Rh(III)-Catalyzed [5+2] Oxidative Annulation of Cyclic Arylguanidines and Alkynes to 1,3-Benzodiazepines. A Striking Mechanistic Proposal from DFT

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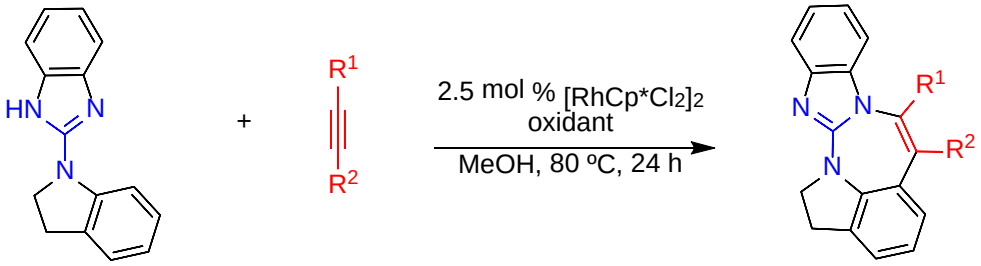
Supporting Information Placeholder



ABSTRACT: A novel and mild Rh(III)-catalyzed [5+2] oxidative annulation between cyclic arylguanidines and alkynes efficiently affords 1,3-benzodiazepines (pentacyclic guanidines). The use of O_2 as the sole oxidant in place commonly used metal oxidants such as AgOAc clearly improves the efficiency of the oxidative annulation process. The mechanism of the cycloaddition most likely involves the formation of an eight-membered rhodacycle. DFT calculations support a striking mechanistic proposal for the [5+2] oxidative annulation.

Benzodiazepines are an important class of benzofused medium-sized dinitrogenated heterocycles,[1] and they are the key structural motifs in many active pharmaceuticals.[2] These compounds comprise several structural derivatives but the most interesting are the 1,4-benzodiazepines, which have attracted significant synthetic effort due to their broad range of clinical applications in the treatment of anxiety, insomnia, agitation, seizures or muscle spasms.[3] Other structural isomers, such as 1,3-benzodiazepines, are less well known despite the fact that these molecules have a wide range of medicinal applications[4] (Figure 1). Accordingly, sustainable catalytic routes for the construction of the 1,3-benzodiazepine core are in high demand.[5]

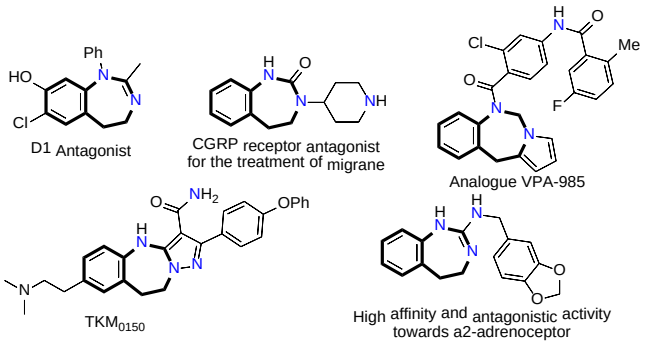
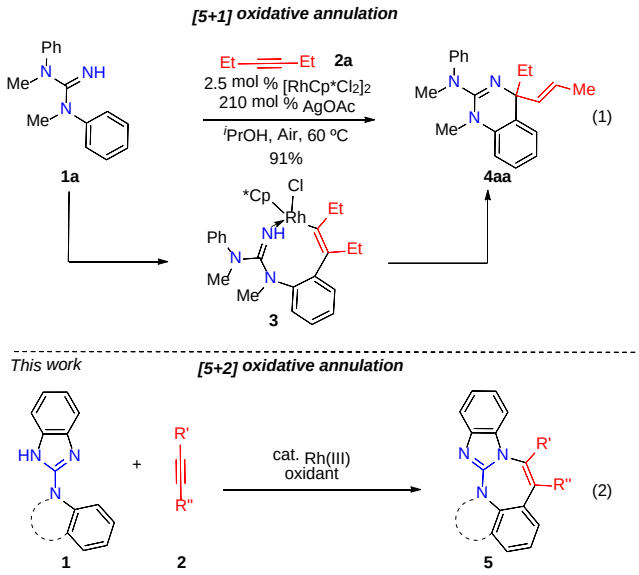


Figure 1. Bioactive 1,3-benzodiazepines.

