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Palladium Catalyzed C8-Arylation of Naphthalenes via C–H Activation: a Combined Experimental and Computational Study

Julian Garrec,^[b] Marie Cordier,^{§[c]} Gilles Frison,^[c] and Sébastien Prévost*^[a]

Abstract: Herein, a direct C8-arylation reaction of 1-amidonaphthalenes is described. Using diaryliodonium salts as arylating agents, the palladium catalyzed C–H activation reaction showed a perfect C8 regioselectivity and a wide functional group tolerance. In most cases, the desired polyaromatic compounds were isolated in good to excellent yields. In order to explain the observed regioselectivity, DFT calculations were performed and highlighted the crucial role of the amide directing group. Finally, the utility of this method is showcased by the synthesis of benzanthrone derivatives.

compound.^[3] However, this strategy based on strongly coordinating directing group suffers from a drawback, the further use or the removal of the directing group. Indeed, most of the time, this directing group can not be transformed. However, the use of weakly coordinating directing group, such as carbonyl derivatives, recently starts to emerge.^[4] In this case, the resulting metallacycle is less thermodynamically stable so the reactions could be more difficult to achieve. On the other hand, carbonyl derivatives can be easily transformed and used for the further construction of complex structures.

Introduction

Naphthalene is a key building block for the synthesis of more complex aromatic structures with a lot of interesting properties such as optical and electrical.^[1] Naphthalene is also a commonly found skeleton in natural products exhibiting various biological activities (Figure 1).^[2]

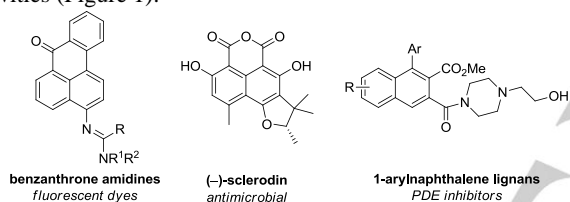
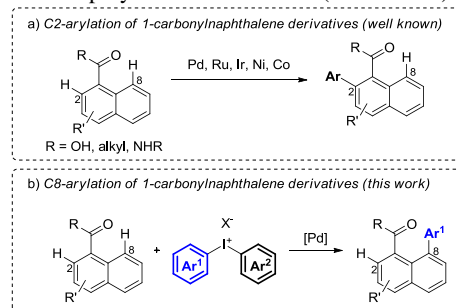


Figure 1. Naphthalene core in active products

In this context, the synthesis of polysubstituted naphthalenes is of considerable interest. Even if their synthesis *via* classical cross-coupling reaction is widely used by the community, naphthalene is a structure of choice to develop new arylation reactions *via* C–H activation. By choosing the suitable conditions, this strategy could allow an access to substituted naphthalenes more easily than going through a pre-functionalization step and is of course very interesting from an atom economy point of view. Traditionally, this kind of reaction has been accomplished using a directing group containing nitrogen, sulfur or phosphorus atom in order to form a stable metallacycle which then reacts to obtain the desired

Regarding arylation reactions of 1-carbonylnaphthalenes *via* C–H activation strategy, several research groups reported a C2 regioselectivity using different transition metals as catalyst such as Pd,^[5] Ru,^[6] Ir,^[7] Ni,^[8] or Co^[9] and carboxylic acid, ketones or amides as directing group (Scheme 1.a). Whereas C2 arylation of 1-carbonylnaphthalenes has been widely observed, the same is not true for the C8 regioselectivity. Considering all kinds of C–H functionalization of 1-carbonylnaphthalene derivatives, few examples of C8 regioselectivity have been reported,^[10] while a mixture of C2 and C8 regioisomers have been observed in certain cases.^[11] However, with respect to C8 regioselectivity, there is a lack of method achieving this. Only the work developed by the group of Xiao and Fu focused on C8-triflation of naphthalenes using ketones and disubstituted amides as directing group.^[12] With this in mind, we were keen to develop the first general method of C8-arylation of 1-carbonylnaphthalenes and to open the door to short synthesis of polyaromatic structures (Scheme 1.b).



