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# Palladium-Catalyzed Regioselective *peri* and *ortho*-Halogenation of 1-Naphthaldehydes: Application to the Synthesis of Polycyclic Natural Product Skeletons

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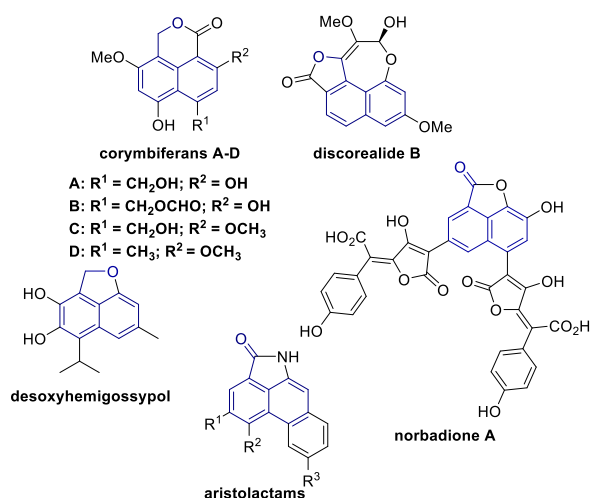
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**Abstract.** Herein, a regioselective bromination or chlorination reaction of 1-naphthaldehydes is described. Without additive, the palladium-catalyzed C–H halogenation showed a C8-regioselectivity, whereas the formation of an aromatic imine intermediate allowed a switch to a C2-reactivity. Mechanistic studies and DFT calculations were performed to explain the regioselectivity and the synthesized halogenated products were used as key building blocks to access polycyclic natural product skeletons.

**Keywords:** C–H activation; 1-naphthaldehydes; halogenation; polycyclic natural products; palladium catalysis

## Introduction

Naphthalene is a key structural core in chemistry as shown by its presence in many bio-active compounds as well as in organic materials.<sup>[1]</sup> Concerning natural products, many different skeletons including a naphthalene moiety have been isolated and identified. Among them, naphthalene annulated with a lactone (e.g. corymbiferans,<sup>[2]</sup> discorealide B,<sup>[3]</sup> norbadione A),<sup>[4]</sup> a dihydrofuran (e.g. desoxyhemigossypol)<sup>[5]</sup> or a lactam (e.g. aristolactams)<sup>[6]</sup> are commonly found moieties with antioxidant, anti-inflammatory, anticancer, antiplatelet or neuro-protective effects (Figure 1). Due to this broad range of biological interests, some research groups have reported interesting synthetic studies, especially on aristolactams,<sup>[7]</sup> but other skeletons have attracted considerably less attention and generally required a large number of steps.<sup>[8]</sup> Therefore, a fast access to these skeletons is still needed. For that, halogenated 1-naphthaldehydes could be a key linchpin due to the further possible transformations.<sup>[9]</sup>

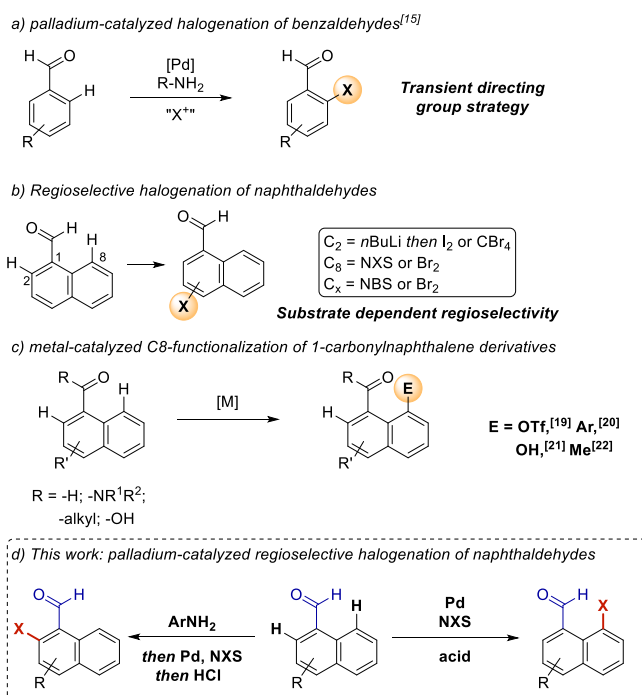


**Figure 1.** Natural products bearing a naphthalene moiety.

In this context, the development of a direct regioselective halogenation reaction of naphthaldehydes is of considerable interest.<sup>[10]</sup> Indeed, the carbonyl group could have a dual role: direct the C–H halogenation reaction and be a heterocycle precursor, whereas the introduced halogen atom could

be used in coupling reactions to form the new cycle of the target skeletons.

