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# Studies on Palladium-Catalyzed [3+2]-Annulation/Domino Reactions

Yang Liu

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## Thèse de doctorat de Sorbonne Université

Spécialité : **Chimie Organique**

École Doctorale de Chimie Moléculaire de Paris Centre – ED406

*Institut Parisien de Chimie Moléculaire / Équipe ROCS*

### Studies on Palladium-Catalyzed [3+2]-Annulation/Domino Reactions

Présentée par

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Pour obtenir le grade de

**Docteur de Sorbonne Université**

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## Abbreviations

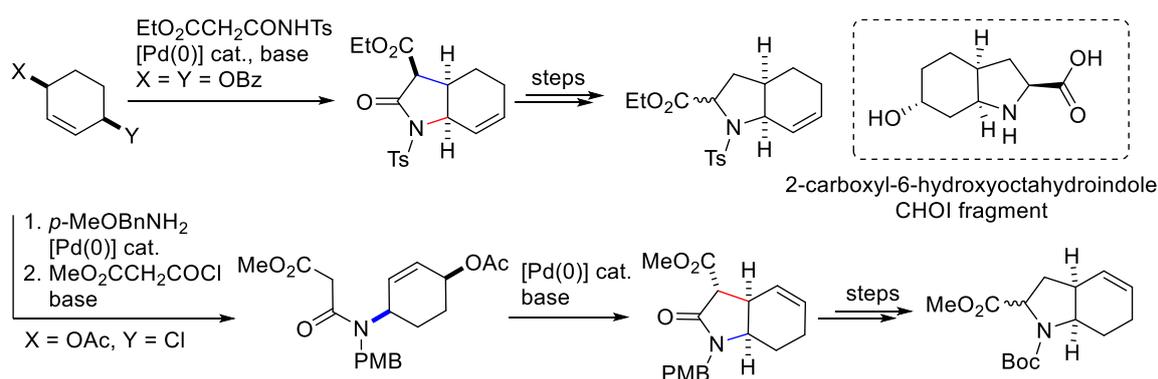
Ac	Acetyl
aq	Aqueous
Ar	Aryl
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene
BINAPO	2,2'-Bis(diphenylphosphinoxy)-1,1'-binaphthalene
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
Boc	<i>Tert</i> -butyloxy carbonyl
BQ	1,4-Benzoquinone
BSA	Bis(trimethylsilyl)acetamide
Bz	Benzoyl
cat	Catalytic or Catalyst
CBz	Carboxybenzyl
Cy	Cyclohexyl
d	Day
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	<i>N,N'</i> -Dicyclohexylcarbodiimide
DCE	Dichloroethane
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano- <i>p</i> -benzoquinone
DMA	<i>N,N</i> -Dimethylacetamide
DMAP	4-(Dimethylamino)pyridine
DMBQ	2,6-Dimethylbenzoquinone
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DPEPhos	Bis[(2-diphenylphosphino)phenyl]ether
dppb	1,4-Bis(diphenylphosphino)butane
dppe	1,4-Bis(diphenylphosphino)ethane
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dppp	1,3-Bis(diphenylphosphino)propane
dr	Diastereomeric ratio
dtbpf	1,1'-Bis(di- <i>tert</i> -butylphosphino)ferrocene
dtpf	1,1'-bis(di- <i>o</i> -tolylphosphino)ferrocene
ee	Enantiomeric excess
Et	Ethyl
EtOAc	Ethyl acetate
EWG	Electron Withdrawing Group
h	Hour

HRMS	High Resolution Mass Spectrometry
<i>i</i> -Pr	<i>iso</i> -Propyl
IR	Infra-Red
JohnPhos	(2-Biphenyl)di- <i>tert</i> -butylphosphine
KHMDS	Potassium bis(trimethylsilyl)amide
LDA	Lithium diisopropylamide
LG	Leaving Group
<i>m</i> -CPBA	3-Chloroperbenzoic acid
Me	Methyl
MePhos	2-Dicyclohexylphosphino-2'-methylbiphenyl
min	Minute
MP	Melting point
Ms	Methanesulfonyl
MW	Microwave
NHC	<i>N</i> -Heterocyclic carbene
NMP	1-Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
Ns	4-Nitrobenzenesulfonyl
Nu	Nucleophile
Oct	Octane
PCC	Pyridinium chlorochromate
Ph	Phenyl
PhBQ	Phenyl- <i>p</i> -benzoquinone
PMB	<i>para</i> -Methoxybenzyl
rt	Room temperature
Salen	<i>N,N'</i> -Bis(salicylidene)ethylenediamine
TBAF	<i>tetra</i> -Butylammonium fluoride
<i>t</i> -Bu	<i>tert</i> -Butyl
TBS	<i>tert</i> -Butyldimethylsilyl
TBSOTf	<i>tert</i> -Butyldimethylsilyl trifluoromethanesulfonate
Tf	Triflyl
TFA	Trifluoroacetic acid
TFP	Tri-2-furanylphosphine
THF	Tetrahydrofuran
TMSCl	Trimethylsilyl chloride
Tol	Toluene
Ts	Toluenesulfonyl
TsOH	<i>para</i> -Toluenesulfonic acid
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

## General introduction

Heteroatom-containing polycyclic structures are molecules of utmost importance that can be found in Nature as well as in Man-made molecules such as ligands for transition-metal catalysis or organocatalysts. Consequently, the search for selective and atom- as well as step-economical ways of synthesizing complex heterocycles is a topic of continuous interest in chemistry. The ability to sequence several bond-forming reactions in a single synthetic operation provides elegance, efficiency and simplicity to organic synthesis, allowing to build up highly functionalized molecules in a minimum amount of steps. In particular, Pd-catalyzed annulation reactions represent a central strategy for the synthesis of heterocycles. However, despite all the reported works, the knowledge of Pd-catalyzed carbo- and hetero-annulations is still far from mature and more work on this topic is desirable.

