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LETTERS

Pd(0)-catalyzed allylic alkylation/Heck coupling in domino sequence[†]

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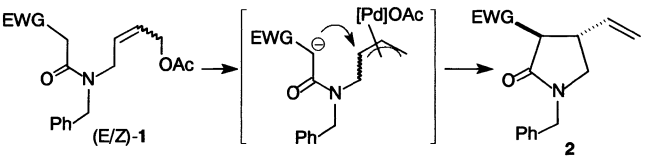
Abstract—A new molecular queuing process has been achieved, in which a single Pd-based catalytic system promotes two unrelated, sequential catalytic cycles in chronologically distinct order. This study demonstrates also that allylic alkylations can be catalyzed by the Herrmann's phosphapalladacycle, a result that further supports the involvement of a Pd(0) species in its mechanism of action. © 2001 Elsevier Science Ltd. All rights reserved.

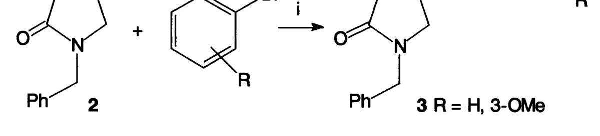
The research in the field of domino reactions is attracting considerable attention in synthetic organic chemistry since it enables the rapid assembly of complex molecules in one-pot processes.[1] In this context, very elegant examples of palladium-catalyzed cascade processes where a single catalytic cycle entails several sequential bond transformations, have been recently reported.[2] On the other hand, multi-step palladium-catalyzed processes belonging to multiple sequential catalytic cycles, albeit synthetically interesting and mechanistically intriguing, have been so far scantily studied,[3] and their success cannot be taken for granted owing to possible incompatibilities between the catalytic cycles.[4]



Scheme 1. *Reagents and conditions*: $Pd_2(dba)_3$ (0.05 equiv.), PPh_3 (0.5 equiv.), BSA (1.2 equiv.), AcOK (0.1 equiv.), THF, reflux, 12 h. EWG: CO_2Me, COMe, CN, SO_2Ph, $PO(OEt)_2$.

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

In this letter, 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 able to promote 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).[6]



Scheme 2. *Reagents and conditions*: (i) NEt_3, $Pd(dba)_2$, $P(o\text{-}Tol)_3$, THF reflux, 28 h. R = H: 46%; R = 3-OMe: 74% yield.

Keywords: palladium and compounds; allylations; Heck reactions.

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[†] Dedicated to Professor Jean F. Normant in honor of his 65th birthday.

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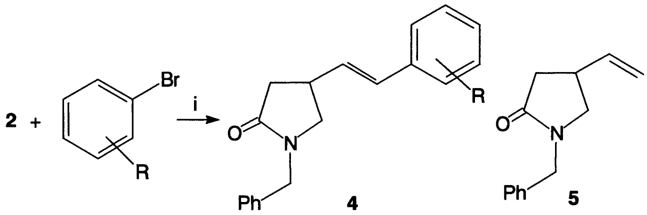
Initial attempts to react the acyclic precursor **1** with an equivalent amount of aryl bromide and a base,[7] under otherwise identical conditions, were disappointing, and produced only the simple cyclization product **2**. The first encouraging result was obtained by adding, in consecutive fashion, the aryl halide and NEt_3 to the reaction mixture, only after detection of the cyclized material **2**. Six examples are illustrated 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)

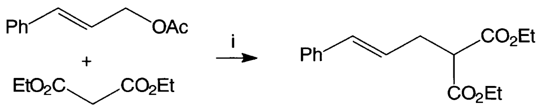
Reagents and conditions: (i) NaH, $Pd_2(dba)_3$ cat., $P(o\text{-Tol})_3$, THF reflux; (ii) ArX, NEt_3, reflux 19 h.

Table 2. Heck coupling between **2** and aryl bromides using the Herrmann's 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)	–

Reagents and conditions: (i) Herrmann's catalyst (0.05 equiv.), AcONa (1.1 equiv.), Me_2NAc, 80→140°C.



