

# Palladium catalyzed molecular cascades for the synthesis of ethyl 2-methyl-2-(4-methyl-3-(morpholinomethyl)-2-oxopent-3-en-1-yl)-1-oxo-1,2,3,4,5,6-hexahydro-3aH-indene-3a-carboxylate

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In memory of Prof. Ronald E. Grigg, Emeritus Professor of the University of Leeds

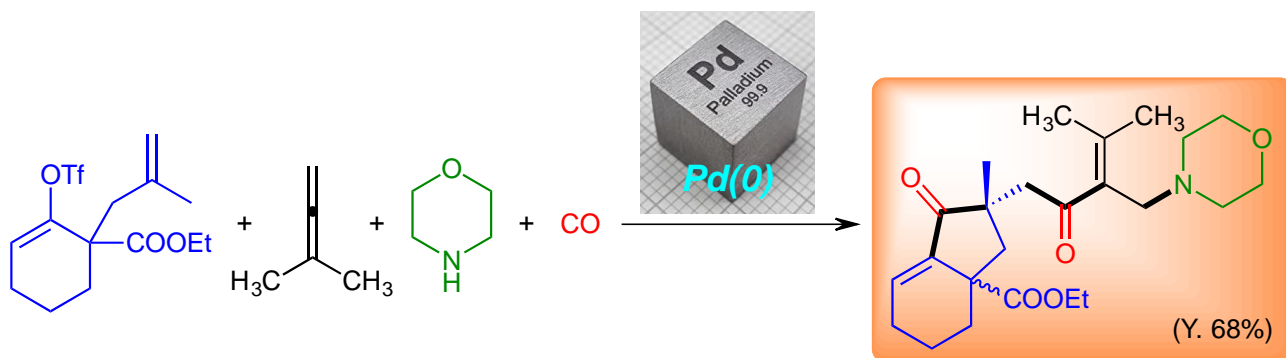
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## Abstract

Regiospecific pentamolecular queuing cascades involving the formation of five new bonds have been investigated. The process employs vinyl triflate as starter species together with excess dimethylallene and CO in the presence of *in situ* generated Pd(0) catalyst and morpholine as capping agent. The investigated reactions were properly tuned up for determining the best conditions allowing to maximizing the desired pentamolecular cascade pathway. The choice of the base, Pd-ligands and reaction temperature as well as the nature of the additive or its presence seem to be pivotal elements that must be tuned for realizing an efficient and reliable process.



**Keywords:** Pd-catalyzed reactions, queuing cascades, triflates, indenone derivatives

## Introduction

The concept of cascade reactions in organic chemistry aspires to develop viable procedures to useful materials with minimum waste and maximum molecular complexity. A careful design of the multi reaction “one-pot” sequences is needed so that the first step creates the functionality to trigger the second reaction and so on.<sup>1</sup> Catalytic cascade ring forming processes offer wide ranging opportunities for substantially leveraging molecular complexity and diversity via multiple insertions, with concomitant introduction of new functional groups. Transition metal catalysts offer the ultimate in clean technology to perform cascade reactions and, in particular, cyclic carbopalladation can be achieved by a group of related reactions, providing versatile and powerful method for the construction of carbocyclic and heterocyclic ring systems.<sup>2</sup>

In the past decades, organic chemistry witnessed significant improvements in synthetic efficiency of cascade reactions, tandem reactions, and related one-pot processes. Palladium-catalyzed cross-coupling reactions, with their well-understood multistep catalytic cycles, form a promising basis for the design of cascade reactions, compatible with a range of functional groups that can be combined with a range of secondary transformations. The resulting palladium-catalyzed cascade reactions have provided access to a plethora of complex small molecules of high medicinal relevance.<sup>3</sup>

Still recently, remarkable examples of palladium-catalyzed cascade cyclizations have been reported in literature. In fact, a palladium-catalyzed cascade cyclization of alkenyl ethers with alkynyl oxime ethers was proposed for the construction of poly-heterocyclic scaffolds. The strategy features excellent regio- and chemoselectivities as well as good functional group tolerance and the newly formed 2-isoxazolyl-2,3-dihydrobenzofuran products can be further transformed into diverse complex heterocycles, with potential applications in medicinal chemistry (Scheme 1a).<sup>4</sup> A highly efficient palladium-catalyzed cascade metallo-ene/metallo-carbene coupling reaction was developed to produce 2,3-dihydropyrrole derivatives where two new Csp<sup>3</sup>-Csp<sup>2</sup> and Csp<sup>2</sup>-Csp<sup>2</sup> bonds were constructed in one-pot. The alkene was one of the most easily functionalized groups, making it possible for these molecules to be transformed into more complex molecules. More importantly, the final product possesses an attractive 1,3,8-trienes scaffold, which is difficult to be synthesized (Scheme 1b).<sup>5</sup>

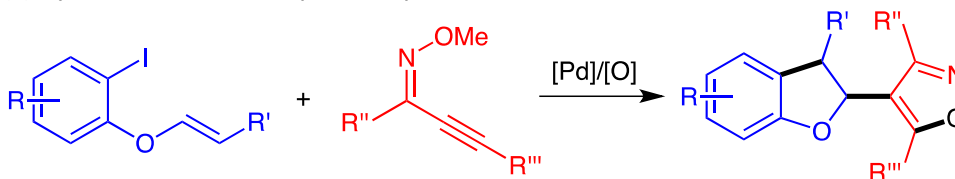
Within this panorama, Grigg's group has provided several examples of tri- and tetra-molecular queuing cascades.<sup>6,7</sup> Typically, a 4-component cyclization anion-cascade reaction requires a starting species that undergoes oxidative addition affording an organopalladium(II) intermediate. This latter undergoes intramolecular cyclization followed by insertion of carbon monoxide (CO), switching the cascade from intra- to intermolecular with termination by capture promoted by a neutral-organometallic reagent providing the final product. Molecular queuing processes require the relative rates of the various desired and other potential processes to be in the correct order. In developing Pd-catalyzed cascades, the Grigg's group has implemented a wide range of starters, relay, terminating and capping agents with the intent to realize new multicomponent queuing cascades leading to an enhanced molecular diversity in automated synthetic approaches.<sup>8</sup>

In particular, a variety of starter species can be proposed, ranging from alkyl-, aryl- vinyl- and allyl-halides, though making the platform of potential structures the widest possible; also triflates were employed and it was demonstrate the advantages in such processes since they can be prepared from the corresponding carbonyl compounds, increasing the molecular diversity in cascade syntheses.<sup>9,10</sup>

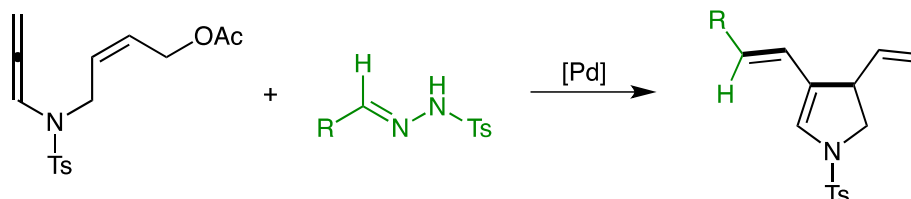
In this contest, aromatic and cycloalkene triflates were used to achieve new goals in Pd-catalyzed cyclization anion-capture methods. Pentamolecular queuing cascades were performed using CO and allene in the relay phase and secondary cyclic amines as capping-agents.<sup>11</sup> Hereby, a detailed study on the use of a six-

membered ring triflate derivative as starter species is presented using CO and allenes in the relay phase and morpholine as capping-agents (Scheme 1c).