The ROCS team has been working on palladium catalysis and domino chemistry for many years.<sup>[1]</sup> Specifically, two years ago, they reported the Pd-catalyzed synthesis of analogues of the 2-carboxyl-6-hydroxyoctahydroindole (CHOI) unit from diverging Pd-catalyzed allylations, starting from bis-allylic cyclohexene derivatives (Scheme 1).<sup>[2]</sup>



Scheme 1. Previous studies on [3+2]-C-C/N-C bond-forming annulations in the team.

As a logical continuation of this work, we decided to extend the study of Pd-catalyzed [3+2]-C-C/N-C bond-forming annulations from bis-allylic cyclohexene derivatives to cyclic  $\alpha,\beta$ -unsaturated- $\gamma$ -oxycarbonyls as bis-electrophiles. This new strategy would imply a first stereoselective Pd-catalyzed intermolecular allylation of a resonance stabilized amide, followed by an aza-Michael addition (Scheme 2, top). Of course, such a planned annulation process may be possible only if the intermolecular Pd-catalyzed allylic alkylation at the electrophilic  $\gamma$ -position of the cyclic carbonyl derivative precedes the intramolecular aza-Michael

<sup>1</sup> For a few examples, see: a) Poli, G.; Giambastiani, G. *J. Org. Chem.* **2002**, *67*, 9456-9459. b) Lorion, M. M.; Gasperini, D.; Oble, J.; Poli, G. *Org. Lett.* **2013**, *15*, 3050-3053. For reviews, see: c) Liron, F.; Oble, J.; Lorion, M. M.; Poli, G. *Eur. J. Org. Chem.* **2014**, 5863-5883. d) Kammerer, C.; Prestat, G.; Madec, D.; Poli, G. *Acc. Chem. Res.* **2014**, *47*, 3439-3447. e) Lorion, M. M.; Oble, J.; Poli, G. *Pure Appl. Chem.* **2016**, *88*, 381-389.

<sup>2</sup> Mao, Z.-Y.; Martini, E.; Prestat, G.; Oble, J.; Huang, P.-Q.; Poli, G. *Tetrahedron Lett.* **2017**, *58*, 4174-4178.

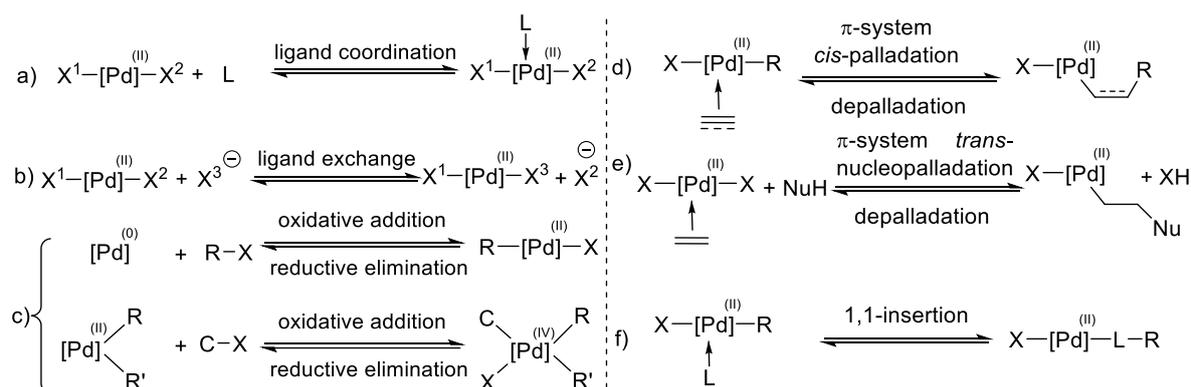


# Chapter 1: Pd-Chemistry and Annulation Reactions

Annulation reactions are among the most important transformations in organic synthesis.<sup>[3]</sup> However, only few of the reported methods are of general scope. In particular, palladium catalysis offers a convenient and versatile way to obtain a wide range of carbo- and hetero-cycles via annulations. This chapter will first give a brief introduction on palladium catalysis. Then, I will try to present the state of the art of Pd-catalyzed annulations through some selected examples. Due to the huge amount of literature existing on this subject, I will mainly focus on three strategies: a) annulations involving bis-nucleophile-bearing vinyl/aryl halides, b) annulations involving bis-nucleophiles and allylic systems, and c) annulations involving zwitterionic trimethylenemethane-palladium complex and cyclopropanes.

## 1. Palladium-catalysis

The construction of complex molecular structures in a facile and efficient method remains an overarching goal of the chemical sciences. Cascade (or domino) reactions allow improved atom and step economy in organic synthesis and therefore represent significant progress toward this goal.<sup>[4]</sup> Palladium is a transition metal of the nickel triad, located in the second row of the periodic table. Except rare exceptions, palladium complexes exist in the three oxidation states: Pd(0), Pd(II), Pd(IV), each oxidation state exhibiting different chemical properties. The main elementary steps involving palladium complexes are: a) dative ligand coordination, b) ligand exchange, c) oxidative addition / reductive elimination [Pd(0)/Pd(II) or Pd(II)/Pd(IV)], d)  $\pi$ -system (alkene/alkyne) *cis*-palladation (migratory insertion), e)  $\pi$ -system *trans*-nucleopalladation and f) dative ligand 1,1-insertion (Scheme 3).<sup>[5]</sup>



Scheme 3. Main elementary steps involved in Pd-catalyzed reactions.

