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[A0061]

First Pd(0)-Catalyzed (Allylic Alkylation / Heck) Domino Sequence

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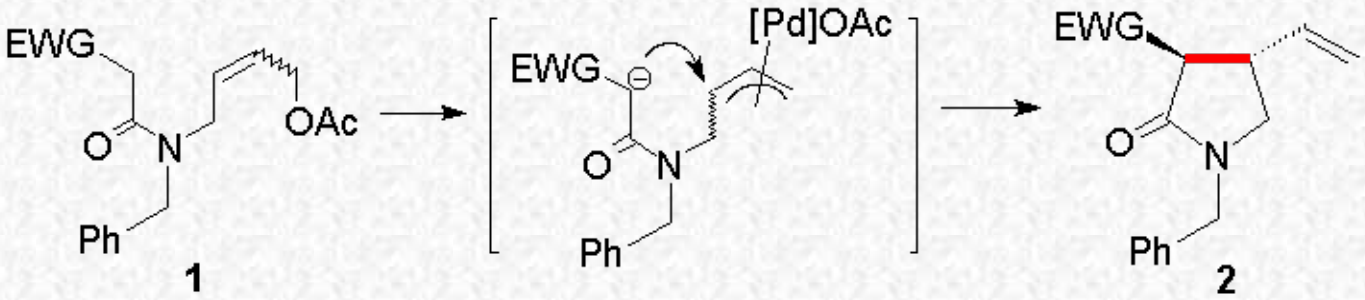
The research in the field of domino reactions is attracting considerable attention in synthetic organic chemistry since it enables the rapid assembly of complex molecules in one-pot processes.[2] In this contest, very elegant examples have been reported in the literature dealing with palladium-catalyzed cascade processes where a single catalytic cycle entails several sequential bond transformations.[3] On the other hand, the development of multistep palladium-catalyzed processes belonging to multiple sequential, but discrete, catalytic cycles, albeit synthetically interesting and mechanistically intriguing, has been so far virtually unexplored.[4]

We recently reported that *trans*-3,4-disubstituted 3-alkenyl-2-pyrrolidones could be easily and stereoselectively obtained via the palladium-catalyzed cyclization of an activated acetamide anion on a properly tethered allylic acetate (**Scheme 1**).[5]



Reagents: $Pd(dba)_2$, (0.05 equiv.), PPh_3, (0.5 equiv.), BSA (1.2 equiv.) AcOK (0.1 equiv.), THF, 70°C, 12h,

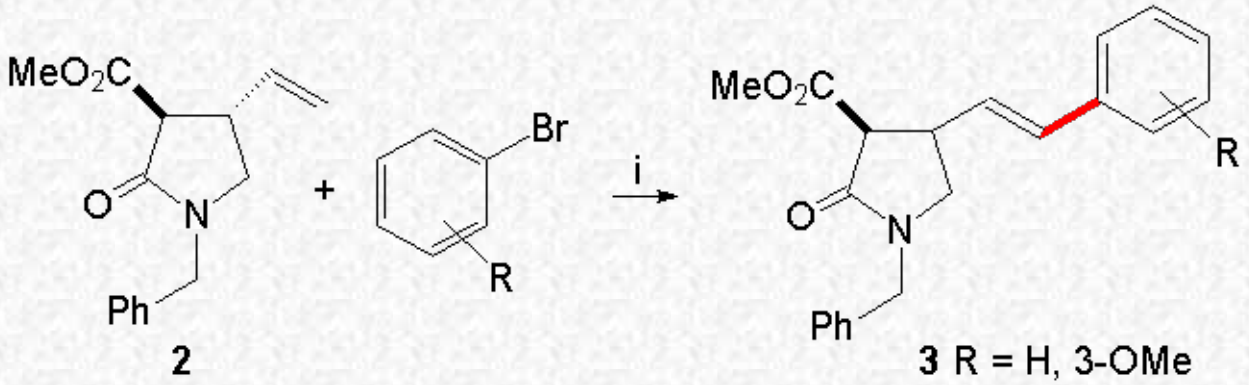
EWG : CO_2Me, COMe, CN, SO_2Ph, $PO(OEt)_2$, PhS

Scheme 1

Here we wish to report that by setting appropriate initial reaction conditions the terminal double bond generated in the allylic alkylation step can further undergo a Heck arylation process. Thus, the same catalytic system is capable of promoting the two different, but

sequential catalytic cycles.

