Amide directed selectivity switch in distal C-H arylation of α-naphthoic acids

Sukumar Pradhan
Indian Institute of Technology (IIT) Bombay
Jyoti Biswas
Indian Institute of Technology Bombay
Mazen Elsaid
Texas Tech University
Haibo Ge
Texas Tech University
Debabrata Maiti (dmaiti@chem.iitb.ac.in)
Indian Institute of Technology Bombay https://orcid.org/0000-0001-8353-1306

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Abstract

Remote C4-H functionalization of a-naphthoic acids is highly challenging due to the presence of proximally more accessible C-H bonds at the C2 and C8 positions. Herein, we report the first palladium-catalysed direct C4 arylation of 1-naphthamides with high regioselectivity and excellent functional group compatibility. The regioselectivity of this one-step reaction could be switched to the C7 position by simply changing the directing group under otherwise identical conditions. Diverse aryl couples were found compatible for both C4 and C7 arylation. Control experiments and kinetic studies were carried out to identify the mechanistic motives of the unique selectivity switch.

full text

The development of regio- and stereo-selective reactions that nevertheless preserve atom-economy is the ultimate goal in the field of organic synthesis. Transition metal catalysis has been ever bringing us closer to this goal by allowing simpler and more efficient pathways to synthesizing large and complex molecules.[1] For instance, the discovery of cross-coupling reactions revolutionized the synthesis of multi-aryl molecules by significantly reducing the number of the synthetic steps needed.[2,3] However, requirement of pre-functionalized reactants is the preeminent pitfall of cross-coupling reactions, especially ones involving complex molecular structures. Traditional multi-step synthesis routes to such precursors are no longer deemed effective and the development of newer methodologies with superior efficiencies is continuously needed. The other main elementary concern in these reaction systems is their control over regio-selectivity. The dilemma caused by the presence of ubiquitous C-H bonds has often been addressed via the directing group strategy.[8-12] In directed approaches, the relatively accessible formation of thermodynamically favourable 5 or 6-membered metallacycles usually leads to proximal functionalization *via* C-H activation.[13-16] In contrast, functionalizing distal C-H bonds remains challenging to a great extent due to thermodynamic and entropic reasons alike. Many efforts have been dedicated to reach such distal positions, primarily through the installation of heavy and rigid directing groups.[8,17-21] Anyways, the processes of installation and post-functionalization removal of the aforementioned directing auxillaries reverts us back to the initial question of efficiency and atom economy. All things considered, development of non-directed methods or ones that involve lighter directing groups is imperative to the context of the current scenario of synthetic chemistry.

Naphthalene is among the simplest of polycyclic arenes and it is found at the core of numerous bioactive and industrially important molecules. Substituted naphthalenes, including a-naphthoic acid derivatives, have diverse applications in the synthesis of pharmaceuticals, photochemicals, plant growth hormones, dyes, and other useful materials. [22] The classical functionalization of naphthalene and their derivatives usually obeys electronic guidance; however, only a limited scope of functional groups could be incorporated, and the presence of two rings often complicates regio-selectivity. Moreover, synthesizing halide substituted naphthalene derivatives for cross-coupling reactions is a challenge in its own right.[23-25]

Therefore, selective distal C-H functionalization of naphthalene derivatives is a stimulating demand in synthetic chemistry.

There are several examples of existing transition metal-catalysed C-H functionalization of a-substituted naphthalene. Most of these examples are directing group-assisted proximal ortho-functionalizations mediated by the formation of thermodynamically stable metallacycles. [26-27] Similarly, diverse peri-C-H functionalizations have been accomplished via the formation of favourable metal coordinated intermediates.[28,29] However, reports of installation of any functional groups at other positions have been scarce. In this direction, the C3-H activation of a-substituted naphthalenes was achieved *via* both the meta-directed approach[30-33] and the Catellani approach[34] using norbornene as a transient mediator. Lu and co-workers reported Cu-catalysed para tosylation of 1-naphthamine via single electron transfer (SET), albeit while offering a narrow scope of reaction substrates.[35] Similarily, palladium catalysed C4 alkylation of 1-naphthaldehyde has been demonstrated via radical intermediacy by Zhou's group.[36] The only example of distal arylation was reported by You's group *via* aryl migration to the C7 position.[37] However, to the best of our knowledge, no examples of C4-arylation of any a-substituted naphthalene derivatives have been reported so far.

