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# A Palladium-Catalyzed Oxa-(4+4)-Cycloaddition Strategy Towards Oxazocine Scaffolds

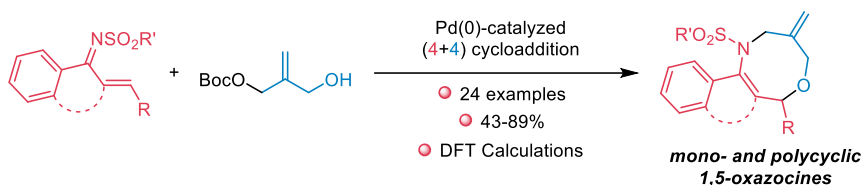
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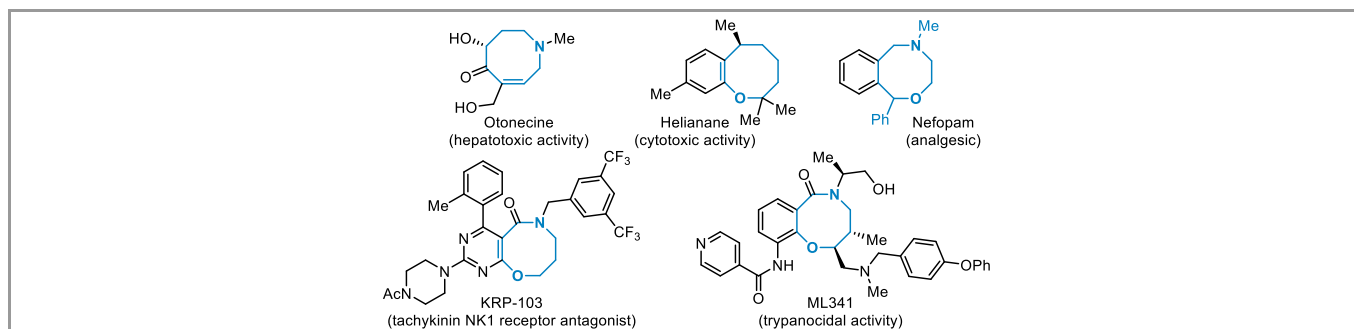
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**Abstract** A Pd-catalyzed oxa-(4+4)-cycloaddition between 1-azadienes and (2-hydroxymethyl)allyl carbonates is described. Aurone-derived azadienes furnished polycyclic 1,5-oxazocines in good yields. Interestingly, linear azadienes have also been involved and yielded monocyclic heterocycles with complete regioselectivity. DFT calculations were carried out to gain insight on this observation.

