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Tandem Reactions | Hot Paper

Palladium-Catalyzed Tandem Cycloisomerization/Cross-Coupling of Carbonyl- and Imine-Tethered Alkylidenecyclopropanes

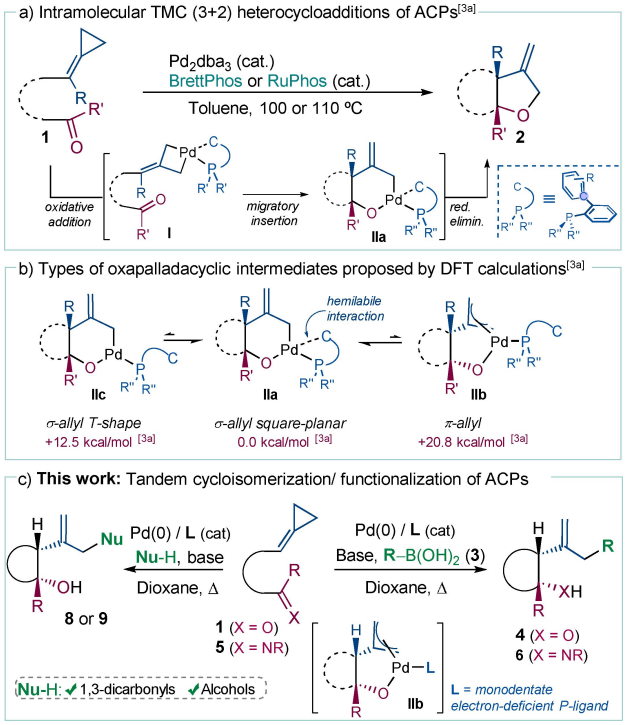
Felipe Verdugo[+], Ricardo Rodiño[+], Martín Calvelo, José Luis Mascareñas, and Fernando López**

Abstract: Pd^0 catalysts featuring phosphorus-based monodentate ligands can detour the reactivity of carbonyl-tethered alkylidenecyclopropanes (ACPs) from standard (3+2) cycloadditions towards tandem cycloisomerization/cross-coupling processes. This new reactivity lies on the formation of key π-allyl oxapalladacyclic intermediates, which are subsequently trapped with external nucleophilic partners, instead of undergoing canonical C–O reductive eliminations. Importantly, the use of imine-tethered ACP's is also feasible. Therefore, the method provides a straightforward and stereoselective entry to a wide variety of highly functionalized cyclic alcohols and amines.

Introduction

Alkylidenecyclopropanes (ACPs) are easily accessible and highly versatile building blocks that have been employed in a number of very appealing synthetic transformations.[1] In particular, they have been extensively used in a wide range of transition-metal catalyzed formal cycloadditions, enabling straightforward entries to a variety of complex (poly)cyclic skeletons.[1,2] While most of these reactions entail carbon-based unsaturated cycloaddition partners,[2] we have recently developed conditions to perform highly efficient (3+2) cycloadditions between ACPs and carbonyls, using Pd^0 catalysts that feature Buchwald type of biaryl phosphines, such as RuPhos or BrettPhos (Scheme 1a).[3] DFT studies revealed that these ligands enable the hetero-cycloadditions by favoring an energetically accessible pathway through key oxapalladacyclic species of type **IIa**. Notably, these σ-allyl square-planar Pd^{II} species, which hold a secondary stabilizing interaction between the Pd center and the biaryl phosphine moiety, are significantly more stable than alternative π- or σ-allyl T-shape tautomers **IIb–IIc**, which lack such hemilabile interactions (Scheme 1b).[3a]

Considering that related, but acyclic Pd^{II} intermediates featuring coordination to both oxygen and carbon atoms have been postulated as intermediates in Suzuki couplings,[4,5] we questioned whether the Pd species of type **II** could be intercepted by an appropriate boron-containing nucleophile, so that the cycloaddition pathway could be diverted towards a cross-coupling process, and eventually deliver 1,2-disubstituted cyclic alcohols, in a stereoselective manner.



Scheme 1. Intramolecular (3+2) heterocycloaddition of ACPs to carbonyls (a); key mechanistic details (b) and the current cascade cycloisomerization involving Pd π-allyl species **IIb**.

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Herein, we demonstrate that this strategy is viable, provided that electron-deficient monodentate phosphorous ligands are used instead of the Buchwald biaryl phosphines. DFT calculations indicate that these ligands favor the formation of π-allyl heteropalladacyclic intermediates of type **IIb** (Scheme 1b), which prefer to evolve through inner or outsphere π-allyl functionalizations, rather than undergoing a C–O reductive elimination towards the (3+2) adducts. The resulting reactivity results in a cycloisomerization/cross-coupling cascade that delivers synthetically relevant five- and six-membered cyclic alcohols bearing vicinal stereocenters with high diastereoselectivity (Scheme 1c, right).[6–8] Importantly, the method can be extended to related imine-tethered ACPs, so that 1,2-disubstituted cyclic amines can also be obtained.