Transition-metal-catalyzed C–H functionalization is nowadays considered to be a powerful synthetic sustainable strategy for a direct access to five- and six-membered azaheterocycles.[6] Typically, the process of heteroannulation of nitrogen-chelating substrates with alkynes involves the formation of six- and seven-membered metallacycles through a C–H activation/alkyne insertion sequence that gives rise to the corresponding azaheterocycles via reductive elimination, which overall can be considered as formal [3+2] or [4+2] oxidative annulations.[6] However, the formation of eight-membered metallacycle intermediates is energetically more unfavorable and this has undoubtedly restricted the direct access to seven-membered azaheterocycles. To the best of our knowledge, only two reports on the direct Pd-catalyzed [5+2] cycloaddition between nitrogen-containing preorganized substrates and alkynes to form 1-benzazepine derivatives have been published.[7] On the other hand, we recently discovered that 1,3-dimethyl-1,3-diphenylguanidine **1a** (i.e., linear arylguanidines) easily undergo catalytic C-H activation/alkyne insertion processes to form the eight-membered rhodacycle **3**, which could be isolated and characterized by X-ray diffraction.[8] In a catalytic process involving 3-hexyne **2a**, the corresponding metallacyclic intermediate **3** evolved via β-elimination to 1,4-dihydroquinazolin-2-amine **4aa**, which is the product of a [5+1] oxidative annulation between the linear arylguanidine and the alkyne (Scheme 1, eq 1).[8] We envisaged that the use of partially and/or fully cyclic arylguanidines **1** would modify the conformational/coordination abilities of rhodacycle inter-

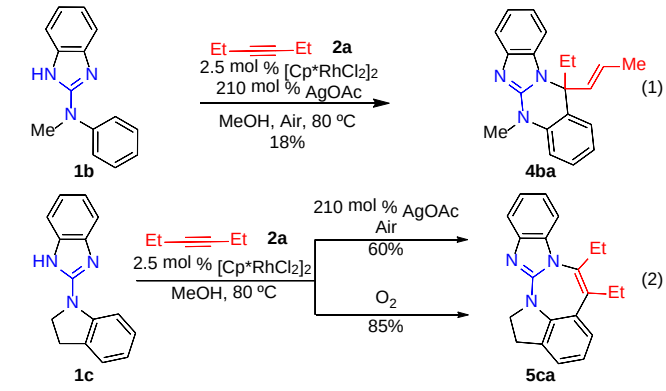
mediates **3** to favor the crucial reductive elimination step to give the desired seven-membered heterocycle. Herein we report the straightforward formation of the seven-membered benzimidazo-1,3-benzodiazepines **5** by a novel Rh(III)-catalyzed [5+2] oxidative annulation of fully cyclic arylguanidines **1** with alkynes **2** (Scheme 1, eq 2).[9] It is noteworthy that in the C-H activation event two nitrogen atoms of the chelate-directing guanidine group were integrated in the final 1,3-benzodiazepine core.

Scheme 1. Rh(III)-catalyzed [5+1] and [5+2] oxidative annulations of arylguanidines with alkynes



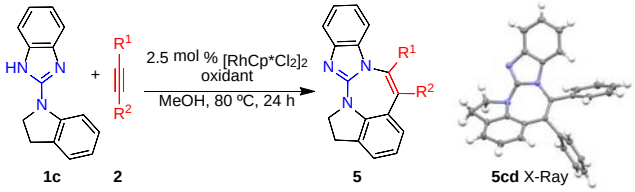
The partially cyclic *N*-methyl-*N*-phenyl-1*H*-benzo[*d*]imidazol-2-amine **1b** reacted sluggishly to give **4ba** in a low 18% yield (Scheme 2, eq 1), with most of the **1b** recovered.[10] Gratifyingly, when the fully cyclic 2-(indolin-1-yl)-1*H*-benzo[*d*]imidazole **1c** was heated in MeOH at 80°C (conditions A), a smooth conversion gave the benzimidazo-1,3-benzodiazepine **5ca** in a respectable 60% yield (Scheme 2, eq 2). To our delight, the yield of the reaction could be improved to 85% when O_2 was used as the sole oxidant (conditions B).[11]

