Pd–Catalyzed (3 + 2) Heterocycloadditions between Alkylidenecyclopropanes and Carbonyls: Straightforward Assembly of Highly Substituted Tetrahydrofurans

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Felipe Verdugo,† Eduardo da Concepción, † Ricardo Rodiño, † Martín Calvelo, † José L. Mascareñas,* † and Fernando López*‡,†

†Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CiQUS) and Departamento de Química Orgánica. Universidade de Santiago de Compostela, 15782, Santiago de Compostela, Spain

‡ Instituto de Química Orgánica General (CSIC), Juan de la Cierva 3, 28006, Madrid, Spain

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ABSTRACT: A Pd catalyst made from a Pd(0) source and a bulky biaryl phosphine ligand promotes highly efficient intramolecular (3 + 2) heterocycloadditions between alkylidenecyclopropanes (ACPs) and carbonyls. The annulations provide a straightforward access to fused polycyclic systems featuring β-methylene tetrahydrofuran moieties. DFT data support a pallada-ene process and shed light on the critical role of hemilabile interactions between the Pd center and the bulky biaryl phosphine. Significantly, these Pd(0) catalysts are also effective for promoting intermolecular formal cycloadditions between ACPs and trifluoromethyl ketones, thus providing for a direct entry to chiral THFs bearing trifluoromethyl–substituted carbons.

Modern organic synthesis demands the development of sustainable methods that allow to transform readily available precursors into complex, target–relevant products.[1] In this context, formal cycloadditions promoted by transition metal catalysts are extremely attractive, as they offer the potential to build relevant (poly)cyclic systems from simple acyclic precursors, in an atom–efficient manner.[2] Most metal-catalyzed cycloadditions involve the coordination/activation of unsaturated C–C bonds,[3] albeit recently, a variety of formal cycloadditions initiated by the activation of C–H and C–C single bonds have attracted great interest, owing to the possibility of generating reactive metalacyclic species from basically inert structures.[4,5]

In this context, we and others have shown that alkylidenecyclopropanes (ACPs) can be employed as three-carbon (3C) components in a variety of transition metal–catalyzed (TMC) formal cycloadditions to afford different types of (poly)carbocyclic systems (Scheme 1a, right).[6,7] Usually, these reactions are initiated by oxidative addition of the metal catalyst –typically featuring Pd, Rh, Ni or Ru– to either the proximal or distal C–C bond of the ACP. The resulting metallacyclobutanes evolve through migratory insertions of C–C unsaturated partners (e.g. alkenes, alkynes, dienes or allenes), prior to a final reductive elimination that delivers the adduct.[8]

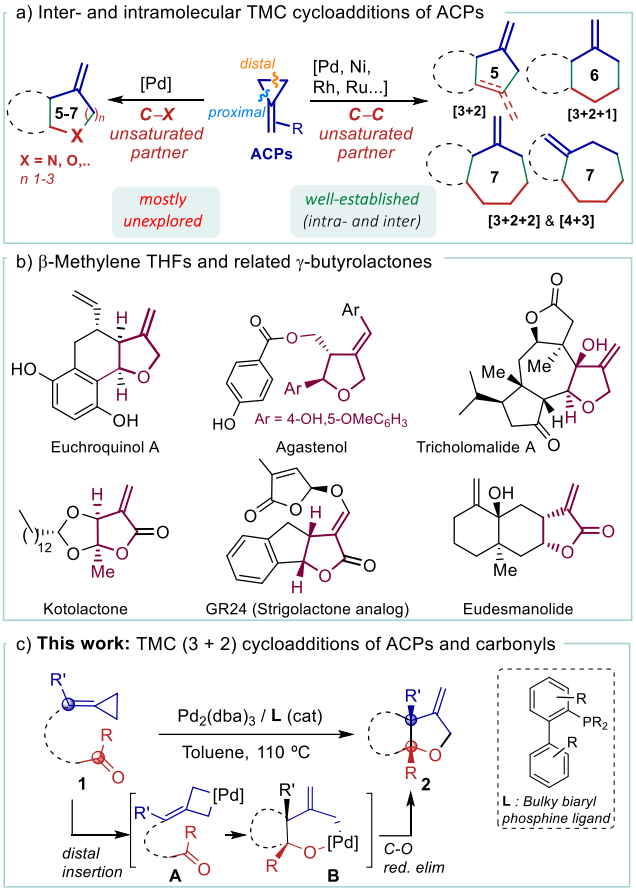
Strikingly, the potential of ACPs in TMC cycloadditions with heteroatom-containing partners is essentially unexplored (Scheme 1a, left).[9] Among the few isolated cases reported, there is only one example of a TMC cycloaddition with carbonyls,[9a] and the method is restricted to intermolecular reactions of specific aromatic aldehydes. Moreover, it requires neat conditions, and the tetrahydrofuran adducts are obtained in low to moderate yields and with poor stereocontrol.

Considering the profusion of β-methylene tetrahydrofuran motifs (THFs), and related γ-butyrolactones in natural and non–natural relevant bioactive molecules,[10] the discovery of cycloaddition methods to build these heterocycles is of major interest.[11,12] In many cases, these scaffolds are fused to other cyclic systems, as part of more complex polycyclic structures (Scheme 1b);[10,13] therefore, the development of stereoselective intramolecular variants that can directly afford fused-THFs is especially attractive.[14]

Herein, we demonstrate that Pd catalysts made from palladium (0) sources and bulky biaryl phosphine ligands are able to promote efficient intramolecular (3 + 2) cycloadditions between ACPs and carbonyls, to give polycyclic systems featuring β-methylene THFs (Scheme 1c). The reaction presents a broad scope, and the adducts can be readily manipulated to provide appealing α-methylene-γ-butyrolactone derivatives and other relevant oxacycles. Moreover, we also demonstrate that these Pd catalysts can promote intermolecular annulations of ACPs with α–trifluoromethyl ketones. This represents the first direct entry to *exo*-methylene THFs bearing CF_3 groups. Finally, we also present DFT data that support pallada-ene type of mechanisms, and shed light on the critical role of hemila-

bile Pd–phosphine interactions to warrant energetically accessible processes.

