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Pd-Catalyzed Domino Synthesis of Heterocycles

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Dissertação

Mestrado em Química

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Orientação: Professora Doutora Maria José Diogo da Silva Calhorda

e

Professor Doutor Giovanni Poli

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Resumo

Foram sintetizados compostos do tipo indole e benzodihidrofuranos, por recurso à catálise com complexos de paládio.

Procurou construir-se uma reacção dominó com vista a incorporar uma etapa de allilação decarboxilativa, quer por inserção de CO na presença de ácool alilíco, quer utilizando um substrato já com um éster alílico na posição desejada.

A alilação do grupo metino do indole malónico foi também explorada, por simples substituição nucleófila ou com activação do substrato alílico com Pd.

A contrução de benzodihidrofuranos, passou numa primeira etapa pela obtenção do iodo-éter capaz de sofrer carbopaladação. Seguiu-se uma metodologia de reactor único identica à do caso dos heterociclos azotados numa primeira etapa para procurar aprisionamento nucleófilo com hidreto, e numa segunda metoxicarbonilação.

Palavras-chave: catálise, paládio, CO, dominó, heterociclos.

Abstract

Indole and benzodihydrofurane type compounds were synthetized by using palladium catalysis.

A domino reaction was constructing looking forward to incorporate a decarboxylative allylation step, either by CO insertion in the presence of allylic alcohol, either byusing a substrate already containing the appropriate allylic ester moiety.

Allylation of the indole malonic methine group was also explored, by simple nucleophilic substitution or activation of the allylic substrate with Pd.

The construction of benzodihydrofuranes underwent in an early stage the synthesis of the iodo-ether substrate to undergo carbopalladation. A one-pot methodology akin to the one used for the nitrogen heterocycles was used in a first time seeking to perform a nucleophilic trapping with hydride and secondly methoxycarbonilation.

Keywords: catalysis, palladium, CO, domino, heterocycle.

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I would like to start by thanking Prof. Giovanni Poli for the opportunity to work in his team, as well as Prof. Maria José Calhorda for her help in making this possible. Also I would like to thank the ERASMUS coordinator in Paris, Dr. Anne Lise Dhimane. I thank as well, to PROALV that through the LLP-ERASMUS program helped fund my stay. Also to the SSO group at IPMC for the funding. To the whole SSO team for their continuing support and good mood. To Fred, for all the guidance and teaching over these few months. To my fellow trainee's for all the good time, in particular Beatriz and Vaizanne. To Mathiew and Melanie, who more than anyone else had the patience to put up with me every day at the lab.

To my parents, for the distance they had to endure over this year.

Joseph "Joey" "DEFINITELY4CHAN" Basha.

José Augusto Nóbrega Lessa.

Abbreviations

AIBN	Azobisisobutyronitrile
aq.	aqueous
Cy	Cyclohexane
d	doublet
dd	doublet of doublets
dt	doublet of triplets
ddd	doublet of doublet of doublets
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
equiv.	equivalent
dppe	1,2-Bis(diphenylphosphino)ethane
HRMS	High resolution mass spectrometry
IR	Infrared
LiHMDS	Lithium hexamethyldisilazide
m	multiplet
NBS	*N*-Bromosuccinimide
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
ppm	parts per million
r.t.	Room temperature
s	singlet
t	triplet
tfp	Tri-2-furylphosphine
THF	Tetrahydrofuran
Tol	Toluene

Contents

Introduction

Carbon monoxide is an attractive building block for a number of processes due to its low price, high reactivity, gaseous nature and versatility. It displays perfect atom economy leaving no waste other than remaining CO gas that can easily be disposed of. Although it has often been coupled in reactions with dihydrogen, due to the easy availability of syngas,[1] it has also been used alone in a wide range of other industrial processes, making it the reagent of choice for the production of high value-added chemicals such as aldehydes, amides and carboxylic acid derivatives.[2]

However there is some reluctance amongst academic organic chemists in making use of gaseous CO as a reagent due to harsh pressurization techniques it might require and its inherent acute toxicity.[3-7]

Transition metal-catalyzed carbonylation reactions are amongst the most efficient processes to introduce a carbonyl moiety into a molecule.[2] If the desired transition metal-catalyzed carbonylation is coupled with one or more other catalytic processes, it results in a domino process displaying step-economy. A domino reaction was defined by Tietze as: «*a process involving two or more bond-forming transformations (usually C─C bonds) which take place under the same reaction conditions without adding additional reagents and/or catalysts and in which the subsequent reactions result as a consequence of the functionality formed in the previous step*».[7] Our group provided a more specific taxonomy for transition metal-catalyzed processes depending on the number of catalytic cycles and on the number of catalysts involved (Figure 1).[8]

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[1] Also known has synthesis gas, it is a fuel gas mixture consisting primarily of hydrogen and carbon monoxide. Its most notable uses are in the production of synthetic natural gas, ammonia, methanol and reagent in the Fischer–Tropsch process to form synthetic petroleum.

[2] Bhaduri, S.; Mukesh, D. *Homogeneous Catalysis: Mechanisms and Industrial Aplications*; John Wiley & Sons, Inc., 2000; Chapter 4, p. 55.

[3] Wu, X.; Neumann, H.; Beller, M. *Chem. Soc. Rev.* **2011**, *40*, 4986–5009.

[4] Wu, X.; Neumann, H.; Beller, M. *Chem. Rev.* **2012**, 113, 1–35.

[5] Brennführer, A.; Neumann, H.; Beller, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 4114–4133.

[6] Barnard, C. F. J. *Organometallics* **2008**, 5402–5422

[7] Tietze, L. F. *Chem. Rev.***1996**, *96*, 115–136.

[8] Poli, G.; Giambastiani, G. *J. Org. Chem.***2002**, *67*, 9456–9459.

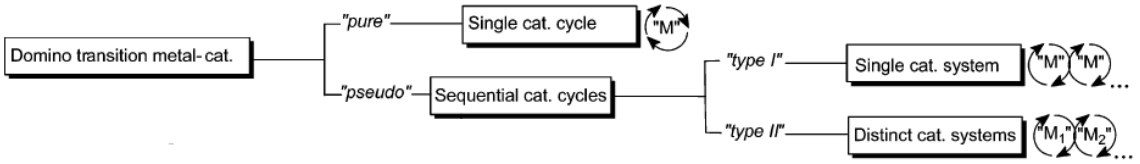
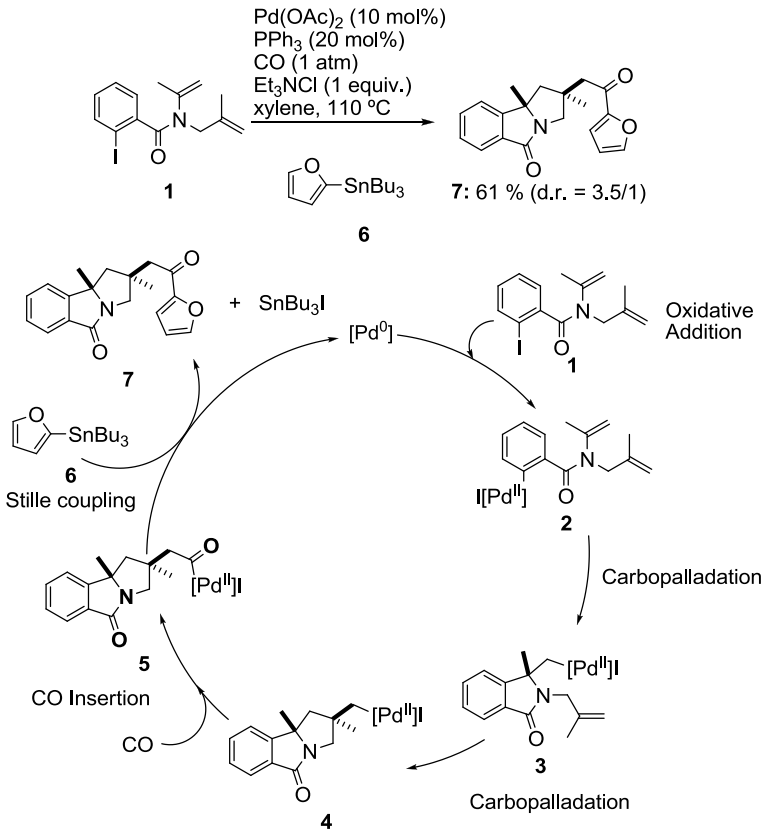


Figure 1 New transition metal-catalyzed domino reaction classification.

