Palladium-Mediated Phosphine-Dependent Chemoselective Bisallylic Alkylation Leading to Spirocarbocycles

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Palladium-mediated phosphine-oriented chemoselective bis allylic alkylation leading to spirocarbocycles

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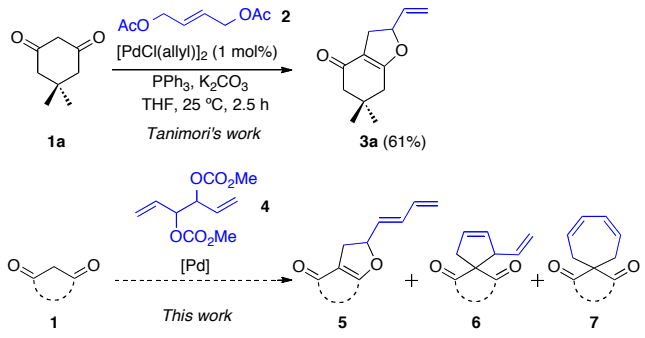
As highlighted by numerous works, allylic substitution is a versatile transformation in organic synthesis and one of the most powerful tools for the formation of carbon-carbon and carbon-heteroatom bonds.[1] Transition-metal-promoted allylic substitutions were found particularly useful since they allow for the installation of stereogenic centers in an enantioselective fashion.[2] Among the various metals competent for this reaction, palladium-catalyzed allylation of soft nucleophiles, so called Tsuji-Trost reaction, has been extensively investigated. Surprisingly, despite the widespread use of this reaction, double allylic substitution sequences have been little explored and limited exclusively to bifunctional allylic diacetates and dicarbonates. As a function of the nucleophile employed, either linear[3] or cyclic products[4] were isolated. Hence, this methodology was applied to the synthesis of furan or piperazine derivatives. For instance, Tanimori reported the preparation of vinyldihydrofuran **3a** *via* a palladium-mediated bis alkylation of dimedone **1a** using the symmetrical allylic diacetate **2** (Scheme 1).[5]

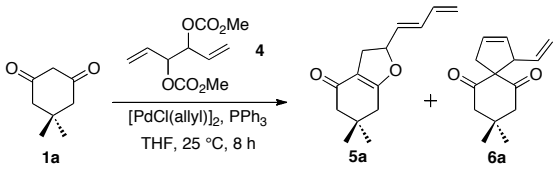


Scheme 1. Palladium-catalyzed bis allylic substitution sequences

Following our continuous interest in metal-promoted formations of carbocycles,[6] we were intrigued by the possibility to use hexadiene dicarbonate **4**[7] in order to form vinylcyclopentene **6** and/or cycloheptadiene **7** in addition of dihydrofuran derivative **5** obtained through sequential C-C then C-C or C-O bond formations (Scheme 1).

As illustrated in Table 1, we started by the examination of the reaction conditions using the benchmark substrates dimedone **1a** and dicarbonate **4**. Through the appropriate choice of conditions, it was possible to isolate selectively either compound **5a** or spiro derivative **6a**. The structure of **6a** was unambiguously confirmed by X-ray determination (Figure 1, left). The use of $[Pd(allyl)Cl]_2$ and PPh_3 as catalytic system allowed for the formation of 64% of vinylcyclopentene **6a** in 8 h at 25°C with traces of **5a** (entry 1). Products selectivity was not affected when using $[Pd(PPh_3)_4]$ or $Pd(OAc)_2$ (entries 5 and 6). In contrast, $Pd_2(dba)_3{\cdot}CHCl_3$ was able to

Table 1. Palladium-catalyzed bis allylic substitution with 1,3-dione **1a**: Effect of Reaction Parameters[a]



