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Regioselective C–H functionalization of naphthalenes: reactivity and mechanistic insights

Sébastien Prévost*^[a]

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Abstract: Naphthalene is a very important skeleton in chemistry as evidenced by the large number of active compounds containing it. For this reason, methods achieving easy functionalization of naphthalene derivatives are of great importance. This review sums up reactions allowing regioselective functionalization of 1-substituted naphthalenes based on a directed C–H activation strategy. Indeed, over the past ten years, a lot of research groups have tried to develop new methodologies to directly introduce different functional groups on every positions of naphthalene. In addition of the possible reactions described in the literature, a special attention has been paid to mechanistic aspects in order to explain the observed regioselectivities.

1. Introduction

Naphthalene is a very important moiety in chemistry. It is commonly found in more or less complex natural product such as guieranone A or mbandakamine A and bioactive compounds (Figure 1).^[1,2] Naphthalene is also an interesting building block for the synthesis of aromatic derivatives with optical and electronic properties or used in the conception of organic materials.^[3]

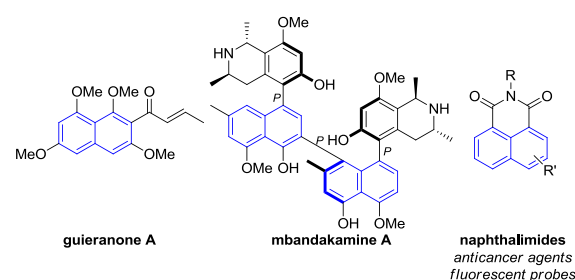
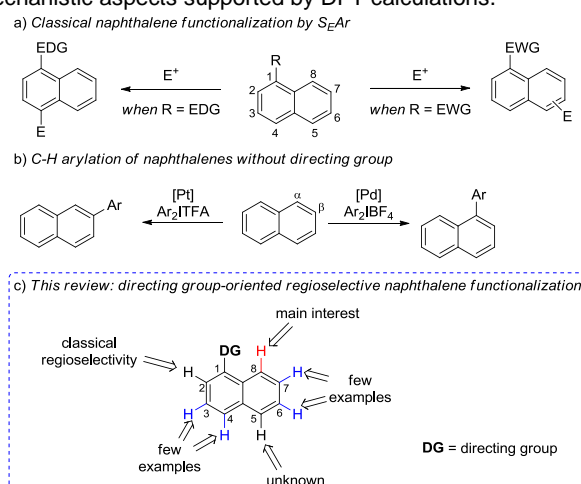


Figure 1. Naphthalene core in natural products and active compounds

Due to all potential applications, synthesis of functionalized naphthalenes has a great interest for the community. Traditionally, disubstituted naphthalenes were synthesized through electrophilic aromatic substitution. However, the regioselectivity of the reaction can be hardly controlled and depends of the already present functional group (Scheme 1.a). Indeed, when naphthalenes bearing an electron-donating group at C1 are submitted to electrophilic aromatic substitution reactions, C4-substituted products are generally obtained whereas an electron-withdrawing group at C1 will favor a functionalization on the electron-richer ring and, in general, at position C5 or C8.^[4]

In the 21st century, C–H activation has known a significant growth of interest^[5] and, in parallel, strategies for direct regioselective functionalization of naphthalenes start to emerge.

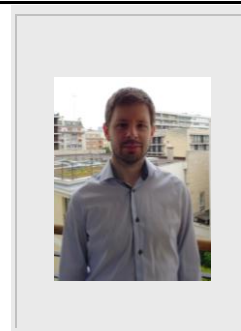
Some research groups tackled the selective arylation of naphthalene and, in particular, Sanford's team showed that, in function of the metal catalyst, it was possible to switch from α to β selectivity (Scheme 1.b).^[6] Concerning naphthalene derivatives substituted at C1 position, a lot of directing group have been demonstrated to achieve a C2-functionalization due to all researches on direct *ortho*-functionalization of arenes.^[7] Very interestingly, almost all the other positions of naphthalenes are now possible to functionalize (Scheme 1.c). In this review, we will describe researches on directed 1-substituted naphthalene C–H functionalization as well as on mechanisms involved in order to explain the observed regioselectivities. A particular attention will be devoted to *peri*-functionalization and to mechanistic aspects supported by DFT calculations.



Scheme 1. Different approaches for regioselective naphthalene functionalization

Dr Sébastien Prévost studied chemistry at ESPCI Paris where he graduated in 2008. He received his PhD in 2011, working under the supervision of Dr Phannarath Phansavath and Dr Virginie Vidal at Chimie ParisTech. After two postdoctoral internships with Prof. Ben List (Max-Planck-Institut für Kohlenforschung) and Prof. Varinder Aggarwal (University of Bristol), he got a CNRS researcher position in 2015 at the National Museum of Natural History in Paris.

In 2017, he moved to the Laboratory of Organic Synthesis of Ecole Polytechnique/ENSTA where his group is working on the development of new catalytic methods and their application in synthesis.



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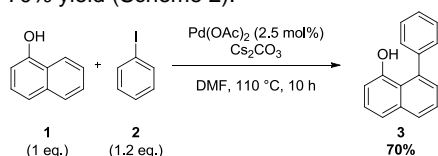
2. C8-functionalization of naphthalene derivatives

While the C2-functionalization of 1-substituted naphthalenes is in general an application of methodologies developed for *ortho*-functionalization of arenes, the *peri*-functionalization is of particular interest since it has been known to be difficult to achieve due to *peri*-strain. We will see in this part the different methods developed to achieve C8-functionalization in function of the directing groups.

