Spiro Compounds

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

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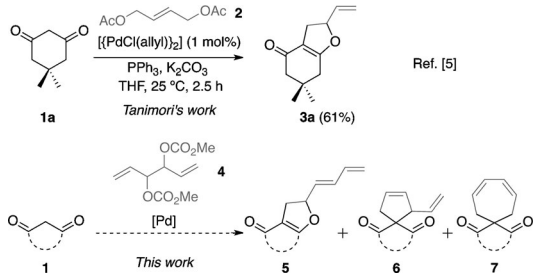
Allylic substitution is a versatile transformation in organic synthesis, as highlighted by numerous works, and one of the most powerful tools for the formation of carbon–carbon and carbon–heteroatom bonds.[1] Transition-metal-promoted allylic substitutions were found to be particularly useful, because they allow the installation of stereogenic centers in an enantioselective fashion.[2] The palladium-catalyzed allylation of soft nucleophiles, the 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. Either linear[3] or cyclic products[4] were isolated, depending on the nucleophile that was employed. Hence, this methodology was applied to the synthesis of furan or piperazine derivatives. For instance, Tanimori reported the preparation of vinyldihydrofuran **3a** through a palladium-mediated bisalkylation of dimedone **1a** using the symmetrical allylic diacetate **2** (Scheme 1).[5]

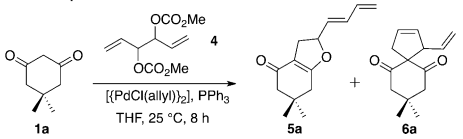


Scheme 1. Palladium-catalyzed bisallylic substitution sequences.

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

We started our investigation by the examination of the reaction conditions using the benchmark substrates dimedone **1a** and dicarbonate **4** (Table 1). We were able to isolate selectively either compound **5a** or spiro derivative **6a** through the appropriate choice of conditions. The structure of **6a** was unambiguously confirmed by X-ray chrystallography (Figure 1, left). The use of $[\{PdCl(allyl)\}_2]$ and PPh_3 as catalytic system allowed the formation of vinylcyclopentene

Table 1: Palladium-catalyzed bisallylic substitution with 1,3-dione **1a**: effect of reaction parameters.[a]



Entry	Change from "standard conditions"	Yield [%][b]	
		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[c]	$Pd(OAc)_2$ instead of $[\{PdCl(allyl)\}_2]$	7	58
7[c]	$Pd(OTFA)_2$ instead of $[\{PdCl(allyl)\}_2]$	–	–
8	1,4-dioxane instead of THF	12	50
9	toluene instead of THF	21	46
10	CH_3CN instead of THF	15	41
11	CH_2Cl_2 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] Yields of isolated products. [c] Palladium and ligand were heated for 15 min at 60 °C before substrates were added. dba = dibenzylideneacetone, TFA = trifluoroacetyl.

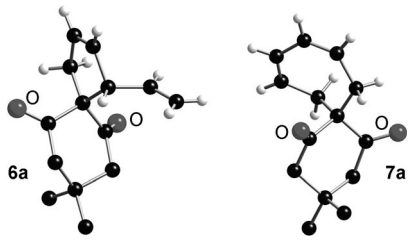


Figure 1. Ball-and-stick representation of compounds **6a** (left) and **7a** (right). Some hydrogen atoms have been omitted for clarity.

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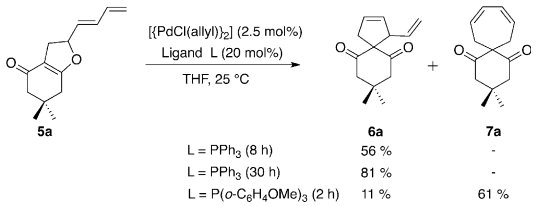
6a in 64% yield in eight hours at 25°C with traces of **5a** (Table 1, entry 1). The selectivity toward the products was not affected when $[Pd(PPh_3)_4]$ or $Pd(OAc)_2$ were used (Table 1, entries 5 and 6). In contrast, we were able to reverse the selectivity by using $[Pd_2(dba)_3]\cdot CHCl_3$ (Table 1, entry 4), whereas $Pd(OTFA)_2$ was found to be ineffective (entry 7). The solvent appeared to play a minor role in the reaction outcome (Table 1, entries 8–11). Because noticeable amounts of unreacted dimedone **1a** were detected at the end of the reaction, the 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 the formation of product **5a** (Table 1, entries 12 and 13). Increasing the temperature led to reduced yields of isolated products as a consequence of degradation processes (Table 1, entry 14).

