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Palladium-Catalyzed Domino Allenamide Carbopalladation/Direct C−H Allylation of Heteroarenes: Synthesis of Primprinine and Papaverine Analogues

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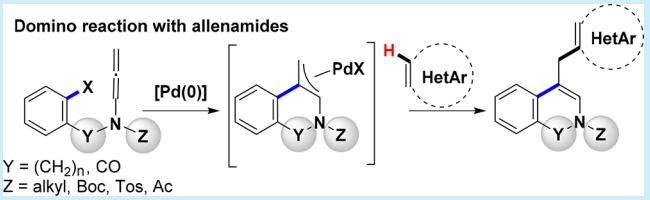
Supporting Information

ABSTRACT: Palladium-catalyzed intramolecular carbopalladation onto allenamides completed by direct C−H allylation of heterocycles is studied. The domino construction/heteroarylation of isoquinolone process is first achieved. A general three-step one-pot strategy, involving in situ generation of allenamide, π-allyl-Pd complex generation, and interception with heteroarenes, has been subsequently set up. This methodology has been extended to the construction/heteroarylation of indoles, dihydroquinolines, isoquinolin(on)es, and medium-sized nitrogen heterocycles, which are known to be key challenging structural motifs with pharmaceutical significance.



The rapid construction of molecular complexity from readily accessible starting material is, inarguably, a subject of central importance in modern organic synthesis. Considerable progress has been made in this area by taking advantage of transition-metal-catalyzed domino reactions, which have proved to be valuable tools for sustainable synthesis and for the powerful construction of complex molecules through the formation of multiple bonds in one sequence.[1]

The domino construction/functionalization of standard important classes of nitrogen-containing heterocycles has been actively studied according to the following pathway: (a) intramolecular or intermolecular *carbopalladation* of halogenated (hetero)aromatics onto standard allenamide, then (b) the *termination step* involving the capture of π-allyl-Pd(II) intermediates with organometallics, nucleophiles, or oxidants (see Figure 1).[2] An ecofriendly, step- and atom-economical added value is to manage the terminal cross-coupling step through direct C−H functionalization reactions.[3,4] Although carbopalladation/intramolecular direct C−H functionalization sequences have been actively developed,[3−5] intermolecular sequences remain sparsely proposed to date. As remarkable examples, the Fagnou, Van der Eycken, Liang and Zhu groups reported the interception of σ-alkyl/vinyl-Pd(II) intermediates with heterocycles.[6]

The present work proposes original sequences of carbopalladation of *ortho*-halogenoallenamides completed by intermolecular direct C−H allylation of azoles (see Figure 1), which are important structural motifs found in many pharmaceuticals, agrochemicals, and natural products.[7] This methodology offers an original step-economical and regiocontrolled synthetic pathway to bis-heteroaryl methylenes embedded in various families of 5-, 6-, 7- and 8-membered nitrogen heterocycles, such as indole, isoquinolin(one),

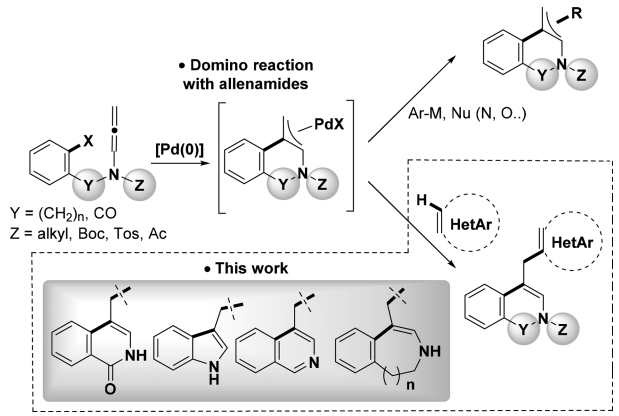


Figure 1. Standard and novel domino reactions with ortho-halogenoallenamides through carbopalladation and interception of π-allyl Pd(II) complexes.

