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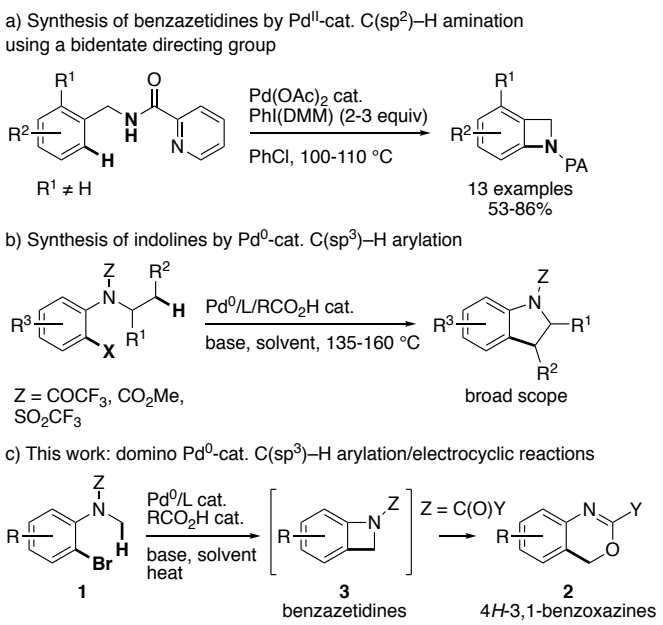
Domino Pd^0-Catalyzed $C(sp^3)$–H Arylation/Electrocyclic Reactions via Benzazetidine Intermediates

*Ronan Rocaboy, David Dailler, Florian Zellweger, Markus Neuburger, Christophe Salomé, Eric Clot, and Olivier Baudoin**

***Abstract**: The Pd^0-catalyzed $C(sp^3)$–H arylation of 2-bromo-N-methylanilides leads to unstable benzazetidine intermediates that rearrange to benzoxazines through 4π electrocyclic ring-opening and 6π electrocyclization. The introduction of a bulky, non-activable amide group on the nitrogen atom was key to favor the challenging reductive elimination step and disfavor undesired reaction pathways.*

Nitrogen heterocycles are omnipresent in small-molecule pharmaceuticals, representing almost 60% of drugs recently approved by the U.S. Food and Drug Administration.[1] However, there is an obvious lack of diversity within the category of (fused) four-membered *N*-heterocycles, with (fused) β-lactams being the quasi-exclusive examples. This matter of fact is likely a consequence of the lack of general synthetic methods to access those compounds, combined with their limited stability.[2] In particular, no truly efficient and general synthesis of benzazetidines is currently available.[3] Indeed, unless they are stabilized by electron-withdrawing or sterically hindered substituents, these highly strained fused *N*-heterocycles tend to readily undergo electrocyclic ring-opening to generate the unstable aza-*ortho*-xylylene forms, which react with nucleophiles and heterodienophiles.[4] In 2016, Chen and co-workers reported a synthesis of benzazetidines by intramolecular $C(sp^2)$–H amination (Scheme 1a).[5] Key to the efficiency of this reaction were the use of the picolinamide directing group initially introduced by Daugulis and co-workers[6] and an oligomeric iodine(III) reagent favoring the desired C–N vs. the undesired C–O bond formation. Good yields were achieved, but the reaction was limited to reactants bearing a bulky substituent (R^1) in *ortho* position to the amidomethyl group. For instance, no benzazetidine product was detected with R^1 = H. In light of our longstanding interest in this field,[7] we considered an alternative synthesis of benzazetidines **3** through Pd^0-catalyzed intramolecular $C(sp^3)$–H arylation from easily accessible 2-bromo-*N*-methylanilides **1** (Scheme 1c). The synthesis of the homologous indolines through this method was initially reported by Ohno and co-wokers,[8a] and its scope has been greatly expanded by various research groups, including enantioselective versions (Scheme 1b).[8b-g] In addition, other strained 4-membered rings such as benzocyclobutenes[9] and β-lactams[10] have been efficiently constructed through this approach.[11] However, until now we have been unable to extend the benzocyclobutene synthesis to benzazetidines. This failure was ascribed to several factors: 1. a difficult C–H activation step, in contrast to benzocyclobutenes that benefited from Thorpe-Ingold effects due to the presence of a quaternary benzylic carbon;[9] 2. a high energy barrier for the C–C reductive elimination leading to the highly strained benzazetidine; 3. the instability of the benzazetidine ring system under the high temperatures that are usually required in such reactions. Herein, we report that the Pd^0-catalyzed reaction of 2-bromo-*N*-methylanilides **1** leads to 4*H*-3,1-benzoxazines **2** via non-isolable benzazetidines **3** through a novel domino sequence of $C(sp^3)$–H arylation/electrocyclic reactions.[12]



Scheme 1. Benzazetidines by C–H activation: state-of-the-art and current work.

