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

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Abstract: Herein, a direct C8-arylation reaction of 1-amidonaphthalenes is described. By using diaryliodonium salts as arylating agents, the palladium-catalyzed C–H activation reaction showed perfect C8 regioselectivity and a wide functional group tolerance. In most cases, the desired polyaromatic compounds were isolated in good to excellent yields. 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.

Introduction

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

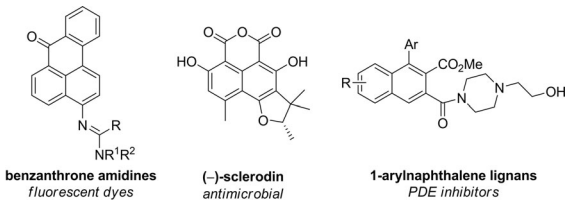
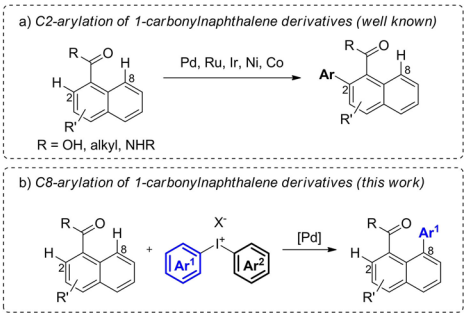


Figure 1. Naphthalene core in active products. PDE = phosphodiesterase.

In this context, the synthesis of polysubstituted naphthalenes is of considerable interest. Even if their synthesis through a classical cross-coupling reaction is widely used by the community, naphthalene is a structure of choice to develop new arylation reactions through C–H activation. By choosing suitable conditions, this strategy could allow access to substituted naphthalenes more easily than going through a prefunctionalization step and is, of course, very interesting from an atom-economy point of view. Traditionally, this kind of reaction has been accomplished by using a directing group containing nitrogen, sulfur, or phosphorus atoms to form a stable metallacycle, which then reacts to obtain the desired compound.[3] However, this strategy, based on strongly coordinating directing group, suffers from a drawback: the further use or removal of the directing group. Indeed, most of the time, this directing group cannot be transformed. However, the use of a weakly coordinating directing group, such as carbonyl derivatives, has recently started to emerge.[4] In this case, the resulting metallacycle is less thermodynamically stable, so the reactions can be more difficult to achieve. On the other hand, carbonyl derivatives can be easily transformed and used for the further construction of complex structures.

Regarding arylation reactions of 1-carbonylnaphthalenes through a C–H activation strategy, several research groups reported C2 regioselectivity with different transition metals as catalysts, such as Pd,[5] Ru,[6] Ir,[7] Ni,[8] or Co,[9] and carboxylic acid, ketones, or amides as the directing group (Scheme 1 a). Whereas C2 arylation of 1-carbonylnaphthalenes has been widely observed, the same is not true for C8 regioselectivity. Considering all kinds of C–H functionalization of 1-carbonyl-



Scheme 1. C2 versus C8 arylation of naphthalene derivatives.

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naphthalene derivatives, few examples of C8 regioselectivity have been reported,[10] although 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 methods to achieve this. Only a study by the group of Fu focused on C8-triflation of naphthalenes by using ketones and disubstituted amides as directing groups.[12] With this in mind, we were keen to develop the first general method for the C8-arylation of 1-carbonylnaphthalenes to open the door to the short synthesis of polyaromatic structures (Scheme 1 b).

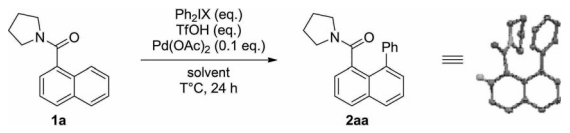
Diaryliodonium salts are known as electrophilic reagents for the introduction of aryl substituents.[13] Since the work of Sanford's group,[14] they have been widely used for the synthesis of biaryl compounds.[15] The oxidative character of iodonium salts make them very interesting candidates for palladium-catalyzed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

Results and Discussion

At the outset, we focused our attention on the C8-phenylation of naphthalen-1-yl(pyrrolidin-1-yl)methanone (**1 a**) by using diphenyliodonium tetrafluoroborate as an arylating agent. From reports in the literature,[12] we anticipated that disubstituted amides would be suitable directing groups to induce C8-regioselectivity. Pleasingly, desired product **2 aa** could be obtained in 26% yield, as determined by means of NMR spectroscopy, with palladium diacetate as the catalyst and 1,2-dichloroethane (DCE) as a solvent after 24 h at 100 °C (Table 1, entry 1). The regioselectivity of the reaction was confirmed by X-ray characterization of **2 aa**. 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; 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 one equivalent of TfOH allowed a yield of 50%, as determined by NMR spectroscopy, to be reached. After extensive screening of the solvents, concentrations, temperatures, and directing groups (see the Supporting Information), we turned our attention to 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 a solvent at 80 °C. After 24 h, 80% yield, as determined by NMR spectroscopy, was observed (Table 1, entry 10).