Arylation is one of the most challenging yet important functionalization processes from both the synthetic and biological points of view. Arylation can enhance bioactivity of a molecule by providing additional non-covalent interactions. In materials science, aryl group incorporation is used to upsurge physicochemical properties and to provide rigidity to organic frameworks. The extended p-conjugation is also advantageous for numerous organic materials.[38-40] Therefore, we pursued selective arylation of 1-naphthoic acids at distal positions. We believed an in-situ produced aryl radical can be directed by the electronic factors of a-naphthoic acid to substitute at the C4 position. At the outset, we employed various metal catalysts and aryl radical precursor combinations with a-naphthoic acid, however, these attempts were met with failure. Careful analysis revealed catalyst poisoning by the acid could be taking place, making it unavailable for catalysis. Therefore, we converted the acid moiety into a less coordinative amide with diisopropylamine. To our delight, 4-nitro-iodobenzene, in the presence of palladium acetate, provided 65% of exclusively C4-arylated product of *N,N*-diisopropyl-1-naphthamide in HFIP, confirmed by X-ray crystallography (**3g**, CCDC in Fig. 2). This is the first example of *para*-arylation of naphthalene derivatives. Subsequently, we began optimizing the initial conditions and varied all possible adjustable parameters to maximize the yield. Changing the palladium catalyst to other complexes did not improve the reaction. The fact that the use of additional ligands either deprived the reaction performance or was otherwise neutral to the yield was indicative of acetate being the most suitable ligand. Various silver based oxidizing agents were tested, however Ag(TFA) remained optimal. Hence, it was evident that acetate has a special role to play in this reaction. We eventually tested a number of different solvents, among which, fluorinated solvents yielded promising results. Anyways, HFIP proved to be supreme compared to these other fluorinated solvents. Finally, temperature and time optimization to 100 °C and 24 h respectively raised the yield to as high as 95%.

With the optimized condition in hand, the scope of the reaction was examined and found to be excellent. At first, a series of electron withdrawing aryl iodides were tested; $-NO_2$, -F, $-CO_2R$, $-CF_3$ groups at different positions were well tolerated and provided good to excellent yields. Various electron donating groups such as –Me, -^{t}Bu, -OMe at the *para*- and/or the *meta*- positions also performed well. Interestingly, biphenyl iodide and naphthyliodide also provided 73% and 69% yields of highly conjugated products respectively. Moreover, bioactive aryl iodides, strychninyl and arbutinyl were also successfully incorporated at the para position of **1a**.

The scope with respect to substituted naphthamides has also been diversified; –Me, -OMe, -Ar substitution at different positions did not compromise the results of the reaction. Remarkably, 1-anthracenamide also provided 81% yield of C4 arylation, exclusively. 2-isopropyl-1H-benzo[de]isoquinoline-1,3(2H)-dione resulted in a para-arylated fluorescent material under the standard reaction conditions. Notably, bulky aryl substituents such as pyrene, trimethylphenyl, dimethoxyphenyl, biphenyl etc. at the C5 position did not prevent the reaction, instead highly conjugated molecules were successfully obtained. Crystallographic studies confirmed that both the substituent aryl rings are parallelly stacked in the solid state. However, installation of a benzyl group at the C5 position completely shuts down the reaction, probably due to sterics.

In order to evaluate the response of other arylating agents towards this protocol, we tested various aryl bromides and aryl boronic acids. We observed that, although all other conditions remained unchanged, an elevated temperature of 130 °C is required for obtaining synthetically useful yields in these cases. Nonetheless, the adjusted conditions delivered selective para arylation of *N,N*-diisopropyl-1-naphthamides with a number of differently substituted aryl bromides and aryl boronic acids in moderate yields. For instance, –COMe, -X, -Ph substituted aryl boronic acids reacted well and as expected –Cl or –F substituted aryl bromides reacted selectively at the C-Br bond.