For the last two decades, a lot of research works have been realized on developing new C–H activation reactions,<sup>[11]</sup> and the use of carbonyl derivative as directing group has recently started to emerge.<sup>[12]</sup> Although the C–H activation step is often more challenging, the utility of carbonyl moiety in synthesis encourages research in this area. Concerning aldehyde as directing group, only few examples of direct C–H functionalization were described,<sup>[13]</sup> but very recently a new strategy based on transient directing groups has emerged.<sup>[14]</sup> In regards to aromatic aldehydes, the addition of catalytic amount of amine was crucial to develop palladium-catalyzed halogenation reactions *via* a transient directing group strategy (Scheme 1.a).<sup>[15]</sup> Although these conditions have been transposed to indol derivatives,<sup>[16]</sup> no general halogenation method exist for naphthaldehydes. The observed regioselectivity with classical halogenation conditions is generally substrate dependent. Moreover, harsh conditions using *n*-butyllithium could be necessary for a C2-selectivity (Scheme 1.b).<sup>[17]</sup> Over the last few years, a lot of progress have been realized on direct metal-catalyzed regioselective functionalizations of naphthalene derivatives.<sup>[18]</sup> Concerning C8-functionalization of 1-carbonylnaphthalenes, we and other groups have recently developed triflation,<sup>[19]</sup> arylation,<sup>[20]</sup> oxygenation<sup>[21]</sup> and methylation reactions (Scheme 1.c).<sup>[22]</sup> With this in mind, we were keen to develop an *peri*- or *ortho*-C–H halogenation reaction of 1-naphthaldehydes in which the addition of an amine could have a crucial role in the regioselectivity (Scheme 1.d).



**Scheme 1.** Halogenation of aromatic aldehydes and metal-catalyzed C8-functionalization of 1-carbonylnaphthalenes.

Herein, we present a palladium-catalyzed C2- or C8-halogenation of 1-naphthaldehydes *via* C–H activation which gives a direct access to key building blocks for natural product synthesis.

## Results and Discussion

At the onset of our investigation, we focused our attention on the C8-bromination of 1-naphthaldehyde **1a** using *N*-bromosuccinimide (NBS) as bromination agent and palladium diacetate (Pd(OAc)<sub>2</sub>) as catalyst. According to literature precedents,<sup>[21b]</sup> several amines were tested as catalytic additive (0.5 equiv) in order to form a transient directing group during the C–H activation reaction, but the best preliminary result was obtained without any amine with a 68% NMR yield of 8-bromo-1-naphthaldehyde **2a** (Table 1, entries 1-4). It is important to notice that 2-bromo-1-naphthaldehyde **3a** and 2,8-dibromo-1-naphthaldehyde **4a** were detected when anilines were employed which could be a promising starting point for a C2-bromination reaction (Table 1, entries 2-3). Encouraged by this result, no amine was added for the C8-bromination reaction and an extensive screening of acids and solvents was realized (see the Supporting Information). The reaction temperature as well as the NBS equivalent were also modified and a 75% NMR yield was reached with 1.05 equivalent of NBS at 110 °C (Table 1, entries 5-8). When 1.5 equivalent of NBS was used, a decrease of the yield of **2a** was observed due to unidentified dibromo-naphthaldehydes (Table 1, entry 7). Finally, in the optimal conditions, the amount of Pd(OAc)<sub>2</sub> could be reduced to 5 mol%, the reaction concentration was increased (C = 0.5 M) and desired 8-bromo-compound **2a** was obtained in 75% NMR yield after 2 hours of reaction (Table 1, entry 9). Importantly, when no palladium was used in the reaction conditions, only a very small amount of desired product **2a** was observed (13% NMR yield) with several side products and starting material (Table 1, entry 10).

**Table 1.** Selected optimization results of the C8-bromination reaction.<sup>[a]</sup>

Entry	NBS ([equiv])	Additive	T [°C]	Yield <sup>[b]</sup>	Yield <sup>[b]</sup>	Yield <sup>[b]</sup>
				of <b>2a</b> [%]	of <b>3a</b> [%]	of <b>4a</b> [%]
1	1.2	-	90	68	0	0
2	1.2	<b>A1</b>	90	21	0	29
3	1.2	<b>A2</b>	90	11	6	9
4	1.2	<b>A3</b>	90	58	0	0