**Key words** Cycloaddition, Catalysis, Heterocycles, Medium-Sized Rings, Oxazocines, Azadienes

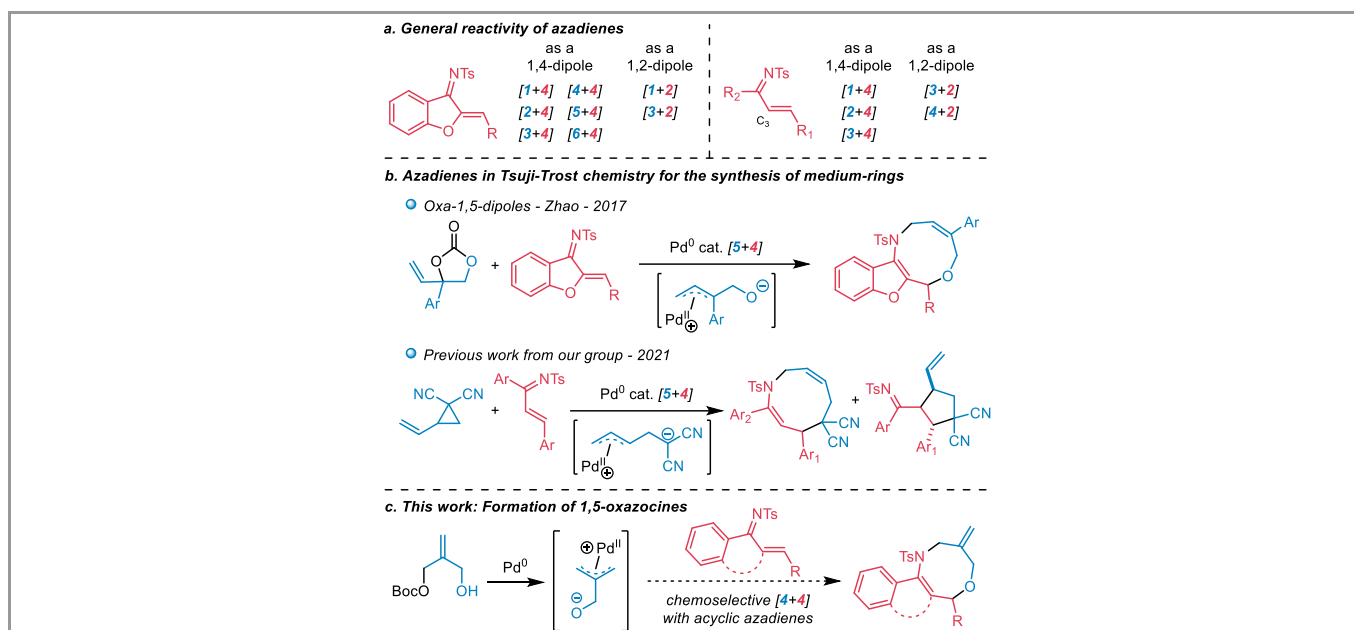
Medium-sized heterocycles are constituents of several biologically active natural products, pharmaceuticals and were successfully incorporated in several drug leads<sup>2</sup> as their structure confers them with favorable pharmacokinetic properties.<sup>3</sup> However, their tedious preparation<sup>4-6</sup> hampers a more thorough investigation of these scaffolds in medicinal chemistry and the development of new methods for their synthesis is of foremost importance (Scheme 1).



**Scheme 1** Examples of oxygenated and nitrogenated 8-membered rings with biological activities.

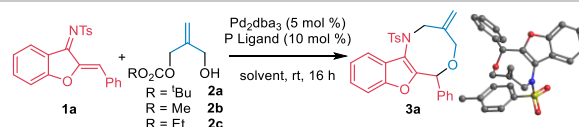
Cycloadditions of 1,*n*-dipoles have recently emerged as an efficient tool towards medium-sized rings. These transformations involve at least one stable partner and aurone-derived azadienes have been exploited in numerous (*n*+4) cycloadditions as an electrophilic 1,4-dipole (Scheme 2a).<sup>7-13</sup> Several catalyzed cycloadditions relying on  $\pi$ -allyl Pd<sup>II</sup> chemistry employed these electrophiles and Trost described the reactivity of a palladium-trimethylenemethane derivative in a (3+4) cycloaddition.<sup>10c</sup> Zhao reported the formation of medium-sized nine and ten-membered heterocycles using vinyl carbonate<sup>12a</sup> and vinyl oxetanes<sup>13</sup> as 1,5- and 1,6-dipoles, respectively (Scheme 2b). Aurone-derived azadienes can also behave as an electrophilic 1,2-dipole (via the C=C or the C=O bond) and spiro compounds have also been prepared via (1+2)<sup>14</sup> and (3+2) cycloadditions.<sup>15</sup>

Linear azadienes, derived from chalcones, display a different reactivity. While they also operate as a 1,4-electrophilic dipole in several (1+4)<sup>16</sup> and in a wide variety of (2+4) cycloadditions (Hetero-Diels-Alder),<sup>17</sup> they generally act as an activated alkene (1,2-dipole with the C=C bond) when opposed to nucleophilic 1,n-dipole (n≥3) to afford the corresponding (n+2) cycloadducts.<sup>18-20</sup> (Scheme 2a). Our group recently reported a Pd-catalyzed (5+4) cycloaddition between azadienes and vinylcyclopropanes highlighting the difficulty to involve linear 1-azadienes with complete regiocontrol as (3+2) side cycloadducts were also obtained (Scheme 2b).<sup>12c</sup> In this context, we became interested in nucleophilic oxa-1,4-dipoles generated *in situ* from (2-hydroxymethyl) allyl carbonates and a Pd<sup>0</sup> catalyst.<sup>21</sup> Herein we report a regioselective palladium-catalyzed (4+4) cycloaddition process involving these intermediates and cyclic or acyclic 1-azadienes (Scheme 2c). During the preparation of this manuscript, Yao and Lin reported a similar study focusing on aurone-derived azadienes.<sup>11c</sup>



