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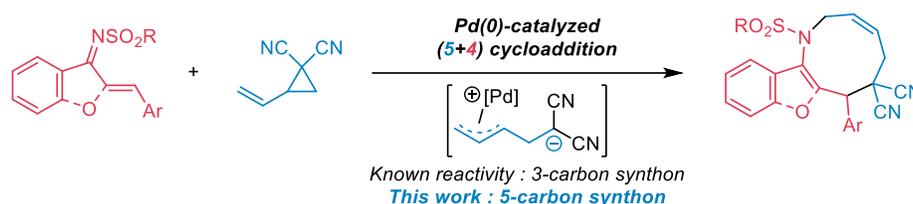
Vinylcyclopropanes as All-Carbon 1,5-Dipoles: A Reactivity Switch for Palladium-Catalyzed (5+4) Cycloadditions

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Supporting Information Placeholder

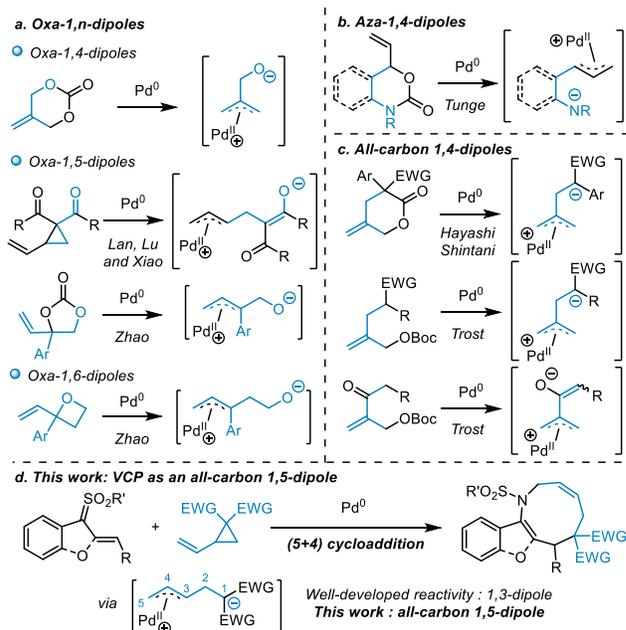


ABSTRACT: Azonanes were prepared by a palladium-catalyzed (5+4) cycloaddition between activated vinylcyclopropanes and 1-azadienes. During this process, the vinylcyclopropane partner displayed an unusual reactivity and behave as an all-carbon 1,5-dipole. A *N,N*-bidentate ligand was required to inhibit the formation of thermodynamic (3+2) cycloadducts.

When a multitude of methods describes the preparation of 3 to 7 membered-rings, the synthesis of medium-sized (8 to 11) heterocycles^{1,2} remains a more demanding task because of the high entropy and enthalpy associated with the cyclization process.³ Our group is interested in the design of new cycloaddition strategies for the preparation of these important structures and we focused our attention on the design and reactivity of 1,*n*-dipoles (*n*≥4) whose application for medium-rings synthesis is still limited.⁴

Transition-metal catalyzed cycloadditions relying on Tsuji-Trost chemistry has recently emerged as a valuable approach towards π -allyl-Pd^{II} 1,*n*-zwitterionic dipoles.⁵⁻⁷