azepine, or azocine, which are known to be key challenging structural motifs with pharmaceutical significance.[8−11] Despite the considerable achievement made in direct C−H (hetero)-arylation, alkenylation, alkynylation, and alkylation of azoles,[12,13] this work proposes original examples of direct C−H allylation of heterocycles based on pioneer developments using allyl phosphates and halides as coupling partners under copper catalysis.[14]

Our initial investigations focused on the Pd-catalyzed domino intramolecular carbopalladation/C−H allylation of 2-phenyl-1,3,4-oxadiazole (**3A**) with *ortho*-halogenoallenamides

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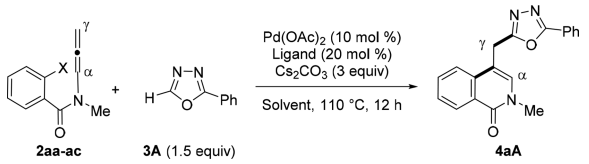
2aa−**2ac**, which were standardly prepared from *ortho*-halogenopropargylbenzamides **1aa**−**1ac** through a basic treatment at room temperature.[2,15] The results are summarized in Table 1. Starting from **2aa** (X = I), the first use of standard

Table 1. Optimization of the Domino Carbopalladation/C−H Allylation Process[a]



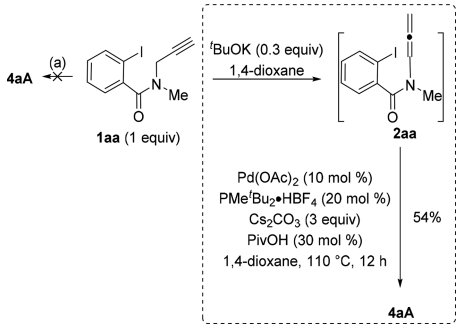
entry	ligand	X	solvent	yield[b] (%)
1	$PCy_3{\cdot}HBF_4$	I	1,4-dioxane	57
2	$PCy_3{\cdot}HBF_4$	I	toluene	51
3	$PCy_3{\cdot}HBF_4$	I	DMAc	32
4	$PMe^tBu_2{\cdot}HBF_4$	I	1,4-dioxane	65
5	$P^tBu_3{\cdot}HBF_4$	I	1,4-dioxane	60
6[c]	$PMe^tBu_2{\cdot}HBF_4$	I	1,4-dioxane	72
7[c]	$PMe^tBu_2{\cdot}HBF_4$	Br	1,4-dioxane	66
8[c]	$PMe^tBu_2{\cdot}HBF_4$	Cl	1,4-dioxane	n.r.

[a]Reaction conditions: **2** (0.435 mmol), **3A** (1.5 equiv), Pd(OAc) (10 mol %), ligand (20 mol %), Cs_2CO_3 (3 equiv), solvent (1 mL), in a sealed tube at 110 °C for 12 h. [b]Yield based on isolated **4aA** after purification by chromatography. [c]0.3 equiv of PivOH was added.

