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2015

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Citation for published version (APA):

Kondrashov, M. (2015). *C–H activation through late transition metal cyclometallation. Addressing selectivity and reactivity problems*. [Doctoral Thesis (compilation), Centre for Analysis and Synthesis]. Department of Chemistry, Lund University.

Total number of authors:

1

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C–H activation through late transition metal cyclometallation

Addressing selectivity and reactivity problems

Mikhail Kondrashov



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AKADEMISK AVHANDLING

som för avläggande av filosofie doktorsexamen vid naturvetenskapliga fakulteten, Lunds universitet, kommer att offentligen försvaras i sal B på Kemicentrum den 4 december 2015, kl. 13.15.

Fakultetsopponent

Prof. Mats Tilset, Universitetet i Oslo, Norge

Organisation LUND UNIVERSITY Faculty of Science Department of Chemistry Centre for Analysis and Synthesis Author(s) Mikhail Kondrashov	Document name DOCTORAL DISSERTATION	
	Date of issue 26-10-2015	
	Sponsoring organisation	
Title and subtitle C—H activation through late-transition metal cyclometallation. Addressing selectivity and reactivity problems.		
Abstract <p>The ligand-directed C—H activation relies on a coordinating donor atom being in proximity to the C—H bond activated. Cyclometallation of 2-(1-naphthyl)-pyridine – a substrate containing both γ- and δ-positions in proximity to the directing nitrogen atom – was studied. Cycloruthenation and cyclopalladation result in γ-substitution and formation of the corresponding 5-membered metallacycles, which is in agreement with published regioselectivities of the corresponding catalytic reactions. Simultaneously, cycloauration and cycloborylation result in δ-substitution and formation of the corresponding 6-membered metallacycles. X-ray structures of all the metallacycles are presented. Deuterium labelling studies show that the cyclopalladation and cycloauration are irreversible, while the cycloruthenation is reversible and happens in both γ- and δ-positions.</p> <p>Attempts to synthesise bimetallic palladium complexes, consisting of two (2-phenyl-pyridine) palladium fragments connected via bridging ligands, resulted predominantly in the formation of monometallic species. While 1,8-naphthyridine and 7-aza-indole bind to palladium in an L-fashion with only one of the two nitrogen atoms, <i>N</i>-piperidine dithiocarbamic acid binds with both sulfur atoms in a chelating, rather than a bridging fashion. 3,3-Dimethylglutaric acid acts as a bridging ligand. X-ray structures of naphthyridine and dithiocarbamate complexes are presented. No increase in the reactivity is observed, when 1,8-naphthyridine, 7-aza-indole and <i>N</i>-piperidine dithiocarbamic acid were used as additives in palladium-catalysed acetoxylation and bromination of 2-phenyl-pyridine.</p> <p>Oxidative anion metathesis was employed as a method of synthesis of organic salts. Trimethylsulfoxonium iodide salts can be converted to tetrafluoroborate, hexafluorophosphate, trifluoroacetate, tosylate and bis-triflimide salts in the presence of hydrogen peroxide and the corresponding acids. The scope of cations, suitable for this reaction also includes <i>N</i>-alkylpyridinium and quaternary phosphonium salts.</p> <p><i>N</i>-acetoxy-pyridinium chloride was employed as an oxidant in the palladium-catalysed C—H functionalisation of 2-aryl-pyridine resulting in the formation of the corresponding chloro-derivative. Trimethylsulfoxonium tetrafluoroborate, hexafluorophosphate and tosylate are unreactive as oxidants towards 2-(phenyl)-pyridine palladium acetate.</p> <p>Cyclopalladation of PCP pincer ligands with aromatic and aliphatic backbones by (PhCN)₂PdCl₂ was shown to proceed at temperatures as low as -62°C. The initial interaction results in the formation of a mixture of coordinated species, only some of which react further to form metallacyclic pincer compounds. The formation of pre-cyclometallation intermediates is kinetically disfavoured. However, C—H activation is fast and not rate-limiting in case of neither sp² nor sp³ C—H bonds.</p>		
Key words: C—H activation; cyclometallation; pincer ligands; anion exchange; bimetallic complexes; oxidative functionalisation		
Classification system and/or index terms (if any)		
Supplementary bibliographical information		Language English
ISSN and key title		ISBN 978-91-7422-418-4
Recipient's notes	Number of pages 79	Price
	Security classification	

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Addressing selectivity and reactivity problems

Mikhail Kondrashov



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Faculty of Science
Department of Chemistry
Centre for Analysis and Synthesis

ISBN 978-91-7422-418-4

Printed in Sweden by Media-Tryck, Lund University
Lund 2015



*“Дайте мне глаз, дайте мне холст,
Дайте мне стену, в которую можно вбить гвоздь -
Ко мне завтра вы придете сами.”
- Борис Гребенщиков*

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List of papers

1. Metal controlled regioselectivity in the cyclometallation of 2-(1-naphthyl)-pyridine, Kondrashov, M.; Raman, S., Wendt, O. F. *Chem Commun.* **2015**, *51*, 911–913.
2. Regioselectivity in C—H Activation: reagent control in cyclometallation of 2-(1-naphthyl)-pyridine, Kondrashov, M.; Provost, D.; Wendt, O. F., *Submitted manuscript*.
3. Crystal structure of (piperidine-1-carbodithioato- κ^2S,S)[2-(pyridin-2-yl)phenyl- κ^2C^1,N]palladium(II) Kondrashov, M.; Fleckhaus, A.; Gritcenko, R.; Wendt, O. F. *Acta Cryst.*, **2015**, *E71* (9), m166
4. Cyclometallated phenyl-pyridine palladium species. Monomeric complex formation with potentially bridging ligands Kondrashov, M.; Gritcenko, R.; Fleckhaus, A.; Wendt, O. F., *Submitted manuscript*.
5. Oxidative anion exchange as a general method for ion metathesis in organic salts. Kondrashov, M.; Wagner, C.; Wendt, O. F. *Manuscript*.
6. Very facile, low-temperature C—H activation in PCP pincer palladation, Kondrashov, M.; Wendt, O. F. *Manuscript*.

Manuscripts not included in the current thesis:

1. Mechanisms of the CO₂ Insertion into (PCP) Palladium Allyl and Methyl σ -Bonds. A Kinetic and Computational Study, Johnson, M. T.; Johansson, R.; Kondrashov, M. V.; Steyl, G.; Ahlquist, M. S. G.; Roodt, A.; Wendt, O. F. *Organometallics*, **2010**, *29* (16), 3521–3529.

Contribution to papers

1. Performed all the experimental work, except for the initial synthesis of the gold metallacycle and X-ray characterisations. Wrote most of the article.
2. Performed most of the experimental work, designed and supervised the initial experiments performed by D. Provost. Wrote most of the manuscript.
3. Designed and supervised all the experiments, except for the X-ray characterisation. Wrote part of the article.
4. Designed and supervised initial experiments. Performed most of the experiments, except for the X-ray characterisation. Wrote most of the manuscript.
5. Designed and supervised all the experiments. Performed the initial experiments. Wrote most of the manuscript, supervised the writing of the rest of the manuscript.
6. Performed all the work presented in the article. Wrote most of the manuscript.

Popular summary

Synthetic chemicals are the basis of the modern civilisation. Nowadays, they have a bad reputation, but it is only due to them that we are able to live healthier, longer, receive improving medical treatments, use the comforts of modern technologies and not die of thirst and starvation, despite the immense population growth. The main task of organic synthesis is to transform molecules into other molecules. Since molecules consist of atoms bound to each other, transforming one molecule into another molecule is essentially a question of breaking some of the existing bonds and making new ones.

One typical recurrent problem in synthesis is breaking C—H bonds. Most of our organic chemical feedstock consists of hydrocarbons (molecules that have only carbon and hydrogen atoms in them). This very special chemical composition makes these molecules suitable for a limited amount of applications. The majority of chemicals we need require nitrogen, oxygen, phosphorus, sulfur, halogens and other elements to be present in the molecule in order to have the required properties. Hence, we need to break C—C and C—H bonds and make new ones to get the molecules we want. At this point we stumble at a problem: not only is a C—H bond, typically, a very strong bond, but it is also fairly unpolar, which makes it difficult for this bond to undergo many interactions. Also, large organic molecules usually contain many C—H bonds, which can have fairly similar properties and only some of them should be broken to produce a certain target molecule. During the past decades metal-catalysed C—H bond activation has emerged as a huge field of research, providing numerous new methods for cheap and facile transformation of C—H bonds into other bonds.

The current work is dedicated to some of the auxiliary problems existing in this field. In order to progress faster in the creation of new methods, we need to know more about the properties of the metal catalysts and their interaction with C—H bonds. In this thesis I was able to study the behaviour of different metal catalysts towards a specific substrate, which could point out the difference between their properties. My attempt to expand the scope of catalysts and reagents used in C—H activation reactions was unsuccessful, but it indicated important specifics of the properties of relevant catalysts. At last, I was able to study an old, well-known reaction and show that it can proceed under completely unexpected conditions, resulting in a C—H activation at one of the lowest temperatures registered.

Abbreviations

Ac	acetyl
acac	acetylacetonate
AO	atomic orbital
Ar	aryl
bipy	2,2'-bipyridyl
BQ	1,4-benzoquinone
Bu ^t	<i>tert</i> -butyl
cod	cyclooctadiene
Cp	cyclopentadienyl
Cp*	pentamethylcyclopentadienyl
<i>-d</i>	deuterated molecule
DCE	1,2-dichloroethane
DCIB	1,2-dichloroisobutane
DCM	dichloromethane
DFT	density functional theory
DMF	dimethylformamide
dppf	1,1'-bis(diphenylphosphino)ferrocene
ESI	electrospray ionisation
Et	ethyl
gCOSY	gradient correlation spectroscopy
HOMO	highest occupied molecular orbital
IPr	1,3-bis-(2,6-diisopropylphenyl)imidazol-2-ylidene
kJ	kilojoule
L	ligand
LDC	ligand-directed C—H activation
Me	methyl
MS	mass-spectrometry
MW	microwave irradiation
NCS	<i>N</i> -chlorosuccinimide

NMP	<i>N</i> -methylpyrrolidone
NMR	nuclear magnetic resonance
NXS	<i>N</i> -halosuccinimide
[Pd]	palladating agent
Ph	phenyl
PhPy	2-(2-pyridyl)-phenylene
Pin	pinacolate
Piv	pivaloyl
Pr ⁱ	isopropyl
py	pyridine
r.t., RT	room temperature
SM	starting material
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMNO	trimethylamine <i>N</i> -oxide
Tol	tolyl
Ts	<i>p</i> -toluenesulfonyl
X-Phos	2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl

Acknowledgements

A lot of people have deliberately or accidentally contributed to this PhD thesis. First of all, I am very grateful for the education that I have received. That would not happen without the help of my parents and my grandfather, they always supported whatever I was interested in and did their very best to make me study hard. My school teachers were an example of ultimate devotion to the children and to their profession. I could not be a chemist without the effort of people like Sergey Ponomarev, Sergey Semenov, Konstantin Vlasenko, Sergey Perchatkin, and Galina Kokueva.

When I entered the university, I enjoyed not only the knowledge and experience which were transferred to me, but also enthusiasm and love for chemistry from lecturers like Dmitry Lemenovsky, Dmitry Roytershtein, Marina Tamm, Vitaly Kotov, Viliam Smit, and Valentin Ananikov. At the time when I met them, I did not appreciate or acknowledge their effort and now it is time to do so. I received the best education I could wish for from them. My classmates at high school and university were a constant support, competition and source of additional motivation, they were the ones who created an atmosphere of knowledge around me.

My first mentors taught me a lot about the experimental chemistry. Sergey Kuklin, Avtandil Koridze and, most of all, Alexey Sheloumov, – thank you for everything! I can only imagine how hard it was to tolerate me for all those years.

A short exchange trip to the University of Missouri-Kansas City, USA in 2005 changed a lot for me. Keith Buszek was my inviting professor and Ekaterina Kadnikova helped me a lot with getting there as well as many more times afterwards. Then I had a stay in Göttingen in 2008 with people like Lutz Ackermann and Rubèn Vicente, where I also learned a lot.

When I arrived to Lund in 2009, I faced the most welcoming atmosphere. I have to thank my supervisor Prof. Ola Wendt for that. He was always supportive and open to new ideas. He offered me the highest degree of freedom in the lab, even if that would include burning ammonium dichromate or playing floorball in the corridor. He was very helpful whenever I had a theoretical or a practical problem, jumping momentarily onto an NMR or X-ray machine with his great skills. The environment he created in the group is so good that I am a little scared to join any other group in the future.

People in the lab were a good company and a good help over the last years. Thank you, Daniel, Klara, Inus, Nagarajan, Sudarkodi, Solomon, Alex, Abdoh, André,

Maitham, Kevin, Sasha, Sheetal, Katya, Rachael, David and all the others. I have to mention Magnus in particular. Magnus was my first supervisor in the lab and a great inspiration behind most of the work-related and non-work-related activities. I am also very grateful to all the students that I had an opportunity to supervise in the lab: Lisa, Mohammed, David, Roma, Joseph and Claudia – you helped me a lot with my work!

The work at the department would have zero efficiency without the people who make the things function and proceed well. Maria, Bodil, Clas, Karl-Erik, Göran, Sofia and Katarina are truly the key contributors to the current thesis.

When I arrived to Sweden, I was a young and naïve student, unaware of any customs and open to any suggestions. After these years, I find myself transformed into an old know-it-all, who has explored every little corner of the town and stays home on a Friday night. On this way I met a lot of people, who were teaching me, learning from me, helping me, getting help from me, making me drunk, forced to drink by me (the latter is more relevant, I guess), telling me how to behave and misbehaving. More importantly, they *made* my way through the PhD. Some of them came and left, some stayed, but most of them made a deep dent in my heart, which would always be there, regardless of where they are. Many people whom I met created communities that were even more memorable, since these communities had their own faces. I do not know a way to rank them, so I will make some kind of a chronological listing, as they did not appear at the same time exactly.

First, there was 6F community: **Sheriff, Alex Z.** (a role model, you were sometimes), **Severine** (to our siblings!), **Sevinç** (salad for dinner?), **Tiago F.** (hope to finish rehearsing “Golden brown” sometime), **Marisa** (a movie late night and “early grey” for breakfast?), **Dawn** (I’ll keep the rice-cooker), **Rodrigo** (wish to come to Bolivia!), **Magda** (how are you, electron?) and **Irem** (I wish you to be happy, sister!).

Then, 6E community: **Tiago M.** (I’d take you scouting, as I already said, just don’t squeeze any eggs!), **Mariano** (“but, who is Moses?”), **Sandra** (“Alabama song”, please!), **Stefano, Rosa, Ryan** (“you, English people, apologise a lot!”), **Rafael, Norbert** and **Dmitry** (killer cook and badminton player).

Then, 6B community: **Steven** (“social parasite club” is still open!), **Steffy** (witchy-witch), **Svetlana, Christopher** (I hope that we will have a chance to take one more walk to Hjärup sometime in the future) and **Gabor** (palinka!).

Also, CAS-community: **Maria-Luisa, Eira** (classy!), **Torbjörn, Eduard, Sergey M., Isa** (what’s the next colour?), **Angelo** (boyade! when will we make at least 85kg?!), **Michaela** (you’re still my best student! Short time passed from me correcting your report to you correcting mine), **Henrik** (more beer!), **Monika** (how was your weekend, after all?) **Björn** (I wish we would have more reports to correct together) and **Kirill**.

And, the last, but not the least – the core crew of the German Embassy, with whom, one sunny afternoon in Bellini pizzeria, we made a decision that changed the social

landscape of Lund for 3.5 years. **Nata**, you are there with me all the way through and I am so grateful that I know you. I hope to know you as a grandma too. **Janina**, you're one inspiring person! (I wish another t-shirt, at least). **Sebastian**, I learnt a lot from you, don't you ever change!

...and so many people, who swarmed around us like a pack angry bees: **Miguel** (you are the best flatmate, I am scared to move away to anyone else now!), **Carlos** (I hope I will be able to hit the right tune sometime), **Sara C** (thanks for the citron crème!), **Bruno S** (seriously, you're the most friendly person, ever), **Robert** (does the band still need some?), **Brian** (simply became a legend), **Lars** (where are the Germs?), **Verena**, **Toby** (you are the fun-producing engine!), **Sonja**, **Uta** (hug!), **Charlotte**, **Jaha** (I solved it: you're actually Mongolian), **Juan Diego**, **Ana**, **Felix F.** (wish you were here), **João** (protect yourself from yourself!), **Maria P.** (at least someone can organise the Portuguese), **Marija K.**, **Alex N.** (join for *the kebab* next time!), **Gabriel C.** (it starts with "Soy un hombre muy honrado"), **Anya E.**, **Claudia Z.**, **Kathrin** (any more carrot cake?), **Vera**, **Tanja L.**, **Gunnar**, **Elinor** and many-many more!

A small, but solid Russian crew: **Коля**, **Женя**, **Миша**, **Леха Карцев**, **Леха Кривцов**, **Галя**, **Олеся**, **Вова**, **Саша** – спасибо вам!

Also, my friends from Moscow were able to support me, whenever I had deep philosophical issues: **Tema**, **Dima** – thank you for all the long conversations!

General Introduction

Most of the commodity chemicals and pharmaceuticals are organic molecules bearing various functional groups and heteroatom substituents. At the same time, the majority of crude carbon sources, available to the chemical industry in large quantities consist of hydrocarbons or other molecules with very low degree of functionalisation (Figure 1). One notable exception is carbohydrates which rather have a too high oxygen content to be used as a general feedstock in organic synthesis. However, normally a task of the organic synthetic chemist is to change molecules in the direction of an increasing degree of functionalisation. That means transforming C—H bonds into C—C or C—heteroatom bonds.