**A1**:

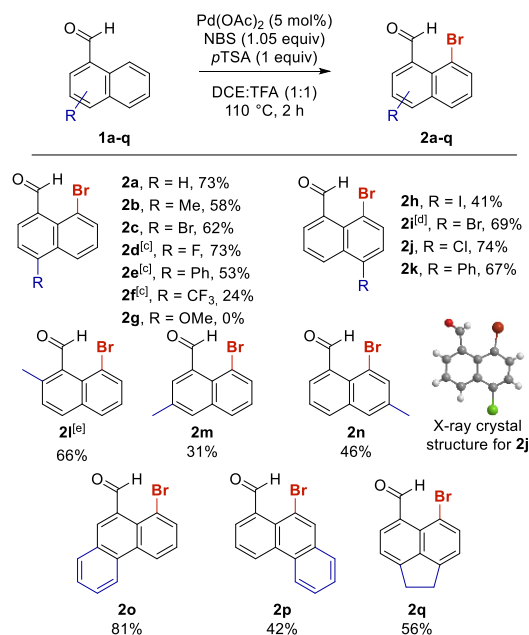
**A2**:

**A3**:

5	1.2	-	70	56	0	0
6	1.2	-	110	70	0	0
7 <sup>[c]</sup>	1.5	-	110	52	0	0
8	1.05	-	110	75	0	0
9 <sup>[d]</sup>	1.05	-	110	75	0	0
10 <sup>[e]</sup>	1.05	-	110	13	-	-

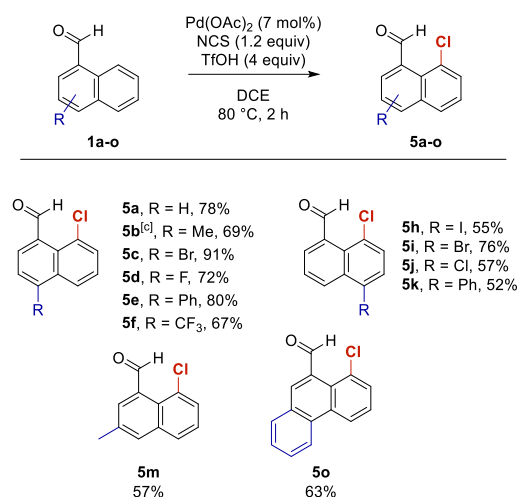
[a] General reaction conditions: **1a** (0.25 mmol, 1 equiv), Pd(OAc)<sub>2</sub> (0.1 equiv), NBS (x equiv), *p*TSA (1 equiv), additive (0.5 equiv), DCE:TFA (1:1, C = 0.2 M), T °C, 18 h. [b] NMR yield determined using 1,3,5-trimethoxybenzene as internal standard. [c] 10% of unidentified dibrominated compound was observed [d] Pd(OAc)<sub>2</sub> (0.05 equiv), DCE:TFA (1:1, C = 0.5 M), 2 h. [e] No palladium source.

With the optimized conditions in hand, we investigated the scope of the C8-bromination reaction and different naphthaldehydes were tested (Scheme 2). First, 8-bromo-1-naphthaldehyde **2a** was isolated in 73% yield which is in line with the previously observed NMR yield. Then, several 4- and 5-substituted naphthaldehydes were tried in the reaction conditions and corresponding 8-bromo derivatives **2b-2k** were obtained in moderate to very good yields. In addition of the disappearance of the clear C8-proton in product NMR spectra, single-crystal X-ray analysis of **2j** confirmed its structure.<sup>[23]</sup> Due to a lower reactivity, some naphthaldehydes needed more reaction time such as 16 hours for 4-fluoro-, 4-phenyl- and 4-(trifluoromethyl)-1-naphthaldehyde **1d-f** or 4 hours for 5-bromo-1-naphthaldehyde **1i**. Alkyl, aryl and halogen groups were compatible with the reaction conditions which show the generality of our reaction. Unfortunately, when 4-methoxy-1-naphthaldehyde **1g** was tested under our bromination conditions, desired 8-bromo derivative **2g** was not isolated. Instead, a bromination in position C3 was observed with or without palladium catalyst (compound **2g'** in the Supporting Information). Then, the substitution position was evaluated. 2-Methyl-, 3-methyl-, and 6-methyl-1-naphthaldehyde were engaged in the reaction and, whatever the methyl group position, desired 8-bromonaphthaldehydes **2l-2n** were isolated in moderate to good yields (31-66%). This time, due to the high reactivity of 2-methyl-1-naphthaldehyde **1l**, the reaction was conducted at 80 °C for only 1 hour. To extend the scope of the reaction, tricyclic 1-naphthaldehydes **1o-1q** were tested and corresponding 8-bromonaphthalenes **2o-2q** were easily obtained (42-81% yield). These latest products are potentially very interesting for a synthesis of aristolactam derivatives.