Scheme 2. Rh(III)-catalyzed oxidative annulations of partially cyclic and fully cyclic arylguanidines (1b, 1c) with alkynes



We proceeded to test the scope and limitations of the new [5+2] annulation using cyclic arylguanidine **1c** as the substrate under both sets of oxidative conditions.[12] In general, reactions performed using O_2 as the sole oxidant (conditions B) gave better yields (Table 1). Thus, other internal aliphatic alkynes, namely 4-octyne **2b** and 5-decyne **2c**, gave the corresponding 1,3-benzodiazepines **5cb-cc** in high yields (entries 2 and 3). Interestingly, unlike the cycloaddition with linear arylguanidines,[8] aromatic alkynes **2d-k** reacted smoothly to give the corresponding 4,5-diarylated 1,3-benzodiazepines **5cd-ck**. In the case of diphenylacetylene **2d**, excellent yields of 1,3-benzodiazepine **5cd** were obtained under both sets of conditions (entry 4). The molecular structure of **5cd** was elucidated by X-ray crystallography.[13] Electron-rich and electron-poor arylalkynes were all tolerated, with insignificant variations in the cycloadditions. Thus, 4-methoxy, 4-methyl and 4-trifluoromethyl arylalkynes **2e-g** gave rise to 1,3-benzodiazepines **5ce-cg** in very good yields (entries 5-7). The case of heteroarylalkyne **2h** was particulary efficient and this gave rise to the thiophenyl derivative **5ch** in high yield (entry 8). Halogenated arylalkynes were also well tolerated, which may lead to future cross-coupling manipulations. For example, 4-Br, 4-Cl and 3-Br arylalkyne derivatives **2i-k** gave moderate to good yields of the corresponding halogenated 1,3-benzodiazepines **5ci-ck** (entries 9-11). Curiously, the [5+2] cycloaddition proved to be non regioselective – in contrast to the regioselective [5+1] cycloaddition with linear arylguanidines.[8] Thus, the alkyne 1-(propynyl)benzene **2l**, bearing C_{sp2} and C_{sp3} substituents, gave rise to a mixture of regioisomers **5cl** and **5cl'** (1.5:1) in a 75% combined yield (entry 12).

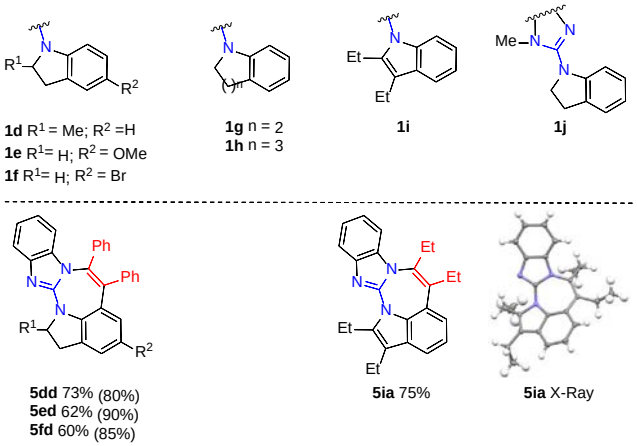
Table 1. Rh(III)-catalyzed [5+2] oxidative annulation of cyclic arylguanidine 1c with alkynes 2 to 1,3-benzodiazepines 5



entry	R^1	R^2	product	yield (%)[a,b]
1	Et	Et	**5ca**	60 (85)
2	*n*-Pr	*n*-Pr	**5cb**	51 (82)
3	*n*-Bu	*n*-Bu	**5cc**	47 (81)
4	Ph	Ph	**5cd**	88 (93)
5	4-MeOPh	4-MeOPh	**5ce**	70
6	4-MePh	4-MePh	**5cf**	57 (84)
7	4-CF_3Ph	4-CF_3Ph	**5cg**	52 (81)
8	2-thiophenyl	2-thiophenyl	**5ch**	82 (82)
9	4-BrPh	4-BrPh	**5ci**	51
10	4-ClPh	4-ClPh	**5cj**	43
11	3-BrPh	3-BrPh	**5ck**	36 (87)
12	Me	Ph	**5cl**:**5cl'** (1.5:1)	66 (75)

[a] *Conditions A*: **1c** (0.3 mmol), **2** (0.33 mmol), $[RhCp^*Cl_2]_2$ (0.0075 mmol), AgOAc (0.63 mmol) in MeOH (3 mL), 80 °C, air, 24h. *Conditions B*: **1c** (0.3 mmol), **2** (0.33 mmol), $[RhCp^*Cl_2]_2$ (0.0075 mmol), in MeOH (3 mL), O_2, 80 °C, 24h. [b] In parenthesis, yields obtained under conditions B.