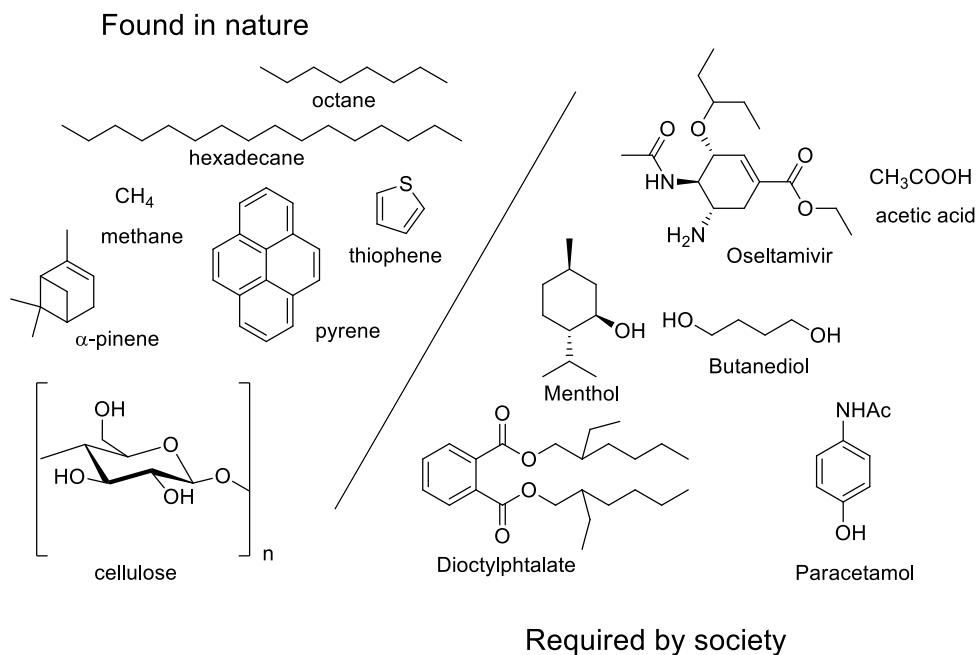


Figure 1. Typical examples of compounds available from natural resources on a large scale (left) and pharmaceuticals and commodity chemicals required by the society (right).

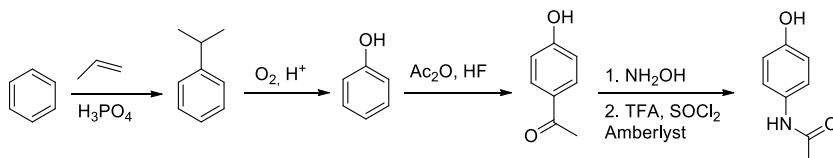
The C—H bond is one of the strongest single bonds. Its typical bond dissociation energy usually lies within the range of 90-110 kcal/mol, sometimes reaching as high as 130 kcal/mol for acetylenic C—H bonds. Thus, the cleavage of such a strong bond remains a critical challenge in many areas of organic chemistry, including organic synthesis and catalysis.

A variety of C—H functionalisation reactions has been developed during the last centuries of organic chemistry research. Normally, the development of a new method of this type faces two challenges:

- 1) low thermodynamic and kinetic reactivity of the C—H bond;
- 2) selection between multiple C—H bonds in the substrate.

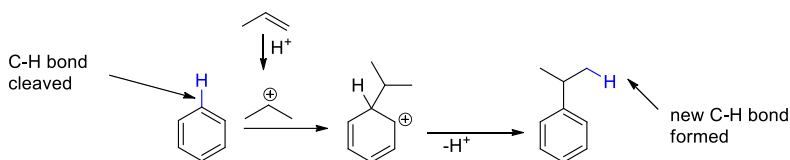
The first challenge is typically resolved by using high-energy reagents and/or catalysts that can form active species (e.g. halogen or oxygen radicals) that would allow to overcome the reaction barriers and in the end form new bonds of comparable strengths (e.g. O—H bond) to compensate for the energy cost of breaking a C—H bond. The second challenge is typically resolved by using a starting material with specific C—H bonds being more prone to be substituted due to special electronic predispositions.

We can take a look on how classical organic synthesis solves these problems, following the example of one of the synthetic pathways from a cheap hydrocarbon available on a large scale towards a common pharmaceutical – paracetamol¹ (Scheme 1). Overall the starting material of this synthesis – benzene – does not contain any heteroatoms, while the product contains three. More specifically, the transformation of the C—H bonds into other bonds happens in the first three steps of this five-step process.



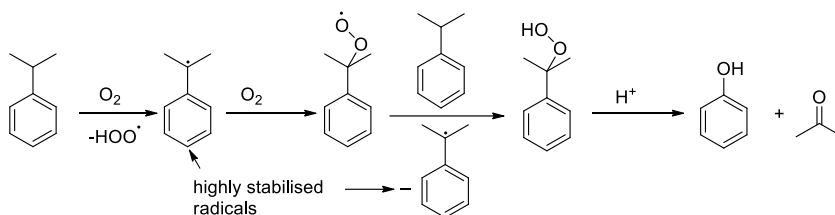
Scheme 1. One of the syntheses of paracetamol.

The first step is a Friedel-Crafts alkylation of benzene which happens via a highly electrophilic carbenium ion (Scheme 2). The C—H bond is being broken during the last part and the restoration of aromaticity is the driving force for this process. Overall the aromatic C—H bond broken in this process is exchanged for a slightly weaker aliphatic C—H bond. There is no issue of regioselectivity in this process, since all the C—H bonds in the substrate benzene are identical.



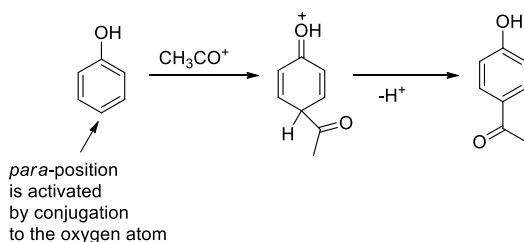
Scheme 2. Simplified mechanism of the alkylation of benzene.

In the second step oxygen is used as a high-energy reagent. The reaction is thermodynamically favoured, since along with the cleavage of the strong C—H bond and relatively weak C—C and O=O bonds, very strong O—H, C—O and C=O bonds are formed. The specific cleavage of the benzylic C—H bond happens due to the activation of this position and corresponding stabilisation of the formed radical with the inductive effect of two methyl group and mesomeric effect of the aromatic ring system. The formed hydroperoxide undergoes the Hock rearrangement to finally form phenol and acetone (Scheme 3).



Scheme 3. Simplified mechanism of the oxidation of cumene.

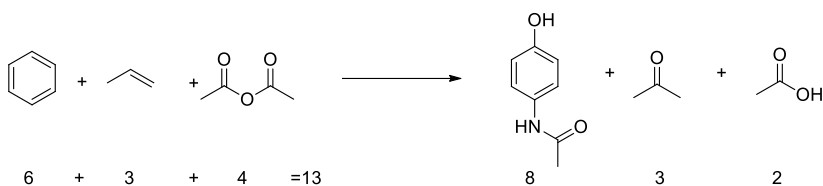
The next step is, again, an electrophilic aromatic substitution, which happens via a strongly electrophilic intermediate. The preference in C—H substitution is due to the strong donating effect of the OH-group, which activates the *para*-position of the phenol (Scheme 4).



Scheme 4. Simplified mechanism of the acetylation of phenol.

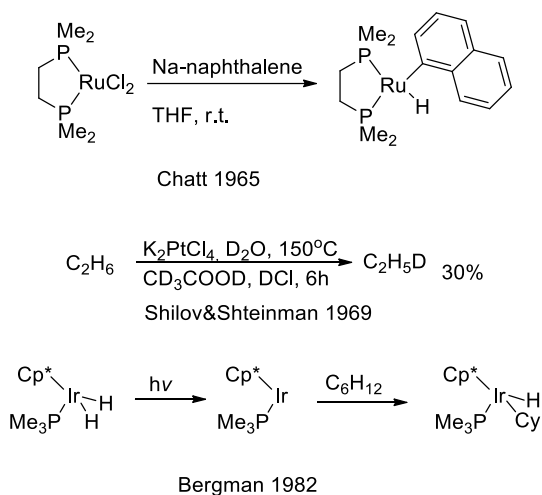
As we can see, this well-developed synthesis requires fairly harsh reagents and conditions. Overall, five steps are needed for what is essentially an installation of two substituents onto a benzene ring. Also, out of 13 carbon atoms of the reactants only 8 end up in the product molecule, which is good but still far from perfect in

terms of atom economy (Scheme 5). That leads to the conclusion that despite the immense development of the field, new methods of functionalisation are still needed for organic synthesis.

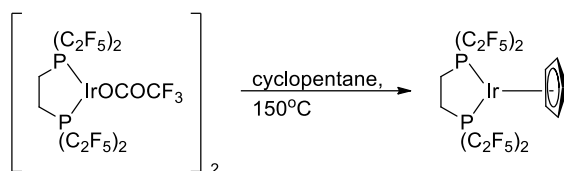


Scheme 5. Atom economy in synthesis of paracetamol.

Transition metals offer an interesting alternative as reagents and catalysts in C—H activation. d-Orbitals lie at rather high energy levels allowing transition metals to be Lewis σ -acids and π -bases at the same time, which causes interactions that are unique for this group of elements. Therefore, transition metals have a long history of C—H bond activation. A few remarkable examples include Ru insertion into a C—H bond of naphthalene by Chatt,² Pt-catalysed H-D exchange published by Shilov and Shteinman in 1969,³ oxidative addition to the Ir atom by Bergman in 1982,⁴ oxidative aromatisation of a saturated carbocycle by Roddick in 1996⁵ and many others (Scheme 6).



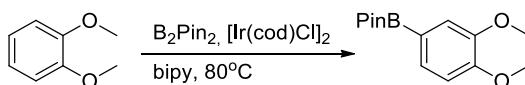
Scheme 6. Some examples of C—H bond cleavage by transition metals.



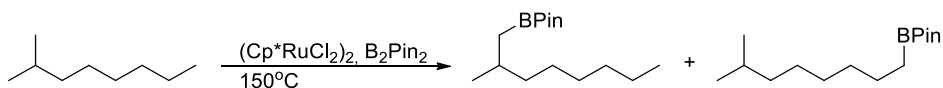
Roddick 1996

Scheme 6. Continued.

Later, a multitude of catalytic C—H activation protocols based on metal-catalysed C—H activation were developed. A few examples include arene⁶ and alkane⁷ borylation by Hartwig, arene acetoxylation by Ebersen and Sanford,⁸ oxidative heteroarene cross-coupling by You⁹ (Scheme 7).

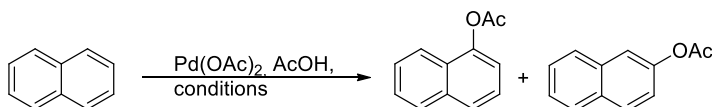


Hartwig 2002

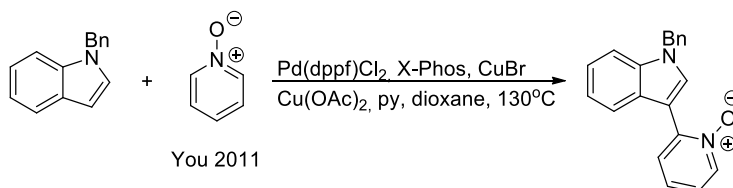


Hartwig 2006

30:70



	Reagents and conditions	Product distribution
Ebersen 1971	O ₂ , 110°C	1:1
Sanford 2010	PhI(OAc) ₂ , Ac ₂ O, 100°C	1.39:1



You 2011

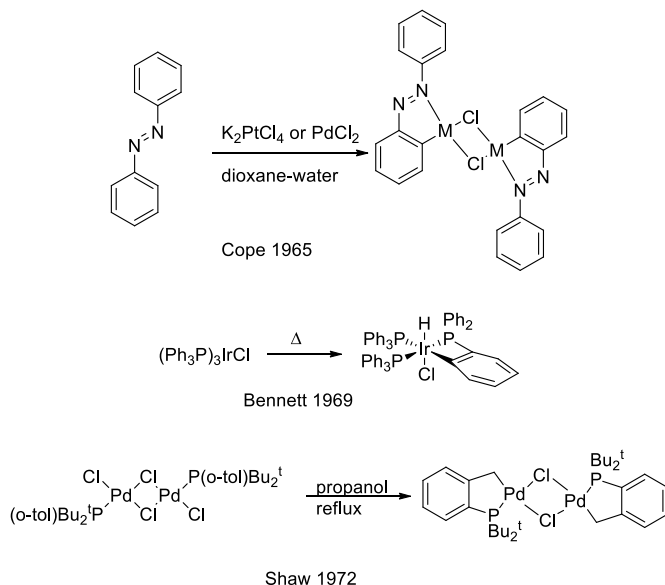
Scheme 7. Some examples of catalytic C—H bond functionalisation by transition metals.

It is notable, that in the reactions mentioned above the issue of discrimination between different C—H bonds is only partly resolved. Thus, the aromatic borylation is guided by a steric repulsion of two substituents in the aromatic ring (a similar

reaction on a mono-substituted benzene results in a mixture of meta- and para-isomers); the Ru-catalysed aliphatic borylation is highly selective towards primary C—H bonds, yet, the discrimination between those is very poor; acetoxylation of arenes is probably guided by the relative electron richness of carbon atoms and also results in a mixture of products. Oxidative arene coupling is relying on high mesomeric effect, increasing the nucleophilicity of the β -position of the indole compared to the other positions.

One very successful approach to the problem of selectivity is the use of coordinating atoms. Heteroatoms with lone pairs of electrons, like N, O, P or S, are able to bind to the vacant orbitals of the metal. After this, the organic molecule becomes bound to the metal atom, reducing the entropic costs for the interaction between the metal and a C—H bond. Also, typically, only one of the C—H bonds becomes located at the position that allows easy interaction with metal atom, thus, solving the issue of selectivity. This reaction results in the formation of a metallacycle and is called cyclometallation.

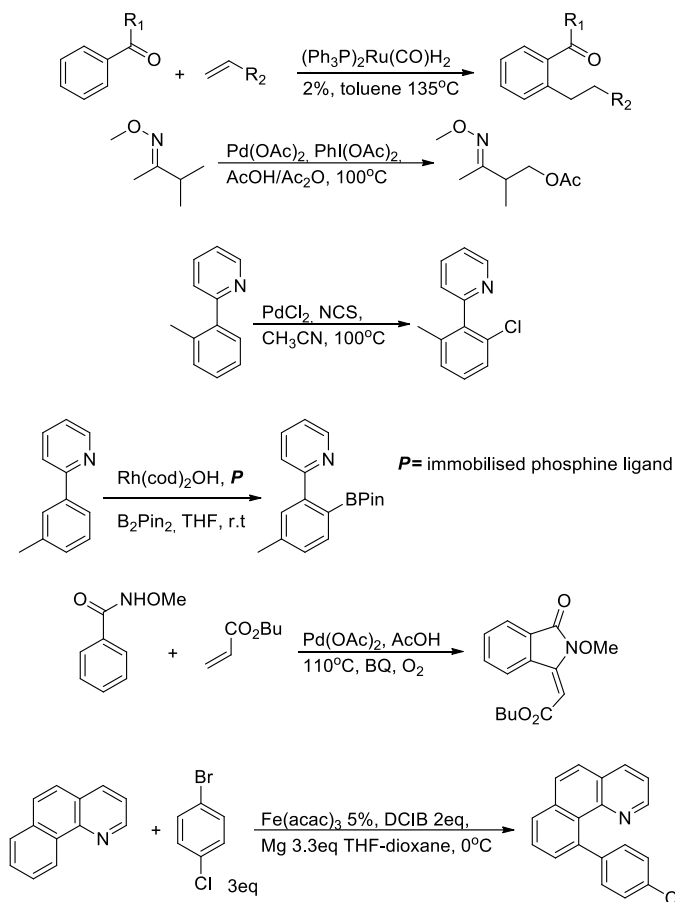
Some of the early examples of cyclometallation include palladation of azobenzene by Cope et al,¹⁰ intramolecular oxidative addition of C—H bond to Ir by Bennett¹¹ and benzylic palladation by Shaw¹² (Scheme 8).



Scheme 8. Some examples of cyclometallation.

If the cyclometallation is coupled with a further C—M bond functionalisation, regenerating the initial metal species, this can result in a catalytic process called ligand-directed C—H activation. A multitude of reactions of this type have been

discovered in last decades and a few examples of those¹³⁻¹⁹ are presented in the Scheme 9.



Scheme 9. Some examples of catalytic ligand-directed C—H activation.

It is noteworthy, that not only are the majority of these methods unique transformations, which are impossible in the absence of transition metals, but also the substituted C—H bonds are located at the carbon atoms which are neither the most electron-rich, nor the most electron-poor, nor the least sterically hindered. Thus, this type of products would not be available without metal catalysis and the directing effect of heteroatoms.

This thesis is dedicated to an analysis of problems remaining in the field of ligand-directed C—H activation, namely: regioselectivity and temperature limits in C—H activation and expanding the scope of catalysts and reagents used in palladium-catalysed reactions. Chapter 1 of the thesis includes an unusual pattern of selectivity in the cyclometallation of a substituted pyridine substrate. In Chapters 2 and 4 our

attempt to expand the scope of reagents and catalysts used in ligand-directed C—H activation is described. Chapter 3 is dedicated to the use of the oxidative anion metathesis as a general method for the synthesis of organic salts. Chapter 5 is dedicated to an exceptionally low-temperature cyclometallation process in the synthesis of pincer complexes.

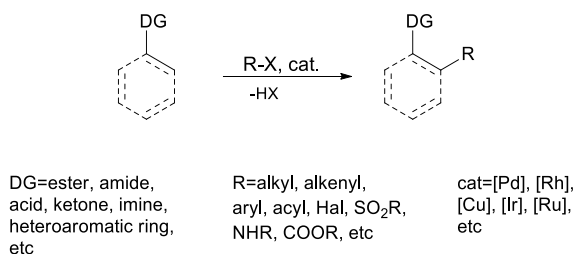
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Chapter 1

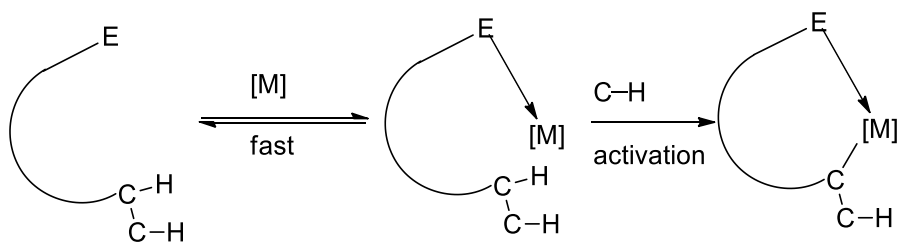
1.1 Introduction

Ligand-directed C—H activation (LDC) is dependent on a functional group with an electron pair available for coordination. Typically this is a heteroatom like N, S, O etc (Scheme 1).