$Pd(OAc)_2$ precatalyst associated with $PCy_3{\cdot}HBF_4$ as a ligand in the presence of 3 equiv of Cs_2CO_3 afforded the heteroarylmethylisoquinolone **4aA** in 57% yield (see Table 1, entry 1). Various bases were tested and turned out to be less efficient.[16] While the reaction was less efficient in more-polar DMAc solvents (32%), a similar performance was obtained in toluene, providing **4aA** in 51% yield (see Table 1, entries 2 and 3). More steric hindered and electron-donor alkyl phosphine ligands, $P^tBu_3{\cdot}HBF_4$ or $PMe^tBu_2{\cdot}HBF_4$, showed superior reactivity, affording **4aA** in better yields, from 60% to 65%, respectively (see Table 1, entries 4 and 5). The beneficial use of PivOH as an additive, which has been previously shown to stabilize the π-allyl Pd(II) complex in transition metal-catalyzed direct allylation,[17] gave the best result, affording **4aA** in 72% yield (see Table 1, entry 6). Under these optimized conditions, we demonstrated that this domino allylation sequence could be successfully performed from the *ortho*-bromoallenamide **2ab**, leading to **4aA** in fair yield (66%) (see Table 1, entry 7). However, no reaction occurred from the *ortho*-chloroallenamide **2ac** (see Table 1, entry 8). Note that only one regioisomer was identified by single-crystal X-ray structure determination; the regioisomer arising from heteroarylation at the α-position of the π−allyl-Pd(II) complex was not observed on the NMR spectrum of the crude reaction. At this stage, we investigated the ability of the propargylamide **1aa** to react with **3A** either by Cs_2CO_3-promoted isomerization, followed by direct C−H allylation reaction,[18] or through intramolecular carbopalladation/exo-dig direct C−H alkenylation, followed by [1,3]-H-shift,[19] to give the desired product **4aA**. In order to preclude both scenarios, a control experiment was performed by reacting the propargylamide **1aa** with **3A** under our optimized conditions (see Scheme 1). However, no annulating product **4aA** was obtained.

With the optimized protocol in hand, the scope of the domino carbopalladation/intermolecular C−H allylation was

Scheme 1. One-Pot Isomerization/Carbopalladation/C−H Allylation



explored from *ortho*-iodoallenamides **2** (see Scheme 2, Method A) using variously substituted 5-arylated 1,3,4-oxadiazoles (**3**) as coupling partners. Overall, the selective capturing of the π-allyl-Pd(II) intermediate with heterocycles was successfully achieved, regardless of the electronic effect or the substitution pattern on the two aromatic units of coupling partners **3** and **2**, affording 4-oxadiazolylmethyl isoquinolones **4aB**−**4aH**, **4bA**, **4cG**, **4dC**, and **4eD** in fair yields. We further examined the selective direct C2−H allylation of various less-acidic 1,3-diazoles (**3I**−**3K**). In this case, replacing 1,4-dioxane by toluene facilitated the coupling with benzoxazole or ethyl oxazole-4-carboxylate to produce the corresponding 4-(benz)-oxazolylmethyl isoquinolinones **4aI** and **4aK**, albeit in low yields. Moreover, the domino coupling of **2aa** was successfully performed with the *tert*-butyl thiazole-4-carboxylate in more-polar solvent (i.e., DMF), leading to the desired thiazolylmethylisoquinolinone **4aJ** in 22% yield. It is also noteworthy that the most acidic pentafluoarene, **3L**, which was previously demonstrated to be suitable for C−H allylation,[20] was successfully employed as a coupling partner in the palladium-catalyzed domino reaction from **2aa** only under CuI assistance, leading to the expected allylated pentafluoroarene **4aL** in good yield (52%). In order to enhance the practical usefulness of our method, we sought to evaluate the possibility of performing a one-pot sequential ^{t}BuOK-catalyzed allenamide generation/Pd-catalyzed domino cross-coupling with **3A** from readily available propargylbenzamides **1** (Scheme 1).

Interestingly, the treatment of *ortho*-iodopropargylbenzamide **1aa** with 30 mol % ^{t}BuOK, for the *in situ* generation of the allenamide **2aa**,[21] followed by the formation of PivOK with the addition of PivOH (0.3 equiv) before the domino C−H coupling, was immediately conclusive. Indeed, this one-pot pathway provided the expected oxadiazolylmethylindole **4aA** in good yield (54%), close to the overall 62% yield previously obtained through the two-step sequential pathway. Based on this result, we decided to evaluate systematically the three-step one-pot sequence, and the results are depicted in Scheme 2 (Method B). Starting from propargylbenzamide **1aa** and using 1,3,4-oxadiazole **3A**−**3H** as coupling partners, a broad set of 4-(1,3,4-oxadiazolyl)methyl isoquinolones **4aB**−**4aH** were successfully produced within the three-step sequential protocol (Method B) in only slightly lower yields than those observed from allenamides **2aa** (Method A). Using the same one-pot procedure, fair yields were also obtained for the synthesis of variously substituted 4-(1,3,4-oxadiazolyl)methyl isoquinolones **4bA**, **4cG**, **4dC**, and **4eD**. In addition, the coupling of less-acidic 1,3-diazoles **3I**−**3K**, as well as the pentafluoroarene **3L**, was successfully performed, leading to the corresponding