As domino processes featuring a carbonylation step display both atom- and step-economy, such processes meet the requirements of "green chemistry" and have therefore received much attention.

The aim of the present study was to develop such a carbonylative domino process to design a new straightforward synthetic approach to functionalized heterocyclic compounds.

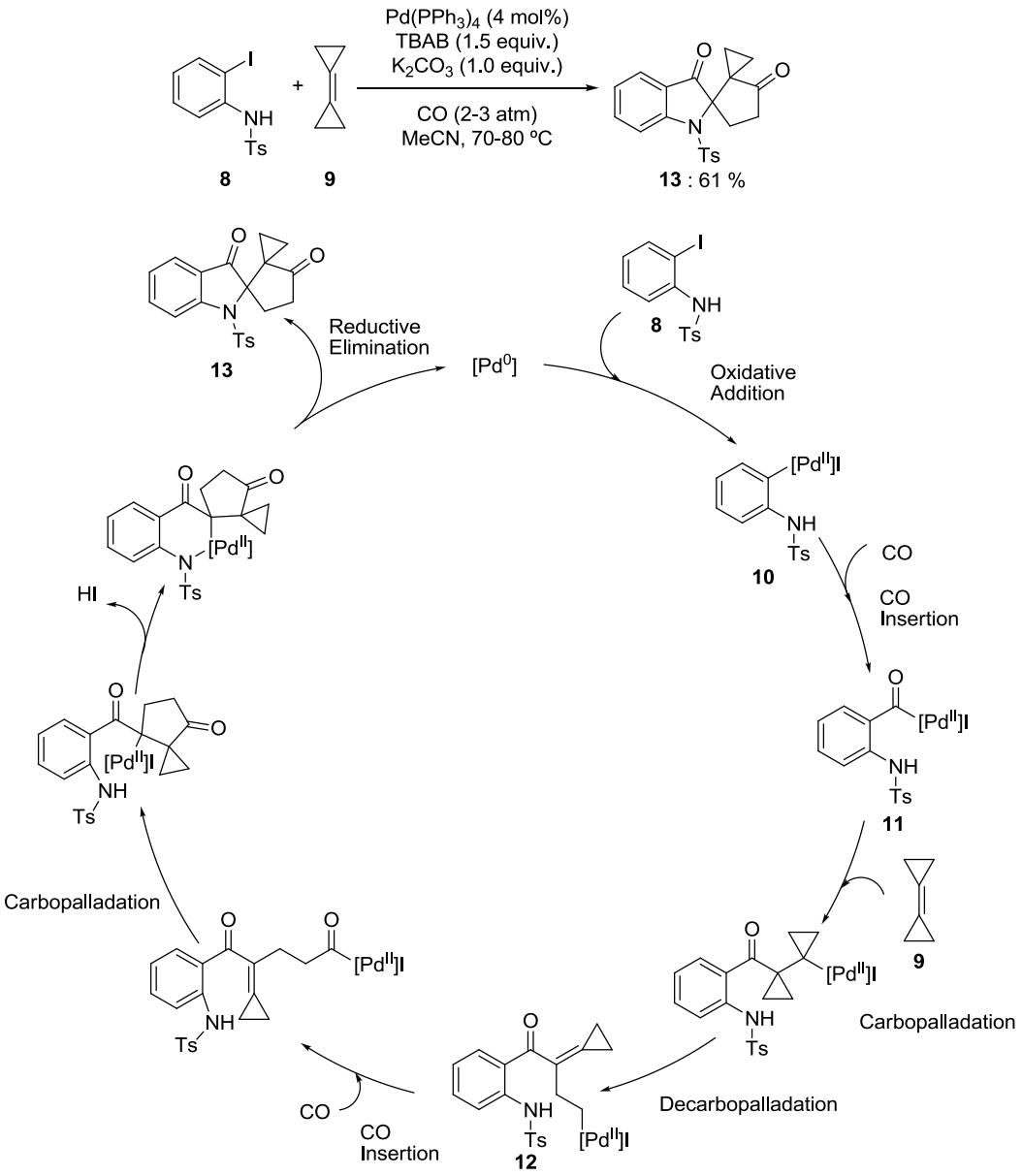
For example, Grigg reported the synthesis of a tricyclic heterocyclic compound from a simple *N*,*N*-bis(methallyl)benzamide (Scheme 1).[9]



Scheme 1 Domino double carbopalladation / carbonylation / transmetallation process.

[9] Brown, S.; Clarkson, S.; Grigg, R.; Thomas, W. A.; Sridharan, V.; Wilson, D. . *Tetrahedron* **2001**, *57*, 1347–1359.

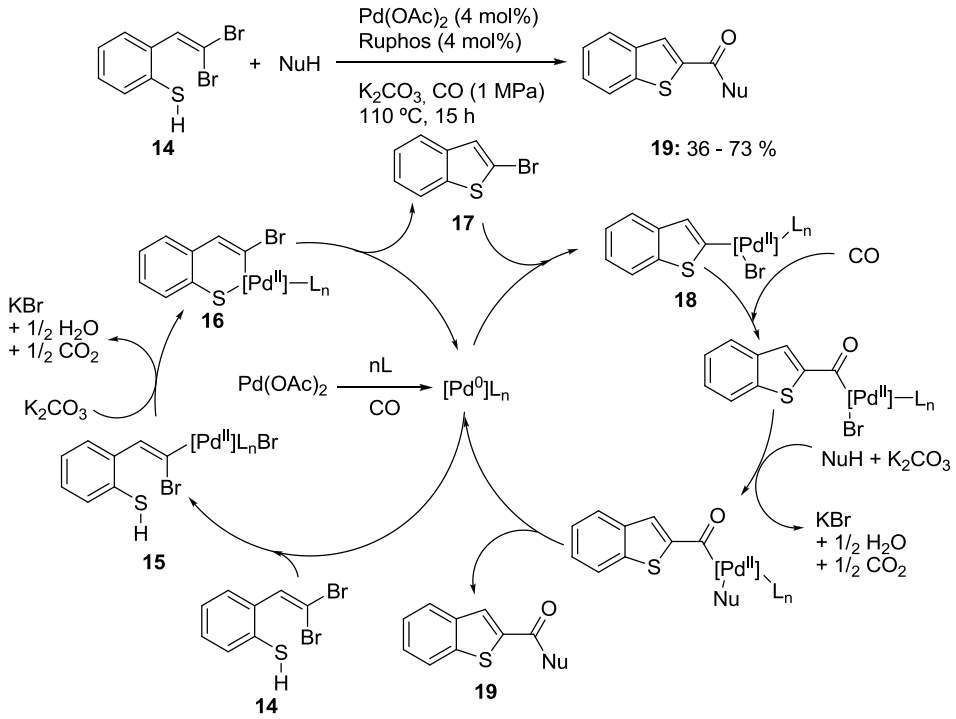
In this transformation, oxidative addition of the iodoarene **1** on the Pd^0 complex led to the Pd^{II} aryl-iodine complex **2** that then underwent two subsequent intramolecular carbopalladations (**2**→ **3**→ **4**). As **3** and **4** are neopentylpalladium intermediates, β-H elimination was impossible. As a result, CO insertion could take place on **4** to give acyl-palladium intermediate **5**. Following transmetallation by means of (2-furyl)tributyltin **6** afforded the final product **7** with regeneration of the Pd^0 catalyst.



Scheme 2 Proposed mechanism for the formation the policyclic spiro indoline.

De Meijere and Grigg reported the preparation of spiro polycyclic systems from an *o*-iodoaniline **8** and cyclopropylidenecyclopropane **9 (**Scheme 2**)**.[10] Oxidative addition of the aryl iodide to the Pd^0 complex generated the corresponding σ-arylpalladium complex **10** that underwent CO insertion to afford acyl-palladium complex **11**. Subsequent carbopalladation / decarbopalladation of **9** led to the cyclopropylidene **12**. Finally a sequence of carbonylation / carbopalladation / nucleophilic trapping afforded the target compound **13**.