**Scheme 2.** Scope of the 8-bromination reaction. [a] Reactions were carried out using **1** (0.5 mmol), NBS (0.525 mmol), *p*TSA (0.5 mmol) and Pd(OAc)<sub>2</sub> (0.025 mmol) in DCE/TFA (0.5 mL: 0.5 mL) for 2 h at 110 °C. [b] Isolated yields were reported. [c] Reaction time was 16 h. [d] Reaction time was 4 h. [e] Reaction carried out for 1 h at 80 °C.

After having developed a C8-bromination reaction, we turned our attention to a C8-chlorination reaction of 1-naphthaldehydes. Based on bromination conditions, 8-chloro-1-naphthaldehyde **5a** was obtained in 80% NMR yield still using Pd(OAc)<sub>2</sub> as catalyst, *N*-chlorosuccinimide (NCS) as chlorination agent and triflic acid as additive for 2 hours at 80 °C (for a full optimization of the reaction see the Supporting Information). It is important to note that a too long reaction time led to significant degradation of the chlorinated product. Having the optimized conditions, they were tested on several 1-naphthaldehyde derivatives (Scheme 3). Again, the isolated yield of 8-chloro-1-naphthaldehyde **5a** (78%) was consistent with the NMR yield previously observed. Several 1-naphthaldehydes bearing functional groups in position 4 or 5 were engaged in the chlorination reaction and the corresponding products were obtained in good to very good yields. The reaction was compatible with alkyl, aryl and halogen substituents exhibiting in general a slightly better yield than the bromination reaction. For instance, 8-chloro-4-(trifluoromethyl)-1-naphthaldehyde **5f** could be isolated in a good 67% yield. All the reactions were conducted at 80 °C for 2 hours except for 4-methyl-1-naphthaldehyde **1b** for which the reaction lasted 4 hours. Finally, 3-substituted naphthaldehyde **1m** as well as 9-phenanthrenecarboxaldehyde **1o** were successfully chlorinated in position 8 in good yields under our conditions (57% and 63% respectively).



**Scheme 3.** Scope of the 8-chlorination reaction. [a] Reactions were carried out using **1** (0.5 mmol), NCS (0.6 mmol), TfOH (2 mmol) and Pd(OAc)<sub>2</sub> (0.035 mmol) in DCE (2.5 mL) for 2 h at 80 °C. [b] Isolated yields were reported. [c] Reaction time was 4 h.

To complete our C8-halogenation study, the C8-iodination reaction was tested on 1-naphthaldehyde **1a** but only poor yields could be observed (see the Supporting Information).

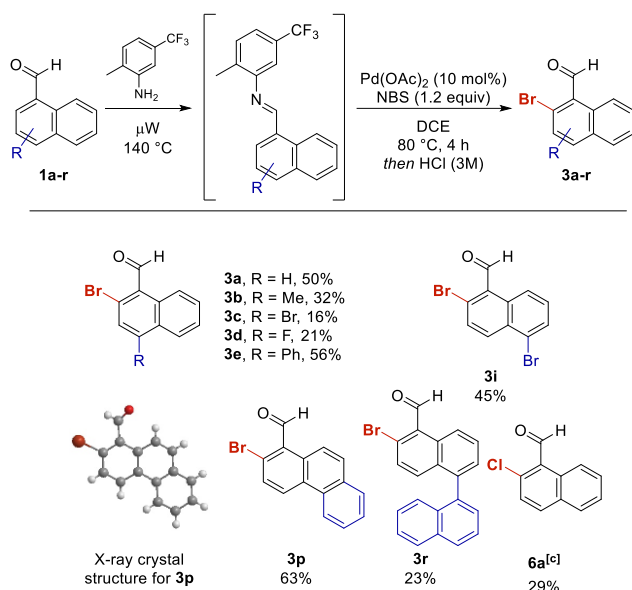
After successfully introducing halogen atoms in position 8, we were keen to study a C2-halogenation reaction. This regioselectivity is also challenging and useful to achieve in order to substitute the lithiation/halogenation method.<sup>[16]</sup> Due to our first amine screening for the C8-bromination, we assumed that the formation of an aromatic imine intermediate was necessary. For that, different imines were generated through micro-wave irradiation without solvent or additive (full conversion was generally observed by NMR analysis) and directly engaged in the bromination reaction using Pd(OAc)<sub>2</sub> as catalyst and NBS in dichloroethane at 110 °C (Table 2). Several *meta*-(trifluoromethyl)anilines were tested (for a full optimization see the Supporting Information), and 2-bromo-1-naphthaldehyde **3a** could be observed in moderate yield after acidic hydrolysis (Table 2, entries 1-5, after 3M HCl treatment, the imine was fully hydrolyzed into the corresponding aldehyde). At best, a 47% NMR yield, with traces of dibromo compound **4a**, was reached when using 2-methyl-5-(trifluoromethyl)aniline as imine precursor (Table 2, entry 4). When other types of anilines were employed, only small amounts of desired product **3a** were detected (Table 2, entries 6-8).