Further, we sought to assess the effect of the protecting group on our developed method. The protecting group was found necessary to mitigate the coordination strength of the acid, therefore the extent of coordination with the metal was presumed to be sensitive to the steric bulk and the electronic nature of the alkyl substituents. However, will there be any direct effect on the selectivity and reactivity of the reaction upon varying the protecting group? Accordingly, we considered dimethylamine and monomethylamine at first as protecting groups in decreasing order of steric bulk. Interestingly, *N,N*-dimethyl-1-naphthamide produced a 1:1 mixture of C4:C7 arylated products under optimized condition, whereas *N*-methyl-1-naphthamide resulted in exclusive C7 arylation with excellent yield. Upon introducing a higher order of steric bulk in the form of dicyclohexylamine, the reaction did not proceed at all, indicating that catalyst coordination is necessary for the functionalization and that the extent of coordination dictates site selectivity. A plethora of *N*-substituted amides were then tested, and it was observed that all mono-substituted amides favoured C7 arylation predominantly while di-substituted ones, except dimethylamide and dicyclohexyl amide, resulted in C4 arylation instead.

The scope for C7 arylation was found to be equally excellent. Variation with respect to aryl iodides, naphthalene substituents and protecting groups were carried out, and good to excellent yields were obtained. Strained rings such as cyclopropyl and cyclobutyl amides were also tolerated under the reaction conditions. Notably, compared to the previous report by You with aryl boronic acids, assistance of fluorine ion oxidants was not required in this methodology for C7 arylation.

To get an insight into the underlying mechanism of C4-selective arylation, we performed a number of kinetic studies and controlled experiments. Naturally, in the absence of either the metal catalyst or the silver trifluoroacetate salt, the reaction did not proceed at all. In the presence of added radical scavengers such as (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO), butylated hydroxyanisole (BHT), diphenylstyrene etc., no desired product was obtained neither, although no other scavenged products were observed anyways. The orders of the C4 arylation reaction were found to be 0.9, 0.82 and 0.02 with respect to the catalyst, ArI and naphthamide. Further, the order with respect to AgTFA was observed to be 1.07. This suggests the involvement of $Pd(OAc)_2$, ArI and AgTFA in the rate limiting step and hints that naphthamide presumably enters the cycle at a later stage. Hammett studies with different substituents at the para position of the aryl iodide resulted in a small positive reaction constant of $r = 0.71$, thus discarding the possibility of ionic intermediate formation to a great extent. Based on these evidence, we proposed a mechanism where the aryl iodide first reacts with the catalyst to generate an aryl radical in the presence of the silver species.[36] Subsequently, electronically directed radical addition takes place at the C4 position of the palladium coordinated substrate. The resulted radical species **A** is then oxidized to form the cationic species **B** which undergoes elimination to generate the intermediate **C**. On the contrary, the C7 arylation showed orders of 0.85 and 1.3 with respect to the Pd catalyst and naphthoic acid and 0.19 order with respect to the ArI. This is indicative of catalyst incorporation at the C8 position followed by aryl migration, as depicted by You.[37]

In conclusion, we have developed a straightforward methodology for selective distal C4 and C7 arylation of naphthoic acid derivatives. The reaction regioselectivty can be switched simply by changing the protecting group. The most common arylating reagents i.e. ArI, ArBr and $ArB(OH)_2$ are compatible for the arylation of a wide range of 1-naphthoic acid derivatives. We were able to tabulate a series of protecting groups for both C4 and C7 regio-selectivities, thus providing a higher potential and a broader flexibility towards complexity incorporation at the acid centre as well. Kinetic and controlled experiments are evocative of two different mechanisms depending on the nature of the protecting group. Extensive mechanistic studies are underway in our laboratory in order to achieve further selective functionalization at the remaining positions of naphthalene derivatives.