Other cyclic arylguanidines were also tested (Figure 2). The substituted 2-(methylindolyl)guanidine **1d** also reacted smoothly to give the 1,3-benzodiazepine **5dd** in good yield (80%). Both electron-rich and electron-poor *para*-substituted indolyl units were well tolerated since indolyl guanidines **1e** and **1f** gave the 1,3-benzodiazepines **5ed** and **5fd** in excellent yields.[14] Gratifyingly, the 2-(indol-1-yl)-1,3-benzimidazole derivative **1i** also underwent the [5+2] oxidative annulation[15] to give the indolo-1,3-benzodiazepine **5ia** in fairly good yield.[13]

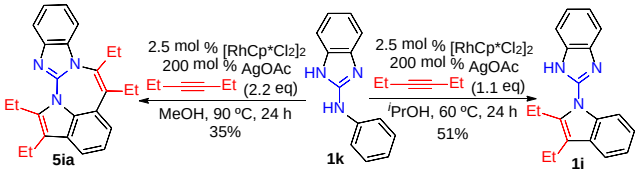


[a] *Conditions A*: **1** (0.3 mmol), **2** (0.33 mmol), $[RhCp^*Cl_2]_2$ (0.0075 mmol), AgOAc (0.63 mmol) in MeOH (3 mL), 80 °C, air, 24h. *Conditions B*: **1** (0.3 mmol), **2** (0.33 mmol), $[RhCp^*Cl_2]_2$ (0.0075 mmol), in MeOH (3 mL), O_2, 80 °C, 24h. [b] In parenthesis, yields obtained under conditions B.

Figure 2. Rh(III)-catalyzed oxidative annulations of other cyclic arylguanidines.[a,b]

The starting indole **1i** could be prepared in moderate yields from the readily available 2-(*N*-phenyl)-1,3-benzimidazole **1k** in a Rh(III)-catalyzed [3+2] oxidative cycloaddition with 3-hexyne (Scheme 3).[8,16] To our delight, the above indolo-1,3-benzodiazepine **5ia** (which was characterized by X-ray diffraction) could also be obtained from the linear benzimidazole **1k** in a cascade process involving tandem [3+2]/[5+2] oxidative annulations[17] with **2a** (Scheme 3).

Scheme 3. Rh(III)-catalyzed [3+2] and tandem [3+2]/[5+2] oxidative annulations of *N*-phenylbenzimidazole 1k



At the outset, the cyclic arylguanidine substrates were selected to favor the crucial reductive elimination step over the β-elimination found for the eight-membered rhodacycle intermediates derived from the linear arylguanidines.[8] We believe that the presence of the NH in the benzimidazole group would trigger the required tautomerism between the nitrogen atoms (L to X-type ligand) to facilitate the reductive elimination step. In fact, the 2-(indolin-1-yl)-1-methyl-1*H*-benzo[*d*]imidazole **1j** failed to react under optimized conditions with total recovery of the starting material.