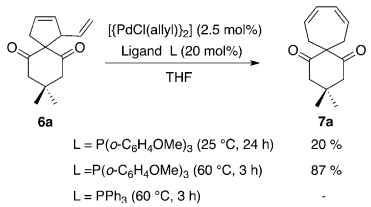
Next, we carefully investigated the effect of ligands on the reaction outcome (Table 2). The use of electron-rich PCy_3 afforded only traces of **5a** (Table 2, entry 3). Electron-poor phosphines, such as trifurylphosphine, $P(OPh)_3$, or $P(C_6F_5)_3$, gave either **6a** or **5a** in low yields (Table 2, entries 4–6). The bulky $P(o\text{-Tol})_3$ led to the formation of spiro product **6a** (Table 2, entry 7). Interestingly, when $P(o\text{-}C_6H_4OMe)_3$ was employed, a new product, cycloheptadiene **7a**, was isolated as the major product (66%) along with **6a** in 11% yield. The structure of **7a** was unambiguously determined by X-ray crystallography (Figure 1, right). In order to understand the factors that govern the formation of **7a**, *meta*- and *para*-substituted tris(methoxyphenyl)phosphines were tested. These ligands afforded product mixtures, in which **6a** appeared to be the major component (Table 2, entries 8–10). Meanwhile, only traces of **5a** were isolated when $P(2,6\text{-}C_6H_3(OMe)_2)_3$ was used. These results suggest that both electron-rich properties and appropriate steric congestion of the ligands favor the formation of **7a**. Examination of bidentate ligands showed that Xantphos gave preferentially cycloheptadiene **7a** (Table 2, entries 12–14). This ligand is well-known to have different 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**.

Examples of palladium-catalyzed 1,3-oxygen-to-carbon alkyl migrations have been reported in the literature,[10] and dihydrofuran **5a** was supposed to be a key intermediate for the formation of spirocarbocycles. 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, the yield and ratio of **6a** to **7a** were found to match 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 attempted (Scheme 3). Unexpectedly, when the catalytic system that includes $P(o\text{-}C_6H_4OMe)_3$ was used, the transformation of **6a**



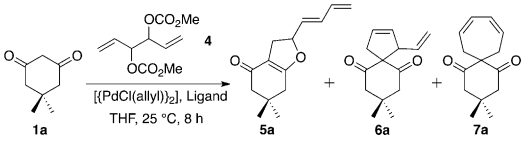
Scheme 3. Transformation of vinylcyclopentene **6a** into cycloheptadiene **7a**.

to **7a** at 25°C which proceeded with a low yield (20%) was significantly improved by increasing the temperature to 60°C (87% yield after 3 h). This result represents one of the rare examples of palladium-promoted C–C allylic bond cleavage, especially at room temperature.[11]

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

Having established the optimal reaction conditions, we next investigated the scope of the formation of vinylcyclopentenes with a range of 1,3-diones or derivatives (Table 3).

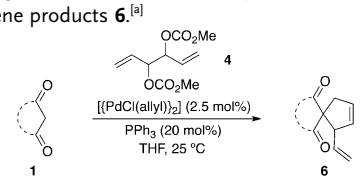
Table 2: Palladium-catalyzed bisallylic substitution with 1,3-dione **1a**: ligand effect.[a]



Entry	Ligand	Yield [%][b]		
		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	**$P(o\text{-}OMeC_6H_4)_3$**	–	**11**	**66**
9	$P(m\text{-}OMeC_6H_4)_3$	6	61	5
10	$P(p\text{-}OMeC_6H_4)_3$	14	28	23
11	$P(2,6\text{-}(OMe)_2C_6H_3)_3$	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. [b] Yields of isolated products. Dpephos = bis[(2-diphenylphosphino)phenyl] ether, dppf = diphenylphosphinoferrocene.

Table 3: Investigation of the substrate scope for the formation of vinylcyclopentene products **6**.[a]



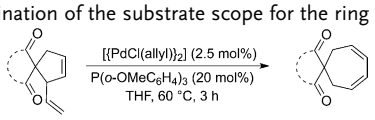
Entry	Substrate	Product	*t* [h]	Yield [%][b]
1			8	72
2			16	72
3			16	83
4			2	85
5			5	53
6			4	70 (d.r.= 1:1.3)
7			5	79
8			2	71
9			2	78
10			4	67 (d.r.= 1:1)
11			24	trace

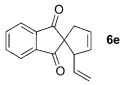
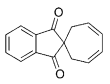
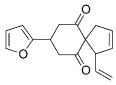
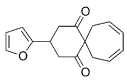
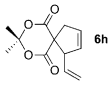
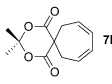
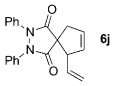
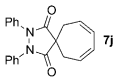
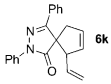
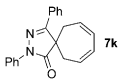
[a] Reaction conditions: [{PdCl(allyl)}$_2$] (2.5 mol%), PPh_3 (20 mol%), **4** (0.5 mmol), **1** (0.5 mmol), THF (5 mL, 0.1 M), 25 °C. [b] Yields of isolated products.

