Unexpected [2 + 2] C–C bond coupling due to photocycloaddition on orthopalladated (*Z*)-2-aryl-4-arylidene-5(4*H*)-oxazolones†

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A [2 + 2] photocycloaddition has been observed in regioselectively orthopalladated 2-aryl-4-arylidene-5(4*H*)-oxazolones, leading to unprecedented cyclobutane-bis(oxazolones).

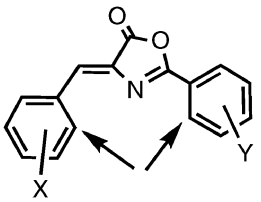
Cyclopalladated complexes are recognized as useful tools in metal-mediated organic synthesis.[1] Several preparative methods are known, but the directed activation of C–H bonds[1] is specially attractive due to its deep implications in functionalization processes.[2,3] The incorporation to a given substrate of aryl,[3a–c] acetate,[3d] halogen,[3e,f] ethoxycarbonyl,[3g] arylsulfonyl[3h] or alkenyl[3i] groups has been reported, among others.[3j,k] Using this methodology new C–C or C–X (X = O, S, N, hal) bonds have been formed in a plethora of molecules.

Oxazolones are important organic precursors and useful building blocks, employed as intermediates in synthesis of compounds of pharmacological interest, in particular of amino acids.[4] Saturated 5(4*H*)-oxazolones have been used in coupling reactions as synthetic equivalents of α-amino acids in the synthesis of peptides. Asymmetric alkylation reactions have been reported for the enantioselective synthesis of acyclic α,α-quaternary amino acids.[5] The outstanding reactivity of the exocyclic double bond of unsaturated 5(4*H*)-oxazolones made them attractive intermediates for the asymmetric synthesis of non-proteinogenic amino acids.[6]

The orthometallation of 5(4*H*)-oxazolones is a scarcely represented process, examples being restricted to saturated compounds with Pd or Ir.[7] The orthometallation of unsaturated 5(4*H*)-oxazolones has never been studied, so our attention has been focussed on the use of the orthopalladation strategy to selectively functionalize these compounds, aiming to design alternative synthetic routes to high-added value modified amino acids. Our first goal is the study of the orthopalladation of oxazolones, the selectivity of the Pd–C bond formation and its reactivity. 2-Aryl-4-arylidene-5(4*H*)-oxazolones (**1a**)–(**1e**) (Fig. 1) were studied. Electron-releasing substituents have been introduced to favour the electrophilic attack to a given ring.

First attempts of orthopalladation of (**1a**)–(**1e**) in standard conditions [$Pd(OAc)_2$, solvent, reflux] were unsuccessful in a wide variety of organic solvents. Under these conditions only **1d**, containing four strong electron-donating OMe groups, two of them at the benzylidene ring, affords **2d** in acetic acid (Scheme 1).

More interestingly, the change of solvent has a noticeable effect on the general course of the reaction.[8] If acetic acid is replaced by trifluoroacetic acid (TFA), all oxazolones shown in Fig. 1 can be orthopalladated. The beneficial effect of the increase in the reaction medium acidity in Pd-mediated C–H bond activations has already been reported, and it is due to the increase in the electrophilicity of the Pd(II) center.[8] Therefore, unsubstituted **1a** reacts easily with $Pd(OAc)_2$ (4 h, 75 °C) to afford **3a**, which is characterized as a TFA-bridged open-book dimer, showing the oxazolone metallated at the benzylidene ring. The presence of strong electron-donating OMe groups at the 2-aryl ring does not alter the regioselectivity of the metallation, since in all cases the Pd is incorporated at the benzylidene ring. This is the case for **3b** and **3c**, which have one or two OMe groups at the 2-aryl ring, respectively. As expected, **3d** is also obtained as a single regioisomer, as was **2d**. The observed regioselectivity is worthy of note, since the obtained six-membered palladacycle seems to be more stable than the hypothetical five-membered ring resulting from C–H bond activation at the 2-phenyl group. In addition, the palladation seems to occur in most cases at the more electron-deficient ring, this fact being hard to justify on the basis of an electrophilic aromatic substitution (S_EAr) mechanism. However, the consideration of a concerted metalation–deprotonation (CMD) pathway, which favours the palladation at the more electron-deficient aryl,[9a–f] together with factors such as the planarity of the cycle or the metalloaromaticity[9g] could help to understand the observed regioselectivity.



X = H; Y = H (**1a**)
3-OMe (**1b**)
3,4-$(OMe)_2$ (**1c**)
X = Y = 3,4-$(OMe)_2$ (**1d**)
X = 4-NO_2 Y = 3,4-$(OMe)_2$ (**1e**)

Fig. 1 5(4*H*)-Oxazolone showing the competitive palladation positions.