Scheme 1. Previous TMC Cycloadditions of ACP's, Relevant Methylene THFs and Related Lactones; This work

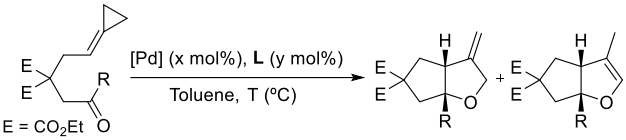


The viability of the transformation was first assessed using aldehyde **1a** as model substrate (Tables 1 and S1). Curiously, conditions that had been very effective in previous (3 + 2) cycloadditions between ACPs and alkenes, allenes or alkynes,[7b,d,e] failed to give satisfactory results. Thus, catalysts generated from $Pd_2(dba)_3$ and $P(O^iPr)_3$ or the bulky aryl phosphite **L1**, led to an untreatable mixture of products (Table 1, entries 1 and 2). A Pd catalyst bearing the phosphoramidite ligand **L2**, previously used for the ACP cycloadditions with dienes,[7d] afforded the desired cycloadduct **2a** (vide infra), albeit in a very low yield (entry 3). Moreover, the catalysts previously used by Yamamoto for the intermolecular cycloadditions with aldehydes, or related imines, [i.e. $Pd(PPh_3)_4$ (12 mol%) / $R_3P{=}O$ (24 mol%)],[9] provided sluggish reactions (Pd black observed), moderate conversions and yields below 35% (entries 4 and 5 and Table S1).

Considering that these fails could be associated to a problematic C(sp^3)–O bond formation,[15] we focused our attention on the use of bulky biaryl phosphines as ancillary ligands, as they had demonstrated to be effective in carbon–heteroatom bond forming reactions involving Pd(0)/Pd(II) catalytic cycles.[16] Gratifyingly, despite these ligands had never been shown successful in related TMC ACP cycloadditions, we found that Pd(0) catalysts generated *in situ* from $Pd_2(dba)_3$ and some of these phosphines enabled a smooth cycloaddition of **1a**, generating the desired product in appreciable yields (entries 6-8 and Table S1). In particular, the reactions using XPhos and BrettPhos as ligands afforded, after 3h in refluxing toluene, the fused–THF adduct **2a** as a single stereoisomer, in good isolated yields (71 and 75%, respectively; entries 7, 8).[17] Traces of the isomeric adduct **2a'**, could also be detected by ^{1}H-NMR in the crude mixtures. Interestingly, the reaction catalyzed by $Pd_2(dba)_3$ / BrettPhos was also efficient with lower catalyst loadings and at lower temperatures (entries 9 and 10). Thus, using just 2 mol% of catalyst, **2a** could be isolated in 74% yield, after 3h at 100 ºC (entry 9). Alternative Pd(0) sources such as CpPd(π–cynnamyl),[7r] led to lower yields (Table S1).

We then evaluated the feasibility of promoting the annulation of a precursor bearing a ketone, instead of the aldehyde, as this would allow the stereoselective assembly of fused–THF skeletons bearing fully substituted carbons at the ring fusion. Gratifyingly, treatment of the methyl ketone **1b** with the catalyst generated from $Pd_2(dba)_3$ and BrettPhos, led to a clean formation of **2b**, which was isolated in 65% yield (entry 11). This value could be further improved by using ^{t}BuXphos (entry 12) and RuPhos (entry 13). In all these cases, the reaction proceeded with complete selectivity towards the *cis*–fused isomer and, importantly, it could also be carried out with equal efficiency by using only 2 mol% of catalyst (entry 14, 90% yield).

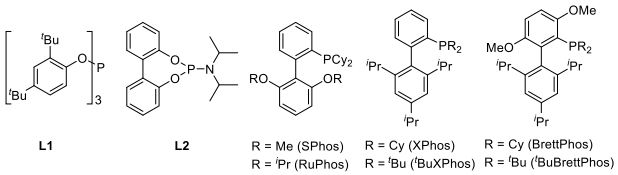
Table 1. Optimization of the (3 + 2) cycloaddition of carbonyl–tethered ACPs 1[a]



