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# Pd-catalyzed domino carbonylative/decarboxylative allylation

Steven Giboulot

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**THESE DE DOCTORAT DE L'UNIVERSITE PIERRE ET MARIE CURIE - PARIS 6**

Spécialité

**CHIMIE ORGANIQUE**

Ecole Doctorale de Chimie Moléculaire de Paris Centre – ED 406

Présentée par

**Mr Steven GIBOULOT**

Pour obtenir le grade de

**DOCTEUR de L'UNIVERSITE PIERRE ET MARIE CURIE**

Sujet de la thèse :

**Pd-Catalyzed Domino Carbonylative / Decarboxylative Allylation**

Soutenue le 24 SEPTEMBRE 2012

Devant le jury composé de :

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Professeur Bartolo GABRIELE  
Professeur André MORTREUX  
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## Abbreviations



|                   |                                      |
|-------------------|--------------------------------------|
| ANR               | Agence Nationale de la Recherche     |
| AcOEt             | Ethyl acetate                        |
| b/l               | Branched / linear ratio              |
| Bmim              | 1-Butyl-3-methylimidazolium          |
| Bn                | Benzyl                               |
| d                 | Doublet                              |
| d                 | Day                                  |
| dba               | Dibenzylidene acetone                |
| BQ                | 1,4-Benzoquinone                     |
| dba               | Dibenzylideneacetone                 |
| DBU               | 1,8-Diazabicyclo[5.4.0]undec-7-ene   |
| dd                | Doublet of doublets                  |
| DMA               | <i>N,N</i> -Dimethylacetamide        |
| DMAN              | 1,8-Bis(dimethylamino)naphthalene    |
| DMAP              | 4-Dimethylaminopyridine              |
| DME               | 1,2-Dimethoxyethane                  |
| DMF               | <i>N,N</i> -Dimethylformamide        |
| DMSO              | 1,2-Bis(methylsulfinyl)ethane        |
| dppb              | 1,4-Bis(diphenylphosphino)butane     |
| dppe              | 1,2-Bis(diphenylphosphino)ethane     |
| dppf              | 1,1'-Bis(diphenylphosphino)ferrocene |
| dppp              | 1,3-Bis(diphenylphosphino)propane    |
| <i>d.r.</i>       | Diastereomeric excess                |
| <i>ee</i>         | Enantiomeric excess                  |
| Et                | Ethyl                                |
| Et <sub>2</sub> O | Ethyl ether                          |
| Fur               | Furyl                                |
| hex               | Hexuplet                             |
| HRMS              | High Resolution Mass Spectrometry    |

|                    |   |
|--------------------|---|
| IR                 | Infrared                                      |
| LDA                | Lithium diisopropylamide                      |
| m                  | Multiplet                                     |
| m.p.               | Melting point                                 |
| Me                 | Methyl  |
| MEK                | Methyl ethyl ketone                           |
| NHC                | <i>N</i> -heterocyclic carbene                |
| NMP                | <i>N</i> -Methyl-2-pyrrolidone                |
| NMR                | Nuclear magnetic resonance                    |
| OAc                | Acetate                                       |
| OTs                | 4-Methylbenzenesulfonate                      |
| P(Cy) <sub>3</sub> | Tricyclohexylphosphine                        |
| PdNPs              | Palladium nanoparticles                       |
| PS-PEO             | Polystyrene-polyethylenoxide block co-polymer |
| pyca               | Pycolinic acid                                |
| r.t.               | Room temperature                              |
| s                  | Singlet                                       |
| t                  | Triplet                                       |
| Tf <sub>2</sub> N  | Bis(methylsulfonyl)amide                      |
| TFA                | Trifluoroacetate                              |
| tfp                | Tri-2-furylphosphine                          |
| THF                | Tetrahydrofuran                               |
| Tol                | Toluene                                       |
| TM                 | Transition-metal-catalyzed domino reaction    |
| TM-DOM             | Pure domino reaction                          |
| TM-PDOM            | Pseudo-domino reaction                        |
| TsOH               | <i>p</i> -Toluenesulfonic acid                |
| y                  | Yield   |

## General Introduction



The environmental impact of mankind through industrial rejections has become an acute issue during last decades. Indeed, pollutant release into the environment, including green-house gases, is no longer acceptable in modern societies.

Among others, the chemical industry had a major contribution to global climate changes and pollution in general. For example, pharmaceutical industries produce 50 to 200 pounds of waste for 2 pounds of pure target product. Such production outcomes are no longer viable. Therefore, new methods based, for example, on green chemistry concepts are highly desirable. Accordingly, step- and atom- economy, by reducing the waste amounts generated, provide appealing, but challenging, solutions. Although the development of highly efficient catalytic processes allowed achievement of high atom-economy, step-economy is still in its infancy. Domino reactions,<sup>1</sup> which allow to perform several chemical transformations without intermediate purifications, have emerged only very recently.

On the one hand, domino reactions have been defined by Tietze.<sup>2</sup> The formation of several bonds in one synthetic step,<sup>3</sup> reduces the number of intermediary work-ups and purification processes, lowering the volume of solvent used and waste generated, thus affording the development of elegant and environmentally-benign reactions.

---

<sup>1</sup> Some authors prefer the words “tandem” or “cascade” instead of domino. For the sake of simplicity, only the word “domino” will be used in this manuscript.

<sup>2</sup> a) Tietze, L. F.; Brasche, G.; Gericke, K. M. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, **2006**. For other reviews of the same author, see: b) Tietze, L. F. *J. Heterocycl. Chem.* **1990**, *27*, 47–69. c) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131–163. d) Tietze, L. F. *Chem. Ind.* **1995**, 453–457. e) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136. f) Tietze, L. F.; Modi, A. *Med. Res. Rev.* **2000**, *20*, 304–322. g) Tietze, L. F.; Haunert, F. Domino reaction in organic synthesis. An approach to efficiency, elegance, ecological benefit, economic advantage and preservation of our resources in chemical transformations. In *Stimulating Concepts in Chemistry*; Vögtle, F.; Stoddart, J. F.; Shibasaki, M. Eds; Wiley-VCH: Weinheim, **2000**, 39–64.

<sup>3</sup> For applications in the synthesis of natural products, see: a) Nicolaou, K. C.; Chen, J. S. *Chem. Soc. Rev.* **2009**, *38*, 2993–3009. b) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195–206. For heterocycle syntheses, see: c) Poulin, J.; Grisé-Bard, C. M.; Barriault, L. *Chem. Soc. Rev.* **2009**, *38*, 3092–3101. For applications in enantioselective synthesis, see: d) Li, H.; Loh, T. *Chem. Asian J.* **2011**, *6*, 1948–1951. e) Fu, X.; Feng, J.; Dong, Z.; Lin, L.; Liu, X.; Feng, X. *Eur. J. Org. Chem.* **2011**, 5233–5236. f) Chapman, C.; Frost, C. *Synthesis* **2007**, 1–21.

On the other hand, transition metal-catalyzed reactions have also witnessed an incredible development, and resulted in the discovery of wide range of highly efficient and selective reactions. The metal complex is used in catalytic rather than stoichiometric amounts, resulting in economy of atoms, compared to a stoichiometric approach. The design of ligand rendered these processes even more powerful.

Moreover, the use of chemicals that can be readily obtained from renewable sources arises as a requirement for a sustainable development. Carbon monoxide is one such chemical compound. Its gaseous nature eliminates any purification issue due to any excess reagent. As it is also highly reactive, carbon monoxide is a reagent of choice for the development of new green processes.

In this work, we will report on the design of a catalytic domino process, thereby benefiting from both atom- (due to catalysis) and step- (thanks to domino reactions) economy. The use of carbon monoxide as a renewable chemical in conjunction with palladium catalysis to achieve alkoxycarbonylations as well as decarboxylative allylations will be described. Accordingly, the first three chapters of this manuscript will introduce and try to describe the state of the art of the topics related to the thesis project. Given the remarkable amount of the published material on these topics, this bibliographical introduction will be necessarily far from being exhaustive.

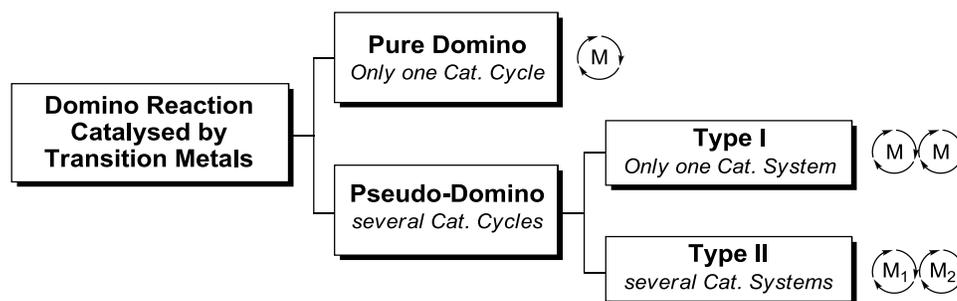
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## CHAPTER I : Transition metal catalyzed domino reactions

Domino reactions have been defined by Tietze in the early 1990's: "a domino reaction is a process involving two or more bond-forming transformations, which take place under the same reaction conditions without adding supplementary reagents and/or catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step".<sup>2</sup> Therefore, domino reactions are in compliance of the principle of step-economy. This definition has led to the classification of radical, anionic, cationic, redox or transition-metal-catalyzed processes. In order to further conceptualize this idea, our team has subsequently proposed an *ad hoc* taxonomy for transition-metal-catalyzed (TM) domino reactions in terms of nature and number of catalytic cycles and metals involved in the domino sequence.<sup>4</sup> Thus, according to this definition, pure domino reactions (TM-DOM) involve only one catalytic cycle entailing several organometallic intermediates, whereas pseudo-domino reactions (TM-PDOM) involve at least two mechanistically independent and succeeding catalytic cycles. The pseudo-domino reaction can be in turn subdivided into two sub-types: the type I and pseudo-domino type II reactions, depending on the numbers of catalytic systems involved (Scheme 1).<sup>2a,2e</sup>



Scheme 1: Classification of domino reactions catalyzed by transition metals

In line with the previously mentioned issues of step-and atom-economy, transition-metal-catalyzed domino reactions have become very popular and have reached a

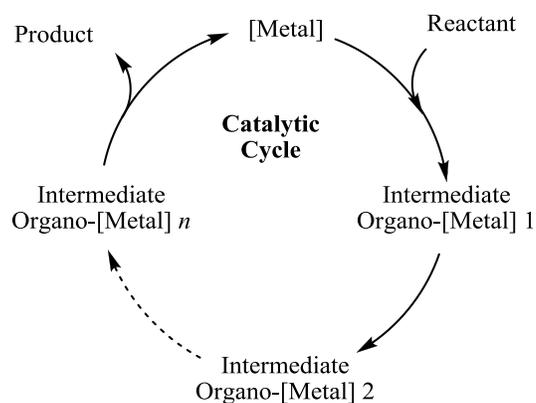
<sup>4</sup> Poli, G.; Giambastiani, G. *J. Org. Chem.* **2002**, *67*, 9456–9459.

high degree of efficiency.<sup>5</sup> Any transition metal may be used (Zr,<sup>6</sup> Co,<sup>7</sup> Cu,<sup>8</sup> La,<sup>9</sup> Ni,<sup>10</sup> Rh,<sup>11</sup> ...), depending on the targeted reactivity, but palladium has emerged as one of the most frequently used.<sup>3c,12-14</sup>

#### a) Pure domino reactions (TM-DOM)

Pure domino reactions are characterized by a single catalytic cycle displaying several elementary steps, creating or cleaving several bonds (Scheme 2).

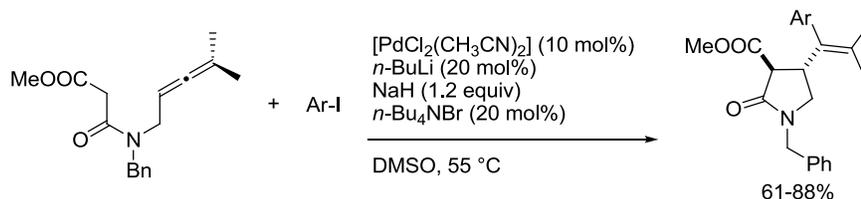
- 
- <sup>5</sup> For reviews see: a) Metal Catalyzed Cascade Reactions. In *Top. Organomet. Chem.*, Vol. 19; Müller, T. J. J. Ed; Springer-Verlag: Berlin, Heidelberg, **2006**. b) de Meijere, A.; Schelper, M. *Actual. Chim.* **2003**, 51–56.
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- <sup>7</sup> Le Floch, C.; Laymand, K.; Le Gall, E.; Léonel, E. *Adv. Synth. Catal.* **2012**, *354*, 823–827.
- <sup>8</sup> a) Cai, S.; Wang, F.; Xi, C. *J. Org. Chem.* **2012**, *77*, 2331–2336. b) Kitching, M. O.; Hurst, T. E.; Snieckus, V. *Angew. Chem. Int. Ed.* **2012**, *51*, 2925–2929.
- <sup>9</sup> Bhatt, R.; Sharma, S.; Nath, M. *Monatsh. Chem.* **2012**, *143*, 309–316.
- <sup>10</sup> Ambe-Suzuki, K.; Ohyama, Y.; Shirai, N.; Ikeda, S. *Adv. Synth. Catal.* **2012**, *354*, 879–888.
- <sup>11</sup> Tsui, G. C.; Lautens, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 5400–5404.
- <sup>12</sup> Handbook of Organopalladium Chemistry for Organic Synthesis, Negishi, E. Ed; Wiley: New York, **2002**.
- <sup>13</sup> For reviews on palladium-catalyzed domino reactions, see: a) Heumann, A.; Réglie, M. *Tetrahedron* **1996**, *52*, 9289–9346. b) Negishi, E.; Copéret, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365–394. c) Grigg, R.; Sridharan, V. *J. Organomet. Chem.* **1999**, *576*, 65–87. d) Poli, G.; Giambastiani, G.; Heumann, A. *Tetrahedron* **2000**, *56*, 5959–5989. f) Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Eur. J. Org. Chem.* **2002**, 2671–2681. g) Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, 4101–4111.
- <sup>14</sup> For recent examples of palladium-catalyzed domino reactions, see: a) de Meijere, A.; von Zezschwitz, P.; Bräse, S. *Acc. Chem. Res.* **2005**, *38*, 413–422. b) Wilhelm, T.; Lautens, M. *Org. Lett.* **2005**, *7*, 4053–4056. c) Grigg, R.; Sridharan, V.; Shah, M.; Mutton, S.; Kilner, C.; MacPherson, D.; Milner, P. *J. Org. Chem.* **2008**, *73*, 8352–8356. d) Petriguet, J.; Boudhar, A.; Blond, G.; Suffert, J. *Angew. Chem. Int. Ed.* **2011**, *50*, 3285–3289.



**Scheme 2: General catalytic cycle for pure domino reaction (TM-DOM)**

Pure domino reactions are by far the most widespread in the literature. This is probably due to the fact that step chronology issues are avoided.

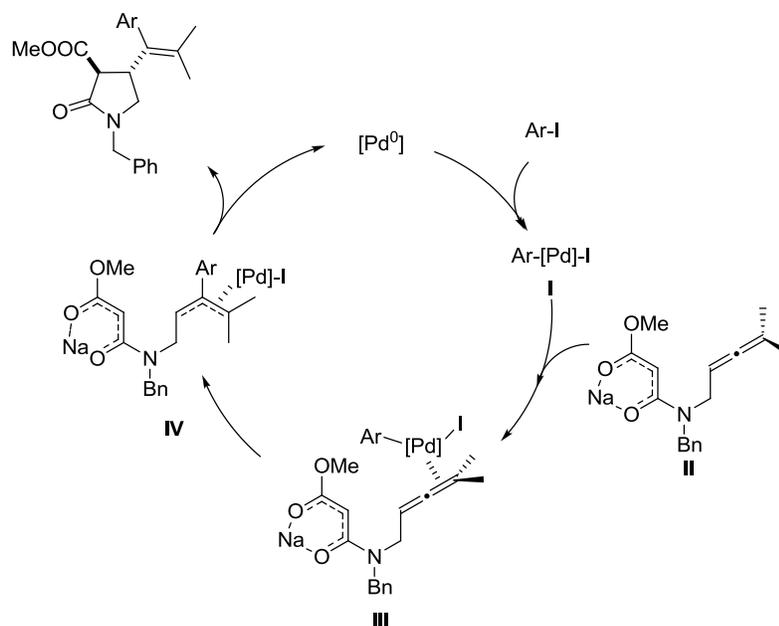
For example, our group has developed a pure domino reaction featuring carbopalladation / allylic alkylation to yield efficiently *trans*  $\gamma$ -lactams (Scheme 3).<sup>15</sup>



**Scheme 3: Example of pure domino reaction**

<sup>15</sup> Kammerer, C.; Prestat, G.; Madec, D.; Poli, G. *Chem. Eur. J.* **2009**, *15*, 4224–4227.

In this phosphine-free process, oxidative addition of the aryl iodide on the palladium (0) complex affords the corresponding  $\sigma$ -aryl palladium species **I**, which undergoes a complexation / carbopalladation sequence to deliver a  $\pi$ -allyl intermediate **IV**. Finally, attack of malonamide sodium enolate to the  $\pi$ -allyl palladium complex produces stereoselectively the desired *trans*  $\gamma$ -lactam (Scheme 4).



**Scheme 4: Mechanism for the pure domino reaction featuring carbopalladation / allylic alkylation**

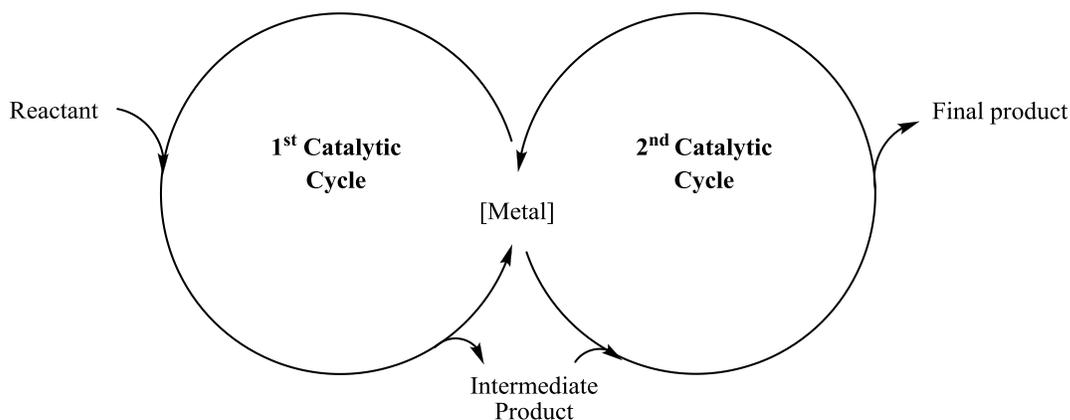
Two carbon-carbon bonds are created along a single catalytic cycle. These features define a pure domino reaction.

#### b) Pseudo-domino reactions (TM-PDOM)

In contrast to pure domino reactions, pseudo-domino reactions involve at least two catalytic cycles. These cycles are mechanistically distinct and occur in a defined chronological order. Pseudo-domino type I reactions involve a single multitask catalyst, whereas pseudo-domino type II reactions involve several catalytic systems. The main difficulty lies in the control of the step chronology.

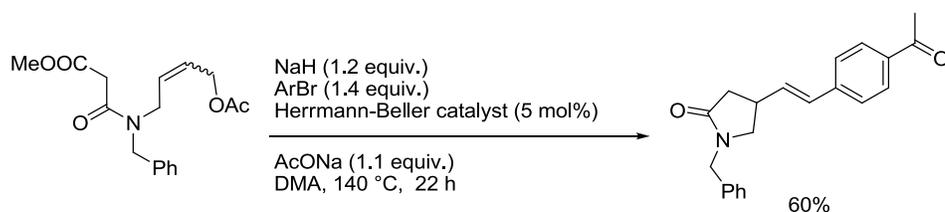
### i. Pseudo-domino type I reactions

Pseudo-domino type I reactions, also called “Auto-tandem catalysis” by Fogg and dos Santos,<sup>16</sup> imply a single metallic complex, which is catalytically-competent for all the cycles. A generic example featuring two catalytic cycles is provided in Scheme 5.



Scheme 5: General catalytic cycle for pseudo-domino type I reaction

Our team has developed several examples of pseudo-domino type I reactions. For example, a sequence including allylic alkylation / Mizoroki-Heck reaction has allowed the synthesis of 3-vinyl substituted  $\gamma$ -lactams (Scheme 6).<sup>17</sup>



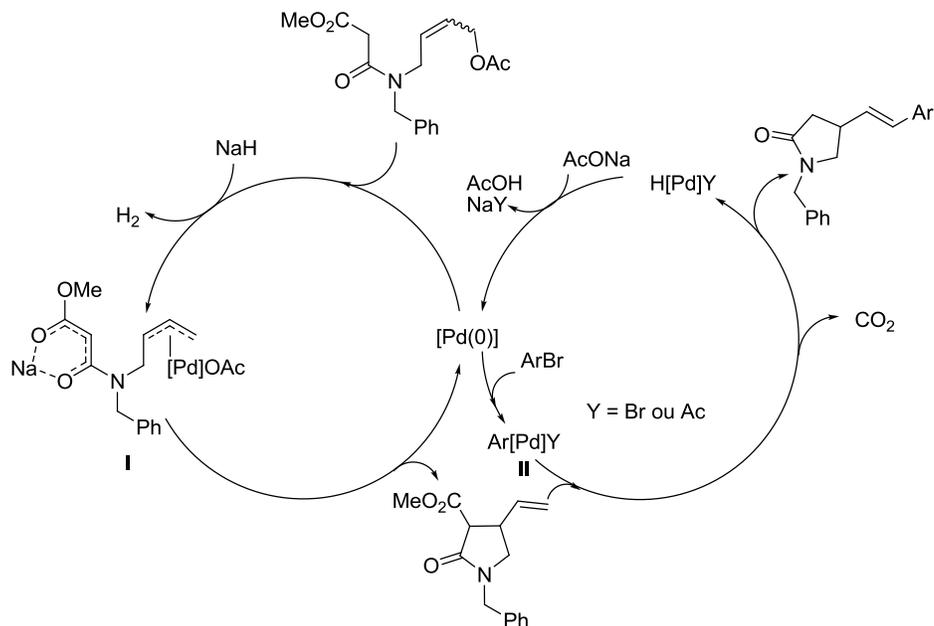
Scheme 6: Example of pseudo-domino type I reaction

Under these conditions, the  $\pi$ -allyl intermediate **1** undergoes nucleophilic attack by the deprotonated malonamide. The thus-generated terminal olefin then enters the 2<sup>nd</sup>

<sup>16</sup> Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365–2379.

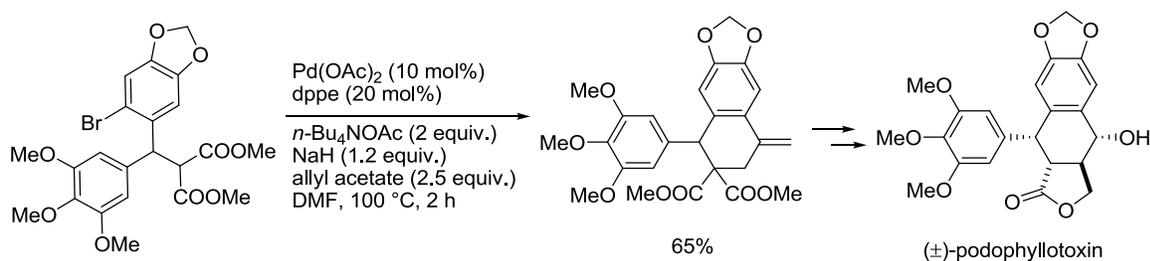
<sup>17</sup> Poli, G.; Giambastiani, G.; Pacini, B. *Tetrahedron Lett.* **2001**, *42*, 5179–5182.

cycle, which involves an intermolecular Mizoroki-Heck reaction with an aryl bromide. Interestingly, the high temperatures required bring about malonamide decarboxylation as a further step of the sequence (Scheme 7).



**Scheme 7: Mechanism for the allylic alkylation / Mizoroki-Heck process**

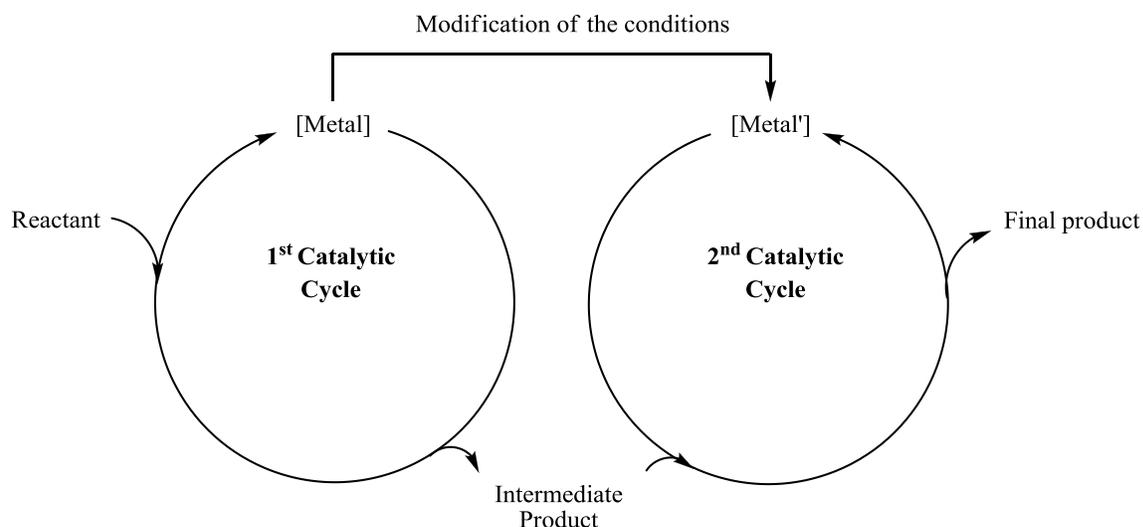
This method has been used for the formal synthesis of podophyllotoxin (Scheme 8).<sup>18</sup>



**Scheme 8: Application to the total synthesis of analogues of podophyllotoxin**

<sup>18</sup> Mingoia, F.; Vitale, M.; Madec, D.; Prestat, G.; Poli, G. *Tetrahedron Lett.* **2008**, *49*, 760–763.

The principal difficulty in pseudo-domino reactions lies in finding conditions that allow the control of the chronological step order. Nevertheless, this difficulty can be circumvented by modifying the conditions at the end of the first catalytic cycle, so as to have an "assisted" as opposed to an "auto" mode pseudo-domino type I sequence (Scheme 9). If a change in the experimental conditions (addition of ligand, or catalyst, oxidation, reduction...) is required for the second catalytic cycle to start, step order can be easier controlled.

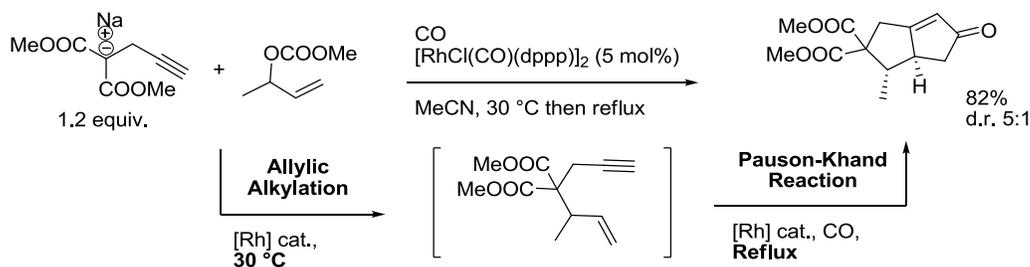


**Scheme 9: General catalytic cycle for "assisted" pseudo-domino type I pseudo-domino sequence**

Evans has described an elegant example of such a pseudo-domino type I reaction, in which a change in the reaction temperature allowed to carry out a rhodium catalyzed allylation reaction in the first step at 30 °C, and a Pauson-Khand reaction in the second one in refluxing acetonitrile (Scheme 10).<sup>19</sup>

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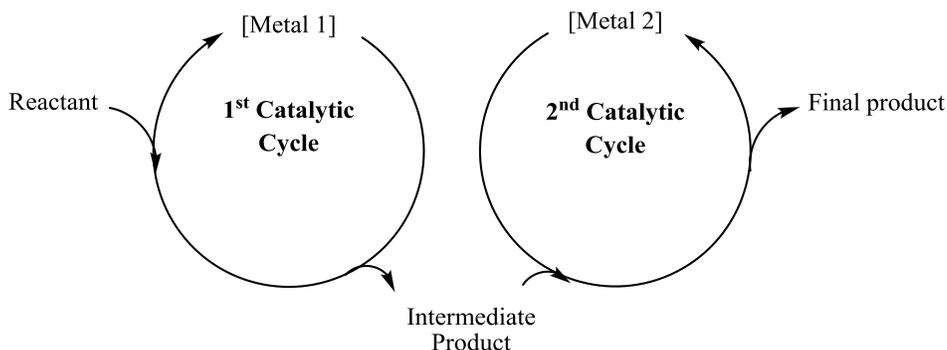
<sup>19</sup> Evans, P. A.; Robinson, J. E. *J. Am. Chem. Soc.* **2001**, *123*, 4609–4610.



Scheme 10: Example of “assisted” pseudo-domino type I reaction

## ii. Pseudo-domino type II reactions

Pseudo-domino type II reactions, alias “orthogonal tandem catalysis”,<sup>16</sup> are composed by two or more catalytic systems driving sequential catalytic cycles (Scheme 11).

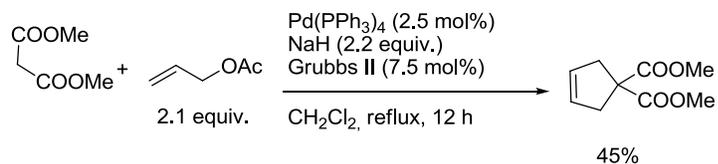


Scheme 11: General catalytic cycle for pseudo-domino type II reaction

Compared to pseudo-domino type I reactions, pseudo-domino type II reactions feature additional difficulties. As catalysts of different nature are involved, they must not interfere with each other. For example, ligand scrambling between metals should not inhibit a given catalytic cycle, and a given intermediate should react selectively with a given catalyst in a given transformation.

The occurrence of all these delicate parameters to control makes pseudo-domino type II reactions highly challenging. Not surprisingly, examples of such processes are scarce in the literature. For example, our group recently described an allylation / ring closing metathesis pseudo-domino type II sequence. A palladium catalyst was required to effect the allylation reaction, whereas a ruthenium complex was the competent catalyst for the ring

closing metathesis step. It goes without saying that each catalyst alone cannot drive both steps (Scheme 12).<sup>20</sup>



**Scheme 12: Example of pseudo-domino type II reaction**

The development of transition-metal-catalyzed domino reactions is an active field of research. As the few preceding examples show such processes allow the straightforward synthesis of complex targets starting from simple precursors.

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<sup>20</sup> Kammerer, C.; Prestat, G.; Gaillard, T.; Madec, D.; Poli, G. *Org. Lett.* **2008**, *10*, 405–408.

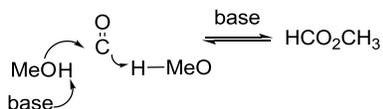


## CHAPTER II : Carbonylation reactions

### a) Foreword

Carbon monoxide can be activated and then incorporated into an organic substrate through transition metal catalysis. This powerful transformation, named nucleocarbonylation reaction, can afford several kinds of carbonyl compounds such as aldehydes, esters, amides, or carboxylic acids, as a function of the nucleophile used, and may take place *via* different pathways (Scheme 14).<sup>21</sup>

Interestingly, in these reactions methyl formate can be used as practical CO precursor, as in the presence of an appropriate base, methyl formate decomposes into CO and MeOH.<sup>22,23</sup> In fact, the industrial synthesis of methyl formate exploits the reverse reaction (Scheme 13).



Scheme 13: General mechanism of the synthesis of methyl formate

Several mechanistic studies have been carried out on this type of carbonylation reactions and yet still some doubts and discrepancies remain regarding the later steps of the mechanism.<sup>24</sup> This is partly due to the number of alternative possible pathways available. Anyway, Scheme 14 outlines a simplified view of three possible mechanisms of the Pd-catalyzed nucleocarbonylation, starting from a generic  $\sigma$ -alkylpalladium complex: routes **A1**,

<sup>21</sup> a) Allen, C. L.; Williams, J. M. *J. Chem. Soc. Rev.* **2011**, *40*, 3405–3415. b) Chaturvedi, D. *Tetrahedron* **2012**, *68*, 15–45. b) *Catalytic Carbonylation Reactions*, (Beller, M. Ed.); Top. in Organomet. Chem.; Springer-Verlag Berlin/Heidelberg, **2006**; Vol. 18.

<sup>22</sup> Pellegrini, S.; Castanet, Y.; Mortreux, A. *J. Mol. Catal. A: Chem.* **1999**, *138*, 103–106.

<sup>23</sup> a) Mohanakrishnan, A. K.; Ramesh, N. *Tetrahedron Lett.* **2005**, *46*, 4577–4579. For example of intramolecular alkoxy carbonylation of benzyl halide see: b) Cowell, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4193–4198. For example of hydroxycarbonylation of benzyl halide see: c) Alper, H.; Hashem, K.; Heveling, J. *Organometallics* **1982**, *1*, 775–778.

<sup>24</sup> Barnard, C. F. J. *Organometallics* **2008**, *27*, 5402–5422.

**A2**, and **B**. Route **A** involves initial CO insertion from the square planar intermediate **II**, to give the acylpalladium complex **III**. This latter can give the final product either *via* direct nucleophilic addition at the acyl moiety (**A1**), or through nucleophilic addition at palladium atom to afford intermediate **IV**, followed by reductive elimination (**A2**). Alternatively, nucleophilic attack at coordinated CO gives intermediate **V**, which can reductively eliminate. The initially formed five-coordinate intermediate **I** is expected to release the four-coordinate species **II**.<sup>25</sup> As to the subsequent steps, the works of Heck,<sup>26</sup> Moser,<sup>27</sup> Milstein<sup>28</sup> and Hidai<sup>29</sup> appear to favor route **A1**, whereas the alternative mechanisms **A2** and **B** were proposed by Yamamoto<sup>30</sup> and Zhang<sup>31</sup>. All in all, it seems likely that the carbonyl insertion reaction prevails for carbonylation reactions yielding acids, esters, and amides. Yet, in some cases the structure of the final product indicates that the alternative path has necessarily to be at work.

The final reductive elimination appears to occur following initial dissociation of one neutral ligand from a *cis* complex, leading to a trigonal (Y shaped) transition state.<sup>32</sup>

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<sup>25</sup> Garrou, P. E.; Heck, R. F. *J. Am. Chem. Soc.* **1976**, *98*, 4115-4127.

<sup>26</sup> Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318-3326.

<sup>27</sup> Moser, W. R.; Wang, A. W.; Kildahl, N. K. *J. Am. Chem. Soc.* **1988**, *110*, 2816-2820.

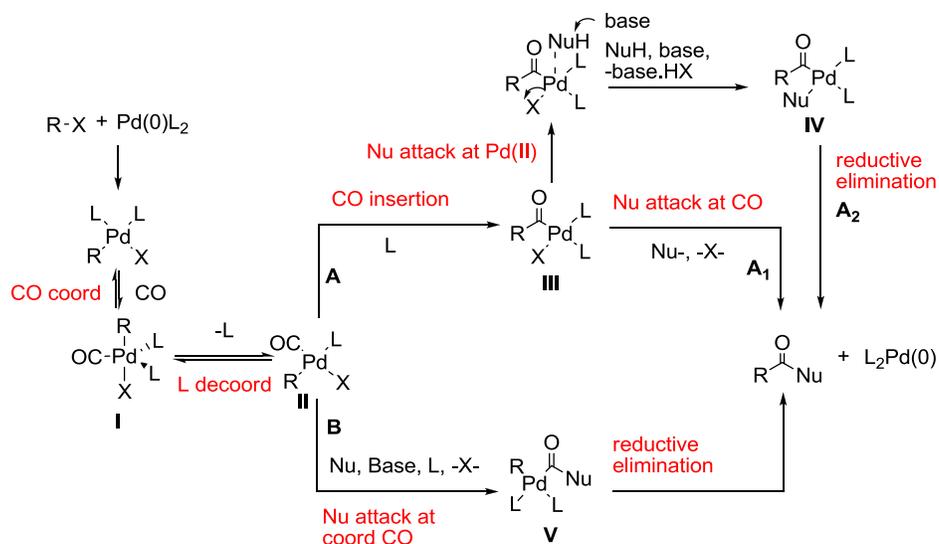
<sup>28</sup> Milstein, D. *J. Chem. Soc., Chem. Commun.* **1986**, 817.

<sup>29</sup> Hidai, M.; Kokura, M.; Uchida, Y. *J. Organomet. Chem.* **1973**, *52*, 431-435.

<sup>30</sup> Ozawa, F.; Kawasaki, N.; Okamoto, H.; Yamamoto, T.; Yamamoto, A. *Organometallics* **1987**, *6*, 1640-1651.

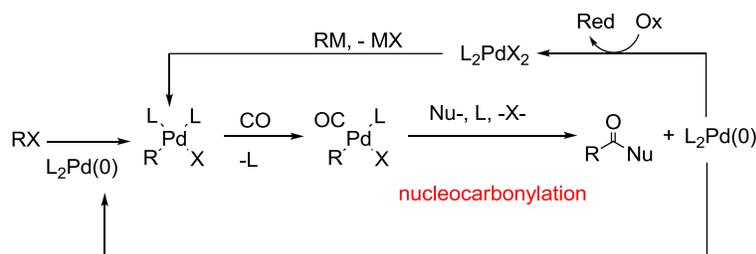
<sup>31</sup> Hu, Y.; Liu, J.; Lü, Z.; Luo, X.; Zhang, H.; Lan, Y.; Lei, J. *J. Am. Chem. Soc.* **2010**, *132*, 3153-3158.

<sup>32</sup> Ozawa, F.; Ito, T.; Nakamura, Y.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1868-1880.



**Scheme 14: Mechanistic insight of nucleocarbonylation**

Interestingly, palladium catalyzed carbonylations can be successfully effected either under non-redox conditions, starting from a  $Pd(0)$  catalyst, or under oxidative conditions, starting from a  $PdX_2$  catalyst. In each case, the carbonylated organic product is produced together with a  $Pd(0)$  complex (Scheme 15).

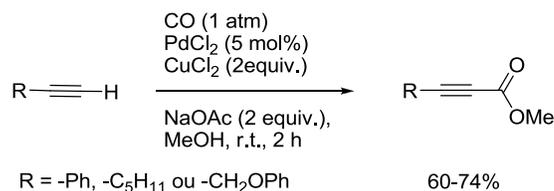


**Scheme 15: Palladium catalyzed nucleocarbonylation general catalytic cycle**

This reaction has been extensively studied, and many reviews can be found in the literature dealing with this topic. Some examples of carbonylation will be first given as a function of the hybridization of the carbon atom undergoing the carbonylation. Indeed, the hybridization parameter plays a key role in the scope and limitations of the carbonylation reaction. Finally, some carbonylative domino and pseudo-domino reactions will also be presented.

## b) Carbonylation of sp-hybridized carbon atoms

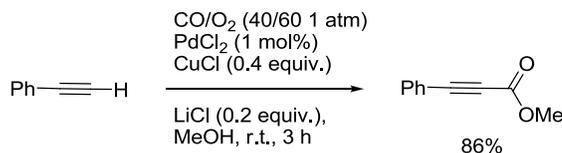
Only few examples of carbonylation at C-sp atoms are described in the literature. The first one was reported by Tsuji in 1980. The carbonylation of phenyl acetylene with palladium chloride for the synthesis of propiolate esters was reported (Scheme 16).<sup>33</sup>



**Scheme 16: Palladium catalyzed alkoxy carbonylation of alkyne, Tsuji's conditions**

The mechanism remains unclear. Palladium acetylides may be involved, and the copper(II) salt should act as the final reoxidant. Jiang extended this reaction to various alcohols (*n*-BuOH, *i*-PrOH) yielding the desired esters in similar yield. The key to success was use of palladium bromide and copper bromide instead of chloride analogues.<sup>34</sup>

Temkin proposed in 1994 a similar carbonylation under aerobic conditions (Scheme 17).<sup>35</sup>



**Scheme 17: Aerobic palladium catalyzed carbonylation of alkyne**

The mechanism starts with generation of the copper(I) acetylide from CuCl and the terminal alkene. Subsequent transmetalation with PdCl<sub>2</sub> produces the corresponding  $\sigma$ -alkynylpalladium(II) complex, which undergoes the carbonylation step. Trapping of the thus

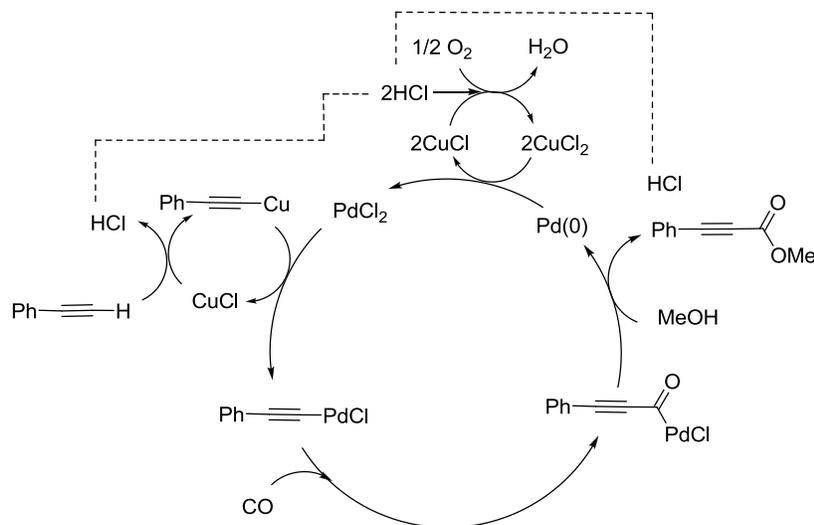
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<sup>33</sup> Tsuji, J.; Takahashi, M.; Takahashi, T. *Tetrahedron Lett.* **1980**, *21*, 849–850.

<sup>34</sup> Li, J.; Jiang, H.; Chen, M. *Synth. Commun.* **2001**, *31*, 199–202.

<sup>35</sup> Zung, T. T.; Bruk, L. G.; Temkin, O. N. *Mendeleev Commun.* **1994**, *4*, 2–3.

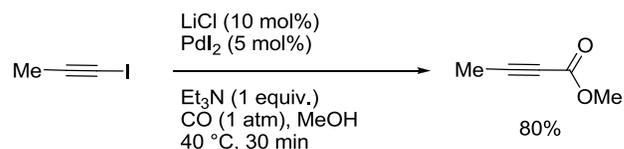
formed  $\sigma$ -acylpalladium complex by methanol delivers the desired product and palladium(0) complex, which is reoxidized by the action of  $\text{CuCl}_2/\text{O}_2$  in a Wacker-type fashion (Scheme 18).



**Scheme 18: Mechanism of Temkin carbonylation**

Phenylacetylene and propyne were suitable alkynes, and methanol was the only alcohol investigated.

One year later, Temkin proposed a copper-free carbonylation of haloalkynes, with palladium catalysts (Scheme 19).<sup>36</sup>



**Scheme 19: Carbonylation of iodoalkyne**

The mechanism proposed by the authors involves the initial reduction of the palladium(II) into palladium(0) complex by carbon monoxide (Scheme 20),<sup>37</sup> followed by

<sup>36</sup> Zung, T. T.; Bruk, L. G.; Temkin, O. N.; Malashkevich, A. V. *Mendeleev Commun.* **1995**, *5*, 3–4.

oxidative addition of the iodoalkyne to the Pd(0) complex to afford the  $\sigma$ -alkynylpalladium(II) complex. The remaining part of the catalytic cycle mimics that previously described (Scheme 18). Moreover, the same scope and limitations were observed.



**Scheme 20: Reduction of palladium(II) into palladium(0) with carbon monoxide**

In conclusion, almost all examples dealing with the carbonylation of C-sp carbon atoms occur under very smooth reaction conditions: atmospheric pressure and room temperature. The lack of diversity regarding the alkyne and the alcohol, is a limitation of this methodology.

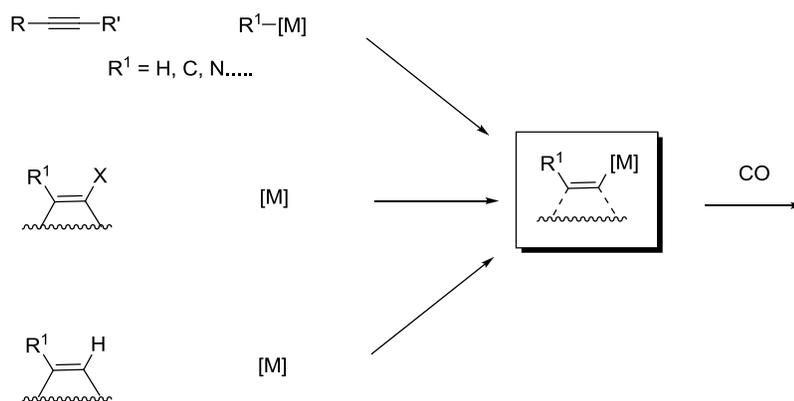
### c) Carbonylation of $\text{sp}^2$ -hybridized carbon atoms

Unlike carbonylation of C-sp hybridized centers, the carbonylation of  $\text{sp}^2$  hybridized carbon atoms is plethora. There are many examples featuring various conditions, catalysts, substrates and resulted in the formation of all possible carbonyl derivatives, from aldehyde to urea or carboxylic acid. Therefore, due to the tremendous amount of published works, only few examples will be described, chosen for their originality, to discuss the possibility of carbonylation.

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<sup>37</sup> a) Phillips, F. C. *Am. Chem. J.*, **1894**, *16*, 255-277. b) Lloyd W. G.; Rowe, D. R. *Environ. Sci. Technol.*, **1971**, *5*, 1133-1134.

The scope and limitations of these carbonylation reactions amply rely on the method (hydro- or carbo-palladation, oxidative addition or C-H activation) used to generate the metallated species (Scheme 21). Accordingly, the examples outlined here below will be classified as a function of the method of generation of the starting metallated species.



Scheme 21: Different ways of generating  $Csp^2$ -M intermediate

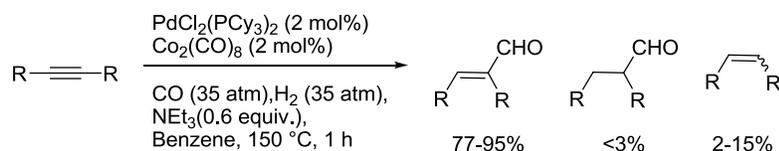
### i. Starting from an alkyne substrate

Addition of a metalhydride to an alkyne leads to the formation of a  $Csp^2$ -[M] complex which can further react with carbon monoxide.

The hydroformylation of alkynes is highly challenging. Indeed, most catalysts reported suffer from low selectivity and/or low yield of the desired unsaturated aldehydes.<sup>38</sup> This is due to the formation of the corresponding saturated aldehydes and non-carbonylated olefin. However, the group of Hidai reported a hydroformylation reaction of acetylenes with a mixture of palladium and cobalt catalysts (Scheme 22).<sup>39</sup>

<sup>38</sup> a) Campi, E.; Jackson, W. *Aust. J. Chem.* **1989**, *42*, 471–478. b) Nombel, P.; Lugan, N.; Mulla, F.; Lavigne, G. *Organometallics* **1994**, *13*, 4673–4675.

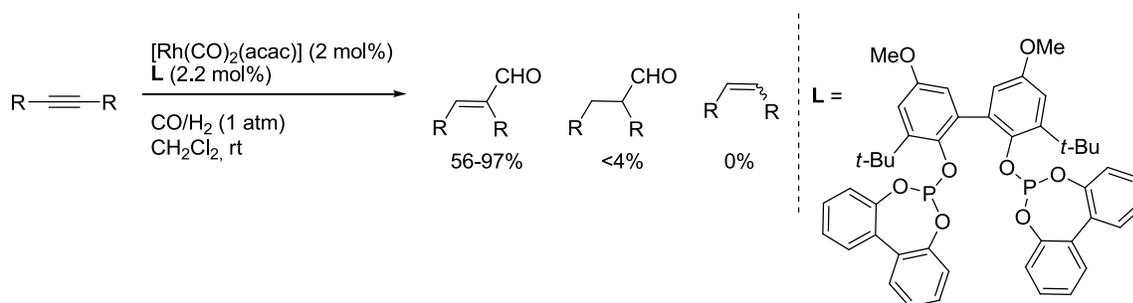
<sup>39</sup> Ishii, Y.; Miyashita, K.; Kamita, K.; Hidai, M. *J. Am. Chem. Soc.* **1997**, *119*, 6448–6449.



**Scheme 22: Hydroformylation of alkyne**

The authors described that the two catalysts formed a bimetallic complex, which is much more active and selective.

Other groups have successfully hydroformylated alkynes. Buchwald for example, has described a Rh-catalyzed carbonylation reaction (Scheme 23).<sup>40</sup>



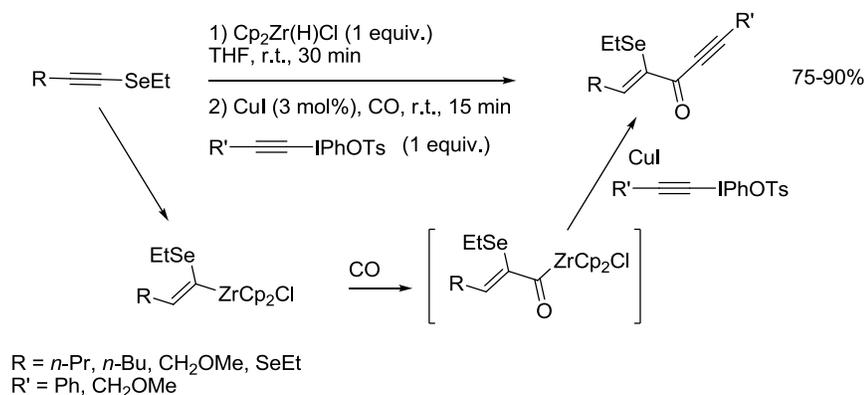
**Scheme 23: Buchwald example of hydroformylation of alkyne**

The reaction conditions are smoother (atmospheric pressure and room temperature) and, except for diphenylacetylene, the authors never observed the alkene resulting from a simple hydrogenation reaction. Only symmetrical alkynes were used, but led to the hydroformylation in medium to excellent yields.

If a different nucleophile from hydrogen gas is used, other carbonyl derivatives other than aldehydes may be formed. For example, the group of Huang succeeded in the hydrozirconation of alkyne. Carbonylation and further reaction of the acylzirconium

<sup>40</sup> Johnson, J. R.; Cuny, G. D.; Buchwald, S. L. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1760–1761.

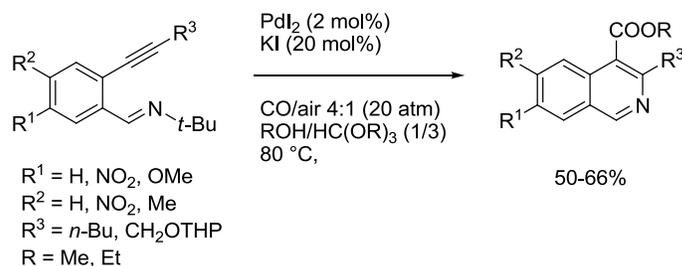
intermediate with copper iodide and alkynyliodonium tosylates led to the corresponding  $\alpha,\beta$ -unsaturated ketone (Scheme 24).<sup>41</sup>



Scheme 24: Carbonylative hydrozirconation

Hydrometallation is not the only way of forming  $\text{Csp}^2\text{-M}$  bond from alkynes. Carbometallation or nucleophilic addition to a metal-activated triple bond, would lead to the formation of the desired intermediate, which would be ready for the carbonylation reaction.

An intramolecular version of a nucleophilic attack on a Pd(II) activated triple bond, followed by a carbonylation reaction has been described by Gabriele, yielding isoquinolines and isochromenes (Scheme 25).<sup>42</sup>

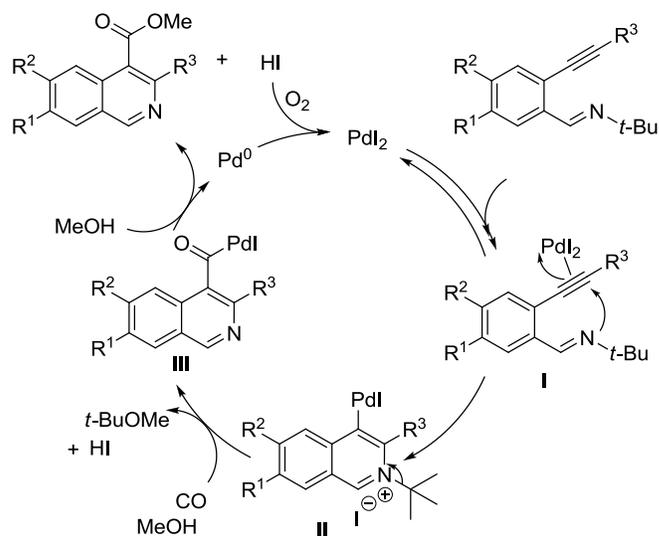


Scheme 25: Gabriele's carbonylation of (2-alkynylbenzylidene)(*tert*-butyl)amines

<sup>41</sup> Sun, A.-M.; Huang, X. *Tetrahedron* **1999**, *55*, 13201–13204.

<sup>42</sup> Gabriele, B.; Veltri, L.; Maltese, V.; Spina, R.; Mancuso, R.; Salerno, G. *Eur. J. Org. Chem.* **2011**, 5626–5635.

6-Endo-dig attack of the nitrogen atom on the palladium(II)-activated alkyne generates the Csp<sup>2</sup>-Pd intermediate II, which undergoes methoxycarbonylation (Scheme 26). The palladium(0) formed during the reaction is reoxidized by the action of oxygen and hydroiodic acid. The imine moiety can be replaced by alcohols,<sup>43</sup> ketones<sup>44</sup> or propargyl acetates.<sup>45</sup>



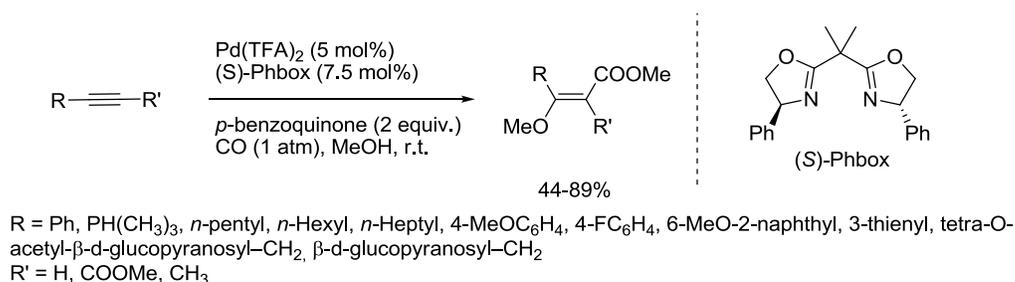
Scheme 26: Mechanism of Gabriele's carbonylation

<sup>43</sup> For examples of cyclisations of 4-alkynols, see: b) Gabriele, B.; Salerno, G.; Pascali, F. D.; Costa, M.; Chiusoli, G. P. *J. Org. Chem.* **1999**, *64*, 7693–7699. c) Gabriele, B.; Salerno, G.; Pascali, F. D.; Costa, M.; Chiusoli, G. P. *J. Organomet. Chem.* **2000**, *593-594*, 409–415. d) Marshall, J. A.; Yanik, M. M. *Tetrahedron Lett.* **2000**, *41*, 4717–4721. e) Nan, Y.; Miao, H.; Yang, Z. *Org. Lett.* **2000**, *2*, 297–299. f) Kato, K.; Matsuba, C.; Kusakabe, T.; Takayama, H.; Yamamura, S.; Mochida, T.; Akita, H.; Peganova, T. A.; Vologdin, N. V.; Gusev, O. V. *Tetrahedron* **2006**, *62*, 9988–9999.

<sup>44</sup> For cyclizations of 4-alkynones, see: a) Kato, K.; Yamamoto, Y.; Akita, H. *Tetrahedron Lett.* **2002**, *43*, 4915–4917. b) Bacchi, A.; Costa, M.; Cà, N. D.; Gabriele, B.; Salerno, G.; Cassoni, S. *J. Org. Chem.* **2005**, *70*, 4971–4979. For asymmetric versions, see: c) Kato, K.; Tanaka, M.; Yamamura, S.; Yamamoto, Y.; Akita, H. *Tetrahedron Lett.* **2003**, *44*, 3089–3092. d) Kusakabe, T.; Kato, K.; Takaishi, S.; Yamamura, S.; Mochida, T.; Akita, H.; Peganova, T. A.; Vologdin, N. V.; Gusev, O. V. *Tetrahedron* **2008**, *64*, 319–327. For cyclization of aldehydes, see: e) Asao, N.; Nogami, T.; Takahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 764–765.

<sup>45</sup> a) Kato, K.; Yamamoto, Y.; Akita, H. *Tetrahedron Lett.* **2002**, *43*, 6587–6590. b) Kato, K.; Nouchi, H.; Ishikura, K.; Takaishi, S.; Motodate, S.; Tanaka, H.; Okudaira, K.; Mochida, T.; Nishigaki, R.; Shigenobu, K.; Akita, H. *Tetrahedron* **2006**, *62*, 2545–2554. For reaction of amides, see: c) Costa, M.; Cà, N. D.; Gabriele, B.; Massera, C.; Salerno, G.; Soliani, M. *J. Org. Chem.* **2004**, *69*, 2469–2477.

Kato and Akita developed an intermolecular version of Gabriele's works. The nucleophilic attack of the activated triple bond led to the vinyl palladium intermediate, which underwent the methoxycarbonylation affording  $\beta$ -methoxyacrylate units in good yields (Scheme 27).<sup>46</sup>



**Scheme 27: Intermolecular methoxycarbonylation of alkynes**

Methanol plays a dual role. It acts as a nucleophile to generate the alkenylpalladium species and traps the final acylpalladium intermediate. With terminal alkynes, the terminal vinylpalladium intermediate is always formed. For internal alkynes with an electron withdrawing group ( $R' = \text{COOMe}$ ) the nucleophilic attack takes place on the more electrophilic carbon of the triple bond. Finally, in the case of an internal alkyne ( $R = n\text{-pent}$ ,  $R' = \text{CH}_3$ ), without any substituent inducing electronic effects, the regioselectivity is not controlled and lead to mixture of isomer ratio = 1.8:1. Various nucleophiles like water<sup>47</sup> or amines<sup>48</sup> have been used, generating the corresponding acids and amides.