2.1. C8-H activation of 1-naphthol

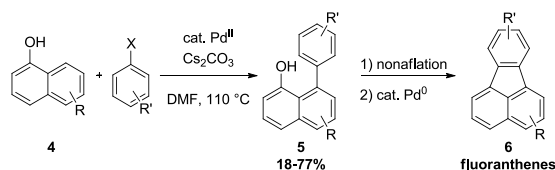
2.1.a. Arylation reactions

The first example of direct C8-functionalization of naphthalene derivative has been reported by the group of Miura in 1997, using 1-naphthol **1** as substrate.^[8] For the first time, a *peri*-selective arylation was described relying on a hydroxyl-directed palladium-catalyzed C–H activation and arylated product **3** was isolated in 70% yield (Scheme 2).



Scheme 2. First example of C8-functionalization of naphthol by Miura

Since this work, naphthols have been used by different groups to functionalize the C8-position. In 2016, Manabe's team combined palladium catalyzed C8-arylation of naphthols with an intra-molecular C–H arylation to obtain fluoranthenes **6** in three steps which constitutes a fast method for the synthesis of polycyclic aromatic hydrocarbons (Scheme 3).^[9] Very recently, Spiewak and Weix reported a similar arylation reaction using a Ru(II) catalyst which allowed the introduction of heteroaryl groups.^[10]

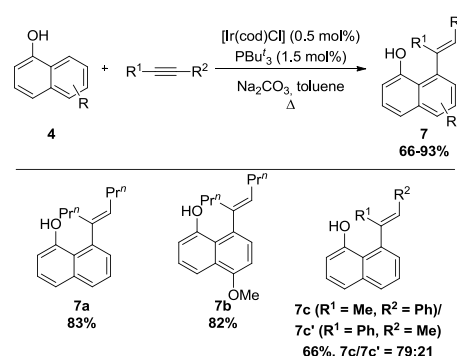


Scheme 3. Fluoranthene synthesis through Pd-catalyzed inter- and intra-molecular C–H arylation

2.1.b. Reaction with alkynes

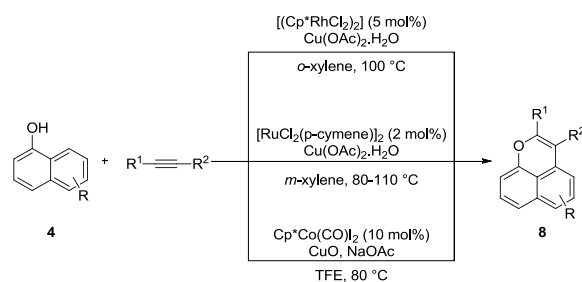
After having studied arylation reaction, the group of Miura focused on the reaction between naphthols and disubstituted alkynes. Thanks to an iridium(I) catalyst, they were able to introduce in good yields substituted vinyl groups in position 8

(Scheme 4).^[11] When non-symmetrical alkynes were used, a mixture of products were obtained.



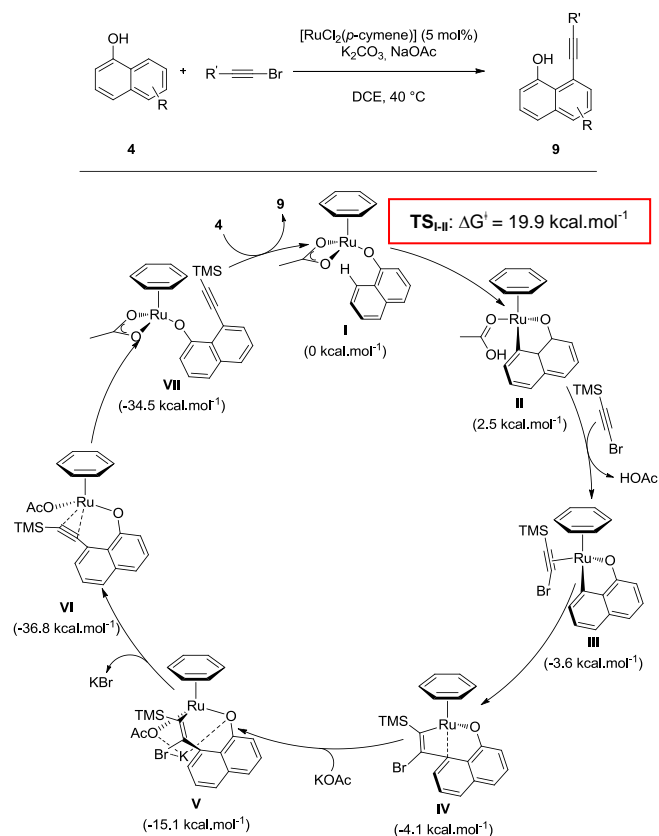
Scheme 4. Iridium-catalyzed C8-alkenylation of naphthols

In the 2010s, several groups used this strategy for the synthesis of naphthopyrans **8** (Scheme 5). Different metals, such as Rh,^[12] Ru,^[13] or Co^[14] were employed to achieve this transformation which gives access to interesting fluorescent pyrans. In 2018, the Ackermann's group was able to develop an electrochemical version of this reaction with a ruthenium catalyst.^[15]



Scheme 5. Naphthopyran synthesis via C8-functionalization

Similarly, Echavarren's team reacted 1-naphthols with bromoalkynes to develop a *peri*-alkynylation reaction (Scheme 6).^[16] In order to have a better understanding of the mechanism involved, some DFT calculations were performed. According to the results, the C–H ruthenation was proposed as the rate-determining step. To explain the observed regioselectivity, the activation energies of the *peri*- and *ortho*-ruthenation steps were calculated ($\Delta G^\ddagger = 19.9 \text{ kcal.mol}^{-1}$ and $26.0 \text{ kcal.mol}^{-1}$ respectively) and had confirmed the preference for the *peri*-metallation. After ruthenacycle II formation, a ligand substitution, an alkyne insertion followed by a bromide elimination was proposed to explain the mechanism.