methods

***para*-arylation of a-naphthamide**: An oven-dried screw cap reaction tube was charged with a magnetic stir-bar, $Pd(OAc)_2$ (7 mol% 1.6 mg for 0.2 mmol), AgTFA (1.5 equiv., 33 mg), a-naphthamide (0.1 mmol, 25.5 mg) and aryl iodide (1.2 equiv., 0.12 mmol). Then 1 mL of HFIP was added. The reaction mixture

was stirred vigorously on a preheated oil bath at 120 °C along. The reaction was carried out for 12 h and the reaction mixture was diluted with EtOAc and filtered through a celite pad. The desired arylation product was isolated by column chromatography using silica gel (100-200 mesh size) and petroleum ether/ethyl acetate as the eluent.

Data availability: The authors declare that the main data supporting the findings of this study are available within the article and its Supplementary information files. Further data are available from the corresponding author on request. Source data are provided with this paper.

Declarations

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Author contributions: SKP, JPB and ME performed of the experiments. DM and HG supervised and directed the progress. JPB, SKP, ME, HG and DM prepared the manuscript.

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Competing interests: The authors declare no competing interests.

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Figures

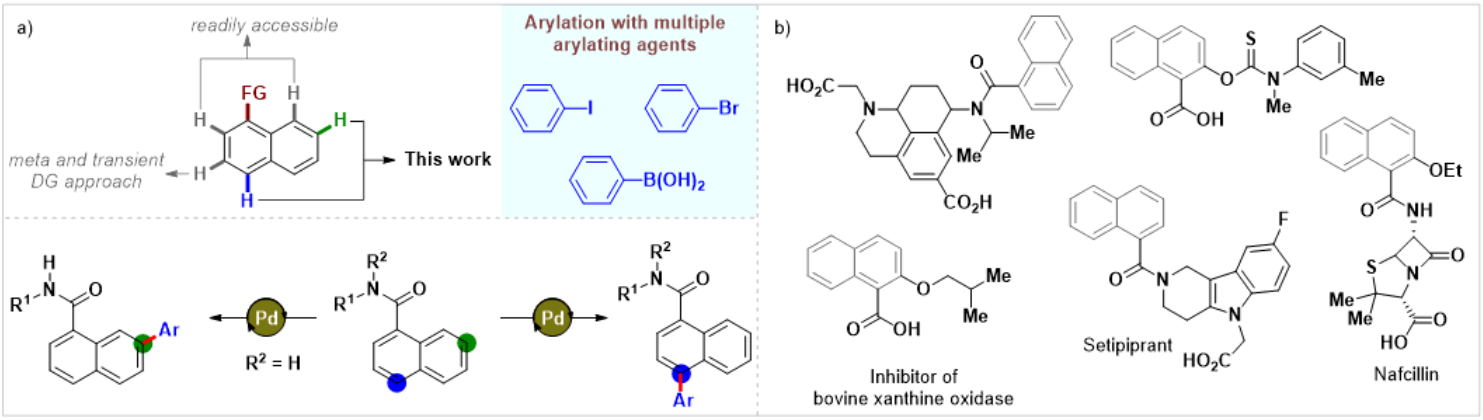

Figure 1

a) Protecting group-dependant C4 and C7 arylation of 1-naphthoic acid, b) Examples of relevant α-naphthoic acid derivatives.