Preliminary tests of the Heck reaction on the already cyclized pyrrolidone **2** indicated that the arylation reaction takes places regioselectively on the terminal olefinic atom, to give an *E*-configurated 1,2-disubstituted alkene (**Scheme 2**).



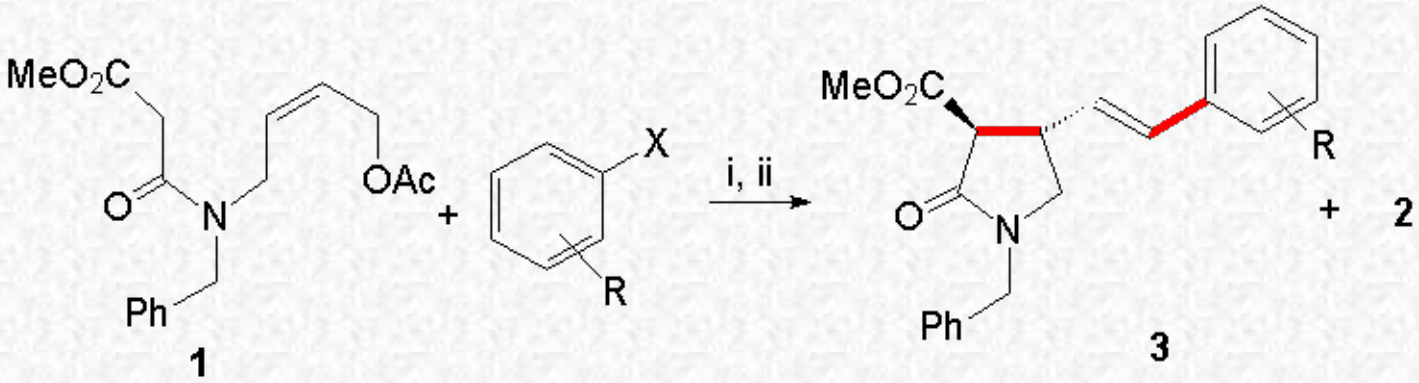
i: NEt_3, $Pd(dba)_2$, P(*o*-Tol)$_3$, THF reflux, 28 h

R = H: 46% yield; R = 3-OMe: 74% yield

Scheme 2

The first attempts to react the precursor **1** with an equivalent amount of aryl bromide and a base,[6] under otherwise identical conditions, produced only the simple cyclization product **2**, the desired Heck coupling product remaining unattained. The first encouraging results have been obtained by adding, in consecutive fashion, the aryl halide and NEt_3 to the reaction mixture only after having detected the correct formation of the cyclized material **2**. Six examples are described in **Table 1**.

Table 1 - The consecutive approach



Entry	X	R	3 (%)	2 (%)
1	Br	3-MeO	**3a** (46)	(23)
2	I	3-MeO	**3a** (32)	(53)
3	Br	4-MeO	**3b** (-)	(30)
4	Br	H	**3c** (61)	(5)
5	Br	3-MeCO	**3d** (-)	(25)