Moreover, we additionally show that the reactivity manifold is not limited to boron-containing nucleophiles, but also viable with other nucleophilic coupling partners, such malonates and phenols, which significantly expands the scope of the methodology (Scheme 1c, left).

Overall, our work demonstrates the enormous power of ligand tuning to control the evolution of palladacyclic intermediates in catalytic processes and provides a new synthetic methodology to build cyclic alcohols and amines in a rapid and efficient manner.

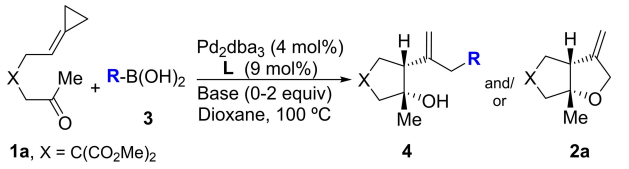
Results and Discussion

We initially tested whether the use of boron-based nucleophiles could allow to trap the palladacyclic intermediates and drive the reaction from a cycloaddition to a cycloisomerization. We selected the ketone **1a** and 4-methoxyphenylboronic acid **3a** as model reactants and screened different types of palladium ligands. When adding 2 equiv of boronic acid **3a** to the milieu, under standard cycloaddition conditions (i.e. using RuPhos or ^{t}BuXPhos as ligands),[3a] we did not observe any product other than the expected cycloadduct **2a** (Table 1, entries 1–3 and Table S1). We then tested simple monodentate ligands which, according to the relative energies indicated in Scheme 1b, may disfavor the cycloaddition path and facilitate the desired alternative pathway. Indeed, treatment of **1a** and **3a** with the catalyst generated in situ from $Pd_2(dba)_3$ (4 mol%) and PPh_3 (9 mol%), in dioxane at 100 °C, provided the desired cyclopentanol **4aa**, which features the hydroxyl group and the allyl moiety in *syn* disposition, with complete diastereselectivity. However, the overall conversion of the process was of only 15% (Table 1, entry 4). In an attempt to further favor the transmetalation process, we tested more electron deficient phosphorus-based ligands.[9] Gratifyingly, the use of the phosphoramidite ligand **L1** (9 mol%), instead of PPh_3, led to **4aa** with an excellent 90% yield and equally complete diastereoselectivity (entry 5). Only traces of the (3+2) cycloadduct **2a** were observed in the crude reaction mixture. A similar result was obtained with the bulky phosphite ligand **L2** (entry 6), while the use of an electron-deficient phosphine ligand, such as **L3**, provided a slightly better yield of **4aa** and negligible amounts of the (3+2) adduct **2a** (entry 7).[10] Furthermore, the amount of Pd catalyst loading could be reduced to 4 mol% without affecting the yield and rate of the process (entry 8). Therefore, these results confirm that by modulating both the coordination, electronic and steric characteristics of the ligand, we can efficiently govern the fate of the organopalladium intermediates.

To preliminary test the generality of these conditions, we evaluated a more challenging boronic acid, the alkenyl derivative **3b**. While using the previous conditions we observed a very poor conversion of **1a**, even after 3 h at 100 °C (entry 9), we were pleased to observe that the addition of an external base led to a significant improvement, likely because of facilitating the transmetalation step (entries 10 and 11). Thus, when an excess of K_3PO_4 (2 equiv) was added to the reaction mixture (entry 11, 80 °C for 1 h), the desired product (**4ab**) was isolated in an excellent 95% yield.

With these optimal conditions in hand, we further analysed the scope of this cycloisomerization/cross-coupling reaction. As can be deduced from Table 2, the reaction tolerates different arylboronic acids bearing electron-donating or withdrawing groups at the *ortho*, *meta* or *para* position of the aromatic ring, affording the corresponding cyclopentanols (**4ac**–**4af**) in yields above 90%. The structure of **4ad** was further determined by X-ray diffraction

Table 1: Optimization of the tandem reaction between keto-ACP **1a** and boronic acids **3a** and **3b**.[a]



1a, X = $C(CO_2Me)_2$ **4** **2a**

Entry	Ligand (**L**)	**3**	Base [equiv]	*t* [h]	**4**, [%] Yield[b]	**2a**, [%] Yield[b]
1	RuPhos	–	–	1	–	90
2	RuPhos	**3a**	–	1	–	90
3	^{t}BuXPhos	**3a**	–	1	–	64
4	PPh_3	**3a**	–	1	**4aa**, (15)	–
5	**L1**	**3a**	–	1	**4aa**, 90	<5
6	**L2**	**3a**	–	1	**4aa**, 90	<5
7	**L3**	**3a**	–	1	**4aa**, 94	<2
8[c]	**L3**	**3a**	–	1	**4aa**, 93	<2
9	**L3**	**3b**	–	3	**4ab**, (25)	–
10	**L3**	**3b**	K_2CO_3 (2)	3	**4ab**, 40 (60)	–
11[d]	**L3**	**3b**	K_3PO_4 (2)	1	**4ab**, 95	–