Scheme 1. C2 vs C8 arylation of naphthalene derivatives

Diaryliodonium salts are known as electrophilic reagents to introduce aryl substituents.^[13] Since the work of Sanford's group,^[14] they have been widely used for the synthesis of biaryl compounds.^[15] The oxidative character of iodonium salts make them very interesting candidates for palladium catalyzed C–H activation reactions where a Pd(II)/Pd(IV) catalytic pathway has been proposed.^[14] Herein, we report a palladium catalyzed C8-arylation reaction of 1-amidonaphthalenes using diaryliodonium salts as arylating agent as well as a computational study of the reaction in order to explain the observed regioselectivity.

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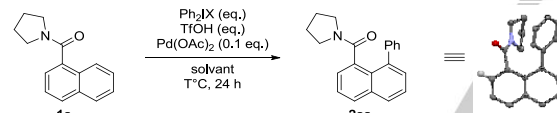
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Results and Discussion

At the outset, we focused our attention on the C8-phenylation of naphthalen-1-yl(pyrrolidin-1-yl)methanone **1a** using diphenyliodonium tetrafluoroborate as arylating agent. Due to literature results,^[12] we were thinking that disubstituted amides would be suitable directing groups to induce a C8-regioselectivity. Pleasingly, desired product **2aa** could be obtained in 26% NMR yield using palladium diacetate as catalyst, 1,2-dichloroethane (DCE) as solvent after 24 h at 100 °C (Table 1, entry 1). The regioselectivity of the reaction was confirmed *via* X-ray characterization of **2aa**. It is worth noting that a large amount of starting material was not converted and the C8-phenylated product was the only one formed during the reaction whereas the C2-phenylated compound was not detected. Encouraged by this preliminary result and taking into account that the addition of triflic acid (TfOH) could enhance the electrophilicity of Pd(II),^[16] different quantities of TfOH were added to the reaction (Table 1, entries 2 and 3) and the use of 1 equivalent of TfOH allowed to reach a 50% NMR yield. After an extensive screening of the solvents, concentrations, temperatures and directing groups (see the Supporting Information), we turned our attention on the diaryliodonium salt (Table 1, entries 7-10). Diphenyliodonium trifluoromethanesulfonate was found to be a better reagent for the reaction (Table 1, entry 8) whereas diphenyliodonium bromide did not show any conversion (Table 1, entry 9). Finally, the optimal reaction conditions involved 3 equivalents of iodonium salt and 1 equivalent of TfOH in DCE as solvent at 80 °C. After 24 h, an 80% NMR yield was observed (Table 1, entry 10).

Table 1. Selected optimization results^[a]



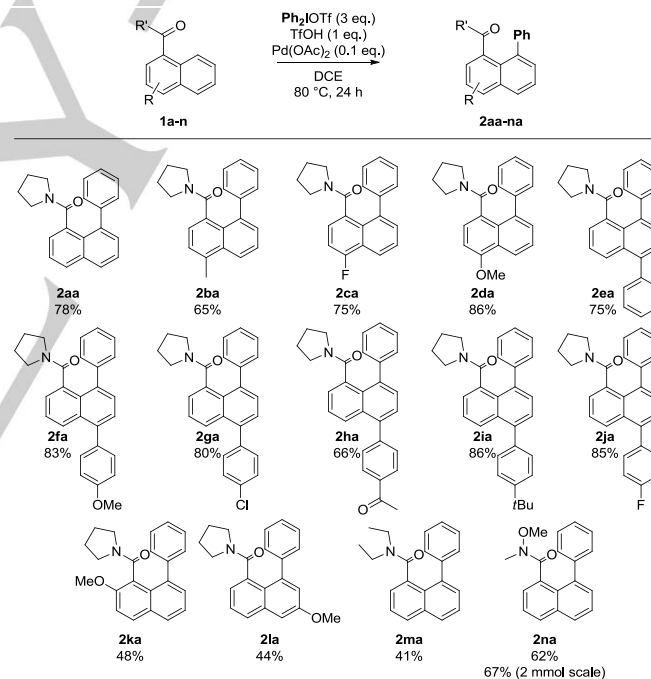
entry	Ph ₂ I _X (eq.)	solvent (C = mol.L ⁻¹)	T (°C)	TfOH (eq.)	yield (%) ^[b]
1	PhI ₂ BF ₄ (2)	DCE (0.1)	100	0	26
2	PhI ₂ BF ₄ (2)	DCE (0.1)	100	1	47
3	PhI ₂ BF ₄ (2)	DCE (0.1)	100	2	30
4	PhI ₂ BF ₄ (2)	toluene (0.1)	100	1	23
5	PhI ₂ BF ₄ (2)	THF (0.1)	100	1	40
6	PhI ₂ BF ₄ (2)	DCE (0.1)	80	1	50
7	PhI ₂ BF ₄ (2)	DCE (0.05)	80	1	53
8	PhI ₂ OTf (2)	DCE (0.05)	80	1	66
9	PhI ₂ Br (2)	DCE (0.05)	80	1	0
10	PhI ₂ OTf (3)	DCE (0.05)	80	1	80