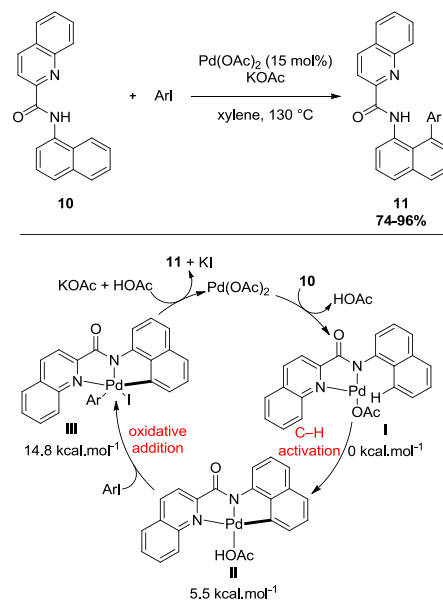
Scheme 6. *Peri*-alkynylation of naphthols and mechanistic study by DFT

2.2. Functionalization of 1-naphthylamine derivatives

The *peri*-functionalization reactions of naphthols are relatively limited in the literature. However, a lot of research groups developed direct C8-functionalization of 1-naphthylamine derivatives which allowed a much wider scope of reactions.

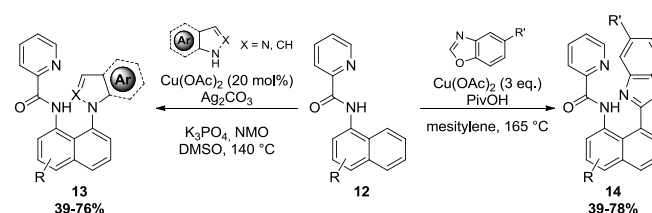
2.2.a. Bidentate directing groups: picolinamide derivatives

In order to achieve C8-functionalization of naphthylamines, a lot of research groups employed a bidentate directing group. Indeed, whereas a monodentate directing group such as *tert*-butylamide showed a C2-regioselectivity,^[17] a bidentate directing group was expected to realize a metal catalyzed C8-H activation. Regarding arylation reaction, the group of Qi developed a method based on quinolinamide and picolinamide directing group. Naphthylquinoline-2-carboxamide **10** was reacted with aryl iodides in presence of Pd(OAc)₂ to achieve the C8-arylation in very good yields (> 74%) (Scheme 7).^[18] Some DFT calculations were also conducted to understand the mechanism of the reaction which concluded to a sequential C-H activation/oxidative addition pathway.



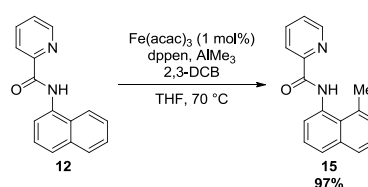
Scheme 7. Palladium catalyzed C8-arylation of naphthylamides

Along with the arylation, the group of Punniyamurthy reported a copper catalyzed C8-introduction of indoles, pyrazoles and pyrroles,^[19] while the group of Miura developed a copper-mediated C8-azolation of naphthylamines (Scheme 8).^[20]



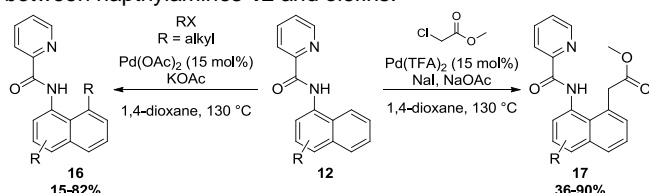
Scheme 8. C8-heteroarylation of naphthylamines

Naphthylamines are compatible with a lot of C-H activation reactions and, for instance, Ilies and Nakamura reported an iron-catalyzed methylation of naphthylamide **12** with trimethylaluminum as alkylating agent (Scheme 9).^[21] C8-methylated naphthalene **15** was isolated in an excellent yield of 97%.



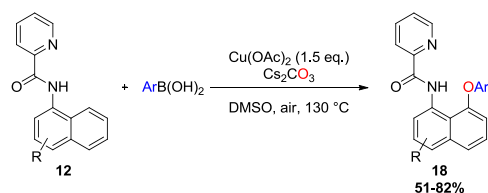
Scheme 9. Iron-catalyzed C8-methylation of naphthylamine

A more general C8-alkylation reaction was reported by Huang *et al.* with alkyl halides and a palladium catalyst (Scheme 10).^[22] This reaction was compatible with alkyl and benzyl halides despite a low yield with secondary iodides. In order to synthesize more functionalized naphthalenes, the group of Wu recently developed an alkoxy carbonylmethylation with α -chloroalkyl esters as alkylating agents.^[23] In 2018, similar C8-alkylated products with wider scope was reported by Chatani's team using rhodium(I)-catalyzed reaction between naphthylamines **12** and olefins.^[24]