[a] *Conditions*: A solution of **1a**, boronic acid (**3**, 2 equiv), base (0–2 equiv), Pd_2dba_3 (4 mol%) and Ligand (**L**, 9 mol%) in dioxane (0.05 M) was heated under Ar at 100 °C, unless otherwise noted. Conversion >99% (by ^{1}H NMR of the crude reaction mixture), unless otherwise noted. [b] Yield determined by NMR with an internal standard. Values of conversion are shown under parenthesis. [c] Carried out with Pd_2dba_3 (2 mol%) and **L3** (5 mol%) and 1.5 equiv of **3a**. [d] Carried out at 80 °C.

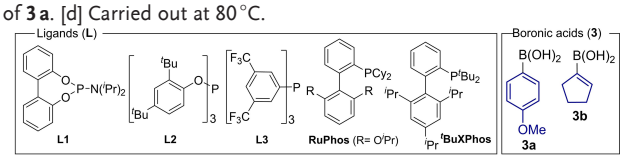


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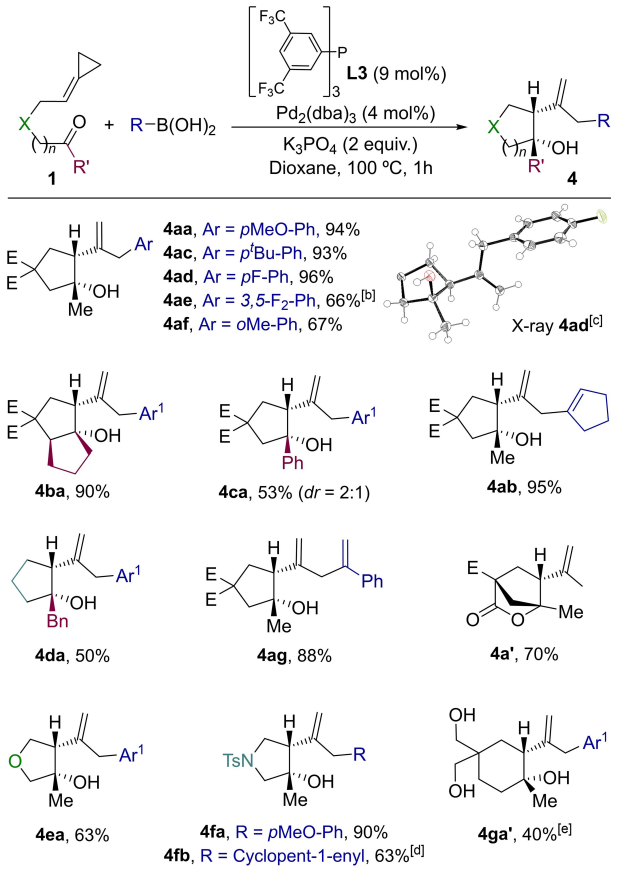
Table 2: Cycloisomerization/Allylic cross-coupling between carbonyl-tethered ACPs **1** and boronic acids **3**.[a]



[a] *Conditions*: A solution of **1**, boronic acid (**3**, 2 equiv), K_3PO_4 (2 equiv), Pd_2dba_3 (4 mol%) and **L3** (9 mol%) in dioxane (0.05 M) was heated under Ar at the indicated temperature. Conversion > 99% (by ^1H NMR of the crude reaction mixture), unless otherwise noted. Isolated yields of **4**. [b] Carried out with K_2CO_3, instead of K_3PO_4. [c] The gem-diester of **4ad** is omitted for clarity. [d] Reaction carried out at 80 °C. [e] Carried out at 90 °C for 16 h with Pd_2dba_3 (6 mol%) and **L3** (9 mol%). Product **4ga′** is obtained after treatment with $LiAlH_4$.[10] E = CO_2Me. Ar^1 = *p*MeO–Ph.

analysis, which confirmed the relative configuration of the stereocenters (Table 2).[11] Notably, the use of an ACP precursor bearing a cyclopentanone moiety, led to the bicyclo[3.3.0]-octanol **4ba**, with complete diastereoselectivity, and with an excellent 90% yield. Likewise, aryl ketones such as **1c** were good reaction partners, providing the product, **4ca**, in 53% yield (*dr* 2:1).