We first studied the influence of the nitrogen substituent, which was deemed crucial to overcome the above-mentioned reactivity issues (Figure 1). First, *N,N*-dimethylaniline **1a** mainly furnished *N*-methylaniline under standard reaction conditions,[13] consistent with previous observations on other *N,N*-dialkylanilines.[14] This result indicated that C–H activation indeed occurred at the methyl group, but also that the conformational bias of the substrate was not sufficiently strong to favor C–C reductive elimination against the competitive demethylation (see Scheme S1 for a proposed mechanism). Various electron-withdrawing substituents were next introduced to both increase the bulk on the nitrogen atom and reduce its donor character, which were both deemed responsible for this

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demethylation side-reaction. A Boc group (Boc = *tert*-butyloxycarbonyl) was found to be unstable under the reaction conditions (**1b**). Methyloxycarbonyl (**1c**), trifluomethanesulfonyl (**1d**) and trifluoroacetyl (**1e**) groups, which were successfully employed in the above-mentioned indoline syntheses (Scheme 1b),[8] were next tested, but only the former gave a trace of product. Cyclobutanamide **1f** bearing a tertiary carbon at the α position to the amide underwent selective C–H arylation at this more acidic site to give spirocyclic γ-lactam **2f**, consistent with precedents of other cyclic amides.[15] To suppress this undesired α-arylation reaction, pivalamide **1g** was tested. However, it underwent exclusive C(sp^3)–H arylation at the *t*-Bu group, leading to the 3,4-dihydroquinolone **2g** in good yield.[16] To disfavor this competing C–H arylation, we sought to replace primary C–H bonds on the amide group with less reactive secondary C–H bonds.[7,17] Indeed, the very bulky 1-adamantylamide **1h** furnished the benzoxazine **2h**[18] as the main product in 54% yield, together with the protodebrominated side-product. Benzazetidine **3h** was not observed even at short reaction times and performing the reaction at lower temperatures only gave incomplete conversions or protodebromination. These results indicate that **3h** is first formed by C(sp^3)–H arylation, but undergoes facile thermal 4π-electrocyclic ring-opening to the aza-*ortho*-xylylene form, followed by 6π-electrocyclization to give benzoxazine **2h** (Figure 1, bottom).[4,19] Indeed, DFT calculations showed that **2h** is much more stable than **3h** and the aza-*ortho*-xylylene, and hence once the opening of the 4-membered ring occurs, only the benzoxazine should be formed.

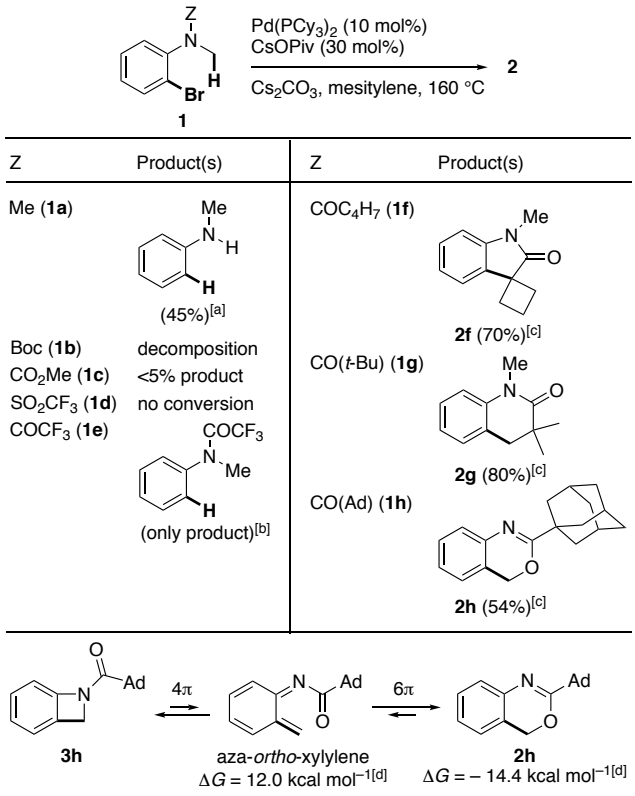
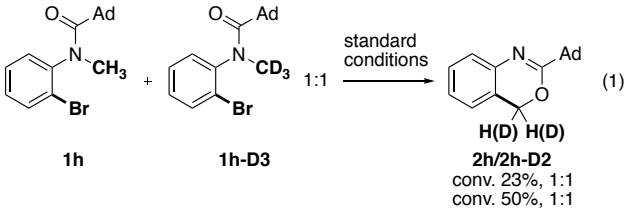