Entry	Change from "the standard conditions"	Isolated yield (%) 5a	6a
1	None	4	64
2	No palladium	-	-
3	$Pd(dba)_2$ instead of $[PdCl(allyl)]_2$	26	39
4	$Pd_2(dba)_3{\cdot}CHCl_3$ instead of $[PdCl(allyl)]_2$	47	10
5	$Pd(PPh_3)_4$ instead of $[PdCl(allyl)]_2$ and PPh_3	7	59
6[b]	$Pd(OAc)_2$ instead of $[PdCl(allyl)]_2$	7	58
7[b]	$Pd(OTFA)_2$ instead of $[PdCl(allyl)]_2$	-	-
8	1,4-dioxane instead of THF	12	50
9	toluene instead of THF	21	46
10	acetonitrile instead of THF	15	41
11	DCM instead of THF	18	38
12	1.5 equiv. of **4**	53	14
13	2 equiv. of **4**	61	4
14	60 °C instead of 25 °C	4	32

[a] Reaction conditions: [Pd] (5 mol%), PPh_3 (20 mol%), **1a** (0.5 mmol), **4** (0.5 mmol), THF (5 mL, 0.1 M), 25 °C, 8 h. [b] Palladium and ligand were heated 15 min. at 60 °C before adding substrates. dba = dibenzylideneacetone; TFA = trifluoroacetyl.

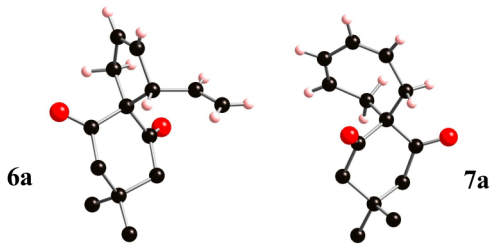


Figure 1. Ball-and-stick representation of compounds **6a** (left) and **7a** (right) (some hydrogen atoms have been omitted for clarity)

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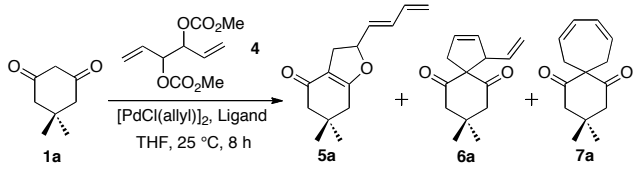
reverse selectivity (entry 4) and $Pd(OTFA)_2$ was found ineffective (entry 7). The solvent appeared to play a minor role on the reaction outcome (entries 8-11). Since noticeable amounts of unreacted dimedone **1a** were observed at the end of the reaction, a degradation of dicarbonate **4** through a reductive elimination to form 1,3,5-hexatriene was assumed.[8] Therefore, an excess of **4** was used to improve product **5a** formation (entries 12 and 13). Increasing the temperature led to reduce isolated yields as a consequence of degradation processes (entry 14).

In a second time, ligand effect has been carefully scrutinized (Table 2). Electron-rich PCy_3 afforded only traces of **5a** (entry 3). Electron-poor phosphines such as trifurylphosphine, $P(OPh)_3$, or $P(C_6F_5)_3$ gave low yields either in **6a** or **5a** (entries 4-6). The bulky $P(o\text{-Tol})_3$ led to the formation of only spiro product **6a** (entry 7). Interestingly, when $P(o\text{-}C_6H_4OMe)_3$ was employed, a new product, cycloheptadiene **7a**, was isolated as major product (66 %) along with 11% of **6a**. The structure of **7a** was unambiguously determined by X-ray crystallography (Figure 2, right). In order to understand the factors governing the formation of **7a**, *meta*- and *para*-substitued tris(methoxyphenyl)phosphines were tested. These ligands afforded mixtures from which **6a** appeared to be the major component (entries 8-10). Meanwhile using $P(2,6\text{-}C_6H_3(OMe)_2)_3$ only traces of **5a** were isolated. These results suggest that both electron-rich properties and appropriate steric congestion of ligands tend to favor the formation of **7a**. Examination of bidentate ligands revealed that Xantphos gave preferentially cycloheptadiene **7a** (entries 12-14). This ligand is well-known to present particular coordination modes with participation of its oxygen atom.[9] Thus, secondary interactions of ligand oxygen atoms, such as $P(o\text{-}C_6H_4OMe)_3$ or Xantphos with the palladium center should be considered to rationalize the formation of **7a**.