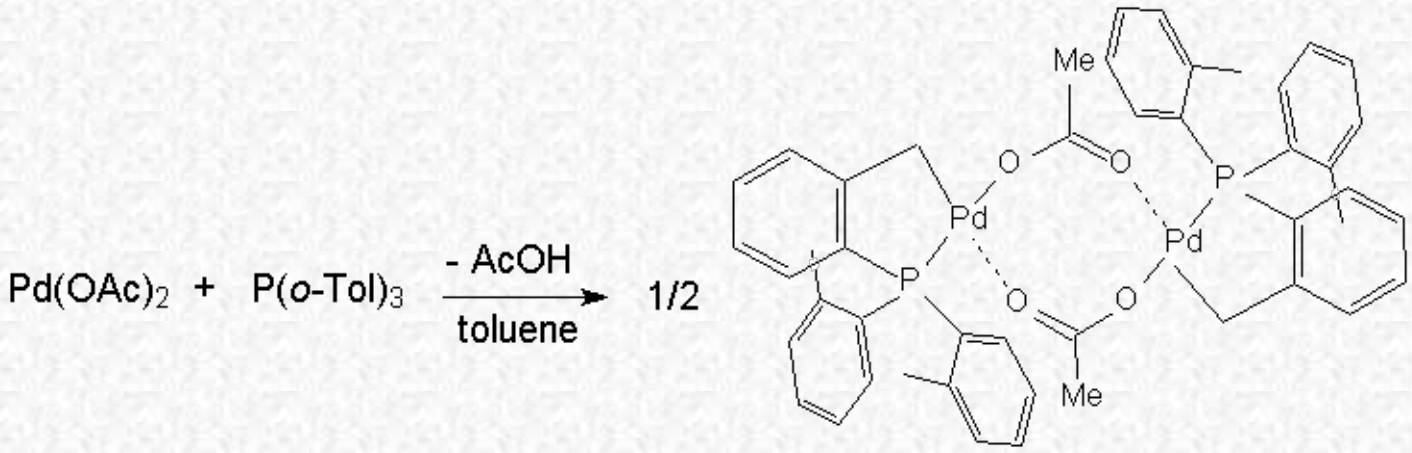
6	Br	4-MeCO	**3e** (21)	(55)

i. NaH, $Pd(dba)_2$ cat., $P(o\text{-}Tol)_3$, THF, 70°C; ii. ArX, NEt_3, 70°C

Inspection of **Table 1** reveals that important amounts of cyclized, but not arylated, product were always detected. Moreover, the Heck reaction did not work at all when *p*-bromoanisole and *m*-bromoacetophenone were used. We believe that these apparently conflicting results may be directly related to the oxidative addition step. In particular, when electron donor groups are present on the aryl halide, oxidative addition is expected to be favored by inductive effect and disfavored by resonance, whereas with electron withdrawing groups the trend is expected to be reversed. Given this assumption, the results of **Table 1** might then be rationalized assuming that inductive effects may dominate with *meta* substitution, whereas mesomeric effects are likely to dominate with *para* substitution.

In order to improve our results we then tested other catalytic systems for the Heck coupling. After some experimentation we found that the Herrmann catalyst,[7] a phosphapalladacycle easily available from $Pd(OAc)_2$ and $P(o\text{-}Tol)_3$, fulfilled our expectations (**Scheme 3**).[8] This catalyst, which is known to efficiently catalyze the Heck reaction with high turnover numbers, has been the object of several mechanistic studies.

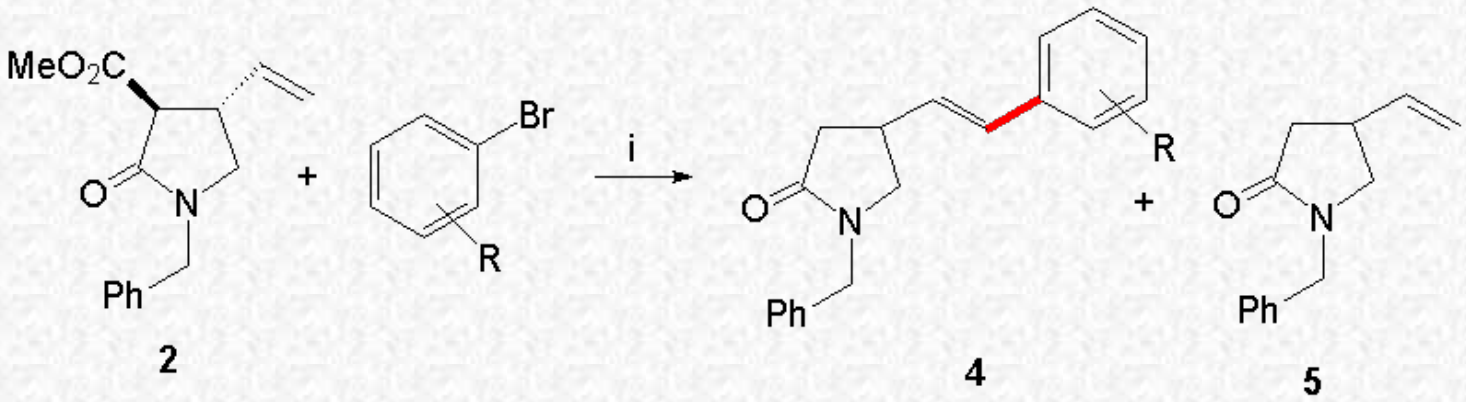
However, although many results indirectly suggest the involvement of a Pd(0) species, such a putative complex has been so far elusive,[9] and an alternative Pd(II)/Pd(IV) redox process cannot be definitively ruled out.[10]