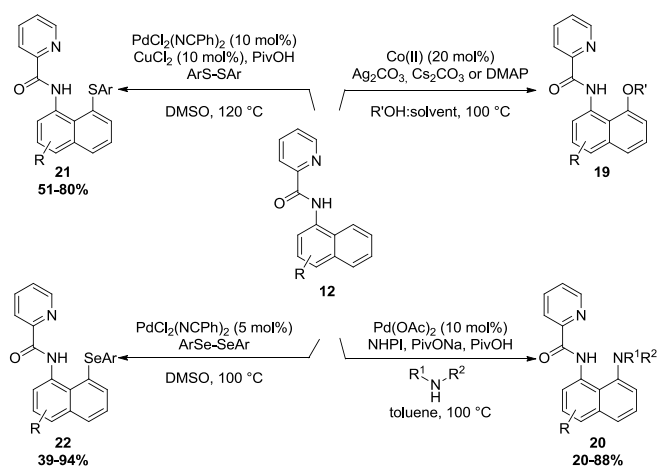
Scheme 10. Palladium-catalyzed C8-alkylation

C8-heterofunctionalization of 1-naphthylamines have also been described. For instance, Punniyamurthy's team reported a copper-mediated etherification reaction with arylboronic acids (Scheme 11).^[25] In this study, thanks to labelling experiments, they were able to show that the water, formed during the reaction from cesium carbonate and acetic acid, was the source of oxygen in product **18**.



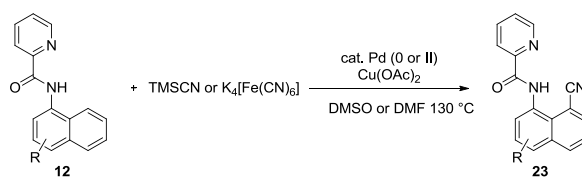
Scheme 11. Copper-mediated C8-etherification

The introduction of several heteroatoms in C8 position has been described in the literature (Scheme 12). Cobalt-catalyzed alkoxylation,^[26] palladium-catalyzed amination,^[27] as well as palladium-catalyzed selenation and thiolation were developed.^[28]



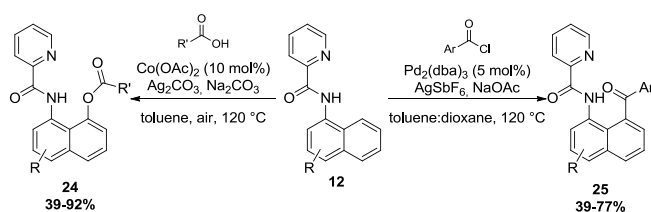
Scheme 12. C8-heterofunctionalization of 1-naphthylamines

Due to the importance of the nitrile moiety in chemistry, some methods were developed to realize a palladium-catalyzed C8-cyanation with low-toxic cyanating reagents (Scheme 13).^[29] The newly introduced cyano group in position C8 could then be converted to carboxylic acid for further transformations.



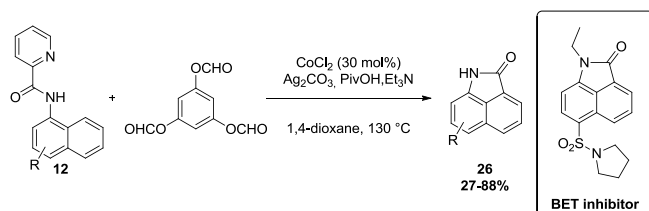
Scheme 13. Palladium-catalyzed cyanation

Carbonyl moieties were also directly introduced in position 8 (Scheme 14). Wu's group reported a palladium-catalyzed acylation of naphthylamines with acyl chlorides.^[30] In 2017, Zeng's group demonstrated a cobalt-catalyzed coupling of naphthylamines with carboxylic acids.^[31] These two methods offers an easy access to 1,8-disubstituted naphthalenes which could be further functionalized.



Scheme 14. C8-esterification and acylation of naphthylamines

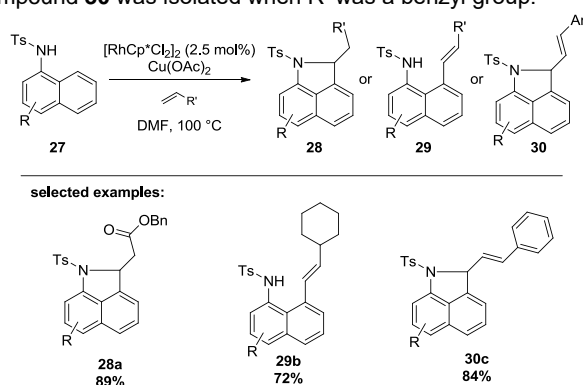
Very recently, a cobalt-catalyzed carbonylation reaction of naphthylamides **12** was developed by the group of Wu to have access to non-protected benzo[*cd*]indol-2(1*H*)-ones **26** in moderate to very good yields (Scheme 15).^[32] Benzene-1,3,5-triyl triformate was used as a solid CO source and this protocol was applied to the synthesis of BET inhibitors.



Scheme 15. Synthesis of benzo[*cd*]indol-2(1*H*)-ones via C8-carbonylation

2.2.b. Monodentate directing groups

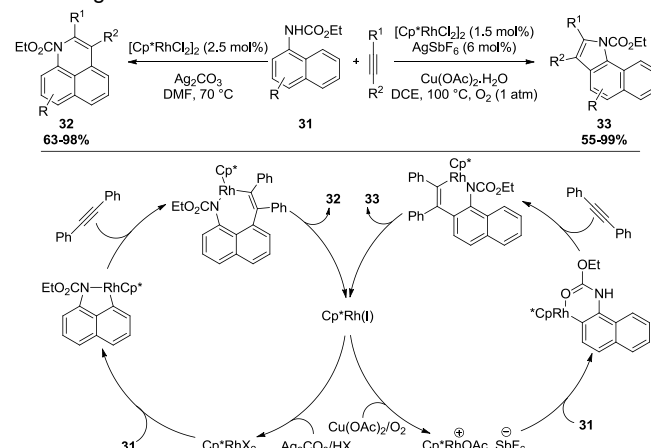
Peri-functionalizations were also possible with monodentate directing groups. For instance, Li's group reported a rhodium-catalyzed olefination of 1-naphthylsulfonamides (Scheme 16).^[33] In function of the olefin partner used in the reaction, different products were obtained. When R' was an electron-withdrawing group, the nitrogen spontaneously cyclized to afford five-membered azacycle **28**. When R' was aryl or an alkyl group, olefination product **29** was obtained whereas oxidized compound **30** was isolated when R' was a benzyl group.