Carbonylation reactions of  $\text{Csp}^2$ -metal bond generated by hydro- or carbometallation of alkynes are powerful methods, which take place under smooth

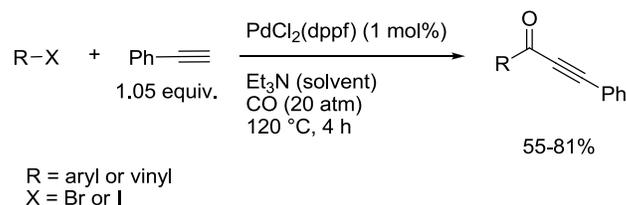
- 
- <sup>46</sup> Kato, K.; Motodate, S.; Mochida, T.; Kobayashi, T.; Akita, H. *Angew. Chem. Int. Ed.* **2009**, *48*, 3326–3328.  
<sup>47</sup> a) Zargarian, D.; Alper, H. *Organometallics* **1991**, *10*, 2914–2921. b) Gabriele, B.; Salerno, G.; Costa, M.; Chiusoli, G.P. *Chem Commun.* **1999**, 1381–1382. c) Sakurai, Y.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **1999**, *40*, 1701–1704. d) Li, J.; Li, G.; Jiang, H.; Chen, M. *Tetrahedron Lett.* **2001**, *42*, 6923–6924. e) Gabriele, B.; Veltri, L.; Salerno, G.; Costa, M.; Chiusoli, G.P. *Eur. J. Org. Chem.* **2003**, 1722–1728.  
<sup>48</sup> a) Gabriele, B.; Costa, M.; Salerno, G.; Chiusoli, G. P. *J. Chem. Soc., Chem. Commun.* **1994**, 1429–1430. b) Bonardi, A.; Costa, M.; Gabriele, B.; Salerno, G.; Chiusoli, G. P. *Tetrahedron Lett.* **1995**, *36*, 7495–7498. c) Gabriele, B.; Salerno, G.; Veltri, L.; Costa, M.; Massera, C. *Eur. J. Org. Chem.* **2001**, 4607–4613.

conditions. Hydroformylation of alkynes is still in its infancy and only few examples have been described. However, the discovery of the most suitable complexes (bimetallic or zwitterionic) and specific ligands has been critical for the success of the reaction. Various acyclic and cyclic derivatives can be prepared *via* this strategy, under very mild reaction conditions.

## ii. By oxidative addition of a carbon-halogen bond

### 1) Cross-coupling reaction

The direct oxidative addition of vinyl or aryl halides directly affords the desired  $Csp^2$ -M bond. This method is the most widely used, although it requires pre-activated substrates. The efficiency of this method is clearly illustrated by the carbonylative version of the classical palladium-catalyzed cross-coupling reactions. For example, the carbonylative Sonogashira reaction has been described as early as 1981 by Tanaka (Scheme 28).<sup>49</sup>

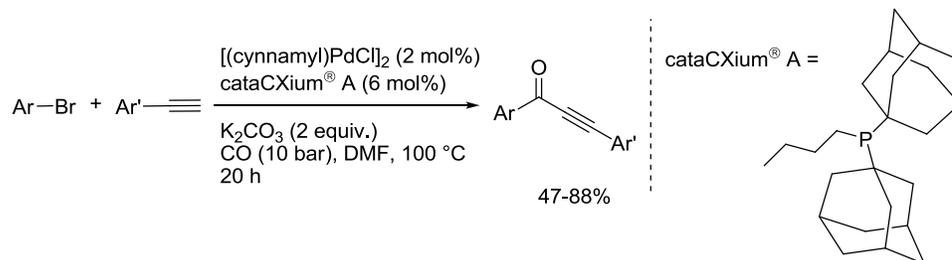


Scheme 28: Carbonylative Sonogashira of aryl and vinyl halogen compound

The reaction occurred in an amine solvent and under harsh conditions (120 °C and 20 atm of carbon monoxide). However, the scope of the reaction is broad and even alkenyl bromides are suitable substrates for the reaction. The electronic effects of the substituents on the aromatic group have little effect on the yield of the reaction. Indeed, both electron-donating and withdrawing groups led to the desired products in equally good yields.

<sup>49</sup> Kobayashi, T.; Tanaka, M. *J. Chem. Soc., Chem. Commun.* **1981**, 333–334.

Many optimization of this reaction has been carried out since Tanaka's work. Beller recently reported the use of an adamantyl-based mono phosphine in carbonylative Sonogashira cross-coupling (Scheme 29).<sup>50</sup>

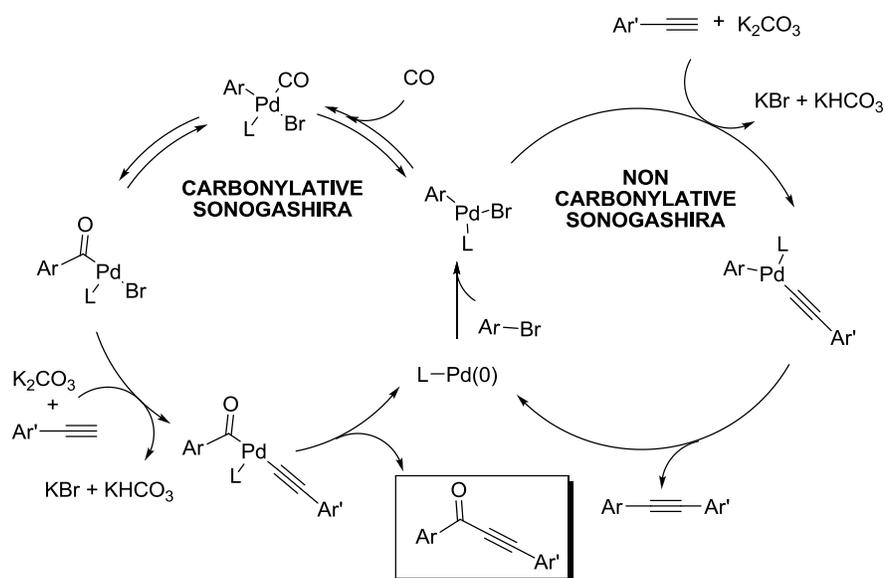


**Scheme 29: Beller's carbonylative Sonogashira reaction**

The use of a bulky ligand (cataCXium<sup>®</sup> A) increased the ease of the insertion of carbon monoxide. This may be accounted for by the number of ligands coordinated to the metal during the process. Indeed, due to the steric hindrance generated, only one ligand can coordinate the metal, leaving a vacant site for solvent or carbon monoxide. However, a high pressure of carbon monoxide (10 bar) is nevertheless required in order to avoid the non-carbonylative coupling (Scheme 30).

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<sup>50</sup> Wu, X.; Neumann, H.; Beller, M. A. *Chem. Eur. J.* **2010**, *16*, 12104–12107.



**Scheme 30: Mechanism of carbonylative Sonogashira using bulky ligands**

The scope of the reaction has been extended to aryl and alkenyl triflates.<sup>51</sup> They have even been able to realize a carbonylative Sonogashira coupling with diazo compounds.<sup>52</sup> In this reaction, an amine was *in situ* transformed into a diazo substrate, which underwent oxidative addition.

Other cross-coupling reactions have also been studied under carbonylative conditions such as Suzuki-Miyaura,<sup>53</sup> Stille coupling,<sup>54</sup> Negishi,<sup>53d-e,55</sup> Heck reaction,<sup>54b,56</sup> ...

<sup>51</sup> a) Wu, X.; Sundararaju, B.; Neumann, H.; Dixneuf, P. H.; Beller, M. *Chem. Eur. J.* **2011**, *17*, 106–110. b) Wu, X.; Sundararaju, B.; Anbarasan, P.; Neumann, H.; Dixneuf, P. H.; Beller, M. *Chem. Eur. J.* **2011**, *17*, 8014–8017.

<sup>52</sup> Wu, X.; Neumann, H.; Beller, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 11142–11146.

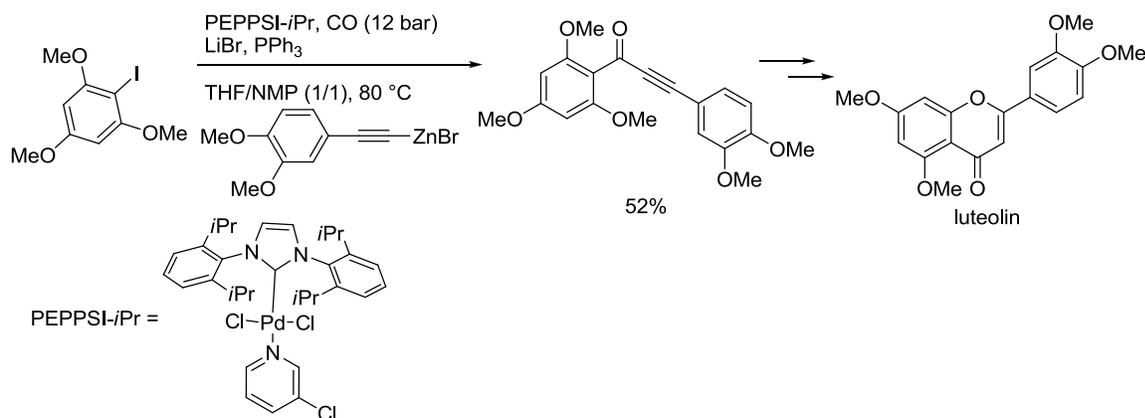
<sup>53</sup> a) Ishiyama, T.; Kizaki, H.; Miyaura, N.; Suzuki, A. *Tetrahedron Lett.* **1993**, *34*, 7595–7598. b) Ishiyama, T.; Kizaki, H.; Hayashi, T.; Suzuki, A.; Miyaura, N. *J. Org. Chem.* **1998**, *63*, 4726–4731. c) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633–9695. d) O’Keefe, B. M.; Simmons, N.; Martin, S. F. *Org. Lett.* **2008**, *10*, 5301–5304. e) O’Keefe, B. M.; Simmons, N.; Martin, S. F. *Tetrahedron* **2011**, *67*, 4344–4351.

<sup>54</sup> a) Tour, J. M.; Negishi, E. *J. Am. Chem. Soc.* **1985**, *107*, 8289–8291. b) Dubbaka, S. R.; Vogel, P. *J. Am. Chem. Soc.* **2003**, *125*, 15292–15293. c) Doi, T.; Inoue, H.; Tokita, M.; Watanabe, J.; Takahashi, T. *J. Comb. Chem.* **2008**, *10*, 135–141. For application in total synthesis see: d) Couladouros, E. A.; Mihou, A. P.; Bouzas, E. A. *Org. Lett.* **2004**, *6*, 977–980.

<sup>55</sup> a) Wu, X.; Schranck, J.; Neumann, H.; Beller, M. *Chem. Asian J.* **2012**, *7*, 40–44. For Nickel catalyzed carbonylative Negishi coupling see: Wang, Q.; Chen, C. *Tetrahedron Lett.* **2008**, *49*, 2916–2921.

Like in the carbonylative Sonogashira reaction, the non-carbonylative coupling is a major competing reaction. The more reactive the organometallic species, the more this side reaction occurs. In order to reverse the reactivity, a higher carbon monoxide pressure is necessary.

Carbonylative cross-coupling reactions lead to the formation of aryl, alkenyl or alkynyl ketones depending on the reagents used. Thus, these reactions have been fairly used for the total synthesis of many compounds. For examples, Negishi cross-coupling has been the key step for the synthesis of Luteolin (Scheme 31).<sup>53e</sup>



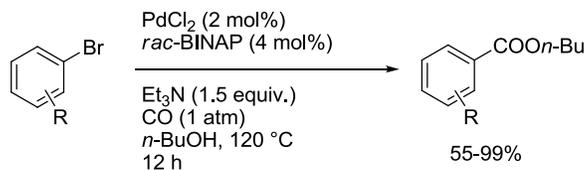
**Scheme 31: Carbonylative Sonogashira reaction in the total synthesis of luteolin**

The aryl iodide was successfully carbonylated even if the three methoxy groups crowded and deactivated the aryl iodide.

<sup>56</sup> a) Negishi, E.; Ma, S.; Amanfu, J.; Copéret, C.; Miller, J. A.; Tour, J. M. *J. Am. Chem. Soc.* **1996**, *118*, 5919–5931. b) Wu, X.-F.; Neumann, H.; Spannenberg, A.; Schulz, T.; Jiao, H.; Beller, M. *J. Am. Chem. Soc.* **2010**, *132*, 14596–14602. c) Wu, X.; Neumann, H.; Beller, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 5284–5288. d) Wu, X.; Jiao, H.; Neumann, H.; Beller, M. *ChemCatChem*, **2011**, *3*, 726–733. e) Schranck, J.; Wu, X.; Neumann, H.; Beller, M. *Chem. Eur. J.* **2012**, *18*, 4827–4831. f) Okuro, K.; Alper, H. *J. Org. Chem.* **2012**, DOI: 10.1021/jo300173g For example of carbonylation with *in-situ* generation of carbon monoxide see: g) Hermange, P.; Gøgsig, T. M.; Lindhardt, A. T.; Taaning, R. H.; Skrydstrup, T. *Org. Lett.* **2011**, *13*, 2444–2447.

## 2) Alkoxy carbonylation

Aryl or alkenyl esters are readily accessible by alkoxy carbonylation of aryl or vinyl halides (Scheme 32).<sup>57</sup>



R = *p*-H, *p*-Ac, *p*-CN, *p*-COOMe, *p*-Cl, *p*-Me, *p*-OMe, *m*-OMe

**Scheme 32: Alkoxy carbonylation of aryl bromide**

The reaction occurred under smooth conditions and the yields were good. The reaction also proceeded smoothly with heteroaromatic substrates (pyridines, thiophene...) and delivered high yields of the desired products. Aryl iodides,<sup>26,31,58</sup> bromides,<sup>59</sup> chlorides<sup>28,60</sup> and sulfonates,<sup>61</sup> can be converted into esters.

Methoxycarbonylation reactions are reliable reactions that have been used at late stage in total syntheses. Roulland used the methoxycarbonylation of an alkenyl iodide in the total synthesis of (-)-exiguolide (Scheme 33).<sup>62</sup> Exiguolide inhibits the fertilization of sea urchin gametes, which indicates that this compound could inhibit the fusion of viruses with cell membranes.<sup>63</sup>

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<sup>57</sup> Yang, W.; Han, W.; Zhang, W.; Shan, L.; Sun, J. *Synlett* **2011**, 2253–2255.

<sup>58</sup> a) Ramesh, C.; Nakamura, R.; Kubota, Y.; Miwa, M.; Sugi, Y. *Synthesis* **2003**, 501–504. b) Beletskaya, I.; Ganina, O. *Reac. Kinet. Mech. Catal.* **2010**, *99*, 1–4. c) Salvadori, J.; Balducci, E.; Zaza, S.; Petricci, E.; Taddei, M. *J. Org. Chem.* **2010**, *75*, 1841–1847.

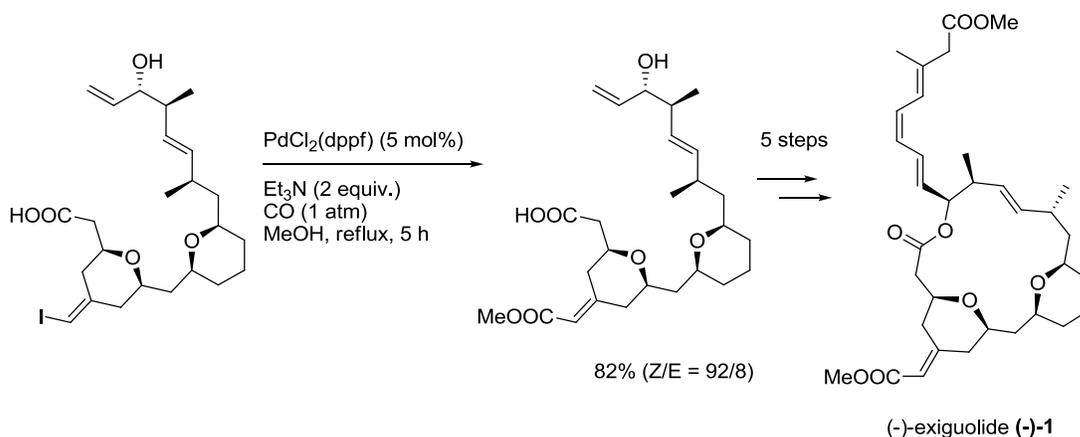
<sup>59</sup> a) Martinelli, J. R.; Watson, D. A.; Freckmann, D. M. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 7102–7107. b) Xin, Z.; Gøgsig, T. M.; Lindhardt, A. T.; Skrydstrup, T. *Org. Lett.* **2011**, *14*, 284–287. c) Yang, W.; Han, W.; Zhang, W.; Shan, L.; Sun, J. *Synlett* **2011**, 2253–2255.

<sup>60</sup> a) Ben-David, Y.; Portnoy, M.; Milstein, D. *J. Am. Chem. Soc.* **1989**, *111*, 8742–8744. b) Portnoy, M.; Milstein, D. *Organometallics* **1993**, *12*, 1655–1664. c) Mägerlein, W.; Indolese, A. F.; Beller, M. A. *Angew. Chem. Int. Ed.* **2001**, *40*, 2856–2859.

<sup>61</sup> a) Kubota, Y.; Nakada, S.; Sugi, Y. *Synlett* **1998**, 183–185. b) Wu, X.; Neumann, H.; Beller, M. *Chem. Eur. J.* **2012**, *18*, 3831–3834.

<sup>62</sup> Cook, C.; Guinchard, X.; Liron, F.; Roulland, E. *Org. Lett.* **2010**, *12*, 744–747.

<sup>63</sup> Ikegami, S.; Kobayashi, H.; Myotoishi, Y.; Ohto, S.; Kato, K. H. *J. Biol. Chem.* **1994**, *269*, 23262–23267.



**Scheme 33: Alkoxy carbonylation of vinyl chloride for the total synthesis of exiguolide**

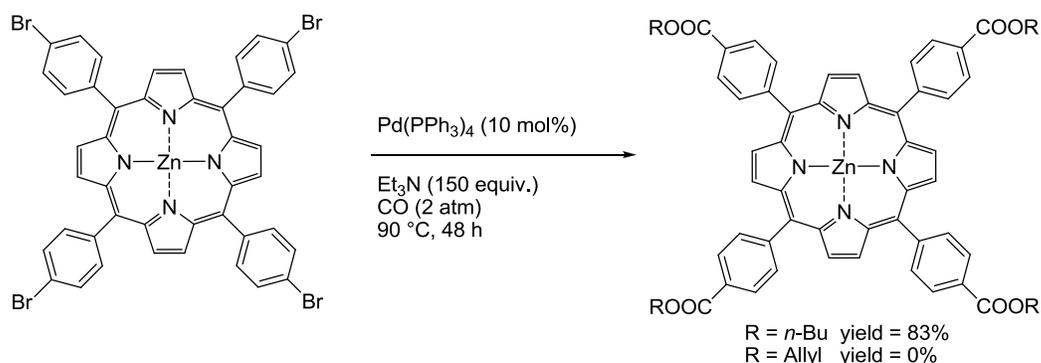
The carbonylation reaction occurred at a late stage of the synthesis, just one step before the Yamaguchi macro-lactonisation. The carbonylation proceeded under mild conditions with a highly functionalized substrate. It proved to be completely chemo- and regioselective, with only minor erosion of the geometry of the alkene. Other groups have used alkoxy carbonylation for their total synthesis, often at a late stage of the synthesis.<sup>64</sup>

Most alkoxy carbonylation reactions have been carried out with simple aliphatic alcohols, and very few examples can be found with more challenging alcohols. Even just the rather simple allyl alcohol led to far less efficient reactions.

For example, Vinogradov has described an alkoxy carbonylation reaction of bromo substituted porphyrins (Scheme 34).<sup>65</sup>

<sup>64</sup> a) Ward, D. E.; Gai, Y.; Qiao, Q.; Shen, J. *Canadian J. Chem.* **2004**, *82*, 254–267. b) Phoenix, S.; Reddy, M. S.; Deslongchamps, P. *J. Am. Chem. Soc.* **2008**, *130*, 13989–13995. c) Trost, B. M.; Dong, G. *J. Am. Chem. Soc.* **2010**, *132*, 16403–16416. d) Trost, B. M.; Yang, H.; Dong, G. *Chem. Eur. J.* **2011**, *17*, 9789–9805.

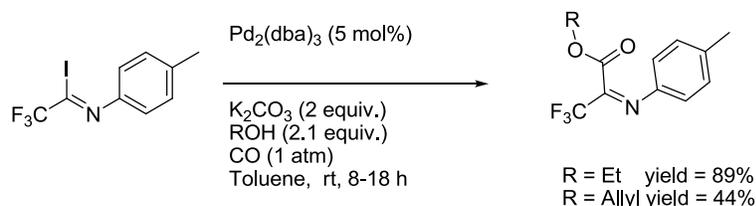
<sup>65</sup> Vinogradov, S. A.; Wilson, D. F. *Tetrahedron Lett.* **1998**, *39*, 8935–8938.



**Scheme 34: Attempt of allyloxycarbonylation**

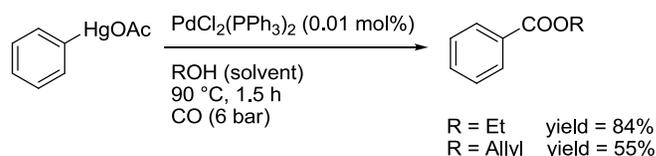
Although the reaction carried out in *n*-BuOH proceeded efficiently, the reaction with allyl alcohol did not proceed at all.

The allyloxycarbonylation of trifluoroacetimidoyl substrates was more efficient, but remained however far less productive than ethoxycarbonylation (Scheme 35).<sup>66</sup>



**Scheme 35: Allyloxycarbonylation of trifluoroacetimidoyl iodides**

Finally, the last example of allyloxycarbonylation of  $\text{Csp}^2$  carbon atoms found in the literature describes the alkoxy- or allyloxycarbonylation of phenylmercuric acetate (Scheme 36).<sup>67</sup> The conditions are harsher than those previously described, but the allyloxycarbonylation reaction proceeded in synthetically useful yield.



**Scheme 36: Allyloxycarbonylation of organomercury compounds**

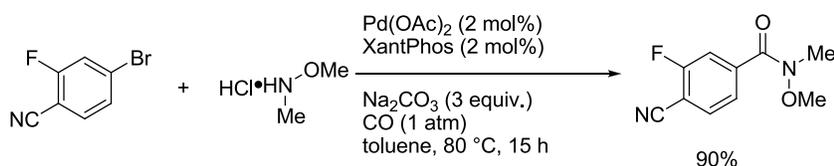
<sup>66</sup> Watanabe, H.; Hashizume, Y.; Uneyama, K. *Tetrahedron Lett.* **1992**, *33*, 4333–4336.

<sup>67</sup> Baird, W. C.; Hartgerink, R. L.; Surridge, J. H. *J. Org. Chem.* **1985**, *50*, 4601–4605.

### 3) Aminocarbonylation

The product of aminocarbonylation could be obtained directly without the formation of any ester intermediate, if the amine is used alone.

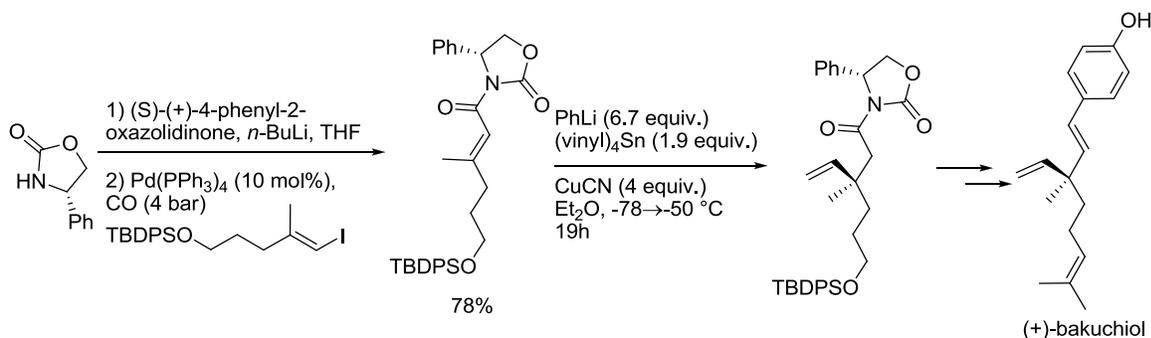
Buchwald optimized an aminocarbonylation reaction using *N,O*-bisdimethylhydroxylamine as a nucleophile (Scheme 37).<sup>59a</sup>



**Scheme 37: Aminocarbonylation of aryl bromide**

The chosen amine led to the formation of the corresponding Weinreb amide in good yield.

Fukuyama achieved an aminocarbonylation reaction between a chiral deprotonated oxazolidinone as nucleophile and an alkenyl iodide, leading to the desired unsaturated amide (Scheme 38).<sup>68</sup>

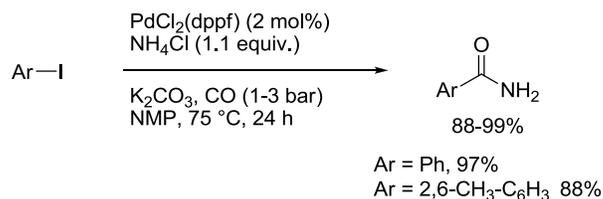


**Scheme 38: Carbonylation of vinyl iodide with chiral oxazolidinone**

The carbonylation proceeded here at an early stage of the synthesis of (+)-bakuchiol, but allowed the efficient introduction of a chiral auxiliary for the control of the stereogenic center during the following step of the synthesis (Scheme 38).

<sup>68</sup> Esumi, T.; Shimizu, H.; Kashiya, A.; Sasaki, C.; Toyota, M.; Fukuyama, Y. *Tetrahedron Lett.* **2008**, *49*, 6846–6849.

The preparation of primary amides by aminocarbonylation is highly challenging. Indeed, gaseous ammonia could be used, but it requires to handle two very toxic and harmful gases. Moreover, ammonia itself is often not nucleophilic enough to react in such reactions. As an alternative, ammonium chloride can be used (Scheme 39).<sup>24</sup>



**Scheme 39: Aminocarbonylation of aryl iodide with ammonia**

The scope of the reaction is broad. Electron-rich and electron-poor substituents on the aromatic ring afford the corresponding primary amide in good yield. Steric hindrance has little effect as 2,6-dimethyliodobenzene affords the corresponding amide in 88% yield. Aryl bromides, chlorides and tosylates are also successful in this reaction.<sup>24</sup>

Formamide,<sup>69</sup> hexamethyldisilazane,<sup>70</sup> and hydroxylamine<sup>71</sup> in conjunction with titanium complexes<sup>72</sup> were also successful.

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<sup>69</sup> Schnyder, A.; Beller, M.; Mehlretter, G.; Nsenda, T.; Studer, M.; Indolese, A. F. *J. Org. Chem.* **2001**, *66*, 4311–4315.

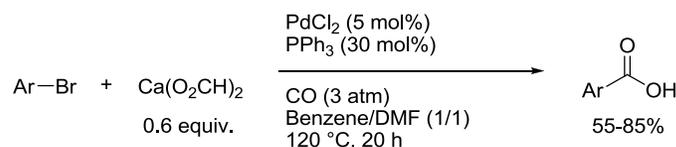
<sup>70</sup> Morera, E.; Ortar, G. *Tetrahedron Lett.* **1998**, *39*, 2835–2838.

<sup>71</sup> Wu, X.; Wannberg, J.; Larhed, M. *Tetrahedron* **2006**, *62*, 4665–4670.

<sup>72</sup> Ueda, K.; Sato, Y.; Mori, M. *J. Am. Chem. Soc.* **2000**, *122*, 10722–10723.

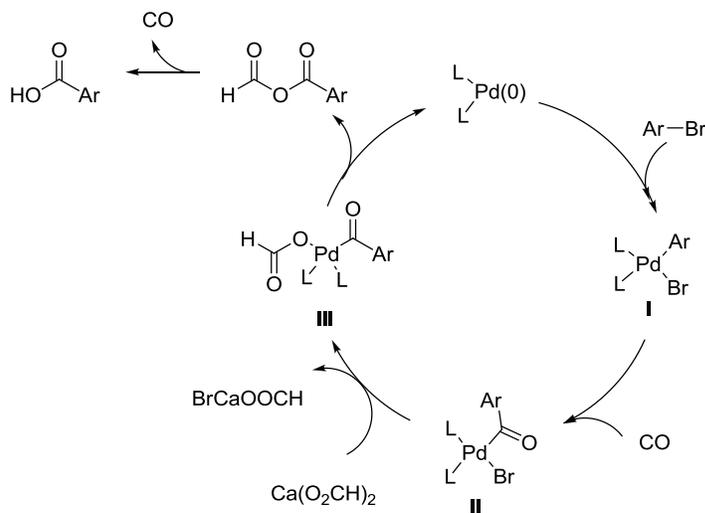
#### 4) Carboxylic acids formation

Carboxylic acids are also accessible by using calcium formate, in a DMF / benzene solvent mixture (Scheme 40).<sup>73</sup>



**Scheme 40: Carboxylic acid formation via carbonylation with calcium formate**

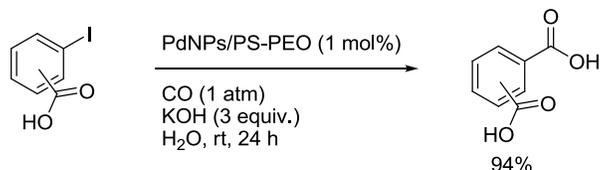
The mechanism of the reaction begins with the oxidative addition of an arylbromide to palladium(0) complex which affords the arylpalladium intermediate **I**. Complexation and migratory insertion of carbon monoxide deliver the acylpalladium intermediate **II**. Then, the transmetalation of calcium formate with acyl palladium species furnishes acylpalladium formate **III**. Reductive elimination delivers the mixed formic anhydride. Due to its thermal instability, decarbonylation occurs and gives the benzoic acid derivative.



**Scheme 41: Mechanism of carbonylation with calcium formate**

<sup>73</sup> Pri-Bar, I.; Buchman, O. *J. Org. Chem.* **1988**, *53*, 624–626.

Beletskaya used water instead of calcium formate as the nucleophile. This strategy allows the direct preparation of acids, avoiding the need for a decarboxylation step (Scheme 42).<sup>58c</sup>



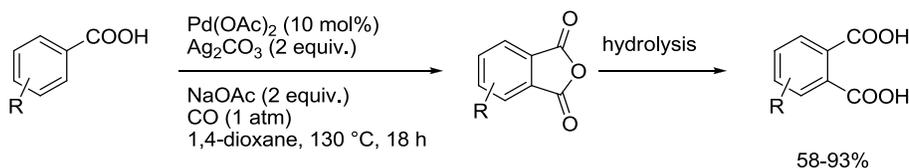
**Scheme 42: Carbonylation in water media**

The ligandless palladium nanoparticles (NPs) used was supported on polymer (polystyrene-polyethylene oxide block co-polymer) and can be reused eleven times without loss of yield.

### iii. By C-H activation

Direct generation of palladated species by means of catalytic C-H activation pathways is very attractive, because it avoids the need for a pre-oxidized substrate. However, such methods have emerged as efficient ones only recently. Examples dealing with subsequent carbonylation reactions are scarce.

The first example of palladium-catalyzed C-H activation/carbonylation sequence has been published in 2008 by Yu.<sup>74</sup> An acid moiety was necessary as a directing group (Scheme 43).



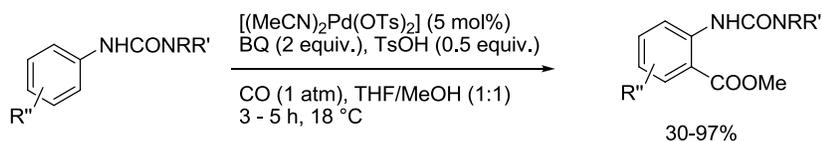
**Scheme 43: Palladium catalyzed carbonylative C-H activation**

The reaction tolerated electron-donating and moderately electron-withdrawing groups on the aromatic ring. Strong electron-withdrawing groups resulted in a decreased

<sup>74</sup> Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14082–14083.

yield.  $\alpha,\alpha$ -Disubstituted phenylacetic acid derivatives are also good substrates for the *o*-carboxylation, but the dicarboxylic acid products cyclize to form the corresponding anhydride derivatives.

Carbonylation of aniline derivatives was achieved by Lloyd-Jones and Booker-Milburn (Scheme 44).<sup>75</sup>



**Scheme 44: C-H activation of Milburn**

The reaction proceeds under very smooth conditions (atmospheric pressure of carbon monoxide and room temperature) compared to those previously described. The reaction suffered the same limitations with electron-withdrawing groups, but with less drastic effects (*p*-CF<sub>3</sub> and *p*-COOMe yield respectively 30 and 46%, for *p*-NO<sub>2</sub> the reaction did not proceed).

#### d) Carbonylation of sp<sup>3</sup> hybridized carbon atoms

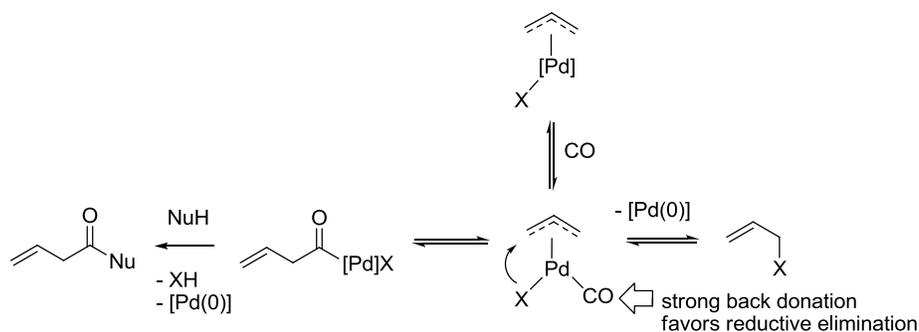
As briefly described, palladium-catalyzed carbonylation reactions of Csp<sup>2</sup> centers has been extensively studied. To the contrary, such carbonylation reactions involving Csp<sup>3</sup> centers are rather scarce. Two main factors may explain this matter of fact: the possibility of  $\beta$ -hydride elimination and the difficulty of oxidative addition of Csp<sup>3</sup>-X bonds to palladium.

##### i. Carbonylation of $\pi$ -allyl systems

Carbon monoxide coordination to the Pd atom of an  $\eta^3$ -allyl complex can in principle either trigger reductive elimination to generate the organic allyl-X and Pd(0) (Scheme 45, right) or insert into the allyl moiety to promote a successive nucleocarbonylation, if an appropriate nucleophile is present (Scheme 45, left).

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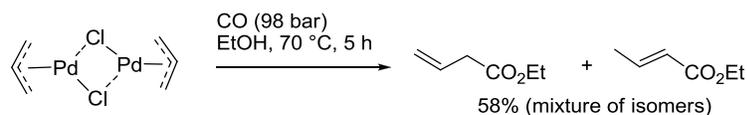
<sup>75</sup> Houlden, C. E.; Hutchby, M.; Bailey, C. D.; Ford, J. G.; Tyler, S. N. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Angew. Chem. Int. Ed.* **2009**, *48*, 1830–1833.



**Scheme 45: General mechanism of  $\pi$ -allyl carbonylation**

Although the equilibrium of this process is highly dependent on factors such as CO pressure, or the nature of the counterion X, the back-donating ( $\pi$  acidic) character of this ligand strongly favors the equilibrium to lie toward the right side as for example in the case of X = OAc (Scheme 45).<sup>76</sup>

The seminal example of carbonylation of a  $\pi$ -allyl palladium complex was described by Tsuji and involved a stoichiometric ethoxycarbonylation (Scheme 46).<sup>77</sup>



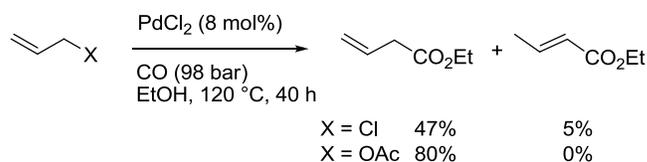
**Scheme 46: Carbonylation of allyl palladium complex**

A catalytic version of this transformation was reported one year later, using PdCl<sub>2</sub> and allylic chlorides or acetates (Scheme 47).<sup>78</sup>

<sup>76</sup> a) Takahashi, Y.; Tsujiyama, K.; Sakai, S.; Ishii, Y. *Tetrahedron Lett.* **1970**, 1913-1916. b) Bäckvall, J.-E.; Nordberg, R. E.; Björkman, E. E.; Moberg, C. *J. Chem. Soc., Chem. Commun.* **1980**, 943-944. c) Yamamoto, T.; Akimoto, M.; Saito, O.; Yamamoto, A. *Organometallics* **1986**, *5*, 1559-1567. d) Yamamoto, T.; Saito, O.; Yamamoto, A. *J. Am. Chem. Soc.* **1981**, *103*, 5600-5602.

<sup>77</sup> a) Tsuji, J.; Kiji, J.; Morikawa, M. *Tetrahedron Lett.* **1963**, *4*, 1811-1813. b) See also: Soderberg, C.; Åkermark B.; Hall, S. S. *J. Org. Chem.*, **1988**, *53*, 2925-2937.

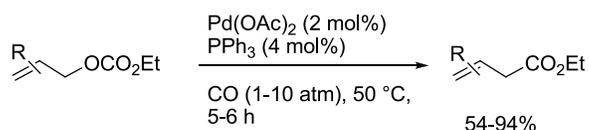
<sup>78</sup> a) Tsuji, J.; Kiji, J.; Imamura, S.; Morikawa, M. *J. Am. Chem. Soc.* **1964**, *86*, 4350-4353. See also: b) Milstein, D. *Organometallics* **1982**, *1*, 888-890. c) Milstein, D. *Acc. Chem. Res.* **1988**, *21*, 428-434.



**Scheme 47: Carbonylation of allyl halide**

The mechanism is expected to involve the initial reduction of PdCl<sub>2</sub> into Pd(0) by CO, followed by oxidative addition of the allyl system to Pd(0), to form a π-allylpalladium complex, which undergoes CO insertion and nucleophilic trapping. Harsh conditions (98 bar and 120 °C) are required to counterbalance the unfavorable equilibrium of the reductive elimination, due to back donation from Pd to CO, as pointed out above (Scheme 45, right).<sup>76</sup>

Allyl carbonates<sup>79</sup> or phosphates<sup>80</sup> were suitable substrates in this reaction. When the η<sup>3</sup>-allylpalladium intermediate generated is not symmetric, the linear product is usually the only isomer observed (Scheme 48). Interestingly, even allyl acetates could be used under these mild conditions.



**Scheme 48: Carbonylation of allylcarbonate**

Alkenyloxiranes<sup>81</sup> are also suitable precursors of π-allyl intermediates but reaction conditions are harsher.

## ii. With β-hydrogen atoms

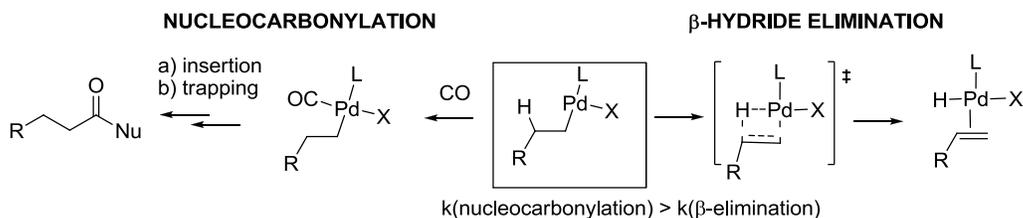
β-Hydride elimination can take place easily on a σ-alkylpalladium intermediate when the β-H atom is linked to a Csp<sup>3</sup> atom, and if a HCCPd synoplanar conformation can be easily adopted, as imposed by the mechanism of this reaction. Indeed, a free vacant site on the metal has to be present.

<sup>79</sup> Tsuji, J.; Sato, K.; Okumoto, H. *J. Org. Chem.* **1984**, *49*, 1341–1344.

<sup>80</sup> Murahashi, S.-I.; Imada, Y.; Taniguchi, Y.; Higashiura, S. *J. Org. Chem.* **1993**, *58*, 1538-1545.

<sup>81</sup> Shimizu, I.; Maruyama, T.; Makuta, T.; *Tetrahedron Lett.* **1993**, *34*, 2135–2138.

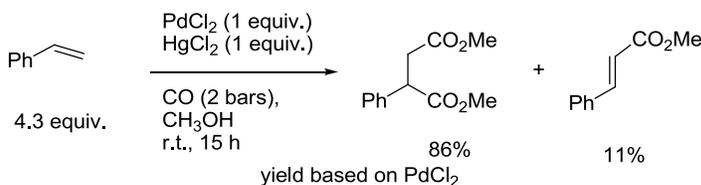
Therefore, a requirement for a successful carbonylation is that the global sequence (CO coordination / CO insertion / nucleophilic trapping) is faster than  $\beta$ -hydride elimination (Scheme 49).



**Scheme 49:  $\beta$ -Hydride elimination versus nucleocarbonylation**

### 1) Via carbopalladation

Heck pioneered the carbonylation reaction involving a  $Csp^3$ -Pd bond, generating the intermediate by methoxycarbonylpalladation of alkenes. An example is shown in Scheme 50.<sup>82</sup> It has to be noted that this reaction required a stoichiometric amount of  $PdCl_2$ .

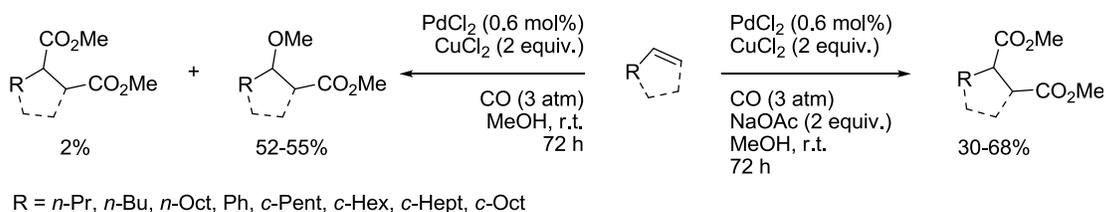


**Scheme 50: Double carbonylation of alkene**

The above described olefin carbonylation was later investigated by James and Stille, under oxidative conditions ( $CuCl_2$ ). Such conditions allowed to use a catalytic amount of palladium (Scheme 51).<sup>83</sup>

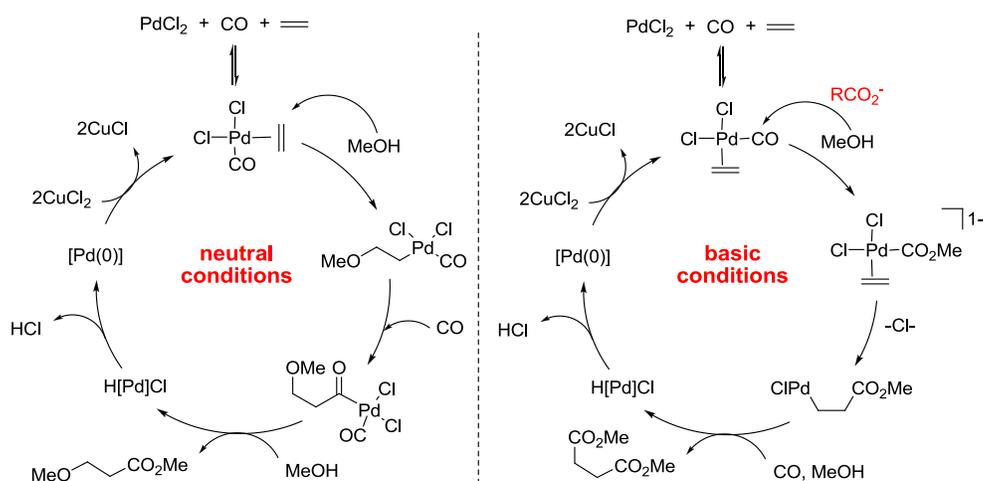
<sup>82</sup> Heck, R. F. *J. Am. Chem. Soc.* **1972**, *94*, 2712–2716.

<sup>83</sup> James, D. E.; Stille, J. K. *J. Am. Chem. Soc.* **1976**, *98*, 1810–1823.



**Scheme 51: The effect of the base: double carbonylation versus monocarbonylation**

In particular, they discovered that in the absence of a base the  $\beta$ -methoxy ester is selectively obtained, whereas in the presence of a carboxylate base the reaction cleanly underwent double carbonylation. The respective postulated mechanisms are depicted in Scheme 52.



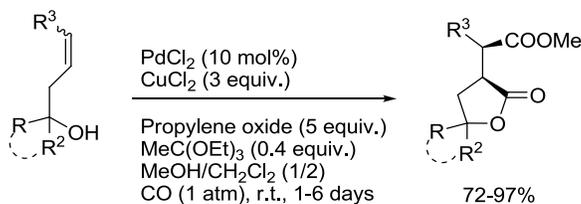
**Scheme 52: Mechanism of double carbonylation compared to monocarbonylation**

Semmelhack developed an intramolecular version in order to achieve the synthesis of tetrahydro-furane and pyrane derivatives.<sup>84</sup> Carbamates and ureas are also

<sup>84</sup> a) Semmelhack, M. F.; Bodurow, C. *J. Am. Chem. Soc.* **1984**, *106*, 1496–1498. b) Semmelhack, M. F.; Bodurow, C.; Baum, M. *Tetrahedron Lett.* **1984**, *25*, 3171–3174.

suitable nitrogen based-nucleophiles in this reaction.<sup>85</sup> Pyrrolidines and cyclic carbamates were obtained in good yield.

Tamaru proposed a Pd(II)-catalyzed oxidative double carbonylation of various 3-buten-1-ol derivatives, based on an intramolecular alkoxy carbonylation followed by a carbonylative trapping of the resulting alkylpalladium complex (Scheme 53).<sup>86</sup>



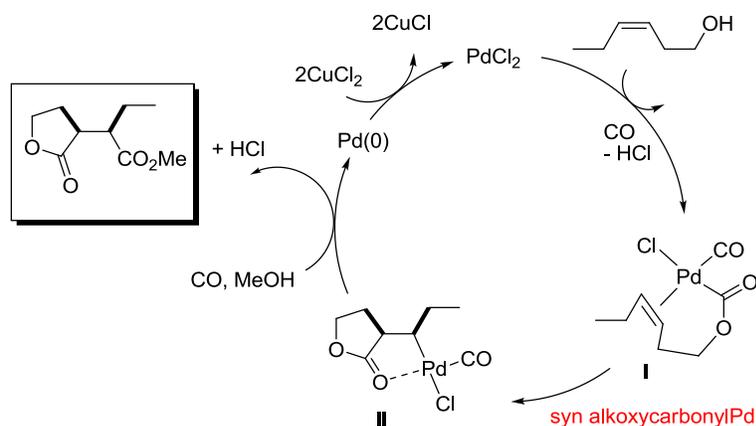
**Scheme 53: Intramolecular double carbonylation**

The mechanism is expected to involve formation of the alkoxy carbonylpalladium chloride complex **I**. Intramolecular *syn* alkoxy palladation provides a new  $\text{Csp}^3$  alkylpalladium complex **III**, which, after a second CO insertion and MeOH trapping delivers the desired  $\gamma$ -lactone (Scheme 54). Propylene oxide traps HCl (by formation of chlorhydrine) so as to allow carbonylative termination (second carbonyl insertion), whereas trimethylorthoformate is used as water scavenger to avoid premature Pd reduction by adventitious water and CO (Scheme 20).<sup>37</sup> Indeed, the rate of the Pd(II)-catalyzed carbon monoxide oxidation in the presence of water is much faster than that of the olefin carbonylation reaction.<sup>87</sup>

<sup>85</sup> a) Tamaru, Y.; Kobayashi, T.; Kawamura, S.; Ochiai, H.; Hojo, M.; Yoshida, Z. *Tetrahedron Lett.* **1985**, *26*, 3207-3210. b) Harayama, H.; Abe, A.; Sakado, T.; Kimura, M.; Fugami, K.; Tanaka, S.; Tamaru, Y. *J. Org. Chem.* **1997**, *62*, 2113-2122.

<sup>86</sup> Tamaru, Y.; Hojo, M.; Yoshida, Z. *J. Org. Chem.* **1991**, *56*, 1099-1105.

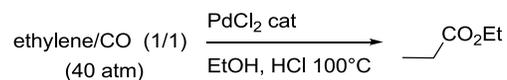
<sup>87</sup> a) Fenton, D. M.; Steinwand, P. J. *J. Org. Chem.* **1972**, *37*, 2034-2035. b) Fenton, D. M.; Steinwand, P. J. *J. Org. Chem.* **1974**, *39*, 701-704.



Scheme 54: Mechanism of intramolecular double carbonylation

## 2) Via hydropalladation

Tsuji studied the carbonylative hydropalladation of alkenes (Scheme 55).<sup>88,89</sup> In his pioneering work he found that treatment of a mixture of ethylene and CO with catalytic amount of PdCl<sub>2</sub> in the presence of HCl in ethanol afforded ethyl propionate.



Scheme 55: Palladium catalyzed carbonylation of ethylene

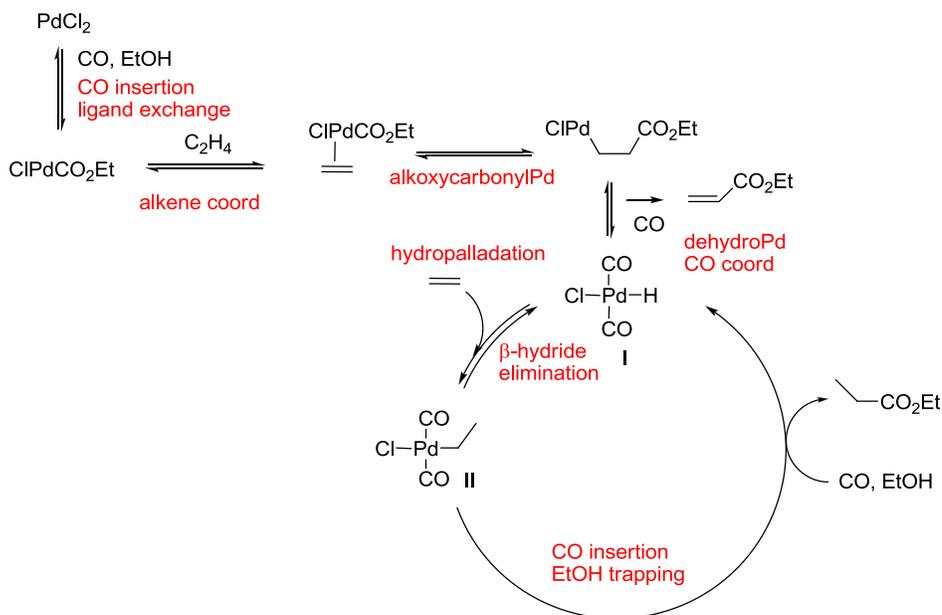
Pd(0) is first formed by reduction of PdCl<sub>2</sub> in the presence of CO and subsequent oxidative addition of HCl is expected to generate the real hydride catalyst I.<sup>90</sup> Subsequent ethylene hydropalladation affords the  $\sigma$ -alkylpalladium intermediate II. Finally, CO insertion

<sup>88</sup> a) Tsuji, J.; Morikawa, M.; Kiji, J. *ins. Tetrahedron Lett.* **1963**, *4*, 1437–1440. b) Tsuji, J. *Acc. Chem. Res.* **1969**, *2*, 144–152. See also: b) Alderson T. Engelhardt, V. A.; U. S. Pat. 3,065,242 (1962); C. A. *2*, 8912 (1963).

<sup>89</sup> The first example of Csp<sup>3</sup>-Pd intermediate carbonylation was reported by Tsuji, and was obtained by alkene chloropalladation under stoichiometric conditions: Tsuji, J.; Morikawa, M.; Kiji, J. *Tetrahedron Lett.* **1963**, *4*, 1061-1064.

<sup>90</sup> Blanco, C.; Godard, C.; Zangrando, E.; Ruiz, A.; Claver C. *Dalton Trans*, **2012**, ASAP. DOI: 10.1039/c2dt30267e

and EtOH trapping generates ethyl propionate (Scheme 56). Notice that in this case the Pd(II) oxidation state level is maintained throughout the cycle. Yields depend on the bulkiness of the alcohol used.<sup>91</sup>

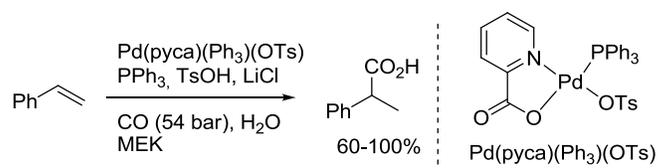


Scheme 56: Mechanism of the carbonylation of ethylene

Recently, Chaudhari reported a related hydroxycarbonylation-terminated hydropalladation of alkenes to afford the corresponding carboxylic acids (Scheme 57).<sup>92</sup>

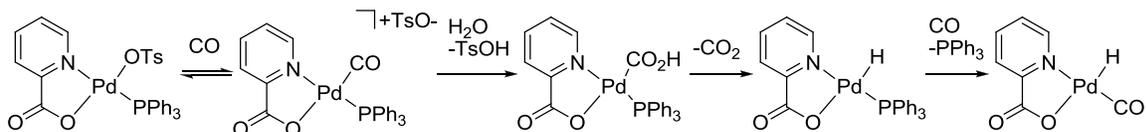
<sup>91</sup> a) Alper, H.; Hartstock, F. W.; Despeyroux, B. *J. Chem. Soc., Chem. Commun.* **1984**, 905. b) Lee, C. W.; Alper, H. *J. Org. Chem.* **1995**, *60*, 250–252. c) Lee, B.; Alper, H. *J. Mol. Catal. A: Chem.* **1996**, *111*, L3–L6. With chiral ligands see: d) Alper, H.; Hamel, N. *J. Am. Chem. Soc.* **1990**, *112*, 2803–2804. With formate as hydride source instead of hydrochloric acid see: e) Ajjou, A. N.; Alper, H. *Macromolecules* **1996**, *29*, 1784–1788.

<sup>92</sup> a) Jayasree, S.; Seayad, A.; Chaudhari, R. V. *Org. Lett.* **1999**, *2*, 203–206. b) Sarkar, B. R.; Chaudhari, R. V. *Catal. Surv. Asia* **2005**, *9*, 193–205.



**Scheme 57: Palladium catalyzed carbonylation of styren in water media**

The scope of the reaction was extended to various styrene derivatives and aliphatic alkenes. In particular, it was found that, in the case of styrenes, addition of lithium chloride greatly improves the regioselectivity. Generation of the competent hydride catalyst from the Pd(pyca)(PPh<sub>3</sub>)(OTs) precatalyst is expected to take place according to the following steps (Scheme 58).<sup>93</sup>



**Scheme 58: Generation of active palladium hydride for the hydroxycarbonylation**

Very recently, Clarke designed special phosphines to develop enantioselective alkene hydroxycarbonylations and alkoxy carbonylations under Chaudhari's conditions.<sup>94</sup>

### iii. Case of benzyl halides

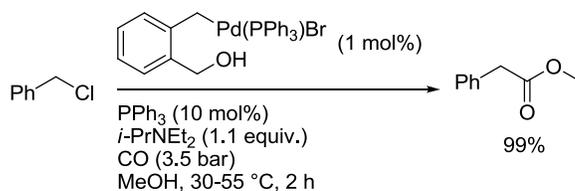
Benzyl halides are highly activated toward oxidative addition to a Pd(0) complex, and the thus generated benzylpalladium complex cannot undergo β-hydride elimination. Therefore, they are ideal substrates for carbonylative transformations.

In 1973, Heck described the first Pd-catalyzed alkoxy carbonylation of benzyl chloride, obtaining *n*-butyl phenylacetate in moderate yield (Scheme 59).<sup>26</sup>

<sup>93</sup> Li, Y.; Chaudhari R. V. *Ind. Eng. Chem. Res.* **2011**, *50*, 9577-9586.

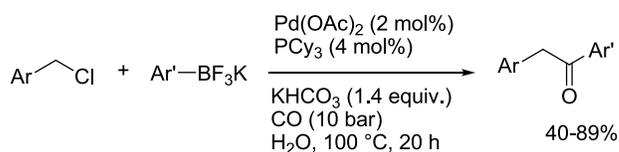
<sup>94</sup> a) Grabulosa, A.; Frew, J. J. R.; Fuentes, J. A.; Slawin, A. M. Z.; Clarke, M. L. *J. Mol. Catal. A: Chem.* **2010**, *330*, 18–25. b) Konrad, T. M.; Fuentes, J. A.; Slawin, A. M. Z.; Clarke, M. L. *Angew. Chem. Int. Ed.* **2010**, *49*, 9197–9200. c) Fuentes, J. A.; Slawin, A. M. Z.; Clarke, M. L. *Catal. Sci. Technol.* **2012**, *2*, 715-718.





**Scheme 61: Whitton's alkoxy carbonylation of benzyl chloride**

Benzyl halides have also been reacted in carbonylative cross-coupling reactions. For example, the carbonylative Suzuki-Miyaura and Sonogashira couplings have been well studied. An example is described in Scheme 62.<sup>53b,99,100</sup>

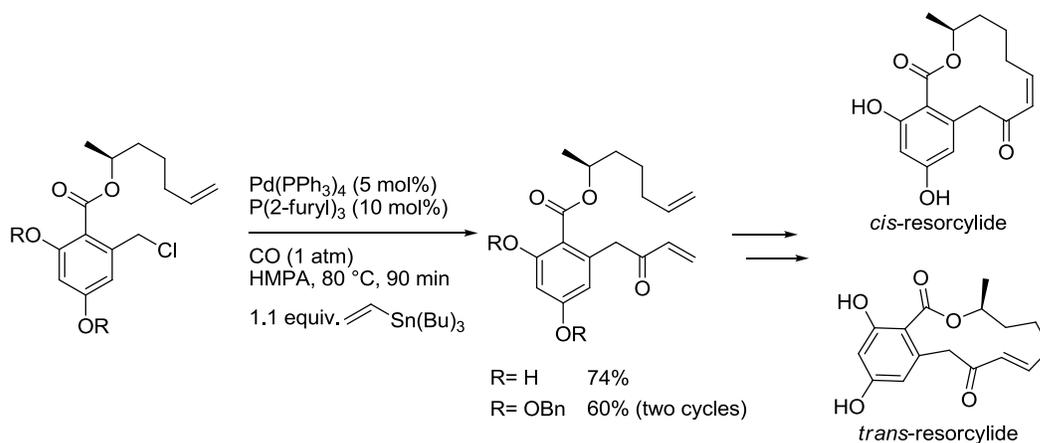


**Scheme 62: Carbonylative Suzuki coupling of benzyl chloride**

The carbonylative Stille coupling was effectively used for total synthesis of *trans*- and *cis*-resorcylic acid (Scheme 63).<sup>54d</sup>

<sup>99</sup> Wu, X.-F.; Neumann, H.; Beller, M. *Adv. Synth. Catal.* **2011**, *353*, 788–792.

<sup>100</sup> a) Wu, X.-F.; Neumann, H.; Beller, M. *Org. Biomol. Chem.* **2011**, *9*, 8003-8005. b) Sans, V.; Trzeciak, A. M.; Luis, S.; Zi'olkowski, J. J. *Catal. Lett.*, **2006**, *109*, 37-41. c) Perrone, S.; Bona, F.; Troisi, L. *Tetrahedron*, **2011**, *67*, 7386–7391.