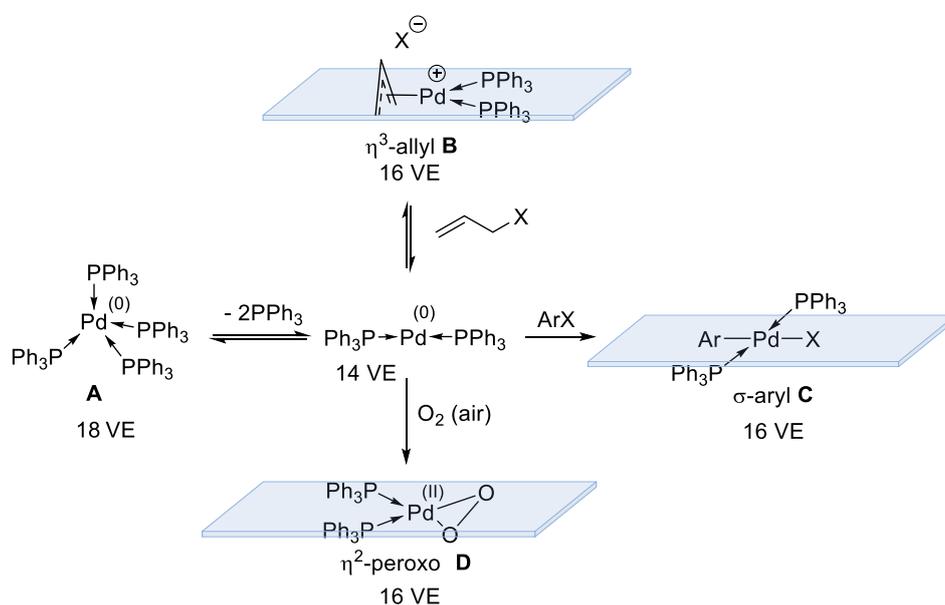
<sup>3</sup> Bering, L.; Manna, S.; Antonchick, A. P. *Chem. Eur. J.* **2017**, *23*, 10936-10946.

<sup>4</sup> a) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 7134-7186. b) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, *38*, 3010-3021.

<sup>5</sup> Throughout the manuscript: a) brackets around palladium atom intend to render implicit the dative ligand(s); b) R: covalent carbon-based ligand, X: covalent heteroatom-based ligand, L: dative ligand.

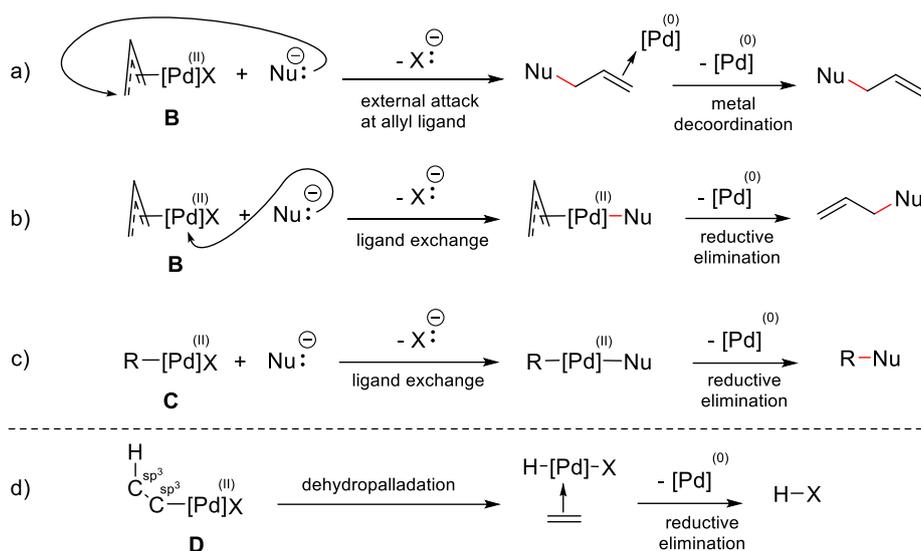
As a function of the nature of the ligands and reagents involved, the equilibria of these reactions may be more or less displaced to the left or right side, reversible or irreversible. All the Pd-catalyzed reactions feature a combination of the above elementary steps. The starting elementary step of the catalytic cycle can be the oxidative addition, the ligand coordination, or the ligand exchange, while the closing elementary step may be the reductive elimination or the depalladation step (usually dehydropalladation).

Thus, for example, phosphine- or NHC-ligated Pd(0) complexes are  $d^{10}$  electron-rich, nucleophilic species and can oxidatively add to electrophilic partners to give square planar Pd(II) 16 valence-electron (VE) complexes. This is for example the case of: a) allylic derivatives, which form  $\eta^3$ -allylpalladium(II) complexes **B**; b) aryl halides (or pseudo-halides), which form  $\sigma$ -arylpalladium(II) halides **C**; and c) molecular oxygen, which forms the  $\eta^2$ -peroxopalladium(II) complex **D** (Scheme 4).



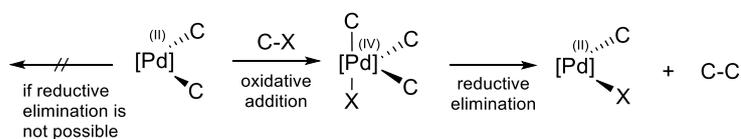
Scheme 4. Oxidative addition of Pd(0) complexes.

The  $\eta^3$ -allylpalladium(II) complexes **B** and the  $\sigma$ -arylpalladium(II) halides **C** are important electrophilic intermediates in organic chemistry. The former ones, reversibly formed by oxidative addition of Pd(0) complexes and allylic systems (see above), as a function of the nature of the nucleophile, can suffer two types of allylic substitution: a) exterior attack of the nucleophile at the allylic ligand, anti to the Pd atom (*alias* anti-reductive elimination) (observed with soft nucleophiles); or b) ligand displacement at Pd atom, followed by *syn*-reductive elimination (observed with hard nucleophiles).  $\sigma$ -Arylpalladium(II) halides **C**, usually irreversibly formed by oxidative addition of Pd(0) to aryl halides or pseudo-halides (see above), also suffer ligand substitution on palladium followed by reductive elimination. On the other hand,  $C(sp^3)$  organopalladium complexes bearing a  $\beta$ -H atom, tend to undergo a very easy dehydropalladation (Scheme 5).



Scheme 5. Evolution of organopalladium(II) complexes with nucleophiles.

Pd(IV) complexes are quite rare, although a few complexes are known. These complexes have hardly been isolated, but transient Pd(IV) species are increasingly considered as intermediates in palladium-catalyzed reactions (Scheme 6).



Scheme 6. Evolution of transiently formed Pd(IV) complexes.

Palladium-catalyzed couplings have proven to be powerful and key reactions for the synthesis of a great number of targets, including carbo- and heterocycles.<sup>[6]</sup> In the following sections, I will review a selection of published works dedicated to Pd-catalyzed annulations.