In an effort to gain an insight into the selectivity of the reaction between guanidines **1b** (partially cyclic) and **1c** (fully cyclic) with alkyne **2a** to form [5+2] cycloadducts, i.e., benzodiazepines **5,** or [5+1] cycloadducts, i.e., quinazolines **4,** DFT calculations[18] were performed starting with the key eight-membered rhodacycles **I**[19] which lie 14.1 (**1b,** blue line) and 9.9 (**1c,** red line) Kcal mol^{-1} below the free energy of the corresponding starting materials (Figure 3). To our surprise, calculations showed that the formation of [5+2] cycloadducts, i.e., benzodiazepines **5**, occurs by an initial decoordination of the imidazole moiety from the metal center to complex **II**, followed by a nucleophilic attack of the iminic nitrogen to the C_{sp2}-Rh bond to afford protonated Rh(I)-coordinated benzodiazepines **III** ($\Delta G^{\ddagger}$ = 20.9 and 11.5 Kcal mol^{-1}, ΔG^{o} = 6.6 and -0.1 Kcal mol^{-1}) rather than the expected direct reductive elimination from **I** ($\Delta G^{\ddagger}$ = 29.5 and 26.4 Kcal mol^{-1}, ΔG^{o} = 12.2 and 10.2 Kcal mol^{-1}).[20] Exergonic deprotonation and reoxidation of the Rh(I) to Rh(III) with AgOAc would give the final benzodiazepines **5ba** and **5ca** (ΔG^{o} = -21.5 and -16.2 Kcal mol^{-1}) for the overall transformations. On the other hand, formation of [5+1] cycloadducts,[21] i.e., quinazolines **4**, starts with coordination of acetate to the eight-membered cationic rhodacycles **I** to give neutral complexes **IV** (ΔG^{o} = 4.9 and 11.5 Kcal mol^{-1}), which after acetate-assisted β-hydride elimination afford allene intermediates **V** ($\Delta G^{\ddagger}$ = 11.1 and 3.9 Kcal mol^{-1}, ΔG^{o} = 7.2 and 1.4 Kcal mol^{-1}). Protonation of **V** by the acetic acid ligand affords the cationic π-allyl Rh (III) species **VI** after acetate release ($\Delta G^{\ddagger}$ = 7.6 and 7.8, ΔG^{o} = -15.4 and -15.6 Kcal mol^{-1}) where Rh(III) is stabilized by an agostic interaction involving a C_{sp3}-H bond of the ethyl substituent. Finally, nucleophilic attack of the iminic nitrogen to the π-allyl moiety ($\Delta G^{\ddagger}$ = 21.3 and 21.1 Kcal mol^{-1}) followed by exergonic deprotonation and reoxidation of the Rh(I) to Rh(III) by AgOAc affords the quinazolines **4ba** and **4ca** (ΔG^{o} = -24.9 and -18.8 Kcal mol^{-1}) for the overall processes.

These calculations described above show the preference for the [5+2] over the [5+1] cycloaddition pathway for the fully cyclic guanidine **1c** to benzodiazepine **5ca** ($\Delta\Delta G^{\ddagger}$ is 9.2 Kcal mol^{-1}), while the opposite is observed from the partially cyclic guanidine **1b** to quinazoline **4ba** ($\Delta\Delta G^{\ddagger}$ is 1.2 Kcal mol^{-1}). These findings are in complete agreement with the experimental results found. We believe that the rigidity/planarity of the indolyl moiety in **1c** (as compared to the linear **1b**) enables the formation of complex **II** with an appropriate spatial disposition between the reactive centers (0.54 Å closer for fully cyclic than partially cyclic **II** due to the planarity imposed by the indolyl ring, 15.4° against 42.4°) that are prone to undergo the formation of the seven-membered heterocycle (Figure 4).