Scheme 16. Rhodium-catalyzed olefination of 1-naphthylamines

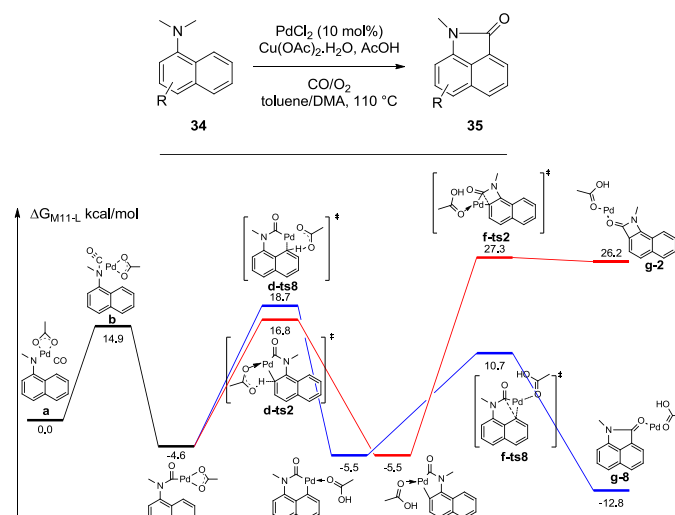
In 2014, Jin's team described a regioselective functionalization of 1-naphthylcarbamates **31** (Scheme 17).^[34] When [Cp**Rh*Cl₂]₂ was used with silver carbonate in DMF, a C8-regioselectivity was observed to deliver benzoquinolines **32** whereas, when silver hexafluoroantimonate was added in presence of copper acetate in dichloroethane, benzoindole **33** were obtained. The C8-selectivity was explained by the formation a five-membered azarhodacycle which then reacts with the alkyne through insertion/elimination steps. The switch of regioselectivity was explain by the formation of a cationic Rh(III) specie in presence of AgSbF₆ in dichloroethane which exhibit a higher Lewis acidity

compared to the Rh(III) catalyst in DMF and which favors a coordination with the oxygen atom of the carbamate instead of the nitrogen.



Scheme 17. Regioselective rhodium-catalyzed annulation with alkynes

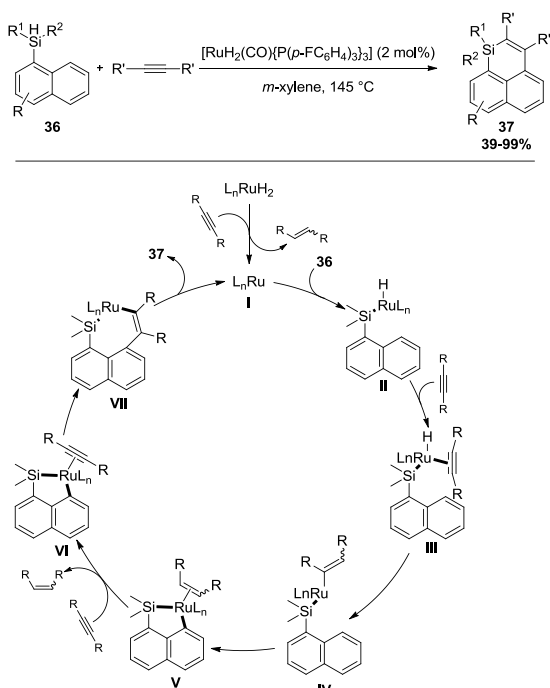
In 2016, Lei's group reported a palladium-catalyzed C8-dealkylative carbonylation of naphthylamines **34** to synthesize methyl protected benzo[*cd*]indol-2(1*H*)-ones **35** (Scheme 18).^[35] This method represents a straightforward way to access biologically active scaffolds. In order to understand the mechanism and the regioselectivity (C8 vs C2), DFT calculations were performed. The activation free energies of both transition states **d-ts2** and **d-ts8** were found to be very similar. However, the observed regioselectivity was explained by the reductive elimination step which has a much higher energy barrier in case of the C2 selectivity.



Scheme 18. Lactam formation via palladium-catalyzed carbonylation

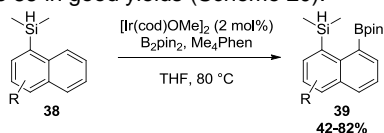
2.3. Peri-functionalization of 1-hydrosilyl naphthalenes

Similarly to 1-naphthols, 1-hydrosilyl naphthalenes were used as substrates to realize direct C8-functionalization. In 2015, Tokoro and Fukuzawa's group reported a ruthenium-catalyzed annulation reaction between 1-naphthylsilanes **36** and internal alkynes to deliver interesting silaphenalenenes **37** (Scheme 19).^[36] The catalytic cycle, supported by DFT calculations, proposed first an oxidative addition of Ru⁰, generated by the reduction of Ru^{II} with the alkyne, into hydrosilane followed by the alkyne insertion leading to intermediate **IV**. Then, the C–H activation step to form metallacycle **V** happens. Ligand exchange with the alkyne generates **VI** which, after alkyne insertion and reductive elimination, finally liberates product **37**.



