyrrole.

Table 4. Scope of palladium-catalyzed reductive cyclization of β-nitrostyrenes.



1 **2**

a. X = CH, R^1 = Me, R^{2-4} = H, R^5 = Me

b. X = CH, R^1 = Me, R^2 = H, R^{3-4} = -CH=CH-CH=CH-, R^5 = H

c. X = N, R^1 = Me, R^{2-4} = H, R^5 = H

d. X = CH, R^1 = Me, R^{2-4} = H, R^5 = OMe

e. X = CH, R^1 = Me, R^{2-4} = H, R^5 = Cl

f. X = CH, R^1 = Me, R^{2-3} =H, R^4 = Cl, R^5 = H

g. X = CH, R^1 = Me, R^{2-4} = H, R^5 = Br

h. X = CH, R^1 = H, R^{2-5} = H

i. X = CH, R^1 = H, R^2 = Ph, R^{3-5} = H

l. X = CH, R^1 = Me, R^{2-3} =H, R^4 = H, R^5 = NEt_2

Entry	Substrate	Product	Conv (%)	Sel (%)[a]
1	1a	2a	99.6	77.5
2	1b	2b	99.6	68.7
3	1c	2c	94.8	64.0[b]
4	1d	2d	94.1	68.6
5	1e	2e	100	55.0
6	1f	2f	100	34.6[c]
7	1g	2g	100	43.6
8	1h	2h	64.5	3.6
9	1i	2i	100	92.9
10	1l	2l	15.7	-

Experimental conditions: $[Pd(Phen)_2][BF_4]_2$ = 11.0×10^{-3} mmol, molar ratios Pd/Phen/substrate = 1:16:100, T = 150°C, t = 2h 30', P_{CO} = 20 bar, Et_3N = 0.356 mL. [a]Indole selectivity based on the reacted nitrostyrene [b]The reported selectivity is the sum of the selectivities of the two isomers: 2-methyl-*1H*-pyrrolo[2,3-b]pyridine (51.0%) and 2-methyl-1*H*-pyrrolo[3,2-c] (13.0%), from integration of the ^{1}H NMR signal of the CH of the pyrrole ring, [c]The reported selectivity is the sum of the selectivities of the two isomers: 7-chloro-2-methyl-*1H*-indole (17.8%) and 5-chloro-2-methyl-*1H*-indole (16.8%).

As expected the electron-rich 4-methoxy-β-methyl-β-nitrostyrene showed a reduced reactivity due to a decreased rate of nitro group reduction (Table 4, Entry 4) for the same reason the diethylamino substituted nitrostyrene was almost not reactive (Table 4, Entry 10) and no traces of the product were detected by GC-MS analysis. Also 2-nitro(3-pyridyl)propene (Table 4, Entry 3), showed a reduced reactivity probably due to a partial coordination of the substrate to the metal center. For this substrate the total indole selectivity was 64% with a 80% regioselectivity in 2-methyl-1*H*-pyrrolo[2,3-b]pyridine. On the contrary for 3-chloro-β-methyl-β-nitrostyrene the reaction is almost completely not regioselective and the total indole selectivity is surprisingly low (Table 4, Entry 6). In general slightly lower selectivities were obtained for halogen substituted

substrates. The oxidative addition of the halogen on palladium center is the most probable explanation for this behavior.

5.2.3 Effect of iron compounds

As mentioned above, in some cases the impurities of $Fe(CO)_5$ in the carbon monoxide could affect the reproducibility of the catalytic reaction due to a catalytic activity of the iron itself. Therefore we performed some tests adding $Fe(CO)_5$ in the reaction mixture together with the palladium catalysts (Table 5). The tests were conducted on the reaction of reductive cyclization of β-methyl-β-nitrostyrene under unoptimized conditions. The results showed that the system activity increases with $Fe(CO)_5$ concentration. The main by-product identified was dimethyl-diphenylpyrrole. Note that the pyrrole selectivity is only a very approxymate indication of the real yield and the values reported are only useful to indicate a trend. Indeed, the response factor at the GC was not available. The pyrrole amount was calculated by assuming the same response factor than indole (it should be lower) but the reported amounts were not corrected for the fact that two equivalents of nitrostyrene are necessary to generate one equivalent of pyrrole (so the selectivity should be doubled).

Table 5. Reactions of β-methyl-β-nitrostyrene catalyzed by $[Pd(Phen)_2][BF_4]_2$, in the presence of variable amounts of $Fe(CO)_5$.

Entry	cat/Phen/stirene mol ratio	cat/$Fe(CO)_5$ mol ratio	Et_3N(mL)	Conv (%)	Indole sel. (%)[a]	Pyrrole sel. (%)[b]
1	1:16:100	-	0.07	13.3	26.0	-
2	1:16:100	1:7.8	0.07	71	50	3
3	1:16:100	1:10	0.07	62	49	-
4	1:16:100	1:15	0.07	100	64	1.2
5[c]	-	-	0.07	99.6	40	5.6
6	1:48:300	1:15	0.21	100	27	42

Experimental condition: $[Pd(Phen)_2][BF_4]_2 = 2.3 \times 10^{-3}$ mmol, molar ratios Pd/Phen/substrate = 1:16:100, T = 170°C, t = 4 h, P_{CO} = 60 bar, Et_3N = 0.07 mL, CH_3CN = 10 mL. [a]Indole selectivity based on reacted nitrostyrene [b]Pyrrole selectivity was calculated by comparison with chromatographic area of the indole signal. [c]No Pd catalyst was added, $Fe(CO)_5 = 3.4\times10^{-2}$ mmol. Phen and substrate concentrations were unvaried with respect to the general experimental conditions.

In the absence of the catalyst, the reaction with $Fe(CO)_5$ gave almost complete conversion, but a lower selectivity was obtained, because of pyrrole formation (Table 5, Entry 5), identified as the main by-product also for the not substituted β-nitrostyrene (Table 4, Entry 8). Increasing three fold

the concentration of triethylamine, substrate and ligand the amount of pyrrole increased, becoming the main product (Table 4, Enty 6).

The effect of iron compounds on the catalytic reaction is very interesting and it will be further investigated in the future.

5.3 Conclusions

A synthetic route to substituted indoles has been reinvestigated. The new optimization performed on β-methyl-β-nitrostyrene as the model substrate allowed an improvement of 13 % in indole selectivity obtained at a lower temperature, reaction time and pressure. The superiority of the found reaction conditions with respect to that previously reported in the literature[20] have been demonstrated by the extension of the scope of the reaction to α-alkyl substituted substrates. Moreover the identification of a strong effect of iron compounds on the catalytic reaction unravel the inconsistencies of the obtained data with the optimization previously performed in our laboratories.

5.4 Experimental section

5.4.1 General procedures.

Unless otherwise stated, all reactions were conducted under a dinitrogen atmosphere. Acetonitrile and DMF, used in catalytic reactions, were dried by distillation over CaH_2 and stored under a dinitrogen atmosphere. All other solvents were used as purchased. All glassware and magnetic stirring bars were kept in an oven at 125 °C for at least two hours and let to cool under vacuum before use. β-methyl-β-nitrostyrene and β-nitrostyrene were purchased from Sigma-Aldrich. 1,10-phenanthroline (Phen), purchased as hydrate, was dried over Na_2SO_4 after dissolution in CH_2Cl_2 followed by filtration under dinitrogen atmosphere and evaporation in vacuo. Then it was stored under dinitrogen. Phenanthroline can be weighed in the air without problems, but must be stored in an inert atmosphere to avoid water uptake. $[Pd(Phen)_2][BF_4]_2$, was synthesized following the procedure reported in the literature.[36]

^1H NMR spectra were recorded on a Bruker AC 300 FT or on an Avance Bruker DPX 300, operating at 300 MHz. Mass spectra were obtained by GC mass spectrometry (Shimadzu GC - 17A / QP5050, equipped with SUPELCO SLB^{TM}-5ms capillary column). Quantitative analyses of catalytic reactions were performed using fast gas chromatography (Shimadzu GC – 2010, equipped with SUPELCO EQUITY^{TM}-5ms capillary column).

5.4.2 Catalytic reactions.

General procedures. For a typical catalytic reaction, the catalyst, the ligand and nitrostyrene were weighed in the air in a glass liner and then placed inside a Schlenk tube with a wide mouth under a dinitrogen atmosphere. The solvent and triethylamine were added by volume and the liner was closed with a screw cap having a glass wool-filled open mouth which allows gaseous reagents to exchange. The Schlenk tube was immersed in liquid nitrogen until the solvent froze and evacuated and filled with dinitrogen for three times. The liner was rapidly transferred to a 200 mL stainless steel autoclave equipped with magnetic stirring. The autoclave was then evacuated and filled with dinitrogen three times, CO was charged at room temperature at required pressure and the autoclave was immersed in an preheated oil bath. The experimental conditions are reported in the captions to the table in the text. At the end of the reaction the autoclave was quickly cooled with an ice bath, and vented. Some of the reactions were performed in parallel in three 10 mm wide × 40 mm high test tubes were employed instead of the glass liner, each having a miniature glass wool-filled screw cap similar to the one of the larger liner. The three test tubes were located in the holes of an aluminum block designed to fit the autoclave. Other operations were analogous to the ones described above except that stock solutions of the catalyst, phenanthroline and triethylamine in acetonitrile (or DMF) were prepared and added by volume to avoid the errors in weighing very small amounts of materials. Moreover, the Schlenk tube was not frozen during the addition of reactant to the test tubes, to avoid excessive water condensation on the aluminum support, and the autoclave was then purged from air, charging and discharging it with CO (20 bar) one time before performing the reaction.

General analysis method of catalytic reactions. Quantitative analyses of reaction mixtures were carried out by fast gas chromatography using naphthalene as internal standard (1/4 by weight with respect to the initial nitrostyrene). For the indoles that are not commercially available, after GC analysis, the solvent was evaporated in vacuo and an appropriate internal standard was added (2,4-dinitrotoluene or anisole) in 1:1 molar ratio with respect to the initial nitrostyrene. The residue was dissolved in anhydrous $CDCl_3$ and analyzed by ^1H NMR using a relaxation delay of 10 seconds. The references for ^1H NMR signals related to CH_3 groups of indoles used to calculate the selectivities, are reported in Appendix (Table A5.1).

For compound **1c** two regioisomer were obtained (2-methyl-*1H*-pyrrolo[2,3-*b*]pyridine and 2-methyl-*1H*-pyrrolo[2,3-*b*]pyridine). Due to the high concentration of the products in the solution analyzed by NMR, the characteristic peaks of the indole (-CH_3 and -CH of the pyrrole ring) were

shifted downfield of 0.1 ppm and it was not easy to distinguish between the two regioisomer only by $–CH_3$ chemical shift. Since the difference in the chemical shifts of the two regioisomers was more marked for the $–CH_{pyrrole}$ signals, these were integrated for more reliable quantification instead of CH_3.

5.4.3 Synthesis of β-nitrostyrenes.

General procedure. The general procedure was adapted from a procedure reported in the literature.[34] In a Schlenk flask equipped with a bubble condenser, aryl aldehyde and ammonium acetate were dissolved in nitroethane. The mixture was stirred at reflux for 4-25 hours and the conversion of the aldehyde checked by TLC on silica. The solvent was evaporated and the residue was taken up with methylene chloride (15 mL) and washed with HCl 3 M (3 x 15 mL) and then with water (2 x 10 mL). The organic layer was dried with Na_2SO_4, filtered and evaporated in vacuo.

4-methyl- β-methyl-β-nitrostyrene (1a). Yellow needles (crystallized from hexane, 32 % yield). ^{1}H NMR (400 MHz, $CDCl_3$, 400 K): δ = 8.11 (s, 1H, CH alkenyl), 7.35 (d, j = 8.1, 1H, H2, H3), 7.27 (d, J = 8, 1H, H1,H4), 2.49 (s, 3H, CH_3) 2.44 (s, 3H, CH_3) ppm. GC-MS m/z = 177 (M^+), 160, 149, 129, 115, 91, 77, 51, 40

1-(2-nitroprop-1-en-1-yl)naphthalene (1b). Yellow solid (crystallized from EtOH, 33 % yield). ^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ = 8.62 (s, 1H, CH alkenyl), 7.91 (m, 4H, H7, H8, H9, H10), 7.52 (m, 4H, H4, H5, H6), 2.46 (d, 3H, J = 1.0 Hz, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 300 K): δ = 149.7 (C1) 133.89 (C3), 122.32 (C2), 131.86 (C6a), 130.60 (C7), 130.13 (10a), 129.20 (C6), 127.58 (C5), 127.53 (C9), 127.05 (C8), 125.57 (C10), 124.57 (C4), 14.58 (CH_3) ppm. GC-MS m/z = 213 (M^+), 198, 167,127, 91, 77, 51, 40

3-(2-nitroprop-1-en-1-yl)piridine (1c). Ocher solid (purified by flash chromatography on silica gel CH_2Cl_2 / Hexane = 1:9, 7 % yield). ^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ =8.69 (s, 1H, CH), 8.65 (d, J = 3.8 Hz, 1H, H2), 8.04 (s, 1H, CH), 7.75 (J=8.0 Hz, 1H, H4), 7.40 (dd, J = 4.49 Hz, J = 4.7 Hz, H3), 2.45 (s, 3H, CH_3) ppm. GC-MS m/z = 164 (M^+),147, 117, 91, 77, 51, 40

4-methoxy-β-methyl-β-nitrostyrenes (1d). Yellow solid (crystallized from diisopropyl ether, 27 % yield). ^{1}H NMR (300 MHz, $CDCl_3$, 300 K): δ = 8.07 (s, 1H, CH alkenyl), 7.43 (d, J = 8.9 Hz,

2H,H1, H4), 6.98 (d, J = 10.7 Hz, 2H,H2, H3), 3.86 (s, 3H), 2.47 (s, 3H) ppm. GC-MS m/z = 193 (M^+), 177, 161, 146, 131, 103, 91, 77, 51, 40

4-chloro-β-methyl-β-nitrostyrene (1e). Yellow solid (crystallized from EtOH, 51 % yield). ^{1}H NMR (300 MHz, $CDCl_3$, 400 K): δ = 8.02 (s, 1H, CH alkenyl), 7.45 (d, J = 8.6 Hz, 2H, H1, H4), 7.36 (d, J = 8.6 Hz, 2H, H2,H3), 2.43 (s, 3H, CH_3).ppm. GC-MS m/z = 197 (M^+), 180, 150, 125, 115, 91, 89, 77, 51, 40

3-chloro-β-methyl-β-nitrostyrene (1f). Yellow oil (purified by flashchromatography on silica gel CH_2Cl_2 / Hexane = 7:3, 29 % yield). ^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ = 7.97 (s, 1H, CH alkenyl), 7.38 (d, J = 3.2 Hz, 1H, H4), 7.27-7.31 (m, 3H, H1, H2, H3), 2.41 (s, 3H, CH_3) ppm. GC-MS m/z = 197 (M^+), 180, 150, 125, 115, 91, 89, 77, 51, 40

4-bromo-β-methyl-β-nitrostyrene (1g). Yellow solid (crystallized from EtOH, 43 % yield). ^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ = 8.01 (s, 1H, CH alkenyl), 7.60 (d, J = 8.5 Hz, 1H, H1,H4), 7.30 (d, J = 8.4 Hz, 1H, H2,H3), 2.43 (s, 3H, CH_3) ppm. GC-MS m/z = 242 (M^+), 194, 162, 132, 91, 77, 51, 40

Synthesis of 1,1-diphenyl-2-nitroethene (1i). The synthesis was performed following the procedure reported in the literature.[35] In a Schlenk flask equipped with a bubble condenser, benzophenone imine (1.0 mL, 6.0 mmol) was dissolved in nitromethane (3.0 mL, 55.5 mmol) and the solution was stirred at reflux for 43 h. The yellow mixture was allowed to cool at room temperature and nitromethane was evaporated in vacuo yielding a yellow solid. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2 / Hexane = 6:4) obtaining 0.95 g of a yellow solid (4.20 mmol, 70 %).^{1}H NMR (400 MHz, $CDCl_3$, 300 K): δ = 7.48-7.37 (m, 7H), 7.30-7.21 (m, 4H) ppm. GC-MS m/z = 225 (M^+), 193, 178, 165, 152, 142, 91, 77, 51, 40

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Chapter 6

Synthesis and characterization of Ar-BIAN based polyimine ligands

6.1 Introduction

Ar-BIANs (Ar-BIAN = bis(aryl)acenaphthenequinonediimine) constitute a class of nitrogen compounds that have been extensively used in the last two decades as ligands in the formation of complexes with transition metals employed in different branches of chemical research. In particular those with palladium, ruthenium and nickel found application in various different homogeneously catalyzed reactions. In particular, in our group, they were used in organic transformations involving the reduction of nitroarenes by carbon monoxide. The most important among these are allylic amination of olefines by nitroarenes,[1-3] selective reduction of the nitro group by CO/H_2O systems,[4-6] the synthesis of pyrroles and oxazines from dienes, nitroarenes and CO[7] and the synthesis of other heterocycles from functionalized *o*-nitroarenes.[8] Compared with other α-diimine, Ar-BIAN ligands show a high rigidity, given by an *s-cis* diimine unit, coupled with the extensive π-system of the acenaphthene skeleton. These characteristics favor the chelation to a metal center and impart a high chemical stability with respect to hydrolysis and rupture of the central C–C bond. The latter is a common problem with most diimine and prevents their use as ligands for many catalytic systems when long catalyst life times are a requisite.

The stability of the Ar-BIAN ligands makes them very interesting candidates for heterogenization of homogeneous catalytic systems. In this thesis we explored the possibility of synthesizing a functional chelating polyimine based on the condensation of an aromatic diamine and acenaphthenequinone. This kind of macromolecules is interesting mainly for two reasons: 1) their expected partial or total insolubility in common reaction solvents used for nitroarenes reduction and allylic amination reaction and thus the possibility of catalyst recovery without the need of an external polymeric or inorganic support; 2) the presence of close coordination sites that allow the preparation of bi- or multi- nuclear catalysts that are very active in some cases.[9]

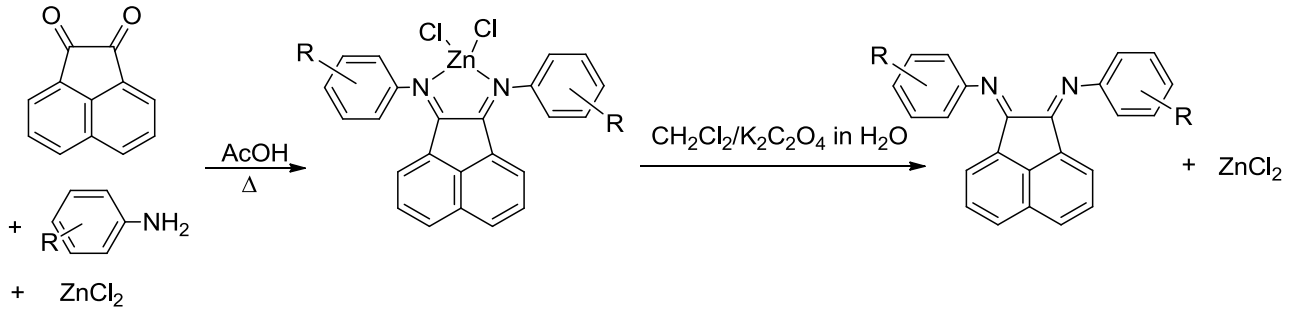
6.2 Results and discussion

6.2.1 Synthesis of polyimine

Only two examples of polyimine based on the Ar-BIAN subunit have been reported in the literature. However one of them is a patent in which no characterization of the obtained compounds is reported, [10] thus there is no evidence of its polymeric nature and the second, published more recently, reports a synthesis of an hexamer based on the use of $TiCl_4$.[11] The procedure was adapted from a previous paper which report the use of $TiCl_4$ in the synthesis of non-chelating polyimines from anthraquinone.[12] It consists on the reaction of *p*-phenylenediamine and acenaphthenequinone, in the presence of DABCO (1,4-diazabicyclo[2.2.2]octane). The condensing agent used in that reaction is $TiCl_4$, added to a toluene solution of the reagents at 90 °C. However the cited paper lacks of a good characterization of the product (the obtainment of an examer is claimed on the basis of a single molecular ion of 1 % of relative intensity), no mention of other oligomeric species and the titanium ligated species is done. Moreover the procedure is a bit troublesome since $TiCl_4$ is highly reactive even when added to the reaction mixture at room temperature. Thus we decided to employ different synthetic strategies

Among the possible aromatic diamine, 4,4'-methylenedianiline (MDA) was chosen due to its commercial availability, low cost and relatively high flexibility.