Scheme 1. General description of the ligand-directed C—H activation.

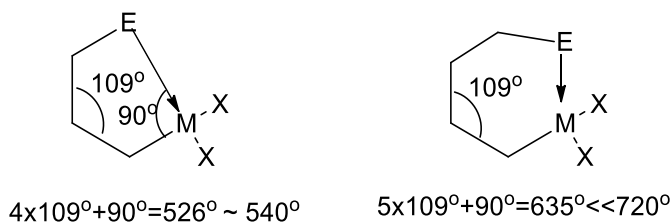
A typical mechanism of LDC starts with coordination of the heteroatom, which is usually fast and reversible. Then, a C—H bond cleavage event might take place. If several C—H bonds are in the proximity of the metal atom, the question of regioselectivity arises (Scheme 2).



Scheme 2. A typical two-step mechanism of the cyclometallation.

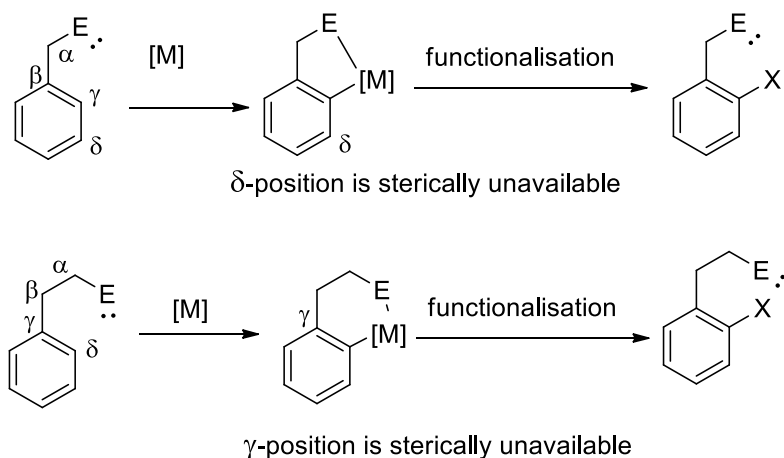
In this respect, 5-membered cycles are fastest to form for kinetic reasons in the case of alicyclic systems.¹ Also, in case of square-planar, square-pyramidal and octahedral chelates, 5-membered rings are preferred thermodynamically since a 90° angle is better matching the polygon formed. The sum of preferred angles for the

sp^3 -atoms of the ligand and a square-planar metal equals 526° which is almost equal to 540° (an ideal sum of angles of a flat pentagon), while in the case of a six-membered ring the corresponding difference becomes more significant (Scheme 3).



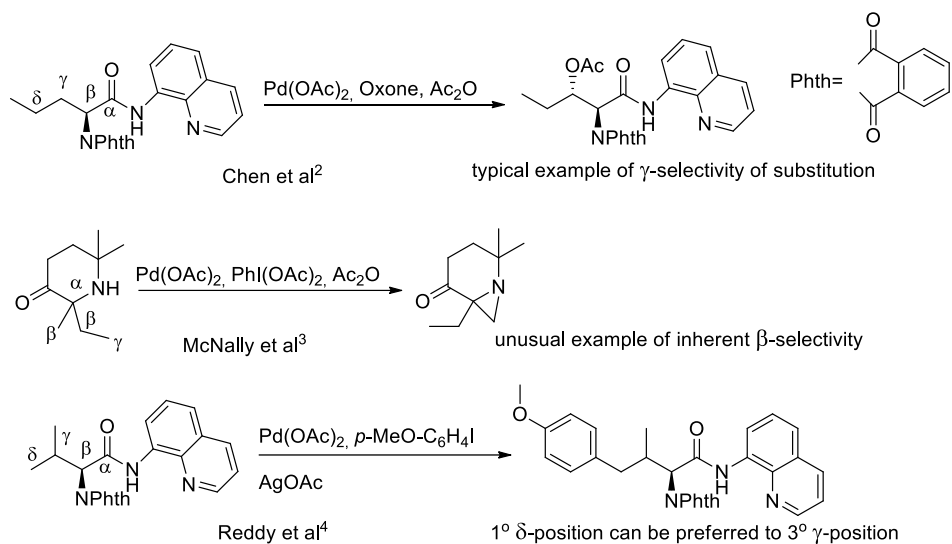
Scheme 3. 5- and 6-membered metallacycles with square-planar geometries.

The most widely studied substrates of LDC have a structure of an aromatic ring with a donor heteroatom substituent at the benzylic position (Scheme 4). γ -Substitution normally happens via a five-membered ring intermediate, formally proving the former statement. However, due to the lack of flexibility in the aromatic rings, the δ -position of these substrates cannot rotate towards the atom of the metal and is not really available for substitution. Similarly, substrates that do not possess a γ -position available for substitution can undergo preferential δ -substitution via a 6-membered ring.



Scheme 4. γ - and δ - substitution in the case of aromatic substrates.

In order to compare γ - and δ -substitutions, flexible aliphatic systems can be used. The vast majority of sp^3 LDC's also happen with γ -selectivity. However, different factors can play important roles, e.g. the rate of C—H activation is dropping in the row of $1^\circ > 2^\circ > 3^\circ$ C—H bonds, which, sometimes, allows a preferential formation of 6-membered metallacycles (Scheme 5).



Scheme 5. Selectivity in sp^3 -LDC.

In order to have a more general comparison between γ - and δ -substitutions in sp^2 LDC, it is required to design a new system. One possibility is to use a terminal or a trans-disubstituted alkene with a heteroatom in a homoallylic position. However, the use of this type of substrates would be problematic, since double bonds of alkenes are prone to side reactions, e.g. π -bond migration and oxidation. In our work we have decided to study the cyclometallation of 2-(1-naphthyl)-pyridine (**1**) (Figure 1).

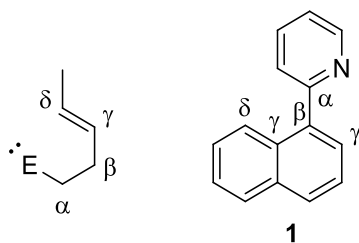
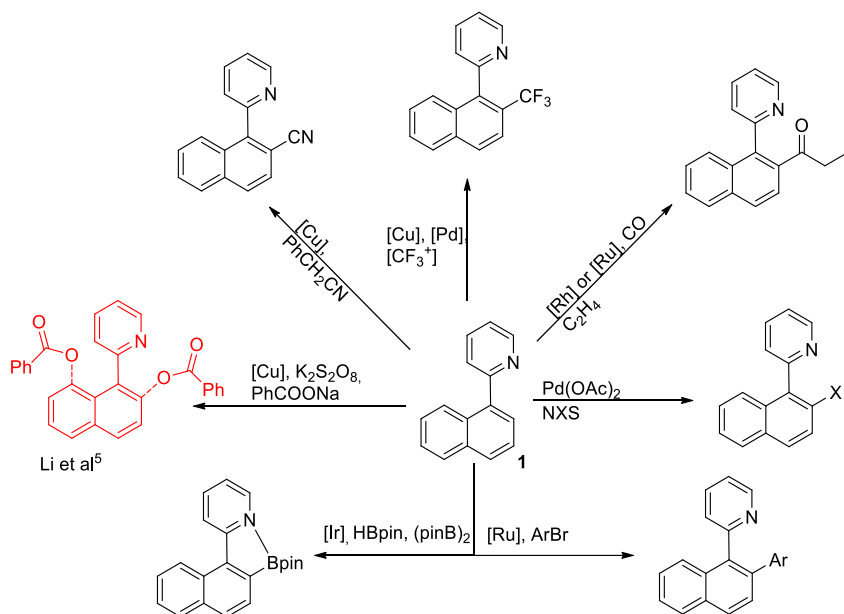


Figure 1. Structures with γ - and δ - sp^2 C—H bonds sterically available for substitution.

This substrate is a fairly robust aromatic compound possessing both γ - and δ -C—H bonds in close proximity of a potentially coordinating atom of metal. A number of publications on metal-catalysed LDC protocols employed this compound in their substrate scope (Scheme 6).^{5,6}

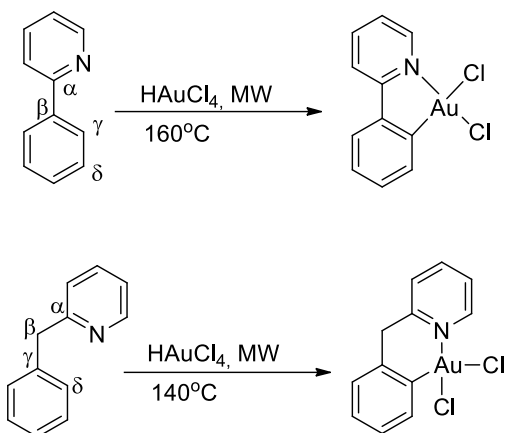


Scheme 6. Selected examples of LDC of **1**.

It is important to mention that in the majority of the articles the presence of two possible sites for activation is not discussed. Also, 1D ^1H NMR of the products is usually the only spectroscopic method of analysis presented. In our experience, elucidation of the structure of derivatives of 2-(1-naphthyl)-pyridine is problematic even with help of 2D NMR spectroscopy, and thus the validity of the structure elucidation of most of the published derivatives of **1** remains under question. The article published by Li et al⁵ is remarkable, since it claims the formation of a δ -substituted product in the main text of the article, but the supporting information of the same article states an opposite regioselectivity.

1.2 Cycloauration

Our study started with the cycloauration reaction. The cycloauration of 2-(aryl)-pyridines is a well-known reaction that usually proceeds under fairly harsh conditions⁷ with moderate to good yields. We decided to use the microwave-heating procedure by Tilset and Heyn and co-workers⁸ due to its remarkable simplicity and fairly short reaction time (Scheme 7). Interestingly, this study also displays an example of the formation of 5-membered and 6-membered rings due to the availability of the corresponding positions for the substitution.



Scheme 7. Formation of 5- and 6-membered rings in the example from Tilset and Heyn.⁸

Cycloauration of **1** proceeds, albeit in moderate yield at 140°C in 30 minutes. In order to analyse the structure of the product, gCOSY NMR was employed. The spectrum (Figure 2) shows cross-resonances between neighbouring protons. Exact assignment of different protons remains troublesome, but one can easily study the chains of resonances.

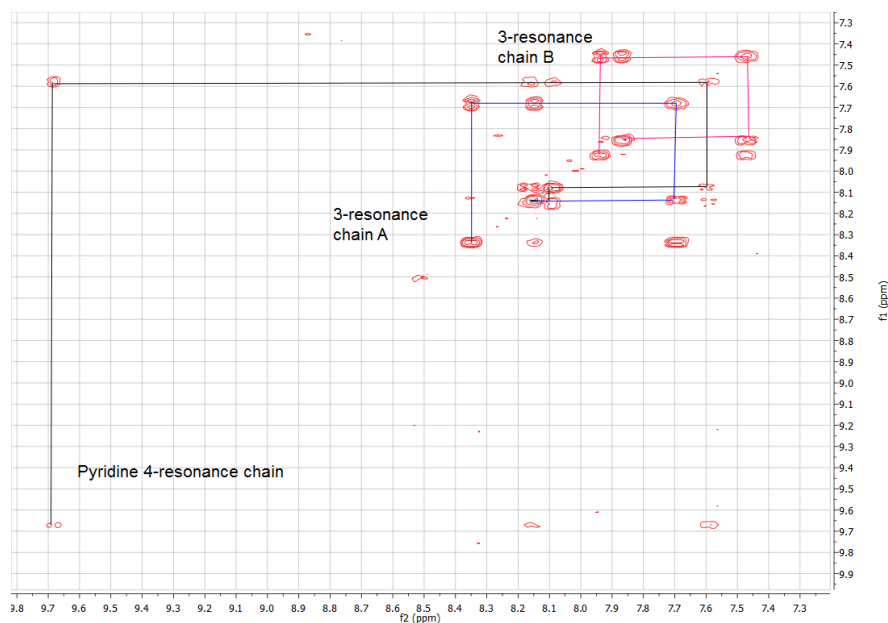
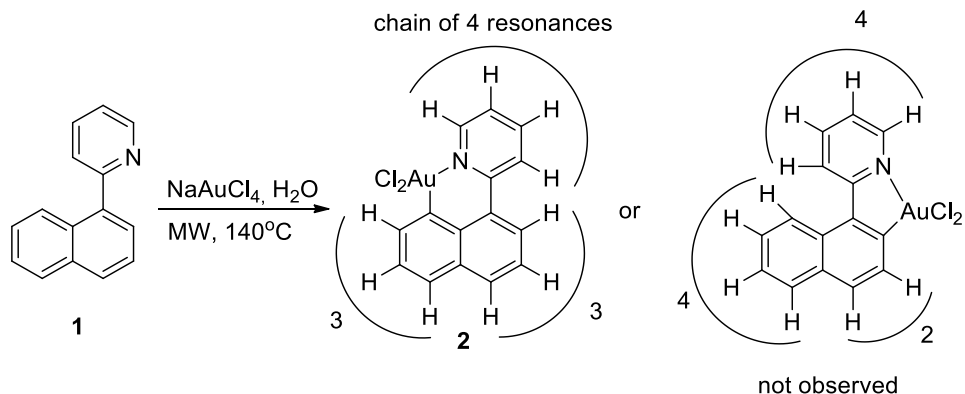


Figure 2. gCOSY spectrum of the cycloauration product in CD_2Cl_2 .

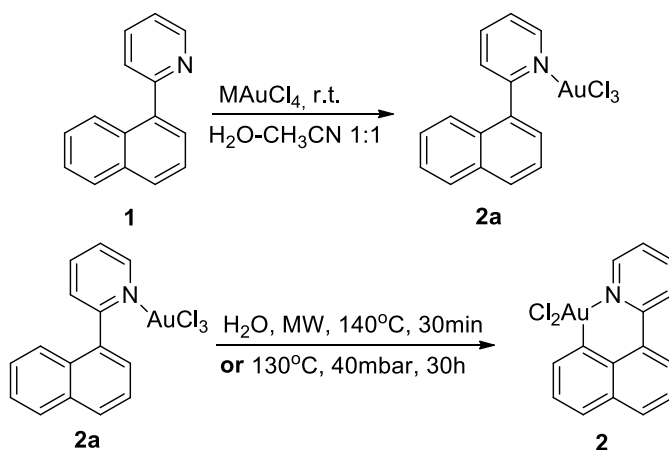
The most downfield resonance corresponds to the α -proton of the pyridine system and couples to the neighbouring proton which couples to the next proton etc. The

chain, expectedly, ends at 4 resonances, corresponding to the 4 protons of the pyridine system. The other resonances form two chains, consisting of 3 resonances each, which means that the product contains a 6-membered ring and the cyclometallation proceeded with δ -selectivity! If, in contrast, the standard five-membered ring was formed, a 4-4-2 chains of resonances would be observed in gCOSY NMR (Scheme 8).



Scheme 8. Synthesis of **2** and gCOSY correlations expected in the two possible isomers.

Alternatively, **2** could be synthesised via a two-step procedure with the intermediate isolation of a non-metallated coordination complex **2a**. This turned out to be easy to handle and also allowed the use of an alternative, higher-yielding, solvent-free procedure (Scheme 9).



Scheme 9. Alternative procedures for the synthesis of **2**.

The structure was further confirmed by an X-ray analysis of a single crystal (Figure 3).

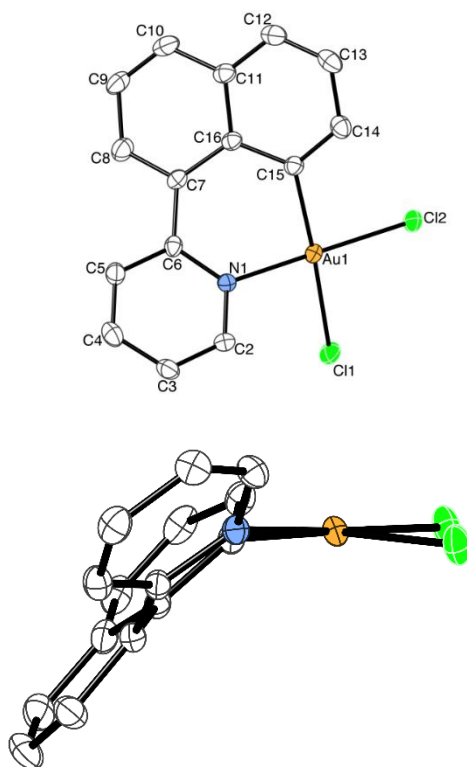


Figure 3. Molecular structure of **2** at the 30% probability level. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and bond angles (°) with estimated standard deviations: C15—Au1 2.024(3); N1—Au1 2.024(3); Cl1—Au1 2.3963(9); Cl2—Au1 2.2771(9); Cl2—Au1—Cl1 89.76; Cl1—Au1—N1 90.89; N1—Au1—C15 88.68; C15—Au—Cl2 90.95; Au1—C15—C7—C6 39.68.

Since the 90° angle at the Au centre does not fit into a flat hexagon with 5 sp² C-atoms, we could expect a distortion in either the square-planar surrounding of the atom of gold or in the ligand. In fact, we observe an almost perfect retention of the 90° angles at Au and a highly puckered organic ligand backbone. Not only is the pyridine ring rotated away from the plane of the naphthalene system, but the planarity of the naphthalene itself is disturbed. With the all-sp² carbon skeleton, the carbon atoms of the rings and the directly bound substituents are normally located in the same plane. However, in the structure of **2** we observe a 40° dihedral angle between the exocyclic C—C and C—Au bonds, which indicates an extreme distortion of the naphthalene ring system. The corresponding 2-(phenyl)-pyridine

analogues of this compound demonstrate almost planar configuration of the aromatic rings.⁹

Apart from the controversial study by Li et al,⁵ this is the first example of δ -substitution of **1**. One possible explanation of this result is the relatively high nucleophilicity of the α -position of the unsubstituted aromatic ring in comparison with the β -position of the substituted aromatic ring, since the pyridine coordinated to the Lewis acidic gold atom acts as an electron-withdrawing substituent (Figure 4).

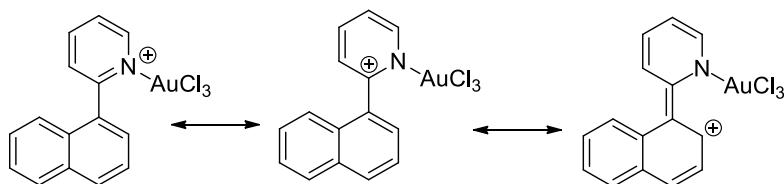


Figure 4. Resonance structures of the pre-cyclometallation intermediate.