Scheme 3

This catalyst allowed the Heck coupling to take place with all the aryl halides tested, including those which failed to react with the previous catalytic systems. On the other hand, the high reaction temperatures required caused the demethoxycarbonylation of the arylated adducts (**Table 2**).[11]

Table 2 - Heck coupling using the Herrmann catalyst

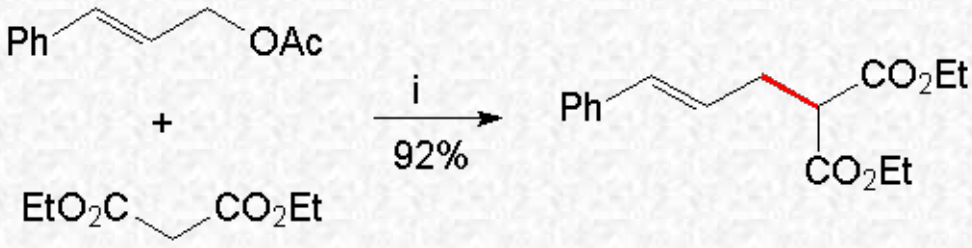


Entry	ArBr	time (h)	4 (%)	5 (%)
1	3-MeO	31	**4a** (68)	-
2	4-MeO	51	**4b** (48)	(29)
3	H	30	**4c** (43)	(51)
4	3-MeCO	24	**4d** (59)	-
5	4-MeCO	23	**4e** (60)	-

i: Herrmann catalyst (0.1 equiv.), AcONa (1.1 equiv.), Me_2NAc, 80 ® 140° C

Given the positive results obtained in the simple Heck coupling we were thus intrigued to also try the same catalyst for the preceding intramolecular allylic alkylation, so as to accomplish a global domino transformation. To our knowledge, phosphapalladacycle-catalyzed allylic alkylations have not been investigated so far.[12] Moreover, since the allylic alkylations under study are known to proceed via oxidative addition of the allylic acetate to a Pd(0) species, the success of such an experiment could not be given for granted at the outset.

It was thus gratifying to observe that the Herrmann phosphapalladacycle was capable of catalyzing the reaction between an active methylene and an allylic acetate, as exemplified in the model reaction between diethyl malonate and cinnamyl acetate (**Scheme 4**). Such a positive result appears not only to be important from the synthetic point of view, but it also strongly supports the implication of a Pd(0) species.



i: NaH (1.2 equiv.), NaOAc (1.1 equiv.), Herrmann cat. (0.1 equiv.) Me_2NAc, 90°C, 2h

Scheme 4

Such a positive result led us to investigate next the intramolecular alkylation of **1** . This transformation turned out to be quite temperature dependent. Thus, at 60°C (**Table 3**, entry 1) the reaction proceeded very slowly (40% of conversion after 23 h), whereas heating at 90°C for 1.5h (**Table 3**, entry 2) afforded the cyclized product in 72% yield. Total demethoxycarboxylation to give **5** was obtained either