Figure 1. Influence of the nitrogen substituent on the reaction outcome. [a] NMR yield. [b] Based on GCMS analysis. [c] Yield of the isolated product. [d] Gibbs free energies relative to **3h** [DFT, ωB97X-D/6-311G**]. Ad = 1-adamantyl.

The demethylation of **1a** hinted that the C–H activation step was facile under these conditions, and that the reductive elimination leading to a highly strained 4-membered ring could be the rate-determining step of the C–H arylation. Indeed, the absence of isotopic effect in intermolecular competition experiments between protiated (**1h**) and deuterated (**1h-D3**) substrates showed that the C–H activation step is not rate-determining [Eq. (1)].[20]



To get additional insights, DFT calculations were conducted for the reductive elimination step with Z = Me, CO_2Me and CO(Ad).[21] The activation barriers ($\Delta G^{\ddagger}$) for these groups were found to be 27.6, 26.8 and 21.7 kcal mol^{-1}, respectively (Figure 2, see also Scheme S2 for more details). Non-covalent interaction maps[22] showed stabilizing dispersive forces[23] between the adamantyl and one cyclohexyl group of the ligand at the transition state, which do not exist for the Me and CO_2Me groups and hence might be at the origin of the lower activation energy observed for the Ad group.

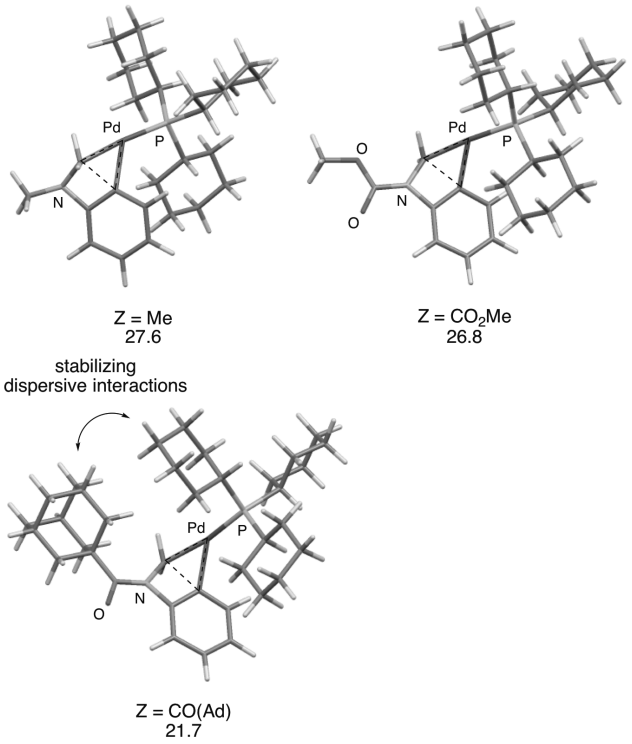
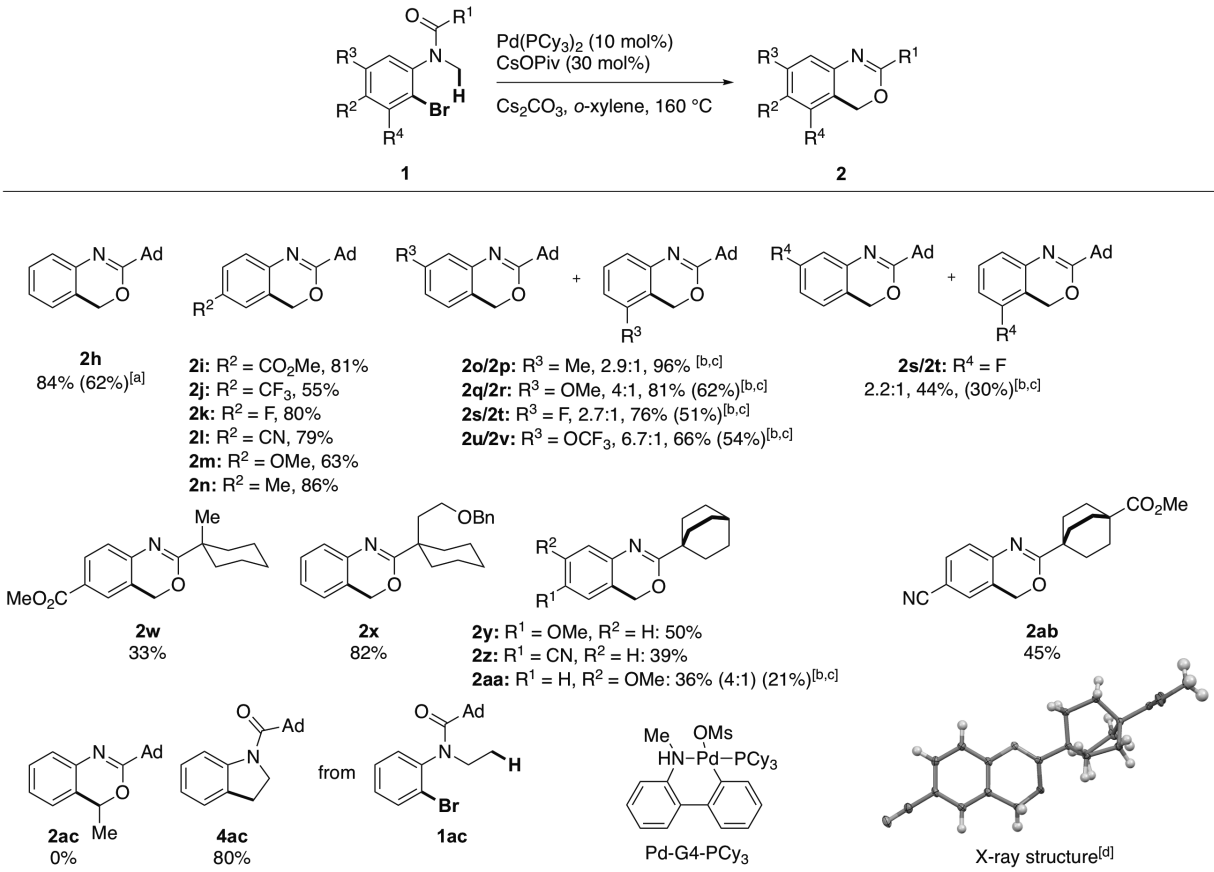