This qualitative argument is supported by a DFT calculation giving the HOMO of the pre-cyclometallation intermediate L—AuCl₃ (**2a**). The coefficient of atomic orbital input into the HOMO at the position δ - to the N-atom is significantly higher than at the competing γ -position (Figure 5).

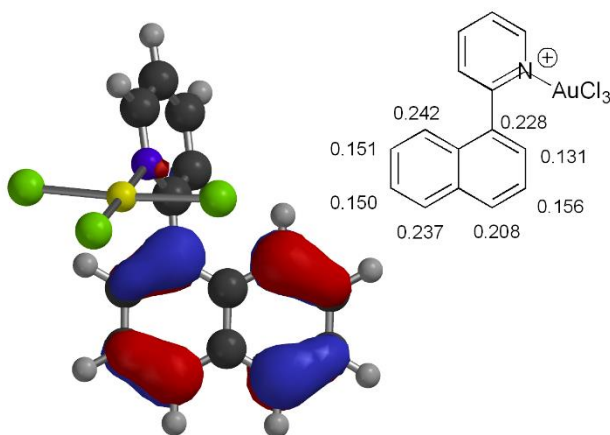
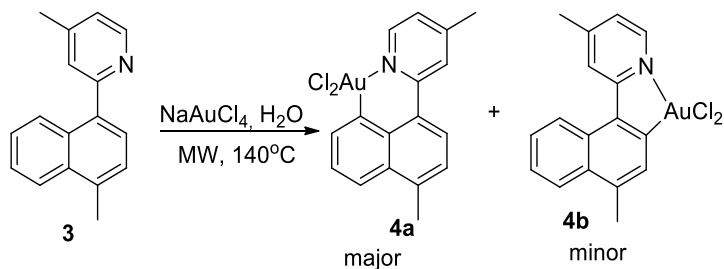


Figure 5. Graphic representations of the AO input into HOMO of **2a**.

Whether the relative nucleophilicity of the aromatic positions can fully explain the observed selectivity remains unclear, particularly since the general mechanism of the cycloauration is still unknown.

Electron-donating substituents at the pyridine and the substituted naphthalene ring might compensate for the electron deficiency of the substituted ring as discussed

above. In the course of our studies on luminescent properties of iridium complexes we have synthesised the 2-(4-methyl-naphth-1-yl)-4-methyl-pyridine (**3**). Thus we decided to run a cycloauration experiment with this substrate. The product of the reaction was a mixture of compounds, where the minor component (~10%) seemed to be γ -substituted isomer **4b**,¹⁰ while the major product **4a** was still δ -substituted, according to a gCOSY analysis (Scheme 10).

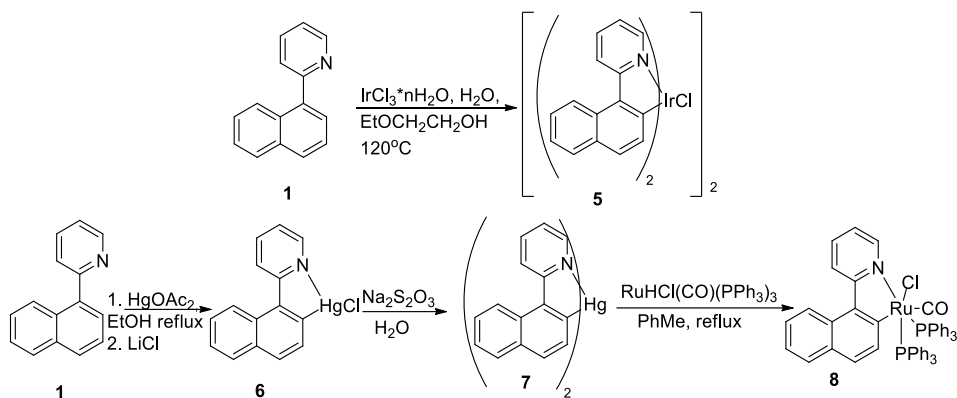


Scheme 10. Cycloauration of **3**.

Whether it could be possible to completely revert the selectivity with even stronger-donating substituents is a question for a further investigation.

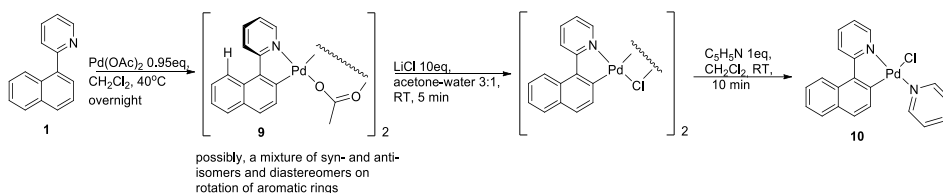
1.3 Other cyclometallations

After receiving these unusual results of cycloauration, we decided to study the reactions of **1** with other standard cyclometallating agents. The reactions presented in Scheme 6 mostly proceed via the cyclometallation step, but there were only a few metallacycles of **1** isolated (Scheme 11). The list includes iridacycle **5**,^{6r,ad} mercuracycles **6** and **7**, and ruthenacycle **8**.^{6ab} The latter, however, was synthesised not via cyclometallation, but via transmetallation from **7**.



Scheme 11. Previously known metallacycles based on **1**.

Our study continued with the cyclopalladation. Sanford and co-workers^{6a} published a palladium-catalysed protocol of halogenation of **1**. The reaction proceeds with γ -selectivity, and we were expecting a formation of a five-membered cycle in the reaction with palladium acetate, which is a standard cyclopalladation agent. However, the direct product of the reaction was difficult to analyse, since we were unable to grow an X-ray quality crystal and the NMR of the compound was too complicated to interpret. The 2-(aryl)-pyridyl palladium acetates are known to be dimeric.¹¹ The most likely explanation for the complexity of the NMR spectrum of **9** is the formation of a mixture of syn- and anti- isomers and diastereomers on the restricted rotation of aromatic rings. The problem was resolved by a sequence of straightforward ligand exchanges, which resulted in the monomeric compound **10** (Scheme 12), which was studied by gCOSY NMR and X-ray crystallographic methods (Figure 6).



Scheme 12. Cyclometallation of **1**.

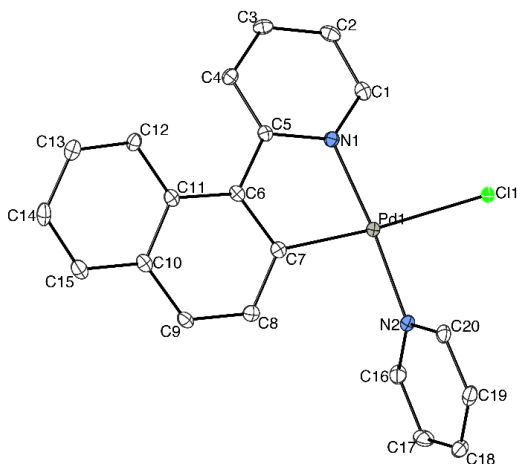
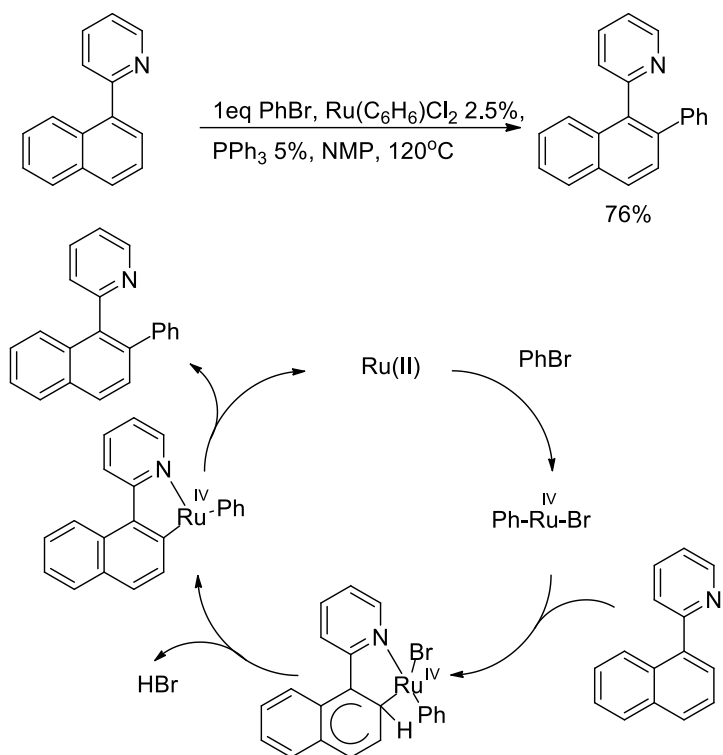


Figure 6. Molecular structure of **10** at the 30% probability level. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and bond angles (°) with estimated standard deviations: Pd1—C7 1.992(3); Pd1—N1 2.017(2); Pd1—N2 2.037(2); Pd1—Cl1 2.4204(7); C11—Pd1—N2 88.95; N2—Pd1—C7 94.53; N1—Pd1—C7 81.03; N1—Pd1—Cl1 95.57; C5—C6—C7—Pd1 16.29.

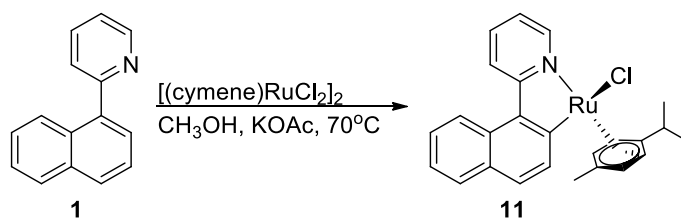
The X-ray structure of compound **10** shows a drastic difference with the structure of **2**. The five-membered ring is a lot closer to planarity, the dihedral angle between the exocyclic C—C and C—Pd bonds being only 16°. Interestingly, the C(7)—Pd—N(1) angle is only 81°, which deviates significantly from the requirements of a square-planar configuration.

Oi et al^{6d} published a ruthenium-catalysed arylation procedure, which they suggested to proceed via an initial oxidation of the Ru(II) precatalyst followed by a cyclometallation with the resulting Ru(IV) intermediate (Scheme 13).



Scheme 13. General scheme of catalytic reaction and the mechanism suggested by Oi.^{6d}

However, since this study it was demonstrated¹² that even Ru(II) compounds, e.g. (*p*-cymene)RuX₂ type compounds, can easily cyclometallate 2-(aryl)-pyridines. We chose [(*p*-cymene)RuCl₂]₂ as a stable and easy-to-handle metallation agent. The reaction with **1** proceeded smoothly in methanol as a solvent, and resulted in a formation of a new metallacycle (Scheme 14) which could be studied by means of gCOSY NMR and X-ray crystallography (Figure 7).



Scheme 14. Cycloruthenation of **1**.

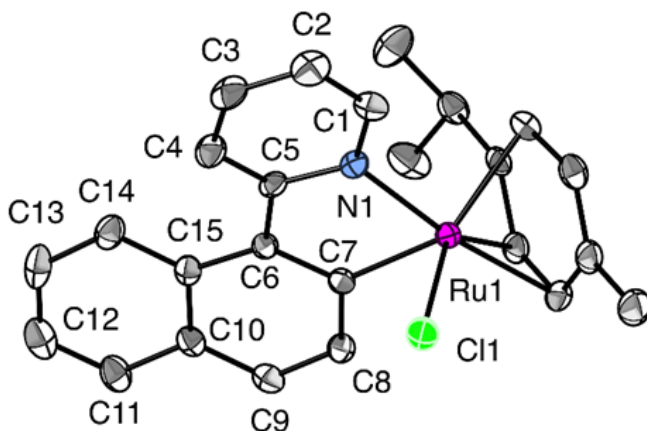
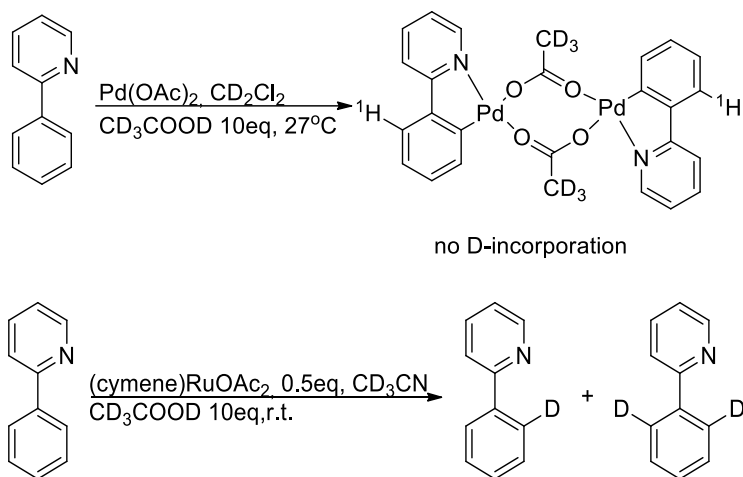


Figure 7. Molecular structure of **11** at the 30% probability level. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and bond and torsion angles (°) with estimated standard deviations: Ru1—N1 2.088(3), Ru1—C7 2.051(3), C7—Ru1—N1 76.6(1), C5—C6—C7—Ru1 6.2, C5—C6—C14—H14 14.3.

The metallation proceeds with expected γ -selectivity and forms the five-membered ring product. The structure of **11** is fairly similar to the structure of palladacycle **10**. The five-membered ring is even closer to planarity: the pyridine ring is rotated at 10° towards the naphthalene ring (N1—C5—C6—C7) and the dihedral angle at the exocyclic bonds of the substituted naphthalene ring (C5—C6—C7—Ru) is only 6° . The Ru—C7 and Ru—N bonds are longer by approximately 0.06 \AA and the angle C7—Ru—N of 77° is even smaller than in the Pd analogue and substantially smaller than 90° , which is expected in an octahedral system.

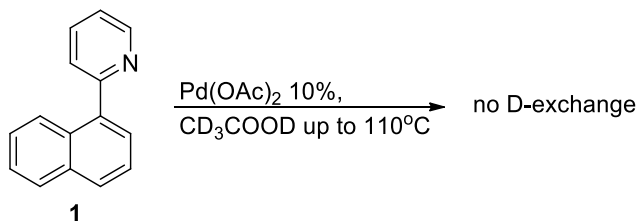
1.4 Reversibility

Fabre et al¹² studied the mechanisms of the cycloruthenation and cyclopalladation with similar substrates and found that while the cyclopalladation was irreversible, the cycloruthenation was reversible and could easily result in H-D exchange in presence of deuterated protic solvents (Scheme 15).



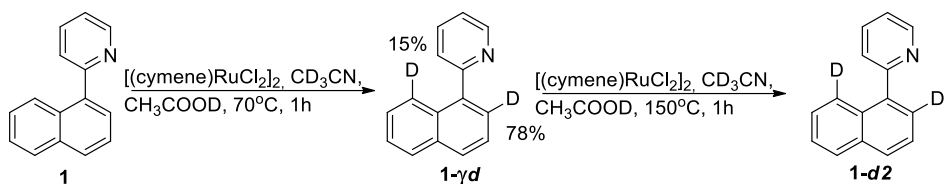
Scheme 15. D-exchange study by Fabre et al.¹²

We decided to set up similar experiments for our substrate. We used a catalytic amount of palladium acetate in order to avoid the stoichiometric formation of the corresponding palladacycle, which exhibits a very complex NMR spectrum. If the D-exchange was to happen we would observe a drop in intensity of the ¹H signals corresponding to γ - and potentially δ -protons. However, the cyclopalladation was irreversible, as expected, and no deuterium-exchange was observed (Scheme 16).



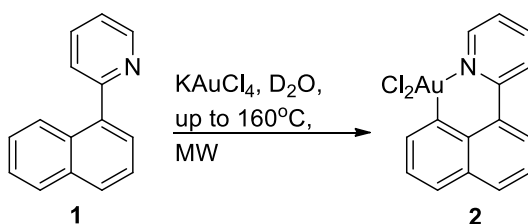
Scheme 16. Attempt of Pd-catalysed D-exchange.

The cycloruthenation was reversible, and, surprisingly, the H-D exchange was observed in both γ - and δ -positions. While in methanol-*d*₄, it was too fast to study even at room temperature, the experiment in acetonitrile-*d*₃ showed that the γ -substitution is faster at 70°C, but at higher temperatures or longer reaction times, the D-content is completely equilibrated (Scheme 17).



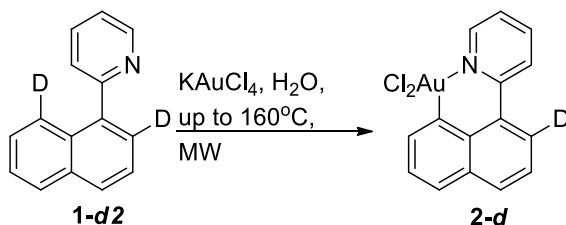
Scheme 17. Ru-catalysed D-exchange.

Setting up a similar experiment for the cycloauration was troublesome, since neither **1** nor the product of the reaction are soluble in the reaction solvent at room temperature. Hence, we decided to run a stoichiometric reaction between 2-(1-naphthyl)-pyridine and tetrachloroaurate in D_2O . The product of the reaction was identical to the product of the reaction in H_2O (Scheme 18).



Scheme 18. D-exchange attempt in the synthesis of **2**.

To confirm this result an “inverse” experiment was set up with **1-d2**, which we received from Ru-catalysed D-exchange, in $^1\text{H}_2\text{O}$ (Scheme 19). Now, we could synthesise a D-analogue of the auracycle (**2-d**).

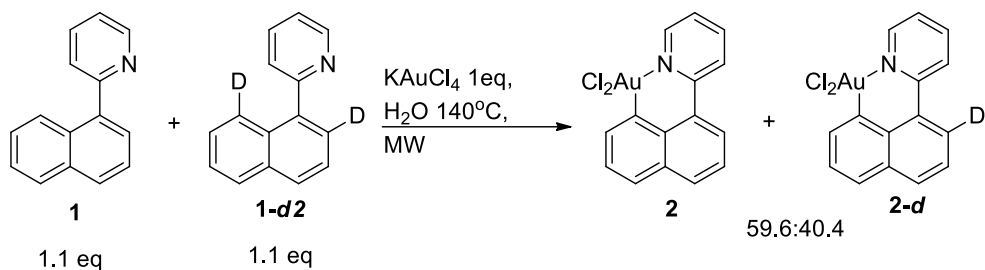


Scheme 20. Attempt of catalytic D-exchange with Au.