**Scheme 63: Carbonylative Sonogashira coupling of benzyl chloride for the total synthesis of Resorcylic acid**

#### iv. With $\alpha$ -carbon-bound resonance stabilized electron withdrawing groups

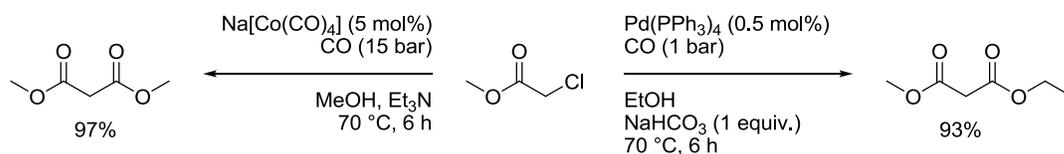
Surprisingly, generation and carbonylation of  $\sigma$ -alkylmetal complexes bearing  $\alpha$ -carbon-bound resonance stabilized electron withdrawing groups has been only poorly studied. Indeed, only few examples of generation of such compounds, *via* oxidative addition / carbonylation of  $\alpha$ -haloesters and  $\alpha$ -haloketones are described. As expected, such compounds are electronically highly activated toward oxidative addition. As this topic is strongly related to the experimental work of this thesis, exhaustive bibliographic report of such carbonylations will be presented.

##### 1) Carbonylation of $\alpha$ -haloacetates

Malonate esters are among the most popular building blocks in organic synthesis, and their access *via* transition metal-catalyzed carbonylation of chloroacetates in alcohol is a straightforward approach.

In the same pioneering work as that describing carbonylation of benzyl chloride (Scheme 59), Heck showed that methoxycarbonylation of methyl chloroacetate affords dimethylmalonate in 20% yield.<sup>26</sup>

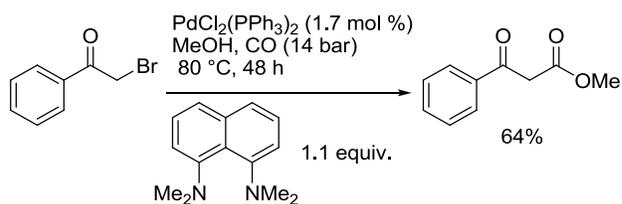
More recently, Jiang published a high yielding alkoxy carbonylation of 2-chloroacetates under cobalt<sup>101</sup> (Scheme 64, left) and palladium<sup>102</sup> (Scheme 64, right) catalysis. The reaction temperature is much smoother than that of the previous example (70 °C vs 200-300 °C), although 15 bar of carbon monoxide were required in the case of cobalt catalysis (Scheme 64).



**Scheme 64: Cobalt catalyzed alkoxy carbonylation of  $\alpha$ -haloacetates**

## 2) Carbonylation of $\alpha$ -haloketones

The Pd-catalyzed alkoxy carbonylation of  $\alpha$ -haloketones allows the synthesis of  $\beta$ -ketoesters, versatile precursors for the synthesis of many products such as ligands for homogenous catalysis or drugs. However, this reaction was scarcely studied. The first report was published in 1975 by Stille,<sup>95</sup> who was able to convert bromoacetophenone into methyl benzoacetate in 64% yield, under 14 bar of carbon monoxide and in the presence of proton sponge as the base (Scheme 65).

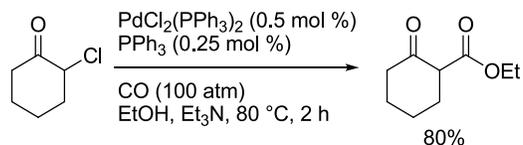


**Scheme 65: Palladium catalyzed alkoxy carbonylation of  $\alpha$ -haloketones**

<sup>101</sup> Song, W. H.; Jiang, X. Z. *Chin. Chem. Lett.* **2001**, *12*, 207-210.

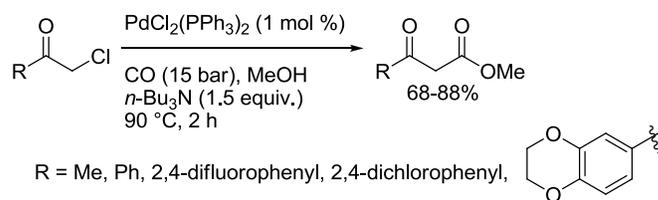
<sup>102</sup> Song, W. H.; Jiang, X. Z. *Chin. Chem. Lett.* **2000**, *11*, 1035-1036.

More recently, Toniolo studied in detail the carbonylation of 2-chlorocyclohexanone.<sup>103</sup> This transformation proceeded at 80 °C, under 100 atmospheres of carbon monoxide and required a phosphine / palladium ratio of 2.5 (Scheme 66).



**Scheme 66: Palladium catalyzed ethoxycarbonylation of  $\alpha$ -chlorocyclohexanone**

Beletskaya<sup>104</sup> investigated this reaction, too, and found that an inorganic base was less efficient than an amine, the best being tri-*n*-butylamine. Triphenylphosphine revealed to be the best ligand (Scheme 67).



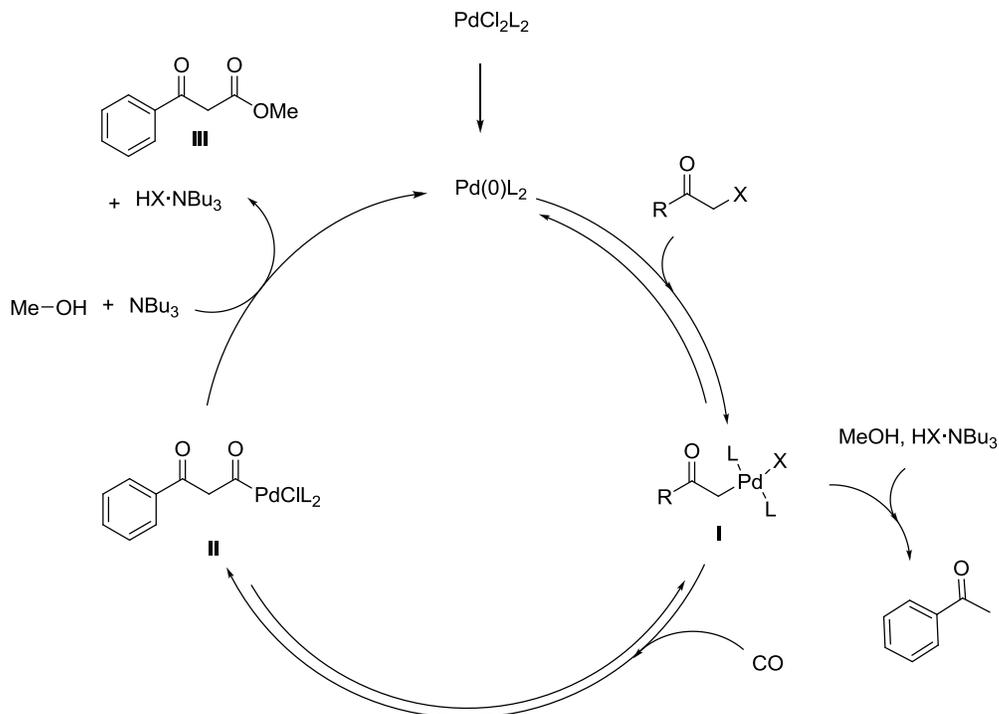
**Scheme 67: Beletskaya's alkoxy carbonylation of  $\alpha$ -haloketones**

The optimized reaction conditions were applied to various substituted ketones. The desired products were obtained in good yields. Even activated dichloroaryl derivatives underwent the desired carbonylation selectively at the  $\alpha$  position of the carbonyl group. On the other hand,  $\alpha$ -bromoketones gave substantial protodehalogenated compounds. In the proposed mechanism, oxidative addition of the  $\alpha$ -haloketone to the palladium(0) complex first forms the alkylpalladium(II) intermediate **I**. After coordination and migratory insertion of carbon monoxide, the acylpalladium(II) intermediate **II** is formed, which, after nucleophilic

<sup>103</sup> Cavinato, G.; Toniolo, L. *J. Mol. Catal. A: Chemical* **1999**, *143*, 325-330.

<sup>104</sup> a) Lapidus, A. L.; Eliseev, O. L.; Sizan, O. E.; Ostapenko, E. G.; Beletskaya, I. P. *Synthesis* **2002**, 317-319. b) Lapidus, A. L.; Eliseev, O. L.; Sizan, O. E.; Ostapenko, E. G.; Beletskaya, I. P. *Kinetics and Catalysis* **2004**, *45*, 234-238.

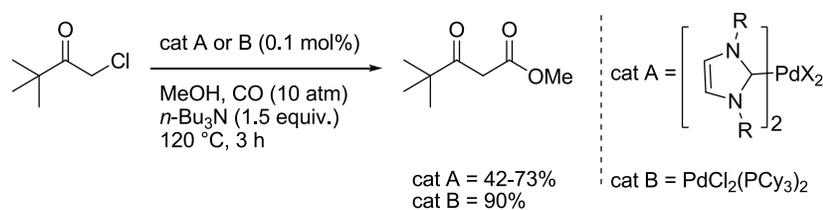
trapping by methanol, generates the desired  $\beta$ -ketoester **III**. On the other hand, undesired protonation of complex **I** by methanol or the ammonium formed during the reaction generates the protodehalogenated side product (Scheme 68).



**Scheme 68: Mechanism of alkoxy carbonylation of  $\alpha$ -haloketones**

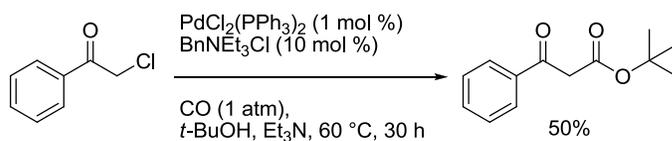
In 2006, Zoeller patented works dealing with the Pd-catalyzed alkoxy carbonylation of  $\alpha$ -chloroketones in the presence of [NHC-Pd]- or [phosphine-Pd]-based catalytic systems (Scheme 69).<sup>105</sup> The two methods allowed reaching yields up to 73% and 90%, respectively. However, the dehalogenated product was identified as side product.

<sup>105</sup> a) Zoeller, J. R. *Eur. Pat. App.* **2006**, EP 1676830 A1. b) Zoeller, J. R. *US Pat. App.* **2006**, USP 200601149094 A1.



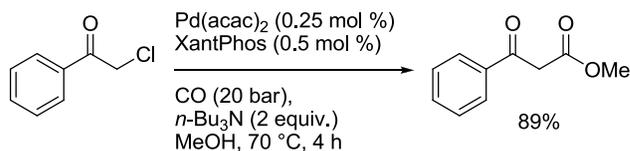
**Scheme 69: Patent on the alkoxycarbonylation of  $\alpha$ -haloketones with NHC-ligands**

Adapa reported a protocol of Pd-catalyzed  $\alpha$ -haloketone carbonylation under atmospheric CO pressure (Scheme 70).<sup>96,106</sup> This method, which makes use of a phase transfer agent, is, to the best of our knowledge, the only one allowing to carry out this transformation without a high CO pressure.



**Scheme 70: Carbonylation of  $\alpha$ -haloketones under atmospheric pressure of carbon monoxide**

Finally, in the frame of an ANR joint project between our research group and that directed by Professor André Mortreux (UL1, Unité de Catalyse et de Chimie du Solide, Lille),<sup>107</sup> developed an efficient alkoxycarbonylation of  $\alpha$ -chloroketones.<sup>108</sup> The optimization showed the crucial role played by the ligand. XantPhos was the most active ligand. An 0.25 mol% catalyst loading afforded the desired  $\beta$ -ketoester in 89% yield (Scheme 71).



**Scheme 71: Mortreux's update of the alkoxycarbonylation of  $\alpha$ -chloroketones**

<sup>106</sup> Raju, P. V. K.; Adapa, S. R. *Indian J. Chem.* **1992**, *31B*, 363-365.

<sup>107</sup> Collaboration within the frame of the project ANR joint CP2D: DOMINO-CO.

<sup>108</sup> Wahl, B.; Bonin, H.; Mortreux, A.; Giboulot, S.; Liron, F.; Poli, G.; Sauthier, M. *Adv. Synt. Catal.* *In press.*

The scope of the reaction was successfully extended to various aromatic, aliphatic ketones and alcohols (*n*-BuOH, *i*-PrOH, *t*-BuOH, ethylene glycol, 1-chloro-2-ethanol, and *o*-tolylmethanol).

#### e) Carbonylation within domino reactions

*Stricto sensu* transition metal-catalyzed carbonylation reactions are *per se* pure domino reactions, in that the final nucleophilic trapping (C-C, C-O...) depends on the prior CO insertion step (see chapters II-b) to II-d) pages 20-54). However, carbonylations have been used in more challenging domino reactions, involving the *in situ* formation of several bonds. In this section, the carbonylation reaction will be considered as a simple step reaction in a more global domino reaction.

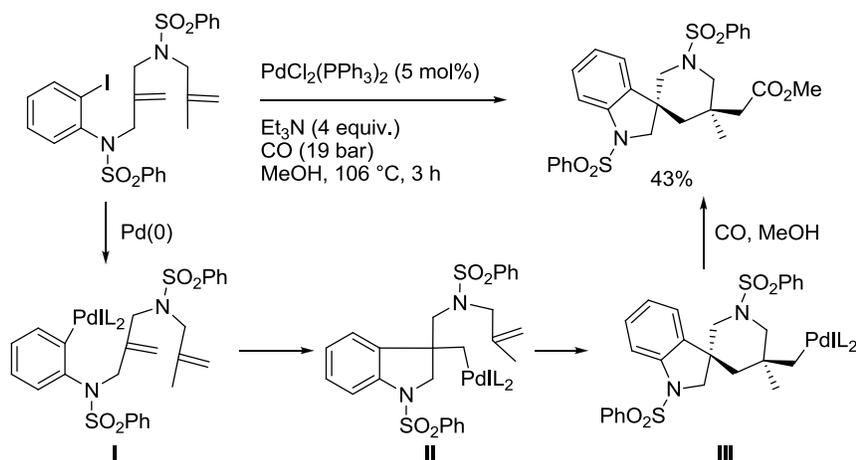
Domino reactions involving carbon monoxide can be incorporated in many types of one-pot multistep sequences, including radical transformations,<sup>109</sup> or transition metal-catalyzed processes such as hydroformylations.<sup>110</sup> However, in this section we will focus on domino reactions where at least one step is catalyzed by palladium.

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<sup>109</sup> a) Brinza, I. M.; Fallis, A. G. *J. Org. Chem.* **1996**, *61*, 3580–3581. b) Tsunoi, S.; Tanaka, M.; Tsunoi, S.; Ryu, I.; Yamasaki, S.; Sonoda, N.; Komatsu, M. *Tandem. Chem. Commun.* **1997**, 1889–1890. c) Ryu, I.; Kuriyama, H.; Minakata, S.; Komatsu, M.; Yoon, J.-Y.; Kim, S. *J. Am. Chem. Soc.* **1999**, *121*, 12190–12191. d) Ryu, I.; Tani, A.; Fukuyama, T.; Ravelli, D.; Fagnoni, M.; Albini, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 1869–1872.

<sup>110</sup> a) Wuts, P. G. M.; Obrzut, M. L.; Thompson, P. A. *Tetrahedron Lett.* **1984**, *25*, 4051–4054. b) Dong, Y.; Busacca, C. A. *J. Org. Chem.* **1997**, *62*, 6464–6465. c) Roggenbuck, R.; Eilbracht, P. *Tetrahedron Lett.* **1999**, *40*, 7455–7456. d) Lazzaroni, R.; Settambolo, R.; Caiazza, A.; Pontorno, L. *J. Organomet. Chem.* **2000**, *601*, 320–323. e) Kranemann, C. L.; Eilbracht, P. *Eur. J. Org. Chem.* **2000**, 2367–2377. f) Settambolo, R.; Savi, S.; Caiazza, A.; Lazzaroni, R. *J. Organomet. Chem.* **2001**, *619*, 241–244. g) Mizutani, N.; Chiou, W.-H.; Ojima, I. *Org. Lett.* **2002**, *4*, 4575–4578. h) Ahmed, M.; Jackstell, R.; Seayad, A. M.; Klein, H.; Beller, M. *Tetrahedron Lett.* **2004**, *45*, 869–873. i) Linnepe, P.; Schmidt, A. M.; Eilbracht, P. *Org. Biomol. Chem.* **2006**, *4*, 302–313. j) Cini, E.; Airiau, E.; Girard, N.; Mann, A.; Salvadori, J.; Taddei, M. *Synlett* **2011**, 199–202.

In 1992, Grigg described an outstanding domino reaction involving a double carbopalladation / methoxycarbonylation sequence. The whole sequence is described here below (Scheme 72).<sup>111</sup>



**Scheme 72: Double carbopalladation / methoxycarbonylation domino sequence of Grigg**

First, oxidative addition of aryl halide onto the palladium(0) complex leads to the aryl palladium intermediate **I**, which undergoes two sequential intramolecular (*5-exo-trig* and *6-exo-trig*) carbopalladations.<sup>112</sup> The thus formed “living”<sup>113</sup> σ-alkylpalladium complex **III**, deriving in turn from “living” complex **II**, eventually undergoes carbonylation and nucleophilic trapping. Notice that for reasons of appropriate differential reaction rates between intra- and intermolecular reaction, carbonylation takes selectively place only on intermediate **III**, as opposed to **I** and **II**. This concept is known under the name of "molecular

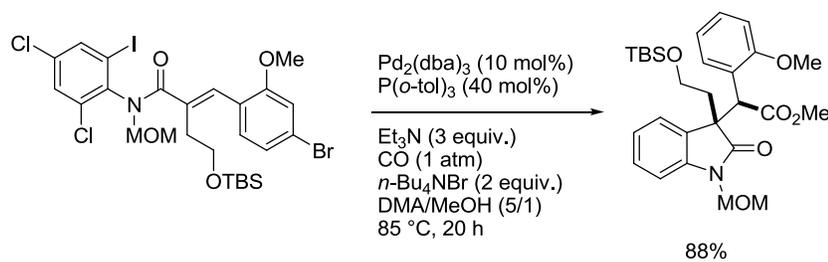
<sup>111</sup> Grigg, R.; Kennewell, P.; Teasdale, A. J. *Tetrahedron Lett.* **1992**, *33*, 7789–7792.

<sup>112</sup> a) Grigg, R.; Sridharan, V.; Stevenson, P.; Worakun, T. *J. Chem. Soc., Chem. Commun.* **1986**, 1697-1699. b) Grigg R.; Sridharan, V.; Stevenson, P., Sukirthalingam, S. *Tetrahedron*, **1989**, *45*, 3557-3568. c) Grigg, R.; Stevenson, P.; Worakun, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1073-1075. d) Grigg, R.; Malone, J. F.; Mitchell, T. R. B.; Ramasubba, A.; Scott, R. M. *J. Chem. Soc., Perkin Trans.1*, **1984**, 1745-1754. e) Grigg, R.; Stevenson, P.; Worakun, T. *Tetrahedron*, **1988**, *44*, 2033-2048.

<sup>113</sup> The "living" nature of organopalladium species is pointed out by Professor Ei-ichi Negishi. The "living" is used for the species of alkynyl-, alkenyl-, allyl-, and alkylpalladiums lacking β-hydrogens which don't readily undergo dehydropalladations. See: a) Negishi, E. *Pure Appl. Chem.* **1992**, *64*, 323-334. b) Negishi, E.; Ay, M.; Sugihara, T. *Tetrahedron*, **1993**, *49*, 5471.

queuing". During the course of his work, Grigg described several domino reactions involving alkoxyacylations,<sup>14c,114</sup> as well as carbonylative cross-coupling reactions.<sup>115</sup>

A similar methodology was followed by Weinreb in the synthesis of perophoramidine, exploiting a carbopalladation / alkoxyacylation domino sequence taking place at atmospheric CO pressure (Scheme 73).<sup>116</sup>



Scheme 73: Weinreb's carbopalladation / alkoxyacylation domino sequence

The substrate undergoes the a 5-*exo-trig* carbopalladation step on the activated double bond to form an alkyl neopentyllic palladium intermediate that could achieve the methoxycarbonylation under atmospheric pressure of carbon monoxide.

Alper described the formation of highly substituted endocyclic enollactones in ionic liquid, starting from simple 1,3-diketones, and alkynes (Scheme 74).<sup>117</sup> Oxidative addition of the enol form of the starting diketone leads to the oxopalladium intermediate I.

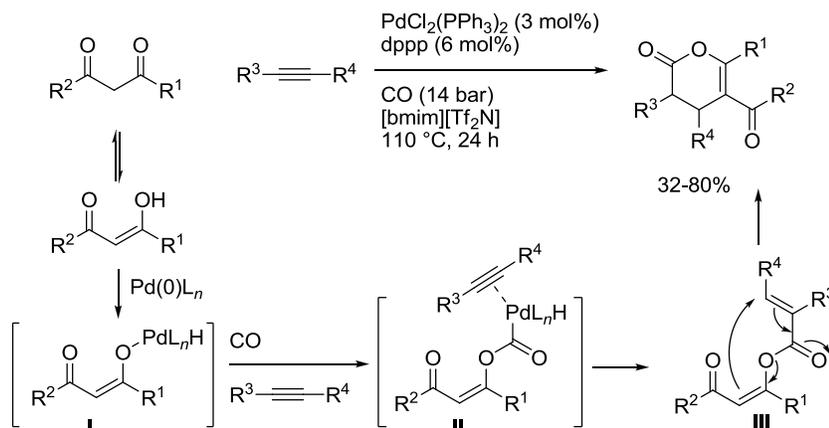
<sup>114</sup> a) Brown, A.; Grigg, R.; Ravishankar, T.; Thornton-Pett, M. *Tetrahedron Lett.* **1994**, *35*, 2753–2756. b) Grigg, R.; Putnikovic, B.; Urch, C. J. *Tetrahedron Lett.* **1996**, *37*, 695–698. For example with aminocarbonylation see: c) Evans, P.; Grigg, R.; Ramzan, M. I.; Sridharan, V.; York, M. *Tetrahedron Lett.* **1999**, *40*, 3021–3024.

<sup>115</sup> For domino reactions with carbonylative Heck coupling examples see: a) Grigg, R.; Khalil, H.; Levett, P.; Virica, J.; Sridharan, V. *Tetrahedron Lett.* **1994**, *35*, 3197–3200. With carbonylative Suzuki and Stille coupling see: b) Grigg, R.; Redpath, J.; Sridharan, V.; Wilson, D. *Tetrahedron Lett.* **1994**, *35*, 4429–4432. c) Grigg, R.; Redpath, J.; Sridharan, V.; Wilson, D. *Tetrahedron Lett.* **1994**, *35*, 7661–7664. d) Anwar, U.; Casaschi, A.; Grigg, R.; Sansano, J. M. *Tetrahedron* **2001**, *57*, 1361–1367. e) Brown, S.; Clarkson, S.; Grigg, R.; Thomas, W. A.; Sridharan, V.; Wilson, D. *Tetrahedron* **2001**, *57*, 1347–1359.

<sup>116</sup> a) Seo, J. H.; Artman, G. D.; Weinreb, S. M. *J. Org. Chem.* **2006**, *71*, 8891–8900. b) Evans, M. A.; Sacher, J. R.; Weinreb, S. M. *Tetrahedron* **2009**, *65*, 6712–6719.

<sup>117</sup> Li, Y.; Yu, Z.; Alper, H. *Org. Lett.* **2007**, *9*, 1647–1649.

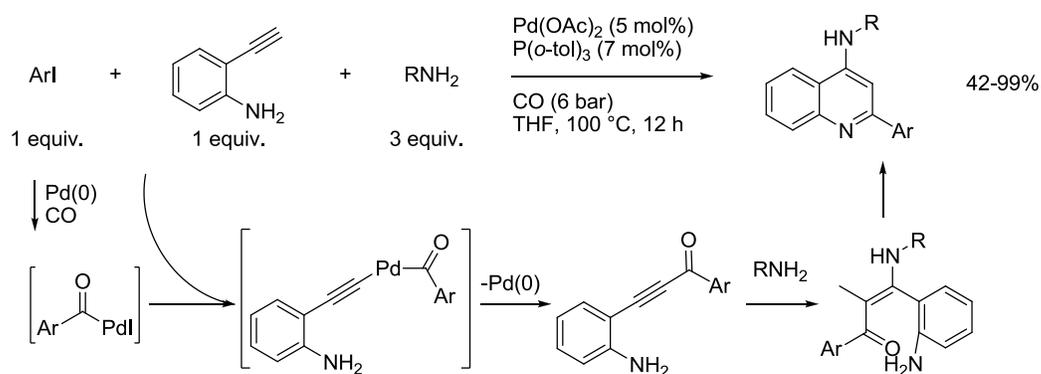
Subsequent migratory insertion of carbon monoxide and complexation of the alkyne affords the acylpalladium intermediate **II**, which can undergo alkoxyacetyl palladation and reductive elimination in order to give the intermediate product **III**. Finally, intramolecular attack of the enol on the Michael acceptor furnishes the desired lactone.



**Scheme 74: Alper's formation of lactone with carbonylative domino sequence**

A four-component domino reaction generating 2-aryl-4-aminoquinolines and 2-aryl-4-amino[1,8]naphthyridines was reported by Rossi.<sup>118</sup> Here, a carbonylative Sonogashira reaction involving *o*-alkynyl aniline is followed by nucleophilic addition of a second external amine on the activated triple bond. Intramolecular imine formation delivers the heterocycle in acceptable yields (Scheme 75).

<sup>118</sup> Abbiati, G.; Arcadi, A.; Canevari, V.; Capezuto, L.; Rossi, E. *J. Org. Chem.* **2005**, *70*, 6454–6460



**Scheme 75: Carbonylative Sonogashira within domino sequence**

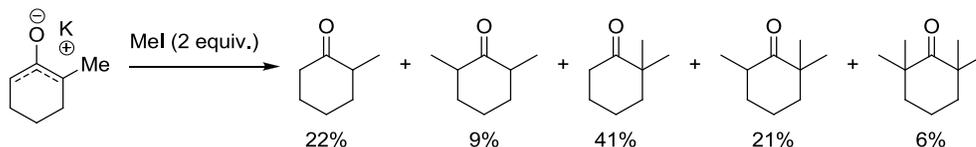
In conclusion, we have seen that CO is a superior reagent entering the mechanism of many catalytic transformations and capable of incorporating the carbonyl function in strategic positions in the final products.



## CHAPTER III : Decarboxylative Allylation

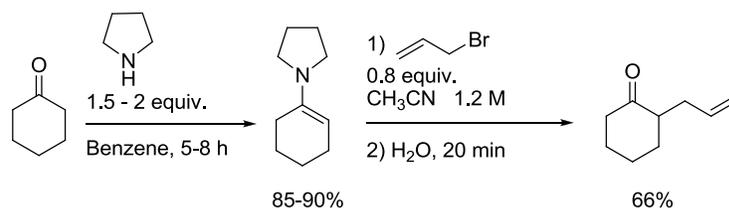
### a) Introduction

The reaction of ketone enolate with an electrophile such as an alkyl halide generally affords mixtures of mono- and poly- functionalized ketones (Scheme 76).<sup>119</sup>



Scheme 76: Selectivity issue for the alkylation of enolate

Methods exist in order to obtain selectively the monoallylated product. For example, the Stork enamine strategy is straightforward and highly efficient (Scheme 77).<sup>120</sup> However, the intermediate enamine is not always stable and cannot be stored.



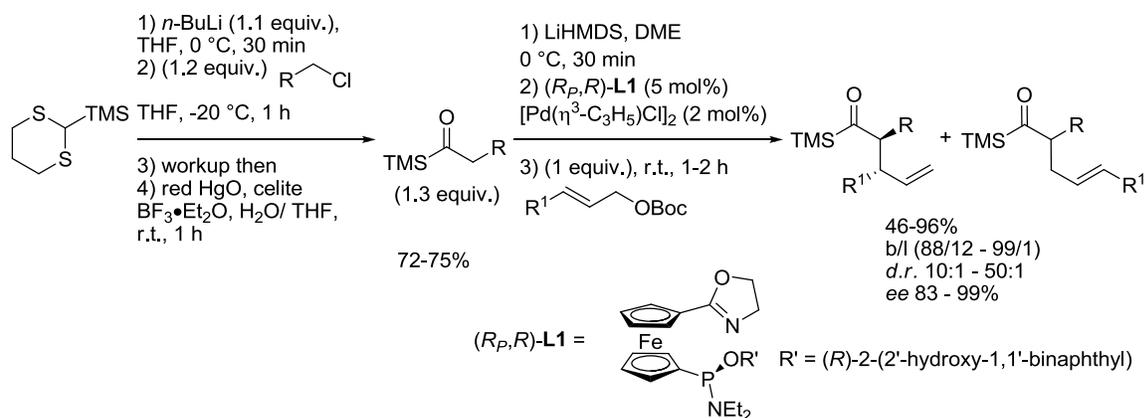
Scheme 77: Stork enamine strategy for the synthesis of monoallylated ketone

Acylsilanes behave well as pronucleophiles and can be used in palladium catalyzed regio-, diastereo-, and enantioselective allylic alkylations before being converted into the desired allylated ketones (Scheme 78).<sup>121</sup>

<sup>119</sup> House, H. O.; Kramar, V. *J. Org. Chem.*, **1963**, *28*, 3362-3379.

<sup>120</sup> a) Stork, G.; Terrell, R. Szmuszkovicz, J. *J. Am. Chem. Soc.* **1954**, *76*, 2029-2030. b) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207-222.

<sup>121</sup> Chen, J.-P.; Ding, C.-H.; Liu, W.; Hou, X.-L.; Dai, L.-X. *J. Am. Chem. Soc.* **2010**, *132*, 15493-15495.



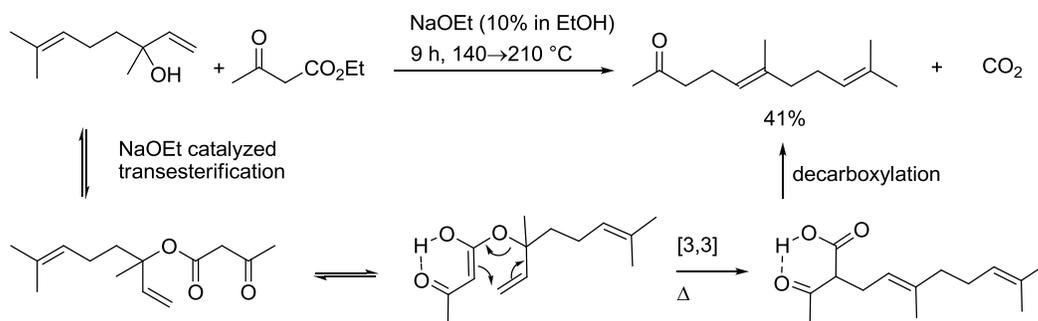
**Scheme 78: Acyl silyl strategy for the synthesis of monoallylated ketone**

The products are easily functionalizable. The yields are moderate to excellent and the selectivities are good depending on the substitution of the acylsilane and the carbonate precursor for  $\pi$ -allyl complex ( $R^1$  = Me, Ph, Et, *i*-Pr, (CH<sub>2</sub>)<sub>2</sub>-Ph, Bn, *p*-BrC<sub>6</sub>H<sub>4</sub>, *p*-ClC<sub>6</sub>H<sub>4</sub>, *p*-MeOC<sub>6</sub>H<sub>4</sub>, 2-furyl). However the synthesis of the acylsilane is long and tedious.

The decarboxylative allylation is a simple and efficient reaction allowing allylation of a carbonyl compounds through CO<sub>2</sub> extrusion. This transformation was first discovered by Carroll in 1940<sup>122</sup> when he reacted an allylic alcohol with ethyl acetoacetate in the presence of an alcoholate, unexpectedly obtaining the corresponding  $\gamma,\delta$ -unsaturated ketone with concomitant decarboxylation. This result can be accounted for on the basis of a transesterification step followed by a thermal [3,3]-sigmatropic rearrangement, and a final decarboxylation (Scheme 79). Due to the drastic thermal conditions, this reaction remained neglected for many years, until the discovery that transition metals could catalyze it.

<sup>122</sup>

a) Carroll, M. F. *J. Chem. Soc.* **1940**, 704-706. b) Carroll, M. F. *J. Chem. Soc.* **1940**, 1266-1268. c) Carroll, M. F. *J. Chem. Soc.* **1941**, 507-511.



Scheme 79: Carroll rearrangement

### b) Catalysis by the transition metals

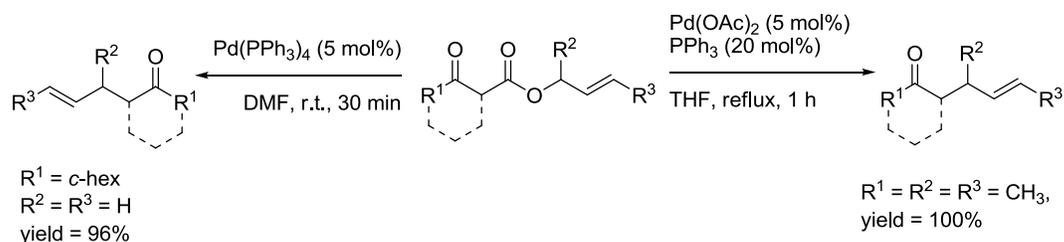
Transition metals are capable of catalyzing a great number of decarboxylative transformations,<sup>123</sup> and *inter alia* the decarboxylative allylation of  $\beta$ -oxoesters. In the 1980's the groups of Tsuji (Scheme 80, right)<sup>124</sup> and Saegusa (Scheme 80, left)<sup>125</sup> discovered independently and at the same time that the decarboxylative allylation of  $\beta$ -oxoesters could be catalyzed by Pd(0) complexes and a few years later Tsuji reported that the same type of reactivity could be obtained starting from allyl enol carbonates.<sup>126</sup> The regioselectivity of this Pd-catalyzed version of the Carroll rearrangement is usually total in favor of the linear product and in certain cases bis-allylated products are obtained in significant quantity. This catalytic variant brings about several advantages over the original thermal reaction, in terms of milder reaction conditions, better yields, and possibility to develop enantioselective variants using chiral ligands.

<sup>123</sup> Weaver, J. D.; Recio III, A.; Grenning, A. J.; Tunge, J. A. *Chem. Rev.* **2011**, *111*, 1846-1913

<sup>124</sup> Shimizu, I.; Yamada, T.; Tsuji, J. *Tetrahedron Lett.* **1980**, *21*, 3199-3202.

<sup>125</sup> Tsuda, T.; Chujo, Y.; Nishi, S.; Tawara, K.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 6381-6384.

<sup>126</sup> Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1983**, *24*, 1793-1796.



Scheme 80: Palladium catalyzed decarboxylative allylation

### c) Mechanism

The mechanism of the Pd(0)-catalyzed reaction entails an initial oxidative addition of the allyl moiety of the substrate onto the palladium(0) catalyst to generate a  $\eta^3$ -allylpalladium complex in equilibrium with the neutral  $\sigma$ -allyl complex.

At this point, the mechanism may differ in chronology of decarboxylation / allylation depending on its substitution. If the substrate has no acidic hydrogens, a likely turnover-limiting decarboxylation step takes place first, to form the corresponding  $\eta^3$ -allylpalladium enolate **V** (Scheme 81, right) and attack of the carbanion on the allyl ligand yields the  $\alpha$ -allylated ketone and releases the active catalytic species.<sup>127, 128</sup>

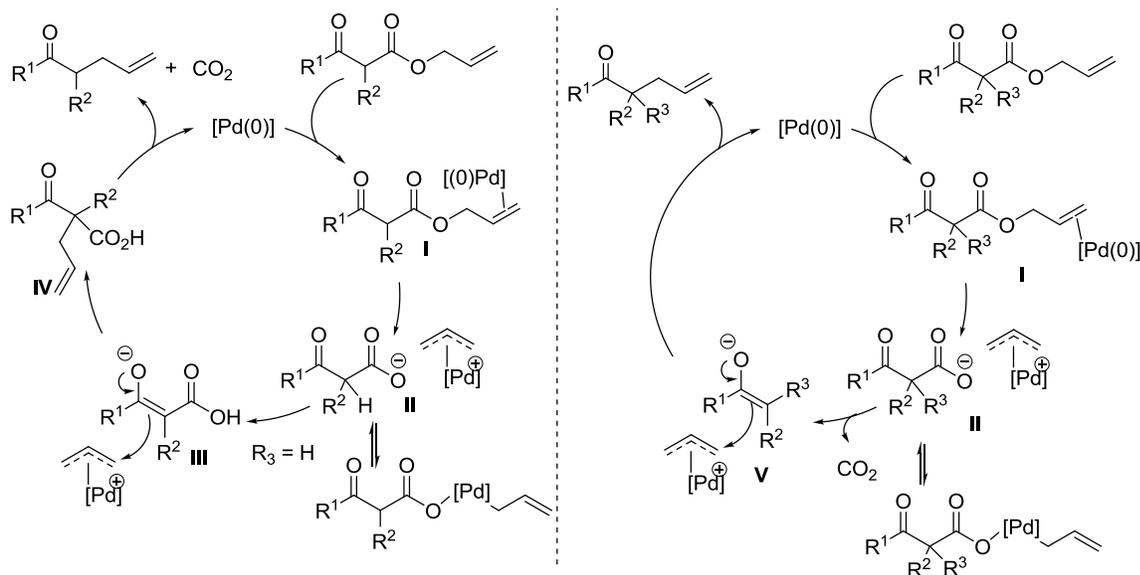
However, in  $\beta$ -oxoesters that bear  $\alpha$ -hydrogen atoms, the intermediate carboxylate can undergo a very fast intramolecular proton transfer to form the stabilized enolate carboxylic acid **III**, which can undergo allylation followed by decarboxylation of the  $\beta$ -oxo acid, to form the product (Scheme 81, left).<sup>129</sup> Whether enol carbonates undergo decarboxylation prior to or after allylation remains to be answered. Also, concerning the detailed mechanism of the decarboxylation, several paths are possible.

<sup>127</sup> Fiaud, J.-C.; Aribi-Zouieueche, L. *Tetrahedron Lett.* **1982**, 23, 5279–5282.

<sup>128</sup> For a recent example from our group of Pd-catalyzed decarboxylative allylation of *O*- $\alpha$ -allyl esters see: Kammerer-Pentier, C.; Diez Martinez, A.; Oble, J.; Prestat, G.; Merino, P.; Poli, G. *J. Organomet. Chem.* **2012**, 714, 53-59.

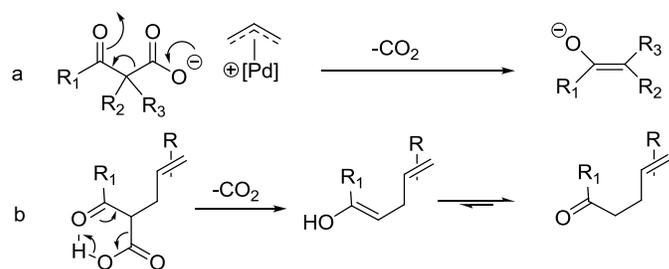
<sup>129</sup> Chattopadhyay, K.; Jana, R.; Day, V. W.; Douglas, J. T.; Tunge, J. A. *Org. Lett.* **2010**, 12, 3042–3045.

In contrast with the thermal reaction, which, as said, is a pure [3,3]-sigmatropic rearrangement, this Pd-catalyzed catalytic variant does not possess a stereospecific mechanism. As a consequence, mixtures of allylated isomers can be obtained. Usually, where possible, regioselectivity favors the linear isomers.



**Scheme 81: Mechanisms of the palladium catalyzed decarboxylative allylation of  $\beta$ -oxo-esters**

The detailed mechanism of the decarboxylation remains an open question. An ionic mechanism involving the transition metal, akin to the decarboxylation mechanism of other  $\beta$ -ketocarboxylates, appears to be the preferred path, at least in the case of disubstituted  $\beta$ -oxoesters (Scheme 82, a). However, in the case of  $\beta$ -oxoesters bearing  $\alpha$ -hydrogen atoms, the carboxyl group gets protonated, forming a  $\beta$ -oxocarboxylic acid after the allylation step. As a consequence, in this latter case the classical cyclic decarboxylation mechanism of  $\beta$ -oxocarboxylic acids is likely to be at work (Scheme 82, b).

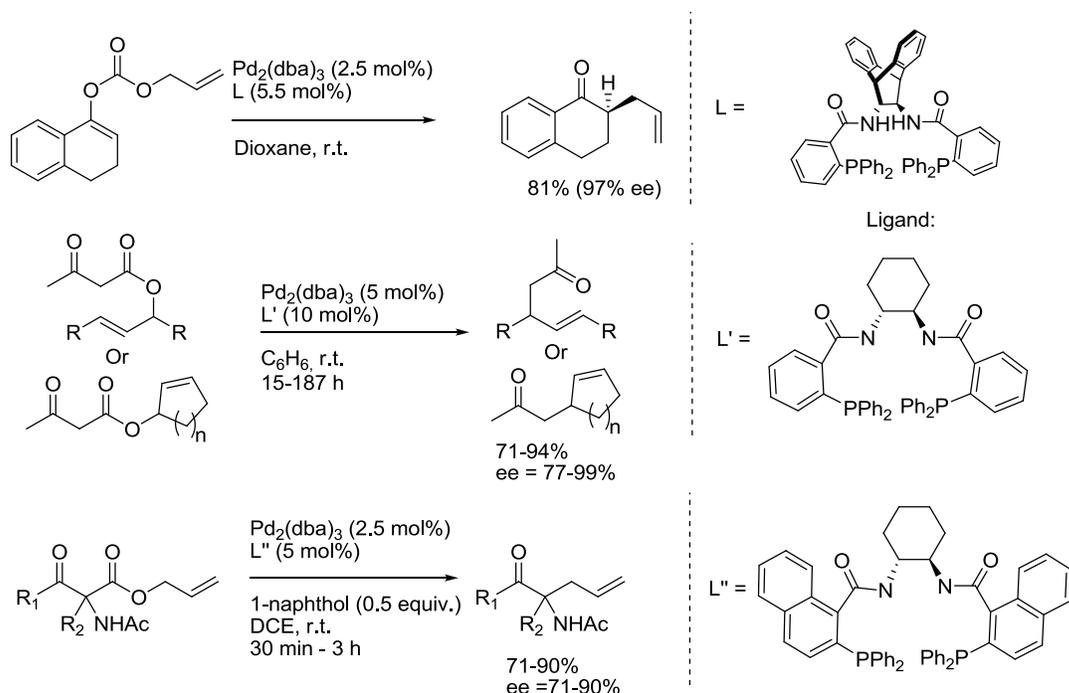


Scheme 82: Possible decarboxylation mechanisms

Using chiral ligands for palladium, this catalytic variant offers the possibility to develop enantioselective decarboxylative allylations, as recently shown by Trost,<sup>130</sup> Tunge<sup>123,131a,132</sup>, Dai,<sup>133</sup> Murakami<sup>131b</sup> and Stoltz<sup>134</sup> (Scheme 83).

Some examples are reported here below.

- 
- <sup>130</sup> Trost, B. M.; Xu, J.; Schmidt, T. J. *J. Am. Chem. Soc.* **2009**, *131*, 18343–18357.
- <sup>131</sup> a) Burger, E. C.; Tunge, J. A. *Org. Lett.* **2004**, *6*, 4113–4115. b) Kuwano, R.; Ishida, N.; Murakami, M. *Chem. Commun.* **2005**, 3951–3952.
- <sup>132</sup> Tunge, J. A.; Burger, E. C. *Eur. J. Org. Chem.* **2005**, 1715–1726.
- <sup>133</sup> You, S.-L.; Dai, L.-X. *Angew. Chem. Int. Ed.* **2006**, *45*, 5246–5248.
- <sup>134</sup> a) Behenna, D. C.; Liu, Y.; Yurino, T.; Kim, J.; White, D. E.; Virgil, S. C.; Stoltz, B. M. *Nat. Chem.* **2012**, *4*, 130–133. b) Behenna, D. C.; Mohr, J. T.; Sherden, N. H.; Marinescu, S. C.; Harned, A. M.; Tani, K.; Seto, M.; Ma, S.; Novák, Z.; Krout, M. R.; McFadden, R. M.; Roizen, J. L.; Enquist, J. A.; White, D. E.; Levine, S. R.; Petrova, K. V.; Iwashita, A.; Virgil, S. C.; Stoltz, B. M. *Chem. Eur. J.* **2011**, *17*, 14199–14223.



**Scheme 83: Enantioselective decarboxylative allylations**

As expected, transition metals other than palladium, such as molybdenum,<sup>135</sup> rhodium,<sup>135</sup> nickel,<sup>135</sup> iridium<sup>136</sup> and ruthenium<sup>137</sup> are capable of catalyzing this transformation, with different features.

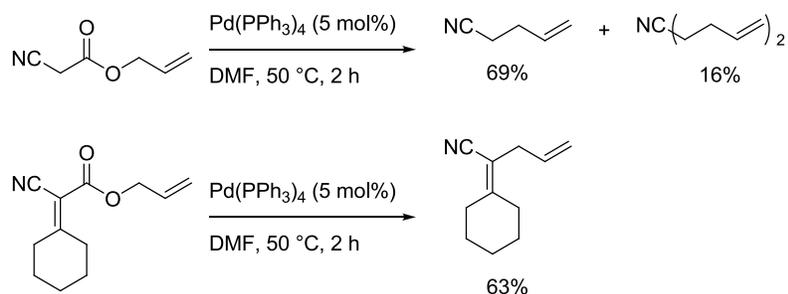
#### d) Decarboxylative allylation with other electron withdrawing groups

The Pd-catalyzed decarboxylative allylation was originally described with  $\beta$ -ketoesters. However successful examples have been published also with ester, amide and cyano groups as the assisting vicinal group. The first of such examples was reported by Saegusa with  $\beta$ -cyanoesters (Scheme 84).<sup>125</sup>

<sup>135</sup> Tsuji, J.; Minami, I.; Shimizu, I. *Chem. Lett.* **1984**, 1721-1724.

<sup>136</sup> He, H.; Zheng, X.-J.; Li, Y.; Dai, L.-X.; You, S.-L. *Org. Lett.* **2007**, *9*, 4339-4341.

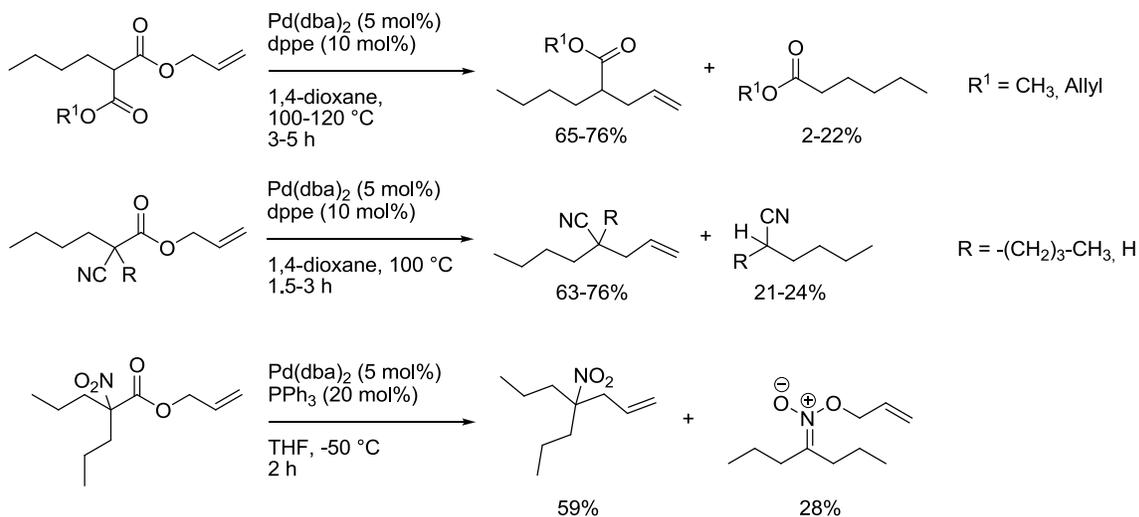
<sup>137</sup> a) Burger, E. C.; Tunge, J. A. *Org. Lett.* **2004**, *6*, 2603-2605. b) Burger, E. C.; Tunge, J. A. *Chem. Commun.* **2005**, 2835-2837. c) Constant, S.; Tortoioli, S.; Müller, J.; Lacour, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 2082-2085. d) Constant, S.; Tortoioli, S.; Müller, J.; Linder, D.; Buron, F.; Lacour, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 8979-8982. e) Linder, D.; Buron, F.; Constant, S.; Lacour, J. *Eur. J. Org. Chem.* **2008**, 5778-5785. f) Linder, D.; Austeri, M.; Lacour, J. *Org. Biomol. Chem.* **2009**, *7*, 4057-4061.



**Scheme 84: Decarboxylative allylation of cyanoester derivatives**

The reaction rapidly delivers the desired cyano compounds in good yields. However, the problem of bis allylation still remains an issue.

Few years later, Tsuji addressed a systematic study of allyl ester decarboxylative allylation using different activating functions such as ester, cyano and nitro derivatives<sup>138</sup> and could propose the following reactivity scale: nitroacetate >  $\beta$ -ketoacetate > cyanoacetate > malonate (Scheme 85).



**Scheme 85: Decarboxylative allylation with various electron withdrawing groups**

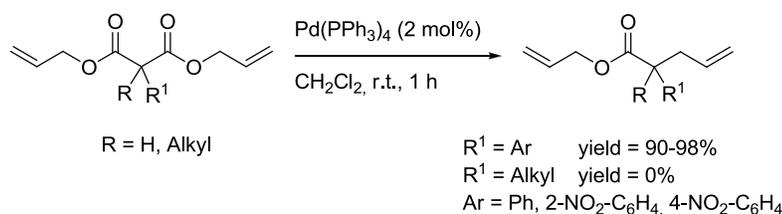
<sup>138</sup>

Tsuji, J.; Yamada, T.; Minami, I.; Yuhara, M.; Nisar, M.; Shimizu, I. *J. Org. Chem.* **1987**, *52*, 2988–2995.

Interestingly, for these newly tested electron-withdrawing groups, no product of bis allylation was observed. However, the product of protodecarboxylation was observed for the malonate and the cyanoacetate derivatives. Concerning the nitroacetate derivative, *O*-allylation of the nitro acid form was an important side reaction.

Recently, Tunge studied in detail the decarboxylative allylation of nitrile derivatives, using *rac*-BINAP as ligand. Despite the fact that the reaction created a new stereogenic center, study of enantioselection using the enantiopure ligand was not addressed.<sup>139</sup>

Ohta<sup>140</sup> studied the Pd-catalyzed decarboxylative allylation of disubstituted malonate derivatives, and showed that the presence of an aromatic ring as one of the substituents allowed performing the decarboxylative allylation at room temperature. This result strongly suggests that the ease of decarboxylation is related to the stability of the incipient enolate (Scheme 86).

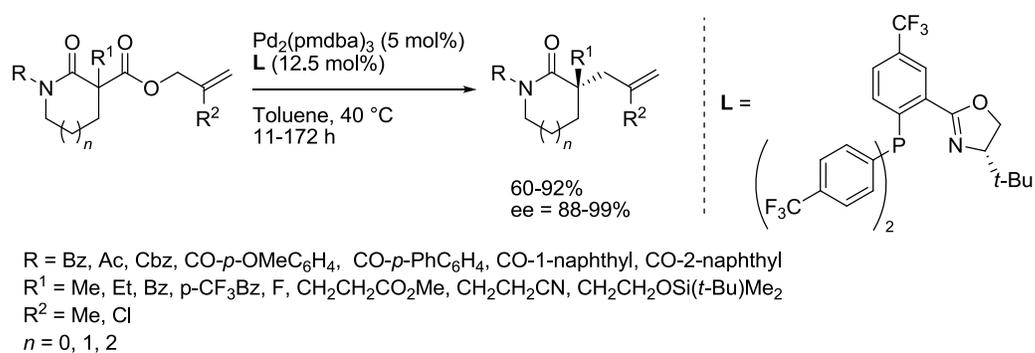


**Scheme 86: Decarboxylative allylation of diallyl malonate derivative**

Decarboxylative allylation has also been recently described with amide as electron-withdrawing group, for the enantioselective synthesis of *N*-heterocycles (Scheme 87).<sup>134a</sup>

<sup>139</sup> Recio, A.; Tunge, J. A. *Org. Lett.* **2009**, *11*, 5630–5633.

<sup>140</sup> Imao, D.; Itoi, A.; Yamazaki, A.; Shirakura, M.; Ohtoshi, R.; Ogata, K.; Ohmori, Y.; Ohta, T.; Ito, Y. *J. Org. Chem.* **2007**, *72*, 1652-1658.



**Scheme 87: Enantioselective decarboxylative allylation of malonamide**

Interestingly, PHOX ligand derivatives were used instead of Trost ligands. The ligand allows an effective control of enantioselectivity at the quaternary center. The key parameter of the reaction is the protecting group on the nitrogen atom of the amide. Indeed, strong electron-withdrawing protective groups have to be used in order to increase the reactivity of malonamides. However, the strength of the protective group has to be fine-tuned in order to obtain good enantioselectivity. For example tosyl group leads to almost racemic product and for acyl group the enantioselectivity is nearly perfect.

In conclusion, the decarboxylative allylation is an efficient method for the monoallylation of ketones and acid derivatives. The reaction conditions are usually smooth and the yields are good. The used of chiral ligands (Trost or PHOX ligands) allows a control of the stereogenic center formed during the reaction.

## Results and Discussion

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## CHAPTER IV : Execution of the project

### a) Development of new Pd-catalyzed domino sequences involving carbon monoxide

In the frame of the ANR project,<sup>107</sup> the aim of the present project thesis work is to develop original Pd-catalyzed domino sequences involving carbon monoxide as a cheap and readily available carbonyl source.<sup>141</sup> Indeed, the Parisian team has a sizeable knowhow in palladium chemistry and domino sequences, whereas the Lille group enjoys a longstanding expertise in catalysis and carbonylations.

Combination of the benefits of CO chemistry with the concepts of domino reactions has already some precedents<sup>13a</sup> such as multicomponent carbonylative coupling reactions<sup>142</sup> 1,3-dipolar cycloadditions involving münchnones,<sup>143</sup> carbopalladation/carbonylation sequences,<sup>144</sup> and allylic alkylation/Pauson-Khand sequences.<sup>145</sup> However, none of these works included a palladium-catalyzed allylation reaction wherein the nucleophile  $\beta$ -oxoester is in turn derived from a Pd-catalyzed alkoxy carbonylation. Accordingly, we decided to set out a collaborative project wherein the Lille group would have tackled domino alkoxy carbonylation / allylation sequences (Scheme

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<sup>141</sup> a) Chiusoli, G. P.; Costa, M. in: Handbook of Organopalladium Chemistry for Organic Synthesis, (Ed.: E. Negishi), John Wiley & Sons, Hoboken, N.J., **2002**, Vol. 2, pp 2595–2621; b) Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Soc. Rev.* **2011**, *40*, 4986-5009, and references quoted therein.

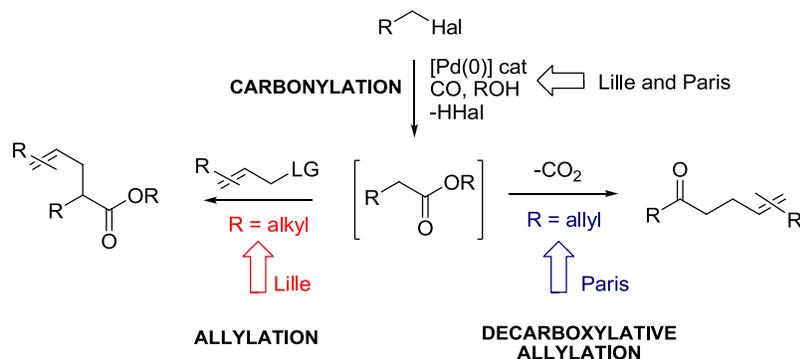
<sup>142</sup> Mihovilovic, M. D.; Stanetty, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 3612–3615.

<sup>143</sup> a) Siamaki, A. R.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2006**, *128*, 6050–6051. b) Dhawan, R.; Dghaym, R. D.; St. Cyr, D. J.; Arndtsen, B. A. *Org. Lett.* **2006**, *8*, 3927-3930.

<sup>144</sup> a) Sugihara, T.; Copéret, C.; Owczarczyk, Z.; Harring, L. S.; Negishi, E.-i. *J. Am. Chem. Soc.* **1994**, *116*, 7923-7924. b) Negishi, E.-i.; Wang, G.; Zhu, G. *Top. Organomet. Chem* **2006**, *19*, 1–48.

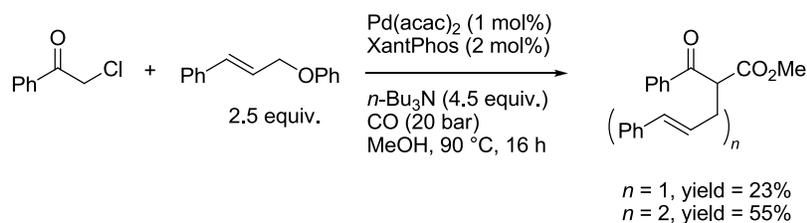
<sup>145</sup> a) Jeong, N.; Seo, S. D.; Shin, J. Y. *J. Am. Chem. Soc.* **2000**, *122*, 10220-10221. b) Son, S. U.; Park, K. H.; Chung, Y. K. *J. Am. Chem. Soc.* **2002**, *124*, 6838–6839.

88, left)<sup>146</sup> and ours, domino allyloxycarbonylation / decarboxylative allylation sequence<sup>147</sup> (Scheme 88, right).