**Table 2.** Aniline optimization results for the C2-bromination reaction.<sup>[a]</sup>

Entry	Amine	Yield <sup>[b]</sup>		
		of <b>2a</b> [%]	of <b>3a</b> [%]	of <b>4a</b> [%]
1	<b>A1</b>	0	44	16
2	<b>A4</b>	2	40	1
3	<b>A5</b>	0	39	1
4	<b>A6</b>	0	47	2
5	<b>A7</b>	0	2	0
6	<b>A8</b>	3	22	6
7	<b>A9</b>	0	10	0
8	<b>A10</b>	0	11	0

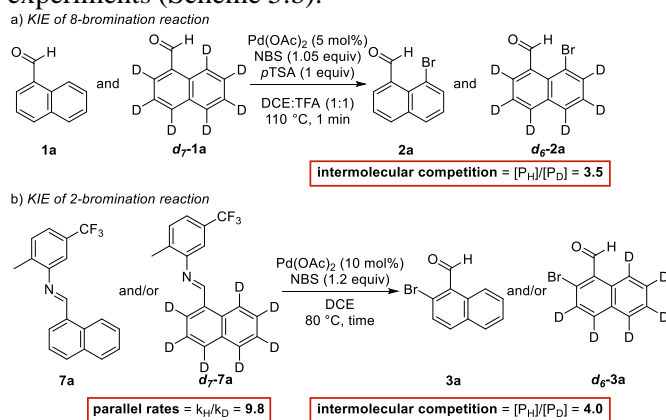
[a] General reaction conditions: **1a** (0.25 mmol, 1 equiv), aniline (0.26 mmol, 1.05 equiv), micro-wave 140 °C then Pd(OAc)<sub>2</sub> (0.1 equiv), NBS (1.2 equiv), DCE (1.25 mL), 110 °C, 16 h then HCl<sub>aq</sub> (3M), r.t., 30 min. [b] NMR yield determined using 1,3,5-trimethoxybenzene as internal standard.

After optimization (see the Supporting Information), the reaction temperature was decreased to 80 °C to avoid any dibromo derivative **4a** which was very difficult to separate from desired compound **3a**, the reaction time was fixed to 4 hours and a 53% NMR yield of 2-bromo-1-naphthaldehyde **3a** was reached. It is interesting to note that, due to our previous results, acid additives should not be used to avoid imine hydrolysis and therefore C8-bromination. Moreover, when the reaction conditions were applied to the purified imine, similar yield was observed. The optimized conditions were applied to a range of 1-naphthaldehydes **1a-r** and corresponding 2-brominated naphthaldehydes **3a-r** were delivered in low to moderate yields (Scheme 4). In accordance with the NMR yield, 2-bromo-1-naphthaldehyde **3a** was isolated in 50% yield. Several 4-substituted naphthaldehydes were engaged in the reaction and corresponding 2-brominated products were got (16-56% yields). Naphthaldehydes brominated or arylated in position 5, respectively **1i** and **1r**, were also compatible with the reaction conditions. Very interestingly, 2-bromophenanthrene-1-carbaldehyde **3p** was obtained in a good 63% yield. As for the C8-bromination, a single-crystal X-ray analysis of **3p** was conducted, confirming the C2-selectivity.<sup>[23]</sup> Finally, NCS instead of NBS was tried in the reaction and 2-chloro-1-naphthaldehyde **6a** could be isolated in 29% yield.