**Scheme 2** General reactivity of acyclic and aurone-derived azadienes.

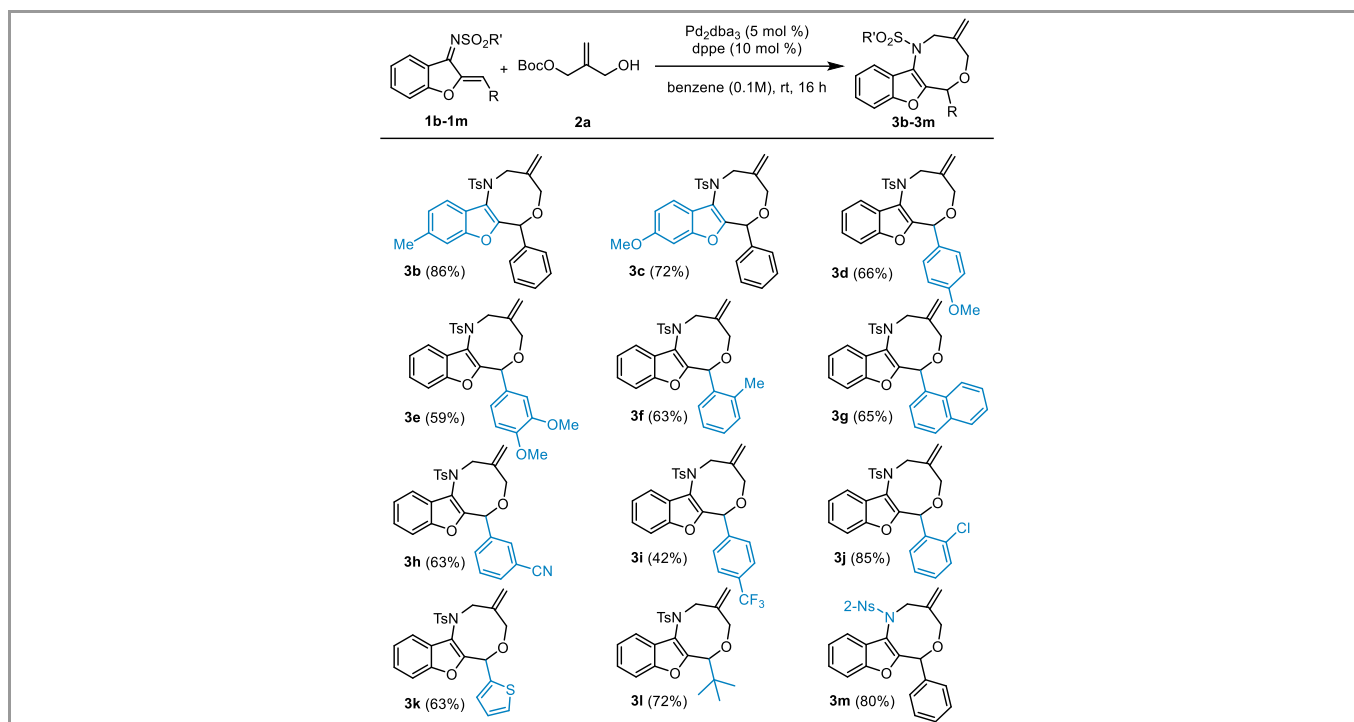
To conduct this study, we selected aurone-derived azadiene **1a** and allyl *tert*-butyl carbonate **2a** as our test substrates. Using dppe as a diphosphine ligand in the presence of Pd<sub>2</sub>dba<sub>3</sub> as the palladium(0) source, we were delighted to observe, at room temperature (toluene), the efficient formation of eight-membered oxazocine **3a** as the sole product of the (4+4) cycloaddition (81% yield). Methyl and ethyl carbonates **2b** and **2c**, respectively, displayed a similar behaviour under the same conditions but furnished **3a** in a slightly lower yield. The optimization was then pursued, and an array of phosphine ligands was examined. While PPh<sub>3</sub> and XantPhos failed to generate efficiently the expected cycloadduct (Table 1, Entry 4 and 5), 1,2-bis(diphenylphosphino)benzene (dppbz) also proved to be suitable for this transformation. We selected dppe for economic reasons and performed a screening of solvents which revealed benzene as the solvent of choice in our case as 1,4-oxazocine **3a** was isolated in 86% yield (Table 1, Entry 7). The structure of this new medium-sized heterocycle was then confirmed by XRD analysis.<sup>22</sup>