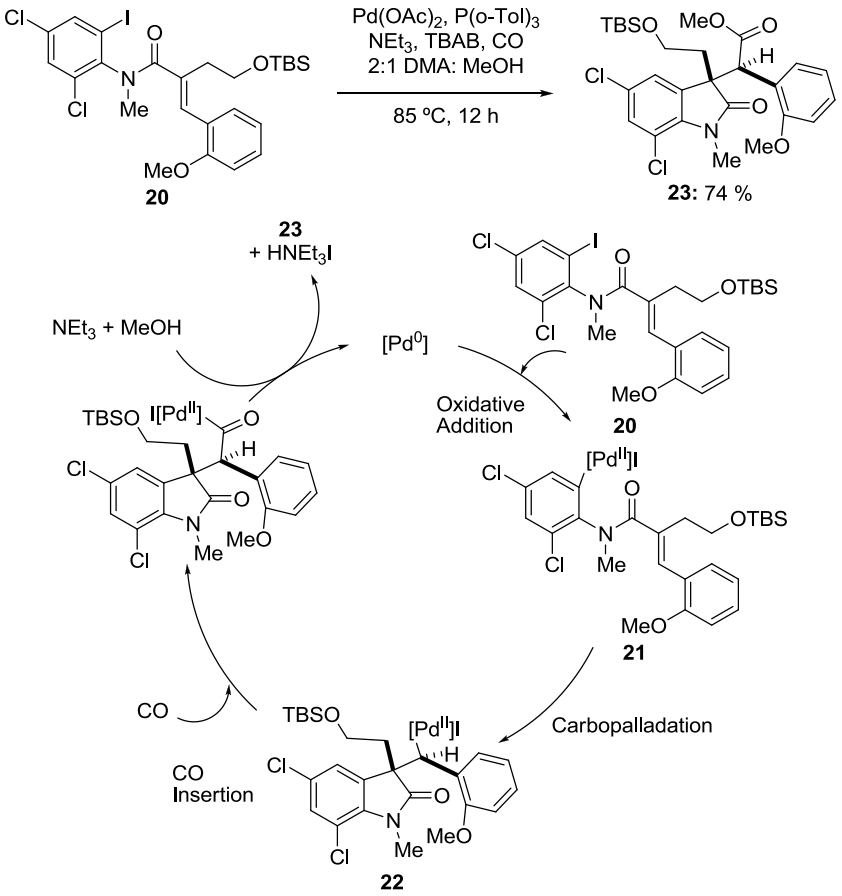
Alper reported the synthesis of 2-acylbenzothiophenes from a substituted 2-*gem*-dibromovinylthiophenol **14** (Scheme 3).[11] The mechanism can be rationalized as follows: oxidative addition of the substrate to the Pd^0 complex generated the vinyl-palladium complex **15** that suffers ligand displacement by the thiol function to give the palladacycle **16**. Then, reductive elimination gives the 2-halobenzothiophene **17** thereby closing the former catalytic cycle. The latter catalytic cycle is started by oxidative addition of bromide **17** to Pd^0 to afford the corresponding benzothiophen-2-yl palladium complex **18**. Finally, CO insertion and nucleophilic trapping delivered the final product **19**.



Scheme 3 Proposed mechanism for the pseudo-domino process for benzotiophene construction.

[10] Von Seebach, M.; Grigg, R.; de Meijere, A. *Eur. J. Org. Chem.* **2002**, 3268–3275.
[11] Zeng, F.; Alper, H. *Org. Lett.* **2011**, *13*, 2868–2871.

Natural product synthesis can also make use of this powerful synthetic tool, such as reported by Weinreb in the construction of intermediates en route to peophoramidine (Scheme 4).[12,13] Substrate **20** underwent oxidative addition to Pd^0 to give the aryl palladium complex **21**. Intramolecular carbopalladation followed to give intermediate **22**. Carbonylation and nucleophilic trapping by methanol furnished the final product **23**.



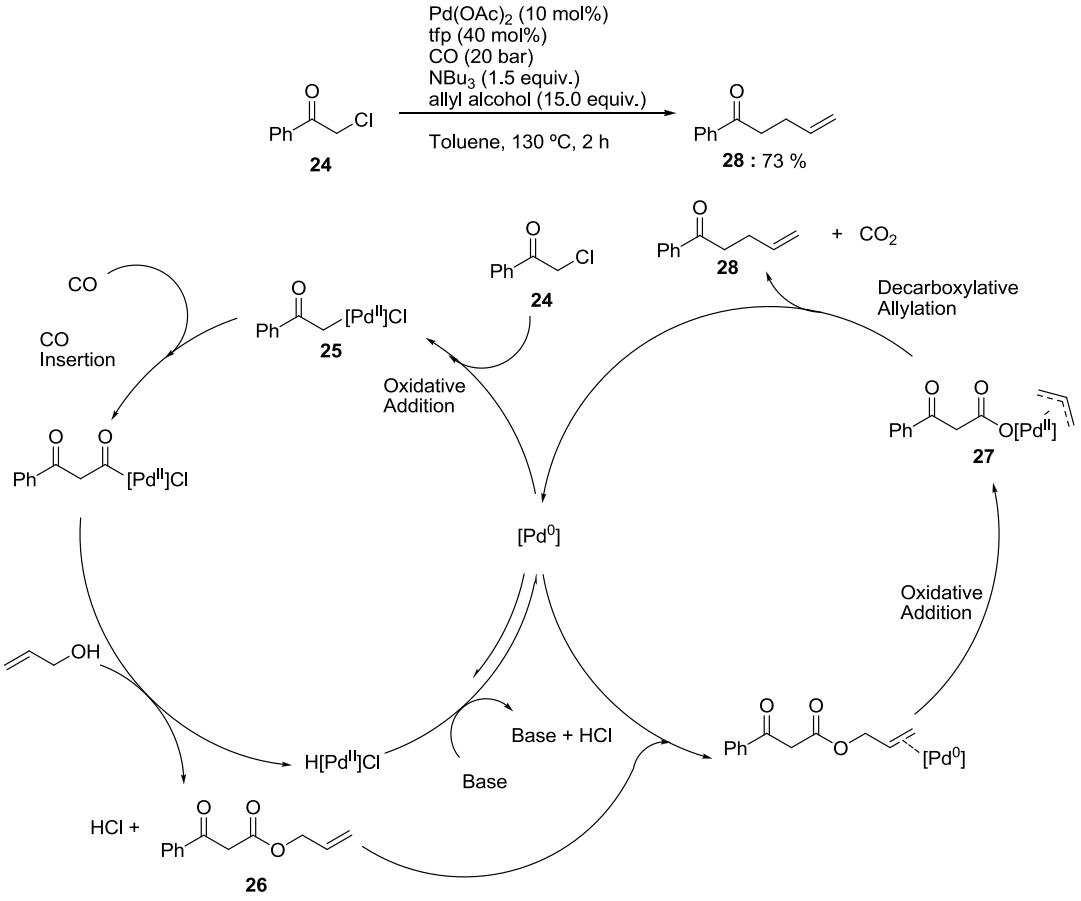
Scheme 4 Carbopalladation / methoxycarbonylation domino process in total synthesis.

Our group recently reported a carbonylative / decarboxylative allylation of α-chloroketones starting from α-chloroacetophenones.[14] The mechanism can be rationalized as follows: oxidative addition of chloroacetophenone **24** to Pd^0 afforded intermediate **25** that underwent carbonylation followed by allyl alcohol trapping to give allyl benzoacetate **26** with regeneration of Pd^0. The second catalytic cycle is started by

[12] Artman, G. D.; Weinreb, S. M. *Org. Lett.* **2003**, *5*, 1523–1526.
[13] Evans, M. a.; Sacher, J. R.; Weinreb, S. M. *Tetrahedron* **2009**, *65*, 6712–6719.
[14] Giboulot, S.; Liron, F.; Prestat, G.; Wahl, B.; Sauthier, M.; Castanet, Y.; Mortreux, A.; Poli, G. *Chem. Comm.* **2012**, *48*, 5889–5891.

oxidative addition of **26** to Pd^0 to give the π-allyl species **27**. Finally, decarboxylative allylation gives the target product **28** (Scheme 5).