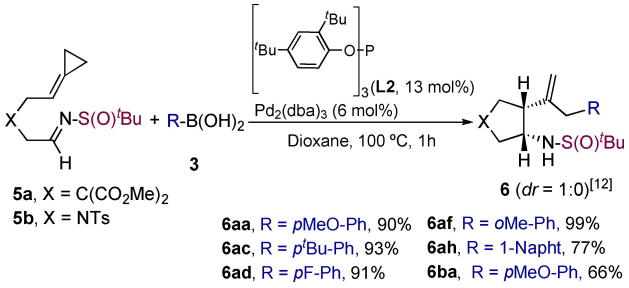
Besides the cyclopentenyl boronic acid **3b**, which afforded **4ab** in 95% yield, other alkenyl derivates such as 1-(phenylvinyl)boronic acid (**3e**) were also suitable partners, delivering the corresponding 1,4-diene product, **4ag**, in an excellent 88% yield and with complete diastereoselectivity.

Curiously, alkylboron species such as *n*-butylboronic acid, also participated in the reaction but, instead of the expected product, it provided the lactone **4a′**, resulting from the interception of the allylic system with a hydride followed by an intramolecular transesterification. This result suggests that after the corresponding transmetalation of the alkyl boron reagent, the resulting alkyl Pd^{II} species evolves by β-hydride elimination, rather than through Csp^3–Csp^3 reductive elimination. The resulting π-allyl Pd^{II} hydride species delivers **4a′** through a C–H reductive elimination, followed by transesterification.[10]

Importantly, the reaction is not restricted to the synthesis of five-membered carbocycles bearing *gem*-diesters at the connecting tether. Indeed, a precursor bearing an unsubstituted carbon chain afforded the 1,2-disubstituted cyclopentanol **4da** in 50% yield, whereas oxygen- or nitrogen-tethered ACPs provided the corresponding tetrahydrofuran (**4ea**) and pyrrolidine derivatives (**4fa–4fb**) in good to excellent yields (63–90%). Finally, the use of a precursor bearing an additional methylene group at the connecting tether, allows to obtain six-membered carbocyclic counterparts, like **4ga′**, as a single diastereoisomer, in 40% yield.

At this point, we wondered whether related cycloisomerizations could be performed using imines, instead of carbonyl partners. Gratifyingly, after screening different imine derivatives and reaction conditions, we found that treatment of the sulfinyl imine **5a** with Pd_2dba_3 (4 mol%), the bulky phosphite **L2** (9 mol%) and K_3PO_4 (2 equiv) gives the desired cyclopentylamine **6aa** in 90% yield, with complete diastereoselectivity at the carbon stereocenters (Scheme 2).[12] Moreover, the reaction tolerated different aryl boronic acids (**6ac–6ad**, **6af–6ah**), as well as the presence of other connecting tethers between the imine and the ACP (**6ba**), delivering in all cases the corresponding products in good yields and complete diasteresoselectivity at the carbocycle.

To shed light into the particular characteristics of these cascade cycloisomerization/coupling processes, and find out the reasons behind the suppression of the (3+2) cycloaddition pathway, we performed a detailed DFT analysis of the reaction between the boronic acid **3a** [*p*(MeO)Ph–B(OH)$_2$] and **1d′**, a precursor very similar to **1a** and **1d** (Figure 1 and Figure S21).[13] We chose as model catalytic species a Pd^0 complex with one $P(OMe)_3$ ligand, since it should mimic the behavior of the active Pd catalysts bearing electron-deficient phosphorous-based ligands (**L1–L3**). Coordination of this Pd complex to the distal position of the cyclopropane (**Int-1**, Figure S21),[10] followed by oxidative addition leads to a palladacyclobutane intermediate **Int-2** ($\Delta\Delta G = 6.9$ kcal mol^{-1}, Figures 1 and S21).[14] At this point, a migratory insertion of the carbonyl might occur via **TS2-3**



Scheme 2. Cycloisomerization/Allylic cross-coupling between imine-tethered ACP's **5** and boronic acids **3**.