Scheme 19. Ruthenium-catalyzed annulation between 1-naphthylsilanes and alkynes

More recently, 1-hydrosilyl naphthalenes were involved in *peri*-borylation reactions.^[37] For instance, Hartwig's team realized an iridium-catalyzed *peri*-borylation of naphthalenes **38** with B₂pin₂ as borylating agent to synthesize very versatile borylated naphthalenes **39** in good yields (Scheme 20).

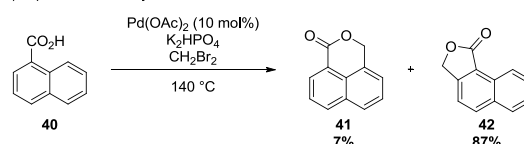


Scheme 20. *Peri*-borylation of hydrosilyl naphthalenes

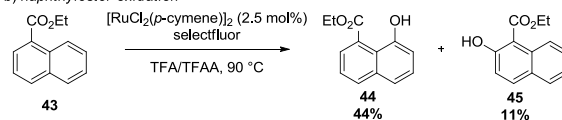
2.4. 1-carbonylnaphthalene derivatives in C8-functionalization

Carbonyl moiety is an interesting weakly coordinating directing group due to the possible further transformations. Its interest in C–H activation recently starts to emerge.^[38] However, regarding naphthalene derivative direct functionalization, the first examples reported in literature were not very conclusive due to an observed mixture of regioisomers (Scheme 21). For instance, in 2009 the group of Yu developed a palladium-catalyzed alkylation reaction of benzoic acid but, when they applied the conditions to 1-naphthoic acid **40**, a mixture of regioisomers **41** and **42** were obtained in favor of the C2-alkylated product (Scheme 21.a).^[39] Examples of oxidation and olefination were reported with ester and ketone as directing group but in both cases a mixture of C2- and C8-functionalized products were obtained (Scheme 21.b,c).^[40,41]

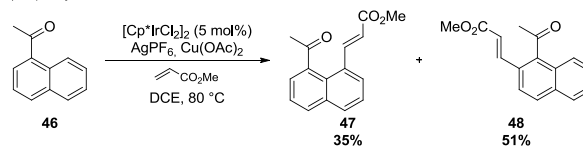
a) naphthoic acid alkylation



b) naphthylester oxidation

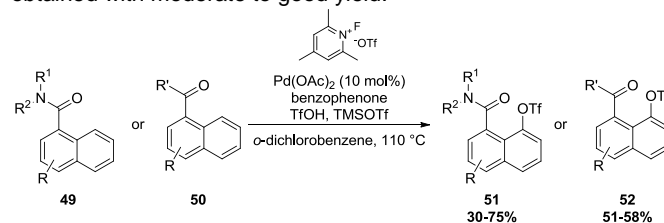


c) naphthylketone olefination



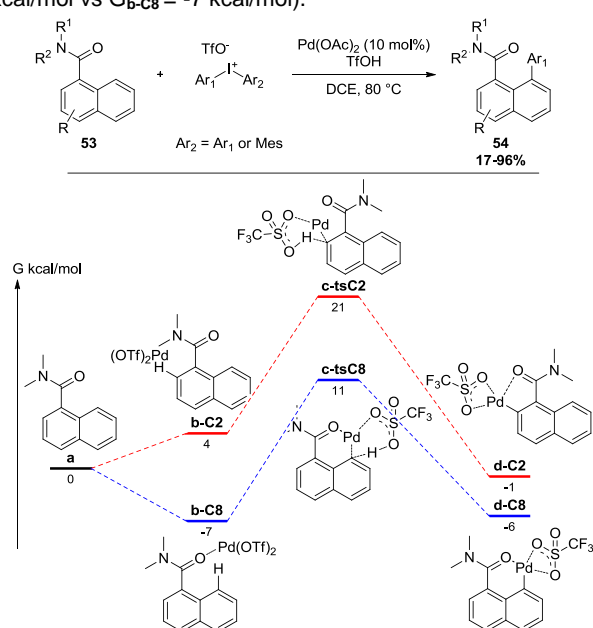
Scheme 21. C–H activation reactions delivering a C2/C8 mixture

Despite one example of halogenations reported in 2013,^[42] carbonyl-directed C8-functionalization is quite rare in the literature. In 2016, Xia and Fu's team developed a palladium-catalyzed C8-triflation of naphthalenes (Scheme 22).^[43] Disubstituted amides and hindered ketones were used as directing group and C8-triflated products **51** and **52** were obtained with moderate to good yield.



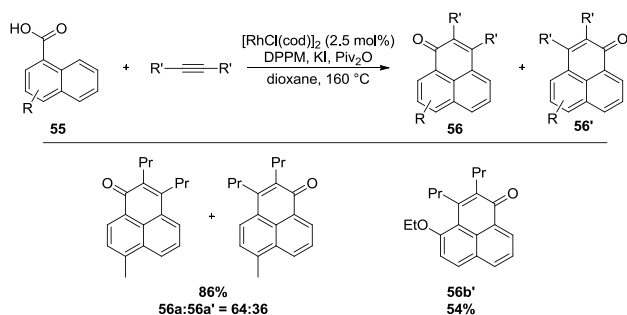
Scheme 22. Palladium-catalyzed C8-triflation of naphthalenes

Very recently, Prévost's group described a C8-arylation of naphthalenes using disubstituted amides as directing group and diaryliodonium salts as arylating agent (Scheme 23).^[44] In order to explain the C8-regioselectivity some DFT calculations were performed and it was shown that the structure of the free substrate, where the carbonyl moiety points toward the C8-H bond, favors the approach of the palladium catalyst in C8-position due to a stabilizing interaction between the catalyst and the carbonyl oxygen which is not possible in case of C2 ($G_{b-C2} = 4\text{kcal/mol}$ vs $G_{b-C8} = -7\text{kcal/mol}$).