Scheme 88: Project DOMINO-CO

Mortreux's group described a pseudo-domino type I sequence featuring the carbonylation of  $\alpha$ -chloroketones and subsequent allylation of the formed  $\beta$ -ketoester (Scheme 89).<sup>146</sup>



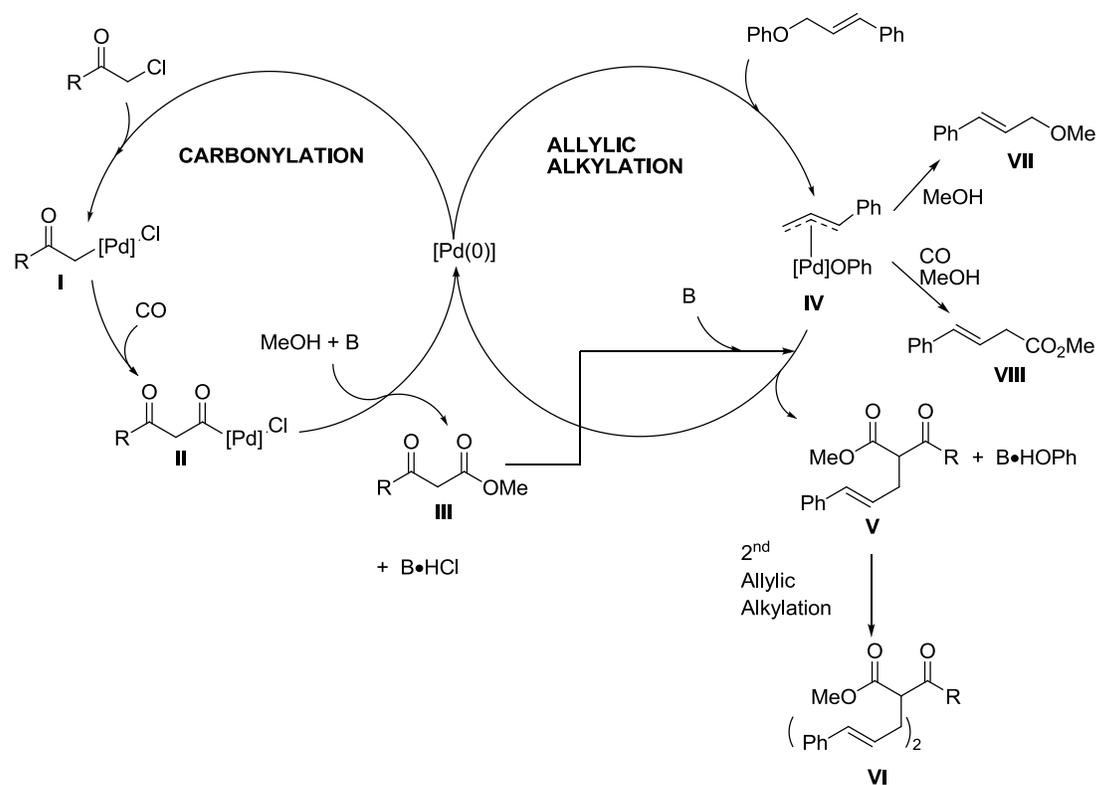
Scheme 89: Mortreux's pseudo-domino type I reaction methoxycarbonylation / allylation of  $\alpha$ -chloroketones

The key to success was the fine-tuning of the leaving group of the allyl moiety. Indeed, the more reactive allyl acetate or allyl halide gave rise mainly to the carbonylation or the substitution on the allyl part, leading to the products **VII** and **VIII**, thereby resulting in the consumption of the reactant (Scheme 90). The reaction starts with the oxidative addition of

<sup>146</sup> Wahl, B. Giboulot, S. Mortreux, A. Castanet, Y. Sauthier, M. Liron F. Poli, G. *Adv. Synth. Catal.*, **2012**, 1077-1083

<sup>147</sup> Giboulot, S.; Liron, F.; Prestat, G.; Wahl, B.; Sauthier, M.; Castanet, Y.; Mortreux, A.; Poli, G. *Chem. Commun.* **2012**, 48, 5889-5891.

the chloroketone to palladium(0) complex leading to the alkylpalladium(II) intermediate **I**. Subsequent complexation and migratory insertion of carbon monoxide generate the acylpalladium intermediate **II**. After nucleophilic trapping with MeOH,  $\beta$ -ketoester **III** is formed. On the other hand, the phenate also undergoes the oxidative addition to palladium(0) complex to form the  $\pi$ -allyl intermediate **IV**, which can be trapped by the enolate form of **III** to afford intermediate **V**. This allylated  $\beta$ -ketoester can undergo a second allylation reaction to provide the diallylated product **VI**. Bulky R groups (*t*-Bu or 2,5-dimethyl-1-phenylpyrrole) allowed the isolation of monoallylated products.



**Scheme 90: Mechanism of the type I domino sequence alkoxy carbonylation / allylic alkylation**

Hence, we decided to study the Pd-catalyzed allyloxy carbonylation of  $\alpha$ -chloroketones and to submit *in situ* the thus formed allyl  $\beta$ -ketoesters to decarboxylative allylation. Such a protocol, if successful, would thus allow obtaining mono-allylated ketones in a single step starting from simple  $\alpha$ -chloroketones. Moreover, in this procedure no stoichiometric amount of metallic salts would be generated.

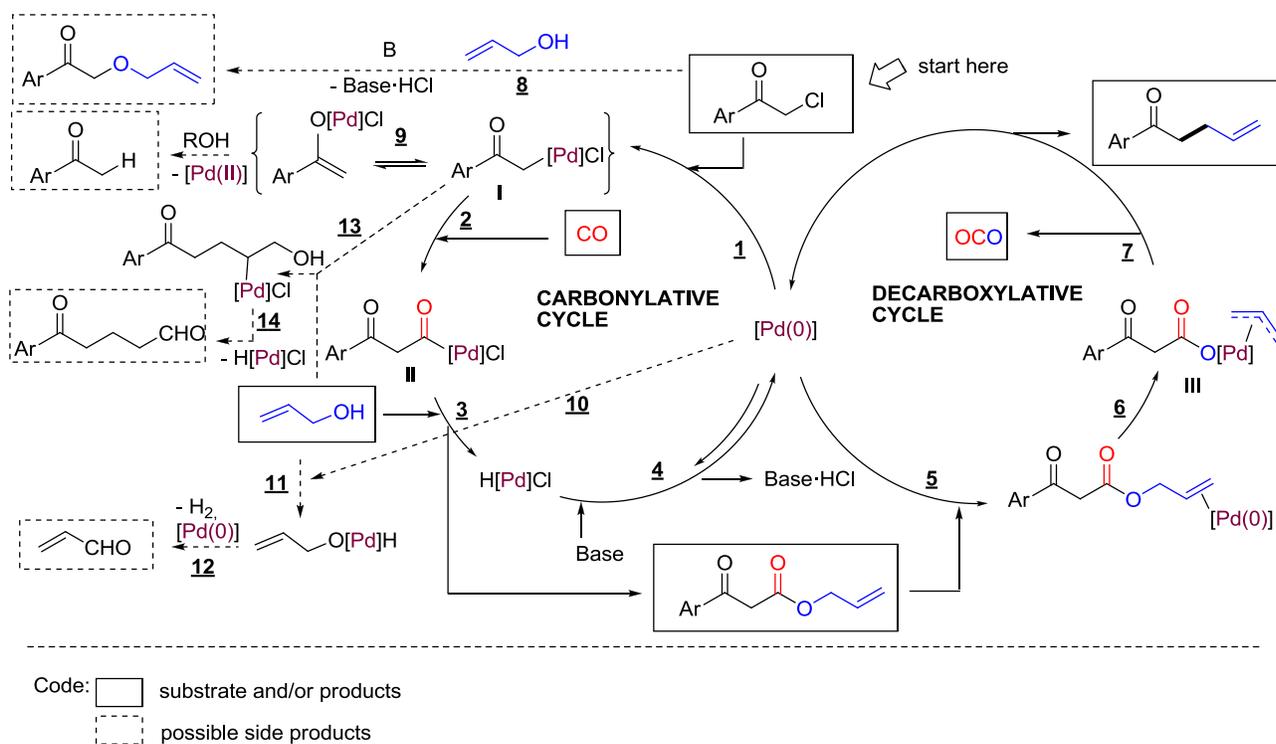
The mechanism of this pseudo-domino type I sequence is expected to follow elementary steps from **1** to **7** incorporated in the two consecutive catalytic cycles sharing Pd(0) (Scheme 91). Oxidative addition of the  $\alpha$ -chloroketone to palladium(0) leads to the alkyl palladium intermediate **I**. Complexation and migratory insertion of carbon monoxide should form the acylpalladium intermediate **II**. Then, trapping by the allyl alcohol delivers the allyl  $\beta$ -ketoester intermediate product. This latter undergoes a second oxidative addition into palladium(0) to form the  $\pi$ -allyl intermediate **III**. Decarboxylation and addition of the enolate on the  $\pi$ -allyl moiety would deliver the desired monoallylated ketone. However, a deep inspection of the potential unwished reactivities (dotted paths) unveils the warnings that make such a catalytic enchainment rather tricky. First, an undesired nucleophilic substitution between allyl alcohol and the halide might generate the corresponding ether, thereby directly subtracting the two components of the reaction (step 8). Furthermore, early protonation of the palladium complex deriving from oxidative addition of the halide may also take place, directly, or *via* its palladium enolate (step 9).<sup>148</sup> Competitive oxidative addition of the alcohol to Pd(0) may, after  $\beta$ -elimination, generate acrolein, thus consuming the alcohol (step 12).<sup>149</sup> Finally, carbopalladation of the alkylpalladium intermediate **I** on the allyl alcohol (step 13), followed by a  $\beta$ -hydride elimination and a tautomerization (step 14), could afford a ketoaldehyde.<sup>150</sup>

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<sup>148</sup> a) Albéniz, A. C.; Catalina, N. M.; Espinet, P.; Redón, R. *Organometallics* **1999**, *18*, 5571–5576. b) Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 5816–5817.

<sup>149</sup> Murahashi S.-I. Komiya, N. in *Handbook of Organopalladium Chemistry for Organic Synthesis*, ed. Negishi, E.-i. John Wiley & Sons, Inc, **2002**, ch. VIII.3.2, pp. 2881-2894.

<sup>150</sup> a) Melpolder, J. B.; Heck, R. F. *J. Org. Chem.* **1976**, *41*, 265-272. b) Buntin, S. A.; Heck, R. F. *Org. Synth. Coll. Vol.* **1990**, *7*, 361.



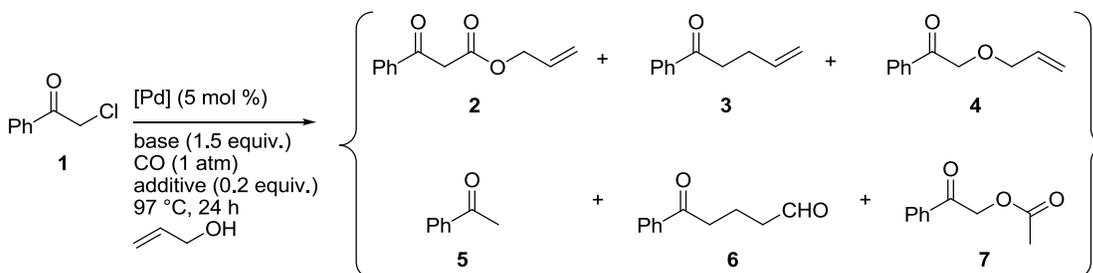
Scheme 91: Mechanism of the type I domino sequence allyloxycarbonylation / decarboxylative allylation

## b) The requirement of a sequential study

### i. Trials at atmospheric pressure

Our study began by treating  $\alpha$ -chloroacetophenone with catalytic amounts of different palladium/ligand systems in allyl alcohol as solvent, under carbon monoxide at atmospheric pressure, and in the presence of different bases or additives (Table 1).

Table 1

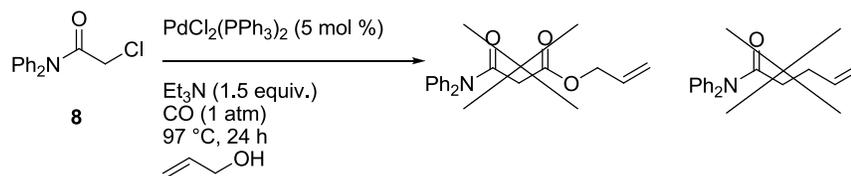


| Entry | Catalyst   | base                        | additive              | Products (yields) <sup>a</sup>                   |
|-------|--|-----------------------------|-----------------------|--|
| 1     | PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> | Et <sub>3</sub> N           | -                     | <b>5</b> (100%)                                  |
| 2     | PdCl <sub>2</sub> dppf                             | Et <sub>3</sub> N           | -                     | <b>5</b> (62%) + <b>6</b> (38%)                  |
| 3     | Pd(dba) <sub>2</sub> + dppe                        | Et <sub>3</sub> N           | -                     | <b>4</b> (81%) + <b>5</b> (19%)                  |
| 4     | PdCl <sub>2</sub> dppp                             | Et <sub>3</sub> N           | -                     | <b>4</b> (65%) + <b>5</b> (35%)                  |
| 5     | Pd(dba) <sub>2</sub> + dppb                        | Et <sub>3</sub> N           | -                     | <b>4</b> (28%) + <b>5</b> (72%)                  |
| 6     | Pd(dba) <sub>2</sub> + PCy <sub>3</sub>            | Et <sub>3</sub> N           | -                     | <b>4</b> (73%) + <b>5</b> (27%)                  |
| 7     | Pd(dba) <sub>2</sub> + P(2-fur) <sub>3</sub>       | Et <sub>3</sub> N           | -                     | <b>5</b> (100%)                                  |
| 8     | PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> | NaOAc                       | -                     | <b>4</b> (29%) + <b>5</b> (43%) + <b>7</b> (28%) |
| 9     | PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> | NaOAc                       | BnNEt <sub>3</sub> Br | <b>5</b> (11%) + <b>6</b> (21%) + <b>7</b> (28%) |
| 10    | PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> | <i>n</i> -Bu <sub>3</sub> N | -                     | <b>4</b> (54%) + <b>5</b> (30%) + <b>6</b> (16%) |

<sup>a</sup> based on <sup>1</sup>H NMR analysis of the crude reaction mixture

NMR analysis of the crude reaction mixture showed neither detectable amounts of the intermediate product **2**, nor of the desired ketone **3** (Table 1, entry 1). On the other hand, acetophenone **5** was always present (11 to 100%). Moreover, when bidentate ligands with a small bite angle were used, ether **4** deriving from nucleophilic substitution of the chloride atom by the alcohol, were observed in important amounts (entries 3-5). Furthermore, sodium acetate, used as base, proved to be sufficiently nucleophilic to displace the chloride in 28% (entry 8). The use of an ammonium salt, as described by Adapa,<sup>106</sup> did not improve the results (entry 9). Finally, ketoaldehyde **6** was obtained in some cases (entries 2, 9, 10).

In the hope that with other substrates protodehalogenation did not compete with (CO complexation / migratory insertion) we then tested chloroamide **8**. However, submission of **8** to the reaction conditions gave no reaction, suggesting that the oxidative addition in this case did not take place (Scheme 92).



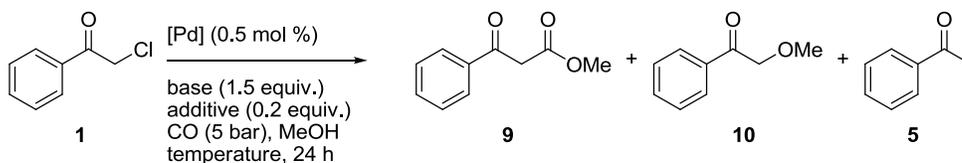
**Scheme 92: Try with  $\alpha$ -chloroamide derivative**

Given these disappointing results, we decided to optimize the reaction conditions for the alkoxy carbonylation and then for the decarboxylative allylation step, separately.

## ii. Carbonylation of $\alpha$ -chloroketones

We decided to start investigation of the alkoxy carbonylation step using 0.5 mol% of catalyst, at 5 bar of CO, in methanol.

**Table 2**



| Entry | Catalyst   | Base                        | Additive              | T (°C) | Products (yields) <sup>a</sup>                                |
|-------|--|-----------------------------|-----------------------|--------|---|
| 1     | PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> | Et <sub>3</sub> N           | -                     | 100    | <b>9</b> (16%) + <b>10</b> (18%) + <b>5</b> (66%)             |
| 2     | PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> | Et <sub>3</sub> N           | -                     | 130    | <b>10</b> (45%) + <b>5</b> (55%)                              |
| 3     | PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> | <i>n</i> -Bu <sub>3</sub> N | -                     | 100    | <b>9</b> (11%) + <b>10</b> (7%) + <b>5</b> (82%)              |
| 4     | PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> | DMAN <sup>b</sup>           | -                     | 100    | <b>9</b> (49%) <sup>c</sup> + <b>10</b> (6%) + <b>5</b> (45%) |
| 5     | PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> | DMAN <sup>b</sup>           | BnNEt <sub>3</sub> Br | 100    | <b>9</b> (21%) + <b>10</b> (9%) + <b>5</b> (70%)              |
| 6     | PdCl <sub>2</sub> dppf                             | DMAN <sup>b</sup>           | -                     | 100    | <b>9</b> (16%) + <b>10</b> (8%) + <b>5</b> (76%)              |

<sup>a</sup> based on <sup>1</sup>H NMR analysis of the crude reaction mixture; <sup>b</sup> 1,8-bis(dimethylamino)naphthalene; <sup>c</sup> isolated yield 38%

Treatment of chloracetophenone **1** with PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> and triethylamine at 100°C afforded the desired β-oxoester **9** in minor amounts (16%), together with acetophenone **5** (66%) and methoxyacetophenone **10** (Table 2, entry 1). Raising the temperature to 130 °C did not improve the result (entry 2 vs 1). Different bases were investigated. Tri-*n*-butylamine, used by Beletskaya, gave no improvement (entry 3), while 1,8-bis(dimethylamino)naphthalene successfully afforded the desired ester in 38% isolated yield (entry 4). Addition of an ammonium salt or the use of ferrocenyl ligand were less efficient (entries 5 and 6).

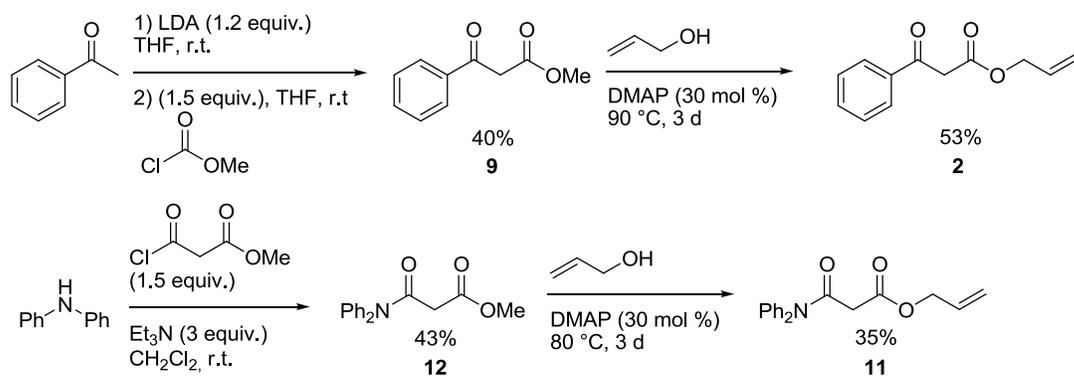
Thus, in methanol, α-chloroacetophenone underwent methoxycarbonylation to afford the desired β-ketoester in moderate yield. At this point, the reaction was not further studied, as we were more interested into the domino process. We then turned our attention to the decarboxylative allylation.

### iii. Decarboxylative allylation

In order to study the decarboxylative allylation, β-ketoester **2** and β-ketoamide **11** were synthesized according to the following procedure (Scheme 93). Addition of lithium enolate of acetophenone on methyl chloroacetate afforded methyl β-ketoester **9**. Then, transesterification in allyl alcohol and in the presence of a substoichiometric amount of DMAP afforded the desired allyl β-ketoester **2**.<sup>151</sup> Malonamide **11** was obtained in a similar manner by addition of diphenylamine to methyl 3-chloro-3-oxopropanoate, to give methyl malonamide **12**. Then, transesterification with allyl alcohol led to allyl malonamide **11**.

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<sup>151</sup> Yadav, J. S.; Reddy, B. V. S.; Krishna, A. D.; Reddy, C. S.; Narsaiah, A. V. J. *Mol. Catal. A: Chemical*, **2007**, *261*, 93-97.



**Scheme 93: Synthesis of allyl  $\beta$ -ketoester and allyl malonamide**

The decarboxylative allylation of malonamide **11** was first studied with  $\text{Pd}(\text{dba})_2$  and  $\text{PPh}_3$  as ligand in different solvents and at different temperatures. At room temperature in THF, the reaction did not occur, the major part of the starting material being recovered after 16 h (Table 3, entry 1). In refluxing THF, after 45 min, 17% of the desired product **13** was isolated (entry 2). Finally, after 45 min at 90 °C, in toluene, 56% of 4-pentenamide was obtained (entry 3).

**Table 3**

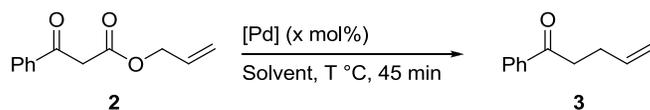
| Entry | Solvent | T (°C) | Time   | yields (%) <sup>a</sup> |
|-------|---------|--------|--------|-------------------------|
| 1     | THF     | 25     | 16 h   | 7                       |
| 2     | THF     | 60     | 45 min | 17                      |
| 3     | toluene | 90     | 45 min | 56                      |

<sup>a</sup> Isolated yields

Then, we tested the decarboxylative allylation of the  $\beta$ -ketoester derivative in presence of  $\text{Pd}(\text{dba})_2$  and  $\text{PPh}_3$  as ligand. Similarly, after 45 min, the use of toluene at 90 °C instead of THF at 60 °C increased the yield (Table 4, entries 1 and 2). A reaction carried out at 90 °C in allyl alcohol, the solvent planned for the future domino reaction, gave also a good result (entry 3).  $\text{Dppf}$  as ligand was also tested, in toluene at 90 °C. In this case, the catalyst loading could be decreased to 0.5 mol% obtaining an almost quantitative yield (entries 4 and

5). Finally, a blank test, conducted without palladium catalyst, and in conditions otherwise identical to the previous experiment, did not lead to decarboxylative allylation, thereby confirming that under these conditions Pd catalysis is needed (entry 6).

**Table 4**



| Entry | Catalyst                                  | x (mol%) | Solvent       | T (°C) | Yields (%) <sup>a</sup> |
|-------|---|----------|---------------|--------|-------------------------|
| 1     | Pd(dba) <sub>2</sub> + 4 PPh <sub>3</sub> | 5        | THF           | 60     | 64%                     |
| 2     | Pd(dba) <sub>2</sub> + 4 PPh <sub>3</sub> | 5        | Tol           | 90     | 78%                     |
| 3     | Pd(dba) <sub>2</sub> + 4 PPh <sub>3</sub> | 5        | allyl alcohol | 90     | 72%                     |
| 4     | Pd(dba) <sub>2</sub> + dppf               | 5        | Tol           | 90     | 83%                     |
| 5     | Pd(dba) <sub>2</sub> + dppf               | 0,5      | Tol           | 90     | 94%                     |
| 6     | -   | -        | Tol           | 90     | 0%                      |

<sup>a</sup> isolated yields

This study showed that both steps can be achieved separately, and the decarboxylative allylation appears to take place under smoother reaction conditions and lower catalytic loadings than the alkoxyacylation reaction. However, no further optimizations were performed, as, at this stage, we decided to pass to the study of the domino process.

### c) Optimization

#### i. Preliminary results

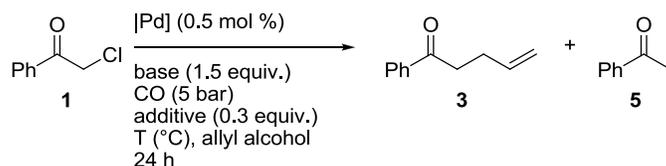
Having in our hands appropriate reaction conditions allowing the decarboxylative allylation, the next task was to merge the reaction conditions of the two protocols so as to accomplish the target domino reaction. With this in mind, we submitted  $\alpha$ -chloroacetophenone to a Pd catalyst system, in the presence of a base, CO (5 bar) and allyl alcohol (Table 5).

Unfortunately, using PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> and DMAN as base at 100 °C, under 5 bar of carbon monoxide, only acetophenone was obtained (entry 1). Increasing the temperature to 130 °C the desired ketone was obtained in 11% yield (entry 2).

Modification of the Pd/ligand catalytic system allowed improving the yield to 20% (Table 5, entries 3-7), Pd(OAc)<sub>2</sub>/PPh<sub>3</sub> being the best combination (entry 5). On the other hand, inorganic bases (entries 9-11) and the Hünig's base (entry 8) gave deceiving results.

Finally, we tried the reaction in a mixture of methanol and allyl alcohol (1/1) and in the presence of DMAN and DMAP. These conditions were tested in the hope of obtaining first a methoxycarbonylation followed by an *in situ* transesterification, and final decarboxylative allylation. However, under these conditions, only 3% of the desired product was isolated (Table 5, entry 12).

Table 5



| Entry | Catalyst   | Base                           | additive | T (°C) | Products | Yields (%) <sup>a</sup> |
|-------|--|--------------------------------|----------|--------|----------|-------------------------|
| 1     | PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>     | DMAN <sup>b</sup>              | -        | 100    | <b>5</b> | 100                     |
| 2     | PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>     | DMAN <sup>b</sup>              | -        | 130    | <b>3</b> | 11                      |
| 3     | PdCl <sub>2</sub> dppf                                 | DMAN <sup>b</sup>              | -        | 130    | <b>3</b> | 19                      |
| 4     | Pd(dba) <sub>2</sub> + 4 PPh <sub>3</sub>              | DMAN <sup>b</sup>              | -        | 130    | <b>3</b> | 6                       |
| 5     | Pd(OAc) <sub>2</sub> + 4 PPh <sub>3</sub>              | DMAN <sup>b</sup>              | -        | 130    | <b>3</b> | 20                      |
| 6     | Pd(OAc) <sub>2</sub> + dppb                            | DMAN <sup>b</sup>              | -        | 130    | <b>3</b> | 12                      |
| 7     | Pd(OAc) <sub>2</sub> + dppf                            | DMAN <sup>b</sup>              | -        | 130    | <b>3</b> | 1                       |
| 8     | Pd(OAc) <sub>2</sub> + 4 PPh <sub>3</sub>              | <i>i</i> -Pr <sub>2</sub> NEt  | -        | 130    | <b>3</b> | 8                       |
| 9     | Pd(OAc) <sub>2</sub> + 4 PPh <sub>3</sub>              | NaOAc                          | -        | 130    | <b>3</b> | 7                       |
| 10    | Pd(OAc) <sub>2</sub> + 4 PPh <sub>3</sub>              | K <sub>2</sub> CO <sub>3</sub> | -        | 130    | <b>3</b> | 8                       |
| 11    | Pd(OAc) <sub>2</sub> + 4 PPh <sub>3</sub>              | K <sub>3</sub> PO <sub>4</sub> | -        | 130    | <b>3</b> | 4                       |
| 12    | Pd(OAc) <sub>2</sub> + 4 PPh <sub>3</sub> <sup>c</sup> | DMAN <sup>b</sup>              | DMAP     | 130    | <b>3</b> | 3                       |

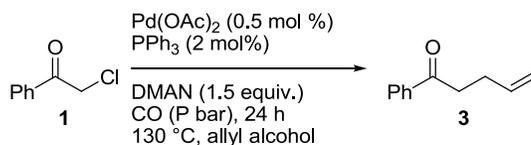
<sup>a</sup> isolated yields. The major side product is acetophenone. <sup>b</sup> 1,8 bis(dimethylamino)naphthalene. <sup>c</sup> methanol/allyl alcohol (1/1) used as solvent.

In this optimization, the major side product was the acetophenone and no trace of the intermediate  $\beta$ -ketoester **2** was ever observed. The most difficult step seems to be the allyloxypalladation (Scheme 91). Accordingly, we decided to use a higher pressure of carbon monoxide.

## ii. Pressure

The purchase of a high pressure relief valve allowed us to undertake a study of CO pressure on the reaction under study (Table 6).

Table 6



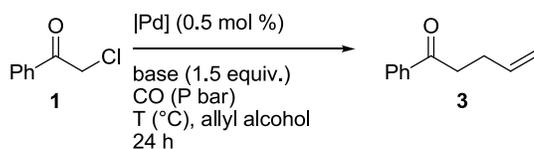
|                         |    |    |    |    |    |    |    |    |
|-------------------------|----|----|----|----|----|----|----|----|
| P (bar)                 | 5  | 10 | 15 | 20 | 25 | 30 | 50 | 80 |
| yields (%) <sup>a</sup> | 20 | 7  | 12 | 27 | 18 | 14 | 18 | 0  |

<sup>a</sup> isolated yields.

Beletskaya observed a clean parabolic curve with an apex in the range of 10 to 20 bar. Indeed, as CO coordination on a metal is a reversible process, it is conceivable that a certain CO pressure is needed to speed up its insertion with respect to other competing steps; yet, an exaggerated CO pressure can reversibly generate CO-saturated inactive complexes, lying outside the catalytic cycle. Accordingly, a precise CO pressure window may be the ideal compromise to maximize efficiency of the process. In our case, the best yield was also achieved with 20 bar of carbon monoxide, although our curve is not parabolic. This fact suggests a problem of reproducibility in our work. To fix this issue, another optimization of reaction conditions (base, ligand, temperature...) was undertaken under different CO pressures (Table 7). Whatever the catalyst or the ligand used, at 130°C and 20 bar of carbon monoxide the yield did not improve. Moreover, the best ratio phosphine/palladium seems

to be 4/1 (Table 7, entries 1-4). Decreasing the temperature to 50 °C at 20 bar CO, or using 10 bar of CO at 50°C resulted in recovered starting material (Table 7, entry 7).

**Table 7**



| Entry | Catalyst   | Base              | T (°C) | P (bar) | Yields (%) <sup>a</sup> |
|-------|--|-------------------|--------|---------|-------------------------|
| 1     | Pd(OAc) <sub>2</sub> + 4 PPh <sub>3</sub>          | DMAN <sup>b</sup> | 130    | 20      | 27                      |
| 2     | Pd(OAc) <sub>2</sub> + 5 PPh <sub>3</sub>          | DMAN <sup>b</sup> | 130    | 20      | 20                      |
| 3     | Pd(OAc) <sub>2</sub> + 3 PPh <sub>3</sub>          | DMAN <sup>b</sup> | 130    | 20      | 16                      |
| 4     | Pd(OAc) <sub>2</sub> + 2.5 PPh <sub>3</sub>        | DMAN <sup>b</sup> | 130    | 20      | 10                      |
| 5     | Pd(OAc) <sub>2</sub> + 4 PPh <sub>3</sub>          | DMAN <sup>b</sup> | 50     | 20      | 2 <sup>c</sup>          |
| 6     | Pd(OAc) <sub>2</sub> + 4 PPh <sub>3</sub>          | DMAN <sup>b</sup> | 90     | 50      | 0                       |
| 7     | Pd(OAc) <sub>2</sub> + 4 PPh <sub>3</sub>          | DMAN <sup>b</sup> | 50     | 10      | 0 <sup>c</sup>          |
| 8     | PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> | DMAN <sup>b</sup> | 130    | 20      | 10                      |
| 9     | Pd(OAc) <sub>2</sub> + dppf                        | DMAN <sup>b</sup> | 130    | 20      | 2                       |
| 10    | Pd(acac) <sub>2</sub> + 4 PPh <sub>3</sub>         | DMAN <sup>b</sup> | 130    | 20      | 15                      |
| 11    | Pd(OAc) <sub>2</sub> + BINAP                       | DMAN <sup>b</sup> | 130    | 20      | 16                      |
| 12    | Pd(OAc) <sub>2</sub> + 4 PPh <sub>3</sub>          | <i>t</i> -BuOK    | 130    | 20      | 0                       |

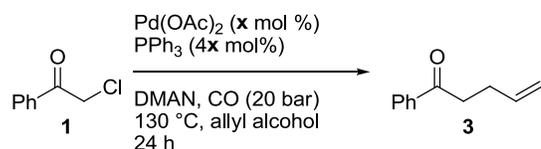
<sup>a</sup> isolated yields. Unless noted otherwise the major side product is acetophenone. <sup>b</sup> 1,8 bis(dimethylamino)naphtalene. <sup>c</sup> starting material was recovered at the end of the reaction.

Still in quest of reproducible results, we decided to focus on catalyst loading.

### iii. Catalyst loading

The catalyst loading parameter appeared to be crucial (Table 8). Indeed, although a tenfold increase of the catalyst loading did not improve the yield, a further twofold boosted the yield to 52%. Further variations were then undertaken.

**Table 8**



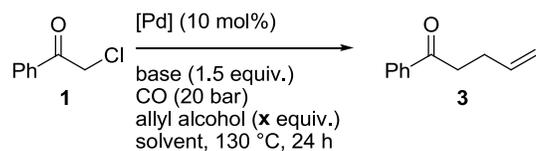
|                         |     |    |                    |
|-------------------------|-----|----|--------------------|
| $x$ (mol %)             | 0.5 | 5  | 10                 |
| Yields <sup>a</sup> (%) | 27  | 25 | 49/52 <sup>b</sup> |

<sup>a</sup> Isolated yields. <sup>b</sup> Second run in the same conditions.

#### iv. Used of a co-solvent and influence of the base

Almost all the carbonylation reactions reported in the literature used the alcohol as solvent. For cheap alcohols like methanol, ethanol or even allyl alcohol, this is not an issue. However, this is not the case for more expensive alcohols. Accordingly, we decided to minimize the amount of allyl alcohol (Table 9). Indeed, in the previous optimization, allyl alcohol was used as solvent (37 equivalents). We first reduced this amount to 15 equivalents using different co-solvents, in the presence of various palladium sources and bases, under CO at 20 bar.

Table 9



| Entry | [Pd]  | Base                        | x equiv. | Solvent     | Yields (%) <sup>a</sup> |
|-------|---|-----------------------------|----------|-------------|-------------------------|
| 1     | Pd(OAc) <sub>2</sub> + 4 PPh <sub>3</sub>                               | DMAN <sup>b</sup>           | 37       | -           | 52                      |
| 2     | Pd(OAc) <sub>2</sub> + 4 PPh <sub>3</sub>                               | DMAN <sup>b</sup>           | 15       | Toluene     | 57                      |
| 3     | Pd(OAc) <sub>2</sub> + 4 PPh <sub>3</sub>                               | DMAN <sup>b</sup>           | 15       | cyclohexane | 54                      |
| 4     | Pd(OAc) <sub>2</sub> + 4 PPh <sub>3</sub>                               | DMAN <sup>b</sup>           | 15       | THF         | 39                      |
| 5     | Pd(OAc) <sub>2</sub> + 4 PPh <sub>3</sub>                               | DMAN <sup>b</sup>           | 15       | DMF         | 3                       |
| 6     | Pd(OAc) <sub>2</sub> + 4 PPh <sub>3</sub>                               | DMAN <sup>b</sup>           | 6        | Toluene     | 5                       |
| 7     | Pd(OAc) <sub>2</sub> + 4 PPh <sub>3</sub>                               | DMAN <sup>b</sup>           | 2        | Toluene     | 8                       |
| 8     | Pd(acac) <sub>2</sub> + 4 PPh <sub>3</sub>                              | DMAN <sup>b</sup>           | 15       | Toluene     | 52                      |
| 9     | Pd(PPh <sub>3</sub> ) <sub>4</sub>                                      | DMAN <sup>b</sup>           | 15       | Toluene     | 57                      |
| 10    | PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> + 2 PPh <sub>3</sub> | DMAN <sup>b</sup>           | 15       | Toluene     | 53                      |
| 11    | PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>                      | DMAN <sup>b</sup>           | 15       | Toluene     | 20                      |
| 12    | Pd(OAc) <sub>2</sub> + 4 PPh <sub>3</sub>                               | Et <sub>3</sub> N           | 15       | Toluene     | 29                      |
| 13    | Pd(OAc) <sub>2</sub> + 4 PPh <sub>3</sub>                               | <i>n</i> -Bu <sub>3</sub> N | 15       | Toluene     | 54                      |

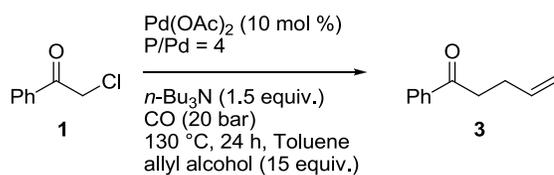
<sup>a</sup> Isolated yields. <sup>b</sup> 1,8 bis(dimethylamino)naphthalene.

The results showed that non polar solvents, like toluene and cyclohexane, were the best co-solvents for the reaction, yielding 57 and 54% of the desired product (Table 9 entries 2 and 3), compared to polar solvent, like THF and DMF, affording only 39 and 3% of the monoallylated ketone **3** (entries 4 and 5). Then, when we tried to reduce the amount of alcohol to 6 and 2 equivalents the yields dropped to 6 and 8%, respectively (entries 6 and 7). Test of different catalytic systems showed that the nature of the starting Pd complexes is of little importance (compare entry 2 with entries 8-10), and, as we saw previously, a 4/1 phosphine/palladium ratio gave the best results (entries 10 and 11). Finally, among the bases

tested, tri-*n*-butylamine gave results similar to DMAN (compare entries 2 and 13). For the ease of work-up and purification, tri-*n*-butylamine was chosen for the rest of the optimization.

#### v. Screening of ligands

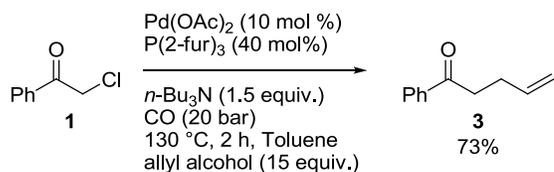
The effect of the ligand was then investigated (Table 10). This study showed that  $\pi$ -acidic ligands gave the best results. Indeed, electron rich phosphines (entries 1-5) led to no reaction or poor yields. Phosphines with no clear electronic (donating or withdrawing) effects furnished average yields (entries 6 to 8), while the  $\pi$ -acidic trifurylphosphine gave good results (entry 9). However, this trend is limited, as a highly  $\pi$ -acidic phosphite yielded only 13% yield (entry 10). XantPhos was the only bidentate ligand tried in this optimization that led to a good result (entry 11). In conclusion, trifurylphosphine appeared to be the best ligand for this domino sequence, leading to 76% of the desired product.

**Table 10**

| Entry | L                            | Yields (%) <sup>a</sup> |
|-------|------------------------------|-------------------------|
| 1     | $\text{P}(t\text{-Bu})_3$    | 0                       |
| 2     | dppf                         | 0                       |
| 3     | Bis sulfoxide <sup>b</sup>   | 0                       |
| 4     | $\text{PCy}_3$               | 13                      |
| 5     | X-Phos                       | 25                      |
| 6     | $\text{PPh}_3$               | 54                      |
| 7     | $\text{PPh}_2\text{fur}$     | 50                      |
| 8     | $\text{PPh}(2\text{-fur})_2$ | 65                      |
| 9     | $\text{P}(\text{fur})_3$     | 76                      |
| 10    | $\text{P}(\text{OEt})_3$     | 13                      |
| 11    | Xantphos                     | 56                      |

<sup>a</sup> Isolated yields. <sup>b</sup> 1,2-bis(phenylsulfinyl)ethane.

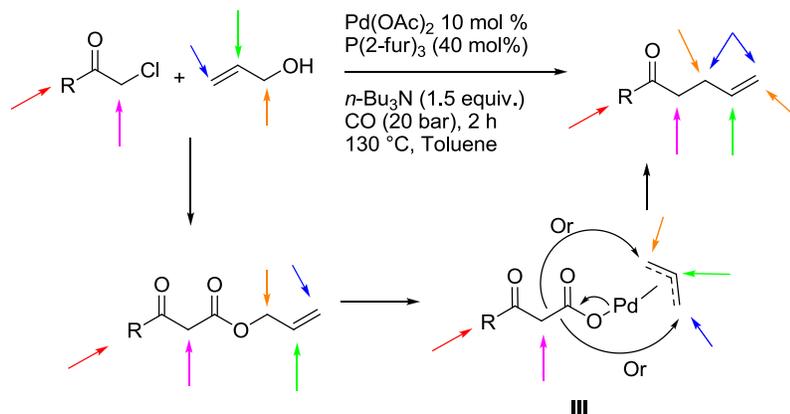
Finally, the optimized conditions were tested with a reaction time of 2 h, obtaining a similar yield of 73% (Scheme 94).

**Scheme 94: Optimized reaction conditions of the domino sequence**

With these optimized conditions, the scope of the reaction was then studied.

#### d) Scope and limitation of the pseudo-domino sequence

Of course, different positions of the chloroketone and the allylic alcohol can be functionalized. Furthermore, with allylic alcohols different from the parent allyl alcohol, the allylation step can show different regioselectivities (Scheme 95).



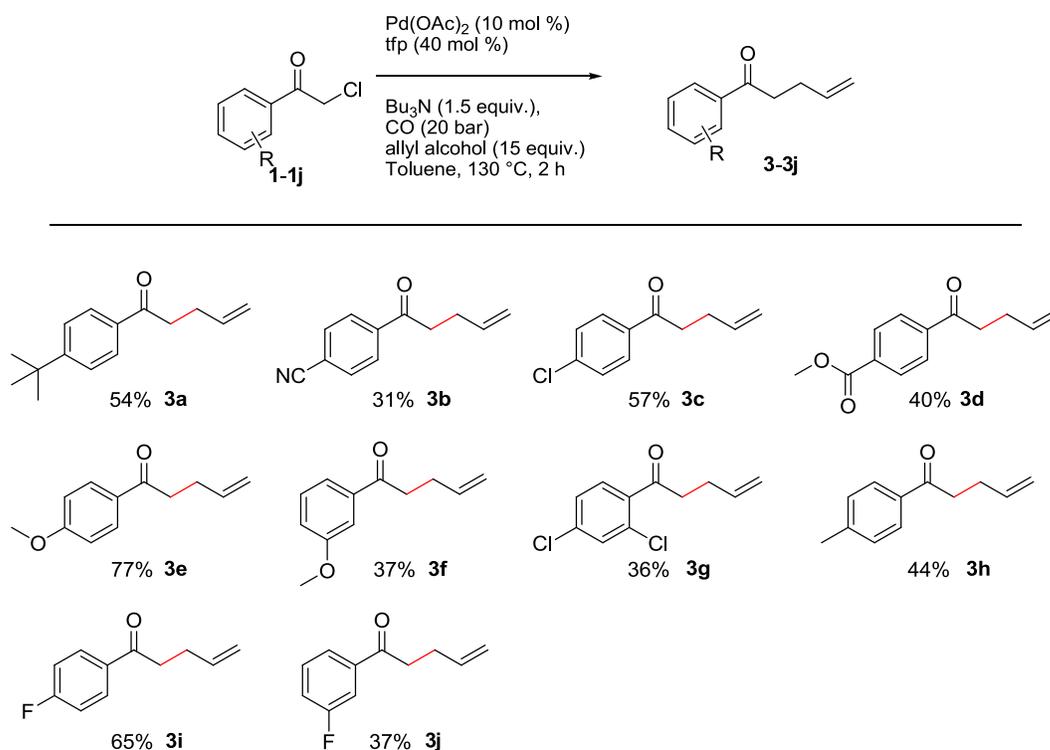
Scheme 95: Selectivity issue for substituted allyl alcohol

Previous studies showed that this type of Pd-catalyzed allylation takes place mostly at the less hindered terminus of the allyl system. In our study, we tested first differently substituted  $\alpha$ -chloroketones (Scheme 95), then, different allylic alcohols.

## i. Functionalization of $\alpha$ -chloroketones

### 1) Substitution on the aromatic ring

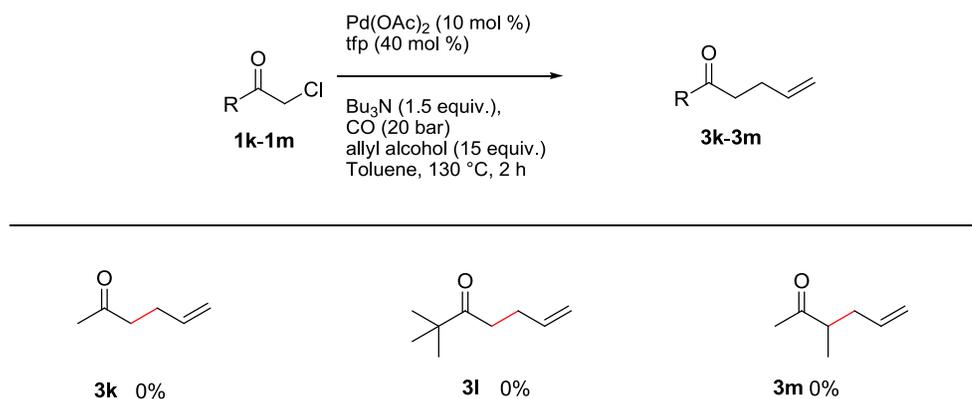
We started our study testing  $\alpha$ -chloroketones bearing differently substituted aromatic rings (Scheme 96).



Scheme 96: Substitution on the aromatic ring

Electron-donating and withdrawing groups in *para* position of the aromatic ring gave good yields, ranging from 31% for cyano substituent to 77% for methoxy substituent. However, *meta* substitution gave poorer results for both electron-donating and withdrawing substituents. Indeed, a yield of 37% was obtained for methoxy and fluoro substituent in *meta* position. Finally, a chlorine atom in *ortho* position gave the product with a lower yield (36%) compared to *para* substitution, likely due to a steric effect. For all the reactions, the only side product observed was the protodehalogenated ketone, resulting from hydrolysis of either enolate- **IV** of alkyl- **I** palladium intermediates (Scheme 91).

Aliphatic ketones were also tested (Scheme 97). However, due to their volatility, their isolation failed.

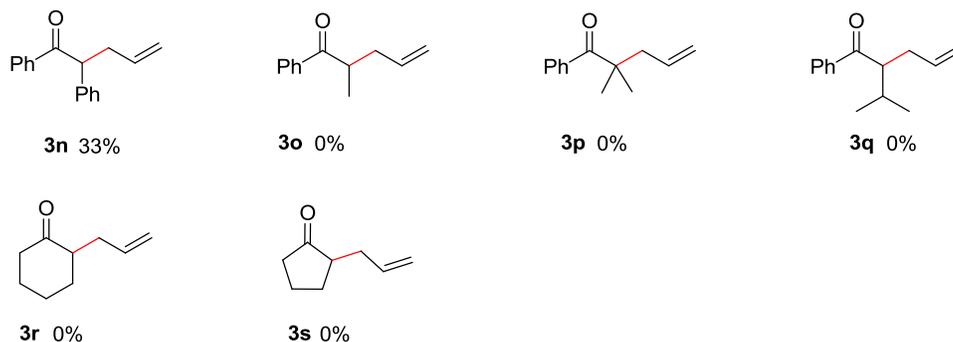
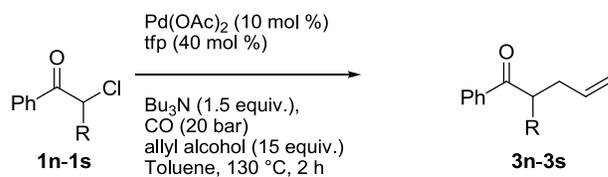


Scheme 97: Extension to aliphatic ketones

## 2) Substitution of the chloro ketone at the $\alpha$ -position

We next focused at the substitution of the  $\alpha$ -carbon. Although literature describes several examples wherein carbonylation wins over potential  $\beta$ -elimination, we were aware that, if the intermediate  $\sigma$ -alkylpalladium complex bears a  $\beta$ -hydrogen, dehydropalladation may seriously compete with the desired carbonylation path. Indeed, our domino process was successful only when no  $\beta$ -H atom was present, the other cases leading to either the protodehalogenated ketone and/or the corresponding  $\alpha,\beta$ -unsaturated ketone (Scheme 98). The formation of the latter product is in accord with the Saegusa reaction.<sup>152</sup>

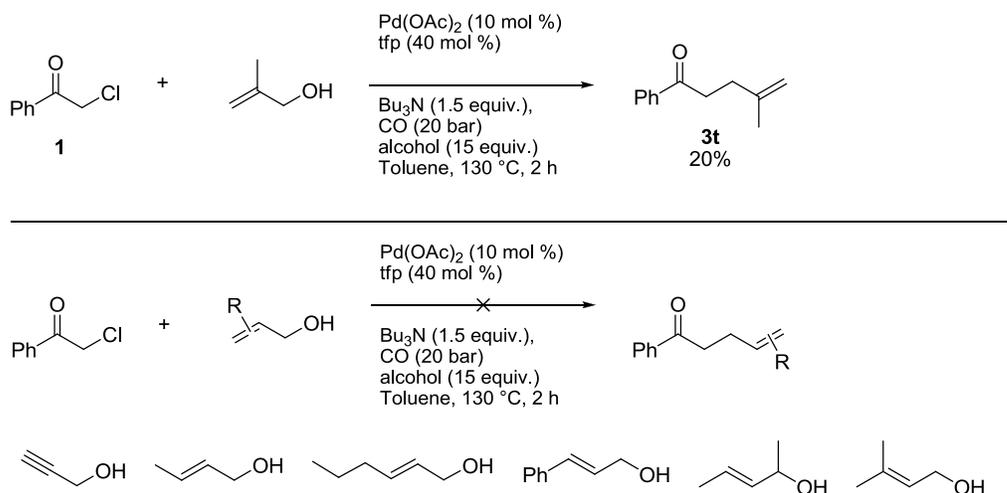
<sup>152</sup> Ito, Y.; Hirao T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011-1013.



**Scheme 98: Substitution on  $\alpha$  position**

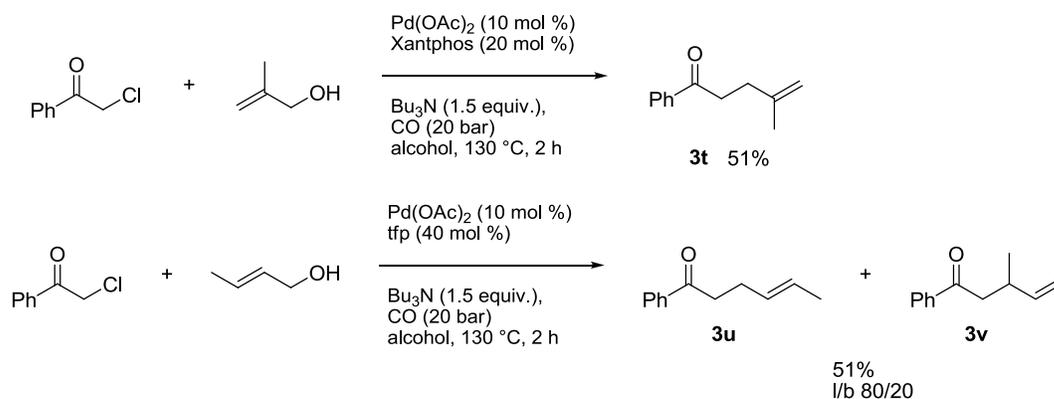
## ii. Substituted allylic alcohols

Various substituted allylic alcohols were tested in the above domino process. However, under the optimized conditions, we were never able to isolate the desired products, except in the case of 2-methylallyl alcohol, which yielded the expected product **3t** in 20% yield (Scheme 99).



**Scheme 99: Scope of various allyl alcohols**

In view of these deceiving results we decided to reoptimize the process, working again in pure alcohol. In the event, 2-methylallyl alcohol in the presence of Xantphos afforded the desired product **3t** in 51% yield, while crotyl alcohol in presence of trifurylphosphine, afforded the expected products **3u/3v** in 51% and a 80/20 linear/branched ratio (Scheme 100).



**Scheme 100: Optimized reaction condition for metallyl and crotyl alcohols**

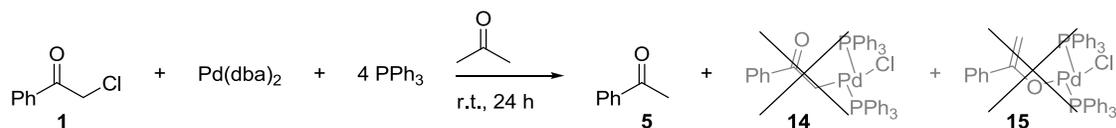
For all tested alcohols the only side product was acetophenone, resulting from the hydrolysis of either the enolpalladium **IV** or the alkylpalladium **I**. To corroborate this hypothesis, some kinetic and theoretical studies were realized.

### e) Mechanistic studies of the pseudo-domino sequence

#### i. Oxidative addition at room temperature

With the aim of obtaining relevant information on the minimal temperature required for the oxidative addition step to take place and the behavior of the supposedly formed  $\sigma$ -alkylpalladium complex, we reacted  $\alpha$ -chloroacetophenone with a stoichiometric amount of  $\text{Pd(dba)}_2$  complex and  $\text{PPh}_3$  in acetone at room temperature and in the absence of

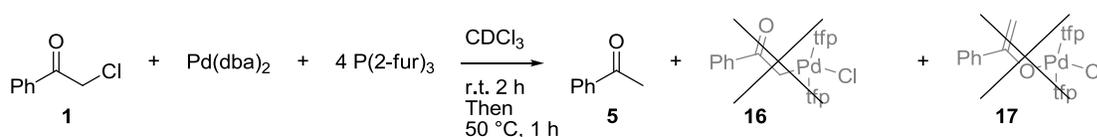
CO atmosphere (Scheme 101).<sup>153</sup> Such experiment afforded acetophenone, which suggests that: a) oxidative addition takes place at room temperature and b) the  $\sigma$ -alkylpalladium complex **37** and/or its corresponding enolate **38** are unstable and undergo immediate protonation with adventitious water generating acetophenone.



Scheme 101: Try to isolated alkyl **14** of enolated **15** of palladium

## ii. Kinetic studies

An analogous experiment (Scheme 102) was performed using  $P(2\text{-fur})_3$  as the ligand. The evolution of the mixture composition was monitored by  $^1\text{H}$  NMR (Figure 1).



Scheme 102: Conditions for the kinetic study

Such kinetic analysis showed the progressive formation of acetophenone since the beginning of the reaction. The amount of acetophenone increases continuously, at room temperature, and so does it significantly when the temperature is raised to 50 °C (Figure 1). Unfortunately, intermediates **16** and **17** were too unstable and underwent immediate decomposition, generating acetophenone **5**.

<sup>153</sup> a) Suzuki, K.; Yamamoto, H. *Inorg. Chim. Acta*, **1993**, *208*, 225–229. b) Veya, P.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, C. *Organometallics* **1993**, *12*, 4899–4907.

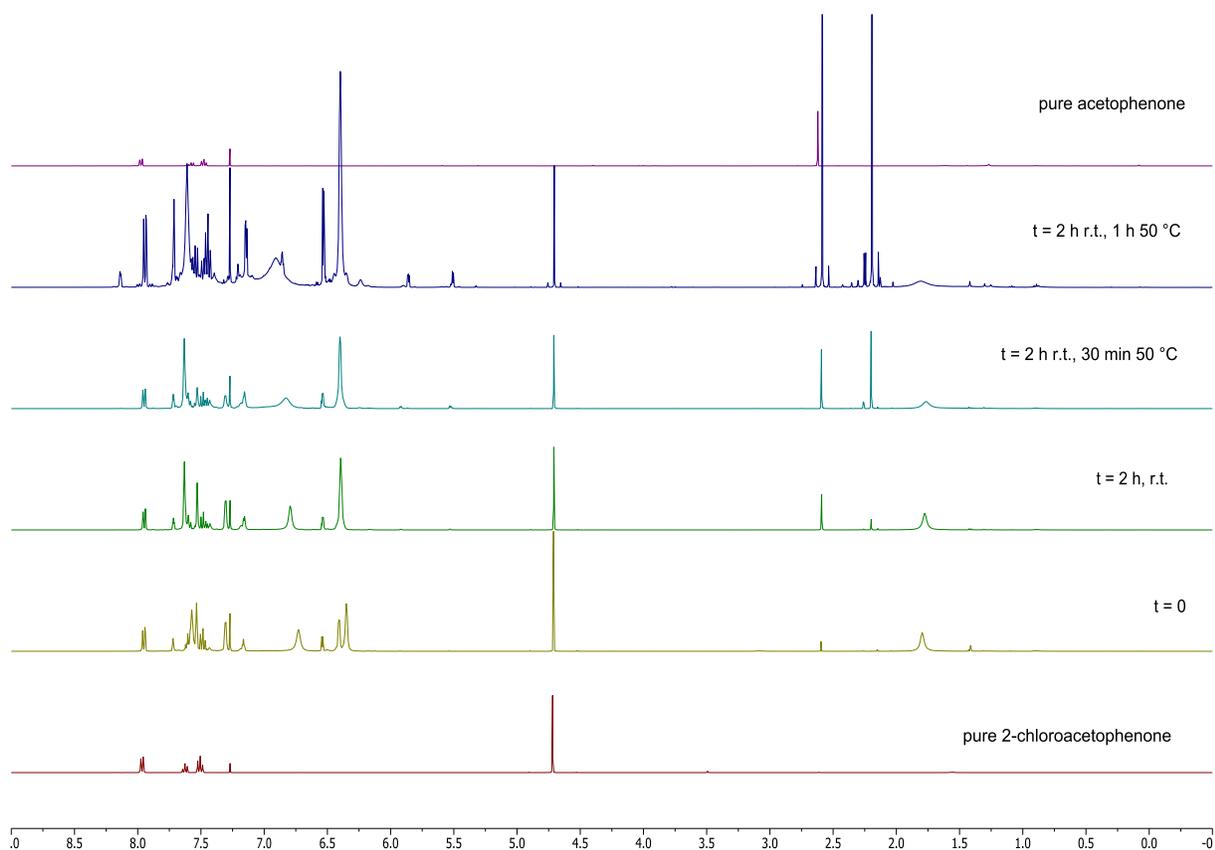


Figure 1:  $^1\text{H}$  NMR kinetic study

At room temperature, only acetophenone could be observed. However, after 30 min at 50 °C, a second singlet appears at 2.19 ppm, which seems to belong neither to the desired complex **16** (in this case the  $\alpha$ -located  $\text{CH}_2$  should be seen as a triplet, due to  $J_{\text{HP}}$  coupling), nor to complex **17**, which should display vinylic hydrogen atoms.

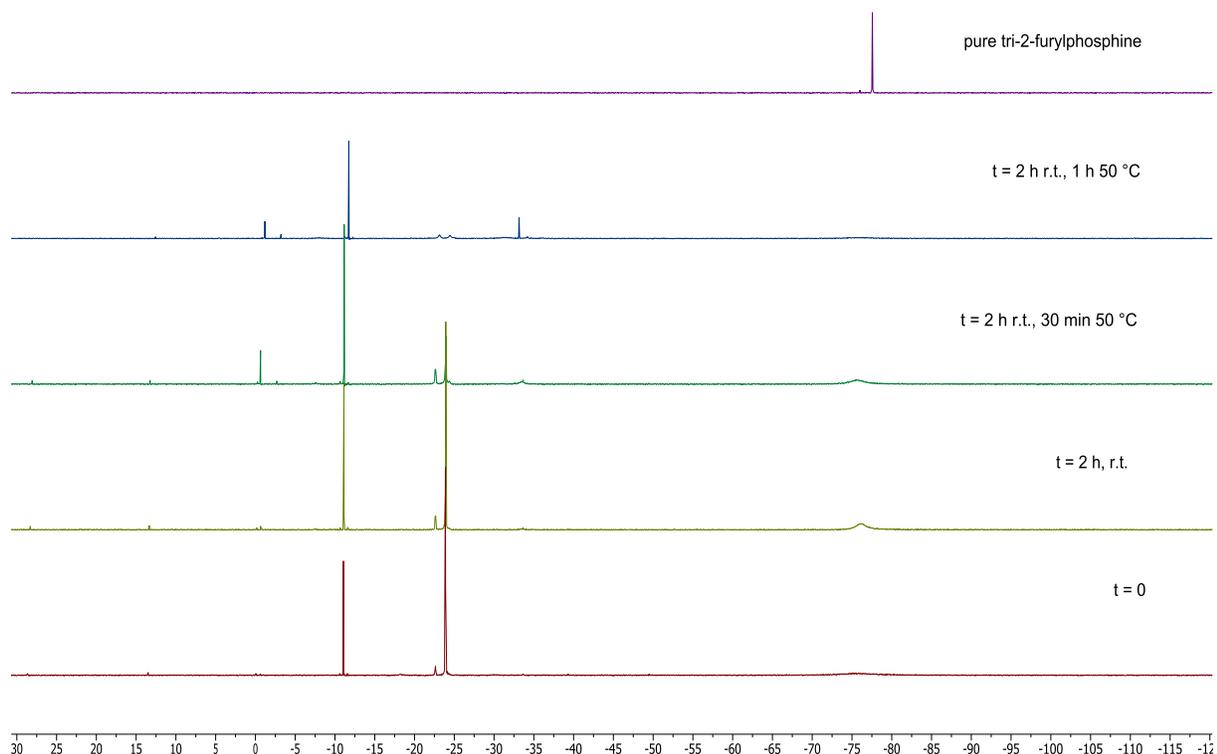
$^{31}\text{P}$ -NMR experiments were also conducted at the same time (Figure 2). Jutand studied the formation of Pd(0) complexes from tri-2-furylphosphine by  $^{31}\text{P}$  NMR. Their subsequent reactivity in oxidative addition of iodobenzene was studied.<sup>154</sup> She observed complex  $\text{Pd}(0)(\text{P}(2\text{-fur})_3)_3$  generated from  $\text{Pd}(\text{dba})_2$  after addition of excess  $\text{P}(2\text{-fur})_3$ , which was characterized as a broad signal at -66.6 ppm, due to the equilibrium between  $\text{Pd}(0)(\text{P}(2\text{-}$

<sup>154</sup> a) Amatore, C.; Jutand, A.; Khalil, F. *Arkivoc*, **2006**, iv, 38-48. b) Amatore, C.; Jutand, A.; Meyer, G.; Atmani, H.; Khalil, F.; Chahdi, F. O. *Organometallics* **1998**, 17, 2958–2964.

fur)<sub>3</sub>)<sub>3</sub>, Pd(0)(P(2-fur)<sub>3</sub>)<sub>2</sub>, and P(2-fur)<sub>3</sub>. The *trans*-PhPd(OAc)(P(2-fur)<sub>3</sub>)<sub>2</sub> generated after oxidative addition is characterized by a singlet at -23.6 ppm. In our experiment, at t=0, 3 peaks could be observed at  $\delta = -11.7$ ,  $\delta = -23.9$  ppm and  $\delta = -75.0$  ppm. The signal at  $\delta = -11.7$  ppm was assigned to tri-2-furylphosphine oxide. The signal at  $\delta = -75.0$  ppm corresponds to free P(2-fur)<sub>3</sub>, whereas no signal corresponds to Pd(0)(P(2-fur)<sub>3</sub>)<sub>3</sub> complex.<sup>148a,155</sup> The signal observed at  $\delta = -23.9$  ppm does not seem to belong to the corresponding alkyl or palladium enolate complex of type **16** or **17**, because no traces of such complexes could be observed in <sup>1</sup>H NMR experiments. Similarly, at 50 °C, two other signals at  $\delta = -0.5$  and  $\delta = -33.2$  ppm were detected, but until now, we were unable to assign them to specific complexes. The tri-2-furylphosphine oxide ( $\delta = -11.7$  ppm) observed can be explained by phosphine oxidation upon storage.