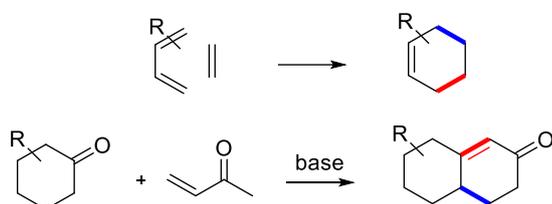
<sup>6</sup> a) Bolm, C. J. *Org. Chem.* **2012**, *77*, 5221-5223. b) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley: New York, **2002**. c) *Cross-Coupling Reactions. A Practical Guide*; Miyaura, N., Ed. *Top. Curr. Chem.* **2002**, *219*. d) *Metal-Catalyzed Cross-Coupling Reactions, 2nd ed.*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, **2004**. e) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4442-4489. f) Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651-2710. g) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417-1492. h) van Leeuwen, P. W. N. M. and Chadwick, J. C. **2011**, *Metal-Catalyzed Cross-Coupling Reactions* (chapt 9), in *Homogeneous Catalysts: Activity - Stability - Deactivation*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany. i) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem. Int. Ed.* **2012**, *51*, 5062-5085. k) *Chemical Society Reviews*, themed collection: *Cross coupling reactions in organic synthesis*, **2011**, Issue 10, 4877-5208. l) Colacot, T. (Ed.) *New Trends in Cross-Coupling: Theory and Applications* **2015**, RSC press. m) Tsuji, J. *Palladium Reagents and Catalysts*, J. Wiley and Sons, **2004**. n) Tsuji, J. Ed. *Palladium in Organic Synthesis*, Springer, **2005**.

## 2. Annulation reactions

### 2.1 Pioneering works

Out of the more than nine million organic compounds present on earth, many of them are, or incorporate, cyclic structures, and some of them are of relevance for steric or electronic properties, biological or pharmacological activity. Furthermore, occurrence of ring compounds in Nature is very high. For this reason, methods for the selective generation of cyclic structures are of utmost importance in organic chemistry and the development of new ones is more than justified.

In this context, annulation reactions are the most efficient methods for the generation of cyclic molecules. Pioneered by O. Diels and K. Alder,<sup>[7,8]</sup> and Sir R. Robinson,<sup>[9]</sup> (Scheme 7) allow building up a cyclic structure through the concerted or stepwise creation of two new bonds from two separated components.



Scheme 7. Pioneering annulation reactions.

A brief history of the definition of the annulation reaction is given here below. In 1973, B. P. Mundy<sup>[10]</sup> wrote a review on this type of reaction, naming it “annelation”. Three years later, M. E. Jung wrote another essay, changing the term from annelation to annulation (from the Latin word *annulatus* (ringed)).<sup>[11]</sup> In 1982, R. L. Danheiser proposed to define annulations as *ring-forming processes in which two molecular fragments are joined with the formation of two new bonds*,<sup>[12]</sup> and this same definition was later followed by D. P. Curran *et al.*<sup>[13]</sup> as well as by the International Union of Pure and Applied Chemistry (IUPAC).<sup>[14]</sup> In 1998, G. A. Molander<sup>[15]</sup> perfected the definition, stating that from the mechanistic viewpoint, the created bonds may be the result of a concerted process, or of two sequential elementary steps, as long as regiochemistry and stereochemistry can be controlled. In this latter case, the first elementary step is bimolecular, while the

<sup>7</sup> Diels, O.; Alder, K. *Liebigs Ann. Chem.* **1928**, *460*, 98-122.

<sup>8</sup> The Diels-Alder reaction is also a pericyclic reaction. Pericyclic reactions are transformations featuring an aromatic transition state and involving a rearrangement between  $\sigma$  and  $\pi$  bonds.

<sup>9</sup> Rapson, W. S.; Robinson, R. *J. Chem. Soc.* **1935**, 1285-1288. Sir Robert Robinson, Nobel Laureate in 1947.

<sup>10</sup> Mundy, B. P. *J. Chem. Ed.* **1973**, *50*, 110.

<sup>11</sup> Jung, M. E. *Tetrahedron* **1976**, *32*, 3-31.

<sup>12</sup> Danheiser, R. L. *J. Am. Chem. Soc.* **1982**, *104*, 7670-7672.

<sup>13</sup> Curran, D. P.; Chen, M.-H.; Spletzer, E.; Seong, C. M.; Chang, C.-T. *J. Am. Chem. Soc.* **1989**, *111*, 8872-8878.

<sup>14</sup> a) Muller, P. *Pure Appl. Chem.* **1994**, *66*, 1107-1184; b) IUPAC. Compendium of Chemical Terminology, 2nd ed. (the "Gold Book"). DOI: <https://doi.org/10.1351/goldbook.A00367>.

<sup>15</sup> Molander, G. A. *Acc. Chem. Rec.* **1998**, *31*, 603-609.

second one is unimolecular.

Many other annulation methods have been reported since, and this type of reaction constitutes a superior method to build-up cyclic structures from simpler components.<sup>[16]</sup>

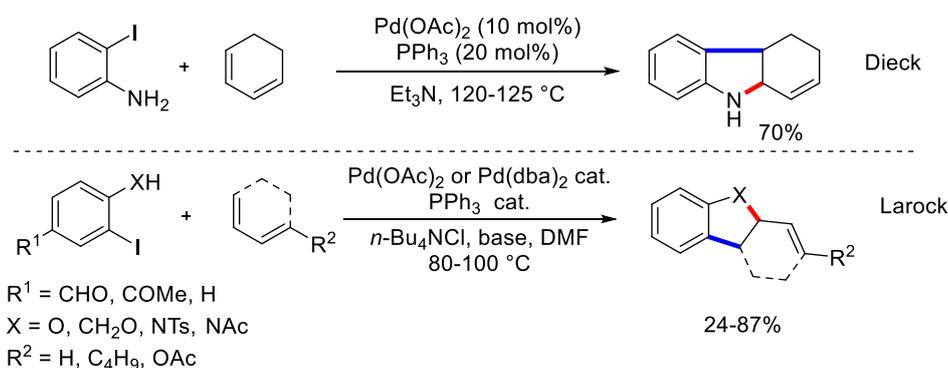
## 2.2 Annulation reactions involving Pd-chemistry

### 2.2.1 Bis-nucleophile-bearing vinyl/aryl halides<sup>[17]</sup>

The palladium-catalyzed annulation between vinyl/aryl halides and  $\pi$ -systems as electrophiles, such as dienes, alkynes, alkenes, and arenes provides a very valuable route to a wide variety of heterocycles, which will be discussed in the following sections. It is worth noting that R. C. Larock made an undeniable contribution to the development of this chemistry.