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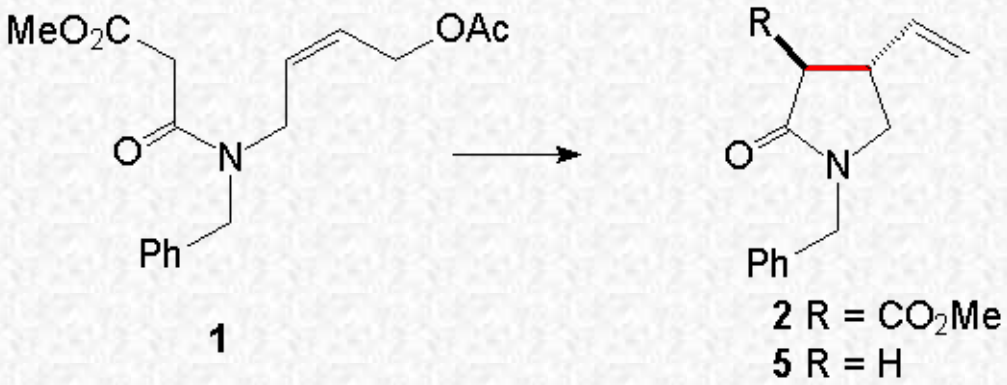
heating the reaction mixture to 140 C for 2.5h (**Table 3**, entry 3) or at 90 C for a more prolonged period (**Table 3**, entry 4).

Table 3 - Intramolecular allylic alkylation using the Herrmann catalyst

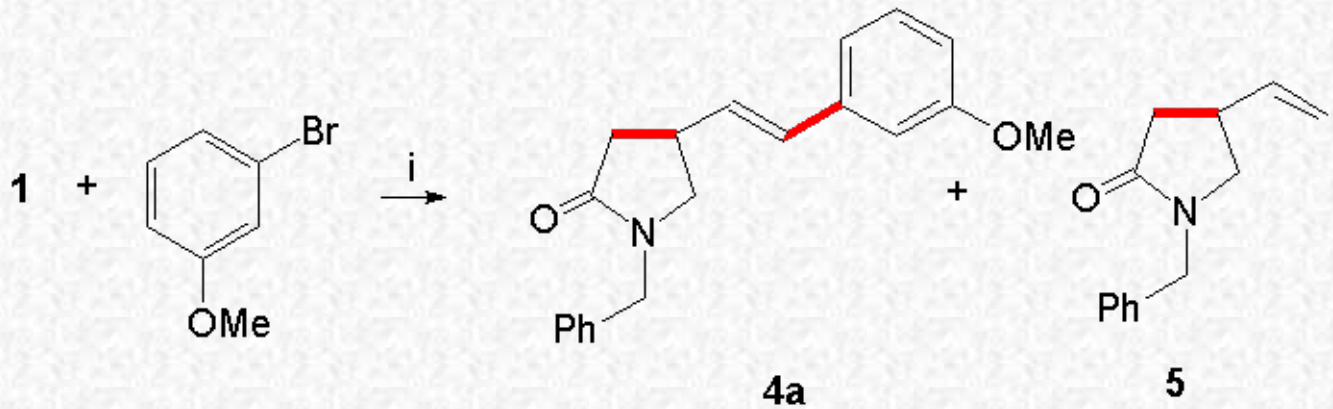


Entry	T (^oC)	time (h)	Prod.	Yield (%)
1	60	23	2	not det.
2	90	1.5	2	72
3	140	2.5	5	66
4	90	48	5	36

i: NaH (1.2 equiv.), NaOAc (1.1 equiv.), Herrmann cat. (0.1 equiv.) Me_2Nac

The finding that a phosphapalladacycle was able to catalyze the allylic alkylation opened the way towards its use in discrete sequential processes (**Table 4**). A first experiment was conducted by performing the allylic alkylation at 90^{o}C, followed by *in situ* addition of 3-bromoanisole at 140^{o}C (entry 1). By following the course of the reaction it could be inferred that the demethoxycarboxylation stage precedes the more sluggish vinylation step. Most importantly, the presence of the aryl halide at the outset of the cyclization step was found to be not detrimental to the global process. In particular, **4a** could be attained at will, either raising the temperature from 90^{o}C to 140^{o}C after the cyclization step (entry 2), or directly, by setting the temperature at 140^{o}C from the outset (entry 3). This result indicates that there is no interference between the oxidative addition of the allylic acetate and that of the aryl bromide, the former process being much faster than the latter one.