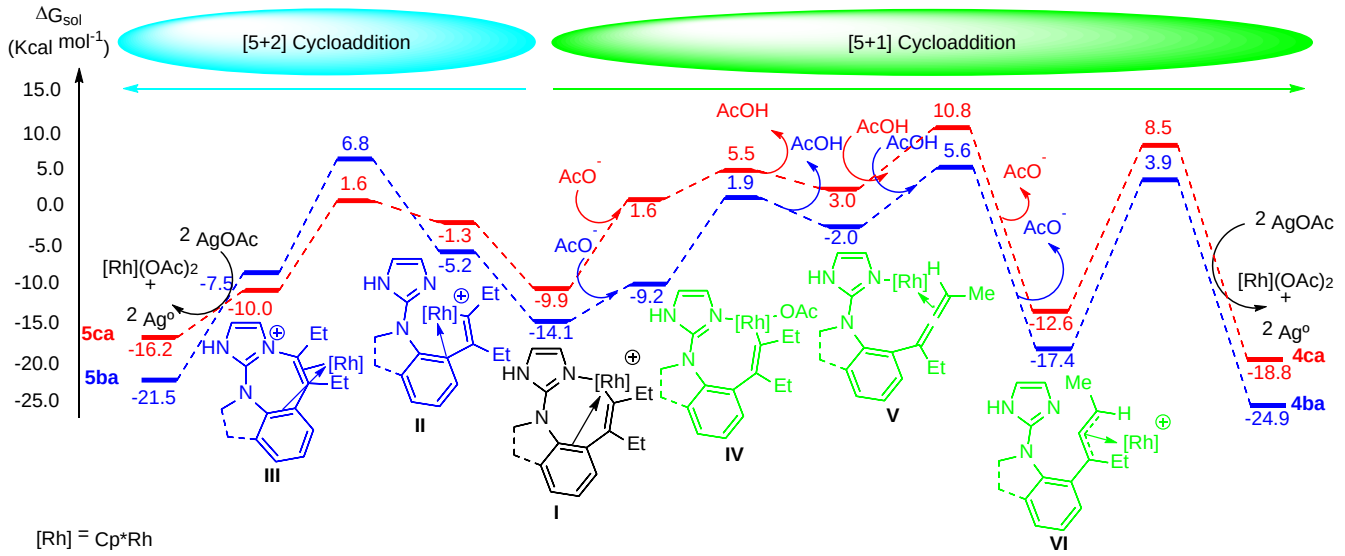


Figure 3. Free energy profile for the formation either of benzodiazepines **5ba** and **5ca** or quinazolines **4ba** and **4ca**[21] from eight-membered rhodacycles **I**. Energies are relative to catalytic active species $Cp^*Rh(OAc)_2$ combined with those of the relevant substrates. The phenyl ring of the benzimidazole moiety is omitted for clarity.

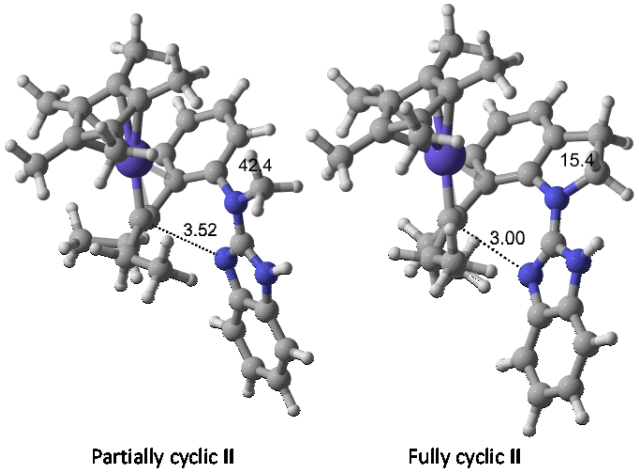
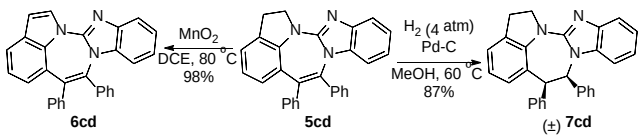


Figure 4. Calculated geometries for intermediates **II** in guanidine **1b** (partially cyclic) and **1c** (fully cyclic).

Redox reactions of indoline-1,3-benzodiazepines **5** were performed to get a straightforward access to *N*-doped aromatic scaffolds containing [4n+2]π-e- with potential electroluminescent properties.[22] Treatment of **5cd** with MnO_2 at 80 °C promotes the oxidation of the indoline moiety to give the indole-1,3-benzodiazepine **6cd** in excellent yield (Scheme 4).[23] Careful hydrogenation of **5cd** in MeOH(H_2 4atm, 60°C) affected only to the enamine unit to give the dihydro-1,3-benzodiazepine **7cd** in fairly good yield.

Scheme 4. Oxidation and reduction of benzodiazepine 5cd.



In summary, we have successfully developed a new and efficient rhodium-catalyzed [5+2] oxidative cycloaddition between fully cyclic arylguanidines and alkynes to give 1,3-benzodiazepines. The use of O_2 as the sole oxidant in place of commonly used metal oxidants like AgOAc clearly improves the efficiency of the oxidative annulation process. The reaction tolerates functional groups in both the guanidine and alkyne partners and provides an easy access to relevant pentacyclic guanidine derivatives. In addition, an indolo-benzazepine skeleton is smoothly assembled by a remarkable cascade process involving [3+2]/[5+2] oxidative annulations of linear benzimidazole **1k** with alkyne **2a**. A striking mechanistic rationale for the [5+2] oxidative annulation is proposed based on DFT calculations. Redox reactions of the indoline-benzodiazepines have been successfully achieved. Further applications of this novel oxidative process are currently being explored in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Detailed experimental procedures and compound characterization data (PDF)

