COMMUNICATION

Pd-catalyzed cascade reactions involving skipped dienes: from double carbopalladation to remote C–C cleavage

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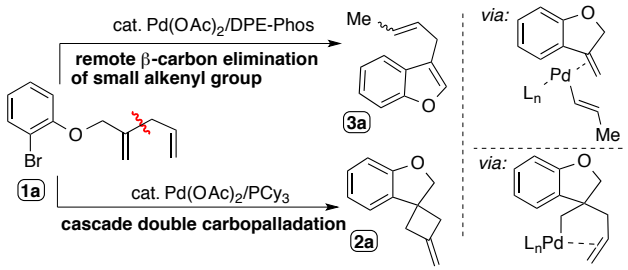
We report two ligand-controlled cascade reactions relying on the intramolecular carbopalladation of skipped dienes. The use of a bulky monodentate phosphine ligand affords [4,5]-spirocycles via sequential double carbopalladation, however bidentate phosphines promote a remote β-C-elimination process which does not rely on the use of strained or sterically hindered substrates.

One of the driving forces that has prompted the study of new synthetic methodologies is the cleavage of ubiquitous C–C bonds.[1] Certainly, harnessing the routes to functionalize these linkages can boost the possibilities to use common carbon skeletons as suitable starting materials, therefore facilitating access to specific molecular substitution patterns. There are two main approaches to tackle the C–C bond functionalization by transition metals: direct C–C activation[2] and β-carbon elimination.[3] The cleavage of C–C bonds becomes specially challenging when they are not involved in strained systems or are located in distal positions to suitable coordinating groups.

The functionalization of remote molecular moieties by means of transition metal catalysis has attracted great interest in recent years.[4] This field relies mainly on: a) the installation of suitable directing groups, and b) cascade reactions where an initial reactive site moves within the molecular skeleton. While these strategies have been deeply studied for the functionalization of remote C–H bonds,[5] they have barely been applied to remote C–C cleavage.[6]

Transient σ-alkyl Pd(II) intermediates arising from intramolecular carbopalladation of alkenes have proven to be a versatile tool for the synthesis of carbo- and heterocyclic scaffolds[5b,7] since they can be directly cross-coupled with a variety of reagents.[8] Moreover, they can perform a remote C–H activation on a pending aryl or alkyl group present in the core structure, giving rise to interesting spirocycles.[5,9] Nevertheless, their potential to promote the C–C cleavage is underexplored.[10]



Scheme 1. Ligand-controlled divergent cascade from skipped dienes.

In 2017, Lautens and co-workers showed that unstrained σ-alkyl-Pd(II) species (generated via intramolecular cascade process) could effectively undergo a β-aryl elimination.[6b] In analogy to the Catellani chemistry,[11] the bulkiness of a sterically demanding 2,6-disubstituted arene on the β-carbon was the driving force of the reaction. Intrigued by these results, and in connection with our interest in the field,[9,12] we set to study the behaviour of 2-haloaryl-substituted ethers (**1a**, Scheme 1) bearing a skipped diene moiety toward Pd(0) catalysis.

We uncovered a ligand-controlled cascade reaction taking place on skipped dienes, which renders either [4,5]-spirocycles upon double carbopallation of the substrate, or 3-allyl substituted benzofurans generated *via* remote C–C cleavage from an unstrained σ-alkyl-Pd(II) intermediate (Scheme 1).

An initial reaction of **1a** in the presence of 10 mol% of $Pd(OAc)_2$, 20 mol% of PPh_3 and 1.5 equiv of Cs_2CO_3 in toluene at 80 ºC gave nearly full conversion of the starting material, affording a 1:2 mixture of the products **2a** and **3a** (Scheme 1). The [4,5]-spirocycle **2a** was the expected product arising from sequential double carbopalladation of the skipped diene followed by β-hydrogen elimination (path **a**, Scheme 2). Intramolecular cascade carbopalladation of alkenes constitute a powerful tool that has allowed the synthesis of [5,6]- and [6,6]-spirocyclic scaffolds.[5] Nevertheless they have barely been applied to the synthesis of the [4,5]-analogues,[13] probably due to the scarce number of published works on 4-exo-trig-

