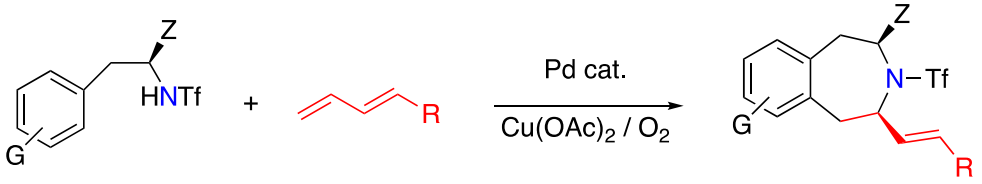
Palladium-Catalyzed [5+2] Heteroannulation of Phenethylamides with 1,3-Dienes to Dopaminergic 3-Benzazepines

Álvaro Velasco-Rubio, Jesús A. Varela and Carlos Saá*

Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CiQUS), Departamento de Química Orgánica, Universidade de Santiago de Compostela, 15782 Santiago de Compostela, Spain

KEYWORDS. C-H Activation, Benzazepines, 1,3-Dienes, Heteroannulation, Palladium catalysts



ABSTRACT: Phenethyltriflamides react with 1,3-dienes upon treatment with a catalytic amount of $Pd(OAc)_2$ and $Cu(OAc)_2/O_2$ as oxidant to afford chemo-, regio- and diastereoselectively 2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepines (3-benzazepine derivatives) in good to excellent yields. A DFT study of the [5+2] heteroannulation suggests a mechanistic pathway starting by the formation of the six-membered palladacycle *cis*-PdX_2L_2 via a CMD process followed by η^2 coordination and insertion of the 1,3-diene unit in a diastereoselective manner.

3-Benzazepines, benzofused seven-membered azaheterocycles, are privileged structures present in a large variety of natural products and important pharmaceuticals.[1] These compounds are among the most reliable structures in terms of affinity and selectivity for dopamine D_1 receptors,[2] that regulate neuronal growth and development and mediate/modulate other behavioral events. As CNS drugs, dopaminergic 3-benzazepines possess selective D_1 agonist or antagonist properties that led to useful pharmaceuticals against Parkinson's disease,[3] leukemia,[4] cocaine addiction[5] or obesity[6] (Figure 1).

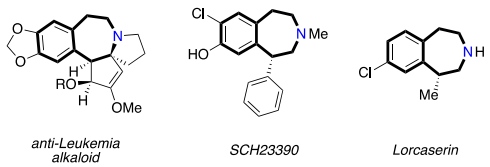
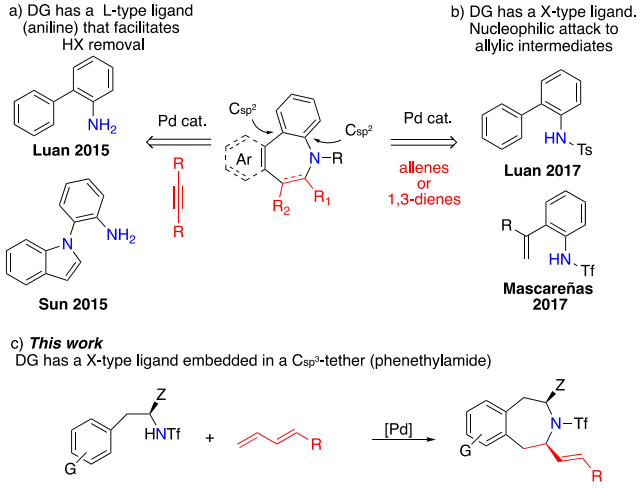


Figure 1. Biologically active 3-benzazepines

The remarkable biological activity of the 3-benzazepines has stimulated a great variety of synthetic approaches throughout the years. The standard strategies to access to these seven-membered azaheterocycles are based on intramolecular processes such as polar cyclizations,[7] Friedel-Crafts cyclizations,[8] oxidative C-H functionalization-ring expansions,[9] metal catalyzed Heck cyclizations[10] or intramolecular hydroamin(d)ations.[11] Although each one could be considered relatively useful, indeed, they are very strong substrate dependent requiring multistep synthesis of starting materials, which somehow limit the scope of the reactions. On the other hand, an elegant intermolecular approach based on Rh-catalyzed cascade reactions of *N*-bridged yne-enoates has been recently developed.[12]

