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

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c01053 Read Online

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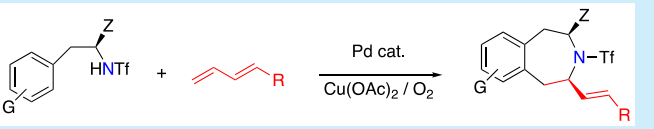
ABSTRACT: Phenethyltriflamides react with 1,3-dienes upon treatment with a catalytic amount of $Pd(OAc)_2$ and $Cu(OAc)_2/O_2$ as oxidant to afford chemo-, regio- and diastereoselectively 2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepines (3-benzazepine derivatives) in good to excellent yields. A DFT study of the [5 + 2] heteroannulation suggests a mechanistic pathway starting with 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, benzo-fused 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).

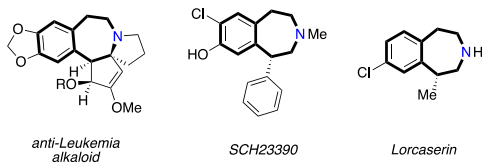
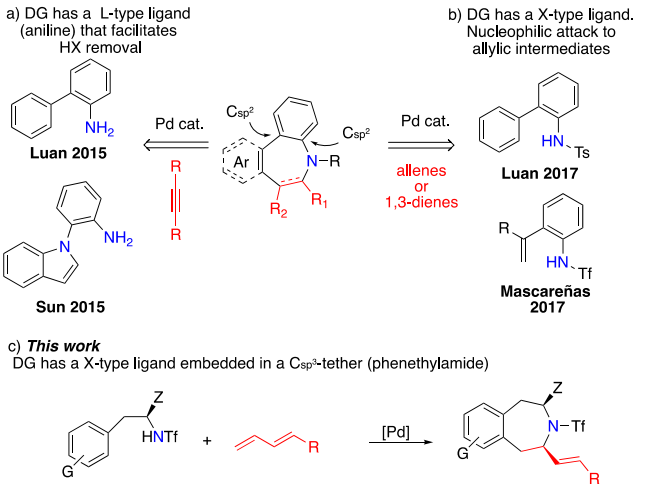


Figure 1. Biologically active 3-benzazepines.

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 strongly substrate dependent requiring a multistep synthesis of starting materials, which somehow limits 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



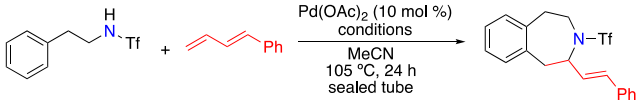
Received: March 23, 2020

https://dx.doi.org/10.1021/acs.orglett.0c01053
Org. Lett. XXXX, XXX, XXX–XXX

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 nonrigid 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/

Table 1. Optimization of Reaction Conditions[a]



1a **2a** (2 equiv) **3aa**

entry[a]	conditions	yield[b] (%)
1	BQ (2 equiv), Et_3N (2 equiv)	
2	$Cu(OAc)_2·H_2O$ (2 equiv), Et_3N (2 equiv)	35
3	$Cu(OAc)_2·H_2O$ (2 equiv), Et_3N (2 equiv), DMF (10 equiv)	50
4[c]	$Cu(OAc)_2·H_2O$ (0.5 equiv), Et_3N (0.1 equiv), DMF (10 equiv), air	40
5[d]	$Cu(OAc)_2·H_2O$ (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 of MeCN. [b]Internal standard 3,5-dinitromethylbenzoate. [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.

benzoquinone oxidative combinations or using other oxidants such as PIFA or PIDA the cycloaddition failed (entry 1 and Supporting Information).[23] Pleasingly, the use of 2 equiv of $Cu(OAc)_2·H_2O$ as oxidant allowed the isolation of 3-benzazepine **3aa** 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 $Cu(OAc)_2·H_2O$ 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 **3aa** (entry 5).[25]

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 heteroaromatic 1,3-dienes in any position. In the case of electron-poor aryl dienes, *o*-bromo (**2b**), *o*-nitro (**2d**), and *p*-trifluoromethyl (**2f**) substituents worked very well. In the case of electron-rich aryl dienes, *o*-methyl (**2c**), *m*-methoxy (**2e**), and heteroaromatic *p*-thiophene-yl (**2i**) substituents worked relatively well, but a *p*-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 nonsubstituted 1,3-butadiene **2j** or 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 fairly 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 as 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**) (Scheme 2). 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. Interestingly, both substitutions in the alkyl chain and the aromatic ring are well-tolerated, giving **3ia** (80%) and **3ja** (70%) as single diastereoisomers.