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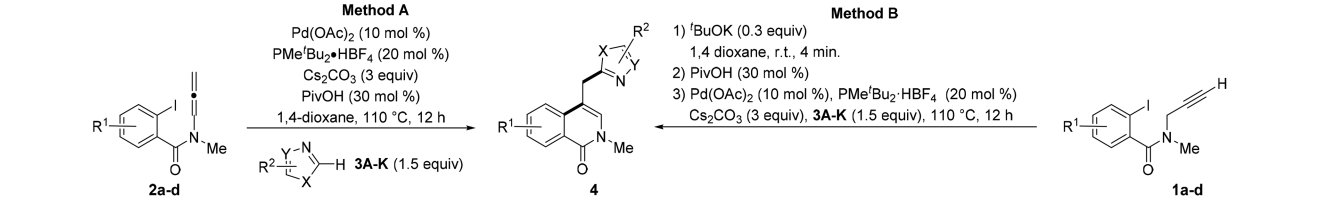
Scheme 2. Synthesis of 1,3-diazolylmethylisoquinolinones 4 by Domino Intermolecular Carbopalladation/C−H Allylation (Method A) or One-Pot Sequential Allenamide Generation/Domino Process (Method B)



	Method A	Method B
4aB, R^2 = 4-MeOC$_6$H$_4$	(46%)	(42%)
4aC, R^2 = 4-MeC$_6$H$_4$	(47%)	(37%)
4aD, R^2 = 2-Naph	(57%)	(53%)
4aE, R^2 = 4-CF$_3$C$_6$H$_4$	(59%)	(54%)
4aF, R^2 = 3,4-diMeOC$_6$H$_3$	(53%)	(50%)
4aG, R^2= (CH$_2$)$_2$Ph	(58%)	(50%)
4aH, R^2 = 2-FC$_6$H$_4$	(51%)	(45%)

	Method A	Method B
4bA, R^1 = 7-Me, R^2 = Ph	(53%)	(50%)
4cG, R^1 = 6,7-diMe, R^2 = (CH$_2$)$_2$Ph	(40%)	(33%)
4dC, R^1 = 7-F, R^2 = 4-MeC$_6$H$_4$	(48%)	(40%)
4eD, R^1 = 6-CF$_3$, R^2 = 2-Naph	(37%)	(32%)

4aI[a]: **Method A** (20%), **Method B** (15%)

4aJ[b]: **Method A** (22%), **Method B** (25%)

4aK[a]: **Method A** (38%), **Method B** (34%)

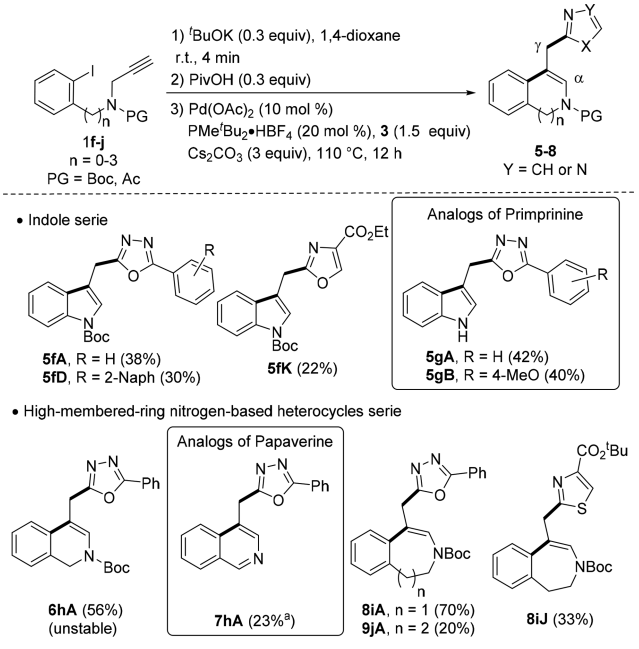
4aL[a, c]: **Method A** (52%), **Method B** (29%)