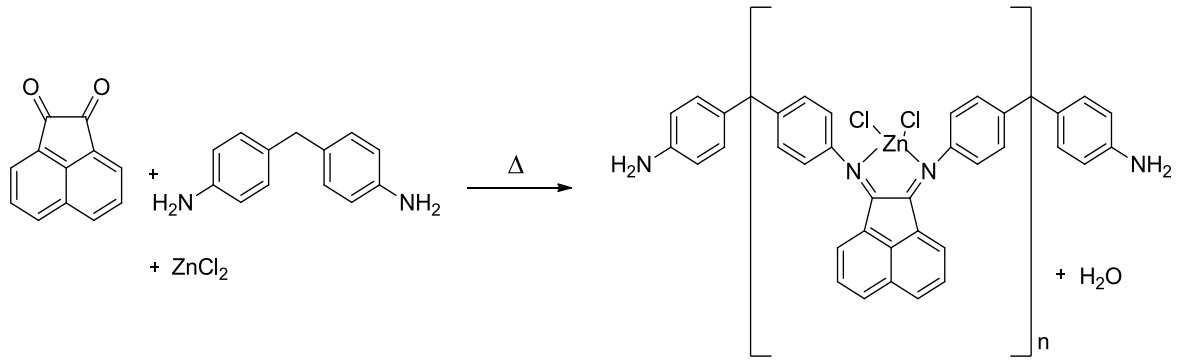
The synthetic method previously optimized in our laboratories for the synthesis of Ar-BIAN consists in the use of $ZnCl_2$ as condensing agent in refluxing acetic acid.[13] The so formed complex precipitates shifting the condensation equilibrium towards the products. Decomplexation with potassium oxalate affords the free ligand (Scheme 1).



Scheme 1

At first this synthetic strategy was employed for the synthesis of the polyimine (Scheme 2). However acetic acid was not suitable as the solvent for the synthesis of the polymeric ligand since the product precipitated before a polymerization occurred, thus we tested different solvents with higher solvating power towards the polymeric metallorganic complex. Ethylene glycol was tested

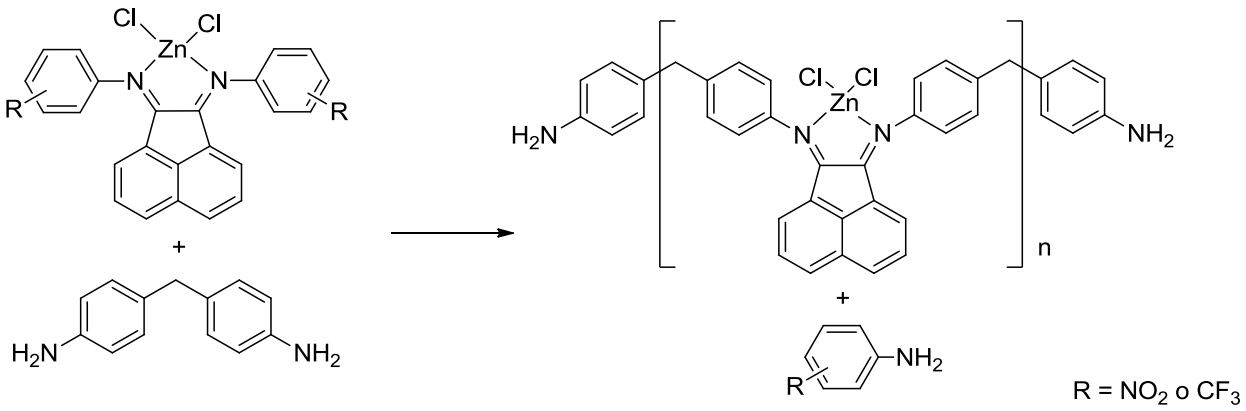
either neat, in mixture 4:1 with *m*-cresol, used as solvent in some polyimine synthesis,[14] or in biphasic systems with 1,2-dichlorobenzene. The presence of a protic aliphatic solvent is always needed to solubilize $ZnCl_2$ while the addition of an aromatic co-solvent was done to increase the solubility of the formed oligomers. Surprisingly the biphasic systems gave the best results and an insoluble red matter was isolated from the reaction mixture. Decomplexation of the obtained polymer from $ZnCl_2$ was not obvious due to the insolubility of the product. Removal of the coordinated zinc chloride was obtained by refluxing the product in acetonitrile in the presence of $K_2C_2O_4$, however there we do not have any evidence that the decomplexation occurred in an exhaustive way. ESI-MS analysis of the product evidenced that the prevalent species was a tetramer but extensive decomposition of the product mixture had occurred.



Scheme 2

A second synthetic strategy was based on the transimination reaction that is the exchange of substituents between an imine and an amine.

The reaction was performed between an Ar-BIAN having electron-withdrawing substituents on the aryl rings and MDA (Scheme 2). As previously reported by our group the reaction was at first conducted in MeOH at room temperature but it was possible to obtain only mixtures in which monomers and dimers were the major species, in addition some non identified species were present. The raise of the temperature above 100 °C coupled with the use of an high boiling point solvent as ethylene glycol, 1,2-dichlorobenzene or a mixture of them resulted in an enhancement of the amount of byproduct while not improving the polymerization degree .



Scheme 3

The main problem encountered with both the employed strategies was the partial decomposition of the product/reagents mixture at high temperature maintained for long reaction times. On the other hand short reaction times resulted in a very low polymerization degrees and the preferential complexation of MDA instead of the condensation product with $ZnCl_2$.

Given the difficulties encountered in the use of a metal as the promoter of the condensation, we shifted our attention towards synthetic methods in which the use of a metal species was not required. At first we tried to apply the "classical" synthesis of imines by acid promoted condensation of a ketone and an amine using a Dean-Stark trap to continuously remove the water formed from the condensation. The reaction solvent was toluene and the acidic promoter *p*-toluenesulfonic acid. The method was successful when employed for the synthesis of *p*-tolyl-BIAN, however, when applied to the polymers synthesis, the reaction times had to be prolonged in order to obtain the chain growth. The ESI-MS analysis of the product showed a low degree of polymerization, with the trimer as the predominant species; however in the spectrum were present also other very intense signals related to byproducts formation. In a recent paper,[15] the reaction of acenaphthenequinone and arenes is reported to occur in superacids at room temperature,[15] however it is not improbable that those kind of reaction could occur to a certain extent also with acids with lower pKa when the temperature is raised as in this case.

Due to the easy formation of byproducts at high temperature we decided to perform the condensation at room temperature. The reaction between MDA and acenaphthenequinone was thus carried on in dry methanol using concentrated H_2SO_4 as a promoter. A similar synthetic method was previously employed for the preparation of Ar-DAB (DAB = diazabuta-1,3-diene)[16] but we are not aware of its use in the synthesis of Ar-BIAN, in which the double condensation is much more difficult.

To avoid monomer formations an amine/quinone ratio of 1.2 was used. The reaction times were long and the proceeding of the reaction was checked by thin-layer chromatography. After a few

minutes the mono-base initiated to form, and after 24 h the main product was the monomer species. However only after 48 h the mono-imine and acenaphthenequinone were completely consumed. After four days the main product was composed by oligomeric species that are not eluted in TLC, however the monomer was still present and it was not completely consumed also by further prolonging the reaction times. The obtained mixture was then treated with triethylamine to neutralize the acid and then the mixture of oligomers and monomer was washed with hot CH_2Cl_2 to remove most of the low molecular weight species. An ESI-MS of the mother liquor evidenced that the most soluble species in CH_2Cl_2 are those in which both termination are $–NH_2$ groups and in particular the most abundant was the monomer, m/z (M+1) = 543.4.

6.2.2. Characterization of oligomeric species

A first rough analysis of the product was performed employing IR spectroscopy in Nujol mull. The presence of a weaker bands at 1729 cm^{-1} (C=O stretching) and two very weak broad bands over 3300 cm^{-1} (-NH_2 stretching) with respect to the bands at 1657, 1625 and 1591 attributed to C=N and C=C stretching indicates the prevalence of polymerization products over the ketonic and aminic termination.

The product was insoluble in most common solvent used for NMR and mass analysis. However we found that by dissolving it in nitrobenzene and then diluting the so obtained solution with acetonitrile it was possible to perform an ESI-MS analysis. This technique was suitable for our purpose in particular because electron-spray ionization sources do not induce a high fragmentation degree on the molecules, thus permitting us to distinguish among the various oligomeric species present in the product mixture and their relative amounts. The relative abundance in a mass analysis is not a good quantitative measure of the real abundance of a certain species, since it depends also on the tendency of the molecule to be ionized. However, it is at least an index of the dispersity of the oligomers.

The most intense peak was found at m/z (M+1) = 1231.6 corresponding to the molecular mass of the trimer with two aminic termination. Very intense are also the peaks at m/z (M+1) = 1051.5 and 1395.5 attributed respectively to the trimer and tetramer with one ketonic and one aminic terminations. Peaks with minor intensities are detected also for tetramer with two terminal -NH_2 and for pentamer with both -NH_2/-NH_2 and -NH_2/=O termination. Moving to higher molecular weight, the presence of peaks related to double charge molecular ions increase. Thus also these peaks have to be taken into account doing a balance of the predominant species in the mixture. Among these, the peak at m/z (M+2) = 788.7, corresponding to the tetramer with two aminic terminatinos, was the most intense with a relative abundance only half of that of the trimer. The species with the highest

molecular weight that was detected was a hexamer. The main molecular peaks are reported in Table 1 and the complete spectrum in Appendix (Figure A6.2). Summing up the relative intensities of the molecular ions and the double charged ions, results that the predominant species is a tetramer =O/-NH_2 terminated, however if the termination of the oligomer is not taken into account, the product could be described as a mixture in which trimers and tetramers are the most abundant species in a ratio close to 1:1.

Although the polymerization degree of the product is not high, its insolubility in the solvents usually employed for the reaction mentioned in the introduction make it suitable for our aim of homogeneous catalyst heterogenization.

Table 1. Molecular peaks and their assignment of ESI-MS analysis of the oligomeric polyBIAN species.

Assignment	**m/z:**	**m/z ($M+H^+$):**	**m/z ($M+2H^{2+}$):**	**Relative intensity**
Dimer (2 x =O)	526.48			9.1
Monomer (2 x NH2)		543.40		26.5
Trimer (2 x NH2)			616.46	24.5
Ciclic dimer		689.49		26.3
Tetramer (=O/NH2)			699.21	26.7
Dimer (=O/NH2)		707.45		27.2
Tetramer (2 x NH2)			788.79	51.9
Trimer (2 x =O)		871.31		31.4
Dimer (2 x NH2)		887.41		71.2
Pentamer (2 x NH2)			961.14	15.2
Hexamer (2 x NH2)			1042.80	16.9
Trimer (=O/NH2)		1051.45		83.4
Tetramer (2 x =O)		1215.50		29.9
Trimer (2 x NH2)		1231.58		100.0
Tetramer (=O/NH2)		1395.51		95.2
Pentamer (2 x =O)	1559.57			22.3
Tetramer (2 x NH2)		1575.93		16.1
Pentamer (=O/NH2)		1739.36		25.5
Pentamer (2 x NH2)		1920.64		13.6

6.3 Conclusions

In spite of the illusory ease of the synthesis of polyimine, the condensation of a ketone and an amine is not obvious. Some condensing agents can be used in some cases (as $TiCl_4$ or $ZnCl_2$) but the removal of the employed metal is not always easy when a chelating polyimine is the target product. In this thesis an easy method for the synthesis of oligomeric Ar-BIAN has been developed and the oligomeric product was characterized. The product shows interesting properties for the future development of heterogenized homogeneous catalytic systems. Moreover the presence of terminal aminic moiety allow the possibility of further expansion of the polymeric structure using opportune cross-linking molecules.

6.4 Experimental section

General procedures. Where not specified solvents and reagent were employed as purchased from Sigma-Aldrich or Alfa-Aesar. Methanol was dried over $Mg(OCH_3)_2$. CH_2Cl_2 and triethylamine were dried over CaH_2. Acenaphthenequinone was purified by recrystallization from toluene and MDA from ethanol. Nitrobenzene was purified by drying with Na_2SO_4 followed by distillation under reduced pressure. IR spectra were recordered on a Varian Scimitar FTS-1000 spectrophotometer. Mass spectra were recorded on an ESI- MS Thermo Finnigan LCQ Advantage and the samples were dissolved in nitrobenzene and diluted with acetonitrile (HPLC grade solvents - CHROMASOLV®).

Oligomer synthesis. Acenaphthenequinone (0.507 g, 2.78 mmol) and 4,4'-methylenedianiline (0.695 g, 3.5 mmol) were placed in a Schlenk flask under a dinitrogen atmosphere. Methanol (50 mL) was added and the mixture stirred at room temperature for one hour. The color of the suspended solid did not change during this time suggesting that no reaction take place without acid addition. 96 wt. % H_2SO_4 (50 μL, 0.94 mmol) was added while stirring. After 15 minutes the color of the mixture begins to change from yellow to orange. The reaction was stirred at room temperature (25 °C) for four days after which the solid was filtered on a Buchner funnel. The filter cake was dried in vacuum and suspended in anhydrous CH_2Cl_2 under a dinitrogen atmosphere. Et_3N (5 mL, 36 mmol) was added and the mixture stirred for 2 h (the anhydrous environment during neutralization of the acid was maintained in order to avoid hydrolysis of the oligomers). The organic phase containing the polymer suspension was then washed with water (2 × 50 mL) and then the solvent evaporated affording 1.08 g of crude orange product.

The solid was then refluxed in CH_2Cl_2 for 1h 30' affording 0.36 g of an insoluble mixture of oligomers as a red solid.

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APPENDICES

Tables containing all catalytic reaction data, NMR spectra for the new compounds, IR and NMR spectra of palladium complexes and IR and MS spectra of polymeric Ar-BIAN are reported in the appendices below.

Appendix to Chapter 2

Note to all tables.

As mentioned in the text, during the reaction diphenylurea is intermediately accumulated, which cannot be detected by gas-chromatography and is later alcoholyzed yielding methyl henylcarbamate and aniline. The latter re-enter the catalytic cycle. Short reactions times were always employed in order to avoid approaching complete conversion as this would not allow comparing catalytic activities. However, under these conditions a relatively large amount of diphenylurea accumulates, which accounts for most of the missing mass balance in the tables. In the tables some abbreviation for the product of the reaction are reported: methyl *N*-phenylcarbamate (MPC), azobenzene (azo), azoxybenzene (azoxy) and methyl *N*-(*p*-methoxy)phenylcarbamate (*p*-MeO-MPC).

Table A2.1. Nitrobenzene carbonylation reactions catalyzed by [Pd(Phen)2][BF4]2, in the presence of variable amounts of differently substituted phenanthrolines.[a]

Entry	Ligand	L/Pd mol ratio	$PhNO_2$ conv.[%][b]	$PhNH_2$ conv.[%][c]	MPC sel.[%][d]	Azo sel.[%][d]	Azoxy sel.[%][d]	*p*-MeO-MPC sel.[%][d]	TOF [h^{-1}][e]
1	Phen	35	30.6	56.4	57.0	0.5	3.9	3.6	3091
2	Phen	75	46.3	32.4	75.9	0.5	4.5	3.6	4680
3	Phen	150	47.6	30.2	74.9	0.4	2.9	2.9	4803
4	Phen	300	43.8	41.0	71.1	0.4	3.7	2.9	4419
5	Phen	500	35.8	39.8	73.7	0.5	5.6	3.6	3620
6	4-MeOPhen	15	8.5	57.7	24.3	<0,1	3.7	0.0	857
7	4-MeOPhen	35	34.7	41.1	68.7	<0,1	5.6	3.6	3502
8	4-MeOPhen	75	50.6	30.1	72.4	0.5	4.0	2.8	5111
9	4-MeOPhen	155	54.8	(0,7)[g]	70.2	0.7	6.7	3.2	5575
10	4-MeOPhen	225	56.1	(0,4)[g]	71.1	0.7	5.8	3.3	5710
11	4-MeOPhen	500	49.8	56.4	82.2	0.8	7.4	2.0	5025
12	4-C_5H_{10}NPhen	15	11.0	79.1	7.4	0.5	3.1	0.4	1122
13	4-C_5H_{10}NPhen	39	13.4	65.1	26.3	0.7	6.3	2.1	1362
14	4-C_5H_{10}NPhen	75	21.3	71.5	55.8	0.8	8.9	3.1	2163