**Table 1** Optimization of the reaction conditions<sup>a,b</sup>

Entry	Substrate	R	Ligand	Solvent	Yield (%) <sup>b</sup>
1	2a	<i>t</i> -Bu	dppe	Toluene	81
2	2b	Me	dppe	Toluene	77
3	2c	Et	dppe	Toluene	74
4	2a	<i>t</i> -Bu	PPh <sub>3</sub> <sup>c</sup>	Toluene	-
5	2a	<i>t</i> -Bu	XantPhos	Toluene	12
6	2a	<i>t</i> -Bu	dppbz	Toluene	80
7	2a	<i>t</i> -Bu	dppe	Benzene	92 (86) <sup>d,e</sup>
8	2a	<i>t</i> -Bu	dppe	CH <sub>2</sub> Cl <sub>2</sub>	25
9	2a	<i>t</i> -Bu	dppe	THF	61
10	2a	<i>t</i> -Bu	dppe	MeCN	-

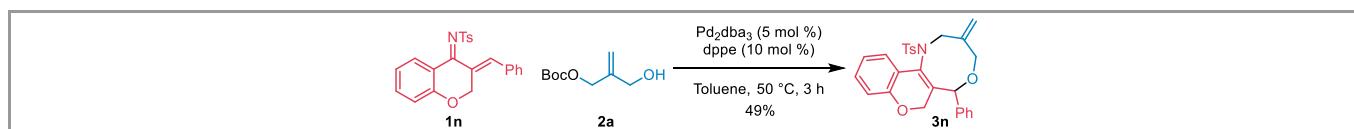
<sup>a</sup>Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), Pd<sub>2</sub>dba<sub>3</sub> (0.005 mmol), ligand (0.01 mmol) in solvent (1 mL) for 16 h at room temperature. <sup>b</sup>NMR yields, isolated yields under parenthesis. <sup>c</sup>Isolated yield under parenthesis.

With these optimized conditions in hand, an evaluation of the scope of this transformation was then carried out. We demonstrated that the presence of an electron-donating group on the benzofuran moiety of azadienes **1b** and **1c** seem to have little influence on the outcome of this transformation as cycloadduct **3b** (86%) and **3c** (72%) were isolated in good yields. The behaviour of several aurone-derived 1-azadienes with different aryl group at the C<sub>4</sub> position was then interrogated. Oxazocines bearing electron-rich *para*-methoxy-phenyl (**3d**) and 3,4-dimethoxyphenyl (**3e**) rings were generated smoothly under the previously optimized set of conditions. The steric hindrance occasioned by an *ortho*-methyl or a 1-naphthyl group did not alter the cycloaddition process which afforded smoothly eight-membered rings **3f** and **3g**, respectively. Electron-deficient aryl groups are also tolerated: azadiene **1h** derived from *meta*-cyanobenzaldehyde proved to be a suitable substrate. However, the introduction of the strong inductive electron-withdrawing *para*-trifluoromethyl group came with a slight yield decrease as our catalytic process furnished **3i** (42%) in moderate yield. The presence of an aromatic halogen atom was also examined and oxazocine **3j** bearing an *ortho*-chlorine substituent, suitable for further functionalization, was prepared in good yield (85%). Gratifyingly, a heteroaromatic moiety such as 2-thiophenyl was also introduced and the (4+4) cycloaddition proceeded smoothly to furnish oxazocine **3k**. We tackled the challenge of introducing an alkyl group at the C<sub>4</sub> position. While this study was limited by the instability of the corresponding starting material, we were delighted to prepare oxazocine **3l** bearing a *tert*-butyl group in 72% yield. Finally, the sulfonamide moiety was also modified and oxazocine **3m** (80%) with a 2-nitrosulfonamide was efficiently generated. (Scheme 3).