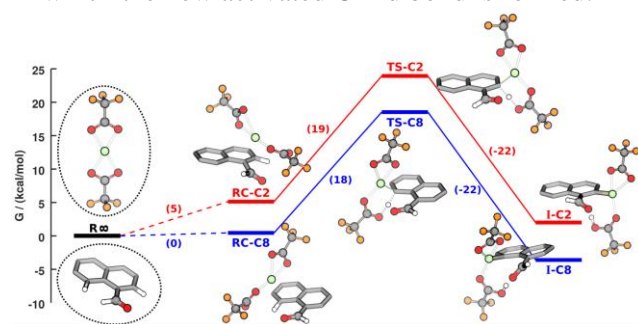
**Scheme 4.** Scope of the 2-bromination reaction. [a] Reactions were carried out using **1** (0.5 mmol), 2-methyl-5-(trifluoromethyl)aniline (0.525 mmol) then NBS (0.6 mmol) and Pd(OAc)<sub>2</sub> (0.05 mmol) in DCE (2.5 mL) for 4 h at 80 °C then HCl<sub>aq</sub> (3M), r.t., 30 min. [b] Isolated yields were reported. [c] NCS was used instead of NBS.

In order to better understand the C–H activation step and especially the regioselectivity, kinetic isotope effect (KIE) experiments were carried out (Scheme 5). A significant primary KIE ( $KIE_{\text{competition}} = 3.5$ ) was observed during intermolecular competition experiment on non-deuterated and deuterated 1-naphthaldehydes (Scheme 5.a),<sup>[24]</sup> which indicates that the C–H bond cleavage is probably linked to the turnover limiting step. Similar observations were made with the 2-bromination reaction for which substantial KIE was measured in both parallel ( $KIE_{\text{parallel}} = 9.8$ ) and competition ( $KIE_{\text{competition}} = 4.0$ ) experiments (Scheme 5.b).



**Scheme 5.** K.I.E. using 1-naphthaldehyde, 1-naphthaldehyde-*d*<sub>7</sub>, imine **7a** and deuterated imine **d**<sub>7</sub>-**7a**.

To go deeper in our study of the regioselectivity of the system, we completed our KIE experiments with density functional theory (DFT) calculations. Following our findings that the C–H activation step is the rate limiting step of the reaction, we focused on the calculations of the free energy profiles of the C–H activations on positions C8 and C2. Concerning the C2-selectivity observed with imine derivatives, it can be explained by similar DFT calculations done by the group of Zhang for their oxygenation reaction.<sup>[21b]</sup> Therefore, we only performed DFT calculations on 1-naphthaldehyde, with palladium trifluoroacetate as catalyst to rationalize the observed C8-regioselectivity. The molecular system was embedded in a dielectric cavity that mimics dichloroethane, following the same approach as in our previous computational study of C8- vs C2- arylation of *N,N*-dimethyl-1-naphthamide (see Computational Methods section for more details).<sup>[20a]</sup> Our results are summarized in Figure 2. It is worth stressing that the directing carbonyl group is oriented toward the C8–H (or C2–H) group in a very similar fashion within 1-naphthaldehyde and *N,N*-dimethyl-1-naphthamide. As a result, the reaction mechanism of C–H activation of 1-naphthaldehyde that we are studying here is virtually the same as the one we found previously for *N,N*-dimethyl-1-naphthamide:<sup>[20a]</sup> starting from the reactants at infinite separation ( $R_{\infty}$ ), two reactive complexes (RC) can be formed, RC-C8 or RC-C2, depending on whether the palladium catalyst approaches the C8–H or the C2–H bond, respectively. This leads to two distinct chemical steps, namely RC-C8  $\rightarrow$  TS-C8  $\rightarrow$  I-C8 and RC-C2  $\rightarrow$  TS-C2  $\rightarrow$  I-C2, where TS- and I- correspond to the transition state and the resulting reaction intermediate in which the new activated C–Pd bond is formed.