Intermolecular processes like oxidative cycloadditions based on metal-catalyzed C-H activations have recently emerged as a key step to build-up medium sized heterocycles in a more sustainable manner.[13] In the case of [5+2] oxidative cycloadditions of phenethylamin(d)es to give 3-benzazepine derivatives, the nature of the directing group and the rigidity of the structure play an important role in order to achieve high selectivity during the C-H activation (Scheme 1). In fact, only examples with substrates bearing all carbon Csp^2 in its phenethylamin(d)e moiety or with an embedded nitrogen to facilitate a certain Thorpe-Ingold effect have been described.[14]

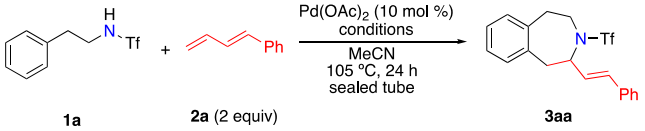
Scheme 1. Metal-catalyzed [5+2] oxidative cycloadditions to 3-benzazepine cores



Pd(II) complexes are well known to form palladacycle derivatives by Csp^2-H activation reactions in phenethylamine derivatives.[15] In 2015 Luan[16] and Sun[17] reported the first Pd-catalyzed [5+2] oxidative cycloadditions of arylanilines and indolo-anilines with alkynes to benzazepines (Scheme 1, eq a).[18] In both cases the directing group is an aniline, a L-type ligand, that possess the correct rigidity (biaryl-type) to facilitate the C-H bond activation, the insertion of the alkyne into the corresponding metallacycle and also the final reductive elimination step via removal of HX.[19] In the case of X-type anilide ligands as directing groups, Luan[20] and Mascareñas[21] reported the Pd-catalyzed [5+2] oxidative cycloaddition with 1,3-dienes and allenes, respectively (Scheme 1, eq b). In both cases the nature of the directing group and, therefore, the rigidity of the corresponding metallacycle did not allow the insertion of alkynes, however, 1,3-dienes[22] or allenes[14] could be inserted to form more stable allylic intermediates. We herein report that phenethyltriflamides (X-type ligands), with a non-rigid Csp^3 tether between the two reacting centers, efficiently undergo chemo-, regio- and diastereoselective Pd-catalyzed [5+2] heteroannulations with 1,3-dienes to afford bioactive 2-alkenyl-3-benzazepines (Scheme 1, eq c) in good to excellent yields.[15b] The best conditions found for the catalytic cycle involve the combination of $Cu(OAc)_2$ and O_2 as oxidant system.

Initially, we began our investigation by examining the intermolecular Pd-catalyzed [5+2] cycloaddition between phenethyl *N*-triflamide **1a** and (*E*)-buta-1,3-dien-1-ylbenzene (**2a**) as model partners (Table 1). Under classical palladium/benzoquinone oxidative combinations or using other oxidants such as PIFA or PIDA the cycloaddition failed (entry 1 and Supp Info).[23] Pleasingly, the use of 2 equiv of $Cu(OAc)_2{\cdot}H_2O$ as oxidant allowed the isolation of 3-benzazepine **3a** albeit in low yield (entry 2).[21] It could be increased up to 50% using the same oxidant in the presence of 10 equiv of strong coordinating solvents such as DMF or DMSO (entry 3). These solvents might help to reoxidize Pd(0) to Pd(II) and, therefore, restart the catalytic cycle avoiding the polymerization of Pd(0) to ineffective dark palladium.[24] Interestingly, the amount of base and oxidant could be reduced when the solution was saturated in air keeping a moderate 40% yield (entry 4) and, to our delight, with only 0.5 equiv of $Cu(OAc)_2{\cdot}H_2O$ and 0.1 equiv of Et_3N in CH_3CN saturated with O_2 (to facilitate a better reoxidation system) gave an excellent yield of **3a** (entry 5).[25]

Table 1. Optimization of reaction conditions[a]



entry[a]	conditions	yield (%) [b]
1	BQ (2 equiv), Et_3N (2 equiv)	-
2	$Cu(OAc)_2{\cdot}H_2O$ (2 equiv), Et_3N (2 equiv)	35
3	$Cu(OAc)_2{\cdot}H_2O$ (2 equiv), Et_3N (2 equiv), DMF (10 equiv)	50
4[c]	$Cu(OAc)_2{\cdot}H_2O$ (0.5 equiv), Et_3N (0.1 equiv), DMF (10 equiv), Air	40
5[d]	$Cu(OAc)_2{\cdot}H_2O$ (0.5 equiv), Et_3N (0.1 equiv), DMF (10 equiv), O_2	95