Subsequent work led us to obtain the key β-oxo palladium intermediate **27** by means of a carbopalladation step of a Michael acceptor, rather than by direct oxidative addition of a C─X bond. In this context, a palladium-catalyzed *N*-allylation / carbopalladation / methoxycarbonylation pseudo-domino sequence involving *o*-iodoanilines and γ-haloacrylates to give a dihydroindole structure was conceived and successfully developed (Scheme 6).[15]



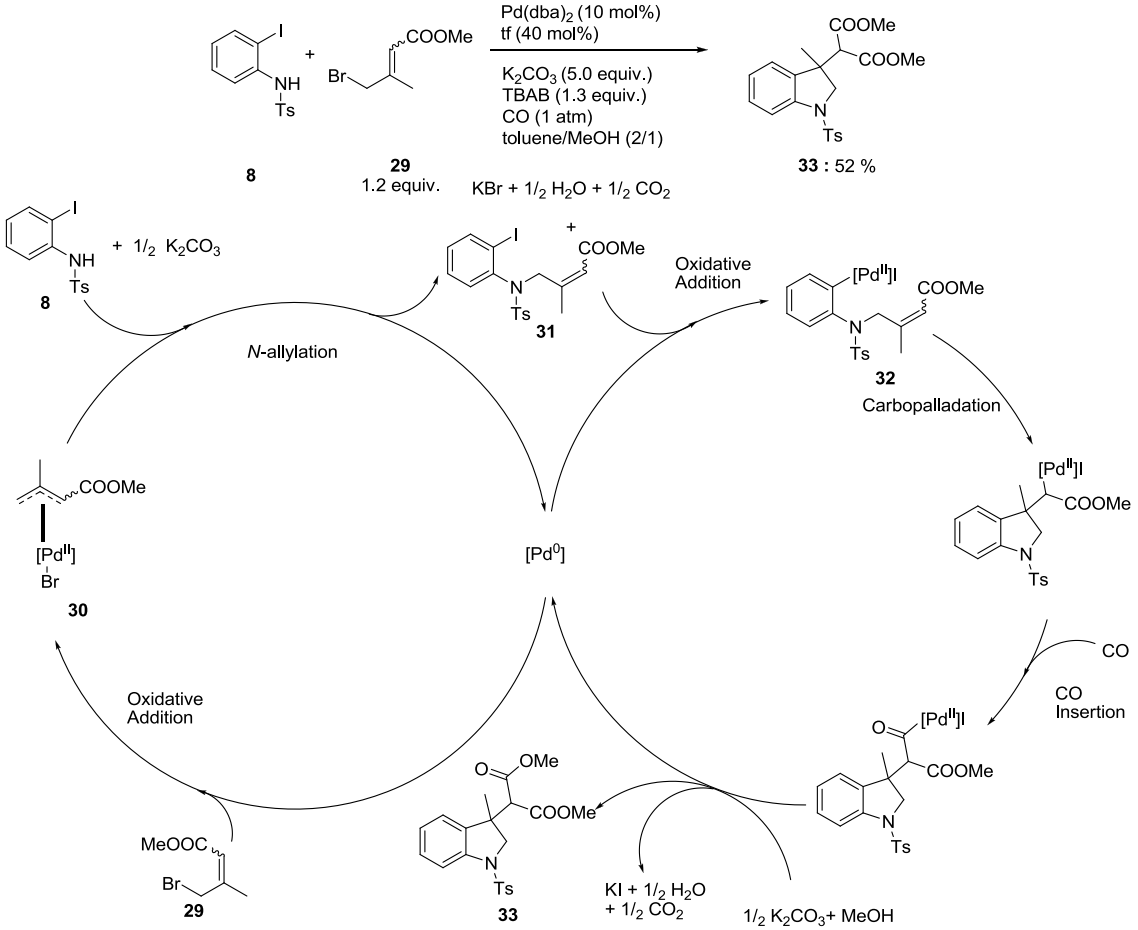
Scheme 5 Proposed mechanism for the decarboxylative allylation of α-chloroketones.

The mechanism can be interpreted as follows: oxidative addition of the γ-bromoacrylate **29** to Pd^0 generates the π-allyl intermediate **30**, which is intercepted by *N*-tosyl-*o*-iodoaniline **8** to generate the *N*-allylamine **31** and Pd^0.The second cycle starts with oxidative addition of **31** to Pd^0 to afford the aryl palladium complex **32**. Subsequent intramolecular carbopalladation generates the α-palladoester containing the

[15] Giboulot, S. Pd-Catalyzed Domino Carbonylative / Decarboxylative Allylation, Université Pierre et Marie Curie - Paris 6, 2012, Ph. D. Thesis.

indoline motif. With no β-H available for β-elimination, a carbonylation / nucleophilic trapping sequence takes place to give the final malonate **33**.

In view of the pressing demand of the fine chemistry industry for better (environmentally / financially) ways to access heterocycles[16] the project aims at pursuing the above cited studies so as to develop further and more efficient ways toward heterocyclic molecules by palladium-catalyzed domino carbonylative sequences. With this in mind we decided to study: a) alternative variations of Scheme 6 so has to obtain other dihydroindole structures, b) switch from *o*-iodoanilines to *o*-iodophenols in the domino sequence so as to end-up with bezofuran structures.



Scheme 6 Proposed mechanism for the palladium-catalyzed pseudo-domino type I sequence: allylic amination / 5-*exo* carbopalladation / metoxycarbonylation to give a malonic indoline structure.

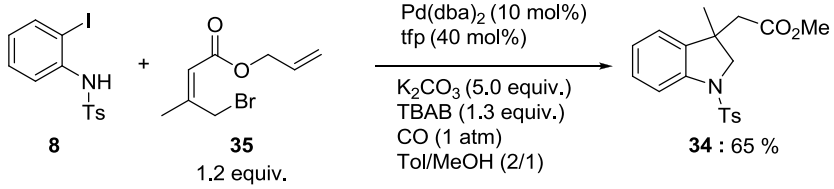
[16] Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, Jr., J. L.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. a.; Wells, A.; Zaks, A.; Zhang, T. Y. *Green Chem.* **2007**, *9*, 411.

Results and discussion

Decarboxylative allylation

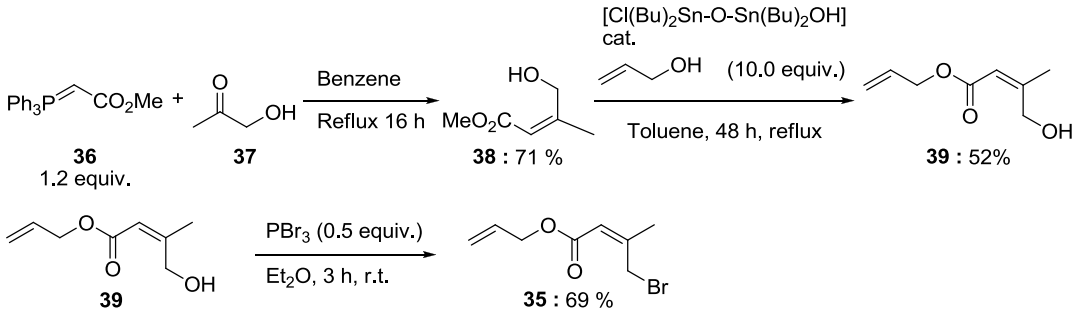
As previously mentioned, the Pd-catalyzed pseudo-domino synthesis of indolines featuring an *N*-allylation / carbopalladation / methoxycarbonylation sequence was successful (Scheme 6).[15]

Surrprisingly, use of MeOH instead of allyl alcohol in the above sequence led to the methyl ester **34** indicating that the intermediate α-pallado-ester gets protonated rather than undergoing methoxycarbonylation (Scheme 7).



Scheme 7 Pseudo-domino cyclisation with unexpected methyl ester product.

However, the analogous sequence starting from allyl acrylate in allyl alcohol had not been studied. To study this reaction, we first had to prepare the allyl 4-bromo-3-methylbut-2-enoate **35** (Scheme 8). Wittig reaction[17] between the ylide $Ph_3P{=}CHCO_2Me$ **36** and 1-hydroxypropan-2-one **37** led to the α,β-unsaturated ester (*Z* isomer only) **38** which then underwent Otera[18,19] transesterification to give the corresponding allyl acrylate **39**. Bromination of **39** with PBr_3 afforded the desired allylic acrylate **35** (Scheme 8).