Table 4 - Domino intramolecular allylic alkylation / Heck coupling (3-bromoanisole)



Entry	**4a** (%)	**5** (%)

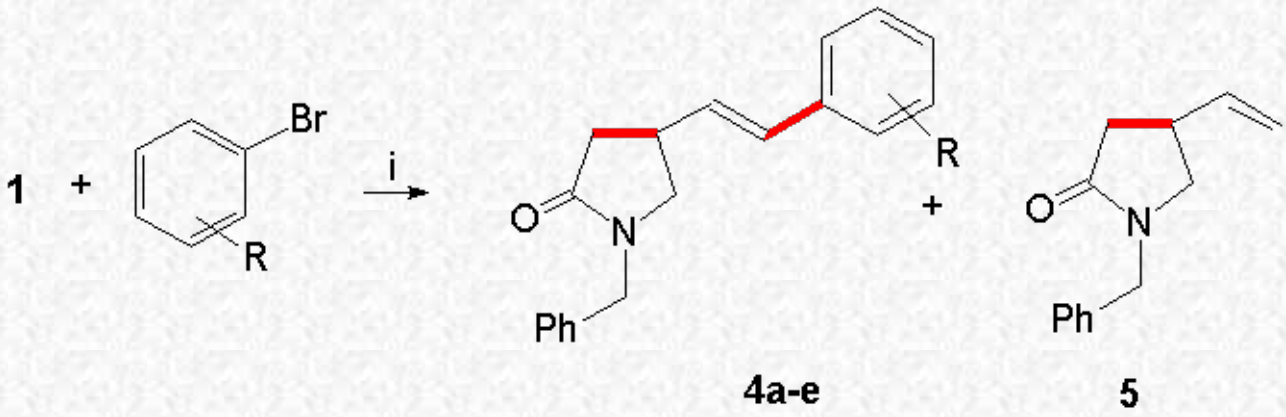
1	44	38
2	59	26
3	58	36

i :Entry 1 : a) NaH (1.2 equiv.), AcONa (1.1 equiv.), Herrmann cat (0.1 equiv.), Me_2NAc, 90°C, 1.5h; b) 3-$MeOC_6H_4Br$ (1.4 equiv.), 90°C® 140°C, 29h. Entry 2 :a) NaH (1.2 equiv.), 3-$MeOC_6H_4Br$ (1.4 equiv.), AcONa (1.1 equiv.), Herrmann cat (0.1 equiv.), Me_2NAc, 90°C, 1.5h; b) 90°C® 140°C, 29h. Entry 3 : NaH (1.2 equiv.), 3-$MeOC_6H_4Br$ (1.4 equiv.), AcONa (1.1 equiv.), Herrmann cat (0.1 equiv.), Me_2NAc, 140°C, 47h.

The same reaction conditions used in entry 3 of **Table 4** have then been applied to other aryl bromides. The results are shown in **Table 5**. It is interesting to note that in the case of the bromoacetophenones the conversion is now complete.