[a]Toluene was used instead of 1,4-dioxane. [b]DMF was used instead of 1,4-dioxane. [c]CuI (30 mol %) was added.

4-(1,3-diazolyl)methyl isoquinolinones **4aI**−**4aK** and 4-(pentafluoroaryl)methy isoquinolone **4aL** in satisfactory yields.

At this stage, we further investigated the construction/heteroarylation of various families of 5-, 6-, and high-membered nitrogen-containing heterocycles. We first turned our attention to the indole scaffold, a privileged structure occurring in numerous natural products and biologically active molecules designed for agricultural and medicinal applications (see Scheme 3).[9] In particular, we focused our methodology on the synthesis of indolyl[1,3-diazolyl]methylene as the framework of pimprinine that displays antifungal activities.[22] To this end, the one-pot three-step procedure (Method B) was envisaged to avoid purification and stability issues. Interestingly, three *N*-Boc indolyl-1,3-azolylmethyles **5fA**, **5fD**, and **5fK** were successfully prepared from the corresponding *N*-Boc *ortho*-iodopropargylamide **1f** using 1,3,4-oxadiazoles, **3A** and **3D**, and ethyl oxazole-4-carboxylate **3K** as coupling partners in a range of yields of 22%−38% over three steps (see Scheme 3). The heteroarylation was regioselective at the γ-position of the π-allyl-Pd(II) complex. Moreover, two analogues of primprinine **5gA** and **5gB** were obtained from the acetamide **2g** in good yields (40%−42%) within a four-step one-pot process including a spontaneous *N*-deprotection step.

Scheme 3. Scope of the One-Pot *t*BuOK-Mediated Allenamide Generation Followed by Pd-Catalyzed Carbopalladation/Direct C−H Allylation of 1,3-Diazoles



[a]Additional treatment was required using DDQ in MeOH at reflux for 2 h.

Pursuing our investigations into the construction/heteroarylation of isoquinolines, the one-pot three-step sequence was then envisaged with *N*-(2-iodobenzyl)prop-2-yn-1-amine (**2h**) and 5-phenylated 1,3,4-oxadiazole (**3A**) as coupling partners. The expected heteroarylmethyldihydroquinoline (**6hA**) was isolated in 56% yield. However, it turned out to be highly unstable in air, leading to rapid degradation. To circumvent this instability issue, an additional treatment with DDQ[23] as oxidant was included in our one-pot strategy, leading to the 1,3,4-oxadiazolylmethylisoquinolin **7hA** in 23% yield over four steps. This product can be considered as a novel 1,3,4-oxadiazole analogue of papaverine (see Scheme 3).[24] Finally, to further evaluate the scope of the strategy, we turned our attention to the construction/heteroarylation of innovative medium-sized nitrogen heterocycles, which remains currently very sparsely explored. Interestingly, the one-pot strategy developed above was successfully applied for the synthesis of stable heteroarylmethylated dihydro-1*H*-benzo[*d*]azepine **8iA** and **8iJ**, as well as tetrahydro-1*H*-benzo[*d*]azocine **9jA** in a yield range from 20% to 70%, starting with *N*-(3-phenylethyl)-prop-2-yn-1-amine (**1i**) and *N*-(3-phenylpropyl)prop-2-yn-1-amine (**1j**), respectively.