Analysing these results we also took into account that the γ -metallation is possible for very similar substrates (e.g. 2-phenyl-pyridine) at similar conditions and, in all likelihood, the activation energy for this process cannot be expected to be significantly higher. DFT calculations comparing gas-phase enthalpies of two possible isomeric products of cycloauration even predict the five-membered metallacycle to be more stable by a difference of 5.3 kcal/mol. From this we conclude, that the δ -selectivity of this reaction is kinetic in origin, and that the

reaction is irreversible at given conditions since, if it were reversible, the γ -metallation would be expected to happen and result in the partial formation of the product **2** with the alternate H-isotope in the γ -position.

Since the mechanism of cycloauration has not been studied extensively, we also decided to run a competition experiment to determine the kinetic isotope effect of this process. 2.3 Equivalents of an equimolar mixture of **1** and **1-d2** were reacted with sodium tetrachloroaurate. The ratio of **2** and **2-d** products were measured with the help of ^1H NMR spectroscopy and ESI-MS and found to be 60:40. Since the D-exchange does not happen at these conditions, the ratio between these two products corresponds to the ratio of **1** and **1-d2** consumed in the reaction, which, in turn, corresponds to a kinetic isotope effect of 1.5 (Scheme 21). The actual k.i.e. value, however, may be somewhat higher, since the concentration of the non-deuterated starting material, should be dropping faster than the concentration of the deuterated analogue. However, this effect is of negligible importance, since the conversion in the C—H activation at given conditions is only 22%, which means that the concentrations of **1** and **1-d2** do not change significantly. The value of $1.5 > 1$ indicates that the C—H activation event must take place during or before the rate-determining step. However, in the former case, the reaction should pass through an early transition state, since the value is fairly low.

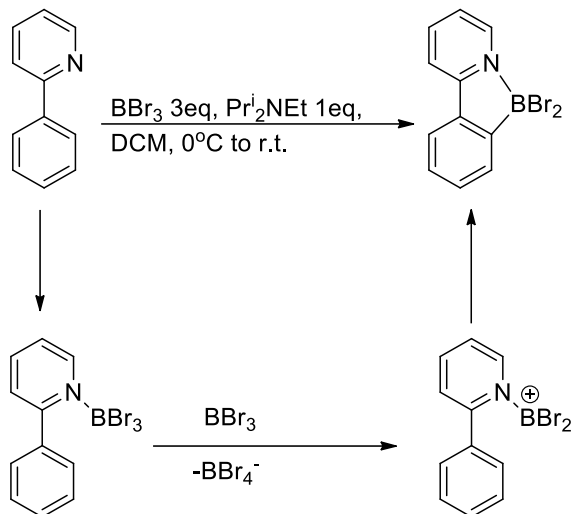


Scheme 21. Competition experiment for the measurement of k.i.e.

1.5 Cycloborylation

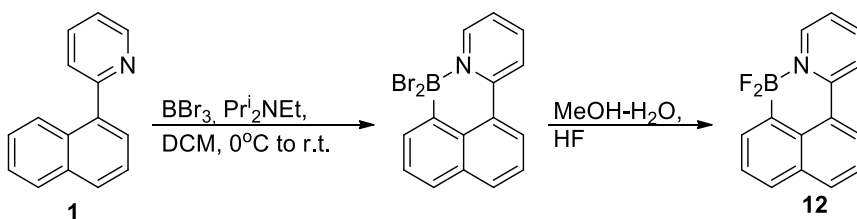
Finally, we wanted to compare the behaviour of the 2-(1-naphthyl)-pyridine towards transition metal precursors with its behaviour towards a non-transition metal cyclometallating agent. In our view, the cycloborylation, developed by Ishida et al¹³ for 2-aryl-pyridines seemed very attractive (Scheme 22). This method was published in 2010 and presents an unusual d-metal-like cyclosubstitution reaction performed with a non-metallic p-element. The proposed reaction mechanism proceeds via a highly electrophilic borenium cation and is unique, since the absence

of d-electrons at the boron atom excludes the possibility of oxidative addition or any kind of back-donation interaction with the C—H bond.



Scheme 22. Cycloborylation protocol by Ishida and its proposed mechanism.

The product of direct reaction of **1** with boron tribromide was too unstable to withstand a column chromatography purification. However, after an easy exchange of the halogen substituents at the boron atom, the more stable difluoroderivative was obtained (Scheme 23). The COSY and X-ray analyses showed, that, like the auracycle **2**, the only isolated product contained a six-membered ring (Figure 8).



Scheme 23. Cycloborylation of **1**.

This selectivity is remarkable, proving our initial assumption of the relatively high nucleophilicity of the δ -position, since the extremely electrophilic borenium cation intermediate should have a preference for a more electron-rich position.

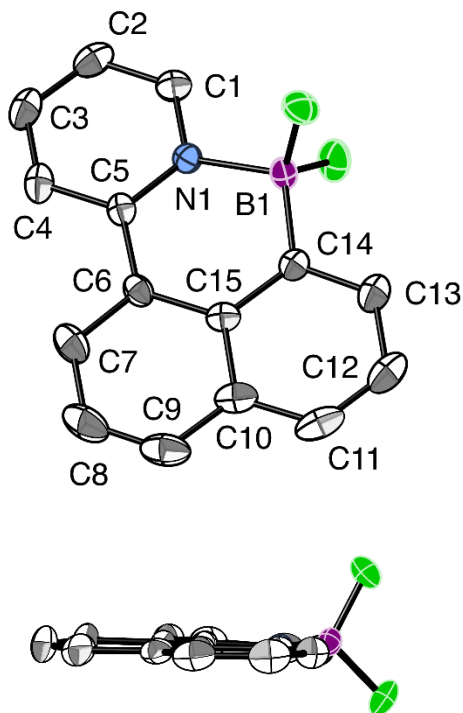


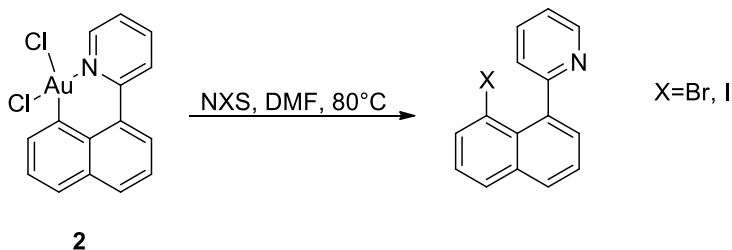
Figure 8. Molecular structure of **11** at the 30% probability level. Selected bond lengths (Å) and bond and torsion angles (°) with estimated standard deviations: B1—N1 1.604(2), B1—C14 1.576(2), N1—B1—C14 110.3(1), B1—C14—C6—C5 4.7, C5—N1—B1—C14 12.3.

It is important to mention, that, unlike the square-planar gold atom, the sp^3 -hybridised boron atom fits almost perfectly into an all- sp^2 six-membered cycle, which remains essentially flat.

1.5 Further functionalisation

We were very encouraged by the observed differences in the regioselectivities, and, since the γ -selectivity for this substrate was usual and the corresponding pallada- and ruthenacycles are the most probable intermediates in a few catalytic protocols, we wanted to employ the novel δ -selectivity of the cycloborylation and cycloauration as the means of further functionalisation.

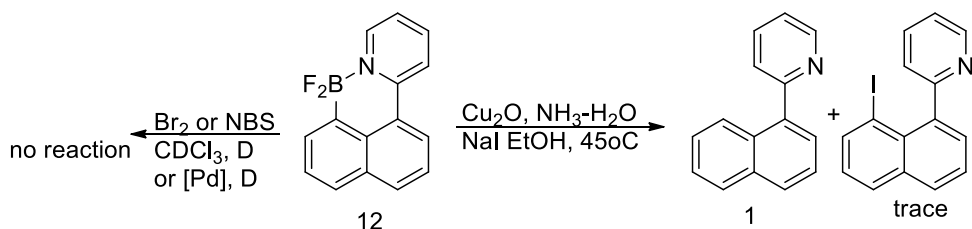
Compound **2** was very difficult to work with, mostly due to its extremely poor solubility in the majority of common organic solvents and water. After a long investigation, we were pleased to observe a reaction between auracycle **2** and N-halosuccinimides in DMF, leading to the corresponding halo-derivatives, which are isomeric to the products of the palladium-catalysed protocol by Sanford (Scheme 24).^{6a}



Scheme 24. C—Au bond cleavage in **2**.

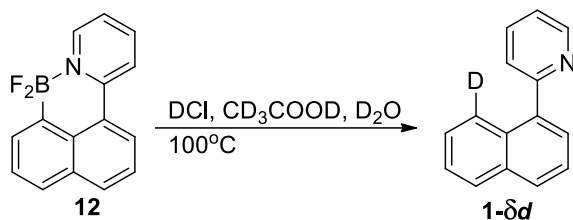
Unfortunately, we have failed to create a catalytic protocol based on this reaction. Our observations lead to the conclusion that the cyclometallation is only viable at high temperatures in water as a solvent, while DMF is crucial for the halogenation step. At the same time, at elevated temperatures, the metal-free non-regioselective halogenation of **2** takes place, making the potential catalytic cycle redundant.

The boracycle **12** was found unreactive in potential trans-metallation reactions with Pd precursors and in electrophilic bromination, while a copper-catalysed iodination, which was published for similar 2-phenyl-pyridine derivatives,¹⁴ lead to the hydrolysis of the C—B bond and only traces of the desired product (Scheme 25).



Scheme 25. Attempts of functionalisation of **12**.

The only transformation of **12** that we could successfully perform, was deuteration in hydrochloric acid, which led to the δ -deutero-substituted **1**, formally isomeric to the product of the low-temperature Ru-catalysed deuteration (Scheme 26).



Scheme 26. Acid-catalysed deuterolysis of **12**.

1.6 Conclusions

The presented study describes the pattern of reactivity of the same substrate with a variety of standard cyclometallating agents. In our view, substrate **1** is a unique compound which allows to compare the preference between sp^2 C—H bonds in γ - and δ -positions in ligand-directed substitution. Even more fascinating is the observed ambiguity, dependent on the choice of a metal precursor. We can observe a whole range of reactivities, from the palladium precursor which activates the γ -position selectively and irreversibly to the ruthenium complex which activates both positions reversibly, and yet demonstrates a kinetic and thermodynamic preference towards the γ -position, and to the gold precursor which demonstrates irreversible δ -substitution.

1.7 References

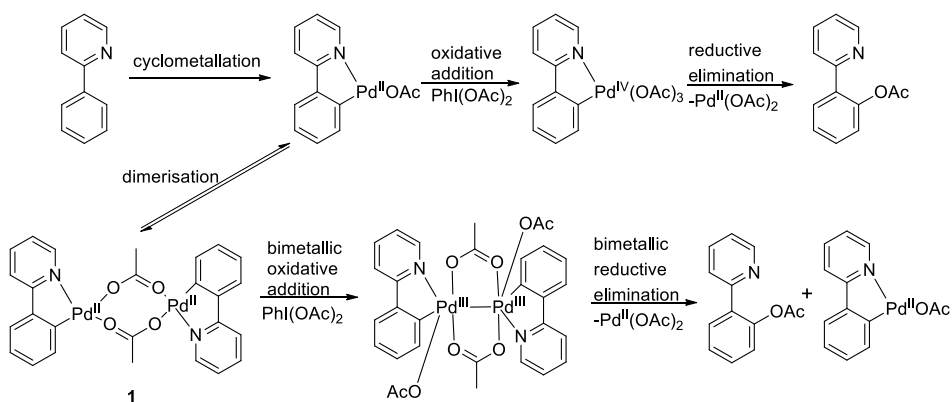
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Chapter 2

2.1 Introduction

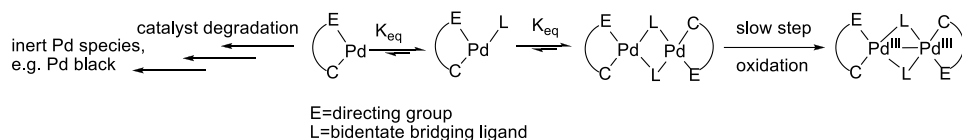
Despite the development of a multitude of Pd-catalysed LDC reactions, there is no general view on their mechanisms. Most mechanistic proposals depict the cyclometallation of the organic substrate followed by an oxidation of the Pd(II) metal centre to Pd(IV) and consecutive reductive elimination. Some of the studies of stoichiometric C—H activation reactions prove the possibility of such a mechanism.¹ At the same time, several publications²⁻⁶ (including thorough kinetic studies)^{3,4} show that the reactions proceed via bimetallic, dimeric Pd(II) species that are oxidised to dimers containing two Pd(III) centres which are bound covalently (Scheme 1). The most probable reason for such a kinetic preference is the high oxidation potential of Pd(II) which may be impassable for a Pd(II) – Pd(IV) transition and is somewhat lower for a Pd(II) – Pd(III) transition. Thus, even in the cases where the Pd(II) – Pd(IV) route is proven to be possible, it cannot be excluded that the Pd(II) – Pd(III) route has a major contribution.



Scheme 1. Pd(II)-Pd(IV) and bimetallic Pd(III)-Pd(III) mechanisms on example of acetoxylation of 2-phenylpyridine.

Due to the high oxidation potential the oxidative addition is often rate-limiting. Hence, in order to improve the catalytic efficiency the first goal is to improve this step. Here it is easy to notice an important role of bridging ligands which keep the

two palladium centres adjacent to each other making the oxidation easier. In the majority of cases these bridging ligands are acetates, which have a perfect geometry. However, acetate is an electron-poor ligand with a very weak interaction with the metal centre. The succinimide ligand which is found in such structures occasionally is only slightly better. Creating a ligand that would keep the two metal atoms at a close distance and at the same time have a stronger binding to the metal may: i) increase the equilibrium concentration of the catalytically active species and proportionally increase the rate of the reaction, ii) block the catalyst degradation pathway via the loss of the ligand, iii) decrease the activation energy of the oxidation which will lead to an exponential increase of the rate constant of this step (Scheme 2).



Scheme 2. Transformations of the metallacycle before the rate-limiting step of the catalytic process.

This approach directly addresses the main drawbacks of the C—H activation protocols: poor reaction rates and catalyst degradation, which lowers the turnover number and frequency. Simultaneously, if a ligand of choice would be binding two Pd atoms at even closer distance, “forcing” an interaction, that might decrease the activation energy of the rate limiting step. That, in turn, will allow the use of a broader scope of weaker oxidants at lower temperatures, increasing the functional group tolerance of the reaction.

2.2 Proposed ligands

The ligand chosen for creating such a bimetallic complex has to fit several requirements: it should be a bidentate ligand with a preferential binding of two metal atoms over the chelation of one atom and it should have a rigid structure that would keep the two metal atoms bound at a distance optimal for the formation of a Pd—Pd bond ($\sim 2.6\text{--}2.9\text{\AA}$)⁷. These requirements can be fulfilled only if the donor atoms are directly bound (in 1,2-position), linked by one atom (1,3-position) or linked by 2 atoms in a rigid structure with a large bite angle (1,4-position). In cases of larger and more flexible chains, the chelation of one metal atom is expected to be predominant. Furthermore, the ligating atoms should form a strong (in comparison with acetate) bond to palladium. Most of the standard ligating atoms, e.g. C, N, P or S fit to this requirement. It also has to be compatible with the oxidative addition step, and thus a strong electron donor, stable to oxidants that can be used in the

reaction, is needed – a requirement that excludes most of the phosphine ligands. The formal electron count is not important since it is not necessary to have two ligands in the place of acetates, one strongly binding ligand may be sufficient. Thus it can be a formal 2-electron ligand (an X,X-ligand), a 3-electron ligand like acetate (X,L-ligand) or a 4-electron ligand (L,L). Finally, the ligand should be of a simple, symmetric structure in order to facilitate its synthesis and the mechanistic studies of the complex bimetallic systems by NMR spectroscopy. Several known ligand types fit these requirements (Figure 1). Some of these ligands are known to form bimetallic complexes with d-block metals.⁸⁻¹⁰

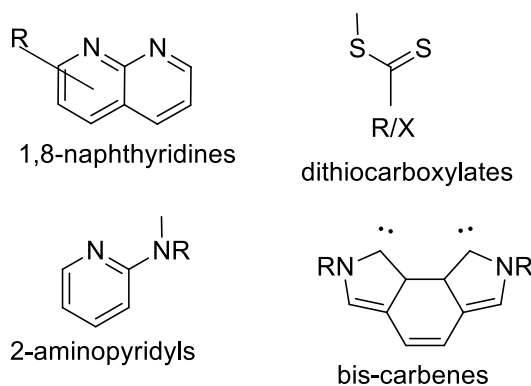
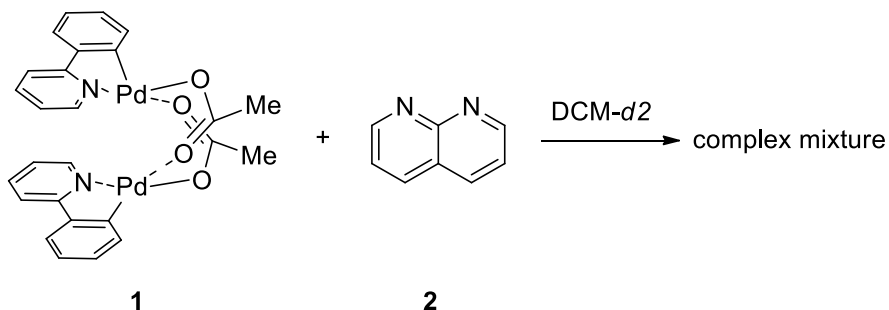


Figure 1. Ligand types potentially suitable for stabilising bimetallic species.