[a] Reactions were run on 0.1 mmol scale. [b] NMR yield determined using 1,3,5-trimethoxybenzene as internal standard.

With the optimized conditions in hand, we investigated the scope of the reaction and different naphthalene derivatives were tested (Table 2). (8-phenylnaphthalen-1-yl)(pyrrolidin-1-yl)methanone **2aa** was isolated in 78% yield which is in line with the NMR yield previously observed. The reaction proved to be remarkably general.

1-Amidonaphthalenes **1b-d**, substituted in position 4 with a methyl, fluorine or methoxy group, were compatible with the reaction conditions and delivered the desired products in very good yields (65-86%). Amides **1e-j**, bearing an aryl group in position 5, were engaged in the reaction. Whether with electron donating or electron withdrawing substituents, desired phenylated naphthalenes **2ea-2ja** were isolated in excellent yields (66-86%). To extend the scope of our reaction, naphthalenes substituted in position 2 and 6 by a methoxy group were tried and showed reactivity under the optimal conditions with a moderate isolated yield (48% and 44% respectively). Finally, we were wondering if different directing group could be used in the reaction. From the optimization results,^[17] we knew that esters and carboxylic acid were not suitable for the reaction. However, non cyclic amide such as *N,N*-diethylamide was able to direct the phenylation reaction even if phenylated compound **2ma** was obtained in a moderate 41% yield. Very interestingly, Weinreb amide could also be used as directing group and **2na** was synthesized in 62% yield. This last reaction was scale up to 2 mmol and the yield reached 67%. This latter example offers interesting transformation opportunities thanks to all the known chemistry related to Weinreb amide derivatives.^[18]

Table 2. Scope of the naphthalene derivatives^[a,b]

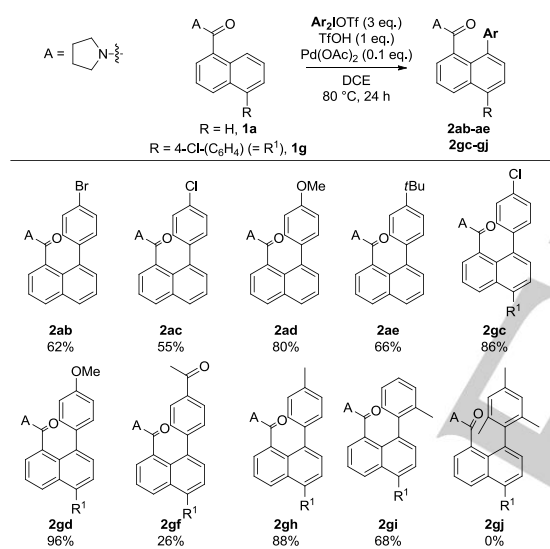


[a] Reactions were carried out using **1** (0.2 mmol), Ph₂IOTf (0.6 mmol), TfOH (0.2 mmol) and Pd(OAc)₂ (0.02 mmol) in 1,2-dichloroethane (4 mL) for 24 h at 80 °C. [b] Isolated yields were reported.