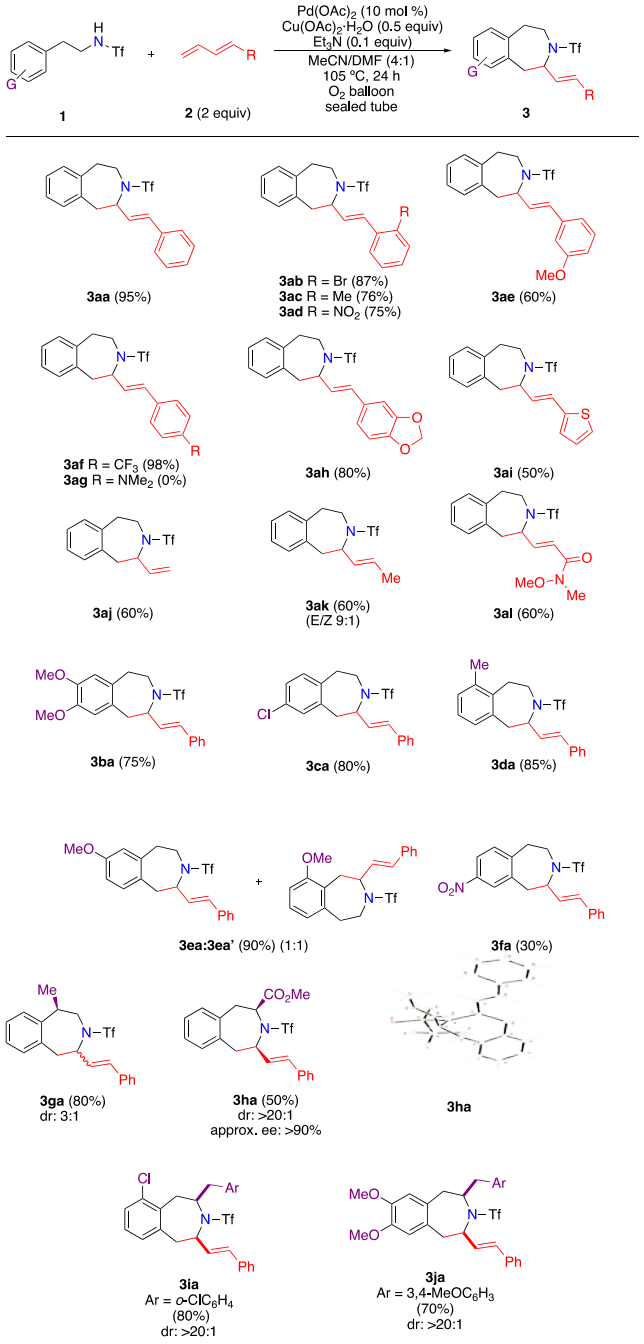
[a] Typical conditions: **1a** (0.2 mmol, 1 equiv), **2a** (0.4 mmol, 2 equiv), 0.5 mL MeCN. [b] Internal standard 3,5-dinitro methylbenzoate. [c] The solution was bubbled with an air balloon for 10 min. [d] The solution was bubbled with an O_2 balloon for 10 min.

Having established optimal conditions, we next investigated the scope of the two reaction partners. Using phenethyltriflamide **1a** as a standard substrate, the scope of 1-aryl-1,3-dienes **2** was explored and found to be very broad, encompassing a wide range of electron-rich, electron-poor and heteroaroamatic 1,3-dienes in any position. In the case of electron-poor aryl dienes, *ortho*-bromo (**2b**), *ortho*-nitro (**2d**) and *para*-trifluoromethyl (**2f**) substituents worked very well. In the case of electron-rich aryl dienes, *ortho*-methyl (**2c**), *meta*-methoxy (**2e**) and the heteroaromatic *para*-thiophenyl (**2i**) substituents worked relatively well, but a *para*-dimethylamino substituted aryl diene (**2g**) failed to react due to extensive polymerization. Electron-rich *meta*-and *para* disubstituted aryl diene **2h** gave also fairly good yields. Either simple non-substituted 1,3-butadiene **2j** and alkyl substituted penta-1,3-diene **2k** (as a 1:1 mixture of isomers) worked in relatively good yields. The 3-benzazepine **3ak** was obtained as a 9:1 mixture of *E*/*Z* isomers, which confirms the regio- and chemoselectivity of the reaction giving the more stable alkenyl-substituted product as the major one. Interestingly, functionalized dienamide **2l** gave the corresponding 3-benzazepine **3al** in a fair good yield, that foresees interesting derivatization of the installed Weinreb amide. Unfortunately, 2-susbtituted 1,3-dienes (e.g. isoprene), and 1,2- or 1,4-disubstituted dienes failed to react like happened in other cycloadditions.[26,22]