entry	[Pd] (x mol%)	L (y mol%)	R	T (ºC)	*t* (h)	**2** (%)[b]	**2'** (%)[b]
1	$Pd_2(dba)_3$ (6)	$P(O^iPr)_3$ (13)	H	110	3	–	–
2	$Pd_2(dba)_3$ (6)	**L1** (13)	H	110	3	–	–
3	$Pd_2(dba)_3$ (6)	**L2** (13)	H	110	3	20	5
4[c]	$[Pd(PPh_3)_4]$(12)	$P(O)Bu_3$ (24)	H	120	3	35 (40)	–
5[c]	$[Pd(PPh_3)_4]$(12)	$P(O)Ph_3$ (24)	H	120	3	30 (55)	–
6	$Pd_2(dba)_3$ (6)	RuPhos (13)	H	110	3	45	<5
7	$Pd_2(dba)_3$ (6)	XPhos (13)	H	110	3	71[d]	<5
8	$Pd_2(dba)_3$ (6)	BrettPhos (13)	H	110	0.5	75[d]	<5
9	**$Pd_2(dba)_3$ (1)**	**BrettPhos(3)**	**H**	**100**	**3**	**74[d]**	-
10	**$Pd_2(dba)_3$ (2.5)**	**BrettPhos (6)**	**H**	**80**	**4**	**71[d]**	–
11	$Pd_2(dba)_3$ (6)	BrettPhos (13)	Me	110	3	65	–
12	$Pd_2(dba)_3$ (6)	^{t}BuXPhos (13)	Me	110	3	80	–
13	$Pd_2(dba)_3$ (6)	RuPhos (13)	Me	110	3	90	–
14	**$Pd_2(dba)_3$ (1)**	**RuPhos (3)**	**Me**	**110**	**4**	**90[d]**	–

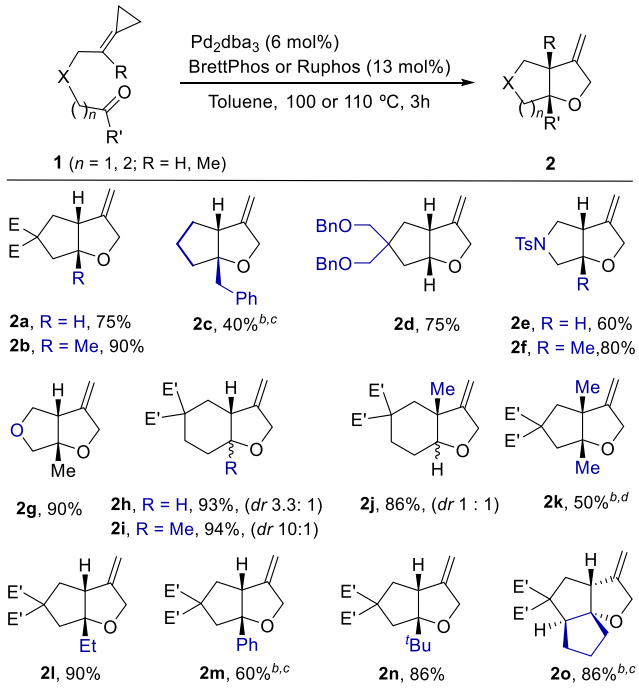
[a] *Conditions*: A solution of [Pd] (x%), L (y%) and **1** in toluene was heated under Ar at the indicated temperature. Conversion > 99% (by ^{1}H–NMR of the crude mixture), unless otherwise noted. [b] Yield determined by NMR with an internal

standard. Conversions under parenthesis. [c] Conditions adapted from references. 9a and 9b. [d] Isolated yields.



With these optimal conditions at hand, we evaluated the scope of the method by using $Pd_2(dba)_3$ and BrettPhos, for aldehyde–containing precursors, or RuPhos, for the ketone counterparts (Table 2). Gratifyingly, the cycloaddition works in precursors bearing nitrogen– and oxygen–containing tethers, to give fused bicyclic THFs such as **2c–2g** in good to excellent yields and complete stereoselectivity. It is also possible to increase the length of the connector (**1h**, R' = H, *n* = 2) to produce cyclohexane–fused methylene-THFs like **2h** (93%, 3:1 mixture of *cis*– and *trans*–fused isomers) or **2i** (R' = Me, *n* = 2, 94% yield, *cis*:*trans* ratio = 10:1).[18] Notably, the annulation could also be carried out with a precursor that bears a methyl group at the internal alkene position of the ACP (**1j**, R = Me, *n* = 2), to afford the corresponding bicyclic product **2j**, featuring a quaternary carbon stereocenter at the ring fusion (86% yield). Additionally, the related ketone precursor **1k** (R, R' = Me, *n* = 1) delivered the fused–THF **2k** which holds two quaternary centers at the ring fusion. This reaction requires a somewhat higher temperature but takes place with full stereoselectivity towards the *cis*–fused isomer, as judged by NMR and X–ray analysis (Figure 1).[18]

Table 2. (3 + 2) intramolecular cycloaddition between ACPs and carbonyls[a]



[a] *Conditions*: A solution of **1**, Pd_2dba_3 (6 mol%) and Ligand (13 mol%; BrettPhos for aldehydes, and Ruphos for ketones) in toluene was heated (at 100 ºC for aldehydes or reflux for ketones) for 3h, unless otherwise noted; Conversions > 99%; dr's (1:0, unless otherwise noted) determined by ^{1}H–NMR of the crude mixture. Isolated yields of **2** are provided. [b] The mixture was degasified before heating. [c] Carried out at 100 ºC for 5 h. [d] Carried out at 130 ºC for 5 h. E' = CO_2Me; E = CO_2Et.

Notably, the reaction tolerates different substituents at the carbonyl moiety, such as ethyl, benzyl, phenyl and even a *t*–butyl group. The expected cycloadducts (**2c**, **2l–n**) were obtained with good to excellent yields and complete diastereoselectivities. The relative configuration of the adducts was established by NMR, and that of **2n** was further verified by X–ray analysis (Figure 1).[18]

Finally, we also tested the cycloaddition of a substrate bearing the ACP tethered to a cyclopentanone moiety through its α– carbonyl position (**10**). Despite this precursor already holds a stereocenter, the cycloaddition proceeded smoothly, delivering the tricyclic adduct **20**, which exhibits three consecutive stereocenters, in excellent yield and complete diastereoselectivity. Its relative stereochemistry was determined by X–ray analysis, which confirmed the *cis* fusion (Figure 1).