Figure 2. Calculated transition state geometries and activation barriers ($\Delta G^{\ddagger}$, kcal mol^{-1}) for the reductive elimination step with three Z groups [PBE0-D3(BJ)/def2-QZVP*+SMD, 433K].

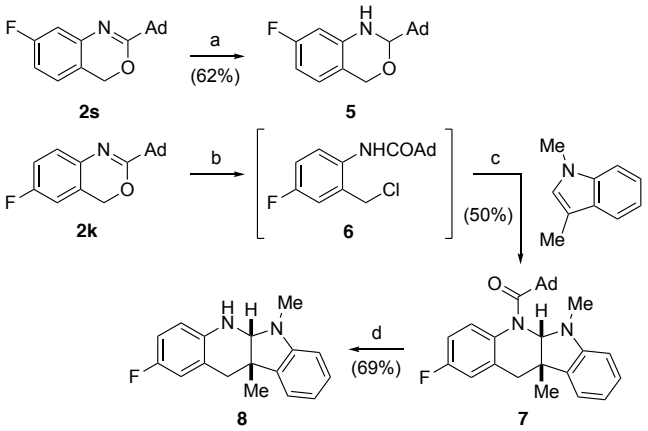
Further optimization of the reaction conditions, and in particular performing the reaction in *o*-xylene (Table S1), led to the isolation of benzoxazine **2h** in very good (84%) yield (Scheme 2). Of note, the well-defined complex [Pd(PCy_3)$_2$] is air-sensitive, but the reaction was successfully scaled-up using a combination of the air-stable palladacycle [Pd-G4-PCy_3][24] and free PCy_3 to give 1g of benzoxazine **2h** in 62% yield.