Electronic effects of the ring substituents in phenethyltriflamide **1** were then analyzed in the reaction with diene **2a** and were found to be similarly broad in terms of electron-withdrawing and electron-donating capability in any position (**3ba-3fa**). When *p*-OMe phenethyltriflamide **1e** was used, a 1:1 mixture of 3-benzazepines **3ea** and **3ea'** was obtained. The strongly polarized *p*-NO_2 substituent is poorly tolerated in the reaction giving rise to the corresponding 3-benzazepine **3fa** in a low 30% yield. Substitution on the tether alkyl chain was then pursued, which allowed us to analyze the diastereoselectivity of the reaction. Thus, the β–substituted phenethyltriflamide **1g** gave rise to **3ga** in a good 80% yield as a 3:1 mixture of diastereomers. To our delight, the α-substituted *L*-phenylalaninate **1h**, with a substituent closer to the coordinating nitrogen atom, reacted smoothly with the diene **2a** to afford **3ha** (50% yield) as a

single diastereoisomer without racemization as confirmed by NMR experiments and X-Ray crystallography.[27] Interestingly, both substitutions in the alkyl chain and the aromatic ring are well-tolerated giving **3ia** (80%) and **3ja** (70%) as single diastereoisomers.

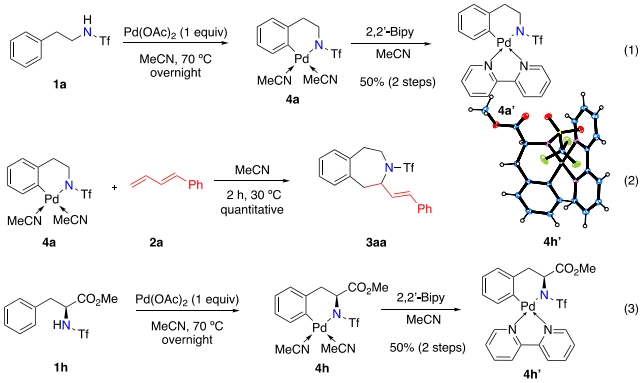
Scheme 2. Scope of the reaction



Reaction conditions: **1** (0.2 mmol, 1 equiv), **2** (0.4 mmol, 2 equiv), 0.5 mL MeCN/DMF (4:1). ORTEP drawing of **3ha** showing ellipsoids at the 30% contour probability level.

In an effort to gain an insight into the reaction mechanism, several stoichiometric experiments to form the cyclometallated palladium *cis*-PdX_2L_2 complexes were conducted.[28] The six-membered cyclometallated Pd(II) complex **4a** was formed by heating **1a** with 1 equiv of $Pd(OAc)_2$ in MeCN for 12 h that could be characterized by ^{1}H-NMR (Scheme 3, eq 1). Gratifyingly, X-ray structural characterization was possible when complex **4a** was stirred in the presence of 2,2'-bipy ligand to give **4a'** as off-white crystals.[27] Furthermore, **4a** reacts with 1 equiv of **2a** to give 3-benzazepine **3aa** in quantitative yield after heating at 30 °C for 2 hours (Scheme 3, eq 2).[29] To gain further information about the diastereoselectivity, the palladacycle **4h'** was also isolated and crystallized as off-white crystals (Scheme 3, eq 3).[27]