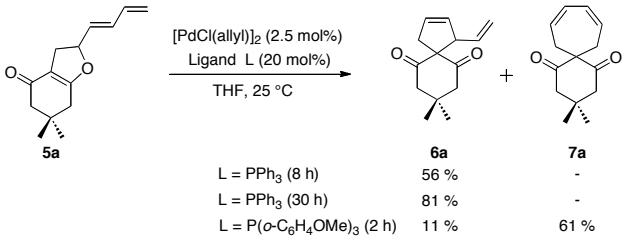
Table 2. Palladium-catalyzed bis allylic substitution with 1,3-dione **1a**: Ligand Effect [a]



Entry	Ligand	Isolated yield (%)		
		5a	**6a**	**7a**
1	None	-	-	-
2	**PPh_3**	**4**	**64**	-
3	PCy_3	6	-	-
4	$P(2\text{-Fu})_3$	-	38	-
5	$P(OPh)_3$	12	-	-
6	$P(C_6F_5)_3$	14	-	-
7	$P(o\text{-Tol})_3$	-	26	-
8	**$P(o\text{-}C_6H_4OMe)_3$**	-	**11**	**66**
9	$P(m\text{-}C_6H_4OMe)_3$	6	61	5
10	$P(p\text{-}C_6H_4OMe)_3$	14	28	23
11	$P(2,6\text{-}C_6H_3(OMe)_2)_3$	5	-	-
12	dppf	16	6	-
13	Xantphos	13	10	31
14	Dpephos	7	67	2

[a] Reaction conditions: $[PdCl(allyl)]_2$ (2.5 mol%), Ligand (20 mol% for monodentate, 10 mol% for bidentate), **1a** (0.5 mmol), **4** (0.5 mmol), THF (5 mL, 0.1 M), 25 °C, 8 h.

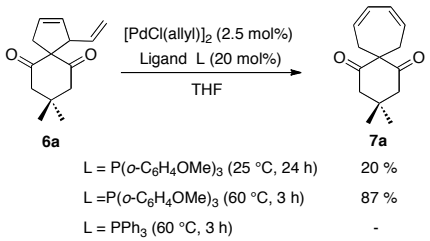
Because examples of palladium-catalyzed 1,3-oxygen-to-carbon alkyl migrations have been reported in the literature,[10] dihydrofuran **5a** was supposed to be a key intermediate for spirocarbocycles formation. Treatment of **5a** under the usual reaction conditions and PPh_3 led to vinylcyclopentene **6a** (Scheme 2). When $P(o\text{-}C_6H_4OMe)_3$ was employed, yields and ratio **6a**/**7a** was found matching with those obtained from dimedone **1a** and **4**.



Scheme 2. Conversion of dihydrofuran derivative **5a** into carbocycles **6a** and **7a**

Following our efforts to study rearrangement processes, the conversion of **6a** into cycloheptadiene **7a** was undertaken (Scheme 3). Unexpectedly, the catalytic system including $P(o\text{-}C_6H_4OMe)_3$ proceeded to the transformation of **6a** into **7a** at 25 °C with a low yield (20%) that was improved further by increasing temperature to 60 °C (87 % yield after 3 h). This represents one of the rare examples of palladium-promoted C-C allylic bond cleavage, specially at room temperature.[11]

When PPh_3 was used in the same reaction conditions, no traces of **7a** were detected; 80 % of the starting material was recovered. This confirms that the formation of 7-membered ring occurs only in presence of $P(o\text{-}C_6H_4OMe)_3$ in the catalytic system.[12]