With the optimized conditions in hand, we investigated the scope of the reaction and tested different naphthalene derivatives (Table 2). (8-Phenylnaphthalen-1-yl)(pyrrolidin-1-yl)methanone (**2 aa**) was isolated in 78% yield, which was in line with the yield previously observed by NMR spectroscopy. The reaction proved to be remarkably general. 1-Amidonaphthalenes **1 b**–**d**, substituted in position 4 with a methyl, fluorine, or methoxy group, respectively, were compatible with the reaction conditions and delivered the desired products in very good yields (65–86%). Amides **1 e**–**j**, with an aryl group in position 5, were engaged in the reaction. Whether with electron-donating or -withdrawing substituents, desired phenylated naphthalenes

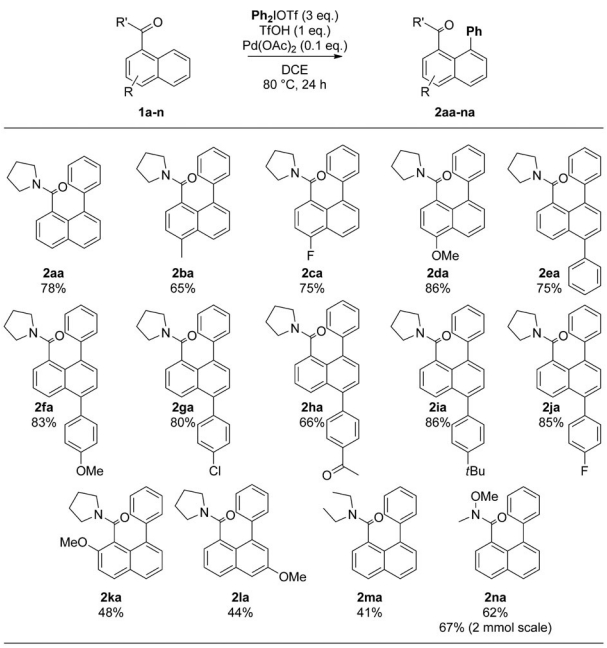
Table 1. Selected optimization results.[a]



Entry	Ph_2IX ([equiv])	Solvent (C = mol L^{-1})	T [°C]	TfOH [equiv]	Yield[b] [%]
1	PhI_2BF_4 (2)	DCE (0.1)	100	0	26
2	PhI_2BF_4 (2)	DCE (0.1)	100	1	47
3	PhI_2BF_4 (2)	DCE (0.1)	100	2	30
4	PhI_2BF_4 (2)	toluene (0.1)	100	1	23
5	PhI_2BF_4 (2)	THF (0.1)	100	1	40
6	PhI_2BF_4 (2)	DCE (0.1)	80	1	50
7	PhI_2BF_4 (2)	DCE (0.05)	80	1	53
8	PhI_2OTf (2)	DCE (0.05)	80	1	66
9	PhI_2Br (2)	DCE (0.05)	80	1	0
10	PhI_2OTf (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.

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



[a] Reactions were carried out by using **1** (0.2 mmol), Ph_2IOTf (0.6 mmol), TfOH (0.2 mmol), and $Pd(OAc)_2$ (0.02 mmol) in DCE (4 mL) for 24 h at 80 °C. [b] Yields of products isolated were reported.