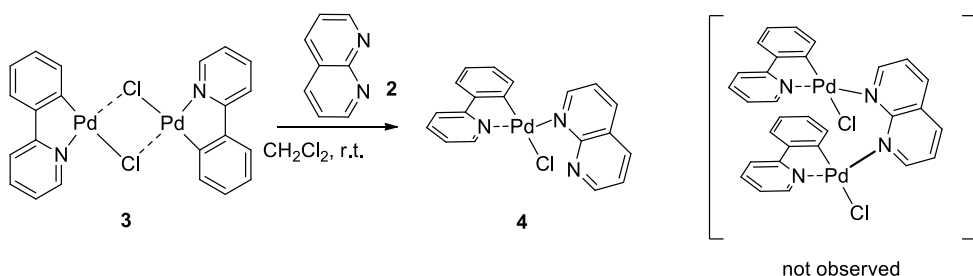
2.3 N,N-ligands

We decided to isolate bimetallic species with some of these ligands to study their oxidation on a stoichiometric level, rather than applying the ligands directly in the catalytic reactions. While the synthesis of the bis-carbene structure poses a major difficulty, we could easily obtain a few ligands of the other types. We started with the 1,8-naphthyridine (**2**) which was synthesised according to a published procedure.¹¹ The reaction between this ligand and diacetate-bridged dimer **1** led to a complex mixture (Scheme 3).



Scheme 3. Reaction between **1** and naphthyridine.

The interaction of a chloro-bridged dimer **3** proceeded cleanly and was easy to follow, since the chloro-bridged dimer is insoluble in DCM and only dissolves upon a reaction with a coordinating ligand. We could isolate the product, but the NMR analysis showed that the product contains only one naphthyridine ligand per one cyclometallated ligand. Hence, the structure is monomeric and only one of two nitrogen atoms of **2** are coordinated to the metal (Scheme 4).

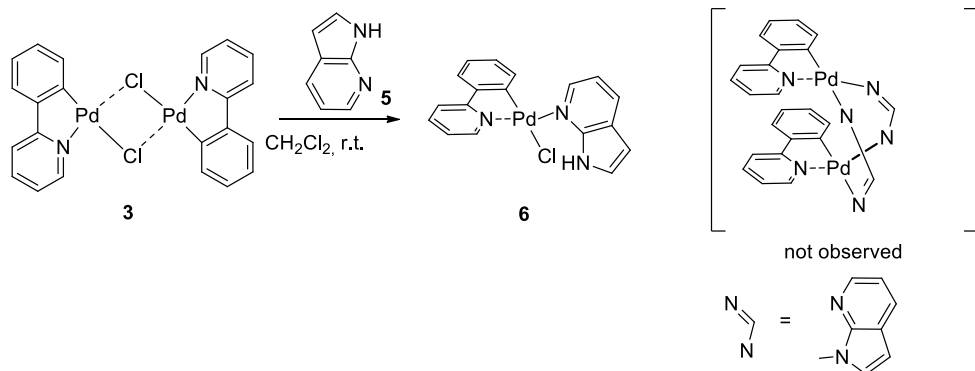


Scheme 4. Reaction between **3** and naphthyridine.

We were unable to vary the reaction conditions in a way that would lead to the formation of a desired product. This result was somewhat unexpected, but it can be rationalised as a consequence of steric repulsion between two phenyl-pyridine fragments in the dimeric structure, which would make the second Pd—N bond weaker than the Pd—Cl bond in a bridged dimer **3**.

We moved on to the second general ligand type – 2-aminopyridyl. We decided to use 7-azaindole (**5**) as an analogue, since it contains only one labile H-atom, which would make the potential product less susceptible to side reactions. At the same time, the N—H nitrogen atom is contained within a cycle which creates little steric hindrance. Also, the labile hydrogen atom would be expected to have a substantially higher acidity, so it would be more prone to deprotonation and consequent metallation. The reaction between this ligand and **1** was again not fruitful, unlike the reaction with **3**. The latter, unfortunately, led to the formation of a new

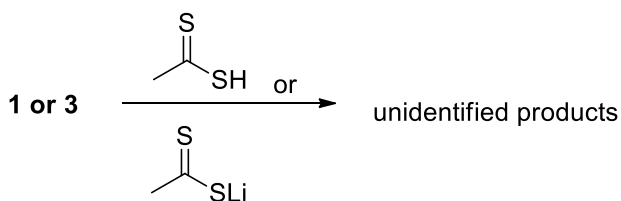
monometallic species, which was obvious from the presence of the N—H nitrogen in the ^1H NMR spectrum (Scheme 5).



Scheme 5. Reaction between **3** and azaindole.

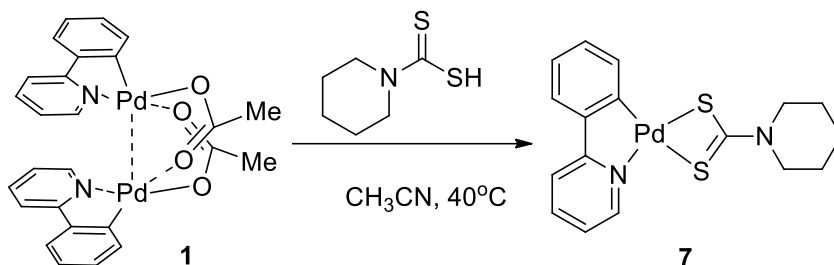
2.4 Dithiocarbamates

Next, we moved on to the dithio-ligands. A simple analogy with acetate would suggest the use of a dithioacetate ligand. However, the reaction with both dithioacetic acid and its lithium salt led to complex mixtures (Scheme 6). In addition, these compounds were very smelly and prone to oxidation.



Scheme 6. Reaction between **1** and **3** and dithioacetic derivatives.

Dithiocarbamates were found to be a more stable and easy-to-handle alternative. *N*-piperidine-dithiocarbamic acid could be easily synthesised from the corresponding secondary amine and carbon disulfide. The ligand exchange from **1** to **7** was straightforward, but the product was monomeric, since the dithioligand was bound in a chelate fashion, rather than a bridging fashion (Scheme 7).

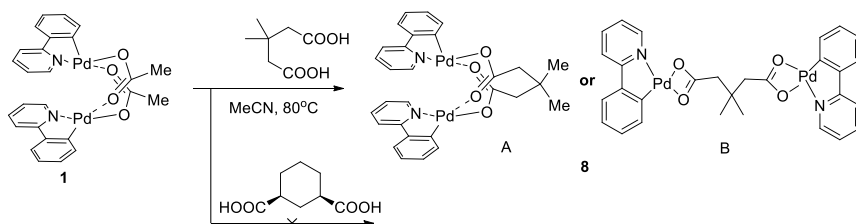


Scheme 7. Reaction of **4** with *N*-piperidine-dithiocarbamic acid.

Overall this result was not completely unexpected since binding in a chelate mode is typical for this type of ligands.¹²

2.5 Dicarboxylate ligands

After failing to isolate the dimeric complexes with the *N,N*- and *S,S*-ligands we were in doubt, whether any alternative to the acetate can be found. Hence, we decided to find a ligand that would bear maximum similarity to the acetate ligand, yet be somewhat more stabilising for the dimeric structure. A dicarboxylate ligand was an obvious choice. The binding properties would be essentially the same as for acetate, yet the equilibrium monomer- dimer would be shifted somewhat to the right as described in 2.1 (Scheme 2). Two carboxylate moieties must be connected with a spacer that would allow them to be bound to the same atoms of palladium at a $\sim 90^\circ$ O—Pd—O angle. 3,3-Dimethylglutaric acid was available and the direct ligand exchange from **1** was an easy way to produce a corresponding complex. The 2:1 ratio of the PhPy and glutarate resonances indicated that the product was indeed bimetallic (Scheme 8). Another indirect evidence was the incredibly low solubility of the compound that did not allow us to establish, whether the carboxylates were bound in an acetate-like bridging mode (structure A) or in a dithiocarbamate-like chelate mode (B). Interestingly, a similar reaction with another 1,5-diacid – *cis*-1,3-cyclohexane dicarboxylic acid – did not lead to any ligand exchange, probably due to the steric effect of a rigid CH₂-group at position 2 of the cyclohexane ring, which would exclude the bimetallic binding mode A. This is an indirect evidence for the higher probability of structure A for compound **8**.



Scheme 8. Reaction of **1** with dicarboxylic acids.

2.6 Catalytic trials

Despite our failure with dinitrogen- and dithio-ligands we decided to still try the ligands in the reactions of catalytic acetoxylation and bromination of 2-(phenyl)-pyridine. The ligands were simply added to the reaction mixture consisting of 2-(phenyl)-pyridine, palladium acetate and the oxidant (diacetoxyiodobenzene in the case of acetoxylation or *N*-bromosuccinimide in the case of bromination). Addition of naphthylridine **2** drastically increased the selectivity towards a mono-acetoxylated product, but at higher concentrations the conversion of the starting material also dropped (Figure 2). The same trend was observed for the dithiocarbamate ligand (Figure 3). In the case of bromination reactions all three ligands showed rather deactivating than activating properties – the addition of **3**, **5** or **7** resulted in a drop in dibromo:monobromo product ratio and increase of the relative amounts of the starting material (Figure 4).

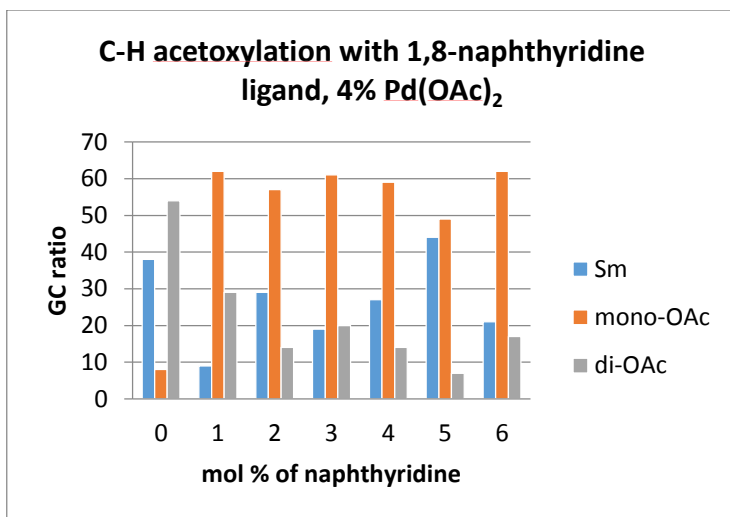


Figure 2. Acetoxylation in the presence of different concentrations of naphthyridine.

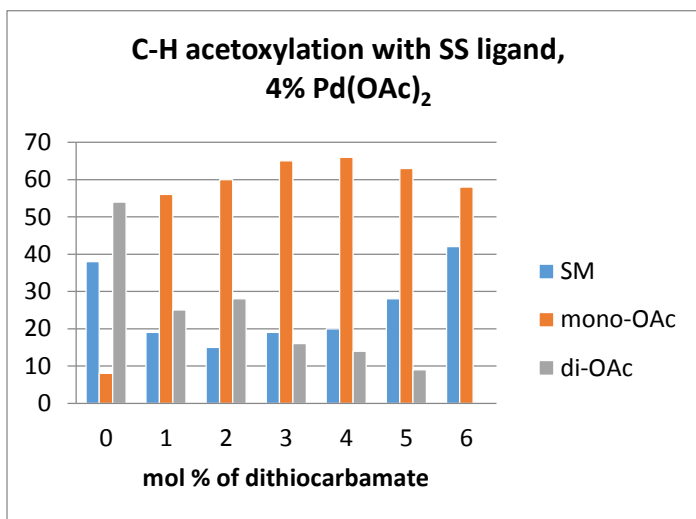


Figure 3. Acetoxylation in the presence of different concentrations of dithiocarbamate.

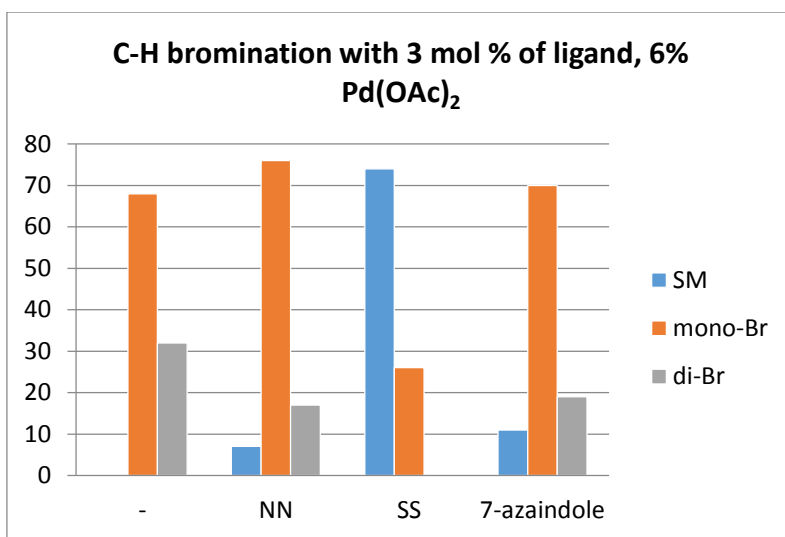


Figure 4. Bromination in the presence or absence of the 3 ligands in question.

2.7 Conclusions

In conclusion, we have shown that designing a ligand, which would stabilise a bimetallic structure of two metallacyclic fragments was more difficult than expected. We exclusively obtained monomeric complexes with potentially bridging *N,N*- and *S,S*-ligands and only the 3,3-dimethylglutarate ligand formed a bimetallic structure. An exploratory catalytic study indicated that the proposed ligands played a mainly deleterious role in the standard conditions of LDC.

2.8 References

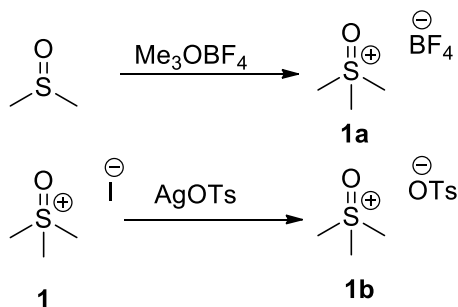
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Chapter 3

3.1 Introduction

In our search for new oxidative reagents, we were interested in the synthesis of trialkylsulfoxonium salts. Trimethylsulfoxonium iodide (**1**) is a commercially available reagent, but the iodide anion binds strongly to Pd(II) compounds and may potentially reduce Pd(IV) reaction intermediates. Hence, we needed trimethylsulfoxonium salts with non-nucleophilic counterions. The syntheses of trimethylsulfoxonium tosylate¹ and tetrafluoroborate² were already published, but we did not find them satisfying, since they relied on the use of silver-induced halide-abstraction or the use of a corresponding strong alkylation agent (Scheme 1).



Scheme 1. Published syntheses of trimethylsulfoxonium tosylate and tetrafluoroborate.

Both of these reagents are fairly costly and have other drawbacks. Reactions with silver salts are somewhat inconvenient due to the light-sensitivity of the precipitating silver halides. Synthesis via alkylation as shown for the tetrafluoroborate² would require the use of a specific alkylation agent for each possible anion.

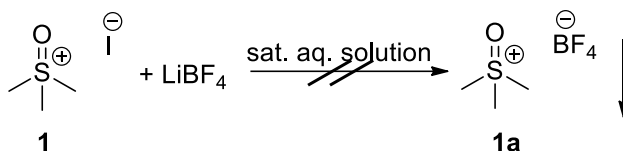
3.2 Direct anion exchange

Direct anion exchange is sometimes feasible, if the required product has a significantly lower solubility than the starting material. Exact prediction of the solubility of salts is troublesome. However, as a rule of thumb, it is possible to use an assumption that anions and cations of similar radii pack better in the crystal lattice, which results in lower solubility of the corresponding salts. Or, more simply, larger cations “prefer” larger anions and vice versa. An apparent demonstration of this rule is the relative solubility of alkali metal halides in water³ (Table 1).

Table 1. Solubility of alkali metal halides in water at 20°C in mol/kg of water. The bold numbers mark the lowest solubilities in each respective row or column.

	Li	Na	K	Rb	Cs
F	0.12	0.98	16	29	37
Cl	18	6.2	4.6	7.5	11
Br	20	10	5.5	5.9	5.4
I	12	12	8.7	7.1	3.0

Our attempt to use this method for synthesising trimethylsulfoxonium tetrafluoroborate, therefore predictably failed (Scheme 2).

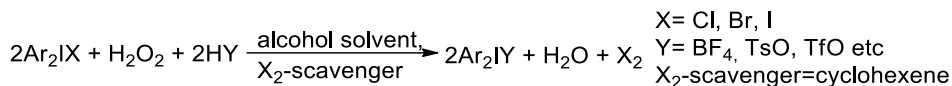


Scheme 2. Failed attempt of a direct anion exchange.

3.3 Oxidative anion metathesis

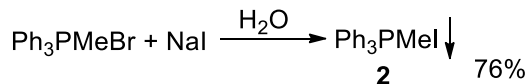
In search of a cheaper and more general method, we found the procedure by Skulski and co-workers.⁴ These authors were facing a similar problem while trying to synthesise diaryliodonium salts with non-nucleophilic anions. That led to a development of the oxidative anion metathesis of halides. Employing the fact that halides (except for the fluoride) can be oxidised to the corresponding halogens by hydrogen peroxide in acidic media, Skulski could exchange the halides to the non-nucleophilic counter-ions using the corresponding acids (Scheme 3). We decided to

use this method for our system. The anion exchange of the trimethylsulfoxonium iodide to the corresponding tetrafluoroborate proceeded smoothly.



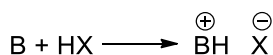
Scheme 3. General scheme for oxidative anion exchange by Skulski.

Skulski and co-workers⁴ used this method for a variety of anions, but only for diaryliodonium and, on two occasions, tetraalkylammonium^{4b} cations. Realising that this method is, potentially, general, we decided to expand the scope of cations used. Several alterations were done to the original procedure. First of all, we could show that water can be used as a reaction solvent. Also, Skulski has used chlorides, bromides and iodides as starting materials. We had an initial interest in iodides (since only the trimethylsulfoxonium iodide is available at major commercial sources). Performing this reaction, we realised that the reaction did not require high temperatures, unlike the oxidation of the corresponding bromides and chlorides. Also, no halogen scavengers were needed, since the iodine is fairly inert. When large organic cations are used, iodides are expected to be made easily from the chlorides and the bromides via direct anion exchange, as described above. This is demonstrated by our synthesis of methyl(triphenyl)phosphonium iodide from the corresponding bromide (Scheme 4).



Scheme 4. Synthesis of **2**.

Thus, we decided to use only iodides. Regarding the cations suitable for this reactions, we decided to stick to organic aprotic cations, since the synthesis of salts of protic cations can usually be performed via a simple acid-base reaction (Scheme 5).



Scheme 5. Typical synthesis of salts of protic cations.