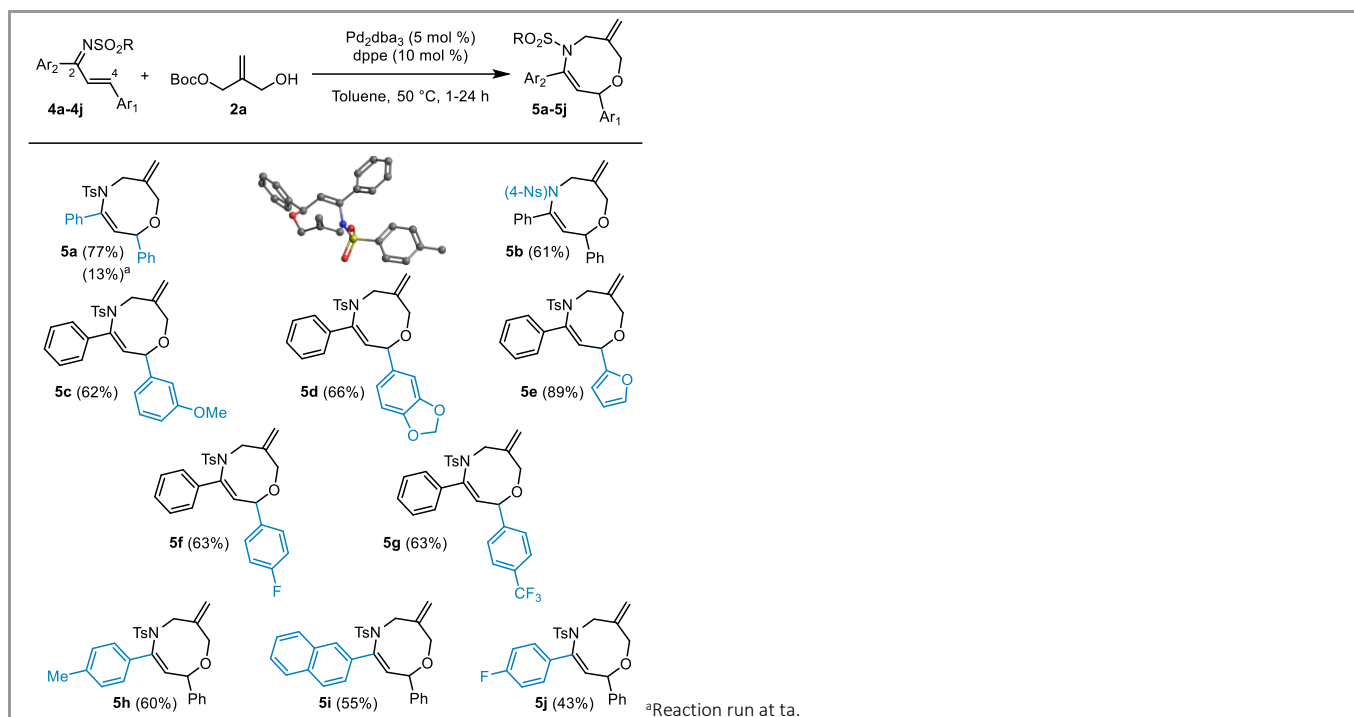
**Scheme 3** Formation of benzofuran-fused oxazocines.

The reactivity of chromanone-derived azadiene **1n** was then questioned. It was here necessary to work at higher temperature (toluene, 50 °C) to isolate the expected polycyclic oxazocine **3n** (49%). A putative (4+4) cycloaddition does not come with a concurrent aromatisation, unlike the previous case of aurone-derived azadienes (Scheme 4).