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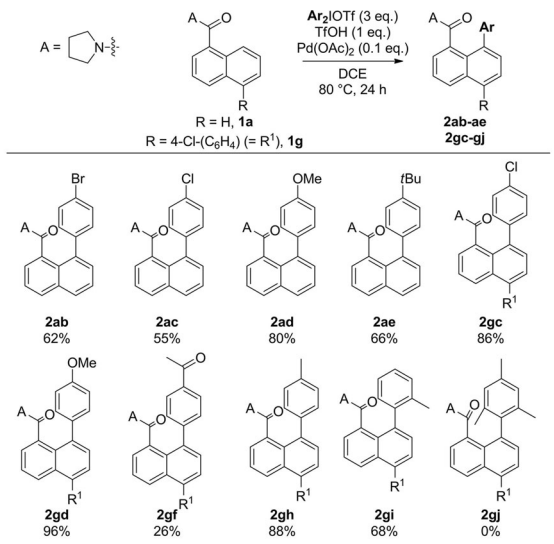
2ea–**ja** were isolated in excellent yields (66–86%). To extend the scope of our reaction, naphthalenes substituted in positions 2 or 6 by a methoxy group were tested and showed reactivity under the optimal conditions with moderate isolated yields (48 and 44%, respectively). Finally, we wondered if different directing groups could be used in the reaction. From the optimization results,[17] we knew that esters and carboxylic acids were not suitable for the reaction. However, noncyclic amides, such as *N*,*N*-diethylamide, were able to direct the phenylation reaction, even if phenylated compound **2ma** was obtained in a moderate yield of 41%. Interestingly, a Weinreb amide could also be used as a directing group and **2na** was synthesized in 62% yield. This last reaction was scaled up to 2 mmol and the yield reached 67%. This latter example offers interesting transformation opportunities thanks to all known chemistry related to Weinreb amide derivatives.[18]

After that, we turned our attention to the transferred aryl group and naphthalenes **1a** and **1g** were used as model substrates. Several symmetrical diaryliodonium derivatives were synthesized and tested under our reaction conditions (Table 3).

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

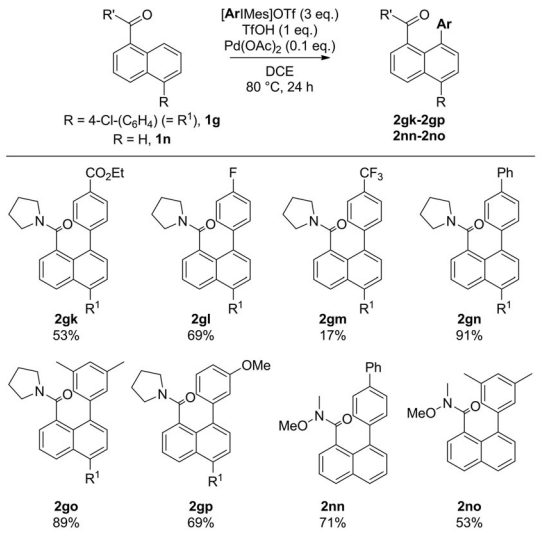


[a] Reactions were carried out by using **1** (0.2 mmol), Ar_2IOTf (0.6 mmol), TfOH (0.2 mmol), and $Pd(OAc)_2$ (0.02 mmol) in DCE (4 mL) for 24 h at 80 °C. [b] Yields of products isolated were reported.

First, aryls with a *para* substituent were introduced, with success, under our standard conditions. Products **2ab**–**ae**, bearing bromine, chlorine, methoxy, or *tert*-butyl groups in the *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 to synthesize more complex polyaromatic derivatives. The reaction also worked very well on naphthalene **1g** with different *para*-substituted diaryliodonium derivatives (products **2gc**–**2gh**). Indeed, aryls substituted with chlorine, methoxy, methyl, or acetyl groups were successfully introduced into the C8 position of naphthalene **1g**, despite a moderate yield for the last derivative (26%). Then, *ortho*-methylated diaryliodonium was tested in the reaction and product **2gi** was isolated in 68% yield, even if the conversion was not complete, probably due to steric hindrance induced by the methyl group. Finally, the reaction was tested with the dimesityliodonium trifluoromethanesulfonate, but no reaction was observed because of steric hindrance. In the literature,[19] many nonsymmetrical diaryliodonium derivatives with one mesityl group are described, so this negative result is very promising to extend our scope because it means that [aryl–I–Mes]OTf (Mes = mesityl) could probably be used to transfer the aryl group selectively thanks to steric difference between the aryl and Mes groups.

With this last result in mind, different [aryl–I–Mes]OTf derivatives were engaged in the reaction with naphthalene **1g** (Table 4). The obtained results confirmed our hypothesis.

Table 4. Naphthalene functionalization with [aryl–I–Mes]OTf.[a,b]



[a] Reactions were carried out by using **1** (0.2 mmol), [aryl–I–Mes]OTf (0.6 mmol), TfOH (0.2 mmol), and $Pd(OAc)_2$ (0.02 mmol) in DCE (4 mL) for 24 h at 80 °C. [b] Yields of products isolated were reported.

