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

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Abstract

A Pd-catalyzed oxa-(4+4)-cycloaddition between 1-aza-dienes 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 and pharmaceuticals and were successfully incorporated in several drug leads as their structure confers them with favorable pharmacokinetic properties. However, their tedious preparation hampers a more thorough investigation of these scaffolds in medicinal chemistry and the development of new methods for their synthesis is of foremost importance (Figure 1).

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 beenexploited in numerous (n+4) cycloadditions as an electrophilic 1,4-dipole (Scheme 1a). Several catalyzed cycloadditions relying on π-allyl Pd chemistry employed these electrophiles and Trost described the reactivity of a palladium-trimethylenemethane derivative in a (3+4) cycloaddition. Zhao reported the formation of medium-sized nine- and ten-membered heterocycles using vinyl carbonate and vinyl oxetanes as 1,5- and 1,6-dipoles, respectively (Scheme 1b). 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) and (3+2) cycloadditions.

Linear azadienes, derived from chalcones, display a different reactivity. While they also operate as a 1,4-electrophilic dipole in several (1+4) and in a wide variety of (2+4) cycloadditions (hetero-Diels–Alder), 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. 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 (Scheme 1b). In this context, we became interested in nucleophilic oxa-1,4-dipoles generated in situ from (2-hydroxymethyl) allyl carbonates and a Pd catalyst. Herein we report a regioselective palladium-catalyzed (4+4)-cycloaddition process involving these intermediates and cy-
clic or acyclic 1-azadienes (Scheme 1c). During the preparation of this manuscript, Yao and Lin reported a similar study focusing on aurone-derived azadienes.10c

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 Pd2(dba)3 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 $\left(4+4\right)$ cycloaddition (81% yield). Methyl and ethyl carbonates 2b and 2c, respectively, displayed a similar behavior 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 PPh3 and XantPhos failed to generate efficiently the expected cycloadduct (Table 1, entries 4 and 5), 1,2-bis(diphenylphosphino)benzene (dpbbz) 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.21

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 seems to have little influence on the outcome of this transformation as cycloadduct 3b (86%) and 3c (72%) were isolated in good yields. The behavior of several aurone-derived 1-azadienes with different aryl group at the C4 position was then interrogated. Oxazocines bearing electron-rich p-methoxyphenyl (3d) and 3,4-dimethoxyphenyl (3e) rings were generated smoothly under the previously optimized set of conditions. The sterically hindered 1-aryl 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 m-cyanobenzaldehyde proved to be a suitable substrate. However, the introduction of the strong inductive electron-withdrawing p-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 o-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 $\left(4+4\right)$ cycloaddition proceeded smoothly to furnish oxazocine 3k. We tackled the challenge of introducing an alkyl group at the C4 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 2).

<table>
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<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R</th>
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<th>Solvent</th>
<th>Yield (%)</th>
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<td>dppe</td>
<td>toluene</td>
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<tr>
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<tr>
<td>3</td>
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<tr>
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<tr>
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<tr>
<td>10</td>
<td>2a</td>
<td>t-Bu</td>
<td>dppe</td>
<td>–</td>
<td>–</td>
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</table>

*Reaction conditions: 1a (0.1 mmol), 2a (0.15 mmol), Pd2(dba)3 (0.005 mmol), ligand (0.01 mmol) in solvent (1 mL) for 16 h at room temperature. NMR yields, isolated yield in parentheses.

## Table 1 Optimization of the Reaction Conditions

![Scheme 1 General reactivity of acyclic and aurone-derived azadienes](image_url)

**a. General reactivity of azadienes**

Table 1, **b. Azadienes in Tsuji–Trost chemistry for the synthesis of medium-sized rings**

**c. This work: Formation of 1,5-oxazocines**

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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 aromatization, unlike the previous case of aurone-derived azadienes (Scheme 3).