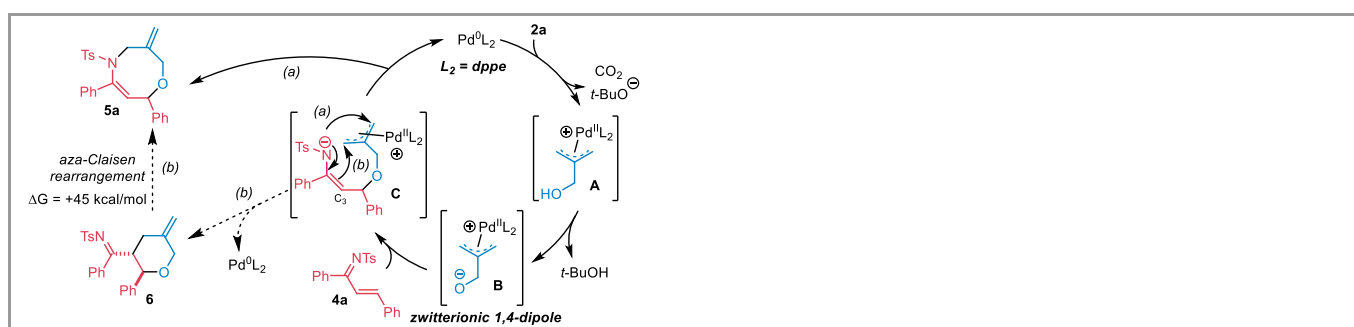
**Scheme 4** General reactivity of acyclic and aurone-derived azadienes.

This encouraging result prompted us to investigate the behaviour of acyclic 1-azadienes derived from chalcones under our (4+4) cycloaddition conditions. Azadiene **4a** was prepared from benzylideneacetophenone and selected as our test substrate. An elevation of the temperature (50 °C, toluene) was also required to achieve a smooth (4+4) cycloaddition towards the corresponding monocyclic 1,5-oxazocine **5a** (77%), whose structure has been confirmed by XRD analysis.<sup>23</sup> The azadiene **4b**, bearing a *para*-nitrobenzene sulfonamide moiety, was a suitable substrate under the same reaction conditions and led to the corresponding medium-sized heterocycle **5b** (61%). The ease of preparation of acyclic 1-azadienes bearing different aryl group at C<sub>2</sub> and C<sub>4</sub> allowed us to further review the scope of this monocyclic oxazocine synthesis. Under the previously described reaction conditions, azadienes **4c** and **4d**, bearing electron-donating substituents (3-OMe; 3,4-OCH<sub>2</sub>O) on the Ar<sub>1</sub> group, were readily converted to the expected cycloadducts. An electron-rich heteroaromatic 2-furane was well-tolerated and our method furnished oxazocine **5e** (89%) in very good yield. Electron-withdrawing substituent (*para*-F, *para*-CF<sub>3</sub>) on Ar<sub>1</sub> did not alter the reaction outcome as oxazocines **5f** (63%) and **5g** (63%) were obtained from the corresponding azadienes. Various substitutions are also tolerated on the Ar<sub>2</sub> ring as 1,5-oxazocines **5h**, **5i** and **5j** bearing an electron-donating *para*-methyl, a 2-naphthyl or an electron-withdrawing *para*-fluoro substituent, respectively, were generated in moderate to good yields (Scheme 5).