Indeed, several aryl groups substituted at the *para* and *meta* positions were successfully transferred. Naphthalenes **2gk**–**2gm**, with electron-withdrawing substituents (CO_2Et, F, CF_3) in the *para* position, were isolated in moderate to good yields (17–69%). Product **2gn**, into which a biphenyl group was inserted, was obtained in excellent yield (91%). Naphthalenes **2go** and **2gp**, with *meta*-substituted aryl groups were also obtained in very good yield. 3,5-Dimethylphenyl was transferred in 89% yield, whereas 3-methoxyphenyl was inserted in 69% yield. [aryl–I–Mes]OTf derivatives were also reacted with naphthalene **1n**, which included the Weinreb amide as a directing group. Desired products **2nn** and **2no** were obtained in good yields (71 and 53%, respectively).

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To shed some light on the observed C8-regioselectivity, we explored both C2- and C8-arylation pathways by using DFT calculations. *N*,*N*-Dimethyl-1-naphthamide was used as a model substrate to prevent conformational difficulties on the pyrrolidine moiety. Due to literature precedents in which the palladium catalyst was first oxidized by the diaryliodonium salt before the C–H activation step,[20] we checked that the preliminary formation of Pd^{IV} was not favorable under our reaction conditions.[21] Then, taking into account that cyclopalladation is typically the rate-limiting step of palladium-catalyzed C–H functionalization,[22] a comparison of the free energy profiles of palladium addition at the two different positions was performed. It turns out that initial palladium addition, during which the C–Pd bond is formed prior to the arylation step, is clearly more favorable at position C8 than that at position C2 (Figure 2). Both reaction pathways start from the reactants at

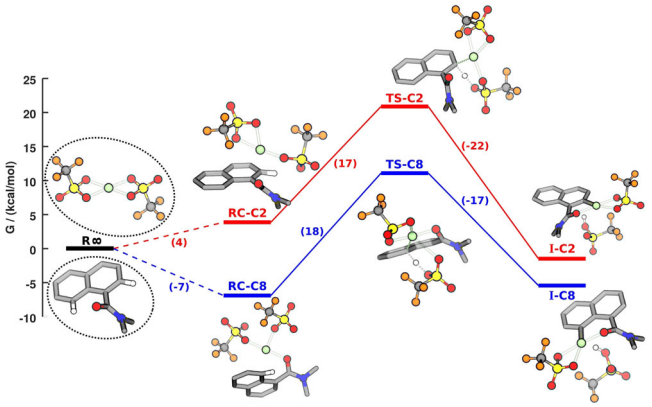
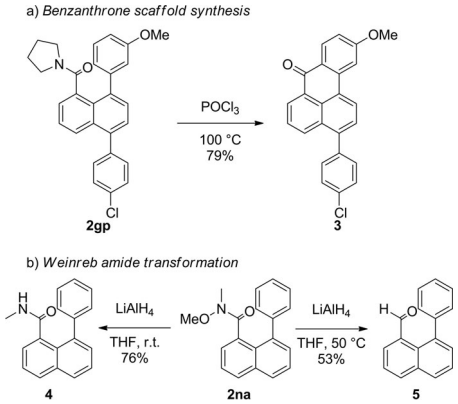


Figure 2. Free energy profiles of palladium addition at the C2- (red) and C8-positions (blue) of *N*,*N*-dimethyl-1-naphthamide. Optimized molecular structures for each stationary state, namely, reactants at infinite separation (R∞), reactant complexes (RCs), transition states (TSs), and reaction intermediates with 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 modeled independently, in their own solvation cavity. For the sake of clarity, most hydrogen atoms of 1-amidonaphthalene are hidden. Only (C2)H and (C8)H atoms are shown, if necessary. Additional molecular representations and all *XYZ* coordinates of each stationary point are provided in the Supporting Information. Energy variation along the formation of the RCs and the chemical steps are represented with dashed and solid lines, respectively.

infinite separation (R∞), namely, palladium(II) triflate (formed from palladium diacetate and TfOH) and *N*,*N*-dimethyl-1-naphthamide in their respective solvent cages. The first stage of the reaction is the formation of a RC, the geometry of which depends on whether the palladium catalyst approaches the C2–H or C8–H bond. Then the reaction proceeds through the actual chemical step, passing through a TS, and leading to the reaction intermediate (I) that contains a newly created C2–Pd or C8–Pd bond.