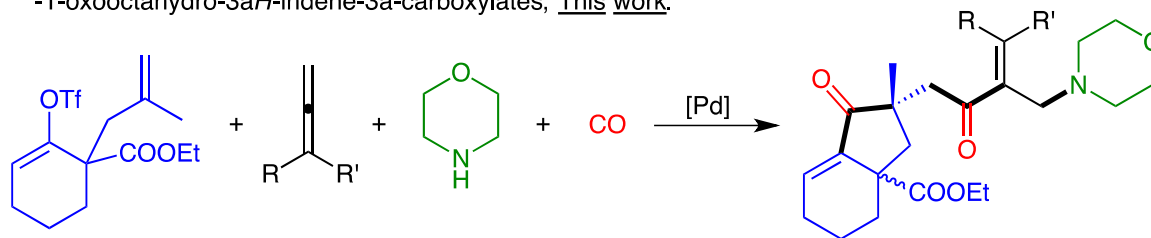
(a) Synthesis of 2-isoxazolyl-2,3-dihydrobenzofurans; [Ref. 4](#).



(b) Synthesis of 2,3-dihydropyrroles; [Ref. 5](#).



(c) Synthesis of ethyl 2-methyl-2-[3-(morpholinomethyl)-2-oxobut-3-en-1-yl]-1-oxooctahydro-3a*H*-indene-3a-carboxylates; [This work](#).



**Scheme 1.** Synthetic approaches using Pd-catalyzed cascade reactions.

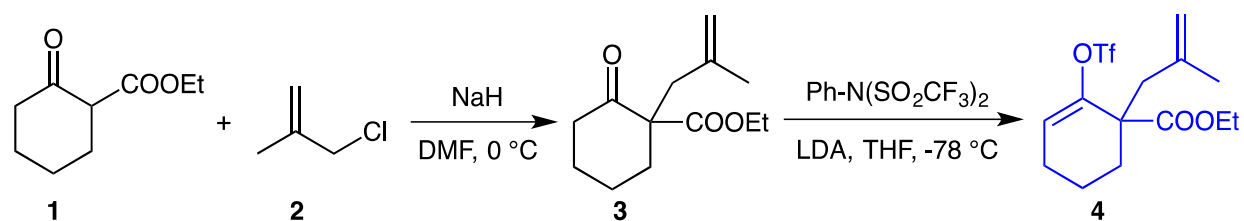
The results are presented and discussed in the light of the experimental conditions applied, using Pd(0) as the catalyst. The products obtained were completely characterized assigning the structure by means of spectroscopic investigations.

## Results and Discussion

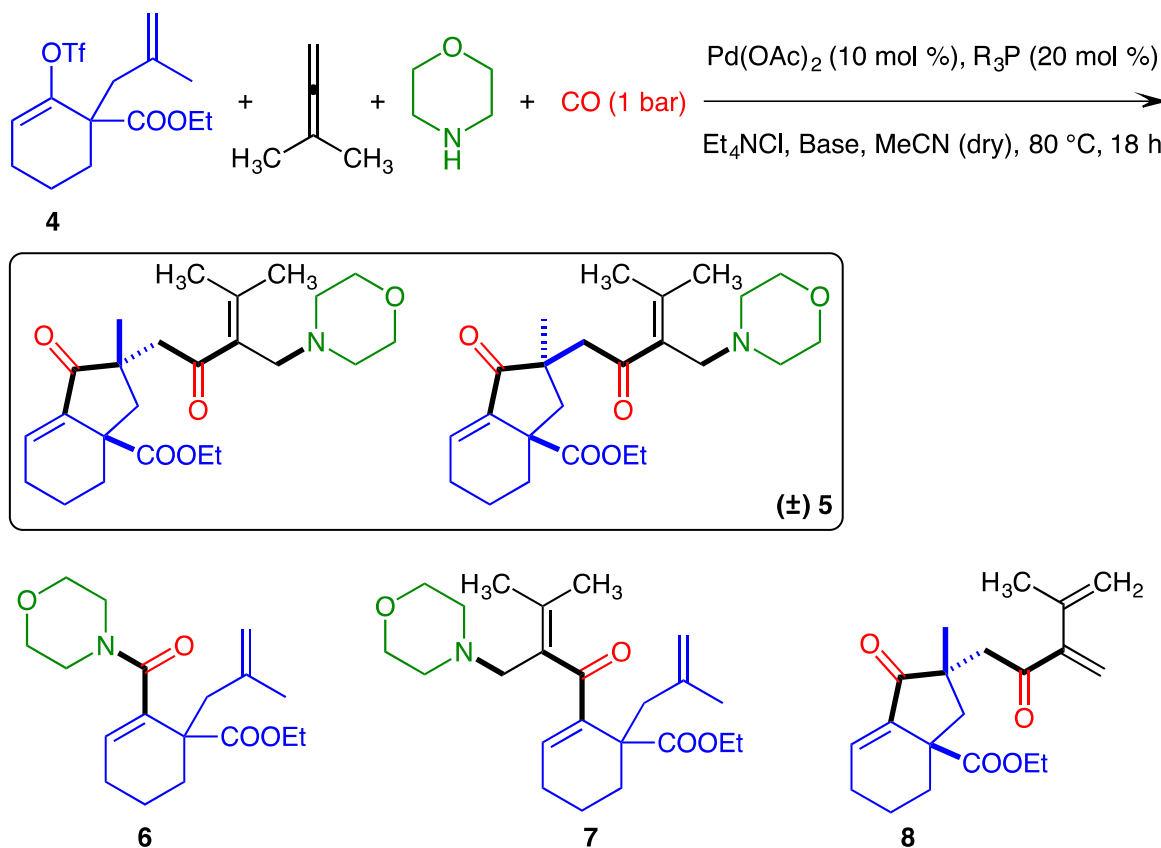
Triflate **4** was used as starter species and the synthesis is reported in Scheme 2. The commercially available  $\beta$ -keto-ester **1** was allylated with methallyl chloride **2** in the presence of NaH in dry DMF affording compound **3** in 60% yield as a colourless oil, according to the known procedure.<sup>12</sup> The allyl ester **3** was then triflated under kinetic control experimental conditions with Ph-NTf<sub>2</sub>,<sup>13</sup> the desired compound **4** was obtained in 76% as a colourless oil, carefully purified to be used in Pd-catalyzed processes (Scheme 2).

Triflate **4** was used in the Pd-catalyzed cascade reactions whose experimental conditions were carefully set-up. The general process is reported in Scheme 3; excess liquid dimethylallene (5 equiv) along with 1 equiv of Et<sub>4</sub>NCl (additive) in the presence of Pd(OAc)<sub>2</sub> (10 mol %) and phosphine ligands (20 mol %). A typical procedure consists in the preparation of a 0.1 M solution of triflate **4** in dry acetonitrile as solvent using a Schlenk tube as reactor; addition of the catalytic system, the additive, an excess of an organic base and the capping agent (morpholine) addition completes the preparation of the reacting mixture. The Schlenk tube is

then sealed and a sequence of vacuum/nitrogen steps is applied at the frozen tube to get rid of air; the reactor is then filled with 1 bar CO and the reaction conducted at 80 °C for 18 h.



**Scheme 2.** Synthesis of ethyl 1-(2-methylallyl)-2-(((trifluoromethyl)-sulfonyl)oxy)-cyclohex-2-ene-1-carboxylate (**4**).