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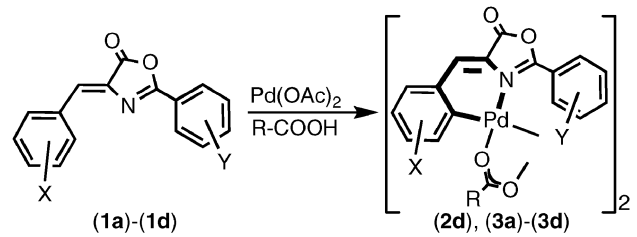
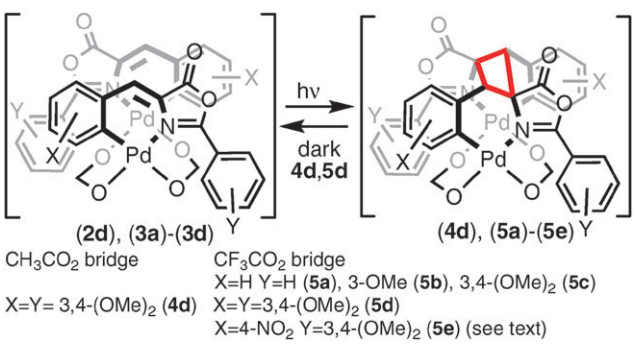


Scheme 1 Synthesis of six-membered orthopalladated oxazolones.

Surprisingly, **2d** and **3a–3d** are not stable in solution (CD_2Cl_2 or $CDCl_3$) when exposed to sunlight, and evolve giving **4d** or **5a–5d** after a [2 + 2] cycloaddition involving the benzylidenic C=C double bond (Scheme 2). As far as we know, only one case of cycloaddition is reported in oxazolones, but it implies the C=N bond.[10] The reaction is unprecedented, not only in oxazolones but in all types of orthopalladated ligands. NMR spectra evidence strong changes on the oxazolone skeleton from the high field shift of the benzylidenic proton H_7 (from ~7.5 ppm in **2–3** to ~4.8 ppm in **4–5**), accompanied with a high field shift of the corresponding ^{13}C signal (C_7 from 138 ppm to 60 ppm), reflecting the hybridization change of this carbon. One of the aromatic protons appears in turn deshielded, this fact explained from the X-ray structure of **5c**.

Complex **5e** is obtained directly from the reaction of **1e** with $Pd(OAc)_2$ in TFA. The intermediate **3e** could not be obtained in pure form since it was always contaminated with **5e**. The latter is the paradigm of how the classical concepts on the orthopalladation do not apply here: the most deactivated 4-nitrobenzylidene ring is regioselectively metallated instead the activated dimethoxyphenyl ring. The necessary role of the sunlight in the cycloaddition is clear, since solutions of **2d**, **3a–3d** do not evolve in the dark. Moreover, solutions of **4d** and **5d** revert partially to the starting **2d** or **3d** when allowed to stand in the dark. The cycloaddition rate seems to be directly related to the nature of the substituents. In the "symmetric" **3d** we observed the slowest photoisomerization (at least 240 h); as the asymmetry on the charge density increases (one OMe in **3b** or two OMe in **3c**) the reaction becomes faster (50 h) and the fastest reaction is observed when the charge density gradient is maximum (**3e**). Therefore, it seems that a higher polarization of the C=C bond implies a faster reaction. The presence of the bridge (acetate or TFA) is clearly essential to promote the



Scheme 2 Photoisomerization of **2–3** and [2 + 2] C–C coupling.

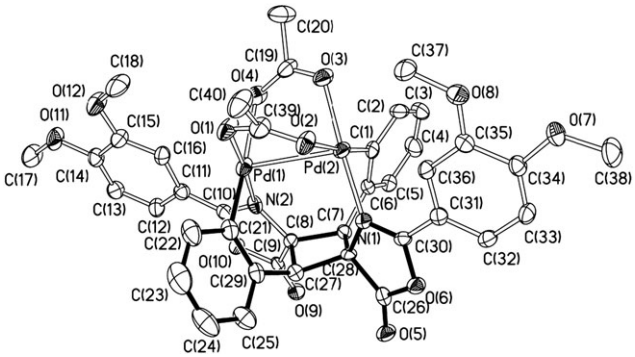


Fig. 2 Molecular drawing (50% ellipsoids) of complex **5c**. H atoms and solvent molecules have been omitted for clarity.

cycloaddition, since the open-book structure ensures the close proximity of the two benzylidenic C=C bonds. In keeping with this, planar (μ-Cl) dinuclear complexes (**6b**, **6c**) or mononuclear acetylacetonate complexes (**7b**, **7c**) (see ESI†) are stable when exposed to natural sunlight. However, the nature of the bridge (OAc *vs.* TFA) seems not to be related to the rate of the cycloaddition since similar rates are obtained for the two bridges (**2d**, **3d**).

The X-ray structure of **5c** has been determined (Fig. 2 and ESI†), showing the presence of the cyclobutane ring on a very distorted bis-oxazolone metallated fragment. In addition, the structure shows two very noteworthy facts. The Pd1–Pd2 bond distance [2.7815(7) Å] is shorter than those found in related carboxylate bridged dinuclear complexes;[11] this fact is probably due to the constraint imposed by the cyclobutane ring. On the other hand, the H atoms bonded to C16, C36, C56 and C76 are in close proximity to the Pd centers (range 2.418–2.692 Å) in such a way that each C–H vector points to the Pd–Pd bond. This type of hydrogen bond interaction, in which the basic Pd center behaves as a proton acceptor has already been described in detail,[12] and it is responsible for the low field shift observed for one aromatic signal in the ^1H NMR spectra.

In conclusion, a regioselective orthopalladation of 5(4*H*)-oxazolones has been achieved. Dimers evolve through [2 + 2] photocycloaddition, giving unprecedented oxazolones.

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