#### 1,3-Dienes as electrophiles

In 1983, H. A. Dieck reported the Pd-catalyzed annulation between 2-iodoaniline and 1,3-cyclohexadiene to give the corresponding tetrahydrocarbazole (Scheme 8, top).<sup>[18]</sup> This pioneering study was later pursued by R. C. Larock, who, from 1990 on, reported the heteroannulation between a wide range of cyclic and acyclic 1,3-dienes and appropriately functionalized 2-iodophenols or 2-iodoanilines (Scheme 8, bottom).<sup>[19]</sup> This strategy was applied some years latter for the synthesis of a variety of biologically interesting compounds such as dihydrofurocoumarins.



Scheme 8. Palladium-catalyzed annulations between nucleophile-bearing aryl halides and 1,3-dienes.

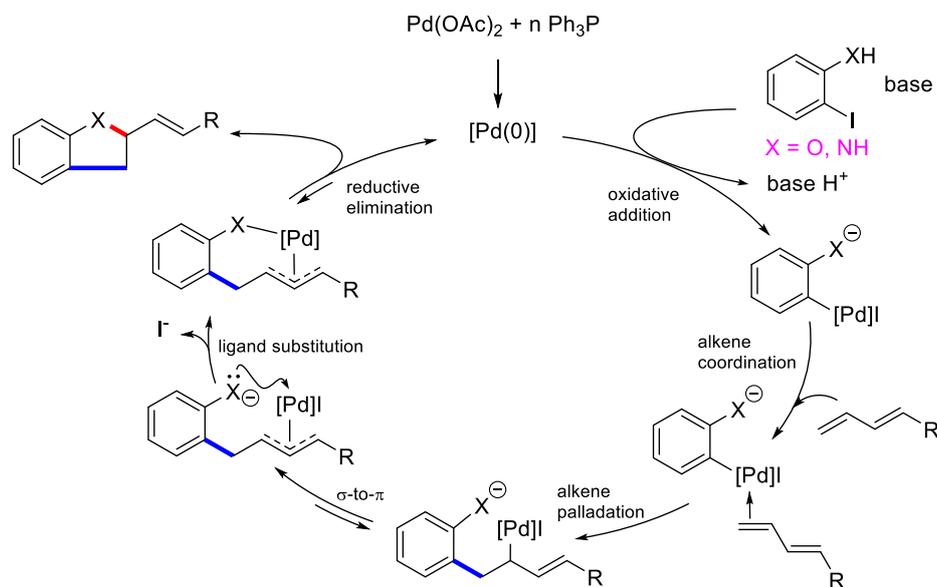
<sup>16</sup> See for example: Gallier, F.; Martel, A. Dujardin, G. *Angew. Chem. Int. Ed.* **2017**, *56*, 12424-12458.

<sup>17</sup> For palladium-catalyzed annulation review, see: a) Larock, R. C. *J. Organomet. Chem.* **1999**, *576*, 111-124. b) Zeni, G.; Larock, R. C.; *Chem. Rev.* **2006**, *106*, 4644-4680.

<sup>18</sup> O'Connor, J. M.; Stallman, B. J.; Clark, W. G.; Shu, A. Y. L.; Spada, R. E.; Stevenson, T. M.; Dieck, H. A. *J. Org. Chem.* **1983**, *48*, 807-809.

<sup>19</sup> a) Larock, R. C.; Peña, N. B.; Narayanan, K. *J. Org. Chem.* **1990**, *55*, 3447-3450. b) Larock, R. C.; Guo, L. *Synlett* **1995**, 465-466. c) Rozhkov, R. V.; Larock, R. C. *Org. Lett.* **2003**, *5*, 797-800. d) Rozhkov, R. V.; Larock, R. C. *J. Org. Chem.* **2010**, *75*, 4131-4134.

This annulation is expected to proceed as follows (Scheme 9). First, Pd(OAc)<sub>2</sub> is reduced *in-situ* to an underligated Pd(0) species by the phosphine.<sup>[20]</sup> Oxidative addition of Pd(0) to the aryl halide generates the corresponding  $\sigma$ -arylpalladium complex. Alkene coordination followed by regioselective arylpalladation of the terminal alkene initially produces an  $\sigma$ -allylpalladium complex, which rapidly rearranges to the more stable  $\eta^3$ -allylpalladium intermediate. Following intramolecular attack at Pd by the nucleophile, followed by reductive elimination forms the product and regenerates the Pd(0) starting catalyst.<sup>[21]</sup>



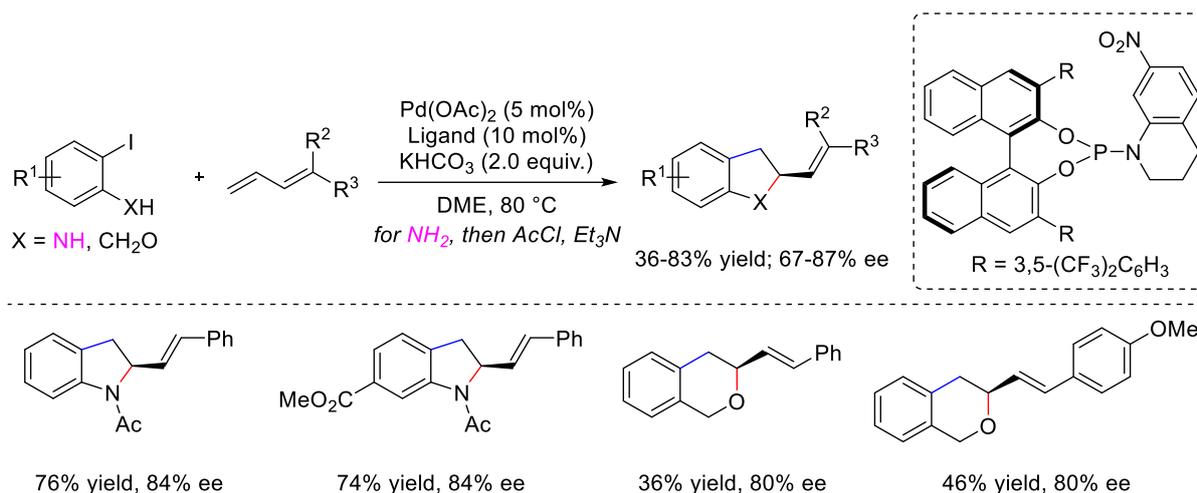
Scheme 9. Mechanism of the Pd-catalyzed annulation between 2-iodoanilines or 2-iodophenols and 1,3-dienes.