Scheme 23. Palladium-catalyzed C8-arylation of naphthalenes

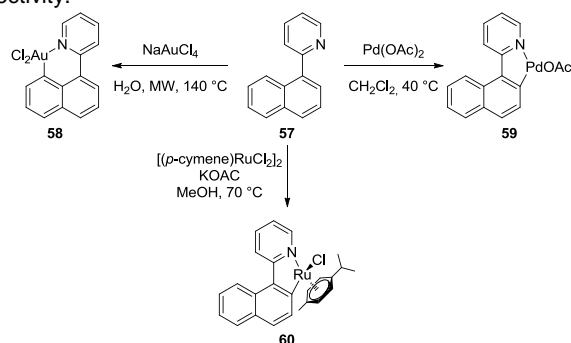
Finally, Fukuyama *et al.* published a rhodium-catalyzed synthesis of perinaphthenones *via* a dehydrative annulations of naphthoic acid **55** with alkynes (Scheme 24).^[45] In some cases a mixture of regioisomers **56** and **56'** was obtained which was explained by a decarbonylation/CO reinsertion sequence.



Scheme 24. Rhodium-catalyzed perinaphthenone synthesis

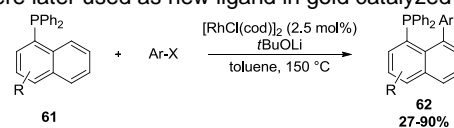
2.5. Miscellaneous directing groups

Other kind of directing groups were used to achieve a *peri*-functionalization of naphthalenes. A very interesting example has been published by the group of Wendt who used 2-(1-naphthyl)-pyridine **57** as substrate. In function of the metal used, the metallacycle could be formed in C2 or C8 position (Scheme 25).^[46] For instance, using palladium diacetate or a ruthenium complex allowed the formation of a palladacycle in C2 position whereas the reaction with a gold complex showed a full C8 selectivity.

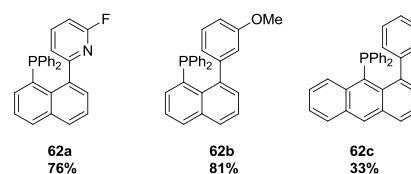


Scheme 25. Regioselective C-H activation with 2-(1-naphthyl)-pyridine

Phosphines were used as directing group to achieve a *peri*-arylation reaction of naphthalenes (Scheme 26).^[47] *Via* a rhodium-catalyzed C-H activation reaction, polyaromatic phosphines **62** were isolated in moderate to very good yields which were later used as new ligand in gold catalyzed reactions.

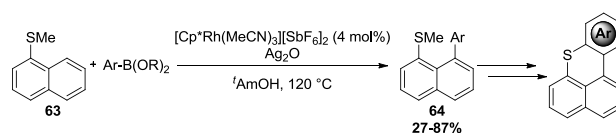


selected examples:



Scheme 26. Rhodium-catalyzed phosphine-directed *peri*-arylation

Thioethers could also be efficient directing groups. Miura's group recently reported a direct C-H arylation of 1-(methylthio)naphthalene **63** with aryl boronic esters as arylating agent (Scheme 27).^[48] In addition, arylated products **64** were easily cyclized to synthesize sulfur-containing polyaromatics.



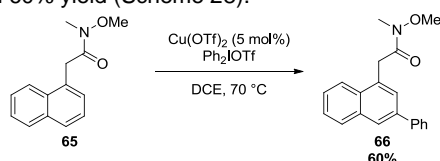
Scheme 27. Rhodium-catalyzed thioether-directed *peri*-arylation

3. Other regioselective functionalizations

While the *peri*-functionalization of naphthalenes is the most studied position, several research groups focused on different regioselectivities. This part gathers the other possible functionalization achieved *via* a C–H activation strategy.

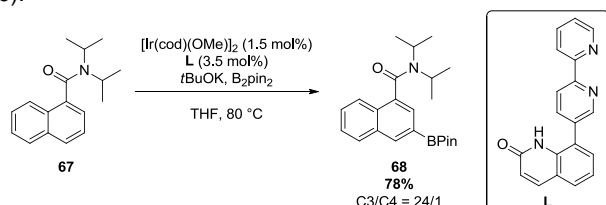
3.1. C3-functionalization

In the 2010's, aryl *meta*-C–H functionalization has attracted the attention of several research groups. When these reactions were applied to naphthalene derivatives, a C3-functionalization was realized. In 2011, the group of Gaunt developed a copper-catalyzed *meta*-arylation of α -aryl carbonyl compounds with diaryliodonium salts as arylating agents.^[49] When naphthalene **65** was used as substrate, C3-phenylated naphthalene **66** was isolated in 60% yield (Scheme 28).