15	4-C_5H_{10}NPhen	150	47.8	50.0	60.9	0.7	8.7	2.7	4857
16	4-C_5H_{10}NPhen	224	52.7	31.8	66.7	0.8	9.3	2.9	5363
17	4-C_5H_{10}NPhen	500	46.2	41.6	65.2	0.8	12.8	2.2	4694
18	4-C_6H_5NHPhen	35	10.8	69.0	9.9	> 0.1	> 0.1	> 0.1	1098
19	4-C_6H_5NHPhen	75	13.9	53.0	53.2	0.8	9.8	3.3	1412
20	4-C_6H_5NHPhen	151	37.6	33.7	66.6	0.8	9.8	2.6	3824
21	4-C_6H_5NHPhen	250	50.2	7.5	83.0	0.8	10.1	2.3	5110
22	4-C_6H_5NHPhen	496	56.5	10.9	70.7	0.9	12.1	1.8	5746
23	4-C_6H_5NHPhen	600	48.7	36.0	66.6	0.8	13.7	1.3	4956
24	3,4-DMPhen	75	30.5	9.5	75.6	0.6	6.2	2.9	3106
25	3,4-DMPhen	150	36.3	0.2	82.8	0.6	6.9	2.8	3695
26	3,4-DMPhen	300	39.3	(1.0)	81.1	0.7	8.2	2.7	3995
27	3,4-DMPhen	500	34.3	5.7	72.4	0.6	7.4	3.4	3489
28	3,4,7,9-TMPhen	15	22.4	33.9	65.4	0.8	5.6		2281
29	3,4,7,9-TMPhen	35	42.5	14.4	66.8	0.7	4.6		4323
30	3,4,7,9-TMPhen	75	43.0	(1,2)[a]	74.6	0.7	5.5		4373
31	3,4,7,9-TMPhen	150	46.7	5.1	69.5	0.7	6.8		4749
32	3,4,7,9-TMPhen	215	48.4	(0,7)[a]	70.8	0.7	7.2		4923
33	3,4,7,9-TMPhen	500	49.3	0.2	65.1	0.9	10.1		5010
34	DPPZ	75	24.2	80.6	20.0	> 0.1	1.4	> 0.1	2458
45	DPPZ	150	26.5	63.9	34.7	> 0.2	2.0	0.5	2694
36	DPPZ	300	49.7	75.4	24.5	> 0.3	1.2	0.6	5052
37	DPPZ	500	26.0	63.3	57.1	0.4	3.8	1.7	2640
38	DPPZ	600	22.5	64.2	50.7	0.5	4.3	1.8	2293
39	PIPhen	10	24.2	69.0	25.7	> 0.1	2.2	> 0.1	2465
40	PIPhen	150	23.3	65.2	49.0	0.6	4.8	0.9	2375
41	PIPhen	300	27.2	70.5	36.8	0.6	5.3	1.1	2769
42	2-MePhen	50	1.7	31.6	< 0.1	< 0.1	< 0.1	< 0.1	170
43	2-MePhen	150	3.5	11.8	< 0.1	< 0.1	< 0.1	< 0.1	351
44	2-MePhen	225	5.7	7.7	< 0.1	< 0.1	< 0.1	< 0.1	571
45	2-MePhen	300	3.6	≈ 100[f]	< 0.1	< 0.1	< 0.1	< 0.1	361
46	2-MePhen	400	1.1	26.9	< 0.1	< 0.1	< 0.1	< 0.1	110
47	2-MePhen	600	0	15	< 0.1	< 0.1	< 0.1	< 0.1	0
48	2,9-Me_2Phen	150	0	34	< 0.1	< 0.1	< 0.1	< 0.1	0
49	2,9-Me_2Phen	300	0	12	< 0.1	< 0.1	< 0.1	< 0.1	0
50	2,9-Me_2Phen	500	0	6	< 0.1	< 0.1	< 0.1	< 0.1	0
51	2-MeOPhen	75	5.9	60.3	<0.1	<0.1	<0.1	<0.1	597
52	2-MeOPhen	150	4.3	57.4	8.6	<0.1	<0.1	<0.1	437
53	2-MeOPhen	300	4.7	58.2	10.1	<0.1	<0.1	<0.1	480
54	2,9-$(MeO)_2$Phen	75	3.4	67.8	7.2	<0.1	<0.1	<0.1	397
55	2,9-$(MeO)_2$Phen	150	2	74.3	5.6	<0.1	<0.1	<0.1	199

56	2,9-$(MeO)_2$Phen	200	2	19.4	7.6	<0.1	<0.1	<0.1	318
57	DMEGqu	10	6.7	≈ 100 [f]	<0.1	<0.1	<0.1	<0.1	670
58	DMEGqu	35	0.5	59.6	<0.1	<0.1	<0.1	<0.1	55
59	DMEGqu	75	1.7	≈ 100 [f]	<0.1	<0.1	<0.1	<0.1	170
60	DMEGqu	150	12.7	≈ 100 [f]	<0.1	<0.1	<0.1	<0.1	1270

[a] Experimental conditions: molar ratios $PhNO_2/PhNH_2/Acid/[Pd(Phen)_2][BF_4]_2$ = 15200:400:1400:1, $[Pd(Phen)_2][BF_4]_2$ = 7.1×10^{-5} mmol , in MeOH (1 mL) + 2,2-dimethoxypropane (34 μL), P_{CO} = 100 bar, at 170 °C for 1.5 h. [b] Calculated with respect to the initial $PhNO_2$ amount. [c] Calculated with respect to the initial $PhNH_2$ amount. [d] Calculated with respect to the sum of the reacted $PhNO_2$ and $PhNH_2$ amounts. [e] TOF = turnover frequency = mol $PhNO_2$ reacted/(mol Pd × h). [f] Since the final amount of $PhNH_2$ was very close to the detection limit, the conversion was considered to be complete. [g] More PhNH2 was found, with respect to the initially added amount. PhNH2 selectivities (with respect to converted PhNO2) are reported in brackets.

Table A2.2. Nitrobenzene carbonylation reactions catalyzed by $[Pd(Phen)_2][BF_4]_2$ and differently substituted phenanthrolines, in the presence of different acidic promoters.[a]

Entry	Ligand	L/Pd mol ratio	Acidic promoter	$PhNO_2$ conv.[%][b]	$PhNH_2$ conv.[%][c]	MPC sel. [%][d]	Azo sel. [%][d]	azoxy sel. [%][d]	*p*-MeO-MPC sel.[%][d]	TOF [h^{-1}][e]
1	Phen	75	$Ph_2P(O)OH$	30.4	42.7	81.9	0.4	2.9	2.5	3093
2	Phen	150	$Ph_2P(O)OH$	33.9	47.3	83.1	0.4	2.6	2.0	3444
3	Phen	225	$Ph_2P(O)OH$	30.4	48.0	90.8	0.3	3.3	2.5	3096
4	Phen	35	$PhP(O)(OH)_2$	33.1	17.1	82.3	0.5	3.0	3.6	3342
5	Phen	75	$PhP(O)(OH)_2$	43.2	(0.6)[g]	75.0	0.4	2.5	3.1	4363
6	Phen	145	$PhP(O)(OH)_2$	40.6	8.5	77.0	0.4	2.6	3.2	4105
7	Phen	300	$PhP(O)(OH)_2$	38.5	25.0	66.7	0.4	2.9	3.1	3892
8	Phen	500	$PhP(O)(OH)_2$	37.5	27.8	69.2	0.5	4.1	3.7	3789
9	4-MeOPhen	75	$Ph_2P(O)OH$	46.9	52.5	79.4	0.3	3.1	1.4	4767
10	4-MeOPhen	150	$Ph_2P(O)OH$	49.0	44.0	87.5	0.4	3.4	1.7	4982
11	4-MeOPhen	225	$Ph_2P(O)OH$	47.1	38.7	91.0	0.4	3.7	1.8	4791
12	4-MeOPhen	500	$Ph_2P(O)OH$	37.5	46.3	80.1	0.3	4.9	1.7	3818
13	4-MeOPhen	40	$PhP(O)(OH)_2$	33.7	44.5	63.9	0.6	4.0	3.2	3399
14	4-MeOPhen	75	$PhP(O)(OH)_2$	39.3	38.7	63.6	0.5	3.6	2.6	3970
15	4-MeOPhen	145	$PhP(O)(OH)_2$	45.7	19.0	73.3	0.5	3.8	2.7	4615
16	4-MeOPhen	300	$PhP(O)(OH)_2$	50.1	21.6	72.9	0.5	3.9	2.3	5060
17	4-MeOPhen	500	$PhP(O)(OH)_2$	47.6	30.9	78.4	0.5	3.9	2.2	4809
18	4-C_5H_{10}NPhen	75	H_3PO_4[h]	14.9	≈ 100 [f]	30.8	1.0	10.9	5.4	1519
19	4-C_5H_{10}NPhen	150	H_3PO_4[h]	27.0	53.9	44.6	1.3	15.0	5.7	2742
20	4-C_5H_{10}NPhen	225	H_3PO_4[h]	47.0	33.8	61.1	1.4	15.5	6.5	4781
21	4-C_5H_{10}NPhen	500	H_3PO_4[h]	51.4	16.8	52.6	1.5	17.7	4.9	5229
22	4-C_5H_{10}NPhen	75	$Ph_2P(O)OH$	29.2	62.2	75.7	0.4	5.2	2.0	2971
23	4-C_5H_{10}NPhen	150	$Ph_2P(O)OH$	38.7	66.2	75.4	0.4	4.7	1.7	3939

24	4-C_5H_{10}NPhen	225	$Ph_2P(O)OH$	36.6	57.9	79.4	0.4	5.4	1.8	3725
25	4-C_5H_{10}NPhen	500	$Ph_2P(O)OH$	31.4	45.3	86.1	0.5	8.9	1.6	3198
26	4-C_5H_{10}NPhen	75	$PhP(O)(OH)_2$	22.0	53.2	41.1	0.6	5.3	2.6	2222
27	4-C_5H_{10}NPhen	145	$PhP(O)(OH)_2$	33.4	38.7	70.6	0.6	6.0	2.7	3375
28	4-C_5H_{10}NPhen	225	$PhP(O)(OH)_2$	40.3	28.3	66.2	0.6	6.1	2.5	4071
29	4-C_5H_{10}NPhen	500	$PhP(O)(OH)_2$	32.2	62.8	60.6	0.6	7.4	1.8	3256
30	4-C_6H_5NHPhen	75	H_3PO_4 [h]	10.8	≈ 100 [f]	27.2	n.d.	11.9	5.8	1102
31	4-C_6H_5NHPhen	150	H_3PO_4 [h]	22.8	≈ 100 [f]	24.0	1.0	11.3	4.6	2316
32	4-C_6H_5NHPhen	251	H_3PO_4 [h]	34.5	66.7	39.5	1.2	15.3	5.4	3510
33	4-C_6H_5NHPhen	501	H_3PO_4 [h]	59.1	20.5	54.4	1.7	17.4	5.2	6013
35	4-C_6H_5NHPhen	600	H_3PO_4 [h]	57.3	3.5	55.4	1.7	18.8	4.5	5828
36	4-C_6H_5NHPhen	75	$Ph_2P(O)OH$	20.0	48.5	35.9	> 0.1	5.4	1.7	2022
37	4-C_6H_5NHPhen	150	$Ph_2P(O)OH$	32.0	50.5	56.4	0.4	5.4	1.6	3236
38	4-C_6H_5NHPhen	251	$Ph_2P(O)OH$	43.5	4.5	64.6	0.4	5.0	1.4	4394
39	4-C_6H_5NHPhen	501	$Ph_2P(O)OH$	36.8	26.8	77.1	0.4	6.9	1.0	3721
40	4-C_6H_5NHPhen	75	$PhP(O)(OH)_2$	11.0	50.9	22.8	0.8	4.0	1.6	1114
41	4-C_6H_5NHPhen	150	$PhP(O)(OH)_2$	18.0	47.8	50.8	0.7	7.1	2.8	1815
42	4-C_6H_5NHPhen	251	$PhP(O)(OH)_2$	37.5	29.4	69.7	0.6	6.0	2.1	3789
43	4-C_6H_5NHPhen	496	$PhP(O)(OH)_2$	44.2	39.9	73.5	0.2	7.4	1.7	4460
44	4-C_6H_5NHPhen	606	$PhP(O)(OH)_2$	43.0	38.2	74.9	0.5	8.0	1.8	4344

[a] Experimental conditions: molar ratios $PhNO_2$/$PhNH_2$/Acid/$[Pd(Phen)_2][BF_4]_2$ = 15200:400:1400:1, $[Pd(Phen)_2][BF_4]_2$ = 7.1×10^{-5} mmol , in MeOH (1 mL) + 2,2-dimethoxypropane (34 μL), P_{CO} = 100 bar, at 170 °C for 1.5 h. [b] Calculated with respect to the initial $PhNO_2$ amount. [c] Calculated with respect to the initial $PhNH_2$ amount. [d] Calculated with respect to the sum of the reacted $PhNO_2$ and $PhNH_2$ amounts. [e] TOF = turnover frequency = mol $PhNO_2$ reacted/(mol Pd × h). [f] Since the final amount of $PhNH_2$ was very close to the detection limit, the conversion was considered to be complete. [g] More PhNH2 was found, with respect to the initially added amount. PhNH2 selectivities (with respect to converted PhNO2) are reported in brackets. [h] The amount of the acid promoter was doubled, molar ratio Acid/$[Pd(Phen)_2][BF_4]_2$ = 2800:1

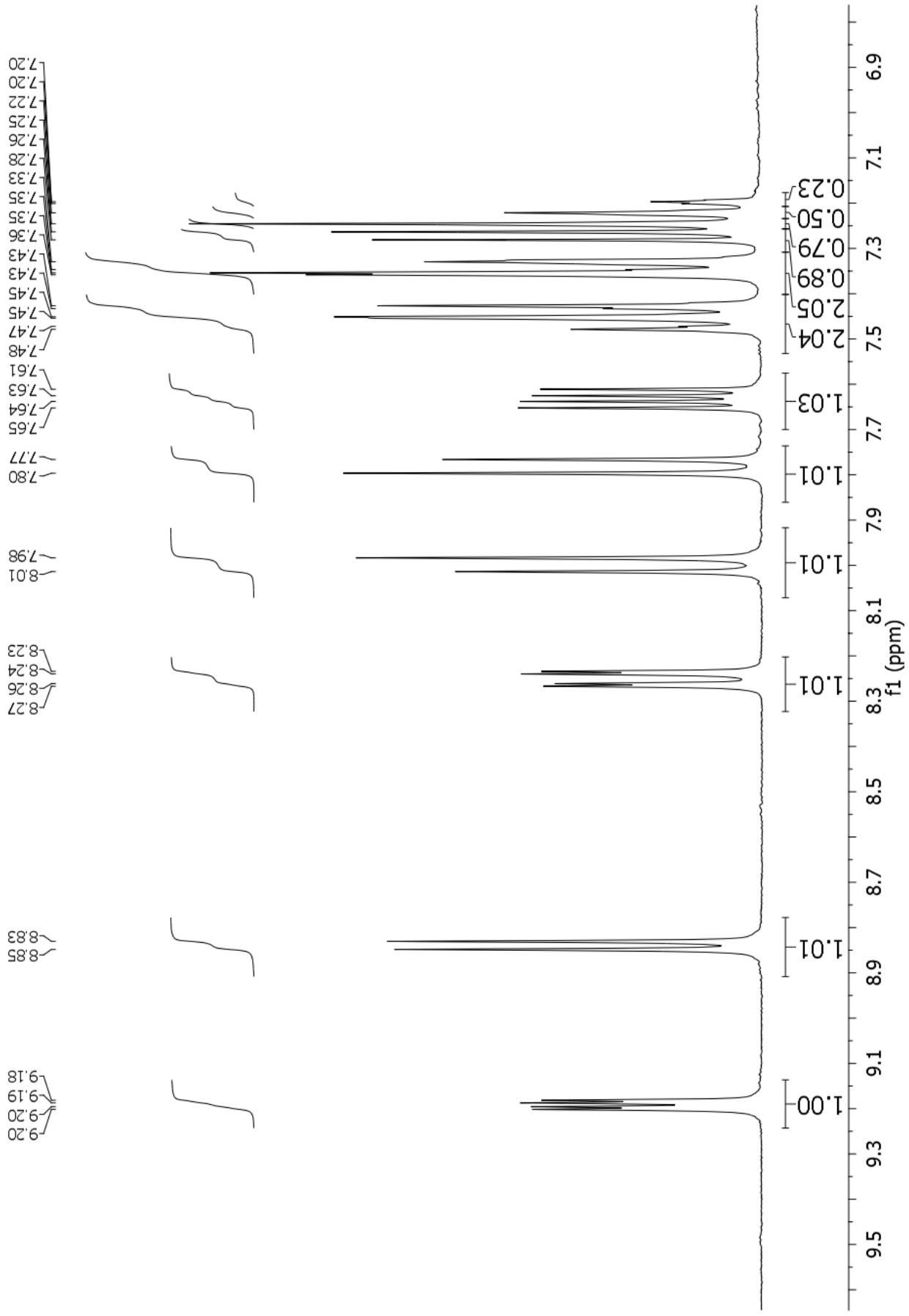

Figure A2.1. ^{1}H NMR (300 MHz, CDCl3, 300 K) 4-anilino-1,10-phenanthroline.

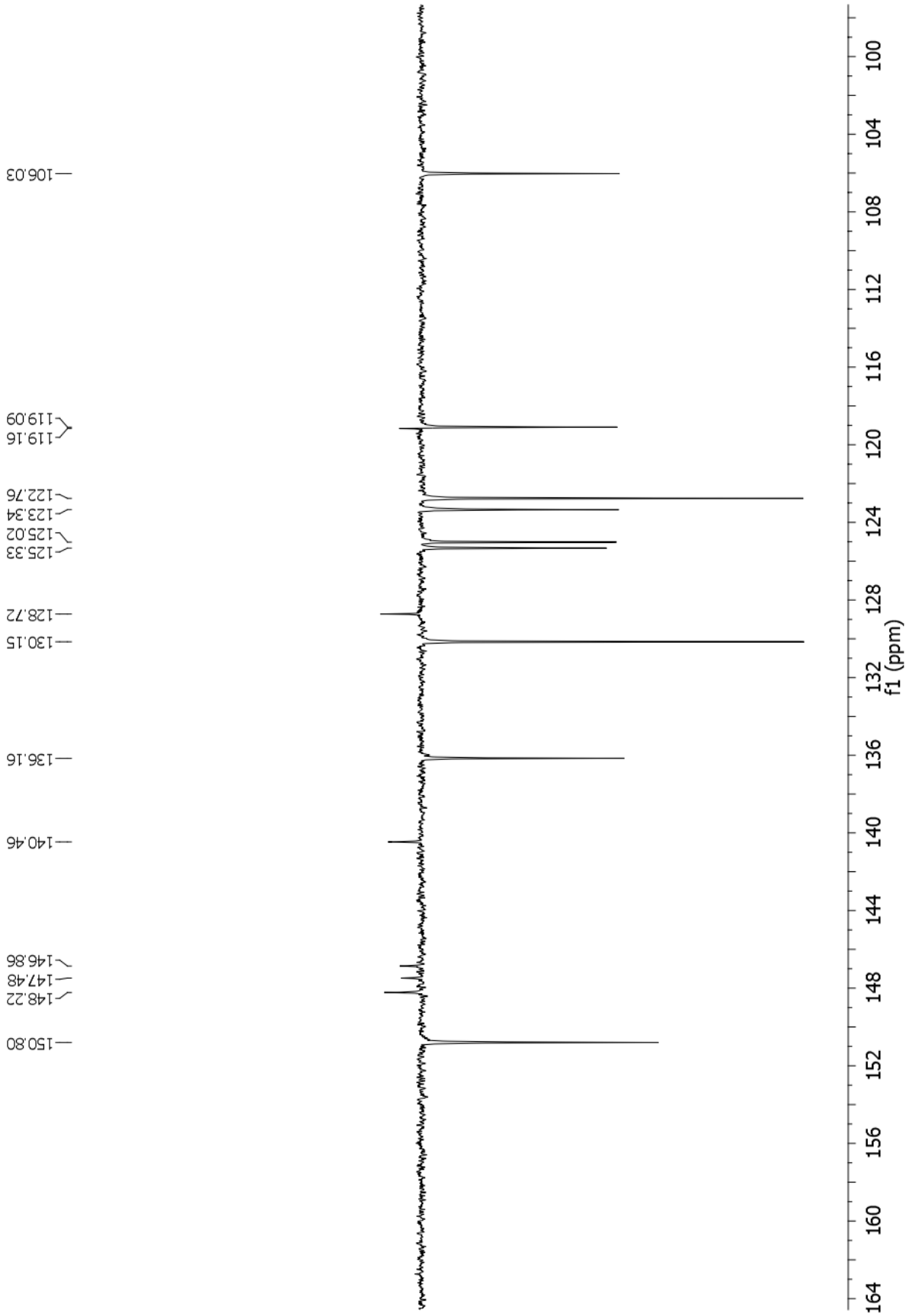

Figure A2.2. ^{13}C APT (75 MHz, CDCl3, 300 K) 4-anilino-1,10-phenanthroline.

