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Expedient Access to 2-Benzazepines by Palladium-Catalyzed C−H activation: Identification of a Unique HSP90 Inhibitor Scaffold

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Abstract: Bioactive 2-benzazepines were accessed in an atom- and step-economical manner by a versatile palladium-catalyzed C−H activation strategy. The C−H arylation featured low catalyst loading and a mild base being reflected by ample scope and high functional group tolerance. Thereby, the benzotriazolodiazepinones were identified as novel HSP90 inhibitor lead compounds, with considerable potential for anti-cancer applications.

Benzazepines, represent key structural motifs of complex naturally occurring molecules of relevant to material sciences and medicinal chemistry (Figure 1a).[1] Indeed, particularly the heterocycle fused 2-benzazepine displays unique biological and pharmacological features, such as inhibition of PI3-kinase, hepatitis C Virus NS5B RNA polymerase, modulation of γ-secretase activity and potential HSP90 inhibition (figure 1b).[2]

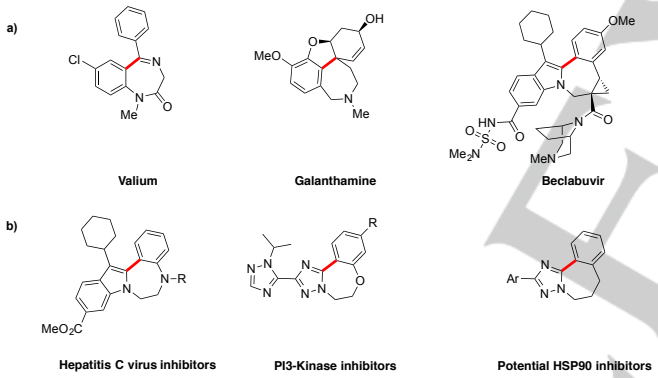

Figure 1. Examples of biologically active 2-benzazepines in nature and pharmaceuticals.

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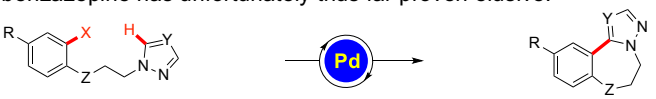
The latter activity is remarkable in light of the key role played by HSP90 client proteins in oncogenic signaling, and in establishing the hallmark traits of malignancy, including proliferation, evasion of apoptosis, immortalization, invasion, angiogenesis and metastasis.[3] Targeting Hsp90 by designed low-molecular weight compounds, constitutes an exciting therapeutic approach and, at the same time, provides access to possible targets, such as specific Hsp90 co-chaperones.[4]

Within our program on sustainable palladium-catalyzed C−H activations,[5] and based on detailed molecular modeling evaluation of literature reported HSP90 inhibitors specifically aimed to uncovering HSP90 inhibitors endowed with a new chemical framework, we identified heterocyclic fused 2-benzazepine derivatives as particularly powerful lead compounds.[6]Thus, we herein report on our recent findings on the step-economical synthesis of multi-annulated rings via a flexible C–H activation strategy affording a new lead compound with a HSP90 nano-molar (nM) inhibition activity.[7] We initiated our studies by exploring approaches towards a general strategy for the preparation of a variety of 2-benzazepines featuring ample chemical diversity. However, despite major advances, classical approaches to access these heterocyclic fused 2-benzazepine derivatives require tedious multi-step sequence largely involving conventional condensation-based and enzymatic strategies.[8] Furthermore, metal-catalyzed cross-coupling strategies have been devised for the construction of N-fused heterocycles. However, despite indisputable progress these cross-couplings require two prefunctionalized starting materials, leading to stoichiometric amounts of undesired byproducts.[9] Moreover, these approaches continue to be limited to specific indoles, pyrroles and arenes, while a flexible strategy for the construction of chemical diverse heterocycles fused 2-benzazepine has unfortunately thus far proven elusive.[10]