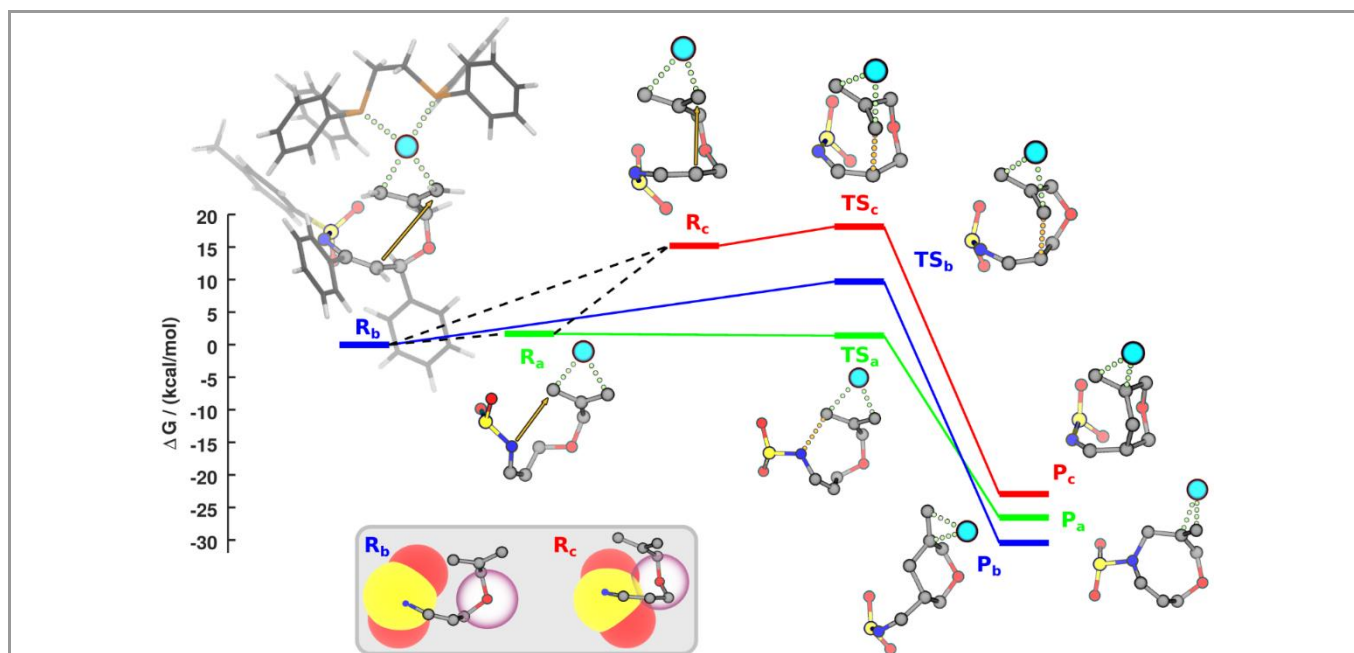
**Scheme 5** Formation of monocyclic oxazocines.

A mechanism was proposed to illustrate this (4+4) process. After complexation (not shown) with the alkene moiety of **2a** followed by an oxidative addition to generate Pd<sup>II</sup>- $\pi$ -allyl complex **A**, the in situ generated tert-butanolate can deprotonate the alcohol moiety and lead to the 1,4-dipole **B**. An oxa-Michael addition into azadiene **4a** then generates the key Pd<sup>II</sup>- $\pi$ -allyl complex intermediate **C**. The eight-membered ring **5a** could result from pathway (a) after addition of the sulfonamide anion to the  $\pi$ -allyl-Pd<sup>II</sup>. As carbon C<sub>3</sub> is not highly congested, one could imagine an alternative pathway (b) involving a (4+2) cycloaddition leading to tetrahydropyran **6**. While this product could never be observed, a fast aza-Claisen rearrangement could also lead to oxazocine **5a** but this reaction pathway has been ruled as DFT calculations showed very high energy barrier of about 45 kcal/mol (Scheme 6).<sup>24</sup>



**Scheme 6** Proposed mechanism.

In order to shed some light on the observed regioselectivity favoring a (4+4) cycloaddition, we explored the microscopic details of the reaction using density functional theory (DFT) calculations. We identified three reactant conformers, namely  $R_a$ ,  $R_b$  and  $R_c$ , which are in thermal equilibrium (represented with dashed line in Figure 1). It turns out that the (4+4) cycloaddition is virtually barrierless ( $G_{TSa} \approx G_{Ra}$ ). Taking a closer look at the structures of  $R_a$  and  $TS_a$ , we notice that they are very similar, which, by virtue of the Hammond principle, provides an explanation for the fact that the two structures have almost the same free energy: reaching the transition state requires a minimal amount of structural reorganization that comes together with only a small increase in cycle tension. It is also worth stressing that there is a stabilizing electrostatic attraction between the negatively charged nitrogen atom and the carbocation in  $R_a$  which is exacerbated by the low dielectric constant of the solvent. A competitive (4+2) pathway (b) could occur from reactant conformer  $R_b$  ( $G_{Rb} \approx G_{Ra}$ ). However, its chemical step is associated with a significantly higher activation barrier ( $G_{TSb} - G_{Rb} \approx 10$  kcal/mol). This is due to the boat conformation of  $TS_b$ , which typically requires more energy to be formed from the reactant. A chair transition state  $TS_c$  can be reached following an other (4+2) pathway (c) with a much lower activation free energy ( $G_{TSc} - G_{Rc} \approx 3$  kcal/mol). However, the overall free energy landscape of this pathway is much higher than the two others due to the high free energy of  $R_c$  with respect to  $R_a$  and  $R_b$ . As highlighted in the gray box, this is due to a strong steric conflict between the sulfonyl group and the endocyclic oxygen atom. Finally, the free energy of the eight-membered ring is only slightly higher than that of the most stable six-membered ring that we obtained ( $G_{Pa} - G_{Pb} \approx 4$  kcal/mol). The overall picture that emerges from our calculations is that the system gets kinetically trapped into the free energy basin corresponding to  $P_a$  (Figure 1).