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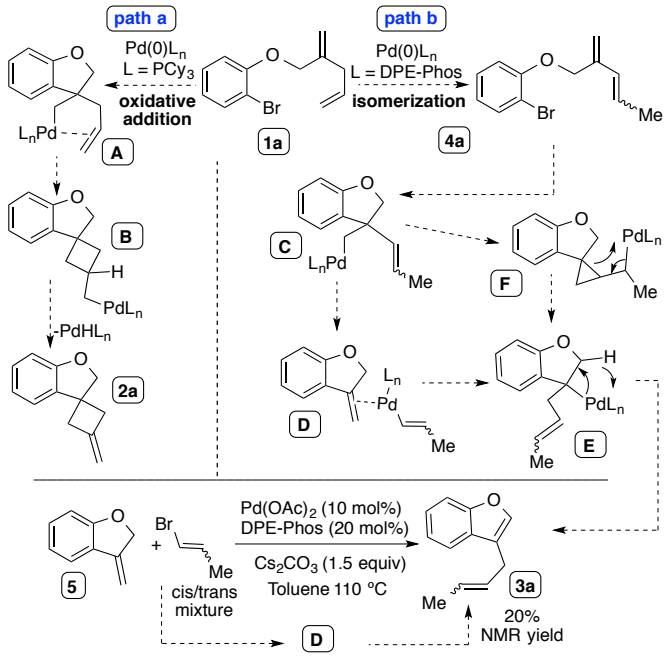
carbopalladation reactions.[14] Noteworthy, cyclobutyl derivatives are valuable starting materials in synthetic methodology,[15a] and more specifically, spirocycles containing four-membered rings have become important moieties in medicinal chemistry discovery programs.[15]

The product **3a** (approx. 10:1 mixture of *E*/*Z* isomers) arose from a more complex molecular rearrangement (*vide infra*). We proceeded to screen the conditions to obtain each type of product selectivity (see full optimization table in the S.I.). We examined the effect of the ligand by using several mono- and bidentate phospines as well as a 1,3-disubstituted imidazolium salt. Gratifyingly, we observed that bidentate phosphines such as Xantphos, DPPF or DPE-Phos dramatically favoured the formation of the benzofuran **3a** with respect to **2a**. The crude ^{1}H-NMR spectra arising from the reactions with Xantphos and DPPF showed variable amounts of a third species, which was identified as the intermediate **4a** (Scheme 2). We then tested the effect of bulky monodentate ligands such as the carbene IMes·HCl or $P(Cy)_3$ and observed a completely reverse selectivity, with the spirocycle **2a** being the main product. The catalytic reaction with the ligand $P(Cy)_3$ showed superior selectivity. No reaction was observed in the absence of $Pd(OAc)_2$ or ligand.

Intrigued by the presence of an intermediate during our optimization studies, we performed the reaction of substrate **1a** in the optimized conditions to get **3a**, and quenched it after 1 h. We observed the isomerization of the skipped diene **1a** into the 1,3-diene **4a** (Scheme 3). The same experiment was repeated with $Pd(OAc)_2$/Xantphos, and $Pd(dba)_2$/DPE-Phos, obtaining similar results. When these reactions were checked after longer reaction times, increasing amounts of **3a** were produced. On the contrary, when the reaction was carried out in the optimized condition to get **2a** ($Pd(OAc)_2/PCy_3$) and stopped after 1 h, only starting material was observed. When the isolated intermediate **4a** was submitted to the $Pd(OAc)_2/PCy_3$ catalytic system, it afforded the benzofuran derivative **3a** (Scheme 3).

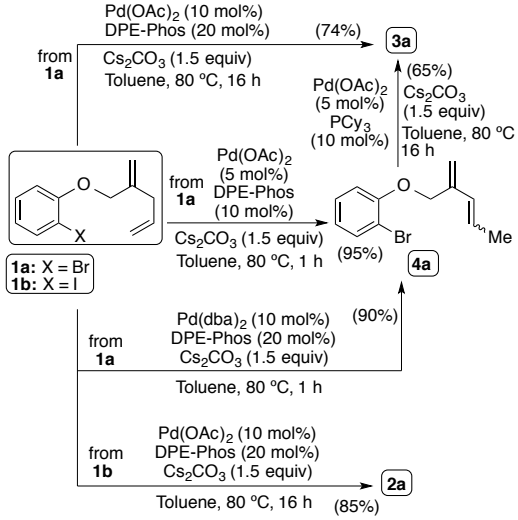
Hence, the ligand must play a crucial role to generate the key Pd species able to promote the initial isomerization leading to the intermediate **4a**, which in turn gives rise to the benzofuran **3a**, since the molecular rearrangement takes place from **4a** irrespectively of the ligand employed (DPE-Phos or PCy_3). Surprisingly, when **1b** was subjected to the reaction conditions with $Pd(OAc)_2$/DPE-Phos, product **2a** was formed in 85% NMR yield (Scheme 3). These results point toward the competition of two Pd-catalyzed processes: the isomerization of the 1,4-diene and the oxidative addition of the aryl–halogen bond. Thus, those factors making the isomerization more difficult (bulky monodentate ligands such as PCy_3 and IMes·HCl) or facilitating the oxidative addition (C–I bond instead of C–Br) favour the selective formation of the spirocycle **2a**.