**Scheme 3.** Pentamolecular queuing cascade reaction: synthesis of racemic compounds **5** and shunt products.

Literature on triflate reactions reports different conditions in Heck reaction and cyclic carbopalladation;<sup>14,15</sup> those reported in Scheme 3 and Table 1 were found to be successful after a number of trial experiments. Dry acetonitrile is the solvent of choice since DMF and toluene did not work; the catalytic system is composed by Pd(II) and a variety of phosphines with different steric demand (*vide infra* for discussion). The additive chosen was Et<sub>4</sub>NCl in accordance with the Jeffery's protocol;<sup>14</sup> experiments conducted with LiCl or other additives did not give any positive result. Table 1 summarizes the obtained results with different bases (structure and equivalents) as well as phosphines; cone angles of these latters are also reported sorted by increasing values. From the experiments performed, five products were isolated. Diastereoisomeric compounds **5** are the products of a pentamolecular queuing cascade pathway, obtained in

the racemic forms, where two molecules of CO are incorporated with the formation of five new bonds (see boldface bonds in the structures of Scheme 3). Compounds **6-8** are typical shunt products: when a single molecule of CO is inserted, the capping agent (morpholine) interrupts immediately the cascade affording the amide **6**, forming two new bonds. Compound **7** corresponds to a step further in the reaction since dimethylallene is inserted after the first CO molecule but capping immediately follows and three bonds are formed. Alternatively, dimethylallene somewhat works as the capping agent leading to compound **8** where four new bonds are formed.

The first experiments were conducted by using simple  $\text{Ph}_3\text{P}$  and  $\text{Et}_3\text{N}$  as a base. The best results in terms of pentamolecular queuing cascade products gave the products **5** in 21% yield along with 11% of the shunt product **8** (single case); this was obtained with 5 equivalents of base and one equivalent of capping agent morpholine (Table 1, entry 2). The increase of the amount of morpholine at 1.5 equiv (Table 1, Entry 1) or at 2 equiv (Table 1, Entry 3) favors somewhat the shunt product **6** where morpholine concludes the cascade just after a single CO insertion. From these results it comes that the equivalents of base has to be up to 5 but the amounts of the capping agent morpholine must not exceed 1.5 equiv. Having  $\text{Ph}_3\text{P}$  a cone angle of 145,<sup>16-21</sup> we started trying different phosphines with increasing cone angle values along with  $n\text{-Bu}_3\text{N}$  as a base aiming to ameliorate the cascade results (*vide infra*). The use of phosphine with lower cone angle (Table 1, Entry 4) determined a lowering of the yields in cascade product **5** (14%) but also poor yields in shunt compounds **6** and **7** (7% and 5%, respectively). Reset of the cone angle values at 145 with  $(p\text{-Tolyl})_3\text{P}$  led to one of the best results in terms of pentamolecular queuing cascade products; compounds **5** were isolated in 28% yield along with the 17% of compound **6** (Table 1, Entry 5). Control experiments were performed by using 1 equiv morpholine for the reaction of Table 1, Entry 5, with a clear decrease of the final yield of compound **5** (12%); for this reason 1.5 equiv were only used in all the other experiments. Furthermore the use of  $\text{PPh}_3$  as ligand in the presence of  $n\text{-Bu}_3\text{N}$  as a base did not give any product, even those from shunt pathways.

**Table 1.** Optimization of the reaction conditions in Pd-catalyzed pentamolecular queuing cascade reaction of **4** in the presence of dimethylallene, morpholine and CO. Chemical yields (%) of products **5**, **6**, **7** and **8**

Entry	Base	(equivs.)	Ligand	Cone Angle <sup>d</sup>	<b>5</b>	Diast. Ratio <sup>e</sup>	<b>6</b>	<b>7</b>	<b>8</b>
1 <sup>a</sup>	$\text{Et}_3\text{N}$	4.5	$\text{PPh}_3$	145	5	Single diast. 1 <sup>st</sup>	28	0	0
2 <sup>b</sup>	$\text{Et}_3\text{N}$	5	$\text{PPh}_3$	145	21	Single diast. 1 <sup>st</sup>	0	0	11
3 <sup>c</sup>	$\text{Et}_3\text{N}$	6	$\text{PPh}_3$	145	12	Single diast. 1 <sup>st</sup>	50	0	0
4 <sup>a</sup>	$n\text{-Bu}_3\text{N}$	4.5	$n\text{Bu}_3\text{P}$	132	14	Single diast. 1 <sup>st</sup>	7	5	0
5 <sup>a</sup>	$n\text{-Bu}_3\text{N}$	4.5	$(p\text{-Tolyl})_3\text{P}$	145	28	Single diast. 1 <sup>st</sup>	17	0	0
6 <sup>a</sup>	$n\text{-Bu}_3\text{N}$	4.5	$(p\text{-MeOPh})_3\text{P}$	145	22	Single diast. 1 <sup>st</sup>	22	0	0
7 <sup>c</sup>	$n\text{-Bu}_3\text{N}$	5	$(p\text{-MeOPh})_3\text{P}$	145	21	Single diast. 1 <sup>st</sup>	36	0	0
8 <sup>a</sup>	$n\text{-Bu}_3\text{N}$	4.5	$(2\text{-Furyl})_3\text{P}$	152	11	1.3 : 1	25	0	0
9 <sup>a</sup>	$n\text{-Bu}_3\text{N}$	4.5	$(\text{C}_6\text{H}_{11})_3\text{P}$	179	30	Single diast. 1 <sup>st</sup>	8	2	0
10 <sup>a</sup>	$n\text{-Bu}_3\text{N}$	4.5	$t\text{Bu}_3\text{P}$	182	11	1 : 2.3	8	0	0
11 <sup>a</sup>	$n\text{-Bu}_3\text{N}$	4.5	$(2,6\text{-MeO}_2\text{Ph})_3\text{P}$	184	36	1 : 5	19	9	0
12 <sup>a</sup>	$n\text{-Bu}_3\text{N}$	4.5	$(\text{C}_6\text{F}_5)_3\text{P}$	184	0	-	17	21	0
13 <sup>a</sup>	$n\text{-Bu}_3\text{N}$	4.5	$(o\text{-Tolyl})_3\text{P}$	194	2	Single Diast. 1 <sup>st</sup>	6	41	0
14 <sup>a</sup>	$n\text{-Bu}_3\text{N}$	4.5	$(2,4,6\text{-MeO}_2\text{Ph})_3\text{P}$	212	24	1 : 16	3	0	0
15 <sup>a</sup>	$n\text{-Bu}_3\text{N}$	4.5	$(\text{Mes})_3\text{P}$	243	0	-	28	30	0

a. Morpholine, 1.5 equiv. b. Morpholine, 1 equiv. c. Morpholine, 2 equiv. d. Cone angle values from Ref. 16-21. e. Diastereoisomeric Ratio (1<sup>st</sup> Eluted : 2<sup>nd</sup> Eluted) compound from column chromatography.

Substantial confirms came from the results of entries 6 and 7 of Table 1 where the (*p*-MeOPh)<sub>3</sub>P was used (cone angle 145°) with different amounts of *n*-Bu<sub>3</sub>N; an increase of the base somewhat depresses the pentamolecular cascade process in favour of the shunt pathway to compound **6** (36%). A further increase of the cone angle with the (2-Furyl)<sub>3</sub>P (Table 1, Entry 8) surprisingly changes again the results; compound **5** was obtained in poor yields (11%) while the larger yields belong to product **6** (25%). Presumably, the presence of a competing coordinating moiety in the phosphine (furan) is detrimental for the catalytic process. Tricyclohexylphosphine (Table 1, Entry 9, cone angle 179°) gave excellent results; compound **5** was obtained as single diastereoisomer in 30% yield along with minor amounts of the shunt products **6** and **7**. Excellent results were also obtained using (2,6-MeO<sub>2</sub>Ph)<sub>3</sub>P as ligand (cone angle 184°) with reversal of the diastereoisomeric ratio; compounds **5** were obtained in 36% yield along with products **6** (19%) and **7** (9%) (Entry 11). Inversion of stereochemical ratio was also observed with (2,4,6-MeO<sub>2</sub>Ph)<sub>3</sub>P as ligand, having a very large cone angle (Table 1, Entry 14, cone angle 212°. In all the other cases (Table 1, Entries 10, 12, 13 and 15) the cascade products were rarely observed while the shunt products largely represent the majority of the reaction mixture components, up to 41% for compound **7** in Entry 13 of Table 1.