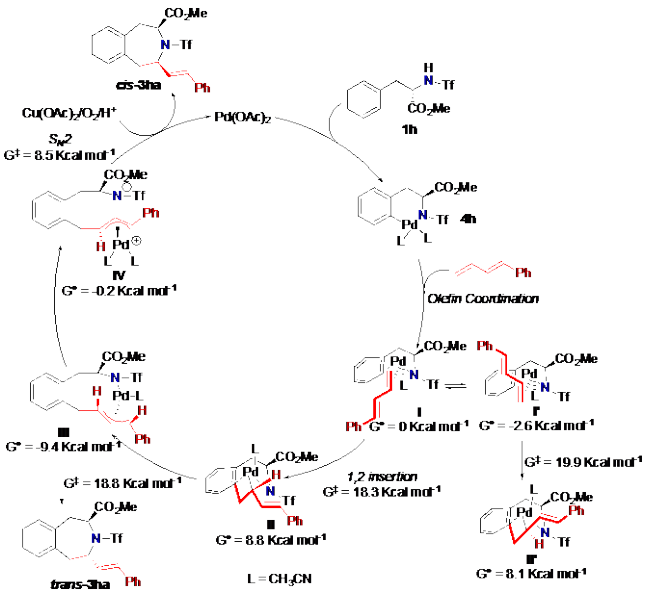
Scheme 3. Isolation of palladacycles and mechanistic experiments



ORTEP drawing of **4h'** showing ellipsoids at the 30% contour probability level.

Diastereoselectivity of the reaction was then analyzed by DFT calculations starting from complex **4h** (Scheme 4).[30] Four possible perpendicular η^2-coordination modes of the less substituted olefin of the 1,3-diene to the palladacycle plane could be considered (substituent left/right and up/down).[31] It was only possible to find the transition states for the 1,2-migratory insertion of the two shown, **I** (left-down)[32] and **I'** (left-up).[33] Even though **I'** is more stable than **I** (ΔG° = 2.6 Kcal mol^{-1}), 1,2- migratory insertion of the coordinated double bond of the diene into the C-Pd bond from **I** to afford the seven-membered palladacycle **II** resulted kinetically more favorable than the same elemental step to afford **II'** from **I'** ($\Delta\Delta G^\ddagger$ = 1.6 Kcal mol^{-1}). Note that a direct route involving a conformational change from **II** to the more stable π-allyl complex **III** followed by reductive elimination affords the *trans*-3-benzazepine ***trans*-3ha** through a high energetic barrier $\Delta G^\ddagger$ = 28.2 Kcal mol^{-1} (this diastereomer was not observed experimentally). However, decoordination of the nitrogen from **III** to a zwitterionic species **IV** followed by a favorable S_N2-type reaction affords the observed *cis* 3-benzazepine ***cis*-3ha** with a relative low barrier ($\Delta G^\ddagger$ = 8.7 Kcal mol^{-1}).[34] Final Pd reoxidation of Pd(0) to Pd(II) would regenerate the catalytic species.

Scheme 4. Proposed catalytic cycle and DFT calculations



In conclusion, an efficient chemo-, regio- and diastereoselective Pd-catalyzed reaction has been developed to obtain highly valuable 2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepines. The use of O_2 as co-oxidant allowed to decrease the amount of oxidant, leading to [5+2] oxidative cycloadditions in good to excellent yields. Stoichiometric experiments allowed the isolation of *cis*-PdX_2L_2 complexes as key intermediates. DFT calculations support both the proposed reaction mechanism and the diastereoselectivity.

ASSOCIATED CONTENT

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AUTHOR INFORMATION

Corresponding Author

*carlos.saa@usc.es

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Dedicated to the memory of our colleague and friend Prof. Kilian Muñiz.

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(26) See Supporting Information for unsuccessful substrates of the Pd-catalyzed [5+2] cycloaddition

(27) Deposition Numbers CCDC 1985306, 1985307 and 1985308 contain the supplementary crystallographic data for the compounds **3ha**, **4a'** and **4h'**, respectively. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

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(29) So far attempts to remove Tf group were unsuccessful. See Supporting Information for details

(30) See Supporting Information for computational details.

(31) For the sake of simplicity, the six-membered palladacycle has been considered plane although its two boat-like conformers have been computed. See Supporting Information for details

(32) We have not observed any coordinating effect by the -CO_2Me group and, therefore, we assume that the steric effect is predominant to locate it at the more stable equatorial position, as shown in X-Ray structure **4h'** and calculated structure **I**, that dictates the regioselectivity found.

(33) The η^4-s-cis coordination mode of the 1,3-diene to the palladacycle was also considered but lead to the corresponding intermediates through higher energy transition states. See Supporting Information for details.

(34) See Supporting Information for the energetic profiles for the reductive elimination and S_N2-type reaction of all the other analyzed isomers.