3.4 Scope

Organic aprotic cations are mostly –onium salts with heteroatom bearing alkyl or aryl substituents. Common central heteroatoms include iodine, sulfur, nitrogen and phosphorus. Since iodonium and tetraalkylammonium salts were already used by Skulski, we decided to employ sulfur in the form of trimethylsulfoxonium, nitrogen in the form of *N*-alkylpyridinium and phosphorus in the form of methyl(triphenyl)phosphonium cations. The results are presented in the Table 2.

Table 2. Scope of the method.

Starting material	Acid	Product	Yield, %
Me ₃ SOI (1)	HBF ₄	Me ₃ SOBF ₄ (1a)	97
Me ₃ SOI (1)	HBF ₄	Me ₃ SOBF ₄ (1a)	77*
Me ₃ SOI (1)	TsOH	Me ₃ SOOTs (1b)	65
Me ₃ SOI (1)	CF ₃ COOH	Me ₃ SOTFA (1c)	54*
Me ₃ SOI (1)	HNTf ₂	Me ₃ SONTf ₂ (1d)	64
Me ₃ SOI (1)	HPF ₆	Me ₃ SOPF ₆ (1e)	77
Me ₃ SOI (1)	C ₁₁ F ₂₃ COOH	Me ₃ SOOCOC ₁₁ F ₂₃ (1f)	41
Ph ₃ PMeI (2)	HBF ₄	Ph ₃ PMeBF ₄ (2a)	78
Ph ₃ PMeI (2)	TsOH	Ph ₃ PMeOTs (2b)	80
C ₅ H ₅ NEtI (3)	HBF ₄	C ₅ H ₅ NEtBF ₄ (3a)	98
C ₅ H ₅ NEtI (3)	TsOH	C ₅ H ₅ NEtOTs (3b)	88
<i>N</i> -octyl-bipyridinium iodide (4)	HBF ₄	<i>N</i> -octyl-bipyridinium tetrafluoroborate (4a)	77

*Water was used as a solvent

All of the cations used produced the expected salts. Since water is difficult to remove, we were mostly using methanol as a solvent. However, the purification of the products was sometimes impossible unless water was used. The extraction of aqueous solutions with diethyl ether was found the best method of removing traces of iodine. Also, some of the products were only obtained as oils from organic solvents and precipitated in crystalline form from water.

In conclusion, we were able to expand the known method of oxidative anion metathesis onto a range of organic aprotic cations and various non-nucleophilic anions.

3.5 References

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Chapter 4

4.1 Introduction

Normally the Pd(II)/Pd(0) redox cycle, that is typical for cross-coupling reactions is not functional in the catalytic LDC processes. Cyclometallation, which is a key step for LDC requires the Pd atom to be fairly electrophilic – this condition is not met by electron-rich Pd(0) species. Thus, the LDC normally runs via oxidative Pd(IV)/Pd(II) or Pd(III)/Pd(II) mechanisms, as previously pointed out. Due to the fairly high oxidation barriers only strong oxidants become active reaction partners.¹ Classical examples include hypervalent iodine (III) reagents,^{2,3} *N*-halosuccinimides,⁴ dibenzothiophenonium salts,⁵ peroxides⁶ etc. One notable exception is the use of aryl iodides for the arylation using bidentate directing groups,⁷ but the mechanism for these reactions remains unclear (Table 1).

Table 1. Examples of reagents used in LDC and the corresponding bonds broken and formed.

Reagent used	Bond broken	Bond formed
PhIX ₂ X=OAc, OTFA	I—O	C—O
Ar ₂ IX X=BF ₄ , OTf etc	I—C	C—C
NXS	N—X X=halogen	C—X X=halogen
C ₅ H ₅ NF ⁺ X ⁸	N—F	C—F
Ar ₂ S—CF ₃ ⁺	S—C	C—C
K ₂ S ₂ O ₈ +NH ₂ COOCH ₃ ⁹	O—O	C—N
ArI+AgX X=OAc, OPiv	C—I	C—C

4.2 C—O bond formation

It is easy to notice that despite the immense development of the field, the scope of reagent types remains fairly narrow. The most sustainable reagent for the creation of C—O bonds is oxygen (or air), peroxides being somewhat worse, but only a limited scope of reactions are suitable for these oxidants. The use of these cheap reagents is restricted by the high temperatures required for reaction to take place, since peroxides have limited stability and oxygen has a low solubility in most of the

solvents used. Also, it poses a threat of explosion of the oxygen-solvent vapour mixture, if the pressure is increased. The most widely used and reliable reagent for the C—O bond formation is diacetoxyiodobenzene. This reagent is fairly convenient, but not efficient in terms of price per mole and *E* factor (Figure 1).¹⁰

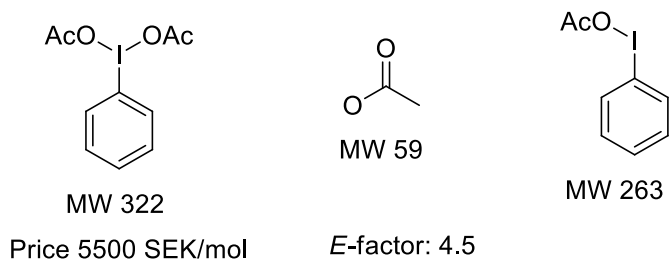


Figure 1. Diacetoxyiodobenzene price and waste efficiency.

Another alternative could be the use of the oxidative potential of N—O bonds. The possible N—O oxidants include nitrates and nitrites, hydroxylamines or quarternary *N*-oxide derivatives (Figure 2).

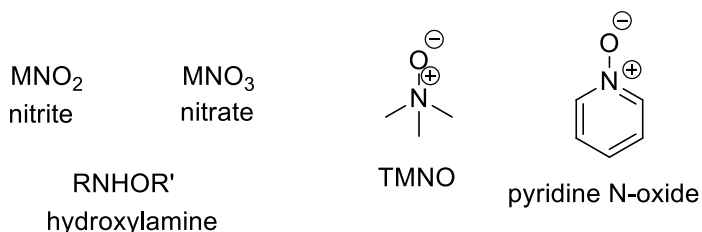
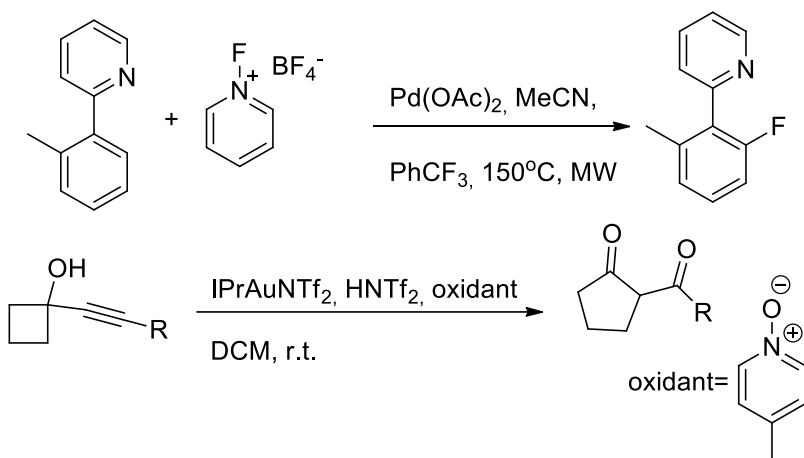


Figure 2. Potential N—O oxidants.

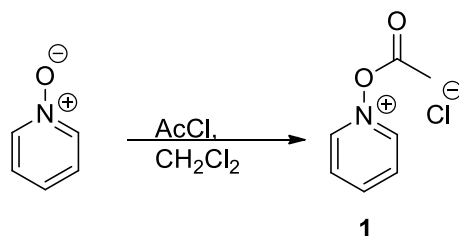
The former two alternatives are inferior: inorganic nitrates and nitrites have poor solubility in organic solvents, are nucleophilic and most likely would have a poor selectivity in oxidation; hydroxylamines are weak oxidants, somewhat unstable and can ligate palladium atoms. *N*-oxides bear only one of the drawbacks - relative nucleophilicity - which can be overrun by an electrophilic substitution at the oxygen atom. Pyridine *N*-oxides are easily available via the oxidation of pyridines with peroxides and offer a wide range of known stable derivatives that could be used as oxidants. Furthermore, very similar cationic *N*-fluoro derivatives have been employed⁸ in Pd-catalysed LDC. Pyridine *N*-oxides as such serve as oxidants in a variety of reactions (Scheme 1).¹¹



Scheme 1. Examples of the use of *N*-substituted pyridines as oxidants by Sanford⁸ and Hashmi.^{11a}

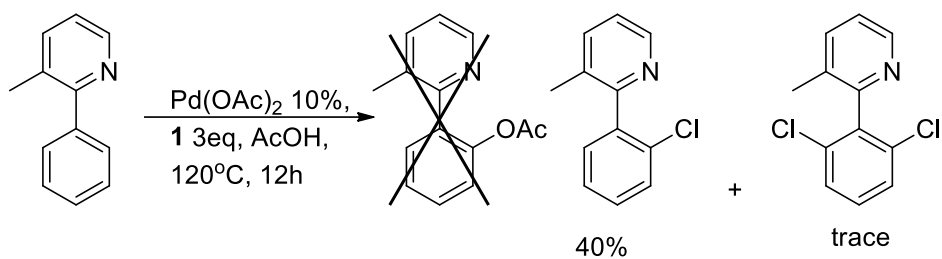
4.3 *N*-oxide reactions

Our study began with the formation of OAc derivatives with acetyl chloride. Pyridine *N*-oxide reacts easily with acetyl chloride forming the corresponding salt (Scheme 2).¹²



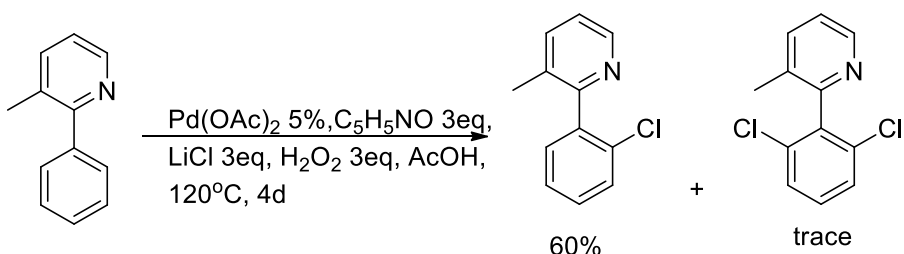
Scheme 2. Synthesis of *N*-acetoxypyridinium chloride.

Using this salt instead of the diacetoxyiodobenzene in a typical reaction of a directed substitution of phenyl-pyridine we observed the chlorinated product instead of the expected acetoxyated product (Scheme 3). Large excess of the *N*-oxonium salt was required to achieve a good conversion, but this was a successful proof of principle – N—O bond can be reduced to oxidise the organic substrate in an LDC reaction.



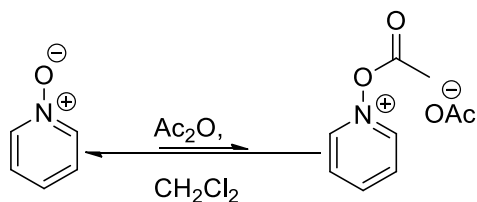
Scheme 3. Reaction with *N*-acetoxypridinium chloride as an oxidant.

Attempts to improve this process led us to the conclusion that the reaction can be performed in the presence of LiCl as a chloride source and H_2O_2 as an oxidant (Scheme 4). However, the yields were still higher in the presence of pyridine *N*-oxide. The effect of this additive remains unclear.



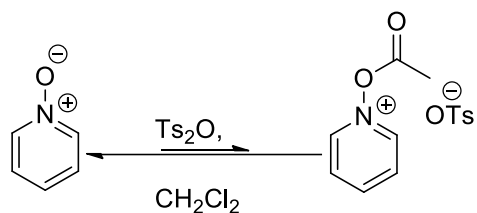
Scheme 4. Optimised protocol using LiCl as a chloride source.

Considering the removal of halide anions from the reaction mixture one can imagine running a similar reaction with the salts of different anions, e.g. acetate. Unfortunately, the equilibrium in the reaction of salt formation lies to the left for the anhydrides, unlike the chloroanhydrides, so we were unable to isolate it (Scheme 5).



Scheme 5. Attempted synthesis of *N*-acetoxypridinium acetate.

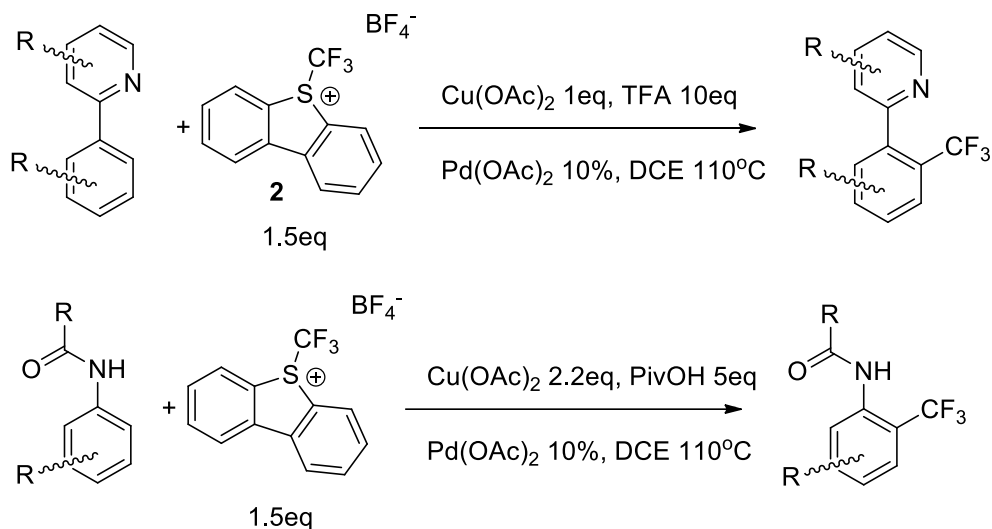
Similarly, the tosylation of *N*-oxides is only successful with tosyl chloride, but not with tosyl anhydride (Scheme 6).



Scheme 6. Attempted synthesis of *N*-tosyloxypyridinium tosylate.

4.4 Sulfoxonium salt reactions

Sulfonium salt **2** (Umamoto's reagent) was used as a source of a trifluoromethyl group in a LDC reaction by Yu⁵ and Shi (Scheme 7).¹³



Scheme 7. Palladium-catalysed trifluoromethylations with Umamoto's reagent.

We sought to expand protocols of this type to other hydrocarbyl substituents, e.g. simple alkyls. The electron density at sulfur would be increased by changing the perfluoroalkyl substituent to a regular alkyl, deteriorating its oxidative power. We expected to compensate for this by increasing the oxidation state of sulfur switching from sulfonium salts to sulfoxonium salts (Figure 3).

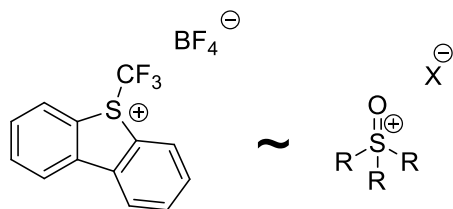
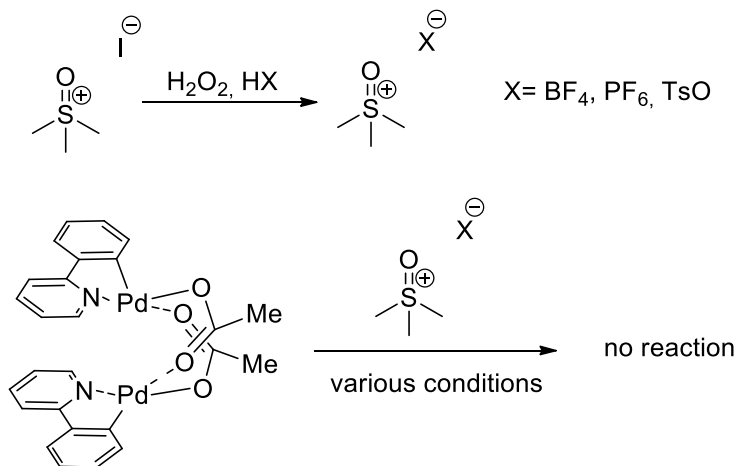


Figure 3. Comparison of Umemoto's reagent and trialkylsulfoxonium salts.

Trimethyl sulfoxonium seemed to be an easily available cation and we could exchange the metallophilic iodide to tosylate, tetrafluoroborate or hexafluorophosphate, as described in Chapter 3. Unfortunately, these salts were found completely unreactive towards the cyclometallated palladium species (Scheme 8).



Scheme 8. Anion exchange of trimethylsulfoxonium salts and attempted reactions with cyclometallated palladium compound.

4.5 Conclusions

In conclusion, we could show that the oxidative potential of the N—O bond of pyridine *N*-oxide derivatives can be used in LDC reactions, but the halide counterion was transferred onto the organic substrate instead of the acetoxy-substituent at nitrogen. Trialkyl sulfoxonium salts were found to be unsuitable for oxidative transformation, probably due to the low oxidation potential of these compounds. After this study was performed, Chang and co-workers succeeded¹⁴ in using the

oxidative potential of an N—O bond of a substituted hydroxylamine in a cobalt-catalysed LDC on 2-aryl-pyridines.

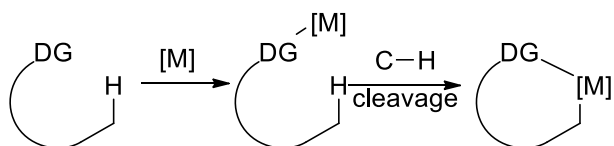
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Chapter 5

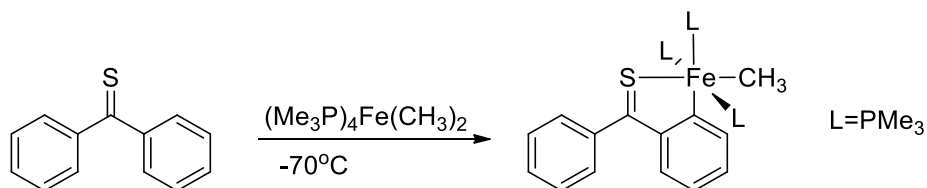
5.1 Introduction

Cyclometallation uses directing heteroatoms, which easily bind d-block metals, thus substantially reducing the value of the entropic contribution, which disfavours the C—H activation event, as discussed in Chapter 1. This results not only in high selectivity for C—H activation, but also in lower activation barriers for this process, which, in turn means that the reaction can proceed at lower temperatures (Scheme 1).