After that, we turned our attention on the transferred aryl group and naphthalenes **1a** and **1g** were used as model substrates. Several symmetrical diaryliodonium were synthesized and tested in our reaction conditions (Table 3). First, aryls with a *para* substituent were introduced with success under our standard conditions. Products **2ab-ae**, bearing a bromine, chlorine, methoxy or *tert*-butyl group in *para* position, were obtained in good yields (55-80%). Compounds **2ab** and **2ac**, with an halogenated aryl group,

open the door to further coupling reactions in order to synthesize more complex polyaromatic derivatives. The reaction worked also very well on naphthalene **1g** with different *para*-substituted diaryliodonium (products **2gc-2gh**). Indeed, aryls substituted with a chlorine, a methoxy group, a methyl group or an acetyl group were successfully introduced in C8 position of naphthalene **1g** despite a moderate yield for this latter (26%). Then, *ortho*-methylated diaryliodonium was tried in the reaction and product **2gi** was isolated in 68% yield even if the conversion was not total probably due to the steric hindrance induced by the methyl group. Finally the reaction was tested with the dimesityliodonium trifluoromethanesulfonate but no reaction was observed because of the steric hindrance. In the literature,^[19] plenty of non-symmetrical diaryliodonium bearing one mesityl group are described, so this negative result is very promising to extend our scope because it means that [Aryl-I-Mes]OTf could be probably used to transfer selectively their aryl group thanks to the steric difference between the aryl group and the mesityl.

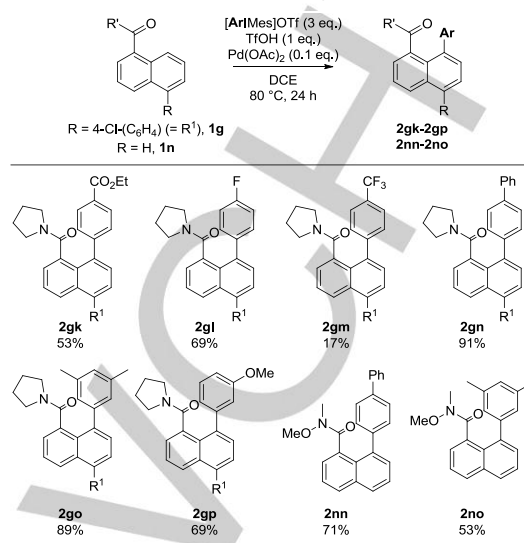
Table 3. Naphthalene functionalization using symmetrical diaryliodonium salts^[a,b]



[a] Reactions were carried out using **1** (0.2 mmol), Ar₂IOTf (0.6 mmol), TfOH (0.2 mmol) and Pd(OAc)₂ (0.02 mmol) in 1,2-dichloroethane (4 mL) for 24 h at 80 °C. [b] Isolated yields were reported.

With this last result in mind, different [Aryl-I-Mes]OTf were engaged in the reaction with naphthalene **1g** (Table 4). The obtained results confirmed our hypothesis. Indeed, several aryl groups substituted in *para* and *meta* position were successfully transferred. Naphthalenes **2gk-2gm** with electronwithdrawing substituents (CO₂Et, F, CF₃) in *para* position were isolated in moderate to good yields (17-69%). Product **2gn**, where a biphenyl group was inserted, was obtained in excellent yield (91%). Naphthalenes **2go** and **2gp** with *meta* substituted aryls were also obtained in very good yield. 3,5-dimethyl phenyl was transferred in 89% yield whereas 3-methoxyphenyl was inserted in 69% yield. [Ar-I-Mes]OTf were also reacted with naphthalene **1n** which includes the Weinreb amide as directing group. Desired products **2nn** and **2no** were obtained in good yields (71% and 53% respectively).

Table 4. Naphthalene functionalization using [Ar-I-Mes]OTf^[a,b]



[a] Reactions were carried out using **1** (0.2 mmol), [Aryl-Mes]OTf (0.6 mmol), TfOH (0.2 mmol) and Pd(OAc)₂ (0.02 mmol) in 1,2-dichloroethane (4 mL) for 24 h at 80 °C. [b] Isolated yields were reported.