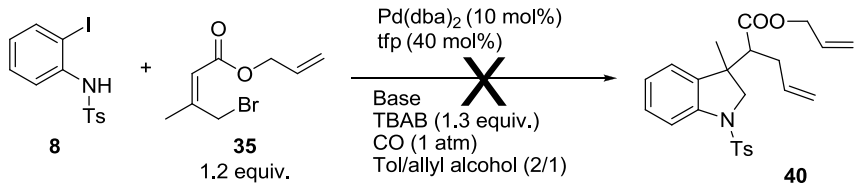


Scheme 8 Synthesis of (*Z*)-allyl-4-bromo-3-methylbut-2-enoate.

[17] Masuda, T.; Osako, K.; Shimizu, T.; Nakata, T. *Org. Lett.* **1999**, *1*, 941–944.
[18] Otera, J.; Yano, T.; Kawabata, A.; Nozaki, H. *Tetrahedron Lett.* **1986**, *27*, 2383–2386.
[19] Otera, J.; Dan-oh, N.; Nozaki, H.; *J. Org. Chem.* **1991**, *56*, 5307–5311.

We then tried to perform the pseudo-domino reaction with **8** and **35** in allyl alcohol. Potassium carbonate as the base (Table 1, entry 1) led only to degradation products. Adding NEt_3 (Table 1, entry 2) gave the same result as did changing K_2CO_3 to the more soluble Cs_2CO_3 (Table 1, entry 3).

Table 1 Pseudo-Domino cyclisation with allylic ester.



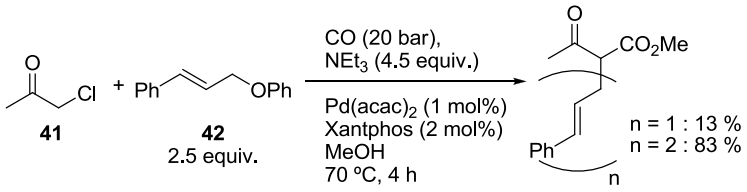
Entry	Organic Base	Inorganic Base	Time (h)	Yield (%)
1	-	K_2CO_3 (2.5 equiv.)	23	0
2	NEt_3 (1.2 equiv.)	K_2CO_3 (5.0 equiv.)	18	0
3	NEt_3 (1.2 equiv.)	Cs_2CO_3 (2.5 equiv.)	19	0

As decarboxylative allylation was not successful, we turned our attention to the reactivity of the active methine group in **33**.

Allylation of activated methine group in 33

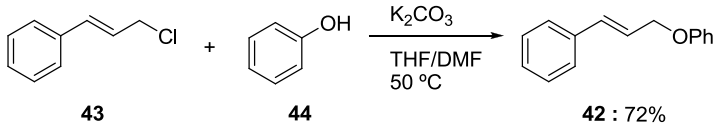
As the pseudo-domino sequence starting from methyl ester **29** involving a methoxycarbonylation step was a productive process, we envisioned to perform a further allylation step following the procedure developed by Mortreux[20] in the frame of the collaborative ANR-funded "Domino-CO" project. In their procedure, an α-chloroketone **41** underwent methoxycarbonylation and the resulting β-ketoester could be allylated *in situ* (Scheme 9). Key to the success of this procedure was the use of the poor phenoxy leaving group on the allylating agent **42**.

[20] Wahl, B.; Giboulot, S.; Mortreux, A.; Castanet, Y.; Sauthier, M.; Liron, F.; Poli, G. *Adv. Synth. Catal.* **2012**, *354*, 1077–1083.



Scheme 9 Conversion of α-chloroketone into β-bisallylated ketoester.

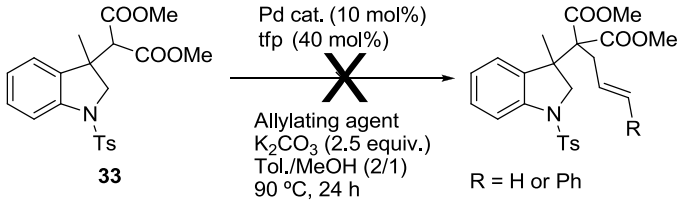
The cinnamyl phenyl ether **42** was prepared by a simple Williamson etherification between cinnamyl chloride **43** and phenol **44** (Scheme 10).

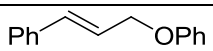
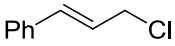
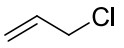


Scheme 10 Preparation of cinnamyl phenyl ether.

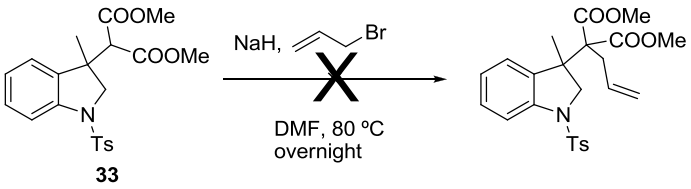
We then prepared the required dihydroindolinyl-malonate **33** as depicted in Scheme 6. However its treatment under Mortreux' conditions in the presence of phenyl cinnamyl ether (**42**, Table 2, entry 1) gave no allylated product. Switching to the more reactive cinnamyl chloride (entry 2) or to the less sterically demanding allyl chloride (entry 3) was also unsuccessful.

Table 2. Allylation of activated methine group.



Entry	Allylating agent	Equiv.	Catalytic Precursor	Yield (%)
1		2.2	$Pd(acac)_2$	0
2		1.2	$Pd(dba)_2$	0
3		1.2	$Pd(dba)_2$	0

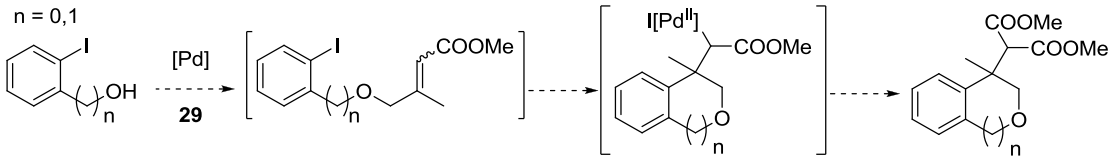
As the position to be allylated is rather sterically encumbered (tertiary neo-pentylic), we tried to allylate the malonate **33** with allylbromide, while using NaH as a base (Scheme 11). Again, no allylation occurred.



Scheme 11 Allylation with allyl bromide.

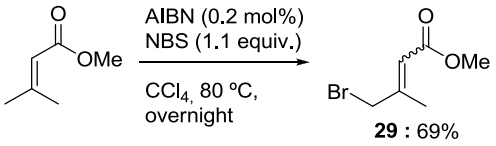
Transposition to O-heterocycle formation

We then decided to extend the pseudo-domino synthesis of indolines to the preparation of the corresponding benzodihydrofuranes and/or benzodihydropyrans (Scheme 12), following the same allylation / carbopalladation / carbonylation sequence.



Scheme 12 General scheme towards the benzodihydrofuran (n = 0) and/or benzodihydropyran (n = 1) units.

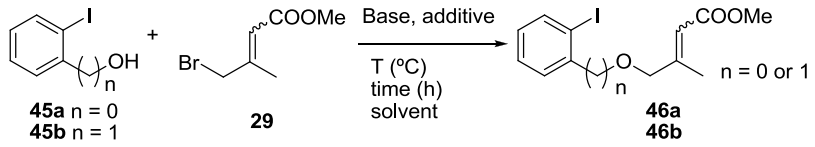
Methyl 4-bromo-3,3-methylbut-2-enoate **29** was prepared by bromination of 3-methylbut-2-enoate with NBS (Scheme 13).



Scheme 13 Free-radical bromination of methyl 3,3-methylbut-2-enoate.

We first decided to separately study the various steps of the envisioned sequence. Accordingly we decided to first prepare the expected intermediate allyl ether under a non-catalyzed condition. However, as *O*-nucleophiles are weaker than *N*-nucleophiles this step was not straightforward and required a short study using **29** as the electrophile.