A plausible mechanism to explain the formation of **2a** and **3a** is depicted in the Scheme 2. The initial oxidative addition of **1a** (path a) leads to a σ-alkyl Pd(II) intermediate **A** that undergoes a second intramolecular carbopalladation followed by a *β*-hydrogen elimination giving **2a**.



Scheme 2. Proposed reaction mechanism.

Nevertheless, when the isomerization of **1a** to the species **4a** takes place in first place, the σ-alkyl Pd(II) species **C** are formed upon intramolecular carbopalladation. **C** could entail a *β*-alkenyl elimination to afford **D** and a migratory insertion leading to a new σ-alkyl Pd(II) species **E**, from which *β*-hydrogen elimination affords the 3-allyl-substituted benzofuran **3a**. Remarkably, the *β*-carbon elimination occurs in a much less sterically hindered scenario than those reported so far in similar species bearing a 2,6-disubstituted bulky arene on that position.[6b] The examples of *β*-vinyl elimination are rather uncommon in the literature[16] compared to the *β*-alkyl,[17] -aryl,[10f,11] -alkynyl,[18] and –allyl[19] elimination, in spite of having similar energy barriers according to DFT studies.[20]

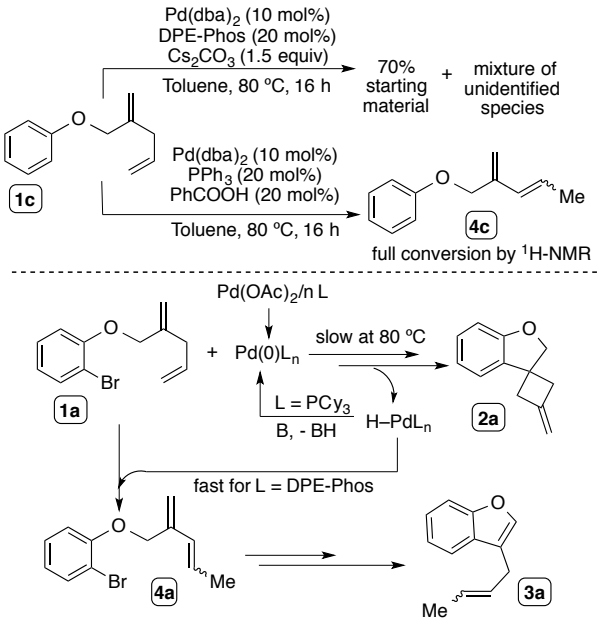


Scheme 3. Detection of intermediate **4a** (^{1}H-NMR yields).

An independent reaction of the dihydrobenzofuran derivative **5** with 1-bromopropene produced the compound **3a** in 20%

NMR yield, proving the feasibility of the step D→E (Scheme 2). The isolation of **4a** excludes the possibility of a retro-allyl mechanism from species **A**, as described in other β-C elimination processes taking place in heteroatomic systems.[19] An alternative 3-exo-trig cyclization occurring via the intermediate **F** can not be ruled out, although this path seems to happen preferentially in olefins involved in cyclic systems.[10]

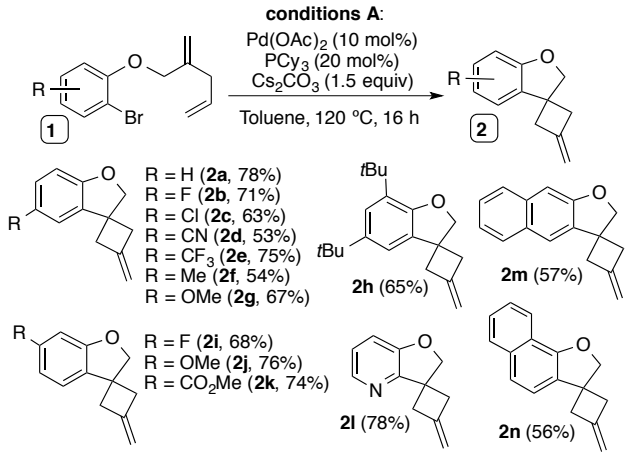
We studied the isomerization of the skipped diene **1a** in order to shed light on the selectivity exerted by the ligand. We submitted the substrate **1c** to Pd(0) catalysis. In contrast to what happened to **1a**, substrate **1c** afforded mainly unreacted starting material (Scheme 4). Pd-catalyzed isomerization of olefins is commonly triggered by Pd–H species.[21] The performance of the reaction in reported conditions to generate Pd-hydride *in situ*[22] proceeded smoothly to give the 1,3-diene **4c** (Scheme 4), analogous to the intermediate **4a**. It seems reasonable to propose that at 80 ºC a slow oxidative addition of small fraction of **1a** to Pd(0)Ln can afford the spirocycle **2a** plus the corresponding H–PdLn complex arising from β-H elimination. When the ligand employed is DPE-Phos, this hydride is able to catalyze the fast isomerization of **1a** to give **4a**. When $P(Cy)_3$ is used instead, the decomposition of the hydride to Pd(0) occurs faster than the isomerization process, hence no intermediate **4a**, and therefore no benzofuran **3a**, is produced.