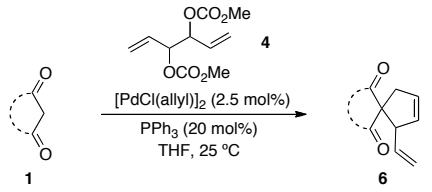


Scheme 3. Transformation of vinylcyclopentene **6a** into cycloheptadiene **7a**

Having established the optimal reaction conditions, we then investigated the scope of the formation of vinylcyclopentenes with a range of 1,3-diones or derivatives (Table 3). Cyclopentane-1,3-dione-based substrates **1b**-**1e** were good candidates affording the expected vinylcyclopentenes **6b**-**6e** in satisfied yields (entries 1-4). For Cyclohexane-1,3-dione **1f**, a moderate yield was obtained (entry 5).[13] Substrate **1g** allowed to determine that the reaction was not diastereoselective (entry 6). More acidic dicarbonyl compounds such as Meldrum's acid **1h**, 1,3-dimethylbarbituric acid **1i** or 1,2-diphenyl-3,5-pyrazolidinedione **1j** were well-tolerated (entries 7-9). This led us to examine 5-pyrazolinone **1k** which gave the expected product without any diastereoselectivity but a satisfactory yield (entry 10). In deep contrast, acyclic 1,3-dione such as **1l** gave rise to only traces amounts of **6l** (entry 11). The bulk of the crude reaction mixture consisted in unreacted **1l** and **4**.

Next, the direct access to cycloheptadienes from various 1,3-diones was attempted. Unfortunately, indanedione **1e** or pyrazolidinedione **1j** were converted only to vinylcyclopentenes **6e** (72 %) and **6j** (55 %) in presence of $[Pd(allyl)Cl]_2/P(o\text{-}C_6H_4OMe)_3$ catalytic system after 2 h at 60 °C. On the other hand, isomerization of a number of vinylcyclopentenes **6** to corresponding cycloheptadienes **7** was achieved under the above conditions in moderate to good yields (Table 4).

Table 3. Scope investigation for the formation of vinylcyclopentene products **6**[a]



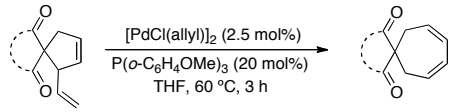
1 **6**

Entry	Substrate	Product	time (h)	Isolated yield (%)
1	**1b**	**6b**	8	72
2	**1c**	**6c**	16	72
3	**1d**	**6d**	16	83
4	**1e**	**6e**	2	85
5	**1f**	**6f**	5	53
6	**1g**	**6g**	4	70 (dr=1:1.3)
7	**1h**	**6h**	5	79
8	**1i**	**6i**	2	71
9	**1j**	**6j**	2	78
10	**1k**	**6k**	4	67 (dr=1:1)
11	**1l**	**6l**	24	traces

[a] Reaction conditions: $[PdCl(allyl)]_2$ (2.5 mol%), PPh_3 (20 mol%), **4** (0.5 mmol), **1** (0.5 mmol), THF (5 mL, 0.1 M), 25 °C.

To illustrate the synthetic potential of vinylcyclopentene substrates **6**, Meldrum's acid derivative **6h** treated with *N*-bromosuccinimide underwent a bromolactonization to give the bicyclic lactone **8** as a 2.5:1 ratio of diastereomers with a good yield. (Scheme 4).[14]

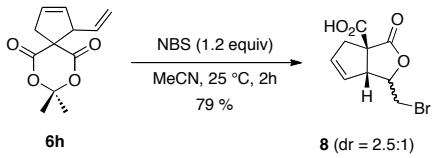
Table 4. Scope examination of the ring expansion[a]



6 **7**

Entry	Substrate	Product	Isolated yield (%)
1	**6e**	**7d**	41
2	**6g**	**7g**	72
3	**6h**	**7h**	75
4	**6j**	**7j**	79
5	**6k**	**7k**	65