**Figure 1** Free energy profiles of the cyclization reactions following a (4+4) cycloaddition mechanism (pathway **(a)** in green), a (4+2) cycloaddition mechanism involving a boat-conformation at the TS (pathway **(b)** in blue) and a (4+2) cycloaddition mechanism involving a chair-conformation at the TS (pathway **(c)** in red). Each free energy is defined relative to the most stable conformer of the reactant, namely  $R_b$ . Conformational transitions and chemical steps are represented with dashed and plain lines, respectively. For the sake of clarity, the full molecular structure is represented only for  $R_b$ . For all the other stationary states, only key backbone atoms involved in the cyclisation process are represented (hydrogen atoms are removed from the representation too). More detailed representations of the same structures are provided in Supporting Information. For each reaction pathway, the nucleophilic attack is represented with an orange arrow and the corresponding forming bond at the TS is depicted with orange dots. The lower gray box provides additional representations of the reactive backbone of  $R_b$  and  $R_c$  in order to emphasize the steric conflict between the sulfonyl group (plain spheres) and the endocyclic oxygen atom (transparent magenta sphere).

In this study, we have disclosed an original pathway to benzofuran-fused [1,5]-oxazocines *via* a palladium-catalyzed (4+4) cycloaddition with (2-hydroxymethyl)allyl carbonates. Acyclic azadienes have also been involved in this process and monocyclic eight-membered rings were obtained with complete regioselectivity and DFT calculations were carried out to rationalize this peculiar finding.

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### Supporting Information

YES (this text will be updated with links prior to publication)

### Primary Data

NO (this text will be deleted prior to publication)

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(25) **General Procedure** for the Pd-catalyzed (4+4) cycloadditions of **2a** with **1a** (benzene, ta): In a screw-cap SVL tube filled with argon, Pd<sub>2</sub>(dba)<sub>3</sub> (13.7 mg, 0.015 mmol, 0.05 equiv) and dppe (12.0 mg, 0.03 mmol, 0.1 equiv) were added in benzene (3 mL, 0.1M) and stirred for 15 minutes at rt. Carbonate **2a** (84.7 mg, 0.45 mmol, 1.5 equiv) and azadiene **1a** (113 mg, 0.30 mmol) were then added, the reaction mixture was stirred at rt for 16 hours, filtered over silica and concentrated under reduced pressure to afford the crude product. The residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc = 85:15) to afford **3a** (109 mg, 81%) as a yellow solid. **Analytical data:** Mp=46 °C; **IR** (neat, cm<sup>-1</sup>) 2922, 1597, 1494, 1452, 1384, 1346, 1180, 1157, 1095, 1069, 747; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>, -20 °C) δ 7.86 (d, *J* = 8.2 Hz, 2H), 7.61-7.58 (m, 1H), 7.41-7.12 (m, 10H), 5.45 (s, 1H), 5.24 (s, 1H), 5.02 (s, 1H), 4.91 (d, *J* = 13.5 Hz, 1H), 4.58 (d, *J* = 12.6 Hz, 1H), 4.24 (d, *J* = 12.6 Hz, 1H), 4.10 (d, *J* = 13.5 Hz, 1H), 2.44 (s, 3H); **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>, -20 °C) δ 154.4, 153.0, 143.5, 139.3, 138.1, 136.4, 129.3 (2C), 128.5, 128.4 (2C), 127.8 (2C), 127.6 (2C), 126.6, 124.6, 123.1, 122.7, 120.0, 116.0, 111.3, 79.0, 75.9, 54.7, 21.6; **HRMS** *m/z* (ESI<sup>+</sup>) [M+H]<sup>+</sup> calculated for C<sub>26</sub>H<sub>24</sub>NO<sub>4</sub>S<sup>+</sup>: 446.1421. Found: 446.1410.