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<sup>155</sup> a) Bertani, R.; Castellani, C. B.; Crociani, B. *J. Organomet. Chem.* **1984**, 269, C15–C18. b) Suzuki, K.; Yamamoto, H. *Inorg. Chim. Acta* **1993**, 208, 225–229.



**Figure 2:**  $^{31}\text{P}$  NMR kinetic study

Being unable to detect the presence of either alkyl or palladium enolate complexes by  $^1\text{H}$  and  $^{31}\text{P}$  NMR, we decided to undertake a computational study. In this context, I had the opportunity to attend at the Ph.D. course "*Molecular Modelling for Experimental Chemists*", a two-week intensive course (from 28/02/2010 to 12/03/2010), given by Professor Per-Ola Norrby at the University of Gothenburg. In this occasion, I learned rudiments of modeling and had the opportunity to start a computational study of the reaction under investigation, then pursued in Paris.

### iii. Study of the C-Pd / O-Pd equilibrium

DFT computations (B3LYP base set LACVP\*\*, benzene solvation) of oxidative addition of chloroacetophenone to  $[(2\text{-fur})_3\text{P}]_2\text{Pd}(0)$ , followed by CO coordination and insertion gave the following results in terms of total free energies (Figure 3).

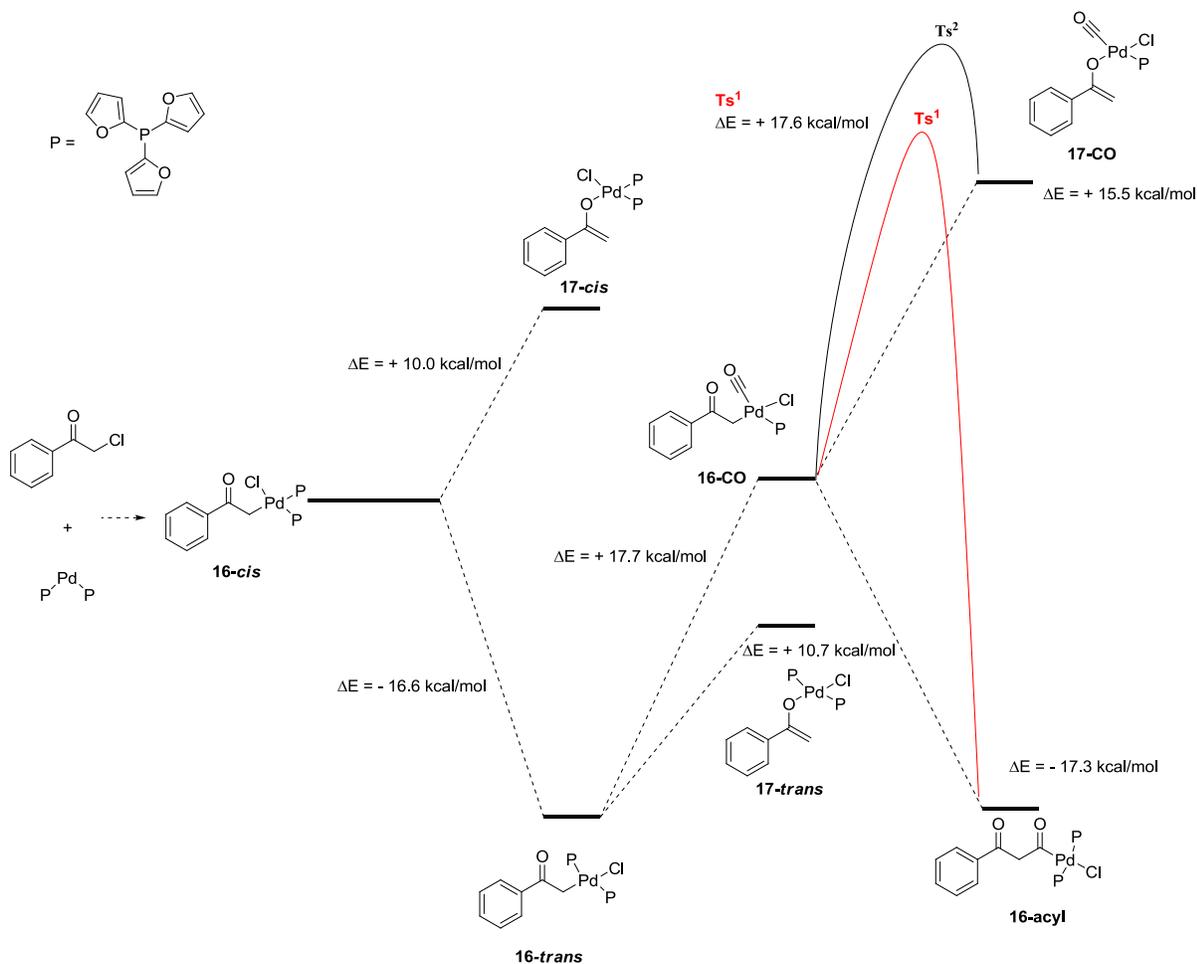


Figure 3: DFT calculation

First of all, the total free energies show that a given C-Pd complex is always more stable than its corresponding O-Pd analogue. Moreover, the transition state **Ts<sup>1</sup>** corresponding to the migratory insertion of carbon monoxide could be located, allowing to calculate the activation barrier. An Activation barrier of 17.6 kcal/mol from **16-CO** to **16-acyl** was calculated for this transformation. To rule out the involvement of palladium enolate in the course of the reaction, further calculations have to be undertaken. First, the transition

state between all alkylpalladium **16** and their corresponding enolate **17**, and calculations concerning the hydrolysis step for both  $\beta$ -oxopalladium and the corresponding palladium enolate. Final nucleophilic trapping by alcohol also needs to be computationally studied. However, Figure 3 clearly shows that the **Ts**<sup>1</sup> is much less stable than the alkyl **16-trans** and the enolate **17-trans**, and the formation of the acetophenone by-product is much likely to come from one of those complexes. Unfortunately, it is not possible to theoretically study the influence of the CO pressure, although it may be an important factor.

#### f) **Conclusion and perspectives**

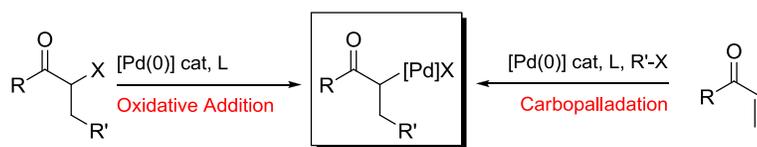
A new Pd-catalyzed domino carbonylative-decarboxylative allylation was developed, which allowed the synthesis of  $\gamma,\delta$ -unsaturated ketones from readily available  $\alpha$ -chloroacetophenones. The key of the success of this domino sequence was the use of relatively high catalyst loading and 20 bar CO. Various aromatic mono-allylated ketones were synthesized in a single step, in moderate to good yields. However, the reaction suffers some limitations. Indeed,  $\alpha$ -substituted ketones bearing  $\beta$ -hydrogen atoms and substituted allyl alcohols gave low yields, if any. Moreover, the conditions had to be re-optimized for each alcohol tested. The only side products of the reactions were the protodehalogenated carbonyl, and, when a  $\beta$ -hydrogen atoms are present, the  $\alpha,\beta$ -unsaturated ketone.

Preliminary studies to isolate the intermediate complexes involved in the process and to calculate their energies have been initiated. Although further investigations will be needed to achieve a satisfactory knowledge of this domino transformation, the results obtained so far indicate that this strategy is synthetically practicable.

## CHAPTER V : Toward a new domino sequence

### a) Introduction

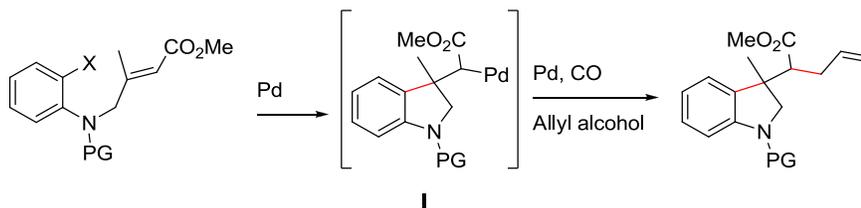
Aware of the limitations of the type I pseudo domino sequence developed in the previous chapter (Scheme 91), we turned our attention to a related carbonylative domino succession wherein the  $\sigma$ -alkyl palladium intermediate would be generated *via* a process other than an oxidative addition (Scheme 103, from left).



Scheme 103: Different way to form alkylpalladium intermediate

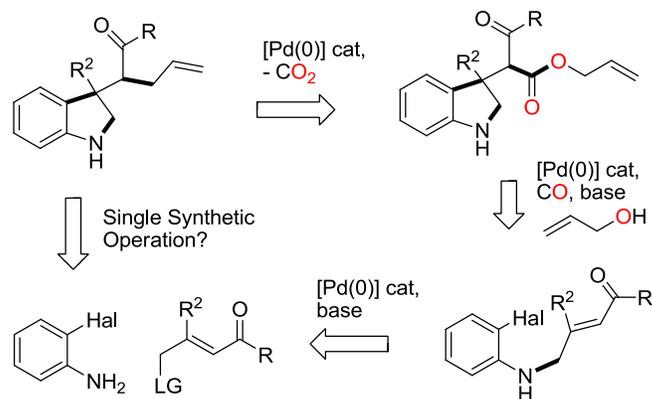
Our reasoning was based on the idea that generation of a similar  $\sigma$ -alkyl palladium intermediate *via* an alternative, possibly milder, path might have avoided the undesired side reactions observed above. After some reasonings, carbopalladation of an  $\alpha,\beta$ -unsaturated carbonyl derivative by an appropriate arylpalladium complex appeared to be a suitable and tempting solution (Scheme 103, from right).

In particular, we thought to carry out the carbopalladation on a  $\beta,\beta$ -disubstituted carbonyl substrate, so as to form a "living"<sup>113</sup> neopentyl  $\sigma$ -alkylpalladium complex of type I. Also, we decided to take profit of this modification to consider a rather appealing intramolecular carbopalladation, so as to end-up with an indoline palladium complex, which could evolve in a carbonylative way, as in the previously studied sequence (Scheme 104).



Scheme 104: General mechanism for the new domino sequence

The starting building block may in turn derive from an allylic substitution between an *o*-halo aniline derivative and a suitable allylic synthon, possibly Pd-catalyzed, too. Hence, one can globally draw the following domino retrosynthetic sequence (Scheme 105). This sequence would entail 3 consecutive mechanistically independent Pd-driven cycles, involving the global generation of 5 new bonds of which 3 are retained into the final product.



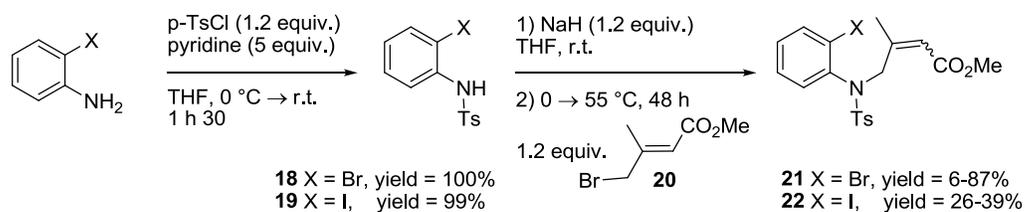
Scheme 105: Retrosynthetic sequence of the new domino sequence

Thus, starting from a simple *o*-halo aniline and an appropriate allylic synthon, a single synthetic operation would generate highly functionalized indolines *via* the concomitant formation of two C-C bonds. We thus engaged in the above synthetic challenge.

## b) Sequential study with incrementation of the domino sequence

### i. Synthesis of the cyclization precursor

To avoid the problem faced in the first domino reaction, we decided to study the sequence step by step. Accordingly, the required *N*-tosyl *o*-bromo- and *o*-iodoanilines **18** and **19** were first prepared by standard tosylation of the corresponding *o*-haloanilines in quantitative yield. Deprotonation of either the bromo or the iodo derivative with sodium hydride, followed by addition of methyl 4-bromo-3-methyl acrylate gave the expected allylic amine as an *E/Z* mixture in a non-reproducible yield for the bromo derivative **21** and a moderate yield for the iodo derivative **22** (Scheme 106).

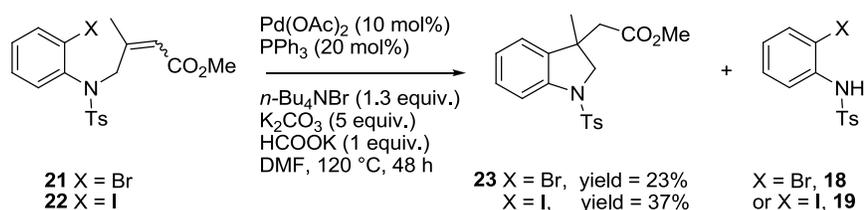


Scheme 106: Synthesis of the cyclisation precursor

Nevertheless, the desired aminoester was obtained in sufficient amount to allow the study of the 5-*exo-trig* cyclization.

## ii. Study of the cyclization, trapping with a hydride

With compounds **21** and **22** in hands, we decided to start the study of the Pd-catalyzed 5-*exo-trig* cyclization trapping intermediate **I** with potassium formate<sup>13c,156</sup> as the hydride source (Scheme 107).



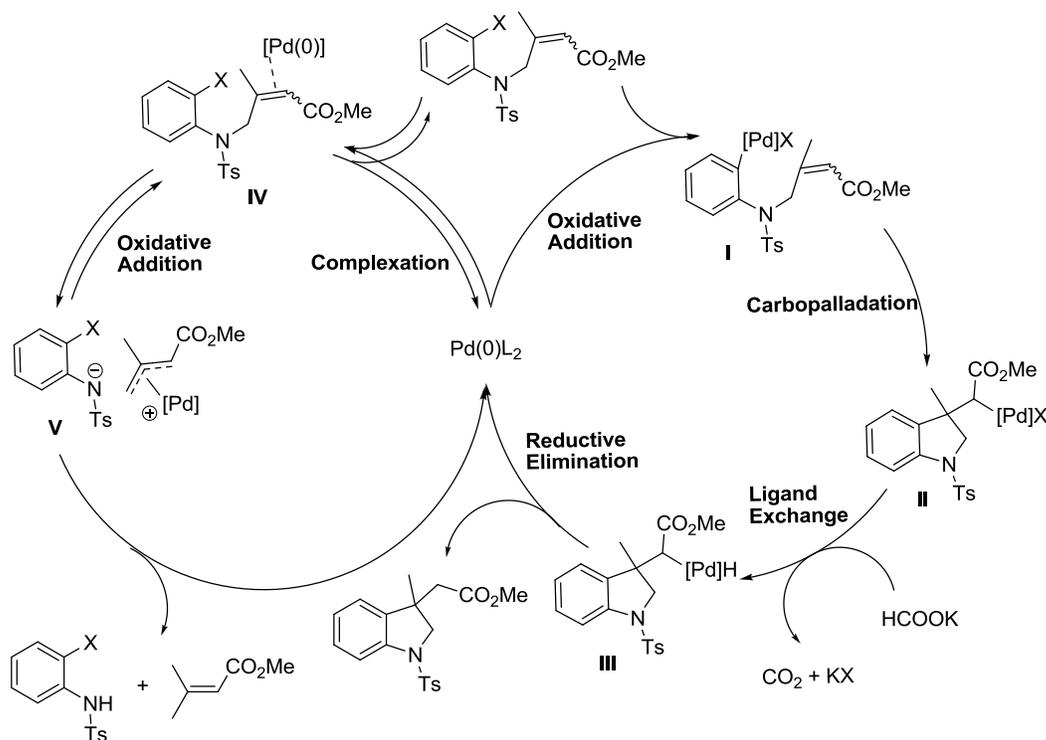
Scheme 107: Carbopalladation reaction

Each of the two substrates was treated with Pd(OAc)<sub>2</sub> (10 mol%), PPh<sub>3</sub> (20 mol%), K<sub>2</sub>CO<sub>3</sub> (5 equiv.) and HCOOK (1 equiv.), *n*-Bu<sub>4</sub>NBr (1.3 equiv.) in DMF at 120 °C for two days. While the bromide **21** gave the desired product in 23% yield, the corresponding iodide **22** gave a slightly improved 37% yield. Importantly, in both cases the cleaved bromide **18** or iodide **19** was detected to a great extent.

<sup>156</sup> a) Burns, B.; Grigg, R.; Sridharan, V.; Worakun, T. *Tetrahedron Lett.* **1988**, 29, 4325–4328. b) Grigg, R.; Loganathan, V.; Sukirthalingam, S.; Sridharan, V. *Tetrahedron Lett.* **1990**, 31, 6573–6576. c) Grigg, R.; Loganathan, V.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T. *Tetrahedron* **1996**, 52, 11479–11502.

The expected mechanism is described in Scheme 108. Oxidative addition of a Pd(0) complex to the C-X bond of the *o*-haloaniline would form intermediate I (Scheme 108). Then, 5-*exo-trig* cyclization on the alkene is expected to generate the indoline structure. Finally, ligand exchange by means of potassium formate followed by reductive elimination of the thus formed hydride would furnish the desired product together with regeneration of the Pd(0) complex.

Interestingly, the cleaved side products **18** and **19** would result from a Pd-catalyzed retro-allylation of the starting material, which would involve formation of the  $\pi$ -allyl complex V (Scheme 108). This result is not surprising, as the strong stabilization of the *N*-tosyl anilinium anion very likely favors reversibility of the *N*-allylation step.



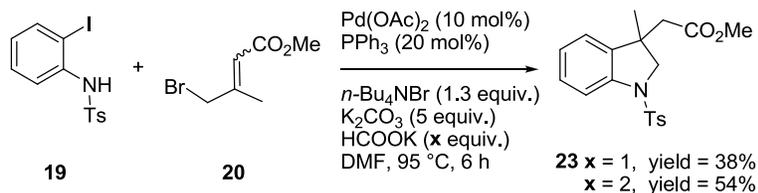
Scheme 108: Mechanism of the carbopalladation versus retro-allylation of aniline

The above result gave us confirmation that the whole process described retrosynthetically in Scheme 108 can, at least in principle, be run in a single synthetic operation as a type I triple pseudo-domino palladium-catalyzed sequence. In fact, independently of the position of the equilibrium of the allylation of the first catalytic cycle,

the subsequent carbopalladation / carbonylative / decarboxylative allylation is expected to irreversibly displace the equilibrium of the entire process toward the right side.

iii. **Toward a new pseudo-domino type I sequence: « N-allylation / carbopalladation / hydride trapping »**

Since the iodo derivative **22** gave a higher yield than the bromoaniline **21**, we decided to optimize the reaction conditions with the former substrate. Accordingly, iodoaniline **19** was treated with the bromoacrylate **20**, applying the same reaction conditions as used previously and using different amounts of potassium formate (Scheme 109).

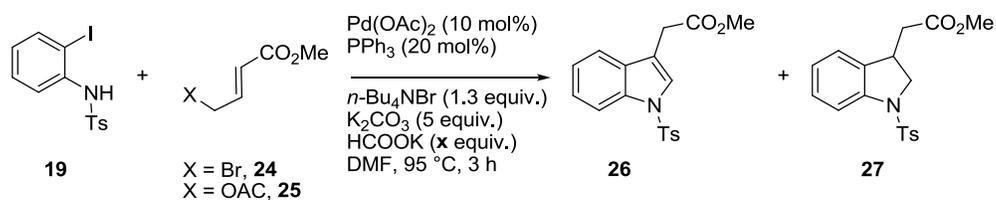


Scheme 109: N-allylation / carbopalladation reaction

In the event, when 1 equivalent of formate were used the reaction yielded the desired compound **23** in 38% yield, while increasing formate to 2 equivalents improved the yield to 54%.

The same protocol was also tested with the  $\beta$ -substituted bromo- and acetoxy-acrylates **24** and **25**, respectively. This variant was tested for comparison purposes, as in this latter case, the  $\sigma$ -alkylpalladium intermediate generated after ring closing carbopalladation is no longer "living" and can easily undergo  $\beta$ -hydride elimination (Table 11).

Table 11



| Entry | X   | HCOOK (x equiv.) | Yields (%) <sup>a</sup> |               |
|-------|-----|------------------|-------------------------|---------------|
|       |     |                  | <b>26</b> (%)           | <b>27</b> (%) |
| 1     | Br  | 0                | 57%                     |               |
| 2     | OAc | 0                | 35%                     |               |
| 3     | Br  | 2                | 40%                     | 33%           |
| 4     | Br  | 6                | 73%                     |               |

<sup>a</sup> isolated yields.

When iodoaniline **19** and acrylates **24** and **25** were engaged in the reaction in the absence of potassium formate, indole **26** was the only product isolated in 57% and 35% yields respectively (entries 1 and 2). Not unexpectedly, this compound results from  $\beta$ -hydride elimination followed by an aromatization-driven isomerization. However, when 2.0 equivalents of formate were introduced, a mixture of indole **26** and indoline **27** were isolated in 40% and 33% yields respectively (entry 3). Puzzlingly enough, when the amount of formate was increased to 6 equivalents to force the trapping of the intermediate **I**, exclusive formation of the indole compound **26** in 73% yield, was observed (entry 4).

This study showed that the new domino sequence allylation / carbopalladation / methoxycarbonylation using either  $\beta,\beta$ -disubstituted or  $\beta$ -substituted acrylates, was successful indeed, and afforded the desired indoline **23** and indole **26** heterocycles in acceptable yields. Not unexpectedly, when using the  $\beta$ -substituted acrylate,  $\beta$ -hydride elimination / aromatization competed with the desired hydride trapping / reductive

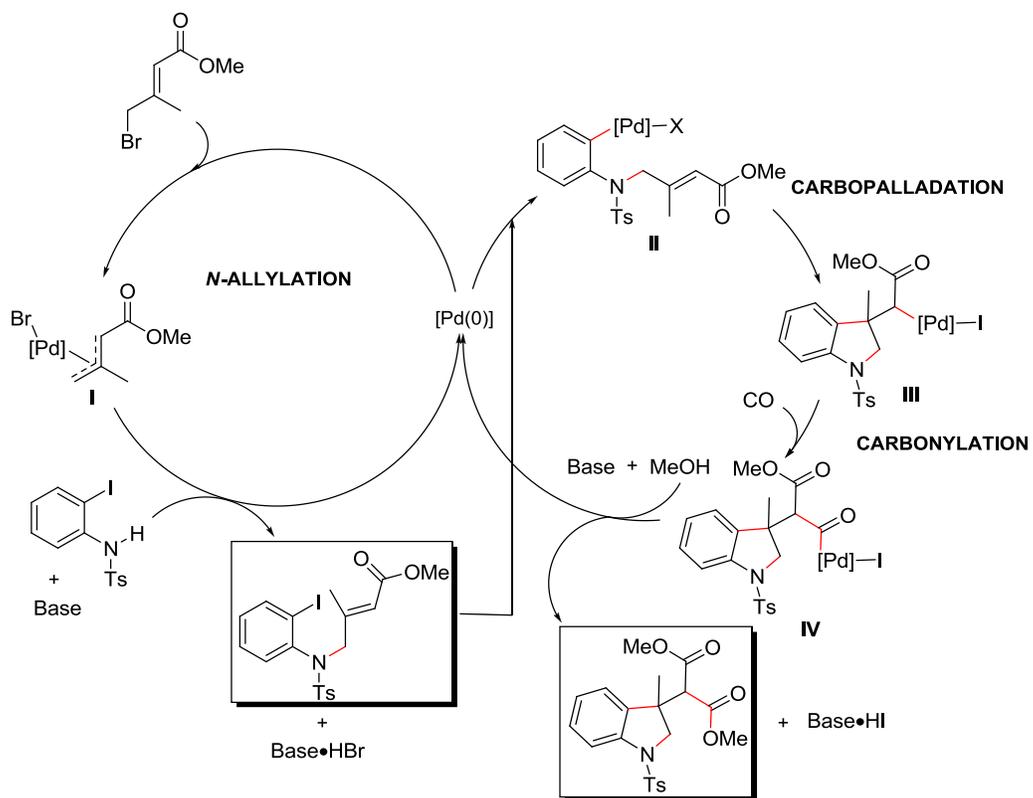
elimination path. With this promising result in hands, we turned our attention to the carbonylative version of this protocol (Scheme 108).

**iv. Toward a new triple pseudo-domino type I sequence: «N-allylation / carbopalladation / methoxycarbonylation»**

The subsequent step in the planned global domino sequence is the carbonylative trapping (Scheme 110). It is known from Grigg's work that neopentyl palladium intermediates are stable and can undergo migratory insertion under carbon monoxide atmospheric pressure. Accordingly, carbon monoxide and methanol was added to the reaction mixture instead of potassium formate. Moreover, to circumvent dehydropalladation problems, the  $\beta,\beta$ -disubstituted acrylate was tested first.

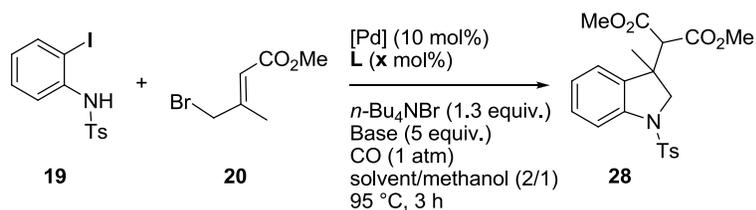
*1) With formation of a neopentyl palladium intermediate*

The *o*-iodo *N*-tosylaniline **19** was reacted with the trisubstituted acrylate **20**, in the presence of palladium complex, a ligand, *n*-Bu<sub>4</sub>NBr and K<sub>2</sub>CO<sub>3</sub> with methanol under an atmospheric pressure of carbon monoxide at 95 °C (Table 12).



Scheme 110: Mechanism of palladium catalyzed allylic amination / carbopalladation / carbonylation

Table 12



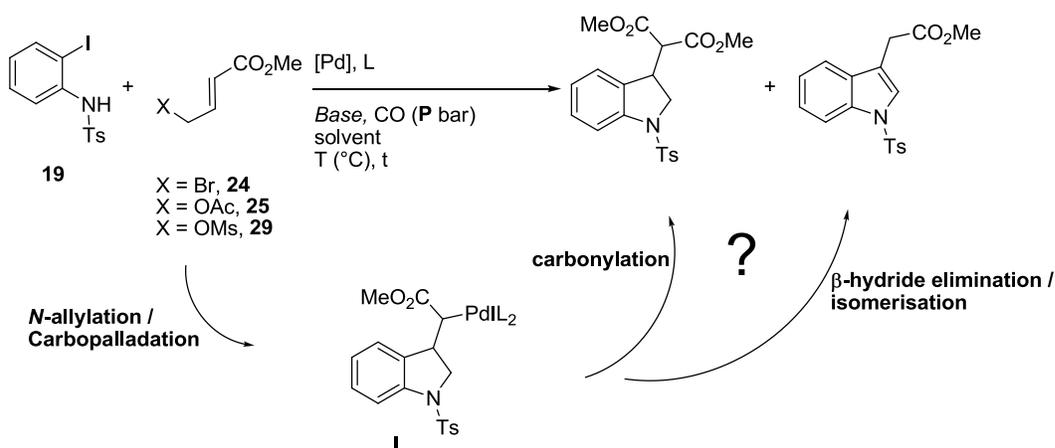
| Entry | [Pd]                               | Base                           | Solvent | Ligand (x mol%)                 | Yields (%) <sup>a</sup> |
|-------|------------------------------------|--------------------------------|---------|---------------------------------|-------------------------|
| 1     | Pd(OAc) <sub>2</sub>               | K <sub>2</sub> CO <sub>3</sub> | DMF     | PPh <sub>3</sub> (20 mol%)      | 14                      |
| 2     | Pd(PPh <sub>3</sub> ) <sub>4</sub> | K <sub>2</sub> CO <sub>3</sub> | DMF     | -                               | 33                      |
| 3     | Pd(PPh <sub>3</sub> ) <sub>4</sub> | K <sub>2</sub> CO <sub>3</sub> | Toluene | -                               | 34                      |
| 4     | Pd(PPh <sub>3</sub> ) <sub>4</sub> | Bu <sub>3</sub> N              | Toluene | -                               | 12                      |
| 5     | Pd(dba) <sub>2</sub>               | K <sub>2</sub> CO <sub>3</sub> | Toluene | PPh <sub>3</sub> (20 mol%)      | 17                      |
| 6     | Pd(dba) <sub>2</sub>               | K <sub>2</sub> CO <sub>3</sub> | Toluene | PPh <sub>3</sub> (40 mol%)      | 21                      |
| 7     | Pd(dba) <sub>2</sub>               | K <sub>2</sub> CO <sub>3</sub> | Toluene | P(2-fur) <sub>3</sub> (40 mol%) | 52                      |

<sup>a</sup> isolated yields.

The effect of the catalyst, the ligand, the solvent and the base were thus studied (Table 12). Use of the previously optimized reaction conditions gave the desired malonate **28** in 14% yield (entry 1). Switch to Pd(Ph<sub>3</sub>)<sub>4</sub> as Pd(0) source improved the yield up to 33% (entry 2). Toluene gave a result comparable to DMF (compare entries 2 and 3). Tri-*n*-butylamine, which was the best base in the previous domino sequence, did not lead to the desired product (entry 4). Pd(dba)<sub>2</sub>/PPh<sub>3</sub> was then tested as the palladium system, with ratios L/Pd of 2 and 4 with deceiving results (entries 5 and 6). Finally, the system Pd(dba)<sub>2</sub>, P(2-fur)<sub>3</sub> with L/Pd of 4 afforded an acceptable 52%. Satisfied by these good results, we next turned our attention to the β-substituted acrylate.

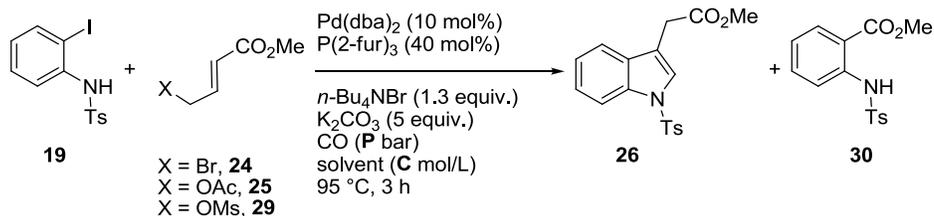
2) Study of the competition between the  $\beta$ -hydride elimination and carbonylation

Switch to the  $\beta$ -substituted acrylate implies generation of a  $\sigma$ -alkylpalladium intermediate **I** susceptible of undergoing easy  $\beta$ -hydride elimination (Scheme 111). The allylic bromide **24**, acetate **25** and mesylate **29** were prepared and tested in reactions with the aniline derivative **19** (Table 13).



Scheme 111: Carbonylation versus  $\beta$ -hydride elimination issue

Table 13



| Entry | X   | P (bar)        | Solvent      | C (mol/L) <sup>b</sup> | Yields (%) <sup>a</sup> |        |
|-------|-----|----------------|--------------|------------------------|-------------------------|--------|
|       |     |                |              |                        | 26 (%)                  | 30 (%) |
| 1     | Br  | 1              | Tol/MeOH 2/1 | 0.03                   | 74%                     | -      |
| 2     | OAc | 1              | Tol/MeOH 2/1 | 0.03                   | 46%                     | -      |
| 3     | OMs | 1              | Tol/MeOH 2/1 | 0.03                   | -                       | 9      |
| 4     | Br  | 5              | Tol/MeOH 2/1 | 0.03                   | -                       | 10     |
| 5     | OAc | 5              | Tol/MeOH 2/1 | 0.03                   | 53%                     | 17     |
| 6     | OMs | 5              | Tol/MeOH 2/1 | 0.03                   | 32%                     | 17     |
| 7     | Br  | 5              | Tol/MeOH 2/1 | 0.1                    | -                       | 17     |
| 8     | Br  | 5              | MeOH         | 0.1                    | -                       | 17     |
| 9     | Br  | 1 <sup>b</sup> | MeOH         | 0.1                    | -                       | 39     |

<sup>a</sup> Isolated yields. <sup>b</sup> in sealed tube. <sup>b</sup> Concentration of **19**.

When the bromide **24** and the acetate **25** were used, the product of allylation / carbopalladation / dehydropalladation / aromatizing isomerization **26** was the only compound isolated (entries 1-2). On the other hand, only a low yield of premature methoxycarbonylation of *o*-iodo *N*-tosyl aniline **30** was observed when using the allylic mesylate **29** (entry 3). The same product **30** was observed when using bromide **24** in the presence of 5 bar of CO at different dilutions (entries 4 and 7). Switching to the acetate or the mesylate, and keeping 5 bar of CO pressure, gave a mixture of the indoline **26** and the carbonylated aniline **30** (entries 5 and 6). Analogous results of premature methoxycarbonylation of the aniline were obtained when working in pure MeOH (entries 8 and 4), or running the reaction in a sealed tube (entry 9).

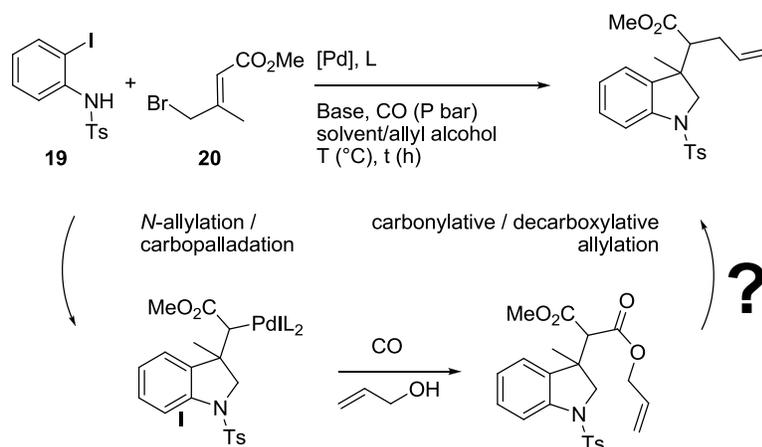
In conclusion, this study showed that the  $\beta$ -monosubstituted acrylates are not suitable compounds for the intended domino carbonylative sequence. Indeed, at variance with Grigg's results,  $\beta$ -hydride elimination revealed to be much faster than CO insertion. Moreover, and not unexpectedly, increase of CO pressure proportionally increased premature carbonylation of the aniline derivative.

Nonetheless, when the domino sequence was applied to the  $\beta,\beta$ -disubstituted acrylate **20** the desired malonate **28** was formed in good yield. Switch from methanol to allyl alcohol, so as to challenge the planned full domino sequence, was the next step.

#### v. Approaches toward the full pseudo-domino sequence

1) Toward the full sequence « *N*-allylation / carbopalladation / carbonylative / decarboxylative allylation »

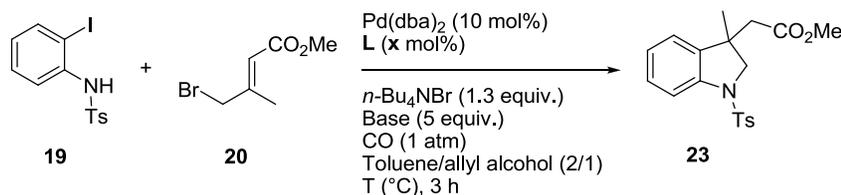
Analogously to the domino transformation studied in the previous chapter, switch from methanol to allyl alcohol, when using a  $\beta,\beta$ -disubstituted acrylate, is expected to set the stage for the full domino sequence involving carbonylative / decarboxylative allylation final steps (Scheme 112).



Scheme 112: General mechanism of the planned *N*-allylation / carbopalladation / allyloxycarbonylation / decarboxylative allylation

It has to be noted that in this case the final decarboxylative allylation is planned to take place on a malonate derivative, while in the majority of these reactions the starting substrate is normally a  $\beta$ -oxoester. The study of this sequence is summarized in Table 14.

**Table 14**



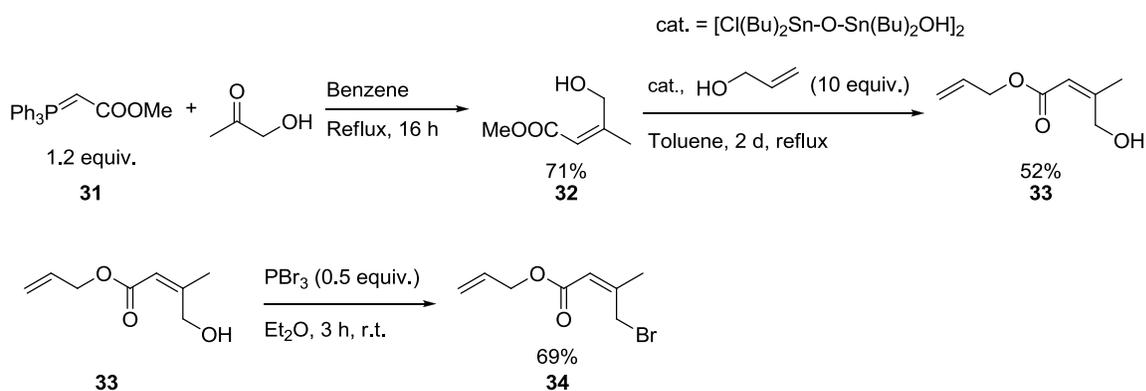
| Entry | Base                           | T (°C) | P (atm) | Ligand                | Yields of <b>23</b> (%) <sup>a</sup> |
|-------|--------------------------------|--------|---------|-----------------------|--------------------------------------|
| 1     | K <sub>2</sub> CO <sub>3</sub> | 95     | 1       | P(2-fur) <sub>3</sub> | 60%                                  |
| 2     | K <sub>2</sub> CO <sub>3</sub> | 130    | 1       | P(2-fur) <sub>3</sub> | 62%                                  |
| 3     | K <sub>2</sub> CO <sub>3</sub> | 130    | 10      | P(2-fur) <sub>3</sub> | 43%                                  |
| 4     | K <sub>2</sub> CO <sub>3</sub> | 130    | 15      | P(2-fur) <sub>3</sub> | 35%                                  |
| 5     | Bu <sub>3</sub> N              | 130    | 10      | P(2-fur) <sub>3</sub> | 29%                                  |
| 6     | Bu <sub>3</sub> N <sup>b</sup> | 130    | 10      | P(2-fur) <sub>3</sub> | 22%                                  |
| 7     | K <sub>2</sub> CO <sub>3</sub> | 130    | 10      | XantPhos              | degradation                          |

<sup>a</sup> Isolated yield. <sup>b</sup> 2.5 equiv.

Switch from methanol to allyl alcohol led always to indoline **23** (Table 14). Running the reaction under 1 atm of CO in the presence of K<sub>2</sub>CO<sub>3</sub> at 95 or 130°C gave indoline **23** in 60% or 62% yield, respectively (entries 1-2). Raising CO pressure to 10 or 15 bar had no beneficial effect (entry 3-4). Tributylamine as the base afforded only indoline **23** and degradation products (entries 5-6). XantPhos afforded only degradation products (entry 7). This result suggests that the allyloxycarbonylation is problematic and undesired protonation of the palladium ester intermediate takes place. We therefore thought to circumvent this difficulty by incorporating the allyl moiety directly into the starting ester. This trick aimed at turning a problematic allyloxycarbonylation into a more promising methoxycarbonylation.

## 2) Switch from allyloxy- to methoxycarbonylation

We therefore had to prepare allyl ester **34**, analogous to methyl ester **20**. A straightforward strategy involving a Wittig reaction between the ylide **31** and  $\alpha$ -hydroxyacetone in refluxing benzene provided the (Z) isomer of the acrylate **32** in 71% yield. Subsequent transesterification following Otera's conditions<sup>157</sup> afforded the desired allylacrylate **33** in 52% yield. Finally, phosphorus tribromide effected the desired allylic bromination to afford the target compound **34** in 69% yield (Scheme 113).

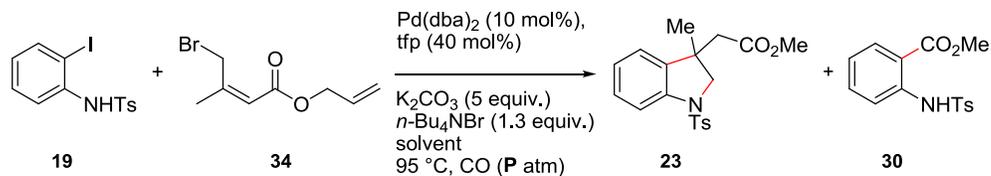


Scheme 113: Synthesis of (Z)-allyl 4-bromo-3-methylbut-2-enoate

We then investigated the full domino sequence featuring a methoxycarbonylation instead of an allyloxycarbonylation (Table 15).

Table 15

<sup>157</sup> a) Otera, J.; Yano, T.; Kawabata, A.; Nozaki, H. *Tetrahedron Lett.* **1986**, *27*, 2383–2386. b) Otera, J.; Danoh, N.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5307–5311.



| Entry | CO (P atm)     | Base                            | solvent      | T (°C) | Yields (%) <sup>a</sup> |               |
|-------|----------------|---------------------------------|--------------|--------|-------------------------|---------------|
|       |                |                                 |              |        | <b>23</b> (%)           | <b>30</b> (%) |
| 1     | 1              | K <sub>2</sub> CO <sub>3</sub>  | Tol/MeOH 2/1 | 95     | 20%                     | -             |
| 2     | 1              | Cs <sub>2</sub> CO <sub>3</sub> | Tol/MeOH 2/1 | 95     | 65%                     | -             |
| 3     | 1 <sup>b</sup> | K <sub>2</sub> CO <sub>3</sub>  | Tol/MeOH 2/1 | 95     | 18%                     | 6%            |
| 4     | 1 <sup>b</sup> | K <sub>2</sub> CO <sub>3</sub>  | MeOH         | 95     | 32%                     | 4%            |
| 5     | 1 <sup>b</sup> | K <sub>2</sub> CO <sub>3</sub>  | Tol/MeOH 2/1 | 130    | 24%                     | 3%            |

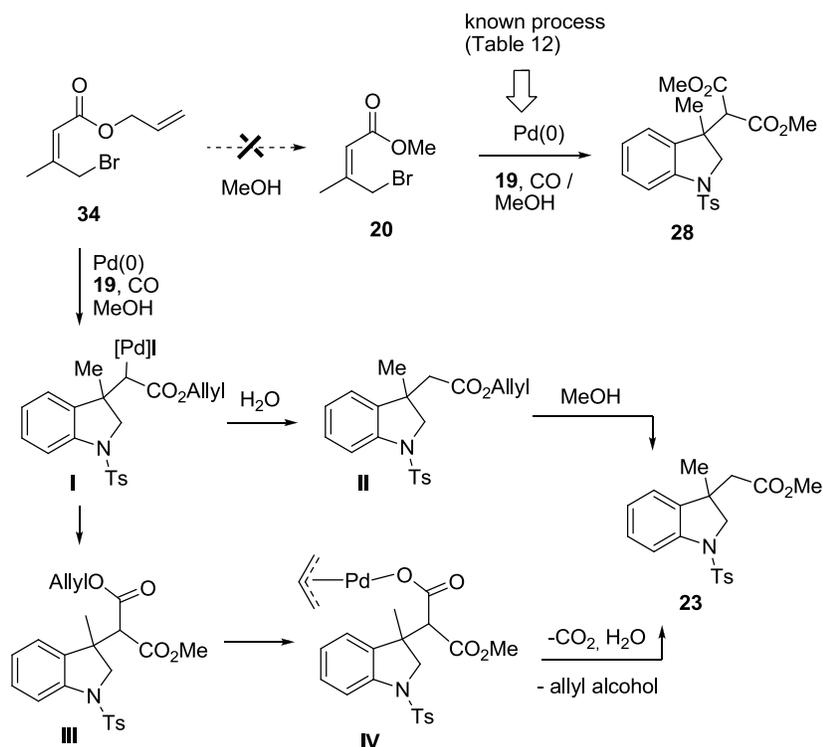
<sup>a</sup> isolated yields. <sup>b</sup> sealed tube

Applying the successful conditions for the methoxycarbonylation reaction (Table 12) led again to indoline **23** (Table 15, entry 1). The more soluble Cs<sub>2</sub>CO<sub>3</sub> base led to the same outcome (entry 2). Increasing methanol molarity or carbon monoxide pressure (sealed tube, entries 3-5) resulted in similar results. Additionally, ester **30** resulting from premature methoxycarbonylation of the aryl iodide was observed. Interestingly, indoline **23** had a methyl ester instead of the initial allyl ester.

### 3) Possible pathways from **34** to **23**

As methanol is present in great excess, undesired transesterification of allyl ester **34** to methyl ester **20** might account for the isolation of indoline **23** (Scheme 114, 1<sup>st</sup> row). However, as the reaction conditions are the same as those described in Table 12, the malonate derivative **28** should be isolated (Scheme 110). Hence, it is more likely that the intermediate from decarbopalladation **I** is initially protonated to give **II**, rather than undergo carbonylation, then suffers transesterification (Scheme 114, 2<sup>nd</sup> row). Alternatively, the

desired allyloxycarbonylation to provide malonate **III** may take place, but inefficient decarboxylative allylation brings about decarboxylative protodeallylation to give **23** (Scheme 114, 3<sup>rd</sup> row).



Scheme 114: Possible pathways from allyl ester **34** to methyl ester **23**

As a transesterification is a slow process normally requiring a nucleophilic catalyst such as DMAP,<sup>158</sup> the third postulated path seems the most probable one.

In order to gain some evidence supporting our hypothesis, we decided to replace the poor electron-withdrawing ester group by a stronger one. Such an electron-withdrawing

<sup>158</sup> Tanaka, R.; Rubio, A.; Harn, N. K.; Gernert, D.; Grese, T. A.; Eishima, J.; Hara, M.; Yoda, N.; Ohashi, R.; Kuwabara, T.; Soga, S.; Akinaga, S.; Nara, S.; Kanda, Y. *Bioorg. Med. Chem.* **2007**, *15*, 1363-1382.

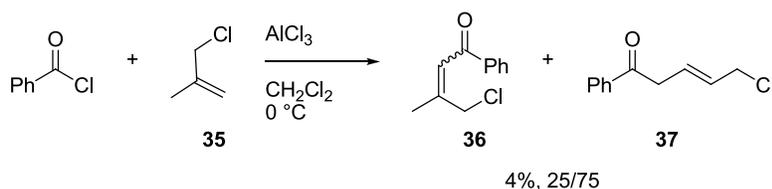
group should be able to better stabilize the carbanionic species resulting from decarboxylation, and thus render the allylation reaction more likely to occur.

#### vi. Extension to different groups than malonate

As showed in the bibliography part, the stronger the electron withdrawing group, the more efficient is the decarboxylative allylation. In particular, Tsuji evidenced the following order of reactivity for the decarboxylative allylation: nitroacetate >  $\beta$ -Ketoacetate > cyanoacetate > malonate.<sup>138</sup> Accordingly, our attention turned naturally toward  $\beta$ -ketoesters and  $\beta$ -cyanoesters.

##### 1) Planning intermediate $\beta$ -ketoesters

Different strategies were envisioned to prepare the requisite  $\alpha,\beta$ -unsaturated ketones bearing a leaving group in allylic position. The most straightforward strategy we found relied on a Friedel-Crafts type acylation reaction between benzoyl chloride and methallyl chloride (Scheme 115).<sup>159</sup> However, following the reported procedure, we were unable to achieve synthetically useful yields of the target ketone **36**.

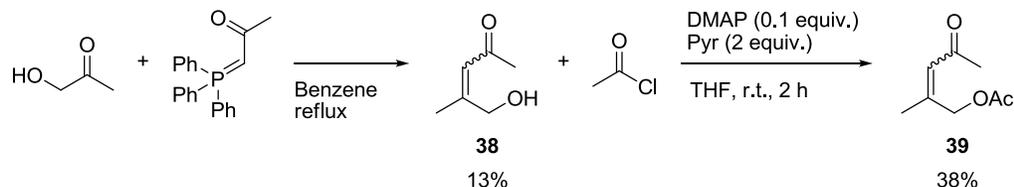


Scheme 115: Attempts of Friedel-Crafts type reaction for the synthesis of  $\alpha,\beta$ -unsaturated ketones

We thus decided to react hydroxyacetone and 1-(triphenylphosphoranylidene)acetone according to a Wittig reaction. The targeted hydroxyketone **38** was isolated in 13% yield. Subsequent protection of the alcohol by reaction with acetyl chloride yielded the desired compound **39** in 38% yield (Scheme 116).

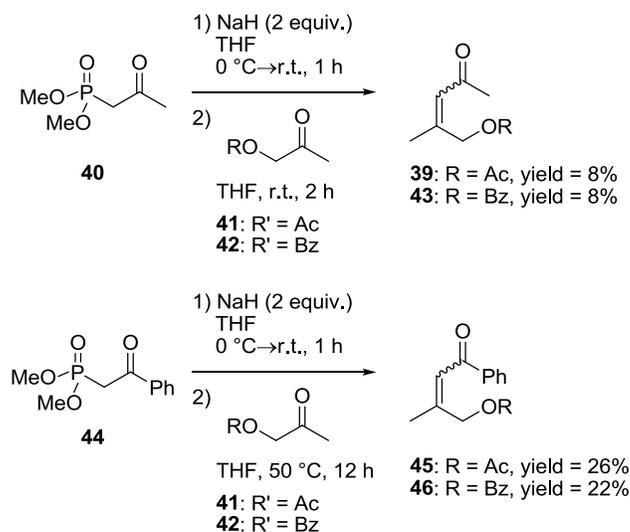
<sup>159</sup> Barbry, D.; Faven, C.; Ajana, A. *Synthetic Commun.* **1993**, *23*, 2647–2658.

The low yields may be accounted for by the volatility of the products and tedious purification protocols, due to triphenylphosphine oxide. Avoiding intermediary purifications and use of protected hydroxyacetone were not more efficient strategies.



**Scheme 116: Synthesis of  $\alpha,\beta$ -unsaturated ketones thanks to Wittig reaction**

A Horner-Wadsworth-Emmons version with variously protected hydroxyacetone derivatives was also investigated. However, the yields obtained remained synthetically ineffective (Scheme 117).

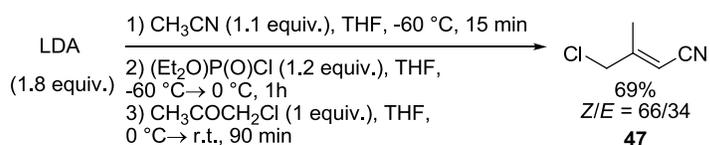


**Scheme 117: Synthesis of  $\alpha,\beta$ -unsaturated ketones thanks to Horner-Wadsworth-Emmons reaction**

We then turned our attention to the synthesis of  $\alpha,\beta$ -unsaturated nitriles bearing an allylic leaving group.

## 2) Planning intermediate malononitriles

The synthesis of 4-chloro-3-methyl-2-butenitrile **47** was realized following Lugtenburg procedure.<sup>160</sup> Acetonitrile was deprotonated with LDA, and the resulting azaenolate was added to diethyl chlorophosphate. *In situ* deprotonation of the thus formed phosphonate with excess LDA and reaction with chloroacetone, according to a Horner-Wadsworth-Emmons reaction, afforded the desired product **47** in 69% yield (Z/E = 66/34, (Scheme 118).



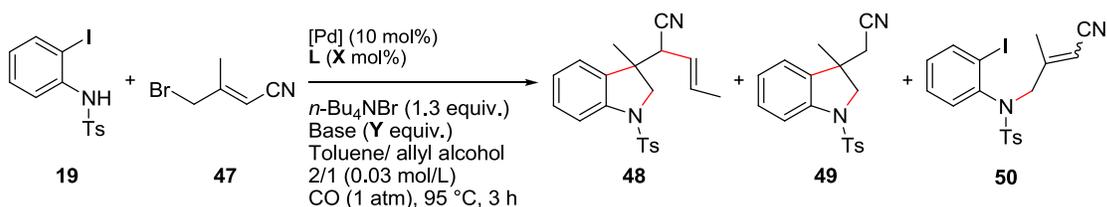
**Scheme 118: Synthesis of  $\alpha,\beta$ -unsaturated nitrile**

The domino sequence involving *N*-allylation / carbopalladation / allyloxycarbonylation / decarboxylative allylation starting from the nitrile-based substrate **47** was then investigated (Table 16).

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<sup>160</sup> Creemers, A. F. L.; Lugtenburg, J. *J. Am. Chem. Soc.* **2002**, *124*, 6324–6334.

Table 16



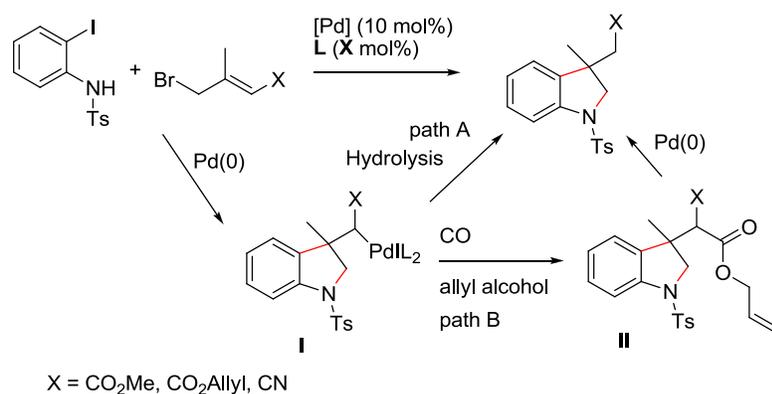
| Entry | [Pd]                 | Base (Y equiv.)                      | Ligand (X mol%)            | Yields (%) <sup>a</sup>  |                    |               |
|-------|----------------------|--------------------------------------|----------------------------|--------------------------|--------------------|---------------|
|       |                      |                                      |                            | <b>48</b> (%)            | <b>49</b> (%)      | <b>50</b> (%) |
| 1     | Pd(dba) <sub>2</sub> | K <sub>2</sub> CO <sub>3</sub> (5)   | P(2-fur) <sub>3</sub> (40) | 10 <sup>c</sup>          | 20                 | -             |
| 2     | Pd(dba) <sub>2</sub> | K <sub>2</sub> CO <sub>3</sub> (2.5) | P(2-fur) <sub>3</sub> (40) | -                        | 40                 | -             |
| 3     | Pd(dba) <sub>2</sub> | K <sub>2</sub> CO <sub>3</sub> (5)   | P(2-fur) <sub>3</sub> (40) | Degradation <sup>d</sup> |                    |               |
| 4     | Pd(dba) <sub>2</sub> | K <sub>2</sub> CO <sub>3</sub> (2.5) | P(2-fur) <sub>3</sub> (40) | Degradation <sup>d</sup> |                    |               |
| 5     | Pd(dba) <sub>2</sub> | Cs <sub>2</sub> CO <sub>3</sub> (5)  | P(2-fur) <sub>3</sub> (40) | Degradation <sup>d</sup> |                    |               |
| 6     | Pd(dba) <sub>2</sub> | Cs <sub>2</sub> CO <sub>3</sub> (5)  | P(2-fur) <sub>3</sub> (40) | -                        | 44                 | -             |
| 7     | Pd(dba) <sub>2</sub> | Et <sub>3</sub> N (5)                | P(2-fur) <sub>3</sub> (40) | -                        | 15                 | 60            |
| 8     | Pd(dba) <sub>2</sub> | K <sub>2</sub> CO <sub>3</sub> (5)   | P(2-fur) <sub>3</sub> (40) | -                        | 35 <sup>e</sup>    | -             |
| 9     | Pd(dba) <sub>2</sub> | K <sub>2</sub> CO <sub>3</sub> (5)   | P(2-fur) <sub>3</sub> (40) | -                        | 60 <sup>b, f</sup> | -             |
| 10    | Pd(dba) <sub>2</sub> | K <sub>2</sub> CO <sub>3</sub> (5)   | XantPhos (10)              | Degradation              |                    |               |
| 11    | Pd(OAc) <sub>2</sub> | K <sub>2</sub> CO <sub>3</sub> (5)   | P(2-fur) <sub>3</sub> (40) | -                        | 43 <sup>f</sup>    | -             |

<sup>a</sup> Isolated yields. <sup>b</sup> Through a "large section tube" instead of a needle. <sup>c</sup> Non-reproducible result, when reapplied the reaction afford only **49** in 44% yield. <sup>d</sup> concentration of 0.1 mol/L instead of 0.03 mol/L of compound **19**. <sup>e</sup> solvent allyl alcohol 0.03 mol/L. <sup>f</sup> Traces of **48** are detected.

Under the successful conditions developed for methoxycarbonylation reactions (Table 12, entry 7), nitrile **48** was isolated in 10% yield (entry 1). This compound may derive from the desired allylated nitrile after olefin isomerization. Besides nitrile **48**, indoline **49** was isolated in 20% yield. An inefficient decarboxylative allylation and competitive protonation (or direct protonation prior to carbonylation) may account for this product. Optimization of the reaction conditions was therefore investigated. We studied the influence of the amount of base (entries 2 and 4), the nature of the base (entries 5-7), the nature of

the ligand (entry 10), the nature of the palladium source (entry 11) and the ease of gas exchange between the reaction medium and the balloon (entry 9). None of these parameters allowed to isolate greater than trace amounts of the desired product. Instead, indoline **49** was recovered. Moreover, the promising result obtained (entry 1) could not be reproduced.