In 2016, the first asymmetric heteroannulation between aryl iodides with 1,3-dienes has been reported by Han and co-workers.<sup>[22]</sup> This strategy provided an efficient way to the construction of enantioenriched indolines and isochromans in the presence of BINOL-derived phosphoramidite ligand bearing electron-withdraw substituents (Scheme 10).

<sup>20</sup> Amatore, C.; Jutand, A.; Khalil, F. *ARKIVOC* **2006**, 38-48.

<sup>21</sup> a) Trost, B. M. *Angew. Chem. Int. Ed.* **1989**, *28*, 1173-1192. b) Frost, C. G.; Howarth, J.; Williams, J. M. J. *Tetrahedron Asymmetry* **1992**, *3*, 1089-1122.

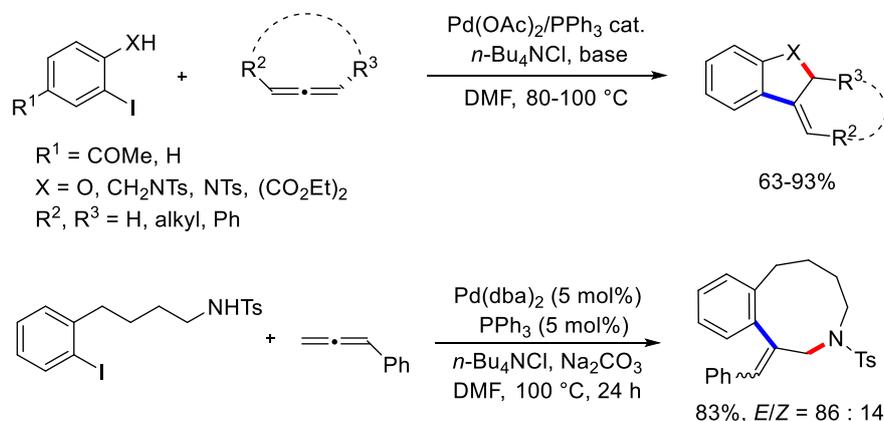
<sup>22</sup> Chen, S.-S.; Meng, J.; Li, Y.-H.; Han, Z.-Y. *J. Org. Chem.* **2016**, *81*, 9402-9408.



Scheme 10. Pd-catalyzed asymmetric heteroannulation between aryl iodides with 1,3-dienes.

### 1,2-Dienes (allenes) as electrophiles

In 1991, the Larock group described related Pd-catalyzed annulations between cyclic and acyclic 1,2-dienes (allenes) and a wide variety of aryl iodides carrying vicinal as well as remote *ortho*-linked pro-nucleophiles such as alcohols, carboxylic acids, amines, phenols, tosylamides, amides and carbon acids, which allowed the formation of seven-, eight- and even nine-membered heterocycles (Scheme 11).<sup>[23]</sup>

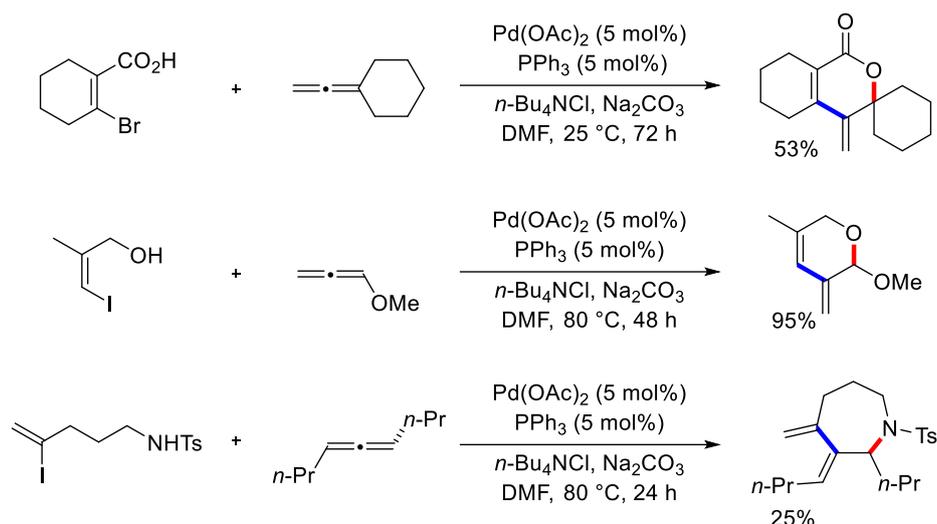


Scheme 11. Palladium-catalyzed annulation between nucleophile-bearing aryl iodides and allenes.

Analogous annulations could be carried out by the Larock group by reacting allenes with vinyl halides (Scheme 12).<sup>[24]</sup>

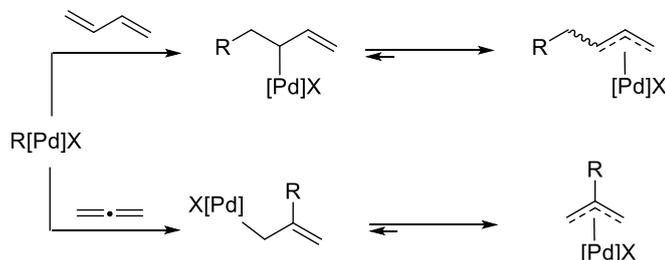
<sup>23</sup> a) Larock, R. C.; Peña, N. G. B.; Fried, C. A. *J. Org. Chem.* **1991**, *56*, 2615-2617. b) Larock, R. C.; Tu, C.; Pace, P. *J. Org. Chem.* **1998**, *63*, 6859-6866.