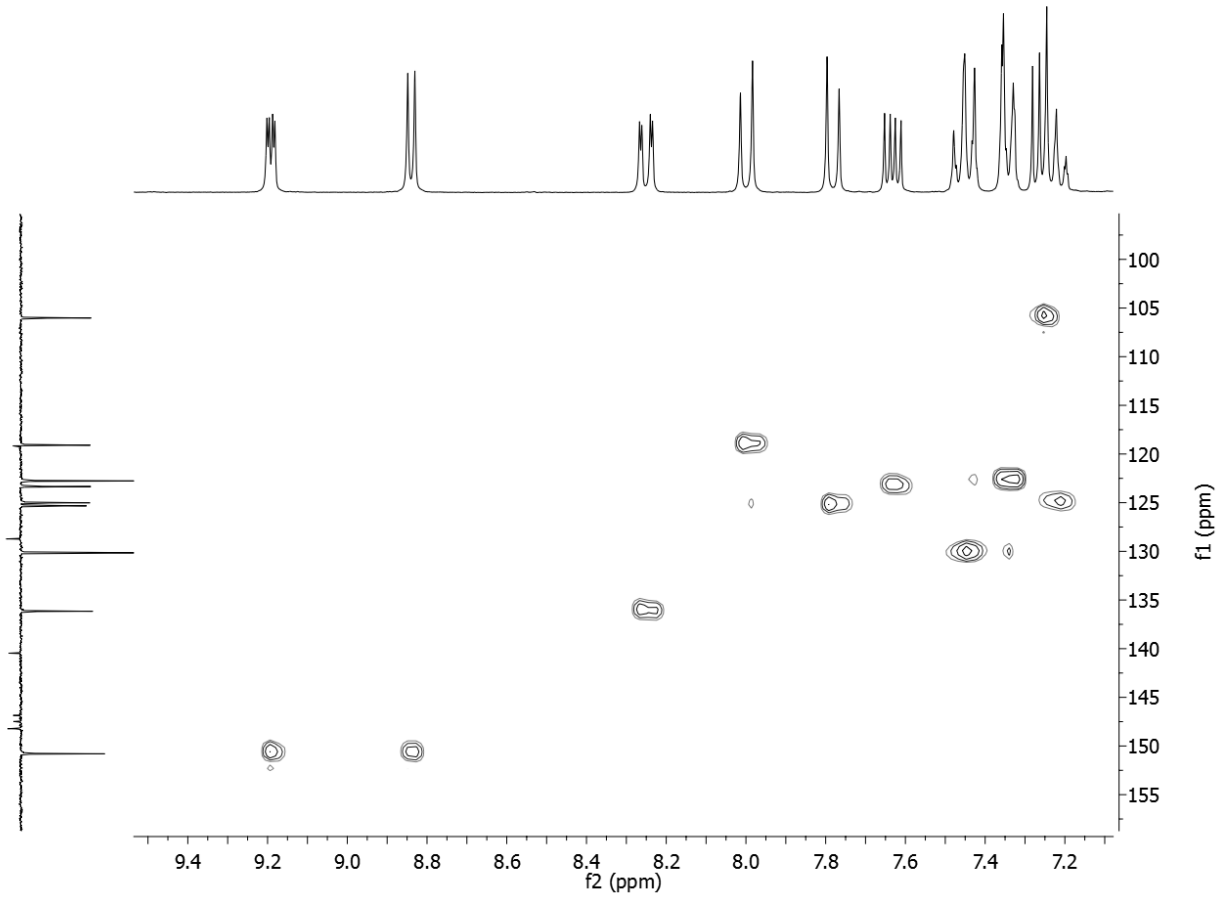

Figure A2.3. ^{1}H-^{13}C HSQC (300 MHz, $CDCl_3$, 300 K) 4-anilino-1,10-phenanthroline.

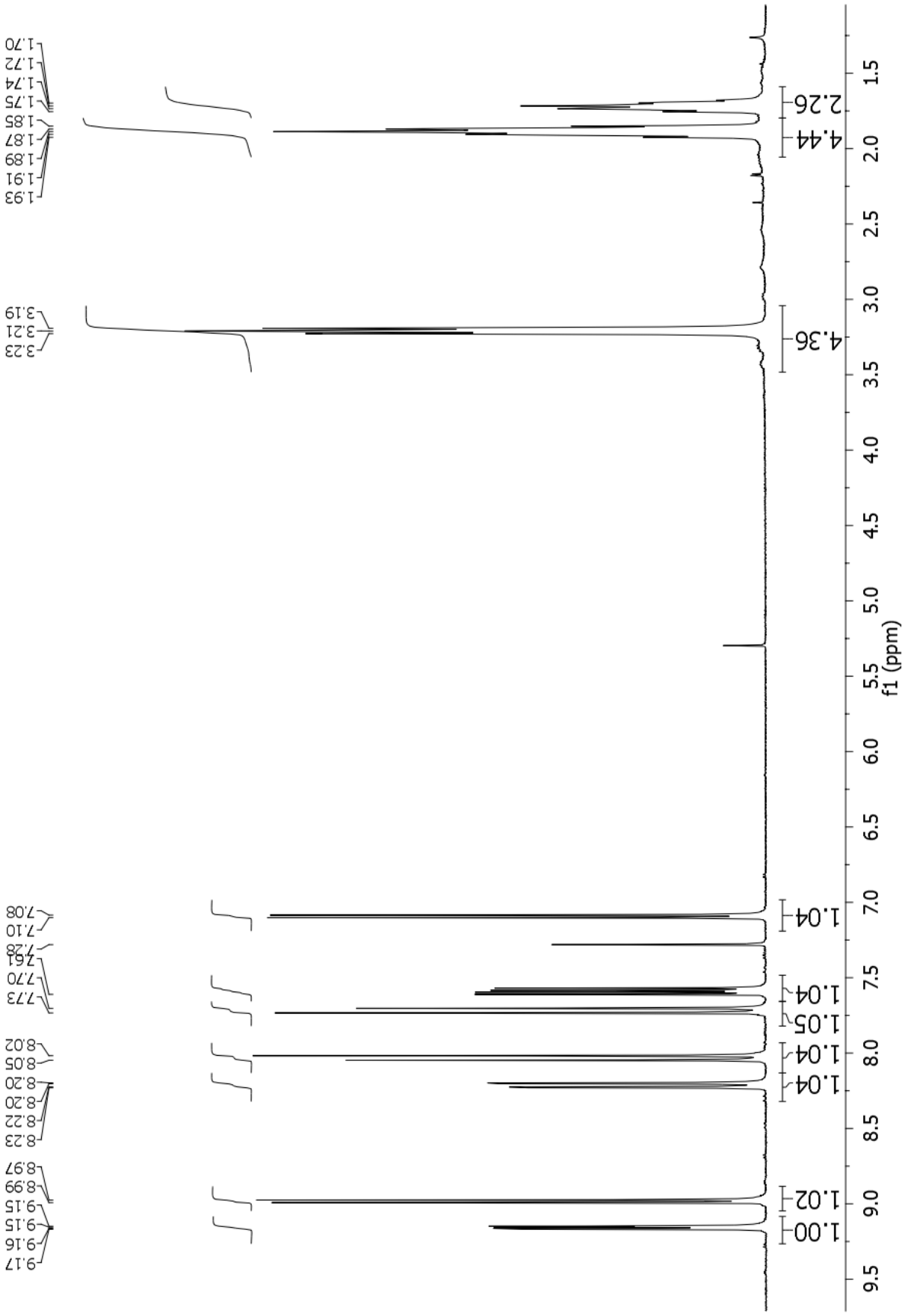

Figure A2.5. ^{1}H NMR (300 MHz, CDCl3, 300 K) 4-piperidyl-1,10-phenanthroline.

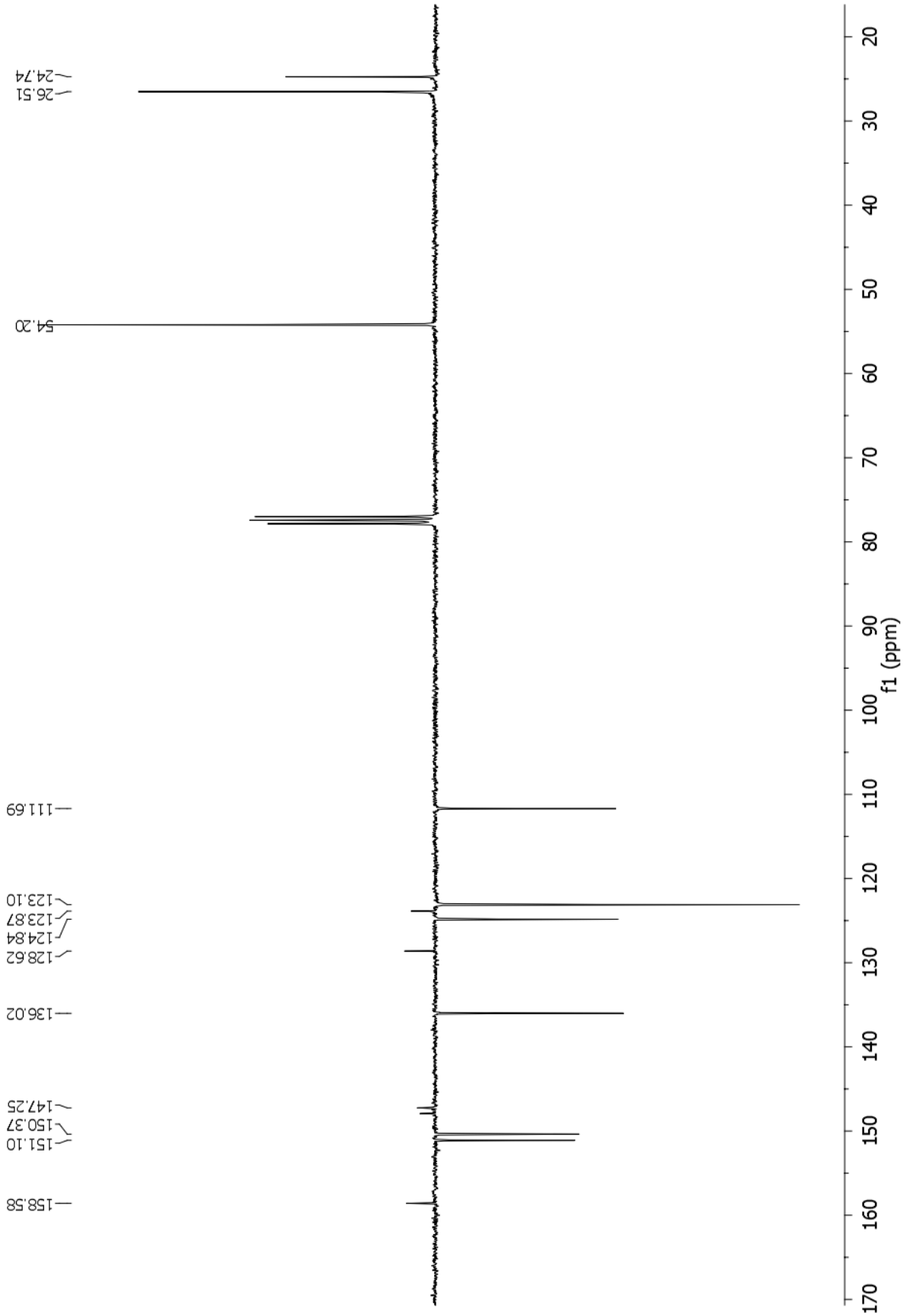

Figure A2.6. ^{13}C APT (75 MHz, CDCl3, 300 K) 4-piperidyl-1,10-phenanthroline.

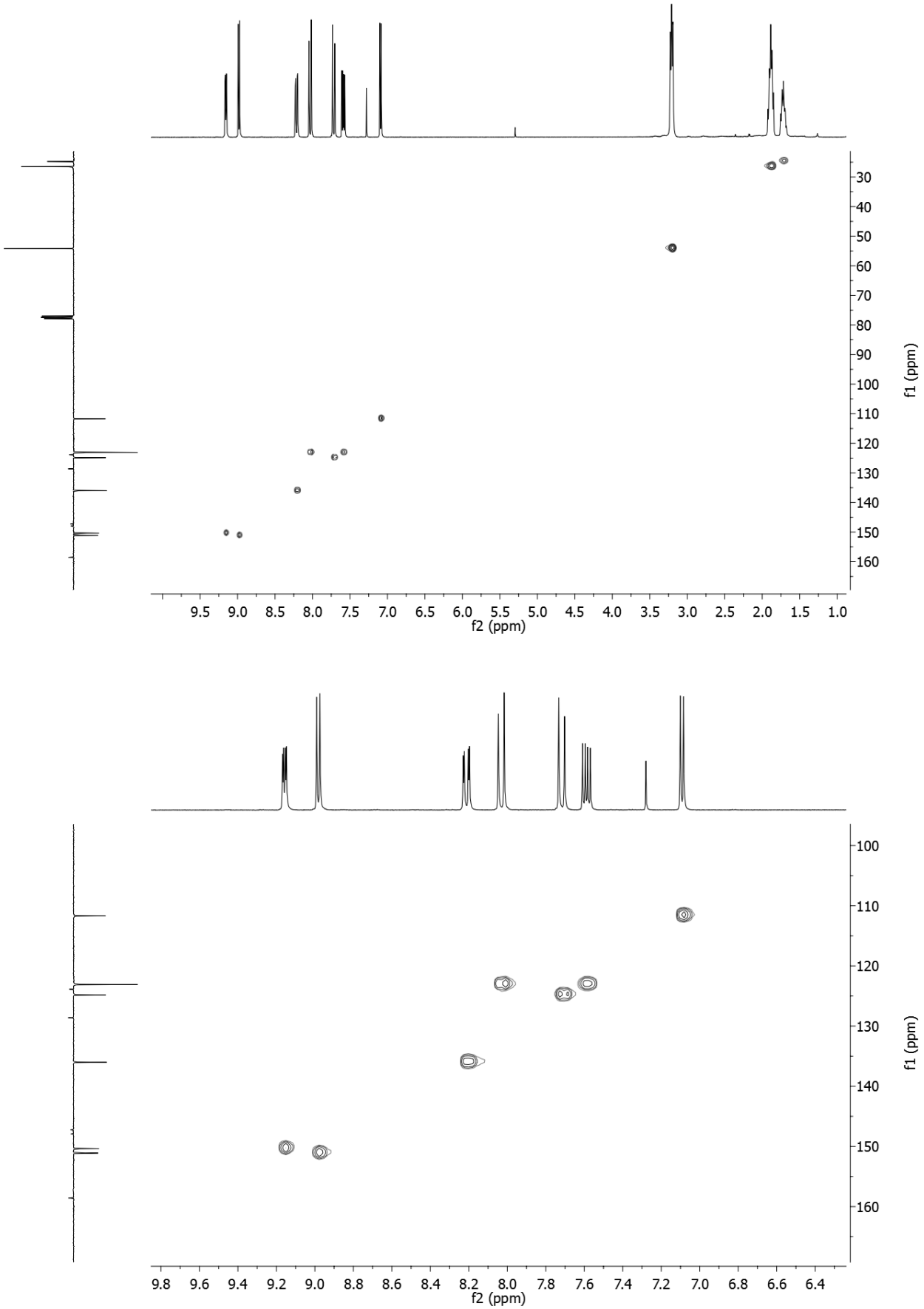

Figure A2.7. ^{1}H-^{13}C HSQC (300 MHz, $CDCl_3$, 300 K) 4-piperidyl-1,10-phenanthroline.

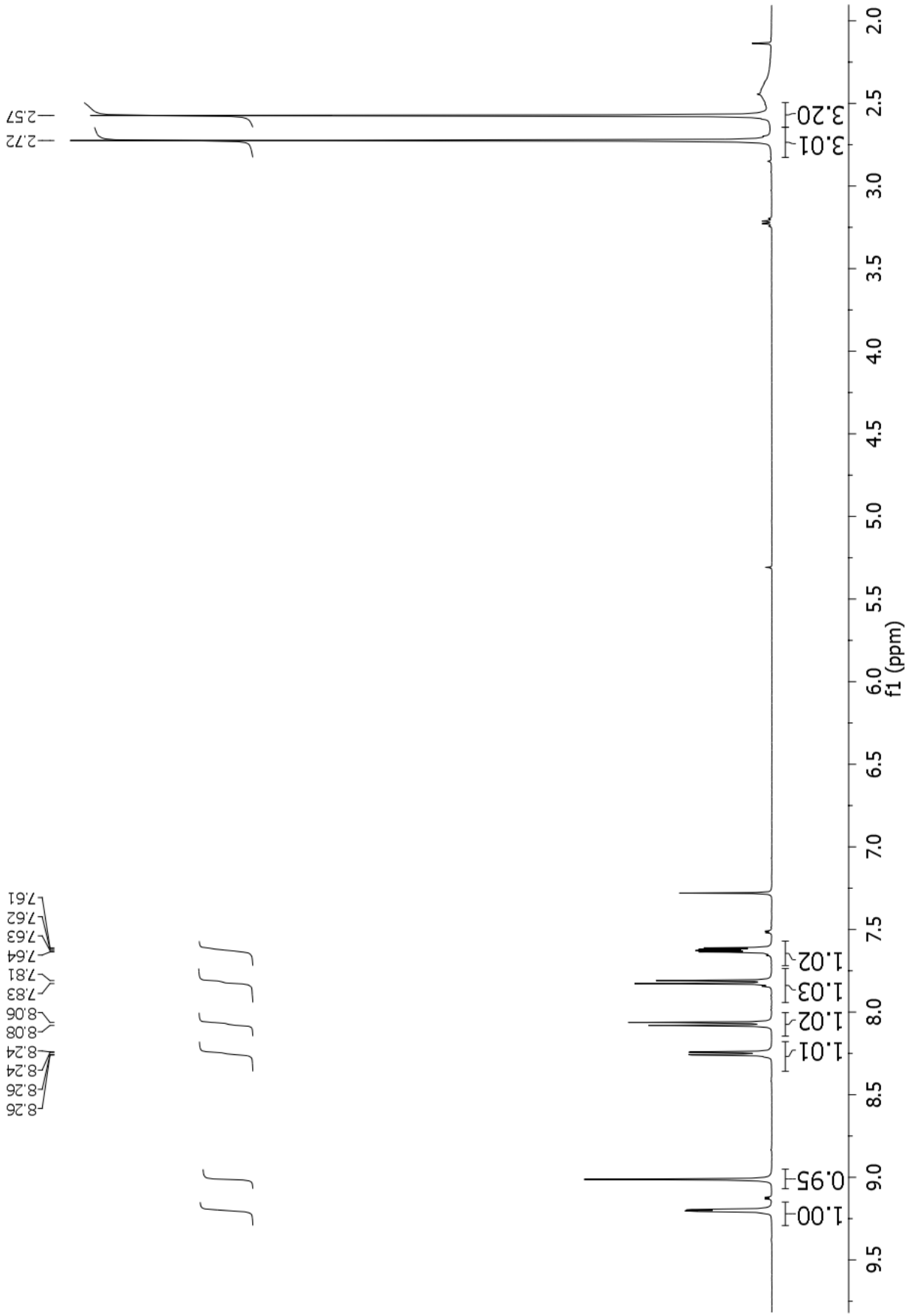

Figure A2.8. ^{1}H NMR (300 MHz, CDCl3, 300 K) 3,4-dimethyl-1,10-phenanthroline.