In order to shed some light on the observed C8-regioselectivity, we explored both C2- and C8-arylation pathways using density functional theory (DFT) calculations. *N,N*-dimethyl-1-naphthamide has been used as model substrate to prevent conformational difficulty on the pyrrolidine moiety. Due to literature precedents where the palladium catalyst was first oxidized by the diaryliodonium salt before the C-H activation step,^[20] we checked that the preliminary formation of a Pd(IV) was not favorable in our reaction conditions.^[21] Then, taking into account that cyclopalladation is typically the rate limiting step of palladium catalyzed C-H functionalizations,^[22] a comparison of the free energy profiles of palladium addition at the two different positions was done. It turns out that the initial palladium addition, during which the C-Pd bond is formed prior to the arylation step, is clearly more favorable at position C8 than at position C2 (Figure 1). Both reaction pathways start from the reactants at infinite separation (R_∞), namely palladium (II) triflate (formed from palladium diacetate and triflic acid) and *N,N*-dimethyl-1-naphthamide in their respective solvent cage. The first stage of the reaction is the formation of a reactive complexes (RC) whose geometry depends on whether the palladium catalyst approaches the C2-H or the C8-H bond. Then the reaction proceeds through the actual chemical step, passing through a transition state (TS) and leading to the reaction intermediate (I) that contains a newly created C2-Pd or C8-Pd bond.

The comparison of the two free energy profiles reveals that the main difference lies in the relative stability of RC-C8 vs RC-C2. The former is indeed 11 kcal/mol lower in free energy than the latter. This preference seems to originate from the structure of the free substrate, in which the amide group points toward the C8-H bonds. Indeed, the amide group is not coplanar with the naphthalene π system, probably due to the steric interactions between the alkyl groups of the amide and the C2-H and C8-H

bonds. The naphthalene skeleton implies that the steric interaction with C2-H is weaker, so a partial conjugation of the amide is observed (dihedral angle C2-C1-C-O = 122.9°) with the N(Me)₂ moiety pointing towards the C2-H bond. This conformation is well adapted to establish a stabilizing interaction between the catalyst and the carbonyl oxygen atom in the RC-C8 complex (Pd^{II}-O = 2.04 Å, see also Figure S2). On the other hand, the positioning of the catalyst above C2 does not allow this interaction (Pd^{II}-O = 3.17 Å, see also Figure S1), which explain the lower energy of RC-C8. This DFT study shows that disubstituted amide directing group allows the regioselectivity control of the palladium insertion and explain our experimental observations.

amide could be deprotected to deliver secondary amide **4** in 76% yield from **2na** (Scheme 2.b). More interestingly, Weinreb amide **2na** was reduced into aldehyde **5** using lithium aluminium hydride which give access to another versatile functional group.