Table 3. Etherification reaction.



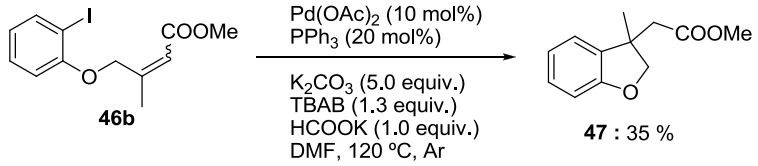
Entry	Nucleophile	Base	Additive	Solvent	Temperature (°C)	Time (h)	Yield (%)[a]
1	**46a**	K_2CO_3	-	DMF	50	24	0
2	**46a**	NaH	-	DMF	50	24	0
3	**46a**	NaH	NaI	DMF	50	72	0
4	**46b**	NaH	KI	DMF	r.t.	72	18
5	**46b**	NaH	NaI	DMF	r.t.	72	39
6	**46b**	K_2CO_3	-	Acetone	56	12	52
7	**46b**	Cs_2CO_3	-	MeCN	82	4	95

[a]Isolated yield.

Conversion of *o*-iodobenzylalcohol **45a** into the corresponding ether **46a** was first studied (Table 3). However, treatment of **45a** with **29** in the presence of K_2CO_3, according to classical S_N2 conditions, gave no reaction (entry 1). Switch to the stronger base NaH (entry 2) resulted in no improvement. Adding NaI to *in situ* generate a transient allylic iodide also met with no success (entry 3).

We then considered conversion of *o*-iodophenol **45b** into the corresponding ether **47b**, which better matches the oxygen-based version with respect to the previously studied protocol starting from the *o*-iodoaniline **8**. In the event, treatment of **45b** with NaH and KI in DMF at 25 °C led, after 72 h of reaction, to a small amount of the desired ether (entry 4). Switching the added iodide salt from KI to NaI slightly improved the yield, which, however, remained unsatisfactory (39 %, entry 5). Switching the base to K_2CO_3 and the solvent to acetone resulted in a further yield increase (52 %, entry 6). Finally, acetonitrile proved to be the solvent of choice, providing a quantitative yield of the desired ether **46b** within only 4 hours (entry 7). Geometric isomer attribution was possible by means of NOESY experiments. With this ether in hand, we then studied its Pd-catalyzed cyclization reaction.

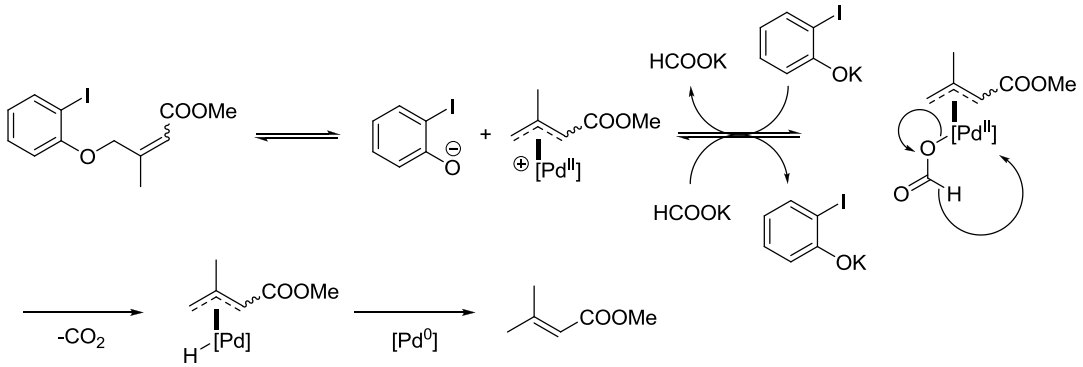
Thus, treatment of **46b** under the conditions previously defined for the reductive cyclization of the nitrogen series (carbopalladation / hydride trapping sequence), led to benzodihydrofuran **47** in comparable yield (35 % for the phenol substrate vs 38 % for the aniline one) (Scheme 14).



Scheme 14 Intramolecular carbopalladation hydride trapping domino sequence.

Although the yield of the cyclized product **47** remained low, this attempt showed the feasibility of the pseudo-domino sequence. Moreover, this low yield may be in part accounted for by the fact that allyl phenyl ethers are potential electrophiles in Pd-catalyzed allylation reactions, the phenoxy group acting as the nucleofuge.[21-23]

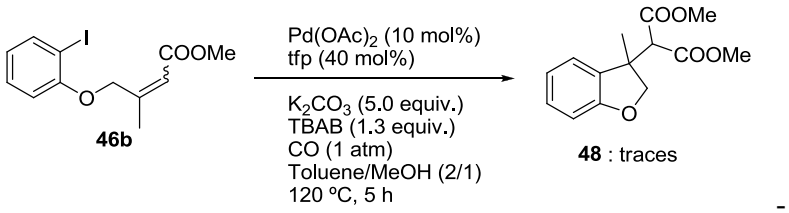
If subsequent protonation can compete with the expected domino sequence, the acrylate moiety might exit the catalytic cycle irreversibly and thus limit the selectivity of the catalytic process (Scheme 15).



Scheme 15 Hydride trapping of the acrylate moiety *in situ* that exits the catalytic cycle.

With this encouraging result in hand, we carried out the carbopalladation / methoxycarbonylation domino sequence. Use of the conditions developed in the azo series led to trace amount of the expected malonate **48** (Scheme 16).

[21] Szlosek-Pinaud, M.; Diaz, P.; Martinez, J.; Lamaty, F. *Tetrahedron* **2007**, *63*, 3340–3349.
[22] Lee, H.-S.; Kim, K.-H.; Lim, J.-W.; Kim, J.-N. *Bull. Korean Chem. Soc.* **2011**, *32*, 1083–1086.
[23] Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley & Sons, Ltd: Chichester, UK, 2004.



Scheme 16 Carbonylative intramolecular carbopalladation / carbonylation / nucleophile trapping.

Due to the basic conditions used for this reaction (K_2CO_3 in methanol), we hypothesized that the methyl ester **46b** may not be stable.

Conclusions

Further development of the indoline constructing pseudo-domino sequence, by incorporation of a decarboxylative allylation step was unsuccessful. Diallyl malonate, expected to be formed as an intermediate leading to the alkylated indoline, was also not observed.

Likewise, allylation of activated methine position on the indoline motif was unsuccessful. Steric hindrance is hypothesized to be the cause of the latter.

The transposition of our system to oxygen type nucleophiles is promising. *o*-Iodophenol as a substrate showed that etherification can take place efficiently in acetonitrile. Carbopalladation / hydride trapping domino sequence of the ether takes place in moderate yield. The reaction has been found to proceed in a one-pot scenario in low yields.

Carbonylation / nucleophilic trapping pseudo-domino sequence took place in trace amounts which is encouraging for the full transposition of *N*-heterocycle formation to *O*-heterocycle formation.

Future work will deal with the use of other nucleophiles as trapping agents, be cynamide, acrylates or organometallic species (stannanes or boronic acids).

Experimental

General

All reactions were carried out under argon or carbon monoxide atmosphere unless otherwise stated.

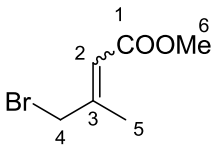
All reagents were used as obtained from commercial suppliers. Acetonitrile, dichloromethane and DMF were dried on a Braun purification system MB SPS-800. Other solvents were purified as described in the literature.[24]

Thin layer chromatographies were performed on Merk 60 F254 silica gel and revealed with an ultra-violet lamp (λ = 254 nm) and a staining reagent ($KMnO_4$ or *p*-anisaldehyde). Merk Geduran SI 60 silica gel (40-63 μm) was used for flash column chromatographies.

Solution NMR spectra (^1H and ^{13}C) were recorded on a Bruker AVANCE 400 or 300 MHz spectrometer. ^1H frequency of 300.16 or 400.13 MHz, respectively; ^{13}C frequency of 75.48 or 100.61 MHz respectively. Chemical shifts (δ) are given in ppm using tetramethylsilane as the internal standard and $CDCl_3$ residual chloroform signal as reference.[25] IR spectra were recorded with a Tensor 27 (ATR diamond) Bruker spectrometer. Only the most important bands were reported, in wavenumbers $\bar{\nu}$ (cm^{-1}). NMR and IR spectroscopy experiments were performed at 300 K. HRMS spectra were recorded at the Institut Parisien de Chimie Moleculaire (FR 2769) of UPMC (electrospray source).