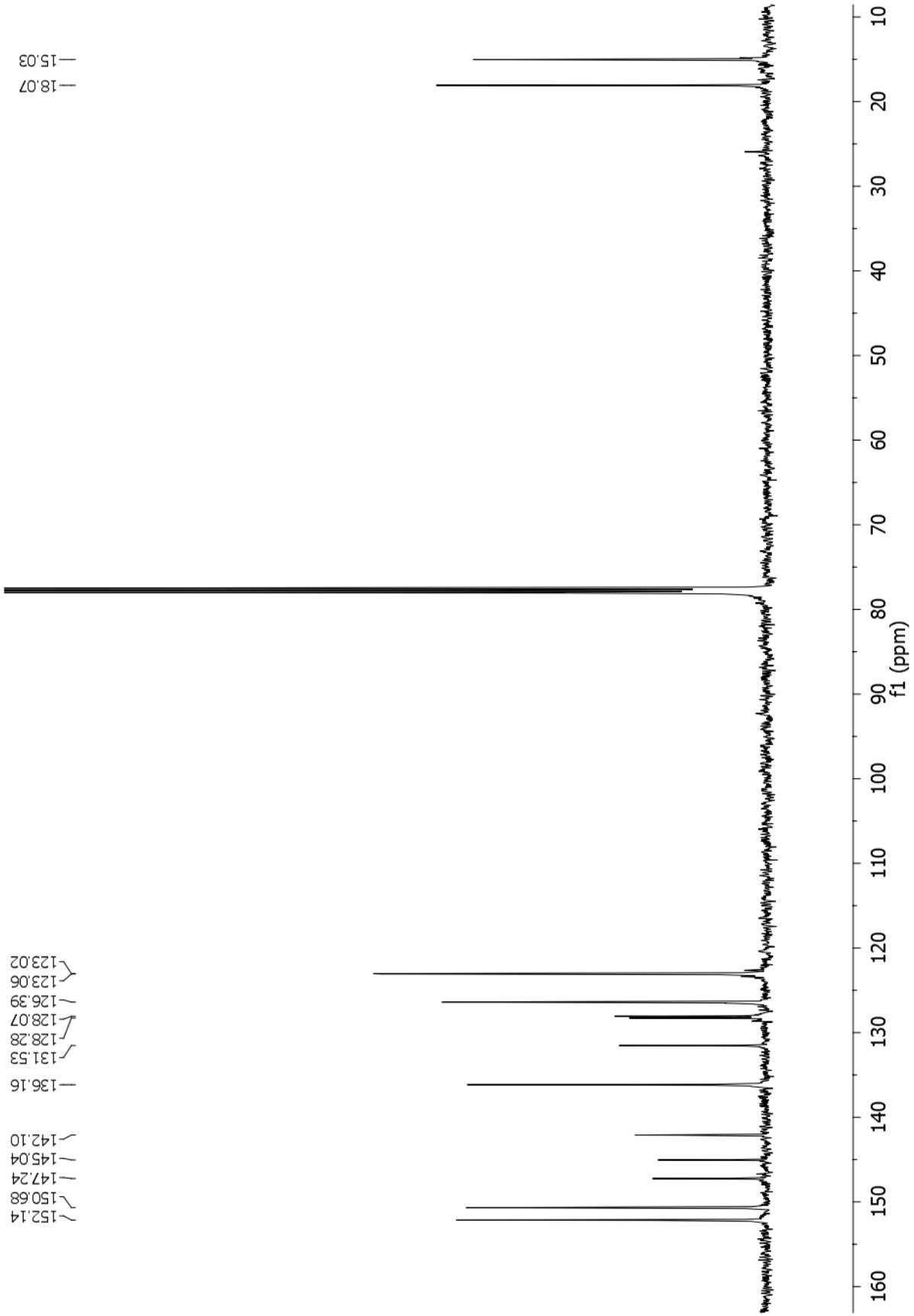

Figure A2.9. ^{13}C NMR (75 MHz, CDCl3, 300 K) 3,4-dimethyl-1,10-phenanthroline.

Appendix to Chapter 3

Figure A3.1. Nitrobenzene carbonylation under thermomorphic conditions: liquid/solid separation.[a]

Ligand	Cycle	$PhNO_2$ conv.[%][b]	$PhNH_2$ conv.[%][c]	MPC sel.[%][d]	Azo sel.[%][d]	Azoxy sel.[%][d]	*p*-MeO-MPC sel.[%][d]	TOF [h^{-1}][e]
C_{19}Phen	1	84.0	24.1	84.0	0.4	1.8	2.4	778
	2	84.8	11.5	84.8	0.4	1.8	2.5	753
	3	78.3	26.0	78.3	0.4	1.7	2.2	688
	4	75.1	38.7	75.1	0.4	2.0	2.5	503
C_{38}Phen	1	60.7	33.2	78.9	0.4	1.2	1.4	817
	2	46.3	45.1	78.5	0.5	1.5	1.2	622
	3	33.9	71.1	67.5	0.3	2.3	1.5	456
	4	28.8	67.0	64.9	0.6	1.8	1.6	386

[a] Experimental conditions: molar ratios $PhNO_2/PhNH_2/H_3PO_4/[Pd(Bipy)_2][BF_4]_2$ = 4000:200:750:1, $[Pd(Bipy)_2][BF_4]_2$ = 1.3×10^{-3} mmol , in MeOH (10 mL) + 2,2-dimethoxypropane (0.5 mL), P_{CO} = 60 bar, at 170 °C for 3 h. [b] Calculated with respect to the initial $PhNO_2$ amount. [c] Calculated with respect to the initial $PhNH_2$ amount. [d] Calculated with respect to the sum of the reacted $PhNO_2$ and $PhNH_2$ amounts. [e]TOF = turnover frequency = mol $PhNO_2$ reacted/(mol Pd × h).

Figure A3.2. Nitrobenzene carbonylation under thermomorphic conditions: liquid/liquid separation.[a]

Ligand/non-polar solvent	Cycle	$PhNO_2$ conv.[%][b]	$PhNH_2$ conv.[%][c]	MPC sel.[%][d]	Azo sel.[%][d]	Azoxy sel.[%][d]	*p*-MeO-MPC sel.[%][d]	TOF [h^{-1}][e]
C_{19}Phen/Decalin[f]	1	77.6	0.0 (6.7)	67.3	0.2	4.4	0.5	978
	2	62.9	9.5	86.5	0.5	4.6	1.0	793
	3	40.9	21.8	72.0	0.5	4.4	1.0	548
	4	24.7	49.7	69.1	0.7	5.4	1.9	319
	5	18.6	55.2	64.1	0.7	5.4	1.7	238
C_{19}Phen/m. oil[g]	1	46.3	21.5	74.8	0.5	2.6	3.0	311
	2	53.0	38.8	81.3	0.5	2.6	2.9	340
	3	59.6	18.2	81.6	0.4	1.9	2.8	396
	4	58.1	40.9	86.4	0.4	2.3	2.6	400
	5	63.0	0.0 (1.2)	84.9	0.9	4.2	4.2	431
	6	28.9	38.9	75.7	0.7	3.7	3.5	197
C_{19}Phen/m. oil[g,h]	1	32.7	49.2	65.6	0.2	2.6	1.6	224
	2	57.4	40.3	99.3	0.2	1.9	0.5	382
	3	46.9	50.4	64.7	0.2	3.6	0.2	316
	4	7.8	68.9	25.0	> 0.1	26.3	> 0.1	51
C_{38}Phen/m. oil[g,i]	1	77.3	32.5	83.0	0.1	0.6	1.2	633
	2	57.3	37.0	81.9	0.2	0.9	1.4	460
	3	41.1	51.1	73.5	0.3	1.5	1.5	337
	4	34.9	64.4	67.2	0.3	1.5	1.5	283
	5	20.2	38.0	68.1	0.4	2.3	2.1	164
	6	13.9	55.3	67.0	0.6	3.4	2.8	113

[a] Experimental conditions: molar ratios $PhNO_2/PhNH_2/H_3PO_4/[Pd(Bipy)_2][BF_4]_2$ = 2000:100:375:1, $[Pd(Bipy)_2][BF_4]_2$ = 2.7×10^{-3} mmol, in MeOH (10 mL) + 2,2-dimethoxypropane (0.5 mL), P_{CO} = 60 bar, at 170 °C for 3 h. [b] Calculated with respect to the initial $PhNO_2$ amount. [c] Calculated with respect to the initial $PhNH_2$ amount, PhNH2 selectivities (with respect to converted PhNO2) are reported in brackets. [d] Calculated with respect to the sum of the reacted $PhNO_2$ and $PhNH_2$ amounts.[e] TOF = turnover frequency = mol $PhNO_2$ reacted/(mol Pd × h). [f] Decalin/methanol volume ratio = 1:1, the amount of catalyst was halved while maintaining unvaried the concentrations of the other reagents [g] Mineral oil/methanol volume ratio = 2:5 [h] Octadecylphosphonic acid was added instead of H_3PO_4. The addition was done only at the first cycle. [i]The reaction was stopped at 2h 20' to avoid complete conversion.

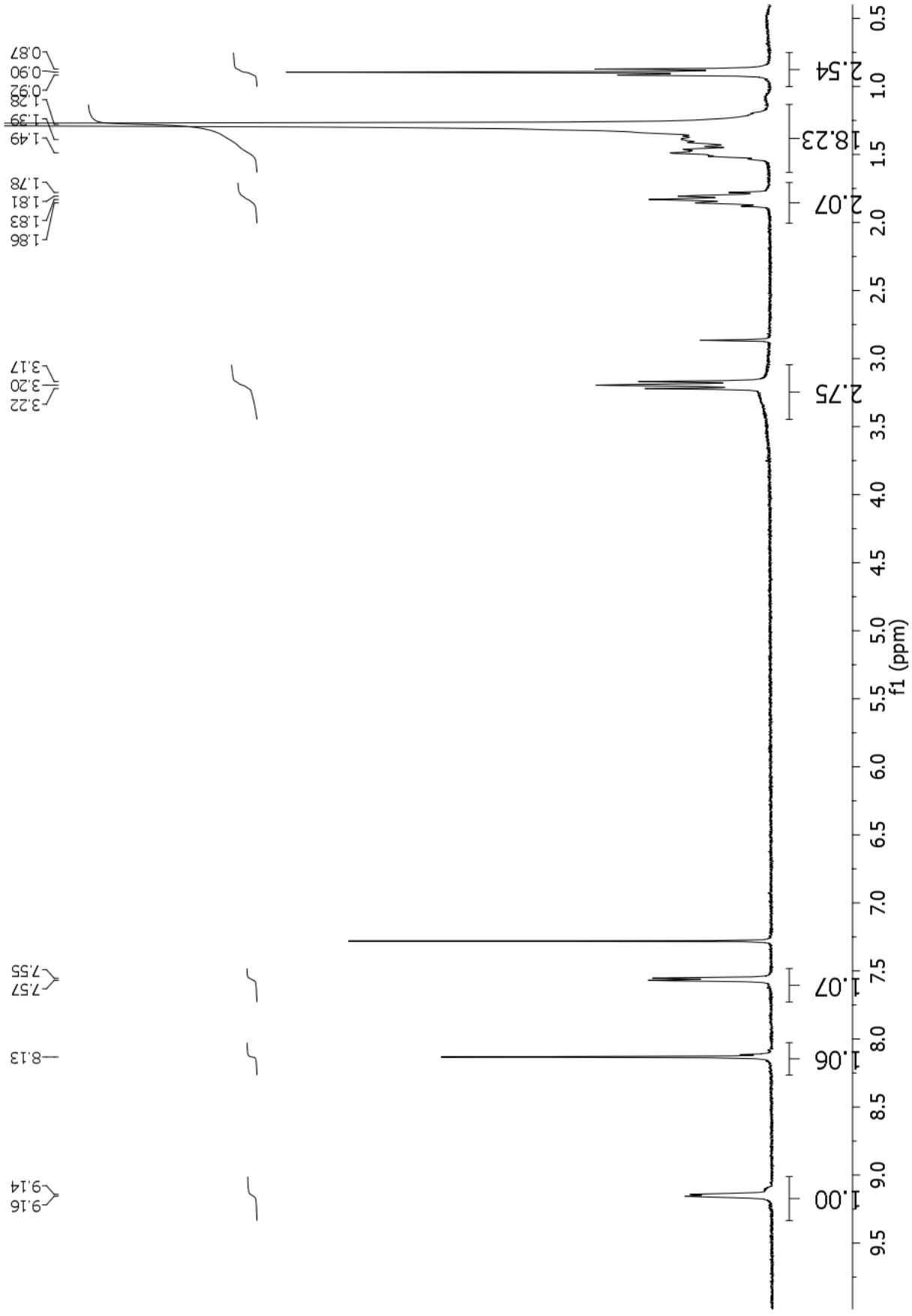

Figure A3.1. ^{1}H NMR (300 MHz, CDCl3, 300 K) C_{13}Phen.

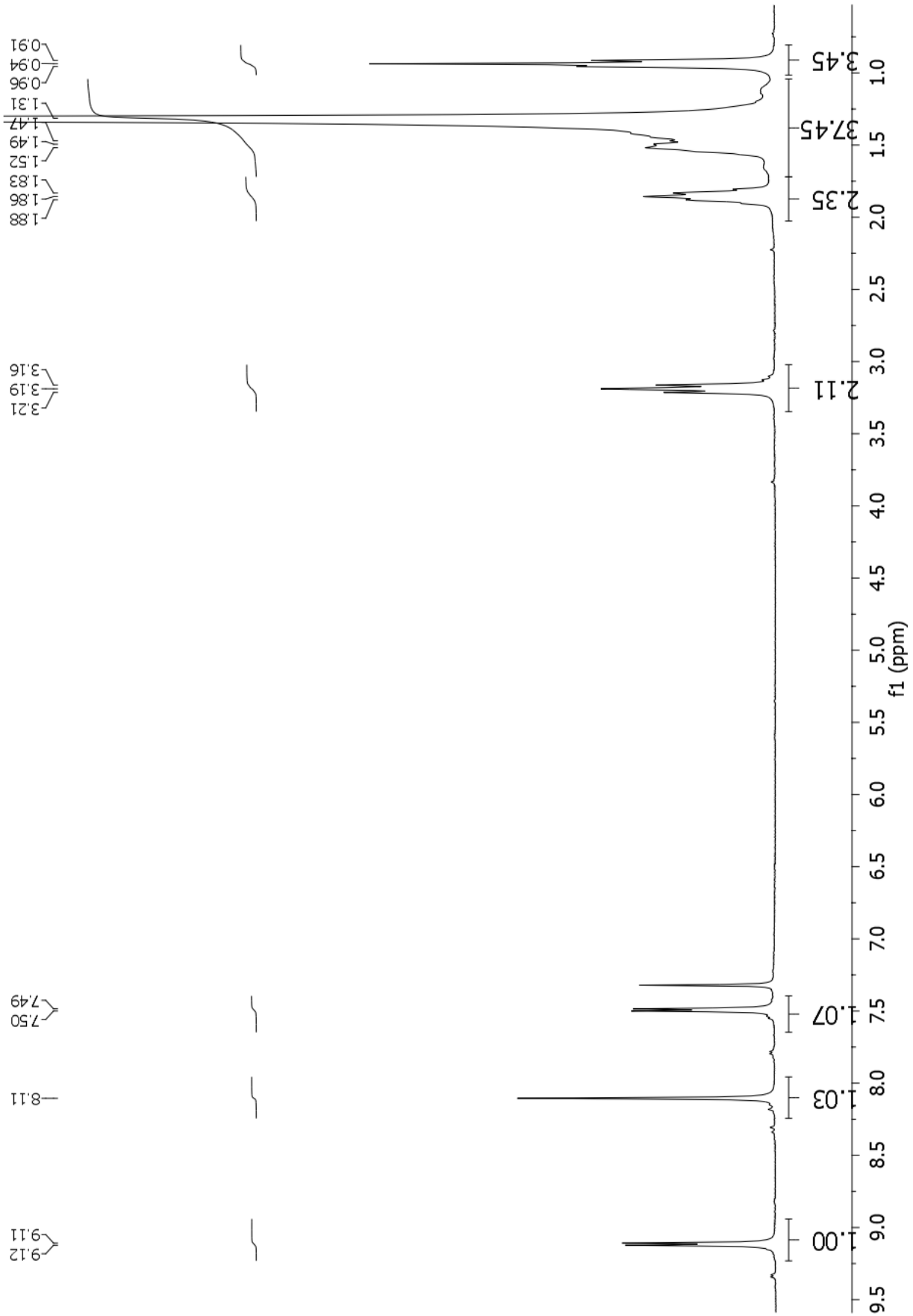

Figure A3.2. ^{1}H NMR (300 MHz, CDCl3, 300 K) C_{19}Phen.