From the mechanistic point of view, Scheme 4 shows a reliable proposal for the products formation; the inherently slow rate of the 4-*exo-trig* cyclopalladation of the initial oxidative addition intermediate **4b** allows the subsequent carbonylation affording **4c** with a considerably enhanced cyclization rate for the 5-*exo-trig* cycloacylpalladation. If the second carbonylation does not occur, the shunt product **6** is formed by means of the capping agent (morpholine).

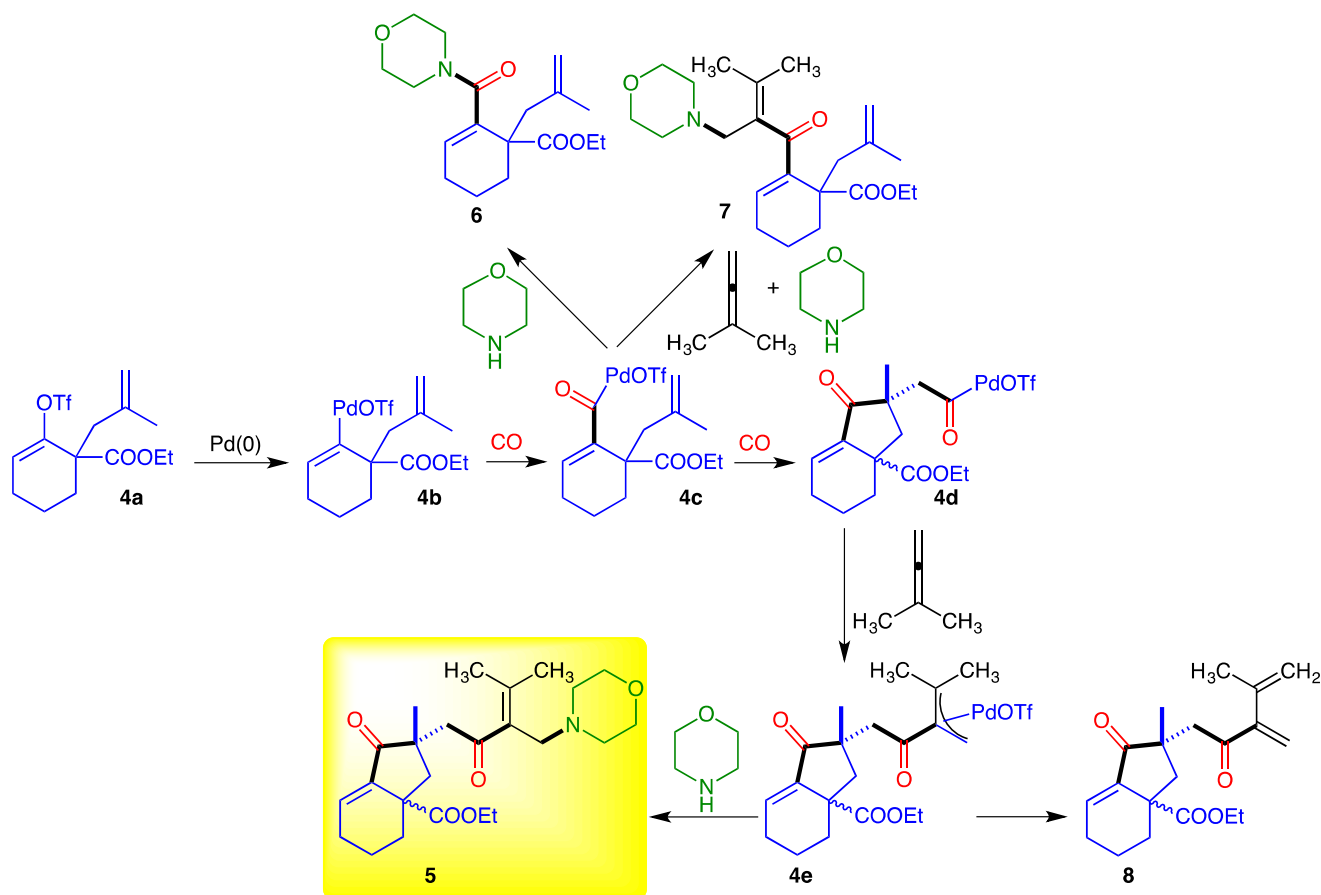
The second carbonylation reaction gives the intermediate **4d** that undergoes acylpalladation of the dimethylallene at the centre carbon atom affording **4e**.<sup>22</sup> Then, anion capture at the least substituted terminus of the  $\pi$ -allyl species occurs by the capping agent (morpholine) affording the desired final compounds **5** with the formation of five new bonds. The formation of compound **7** can be ascribed to the allene insertion and capping by morpholine at the **4c** intermediate formation step. Finally, compound **8** derives from the intermediate **4e** by  $\pi$ -allyl complex elimination.

To explain the results obtained with different ligands, electronic and steric effects must be considered. Good  $\sigma$ -donor ligands, such as phosphines of Entries 5-7, 9, 11 and 14 of Table 1, increase the electron density at the metal centre and facilitate the oxidative addition, leading to the pentamolecular queuing cascade products and related shunt compounds. With phosphines decreasing the electron density at the metal centre (Table 1, Entries 8 and 12), poor yields of the desired products are obtained or these can be also totally absent. From steric reasoning, large cone angle ligands give less stable complexes that readily dissociate in solution and are assumed to be catalytically more active.<sup>18</sup> This explains the results of Entries 4 and 10 of Table 1; *n*-Bu<sub>3</sub>P is a better  $\sigma$ -donor ligand being alkyl phosphine but the cone angle is not large enough as in the case of (C<sub>6</sub>H<sub>11</sub>)<sub>3</sub>P or aromatic phosphines; *t*-Bu<sub>3</sub>P has a large cone angle but is again  $\sigma$ -donor ligand.

Concerning the role of the base, the use of *n*Bu<sub>3</sub>N improved remarkably the products yields in non-aromatic intramolecular carbonylation coupling reactions with respect to Et<sub>3</sub>N. Exploring different reaction conditions we report the results obtained in Table 2. The previously set-up of reaction conditions were maintained, *i.e.* dimethylallene (5 equiv.), 1 equiv. Et<sub>4</sub>NCl (additive), Pd catalyst (10 mol %), phosphine ligands (20 mol %) for a 0.1 M solution of triflate **4** in dry solvents in a Schlenk tube as the reactor, 1 bar CO, reaction conducted at 80 °C for 18 h.

In Entries 1 and 2 of Table 2 (*p*-MeOPh)<sub>3</sub>P was used having a medium range cone angle (145°) and morpholine (6 equiv) replaced the base; no significant improvements were obtained even upon changing the reaction solvent. A more sterically hindered base like *i*Pr<sub>2</sub>EtN (Table 2, Entry 3) and the use of (C<sub>6</sub>H<sub>11</sub>)<sub>3</sub>P as the ligand (cone angle 179°) barely changed the results compared to those obtained with *n*Bu<sub>3</sub>N, affording isomer

**5** as single diastereoisomer (1<sup>st</sup> Eluted) in 28% yield along with compound **6** in 20% yield. Further changes in the type of Palladium catalyst (Table 2, Entry 4) or in the ratio Pd/Ligand to 1:4 (Table 2, Entry 5) were not much effective.