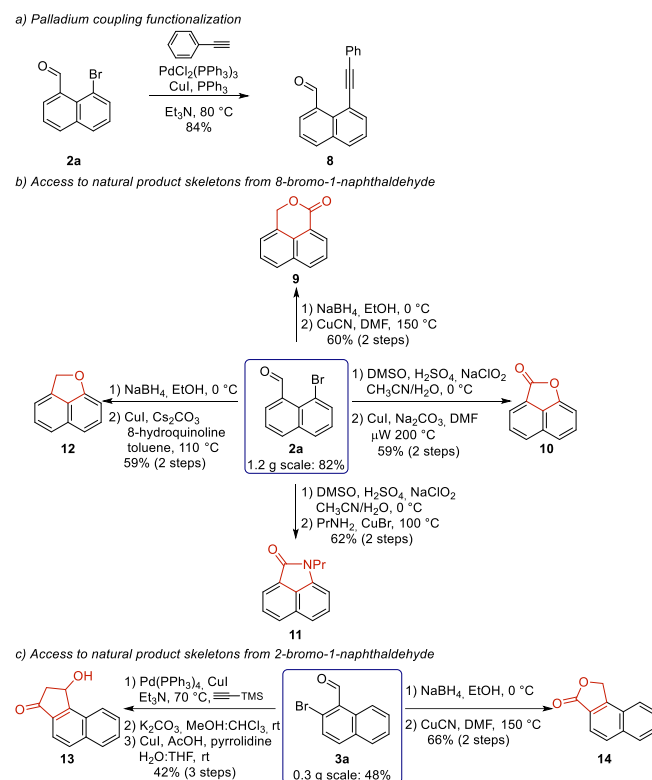


**Figure 2.** Free energy profiles of C8–H (blue) and C2–H activations (red) of 1-naphthaldehyde to explain the regioselectivity in the *peri*-halogenation reaction. Optimized molecular structures are represented for each stationary state, namely, reactants at infinite separation ( $R_{\infty}$ ), reactant complexes (RCs), transition states (TSs), and reaction intermediates (Is). Molecules in the  $R_{\infty}$  state, namely 1-naphthaldehyde and fluoroacetate, 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, all hydrogen atoms of 1-naphthaldehyde, except the reactive ones, are hidden. Free energy variations that correspond to the formation of the RC-C8 and RC-C2 are represented with dashed lines, while solid lines are used for chemical steps.

The comparison of the two free energy profiles in Figure 2 shows that the C8- and C2- pathways exhibit almost the same activation barrier for the chemical step, of 18 and 19 kcal/mol, respectively. However, the initial formation of RC-C8 from  $R_{\infty}$  requires no energy, while the assembly of RC-C2 is unfavorable by 5 kcal/mol. A close inspection of the structure of RC-C8 (see also Fig S2) reveals that the Palladium atom comes at the right position above the C8–H while being correctly positioned with respect to the oxygen lone pair of the directing aldehyde group. The same arrangement is not possible in RC-C2 because there is not enough room to accommodate a proper Palladium-aldehyde interaction. The aldehyde is instead repelled in RC-C2. This difference with RC-C8 can be quantified by the  $\text{PdO}_{\text{aldehyde}}\text{C}_{\text{aldehyde}}$  angle, which is obtuse (and favorable) in RC-C8 and acute (and unfavorable) in RC-C2. Overall, this is again very similar to what we observed in our previous modeling of the C–H activation of *N,N*-dimethyl-1-naphthamide,<sup>[20a]</sup> for which the activation barrier for the chemical step was also of the order of 19 kcal/mol and the main difference between the C8- and C2- pathways also came from a better Palladium-interacting group arrangement in the C8-case. However, we note that here, with an aldehyde as the directing group, RC-C8 is not stabilized with respect to  $R_{\infty}$  which is consistent with the fact that aldehydes are poor directing groups. Nevertheless, the present study indicates that aldehydes can effectively induce the desired regioselectivity.

To show the potential interest of our methodology in synthesis, several transformations were achieved (Scheme 6). First, classical Sonogashira coupling was realized on 8-bromo-1-naphthaldehyde **2a** delivering corresponding alkyne **8** (Scheme 6.a) which has been previously used as key starting material in gold cyclization<sup>[25]</sup> or azafluoranthene synthesis.<sup>[26]</sup> Afterwards, we turned our attention to synthesis of natural product scaffolds and the 8-bromination reaction was performed on a gram-scale with a slightly better yield of 82% compare to our scope (Scheme 6.b). Having this bromo-naphthaldehyde in hand, several transformations were tried. After aldehyde reduction and copper-mediated carbonylative coupling,<sup>[27]</sup> the six-membered ring lactone of corymbiferans was obtained.<sup>[2]</sup> Moreover, after oxidation into carboxylic acid and copper-catalyzed coupling reaction, naphtholactone **10** was isolated in a good 59% yield. The carboxylic acid was also reacted with propylamine in presence of a catalytic amount of copper(I) bromide to deliver naphthylamide **11** which is known to exhibit interesting biological activities.<sup>[28]</sup> Finally, after aldehyde reduction, the corresponding bromo-alcohol **12**, skeleton found in desoxyhemigossypol.<sup>[5]</sup> Some post-functionalizations were also realized on 2-bromo-1-naphthaldehyde **3a** (Scheme 6.c). Pleasingly, the scale of the 2-bromination reaction could be tripled without any yield disruption. Then, after a Sonogashira coupling followed by a silyl deprotection, hydroxyindanone **13** was synthesized *via* a reported copper

catalyzed annulation reaction.<sup>[29]</sup> At last, employing the same sequence as for **2a**, **3a** was easily converted into five-membered lactone **14**, moiety found in discorealide B.<sup>[3]</sup>