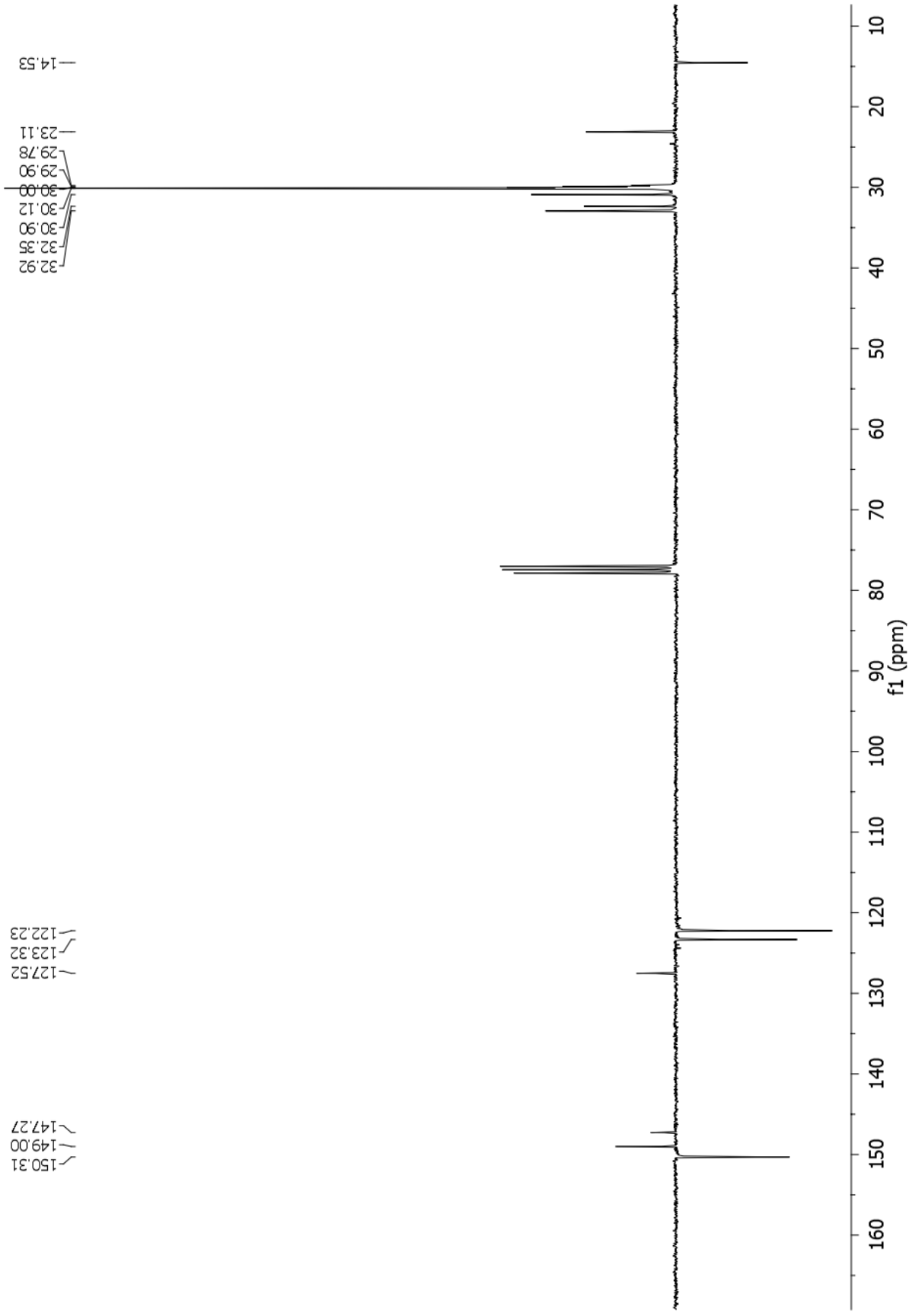

Figure A3.3. ^{13}C APT (75 MHz, CDCl3, 300 K) C_{19}Phen.

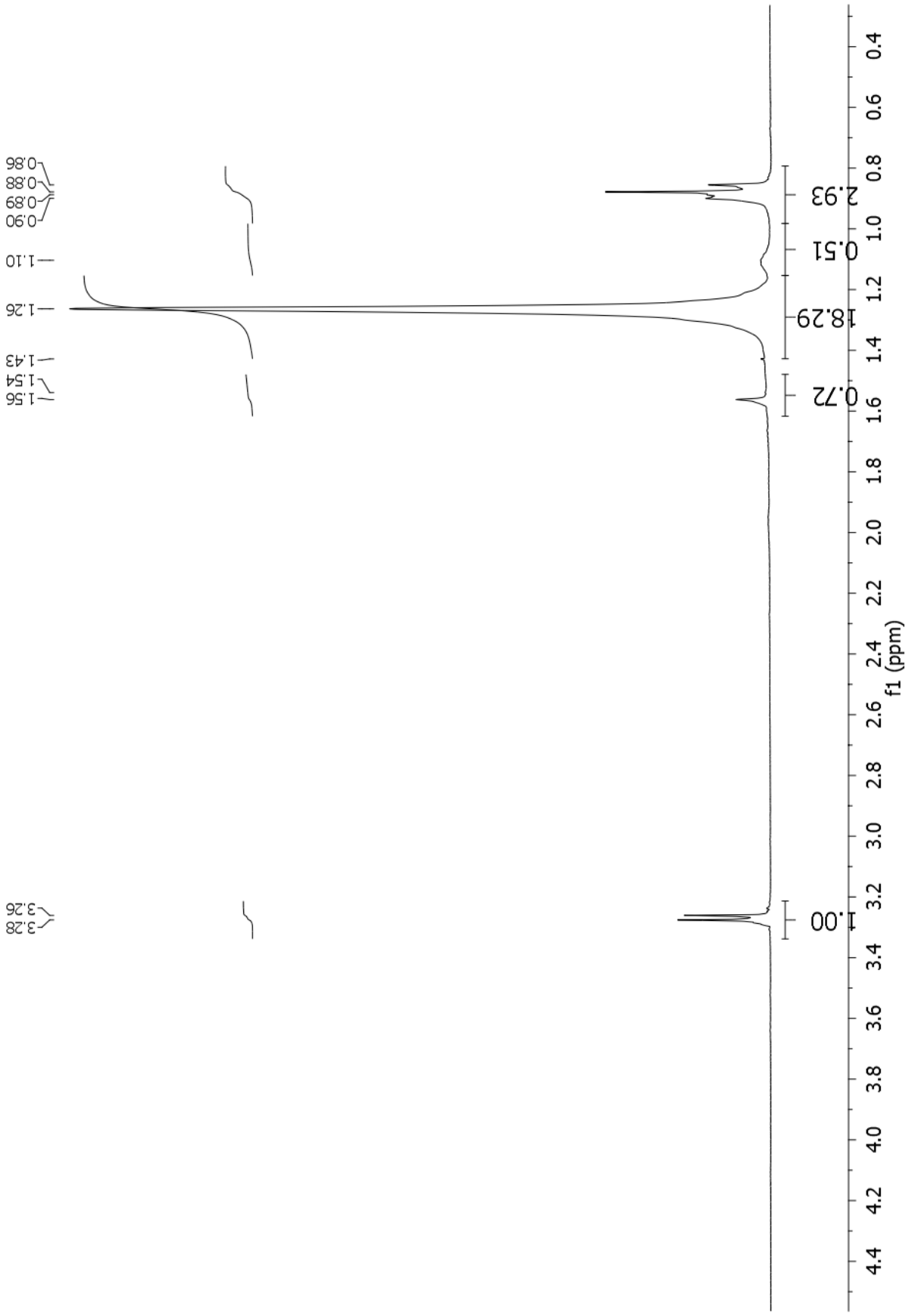

Figure A3.4. ^{1}H NMR (300 MHz, CDCl3, 300 K) 9-(Iodomethyl)nonadecane.

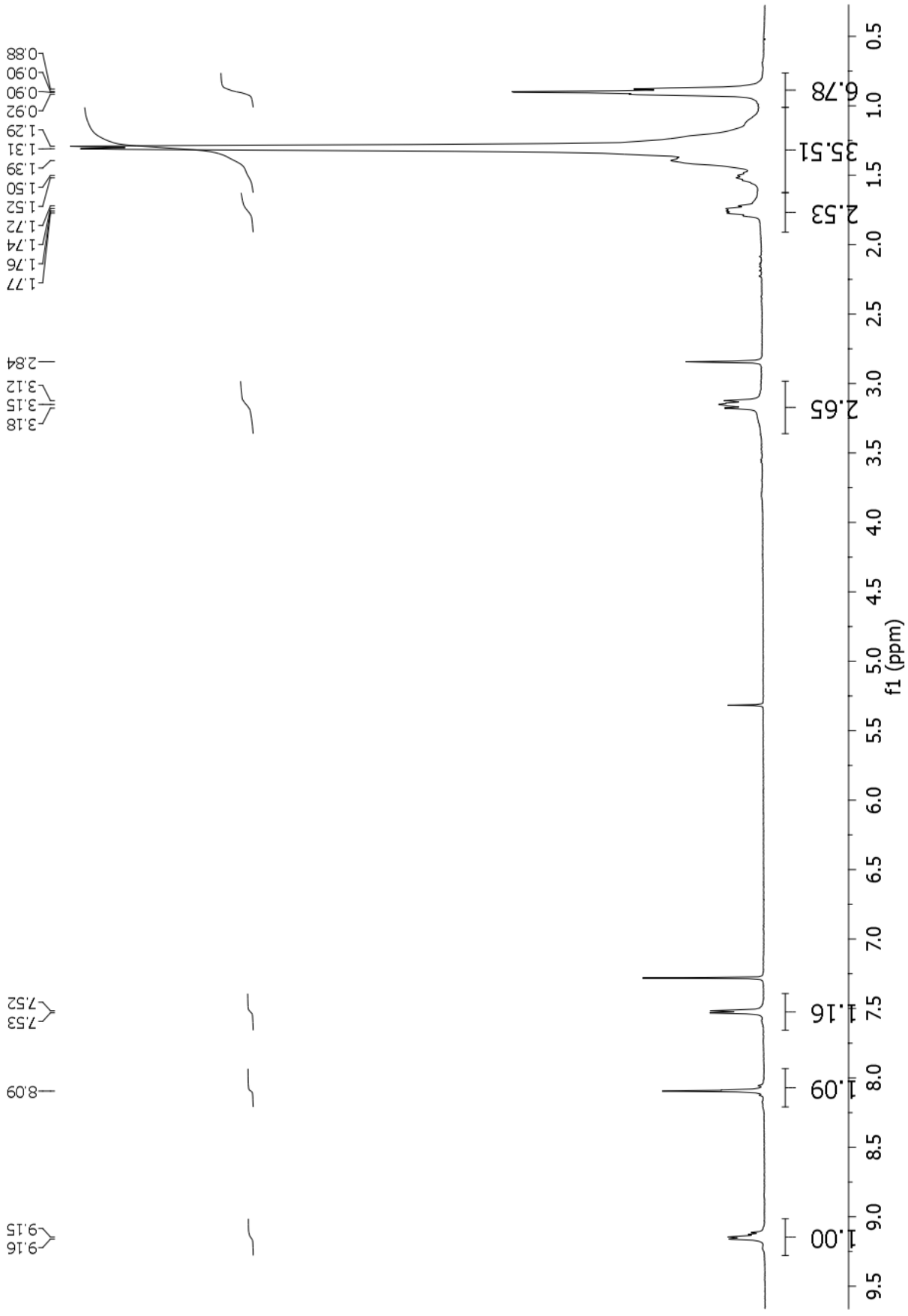

Figure A3.5. ^{1}H NMR (300 MHz, CDCl3, 300 K) C_{21}Phen.

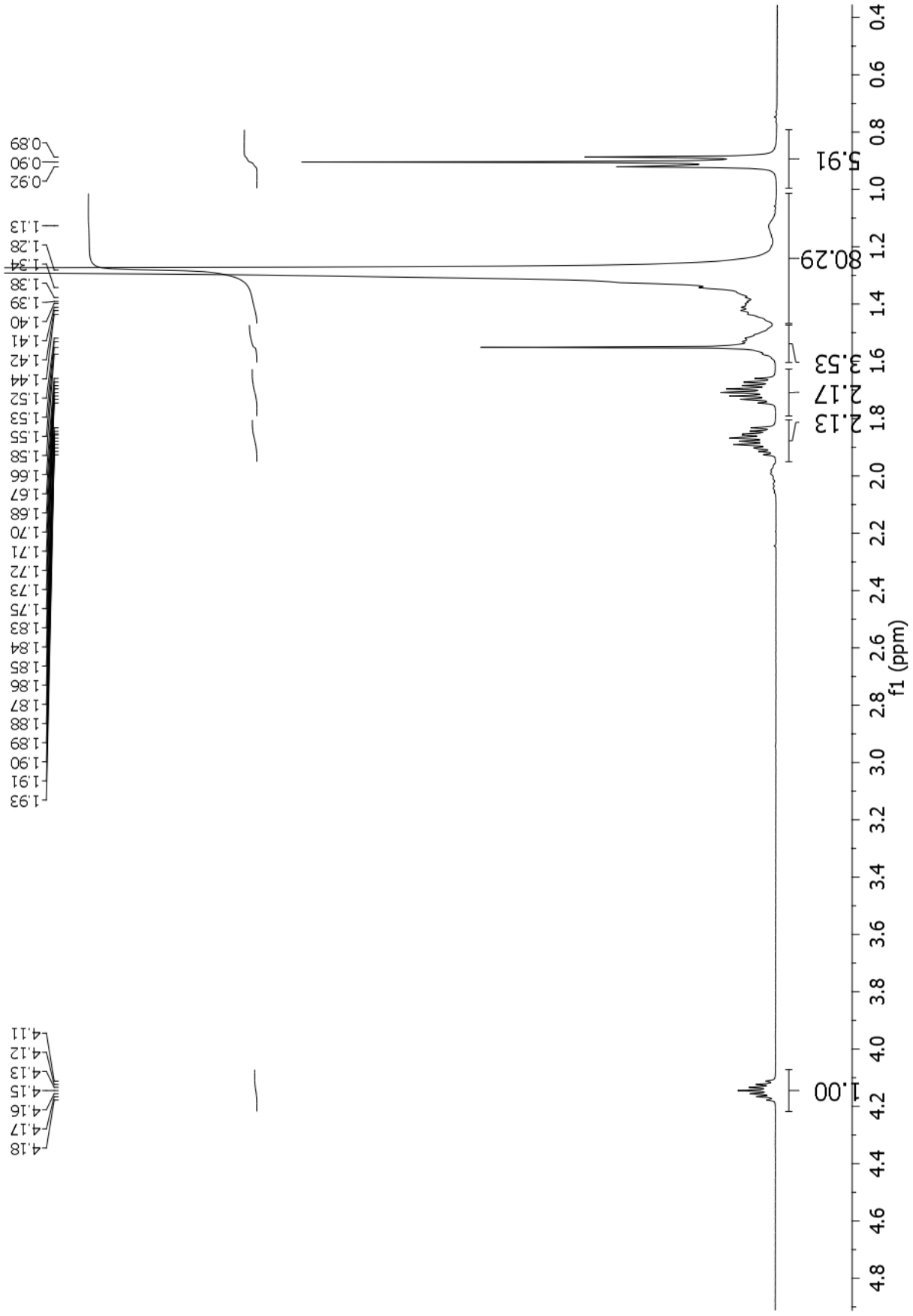

Figure A3.6. ^{1}H NMR (300 MHz, CDCl3, 300 K) 19-iodoheptatriacontane.

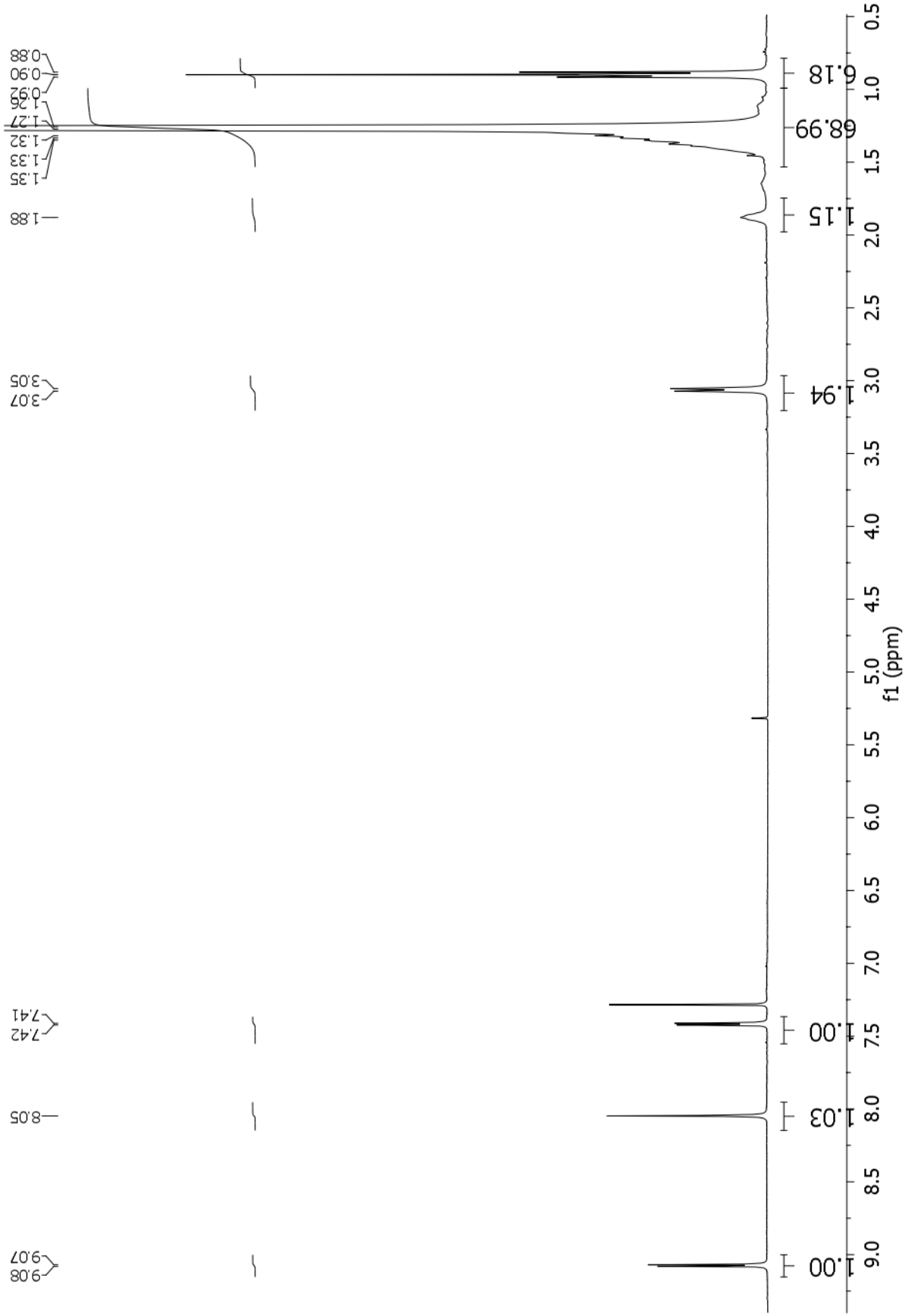

Figure A3.7. ^{1}H NMR (300 MHz, CDCl3, 300 K) C_{38}Phen.