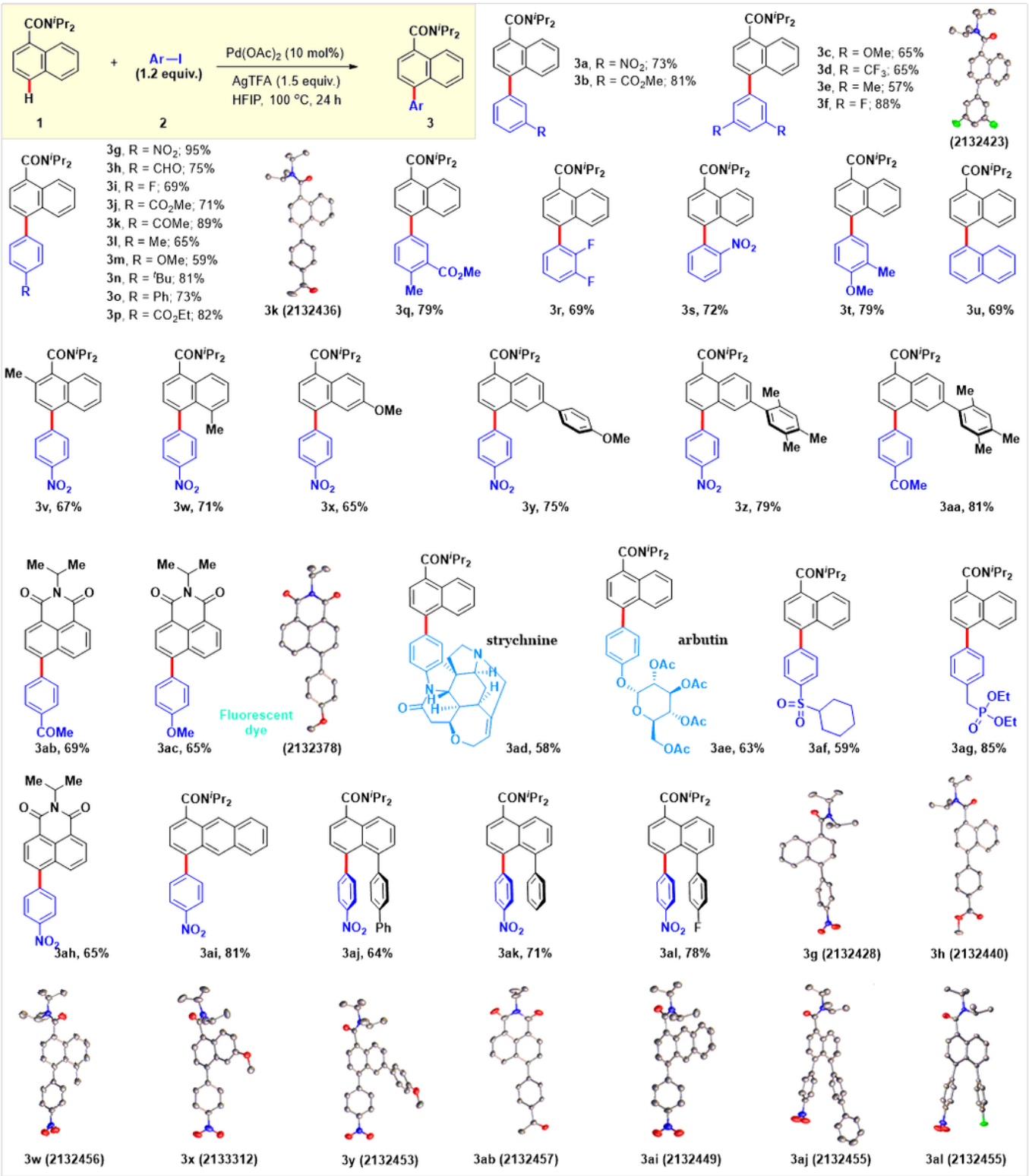

Figure 2

Scope of C4-arylation of *N,N*-diisopropyl-1-naphthamide derivatives with various aryl iodides. (Numbers in the parentheses correspond to the CCDC number of respective crystal structure).