In an effort to gain an insight into the reaction mechanism, several stoichiometric experiments to form the cyclometalated palladium *cis*-PdX_2L_2 complexes were conducted.[27] The six-membered cyclometalated 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 ^1H 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. Furthermore, **4a** reacts with 1 equiv of **2a** to give 3-benzazepine **3aa** in quantitative yield after heating at 30 °C for 2 h (Scheme 3, eq 2).[28] To gain further information about the diastereoselectivity, the palladacycle **4h′** was also isolated and crystallized as off-white crystals (Scheme 3, eq 3).

https://dx.doi.org/10.1021/acs.orglett.0c01053
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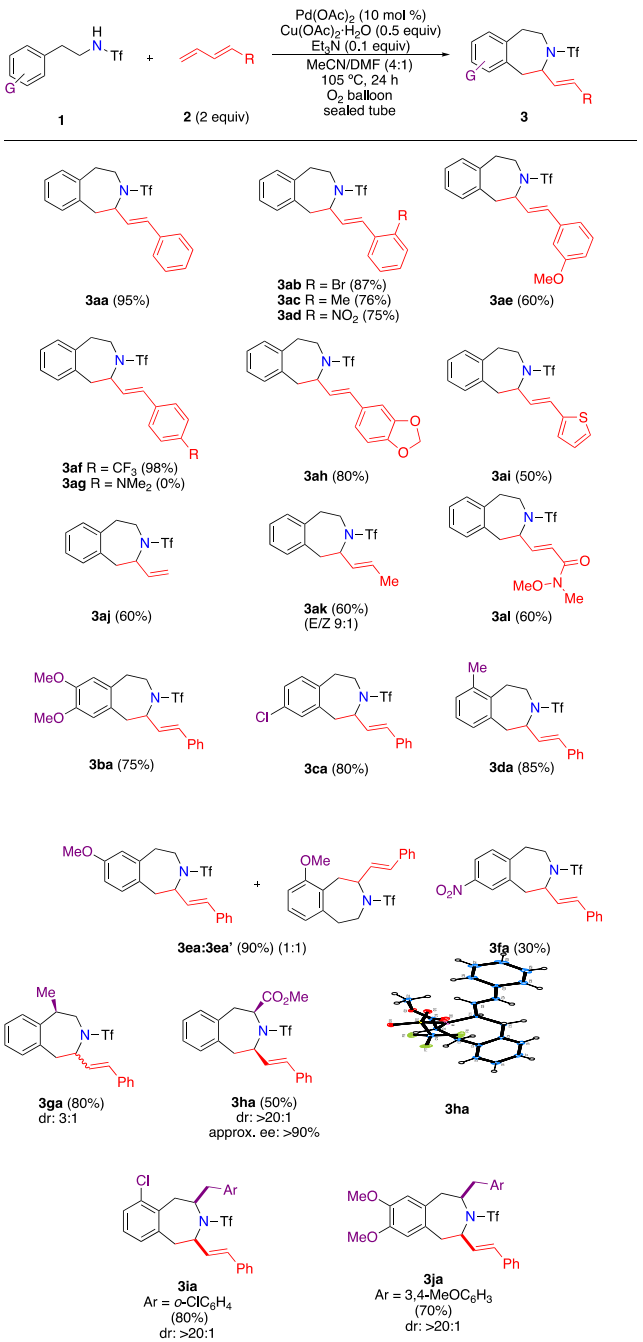
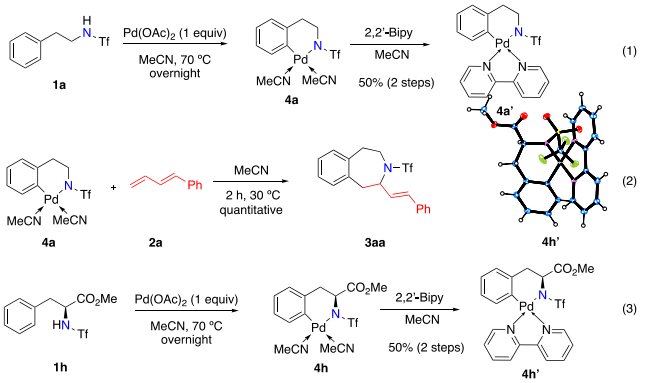
Scheme 2. Scope of the Reaction[a]