Scheme 2. Scope of the domino reaction. [a] Gram-scale reaction performed with [Pd-G4-PCy$_3$] (10 mol%)/PCy$_3$ (10 mol%) as catalyst. [b] Yield of the isolated mixture of isomers; in parentheses: yield of the isolated major isomer. [c] Using AdCO$_2$H (30 mol%) instead of CsOPiv. [d] X-ray structure of **2ab** (shown with 50% probability ellipsoids).[26]

The scope of the domino reaction was next examined. Aryl bromides bearing electron-withdrawing (**2i-l**) or -donating groups (**2m-n**) at the *para* position to the nitrogen atom (R^2) led to the benzoxazines **2i-n** as single isomers with moderate to very good yields. In contrast, with a substituent at the *para* position to the bromine atom (R^3), two isomeric products were obtained, and the yields and isomeric ratios could be significantly improved by using AdCO$_2^-$ instead of PivO$^-$ as the CMD base (CMD = concerted metalation-deprotonation). This formation of isomeric products was already observed in the context of benzocyclobutenes.[9b] Indeed, after the initial C(sp^3)–H activation step, the opening of the palladacycle intermediate is facile and re-closure by C(sp^2)–H activation leads to isomeric benzazetidines (Scheme S1), which eventually provide isomeric mixtures of benzoxazines **2o-v**. A similar mechanism may explain the demethylation of compound **1a** (Figure 1). The same behavior was observed with a substituent in *ortho* position to the bromine atom (R^4), which furnished the same isomeric mixture of benzoxazines **2s/2t** as obtained from a *para* substituent (R^3), albeit in lower yield due to a higher extent of protodebromination.

In addition to the adamantyl group, other large, non-activable groups enabled the reaction (**2w-2ab**). In particular, compound **2x** devoid of primary C–H bonds was obtained with similar efficiency to the adamantyl-substituted product **2h**. Moreover, the cage-like bicyclo[2.2.2]octane motif, bioisosteric to a *p*-substituted benzene ring,[25] proved compatible and provided valuable benzoxazines **2y-2ab** in more moderate yields, presumably due to a lesser thermal stability compared to the adamantyl group. Finally, we also considered replacing the *N*-methyl with an *N*-ethyl group (**1ac**), but the latter only furnished the indoline **4ac** (80% yield), arising from C–H activation at the terminal methyl group and easier reductive elimination from the six-membered palladacycle, without any trace of the corresponding benzoxazine **2ac**.



Scheme 3. Applications of 4*H*-3,1-benzoxazines. Reagents and conditions: a) NaBH$_4$ (3 equiv), THF/MeOH/DMF 1:1:1, 0 °C; b) 4 M HCl, dioxane, reflux; c) *N*-methylskatole (3 equiv), Cs$_2$CO$_3$ (2 equiv), 1,2-dichloroethane, 80 °C; d) NaOH, MeOH, 90 °C.

4*H*-3,1-Benzoxazines are interesting scaffolds for drug discovery,[27,28] but they can also serve as precursors for the

synthesis of other nitrogen heterocycles. For instance, **2s** was reduced to the dihydrobenzoxazine **5** under standard conditions (Scheme 3). In addition, HCl-mediated ring-opening of **2k** and trapping of the resulting chloroanilide **6** with *N*-methylskatole under conditions adapted from Stoltz and co-workers[29] provided tetracyclic compound **7**. Cleavage of the adamantylamide group under basic conditions afforded tetrahydroindoloquinoline **8**, which contains the tetracyclic core of the communesin family of indole alkaloids.[29]

In conclusion, we showed that the Pd^0-catalyzed $C(sp^3)$–H activation of 2-bromo-*N*-methylanilides furnishes valuable benzoxazines, through electrocyclic rearrangement of unstable benzazetidine intermediates. The introduction of a bulky, non-activable amide group on the nitrogen atom was key to favor the challenging reductive elimination step and disfavor undesired reaction pathways.

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Conflict of interest

The authors declare no conflict of interest.

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[26] CCDC1850396 (**2ab**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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C–H Activation

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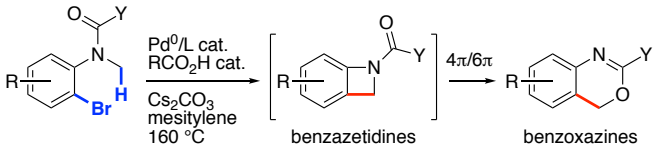
Domino Pd^0-Catalyzed $C(sp^3)$–H Arylation/Electrocyclic Reactions via Benzazetidine Intermediates



Playing dominos: the Pd^0-catalyzed $C(sp^3)$–H activation of 2-bromo-*N*-methylanilides leads to benzoxazines through $4\pi/6\pi$ electrocyclic reactions of unstable benzazetidine intermediates.