<sup>24</sup> Larock, R. C.; He, Y.; Leong, W. W.; Han, X.; Refvik, M. D.; Zenner, J. *J. Org. Chem.* **1998**, *63*, 2154-2160.



Scheme 12. Palladium-catalyzed annulation between nucleophile-bearing vinyl halides and allenes.

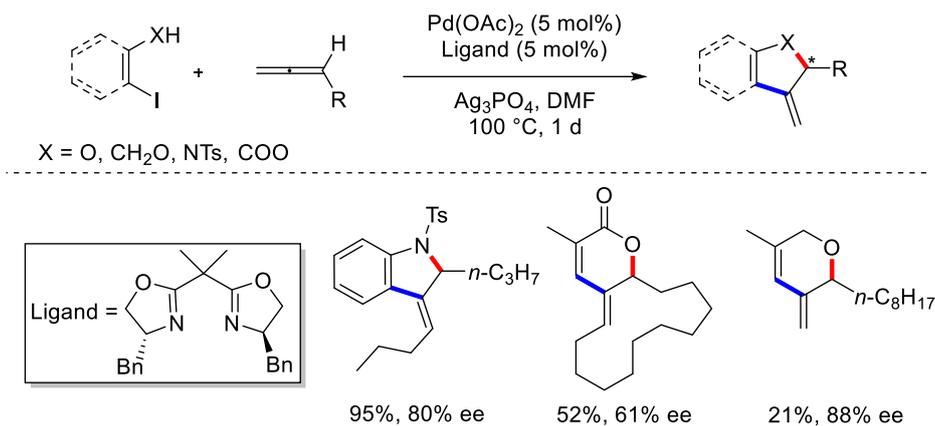
The mechanism of the Pd-catalyzed annulation of allenes is similar to the previously shown mechanism involving 1,3-dienes. In both cases the palladation step generates a  $\eta^3$ -allylpalladium complex, which implies that palladation of allenes leads to a  $\eta^3$ -allylpalladium complex substituted at the central position (Scheme 13).



Scheme 13. Palladation of 1,3- vs 1,2 dienes.

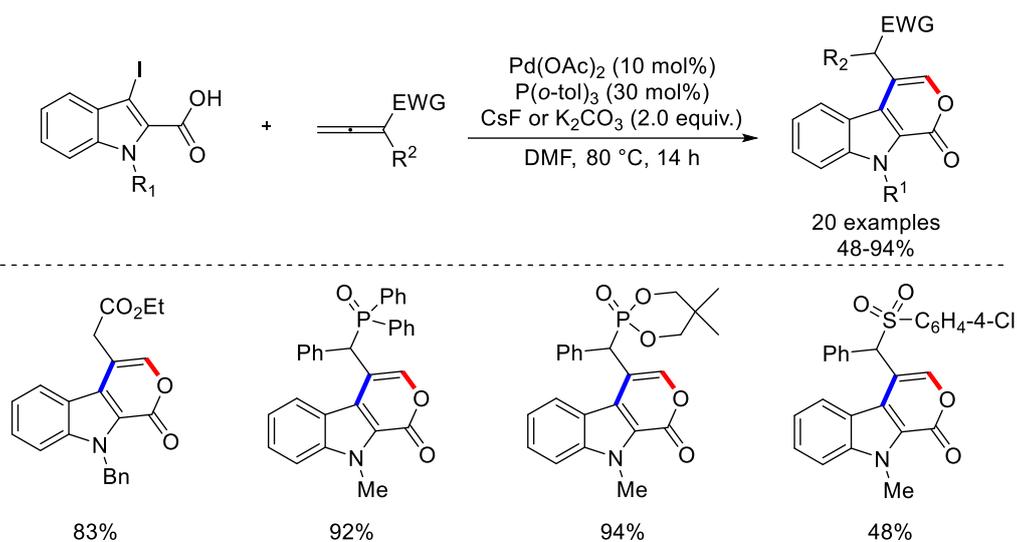
The same group subsequently developed the asymmetric palladium-catalyzed annulation of allenes with nucleophile-bearing aryl and vinylic iodides, accomplished in the presence of a chiral BOX ligand (Scheme 14).<sup>[25]</sup> The generality of this annulation was demonstrated by the use of a wide variety of aryl and vinyl iodides bearing nucleophilic substituents such as alcohols, tosylamides and carboxylic acids.

<sup>25</sup> Zenner, J. M.; Larock, R. C. *J. Org. Chem.* **1999**, *64*, 7312-7322.



*Scheme 14. Enantioselective palladium-catalyzed annulation of allenes.*

Recently, the palladium-catalyzed annulation of allenes with 3-indole-2-carboxylic acid derivatives to produce indolo [2,3-c] pyrane-1-ones was reported by Swamy and co-workers.<sup>[26]</sup> This method was validated by the use of a wide range of allenes (Scheme 15).