**Scheme 4.** Pentamolecular queuing cascade reaction mechanism.

**Table 2.** Effect of the base in Pd-catalyzed pentamolecular queuing cascade reaction of **4** in the presence of dimethylallene, morpholine and CO. Chemical yields (%) of products **5** and **6**

Entry	Base	(equiv.)	Catalyst	Ligand	Solvent	<b>5</b> <sup>c</sup>	<b>6</b>
1 <sup>a</sup>	Morpholine	6	Pd(OAc) <sub>2</sub>	( <i>p</i> -MeOPh) <sub>3</sub> P	MeCN	7	22
2 <sup>b</sup>	Morpholine	6	Pd(OAc) <sub>2</sub>	( <i>p</i> -MeOPh) <sub>3</sub> P	DMF	15	25
3 <sup>c</sup>	<i>i</i> Pr <sub>2</sub> EtN	4.5	Pd(OAc) <sub>2</sub>	(C <sub>6</sub> H <sub>11</sub> ) <sub>3</sub> P	MeCN	28	20
4 <sup>a</sup>	<i>n</i> Bu <sub>3</sub> N	4.5	Pd <sub>2</sub> (dba) <sub>3</sub>	<i>n</i> Bu <sub>3</sub> P	MeCN	9	3
5 <sup>b</sup>	<i>n</i> Bu <sub>3</sub> N	4.5	Pd(OAc) <sub>2</sub>	( <i>p</i> -MeOPh) <sub>3</sub> P	MeCN	26	22

a. Typical reaction conditions: dimethylallene (5 equivs.), 1 equiv. Et<sub>4</sub>NCl (additive), Pd catalyst (10 mol %), phosphine ligands (20 mol %) for a 0.1 M solution of triflate **4** in dry solvents in a Schlenk tube as the reactor, 1 bar CO, reaction conducted at 80 °C for 18 h. b. Pd catalyst (10 mol %), phosphine ligands (40 mol%). c. Single diastereoisomer 1<sup>st</sup> Eluted

According to Jeffery's protocol,<sup>14,15,23</sup> Et<sub>4</sub>NCl and in general ammonium chlorides are used as additives as phase transfer catalysts facilitating both the regeneration of Pd(0)-catalyst and the Heck coupling. We

performed a few experiments by removing this reaction component and the results are summarized in Table 3. The chosen catalytic system refers to the best result in Table 1, Entry 11, and for this reason (2,6-MeO<sub>2</sub>Ph)<sub>3</sub>P was used. The reaction temperature was also varied and excellent results were obtained. Among the products deriving from direct capture process, the sole compound **6** was isolated with chemical yields ranging from 6% up to 22%. The 2<sup>ns</sup> Eluted stereoisomer **5** is the major component of the pentamolecular queuing cascade products (Table 3, Entries 1 and 2) and single stereoisomer in Entries 3-6 of Table 3. *N*-Bu<sub>3</sub>N is confirmed as best base for performing this type of cascade reactions, since the use of Et<sub>3</sub>N (Table 3, Entry 5) could not reproduce the result of Entry 2 of Table 3 that afforded compounds **5** in 60% yield with 6% only for compound **6**. The change of the reaction solvent (Table 3, Entry 4, DMF) and the increase of reaction temperatures are somewhat detrimental for the catalyzed process. A fine tuning of the reaction temperature led to site the value at 70 °C. The best result ever obtained is reported in Table 3, Entry 6 where a double amount of catalyst was used; under these conditions stereoisomer **5b** was obtained in 68% yield.

A possible rationale for these results acknowledges that triflates are better leaving groups than halides, readily dissociating to give the cationic complexes. This positive effect might be depreciated by the ammonium chloride of the additive since the chloride anion can be a ligand for the zero-valent Pd complexes even in the presence of phosphines.<sup>23,24,25</sup>

**Table 3.** Pd-catalyzed pentamolecular queuing cascade reaction of **4** in the presence of dimethylallene, morpholine and CO without additives. Chemical yields (%) of products **5** and **6**

Entry	Base <sup>c</sup>	Solvent	T (°C)	<b>5</b>	Diast. Ratio <sup>d</sup> 1 <sup>st</sup> : 2 <sup>nd</sup> Eluted	<b>6</b>
1 <sup>a</sup>	<i>n</i> -Bu <sub>3</sub> N	MeCN	80	53	1:8	17
2 <sup>a</sup>	<i>n</i> -Bu <sub>3</sub> N	MeCN	70	60	1:10	6
3 <sup>a</sup>	<i>n</i> -Bu <sub>3</sub> N	MeCN	60	53	Single diast. 2 <sup>nd</sup> eluted	11
4 <sup>a</sup>	<i>n</i> -Bu <sub>3</sub> N	DMF	110	32	Single diast. 2 <sup>nd</sup> eluted	22
5 <sup>a</sup>	Et <sub>3</sub> N	MeCN	70	49	Single diast. 2 <sup>nd</sup> eluted	17
6 <sup>b</sup>	<i>n</i> -Bu <sub>3</sub> N	MeCN	70	68	Single diast. 2 <sup>nd</sup> eluted	6

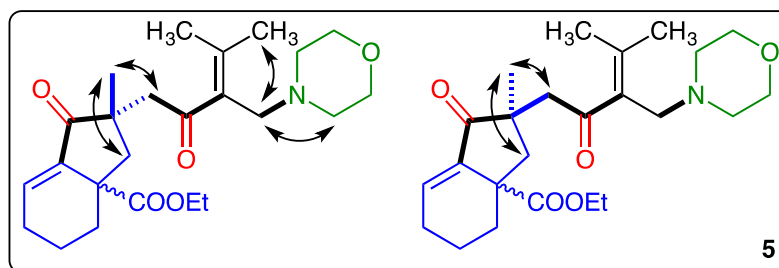
a. Typical reaction conditions: dimethylallene (5 equiv), Pd(OAc)<sub>2</sub> catalyst (10 mol %), (2,6-MeO<sub>2</sub>Ph)<sub>3</sub>P (20 mol %) for a 0.1 M solution of triflate **4** in dry solvents in Schlenk tube as reactor, 1 bar CO, reaction conducted for 18 h.

b. Pd(OAc)<sub>2</sub> catalyst (20 mol %), (2,6-MeO<sub>2</sub>Ph)<sub>3</sub>P (40 mol %). c. Base 4.5 equiv. d. Diastereoisomeric ratio 1<sup>st</sup> Eluted : 2<sup>nd</sup> Eluted compound from column chromatography.

To complete the picture on the pentamolecular queuing cascade reaction above described, we wish to discuss the structural assignments of the obtained products, relying upon their analytical and spectroscopic data that are consistent for the given structure. In particular the correct structures were based upon the NMR data; <sup>1</sup>H, <sup>13</sup>C-NMR spectra as well as COSY, DEPT, HSQC and NOE experiments allowed for determining the structures of the products. Racemic compounds **5**, with uncertain stereochemistry at the carbon atoms 2 and 3a, showed in the <sup>1</sup>H NMR spectra the typical signal corresponding to the CH= proton of the indenone moiety at δ 6.85 and 6.75 (as triplets), respectively for the (first eluted and second eluted) diastereoisomer. The AB systems of the two diastereoisotopic methylenes are also found at δ 3.20 ppm and 2.85 ppm for the 1<sup>st</sup> isomer and at δ 3.12 ppm and (2.87, 2.58 ppm) for the 2<sup>nd</sup> isomer. All the other signals are in the range expected for the type of protons corresponding to the assigned structure.



Figure 1 reports the structures of the diastereoisomers **5** where the curly arrows indicate the NOE effects observed that confirm the skeleton of the molecules with the correct connections derived from the newly formed bonds.



**Figure 1.** Structures of racemic compounds **5**; uncertain relative stereochemistry at the carbon *3a*. NOE correlations indicated by curly arrows.