Cyclopentane-1,3-dione-based substrates **1b**–**1e** were good candidates, which afforded the expected vinylcyclopentenes **6b**–**6e** in satisfactory yields (Table 3, entries 1–4). With cyclohexane-1,3-dione **1f**, product **6f** was obtained in a moderate yield (Table 3, entry 5).[13] The use of substrate **1g** allowed to determine that the reaction was not diastereoselective (Table 3, 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 (Table 3, entries 7–9). These results led us to examine 5-pyrazolinone **1k** as a substrate, which gave the expected product without any diastereoselectivity but in a satisfactory yield (Table 3, entry 10). In deep contrast, acyclic 1,3-dione **1l** gave rise to only trace amounts of **6l** (Table 3, entry 11). The bulk of the crude reaction mixture consisted of unreacted compounds **1l** and **4**.

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

Table 4: Examination of the substrate scope for the ring expansion.[a]

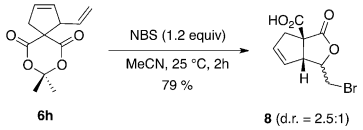


Entry	Substrate	Product	Yield [%][b]
1			41
2			72
3			75
4			79
5			65

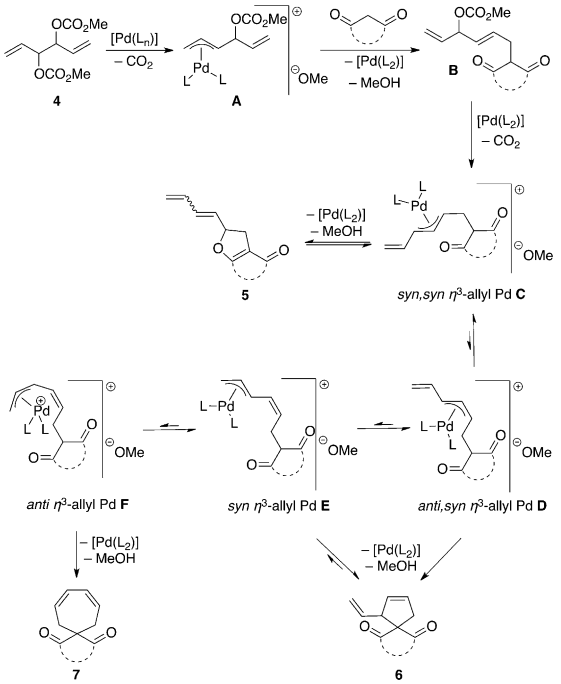
[a] Reaction conditions: [{PdCl(allyl)}$_2$] (2.5 mol%), P(*o*-$OMeC_6H_4)_3$ (20 mol%), **6** (0.5 mmol), THF (5 mL, 0.1 M), 60 °C, 3 h. [b] Yields of isolated products.

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

A plausible mechanism to explain the formation of spirocarbocycles is shown in Scheme 5. At first, an allylic substitution takes place via 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 kinetic product **5** through O-alkylation or evolve into the *anti*,*syn* η^3-allyl intermediate **D** through a π-σ-π isomerization. Intermediate **D** leads to vinylcyclopentene **6** by C-alkylation. Dynamic equilibration of **D** into *syn* η^3-allyl



Scheme 4. Bromolactonization of compound **6h**. NBS = *N*-bromosuccinimide.



Scheme 5. Mechanistic proposal.

complex **E** may give either **6** or the less disfavored *anti* η^3-allyl palladium complex **F**, thus triggering the formation of cycloheptadiene product **7**.

In summary, we have developed a palladium-mediated bisallylic substitution leading to five- and seven-membered carbocycles. The chemoselectivity of the reaction depends on the phosphorous ligand that is used. More importantly, we observed a cleavage of carbon–carbon allylic bonds through activation under mild conditions, thus allowing 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 bisallylic substitution sequence.

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Keywords: allylic substitution · C–C activation · palladium · phosphines · spiro compounds

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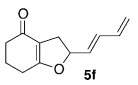

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