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

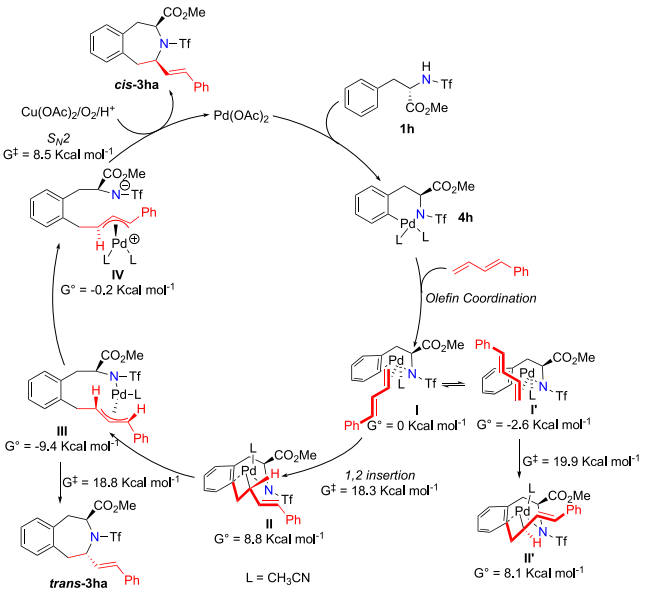
Diastereoselectivity of the reaction was then analyzed by DFT calculations starting from complex **4h** (Scheme 4).[29] Four possible perpendicular η^2-coordination modes of the less substituted olefin of the 1,3-diene to the palladacycle plane could be considered (substituent left/right and up/down).[30] It was only possible to find the transition states for the 1,2-migratory insertion of the two shown, **I** (left-down)[31] and **I′** (left-up).[32] 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

Scheme 3. Isolation of Palladacycles and Mechanistic Experiments[a]



[a]The ORTEP drawing of **4h′** shows ellipsoids at the 30% contour probability level.

Scheme 4. Proposed Catalytic Cycle and DFT Calculations



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 relatively low barrier ($\Delta G^\ddagger$ = 8.7 kcal mol^{-1}).[33] Final Pd reoxidation of Pd(0) to Pd(II) would regenerate the catalytic species.

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.

https://dx.doi.org/10.1021/acs.orglett.0c01053
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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01053.

General experimental procedures, X-ray crystallographic data, NMR spectra (PDF)
DFT calculations (PDF)

Accession Codes

CCDC 1985306−1985308 contain 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, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work has received financial support from MINECO (project CTQ2017-87939R and the ORFEO-CINQA network RED2018-102387-T), the Xunta de Galicia (project ED431C 2018/04 and Centro singular de investigación de Galicia accreditation 2019-2022, ED431G 2019/03), and the European Union (European Regional Development Fund, ERDF). A.V.-R. thanks Xunta de Galicia for a predoctoral fellowship (ED481A-2018/34, 2018-2021). We are also grateful to the CESGA (Xunta de Galicia) for computational time.

■ DEDICATION

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

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(29) See the Supporting Information for computational details.
(30) For the sake of simplicity, the six-membered palladacycle has been considered plane although its two boat-like conformers have been computed. See the Supporting Information for details.
(31) 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.
(32) The η^4-s-cis coordination mode of the 1,3-diene to the palladacycle was also considered but led to the corresponding intermediates through higher energy transition states. See the Supporting Information for details.
(33) See the Supporting Information for the energetic profiles for the reductive elimination and S_N2-type reaction of all the other analyzed isomers.

https://dx.doi.org/10.1021/acs.orglett.0c01053
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