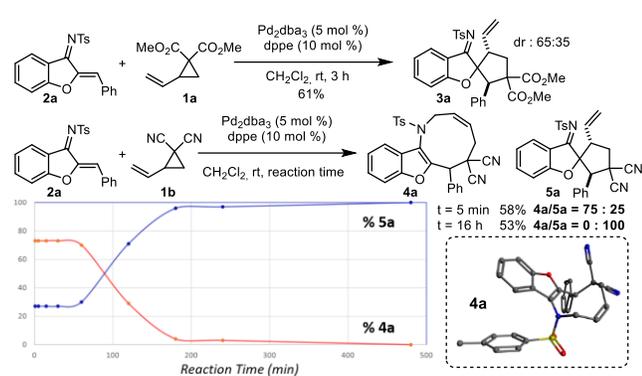
Following the pioneering work of Zhao, vinyl ethylene carbonates (and, to a lesser extent, the corresponding oxiranes) have recently gathered a growing attention as readily available oxa-1,5-dipole precursors (Scheme 1a).^{8,9} The relevance of nitrogenated heterocycles prompted organic chemists to study new aza-dipoles.¹⁰ Tunge and others demonstrated the versatility of vinyl benzoxazinones in a wide array of Pd-catalyzed (4+n) cycloadditions (Scheme 1b).¹¹ The negative charge of the zwitterionic π -allyl-Pd^{II} intermediates could also be stabilized as a soft enolate by electron withdrawing neighboring groups and cycloadditions of all-carbon 1,4-dipoles were pioneered by Hayashi and Shintani using γ -methylidene- δ -valerolactones as readily available substrates.¹² Recently, the group of Trost designed two acyclic substrates, precursors of trimethylenemethane homologues, allowing for the enantioselective formation of diversely substituted cyclohexanes¹³ and cyclohexanones¹⁴ (Scheme 1c). To the best of our knowledge,



Scheme 1. 1,*n*-dipoles (*n*≥4) in Tsuji-Trost chemistry.

cycloadditions of all-carbon 1,5-dipoles relying on Tsuji-Trost chemistry have not been disclosed yet.¹⁵ Acknowledging that such zwitterionic intermediates could contribute to the preparation of new medium-sized cyclic structures, we envisioned to involve VCPs as their precursors.

While these substrates have been well established as 3-carbon synthons in Pd(0) catalysis,¹⁶ we anticipated that steric hindrance at the nucleophilic site of a cycloaddition partner would promote a faster cyclization step at the C₅ carbon. Herein we report a kinetically-controlled Pd-catalyzed (5+4) cycloaddition of activated vinylcyclopropanes with 1-azadienes^{8a,8b,9a} for the synthesis of azonane heterocycles (Scheme 1d).



Scheme 2. Preliminary studies

to conduct this study, we initially involved VCP **1a** bearing two methyl ester groups and benzofuran-derived 1-azadiene **2a** as test substrates. Under usual conditions (Pd₂dba₃, dppe, CH₂Cl₂, rt), we observed the formation of spiro compound **3a** originating from a (3+2) cycloaddition involving the VCP as a nucleophilic 1,3-dipole and the C=C bond of the azadiene as an electrophilic 1,2-dipole.¹⁷ A remarkably different outcome was observed with VCP **1b** bearing two cyano electron-withdrawing groups. Under the same conditions, a fast transformation (<1 min) was observed and furnished the expected 9-membered ring **4a**¹⁸ as a major product along with a mixture of diastereomers of the cyclopentane spiro compound **5a** (**4a/5a** = 75:25). Interestingly, **5a** was the only cycloadduct observed after 4 hours (rt) and a careful monitoring of the **4a/5a** ratio by ¹H NMR spectroscopy revealed that (5+4) cycloadduct **4a** was gradually converted to (3+2) cycloadduct **5a** under these reaction conditions (Scheme 2).