A comparison of the two free energy profiles reveals that the main difference lies in the relative stability of RC-C8 versus RC-C2. The former is indeed 11 kcal mol^{-1} lower in free energy than that of the latter. This preference seems to originate from the structure of the free substrate, in which the amide group points toward the C8–H bond. Indeed, the amide group is not coplanar with the naphthalene π system, probably due to 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 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 carbonyl oxygen atom in the RC-C8 complex (Pd···O = 2.04 Å, see also Figure S2 in the Supporting Information). On the other hand, the positioning of the catalyst above C2 does not allow this interaction (Pd···O = 3.17 Å, see also Figure S1 in the Supporting Information), which explains the lower energy of RC-C8. This DFT study shows that a disubstituted amide directing group allows control over the regioselectivity of palladium insertion and explains our experimental observations.

To demonstrate the synthetic utility of our arylation reaction, amide **2gp** was heated at 100 °C in phosphoryl chloride (Scheme 2a) and, through amide activation, benzanthrone **3**



Scheme 2. Product transformations to demonstrate the synthetic utility of our arylation reaction.

was synthesized in 79% yield. This method offers a facile access to the benzanthrone moiety, the fluorescent probe applications,[23] as well as biological properties, of which are well known.[24] Moreover, the arylation reaction was possible by using the Weinreb amide as a directing group, which allowed classical transformations known for this functional group. For instance, the methoxy group of the Weinreb amide could be deprotected to deliver secondary amide **4** in 76% yield from **2na** (Scheme 2b). Interestingly, Weinreb amide **2na** was reduced into aldehyde **5** by lithium aluminum hydride, which gave access to another versatile functional group.

Conclusion

We developed a palladium-catalyzed C8-arylation reaction of 1-amidonaphthalenes based on a C–H activation strategy. This methodology gives efficient access to polyaromatic structures by using diaryliodonium salts as arylating agents. The perfect C8-regioselectivity observed in our reaction was explained

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thanks to DFT calculations. Indeed, we showed that, due to the weakly coordinating tertiary amide directing group, approach of the palladium catalyst was more favorable in the C8 position than that at C2. 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 our laboratory.

Experimental Section

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

General procedure for naphthalene amide 1 a–l formation

thionyl chloride (1.5 equiv) was added dropwise at 0 °C to a solution of 1-naphthoic acid (1 equiv) in dry CH_2Cl_2 ($C = 0.15$ M) and the mixture was stirred at RT for 1 h. At 0 °C, Et_3N (3 equiv) and pyrrolidine (1.2 equiv) were added dropwise and the mixture was stirred at RT for 16 h. At RT, H_2O was added and the layers were separated. The aqueous layer was extracted with Et_2O and 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 C8-arylation

Naphthalene amide **1** (0.2 mmol, 1 equiv), palladium diacetate (4.5 mg, 0.02 mmol, 0.1 equiv), and the desired diaryliodonium salt (0.6 mmol, 3 equiv) were placed in a tube. DCE (4 mL) and TfOH (18 μL, 0.2 mmol, 1 equiv) were added and the tube was closed with a screw cap. The mixture was stirred at 80 °C for 24 h. The mixture was filtered through 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 give compound **2**.

Computational methods

All electronic structure calculations were performed by means of DFT with 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] whereas 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 that mimicked the DCE solvent (polarizable continuum model (PCM)[31]). All relevant reactants, products, and 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 coordinate[32]+and proceeded downhill toward the reactants and products of the elementary step. Graphical representations of the molecules were made with the software VMD.[33]

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Conflict of interest

The authors declare no conflict of interest.

Keywords: arylation · density functional calculations · homogeneous catalysis · palladium · synthesis design

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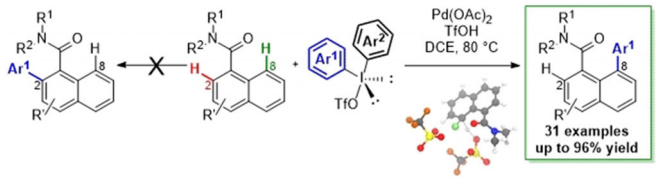

Directing reactions: The development of direct palladium-catalyzed C8-arylation of naphthalene derivatives was achieved by using diaryliodonium derivatives as arylating agents (see scheme). The regioselectivity of the reaction (C8 vs. C2) was studied by DFT calculations and the important role of the tertiary amide directing group was explained.

Synthesis Design

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■■ – ■■

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

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