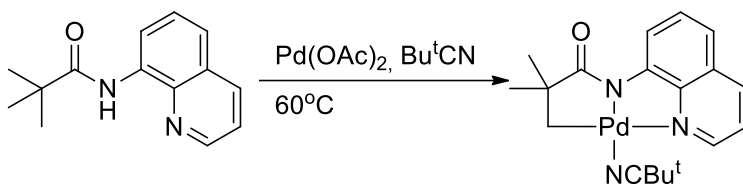
Scheme 1. Cyclometallation – the first step in ligand-directed C—H activation.

In some cases the cleavage of strong C—H bonds can take place at as low temperatures as -40°C ¹ or -70°C in the presence of a very strong internal base (Scheme 2).²



Scheme 2. An example of a low-temperature cyclometallation with an iron-alkyl complex.

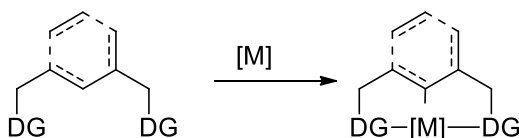
To further ease the interaction between a metal atom and C—H bond, a chelating ligand that contains two directing atoms can be used (Scheme 3); as an example the 8-aminoquinolyl directing group was used in various Pd- and Cu-catalysed reactions, some of which are not possible with monodentate directing groups.³



Scheme 3. Example of a cyclometallation with a bidentate directing group.

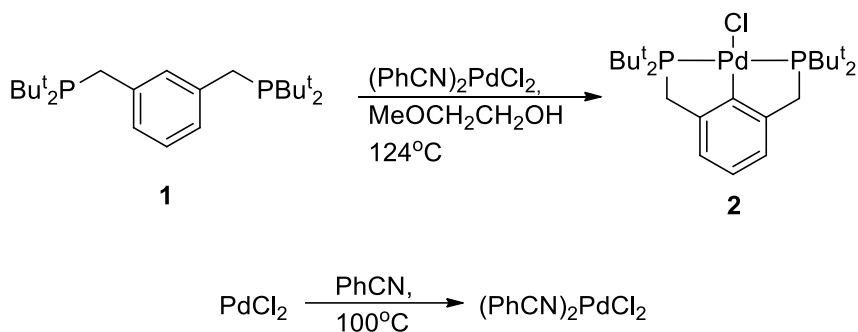
5.2 Pincer complexes

Another classic example of this double-directed C—H activation is the synthesis of pincer complexes (Scheme 4). Pincer complexes typically contain two ligating heteroatoms in γ -positions to the C-atom, which is to be substituted. That creates an almost perfect arrangement for the C—H activation event, since the metal atom is “forced” to form two stable 5-membered rings with chelate angles in the product usually being close to 90° , which is perfect for the typical product ligation arrangements: square planar, square pyramidal, trigonal bipyramidal or octahedral.



Scheme 4. General description of the metallation of a pincer ligand.

The first pincer palladium complex was published by Shaw in 1976.⁴ The product **2** was synthesised via a reaction between pincer preligand **1** and a common palladium precursor – bis(benzonitrile)palladium (II) chloride (Scheme 5). This precursor is very convenient for several reasons: i) it can easily be synthesised from palladium chloride via a fast reaction;⁵ ii) benzonitrile ligands form weak bonds to Pd, and can thus be easily substituted; iii) the compound has a high solubility in many moderately polar organic solvents, e.g. DCM or THF and shows some solubility even in aromatic hydrocarbons. Considering what is said above, it is fairly strange that the synthesis published by Shaw required refluxing in 2-methoxyethanol – a solvent, which is not only inconvenient due to its high toxicity, but also has a fairly high boiling point.⁶



Scheme 5. Syntheses of the first pincer palladium complex and the corresponding palladating agent.

5.3 Room-temperature reactions

While reproducing the procedure published by Shaw,⁴ it is easy to note that the starting materials, particularly the phosphine preligand, have very low solubilities in the highly polar solvent used. To investigate the possibilities for improvements, we decided to perform test reactions between **1** and the palladating agent in different solvents and study the reaction by NMR. Excess of $(\text{PhCN})_2\text{PdCl}_2$ was used to ensure complete conversion of the phosphine. To our surprise, the ^{31}P NMR spectra obtained at room temperature in a minimum time span contained only one resonance, corresponding to a pincer product! Similar spectra were obtained independently of whether CDCl_3 , C_6D_6 or THF were used as a solvent. Our first conclusion was that the reaction proceeds with quantitative yield at room temperature. However, the signal to noise ratio of the resulting NMR spectrum was unexpectedly low. We decided to reproduce the room-temperature reaction, using a capillary with a solution of orthophosphoric acid as an internal standard, using CDCl_3 , since this solvent was convenient, relatively cheap and the solubility of the palladating agent in it was very high. The ^{31}P NMR spectrum indicated that despite the full conversion of the starting material, only 30% of pincer product was formed. Most of the ^{31}P resonances “disappeared” from the spectrum, which we assigned to an exchange process taking place (Figure 1).

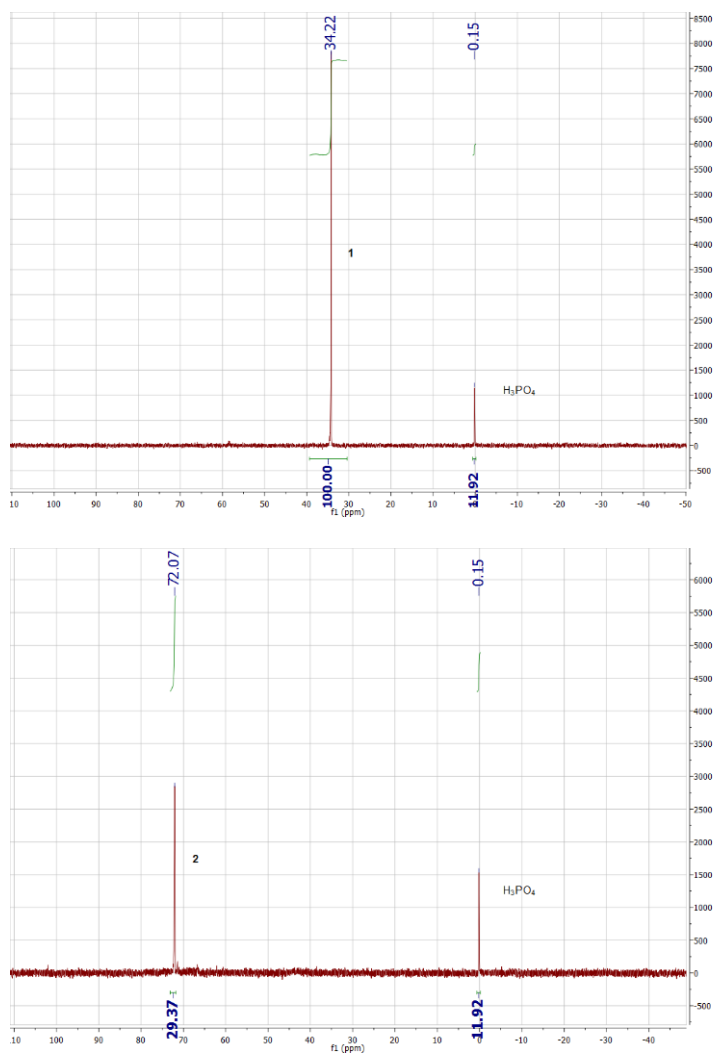
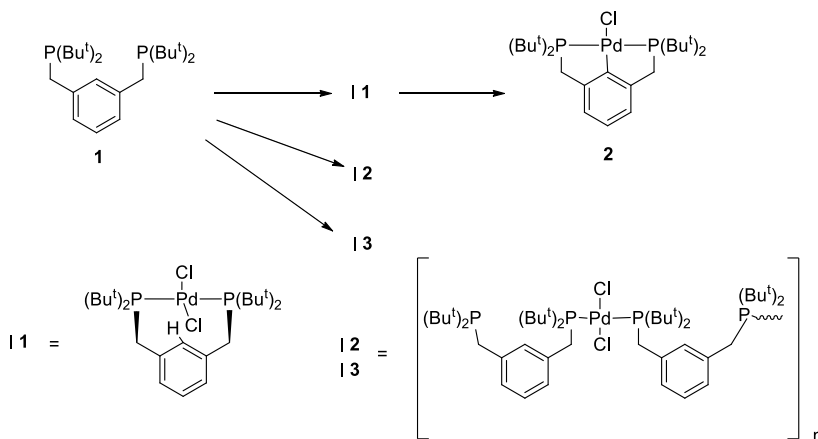


Figure 1. Representative ^{31}P NMR spectra before the addition and 10 minutes after the addition of [Pd].

The intensity of the resonance of **2** increased slowly at room temperature reaching a value of 60% after 3 days without any further increase. The addition of a base did not affect the conversion, indicating that the molecule of HCl formed was not the reason for the moderate yield. In our view, if a single process was to take place, it should have been driven to completion either with addition of a base (if it proceeded under a thermodynamic control) or at prolonged reaction times (if it proceeded under a kinetic control). Our only explanation for the observed behaviour is that there are several parallel reactions taking place, only some of which lead to the formation of the pincer product **2**. Since phosphines easily form strong bonds to

palladium, these parallel processes can be rationalised as formation of many different coordination complexes, only one (e.g. **11**) or few of which lead to the formation of the product **2** (Scheme 6). The alternative intermediates may be mixtures of oligomers or even polymers, which would explain the absence of sharp resonances in the ^{31}P NMR spectrum.



Scheme 6. Proposed formation of multiple intermediates.

5.4 Low-temperature reactions

Next, we were keen to elucidate the lowest temperature at which the C—H activation is happening. NMR spectroscopy was found to be a suitable way. The broadband probe that we used allows cooling down to -80°C and we were certain that the reaction will not happen at such a low temperature. By slowly increasing the temperature we were hoping to register the lowest temperature where the reaction is feasible. Since deuterated chloroform was found suitable, we decided to stick to this solvent. That posed an additional limitation, since the melting point of CDCl_3 is -64°C – that was the lowest temperature we could use. In order to avoid any possibility of the reaction being promoted by an increase of temperature, which might happen during a contact of the NMR tube with air, we devised the following experiment scheme: the solutions of the pincer preligand and an internal standard in CDCl_3 were placed in an NMR tube. Then, the NMR tube was fixed in the spinner and placed in a Dewar container filled with liquid nitrogen until the solvent inside froze and the NMR tube reached the temperature of liquid nitrogen. Then the solution of bis(benzonitrile)palladium (II) chloride in CDCl_3 was added within $\sim 10\text{s}$. This time span allowed the solution of the palladating agent to freeze on the

walls of the NMR tube, without contact with the level of the frozen phosphine solution. At the same time, it was short enough to avoid any significant exchange with outer atmosphere, which could pose a threat of the condensation of liquid oxygen. Then the NMR tube was placed inside an NMR spectrometer as quickly as possible. After that the solution slowly melted inside the probe, which was set to the temperature of -62°C . To our great surprise the first spectrum we could observe already contained a ^{31}P resonance of the pincer product! At these conditions 12% of **1** was still present in the spectrum after 10 minutes as well as a few unidentified broad resonances. However, the sum of the intensities of all the resonances present (excluding Ph_3PO standard) is less than 40% of the original intensity of the pincer preligand (Figure 2).

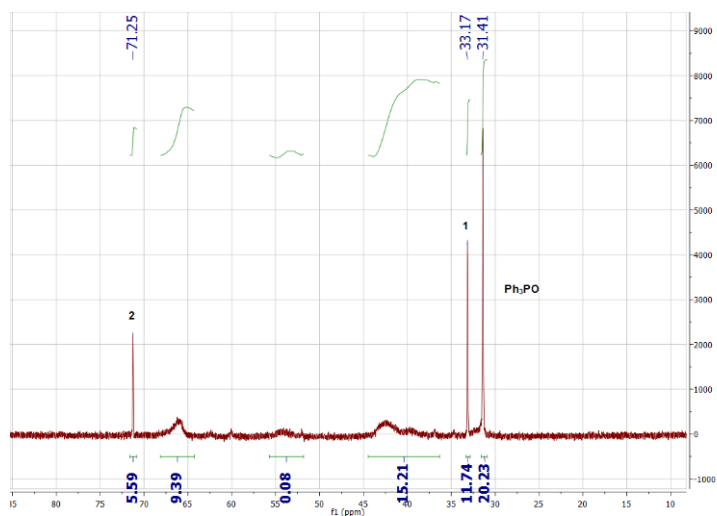


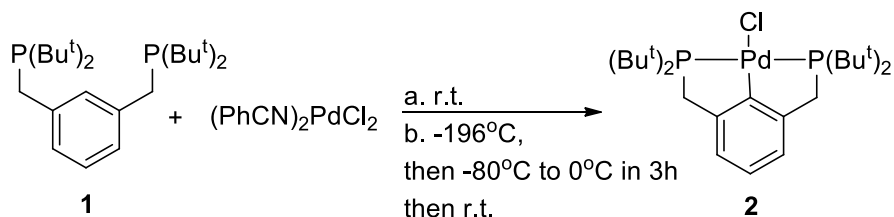
Figure 2. Representative ^{31}P NMR spectra ~10 minutes into the reaction at -62°C .

Even more peculiar was the behaviour of this resonance: its intensity, which reached 6% in about less than 10 minutes did not increase any further in the time of 50 minutes. This behaviour cannot be described in terms of regular 1st, 2nd, etc order kinetics, unless we assume the reaction reaches its endpoint at this yield. The two obvious explanations for this endpoint are i) the reaction proceeds under a thermodynamic control and reaches equilibrium; ii) the reaction proceeds under kinetic control and reaches full conversion, but parallel irreversible (at this temperature) reactions are taking place. The first assumption can almost certainly be ruled out given the fact that the reaction is not under thermodynamic control even at higher temperatures. Hence, we are convinced in our previous conclusion that several parallel reactions are taking place. Another conclusion that can be derived from this data is that the C—H cleavage is very fast. It may still be the rate determining step in the sequence leading to **II** and pincer complex **2** (see Scheme

6), but in the overall reaction scheme, the transformation between different coordination compounds becomes rate-determining. This contradicts the results published by Cox and co-workers,⁷ who proposed the C—H bond cleavage to be the slow step. The calculated activation energy for this step of 92.5 kJ/mol does not match a reaction that proceeds spontaneously at -62°C.

The sample was slowly warmed inside the NMR spectrometer. The intensity of the product resonance increased slightly with increasing temperature, however, it still did not change with time when the reaction mixture was kept at the same temperature. The increase stopped after reaching -25°C and the spectrum of the sample kept for 7 minutes at -15°C was the same.

Overall, we were somewhat disappointed by the fact that, despite the reaction being observed at very low temperatures, the yield was even lower than in the room temperature reaction. To verify this observation, we ran another set of experiments, where identical samples were reacted with the same volumes of the same stock solution of [Pd]. Indeed, the sample, where all the reagents were mixed at room temperature showed higher conversion after 30 min reaction at room temperature, than the sample which was mixed in the NMR tube frozen, slowly warmed up to 0°C, then heated to room temperature and then left for 30 min! Our conclusion is that, if the mixture of coordination complexes was formed (Scheme 6), the formation of **11**, which leads to the pincer complex, is kinetically disfavoured (Scheme 7).

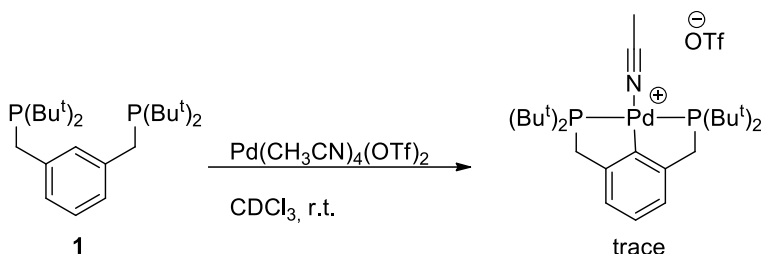


	Time at r.t	Yield	Time at r.t.	Yield
a	30 min	40%	3d	58%
b	30 min	8%	3d	43%

Scheme 7. Comparison of the reactions started at different temperatures.

5.5 Alternative electrophile

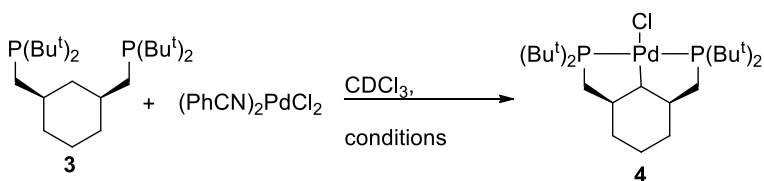
If the metallation was incomplete due to the insufficient electrophilicity of the palladating agent, it can be improved by using an even stronger electrophile. We chose tetrakis(acetonitrile)palladium (II) triflate as an alternative. A similar reaction was performed in CDCl_3 . The conversion of **1** was, again, instant, however, only trace amounts of the corresponding pincer products were observed, along with some unknown low-field resonances, probably resulting from oxidation or even degradation of the pincer backbone (Scheme 8).



Scheme 8. Reaction with the cationic palladation agent.

5.6 Aliphatic preligand

The presence of an aromatic π -electron density might play a beneficial role for the metallation process, since the Pd(II) centre is fairly electrophilic. Thus, we were interested to compare the reactivity of the “standard” aromatic preligand **1** with its aliphatic analogue **3**,⁸ possessing a cyclohexyl ring instead of a phenyl ring, (Scheme 9). The same experiments were repeated and very similar results were obtained: the reaction proceeds at room temperature and at temperatures as low as -62°C , does not reach completion, is unaffected by the presence of bases and the yield of pincer product is increased after refluxing.



Scheme 9. Cyclopalladation of the saturated pincer preligand.

5.7 Conclusions

In conclusion, the processes happening during the cyclopalladation of the first pincer preligand **1** and its saturated analogue **3** are too complicated to study the mechanism in all the details. However, we are able to conclude that the C—H activation easily proceeds at room temperature and is possible at a temperature as low as -62°C. The C—H activation itself is fast and, probably, not rate-limiting in this process. Several processes are running in parallel and only some of those lead the formation of pincer complexes, unless the reaction is heated to a high temperature.

5.8 References

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