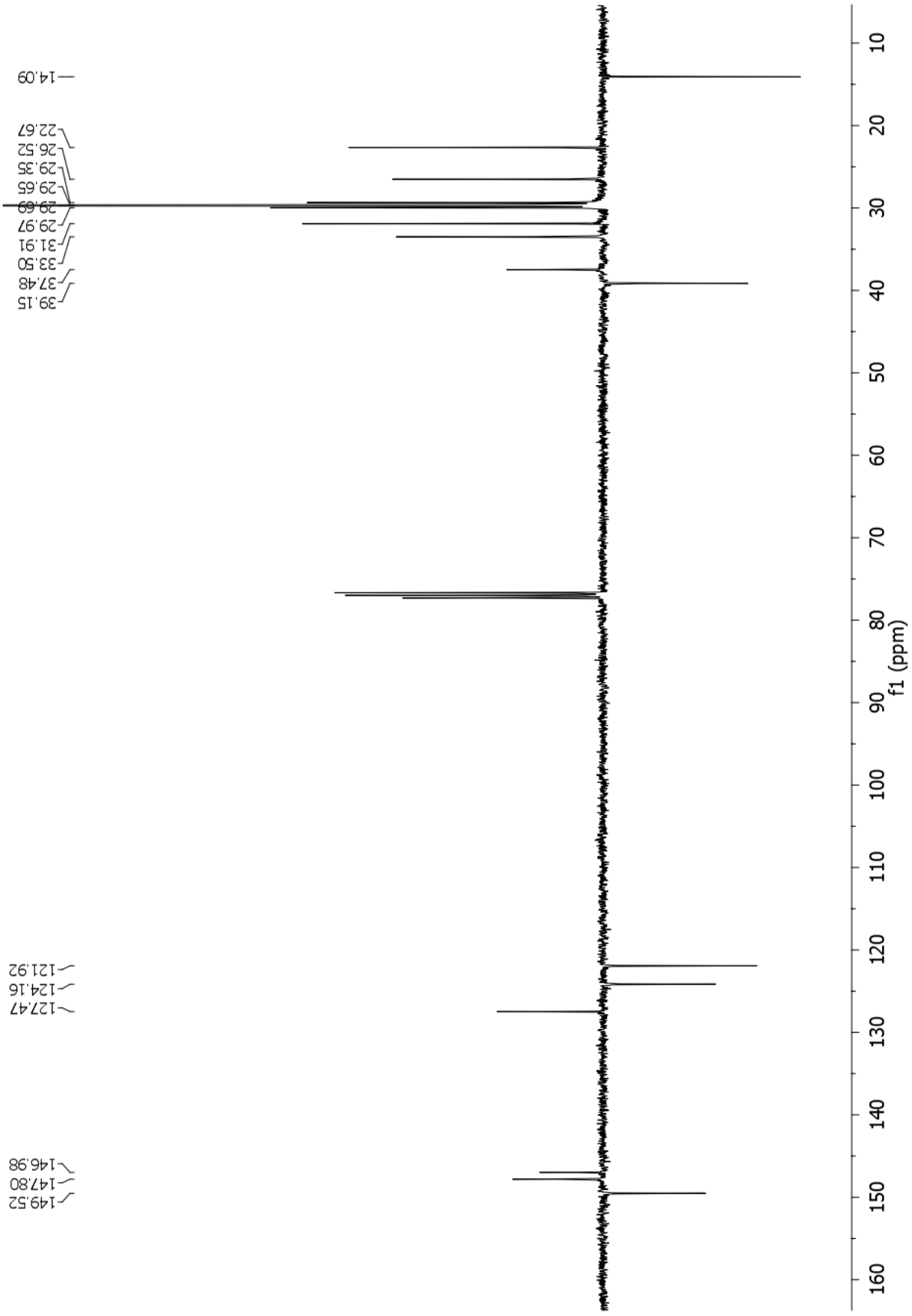

Figure A3.8. ^{13}C APT (75 MHz, CDCl3, 300 K) C_{38}Phen.

Appendix to Chapter 4

Table A4.1. Crystallographic data for compound [$PdBr_3(CO)$][NeocH]

Formula	$C_{14}H_{13}N_2$, CBr_3OPd
Formula Weight	583.37
Crystal System	*Triclinic*
Space group	P-1 (No. 2)
a, b, c [Å]	7.4271(1) 9.2217(1) 13.5184(2)
α, β, γ [˚]	83.746(1) 76.144(1) 71.549(1)
V [$Å^3$]	852.18(2)
Z	2
D(calc) [g/cm^3]	2.273
μ(MoKα) [mm^{-1}]	8.123
F(000)	552
Crystal Size [mm]	0.25 x 0.14 x 0.12
Data Collection	
Temperature (K)	100(2)
Radiation [Å]	MoKα 0.71069
θ Min-Max [˚]	1.5, 48.5
hkl	15:-15 ; 19:-18 ; 28:-27
Tot., Uniq. Data, R_{int}	49480, 15557, 0.025
Observed data [I > 2.0 σ(I)]	11846
Refinement	
Nref, Npar	15557, 203
R_1, wR_2, S	0.0575, 0.1039, 1.02
R_1, wR_2 (I > 2.0 σ(I))	0.0364, 0.0937
Max. and Av. Shift/Error	0.012, 0.001
Min. and Max. Resd. Dens. [$eÅ^{-3}$]	-3.15, 2.90

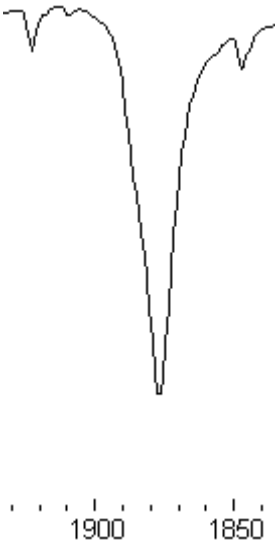

Figure A4.1. IR spectrum (in nujol) of $[Pd(Neoc)Cl]_2(\mu\text{-}CO)_2$ (**3a**) (1921 (w), 1875 (s), 1846 (vw) cm^{-1})

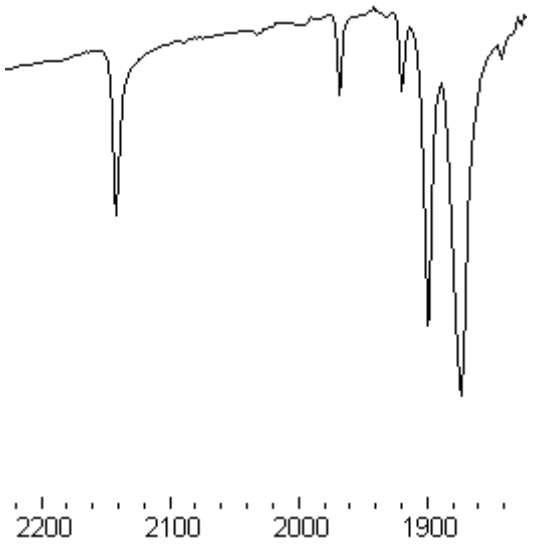

Figure A4.2. IR spectrum (in nujol) of the mixture obtained by carbonylating $Pd(Neoc)Cl_2$ (**1a**) for two weeks and containing $[Pd(Neoc)Cl]_2(\mu\text{-}CO)_2$ (**3a**) (1921 (w), 1875 (s), 1846 (vw) cm^{-1}), $[Pd(CO)Cl_3](NeocH)$ (2143 (m) cm^{-1}), and $[Pd_2Cl_4(\mu\text{-}CO)_2](NeocH)_2$ (1900 (ms) and 1966 (w) cm^{-1}).

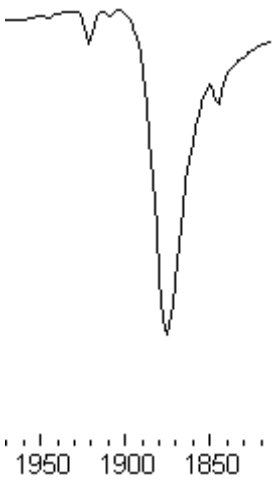

Figure A4.3. IR spectrum (in nujol) of $[Pd(Neoc)Br]_2(\mu\text{-}CO)_2$ (**3c**) (1922 (w), 1877 (s), 1847 (vw) cm^{-1})

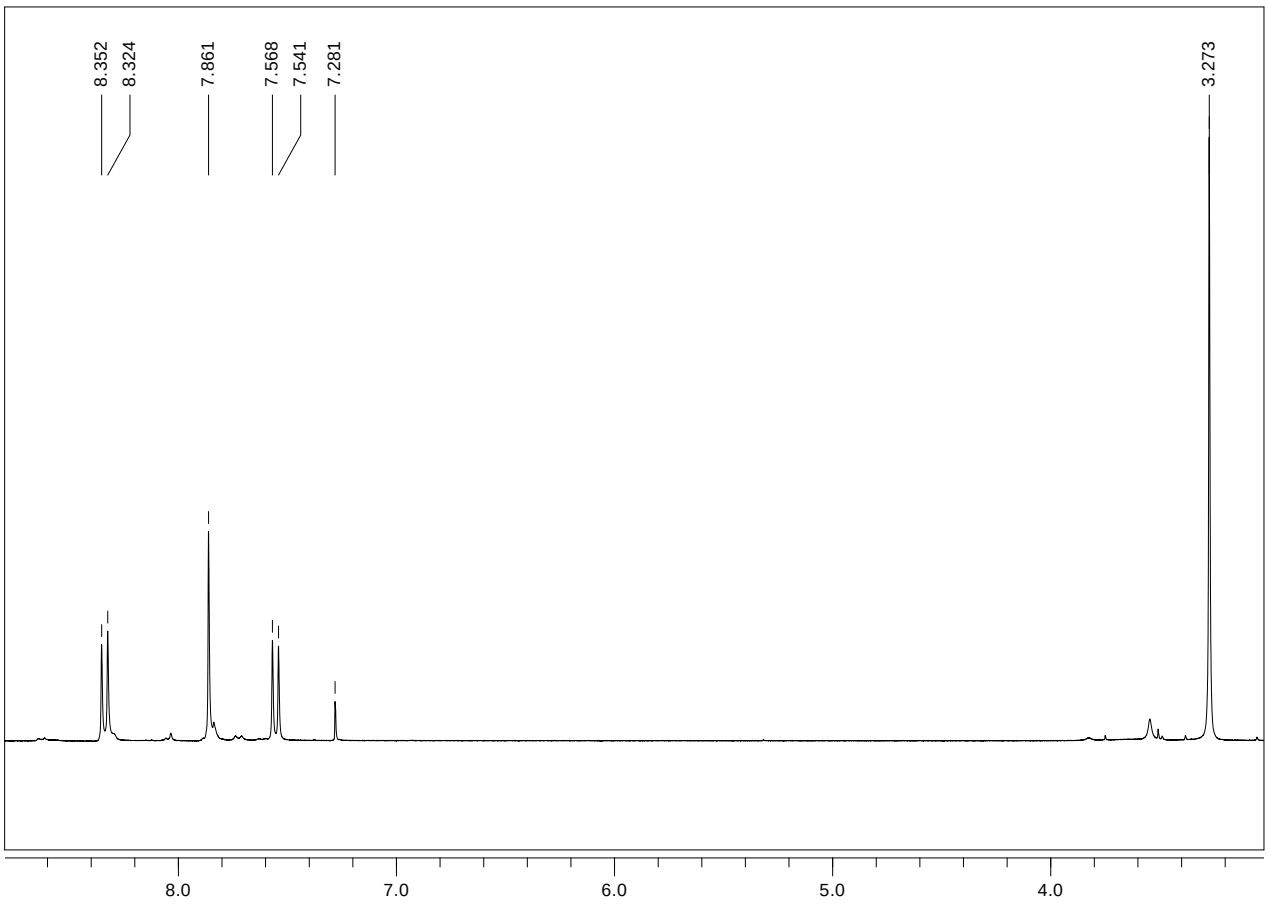

Figure A4.4: ^{1}H NMR (300 MHz, $CDCl_3$, 300 K) of [Pd(Neoc)Cl_2(CO)]: δ 8.34 (d, 2H, H4, H7 or H3, H8, *J* = 8.4 Hz); 7.86 (s, 2H, H5 and H6); 7.55 (d, 2H, H3, H8 or H4, H7, *J* = 8.4 Hz); 3.27 (s, 6H, C*H*$_3$).

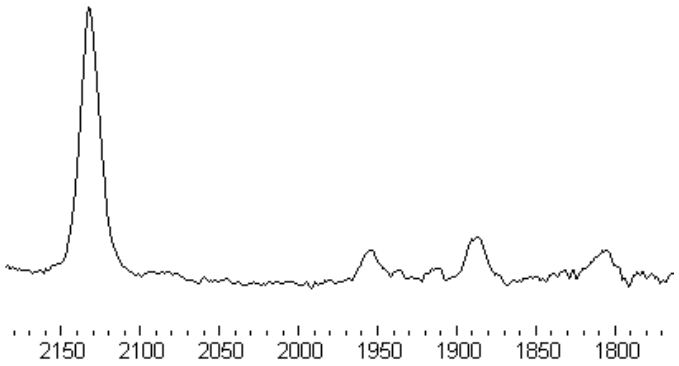

Figure A4.5. IR ($CDCl_3$, RT) of the solution of [Pd(Neoc)Cl_2(CO)] used to record the spectrum in Fig.A4.1. The lower intensity bands are due to decomposition products formed in the timeframe between the recording of the two spectra, in accord with the stability of the complex at RT:) $\nu_{(CO)}$ =2133 cm^{-1} (s) [1955 cm^{-1} (w), 1888 cm^{-1} (w), 1806 cm^{-1} (w)]

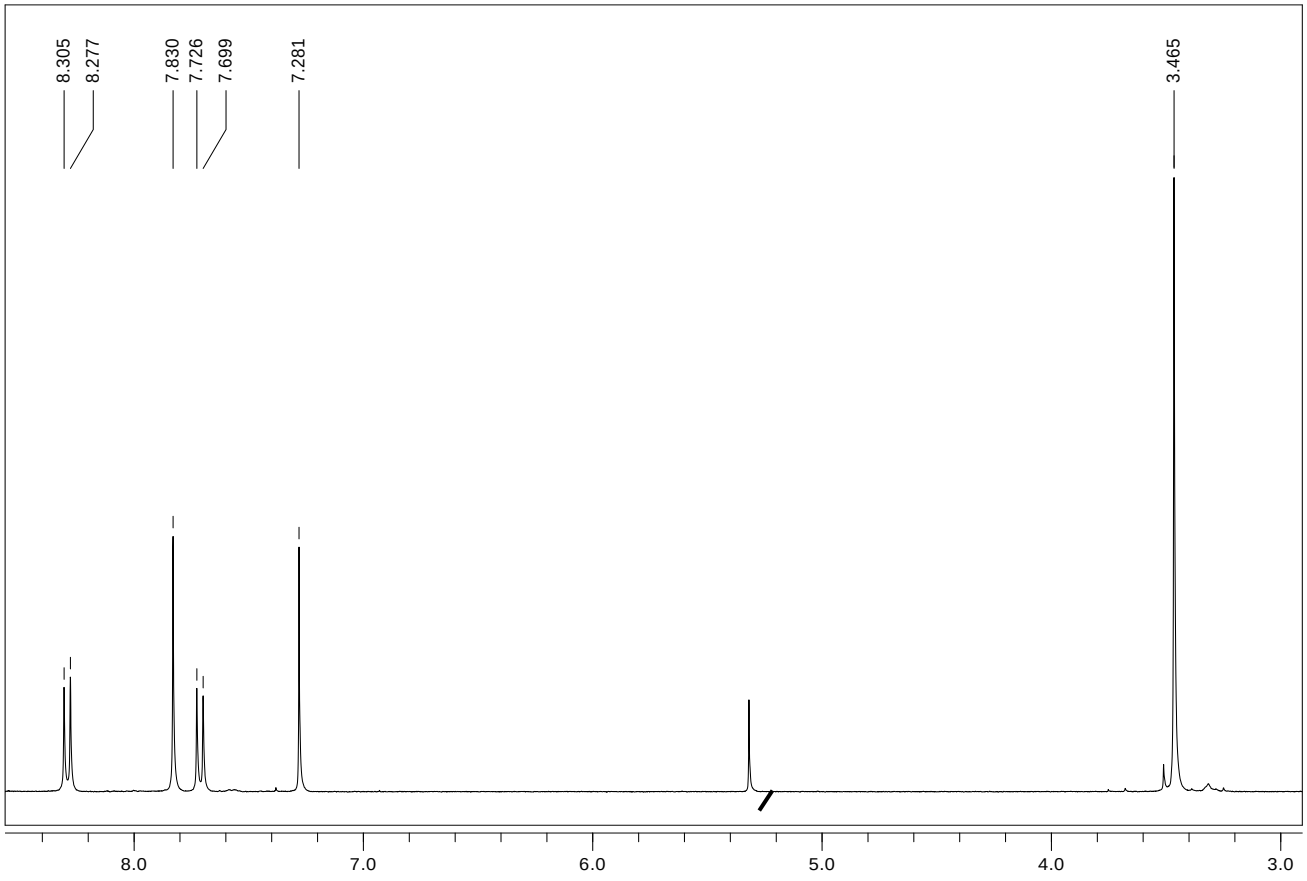

Figure A4.6. ^{1}H NMR ($CDCl_3$, RT) of [Pd(Neoc)Br_2(CO)]: δ 8.29 (d, 2H, H4, H7 or H3, H8, *J* = 8.2 Hz); 7.83 (s, 2H, H5 and H6); 7.71 (d, 2H, H3, H8 or H4, H7, *J* = 8.2 Hz); 3.46 (s, 6H, C*H*$_3$) (the crossed peak is a CH_2Cl_2 impurity).

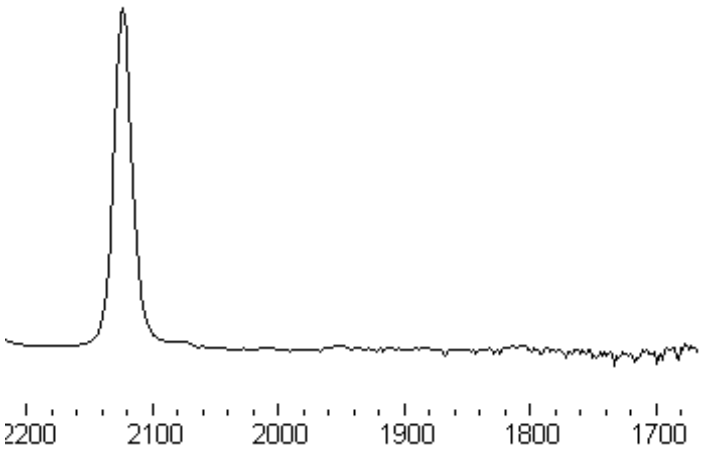

Figure A4.7. IR ($CDCl_3$, RT) of the solution of [Pd(Neoc)Br_2(CO)] used to record the spectrum in Fig.A4.3: $\nu_{(CO)}$ = 2124 cm^{-1} (s)

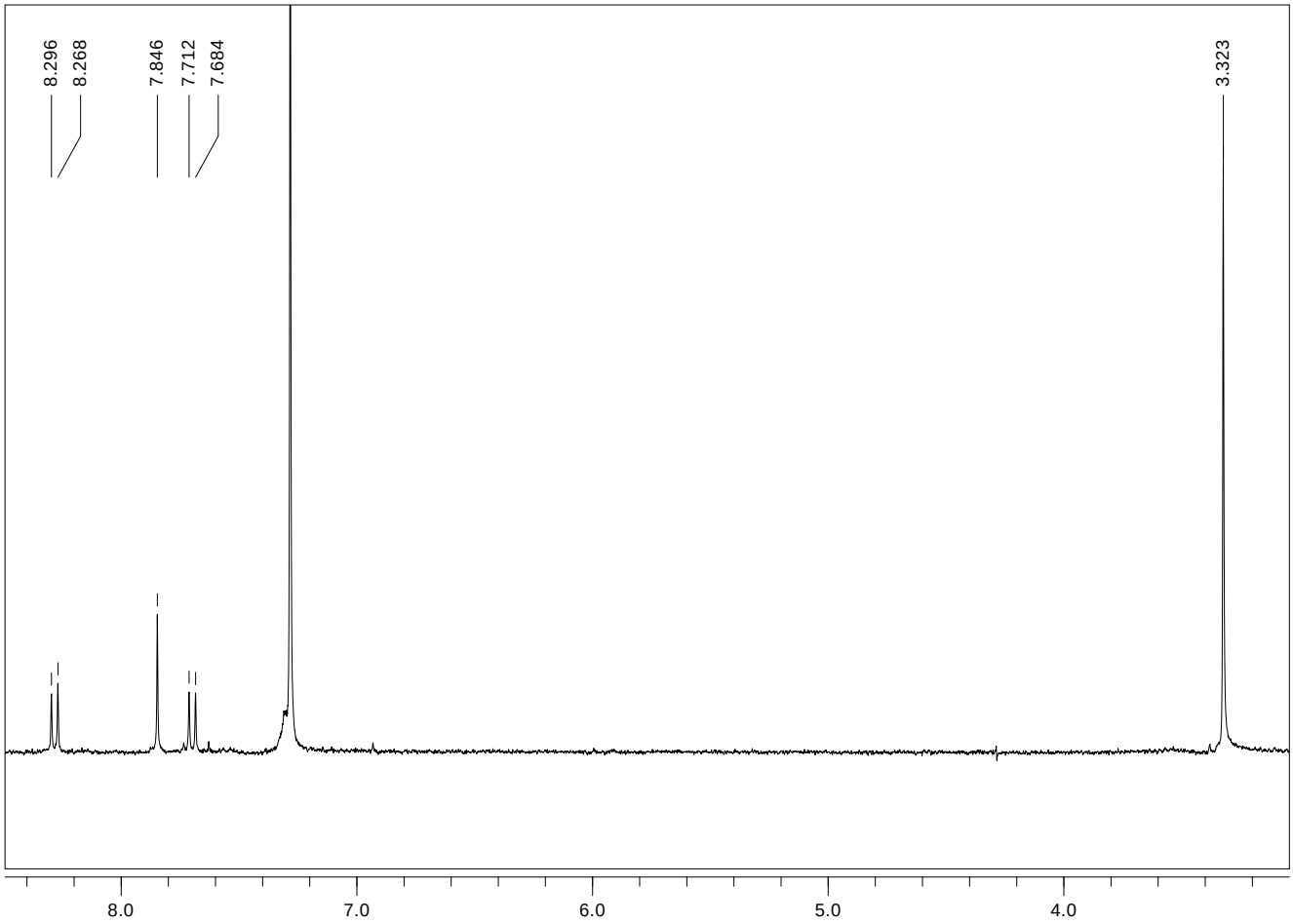

Figure A4.8. ^{1}H NMR ($CDCl_3$, RT) of [Pd(Neoc)I_2(CO)] (**2d**): δ 8.28 (d, 2H, H4, H7 or H3, H8, *J* = 8.2 Hz); 7.84 (s, 2H, H5 and H6); 7.69 (d, 2H, H3, H8 or H4, H7, *J* = 8.2 Hz); 3.32 (s, 6H, C*H*$_3$).