With the exception of one non reproducible result, a nitrile did not allow a more efficient decarboxylative allylation. At this stage it is unclear whether an inefficient decarboxylative allylation of intermediate **II** or a fast competing protonolysis of intermediate **I** (Scheme 119) account for the formation of **49**.

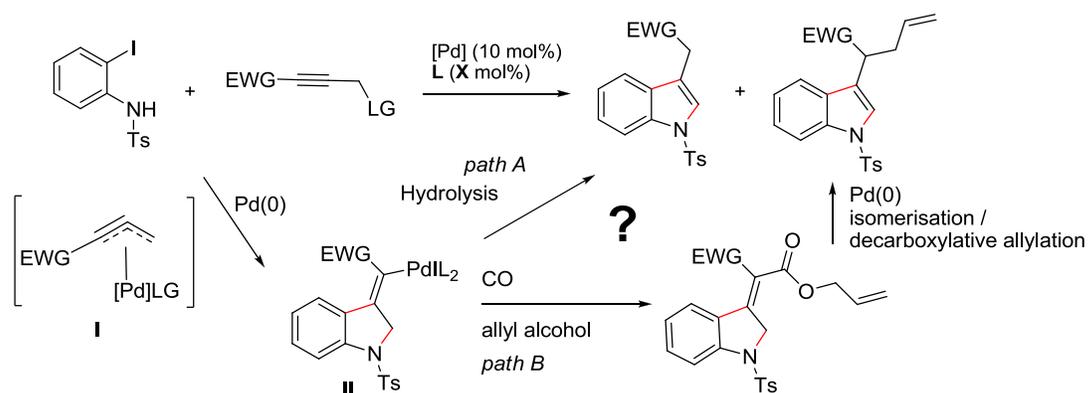


**Scheme 119: Possible origins of the side product**

We thought that an alkenylpalladium intermediate could be less prone to protonation than an alkyl palladium intermediate. We therefore decided to react propiolates instead of acrylates in the domino reaction.

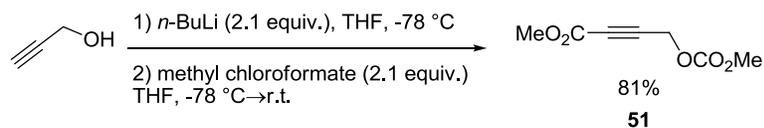
vii. Approach to a triple pseudo-domino type I sequence: « *N*-propargylation / 5-*exo-dig* carbopalladation / carbonylation »

We reasoned that using a propiolate derivative, a propargylation, *via* intermediate **I**,<sup>161</sup> followed by carbopalladation, could generate a vinylpalladium complex **II**, which should be less prone to undergo direct hydrolysis and could have more chances to lead to the desired carbonylation (Scheme 120).



Scheme 120: Postulated paths of the domino sequence with a propiolate derivative

The propiolate derivative **51** was synthesized in a one-step procedure from propargyl alcohol by double deprotonation (alcohol and acetylenic position) and subsequent double condensation with methyl chloroformate (Scheme 121).<sup>162</sup>



Scheme 121: Synthesis of the propiolate

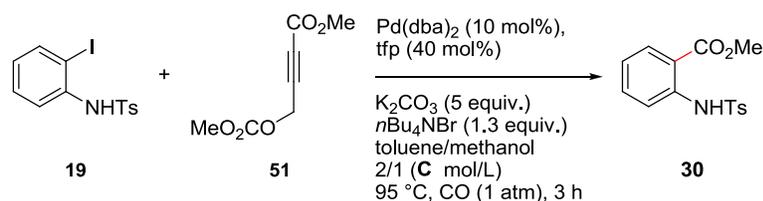
<sup>161</sup> Guo, L. N.; Duan, X.-H.; Liang, Y.-M. *Acc. Chem. Res.*, **2011**, *44*, 111-122.

<sup>162</sup> Trost, B. M.; Taft, B. R.; Masters, J. T.; Lumb, J.-P. *J. Am. Chem. Soc.* **2011**, *133*, 8502-8505.

### 1) Methoxycarbonylation

The propiolate **51** was reacted in the methoxycarbonylation reaction with the protected aniline **19**, following the conditions previously used for the methoxycarbonylation with acrylate derivatives (Table 16, entry 1). The results are shown in Table 17.

Table 17



| Entry | C (mol/L) <sup>b</sup> | Yield (%) <sup>a</sup>            |
|-------|------------------------|-----------------------------------|
| 1     | 0.03                   | <b>30</b> (38%) + <b>19</b> (15%) |
| 2     | 0.1                    | <b>30</b> (40%) + <b>19</b> (20%) |

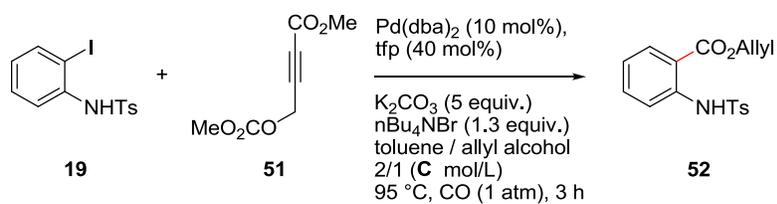
<sup>a</sup> Isolated Yields. <sup>b</sup> Of compound **19**.

In preliminary experiments, under an atmospheric pressure of carbon monoxide, we only observed premature carbonylation of the aryl iodide moiety and propargylation of the aniline nitrogen atom did not occur.

### 2) Allyloxy carbonylation

Analogously, using allyl alcohol instead of MeOH afforded only premature allyloxy carbonylation of the aryl iodide (Table 18). The lower yield of allyl benzoate **52** compared to that of methyl benzoate **30** confirms the poorer reactivity of allyl alcohol compared to methanol.

Table 18



| Entry | C (mol/L) <sup>b</sup> | Yield (%) <sup>a</sup> |
|-------|------------------------|------------------------|
| 1     | 0.03                   | <b>52</b> (18%)        |
| 2     | 0.1                    | Degradation            |

<sup>a</sup> Isolated Yields. <sup>b</sup> Of compound **19**.

### c) Conclusion and perspectives

We have designed a triple pseudo domino type 1 sequence featuring an *N*-allylation, a 5-*exo-trig* carbopalladation and a methoxycarbonylation. The corresponding malonate **28** was isolated in good yield.

We focused on extending this pseudo-domino sequence to a four-step sequence by adding a decarboxylative allylation step. Replacing methanol by allyl alcohol led to unsatisfactory results. Designing substrates bearing the required allyloxy moiety did not improve results. Replacing the enolate-stabilizing ester group by a cyano group did not allow isolation of the expected allylated nitriles in good and reproducible yields.

Finally, we tried to extend the allylation step to propargylic systems. Preliminary results only led to premature carbonylation of the aryl iodide moiety of protected iodoaniline.

## General conclusion



The present thesis work dealt with the development on new palladium-catalyzed pseudo-domino sequences. A first pseudo-domino type I process featuring a carbonylation / decarboxylative allylation was designed with  $\alpha$ -chloroacetophenone. The sequence allowed the selective mono-allylation of readily available ketone derivatives in one single synthetic operation. This pseudo-domino sequence could be applied to variously substituted acetophenones. The reaction was not sensitive to electronic effects, as both electron-donating and withdrawing groups were equally well tolerated. Formal hydrolysis of palladium enolates appeared to be a crucial issue of the transformation. Unfortunately, the carbonylation step proved to be slower than  $\beta$ -hydride elimination, although faster carbonylations have been described. Preliminary computational studies have been carried out to rationalize our experimental findings, and especially to point out possible pathways towards reduced (formally hydrolyzed) compounds.

We also designed a three-step pseudo-domino reaction featuring *N*-allylation / carbopalladation / carbonylation. This sequence allowed us to prepare substituted indolines in one single synthetic operation from readily available substrates. This strategy allows a straightforward synthesis of potentially biologically relevant building blocks.

The extension to a four step pseudo-domino sequence was also envisaged. Switching the alcohol used to allyl alcohol should merge both sequences, by adding a decarboxylative allylation step to the three-step process. Unfortunately, in the presence of allyl alcohol, either nucleophilic trapping or decarboxylative allylation is not an efficient reaction.



## Experimental Section

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a) **General instrumentation:**

All carbonylation and domino reactions were carried out in a stainless steel pressure vessel if pressure higher than 1 atmosphere of carbon monoxide was required. All other reactions were carried out under an argon or carbon monoxide atmosphere in flame-dried glassware. Diethyl ether, THF and dichloromethane were dried on a Braun purification system MB SPS-800. Toluene was distilled over sodium / benzophenone. *N,N*-dimethylacetamide and *N,N*-dimethylformamide was stirred for several days on BaO at room temperature and at reflux for 1 h, then fractionally distilled under reduced pressure. The main fraction was stored on molecular sieves and under argon atmosphere. Allyl alcohol was distilled and stored under argon atmosphere. Silica gel (40-63  $\mu\text{m}$ ) was used for chromatographic purifications. TLC plates were performed on Merck precoated 60 F<sub>254</sub> plates and visualized under UV light and spraying with  $\text{KMnO}_4$  (5 % in water) or vanillin.

NMR spectra were recorded (Bruker 400 MHz or 300 MHz,  $^1\text{H}$ , and 101 or 75 MHz, respectively for  $^{13}\text{C}$ ) in  $\text{CDCl}_3$  (which also provided the lock signal at  $\delta = 7.27$  ppm for  $^1\text{H}$  and  $\delta = 77.16$  ppm for  $^{13}\text{C}$ ). Chemical shifts are reported in ppm and coupling constants  $J$  in Hertz.

IR spectra were recorded on a Bruker Tensor 27 apparatus and only the strongest or the structurally most important peaks were listed. Melting points were measured using a Stuart Scientific SMP3 apparatus. High resolution mass spectrometries were performed on a Thermo Fisher Scientific LTQ-Orbitrap (ESI).

The computational study was realized with the drawing tool *Maestro* and the calculations thanks to the Jaguar software of the Schrödinger Suite software with B3LYP/LACVP\*\* basis set. The method used to obtain total free energies is as follows for each complex. First the optimization of the structure in gas phase delivers the optimized structure and the lower energies for a given complex. Then, *single point energies* of this structure with solvation in benzene, Gibbs frequency, and *self consistent field* (SCF) frequency were calculated. Addition of the difference between Gibbs and SCF frequencies to the single point energy with solvation in benzene delivers the total free energy of the

structure in Hartree unit. Multiplication by 627.5 gives the *total free energy* in kcal/mol. Finally the multiplication by 4.18 affords the total free energy in kJ/mol.

## b) General procedures (GP)

### General procedure for type 1 pseudo-domino reaction under atmospheric pressure of carbon monoxide (GP1):

A flask was charged with  $\alpha$ -chloroacetophenone (1.03 mmol, 1 equiv.),  $\text{PdCl}_2(\text{PPh}_3)_2$  (0.05 mmol, 0.05 equiv.), allyl alcohol (2 mL), and  $\text{Et}_3\text{N}$  (1.51 mmol, 1.5 equiv.). The flask was flushed with CO for 5 min. The solution was stirred for 24 h at 97 °C. The reaction was hydrolyzed and extracted with ethylacetate (3 x 15 mL). The combined organic layers were dried over  $\text{MgSO}_4$  and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (cyclohexane / AcOEt 90 / 10).

### General procedure for the methoxycarbonylation of $\alpha$ -chloroacetophenone (GP2):

A stainless steel pressure vessel was charged with  $\alpha$ -chloroacetophenone (2 mmol, 1 equiv.),  $\text{PdCl}_2(\text{PPh}_3)_2$  (0.01 mmol, 0.5 mol%), methanol (5 mL) and 1,8-bis(dimethylamino)naphthalene (3.00 mmol, 1.5 equiv.). The vessel was carefully closed and flushed with carbon monoxide for 5 min, pressurized to 5 bar of carbon monoxide and warmed to 100 °C during 24 h. The vessel was cooled to room temperature, and the excess of carbon monoxide carefully released. The solution concentrated *in vacuo*, diluted in  $\text{CH}_2\text{Cl}_2$ , hydrolyzed with  $\text{NH}_4\text{Cl}$  and extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 20 mL). The combined organic layers were dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (cyclohexane / AcOEt 90 / 10).

### General procedure for the chlorination of ketones according to the literature

#### (GP3):<sup>163</sup>

A flask was charged with the substrate (4 mmol), NCS (4 mmol, 1 equiv.), and PTSA (0.4 mmol, 0.1 equiv.). The reaction mixture was heated to 80 °C overnight, hydrolyzed and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 10 mL). The combined organic layers were dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel.

### General procedure for the optimized type 1 pseudo domino sequence:

#### carbonylative / decarboxylative allylation (GP4):

The autoclave was charged with  $\alpha$ -chloroketone (1 mmol, 1 equiv.), Pd(OAc)<sub>2</sub> (0.1 mmol, 0.1 equiv.), tri (2-furyl)phosphine (0.4 mmol, 0.4 equiv.), tri-*n*-butylamine (1.5 mmol, 1.5 equiv.), allyl alcohol (14.6 mmol, 15 equiv.) and toluene (1.5 mL). The autoclave was purged with CO and then pressurized (20 bar). The reaction mixture was heated to 130 °C for 2 h. After cooling to room temperature, the pressure was carefully released and the autoclave vented. The reaction was concentrated *in vacuo*, hydrolyzed and extracted with diethyl ether (3 x 15 mL). The combined organic layers were dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel.

### General procedure for the protection of the *o*-halogenoaniline (GP5):

To a solution of 2-halogenoaniline (24 mmol, 1 equiv.) and pyridine (10.1 mL, 125 mmol, 5.1 equiv.) in THF (5 mL) at 0 °C was added *p*-toluenesulfonyl chloride (5.7 g, 30 mmol, 1.2 equiv.). The mixture was allowed to warm up to room temperature and stirred for 4 h. After evaporation of the solvent, the residue was diluted with H<sub>2</sub>O and extracted with CHCl<sub>3</sub>

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<sup>163</sup> Pravst, I.; Zupan, M.; Stavber, S. *Tetrahedron*, **2008**, *64*, 5191-5199.

(3 x 30 mL). The combined organic layer were dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue obtained was purified by column chromatography on silica gel (cyclohexane / CH<sub>2</sub>Cl<sub>2</sub>, 60 / 40).

**General procedure for the cyclization of compounds 21 and 22 (GP6):**

A flask was charged with K<sub>2</sub>CO<sub>3</sub> (2.5 mmol, 5 equiv.), *n*-Bu<sub>4</sub>NBr (0.6 mmol, 1.3 equiv.), HCOOK (0.5 mmol, 1 equiv.), PPh<sub>3</sub> (0.2 mmol, 0.4 equiv.) and DMF (20 mL). Then, a solution of **21** or **22** (0.5 mmol, 1 equiv.) in DMF (5 mL) was added. Finally Pd(OAc)<sub>2</sub> (0.1 mmol, 0.2 equiv.) was introduced and the solution was heated to 120 °C during 19 h. The reaction mixture was cooled to room temperature, hydrolyzed and extracted with Et<sub>2</sub>O (3 x 20 mL). The combined organic layers were dried over MgSO<sub>4</sub>, concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (cyclohexane / AcOEt, 9 / 1).

**General procedure for the pseudo-domino reaction: N-allylation / 5-*exo-trig* carbopalladation (GP7):**

A flask was charged with *N*-(2-iodophenyl)-4-methylbenzenesulfonamide **19** (0.5 mmol, 1 equiv.), Pd(OAc)<sub>2</sub> (0.05 mmol, 10 mol%), PPh<sub>3</sub> (0.10 mmol, 20 mol%), *n*-Bu<sub>4</sub>NBr (0.65 mmol, 1.3 equiv.), K<sub>2</sub>CO<sub>3</sub> (2.50 mmol, 5.1 equiv.) and HCOOK (0.99 mmol, 2 equiv.). A solution of **20**, **24** or **25** (0.55 mmol, 1.1 equiv.) in DMF (20 ml) was added. The solution was heated to 95 °C during 6 h, cooled to room temperature, hydrolyzed and extracted with Et<sub>2</sub>O (3 x 20 mL). The combined organic layers were dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (cyclohexane / AcOEt, 8 / 2).

**General procedure for the domino reaction: allylic alkylation / 5-*exo-trig* carbopalladation / methoxycarbonylation (GP8):**

A flask fitted with a condenser was charged with *N*-(2-iodophenyl)-4-methylbenzenesulfonamide **19** (0.5 mmol, 1 equiv.), Pd(dba)<sub>2</sub> (0.05 mmol, 10 mol%), P(2-fur)<sub>3</sub> (0.20 mmol, 40 mol%), *n*-Bu<sub>4</sub>NBr (0.64 mmol, 1.3 equiv.) and K<sub>2</sub>CO<sub>3</sub> (2.50 mmol, 5 equiv.) under an atmospheric pressure of carbon monoxide atmosphere. Then, a solution of **20**, **24**, **25** or **29** (0.55 mmol, 1.1 equiv.) in toluene (10 mL) was added, followed by the addition of methanol (5 mL). The solution was heated to 95 °C under carbon monoxide atmosphere during 4 h. The reaction was then cooled down to room temperature, filtered on celite. The filtrate was diluted with Et<sub>2</sub>O, hydrolyzed and extracted with Et<sub>2</sub>O (3 x 20 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was then purified by column chromatography on silica gel (pentane / AcOEt, 8 / 2).

**General procedure for the domino reaction: N-allylation / 5-*exo-trig* carbopalladation / allyloxycarbonylation / decarboxylative allylation (GP9):**

A flask fitted with an reflux condenser was charged with *N*-(2-iodophenyl)-4-methylbenzenesulfonamide **19** (0.25 mmol, 1 equiv.), Pd(dba)<sub>2</sub> (0.025 mmol, 10 mol%), P(2-fur)<sub>3</sub> (0.10 mmol, 40 mol%), *n*-Bu<sub>4</sub>NBr (0.32 mmol, 1.3 equiv.) and K<sub>2</sub>CO<sub>3</sub> (1.25 mmol, 5 equiv.) under an atmospheric pressure of carbon monoxide atmosphere. Then, a solution of **20** (0.28 mmol, 1.1 equiv.) in toluene (5 mL) was added, followed by the addition of allyl alcohol (2.15 mL). The solution was heated to 95 °C under carbon monoxide atmosphere during 4 h. The reaction was cooled down to room temperature, filtered on celite. The filtrate was hydrolyzed and extracted with Et<sub>2</sub>O (3 x 20 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was then purified by column chromatography on silica gel (pentane / AcOEt, 8 / 2).

**General procedure for the domino reaction: N-allylation / 5-*exo-trig* carbopalladation / methoxycarbonylation / decarboxylative allylation (GP10):**

A flask fitted with a condenser was charged with **19** (0.2 mmol, 1 equiv.), Pd(dba)<sub>2</sub> (0.03 mmol, 10 mol%), P(2-fur)<sub>3</sub> (0.1 mmol, 40 mol%), *n*-Bu<sub>4</sub>NBr (0.3 mmol, 1.3 equiv.) and Cs<sub>2</sub>CO<sub>3</sub> (1.2 mmol, 6 equiv.) under an atmospheric pressure of carbon monoxide atmosphere. A solution of **34** (0.3 mmol, 1.5 equiv.) in toluene (5 mL) was added, followed by the addition of MeOH (2.5 mL). The solution was heated at 95 °C during 3 h. The solution was cooled to room temperature, hydrolyzed and extracted with Et<sub>2</sub>O (3 x 10 mL). The combined organic layer were dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was then purified by column chromatography on silica gel (cyclohexane / AcOEt, 8 / 2).

**General procedure for the domino reaction with the cyano compound and allyl alcohol (GP11):**

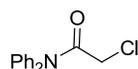
A flask was charged with **19** (0.5 mmol, 1 equiv.), Pd(dba)<sub>2</sub> (0.05 mmol, 10 mol%), P(2-fur)<sub>3</sub> (0.2 mmol, 40 mol%), K<sub>2</sub>CO<sub>3</sub> (2.5 mmol, 5 equiv.) and *n*-Bu<sub>4</sub>NBr (0.65 mmol, 1.3 equiv.) under atmospheric pressure of carbon monoxide. A solution of **47** (0.55 mmol, 1.1 equiv.) in toluene (6.5 mL) was added, followed by the addition of allyl alcohol (8.5 mL). The solution was heated to 95 °C during 3 h. The solution cooled to room temperature, hydrolyzed and extracted with Et<sub>2</sub>O (3 x 15 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was then purified by column chromatography on silica gel (cyclohexane / AcOEt, 8 / 2).

**General procedure for the domino reaction with the propiolate (GP12):**

A flask was charged with **19** (0.5 mmol, 1 equiv.), Pd(dba)<sub>2</sub> (0.05 mmol, 10 mol%), P(2-fur)<sub>3</sub> (0.2 mmol, 40 mol%), K<sub>2</sub>CO<sub>3</sub> (2.5 mmol, 5 equiv.) and *n*-Bu<sub>4</sub>NBr (0.65 mmol, 1.3 equiv.) under carbon monoxide atmosphere. A solution of **51** (0.6 mmol, 1.2 equiv.) in toluene (6.5 mL) was added, followed by the addition of allyl alcohol (8.5 mL). The solution was heated to 95 °C during 3 h. The solution was cooled to room temperature, hydrolyzed

and extracted with Et<sub>2</sub>O (3 x 15 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was then purified by column chromatography on silica gel (cyclohexane / AcOEt, 9 / 1).

c) **Pseudo-domino type I carbonylative / decarboxylative allylation of  $\alpha$ -chloroketones:**

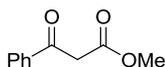


**2-chloro-N,N-diphenylacetamide (8):**

To a solution of diphenylamine (3.47 g, 20.5 mmol, 1 equiv.) in toluene (40 mL) under N<sub>2</sub> atmosphere, was slowly added 2-chloroacetyl chloride (3.2 mL, 40.2 mmol, 2.0 equiv.). The solution was stirred for 1 h at 100 °C, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (cyclohexane / AcOEt, 7 / 3) and yielded 5.1 g (100%) of the expected product **8** as a white powder.

Data for **8**:

**m.p.:** 119-120 °C. **IR:** 3005, 2946, 1676, 1588, 1490, 1362, 1264, 689, 606 cm<sup>-1</sup>. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.30 - 7.40 (m, 10 H), 4.03 (s, 2 H). **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>)  $\delta$  166.4, 141.9, 129.8, 128.5, 126.2, 42.7. **HRMS** (ESI) *m/z* calcd. for C<sub>14</sub>H<sub>12</sub>ClNaNO [M + Na<sup>+</sup>] 268.0495, found 268.0499.



**Methyl 3-oxo-3-phenylpropanoate (9):**

*Synthesize from methoxycarbonylation GP2:*

Reaction performed with  $\alpha$ -chloroacetophenone (309.3 mg, 2.00 mmol, 1.0 equiv.), PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (7.4 mg, 0.01 mmol, 0.5 mol%), methanol (5 mL) and 1,8-

bis(dimethylamino)naphthalene (642.2 mg, 3.00 mmol, 1.5 equiv.) at 100 °C for 24 h. The residue was purified by column chromatography on silica gel (cyclohexane/AcOEt, 9 / 1) and yielded 134 mg (38%) of the expected keto-ester **8** as a colorless oil.

Synthesize from addition of enolate on the formiate derivative:

A flask was charged with *n*-BuLi (9.6 mL, C = 2.5 M in hexane, 24 mmol, 1.2 equiv.) and diisopropylamine (3.65 mL, 26 mmol, 1.3 equiv.) was slowly added. The solution was stirred for 15 min, and THF (20 mL) was added. After 5 min, acetophenone (2.36 mL, 20 mmol, 1 equiv.) was introduced. Methylchloroformiate (2.32 mL, 30 mmol, 1.5 equiv.) was added. The solution was stirred overnight, then hydrolyzed and extracted with ethylacetate (3 x 30 mL). The combined organic layers were dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (cyclohexane/AcOEt, 90 / 10) and yielded 1.453 g (40%) of the expected product as a colorless oil.

Data for **9**:

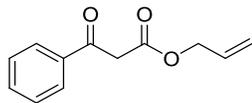
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.95 – 7.93 (m, 2H), 7.61 – 7.57 (m, 1H), 7.50 – 7.46 (m, 2H), 4.00 (s, 2H), 3.75 (s, 3H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 192.4, 168.0, 136.0, 133.9, 128.9, 128.6, 52.5, 45.8.

These data are in good agreement with those reported in the literature.<sup>164</sup>

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<sup>164</sup> Taniguchi, T.; Sugiura, Y.; Zaimoku, H.; Ishibashi, H. *Angew. Chem. Int. Ed.* **2010**, *49*, 10154-10157.

**Synthesis of the allyl keto-ester and the allyl malonamide for the study of the decarboxylative allylation:**



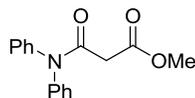
**Allyl 3-oxo-3-phenylpropanoate (2):**

A solution of methyl 3-oxo-3-phenylpropanoate **9** (1.45 g, 8.15 mmol, 1 equiv.), DMAP (301.8 mg, 2.45 mmol, 0.3 equiv.) in allyl alcohol (6 mL, 87mmol, 10 equiv.), was stirred at 90 °C for 3 days. The solution was cooled to room temperature and concentrated *in vacuo*. The residue was hydrolyzed and extracted with ethylacetate (3 x 20 mL). The combined organic layers were dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (cyclohexane / AcOEt, 95 / 5) and yielded 0.875 g (53%) of the expected product **2** as a colorless oil.

Data for **2**:

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.97-7.94 (m, 1H), 7.80 - 7.77 (m, 1H), 7.62-7.58 (m, 1H), 7.51 - 7.40 (m, 2H), 5.90 (ddt, *J* = 5.7, 10.2, 17.2 Hz, 1H), 5.36 - 5.20 (m, 2H), 4.65 (dt, *J* = 1.3, 5.7 Hz, 2H), 4.03 (s, 2H). HRMS (ESI) *m/z* calcd. for C<sub>12</sub>H<sub>12</sub>NaO<sub>3</sub> [*M* + Na<sup>+</sup>] 227.0673, found 227.0679.

These data are in good agreement with those reported in the literature.<sup>151</sup>



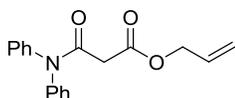
**Methyl 3-(diphenylamino)-3-oxopropanoate (12):**

To a solution of diphenylamine (3.41 g, 20.1 mmol, 1 equiv.) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added Et<sub>3</sub>N (8.4 mL, 60.2 mmol, 3 equiv.) and methyl 3-chloro-3-oxopropanoate (3.2 mL, 29.8 mmol, 1.5 equiv.). The solution was stirred overnight at room temperature, hydrolyzed and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 30 mL). The combined organic layers were dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel

(cyclohexane/AcOEt, 7 / 3) and yielded 2.34 g (43%) of the expected compound **12** as a white powder.

Data for **12**:

**m.p.:** 75 - 76 °C. **IR:** 2940, 1732, 1666, 1489, 1365, 1207  $\text{cm}^{-1}$ .  **$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.52 - 7.14 (m, 10H), 3.69 (s, 3H), 3.41 (s, 2H).  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  168.1, 166.1, 142.5, 142.4, 129.6, 129.1, 128.8, 128.5, 126.6, 126.4, 52.5, 42.6. **HRMS** (ESI)  $m/z$  calcd. for  $\text{C}_{16}\text{H}_{15}\text{O}_3\text{NaN}$  [ $\text{M} + \text{Na}^+$ ] 292.09451, found 292.09441

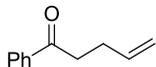


**Allyl 3-(diphenylamino)-3-oxopropanoate (11):**

A solution of methyl 3-(diphenylamino)-3-oxopropanoate **12** (1.53 g, 5.67 mmol, 1 equiv.) and DMAP (203.6 mg, 1.70 mmol, 0.3 equiv.) in allyl alcohol (6 mL) was stirred at 90°C for 3 days and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (cyclohexane / AcOEt, 85 / 15) and yielded 0.312 g (35%) of the expected compound **11** as a colorless oil.

Data for **11**:

**IR:** 1739, 1673, 1594, 1491, 1453, 1410, 1359  $\text{cm}^{-1}$ .  **$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.32 - 7.20 (m, 10H), 5.90 (ddt,  $J = 17.1, 10.5, 5.8$  Hz, 1H), 5.33 (dq,  $J = 17.2, 1.5$  Hz, 1H), 5.25 (dq,  $J = 10.4, 1.2$  Hz, 1H), 4.60 (dt,  $J = 5.8, 1.3$  Hz, 2H), 3.43 (s, 2H).  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  167.2, 165.9, 142.4, 131.7, 130.0, 129.0, 128.7, 128.5, 126.3, 118.8, 66.0, 42.7. **HRMS** (ESI)  $m/z$  calcd. for  $\text{C}_{18}\text{H}_{17}\text{O}_3\text{NaN}$  [ $\text{M} + \text{Na}^+$ ] 318.10946, found 318.11006



### 1-phenylpent-4-en-1-one (3)

Synthesize thanks to the decarboxylative allylation:

A flask was charged with allyl 3-oxo-3-phenylpropanoate **2** (226.4 mg, 1.11 mmol, 1 equiv.), Pd(dba)<sub>2</sub> (3.4 mg, 0.006 mmol, 0.5 mol%), dppf (3.1 mg, 0.006 mmol, 0.5 mol%) and toluene (4 mL). The solution was stirred at 90 °C for 45 min, hydrolyzed and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (cyclohexane / AcOEt, 95 / 5) and yielded 167 mg (94%) of the expected compound **3** as a yellow oil.

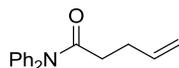
Synthesize thanks to the pseudo-domino type I sequence carbonylative / decarboxylative allylation **GP4**:

Prepared according to **GP4** from α-chloroacetophenone (152.9 mg, 0.99 mmol, 1 equiv.), Pd(OAc)<sub>2</sub> (22.3 mg, 0.10 mmol, 10 mol%), P(2-fur)<sub>3</sub> (92.0 mg, 0.39 mmol, 39 mol%), *n*-Bu<sub>3</sub>N (360 μL, 1.51 mmol, 1.53 equiv.), toluene (1.5 mL) and allyl alcohol (1 mL, 14.6 mmol, 15 equiv.). The residue was purified by column chromatography on silica gel (cyclohexane / AcOEt, 95 / 5) and yielded 116 mg (73%) of the expected product **3** as a yellow oil.

Data for **3**:

**IR**: 3062, 2920, 1684, 1597, 1448, 1208, 913, 690 cm<sup>-1</sup>; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.85 – 7.83 (m, 2H), 7.44 – 7.40 (m, 1H), 7.35 – 7.31 (m, 2H), 5.79 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 4.97 (dq, *J* = 17.1, 1.6 Hz, 1H), 4.90 (ddd, *J* = 10.2, 3.0, 1.3 Hz, 1H), 2.96 – 2.92 (m, 2H), 2.41 – 2.35 (m, 2H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 199.3, 137.3, 137.0, 133.0, 128.6, 128.0, 115.2, 37.7, 28.1. **HRMS** (ESI) *m/z* calcd. for C<sub>11</sub>H<sub>12</sub>NaO [M + Na<sup>+</sup>] 183.0778, found 183.0780.

These data are in good agreement with those reported in the literature.<sup>165</sup>



***N,N*-diphenylpent-4-enamide (13):**

A flask was charged with allyl 3-(diphenylamino)-3-oxopropanoate **11** (75.4 mg, 0.26 mmol, 1 equiv.), Pd(dba)<sub>2</sub> (8.0 mg, 0.01 mmol, 5 mol%), PPh<sub>3</sub> (14.7 mg, 0.06 mmol, 20 mol%) and toluene (2 mL). The solution was stirred at 90 °C for 45 min, hydrolyzed and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (cyclohexane / AcOEt, 90 / 10) and yielded 36 mg (56%) of the expected compound **13** as a yellow solid.

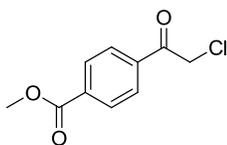
Data for **13**:

**m.p.:** 49 - 50 °C. **IR:** 3061, 1658, 1592, 1490, 1372, 1270 cm<sup>-1</sup>. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.68 - 7.72 (m, 2H), 7.27 - 7.43 (m, 8H), 5.81 (ddt, *J* = 6.4, 10.3, 17.1 Hz, 1H), 5.01 (dq, *J* = 1.6, 17.2 Hz, 1H), 4.97 (ddt, *J* = 1.1, 2.3, 10.2 Hz, 1H), 2.34 - 2.46 (m, 4H). **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 172.5, 142.5, 135.1, 129.1, 128.1, 126.6, 115.3, 34.7, 29.6. **HRMS** (ESI) *m/z* calcd. for C<sub>17</sub>H<sub>17</sub>NaN<sub>3</sub>O [M + Na<sup>+</sup>] 274.1200, found 274.1202.

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<sup>165</sup> Zhang, Y.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 15964-15965.

### Chlorination of ketones:

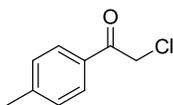


### Methyl 4-(2-chloroacetyl)benzoate (1d):

Prepared according to **GP3** from methyl 4-acetylbenzoate (713.3 mg, 4.00 mmol, 1 equiv.), NCS (535.4 mg, 4.01 mmol, 1 equiv.) and APTS (69.9 mg, 0.41 mmol, 0.1 equiv.). The crude product was purified by column chromatography (CH<sub>2</sub>Cl<sub>2</sub> / cyclohexane, 10 / 1). The desired compound was isolated as white crystals (535 mg, 63%).

Data for **1d**:

**m.p.** = 136 °C. **IR**: 3001, 2947, 1704, 1432, 1401, 1279, 1196, 1108, 762 cm<sup>-1</sup>; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 8.18 – 8.15 (m, 2H), 8.04 – 8.01 (m, 2H), 4.73 (s, 2H), 3.97 (s, 3H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 190.6, 165.9, 137.3, 134.6, 130.0, 128.4, 52.5, 45.8. **HRMS** (ESI) m/z calcd. for C<sub>10</sub>H<sub>9</sub>ClNaO<sub>3</sub> [M + Na<sup>+</sup>] 235.01324, found 235.01325.



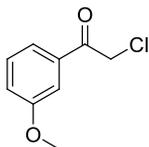
### 2-Chloro-1-*p*-tolylethanone (1h):

Prepared according to **GP3** from 1-*p*-tolylethanone (533.7 mg, 3.98 mmol, 1 equiv.), NCS (538.3 mg, 4.03 mmol, 1 equiv.) and APTS (69.5 mg, 0.40 mmol, 0.1 equiv.). The crude product was purified by column chromatography (CH<sub>2</sub>Cl<sub>2</sub> / cyclohexane, 10 / 1). It afforded the desired compound as a brown solid (539 mg, 80%).

Data for **1h**:

**m.p.** = 41 °C. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.87 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 4.69 (s, 2H), 2.44 (s, 3H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 190.8, 145.1, 131.9, 129.7, 128.7, 46.0, 21.8.

These data are in good agreement with those reported in the literature.<sup>166</sup>

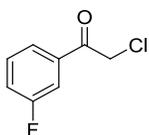


### 2-Chloro-1-(3-methoxyphenyl)ethanone (1f):

Prepared according to **GP3** from 1-(3-methoxyphenyl)ethanone (533.7 mg, 3.98 mmol, 1 equiv.), NCS (538.3 mg, 4.03 mmol, 1 equiv.) and APTS (69.5 mg, 0.40 mmol, 0.1 equiv.). The crude product was purified by column chromatography (CH<sub>2</sub>Cl<sub>2</sub> / cyclohexane, 8 / 2). The desired compound was isolated as a dark red solid (417 mg, 56%).

Data for **1f**:

**m.p.** = 60 °C. **IR**: 2979, 2941, 2844, 1697, 1574, 1433, 1247, 1003, 777 cm<sup>-1</sup>. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.54 – 7.47 (m, 2H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.16 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 4.70 (s, 2H), 3.86 (s, 3H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 190.9, 160.1, 135.6, 129.9, 121.0, 120.5, 112.9, 55.6, 46.2. **HRMS** (ESI) *m/z* calcd. for C<sub>9</sub>H<sub>9</sub>ClNaO<sub>2</sub> [M + Na<sup>+</sup>] 207.01833, found 207.01836.



### 2-Chloro-1-(3-fluorophenyl)ethanone (1j):

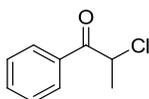
Prepared according to **GP3** from 1-(3-fluorophenyl)ethanone (554.9 mg, 4.02 mmol, 1 equiv.), NCS (536.6 mg, 4.02 mmol, 1 equiv.) and APTS (68.5 mg, 0.40 mmol, 0.1 equiv.). The crude product was purified by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>/cyclohexane, 8 / 2). The desired compound was isolated as a colorless oil (200 mg, 29%).

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<sup>166</sup> Ram, R. N.; Manoj, T. P. *J. Org. Chem.* **2008**, *73*, 5633-5635.

Data for **1j**:

**IR**: 3077, 2946, 1706, 1589, 1484, 1245  $\text{cm}^{-1}$ .  **$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.78 – 7.62 (m, 2H), 7.50 (td,  $J = 8.0, 5.5$  Hz, 1H), 7.33 (tdd,  $J = 8.2, 2.6, 0.9$  Hz, 1H), 4.68 (s, 2H).  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  190.1, 163.0 (d,  $J = 249.0$  Hz), 136.3 (d,  $J = 6.4$  Hz), 130.7 (d,  $J = 7.7$  Hz), 124.4 (d,  $J = 3.1$  Hz), 121.2 (d,  $J = 21.4$  Hz), 115.5 (d,  $J = 22.7$  Hz), 45.8. **HRMS** (ESI)  $m/z$  calcd. for  $\text{C}_8\text{H}_6\text{ClFNaO}$  [ $\text{M} + \text{Na}^+$ ] 194.99834, found 194.99804.



### 2-Chloro-1-phenylpropan-1-one (**1o**):

Prepared according to **GP3** from propiophenone (536.2 mg, 4.00 mmol, 1 equiv.), NCS (536.5 mg, 4.02 mmol, 1 equiv.) and APTS (70.6 mg, 0.41 mmol, 0.1 equiv.). The crude product was purified by column chromatography ( $\text{CH}_2\text{Cl}_2$  / cyclohexane, 10 / 1). It delivered the title compound as a yellow oil (572 mg, 85%).

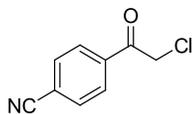
Data for **1o**:

**$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.02 (dd,  $J = 8.5, 1.3$  Hz, 2H), 7.62 – 7.58 (m, 1H), 7.52 – 7.48 (m, 2H), 5.26 (q,  $J = 6.7$  Hz, 1H), 1.75 (d,  $J = 6.7$  Hz, 3H).  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  193.7, 134.2, 133.8, 129.0, 128.8, 52.9, 20.0.

These data are in good agreement with those reported in the literature.<sup>167</sup>

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<sup>167</sup> Hajra, S.; Bhowmick, M.; Maji, B.; Sinha, D. *J. Org. Chem.* **2007**, *72*, 4872-4876.



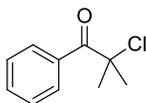
#### 4-(2-Chloroacetyl)benzonitrile (1b):

Prepared according to **GP3** from 4-acetylbenzonitrile (575.5 mg, 3.96 mmol, 1 equiv.), NCS (534.5 mg, 4.00 mmol, 1 equiv.) and APTS (66.6 mg, 0.39 mmol, 0.1 equiv.). The crude product was purified by column chromatography (CH<sub>2</sub>Cl<sub>2</sub> / cyclohexane, 3 / 7). The desired compound was isolated as a white solid (461 mg, 65%).

Data for **1b**:

**m.p.** = 90 °C (lit. = 91-95 °C).<sup>168</sup> **IR**: 3048, 2928, 2855, 2232, 1706, 1398, 1208, 830 cm<sup>-1</sup>. **<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.08 – 8.06 (m, 2H), 7.84 – 7.81 (m, 2H), 4.68 (s, 2H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 190.1, 137.2, 132.8, 129.2, 117.7, 117.4, 45.5. **HRMS** (ESI) m/z calcd. for C<sub>9</sub>H<sub>6</sub>ClNNaO [M + Na<sup>+</sup>] 202.0030, found 202.0037.

These data are in good agreement with those reported in the literature.<sup>169</sup>



#### 2-chloro-2-methyl-1-phenylpropan-1-one (1p):

Prepared according to **GP3** from 2-methyl-1-phenylpropan-1-one (575.0 mg, 3.76 mmol, 1 equiv.), NCS (539.8 mg, 4.04 mmol, 1 equiv.) and APTS (70.5 mg, 0.41 mmol, 0.1 equiv.). The crude product was purified by column chromatography (CH<sub>2</sub>Cl<sub>2</sub> / cyclohexane, 10 / 1). The desired compound was isolated as a colorless oil (507 mg, 74%).

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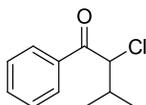
<sup>168</sup> Russell, G. A.; Ros, F. *J. Am. Chem. Soc.* **1985**, *107*, 2506-2511.

<sup>169</sup> See: Olivato, P. R.; Guerrero, S. A.; Rittner, R. *Magn. Reson. Chem.* **1987**, *25*, 179-180. For <sup>13</sup>C spectrum and: Szymanski, W.; Postema, C. P.; Tarabiono, C.; Berthiol, F. Campbell-Verduyn, L.; De Wildeman, S.; De Vries, J. G. Feringa, B. L.; Janssen, D. B. *Adv. Synth. Catal.* **2010**, *352*, 2111-2115. Rieke, R. D.; Brown, J. D.; Wu, X. *Synth. Commun.* **1995**, *25*, 3923-3930. For <sup>1</sup>H spectrum.

Data for **1p**:

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.16 – 8.14 (m, 2H), 7.56 – 7.52 (m, 1H), 7.47-7.43 (m, 2H), 1.90 (s, 6H).  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  197.2, 134.6, 132.6, 130.1, 128.2, 68.4, 30.6.

These data are in good agreement with those reported in the literature.<sup>170</sup>



### **2-chloro-3-methyl-1-phenylbutan-1-one (1q):**

Prepared according to **GP3** from 3-methyl-1-phenylbutan-1-one (642.3 mg, 3.96 mmol, 1 equiv.), NCS (535.9 mg, 4.02 mmol, 1 equiv.) and APTS (69.2 mg, 0.40 mmol, 0.1 equiv.). The crude product was purified by column chromatography ( $\text{CH}_2\text{Cl}_2$  / cyclohexane, 10 / 1). The desired compound was isolated as a colorless oil (779 mg, 91%).

Data for **1q**:

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.00 – 7.97 (m, 2H), 7.62 – 7.58 (m, 1H), 7.51-7.47 (m, 2H), 4.96 (d,  $J = 7.3$  Hz, 1H), 2.53-2.42 (m, 1H), 1.12 (d,  $J = 6.6$  Hz, 3H), 1.04 (d,  $J = 6.7$  Hz, 3H).  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  194.1, 135.2, 133.7, 128.9, 128.8, 65.1, 31.6, 20.3, 18.6.

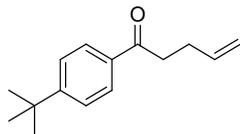
These data are in good agreement with those reported in the literature.<sup>171</sup>

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<sup>170</sup> Wang, Z.; Zhu, L.; Yin, F.; Su, Z.; Li, Z.; Li, C. *J. Am. Chem. Soc.* **2012**, *134*, 4258–4263.

<sup>171</sup> Russell, G. A.; Mudryk, B.; Jawdosiuk, M.; Wrobel, Z. *J. Org. Chem.* **1982**, *47*, 1879–1884.

Scope of the pseudo-domino sequence carbonylative / decarboxylative allylation of  $\alpha$ -chloroketones:

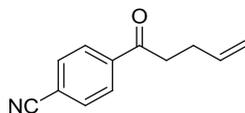


**1-(4-tert-Butylphenyl)pent-4-en-1-one (3a)**

Prepared according to **GP4** from 2-chloro-1-(4-*tert*-butylphenyl)ethanone (212.9 mg, 1.01 mmol, 1 equiv.), Pd(OAc)<sub>2</sub> (22.6 mg, 0.10 mmol, 10 mol%), P(2-fur)<sub>3</sub> (93.8 mg, 0.40 mmol, 40 mol%), *n*-Bu<sub>3</sub>N (360  $\mu$ L, 1.51 mmol, 1.50 equiv.), toluene (1.5 mL) and allyl alcohol (1 mL, 14.6 mmol, 15 equiv.). The residue was purified by column chromatography on silica gel (cyclohexane / AcOEt, 90 / 10) and yielded 118 mg (54%) of the expected product **3a** as a yellow oil.

Data for **3a**:

IR: 3075, 2961, 2358, 1683, 1606, 1407, 1269, 1107, 913  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.93 – 7.90 (m, 2H), 7.50 – 7.47 (m, 2H), 5.92 (ddt,  $J$  = 16.8, 10.2, 6.5 Hz, 1H), 5.10 (dq,  $J$  = 17.1, 1.6 Hz, 1H), 5.02 (dq,  $J$  = 10.2, 1.3 Hz, 1H), 3.08 – 3.05 (m, 2H), 2.54 – 2.48 (m, 2H), 1.35 (s, 9H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  199.2, 156.8, 137.5, 134.5, 128.1, 125.6, 115.3, 37.7, 35.2, 31.2, 28.3. HRMS (ESI)  $m/z$  calcd. for C<sub>15</sub>H<sub>20</sub>NaO [M + Na<sup>+</sup>] 239.14064, found 239.14067.



**4-Pent-4-enoylbenzonitrile (3b)**

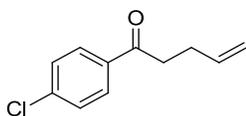
Prepared according to **GP4** from 4-(2-chloroacetyl)benzonitrile (166.7 mg, 0.92 mmol, 1 equiv.), Pd(OAc)<sub>2</sub> (22.5 mg, 0.11 mmol, 10 mol%), P(2-fur)<sub>3</sub> (92.9 mg, 0.40 mmol, 43 mol%), *n*-Bu<sub>3</sub>N (360  $\mu$ L, 1.51 mmol, 1.64 equiv.), toluene (1.5 mL) and allyl alcohol (1 mL, 14.6 mmol, 15 equiv.). The residue was purified by column chromatography on silica gel

(pentane / CH<sub>2</sub>Cl<sub>2</sub>, 20 / 80) but afforded a mixture of the product **3b** and 4-acetylbenzotrile. <sup>1</sup>H NMR with butadiene sulfone as internal standard allows to calculate 51 mg (30%) of the expected product **3b**.

Data for **3b**:

IR: 3077, 2923, 2358, 2231, 1691, 1405, 1282, 1206, 985, 917, 848 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.06 – 8.04 (m, 2H), 7.85 – 7.76 (m, 2H), 5.89 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.09 (dq, *J* = 17.1, 1.6 Hz, 1H), 5.03 (dq, *J* = 10.2, 1.2 Hz, 1H), 3.09 (t, *J* = 7.3 Hz, 2H), 2.54 – 2.48 (m, 2H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 198.1, 134.0, 136.8, 132.6, 128.6, 118.4, 116.5, 115.9, 38.2, 27.9. HRMS (ESI) *m/z* calcd. for C<sub>12</sub>H<sub>11</sub>NNaO [M + Na<sup>+</sup>] 208.07329, found 208.07308.

These data are in good agreement with those reported in the literature.<sup>172</sup>



### 1-(4-Chlorophenyl)pent-4-en-1-one (**3c**)

Prepared according to **GP4** from 2-chloro-1-(4-chlorophenyl)ethanone (190.3 mg, 1.01 mmol, 1 equiv.), Pd(OAc)<sub>2</sub> (22.5 mg, 0.10 mmol, 10 mol%), P(2-fur)<sub>3</sub> (91.9 mg, 0.39 mmol, 39 mol%), *n*-Bu<sub>3</sub>N (360 μL, 1.51 mmol, 1.51 equiv.), toluene (1.5 mL) and allyl alcohol (1 mL, 14.6 mmol, 15 equiv.). The residue was purified by column chromatography on silica gel (cyclohexane / AcOEt, 90 / 10) and yielded 112 mg (57%) of the expected product **3c** as a yellow oil.

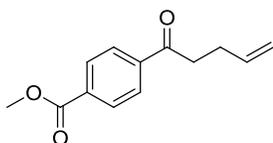
Data for **3c**:

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<sup>172</sup> Hodgson, D. M.; Humphreys, P. G.; Miles, S. M.; Brierley, C. A. J.; Ward, J. G. *J. Org. Chem.* **2007**, *72*, 10009-10021.

**IR:** 3076, 2919, 2358, 1687, 1643, 1403, 1206, 1093, 980, 915, 834  $\text{cm}^{-1}$ ;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.91 – 7.88 (m, 2H), 7.45 – 7.41 (m, 2H), 5.89 (ddt,  $J$  = 16.8, 10.2, 6.5 Hz, 1H), 5.09 (dq,  $J$  = 17.1, 1.6 Hz, 1H), 5.02 (dq,  $J$  = 10.2, 1.3 Hz, 1H), 3.06 – 3.02 (m, 2H), 2.52 – 2.46 (m, 2H).  **$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  198.2, 139.5, 137.1, 135.3, 129.5, 129.0, 115.5, 37.8, 28.1. **HRMS** (ESI)  $m/z$  calcd. for  $\text{C}_{11}\text{H}_{11}\text{ClNaO}$  [ $\text{M} + \text{Na}^+$ ] 217.03906, found 217.03879.

These data are in good agreement with those reported in the literature.<sup>173</sup>

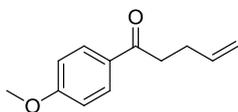


### **Methyl 4-pent-4-enoylbenzoate (3d)**

Prepared according to **GP4** from methyl 4-(2-chloroacetyl)benzoate (212.9 mg, 1.00 mmol, 1 equiv.),  $\text{Pd}(\text{OAc})_2$  (22.6 mg, 0.10 mmol, 10 mol%),  $\text{P}(\text{2-fur})_3$  (93.9 mg, 0.40 mmol, 40 mol%),  $n\text{-Bu}_3\text{N}$  (360  $\mu\text{L}$ , 1.51 mmol, 1.51 equiv.), toluene (1.5 mL) and allyl alcohol (1 mL, 14.6 mmol, 15 equiv.). The residue was purified by column chromatography on silica gel (pentane /  $\text{CH}_2\text{Cl}_2$ , 20 / 80) and yielded 87 mg (40%) of the expected product **3d** as a yellow powder.

Data for **3d**:

**m.p.** = 73  $^\circ\text{C}$ . **IR:** 3077, 2956, 1718, 1675, 1568, 1568, 1432, 1274, 1195, 1104, 755  $\text{cm}^{-1}$ ;  **$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.13 (d,  $J$  = 8.6 Hz, 2H), 8.01 (d,  $J$  = 8.6 Hz, 2H), 5.91 (ddt,  $J$  = 16.8, 10.2, 6.5 Hz, 1H), 5.10 (dq,  $J$  = 17.1, 1.6 Hz, 1H), 5.03 (dq,  $J$  = 10.2, 1.3 Hz, 1H), 3.96 (s, 3H), 3.11 (t,  $J$  = 7.3 Hz, 2H), 2.54 – 2.49 (m, 2H).  **$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  199.0, 166.3, 140.2, 137.1, 133.9, 129.9, 128.0, 115.6, 52.6, 38.2, 28.1. **HRMS** (ESI)  $m/z$  calcd. for  $\text{C}_{13}\text{H}_{14}\text{NaO}_3$  [ $\text{M} + \text{Na}^+$ ] 241.08323, found 241.08352.



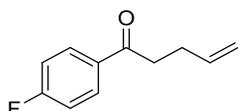
### 1-(4-Methoxyphenyl)pent-4-en-1-one (3e)

Prepared according to **GP4** from 2-chloro-1-(4-methoxyphenyl)ethanone (184 mg, 1.00 mmol, 1 equiv.), Pd(OAc)<sub>2</sub> (22.7 mg, 0.10 mmol, 10 mol%), P(2-fur)<sub>3</sub> (94.3 mg, 0.41 mmol, 41 mol%), *n*-Bu<sub>3</sub>N (360 μL, 1.51 mmol, 1.51 equiv.), toluene (1.5 mL) and allyl alcohol (1 mL, 14.6 mmol, 15 equiv.). The residue was purified by column chromatography on silica gel (cyclohexane / AcOEt, 90 / 10) and yielded 146 mg (77%) of the expected product **3e** as a yellow oil.

Data for **3e**:

**IR**: 3074, 2928, 2843, 1676, 1601, 1511, 1256, 1172, 1028, 836 cm<sup>-1</sup>; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.96 – 7.92 (m, 2H), 6.95 – 6.91 (m, 2H), 5.90 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.08 (dq, *J* = 17.1, 1.6 Hz, 1H), 5.00 (dd, *J* = 10.2, 1.5 Hz, 1H), 3.86 (s, 3H), 3.03 – 3.00 (m, 2H), 2.51 – 2.45 (m, 2H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 198.1, 163.5, 137.6, 130.4, 130.1, 115.2, 113.8, 55.5, 37.5, 28.5. **HRMS** (ESI) *m/z* calcd. for C<sub>12</sub>H<sub>14</sub>NaO<sub>2</sub> [M + Na<sup>+</sup>] 213.08860, found 213.08858.

These data are in good agreement with those reported in the literature.<sup>173</sup>



### 1-(4-Fluorophenyl)pent-4-en-1-one (3i)

Prepared according to **GP4** from 2-chloro-1-(4-fluorophenyl)ethanone (171.6 mg, 0.99 mmol, 1 equiv.), Pd(OAc)<sub>2</sub> (22.9 mg, 0.10 mmol, 10 mol%), P(2-fur)<sub>3</sub> (92.8 mg, 0.40

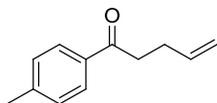
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<sup>173</sup> Hok, S.; Schore, N. E. *J. Org. Chem.* **2006**, *71*, 1736-1738.

mmol, 40 mol%), *n*-Bu<sub>3</sub>N (360 μL, 1.51 mmol, 1.53 equiv.), toluene (1.5 mL) and allyl alcohol (1 mL, 14.6 mmol, 15 equiv.). The residue was purified by column chromatography on silica gel (cyclohexane / AcOEt, 90 / 10) and yielded 115 mg (65%) of the expected product **3i** as a yellow oil.

Data for **3i**:

**IR**: 3076, 2924, 2358, 1686, 1598, 1506, 1411, 1361, 1230, 1156, 984, 916, 841 cm<sup>-1</sup>; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 8.01 – 7.98 (m, 2H), 7.16 – 7.10 (m, 2H), 5.90 (ddt, *J* = 16.9, 10.2, 6.5 Hz, 1H), 5.09 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.02 (dd, *J* = 10.2, 1.3 Hz, 1H), 3.05 (t, *J* = 7.3 Hz, 2H), 2.53 – 2.47 (m, 2H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 197.8, 165.8 (d, *J* = 254.5 Hz), 137.2, 133.4, 130.7 (d, *J* = 9.2 Hz), 115.7 (d, *J* = 38.8 Hz), 115.6, 37.7, 28.2. **HRMS** (ESI) *m/z* calcd. for C<sub>11</sub>H<sub>11</sub>FNaO [M + Na<sup>+</sup>] 201.06861, found 201.06839.



### **1-*p*-Tolyl-pent-4-en-1-one (3h)**

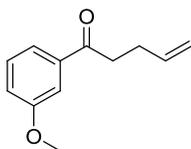
Prepared according to **GP4** from 2-chloro-1-*p*-tolylethanone (170.2 mg, 1.00 mmol, 1 equiv.), Pd(OAc)<sub>2</sub> (22.3 mg, 0.10 mmol, 10 mol%), P(2-fur)<sub>3</sub> (92.4 mg, 0.40 mmol, 40 mol%), *n*-Bu<sub>3</sub>N (360 μL, 1.51 mmol, 1.51 equiv.), toluene (1.5 mL) and allyl alcohol (1 mL, 14.6 mmol, 15 equiv.). The residue was purified by column chromatography on silica gel (cyclohexane / CH<sub>2</sub>Cl<sub>2</sub>, 20 / 80) and yielded 77 mg (44%) of the expected product **3h** as a yellow oil.

Data for **3h**:

**IR**: 2921, 1681, 1607, 1411, 1359, 1277, 1181, 1114, 979, 913, 810 cm<sup>-1</sup>; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.88 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 5.92 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.09 (dq, *J* = 17.1, 1.6 Hz, 1H), 5.02 (dq, *J* = 10.2, 1.3 Hz, 1H), 3.08 – 3.04 (m, 2H), 2.53 – 2.47 (m, 2H), 2.42 (s, 3H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 199.2, 143.8, 137.5, 134.6, 129.4, 128.3,

115.3, 37.7, 28.4, 21.7. **HRMS** (ESI)  $m/z$  calcd. for  $C_{12}H_{14}NaO$  [ $M + Na^+$ ] 197.09369, found 197.09368.

These data are in good agreement with those reported in the literature.<sup>173</sup>



### 1-(3-Methoxyphenyl)pent-4-en-1-one (**3f**)

Prepared according to **GP4** from 2-chloro-1-(3-methoxyphenyl)ethanone (185 mg, 1.00 mmol, 1 equiv.),  $Pd(OAc)_2$  (22.1 mg, 0.10 mmol, 10 mol%),  $P(2-fur)_3$  (91.9 mg, 0.39 mmol, 39 mol%),  $n-Bu_3N$  (360  $\mu$ L, 1.51 mmol, 1.51 equiv.), toluene (1.5 mL) and allyl alcohol (1 mL, 14.6 mmol, 15 equiv.). The residue was purified by column chromatography on silica gel (cyclohexane / AcOEt, 95 / 5) and yielded 70 mg (37%) of the expected product **3f** as a yellow oil.

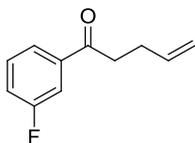
Data for **3f**:

**IR**: 3075, 2938, 2841, 2358, 1685, 1589, 1432, 1260, 1171, 1039, 914, 874, 780  $cm^{-1}$ ;  **$^1H$  NMR** (400 MHz,  $CDCl_3$ )  $\delta$  7.56 – 7.49 (m, 2H), 7.37 (t,  $J = 7.9$  Hz, 1H), 7.11 (ddd,  $J = 8.2, 2.7, 0.9$  Hz, 1H), 5.91 (ddt,  $J = 16.8, 10.2, 6.5$  Hz, 1H), 5.09 (dq,  $J = 17.1, 1.6$  Hz, 1H), 5.02 (dq,  $J = 10.2, 1.3$  Hz, 1H), 3.86 (s, 3H), 3.08 – 3.05 (m, 2H), 2.53 – 2.47 (m, 2H).  **$^{13}C$  NMR** (101 MHz,  $CDCl_3$ )  $\delta$  199.3, 159.9, 138.4, 137.4, 129.6, 120.7, 119.5, 115.4, 112.4, 55.5, 37.9, 28.3. **HRMS** (ESI)  $m/z$  calcd. for  $C_{12}H_{14}NaO_2$  [ $M + Na^+$ ] 213.08860, found 213.08844.

These data are in good agreement with those reported in the literature.<sup>174</sup>

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<sup>174</sup> Overman, L. E.; Renaldo, A. E. *J. Am. Chem. Soc.* **1990**, *112*, 3945-3929.