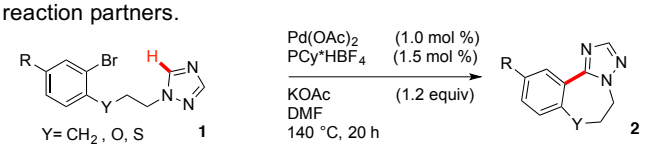
X = Br, Cl
Y = N, CH
Z = CH_2, C=O, O, S

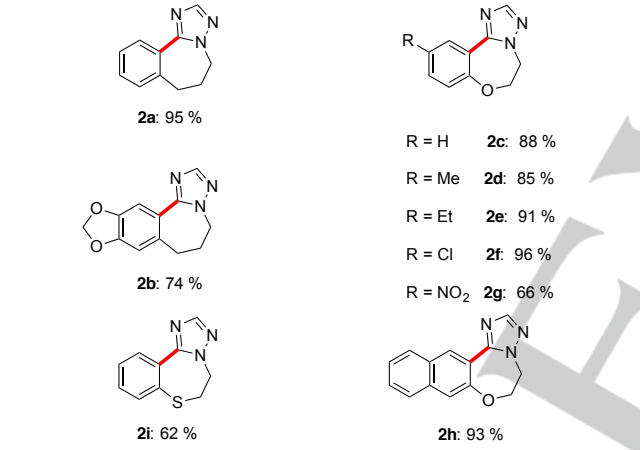
Figure 2. Palladium-Catalyzed C–H arylation towards bioactive azepines.

Our modular strategy for the atom- and step-economical approach for the synthesis of seven-membered azepines derivatives is depicted in Figure 2. Hence, our C−H arylation approach exhibited ample scope and flexibility as to N-heterocycles, functional groups and spacer between the two aromatic moieties. Heteroatoms and carbonyl groups in the side

chains, halogen substituted aromatic rings and a variety of heterocycles were well tolerated.

We commenced our studies by exploring various ligands, bases and solvents for the envisioned C−H arylation of 1,2,4-triazole 1a with $Pd(OAc)_2$ as the catalyst. Ultimately ligand and other parameters (See Supporting Information) established that catalytic $Pd(OAc)_2$ in the presence of PCy_3·HBF_4, using DMF as solvent, was effective for the formation of the new C-C bond leading to compound **2a** in 95 % yield (Scheme 1). It is important to note that the amount of the catalyst could be reduced to only 1 mol % with a mild base, while the C−H arylation occurred with a comparable yield on gram scale. With the optimized conditions for the C−H arylation in hand, we extended the scope of the C−H activation by varying the substituents on the aryl motif and inducing various heteroatoms in the spacer between the two reaction partners.

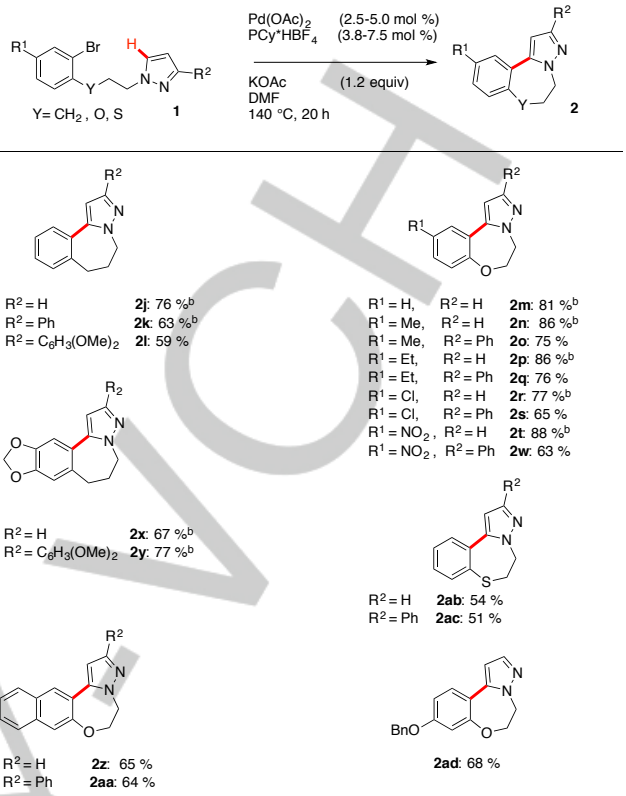




[a] Reactions conditions: **1** (0.5 mmol), $Pd(OAc)_2$ (1.0 mo l%), PCy_3·HBF_4 (1.5 mol %), KOAc (0.6 mmol, 1.2 equiv) in DMF (0.07 M, 7.1 mL) at 140 °C for 20 h.