Scheme 3. *Reagents and conditions*: (i) NaH (1.2 equiv.), NaOAc (1.1 equiv.), Herrmann's cat. (0.05 equiv.), Me_2NAc, 90°C, 2 h (92%).

Table 3. Intramolecular allylic alkylation using the Herrmann's catalyst (**1**→**2** or **5**)

Entry	*T* (°C)	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

Reagents and conditions: (i) NaH (1.2 equiv.), NaOAc (1.1 equiv.), Herrmann's cat. (0.05 equiv.) Me_2NAc.

Inspection of Table 1 reveals that under these conditions the reaction is always plagued by important amounts of the undesired intermediate **2**. Moreover, the Heck reaction did not work at all when *p*-bromoanisole and *m*-bromoacetophenone were used.

In order to improve our results we then tested other catalytic systems for the coupling reaction. After some experimentation we found that Herrmann's catalyst,[8] a phosphapalladacycle easily available from $Pd(OAc)_2$ and $P(o\text{-Tol})_3$, fulfilled our expectations.[9] This catalyst, which is known to efficiently catalyze the Heck reaction with high turnover numbers, has been the object of several mechanistic studies. Although many results indirectly suggest the involvement of a Pd(0) species, such a putative complex has been so far elusive,[10] and an alternative Pd(II)/Pd(IV) redox process has also been considered.[11]

This catalyst allowed the Heck coupling to take place with all the aryl halides tested, including those that failed with the previous catalytic system. On the other hand, the high reaction temperatures required brought about demethoxycarbonylation of the arylated adducts (Table 2).[12]

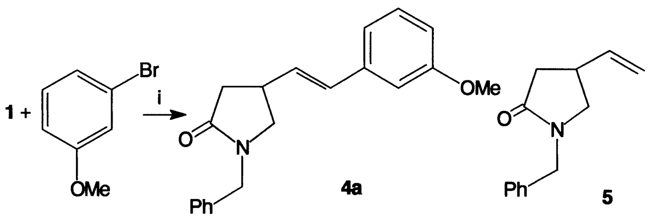
Given the positive results obtained in the simple Heck coupling we were thus intrigued to test the same catalyst also for the preceding intramolecular allylic alkylation, so as to accomplish a global domino transformation. To our knowledge, phosphapalladacycle-catalyzed allylic alkylations have not been investigated so far.[13] 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 taken for granted at the outset.

In the light of what stated above, it was gratifying to observe that Herrmann's phosphapalladacycle was capable indeed 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 3). 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 in its mechanism.

Such a 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 1.5 h (Table 3, entry 2) afforded the cyclized product in 72% yield. Total demethoxycarbonylation, to give **5**, was observed by either heating the reaction at 140°C for 2.5 h (Table 3, entry 3), or at 90°C for a more prolonged period (Table 3, entry 4).

The finding that a phosphapalladacycle was able of catalyzing the allylic alkylation opened the way towards its use in discrete sequential processes (Table 4). A first experiment was conducted by performing the allylic

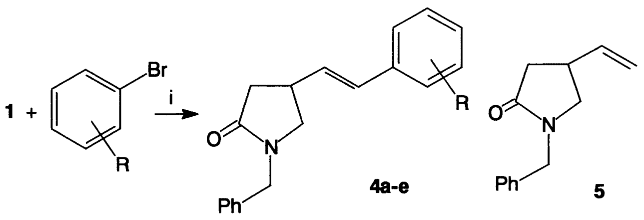
Table 4. Intramolecular allylic alkylation/intermolecular Heck coupling under consecutive and domino conditions



Entry	**4a** (%)	**5** (%)
1	44	38
2	59	26
3	58	36

Reagents and conditions: (i) Entry 1: (a) NaH (1.2 equiv.), AcONa (1.1 equiv.), Herrmann's cat. (0.05 equiv.), Me_2NAc, 90°C, 1.5 h; (b) $3\text{-}MeOC_6H_4Br$ (1.4 equiv.), 90→140°C, 29 h. Entry 2: (a) NaH (1.2 equiv.), $3\text{-}MeOC_6H_4Br$ (1.4 equiv.), AcONa (1.1 equiv.), Herrmann's cat. (0.05 equiv.), Me_2NAc, 90°C, 1.5 h; (b) 90→140°C, 29 h. Entry 3: NaH (1.2 equiv.), $3\text{-}MeOC_6H_4Br$ (1.4 equiv.), AcONa (1.1 equiv.), Herrmann's cat. (0.05 equiv.), Me_2NAc, 140°C, 47 h.