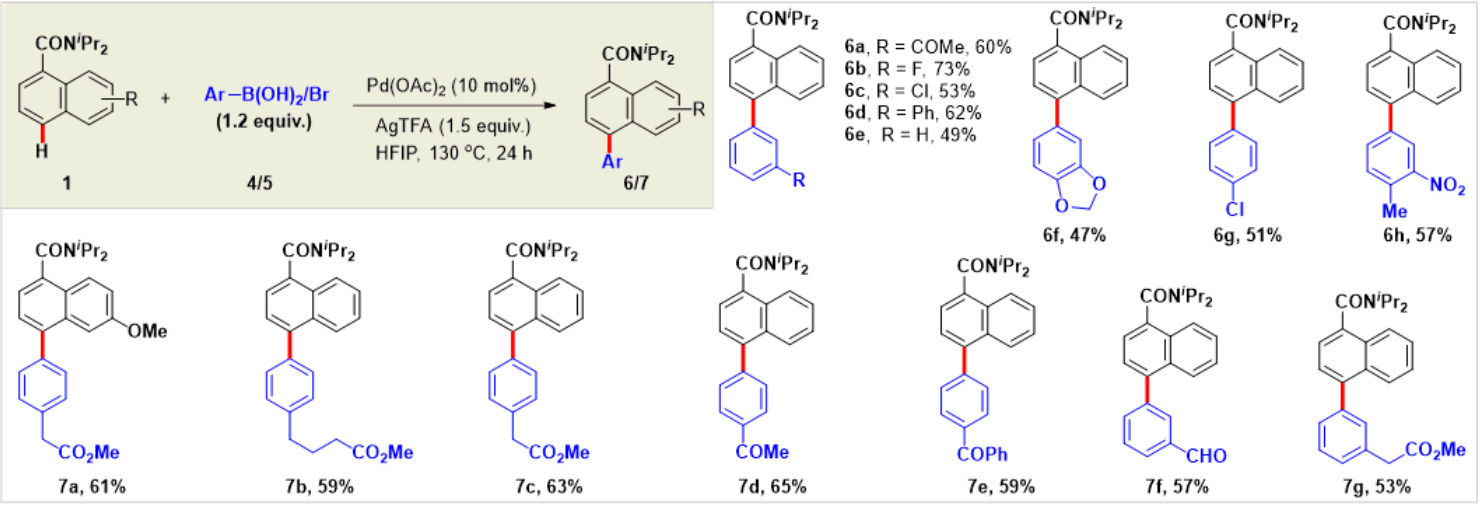

Figure 3

Scope of C4-arylation with aryl boronic acids (**6a**-**h**) and aryl bromides (**7a**-**g**).