The AB systems adjacent to the second C=O group gave the typical signals at  $\delta$  2.85 ppm and (2.87, 2.58 ppm), respectively for the two diastereoisomers, and showed nuclear Overhauser (NO) Effects with the methyls at the carbon C2 of the indanone moieties. One of the methyls of the allene moieties gave also NO Effects with the methylene attached to the morpholine. Other connections were found but, unfortunately, no effects were found between the ethyls of the COOEt groups in the two structures that could give information relative to the stereochemistry of the two isomers of **5**. This is the reason why compounds **5**, even though separable by column chromatography, were considered together in terms of chemical yields and the diastereoisomeric ratios were only given.

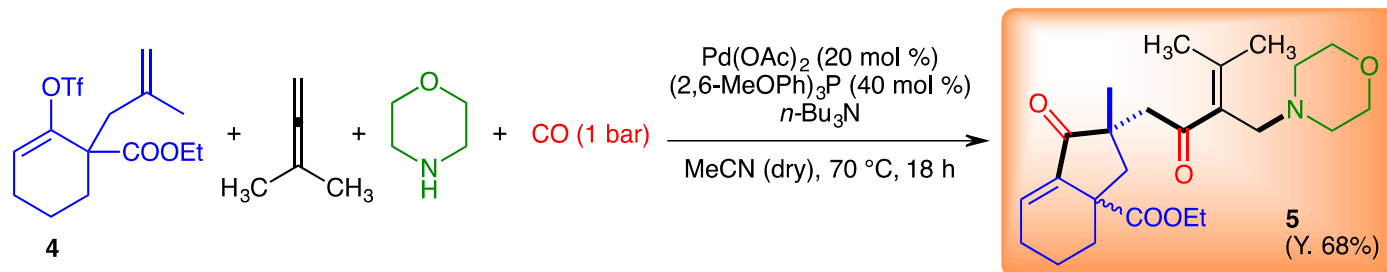
In the  $^1\text{H}$  NMR spectrum of compound **6** the CH= proton of the indenone moiety is found at  $\delta$  5.90 ppm (as triplet) and the new signals corresponding to the CH<sub>2</sub>= terminus are found at  $\delta$  4.83 ppm and 4.70 ppm, as singlets. Compound **7**  $^1\text{H}$  NMR spectrum showed again the CH= proton of the indenone moiety at  $\delta$  7.48 ppm (as triplet) and the signals corresponding to the CH<sub>2</sub>= terminus are found at  $\delta$  4.67 and 4.63 ppm, as singlets, along with the methyls corresponding to the dimethylallene insertion ( $\delta$  1.70 ppm, as singlets). Finally, compound **8**  $^1\text{H}$  NMR spectrum showed the CH= proton of the indenone moiety at  $\delta$  6.89 ppm (as triplet) and the signals corresponding to two CH<sub>2</sub>= groups, found at  $\delta$  (5.60 and 5.55 ppm) and  $\delta$  5.03 ppm.

A series of other reactions were also conducted with different Pd-based catalysts, ligands, allenes, bases and solvents, also changing the additives, but with no or negligible results with respect to those here reported.

## Conclusions

Regiospecific pentamolecular queuing cascades involving the formation of five new bonds and cyclopalladation have been achieved. The process employs vinyl triflate **4** as starter species together with excess dimethylallene and 1 bar CO in the presence of *in situ* generated Pd(0)-catalyst and morpholine as capping agent (Scheme 5).

The investigated processes were properly tuned up for determining the best reaction conditions allowing to reducing shunt reactions and maximizing the desired pentamolecular cascade reaction. Scheme 5 reports the best result under the optimum reaction conditions. The choice of the base, Pd-ligands and reaction temperature as well as the nature of the additive or their presence seem to be pivotal elements that must be tuned for realizing an efficient and reliable formation of 5 new chemical bonds.



**Scheme 5.** Regiospecific pentamolecular queuing cascades involving the formation of 5 new bonds.

We developed this exciting chemistry at Leeds University with Marie Curie Fellowship (Grant n. ERBFMBiCT961350) under the guidance of Prof. Ronald Grigg who wrote in a review<sup>2</sup> published in 1999:

*Cyclisation-carbopalladation has developed into a formidable reaction at a rapid pace following the demonstration in 1986 that the intramolecular Heck reaction provides access to both fused-, bridged- and spiro-cyclic systems and a reliable and flexible method for generating tetrasubstituted carbon centres. The ongoing development of novel palladium catalysts and additives to promote desirable features or suppress certain undesirable features of the reactions will continue to enhance the precision and scope of the basic cyclisation-carbopalladation and the wide range of processes developing from this. The advent of polycomponent queuing processes offers a new, productive avenue for organic synthesis.*

A deep debt of gratitude I wish to address to a great “Maestro” of organic chemistry.

## Experimental Section

**General.** All melting points (m.p.) were determined on a Koffler hot-stage apparatus and are uncorrected. Elemental analyses were done on a elemental analyzer Carlo Erba Mod. 1106. IR spectra (nujol mulls) were recorded on a spectrophotometer Philips PU 9706 and absorptions ( $\nu$ ) are in  $\text{cm}^{-1}$ .  $^1\text{H}$  and  $^{13}\text{C}$  NMR as well as other NMR spectra were recorded on a Bruker AC 250 and AM 400 spectrometers (solvents specified). Chemical shifts are expressed in ppm from internal tetramethylsilane ( $\delta$ ) and coupling constants ( $J$ ) are in Hertz (Hz): b, broad; s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Mass spectra were obtained from VG Autospec (70 eV). Column chromatography and tlc: silica gel H60 and Whatman PE SIL G/UV washed with  $\text{Et}_2\text{O}/\text{Et}_3\text{N}$  9:1 and dried at room temperature prior to use; eluants: hexane/diethyl ether 9:1 to pure diethyl ether.

**Starting and reference materials.** Ethyl 2-oxocyclohexane-1-carboxylate **1** and methallyl chloride **2** were purchased from Sigma-Aldrich. Ph-NTf<sub>2</sub>, NaH and DMF were purchased from Fluka. Other reagents and solvents were purchased from chemical suppliers and used without any further purification.

Ethyl 1-(2-methylallyl)-2-oxocyclohexane-1-carboxylate (**3**) was prepared according to the known procedure.<sup>12</sup> The product was purified by fractional distillation at reduced pressure as a colorless oil in 60% yield: b.p.  $89\text{--}95^\circ\text{C}/0.2\text{ mmHg}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  = 4.83 and 4.67 (s, 1H+1H,  $\text{C}=\text{CH}_2$ ), 4.17 (q, 2H,  $J$  7 Hz,  $-\text{OCH}_2\text{CH}_3$ ), 2.75 and 2.35 (AB syst.,  $J$  12 Hz, 1H+1H,  $-\text{CH}_2\text{--C}=\text{C}-$ ), 2.60–1.40 (m, 8H,  $-(\text{CH}_2)_4-$ ), 1.66 (s, 3H,  $\text{CH}_3$ ), 1.26 (t, 3H,  $J$  7 Hz,  $-\text{OCH}_2\text{CH}_3$ ).

**Synthesis of the ethyl 1-(2-methylallyl)-2-(((trifluoromethyl)sulfonyl)oxy)cyclohex-2-ene-1-carboxylate (4).**

*n*-BuLi (solution in hexane, 15 mmol) were added dropwise to a stirred solution of 13 mmol of dry *i*.Pr<sub>2</sub>NH in 30 mL of dry THF at 0 °C under nitrogen stream. Half an hour later, the resulting straw coloured solution was cooled down to -78 °C and 9 mmol of the ester **3** dissolved in 30 mL dry THF were added dropwise. The mixture was stirred at -78 °C for 90 min and then 9 mmol Ph-NTf<sub>2</sub> in 30 mL dry THF were added dropwise. The mixture was stirred for further 4 hours at -78 °C and then overnight at room temperature. THF was removed *in vacuo* and the residue dissolved in diethyl ether, washed with water and the organic phase dried over anhydrous MgSO<sub>4</sub>.