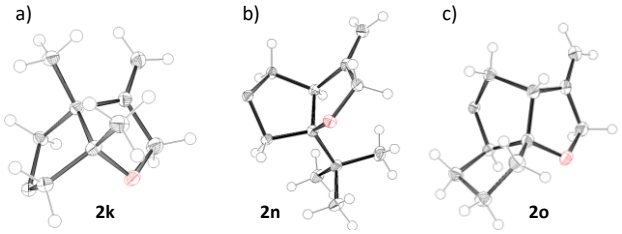
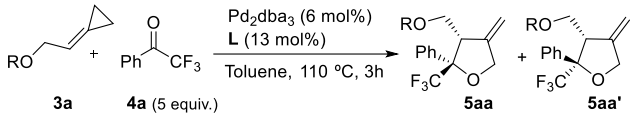


Figure 1. X–ray diffraction analysis of cycloadducts **2k, 2n** and **20** (gem-diesters are omitted for clarity)

Considering the broad scope of the intramolecular processes, we also explored intermolecular variants. Treating ACP **3a** with an excess of carbonyl partners such as benzaldehyde or acetophenone, in the presence of the Pd-Ruphos catalyst, led to complex reaction mixtures in which we could not detect the desired (3 + 2) hetero–adducts (Table S2).[18] Therefore, we turned our attention to trifluoromethyl ketones, assuming that the CF_3 group could inductively activate the carbonyl moiety while hampering potentially competitive β–hydride elimination processes. Furthermore, it is well known that the introduction of trifluoromethyl groups in bioactive molecules is highly relevant from the standpoint of drug discovery.[19] Additionally, the number of catalytic methods for the assembly of THFs featuring these groups is very limited.[20]

Gratifyingly, when ACP **3a** and trifluoroacetophenone (**4a**, 5 equiv.) were refluxed in toluene (0.1 M) in the presence of $Pd_2(dba)_3$ (6%) and Ruphos (13%), the (3 + 2) cycloaddition proceeded smoothly to afford the desired β-methylene THF, as a 1.4: 1 mixture of diastereoisomers (**5aa**:**5aa'**), with complete regioselectivity, and 95% overall yield (Scheme 2).[21] Other ligands such as BrettPhos, ^{t}BuBrettPhos, Xphos or ^{t}BuXPhos also provided similar yields, and diastereomeric ratios varying from 1.4:1 to 1.7:1. Notably, by using Ruphos, the amount of trifluoroacetophenone could be reduced down to 2 equiv., and the catalyst loading to 4 mol%, without any loss of efficiency (93% yield, dr = 1.4.1, Scheme 2).

Scheme 2. Intermolecular (3 + 2) cycloadditions between ACPs and α,α,α-trifluoroacetophenone



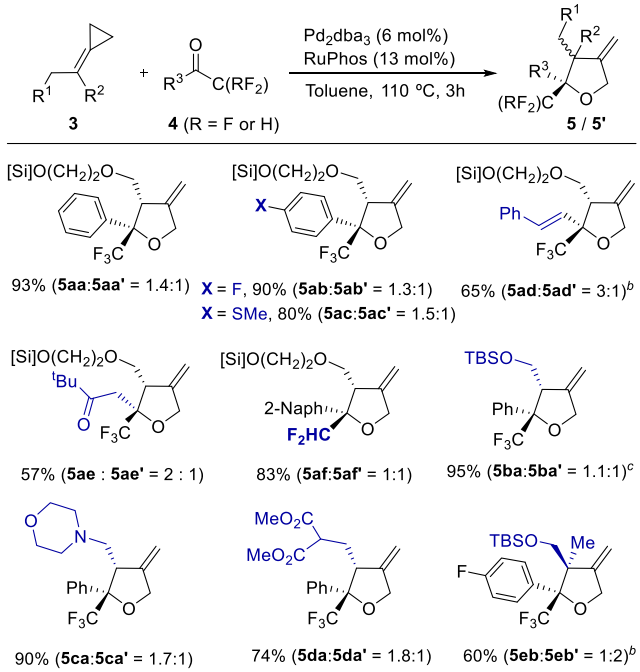
R = $O(CH_2)_2OTBDPS$

L	5aa : 5aa'	yield	L	5aa : 5aa'	yield
Ruphos	1.4 : 1	96	XPhos	1.5 : 1	81
BrettPhos	1.4 : 1	82	^{t}BuXPhos	1.6 : 1	87
^{t}BuBrettPhos	1.7 : 1	90	Ruphos[a]	1.4 : 1	93

[a] Carried out with 2 equiv. of **4a**, Pd_2dba_3 (2%) and Ruphos (4%)

Trifluoroacetophenones bearing electron-donating or withdrawing groups in the phenyl ring are also effective cycloaddition partners, with the more electrophilic derivatives providing somewhat higher yields (X = F: 90% yield *vs* X = SMe: 80% yield, Table 3). Albeit the cycloaddition did not proceed with aliphatic ketones such as trifluoromethyl acetone (decomposition was observed, Table S2), we were pleased to observe that an α,β–unsaturated ketone such as the cinnamyl derivative **4d**, reacts with **3a** to give the desired cycloadduct as a 3 : 1 mixture of isomers (65% yield). Interestingly, the reaction works with 3-oxoalkyltrifluoromethylketones, and thus *exo*-methylene THFs like **5ae** and **5ae'** could be obtained in 57% yield (*dr* 2 : 1). Remarkably, these two examples proceeded with complete chemoselectivity, as adducts resulting from the participation of the C–C double bond of **4d**, or the ^{t}butyl ketone of **4e,** were not detected.