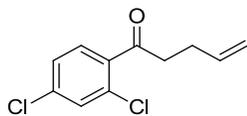
### 1-(3-Fluorophenyl)pent-4-en-1-one (3j)

Prepared according to **GP4** from 2-chloro-1-(3-fluorophenyl)ethanone (193.4 mg, 1.12 mmol, 1 equiv.), Pd(OAc)<sub>2</sub> (22.2 mg, 0.10 mmol, 9 mol%), P(2-fur)<sub>3</sub> (91.4 mg, 0.39 mmol, 35 mol%), *n*-Bu<sub>3</sub>N (360 μL, 1.51 mmol, 1.34 equiv.), toluene (1.5 mL) and allyl alcohol (1 mL, 14.6 mmol, 15 equiv.). The residue was purified by column chromatography on silica gel (cyclohexane / AcOEt, 95 / 5) and yielded 73 mg (37%) of the expected product **3j** as a yellow oil.

Data for **3j**:

**IR**: 3076, 2927, 2358, 1690, 1588, 1442, 1260, 1158, 996, 910, 784 cm<sup>-1</sup>; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.74 (ddd, *J* = 7.8, 1.4, 1.1 Hz, 1H), 7.65 (ddd, *J* = 9.5, 2.5, 1.6 Hz, 1H), 7.45 (td, *J* = 7.9, 5.5 Hz, 1H), 7.32 – 7.22 (m, 1H), 5.90 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.10 (dq, *J* = 17.1, 1.6 Hz, 1H), 5.03 (dq, *J* = 10.2, 1.3 Hz, 1H), 3.08 – 3.05 (m, 2H), 2.54 – 2.48 (m, 2H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 198.2, 163.0 (d, *J* = 247.9 Hz), 139.1 (d, *J* = 6.1 Hz), 137.1, 130.4 (d, *J* = 7.6 Hz), 123.9 (d, *J* = 3.0 Hz), 120.1 (d, *J* = 21.5 Hz), 115.6, 114.9 (d, *J* = 22.3 Hz), 38.0, 28.1. **HRMS** (ESI) *m/z* calcd. for C<sub>11</sub>H<sub>11</sub>FNaO [M + Na<sup>+</sup>] 201.06861, found 201.06835.

These data are in good agreement with those reported in the literature.<sup>174</sup>



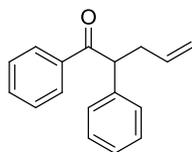
### 1-(2,4-Dichlorophenyl)pent-4-en-1-one (3g)

Prepared according to **GP4** from 2-chloro-1-(2,4-dichlorophenyl)ethanone (220.8 mg, 0.99 mmol, 1 equiv.), Pd(OAc)<sub>2</sub> (22.3 mg, 0.10 mmol, 10 mol%), P(2-fur)<sub>3</sub> (93.6 mg, 0.40 mmol, 40 mol%), *n*-Bu<sub>3</sub>N (360 μL, 1.51 mmol, 1.53 equiv.), toluene (1.5 mL) and allyl alcohol (1 mL, 14.6 mmol, 15 equiv.). The residue was purified by column chromatography on silica

gel (cyclohexane / AcOEt, 90 / 10) and yielded 81 mg (36%) of the expected product **3g** as a yellow oil.

Data for **3g**:

**IR**: 3079, 2923, 2358, 1696, 1582, 1372, 1272, 1200, 1104, 982, 915, 820  $\text{cm}^{-1}$ ;  **$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.45 – 7.42 (m, 2H), 7.32 (dd,  $J = 8.3, 2.0$  Hz, 1H), 5.86 (ddt,  $J = 16.8, 10.2, 6.5$  Hz, 1H), 5.10 – 5.00 (m, 2H), 3.04 (t,  $J = 7.3$  Hz, 2H), 2.50 – 2.45 (m, 2H).  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  201.4, 137.7, 137.4, 136.7, 132.1, 130.5, 130.2, 127.4, 115.8, 42.1, 28.2. **HRMS** (ESI)  $m/z$  calcd. for  $\text{C}_{11}\text{H}_{10}\text{Cl}_2\text{NaO}$  [ $\text{M} + \text{Na}^+$ ] 250.99991, found 251.00009.

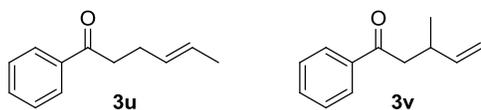


### 1,2-Diphenylpent-4-en-1-one (**3n**)

Prepared according to **GP4** from 2-chloro-1,2-diphenylethanone (230.1 mg, 1.00 mmol, 1 equiv.),  $\text{Pd}(\text{OAc})_2$  (22.1 mg, 0.10 mmol, 10 mol%),  $\text{P}(2\text{-fur})_3$  (91.3 mg, 0.39 mmol, 39 mol%),  $n\text{-Bu}_3\text{N}$  (360  $\mu\text{L}$ , 1.51 mmol, 1.51 equiv.), toluene (1.5 mL) and allyl alcohol (1 mL, 14.6 mmol, 15 equiv.). The residue was purified by column chromatography on silica gel (cyclohexane /  $\text{CH}_2\text{Cl}_2$ , 20 / 80) and yielded 77 mg (33%) of the expected product **3n** as a yellow oil.

Data for **3n**:

**IR**: 3068, 2922, 2358, 1681, 1595, 1493, 1447, 1343, 1245, 1205, 1074, 993, 917, 753, 697  $\text{cm}^{-1}$ ;  **$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.99 – 7.96 (m, 2H), 7.52 – 7.47 (m, 1H), 7.43 – 7.38 (m, 2H), 7.30 – 7.32 (m, 4H), 7.24 - 7.20 (m, 1H), 5.77 (ddt,  $J = 17.1, 10.2, 6.9$  Hz, 1H), 5.06 (dq,  $J = 17.1, 1.5$  Hz, 1H), 4.99 (ddt,  $J = 10.2, 2.0, 1.1$  Hz, 1H), 4.65 (t,  $J = 7.3$  Hz, 1H), 2.97 (dddt,  $J = 14.5, 7.9, 6.9, 1.2$  Hz, 1H), 2.59 (dtt,  $J = 14.3, 6.9, 1.3$  Hz, 1H).  **$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  199.3, 139.2, 136.8, 136.1, 133.0, 129.0, 128.8, 128.6, 128.3, 127.2, 116.8, 53.7, 38.3. **HRMS** (ESI)  $m/z$  calcd. for  $\text{C}_{17}\text{H}_{16}\text{NaO}$  [ $\text{M} + \text{Na}^+$ ] 259.10934, found 259.10973.

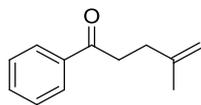


### (E)-1-phenylhex-4-en-1-one (**3u**) and 3-methyl-1-phenylpent-4-en-1-one (**3v**)

Prepared according to **GP4** from  $\alpha$ -chloroacetophenone (77.4 mg, 0.50 mmol, 1 equiv.), Pd(OAc)<sub>2</sub> (10.7 mg, 0.05 mmol, 10 mol%), P(2-fur)<sub>3</sub> (44.5 mg, 0.19 mmol, 38 mol%), *n*-Bu<sub>3</sub>N (180  $\mu$ L, 0.76 mmol, 1.51 equiv.) and (*E*)-but-2-en-1-ol (1.3 mL, 15.2 mmol, 30 equiv.). The residue was purified by column chromatography on silica gel (pentane / CH<sub>2</sub>Cl<sub>2</sub>, 90 / 10) and yielded 44 mg (50%) of a mixture (80 / 20) of the linear **3u** and the branched products **3v** as a yellow oil.

Data for **3u**, **3v**:

**IR**: 2924, 2856, 1733, 1687, 1594, 1448, 1364, 1264, 1205, 968 cm<sup>-1</sup>; **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.98 – 7.95 (m, 2H (**3u**) + 2H (**3v**)), 7.58 – 7.54 (m, 1H (**3u**) + 1H (**3v**)), 7.49 – 7.45 (m, 2H (**3u**) + 2H (**3v**)), 5.86 (ddd, *J* = 17.0, 10.4, 6.4 Hz, 1H (**3v**)), 5.52-5.50 (m, 2H (**3u**)), 5.04 (dt, *J* = 17.3, 1.3 Hz, 1H (**3v**)), 4.99 – 4.94 (m, 1H (**3v**)), 3.06 – 3.02 (m, 2H (**3u**) + 1H (**3v**)), 2.94 – 2.88 (m, 1H (**3v**)), 2.50 (m, 1H (**3v**)), 2.46 – 2.40 (m, 2H (**3u**)), 1.64-1.66 (m, 3H (**3u**)), 1.11 (d, *J* = 6.4 Hz, 3H (**3v**)). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  199.9, 196.4, 143.2, 137.1, 133.0, 133.0, 130.1, 129.9, 128.7, 128.2, 128.1, 126.0, 113.1, 45.3, 38.7, 33.7, 27.3, 19.9, 18.0. **HRMS** (ESI) *m/z* calcd. for C<sub>12</sub>H<sub>14</sub>NaO [M + Na<sup>+</sup>] 197.09369, found 197.09358.



### 4-Methyl-1-phenylpent-4-en-1-one (**3t**)

Prepared according to **GP4** from  $\alpha$ -chloroacetophenone (78.1 mg, 0.50 mmol, 1 equiv.), Pd(OAc)<sub>2</sub> (11.6 mg, 0.10 mmol, 10 mol%), P(2-fur)<sub>3</sub> (57.9 mg, 0.10 mmol, 20 mol%), *n*-Bu<sub>3</sub>N (180  $\mu$ L, 0.76 mmol, 1.50 equiv.) and 2-methylprop-2-en-1-ol (1.3 mL, 15.4 mmol, 30

equiv.). The residue was purified by column chromatography on silica gel (cyclohexane / AcOEt, 95 / 5) and yielded 45 mg (51%) of the expected product **3t** as a yellow oil.

Data for **3t**:

**IR**: 2924, 2853, 2360, 2341, 1725, 1686, 1650, 1558, 1448, 1360, 1202, 967, 888  $\text{cm}^{-1}$ . **<sup>1</sup>H NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.99 – 7.97 (m, 2H), 7.59 – 7.54 (m, 1H), 7.49 – 7.45 (m, 2H), 4.77 (s, 1H) 4.72 (s, 1H), 3.15 – 3.11 (m, 2H), 2.48 – 2.44 (m, 2H), 1.79 (s, 3H). **<sup>13</sup>C NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  199.8, 144.8, 137.1, 133.1, 128.7, 128.1, 110.3, 36.9, 32.0, 22.8. **HRMS** (ESI)  $m/z$  calcd. for  $\text{C}_{12}\text{H}_{14}\text{NaO}$  [ $\text{M} + \text{Na}^+$ ] 197.09369, found 197.09363.

#### **Procedure for the stoichiometric procedure:**

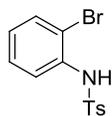
A flask was charged with  $\alpha$ -chloroacetophenone (30.4 mg, 0.2 mmol, 1 equiv.),  $\text{Pd}(\text{dba})_2$  (114.7 mg, 0.2 mmol, 1 equiv.),  $\text{PPh}_3$  (208.7 mg, 0.8 mmol, 4 equiv.) and acetone (10 mL). The reaction mixture was stirred at room temperature overnight, then directly concentrated *in vacuo*.  $^1\text{H}$  NMR of the crude product allowed to identify the acetophenone as the only product formed.

#### **Procedure for the kinetic studies:**

A flask was charged with  $\alpha$ -chloroacetophenone (10 mg, 0.06 mmol, 1 equiv.),  $\text{Pd}(\text{OAc})_2$  (14 mg, 0.06 mmol, 1 equiv.),  $\text{P}(2\text{-fur})_3$  (59.9 mg, 0.26 mmol, 4 equiv.) and  $\text{CDCl}_3$  (1 mL). The reaction mixture was stirred at room temperature for homogenization and directly transferred into an NMR tube. Tube was purged with argon and sealed. An NMR spectrum was immediately measured, then one hour later at room temperature, a second NMR experience was recorded, followed by other experiences after another hour at room temperature, 30 min at 50 °C and another 30 min at 50 C.

#### d) Toward a new domino sequence

##### Protection of *o*-halogenoanilines:



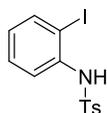
##### ***N*-(2-bromophenyl)-4-methylbenzenesulfonamide (18)**

Prepared according to **GP5** from 2-bromogenoaniline (4.3 g, 24.3 mmol, 1 equiv.), pyridine (10 mL, 124.9 mmol, 5.1 equiv.) and *p*-toluenesufonyl chloride (5.7 g, 30 mmol, 1.2 equiv.). Purification by column chromatography on silica gel afforded 8.06 g (100%) of the desired compound **18** as a white solid.

Data for **18**:

**m.p.** = 94 °C. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.67-7.63 (m, 3H), 7.33-7.30 (m, 1H), 7.25-7.19 (m, 3H), 6.97-6.93 (m, 2H), 2.37 (s, 3H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 144.4, 136.0, 134.9, 132.7, 129.8, 128.7, 127.4, 126.4, 122.6, 115.8, 21.7.

These data are in good agreement with those reported in the literature.<sup>175</sup>



##### ***N*-(2-iodophenyl)-4-methylbenzenesulfonamide (19)**

Prepared according to **GP5** from 2-iodogenoaniline (5.51 g, 25.2 mmol, 1 equiv.), pyridine (10 mL, 124.8 mmol, 5.0 equiv.) and *p*-toluenesufonyl chloride (5.8 g, 30.4 mmol, 1.2 equiv.). Purification by column chromatography on silica gel (cyclohexane / AcOEt, 8 / 2) afforded 9.27 g (99%) of the desired compound **19** as a white solid.

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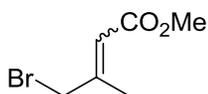
<sup>175</sup> René, O.; Lapointe, D.; Fagnou, K. *Org. Lett.* **2009**, *11*, 4560–4563.

Data for **1c**:

**m.p.** = 88 °C. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.67-7.62 (m, 4H), 7.32-7.28 (m, 1H), 7.22-7.20 (m, 2H), 6.84-6.79 (m, 2H), 2.38 (s, 3H). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 144.4, 139.2, 137.6, 136.0, 129.8, 129.6, 127.6, 127.0, 122.6, 92.4, 21.7.

These data are in good agreement with those reported in the literature.<sup>176</sup>

#### Bromation of the methyl 3-methylbut-2-enoate:



#### Methyl 4-bromo-3-methylbut-2-enoate (**20**)

A flask was charged with methyl 3-methylbut-2-enoate (6.5 mL, 50 mmol, 1 equiv.), CCl<sub>4</sub> (80 mL), NBS (8.9 g, 50.5 mmol, 1 equiv.) and AIBN (18 mg, 0.1 mmol, 0.2 mol%). The solution was heated at reflux overnight, then cooled to 0 °C, and filtered on a celite pad. The filtrate was then washed with Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (2 x 30 mL), NaCl (2 x 30 mL). The organic layer was then dried over MgSO<sub>4</sub>, filtered, concentrated *in vacuo*. The residue was then purified by column chromatography on silica gel (Pentane / Et<sub>2</sub>O, 98 / 2), affording 9.4 g (98%) of the desired compound **20** in a *Z/E* = 55 / 45 mixture.

Data for **20**:

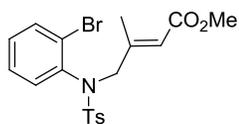
**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 5.96 (s, 1H, *E*), 5.78 (s, 1H, *Z*), 4.55 (s, 2H, *Z*), 3.94 (s, 2H, *E*), 3.72 – 3.71 (m, 6H, *Z + E*), 2.28 (s, 3H, *E*), 2.05 (s, 3H, *Z*). **<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 166.3, 165.8, 152.95, 152.75, 119.1, 118.9, 51.33, 51.27, 38.2, 29.6, 23.5.

These data are in good agreement with those reported in the literature.<sup>177</sup>

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<sup>176</sup> Zenner, J. M.; Larock, R. C. *J. Org. Chem.* **1999**, *64*, 7312–7322.

### Procedure for the alkylation of protected anilines (21,22):



### (*E*)-Methyl 4-(*N*-(2-bromophenyl)-4-methylphenylsulfonamido)-3-methylbut-2-enoate (**21**)

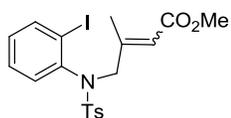
A solution of *N*-(2-bromophenyl)-4-methylbenzenesulfonamide **18** (1.82 g, 5.58 mmol, 1 equiv.) diluted in THF (5 mL) was added dropwise to a suspension of sodium hydride (245.9 mg, 6.15 mmol, 1.1 equiv.) in THF (60 mL). The resulting reaction mixture was stirred at room temperature for 1 h, then cooled to 0 °C and a solution of methyl (*E*)-4-bromo-3-methylbut-2-enoate **20** (1.30 g, 6.7 mmol, 1.2 equiv.) in THF (5 mL) was added. The mixture was then warmed up to 50 °C overnight, and heated at reflux for 7 h. After total conversion of the starting material, the mixture was hydrolyzed and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 20 mL). The combined organic layers were dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (cyclohexane / AcOEt, 80 / 20) and yielded 2.18 g (87 %) of the expected compound **21** as pure isomer.

Data for **21**:

**m.p.** = 89 °C. **IR**: 2949, 1718, 1656, 1597, 1471, 1434, 1351, 1289, 1224 cm<sup>-1</sup>. **<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.57-7.52 (m, 3H), 7.26-7.15 (m, 5H), 5.69 (d, *J* = 1.2 Hz, 1H), 4.26 – 4.24 (m, 2H), 3.63 (s, 3H), 2.42 (s, 3H), 2.20 (d, *J* = 1.3 Hz, 3H). **<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>) δ 166.5, 152.8, 144.0, 137.6, 136.4, 132.8, 130.1, 129.7, 128.2, 128.1, 124.7, 118.8, 58.5, 51.1, 21.7, 17.2. **HRMS** (ESI) *m/z* calcd. for C<sub>19</sub>H<sub>20</sub>INO<sub>4</sub>S [M + Na<sup>+</sup>] 460.0194, found 460.0190.

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<sup>177</sup> Lei, B.; Fallis, A. G. *Can. J. Chem.* **1991**, *69*, 1450–1456.



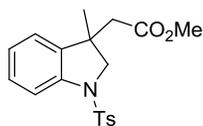
**Methyl 4-(N-(2-iodophenyl)-4-methylphenylsulfonamido)-3-methylbut-2-enoate (22):**

A flask was charged with diisopropylamine (850  $\mu$ L, 6.0 mmol, 1.2 equiv.) and *n*-BuLi (2.7 mL, C = 2.25 M, 6.075 mmol, 1.2 equiv.) was slowly added at room temperature. The resulting wax was dissolved with THF (40 mL) and stirred at room temperature for 20 min. A solution of **19** (1.9 g, 5.0 mmol, 1 equiv.) in THF (10 mL) was slowly added to the freshly prepared LDA. The dark green solution turned slowly to yellow within 20 min. a solution of **44** (1.1 g, 5.9 mmol, 1.2 equiv.) in THF (10 mL) was then slowly added. The mixture was heated to 50 °C overnight. The reaction mixture was then hydrolyzed, extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 30 mL), dried over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by column chromatographie (pentane / AcOEt, 9 / 1), affording 957 mg (39%) of the desired compound **22** as an *E/Z* = 2/1 mixture of isomers. The identifications of the isomers were possible due to the partial separation of the two isomers on the column.

Data for **22**:

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.88 – 7.84 (m, 1H *Z*), 7.86 (dd, *J* = 8.2, 1.2 Hz, 1H *E*), 7.58 (d, *J* = 8.2 Hz, 2H *Z*), 7.56 (d, *J* = 8.2 Hz, 2H *E*), 7.33 – 7.27 (m, 3H *Z*), 7.34 – 7.17 (m, 3H *E*), 7.11 – 6.98 (m, 2H *Z*), 6.97 (dt, *J* = 6.0, 3.2 Hz, 2H *E*), 5.68 (d, *J* = 1.2 Hz, 1H *E*), 5.65 (s, 1H *Z*), 4.96 (d, *J* = 14.6 Hz, 1H *E*), 4.63 (d, *J* = 14.6 Hz, 1H *E*), 4.23 (d, *J* = 7.9 Hz, 2H *Z*), 3.64 (s, 3H *Z*), 3.48 (s, 3H *E*), 2.44 (s, 3H *Z*), 2.44 (s, 3H *E*), 2.25 (s, 3H *Z*), 2.21 (d, *J* = 1.4 Hz, 3H *E*). **13C** NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  166.3 (*Z*), 165.9 (*E*), 152.6 (*E*), 152.3 (*Z*), 144.0 (*E*), 144.0 (*Z*), 141.7 (*E*), 141.1 (*Z*), 140.9 (*Z*), 140.6 (*E*), 136.0 (*Z*), 135.2 (*E*), 131.4 (*Z*), 130.7 (*E*), 130.0 (*Z*), 129.7 (*E*), 129.6 (*Z*), 129.5 (*E*), 128.8 (*Z*), 128.4 (*E*), 128.4 (*E*), 128.2 (*Z*), 119.9 (*E*), 119.2 (*Z*), 102.0 (*E*), 101.0 (*Z*), 59.2 (*Z*), 51.3 (*E*), 51.0 (*Z*), 51.0 (*E*), 24.2 (*E*), 21.6 (*Z*), 21.6 (*E*), 17.6 (*Z*). **HRMS** (ESI) *m/z* calcd. for C<sub>19</sub>H<sub>20</sub>INO<sub>4</sub>S [M + Na<sup>+</sup>] 508.0055, found 508.0059.

### Cyclisation reactions of compounds **21** and **22**:



#### Methyl 2-(3-methyl-1-tosylindolin-3-yl)acetate (**23**):

Cyclisation from **21**:

Prepared according to **GP6** from  $K_2CO_3$  (345.5 mg, 2.5 mmol, 5 equiv.), *n*-Bu<sub>4</sub>NBr (209.5 mg, 0.6 mmol, 1.3 equiv.), HCOOK (42.4 mg, 0.5 mmol, 1 equiv.), PPh<sub>3</sub> (51.8 mg, 0.2 mmol, 0.4 equiv.), **21** (215.9 mg, 0.5 mmol, 1 equiv.) and Pd(OAc)<sub>2</sub> (22.4 mg, 0.1 mmol, 0.2 equiv.). Purification by column chromatography on silica gel (cyclohexane / AcOEt, 9 / 1), afforded 40 mg (23 %) of the desired compound **23** as yellow oil.

Cyclisation from **22**:

Prepared according to **GP6** from  $K_2CO_3$  (342.2 mg, 2.47 mmol, 4.8 equiv.), *n*-Bu<sub>4</sub>NBr (209.1 mg, 0.65 mmol, 1.3 equiv.), HCOOK (42.4 mg, 0.5 mmol, 1 equiv.), PPh<sub>3</sub> (25.5 mg, 0.10 mmol, 0.19 equiv.), **22** (249.4 mg, 0.51 mmol, 1 equiv.) and Pd(OAc)<sub>2</sub> (11.3 mg, 0.05 mmol, 0.1 equiv.). Purification by column chromatography on silica gel (cyclohexane / AcOEt, 9 / 1), afforded 68 mg (37%) of the desired compound **23**.

From Domino sequence N-allylation / 5-*exo-trig* carbopalladation:

Prepared according to **GP7** from **19** (182.8 mg, 0.49 mmol, 1 equiv.), Pd(OAc)<sub>2</sub> (12.4 mg, 0.05 mmol, 10 mol%), PPh<sub>3</sub> (27.6 mg, 0.10 mmol, 20 mol%), *n*-Bu<sub>4</sub>NBr (209.0 mg, 0.65 mmol, 1.3 equiv.),  $K_2CO_3$  (345.6 mg, 2.50 mmol, 5.1 equiv.) and **20** (102.7 mg, 0.53 mmol, 1.1 equiv.), yielding 96 mg (54%) of the desired compound **23**.

From Domino sequence N-allylation / 5-*exo-trig* carbopalladation / allyloxycarbonylation / decarboxylative allylation:

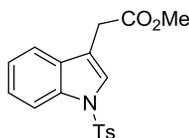
Obtained as side product according to **GP9** from **19** (93.3 mg, 0.25 mmol, 1 equiv.), Pd(dba)<sub>2</sub> (14.8 mg, 0.026 mmol, 10 mol%), P(2-fur)<sub>3</sub> (22.8 mg, 0.10 mmol, 40 mol%),

*n*-Bu<sub>4</sub>NBr (100.5 mg, 0.31 mmol, 1.2 equiv.), K<sub>2</sub>CO<sub>3</sub> (171.8 mg, 1.24 mmol, 4.95 equiv.), and **20** (54.4 mg, 0.28 mmol, 1.1 equiv.). <sup>1</sup>H NMR with butadiene sulfone as internal standard allowed to calculate an NMR yield (72%) of the side product **23**.

Data for **23**:

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.74 – 7.64 (m, 2H), 7.27 – 7.21 (m, 4H), 7.14 – 7.00 (m, 2H), 4.09 (d, *J* = 10.9 Hz, 1H), 3.71 (d, *J* = 10.9 Hz, 1H), 3.63 (s, 3H), 2.51 (d, *J* = 15.3 Hz, 1H), 2.38 (s, 3H), 2.30 (d, *J* = 15.3 Hz, 1H), 1.22 (s, 3H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 171.2, 144.3, 141.0, 138.5, 134.3, 129.8, 128.6, 127.5, 123.9, 121.9, 114.8, 61.6, 51.7, 44.3, 42.2, 25.7, 21.7. HRMS (ESI) *m/z* calcd. for C<sub>19</sub>H<sub>21</sub>NO<sub>4</sub>S [M + Na<sup>+</sup>] 382.1089, found 382.1085.

**Domino sequence N-allylation / 5-*exo-trig* carbopalladation:**



**Methyl 2-(1-tosyl-1H-indol-3-yl)acetate 26:**

From domino sequence N-allylation / 5-*exo-trig* carbopalladation:

Prepared according to **GP7** from **19** (188.7 mg, 0.51 mmol, 1 equiv.), Pd(OAc)<sub>2</sub> (11.6 mg, 0.05 mmol, 10 mol%), PPh<sub>3</sub> (25.9 mg, 0.10 mmol, 20 mol%), *n*-Bu<sub>4</sub>NBr (213.6 mg, 0.65 mmol, 1.3 equiv.), K<sub>2</sub>CO<sub>3</sub> (355.2 mg, 2.50 mmol, 5.1 equiv.) and **24** (92.7 mg, 0.52 mmol, 1 equiv.), affording 100 mg (57%) of the desired compound **26**.

From Domino sequence: N-allylation / 5-*exo-trig* carbopalladation / methoxycarbonylation:

Prepared according to **GP8** from *N*-(2-iodophenyl)-4-methylbenzenesulfonamide **19** (179.8 mg, 0.48 mmol, 1 equiv.), Pd(dba)<sub>2</sub> (28.5 mg, 0.05 mmol, 10 mol%), P(2-fur)<sub>3</sub> (46.9 mg, 0.20 mmol, 40 mol%), *n*-Bu<sub>4</sub>NBr (206.9 mg, 0.65 mmol, 1.3 equiv.) and K<sub>2</sub>CO<sub>3</sub> (349.7 mg, 2.51 mmol, 5.2 equiv.) and **24** (65 μL, *d* = 1.522, 0.55 mmol, 1.1 equiv.). Purification by

column chromatography on silica gel afforded 123 mg (74%) of the side product resulting from  $\beta$ -hydride elimination compound **26**.

Data for **26**:

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.99 (dd,  $J = 8.2, 0.8$  Hz, 1H), 7.79 – 7.76 (m, 2H), 7.58 (s, 1H), 7.51 – 7.49 (m, 1H), 7.35 – 7.31 (m, 1H), 7.25 – 7.21 (m, 3H), 3.72 (s, 3H), 3.71 (d,  $J = 1.0$  Hz, 2H), 2.34 (s, 3H).  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  171.1, 145.0, 135.2, 130.5, 130.0, 127.0, 125.0, 123.4, 119.6, 115.1, 113.8, 52.3, 31.0, 21.7. **HRMS** (ESI)  $m/z$  calcd. for  $\text{C}_{18}\text{H}_{17}\text{NO}_4\text{S}$  [ $\text{M} + \text{Na}^+$ ] 366.0776, found 366.0775.

**Domino sequence N-allylation / 5-*exo-trig* carbopalladation / methoxycarbonylation.**

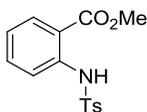


**Dimethyl 2-(3-methyl-1-tosylindolin-3-yl)malonate (**28**):**

Prepared according to **GP8** from *N*-(2-iodophenyl)-4-methylbenzenesulfonamide **19** (181.9 mg, 0.49 mmol, 1 equiv.),  $\text{Pd}(\text{dba})_2$  (28.9 mg, 0.05 mmol, 10 mol%),  $\text{P}(2\text{-fur})_3$  (46.1 mg, 0.20 mmol, 40 mol%), *n*- $\text{Bu}_4\text{NBr}$  (206.9 mg, 0.64 mmol, 1.3 equiv.) and  $\text{K}_2\text{CO}_3$  (349.7 mg, 2.53 mmol, 5.2 equiv.) and **20** (105.2 mg, 0.55 mmol, 1.1 equiv.). Purification by column chromatography on silica gel afforded 106 mg (52%) of the desired compound **28**.

Data for **28**:

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.75 (d,  $J = 8.3$  Hz, 2H), 7.64 (d,  $J = 8.2$  Hz, 1H), 7.28 – 7.20 (m, 3H), 7.03 – 6.95 (m, 2H), 4.50 (d,  $J = 11.1$  Hz, 1H), 3.74 – 3.71 (m, 4H), 3.64 (s, 1H), 3.43 (s, 3H), 2.38 (s, 3H), 1.29 (s, 3H).  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  168.0, 167.3, 144.2, 141.2, 136.0, 134.3, 129.7, 129.0, 127.5, 123.5, 123.5, 114.4, 59.8, 58.3, 52.6, 52.4, 45.0, 26.2, 21.6. **HRMS** (ESI)  $m/z$  calcd. for  $\text{C}_{21}\text{H}_{23}\text{NO}_6\text{S}$  [ $\text{M} + \text{Na}^+$ ] 440.1144, found 440.1149.



### Methyl 2-(4-methylphenylsulfonamido)benzoate (**30**):

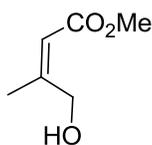
Obtained as side product according to **GP8** from *N*-(2-iodophenyl)-4-methylbenzenesulfonamide **19** (181.9 mg, 0.49 mmol, 1 equiv.), Pd(dba)<sub>2</sub> (28.9 mg, 0.05 mmol, 10 mol%), P(2-fur)<sub>3</sub> (46.1 mg, 0.20 mmol, 40 mol%), *n*-Bu<sub>4</sub>NBr (206.9 mg, 0.64 mmol, 1.3 equiv.) and K<sub>2</sub>CO<sub>3</sub> (349.7 mg, 2.53 mmol, 5.2 equiv.) and **20** (105.2 mg, 0.55 mmol, 1.1 equiv.). Purification by column chromatography on silica gel afforded 34 mg (23%) of the side product **30**.

Data for **30**:

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 10.62 (s, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.75 – 7.68 (m, 3H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.03 (t, *J* = 7.6 Hz, 1H), 3.88 (s, 3H), 2.37 (s, 3H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 168.4, 144.0, 140.7, 136.7, 134.6, 131.3, 129.8, 127.4, 122.9, 119.2, 116.0, 52.6, 21.7.

These data are in good agreement with those reported in the literature.<sup>178</sup>

### Synthesis of allyl acrylate **34**:



### (*Z*)-methyl 4-hydroxy-3-methylbut-2-enoate (**32**):

To a solution of methyl (triphenylphosphoranylidene)acetate **31** (2.29 g, 6.83 mmol, 1.2 equiv.) in benzene (10 mL) was added hydroxyacetone (390 μL, 5.69 mmol, 1

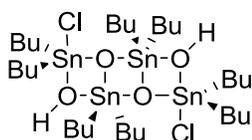
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<sup>178</sup> Li, F.; Nie, J.; Wu, J.-W.; Zheng, Y.; Ma, J.-A. *J. Org. Chem.* **2012**, *77*, 2398–2406.

equiv.). The solution was refluxed overnight, cooled to room temperature and the solvent was removed *in vacuo*. The residue was directly purified by column chromatography on silica gel (cylo / AcOEt, 1 / 1), affording 523 mg (71%) of the desired compound **32**.

Data for **32**:

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  5.94 (hex,  $J = 1.4$  Hz, 1H), 4.08 (s, 2H), 3.66 (s, 3H), 3.03 (s, 1H), 2.03 – 2.02 (m, 3H).  $^{13}\text{C NMR}$  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  167.5, 158.1, 113.1, 66.9, 51.1, 15.6. **HRMS** (ESI)  $m/z$  calcd. for  $\text{C}_6\text{H}_{10}\text{O}_3$  [ $\text{M} + \text{Na}^+$ ] 153.0528, found 153.0524.

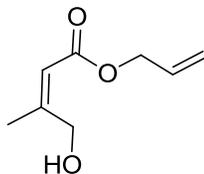


Otera's protocol was followed for the synthesis of the catalyst (**53**).<sup>157</sup>

A solution of  $\text{Bu}_2\text{SnCl}_2$  (6.05 g, 19.9 mmol, 1 equiv.) and  $\text{Bu}_2\text{SnO}$  (15.07 g, 60.5 mmol, 3 equiv.) in EtOH (200 mL) and  $\text{H}_2\text{O}$  (360  $\mu\text{L}$ , 20 mmol, 1 equiv.) was refluxed overnight. The reaction was then cooled to room temperature and the solvent was directly removed *in vacuo*. The white solid was then purified by recrystallization in *n*-hexane, affording 10.5 g (49%) of the desired catalyst **53** as white crystals.

Data for **53**:

**m.p.** = 109 °C.



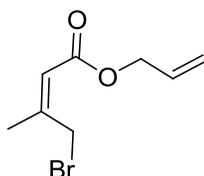
**(Z)-allyl 4-hydroxy-3-methylbut-2-enoate (33)**

Otera's protocol was adapted for the synthesis of compound **33**.<sup>157</sup>

A solution of **32** (522.9 mg, 4.02 mmol, 1 equiv.) in toluene (25 mL) was added to the catalyst **53** (431.3 mg, 0.4 mmol, 0.1 equiv.), followed by the addition of allyl alcohol (2.8 mL, 40.98 mmol, 10.2 equiv.). The solution was refluxed for 2 days, cooled to room temperature and the solvent was removed *in vacuo*. The residue was then purified by column chromatography on silica gel (pentane / AcOEt, 8 / 2), affording 0.33 mg (52%) of the desired compound **33** as a colorless oil.

Data for **33**:

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.99 (hex, *J* = 1.4 Hz, 1H), 5.92 (ddt, *J* = 17.2, 10.5, 5.6 Hz, 1H), 5.30 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.21 (dq, *J* = 10.4, 1.3 Hz, 1H), 4.59 (dt, *J* = 5.6, 1.4 Hz, 2H), 4.11 – 4.10 (m, 2H), 2.72 (s, 1H), 2.06 – 2.05 (m, 3H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 166.7, 158.3, 132.5, 118.0, 113.2, 67.0, 64.6, 15.7. HRMS (ESI) *m/z* calcd. for C<sub>8</sub>H<sub>12</sub>O<sub>3</sub> [M + Na<sup>+</sup>] 179.0684, found 179.0683.



**(Z)-allyl 4-bromo-3-methylbut-2-enoate (34):**

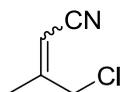
To a cooled (-10 °C) solution of **44** (274 mg, 1.75 mmol, 1 equiv.) in Et<sub>2</sub>O (3 mL) was slowly added PBr<sub>3</sub> (85 μL, 0.90 mmol, 0.5 equiv.). The solution was warmed up to room temperature, and stirred at room temperature during 2 h. The orange solution was hydrolyzed and extracted with Et<sub>2</sub>O (3 x 10 mL). The combined organic layers were dried

over MgSO<sub>4</sub> and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (cyclohexane / AcOEt, 8 / 2), affording 262 mg (69%) of the desired compound **34**.

Data for **34**:

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.99 - 5.98 (m, 1H), 5.94 (ddt, *J* = 17.1, 10.4, 5.7 Hz, 1H), 5.34 (dq, *J* = 17.2, 1.4 Hz, 1H), 5.25 (dq, *J* = 10.4, 1.3 Hz, 1H), 4.63 (dt, *J* = 5.7, 1.3 Hz, 2H), 3.96 – 3.95 (m, 2H), 2.29 (d, *J* = 1.3 Hz, 3H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 165.6, 153.1, 132.3, 119.2, 118.4, 64.9, 38.2, 17.4. HRMS (ESI) *m/z* calcd. for C<sub>8</sub>H<sub>12</sub>BrO<sub>2</sub> [M + Na<sup>+</sup>] 240.9840, found 240.9837.

**Procedure for the synthesis of the cyano derivative 47:**

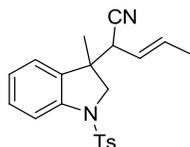


**4-chloro-3-methylbut-2-enitrile 47:**

A flask was charged with *n*-Buli (17 mL, C = 2.26 M, 38.42 mmol, 1.8 equiv.) and DIPA (6.5 mL, 45.98 mmol, 1.2 equiv.) was slowly added at room temperature. The mixture was stirred during 10 min, and diluted with THF (100 mL). The solution was cooled to -60 °C, and acetonitrile (1.2 mL, 23.39 mmol, 1.1 equiv.) was slowly added. The mixture was stirred at -60 °C for 15 min, and diethyl phosphorochloridate (3.6 mL, 24.91 mmol, 1.2 equiv.) was added dropwise. The solution was warmed to 0 °C and stirred for 1 h. Then, 1-chloropropan-2-one (1.7 mL, 21.35 mmol, 1 equiv.) was added. The solution was warmed to room temperature and stirred for 90 min. The solution was then hydrolyzed with saturated NH<sub>4</sub>Cl solution (30 mL), extracted with Et<sub>2</sub>O (3 x 40 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was then purified by column chromatography on silica gel (pentane / Et<sub>2</sub>O, 8 / 2), affording 1.7 g (69%) of the desired compound **47** in mixture of Z/E 75 / 25.

Data for **47**:

$^1\text{H NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$  5.52 (q,  $J = 1.2$  Hz, 1H), 5.30 (d,  $J = 1.5$  Hz, 1H), 4.27 (s, 2H), 4.08 (d,  $J = 1.0$  Hz, 2H), 2.16 (d,  $J = 0.9$  Hz, 3H), 2.07 (d,  $J = 1.6$  Hz, 3H).  $^{13}\text{C NMR}$  (75 MHz,  $\text{CDCl}_3$ )  $\delta$  158.0 (overlap of the two isomers), 116.0 (overlap of the two isomers), 99.1, 98.8, 46.9, 44.3, 21.0, 19.1.



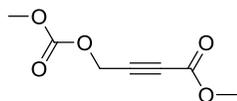
**(E)-2-(3-methyl-1-tosylindolin-3-yl)pent-3-enitrile (48):**

The protocol was followed with **19** (185.2 mg, 0.50 mmol, 1 equiv.),  $\text{Pd}(\text{dba})_2$  (28.9 mg, 0.05 mmol, 10 mol%),  $\text{P}(\text{2-fur})_3$  (47.0 mg, 0.2 mmol, 40 mol%),  $\text{K}_2\text{CO}_3$  (353.3 mg, 2.5 mmol, 5.1 equiv.) and  $n\text{-Bu}_4\text{NBr}$  (209.9 mg, 0.65 mmol, 1.3 equiv.), affording 181.8 mg (10 %) of the desired compound **48** as a yellow oil.

Data for **48**:

$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.84-7.69 (m, 4H), 7.39 – 7.29 (m, 3H), 7.25 – 7.04 (m, 1H), 6.95 (dq,  $J = 14.9, 6.9$  Hz, 1H), 6.34 (dq,  $J = 15.0, 1.6$  Hz, 1H), 4.02 (dd,  $J = 11.2, 2.0$  Hz, 1H), 3.80 (d,  $J = 7.4$  Hz, 1H), 3.57 (d,  $J = 11.0$  Hz, 1H), 2.45 - 2.44 (m, 3H), 1.92 (dd,  $J = 6.9, 1.7$  Hz, 3H), 1.26 (s, 3H). **HRMS** (ESI)  $m/z$  calcd. for  $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_2\text{S}$  [ $\text{M} + \text{Na}^+$ ] 389.1300, found 389.1307.

**Procedure for the synthesis of the propiolate (51):**



**methyl 4-(methoxycarbonyloxy)but-2-ynoate (51):**

To a solution of propargyl alcohol (6.3 mL, 106.8 mmol, 1 equiv.) in THF (200 mL), at  $-78$  °C, was added dropwise  $n\text{-BuLi}$  (95 mL,  $C = 2.37$  M, 225.2 mmol, 2.1 equiv.). The solution was stirred at  $-78$  °C for 15 min, and methyl chloroformate (17.3 mL, 223.9 mmol,

2.1 equiv.) was slowly added. The solution was slowly warmed to room temperature and stirred for 4 h. The solution was hydrolyzed and extracted with Et<sub>2</sub>O (3 x 60 mL). The combined organic layers were then dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (cyclohexane / AcOEt, 85 / 15), affording 14.85 g (81%) of the desired product **51** as a colorless oil.

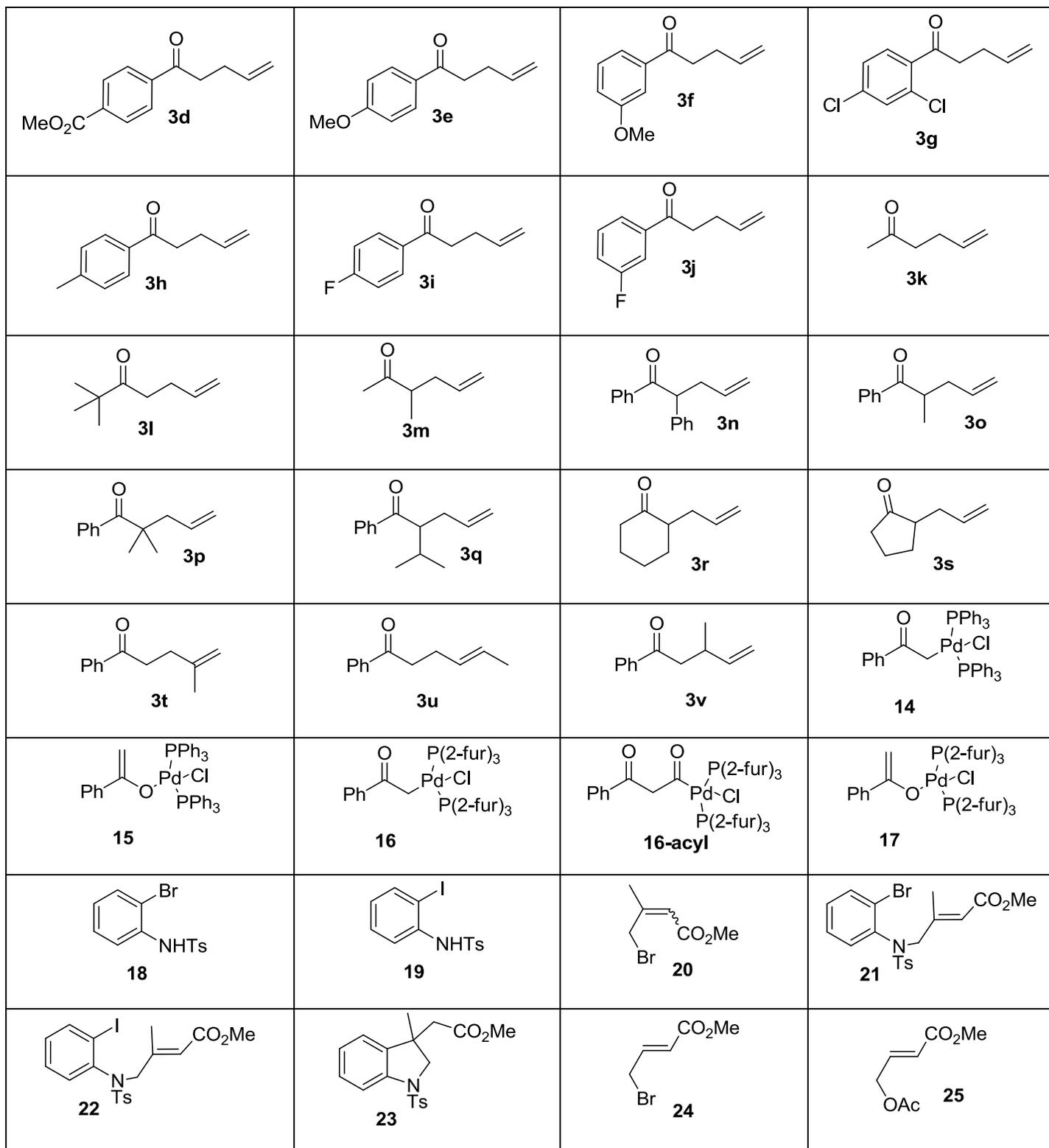
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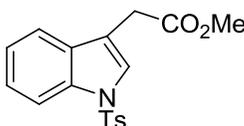
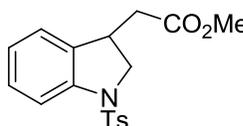
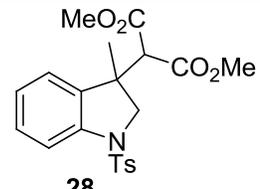
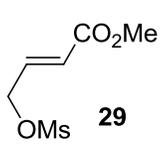
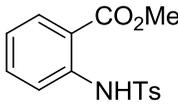
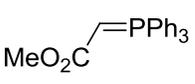
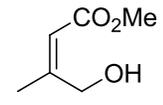
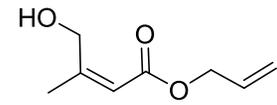
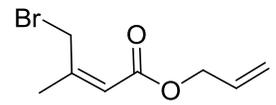
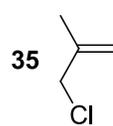
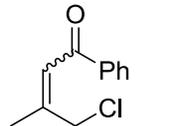
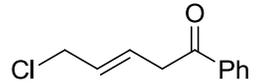
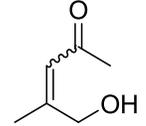
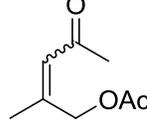
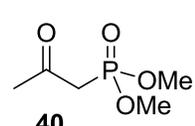
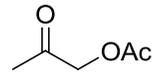
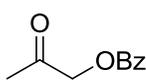
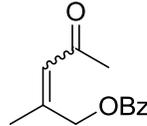
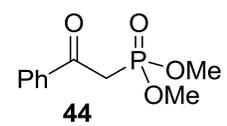
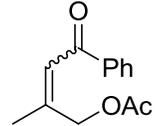
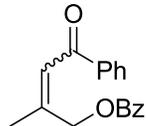
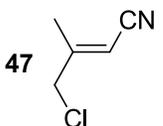
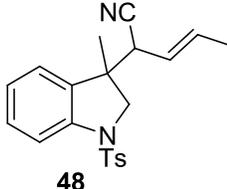
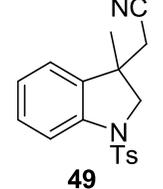
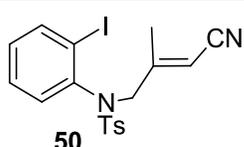
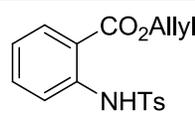
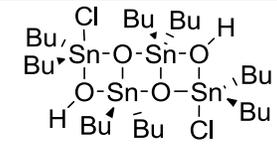
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 4.83 (s, 2H), 3.81 (s, 3H), 3.77 (s, 3H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 155.0, 153.2, 80.5, 78.3, 55.5, 54.6, 53.0. HRMS (ESI) m/z calcd. for C<sub>7</sub>H<sub>8</sub>O<sub>5</sub> [M + Na<sup>+</sup>] 195.0269, found 195.0272.

**Product Index**



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| <br><b>8</b>  | <br><b>11</b> | <br><b>13</b> | <br><b>9</b>  |
| <br><b>10</b> | <br><b>12</b> | <br><b>1a</b> | <br><b>1b</b> |
| <br><b>1c</b> | <br><b>1d</b> | <br><b>1e</b> | <br><b>1f</b> |
| <br><b>1g</b> | <br><b>1h</b> | <br><b>1i</b> | <br><b>1j</b> |
| <br><b>1k</b> | <br><b>1l</b> | <br><b>1m</b> | <br><b>1n</b> |
| <br><b>1o</b> | <br><b>1p</b> | <br><b>1q</b> | <br><b>1r</b> |
| <br><b>1s</b> | <br><b>3a</b> | <br><b>3b</b> | <br><b>3c</b> |



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|  <p><b>34</b></p>   |  <p><b>35</b></p>   |  <p><b>36</b></p>  |  <p><b>37</b></p>   |
|  <p><b>38</b></p>  |  <p><b>39</b></p>  |  <p><b>40</b></p>  |  <p><b>41</b></p>  |
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|  <p><b>46</b></p> |  <p><b>47</b></p> |  <p><b>48</b></p> |  <p><b>49</b></p> |
|  <p><b>50</b></p> |  <p><b>51</b></p> |  <p><b>52</b></p> |  <p><b>53</b></p> |



**References:**



- <sup>1</sup> Some authors prefer the words “tandem” or “cascade” instead of domino. For the sake of simplicity, only the word “domino” will be used in this manuscript.
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## **Publications:**



## Straightforward Synthesis of Allylated Keto Esters: The Palladium-Catalysed Haloketone Alkoxy carbonylation/Allylation Domino Reaction

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**Abstract:** The palladium-catalysed  $\alpha$ -chloro ketone methoxycarbonylation and allylic alkylation reactions can be efficiently combined to provide a new catalytic domino reaction. The first, carbonylative, step generates the  $\beta$ -keto ester, which acts as the nucleophile in a subsequent allylation step. The use of

allyl phenates in combination with Xantphos ligand are the key features allowing one to obtain the allylated  $\beta$ -keto esters in good yields

**Keywords:** allylic alkylation; carbon monoxide; catalysis; domino reaction; selectivity

### Introduction

The multi-step synthesis of complex organic molecules often results in the generation of large amounts of wastes due to the numerous solvent-consuming purification procedures at each stage of the synthesis.<sup>[1]</sup> Domino-type transformations that involve metal-catalysed reactions have consequently emerged as green and efficient synthetic tools as they allow the one-step construction of elaborated molecules with a reduced environmental impact.<sup>[2]</sup> However, the elaboration of a domino reaction may often meet with drastic difficulties and limitations. Indeed, a number of incompatibilities between the reactants and the catalytic system, present from the outset of the reaction, may arise and lead to side products and/or catalyst poisoning. Hence, the consecutive elementary steps building up a domino process have to be carefully and rationally chosen when planning a new such sequence.

We targeted to develop new catalytic domino<sup>[3]</sup> sequences involving carbon monoxide as a cheap and readily available carbonyl source,<sup>[4]</sup> for the straightforward one-pot construction of specific building blocks. The literature witnesses several precedents of domino and/or multicomponent sequences entailing carbonylative steps.<sup>[5]</sup> The following examples represent

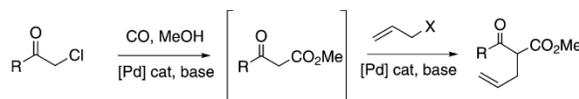
a non-exhaustive list: hydroformylation (with syngas)/acetal formation and related sequences,<sup>[6]</sup> radical reactions involving CO,<sup>[7]</sup> multicomponent carbonylative coupling reactions<sup>[8]</sup> such as 1,3-dipolar cycloadditions involving münchnones,<sup>[9]</sup> carbopalladation/carbonylation sequences,<sup>[10]</sup> and allylic alkylation/Pauson-Khand sequences.<sup>[11]</sup> In most cases the carbonylation step occurs at the end of the sequence, which closes through an intra- or intermolecular trapping of a palladium-carbonyl intermediate.

Our project focussed on the development of a palladium-catalysed *pseudo-domino type I*<sup>[12]</sup> sequence involving the alkoxy carbonylation of an  $\alpha$ -chloro ketone, followed by allylation of the transiently formed  $\beta$ -keto ester (Scheme 1).

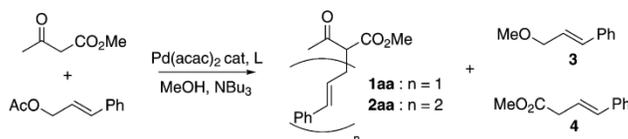
### Results and Discussion

Our primary objective was to find out the common key parameters allowing the achievement of the two consecutive reactions using the same catalytic system and enolising system.

We then settled to study first the second step of our sequence, taking as a model the reaction between



**Scheme 1.** The palladium-catalysed methoxycarbonylation/allylation domino sequence.



**Scheme 2.** The palladium-catalysed reaction between methyl acetoacetate and cinnamyl acetate.

methyl acetoacetate and cinnamyl acetate (Scheme 2 and Table 1).

The palladium-catalysed methoxycarbonylation of  $\alpha$ -chloro ketones<sup>[13]</sup> (that would represent the first step of our sequence) is best effected using  $\text{PPh}_3$  as ancillary ligand, MeOH as the solvent, and tributylamine as the base.<sup>[14]</sup> Accordingly, we started our study using the catalytic system  $[\text{Pd}(\text{acac})_2/\text{PPh}_3$  (1/4 ratio)], MeOH as the solvent, and  $\text{NBu}_3$  as the base.<sup>[15]</sup> We also decided to use an excess of the allyl acetate (2.5 equiv.), as this reaction partner may be involved (and thus consumed) in side reactions (see below). This experiment gave a mixture of mono- and bis-allylated linear  $\beta$ -keto esters **1aa** and **2aa** in 18:82 ratio (entry 1). The reaction also yielded cinnamyl methyl ether<sup>[16]</sup> **3** as side product, resulting from attack of methanol on the  $\eta^3$ -allylpalladium intermediate formed in excess. The starting materials were entirely converted and the overall yield in **1aa** and **2aa** was essentially limited by the competitive formation of the methyl ether **3**. A similar result was obtained on switching from  $\text{PPh}_3$  to Xantphos (entry 2). In view of the need of carbonylative conditions during the de-

sired domino reaction, the allylic alkylation was also performed under a CO atmosphere. Under such conditions, the allylic alkylation still proceeded, although it was accompanied by the formation of methyl ester **4**, arising from the methoxycarbonylation of cinnamyl acetate.<sup>[17]</sup> Interestingly, the selectivity of the reaction was strongly dependent on the nature of the ligand used. In particular, large amounts of **4** were obtained when using  $\text{PPh}_3$  (entry 3), to the detriment of the targeted products **1aa** and **2aa**, whereas the allylation reaction remained efficient with Xantphos (entry 4). This observation is coherent with the fact that monophosphines are more commonly used than diphosphines for the carbonylation of allylic acetates, halides or carbonates.

Although the side products **3** and **4** were formed in non-negligible amounts, the compatibility of the reaction conditions used for  $\alpha$ -chloro ketone methoxycarbonylation in  $\beta$ -keto ester allylation was at this point clearly established.

The feasibility of the complete *pseudo*-domino reaction was studied using chloroacetone as a cheap, commercially available  $\alpha$ -chloro ketone and cinnamyl derivatives bearing various leaving groups (Scheme 3 and Table 2).

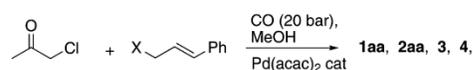
The reactions were performed under 20 bar of carbon monoxide with 1% of palladium catalyst associated with a phosphorus-based ligand (4/1 P/Pd ratio) at 70 °C for 16 h. In line with what was previously observed in the allylation performed under CO pressure (Table 1, entry 3), the reaction with  $\text{PPh}_3$  yielded exclusively the carbonylated product **4** (entry 1). Apparently, with the above reaction condi-

**Table 1.** The allylic alkylation reaction in methanol.<sup>[a]</sup>

| Entry | Ligand <sup>c</sup> | $P_{\text{CO}}$ | mmol (Yield [%]) <sup>[a]</sup> |            |          |          |
|-------|---------------------|-----------------|---------------------------------|------------|----------|----------|
|       |                     |                 | <b>1aa</b>                      | <b>2aa</b> | <b>3</b> | <b>4</b> |
| 1     | $\text{PPh}_3$      | 0               | 0.5 (16)                        | 2.3 (77)   | 0.5      | –        |
| 2     | Xantphos            | 0               | 0.3 (10)                        | 2.4 (80)   | 0.7      | –        |
| 3     | $\text{PPh}_3$      | 20              | 0.7 (23)                        | 0.6 (20)   | 0.1      | 1.2      |
| 4     | Xantphos            | 20              | 0.6 (20)                        | 1.8 (60)   | 0.8      | 0.2      |

<sup>[a]</sup> The reaction was carried out at 70 °C using methyl acetoacetate (3.0 mmol),  $\text{NBu}_3$  (7.5 mmol; 2.5 equiv.),  $\text{Pd}(\text{acac})_2$  (0.03 mmol),  $\text{PPh}_3$  (0.12 mmol) or Xantphos (0.06 mmol) in MeOH (10 mL) for 16 h.

<sup>[b]</sup> Amounts determined by GC with undecane as internal standard. Yields calculated with respect to methyl acetoacetate.



**Scheme 3.** The palladium-catalysed methoxycarbonylation/cinnamylation as a *pseudo*-domino sequence.

**Table 2.** The palladium-catalysed alkoxyacylation/allylation domino reaction.<sup>[a]</sup>

| Entry          | Ligand <sup>c</sup> | X (equiv.) <sup>[c]</sup> | mmol (Yield [%]) <sup>[b]</sup> |            |          |          |
|----------------|---------------------|---------------------------|---------------------------------|------------|----------|----------|
|                |                     |                           | <b>1aa</b>                      | <b>2aa</b> | <b>3</b> | <b>4</b> |
| 1              | PPh <sub>3</sub>    | OAc (2.2)                 | traces                          | traces     | traces   | 4.4      |
| 2              | Xantphos            | OAc (2.2)                 | 0.3 (10)                        | 1.3 (43)   | 2.2      | 0.9      |
| 3              | Xantphos            | OAc (3.5)                 | 0.1 (3)                         | 1.3 (43)   | 4.3      | 1.6      |
| 4 <sup>d</sup> | Xantphos            | OAc (2.2)                 | 0.3 (10)                        | 1.1 (35)   | 2.5      | 0.3      |
| 5              | Xantphos            | Cl (2.2)                  | 0.5 (17)                        | 1.5 (50)   | 2.1      | 1.0      |
| 6              | Xantphos            | MeOCOO (2.2)              | 0.2 (7)                         | 1.8 (60)   | 1.6      | 0.5      |
| 7              | Xantphos            | OPh (2.2)                 | 0.4 (13)                        | 2.5 (83)   | 0.6      | 0.6      |

<sup>[a]</sup> The reaction was carried out at 70 °C using chloroacetone (3.0 mmol), allylic substrate (7.5 mmol, 2.5 equiv.), tributylamine (13.5 mmol; 4.5 equiv.), CO (20 bar), Pd(acac)<sub>2</sub> (0.03 mmol), PPh<sub>3</sub> (0.12 mmol) or Xantphos (0.06 mmol) in 10 mL of MeOH for 16 h.

<sup>[b]</sup> Amounts determined by GC with undecane as internal standard, yields calculated from the amount of chloroacetone used.