Scheme 1. Substrate scope for the 1,2,4-triazole intramolecular C−H activation[a].

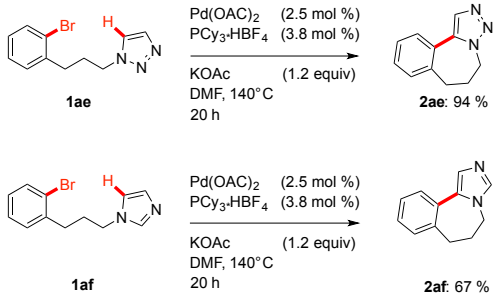
A wide range of spacer-motifs could be employed in the C−H arylation. In particular, the chain containing the sulfur atom is fascinating because it gave access to different class of thiazepine in an innovative fashion. Importantly, the C−H arylation smoothly proceeded with various substituents on both aryl moieties and the nitrogen-containing heterocycle. The versatile catalyst thus proved tolerant of valuable electrophilic functional groups, such as the chloro and nitro substituent. Subsequently, we explored the robustness of our optimized catalyst by testing various pyrazole heterocycles (Scheme 2).



[a] Reactions conditions: **1** (0.5 mmol), $Pd(OAc)_2$ (5.0 mol %), PCy_3·HBF_4 (7.5 mol %), KOAc (0.6 mmol, 1.2 equiv) in DMF (0.07 M, 7.1 mL) at 140 °C for 20 h.[b] $Pd(OAc)_2$ (2.5 mol %) and PCy_3·HBF_4 (3.8 mol %)

Scheme 2. Substrate scope for the pyrazole intramolecular C−H activation[a].

Furthermore, the broadly applicable palladium catalyst enabled the efficient C−H activation on other nitrogen heterocycles likewise, including imidazole **1ae** and 1,2,3-triazole **1af** (Scheme 3).



Scheme 3. Other nitrogen heterocycles.

To our delight, under otherwise identical reaction conditions the palladium catalyst provided versatile access to diversely decorated benzodiazepine **3**, starting from easily accessible 2-bromoanilines (Scheme 4).

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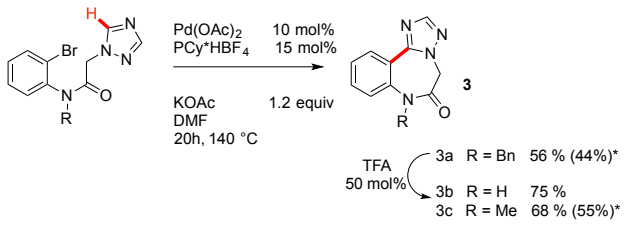


*Reaction performed using 5 mol% of $Pd(OAc)_2$ and 7.5 mol% of PCy_3-HBF_4

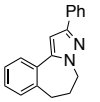
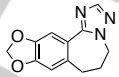
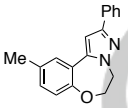
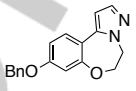
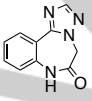
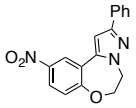
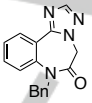
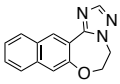
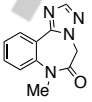
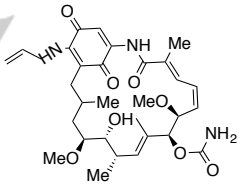
Scheme 4. Synthesis of benzodiazepines.