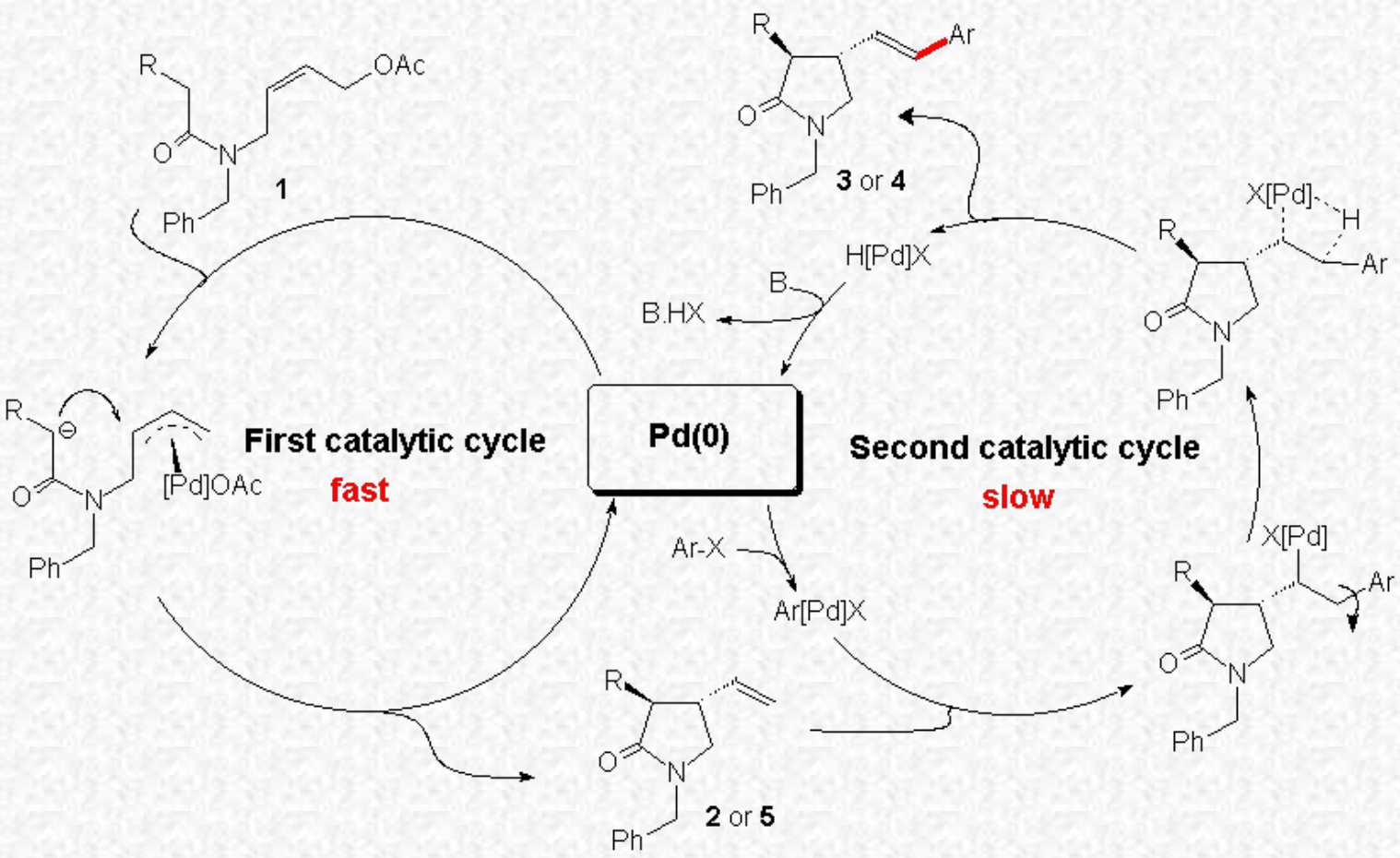
In conclusion, we have shown that the appropriate choice of the reaction conditions allows to perform an allylic alkylation / Heck coupling sequence as a one-pot procedure using a single catalyst. The catalytic system P(o-Tol)$_3$/Pd(dba)$_2$ allows to perform the global process under consecutive conditions, whereas the use of the Herrmann catalyst allows to perform a true domino process with concomitant demethoxycarbonylation. This study demonstrates for the first time that allylic alkylations can be catalyzed by the Herrmann phosphapalladacycle, a result that further supports the involvement of a Pd(0) species in its mechanism of action. Moreover, this study shows that a single catalytic system is capable of promoting two sequential but unrelated catalytic cycles thereby allowing an efficient molecular queuing process.[13]

Table 5 - Domino intramolecular allylic alkylation / Heck coupling (various aryl bromides)



Entry	ArX	time (h)	4	4 (%)	5 (%)
1	3-MeO	47	4a	58	36
2	4-MeO	50	4b	38	42
3	H	31	4c	54	30
4	3-MeCO	22	4d	59	-
5	4-MeCO	22	4e	60	-

i : NaH (1.2 equiv.), ArBr (1.4 equiv.), AcONa (1.1 equiv.), Herrmann cat (0.1 equiv.), Me_2NAc, 140°C, 47h.



Scheme 5

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6. (NaH / NEt_3) or TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene) were tested as bases. These bases were added with the double purpose of enolising the active methylene, as well as capturing HBr from BrPdH.
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11. No attempt has been made to optimize the turnover number in the present study. Such a point will be addressed in future investigations.

12. The Herrmann palladacycle is known to catalyze the Heck, the Suzuki, the Sonogashira, the Stille, and the Grignard / Negishi reactions.

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