Table 3 Pd–catalyzed intermolecular (3 + 2) cycloaddition between ACPs and fluorinated ketones[a]



[a] *Conditions:* A solution of Pd_2dba_3 (6 mol%), Ruphos (13 mol%), ketone (**4**, 2 equiv.) and **3** in toluene was heated at reflux under Ar. Conversions (> 99%) and isomeric ratios determined by ^{1}H–NMR of the crude mixture. Isolated overall yields of **5** / **5'**. The major isomers are those depicted.[21] [b] Carried out at 140 ºC. [c] With 5 equiv. of **3**. [Si] = $Ph_2(t\text{-Bu})Si$.

Difluoromethyl ketones are also efficient partners, and the expected THF's, like **5af** and **5af'**, were formed in 83% yield. The reaction is also viable with ACPs others than **3a**. Therefore, precursors like **3b, 3c** or **3d** with diverse types of substituents, gave the expected cycloadducts with excellent yields and regioselectivity, and modest diasteroselectivities (Table 3). Finally, we also tested an ACP featuring a tetrasubstituted alkene, like **3e** (R^1 = OTBS, R^2 = Me). Gratifyingly, its reaction with *p*–F–trifluoromethyl acetophenone proceeded efficiently at 130 ºC to provide the corresponding THF bearing two adjacent chiral quaternary centers, in 60% yield (**5eb** : **5eb'** = 1 : 2).

Considering prior mechanistic information gathered for the Pd–catalyzed (3 + 2) cycloadditions between ACPs and alkenes (or alkynes),[8c,4g] we hypothesized that the current annulations with carbonyls might proceed by initial insertion of the Pd(0) complex into the distal C–C bond of the cyclopropyl ring, to yield a palladacyclobutane intermediate of type **A** (Figure 2). This species might then undergo a rearrangement to its *exo*–methylene isomer of type **B**, prior to carbonyl coordination and migratory insertion to yield an oxapalladacycle like **C** (Figure 2, route ***a***). Alternatively, the species **A** could engage in a metallo-ene process to directly afford the same species **C** (Scheme 3a, route ***b***), which provides the product through a C–O reductive elimination.

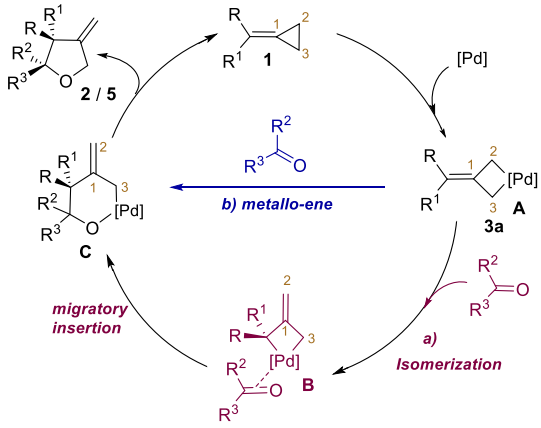
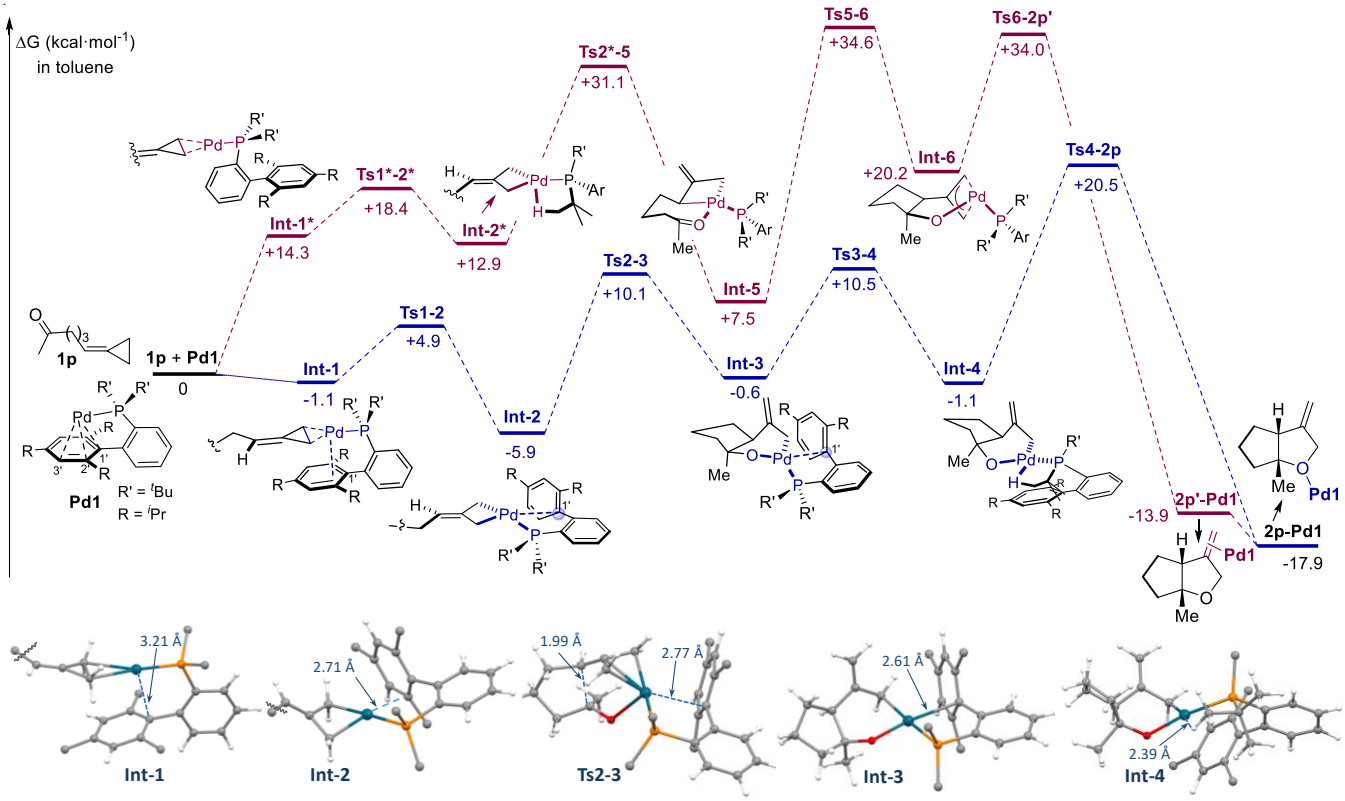