[24] Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; 4th ed.; Butterworth-Heinmann: Woburn, MA, 2000; p. 544.
[25] Fulmer, G. R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Goldberg, K. I. *Organometallics* **2010**, *29*, 2176–2179.

Synthesis of methyl 4-bromo-3-methylbut-2-enonate **29**



Compound **29** was prepared according to a Ph. D. thesis in our group literature[15] (see pg 159).

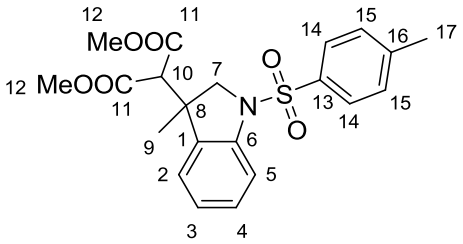
To a mixture of *N*-bromosuccinimide (9.79 g, 55.0 mmol, 1.1 equiv.) in CCl_4 (70 cm^3), a solution of methyl 3,3-dimethylbut-2-enoate (5.45 g, 47.7 mmol, 1.0 equiv.) also in CCl_4 (10 cm^3) was added. To this mixture, AIBN (16.0 mg, 0.10 mmol, 0.2 mol%) was added. The reaction mixture was refluxed overnight. The heating was then stopped and the reaction mixture cooled to 0 °C. Once cooled, the mixture was filtered over celite and the filtrate washed with Na_2SO_3 aq. (2 × 5 cm^3) and NaCl aq. (2 × 5 cm^3). The organic phase was then dried over $MgSO_4$ and concentrated *in vacuo*. The product was purified by column chromatography (*n*-pentane/Et_2O, 98/2) to afford 6.48 g (70 % yield) of product as a yellowish liquid in a *E/Z* = 45 / 55 mixture.

IR ($\bar{\upsilon}$, cm^{-1}): 2950, 2842, 1713, 1644, 1433, 1230, 1189,1039. ^{1}H NMR (δ ppm): 5.95 (s, 1H, H_2, *E*), 5.76 (s, 1H, H_2, *Z*), 4.54 (s, 2H, H_4, *Z*), 3.93 (d, 2H, H_4, *J* = 0.7 Hz, *E*), 3.70-3.68 (m, 6H, H_6, *E* + *Z*), 2.26 (d, 3H, H_5, *J* = 1.3 Hz, *Z*), 2.03 (d, 3H, H_5, *J* = 1.4 Hz, *E*). ^{13}C {^{1}H} NMR (δ ppm): 166.4 (C_1, *Z*), 166.0 (C_1, *E*), 153.0 (C_3, *Z*), 152.8 (C_3, *E*), 119.1(C_2, *E*), 118.9 (C_2, *Z*), 51.3(C_6, *E* + *Z*), 38.2 (C_4, *Z*), 29.6 (C_4, *Z*), 23.5 (C_5, *E*), 17.4 (C_5, *Z*).

These NMR data were in good accordance with those reported in the literature.[26] [27]

[26] Martin, R.; Chapleol, C. B.; Svanholt, K. L.; Dreiding, A. S. *Helv. Chim. Acta* **1976**, *8*, 2724–2727.
[27] Lei, B.; Fallis, A. G. *Can. J. Chem.* **1991**, *69*, 1450–1456.

Synthesis of dimethyl 2-(3-methyl-1-tosylindolin-3-yl)malonate **33**

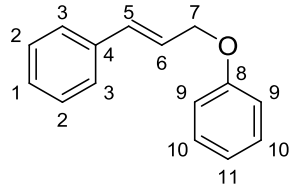


Compound **33** was prepared according to a Ph. D. thesis in our group[15] (see General Procedure 8, pg 135).

A flask was charged with a mixture of *o*-iodoaniline **8** (185.0 mg, 0.50 mmol, 1.0 equiv.), $Pd(dba)_2$ (28.5 mg, 0.05 mmol, 10 mol%), tfp (46.6 mg, 0.20 mmol, 40 mol%), TBAB, (210.7 mg, 0.65 mmol, 1.3 equiv.) and K_2CO_3 (341.6 mg, 2.50 mmol, 5.0 equiv.) in toluene (10 cm^3), to which a solution of methyl 4-bromo-3-methylbut-2-enoate **29** (113.9 mg, 0.6 mmol, 1.1 equiv.) in methanol (5 cm^3) was added. The flask was flushed with an atmospheric pressure of carbon monoxide, heated to 95 °C and stirred for 4 hours. The reaction was then cooled to room temperature, hydrolyzed and extracted with AcOEt (3×20 cm^3). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (eluent system: Cy/AcOEt, 8/2) gave 76.3 mg (39 % yield) of the product as an orange oil.

^{1}H NMR (δ ppm): 7.75 (d, 2H, H_{14}, $J^3_{15,16}$ = 8.3 Hz), 7.64 (d, 1H, H_2, $J^3_{2,3}$ = 8.2 Hz), 7.28 – 7.20 (m, 3H, H_{15} + H_3), 7.03 – 6.95 (m, 2H, H_4 + H_5), 4.50 (d, 1H, H_7, J^2 = 11.1 Hz), 3.74 – 3.71 (m, 4H, $H_{7'}$ + H_{12}), 3.64 (s, 1H, H_{10}), 3.43 (s, 3H, $H_{12'}$), 2.38 (s, 3H, H_{17}), 1.29 (s, 3H, H_9). ^{13}C {^{1}H} NMR (δ ppm): 168.0 ($C_{11'}$), 167.3 (C_{11}), 144.2 (C_{13}), 141.2 (C_6), 136.0 (C_1), 134.3 (C_{16}), 129.7 (C_{15}), 129.0 (C_3), 127.5 (C_{14}), 123.5 (C_4 + C_5), 114.4 (C_2), 59.8 (C_7), 58.3(C_{10}), 52.6 ($C_{12'}$), 52.4 (C_{12}), 45.0 (C_8), 26.1 (C_9), 21.6 (C_{17}). HRMS (ESI) m/z calculated for $C_{21}H_{23}NO_6S$ [M + Na^+] 440.1144, found 440.1149.

Synthesis of phenyl 2-phenyl-1-ene ether **42**



Compound **42** was prepared according as described in the literature.[28]

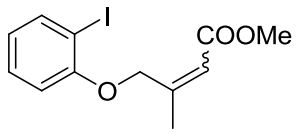
To a mixture of phenol (1.86 g, 19.7 mmol, 1.40 equiv.) and K_2CO_3 (2.24 g. 16.2 mmol, 1.15 equiv.) in DMF/THF (1/1, 4 cm^3 overall) a solution of cinnamyl chloride **45** (2.17 g, 14.2 mmol, 1.00 equiv.), also in DMF/THF (1/1, 2 cm^3 overall) was added. This mixture was then heated to 50 °C for 48 h. The reaction was then hydrolyzed (10 cm^3), diluted in AcOEt (10 cm^3), washed with 1 M HCl aq. (3 × 10 cm^3), 1 M NaOH aq. (3 × 10 cm^3) and H_2O (3 × 10 cm^3). The combined organic layers were then dried over $MgSO_4$ and concentrated *in vacuo* to give pale yellow flakes. Purification by flash column chromatography (eluent system: Cy/Et_2O, 95/5) gave 2.68 g (72 % yield) of the desired compound as a pale yellow solid.

IR ($\bar{\upsilon}$, cm^{-1}): 3057, 3027, 2907, 2862, 1597, 1581, 1498, 1226, 961. ^{1}H NMR (δ ppm): 7.43 (m, 2H, J^3 = 7.0 Hz), 7.35-7.29 (m, 5H), 6.99-6.95 (m, 3H), 6.75 (d, 1H, H_5, $J^3_{5,6}$ = 16.0 Hz), 6.30 (dt, 1H, H_6, $J^3_{6,5}$ = 16.0 Hz $J^3_{6,7}$ = 5.6 Hz), 4.72 (dd, 2H, H_7, $J^3_{7,6}$ = 5.6 Hz, $J^4_{5,7}$ = 1.5 Hz). ^{13}C {^{1}H} NMR (δ ppm): 158.7, 136.5, 129.6, 128.7, 128.0, 126.7, 121.0, 114.9, 68.8.