Table 5. Domino intramolecular allylic alkylation/intermolecular Heck coupling



Entry	ArBr	Time (h)	**4a**–**e** (%)	**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)	–

Reagents and conditions: (i) NaH (1.2 equiv.), ArBr (1.4 equiv.), AcONa (1.1 equiv.), Herrmann's cat. (0.05 equiv.), Me_2NAc, 140°C, 47 h.

alkylation at 90°C, followed by in situ addition of 3-bromoanisole at 140°C (entry 1). By following the course of the reaction it could be inferred that the demethoxycarbonylation stage precedes the more sluggish arylation step. Most importantly, the presence of the aryl halide at the outset of the cyclization step was found to be compatible with the global process. In particular, **4a** could be attained at will, either raising the temperature from 90 to 140°C after the cyclization step (entry 2), or directly, by setting the temperature at 140°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.

The same reaction conditions used in entry 3 of Table 4 were then applied to other aryl bromides. It is interesting to note that in the case of the bromoacetophenones the conversion is now complete (Table 5).

In conclusion, we have shown that the appropriate choice of the reaction conditions allowed to perform an allylic alkylation/Heck coupling sequence, as a one-pot procedure using a single catalyst. The catalytic system $P(o\text{-}Tol)_3/Pd(dba)_2$ allows to perform the global process under *consecutive* conditions, whereas the use of the Herrmann's catalyst permits a *domino* process to take place. In this way, a single catalytic system is capable of promoting two sequential but independent catalytic cycles in the desired chronological order, thereby allowing a new molecular queuing process to take place (Scheme 4).[14,15]

Last but not least, this study demonstrates that allylic alkylations can be catalyzed by the Herrmann's phosphapalladacycle, a result that further supports the involvement of a Pd(0) species in its mechanism of action.

Acknowledgements

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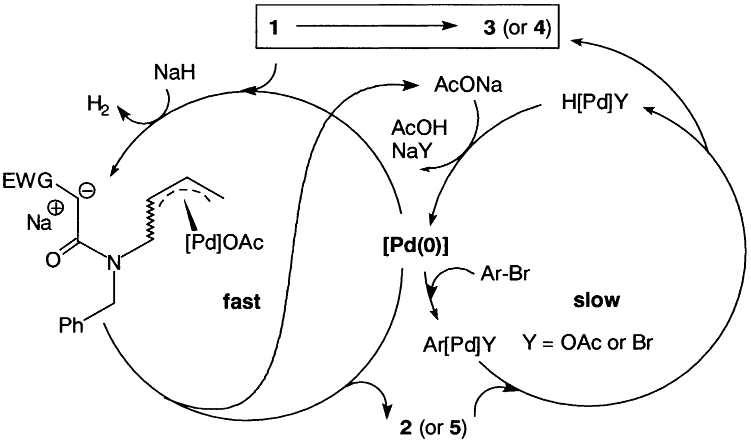

Scheme 4.

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6. The yields given in Schemes 2 and 3 and in Tables 1–5 refer to isolated products. Where partial conversion was observed, chromatographic recovery of the unreacted pyrrolidones was possible.
7. (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 enolizing the active methylene, as well as capturing HX from XPdH.
8. *trans*-Di-(μ-acetate)bis[*o*-(di-*o*-tolylphosphine)benzyl]dipalladium(II).
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12. No attempt has been made to optimize the turnover number in the present study. Such a point will be addressed in future investigations.
13. The Herrmann's palladacycle is known to catalyze the Heck, the Suzuki, the Sonogashira, the Stille, and the Grignard/Negishi reactions (for a review see Ref. 9f).
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15. For mechanistic details on the Heck coupling see Ref. 11c and references cited therein.