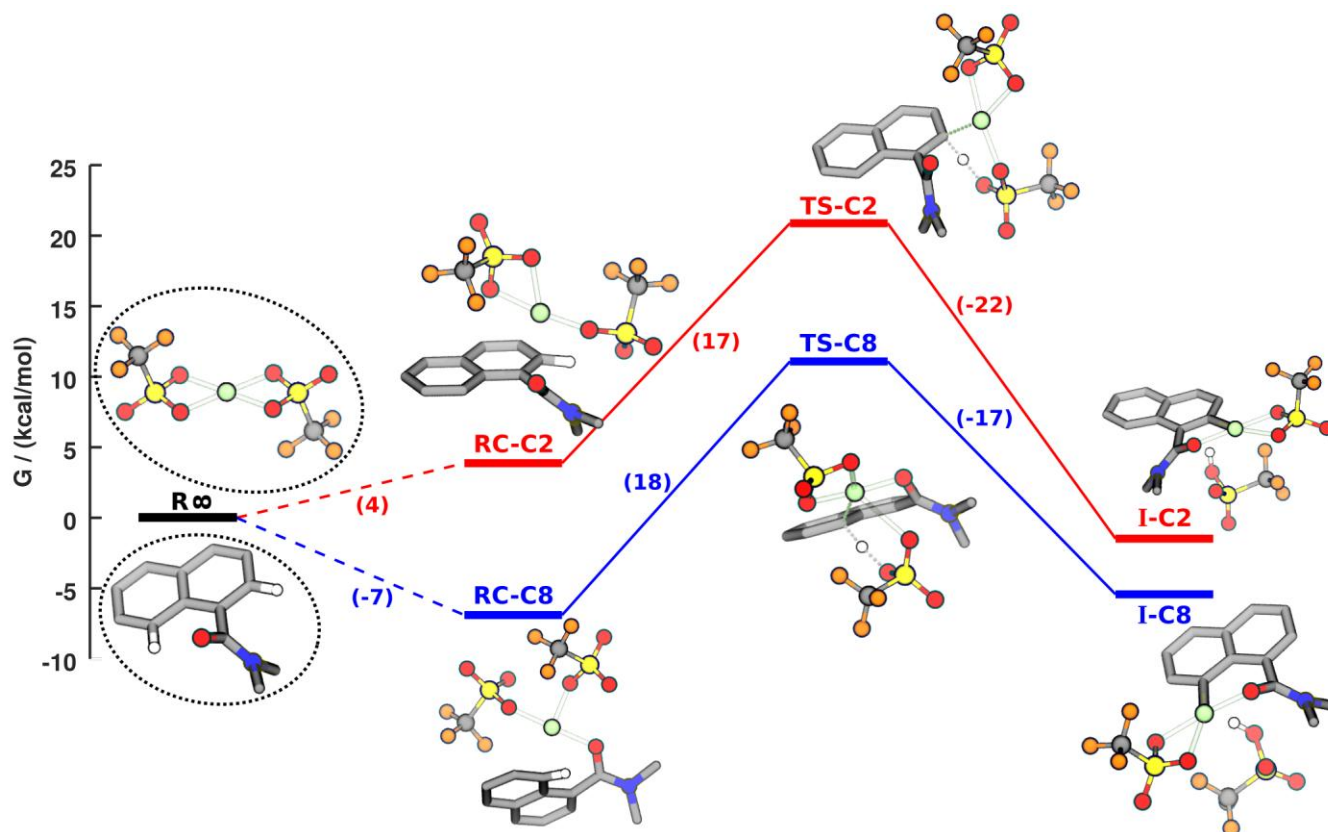
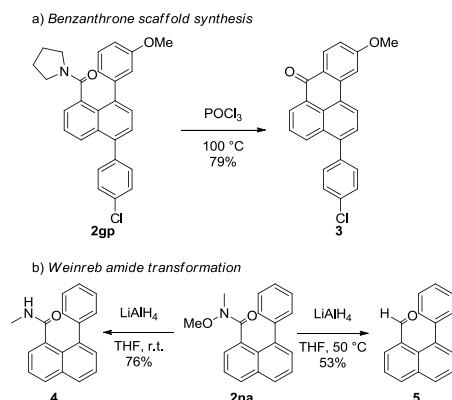


Figure 1. Potential energy surfaces of palladium addition at C2- (red) and C8-positions (blue) of *N,N*-dimethyl-1-naphthamide. Optimized molecular structures for each stationary state, namely reactants at infinite separation (R_{∞}), reactant complexes (RC), transition states (TS) and reaction intermediates bearing a C-Pd bond (I) are shown. Molecules in the R_{∞} state are represented with a surrounding dotted ellipse to highlight the fact that they were modelled independently, in their own solvation cavity. For the sake of clarity, most H atoms of 1-amidonaphthalene are hidden. Only (C2)H and (C8)H atoms are shown when necessary. Additional molecular representations as well as all XYZ coordinates of each stationary points are provided in SI. Energy variation along the formation of the RCs and the chemical steps are represented with dashed and plain lines, respectively.

To demonstrate the synthetic utility of our arylation reaction, amide **2gp** was heated at 100 °C in phosphoryl chloride (Scheme 2.a) and, through amide activation, benzanthrone **3** was synthesized in 79% yield. This methods offers a facile access to the benzanthrone moiety, whose fluorescent probe applications,^[23] as well as biological properties are well known.^[24] Moreover, the arylation reaction was possible using Weinreb amide as directing group which allows classical transformations known with this functional group. For instance, the methoxy group of the Weinreb



Scheme 2. Product transformations

Conclusions

We developed a palladium catalyzed C8-arylation reaction of 1-amidonaphthalenes based on a C–H activation strategy. This methodology gives an efficient access to polyaromatic structures using diaryliodonium salts as arylating agents. The perfect C8-regioselectivity observed in our reaction was explained thanks to DFT calculations. Indeed, we showed that, due to the weakly coordinating tertiary amide directing group, the palladium catalyst approach is more favorable in C8 than in C2 position. Our method represents an effective way to functionalize 1-amidonaphthalenes in position 8 and its utility was demonstrated by the synthesis of the benzanthrone scaffold. Further explorations of C–H activation reactions with naphthalene derivatives are currently in progress in the laboratory.