Chromatographic separation on silica gel of the residue obtained from evaporation to dryness of the organic solvent afforded the triflate **4** as colourless oil. Yield: 2.44 g (76%); colourless oil, purity 96% (NMR). IR  $\nu_{C=O}$  1724 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  = 5.86 (t, *J* 3 Hz, 1H, =CH), 4.90 and 4.78 (s, 1H+1H, =CH<sub>2</sub>), 4.20 (q, *J* 7 Hz, 2H, -OCH<sub>2</sub>CH<sub>3</sub>), 2.60 (AB syst., *J* 10 Hz, 2H, -CH<sub>2</sub>-C=), 2.40-1.50 (m, 6H, -(CH<sub>2</sub>)<sub>3</sub>-), 1.70 (s, 3H, CH<sub>3</sub>), 1.30 (t, = 7 Hz, 3H, -OCH<sub>2</sub>CH<sub>3</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  = 185.0 (C=), 169.1 (C=O), 145.8 (C=), 118.6 (CF<sub>3</sub>), 110.1 (=CH<sub>2</sub>), 104.0 (C=), 62.6 (CH<sub>2</sub>O), 42.9 (C), 37.6 (CH<sub>2</sub>), 26.6, 26.5, 23.5 (CH<sub>2</sub>), 22.9, 14.5 (CH<sub>3</sub>).

Anal. Calcd for C<sub>14</sub>H<sub>19</sub>F<sub>3</sub>O<sub>5</sub>S (356.36): C, 47.19; H, 5.37. Found: C, 47.18; H, 5.38.

**General procedure for the pentamolecular queuing cascade reactions**

In a Schlenk tube perfectly clean and dry under dry nitrogen stream, to a 0.1 M solution of the triflate **4** dissolved in the dry solvent of choice, the following reagents were added:

**Method A.** Pd catalyst 10 mol %, Ligand 20 mol %, additive Et<sub>4</sub>NCl (1 equiv), a base in the amount reported in Table 1, morpholine in the amount reported in Table 1, dimethylallene (5 equiv). The Schlenk is sealed and frozen in liquid nitrogen and then put under high vacuum for 30 min. The temperature is then allowed to rise to ambient maintaining a static vacuum. This operation is repeated until complete elimination of air from inside the Schlenk tube. The reaction vessel is frozen again and finally filled with 1 bar CO. The mixture is vigorously stirred for 18 h heating at the desired temperature. The reaction mixture is filtered and the organic solvent removed at reduced pressure leaving a residue that is taken up in diethyl ether, washed with water and the organic phase dried over anhydrous MgSO<sub>4</sub>. Chromatographic separation on silica of the residue afforded the reaction products.

**Method B.** Pd catalyst 20 mol %, Ligand 40 mol %, a base in the amount reported in Table 2 and 3, morpholine in the amount reported in Table 2 and 3, dimethylallene (5 equiv). The Schlenk is sealed and frozen in liquid nitrogen and then put under high vacuum for 30 min. The temperature is then allowed to rise to ambient maintaining a static vacuum. This operation is repeated until complete elimination of air from inside the Schlenk tube. The reaction vessel is frozen again and finally filled with 1 bar CO. The mixture is vigorously stirred for 18 h heating at the desired temperature. The reaction mixture is filtered and the organic solvent removed at reduced pressure leaving a residue that is taken up in diethyl ether, washed with water and the organic phase dried over anhydrous MgSO<sub>4</sub>. Chromatographic separation on silica of the residue afforded the reaction products.

**Ethyl 2-methyl-2-(4-methyl-3-(morpholinomethyl)-2-oxopent-3-en-1-yl)-1-oxo-1,2,3,4,5,6-hexahydro-3aH-indene-3a-carboxylate, first eluted diastereoisomer 5.** Yield: see Tables in the text; yellowish oil. IR  $\nu_{C=O}$  1710, 1690 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  = 6.85 (t, *J* 3 Hz, 1H, =CH), 4.16 (m, 2H, -OCH<sub>2</sub>CH<sub>3</sub>), 3.60 (bs, 4H, CH<sub>2</sub>-O morph.), 3.20 (AB syst., *J* 13 Hz, 2H, -CH<sub>2</sub>-morph.), 2.85 (AB syst., *J* 12 Hz, 2H, -CH<sub>2</sub>-CO), 2.40 (m, 8H, CH<sub>2</sub>-N morph. and -CH<sub>2</sub>CH<sub>2</sub>-), 2.08 and 2.46 (AB syst., *J* 10 Hz, 2H, C-CH<sub>2</sub>-C), 1.74 (m, 2H, CH<sub>2</sub>), 1.70 and 1.69 (s, 3H+3H, =C-CH<sub>3</sub>), 1.24 (t, *J* 7 Hz, 3H, -OCH<sub>2</sub>CH<sub>3</sub>), 1.04 (s, 3H, -C-CH<sub>3</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  = 207.6, 205.6 and 176.6 (C=O), 135.7, 137.2 and 139.0 (C=), 135.1 (CH=), 66.9 (CH<sub>2</sub>-O morph.), 61.0 (-O-CH<sub>2</sub>CH<sub>3</sub>), 57.2 (CH<sub>2</sub>-

morph.), 53.0 (CH<sub>2</sub>-N morph.), 50.5 (CH<sub>2</sub>-C=O), 48.0 and 45.3 (C), 44.6 (-C-CH<sub>2</sub>-C-), 33.9, 24.9 and 19.0 [-(CH<sub>2</sub>)<sub>3</sub>-], 22.1 and 20.6 (CH<sub>3</sub>-C=), 23.9 (C-CH<sub>3</sub>), 14.1 (-OCH<sub>2</sub>CH<sub>3</sub>). MS (*m/z*): 417 (15), 331 (8), 344 (39), 196 (100).

Anal. Calcd for C<sub>24</sub>H<sub>35</sub>NO<sub>5</sub> (417.55): C, 69.04; H, 8.45; N, 3.35. Found: C, 68.99; H, 8.50; N, 3.34.

**Ethyl 2-methyl-2-(4-methyl-3-(morpholinomethyl)-2-oxopent-3-en-1-yl)-1-oxo-1,2,3,4,5,6-hexahydro-3aH-indene-3a-carboxylate, second eluted diastereoisomer 5.** Yield: see Tables in the text; yellowish oil. IR  $\nu_{C=O}$  1715, 1680 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  = 6.75 (t, *J* = 3 Hz, 1H, =CH), 4.07 (m, 2H, -OCH<sub>2</sub>CH<sub>3</sub>), 3.57 (bs, 4H, CH<sub>2</sub>-O morph.), 3.12 (AB syst., *J* 13 Hz, 2H, -CH<sub>2</sub>-morph.), 2.87 and 2.58 (AB syst., *J* 12 Hz, 2H, -CH<sub>2</sub>-CO), 2.33 (m, 4H, CH<sub>2</sub>-N morph.), 3.02 and 1.63 (AB syst., *J* 10 Hz, 2H, C-CH<sub>2</sub>-C), 2.35 (m, 2H, CH<sub>2</sub>), 1.80-1.40 (m, 4H, -CH<sub>2</sub>CH<sub>2</sub>-), 1.70 and 1.69 (s, 3H+3H, =C-CH<sub>3</sub>), 1.20 (t, *J* 7 Hz, 3H, -OCH<sub>2</sub>CH<sub>3</sub>), 1.10 (s, 3H, -C-CH<sub>3</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  = 207.7, 205.3 and 176.0 (C=O), 139.0, 137.6 and 134.4 (C=), 135.6 (CH=), 66.8 (CH<sub>2</sub>-O morph.), 60.9 (-O-CH<sub>2</sub>CH<sub>3</sub>), 57.1 (CH<sub>2</sub>-morph.), 53.1 (CH<sub>2</sub>-N morph.), 47.6 (CH<sub>2</sub>-C=O), 47.3 and 45.5 (C), 45.0 (-C-CH<sub>2</sub>-C-), 34.0, 24.9 and 19.1 [-(CH<sub>2</sub>)<sub>3</sub>-], 25.0 and 22.1 (CH<sub>3</sub>-C), 20.9 (CH<sub>3</sub>-C=), 14.1 (-OCH<sub>2</sub>CH<sub>3</sub>). MS (*m/z*): 417 (2), 402 (16), 372 (24), 344 (15), 330 (10), 152 (100). Anal. Calcd for C<sub>24</sub>H<sub>35</sub>NO<sub>5</sub> (417.55): C, 69.04; H, 8.45; N, 3.35. Found: C, 69.01; H, 8.48; N, 3.30.