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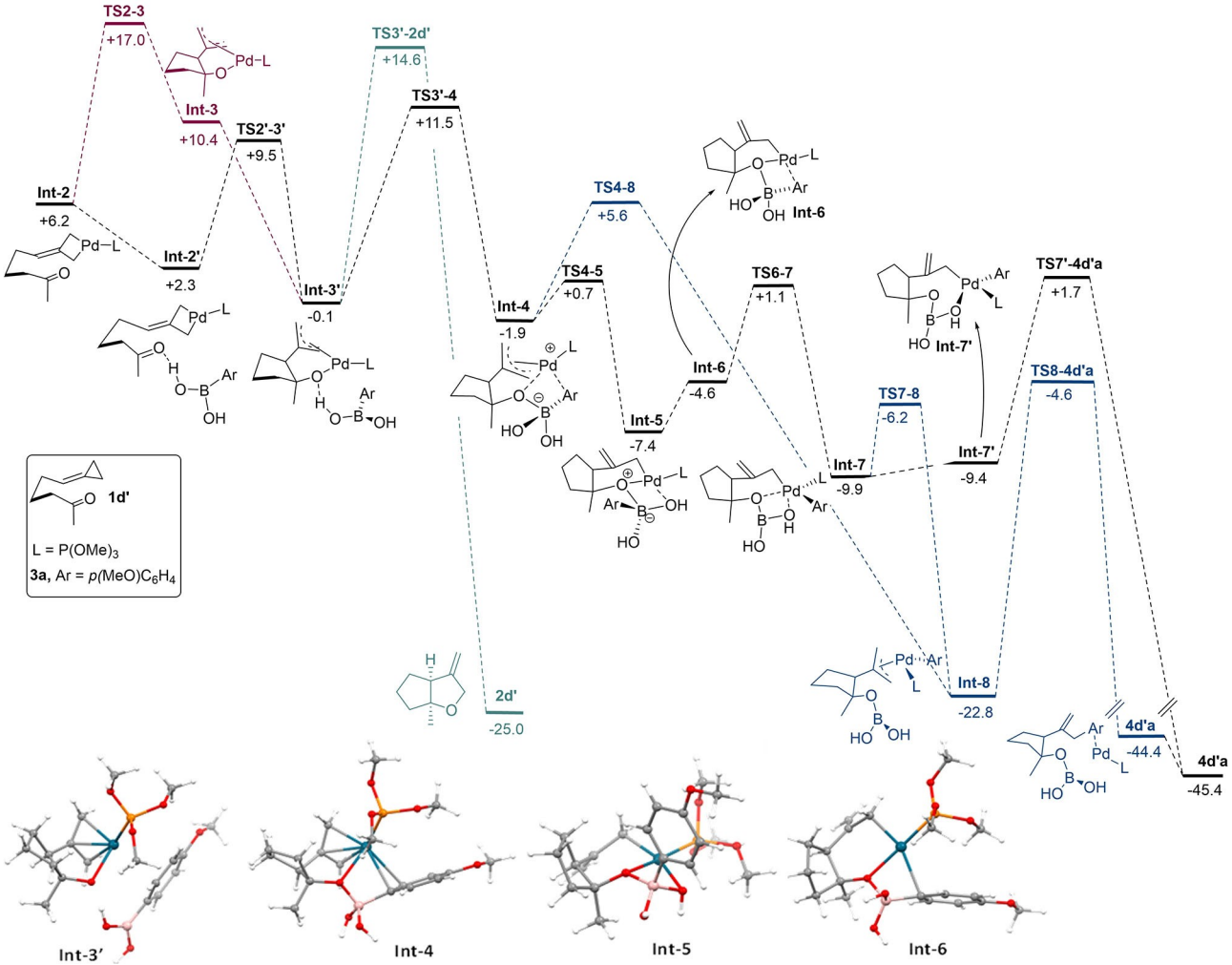

Figure 1. DFT-calculated energy profile ΔG^{solv}(kcal mol^{-1}) for the cycloisomerization/cross coupling of **1 d′** with aryl boronic acid **3 a** [B3LYP/6-31G(d) (LANL2DZ for Pd)//M06/6–311++g(d,p) (SDD for Pd). ΔG values of the stationary points **Int-2**, **TS2-3**, **Int-3**, **2 d′**, **4 da′** include the ΔG value of **3 a**.

(energy barrier of 10.8 kcal mol^{-1}), to deliver the oxapalladacyclic species **Int-3**, analogue to the proposed intermediate **IIb** (Scheme 1b). However, coordination of the boronic acid to the carbonyl oxygen, via hydrogen bonding, enables a more favorable migratory insertion with an energy barrier of only 7.2 kcal mol^{-1} (via **TS2′-3**). The resulting oxapalladacycle, **Int-3′**, similarly to its analog **Int-3**, features a π-allyl ligand that engages the three carbons of the former cyclopropane. The presence of the hydrogen bond accounts for a stabilization of about 10 kcal mol^{-1}. We couldn't identify alternative σ-allyl Pd species (e.g. T-shape tautomers like **IIc**, previously located in the context of the (3+2) cycloaddition using the biaryl phosphine ligand ᵗBuXPhos).[3a]

A reductive elimination from species **Int-3′**, delivering the (3+2) cycloadduct (**4 d′**) can occur with an energy barrier of 14.7 kcal mol^{-1} (via **TS3′-2 d′**, Figure 1). However, we located a significantly more accessible evolution pathway through **TS3′-4** ($\Delta G = 11.6$ kcal mol^{-1}; $\Delta\Delta G = 3.1$ kcal mol^{-1}), to give the aryl boronate intermediate **Int-4**. This new species is readily converted into a σ-allyl palladium(II) complex (**Int-7**), a process which conveys a π-allyl to σ-allyl isomerization (via **Int-5**) and the subsequent transmetalation (**TS6-7**). This intermediate evolves by reductive elimination to the product (**4d′a**) through a very accessible barrier of 11.6 kcal mol^{-1}, a process that initially involves a *cis*—*trans* isomerization at the Pd center to deliver **Int-7′**.