Scheme 28. Copper-catalyzed C3-arylation

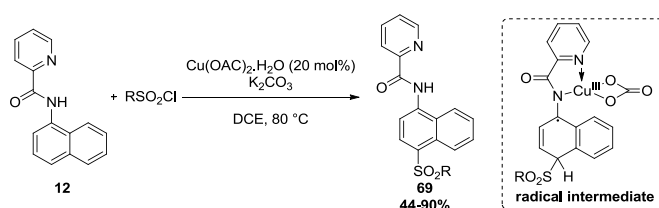
Since this example, several strategies based on directing group design^[50] or using a Pd/norbornene relay process^[51] were reported to achieve *meta*-functionalization and so naphthalene C3-functionalization. An interesting study has been developed by the group of Chattopadhyay who reported a borylation reaction thanks to a L-shaped bifunctional ligand and obtained C3-borylated product **68** in very good regioselectivity (Scheme 29).^[52]



Scheme 29. Iridium-catalyzed C3-borylation thanks to L-shaped ligand design

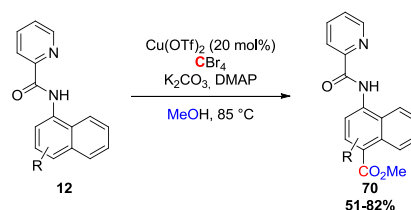
3.2. C4-functionalization

In order to improve the possibilities in regioselective naphthalene synthesis, the C4-functionalization was recently disclosed by the group of Weng and Lu.^[53] A copper-catalyzed C4-sulfonation of naphthylamine **12** was achieved thanks to a single electron transfer mechanism (Scheme 30). Charge analysis as well as the relative free energies of the possible tosyl addition intermediates were in accordance with the C4-regioselectivity.



Scheme 30. Copper-catalyzed C4-sulfonation

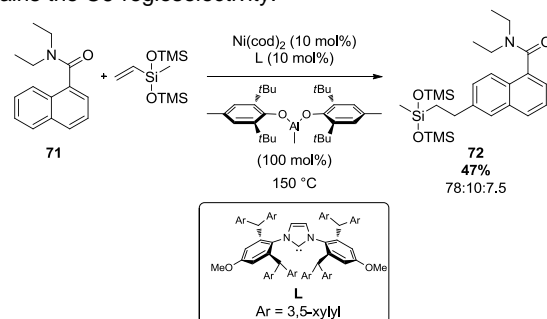
A similar strategy was employed by Ghosh's group to achieve a C4-carboxylation of naphthylamide **12** (Scheme 31).^[54] As previously, a single electron transfer from Cu(II) complex to CBr_4 was proposed in order to achieve the carbon addition in C4 and thus introduce an ester group. The same group developed an extension of this reaction to 8-aminoquinoline derivatives but this time using visible light to promote the reaction with a ruthenium catalyst.^[55]



Scheme 31. Copper-catalyzed C4-carboxylation of naphthylamide

3.3. C6-functionalization

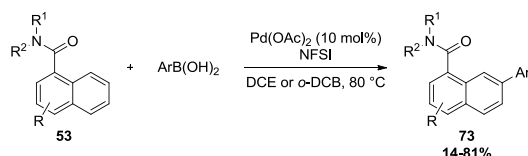
Regarding C6-functionalization, only one example has been reported by the group of Sakaki and Nakao.^[56] A *para*-alkylation of benzamides was developed by a cooperative nickel/aluminium catalysis and, when applied to naphthylamide **71**, C6-alkylated naphthalene **72** was predominantly obtained (Scheme 32). The bulky aluminium Lewis acid coordinates to the amide group and enhances the reactivity of the *para*- (for arenes) or C6-position (for naphthalene) toward the electron rich nickel(0) catalyst as well as hinders the *ortho*-position, which explains the C6-regioselectivity.



Scheme 32. C6-alkylation of naphthalenes by cooperative nickel/aluminium catalysis

3.4. C7-functionalization

Until very recently no example of C7-functionalization was reported in literature, but Zhang *et al.* developed a palladium-catalyzed C7-arylation of naphthamides **53** with aryl boronic acids (Scheme 33).^[57] In the mechanism, NFSI was proposed to generate a cationic Pd(IV) complex which then coordinate to the substrate to form a palladacycle in C8-position. A final aryl migration from Pd center to C7 followed by β -hydride elimination allowed product **73** formation.



Scheme 33. Palladium-catalyzed C7-arylation

4. Summary and outlook

Thanks to the development of C–H activation methodologies, directed-functionalization of naphthalenes starts to be well studied. Originally, C2-functionalization was a simple application of *ortho*-C–H activation of arenes, yet a lot of researches aimed at functionalize all the other positions. Nowadays, a wide range of C8-functionalizations are described and could be applied for the synthesis of naphthalene-containing natural products or drugs. During a long time, C2 and C8-positions were the only one accessible, but, during the last few years, new methodologies were developed to access the other positions. While the C3-functionalization is an application of *meta*-C–H activation of arenes, progresses were made to reach C4-, C6- and C7-positions. However, a lot of development is still required in order to achieve any kind of functionalization of naphthalenes, especially on these latter positions. The study of new catalysts with original ligands or new directing groups could, in theory, be very important for the development of new reactions to functionalize these more distant positions. In addition, a direct C5-functionalization remains still unknown.

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Keywords: C–H activation • density functional theory • directing groups • metal catalysis • naphthalenes

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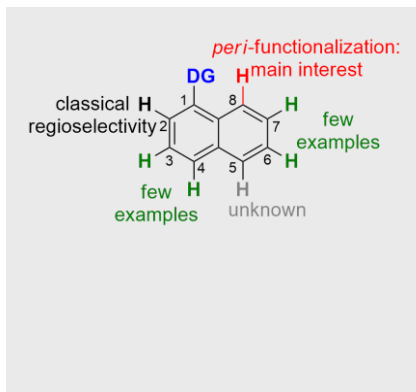
MINIREVIEW

Entry for the Table of Contents (Please choose one layout)

Layout 1:

MINIREVIEW

Regioselective functionalization of naphthalenes has known significant improvements during the last years. This review presents the different methods based on directed C–H activation strategy to introduce different functional groups on naphthalene derivatives. In addition, the mechanisms explaining the observed regioselectivity are especially emphasized.



S. Prévost*

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Regioselective C–H functionalization of naphthalenes: reactivity and mechanistic insights