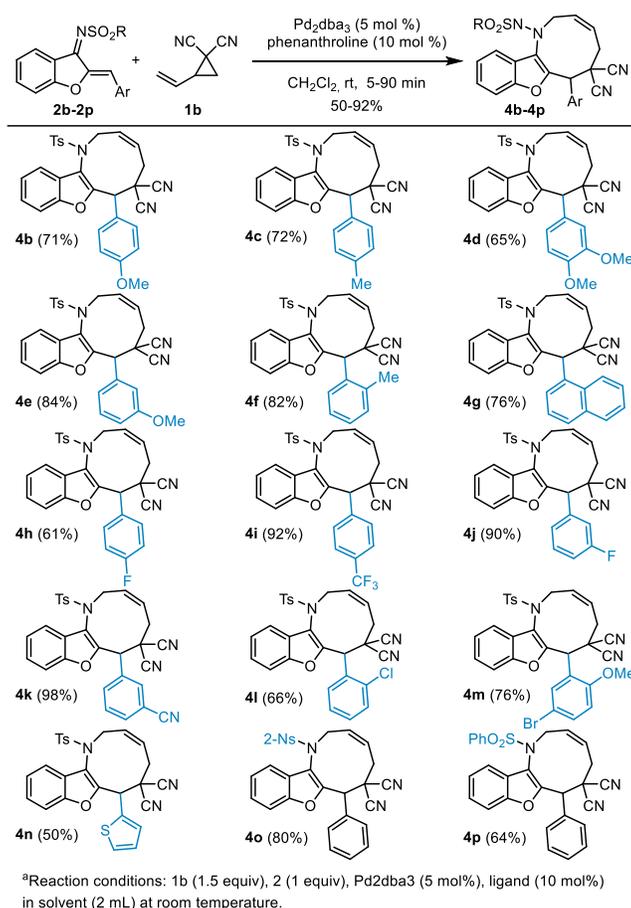
After this encouraging preliminary result, an array of solvents was tested but did not allow for a more selective formation of 9-membered azonane **4a** (Table 1, Entry 1-5). Gratifyingly, a Pd₂dba₃/*N,N*-bidentate ligand catalytic system led to the exclusive formation of the (5+4) cycloadduct **4a** (**4a/5a** > 96:4) which was isolated in good yield (74%) using phenanthroline as ligand (Table 1, Entry 7) and, in this case, no conversion of **4a** to **5a** was observed after 16 hours (Table 1, Entry 8). These conditions proved to be suitable for the gram-scale synthesis (1.10 g, 73%) of **2a** (Table 1, Entry 9). It is worth pointing out that VCP **1a** bearing two methyl esters was exclusively converted to the corresponding spiro compound under these conditions, highlighting the importance of the two cyano groups.¹⁹

Table 1. Optimization of the reaction conditions^a

Entry	Ligand	Solvent	4a/5a	Yield (%)
1	dppe	CH ₂ Cl ₂	75:25	58 ^b
2	dppe	Toluene	72:28	42 ^b
3	dppe	Methanol	65:35	41 ^b
4	dppe	Et ₂ O	65:35	62 ^b
5	dppe	Acetone	63:37	56 ^b
6	bipyridine	CH ₂ Cl ₂	> 96:4	64 ^c
7^d	phenanthroline	CH₂Cl₂	> 96:4	74^c
8 ^e	phenanthroline	CH ₂ Cl ₂	> 96:4	71 ^c
9 ^f	phenanthroline	CH ₂ Cl ₂	> 96:4	73 ^c

^aReaction conditions: **1b** (0.075 mmol), **2a** (0.05 mmol), Pd₂dba₃ (0.0025 mmol), ligand (0.005 mmol) in solvent (0.5 mL) at room temperature. ^bNMR yields ^cisolated yields. ^dReaction time: 5 min. ^eReaction time: 16 h. ^f**2a** (3.00 mmol), Reaction time: 5 min.

Having these optimized conditions in hand, we then examined the scope of this (5+4) cycloaddition by involving benzofuran-derived azadienes bearing an array of aromatic substituents at position C₄. Electron-rich phenyl groups were well tolerated and azonane with *p*-anisyl (**4b**), *p*-tolyl (**4c**), 3,4-dimethoxyphenyl (**4d**) and *m*-methoxyphenyl (**4e**) groups were smoothly generated. Steric hindrance on this aromatic group had little influence on this cycloaddition as azadienes **2f** (82%) and **2g** (76%) with an *o*-tolyl and a 1-naphthyl group, respectively, were readily converted to the corresponding nine-membered heterocycles. We continued to question the importance of the electronic properties of this aromatic moiety and demonstrated that electron-withdrawing substituents such as a fluorine (**4h**) or a trifluoromethyl (**4i**) group at the *para* position could be installed. Substitutions at the *meta* position (3-F for **2j** and 3-CN for **2k**) were also tolerated as the expected azonanes **4j** (90%) and **4k** (98%) were generated in high yields. Halogen atoms are susceptible to alter the course of this reaction as an oxidative insertion of the Pd⁰ catalyst can occur. We were pleased to observe the efficient formation of azonanes **4l** (2-Cl, 66%) and **4m** (5-Br-2-OMe, 76%). Under the same reaction conditions, azadiene **2n** (50%) bearing an electron-rich 2-thiophenyl group was converted to the expected nine-membered ring.