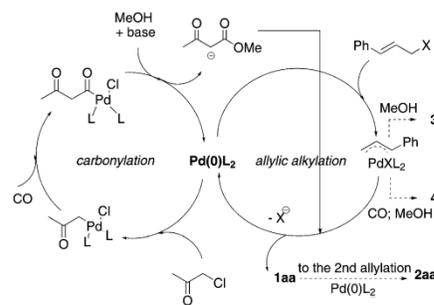
<sup>[c]</sup> Number of equivalents of allylic derivative *versus* chloroacetone.

<sup>[d]</sup> The reaction was performed in the presence of AcONa (2.0 equiv. with respect to chloroacetone).

tions, methoxycarbonylation of chloroacetone did not occur, thereby leaving free access to methoxycarbonylation of cinnamyl acetate. However, when PPh<sub>3</sub> was changed for Xantphos, encouraging amounts of the allylated  $\beta$ -keto esters **1aa** and **2aa** were obtained, although the methyl ether **3** was still the major product (entry 2). This result suggests that in this case methoxycarbonylation of the cinnamyl residue occurs concurrently to alkylation. The use of larger amounts of cinnamyl acetate (entry 3) did not produce better yields, leading essentially to an increase of the side products **3** and **4**. Use of chloride, or methyl carbonate as the allylic leaving group, classically exploited in palladium-catalysed allylic substitutions, allowed only slight improvements in the yield of **1** and **2**, the formation of methyl ether **3** remaining in both cases strongly limiting (entries 5 and 6). Finally, use of the less reactive phenoxy leaving group<sup>[18]</sup> at the allylic position gave the best yields of **1aa** and **2aa**, which almost attained those observed when starting directly from the  $\beta$ -keto ester, to the detriment of the side products **3** and **4** (compare entry 7 of Table 2 with entry 2 of Table 1).

This result indicates that under these conditions methoxycarbonylation of chloroacetone proceeds very efficiently and faster than methoxycarbonylation of the cinnamyl derivative.

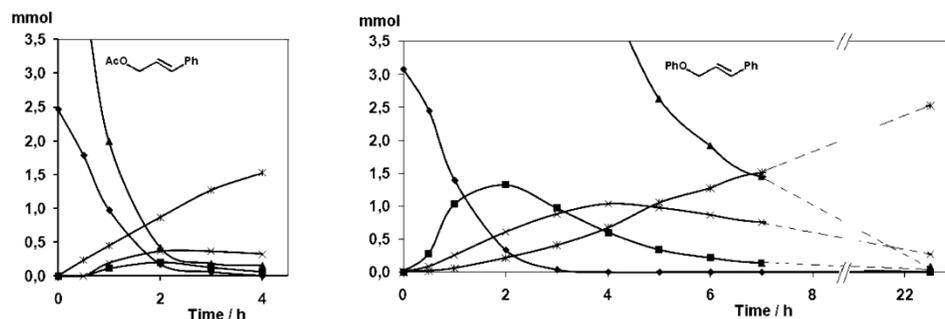
The global transformation involves two sequential catalytic cycles, both initiated by an oxidative addition step at the Pd(0) centre (Scheme 4). The former one is started by the  $\alpha$ -chloro ketone, whereas the latter one by the allylic derivative. As the product of the former catalytic cycle becomes the substrate for the latter one, the success of this *pseudo*-domino sequence depends on the relative rates of the two cycles. More specifically, the carbonylation rate of the ketone derivative has to be higher than leakage of the allyl derivative from the second cycle to give the side



**Scheme 4.** Catalytic cycles involved in the *pseudo*-domino sequence. The dashed arrows emphasise the competing oxidative addition paths.

products. If not, the allylic derivative would be irreversibly transformed into the ether **3** or the methyl ester **4**, and the tardily generated  $\beta$ -keto ester would not find any more  $\eta^3$ -allyl complex intermediate to intercept.

We believe that the rates of oxidative addition of cinnamyl acetate, chloride or methyl carbonate to the palladium (0) centre are higher than or of the same order of magnitude as that of  $\alpha$ -chloroacetone. Consequently, when using these leaving groups, products **3** and **4** are obtained in proportions similar to the allylated derivatives **1aa** and **2aa**. On the other hand, use of the less reactive phenoxy leaving group allows the chloro ketone oxidative addition to take place first, thereby permitting the *pseudo*-domino chain to work efficiently. This picture is clearly confirmed by the comparison of the reaction profiles of catalytic runs performed with cinnamyl acetate and phenyl cinnamyl ether (Figure 1). The reaction with cinnamyl acetate is fast and almost complete within 3 h. Both start-

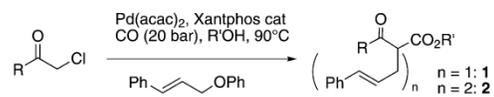


**Figure 1.** Evolution of the allylic starting material (▲), chloroacetone (◆), methyl acetoacetate (■), reactions products **1** (×) and **2** (★), during the domino reaction under 20 bar CO. The dotted lines are drawn to guide the eye. The reaction was performed at 70°C with 6 mmol of chloroacetone, 13.2 mmol of the noted allylic starting material, 27 mmol of tributylamine, 1 mol% of Pd(acac)<sub>2</sub>, 2 mol% of Xantphos, and 20 mL of distilled MeOH.

ing materials are rapidly converted, and products **1aa** and **2aa** are formed from the early minutes of the reaction. Methyl acetoacetate is only obtained in very small amounts and is likely almost instantaneously converted into the allylated products. On the other hand, the reaction with phenyl cinnamyl ether is much slower and appears to be more sequential. Chloroacetone is still relatively rapidly converted into methyl acetoacetate, whose formation reaches a maximum after 2 h. Due to its lower propensity to oxidatively add to the Pd(0) centre, a delayed consumption of phenyl cinnamyl ether is observed. While most of the cinnamyl acetate has reacted within two hours, more than 8 h of reaction were needed to reach a complete conversion of phenyl cinnamyl ether.

Using these optimised conditions, the scope of the domino reaction was studied with various  $\alpha$ -chloro ketones and alcohols (Scheme 5, Table 3).

As MeOH is the main alcohol used in alkoxy-carbonylation reactions, we settled to extend our study to other less common alcohols, featuring different electronic and/or steric properties. In the event, *n*-BuOH and *i*-PrOH showed reactivities similar to that observed with MeOH, affording the mono- and bis-allylated  $\beta$ -keto esters with comparable ratios and yields (entries 2 and 3). However, with the latter solvent, generation of the ether **3** was favored, to the detriment of the alkoxy-carbonylated ester **4**. This fact suggests that *i*-PrOH intercepts more readily the  $\eta^3$ -allyl palladium complex than its corresponding acylpalladium complex.



**Scheme 5.** Scope of the reaction.

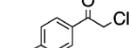
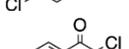
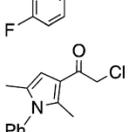
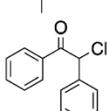
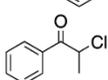
While chloroacetone always led to mixtures of mono- and bis-allylated  $\beta$ -keto esters **1aa** and **2aa**, the analogous reaction with chloropinacolone resulted in the exclusive formation of the mono-allylated product (entry 4). This fact is very likely due to the steric hindrance of the enolate of **1b**, which bears a tetrasubstituted alkene with a vicinal quaternary carbon atom.  $\alpha$ -Chloroacetophenone yielded 23% of **1** and 55% of **2** (entry 5). On the other hand, variable and more balanced proportions of allylation products **1** and **2** were obtained on moving to different aryl-substituted chloro ketones (entries 6 and 7). With 2-chloro-1-(2,5-dimethyl-1-phenyl-1*H*-pyrrol-3-yl)-1-ethanone (entry 8) the bis-allylated derivative **2** is obtained as minor product. No correlation could be drawn between the electronic effect of the ketone substituent and the **1/2** ratio.

Secondary chloro ketones led to the formation of quaternary carbons through the allylic alkylation step. In this case half the amount of allylic starting material was used. The derivatives efficiently yielded the expected products, albeit with lower yields (entries 9–11).

## Conclusions

In conclusion, we have shown that the alkoxy-carbonylation of  $\alpha$ -chloro ketones and their allylic alkylation reactions can be efficiently combined to build a new Pd-catalyzed *pseudo-domino type 1* sequence wherein the same catalytic system drives the two concatenated cycles. The  $\beta$ -keto ester is intermediately generated through a carbonylation reaction before being *in situ* engaged as nucleophile in the final allylic alkylation cycle. Tuning the allylic leaving group in the starting material, as well as the ancillary ligand proved to be keys to attain the successful combination of the two

**Table 3.** Scope of the reaction.<sup>[a]</sup>

| Entry             | $\alpha$ -Chloro ketone   | R'OH           | (Yield [%] <sup>[b]</sup> ) |                 |
|-------------------|---|----------------|-----------------------------|-----------------|
|                   |   |                | <b>1</b>                    | <b>2</b>        |
| 1                 |    | MeOH           | <b>1aa</b> (13)             | <b>2aa</b> (83) |
| 2                 |    | <i>n</i> -BuOH | <b>1ab</b> (14)             | <b>2ab</b> (77) |
| 3 <sup>[c]</sup>  |    | <i>i</i> -PrOH | <b>1ac</b> (12)             | <b>2ac</b> (85) |
| 4                 |    | MeOH           | <b>1b</b> (62)              | <b>2b</b> (0)   |
| 5                 |    | MeOH           | <b>1c</b> (23)              | <b>2c</b> (55)  |
| 6                 |    | MeOH           | <b>1d</b> (37)              | <b>2d</b> (39)  |
| 7                 |    | MeOH           | <b>1e</b> (30)              | <b>2e</b> (54)  |
| 8                 |    | MeOH           | <b>1f</b> (65)              | <b>2f</b> (5)   |
| 9 <sup>[d]</sup>  |    | MeOH           | <b>1g</b> (53)              | –               |
| 10 <sup>[d]</sup> |   | MeOH           | <b>1h</b> (20)              | –               |
| 11 <sup>[d]</sup> |  | MeOH           | <b>1i</b> (23)              | –               |

<sup>[a]</sup> The reaction were carried out at 90 °C using chloro ketone (3.0 mmol), phenylcinamyl phenyl ether (7.5 mmol, 2.5 equiv.), tributylamine (13.5 mmol, 4.5 equiv.), Pd(acac)<sub>2</sub> (0.03 mmol), Xantphos (0.06 mmol) in 10 mL of alcohol for 16 h.

<sup>[b]</sup> Isolated yields calculated from the amount of chloroacetone.

<sup>[c]</sup> With MeOH, **3** (0.6 mmol) and **4** (0.6 mmol); with *i*-PrOH **3** (1 mmol) and **4** (0.1 mmol).

<sup>[d]</sup> Reaction performed with 3.75 mmol of phenyl cinamyl ether.

metal-catalysed reactions in the correct succession. In particular, the use of less reactive phenates allowed great improvements compared to acetates, as revealed by kinetic experiments. Noteworthy, the reaction involves only a single palladium catalyst to promote the two steps at relatively moderate catalyst loadings. Further studies are aimed at applying this procedure to intramolecular domino sequences for the synthesis of highly functionalised cyclic structures.

## Experimental Section

### General Procedure for the Carbonylation/Allylation Domino Reaction (Table 3)

Reactions were performed in a stainless steel autoclave equipped with a magnetic stirrer. 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene (34.7 mg, 0.06 mmol), and (*E*)-cinamyl phenyl ether (1.577 g, 7.5 mmol) were placed in the reactor, and the contents were placed under N<sub>2</sub>. In a Schlenk tube, and under N<sub>2</sub>, a solution of Pd(acac)<sub>2</sub> (9.1 mg, 0.03 mmol), tributylamine (3.2 mL, 13.5 mmol) and chloro ketone (3 mmol) in 10 mL of alcohol was stirred until a homogeneous solution was obtained. Then, this solution was transferred to the reactor with a syringe and the reactor was charged with 15 bar of carbon monoxide. The mixture was stirred at 90 °C for 16 h. Then, the reactor was cooled until room temperature and carefully degassed. The mixture was diluted with diethyl ether, washed with an HCl solution (1 N), followed by an NaOH solution (1 N) until neutralisation, dried over MgSO<sub>4</sub> and concentrated under vacuum. After flash column chromatography on silica gel (petroleum ether/ethyl acetate 100:0 to 90:10), the mono-allylated, bis-allylated, ether and ester were isolated.

**(E)-Methyl 2-acetyl-2-cinnamyl-5-phenylpent-4-enoate (2aa):** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  = 7.27–7.14 (m, 10H, Ph), 6.40 (d, 2H, *J* = 15.0 Hz, Ph-CH), 5.94 (dt, 2H, <sup>3</sup>*J* = 15.0, 7.5 Hz, CH-CH<sub>2</sub>), 3.68 (s, 3H, O-CH<sub>3</sub>), 2.79 (br dd, *J* = 7.5, 14.5 Hz, 2H, CH<sub>2</sub>), 2.72 (br dd, *J* = 7.5, 14.5 Hz, 2H, CH<sub>2</sub>), 2.18 (s, 3H, O=C-CH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  = 204.2 (CH<sub>3</sub>-C=O), 172.1 (O=C=O), 137.0 (C<sub>Ar</sub>), 134.3 (CH=CH-CH<sub>2</sub>), 128.6 (CH<sub>Ar</sub>), 127.6 (CH<sub>Ar</sub>), 126.3 (CH<sub>Ar</sub>), 123.7 (CH=CH-CH<sub>2</sub>), 64.0 (O=C-C=O), 52.6 (O-CH<sub>3</sub>), 35.9 (CH<sub>2</sub>-CH=CH), 27.3 (O=C-CH<sub>3</sub>); HR-MS (ESI): *m/z* = 349.18034, calcd. for C<sub>23</sub>H<sub>25</sub>O<sub>3</sub> [M+H<sup>+</sup>]; 349.17982.

**(E)-Butyl 2-acetyl-2-cinnamyl-5-phenylpent-4-enoate (2ab):** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  = 7.33–7.23 (m, 10H, H<sub>Ar</sub>), 6.47 [d, 2H, *J* = 15.0 Hz, (-CH=CH-CH<sub>2</sub>-)<sub>2</sub>], 6.03 [dt, 2H, *J* = 15.0, 7.5 Hz, (CH=CH-CH<sub>2</sub>-)<sub>2</sub>], 4.18 (t, *J* = 7.2 Hz, 2H, CH<sub>2</sub>), 2.88 (br dd, *J* = 7.5, 14.5 Hz, 2H, CH<sub>2</sub>), 2.80 (br dd, *J* = 7.5, 14.5 Hz, 2H, CH<sub>2</sub>), 2.22 (s, 3H, O=C-CH<sub>3</sub>), 1.63 (quint, *J* = 7.2 Hz, 2H, O-CH<sub>2</sub>-CH<sub>2</sub>), 1.37 (sext, *J* = 7.2 Hz, 2H, O-CH<sub>2</sub>-CH<sub>2</sub>), 0.92 (t, *J* = 7.2 Hz, 3H, CH<sub>2</sub>-CH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  = 204.3 (CH<sub>3</sub>-C=O), 171.7 (O=C=O), 137.0 (C<sub>Ar</sub>), 134.2 (CH=CH-CH<sub>2</sub>), 128.6 (CH<sub>Ar</sub>), 127.6 (CH<sub>Ar</sub>), 126.3 (CH<sub>Ar</sub>), 123.8 (CH=CH-CH<sub>2</sub>), 65.5 (CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>), 64.0 (O=C-C=O), 35.9 (CH<sub>2</sub>-CH=CH), 30.6 (CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>), 27.3 (O=C-CH<sub>3</sub>), 19.3 (CH<sub>2</sub>-CH<sub>3</sub>), 13.7 (CH<sub>2</sub>-CH<sub>3</sub>); HR-MS (ESI): *m/z* = 391.22738, calcd. for C<sub>26</sub>H<sub>31</sub>O<sub>3</sub> [M+H<sup>+</sup>]; 391.22677.

**(E)-Isopropyl 2-acetyl-5-phenylpent-4-enoate (1ac):** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  = 7.23–7.13 (m, 5H, H<sub>Ar</sub>), 6.38 (d, *J* = 16.0 Hz, 1H, -CH=CH-CH<sub>2</sub>-), 6.04 (dt, *J* = 16.0, 6.0 Hz, 1H, -CH=CH-CH<sub>2</sub>-), 5.00 (sept, *J* = 6.3 Hz, 1H, O-CH), 3.48 (t, *J* = 7.4 Hz, 1H, O=C-CH), 3.48 (t, *J* = 7.4 Hz, 2H, CH<sub>2</sub>), 2.18 (s, 3H, O=C-CH<sub>3</sub>), 1.17 (d, *J* = 6.0 Hz, 3H, CH-CH<sub>3</sub>), 1.16 (d, *J* = 6.0 Hz, 3H, CH-CH<sub>3</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  = 202.7 (CH<sub>3</sub>-C=O), 168.9 (O=C=O), 137.1 (C<sub>Ar</sub>), 132.8 (CH=CH-CH<sub>2</sub>), 128.6 (CH<sub>Ar</sub>), 127.5 (CH<sub>Ar</sub>), 126.3 (CH<sub>Ar</sub>), 125.9 (CH=CH-CH<sub>2</sub>), 69.3 [(CH<sub>3</sub>)<sub>2</sub>-CH], 59.9 (CH<sub>2</sub>-CH-C=O), 31.6 (CH<sub>2</sub>-CH=CH),

29.3 (O=C-CH<sub>3</sub>), 21.9 (CH-CH<sub>3</sub>), 21.8 (CH-CH<sub>3</sub>); HR-MS (ESI): *m/z* = 261.14857, calcd. for C<sub>16</sub>H<sub>21</sub>O<sub>3</sub> [M+H<sup>+</sup>]: 261.14852.

**(E)-Isopropyl 2-acetyl-2-cinnamyl-5-phenylpent-4-enoate (2ac):** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ = 7.24–7.15 (m, 10H, H<sub>Ar</sub>), 6.39 [d, 2H, *J* = 15.0 Hz, (-CH=CH-CH<sub>2</sub>-)<sub>2</sub>], 5.95 [dt, 2H, *J* = 15.0, 7.5 Hz, (CH=CH-CH<sub>2</sub>-)<sub>2</sub>], 5.02 (sept, *J* = 6.3 Hz, 1H, O-CH), 2.77 (br dd, *J* = 7.5, 14.5 Hz, 2H, CH<sub>2</sub>), 2.70 (br dd, *J* = 7.5, 14.5 Hz, 2H, CH<sub>2</sub>), 2.13 (s, 3H, O=C-CH<sub>3</sub>), 1.17 [d, *J* = 6.0 Hz, 6H, (CH<sub>3</sub>)<sub>2</sub>]; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ = 204.3 (CH<sub>3</sub>-C=O), 171.0 (O=C=O), 137.0 (C<sub>Ar</sub>), 134.0 (CH=CH-CH<sub>2</sub>), 128.5 (CH<sub>Ar</sub>), 127.5 (CH<sub>Ar</sub>), 126.2 (CH<sub>Ar</sub>), 123.7 (CH=CH-CH<sub>2</sub>), 69.2 [(CH<sub>3</sub>)<sub>2</sub>-CH], 63.8 (O=C-C=O), 35.7 (CH<sub>2</sub>-CH=CH), 27.1 (O=C-CH<sub>3</sub>), 21.7 [(CH<sub>3</sub>)<sub>2</sub>]; HR-MS (ESI): *m/z* = 377.21170, calcd. for C<sub>25</sub>H<sub>32</sub>O<sub>3</sub> [M+H<sup>+</sup>]: 377.21112.

**(E)-Methyl 5-phenyl-2-pivaloylpent-4-enoate (1b):** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ = 7.28 (m, 5H, H<sub>Ar</sub>), 6.46 (d, *J* = 16.0 Hz, 1H, -CH=CH-CH<sub>2</sub>-), 6.12 (dt, *J* = 16.0, 7.0 Hz, 1H, -CH=CH-CH<sub>2</sub>-), 4.07 (dd, *J* = 7.2, 7.2 Hz, 1H, CH), 3.72 (s, 3H, O-CH<sub>3</sub>), 2.77 (ddd, *J* = 7.0, 7.2, 14.5 Hz, 1H, CH<sub>2</sub>), 2.73 (ddd, *J* = 7.0, 7.2, 14.5 Hz, 1H, CH<sub>2</sub>), 1.19 [s, 9H, (CH<sub>3</sub>)<sub>3</sub>]; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ = 209.5 [(CH<sub>3</sub>)<sub>3</sub>C=O], 169.8 (O=C=O), 137.1 (C<sub>Ar</sub>), 132.8 (CH=CH-CH<sub>2</sub>), 128.6 (CH<sub>Ar</sub>), 127.5 (CH<sub>Ar</sub>), 126.2 (CH=CH-CH<sub>2</sub> and CH<sub>Ar</sub>), 52.5 (O-CH<sub>3</sub> and CH-C=O), 45.5 [C(CH<sub>3</sub>)<sub>3</sub>], 33.5 (CH<sub>2</sub>-CH=CH), 26.2 [(CH<sub>3</sub>)<sub>3</sub>]; HR-MS (ESI): *m/z* = 275.16441, calcd. for C<sub>17</sub>H<sub>25</sub>O<sub>3</sub> [M+H<sup>+</sup>]: 275.16417.

**(E)-Methyl 2-benzoyl-5-phenylpent-4-enoate (1c):** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ = 7.94 (d, *J* = 8.0 Hz, 2H, H<sub>ortho</sub>), 7.52 (t, *J* = 7.5 Hz, 1H, H<sub>para</sub>), 7.42 (t, *J* = 7.6 Hz, 2H, H<sub>meta</sub>), 7.22–7.13 (m, 5H, H<sub>Ar</sub>), 6.40 (d, *J* = 16.0 Hz, 1H, -CH=CH-CH<sub>2</sub>-), 6.14 (dt, *J* = 16.0, 7.0 Hz, 1H, -CH=CH-CH<sub>2</sub>-), 4.42 (dd, *J* = 7.2, 7.2 Hz, 1H, CH), 3.62 (s, 3H, O-CH<sub>3</sub>), 2.85 (ddd, *J* = 7.0, 7.2, 14.5 Hz, 1H, CH<sub>2</sub>), 2.83 (ddd, *J* = 7.0, 7.2, 14.5 Hz, 1H, CH<sub>2</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ = 194.5 (Ph-C=O), 170.0 (O=C=O), 137.2 (C<sub>Ar</sub>), 136.2 (C<sub>Ar</sub>), 133.8 (CH=CH-CH<sub>2</sub>), 132.9 (CH<sub>Ar</sub>), 129.0 (CH<sub>Ar</sub>), 128.8 (CH<sub>Ar</sub>), 128.6 (CH<sub>Ar</sub>), 127.5 (CH<sub>Ar</sub>), 126.3 (CH<sub>Ar</sub>), 126.1 (CH=CH-CH<sub>2</sub>), 54.2 (CH<sub>2</sub>-CH-C=O), 52.7 (O-CH<sub>3</sub>), 32.6 (CH<sub>2</sub>-CH=CH); HR-MS (ESI): *m/z* = 295.13306, calcd. for C<sub>19</sub>H<sub>19</sub>O<sub>3</sub> [M+H<sup>+</sup>]: 295.13287.

**(E)-Methyl 2-benzoyl-2-cinnamyl-5-phenylpent-4-enoate (2c):** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ = 7.88 (d, *J* = 8.0 Hz, 2H, H<sub>ortho</sub>), 7.57 (t, *J* = 7.5 Hz, 1H, H<sub>para</sub>), 7.47 (t, *J* = 7.6 Hz, 2H, H<sub>meta</sub>), 7.34–7.22 (m, 10H, H<sub>Ar</sub>), 6.38 [d, *J* = 16.0 Hz, 2H, (-CH=CH-CH<sub>2</sub>-)<sub>2</sub>], 6.02 [dt, *J* = 16.0, 7.5 Hz, 2H, (-CH=CH-CH<sub>2</sub>-)<sub>2</sub>], 3.69 (s, 3H, O-CH<sub>3</sub>), 3.06 (br dd, *J* = 7.5, 14.5 Hz, 2H, CH<sub>2</sub>), 2.99 (br dd, *J* = 7.5, 14.5 Hz, 2H, CH<sub>2</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ = 196.2 (Ph-C=O), 176.3 (O=C=O), 137.2 (C<sub>Ar</sub>), 136.0 (C<sub>Ar</sub>), 134.4 (CH=CH-CH<sub>2</sub>), 133.0 (CH<sub>Ar</sub>), 128.8 (CH<sub>Ar</sub>), 128.6 (CH<sub>Ar</sub>), 128.5 (CH<sub>Ar</sub>), 127.6 (CH<sub>Ar</sub>), 126.4 (CH<sub>Ar</sub>), 123.6 (CH=CH-CH<sub>2</sub>), 61.4 (O=C-C=O), 52.6 (O-CH<sub>3</sub>), 37.1 (CH<sub>2</sub>-CH=CH); HR-MS (ESI): *m/z* = 411.19575, calcd. for C<sub>28</sub>H<sub>27</sub>O<sub>3</sub> [M+H<sup>+</sup>]: 411.19547.

**(E)-Methyl 2-(4-chlorobenzoyl)-5-phenylpent-4-enoate (entry 1d):** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ = 7.88 (d, *J* = 8.0 Hz, 2H, H<sub>ortho</sub>), 7.38 (d, *J* = 8.0 Hz, 2H, H<sub>meta</sub>), 7.22–7.14 (m, 5H, H<sub>Ar</sub>), 6.40 (d, *J* = 16.0 Hz, 1H, -CH=CH-CH<sub>2</sub>-), 6.09 (dt, *J* = 16.0, 7.0 Hz, 1H, -CH=CH-CH<sub>2</sub>-), 4.36 (dd, *J* = 7.2, 7.2 Hz, 1H, CH), 3.62 (s, 3H, O-CH<sub>3</sub>), 2.83 (ddd, *J* = 7.0, 7.2, 14.5 Hz, 1H, CH<sub>2</sub>), 2.81 (ddd, *J* = 7.0, 7.2,

14.5 Hz, 1H, CH<sub>2</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ = 193.3 (Ar-C=O), 169.7 (O=C=O), 140.4 (C<sub>Ar</sub>), 137.0 (C<sub>Ar</sub>), 134.5 (C<sub>Ar</sub>), 133.0 (CH=CH-CH<sub>2</sub>), 130.2 (CH<sub>Ar</sub>), 129.3 (CH<sub>Ar</sub>), 128.6 (CH<sub>Ar</sub>), 127.6 (CH<sub>Ar</sub>), 126.3 (CH<sub>Ar</sub>), 125.8 (CH=CH-CH<sub>2</sub>), 54.2 (CH<sub>2</sub>-CH-C=O), 52.8 (O-CH<sub>3</sub>), 32.5 (CH<sub>2</sub>-CH=CH); HR-MS (ESI): *m/z* = 329.09433, calcd. for C<sub>19</sub>H<sub>18</sub>ClO<sub>3</sub> [M+H<sup>+</sup>]: 329.09390.

**(E)-Methyl 2-(4-chlorobenzoyl)-2-cinnamyl-5-phenylpent-4-enoate (2d):** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ = 7.74 (d, *J* = 8.0 Hz, 2H, H<sub>ortho</sub>), 7.35 (d, *J* = 8.0 Hz, 2H, H<sub>meta</sub>), 7.22–7.13 (m, 10H, H<sub>Ar</sub>), 6.29 [d, *J* = 16.0 Hz, 2H, (-CH=CH-CH<sub>2</sub>-)<sub>2</sub>], 5.89 [dt, *J* = 16.0, 7.5 Hz, 2H, (-CH=CH-CH<sub>2</sub>-)<sub>2</sub>], 3.60 (s, 3H, O-CH<sub>3</sub>), 2.95 (br dd, *J* = 7.5, 14.5 Hz, 2H, CH<sub>2</sub>), 2.87 (br dd, *J* = 7.5, 14.5 Hz, 2H, CH<sub>2</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ = 195.0 (Ar-C=O), 173.2 (O=C=O), 139.6 (C<sub>Ar</sub>), 137.1 (C<sub>Ar</sub>), 134.6 (C<sub>Ar</sub>), 134.3 (CH=CH-CH<sub>2</sub>), 130.0 (CH<sub>Ar</sub>), 129.2 (CH<sub>Ar</sub>), 128.7 (CH<sub>Ar</sub>), 127.7 (CH<sub>Ar</sub>), 126.4 (CH<sub>Ar</sub>), 123.3 (CH=CH-CH<sub>2</sub>), 61.4 (O=C-C=O), 52.7 (O-CH<sub>3</sub>), 37.1 (CH<sub>2</sub>-CH=CH); HR-MS (ESI): *m/z* = 445.15802, calcd. for C<sub>28</sub>H<sub>26</sub>ClO<sub>3</sub> [M+H<sup>+</sup>]: 445.15650.

**(E)-Methyl 2-(4-fluorobenzoyl)-5-phenylpent-4-enoate (1e):** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ = 8.07 (m, 2H, H<sub>Ar</sub>), 7.38–7.14 (m, 7H, H<sub>Ar</sub>), 6.50 [d, *J* = 16.0 Hz, 2H, (-CH=CH-CH<sub>2</sub>-)<sub>2</sub>], 6.19 [dt, *J* = 16.0, 7.0 Hz, 2H, (-CH=CH-CH<sub>2</sub>-)<sub>2</sub>], 4.47 (dd, *J* = 7.2, 7.2 Hz, 1H, CH), 3.72 (s, 3H, O-CH<sub>3</sub>), 2.94 (ddd, *J* = 7.0, 7.2, 14.5 Hz, 1H, CH<sub>2</sub>), 2.92 (ddd, *J* = 7.0, 7.2, 14.5 Hz, 1H, CH<sub>2</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ = 192.8 (Ar-C=O), 169.7 (O=C=O), 137.0 (C<sub>Ar</sub>), 132.9 (C<sub>Ar</sub>), 131.5 (C<sub>Ar</sub>), 131.4 (CH=CH-CH<sub>2</sub>), 128.5 (CH<sub>Ar</sub>), 127.4 (CH<sub>Ar</sub>), 126.2 (CH<sub>Ar</sub>), 125.8 (CH<sub>Ar</sub>), 116.2 (CH<sub>Ar</sub>), 115.9 (CH=CH-CH<sub>2</sub>), 54.1 (CH<sub>2</sub>-CH-C=O), 52.7 (O-CH<sub>3</sub>), 32.4 (CH<sub>2</sub>-CH=CH); HR-MS (ESI): *m/z* = 313.12385, calcd. for C<sub>19</sub>H<sub>18</sub>FO<sub>3</sub> [M+H<sup>+</sup>]: 313.12345.

**(E)-Methyl 2-cinnamyl-2-(4-fluorobenzoyl)-5-phenylpent-4-enoate (2e):** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ = 7.93 (m, 2H, H<sub>Ar</sub>), 7.38–7.21 (m, 10H, H<sub>Ar</sub>), 7.15 (m, 2H, H<sub>Ar</sub>), 6.39 [d, *J* = 16.0 Hz, 2H, (-CH=CH-CH<sub>2</sub>-)<sub>2</sub>], 5.99 [dt, *J* = 16.0, 7.5 Hz, 2H, (-CH=CH-CH<sub>2</sub>-)<sub>2</sub>], 3.69 (s, 3H, O-CH<sub>3</sub>), 3.05 (br dd, *J* = 7.5, 14.5 Hz, 2H, CH<sub>2</sub>), 2.98 (br dd, *J* = 7.5, 14.5 Hz, 2H, CH<sub>2</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ = 194.6 (Ar-C=O), 173.3 (O=C=O), 137.1 (C<sub>Ar</sub>), 134.6 (C<sub>Ar</sub>), 131.4 (C<sub>Ar</sub>), 131.2 (CH=CH-CH<sub>2</sub>), 128.7 (CH<sub>Ar</sub>), 127.6 (CH<sub>Ar</sub>), 126.4 (CH<sub>Ar</sub>), 123.4 (CH<sub>Ar</sub>), 116.1 (CH<sub>Ar</sub>), 115.8 (CH=CH-CH<sub>2</sub>), 61.3 (O=C-C=O), 52.7 (O-CH<sub>3</sub>), 37.1 (CH<sub>2</sub>-CH=CH); HR-MS (ESI): *m/z* = 429.18749, calcd. for C<sub>28</sub>H<sub>26</sub>FO<sub>3</sub> [M+H<sup>+</sup>]: 429.18605.

**(E)-Methyl 2-(2,5-dimethyl-1-phenyl-1H-pyrrole-3-carbonyl)-5-phenylpent-4-enoate (1f):** <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ = 7.52–7.46 (m, 3H, H<sub>Ar</sub>), 7.34–7.16 (m, 7H, H<sub>Ar</sub>), 6.49 (d, *J* = 16.0 Hz, 1H, -CH=CH-CH<sub>2</sub>-), 6.40 (s, 1H, CH<sub>pyrrole</sub>), 6.23 (dt, *J* = 16.0, 6.0 Hz, 1H, -CH=CH-CH<sub>2</sub>-), 4.20 (t, *J* = 7.2 Hz, 1H, CH), 3.74 (s, 3H, O-CH<sub>3</sub>), 2.90 (ddd, *J* = 7.0, 7.2, 14.5 Hz, 1H, CH<sub>2</sub>), 2.88 (ddd, *J* = 7.0, 7.2, 14.5 Hz, 1H, CH<sub>2</sub>), 2.32 (s, 3H, CH<sub>3pyrrole</sub>), 1.98 (s, 3H, CH<sub>3pyrrole</sub>); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ = 190.3 (pyrrole-C=O), 170.8 (O=C=O), 138.0 (C<sub>Ar</sub>), 137.4 (C<sub>Ar</sub>), 137.1 (C<sub>Ar</sub>), 132.1 (C<sub>Ar</sub>), 129.5 (C<sub>Ar</sub>), 129.2 (CH=CH-CH<sub>2</sub>), 128.8 (CH<sub>Ar</sub>), 128.5 (CH<sub>Ar</sub>), 128.0 (CH<sub>Ar</sub>), 127.2 (CH<sub>Ar</sub>), 127.1 (CH<sub>Ar</sub>), 126.2 (CH<sub>Ar</sub>), 119.3 (CH=CH-CH<sub>2</sub>), 107.6 (CH<sub>pyrrole</sub>), 56.0 (O=C-CH-), 52.3 (O-CH<sub>3</sub>), 32.7 (CH<sub>2</sub>), 13.2 (CH<sub>3pyrrole</sub>), 12.8 (CH<sub>3pyrrole</sub>); HR-MS (ESI): *m/z* = 388.19156, calcd. for C<sub>25</sub>H<sub>26</sub>NO<sub>3</sub> [M<sup>+</sup>]: 388.19072.

**(E)-Methyl 2-acetyl-2-methyl-5-phenylpent-4-enoate (1g):**  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 300 MHz):  $\delta = 7.33\text{--}7.23$  (m, 5H,  $\text{H}_{\text{Ar}}$ ), 6.45 (d,  $J = 16.0$  Hz, 1H,  $-\text{CH}=\text{CH}-\text{CH}_2-$ ), 6.06 (dt,  $J = 16.0$ , 6.0 Hz, 1H,  $-\text{CH}=\text{CH}-\text{CH}_2-$ ), 3.76 (s, 3H,  $\text{O}-\text{CH}_3$ ), 2.81 (br dd,  $J = 7.5$ , 14.5 Hz, 2H,  $\text{CH}_2$ ), 2.67 (br dd,  $J = 7.5$ , 14.5 Hz, 2H,  $\text{CH}_2$ ), 2.20 (s, 3H,  $\text{O}=\text{C}-\text{CH}_3$ ), 1.41 (s, 3H,  $\text{CH}_3$ );  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 75 MHz):  $\delta = 205.1$  ( $\text{CH}_3-\text{C}=\text{O}$ ), 173.0 ( $\text{O}-\text{C}=\text{O}$ ), 137.0 ( $\text{C}_{\text{Ar}}$ ), 134.0 ( $\text{CH}=\text{CH}-\text{CH}_2$ ), 128.5 ( $\text{CH}_{\text{Ar}}$ ), 127.4 ( $\text{CH}_{\text{Ar}}$ ), 126.2 ( $\text{CH}_{\text{Ar}}$ ), 124.2 ( $\text{CH}=\text{CH}-\text{CH}_2$ ), 59.9 ( $\text{O}=\text{C}-\text{C}-\text{O}$ ), 52.5 ( $\text{O}-\text{CH}_3$ ), 38.7 ( $\text{CH}_2-\text{CH}=\text{CH}$ ), 26.4 ( $\text{O}=\text{C}-\text{CH}_3$ ), 19.2 ( $\text{CH}_3$ ); HR-MS (ESI):  $m/z = 247.13340$ , calcd. for  $\text{C}_{15}\text{H}_{19}\text{O}_3$  [ $\text{M}+\text{H}^+$ ]: 247.13287.

**(E)-methyl 2-benzoyl-2,5-diphenylpent-4-enoate (1h):**  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 300 MHz):  $\delta = 7.65$  (d,  $J = 8.0$  Hz, 2H,  $\text{H}_{\text{Ar}}$ ), 7.53 (d,  $J = 8.0$  Hz, 2H,  $\text{H}_{\text{Ar}}$ ), 7.33–7.11 (m, 11H,  $\text{H}_{\text{Ar}}$ ), 6.18 (d,  $J = 16.0$  Hz, 1H,  $-\text{CH}=\text{CH}-\text{CH}_2-$ ), 6.06 (dt,  $J = 16.0$ , 6.0 Hz, 1H,  $-\text{CH}=\text{CH}-\text{CH}_2-$ ), 3.51 (s, 3H,  $\text{O}-\text{CH}_3$ ), 3.25 (br dd,  $J = 7.5$ , 14.5 Hz, 2H,  $\text{CH}_2$ ), 2.96 (br dd,  $J = 7.5$ , 14.5 Hz, 2H,  $\text{CH}_2$ );  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 75 MHz):  $\delta = 195.1$  ( $\text{Ph}-\text{C}=\text{O}$ ), 171.5 ( $\text{O}-\text{C}=\text{O}$ ), 138.2 ( $\text{C}_{\text{Ar}}$ ), 137.4 ( $\text{C}_{\text{Ar}}$ ), 135.8 ( $\text{C}_{\text{Ar}}$ ), 133.8 ( $\text{CH}-\text{CH}-\text{CH}_2$ ), 132.7 ( $\text{CH}_{\text{Ar}}$ ), 129.7 ( $\text{CH}_{\text{Ar}}$ ), 128.7 ( $\text{CH}_{\text{Ar}}$ ), 128.6 ( $\text{CH}_{\text{Ar}}$ ), 128.3 ( $\text{CH}_{\text{Ar}}$ ), 128.0 ( $\text{CH}_{\text{Ar}}$ ), 127.6 ( $\text{CH}_{\text{Ar}}$ ), 127.4 ( $\text{CH}_{\text{Ar}}$ ), 126.3 ( $\text{CH}_{\text{Ar}}$ ), 124.9 ( $\text{CH}=\text{CH}-\text{CH}_2$ ), 66.3 ( $\text{O}=\text{C}-\text{C}-\text{O}$ ), 52.5 ( $\text{O}-\text{CH}_3$ ), 43.6 ( $\text{CH}_2-\text{CH}=\text{CH}$ ); HR-MS (ESI):  $m/z = 371.16519$ , calcd. for  $\text{C}_{25}\text{H}_{25}\text{O}_3$  [ $\text{M}+\text{H}^+$ ]: 371.16417.

**(E)-Methyl 2-benzoyl-2-methyl-5-phenylpent-4-enoate (1i):**  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 300 MHz):  $\delta = 7.86$  (d,  $J = 8.0$  Hz, 2H,  $\text{H}_{\text{ortho}}$ ), 7.56 (t,  $J = 7.5$  Hz, 1H,  $\text{H}_{\text{para}}$ ), 7.46 (t,  $J = 7.6$  Hz, 2H,  $\text{H}_{\text{meta}}$ ), 7.31–7.22 (m, 5H,  $\text{H}_{\text{Ar}}$ ), 6.39 (d,  $J = 16.0$  Hz, 1H,  $-\text{CH}=\text{CH}-\text{CH}_2-$ ), 6.07 (dt,  $J = 16.0$ , 6.0 Hz, 1H,  $-\text{CH}=\text{CH}-\text{CH}_2-$ ), 3.67 (s, 3H,  $\text{O}-\text{CH}_3$ ), 2.98 (br dd,  $J = 7.5$ , 14.5 Hz, 2H,  $\text{CH}_2$ ), 2.89 (br dd,  $J = 7.5$ , 14.5 Hz, 2H,  $\text{CH}_2$ ), 1.59 (s, 3H,  $\text{CH}_3$ );  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 75 MHz):  $\delta = 197.0$  ( $\text{Ph}-\text{C}=\text{O}$ ), 174.3 ( $\text{O}-\text{C}=\text{O}$ ), 137.1 ( $\text{C}_{\text{Ar}}$ ), 135.4 ( $\text{C}_{\text{Ar}}$ ), 134.0 ( $\text{CH}=\text{CH}-\text{CH}_2$ ), 132.8 ( $\text{CH}_{\text{Ar}}$ ), 128.7 ( $\text{CH}_{\text{Ar}}$ ), 128.6 ( $\text{CH}_{\text{Ar}}$ ), 128.5 ( $\text{CH}_{\text{Ar}}$ ), 127.4 ( $\text{CH}_{\text{Ar}}$ ), 126.3 ( $\text{CH}_{\text{Ar}}$ ), 124.1 ( $\text{CH}=\text{CH}-\text{CH}_2$ ), 57.3 ( $\text{O}=\text{C}-\text{C}-\text{O}$ ), 52.5 ( $\text{O}-\text{CH}_3$ ), 40.4 ( $\text{CH}_2-\text{CH}=\text{CH}$ ), 21.3 ( $\text{CH}_3$ ); HR-MS (ESI):  $m/z = 309.14909$ , calcd. for  $\text{C}_{20}\text{H}_{21}\text{O}_3$ ; 309.14852 [ $\text{M}+\text{H}^+$ ].

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## COMMUNICATION

**Pd-catalyzed domino carbonylative–decarboxylative allylation: an easy and selective monoallylation of ketones†**Steven Giboulot,<sup>a</sup> Frédéric Liron,<sup>\*a</sup> Guillaume Prestat,<sup>‡a</sup> Benoit Wahl,<sup>b</sup> Mathieu Sauthier,<sup>b</sup> Yves Castanet,<sup>b</sup> André Mortreux<sup>b</sup> and Giovanni Poli<sup>\*a</sup>

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In the presence of an allyl alcohol,  $\alpha$ -chloroacetophenones undergo an allyloxy-carbonylation reaction followed by *in situ* decarboxylative allylation to selectively afford the corresponding monoallylated ketones via a Pd-catalyzed domino sequence. The scope of the reaction was extended to substituted  $\alpha$ -chloroacetophenones as well as various allyl alcohols.

Monoallylation of ketones remains challenging in organic synthesis. Direct allylation of enolates is not selective and normally results in mixtures of mono- and diallylated ketones.<sup>1</sup> The Stork enamine strategy is highly efficient, but requires the stoichiometric formation of an enamine, which may not be stable.<sup>2</sup> Pd-catalyzed allylation reactions have recently emerged, but the need for a special ferrocene-based ligand<sup>3</sup> makes these multi-step syntheses tedious.

To the best of our knowledge, palladium-catalyzed alkoxy-carbonylation of  $\alpha$ -chloroketones has been so far limited to the preparation of simple, saturated esters, using the required alcohol as the solvent.<sup>4</sup> We anticipated that, in the presence of an allyl alcohol, the resulting allyl  $\beta$ -ketoester could undergo *in situ* Pd-catalyzed decarboxylative allylation.<sup>5</sup> In such a case, a Pd(0) complex would catalyze the carbonylation step as well as the decarboxylative allylation in a *pseudo-domino type I* manner,<sup>6</sup> thereby selectively generating the desired monoallylated ketone via a doubly catalytic one-pot process. Scheme 1 shows the prospective overall mechanism of this new *pseudo-domino* sequence.<sup>7</sup> The desired path follows elementary steps from *I* to *7* incorporated in the two consecutive catalytic cycles sharing Pd(0). However, an accurate perusal at the possible undesired reactivities (Scheme 1, dotted paths) unveils the *caveat* that makes such a sequence challenging. First, an undesired nucleophilic substitution between allyl alcohol and the halide might generate the corresponding ether, thereby directly subtracting

the two components of the reaction (step *8*). Furthermore, premature protonation of the palladium complex deriving from oxidative addition of the halide may also take place, directly, or via its palladium enolate<sup>8</sup> (step *9*). Finally, competitive oxidative addition of the alcohol to Pd(0) may, after  $\beta$ -elimination, generate acrolein, thereby consuming the alcohol (step *12*).<sup>9</sup>

We first studied both steps separately. On the one hand, in MeOH and under a CO atmosphere (10 bar),  $\alpha$ -chloroacetophenone **1a** provided the expected methyl  $\beta$ -ketoester **2**. Unfortunately, the reaction did not proceed at atmospheric pressure.<sup>4f,g</sup>

On the other hand, treatment of allyl  $\beta$ -ketoester **3** with catalytic Pd(dba)<sub>2</sub>/4PPh<sub>3</sub> at 90 °C in allyl alcohol gave readily the allylated acetophenone **4a** in high yield (Scheme 2).

We next focused on the *pseudo-domino* process. Accordingly, we investigated the reactivity of **1a** in the presence of allyl alcohol, a base, a catalytic amount of a palladium complex, and under a CO atmosphere (Table 1).

Under the conditions suitable for the methoxycarbonylation reaction, neither allylated acetophenone **4a**, nor allyl  $\beta$ -ketoester **3** was observed (entry 1). Raising the temperature to 130 °C led to 11% isolated yield of allylated acetophenone **4a** (entry 2).

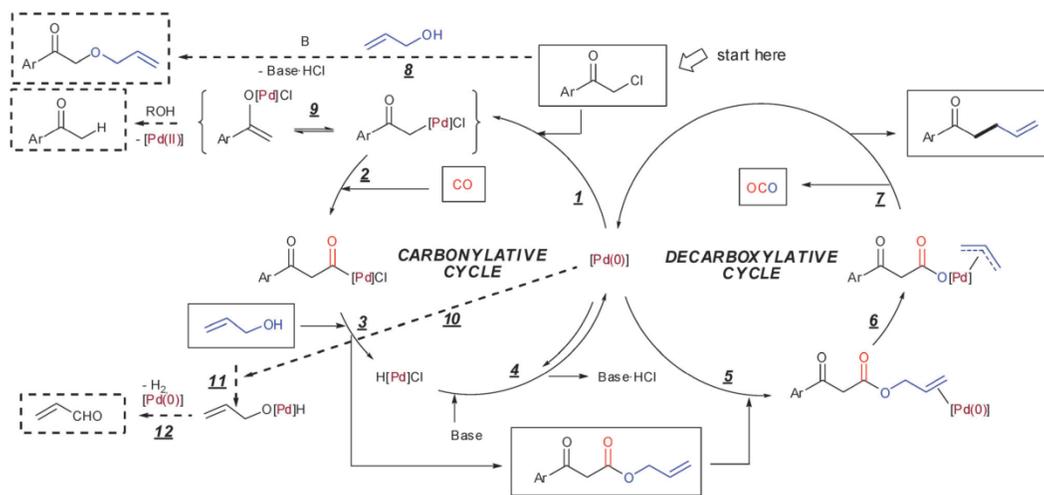
Use of a combination of Pd(OAc)<sub>2</sub> and PPh<sub>3</sub> (1 : 4) resulted in a slightly better yield (20%, entry 3). Raising CO pressure to 20 bar gave the desired product in 27% yield (entry 4). Although an increase in the catalyst loading to 5 mol% showed no improvement (25%, entry 5), further increase to 10 mol% Pd resulted in a doubled isolated yield (52%, entry 6). So far, allyl alcohol was used as the solvent (30 equiv.). Next, we reduced the amount of allyl alcohol to 15 equivalents, in the presence of an additional solvent, so as to keep the molarity constant. THF and DMF were less efficient, affording 39% and 3% yield of **4a**, respectively (entries 7 and 8), whereas toluene was suitable (57%, entry 9). Tributylamine as the base was as efficient as 1,8-bis(dimethylamino)naphthalene (DMAN) (54%, entry 10), yet, allowing an easier workup. A decrease in the amount of allyl alcohol to 6 equiv. led to the exclusive formation of acetophenone (entry 11). A ligand screening revealed that tri(2-furyl) phosphine (TFP) was the best one (76%, entry 12). Finally, the reaction proceeded with equal efficiency reducing the reaction time to 2 h (73%, entry 13). All electron-rich phosphines studied, but Xantphos, led to

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† Electronic supplementary information (ESI) available: Full optimization details and full spectroscopic characterization of all new compounds. See DOI: 10.1039/c2cc32391e

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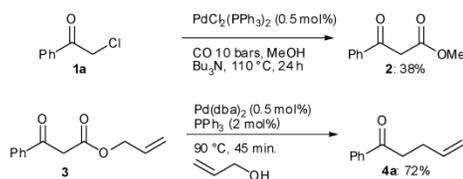


**Scheme 1** Mechanism of the Pd-catalyzed carbonylative-decarboxylative allylation pseudo-domino sequence, and the possible side reactions.

unsatisfactory results.<sup>10</sup> Triethyl phosphite led to disappointing results, too (entry 14). Generating CO from methyl formate<sup>11</sup> was also not efficient.§

With these optimized conditions in hand (Table 1, entry 13), substituted acetophenones **1b–n** were tested as substrates (Scheme 3).

Monoallylated aryl ketones bearing an electron-withdrawing group at the *para* position were isolated in moderate to acceptable yields (**4b–e**, 31–65%). The reaction was equally successful for ketones bearing electron-donating groups at the *para* position (**4f–h**, 44–77%). An EWG or EDG group at the *meta* position was also well tolerated (**4i–j**, 37%). However, our procedure proved to be sensitive to steric hindrance. Allylated acetophenone **4k**, bearing chlorine atoms at *para* and *ortho* positions was obtained in a lower yield than allylated acetophenone **4c** bearing only the *para* chlorine atom (36% vs. 57%, respectively). Desyl chloride also furnished the desired monoallylated ketone, albeit in moderate yield (**4l**, 33%).  $\alpha$ -Chloro cycloalkanones and  $\alpha$ -chloroketones bearing  $\beta$ -hydrogen atoms led to mixtures of  $\beta$ -hydride elimination and/or reduction products. Finally,  $\alpha$ -chloroacetophenone **1a** was reacted with substituted allyl alcohols. These alcohols were used as the solvent. Indeed, use of 15 equiv. of the desired alcohol in toluene led to unsatisfactory results. Monosubstitution at either the 2- or 3-position of the allylic motif was tolerated, affording the desired allylated ketones **4p–r** in good yields (51%, Scheme 4).



**Scheme 2** Pd-catalyzed methoxycarbonylation and decarboxylative allylation, separately.

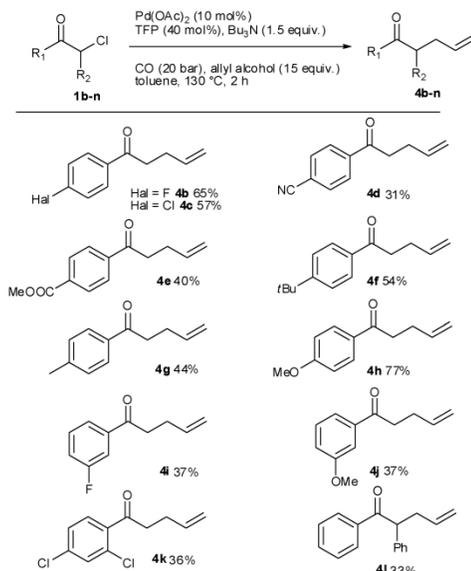
In the case of crotyl alcohol, mixtures of regioisomeric allylated acetophenones **4p** and **4q** were obtained. Worthy of note, in the case of methyl allyl alcohol, Xantphos revealed to be the ligand of choice.

In conclusion, we have developed a synthetic protocol for the selective generation of  $\gamma,\delta$ -unsaturated aromatic ketones

**Table 1** Optimization of the reaction conditions for the domino sequence

| Entry           | [Pd] <sup>a</sup>                                  | Ligand              | Base              | Solvent <sup>b</sup> | T/ <sup>c</sup><br>°C | P <sub>CO</sub> /<br>bar | Yield <sup>d</sup><br>(%) |
|-----------------|--|---------------------|-------------------|----------------------|-----------------------|--------------------------|---------------------------|
| 1               | PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> | —                   | DMAN              |                      | 100                   | 10                       | 0                         |
| 2               | PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> | —                   | DMAN              |                      | 130                   | 10                       | 11                        |
| 3               | Pd(OAc) <sub>2</sub>                               | PPh <sub>3</sub>    | DMAN              |                      | 130                   | 10                       | 20                        |
| 4               | Pd(OAc) <sub>2</sub>                               | PPh <sub>3</sub>    | DMAN              |                      | 130                   | 20                       | 27                        |
| 5               | Pd(OAc) <sub>2</sub>                               | PPh <sub>3</sub>    | DMAN              |                      | 130                   | 20                       | 25                        |
| 6               | Pd(OAc) <sub>2</sub>                               | PPh <sub>3</sub>    | DMAN              |                      | 130                   | 20                       | 52                        |
| 7               | Pd(OAc) <sub>2</sub>                               | PPh <sub>3</sub>    | DMAN              | THF                  | 130                   | 20                       | 39                        |
| 8               | Pd(OAc) <sub>2</sub>                               | PPh <sub>3</sub>    | DMAN              | DMF                  | 130                   | 20                       | 3                         |
| 9               | Pd(OAc) <sub>2</sub>                               | PPh <sub>3</sub>    | DMAN              | Toluene              | 130                   | 20                       | 57                        |
| 10              | Pd(OAc) <sub>2</sub>                               | PPh <sub>3</sub>    | Bu <sub>3</sub> N | Toluene              | 130                   | 20                       | 54                        |
| 11 <sup>d</sup> | Pd(OAc) <sub>2</sub>                               | PPh <sub>3</sub>    | Bu <sub>3</sub> N | Toluene              | 130                   | 20                       | 0                         |
| 12              | Pd(OAc) <sub>2</sub>                               | TFP <sup>e</sup>    | Bu <sub>3</sub> N | Toluene              | 130                   | 20                       | 76                        |
| 13 <sup>f</sup> | Pd(OAc) <sub>2</sub>                               | TFP                 | Bu <sub>3</sub> N | Toluene              | 130                   | 20                       | 73                        |
| 14              | Pd(OAc) <sub>2</sub>                               | P(OEt) <sub>3</sub> | Bu <sub>3</sub> N | Toluene              | 130                   | 20                       | 0                         |

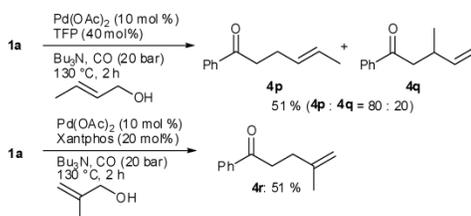
<sup>a</sup> Entries 1–4: 0.5 mol%; entry 5: 5 mol%; entries 6–14: 10 mol%; in all cases, 4 equiv. of ligand with respect to [Pd] were used. <sup>b</sup> For allyl alcohol: 30 equiv. allyl alcohol. For other solvents: 15 equiv. allyl alcohol unless otherwise noted. <sup>c</sup> Isolated yields. The mass balance to 100% was essentially acetophenone. Traces of aldehydes were sometimes noticed. <sup>d</sup> 6 equiv. of allyl alcohol. <sup>e</sup> Tri(2-furyl)phosphine. <sup>f</sup> 2 h.



**Scheme 3** Scope and limitations of the pseudo-domino sequence.<sup>12</sup>

starting from readily accessible  $\alpha$ -chloroacetophenones. The method, which is based on a Pd-catalyzed carbonylative-decarboxylative allylation pseudo-domino process, was insensitive to the electronic properties of the substituents on the aromatic ring. As this new concept could be extended to substituted  $\alpha$ -chloroacetophenones, further synthetic applications involving  $\gamma,\delta$ -unsaturated aromatic ketones can be foreseen.

We are grateful to ANR CP2D programme ('Domino-CO' project), the CNRS and the Ministry of Research and Technology (UPMC and Lille University) for their financial support.



**Scheme 4** Influence of the substitution pattern of the allyl alcohol.

## Notes and references

§ Representative experimental procedure: an autoclave was charged with Pd(OAc)<sub>2</sub> (10 mol%), P(2-furyl)<sub>3</sub> (40 mol%), Bu<sub>3</sub>N (1.5 equiv.),  $\alpha$ -chloroacetophenone (1.0 mmol), allyl alcohol (1 mL) and toluene (1.5 mL). The autoclave was purged with CO, sealed and pressurized to 20 bar and heated at 130 °C for 2 h. After cooling to r.t., pressure was released. The reaction mixture was diluted with ether (10 mL) and water (20 mL) was added. After extraction with Et<sub>2</sub>O (3 × 20 mL), drying over MgSO<sub>4</sub> and concentration *in vacuo*, the residue was purified by column chromatography, affording the desired product.

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## **Pd-Catalyzed Pseudo Domino Carbonylative / Decarboxylative Allylation**

The present thesis work dealt with the development on new palladium-catalyzed pseudo-domino sequences.

A first pseudo-domino type I process featuring a carbonylation / decarboxylative allylation was designed with  $\alpha$ -chloroacetophenone. The sequence allowed the selective monoallylation of readily available  $\alpha$ -chloroketones derivatives in one single synthetic operation. This pseudo-domino sequence could be applied to variously substituted acetophenones.

We also designed a three-step pseudo-domino reaction featuring *N*-allylation / carbopalladation / carbonylation. This sequence allowed us to prepare substituted indolines in one single synthetic operation from readily available substrates. The extension to a four step pseudo-domino sequence was also envisaged. Switching the alcohol used to allyl alcohol should merge both sequences, by adding a decarboxylative allylation step to the three-step process.

**Keywords:** Catalysis. Carbonylation. Decarboxylative allylation. Palladium. Domino reaction.

## **Séquences pseudo-domino Carbonylation / allylation décarboxylante catalysées au Palladium**

Le travail décrit dans ce manuscrit est consacré au développement de nouvelles séquences domino catalysées par le palladium impliquant une carbonylation suivie d'une allylation décarboxylante.

Dans un premier temps, la séquence pseudo-domino type I carbonylation / allylation décarboxylante a été optimisée sur des  $\alpha$ -chlorocétone. La séquence domino a permis d'obtenir des cétones mono-allylées avec de bons rendements, et ce en une seule étape synthétique.

Dans un deuxième temps, nous avons optimisée une seconde séquence pseudo domino type I impliquant cette fois-ci la *N*-allylation / carbopalladation / carbonylation d'anilines. Cette séquence a permis de synthétiser des dérivés indolines et indoles hautement fonctionnalisés à partir de substrats simples et toujours en une seule étape synthétique. Des essais afin d'étendre cette séquence domino à une séquence pseudo-domino quadruple ont été envisagés, en remplaçant le méthanol utilisé par de l'alcool allylique. Ceci permettrait de réunir les deux séquences optimisées et rajouterait l'allylation décarboxylante au processus domino triple.

**Mots clés :** Catalyse. Carbonylation. Allylation Décarboxylante. Palladium. Réaction domino