Figure 2. Initial mechanistic hypothesis based on prior work

To shed light on the particular characteristics of the heterocycloaddition, and to discern between these two mechanistic alternatives, we performed a detailed DFT analysis of the intramolecular cycloaddition of **1p**, a methyl ketone similar to **1b** (Scheme 3 and Figures S20-S24).[22] We chose the Pd(0)-^{t}BuXPhos complex (**Pd1**) as model catalyst (Table 1, entry 12, 80% yield). In consonance with previous reports on related Pd-complexes of Buchwald biaryl phosphines,[23] the *in silico* analysis of **Pd1** revealed the bidentate character of the ligand, which coordinates the Pd through the phosphorous and its *ortho*-aryl ring (in particular through C2' and C3', Scheme 3).

Scheme 3. Gibbs energy profile (kcal·mol⁻¹) of the reaction of 1p with the Pd-^{t}BuXPhos complex Pd1, in toluene. Optimized structures of selected stationary points of the preferred pathway (^{i}Pr groups of the biaryl moiety, ^{t}Bu groups of the phosphine, and the carbonyl tether (in Int-1 and Int-2) are truncated for clarity[18,22]



Upon coordination of the alkylidenecyclopropane moiety through its distal C–C bond (**Int-1**), the hemilabile Pd–arene interaction is partially loosen, but the aryl ring remains blocking one side of the ACP–Pd complex, almost perpendicular to the Pd center [d(Pd–C1) = 3.21 Å]. The stabilization provided by such Pd(0)-interaction is significant, since the energetically closest intermediate lacking this interaction, **Int-1***, turned out to be >10 kcal·mol⁻¹ less stable than **Int-1** (Scheme 3, Figures S20 and S22).[24]

From intermediate **Int-1**, the oxidative addition of the ACP takes place through a very accessible activation barrier (**Ts1-2**, ΔG = 6.0 kcal·mol⁻¹), to yield the palladacyclobutane species **Int-2**, a square planar (distorted) intermediate wherein the *ipso* carbon of the biaryl group (C1') occupies the fourth coordination site [d(C1'- Pd) = 2.7 Å].[25] This Pd–C$_{ipso}$ interaction seems essential for the stability of this palladacyclobutane. Indeed, alternative square planar complexes bearing a γ–agostic interaction with the ^{t}Bu group of the phosphine (**Int-2***, Scheme 3) or related three-coordinate T-shape isomers lacking any kind of hemilabile interactions (**Int-2****, Figure S20), were found to be more than 18 kcal·mol⁻¹ less stable than **Int-2**. In consonance with the high stability of **Int-2**, the oxidative addition step via **Ts1-2** is exergonic by almost 5 kcal·mol⁻¹.[26]

From the palladacyclobutane intermediate **Int-2**, the migratory insertion of the methyl ketone, through a palladoene pathway (route ***b***) was found to involve an energy barrier of 16.0 kcal·mol⁻¹ (via **Ts2-3**). The resulting σ-allyl oxapalladacycle intermediate **Int-3,** is a square planar complex that holds the oxygen and the phosphorus atoms *cis* to each other. The Pd–C1' interaction, which is now *trans* to the oxygen, has been strengthened, as judged by the shorter Pd–C1' distance (2.61 versus 2,71 Å in **Int-2**, Scheme 3).

An alternative path, based on a stepwise process involving an initial isomerization to the *exo*-methylene palladacyle of type **B** and a subsequent migratory insertion of the carbonyl moiety could not be located from **Int-2**; however, this pathway is feasible from the isomeric metallacyclobutane species **Int-2*** (via **Int-5**, Scheme 3), which features a weak Pd–H γ-agostic interaction. Curiously, the generated oxapalladacycle **Int-6** features a π–allyl ligand (engaging the three carbons of the former cyclopropane), a type of intermediate that was not computationally located from palladacyclobutane intermediate **Int-2**, bearing the Pd-C$_{ipso}$ coordination.[27] Nonetheless, the significant energetic differences in the paths to **Int-3** and **Int-6** ($\Delta\Delta G_{(Ts5\text{-}6\ -\ Ts2\text{-}3)}$ = 24.5 kcal·mol⁻¹), allows to propose the metallo-ene process as the most favorable migratory insertion route.[28]

Intriguingly, all attempts to locate a reductive elimination step from intermediate **Int-3** were not successful. Instead, we observed that this step is possible from the isomeric *trans* intermediate (**Int-4**, O and P are now *trans* to each other). This complex, exhibiting a weak γ-agostic interaction between the Pd and a hydrogen atom of one of the ^{t}butyl groups of the ligand,[29] is easily accessible (11.1

kcal·mol^{-1}) from **Int-3**. The energetic value of the reductive elimination, 21.6 kcal·mol^{-1} (via **Ts3-4**), fits with the heating requirements of the reaction, and suggests that it is the turnover limiting step.