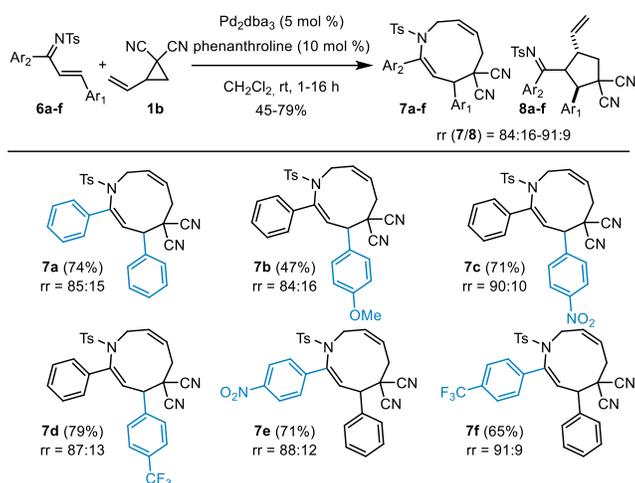


Scheme 3. Formation of benzofuran-fused azonanes^a

Finally, the reactivity of benzofuran-derived azadienes with different sulfonamide groups was examined and 2-nitrosulfonamide **4o** (80%) as well as benzenesulfonamide **4p** (64%) were isolated (Scheme 3).

We then focused our attention towards linear 1-azadienes **6a-f** derived from various chalcones. These substrates present an ambitious challenge as the (5+4) cycloaddition does not come with an aromatization step driving the azadiene to act as a 4-atoms synthon rather than a 2-atom synthon. We first interrogated the behavior of *N*-Ts-azadiene **6a** derived from benzylideneacetophenone and were pleased to observe that the nine-membered heterocycle remained the major product under the previously optimized reaction conditions as a 85:15 mixture of the expected (5+4) cycloadduct **7a** along with cyclopentane **8a** was obtained (74%). The presence of an electron-rich aryl Ar₁, substituted with a methoxy group at the *para* position, did not influence the **7b/8b** (84:16) isomeric ratio but the mixture was isolated in a moderate yield of 47%. Electron-withdrawing groups on Ar₁ restored the

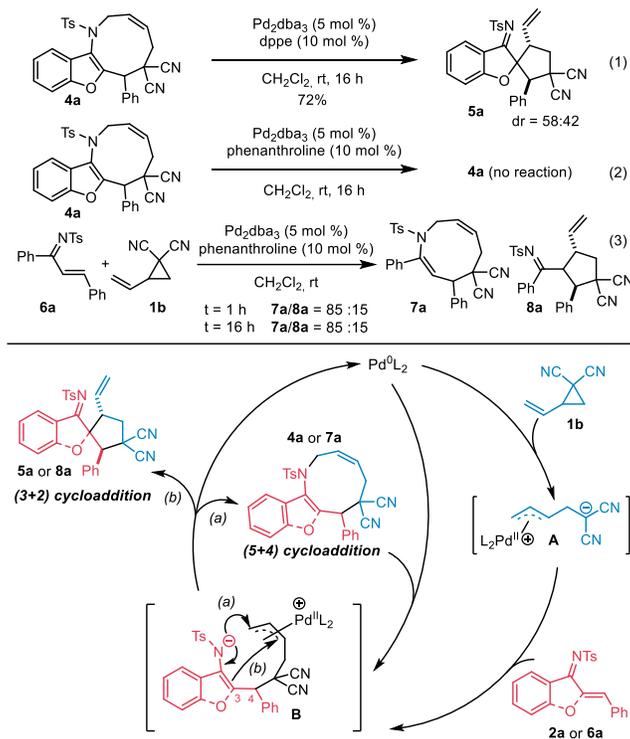
reactivity: azonanes **7c** and **7d** were isolated as the major products with a better selectivity of 90:10 and 87:13, respectively. The ease of preparation of acyclic 1-azadienes bearing different Ar₂ aryl groups allowed us to further review the scope of this monocyclic azonane synthesis. In this case, electrophilic partners with an electron-deficient *p*-nitrophenyl and *p*-trifluoromethylphenyl substituents also reacted promptly to generate **7e** (**7e/8e** = 88:12) and **7f** (**7f/8f** = 91:9) with similar selectivities, showing that electronic properties of these 1-azadienes had little influence on the outcome of the transformation (Scheme 4).