Scheme 4. Proposed pathway for the selective formation of **2a** and **3a**.

Upon establishing the optimized conditions to obtain selectively each type of product, we studied the scope and limitations of the reaction. We found that aryl substituted ethers **1a**–**p** bearing both electron-donating/withdrawing groups gave moderate to good yields of the [4,5]-spirocycles **2a**–**n** under the $Pd(OAc)_2/PCy_3$ catalysis (Scheme 5).

While substrate **1a** afforded the corresponding products **2a** smoothly at 80 ºC, most of the substrates required higher

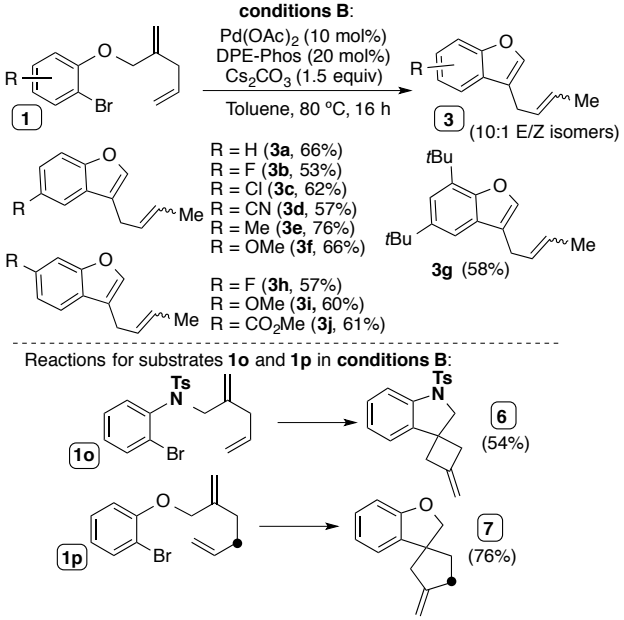


Scheme 5. Substrate scope for the synthesis of [4,5]-spirocycles **2a-n**.

temperatures (120 ºC) for full conversion of the starting materials. Naphthalene derivative **2n** was better obtained at 105 ºC to avoid the formation of by-products.

Next, we turned our attention to the Pd-catalyzed remote β-C elimination cascade. A range of 3-allyl-substituted benzofurans **3a–j** were obtained in moderate to good yields from the corresponding substrates **1** under catalytic $Pd(OAc)_2$/DPE-Phos conditions (Scheme 6).

While the crude reaction mixtures for most of the reactions showed only traces of the corresponding spirocycles **2**, substrate **1k** gave a 4:1 mixture of **3j** and **2k** respectively, probably due to the easier oxidative addition of the C–Br bond in this case. We examined the effect of the variability in the aliphatic chain by submitting the substrates **1o** and **1p** to the $Pd(OAc)_2$/DPE-Phos catalysis. In both cases, the spirocycles **6** and **7** arising from the double carbopalladation process were obtained, instead of the expected allyl-derivatives. These results suggest that the initial 1,4- to 1,3-diene isomerization is



Scheme 6. Substrate scope in conditions to get benzofuran derivatives **3**.

rather sensitive to the bulkiness of the fragment bearing the aryl group, and to the coordination capability of the diene to the metal.

In conclusion, we have shown the control of the selectivity of two competitive Pd-catalyzed processes (oxidative addition and isomerization of olefins) happening on the same substrate in a cascade reaction. This work may serve to show the versatility of Pd-catalyzed cascade reactions in organic synthesis, with special focus on the synthesis of spirocycles and heteroaromatic cores, either via double carbopalladation or carbopalladation/C–C cleavage cascade processes.

This paper is dedicated to Prof. M. Lautens on the occassion of his 60th birthday.

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Conflicts of interest

The results dealing with the synthesis of [4,5]-spirocycles are under protection with a patent application priority number P201930308.

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