In order to exploit the biological activity of the new benzazepines **3a**, **3b** and **3c**, various biological tests were carried out. First, in light of the chemical similarity,[2a] we explored their inhibitory potential against PI3-β kinase without any positive results. Thus, we were delighted to find that the newly synthesized compounds showed considerable binding to recombinant human Hsp90α protein in a surface plasmon resonance (SPR) assay in which 17-AAG was used as a positive control.[11] Analysis of the SPR sensorgrams indicated that the six compounds **2b**, **2h**, **2o**, **2k**, **2ae** and **3a** interacted with the protein in the μM range (Table 1). Compounds **2k** and especially secondary amide **3b** were shown to display a high affinity towards the chaperone, as reflected by the measured K_D values in the nM range. Thus, 5*H*-benzo-triazolodiazepinone **3b** exhibited an affinity that was even higher than the one of NVP-AUY922, one of the most active reference compounds.[12]

In order to gain detailed insights and rationalize the role of the different functionalities for the ligand affinities at the receptor, we selected a subset of molecules having the same scaffold of the most active compound, which interestingly showed a wider range of K_D, for structural studies. In particular, we focused on molecules **3b, 2i, 3a, 3c, 2b** and **2h** to model the possible binding modes with Hsp90. Docking calculations were performed in the nucleotide binding pocket of the N-terminal domain of human-Hsp90. The crystal structure of the receptor was obtained from the RCSB Protein Data Bank (PDB), PDB code 2CCS (resolution 1.79 Å), where the *N*-terminal domain of Hsp90 was co-crystalized with a piperazine-containing compound. We first set up a docking procedure that was able to reproduce the binding pose of this crystal structure (see Docking section in Supporting Information, Figure S-1) and then we used the same protocol for modelling the binding of molecules **3b**, **2i**, **3a**, **3c**, **2b** and **2h** in the ATP binding site of Hsp90, the molecular interaction of which is highlighted in Figure S-2.

Hence, a magnesium ion is coordinated by oxygen atoms of the α-, β-, and γ-phosphate groups, the side chain of ASN51 and two water molecules. The most active compound **3b** showed five possible binding poses within 3 kcal/mol from the lowest energy mode. The lowest energy binding pose is also the most represented among the 20 poses that were retained at the end of the docking run. Docking calculations of stage (4) described in the Material and Methods section were performed using two different methodologies, SP and XP. XP does more extensive sampling than SP and it uses a more sophisticated scoring function, with stricter requirements for ligand-receptor shape complementarity.

Table 1. Pseudo-thermodynamic dissociation constants measured by SPR.

	Compound	K_D (μM)		Compound	K_D (μM)
2k		0.105 ± 0.012	**2b**		4.48 ± 5
2o		5.71 ± 0.77	**2ad**		0.63 ± 0.16
2i		15 ± 0.2	**2af**		10.2 ± 2.3
3b		0.005 ± 0.026	**2w**		1.96 ± 2.1
3a		15 ± 0.7	**2h**		3.59 ± 1.4
3c		13.2 ± 1.6	**2ae**		3.57 ± 1.4
				**17-AAG**	
				Ref compound	
				K_D (μM) 0.330 ± 0.27	

The XP run confirmed that the most represented binding pose corresponds to the most represented one observed in the SP run. In this binding pose compound **3b** establishes a network of HB interactions with the critical residue ASP93 and residues ASN51 and THR184 (Figure 3) and accommodates its benzene ring in a hydrophobic pocket defined by LEU107, PHE138, VAL150, VAL186 (pocket A).

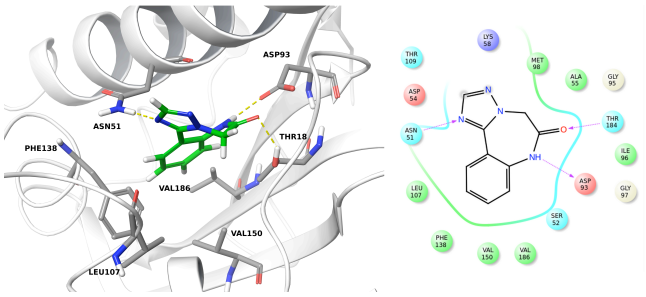


Figure 3. 3D and 2D best binding pose of compound 3b (green) in complex with NTD of Hsp90. In the 2D representation, amino acids are colored according to hydrophobicity, charge, and polarity (Gray- GLY, dark green- hydrophobic, cyan- polar uncharged, blue – positives, red – negatives). Yellow dashed lines represent H-bond interactions.