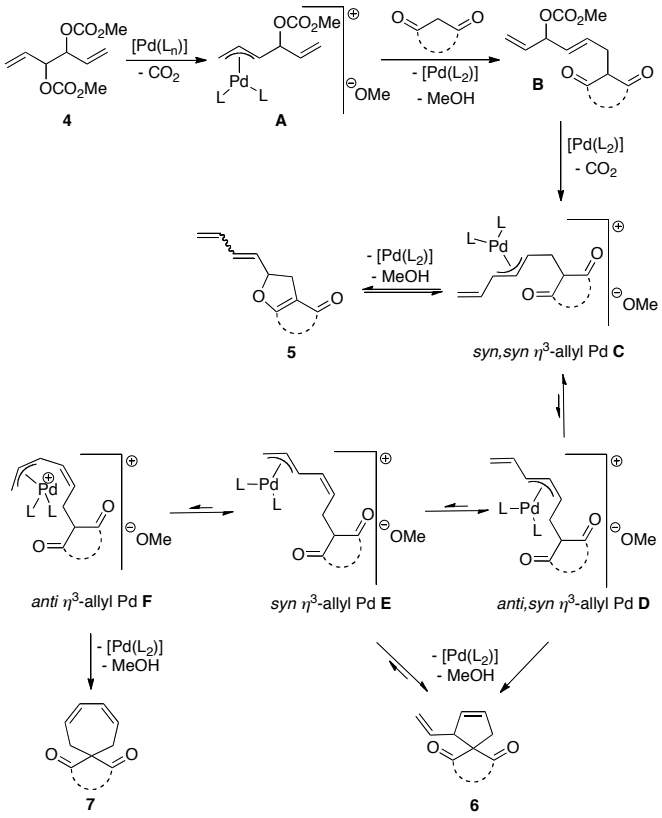
[a] Reaction conditions: $[PdCl(allyl)]_2$ (2.5 mol%), $P(o\text{-}C_6H_4OMe)_3$ (20 mol%), **6** (0.5 mmol), THF (5 mL, 0.1 M), 60 °C, 3 h.



6h **8** (dr = 2.5:1)

Scheme 4. Bromolactonization of compound **6h**

A plausible mechanism to explain the formation of spirocarbocycles is depicted in scheme 5. At first, an allylic substitution takes place through the intermediate **A** to afford monocarbonate **B**. Then, the oxidative addition process gives rise to the *syn*,*syn* η^3-allyl palladium complex **C** which can release the kinetic product **5** through *O*-alkylation or evolves into the *anti*,*syn* η^3-allyl intermediate **D** through a π-σ-π isomerization. By a *C*-alkylation, **D** leads to vinylcyclopentene **6** formation. Dynamic equilibration of **D** into *syn* η^3-allyl complex **E** may evolves towards either **6** or the less disfavored *anti* η^3-allyl palladium **F** that triggers the formation of cycloheptadiene product **7**.



Scheme 5. Mechanistic proposal

In summary, we have developed a palladium-mediated bis allylic substitution leading to 5- and 7 membered carbocycles. The chemoselectivity of the reaction depends on the phosphorous ligand used. More importantly, we observed a cleavage of carbon-carbon allylic bond activation under mild conditions allowing for the isomerization of vinylcyclopentenes into cycloheptadienes. To the best of our knowledge, this metal-catalyzed ring expansion process is unprecedented. Further investigations are underway in our laboratories to better apprehend the mechanism and develop an asymmetric version of this bis allylic substitutions sequence.

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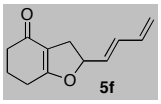
[12] Various experiences to obtain **6a** from **7a** were unsuccessfully conducted.

[13] Small amounts of **5f** were also isolated (< 10 %).



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Layout 2:

Cycles story

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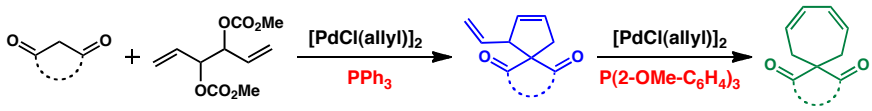
Palladium-mediated phosphine-oriented chemoselective bis allylic alkylation leading to spirocarbocycles



The palladium-catalyzed bis allylic alkylations of 1,3-dione derivatives to afford carbocycles has been investigated. In this transformation, it has been observed that the reaction selectivity was strongly dependent of the phosphine employed. Moreover, it has been demonstrated that vinylcyclopentenes synthesized could be easily transformed into cyclohexadiene derivatives through a carbon-carbon allylic bond cleavage.