We also found two energetically related conformers of **Int-4** (namely **Int-4^{II}** and **Int-4^{III}**, ± 4 kcal·mol^{-1}), also entailing Pd–H γ-agostic interactions, which can undergo energetically feasible reductive eliminations towards **2p** with similar barriers (ΔG's of 23.1 and 23.9 kcal·mol^{-1}, respectively, Figure S21).[30]

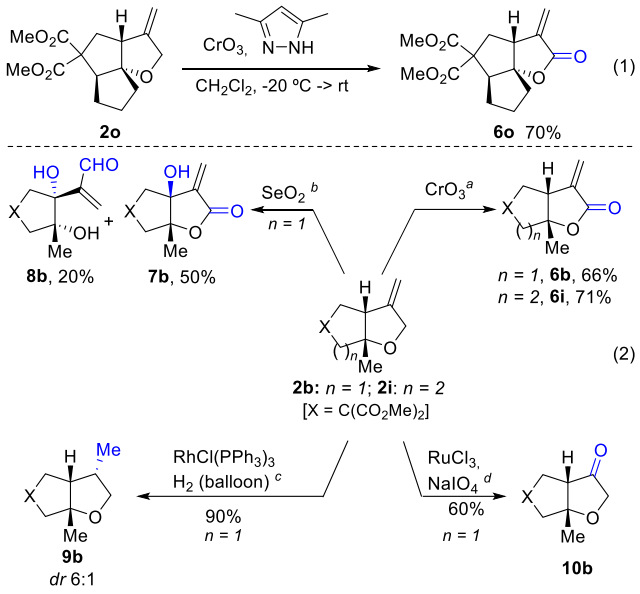
Therefore, our DFT calculations suggest that the use of bulky biaryl ligands such as ^{t}BuXphos, RuPhos or BretPhos is instrumental to facilitate the oxidative addition of the cyclopropane as well as the migratory insertion of the carbonyl moiety. Moreover, they also favor the reductive elimination when compared with regular monodentate phosphines.[31]

We have also performed preliminary calculations for the intermolecular process, using the ACP **3b**, and trifluoroacetophenone (**4a**) or acetophenone as partners, in order to obtain insights into the role of the fluorine atoms in the reaction (Figure S24). Remarkably, the calculations revealed that the electronic effects associated to the trifluoromethyl group allow for an impressive decrease in the activation barrier of the migratory insertion step (ΔΔG > 17.9 kcal·mol^{-1}, Figure S24). The reductive elimination was not significantly affected by the presence of the CF_3. These theoretical data are in consonance with the exclusive but excellent reactivity achieved with trifluoromethylketones, which might be extrapolated for other reactions with similar fluorinated partners.

Finally, considering the prevalence of fused α-methylene-γ-butyrolactone scaffolds in many bioactive products with antitumoral, antiviral, or antimalarial activities, among others,[10a] we explored the viability of installing this motif by direct allylic oxidation of the fused-THF adducts. Gratifyingly, treatment of the tricyclic adduct **2o** with CrO_3/3,5–dimethylpyrazole,[32] provided the butyrolactone **6o** in 70% yield (Scheme 4, eq. 1). Bicyclic adducts like **2b** and **2i** can also be readily transformed into their corresponding γ–butyrolactones **6b** and **6i** in an efficient manner (Scheme 4, eq. 2). Alternatively, treatment of **2b** with an excess of SeO_2,[33] afforded the double–oxidized butyrolactone **7b** (50% yield, Scheme 4, eq. 2, top left), which holds a hydroxyl group at the ring fusion.

The fused–THFs adducts are susceptible of alternative manipulations. Thus, treatment of the adduct **2b** with H_2 (1 atm) and the Wilkinson´s catalyst allowed a selective hydrogenation of the *exo*–methylene group (product **9b**, 90% yield, 6:1 mixture of isomers, Scheme 4, eq. 2, bottom), Alternatively, reaction of **2b** with $RuCl_3$ / $NaIO_4$ gave the corresponding ketone (**10b**), which was isolated in 60% yield. Overall, all these results confirm the synthetic potential of the intramolecular (3+2) cycloaddition and augurs well for its application in the synthesis of complex molecules bearing these motifs.

Scheme 4. Synthetic derivatization of the products[a]



[a] *Conditions*: [a] CrO_3, 3,5–dimethylpyrazole, CH_2Cl_2, –20 ºC, 1h, then NaOH, 0 ºC, 1h. [b] SeO_2, dioxane, reflux, 8h; [c] $RhCl(PPh_3)_3$ (15 mol%), H_2 (balloon), toluene, rt, 4h; [d] 15 mol% $RuCl_3$, $NaIO_4$, EtOAc, CH_3CN, H_2O, rt, 5min.