In the most represented binding pose, compound **2i** overlaps almost perfectly with compound **3b**. The N2 and N4 atoms of the triazole ring are able to establish HB interactions with LYS58 and ASN51, and the benzene ring accommodates in hydrophobic pocket A as observed for compound **3b**, however compound **2i** lacks of the possibility of establishing any interactions with ASP93 and THR184 (Figure S-4). The binding pose of compound **3a** is slightly different compared to the binding mode of compound **3b**. In particular, compound **3a** is rotated in the binding site so that the carboxyl group in the azepine ring still engages in HB to THR184, but the benzyl group accommodates more deeply in the hydrophobic pocket compared to the benzene ring of compound **3b**. The N2 and N4 atoms of the triazole ring can establish HB interactions with LYS58 and GLY97 (Figure S-5). Compound **3c** shows a very similar binding mode to compound **3a**. The N2 atom of the triazole ring can establish a HB interaction with LYS58, while the carbonyl group of the azepine ring can bind residue THR184. The entire scaffold is slightly shifted in respect to compound **3a**, and this shift orients the methyl group in the azepine ring towards the hydrophobic pocket A. However, this group cannot accommodate inside pocket A, unlike the long benzyl group of compound **3a** (see Figure S-6). Compound **2h** flips the triazole ring which engages a HB interaction with THR184 and improves the hydrophobic interaction with pocket A through its benzene rings; moreover, one of the benzene rings can reach residue PHE138, with whom it establishes a π,π-stacking interaction (see Figure S-7). Compound **2b** still establishes a HB interaction with THR184 with the triazole ring, while it points the azepine ring toward the hydrophobic pocket A and it rotates the order to orient the dioxolane ring into a polar cavity (see Figure S-8). From this analysis the interactions that appear to foster binding are the H bonds with ASP93 and THR184 (see the comparison between **2i** and **2b**).

In summary, we have reported on an unprecedented palladium-catalyzed C−H activation strategy to provide step-economical access to a heterocyclic fused 2-benzazepine. The C−H arylation strategy is characterized by low catalyst loading, a mild base and ample substrate scope towards various azepines, benzoxazepines, thiazepines, and even benzodiazepines. In contrast to cross-coupling-based strategies, our approach involves the direct activation of otherwise inert C−H bonds without the need for tedious prefunctionalizations. The identified compounds are low molecular weight inhibitors of HSP90 featuring a novel, and so far underappreciated, scaffold. Our computational studies provide a model that not only rationalizes the distinct activities of the various compounds, but provides novel guidance for structural modifications aimed to further lead development.

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Keywords: C-H arylation • HSP90 • Inhibitors • benzazepines • docking analysis.

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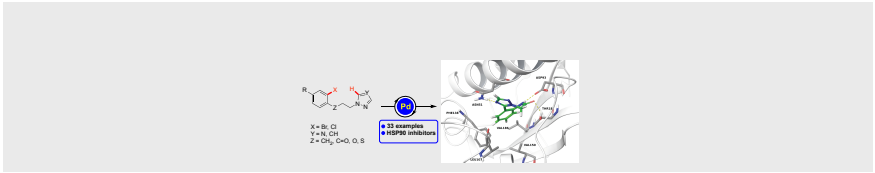

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Expedient Access to 2-Benzazepines by Palladium-Catalyzed C−H activation: Identification of a Unique HSP90 Inhibitor Scaffold

Bioactive 2-benzazepines were accessed in an atom- and step-economical manner by a versatile palladium-catalyzed C−H activation strategy. The C−H arylation featured low catalyst loading and a mild base being reflected by ample scope and high functional group tolerance. Thereby, one of our benzotriazolodiazepinones was identified as novel HSP90 nanomolar inhibitor, with considerable potential for future anti-cancer applications.