These data are in good agreement with those reported.[28]

[28] Wahl, B. (2011). *Nouvelle réaction domino pallado-catalysée : alcoxycarbonylation / allylation pour la synthèse d 'esters alpha-allylés*. Université de Lille 1 Sciences et Technologies, Ph. D. Thesis.

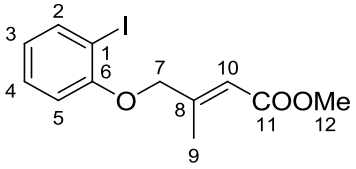
Synthesis of methyl 4-*o*-iodophenol-3-methylbut-2-enoate **46b**



Compound **46b** was prepared according to a procedure described in the literature.[21]

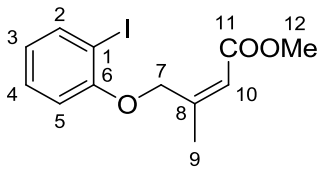
To a solution of *o*-iodophenol (439.3 mg, 2.00 mmol, 1.0 equiv.) in MeCN (25 cm^3), Cs_2CO_3 (918.0 mg, 2.82 mmol, 1.4 equiv.) was added, followed by a solution of **29** (684.4 mg, 3.55 mmol, 1.75 equiv.), also in MeCN (3 cm^3). The resulting milky white mixture was refluxed for 4 h. The mixture was then allowed to cool to r.t., diluted in Et_2O (25 cm^3), filtered over celite and washed with brine (3 × 10 cm^3). The organic layer was then dried over $MgSO_4$ and concentrated *in vacuo* to give a pale yellow oil. Flash chromatography (eluent system: Cy/AcOEt, 8/2) afforded 410.0 mg (57 % yield) of **46b-(*E*)** and 272.0 mg (38 % yield) of **46b-(*Z*)** as colourless oils.

46b-(E)



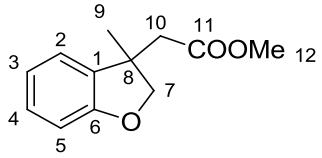
IR ($\bar{\upsilon}$, cm^{-1}): 2947, 2844, 1705, 1661, 1472, 1433, 1223, 1016. ^{1}H NMR (δ ppm): 7.77 (dd, 1H, H_2, $J^3_{2,3}$ = 7.8 Hz, $J^4_{2,4}$ = 1.6 Hz), 7.28 (ddd, 1H, H_4, $J^3_{4,5}$ = 8.3 Hz, $J^3_{4,3}$ = 7.5 Hz, $J^4_{4,2}$ = 1.6 Hz) 6.89 (dd, 1H, H_5, $J^3_{4,5}$= 8.3 Hz, $J^4_{5,3}$ = 1.2 Hz), 6.72 (ddd, 1H, H_3, $J^3_{3,4/5}$ = 7.6 Hz, $J^4_{3,5}$ = 1.2 Hz), 5.85 (m, 1H, H_{10}), 5.25 (m, 2H, H_7), 3.72 (s, 3H, H_{12}), 2.16 (m, 3H, H_9). ^{13}C {^{1}H} NMR (δ ppm): 22.0 (C_9), 51.3 (C_{12}), 68.4 (C_7), 86.3 (C_1), 112.2 (C_5), 116.9 (C_{10}), 122.9 (C_3), 129.7 (C_4), 139.6 (C_2), 156.2 (C_8), 157.0 (C_6), 166.5 (C_{11}). HRMS (ESI) m/z calculated for $C_{12}H_{13}IO_3$ [M + Na^+] 354.9802, found 354.9795.

46b-(Z)



IR ($\bar{\upsilon}$, cm^{-1}): 2983, 2944, 2847, 1715, 1657, 1472, 1435, 1327, 1222, 1147, 1015. ^{1}H NMR (δ ppm): 7.79 (dd, 1H, H_2, $J^3_{2,3}$ = 7.8 Hz, J^4 = 1.6 Hz), 7.28 (ddd, 1H, H_5, J^3 = 7.4 Hz, J^3 = 8.3 Hz , $J^4_{5,2}$ = 1.6 Hz), 6.76-672 (m, 2H, H_3/H_4), 6.23 (m, 1H, H_{10}), 4.55 (m, 2H, H_7), 3.73 (s, 3H, H_{12}), 2.23 (m, 3H, H_9). ^{13}C {^{1}H} NMR (δ ppm): 15.8 (C_9), 51.2 (C_{12}), 72.5 (C_7), 86.6 (C_1), 112.4 (C_3 or C_4), 116.0 (C_{10}), 123.2 (C_3 or C_4), 129.76(C_5), 139.8 (C_2), 152.2 (C_8), 156.7 (C_6), 167.0 (C_{11}). HRMS (ESI) m/z calculated for $C_{12}H_{13}IO_3$ [M + Na^+] 354.9802, found 354.9795.

Synthesis of methyl 2-(3-methyl-2,3-dihydrobenzofuran-3-yl)acetate **47**.



A flask was charged with a mixture of PPh_3 (51.3 mg, 0.20 mmol, 0.2 equiv.), TBAB (212.0 mg, 0.66 mmol, 1.3 equiv.), K_2CO_3 (340.1 mg, 2.50 mmol, 5.0 equiv.) and HCOOK (34.7 mg, 0.51 mmol, 1.0 equiv.) in DMF (22 cm^3), a solution of **46b** (163.9 mg, 0.50 mmol, 1.0 equiv.) also in DMF (3 cm^3) was added. Last, $Pd(OAc)_2$ (26.1 mg, 0.10 mmol, 0.10 equiv.) was added. The yellow mixture was then heated to 120 °C and stirred for 5 h. The mixture was then cooled to r.t., hydrolysed (50 cm^3), filtered over celite and extracted with Et_2O (5 × 15 cm^3). The organic phase was then concentrated *in vacuo*, diluted with H_2O (30 cm^3), again extracted with Et_2O (5 × 15 cm^3). The organic phase was dried over $MgSO_4$, concentrated *in vacuo* to give a colourless oil. Flash column chromatography (eluent system: Cy/AcOEt, 8/2) afforded 31.2 mg (35 % yield) of the product as a colourless oil.

IR ($\bar{\upsilon}$, cm^{-1}): 2952, 2885, 1730, 1480, 1226. ^{1}H NMR (δ ppm): 7.14 (ddd, 1H, H_3, $J^3_{3,4}$ = 8.2 Hz, $J^3_{3,2}$ = 7.6 Hz, $J^4_{3,5}$ = 1.3 Hz, 7.11 (dd, 1H, H_5, $J^3_{5,4}$ = 7.5 Hz, $J^4_{5,3}$ = 1.3 Hz), 6.88 (ddd, 1H, H_4, $J^3_{4,3}$ = 8.2 Hz, $J^3_{4,5}$ = 7.5 Hz, $J^4_{4,2}$ = 1.0 Hz), 6.80 (dd, 1H, H_2, $J^3_{2,3}$ = 7.6 Hz,

$J^4_{2,4}$ = 1.0 Hz), 4.62 (d, 1H, H_7, J^2 = 9.0 Hz), 4.31 (d, 1H, $H_{7'}$, J^2 = 9.0 Hz), 3.73 (s, 3H, H_{12}), 2.72 (d, 1H, H_{10}, J^2 = 15.3 Hz), 2.65 (d, 1H, H_{10}, J^2 = 15.3 Hz), 2.23 (s, 3H, H_9). ^{13}C {^1H} NMR (δ ppm): 171.7 (C_{11}), 161.1 (C_1), 159.3 (C_6), 134.3 (C_8), 128.7 (C_3), 122.9 (C_5), 120.8 (C_4), 110.1 (C_2), 82.5 (C_7), 51.7 (C_{12}), 44.3 (C_{10}), 25.2 (C_9). HRMS (ESI) m/z calculated for $C_{12}H_{14}IO_3$ [M + Na^+] 229.0835, found 229.0828.