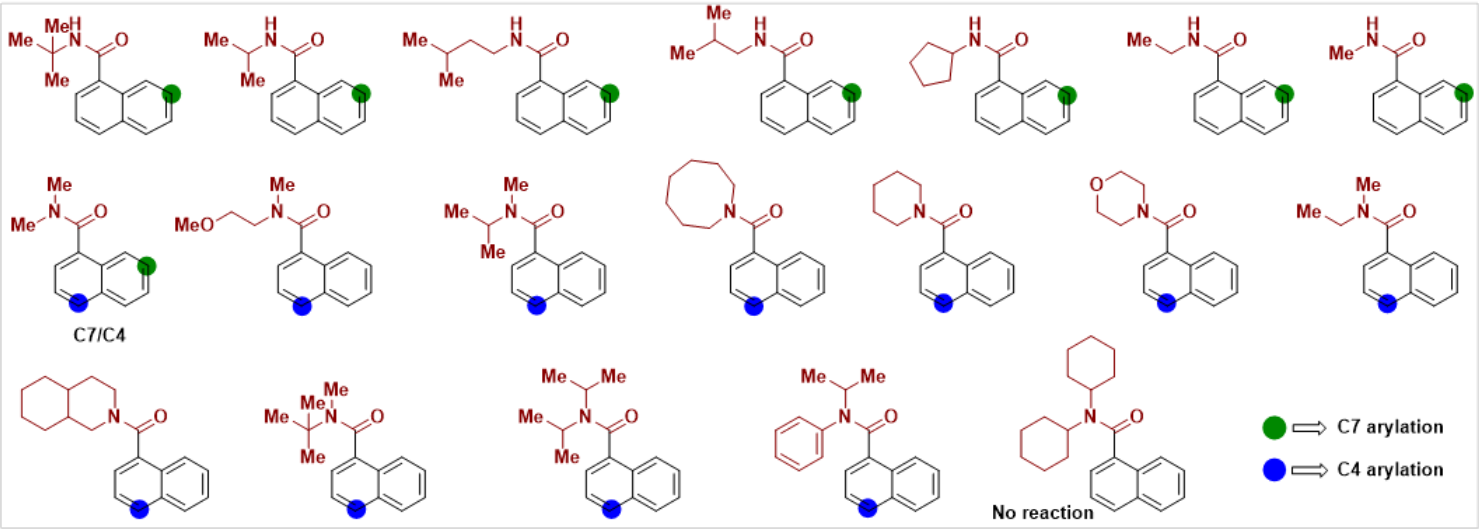

Figure 4

C4/C7 regio-selectivity dependence of amide protecting group.