**Scheme 6.** Post-functionalization and access to natural product skeletons.

## Conclusion

In summary, we have developed a palladium-catalyzed regioselective halogenation reaction of 1-naphthaldehydes based on a C–H activation strategy. Under acidic conditions, a C8-halogenation was observed, whereas going through an imine intermediate allowed a C2-selectivity. KIE experiments coupled to DFT calculations could explain the observed regioselectivity. Finally, halogenated 1-naphthaldehydes were engaged in derivatization reactions to access natural product skeletons such as the tricyclic core of corymbiferan. Further explorations of C–H functionalization of naphthalenes are currently in progress.

## Experimental Section

Additional references cited within the Supporting Information.<sup>[39-59]</sup>

**C8-bromination:** Naphthaldehyde derivative **1** (1 equiv), NBS (1.05 equiv),  $\text{Pd}(\text{OAc})_2$  (5 mol%) and *p*TSA (1 equiv) were dissolved in a mixture of DCE:TFA (1:1, 0.5 M). The reaction was stirred at  $110^\circ\text{C}$  for 2–16 h. After completion, the reaction was cooled to room temperature dissolved with DCM and quenched with a saturated aqueous solution of  $\text{NaHCO}_3$ . Extraction was performed three times with DCM.

Organic phases were gathered, dried over MgSO<sub>4</sub>, filtered and then concentrated *in vacuo*. The residue was purified by flash chromatography.

**C8-chlorination:** Naphthaldehyde derivative **1** (1 equiv), Pd(OAc)<sub>2</sub> (7 mol%) and NCS (1.2 equiv) were dissolved in DCE (0.2 M). TfOH (4 equiv) was added to the mixture. The reaction was stirred at 80 °C for 2-16 h. After completion, the reaction was dissolved with DCM and quenched with a saturated aqueous solution of NaHCO<sub>3</sub>. Extraction was performed three times with DCM. Organic phases were gathered, dried over MgSO<sub>4</sub>, filtered and then concentrated *in vacuo*. The residue was purified by flash chromatography.

**C2-halogenation:** Naphthaldehyde derivative **1** (1 equiv) and 2-methyl-5-(trifluoromethyl)aniline (1.05 equiv) were introduced in a micro-wave tube. The reaction was stirred at 140 °C for 6 to 10 h under microwave irradiation. Then, the imine derivative was dissolved in distilled DCE (0.2 M) with NXS (1.2 equiv) and Pd(OAc)<sub>2</sub> (10 mol%). The reaction was stirred at 80 °C for 4 h. The mixture was cooled down to r.t. and an aqueous solution of HCl (3 M) was added and the mixture was vigorously stirred during 15 min. The aqueous phase was extracted with DCM, the organic phases were gathered, dried over MgSO<sub>4</sub>, filtered and then concentrated *in vacuo*. The residue was purified by flash chromatography.

**Computational methods:** All electronic structure calculations were performed by means of DFT with the M062X functional,<sup>[30]</sup> as implemented in the Gaussian 09 suite of programs.<sup>[31]</sup> All atoms except palladium were represented with the 6-31+G(d,p) basis set,<sup>[32-34]</sup> whereas the LANL2DZ basis set, together with the corresponding effective core potential,<sup>[35]</sup> were used for palladium. The molecular system was embedded in a dielectric cavity that mimicked the DCE solvent (polarizable continuum model (PCM)).<sup>[36]</sup> 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<sup>[37]</sup> and proceeded downhill toward the reactants and products of the elementary step. Graphical representations of the molecules were made with the software VMD.<sup>[38]</sup>

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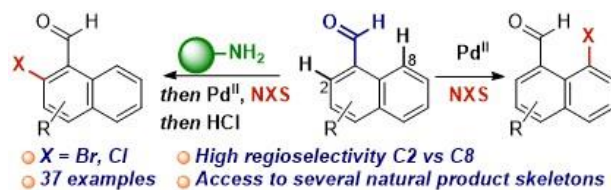
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Palladium-Catalyzed Regioselective *peri*- and *ortho*-Halogenation of 1-Naphthaldehydes: Application to the Synthesis of Polycyclic Natural Product Skeletons

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A palladium-catalyzed regioselective halogenation reaction of 1-naphthaldehydes was disclosed. When aldehyde was used as directing group, a C8-selectivity was observed whereas an imine formation was necessary to achieve C2-halogenation. The mechanism as well as the regioselectivity of the reaction were studied and the halogenated products were used in the synthesis of natural product skeletons.

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