Interestingly, we also located a second route based on a direct transmetalation at the π-allyl intermediate **Int-4**, to yield a π-allyl Pd^{II} species, **Int-8** ($\Delta\Delta G = 7.5$ kcal mol^{-1}). This stable intermediate can also be obtained from **Int-7**, via **TS7-8** ($\Delta G = 3.7$ kcal mol^{-1}). Both reductive eliminations, from **Int-7** and **Int-8**, are compatible with the reaction conditions, and provide the experimentally observed product (**4 d′a**). Probably, the precise structure and electronic properties of the ancillary ligand determine which is the majoritarian reductive elimination path.

Worth to note, we could locate two alternative pathways that deliver the (3+2) cycloadduct **2 d′**, respectively from **Int-4** and **Int-5**, but both of them were significantly less

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favorable than the transmetalation pathway through **Int-7** ($\Delta\Delta G = 4.3$ and 5.8 kcal mol^{-1}, see Figure S22).[10]

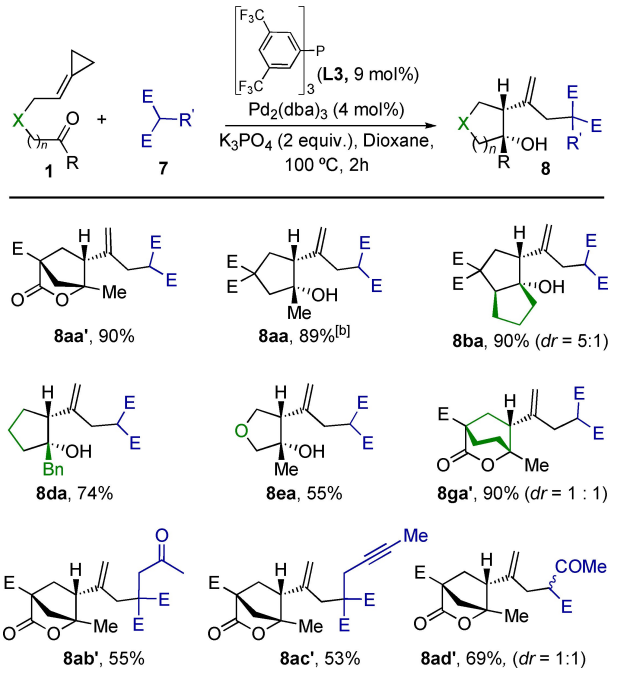
We also calculated key mechanistic steps using a *N*-sulfinyl imine precursor **5b′** (Figure S23, S24). The overall process follows the same steps as for the carbonyl precursor **1d′**; the major difference is related to the migratory insertion of the imine double bond, which is slightly more demanding than that of the methyl ketone ($\Delta\Delta G \approx 2$ kcal mol^{-1}).

Whereas the above data suggest that the tandem reaction requires boronate type of nucleophiles, for promoting the transmetalation/reductive elimination sequence, we wondered if π-allyl palladium(II) species of type **IIb** could be also intercepted by soft nucleophiles, such as malonate anions, as in canonical Pd-catalyzed allylic substitution reactions.[15] Despite this type of nucleophiles usually react through outer- rather than inner-sphere pathways, we were glad to see that the conditions used for the coupling with boronic acids also enable the reaction between ACP **1a** and dimethylmalonate (**7a**), to afford the lactone **8aa′**, in 90 % yield (Table 3). The intramolecular transesterification of the initially expected cyclopentanol (**8aa**) can be avoided by using K_2CO_3 instead of K_3PO_4, so that **8aa** could be isolated in 89 % yield.[10] The precursor bearing a cyclopentanone moiety afforded the bicyclo[3.3.0]octanol derivate **8ba** in 90 % yield (*dr* 5:1).