Experimental Section

For a detailed description of the starting material synthesis, the arylation reaction and the product transformations, see the Supporting Information.

General procedure for naphthalene amide 1a-l formation: To a solution of 1-naphthoic acid (1 eq.) in dry CH_2Cl_2 ($C = 0.15 \text{ M}$) was added thionyl chloride (1.5 eq.) dropwise at 0°C and the mixture was stirred at r.t. during 1 h. At 0°C , Et_3N (3 eq.) and pyrrolidine (1.2 eq.) were added dropwise and the mixture was stirred at r.t. during 16 h. At r.t., H_2O was added and the layers were separated. The aqueous layer was extracted with Et_2O , the combined organic layers were dried over MgSO_4 and concentrated in vacuo. The residue was purified by flash chromatography to deliver amide 1.

General procedure for the C8-arylation: Naphthalene amide 1 (0.2 mmol, 1 eq.), palladium diacetate (4.5 mg, 0.02 mmol, 0.1 eq.) and the desired diaryliodonium salt (0.6 mmol, 3 eq.) were placed in a tube. 1,2-Dichloroethane (4 mL) and triflic acid (18 μL , 0.2 mmol, 1 eq.) were added and the tube was closed with a screw cap. The mixture was stirred at 80°C during 24 h. The mixture was filtered on a pad of celite and washed with CH_2Cl_2 . The organic phase was washed with a saturated aqueous solution of NaHCO_3 , dried over MgSO_4 and concentrated in vacuo. The residue was purified by flash chromatography to furnished compound 2.

Computational methods: All electronic structure calculations were performed by means of density functional theory (DFT) using the M062X functional,^[25] as implemented in the Gaussian 09 suite of programs.^[26] All atoms except palladium were represented with the 6-31G(d,p) basis set^[27-29] while the LANL2DZ basis set together with the corresponding effective core potential^[30] were used for palladium. The molecular system was embedded in a dielectric cavity mimicking the dichloroethane solvent (polarizable continuum model (PCM))^[31]. All relevant reactants, products and transition states (TS) geometries were optimized including solvent effects and then validated by means of normal mode analysis. For each TS, the single mode corresponding to an imaginary frequency was used to define an intrinsic reaction coordinates (IRC)^[32] and proceed downhill toward the reactants or products of the elementary step. Graphical representation of the molecules were made with the software VMD.^[33]

Acknowledgements

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Keywords: C–H arylation • 1-carbonylnaphthalenes • diaryliodonium salts • density functional theory • palladium-catalysis

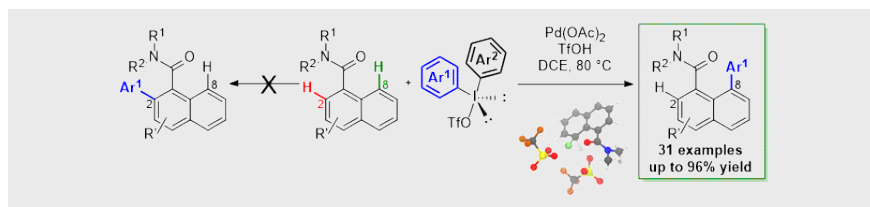
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FULL PAPER



Julian Garrec, Marie Cordier, Gilles Frison and Sébastien Prévost*

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Palladium Catalyzed C8-Arylation of Naphthalenes via C–H Activation: a Combined Experimental and Computational Study

The development of a direct palladium catalyzed C8-arylation of naphthalene derivatives was achieved using diaryliodoniums as arylating agents. The regioselectivity of the reaction (C8 vs C2) has been studied thanks to DFT calculation and the important role of the tertiary amide directing group was explained.