This encouraging result prompted us to investigate the behavior 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. The azadiene 4b, bearing a p-nitrobenzene sulfonylamine 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 C2 and C4 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-OCH2O) on the Ar1 group, were readily converted into the expected cycloadducts. An electron-rich heteroaromatic 2-furan was well-tolerated and our method furnished oxazocine 5e (89%) in very good yield. Electron-withdrawing substituent (p-F, p-CF3) on Ar1 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 Ar2 ring as 1,5-oxazocines 5h, 5i, and 5j bearing an electron-donating p-methyl, a 2-naphthyl, or an electron-withdrawing p-fluoro substituent, respectively, were generated in moderate to good yields (Scheme 4).

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 PdIV, the in situ generated tert-butanolate can deprotonate the alcohol moiety and lead to the 1,4-dipole B. An oxo-Michael addition into azadiene 4a then generates the key PdIIπ-allyl complex intermediate C. The eight-membered ring 5a could result from pathway (a) after addition of the sulfonamide anion to the π-allyl-PdIII. As carbon C3 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 a very high energy barrier of about 45 kcal/mol (Scheme 5).23

**Scheme 5 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 2). It turns out that the (4+4) cycloaddition is virtually barrierless (\(G_{TSa} = \text{ca. } G_{Ra}\)). 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 (\(G_{Rb} = \text{ca. } G_{Ra}\)). However, its chemical step is associated with a higher activation barrier (\(G_{TSb} - G_{Rb} = \text{ca. } 10 \text{ kcal/mol}\)). 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 another (4+2) pathway (c) with a much lower free-energy barrier (\(G_{TSc} - G_{Rc} = \text{ca. } 3 \text{ kcal/mol}\)). 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 oxygen atom to which the carbocation is attached in R_c. 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 (\(G_{Pa} - G_{Pb} = \text{ca. } 4 \text{ kcal/mol}\)). 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 2).

**Figure 2** 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_a. 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_a. As highlighted in the gray box, this is due to a strong steric conflict between the sulfonyl group and the oxygen atom to which the carbocation is attached in R_c. 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 (\(G_{Pa} - G_{Pb} = \text{ca. } 4 \text{ kcal/mol}\)). 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 2).
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.

Conflict of Interest
The authors declare no conflict of interest.

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Supporting Information
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(g) Choury, M.; Basilio Lopes, A.; Blond, G.; Gulea, M. Molecules 2020, 25, 3147.
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(21) CCDC 2040269 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures

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(23) See the Supporting Information.

(24) **Typical Procedure for the Pd-Catalyzed (4+4) Cycloadditions of 2a with 1a (Benzene, rt)**

In a screw-cap SVL tube filled with argon, Pd{db}a$_3$ (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, 0.1 M) and stirred for 15 min 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 h, 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; mp 46 °C.

IR (neat): 2922, 1597, 1494, 1452, 1384, 1346, 1180, 1157, 1095, 1069, 747 cm$^{-1}$. 1H NMR (400 MHz, CDCl$_3$, –20 °C): $\delta$ = 7.86 (d, $J = 8.2$ Hz, 2 H), 7.61–7.58 (m, 1 H), 7.41–7.12 (m, 10 H), 5.45 (s, 1 H), 5.24 (s, 1 H), 5.02 (s, 1 H), 4.91 (d, $J = 13.5$ Hz, 1 H), 4.58 (d, $J = 12.6$ Hz, 1 H), 4.24 (d, $J = 12.6$ Hz, 1 H), 4.10 (d, $J = 13.5$ Hz, 1 H), 2.44 (s, 3 H). 13C NMR (101 MHz, CDCl$_3$, –20 °C): $\delta$ = 154.4, 153.0, 143.5, 139.3, 138.1, 136.4, 129.3 (2 C), 128.5, 128.4 (2 C), 127.8 (2 C), 127.6 (2 C), 126.6, 124.6, 123.1, 122.7, 120.0, 116.0, 111.3, 79.0, 75.9, 54.7, 21.6. HRMS (ESI+): $m/z$ [M + H]$^+$ calcld for C$_{26}$H$_{24}$NO$_4$S$: 446.1421; found: 446.1410.