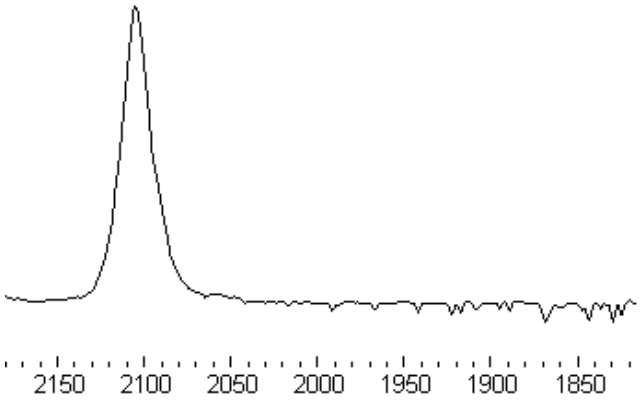

Figure A4.9. IR ($CDCl_3$, RT) of the solution of [Pd(Neoc)I_2(CO)] (**2d**) used to record the spectrum in Fig.A4.5: $\nu_{(CO)}$ = 2105 cm^{-1} (s)

Appendix to Chapter 5

Table A5.1. Indoles ^{1}H NMR reference and -CH_3 chemical shifts.

Substrate	Product	-CH_3 chemical shift (ppm)	Ref.
1a	2a	2.43	[1]
1b	2b	2.46	[2]
1c	2c	2.55	[3]
1d	2d	2.49	[4]
1e	2e	2.36	[5]
1f	1f	2.42	[6]
1g	1g	2.38	[7]
1i	2i[a]	-	-
1l	1l[a]	-	-

[a] The products were analyzed by GC-MS and GC-FID using pure compound as reference.

[1] M. C. Pirrung, L. Deng, Z. Li, K. Park, *J. Org.Chem.* **2002**, *67*, 8374-8388.

[2] H. Inui, S. Murata, *J. Am. Chem. Soc.* **2005**, *127*, 2628-2636.

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[4] Y. Kasaya, K. Hoshi, Y. Terada, A. Nishida, S. Shuto, M. Arisawa, *Eur. J. Org. Chem.* **2009**, *2009*, 4606-4613.

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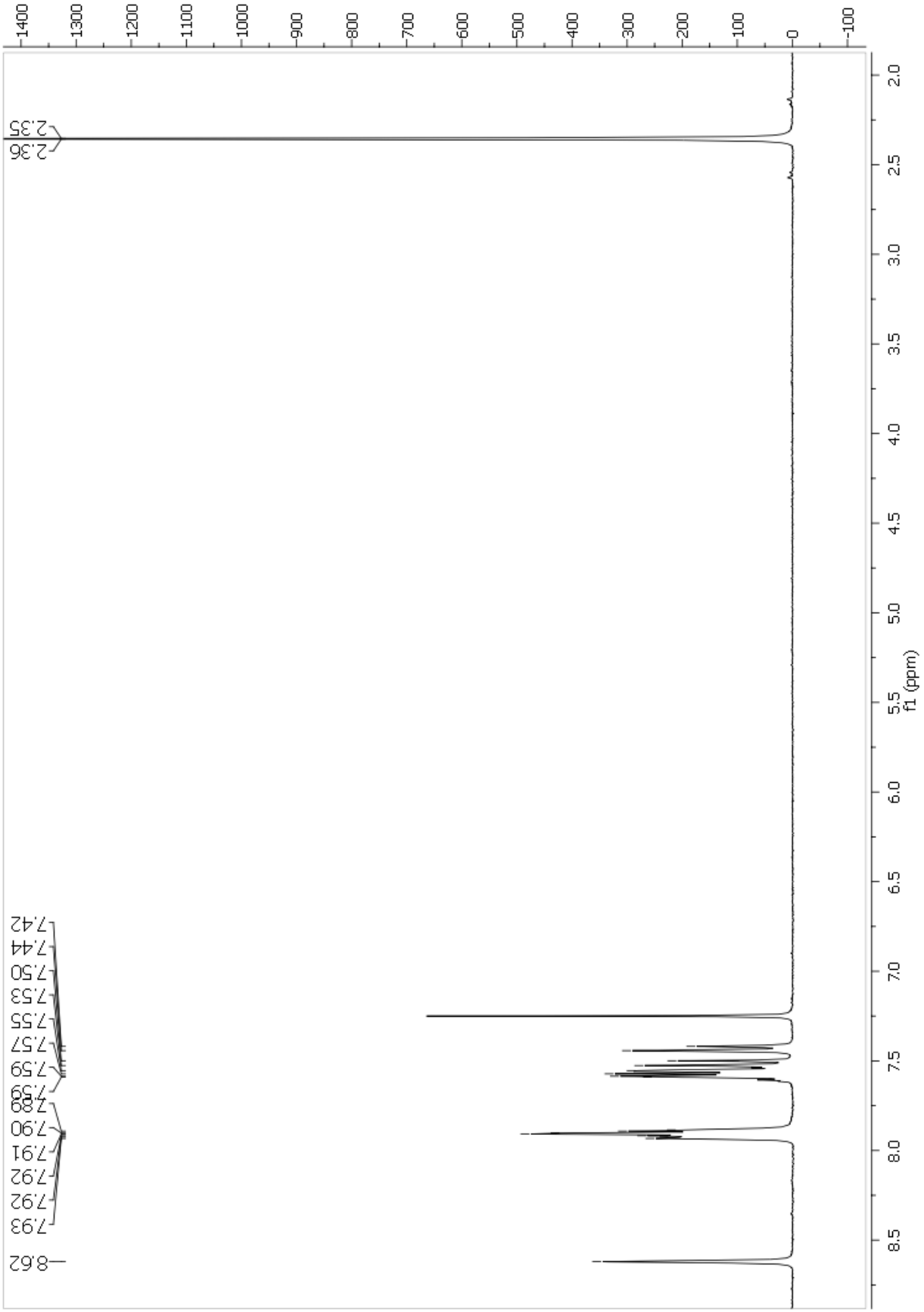

Figure A5.1. ^{1}H NMR (300 MHz, CDCl3, 300 K) 1-(2-nitroprop-1-en-1-yl)naphthalene.

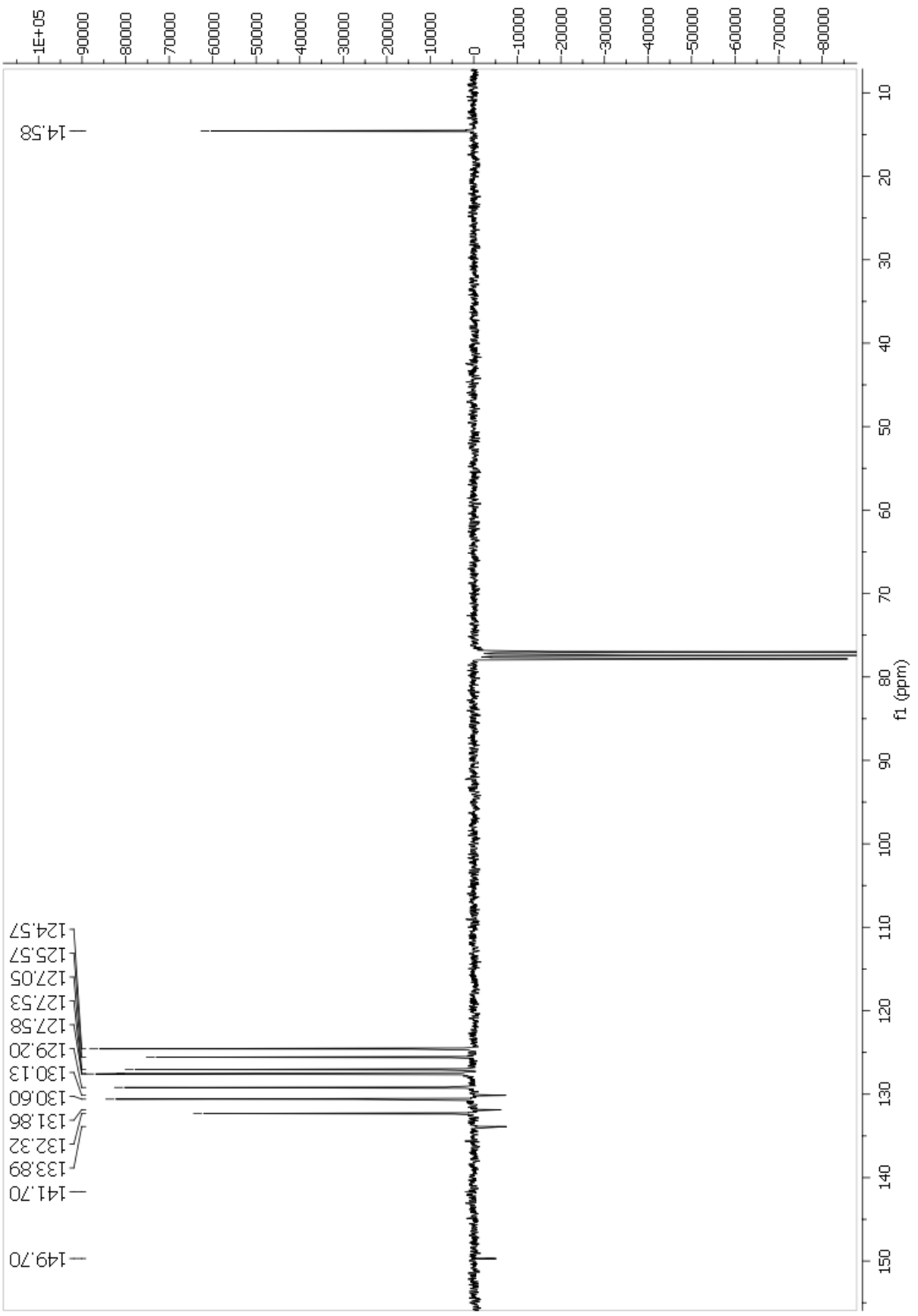

Figure A5.1. ^{13}C APT (75 MHz, CDCl3, 300 K) 1-(2-nitroprop-1-en-1-yl)naphthalene.

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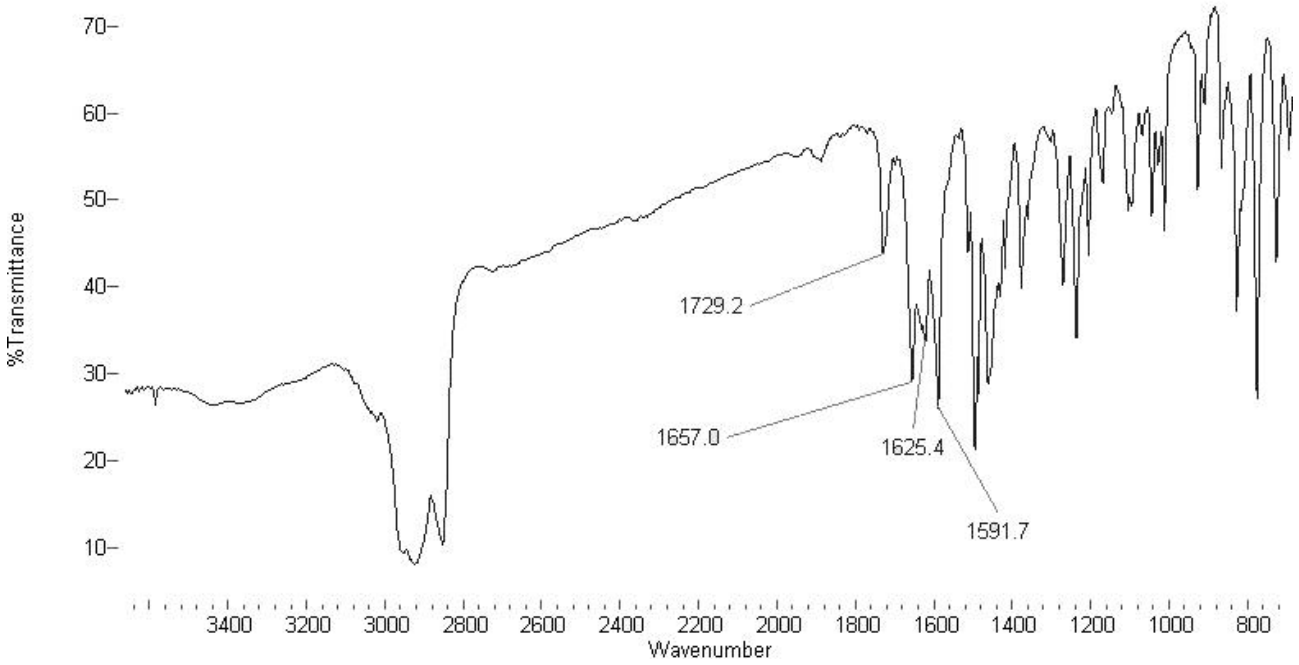

Figure A6.1. IR (Nujol mull, RT) of the mixture of Ar-BIAN oligomers.

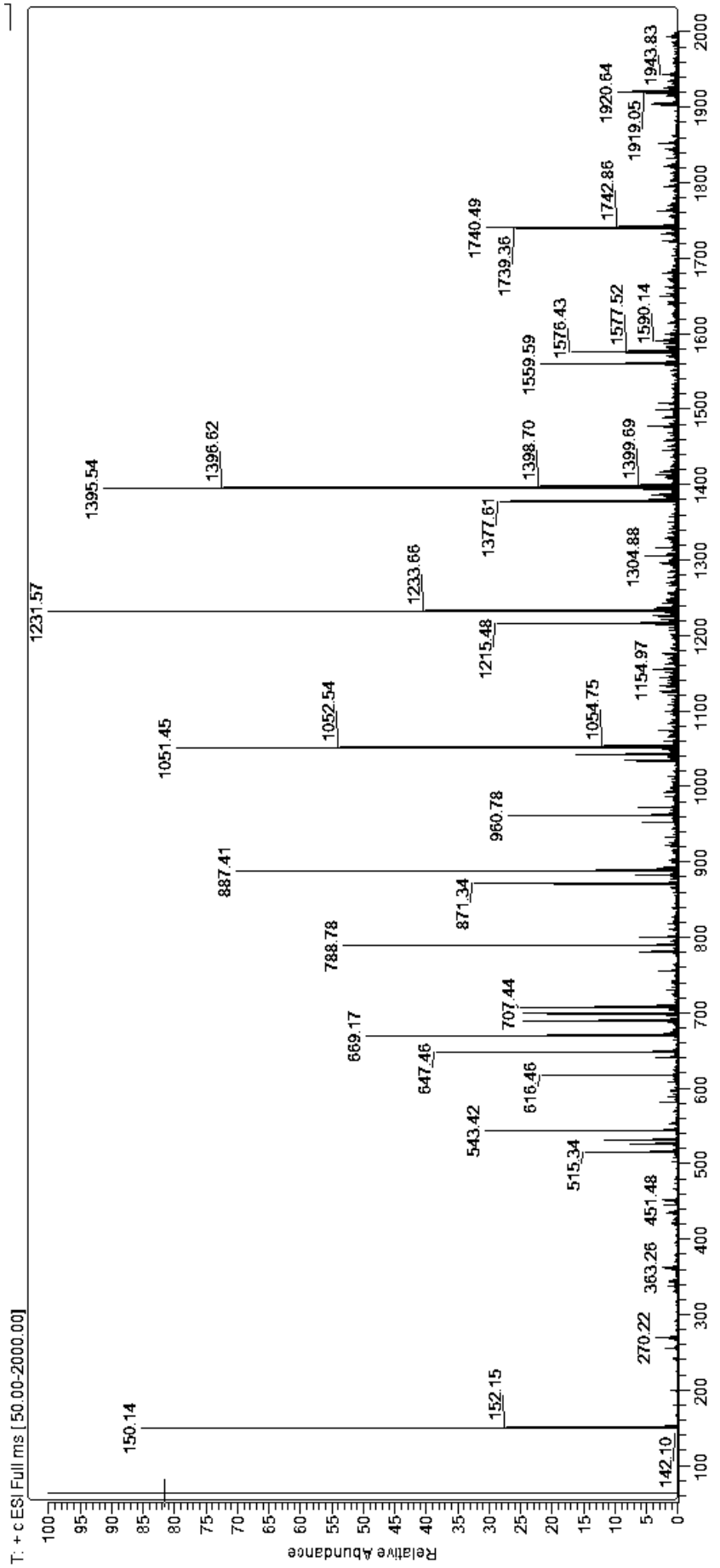

Figure A6.2. MS spectra of the mixture of Ar-BIAN oligomers.

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Francesco Ferretti

Sommario