A catalytic cycle based on experimental results and previous reports on cyclocarbopalladation with allenamide is proposed

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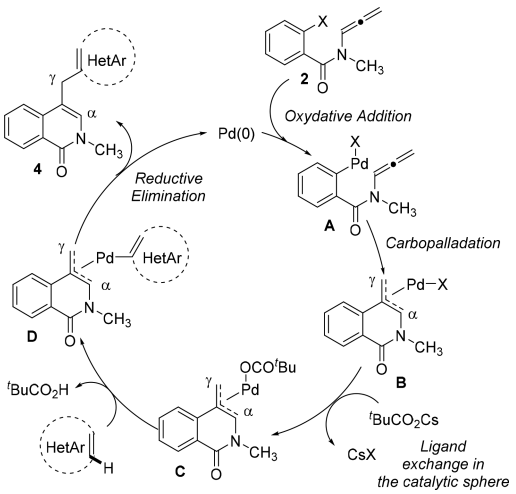
in Scheme 4.[2] Initially, the oxidative addition of allenamide **2** by the ligated Pd(0) species generates the Pd(II) complex **A**.

Scheme 4. Proposed Mechanistic Pathway



The subsequent cyclocarbopalladation step leads to the π-allylpalladium intermediate **B**. The latter then rapidly undergoes an exothermic inner-sphere pivalate-halide exchange,[25,17] leading to the more stable and less electron-rich π-allylpalladium **C**. The next step concerns heterocycle C−H activation by the π-allylpalladium system. In agreement with previous observations, Grigg's group demonstrated that an outer sphere nucleophilic attack is only favored from a halogenated (π-allyl)Pd complex using Ag_2CO_3 as an additive for the generation of a highly electrophilic and cationic (π-allyl)Pd system.[26] In addition, the branched product can be expected under this typical charge-controlled outer-sphere mechanism. In the present case, the employment of pivalate, combined with the PMe^{t}Bu$_2$·HBF$_4$, electron-rich phosphine as ligand significantly decreases the positive charge of the (π-allyl)Pd complex **C**. As an additional experiment, the reaction was found to be fully inhibited in the presence of the Ag_2CO_3 additive with or without Cs_2CO_3.[16] Thus, an S_N2-type attack of a C2-metalated heterocycle on the (π-allyl)Pd complex C is precluded in favor of inner-sphere based-mediated concerted or carbanionic-type metalation deprotonation of 1,3-diazoles.[12e,25b,27] It proceeds by generating a second heteroaryl (π-allyl)Pd complex (**D**), which delivers the expected product through a final reductive elimination step while regenerating the Pd(0) catalyst.

In summary, we have first reported an original Pd-catalyzed domino carbopalladation of allenamides/direct C−H allylation of (oxa)diazoles. Simultaneously, a one-pot strategy over three steps, including the in situ generation of allenamide in the domino process, was also developed to avoid allenamide stability issues. The two approaches were first validated and then applied to the design of a novel library of 3-heteroarylmethylisoquinolinones, which is a key structural motif with potential pharmaceutical significance. This methodology was then successfully expanded to the construction/heteroarylation of indole, dihydroquinoline, and isoquinoline, as well as original medium-sized nitrogen heterocycles, 7- and 8-membered azepine and azocine derivatives. As an application, three structural analogues of papaverin and pimprinine were prepared. Therefore, this construction/heteroarylation methodology involving the consecutive formation of C(sp^2)−C(sp^2) and C(sp^3)−C(sp^2) bonds through trapping a σ-allyl-Pd(II) intermediate with (oxa)diazoles constitutes a straightforward and general route to prepare a great variety of bis-heteroarylmethyle frameworks.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02365.

Experimental procedures, characterization data of new compounds, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 1822929 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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