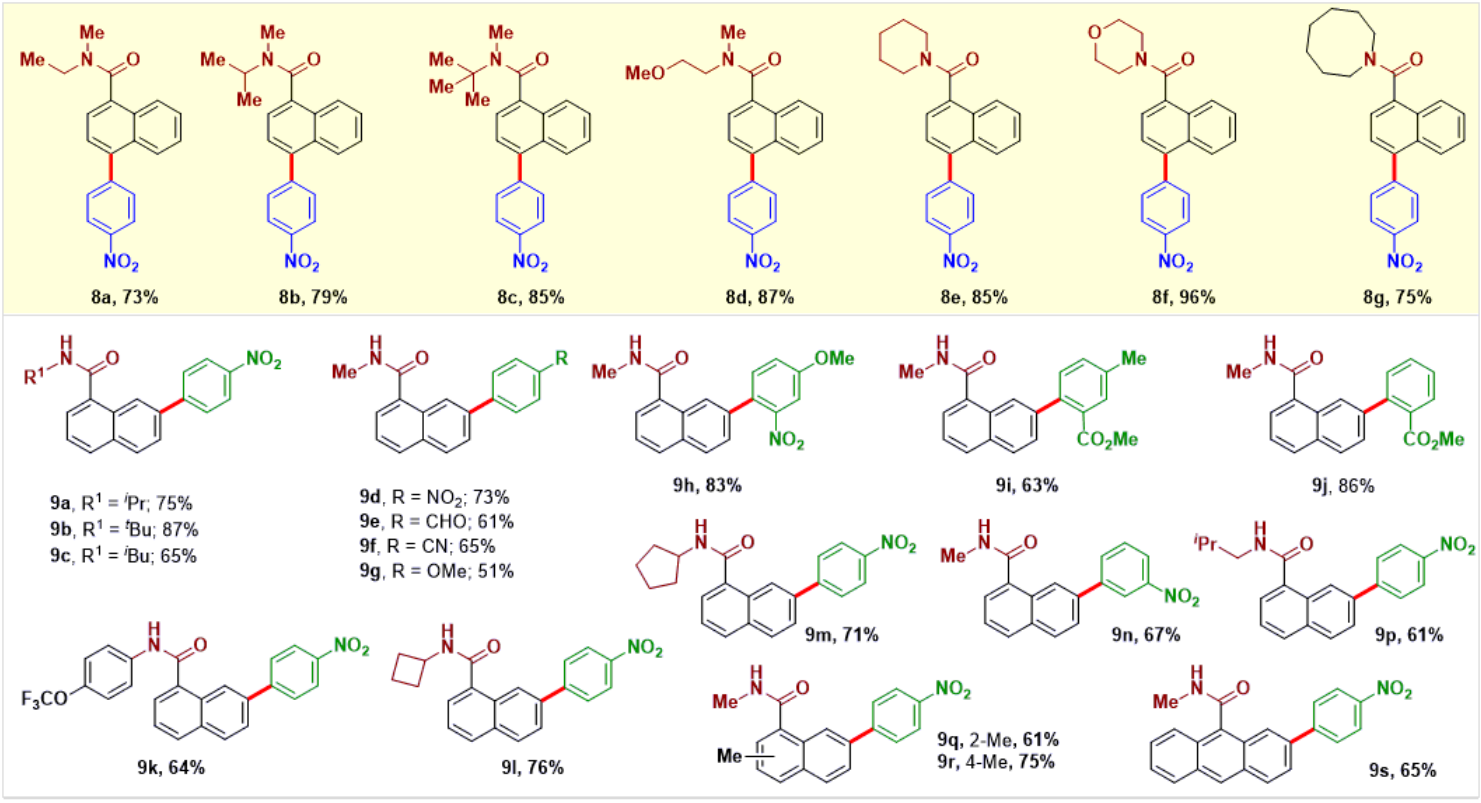

Figure 5

Arylation of different 1-naphthamides derived from various amines.

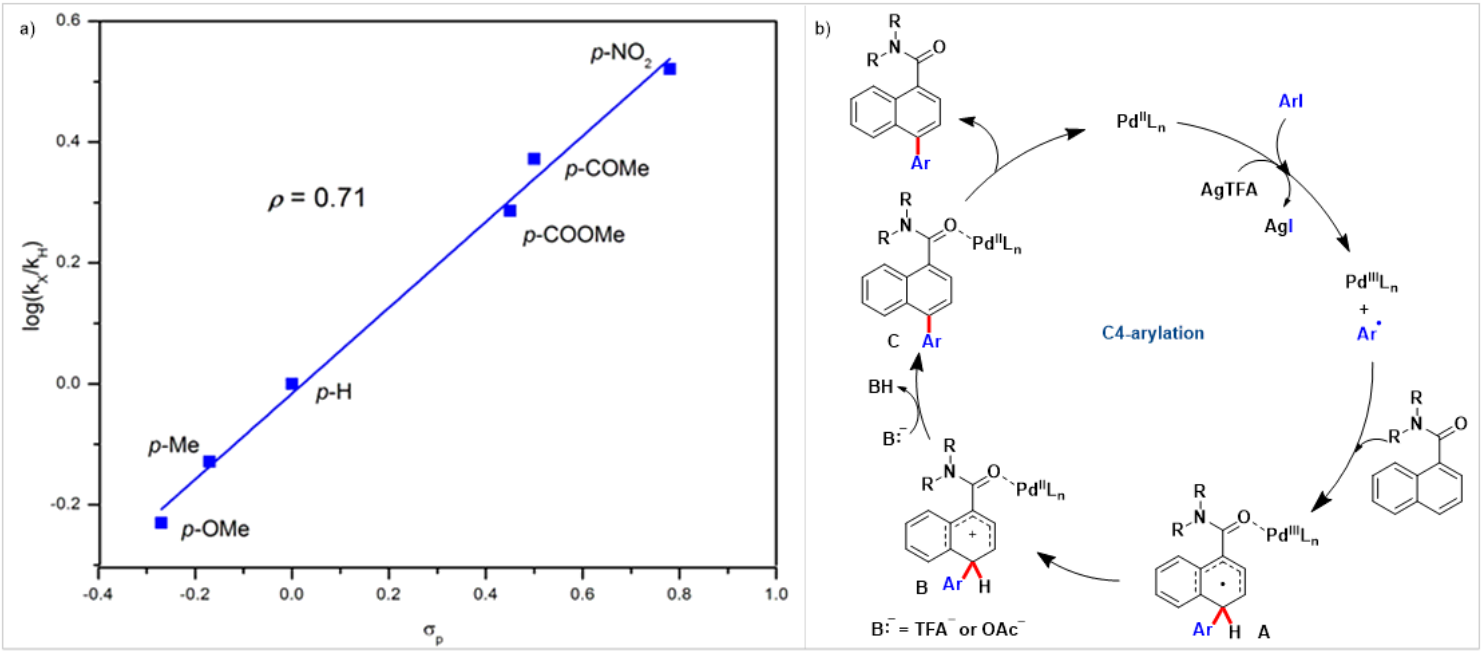

Figure 6

a) Hammett plot for C4-arylation, b) Probable mechanism for C4 arylation in a radical pathway.

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