**Ethyl 1-(2-methylallyl)-2-(morpholine-4-carbonyl)cyclohex-2-ene-1-carboxylate 6.** Yield: see Tables in the text; yellow oil. IR  $\nu_{C=O}$  1725,  $\nu_{C=C}$  1625 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  = 5.90 (t, *J* = 3 Hz, 1H, =CH), 4.83 and 4.70 (s, 1H+1H, =CH<sub>2</sub>), 4.12 (m, 2H, -OCH<sub>2</sub>CH<sub>3</sub>), 3.70- 3.40 (m, 8H, CH<sub>2</sub> morph.), 3.04 and 2.62 (AB syst., *J* = 12 Hz, 2H, -CH<sub>2</sub>-C), 2.20 and 1.70 (m, 6H, -(CH<sub>2</sub>)<sub>3</sub>-), 1.70 (s, 3H, =C-CH<sub>3</sub>), 1.26 (t, *J* 7 Hz, 3H, -OCH<sub>2</sub>CH<sub>3</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  = 174.6 and 169.7 (C=O), 142.0 and 134.4 (C=), 131.7 (CH=), 114.5 (CH<sub>2</sub>=), 66.5 (CH<sub>2</sub> morph.), 60.8 (-O-CH<sub>2</sub>CH<sub>3</sub>), 47.8 (C), 44.3, 29.4 and 17.8 [-(CH<sub>2</sub>)<sub>3</sub>-], 24.4 (-CH<sub>2</sub>-C=), 23.6 (CH<sub>3</sub>-C=), 13.8 (-OCH<sub>2</sub>CH<sub>3</sub>). MS (*m/z*): 321 (20), 278 (19), 248 (61), 161 (100). Anal. Calcd for C<sub>18</sub>H<sub>27</sub>NO<sub>4</sub> (321.42): C, 67.26; H, 8.47; N, 4.36. Found: C, 67.28; H, 8.48; N, 4.38.

**Ethyl 2-(3-methyl-2-(morpholinomethyl)but-2-enoyl)-1-(2-methylallyl)cyclohex-2-ene-1-carboxylate 7.** Yield: see Tables in the text; yellowish oil. IR  $\nu_{C=O}$  1724, 1716  $\nu_{C=C}$  1624 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  = 7.48 (t, *J* = 3 Hz, 1H, =CH), 4.67 and 4.63 (s, 1H+1H, =CH<sub>2</sub>), 4.10 (q, *J* 7 Hz, 2H, -OCH<sub>2</sub>CH<sub>3</sub>), 3.62 (bs, 4H, CH<sub>2</sub>-O morph.), 3.70 and 3.45 (AB syst., 2H, CH<sub>2</sub>-morph.), 2.90 and 2.68 (AB syst., *J* 12 Hz, 2H, -CH<sub>2</sub>-C=), 2.40 (bs, 4H, CH<sub>2</sub>-N morph.), 2.30 and 1.70 (m, 6H, -(CH<sub>2</sub>)<sub>3</sub>-), 1.70 (s, 9H, =C-CH<sub>3</sub>), 1.20 (t, *J* 7 Hz, 3H, -OCH<sub>2</sub>CH<sub>3</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  = 203.2 and 200.9 (C=O), 143.4, 137.2, 133.9 and 127.1 (C=), 149.2 (CH=), 114.9 (CH<sub>2</sub>=), 66.8 (CH<sub>2</sub>-O morph.), 60.5 (-O-CH<sub>2</sub>CH<sub>3</sub>), 57.1 (CH<sub>2</sub>-morph.), 53.1 (CH<sub>2</sub>-N morph.), 46.0 (C), 43.4, 32.8 and 17.9 [-(CH<sub>2</sub>)<sub>3</sub>-], 26.1 (-CH<sub>2</sub>-C=), 24.6, 22.1 and 21.0 (CH<sub>3</sub>-C=), 14.0 (-OCH<sub>2</sub>CH<sub>3</sub>). MS (*m/z*): 389 (3), 374 (17), 335 (100). Anal. Calcd for C<sub>23</sub>H<sub>35</sub>NO<sub>4</sub> (389.54): C, 70.92; H, 9.06; N, 3.60. Found: C, 70.90; H, 9.10; N, 3.58.

**Ethyl 2-methyl-2-(4-methyl-3-methylene-2-oxopent-4-en-1-yl)-1-oxo-1,2,3,4,5,6-hexahydro-3aH-indene-3a-carboxylate 8.** Yield: see Tables in the text; yellowish oil. IR  $\nu_{C=O}$  1727, 1714  $\nu_{C=C}$  1620 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  = 6.89 (t, *J* 3 Hz, 1H, =CH), 5.60 and 5.55 (s, 1H+1H, =CH<sub>2</sub>), 5.03 (d, *J* 6 Hz, 2H, CH<sub>2</sub>=C-Me), 4.16 (q, *J* 7 Hz, 2H, -OCH<sub>2</sub>CH<sub>3</sub>), 3.03 (d, *J* 6 Hz, 2H, CH<sub>2</sub>-C=O), 2.50 and 2.00 (AB syst., *J* 12 Hz, 2H, CH<sub>2</sub>), 2.40 and 1.30 (m, 6H, -(CH<sub>2</sub>)<sub>3</sub>-), 1.86 (s, 3H, CH<sub>3</sub>), 1.25 (t, *J* 7 Hz, 3H, -OCH<sub>2</sub>CH<sub>3</sub>), 1.05 (s, 3H, CH<sub>3</sub>). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  = 206.8, 203.0 and 176.5 (C=O), 150.9, 140.1 and 138.8 (C=), 135.7 (CH=), 119.2 and 116.8 (CH<sub>2</sub>=), 61.1 (-O-CH<sub>2</sub>CH<sub>3</sub>), 49.1 (CH<sub>2</sub>-C=O), 48.0 and 45.3 (C), 44.4 (-C-CH<sub>2</sub>-C-), 33.9, 24.9 and 18.9 [-(CH<sub>2</sub>)<sub>3</sub>-], 23.9 (CH<sub>3</sub>-C), 22.2 (CH<sub>3</sub>-C=), 14.1 (-OCH<sub>2</sub>CH<sub>3</sub>). MS (*m/z*): 330 (44), 257 (21), 180 (77), 152 (100). Anal. Calcd for C<sub>20</sub>H<sub>26</sub>O<sub>4</sub> (330.42): C, 72.70; H, 7.93. Found: C, 72.69; H, 8.00.

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