Computational details, cartesian coordinates, imaginary frequencies and absolute energies in hartrees for all optimized geometries (PDF)

Crystallographic data for **5cd** (CCDC: 1873638) (CIF)

Crystallographic data for **5ia** (CCDC: 1873637) (CIF)

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gación de Galicia accreditation 2016–2019, ED431G/09) and the European Union (European Regional Development Fund - ERDF). N. M.-Y. thanks MINECO and Xunta de Galicia for a predoctoral contract. We are also grateful to the CESGA (Xunta de Galicia) for computational time.

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(12) Typically, early oxidative conditions employed AgOAc as oxidant (contidions A) that were sometimes replaced with O_2 as the sole oxidant (conditions B).

(13) Data availability. The X-ray crystallographic coordinates for the structure of compound **5cd** (accession code CCDC 1873638) and compound 5**ia** (accession code CCDC 1873637) reported in this article have been deposited at the Cambridge Crystallographic Data Centre (CCDC). This data can be obtained free of charge from the CCDC via https://www.ccdc.cam.ac.uk/structures/.

(14) The size of the heterocyclic amine unit proved to be an essential characteristic of the substrate since six-membered 2-(tetrahydroquinolin-1-yl) and seven-membered 2-(tetrahydrobenzazepin-1-yl)-1,3-benzimidazoles **1g** and **1h** failed to give the desired 1,3-benzodiazepine derivatives. We speculate that the increased conformational mobility in the azaheterocyclic unit (less planar substrate) hampers an effective C-H activation step.

(15) [5+1] cycloadduct **4ia** (18%) was also observed when conditions A were used.

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(17) For a tandem Rh-catalyzed [3+2]/[5+2] annulation to indeno[1,7-*cd*]azepines, see: Yang, Y.; Zhou, M.-B.; Ouyang, X.-H.; Pi, R.; Song, R.-J.; Li, J.-H. *Angew. Chem. Int. Ed.* **2015**, *54*, 6595-6599.

(18) These calculations were performed using AgOAc as oxidant to visualize the different selectivity found for guanidines **1b** ([5+1] cycloadducts) and **1c** ([5+2] cycloadducts). In fact, when O_2 is used as oxidant, only guanidine **1c** reacts to afford [5+2] cycloadduct benzodiazepine **5ca**. See Supporting Information for an explanation and complete computational details.

(19) (a) For the free energy profile including the formation of the eigth-membered rhodacycles **I** from guanidines **1b** and **1c** with alkyne **2a,** see Supporting Information. (b) For similar C-H activation through a CMD process and formation of seven-membered rhodacycles, see: Algarra, A. G.; Cross, W. B.; Davies, D. L.; Khamker, Q.; Macgregor, S. A.; McMullin, C. L.; Singh, K. *J. Org. Chem.* **2014**, *79*, 1954-1970. (c) Carr, K. J. T.; Davies, D. L.; Macgregor, S. A.; Singh, K.; Villa-Marcos, B. *Chem. Sci.* **2014**, *5*, 2340-2346. (d) Davies, D. L.; Ellul, C. E.; Macgregor, S. A.; McMullin, C. L.; Singh, K. *J. Am. Chem. Soc.* **2015**, *137*, 9659-9669.

(20) See Supporting Information for the energetic profile of direct reductive elimination from **I**.

(21) For sake of clarity only key intermediates and transition states are shown in Figure 3 and discussed in the main text. See Supporting Information for complete free energy profile of the formation of quinazolines **4ba** and **4ca** from rhodacycles **I**.

(22) (a) Stępień, M.; Gońka, E.; Zyła, M.; Sprutta, N. *Chem. Rev.* **2017**, *117*, 3479-3716. (b) Narita, A.; Wang, X.-Y.; Feng, X.; Muellen, K. *Chem. Soc. Rev.* **2015**, *44*, 6616-6643. (c) Wang, X.; Sun, G.; Routh, P.; Kim, D.-H.; Huang, W.; Chen, P. *Chem. Soc. Rev.* **2014**, *43*, 7067-7098.

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