In summary, we have discovered a highly diastereoselective Pd–catalyzed intramolecular (3 + 2) cycloaddition between ACPs and aldehydes or ketones that delivers exo-methylene fused–bicyclic THFs. An appropriate selection of Pd ligands (bulky biaryl phosphines) is key to obtain good yields and selectivities. The adducts can be readily manipulated in different ways, including a chemoselective oxidation to highly relevant α–methylene–γ–butyrolactones. Mechanistic DFT studies confirmed that these reactions occur via an initial distal insertion of the Pd complex into the distal C-C bond of the ACP, followed by a metallo-ene rearrangement. Both the palladacyclobutane intermediates and the subsequent oxa-palladacycles feature hemilabile Pd–C or Pd–H interactions, which are instrumental for the evolution of this intermediates. Thus, the use of these ligands might pave the way for the development of alternative, otherwise unviable, metal-catalyzed ACP cycloadditions. Indeed, we also found that the same Pd catalysts can promote challenging intermolecular annulations between ACPs and trifluoromethylated carbonyl partners. Preliminary calculations are fully consistent with the essential role of the CF_3 group to facilitate the migratory insertion step. Further studies on the extension of this findings to develop alternative TMC processes are ongoing.

AUTHOR INFORMATION

Corresponding Authors

Prof. J. L. Mascareñas: joseluis.mascarenas@usc.es,
Dr. F. Lopéz: fernando.lopez@csic.es

ORCID

F. Verdugo: 0000-0002-2466-5643
José L. Mascareñas: 0000-0002-7789-700X

Fernando López: 0000-0002-0235-6858

ASSOCIATED CONTENT

Full experimental procedures, characterization data of all new compounds (including ^{1}H-, ^{13}C-NMR spectra), computational details, and Cartesian coordinates. Are available free of charge via the Internet at http://pubs.acs.org.

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(21) (a) The relative configurations of the isomers were determined by nOe experiments; See the Supporting Information. (b) The isomers cannot be fully separated by standard silicagel flash chromatography.

(22) 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, Si and Cl and the LANL2DZ basis set for Pd. Single–point calculations of the optimized systems were carried out using the hybrid functional M06 together with the 6–3111++g(d,p) basis set for C, H, O, P, Si and Cl, and the Stuttgart–Dresden (SDD) ECP for Pd, in toluene (using SMD model). See the Supp. Info.

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(24) Intermediate **Int-1*** can be transformed into **Int-1** in a stepwise process which involves two consecutive rotations of the phosphine ligand. See the Supp. Info. (Figure S22) for a Potential Energy Surface (PES) scan of **Int-1**. See also reference 23c for a related study.

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(26) When using PH_3 as model phosphine ligand, this oxidative addition step was found to be endergonic by 3.7 kcal·mol^{-1} (ΔG = 5.6 kcal·mol^{-1}). On the other hand, when two PH_3 ligands are considered at Pd, as opposed to the P–C_{ipso} coordination, the energy barrier of the oxidative addition increases up to 21.6 kcal·mol^{-1} and becomes even more endergonic (by 5.7 kcal·mol^{-1}. See Figure S23 for the energy profile with one or two PH_3 ligands.

(27) This type of π–allyl palladacyclic species was neither located in the (3 + 2) cycloadditions between ACPs and alkenes, for which a σ–complex of type **C** was found. See ref 8c.

(28) (a) Remarkably, when considering PH_3 as model ligand, instead of ^{t}BuXPhos, the two pathways become much closer to each other ($\Delta\Delta G$ = 11.3 vs 24.5 kcal·mol^{-1}, see Figure S23). (b) On the other hand, the stepwise route *b* is not feasible with two PH_3 ligands, since the carbonyl oxygen atom coordinates the Pd throughout both steps.

(29) For selected examples on related γ-agostic interactions in Pd(II) complexes, see: (a) Stambuli, J. P.; Incarvito, C. D.; Buhl, M.; Hartwig, J. F. Synthesis, structure, theoretical studies, and ligand exchange reactions of monomeric, T-shaped arylpalladium(II) halide complexes with an additional, weak agostic interaction. *J. Am. Chem. Soc.* **2004**, *126*, 1184-1194. (b) Walter, M. D.; White, P. S.; Brookhart, M. Synthesis, structure and computational studies of a cationic T-shaped Pd-complex. *New. J. Chem.* **2013**, *37*, 1128-1133; See also: (c) Brookhart, M.; Green, M. L. H.; Parkin, G. Agostic interactions in transition metal compounds. *Proc. Nat. Acad. Sci.* **2007**, *104*, 6908-6914.

(30) All attempts to locate the reductive elimination from a three coordinate T-shape conformer, without hemilabile interaction, were not successful (Figure S21).

(31) The corresponding reductive elimination using one PH_3 as model ligand occurs through a T-shape three-coordinate intermediate, with a similar energy barrier to that calculated for the Pd–^{t}BuXPhos profile ($\Delta\Delta G$ < 1 kcal·mol^{-1}). On the contrary, the homologous step with two PPh_3 ligands involves a notably higher energy barrier (ΔG = 25.4 kcal·mol^{-1}, $\Delta\Delta G \approx$ 4 kcal·mol^{-1}, Figure S23).

(32) Salmond, W. G.; Barta, M. A.; Havens, J. L. Allylic oxidation with 3,5-dimethylpyrazole. Chromium trioxide complex steroidal Δ^5-7-ketones. *J. Org. Chem.* **1978**, *43*, 2057–2059.

(33) Umbreit, M. A.; Sharpless, K. B. Allylic oxidation of olefins by catalytic and stoichiometric selenium dioxide with tert-butyl hydroperoxide. *J. Am. Chem. Soc.* **1977**, *99*, 5526–5528.

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