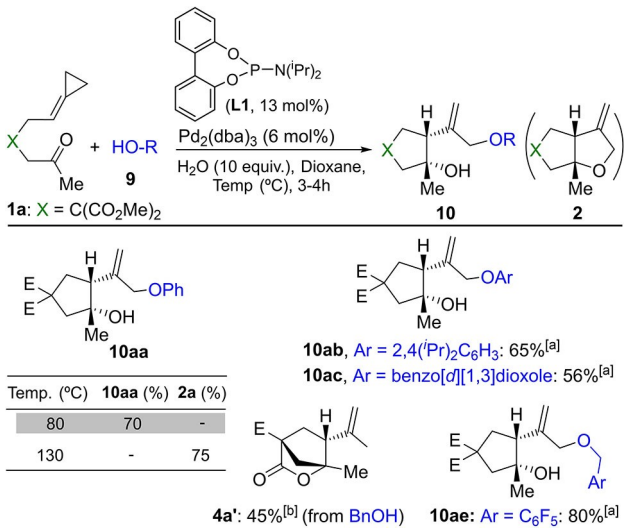
Likewise, the cascade reaction can be implemented in ACPs that lack the *gem*-diester motive at the tether. Therefore, the cyclopentanol **8da** and the tetrahydrofuran derivative **8ea** were obtained in good yields, as single diastereoisomers. The formation of cyclohexanols is also possible, so that the lactone **8ga′**, resulting from an intramolecular transesterification, could be obtained in an excellent 90 % yield (*dr* 1:1). Finally, we confirmed that monoalkylated malonates and other 1,3-dicarbonyl compounds, such as ethyl acetoacetate, are also competent nucleophiles, so that products like **8ab′**, **8ac′** or **8ad′** could be obtained in moderate to good yields (Table 3).[16]

Importantly, besides carbon-based nucleophiles, we tested phenols as intercepting, nucleophilic reagents. After a screening of conditions (Table S2), we found that treating ACP **1a** with phenol (2 equiv), Pd_2dba_3 (6 mol %), phosphoramidite **L1** (13 mol %) and water (10 equiv) at 80 °C, generates the desired product **10aa**, which was isolated in 70 % yield (Scheme 3). The addition of water (10 equiv) was required in this case to warrant reproducibility, probably because it favors the overall homogeneity of the mixture. Curiously, when this reaction was carried out at higher temperatures, such as at 130 °C, the formal cycloadduct **2a** was exclusively obtained (75 % yield). In the absence of phenol (**8a**), under otherwise identical reaction conditions at 130 °C, only traces of **2a** were observed, which confirms that phenol is required to obtain **2a**. Moreover, treatment of **10aa** with the Pd catalyst at 130 °C directly led to the cyclic ether **2a** (70 % yield, 1 h, Figure S20). These and additional control experiments[10] strongly suggest that **10aa** is formed at 80 °C, but at higher temperatures evolves to the tetrahydrofuran derivative **2a**, most probably via insertion of the Pd^0 catalyst into its C–O bond, followed by an intramolecular π-allyl nucleophilic displacement by the hydroxyl group.

Table 3: Cycloisomerization/Nucleophilic addition between ACPs **1** and 1,3-dicarbonyls **7**.[a]



[a] *Conditions*: A solution of **1**, 1,3-dicarbonyl **7** (2 equiv), Base (2 equiv), Pd_2dba_3 (4 mol %) and Ligand (**L3**, 9 mol %) in dioxane (0.05 M) was heated under Ar at the indicated temperature. Conversion > 99 % (by ^{1}H NMR of the crude reaction mixture), unless otherwise noted. Isolated yields of **8** are provided. [b] Reaction carried out using K_2CO_3 as base. E = CO_2Me.



Scheme 3. Cycloisomerization/Cross-coupling between carbonyl-tethered ACP's **1** and alcohols **9**; *Conditions*: A solution of **1**, R–OH, water (10 equiv), Pd_2dba_3 (6 mol %) and **L1** (13 mol %) in dioxane (0.05 M) was heated under Ar at the indicated temperature. [a] Carried out at 80 °C. [b] Carried out at 90 °C. E = CO_2Me.

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The cycloisomerization/etherification cascade reaction could be translated to other aromatic alcohols (**10ab**–**10ac**). Interestingly, the use of benzyl alcohol led to the reduced adduct **4a′** (45 % yield), probably due to a β-hydride elimination at the oxy-allyl-palladium species **III**, which delivers a palladium hydride intermediate (**IV**).[17] This competitive pathway can be deactivated by using an electron deficient benzyl alcohol such as pentafluorobenzyl alcohol, which afforded the product **10ae** in 80 % yield, as a single stereoisomer (Scheme 3).

Finally, we carried out a preliminary DFT analysis of the cycloisomerization/alkylation process with malonate (Figures 2 and S25). As initial species we used the key π-allyl oxapalladacyclic intermediate **Int-3**, which is obtained from **Int-2** after the carbonyl migratory insertion (Figure 1). Our results indicate that the outer-sphere attack of a malonate anion, such **7a**$^-$, to this species (**Int-3**) can occur through a very accessible energy barrier of only 7.9 kcal mol^{-1}, directly leading to **8da′** (Figure 2). On the other hand, the transition state leading to the (3+2) cycloadduct **2d′** lies 1.6 kcal mol^{-1} above (**Int-3**–**2d′**), which is in qualitative agreement with the experimental results.

Overall, the calculations confirmed that when using monodentate phosphorous type of ligands such as **L1**–**L3**, the intramolecular reaction of ACPs and carbonyls (or imines) prefers to proceed through π-allyl oxapalladacyclic intermediates of type **Int-3**, which can be favorably intercepted by nucleophiles through either inner- or outer-sphere pathways.