Reaction conditions: **1b** (0.3 mmol), **2** (0.2 mmol), Pd₂dba₃ (0.01 mmol), ligand (0.02 mmol) in solvent (2 mL) at room temperature.

Scheme 4. (5+4) cycloadditions of linear 1-azadienes.^a

A mechanistic rationale was proposed for this (5+4) process relying on Tsuji-Trost chemistry (Scheme 5). After *in situ* formation of the active 14 electrons complex Pd⁰L₂ (L₂ = phen or dppe), its complexation (not shown) with the alkene moiety of VCP **1b** is then followed by an oxidative addition to generate zwitterionic Pd^{II}-π-allyl complex **A**. A Michael addition into azadiene **2a** then generates the key Pd^{II}-π-allyl complex intermediate **B**. The formation of the observed nine-membered ring **4a** could result from pathway (a) after addition of the sulfonamide anion, acting as a bulky soft nucleophile, to the terminal carbon of the π-allyl moiety. An alternative pathway (b) involving the nucleophilic addition of the C₃ carbon onto the substituted carbon of the π-allyl Pd^{II} complex would then lead to the spiro (3+2) cycloadduct **5a**, observed as the side product of the transformation when L₂ = dppe. In this case, the complete conversion of **4a** to **5a** after 4 h (see Scheme 2) could be explained by the ring-opening of kinetic product **4a** and regeneration of zwitterionic intermediate **B** which then cyclizes towards the thermodynamic product **5a** (Scheme 5, Eq 1). When L₂ = phenanthroline, the complete selectivity for the 9-membered ring **4a** (Scheme 5, Eq 2) could be explained by an inhibition of pathway (b) but could also result from a forbidden ring-opening step. We finally established that the lower selectivity for monocyclic azonane **7a** (1 h, **7a/8a** = 85:15) did not evolve after an extended reaction time (Scheme 5, Eq 3), suggesting that no subsequent ring-opening of **7a** (and by analogy **4a**) occurs with a *N,N*-bidentate ligand.



Scheme 5. Control experiments and proposed mechanism.

In this study, we reported a Pd-catalyzed (5+4) cycloaddition between an activated vinylcyclopropane and 1-azadienes as the electrophilic partner to furnish azonanes, a nine-membered *N*-heterocycle. During this process, the VCP acts as a 5-atom synthon and a *N,N*-ligand was necessary to achieve a complete selectivity and avoid the formation of the undesired thermodynamic product originating from a competing (3+2) process. Mechanistic investigations are underway to better understand the selectivity of this transformation with the aim of involving VCPs in other (5+n) cycloadditions.

ASSOCIATED CONTENT

Supporting Information

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

Experimental procedures and NMR spectra for all new compounds (PDF)

Crystallographic data

CCDC 2058000 (**4a**) contains the supplementary crystallographic data for this paper and can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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Notes

The authors declare no competing financial interest.

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(18) XRD analysis of **4a**: CCDC 2058000.

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