This contrasts with the experimental results obtained using bulky biaryl phosphines (e.g. RuPhos, ^{t}BuXPhos),[3a] which produce the (3+2) cycloadducts, regardless the presence of an excess (2 equiv) of boronic acid in the media (Table 1, entries 1–3 and Table S1). A DFT exploration of the reaction between model ACP **1d′** and the boronic acid **3a**, using ^{t}BuXPhos as ligand confirms that the formation of σ-allyl square planar species of type **IIa** (Scheme 1b), wherein the palladium center establishes a hemilabile interaction with the biaryl moiety, is favored over π-allyl intermediates **IIb** (Figure S26). This selectivity is key to preserve the (3+2) cycloaddition reactivity. Indeed, coordination of the boronic acid to this species leads to significantly less stable intermediates ($\Delta G > 5.5$ kcal mol^{-1}), disfavoring the transmetalation process (Figure S26).

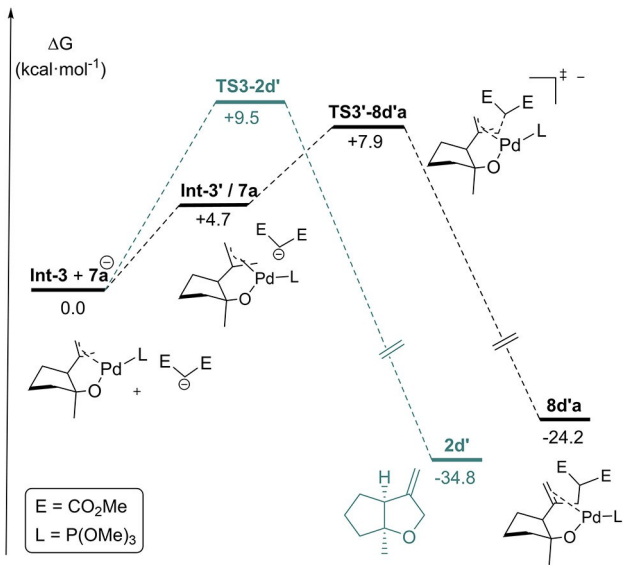

Figure 2. Key step of the DFT-calculated energy profile ΔG^{solv} (kcal mol^{-1}) for the cycloisomerization/alkylation of **1d′** with **7a**.

Conclusion

In summary, we have demonstrated how subtle changes in the characteristics of the ancillary ligand can completely alter the outcome of Pd-catalyzed reactions of ACPs with carbonyls. While Buchwald-type of phosphines, owing to their intrinsic ability to establish a second hemilabile coordination, favor the formation of σ-allyl oxapalladacyclic intermediates that deliver (3+2) cycloadducts, electron-deficient phosphorous-based ligands allow the selective formation of alternative π-allyl oxapalladacyclic species, which can be easily intercepted with different nucleophiles. As a result, highly interesting cyclic alcohols are obtained in a very robust, versatile and stereoselective manner. This highly diastereoselective, Pd-catalyzed cycloisomerization/cross coupling reactions can also be used with imines, instead of carbonyl partners.

In addition to the methodological contribution, our results confirm that metallacyclic species formed in metal catalyzed cycloadditions can be made to evolve through different reaction pathways, just by playing with the properties of the metal ligands. This concept might be extended to other processes that involve similar types of intermediates.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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[10] See the Supporting Information for further details.

[11] Deposition Number 2158745 (for **4da**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

[12] a) The use of ligand **L1** provided somewhat lower yields than **L2**; b) Products **6** consist of a 1:1 mixture of diastereoisomers at the sulfoxide center. They can be separated by chromatography and independently transformed to the same sulphonyl derivative by treatment with mCPBA. See the Supporting Information.

[13] DFT calculations have been carried out with Gaussian 09. The geometries of all species were optimized using the B3LYP hybrid functional together with the 6–31G(d) basis set for C, H, O, P and B, as well as the LANL2DZ basis set for Pd. Single-point calculations of the optimized systems were carried out using the hybrid functional M06 together with the 6–311++g(d,p) basis set for C, H, O, P and B, and the Stuttgart-Dresden (SDD) ECP for Pd, in dioxane and or toluene (using SMD model). See the Supporting Information for further details.

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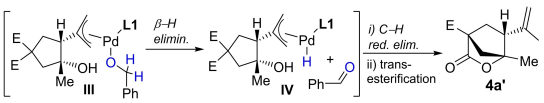
[16] The reactions leading to **8ab′** and **8ac′**, also provided variable amounts of the hydrogen-substituted product **4a′** (20–30 % yield aprox.).

[17] Mechanistic proposal for the formation of **4a′** from **1a** and BnOH



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