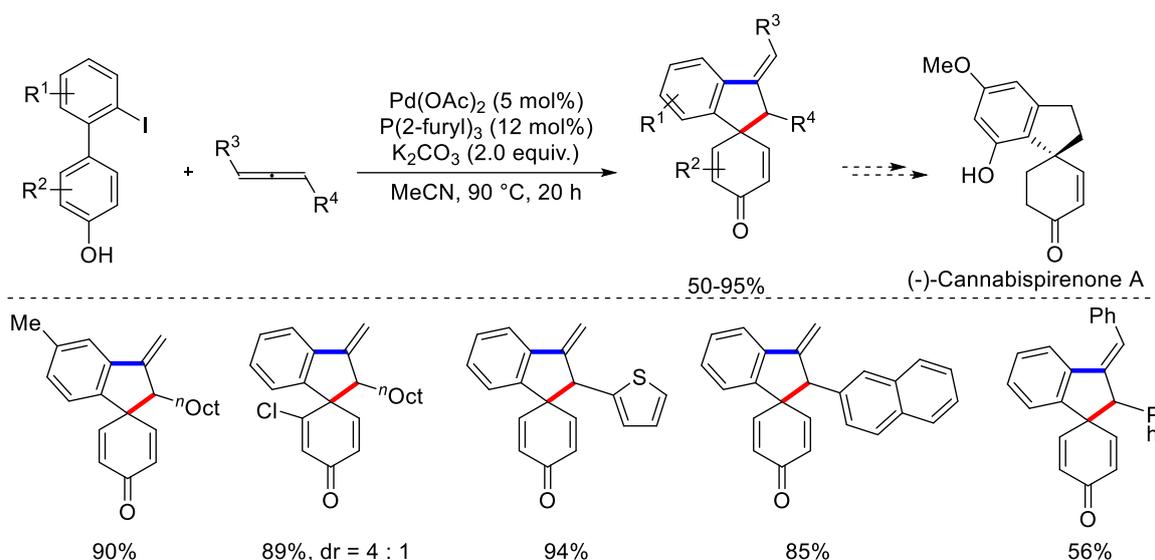
*Scheme 15. Palladium-catalyzed annulation between 3-indole-2-carboxylic acid derivatives and allenes.*

Last year, a novel Pd-catalyzed [3+2] spiroannulation between phenol-based biaryl iodides with allenes was reported by Luan and co-workers.<sup>[27]</sup> This transformation tolerated a range of functional groups and took place with high chemo- and regioselectivity. Moreover, this strategy leads to the straightforward assembly of spiroindene cyclohexadienones, which are found in alkaloids and bioactive compounds such as

<sup>26</sup> Suresh, R. R.; Swamy, K. C. K. *J. Org. Chem.* **2012**, *77*, 6959-6969.

<sup>27</sup> Hu, W.-H.; Wang, H.; Bai, L.; Liu, J.-J.; Luan, X.-J. *Org. Lett.* **2018**, *20*, 880-883.

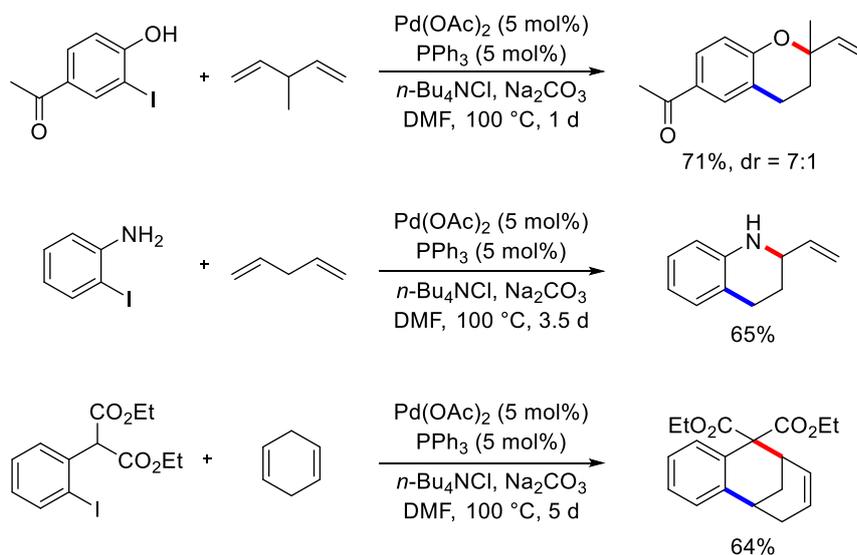
(-)-Cannabispirenone A (Scheme 16).



Scheme 16. Palladium-catalyzed annulation between phenol-based biaryl iodides and allenes.

### 1,4-Dienes as electrophiles

The Larock group reported in 1993 the palladium-catalyzed annulation between 1,4-dienes and a variety of nucleophile-bearing aryl halides.<sup>[28]</sup> The regioselectivity of this annulation reaction was excellent (Scheme 17).



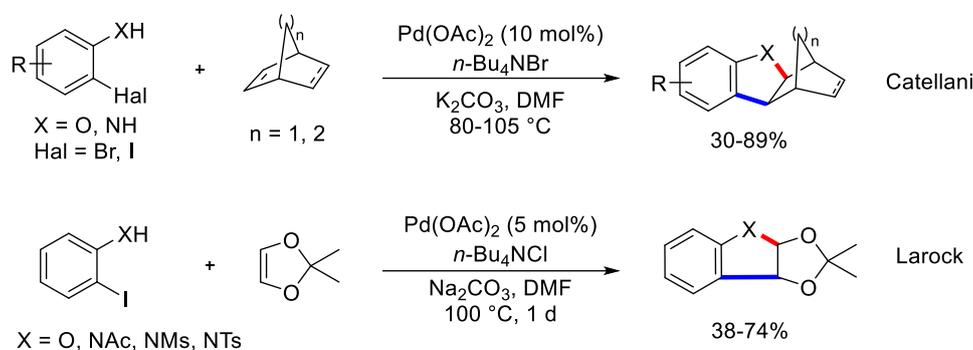
Scheme 17. Palladium-catalyzed annulation of 1,4-dienes.

<sup>28</sup> Larock, R. C.; Peña, N. G. B.; Fried, C. A. Yum, E. K.; Tu, C.; Leong, W. *J. Org. Chem.* **1993**, *58*, 4509-4510.



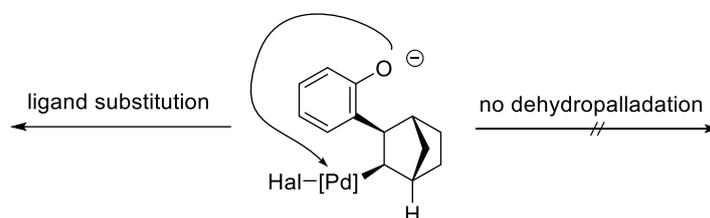
## Cyclic alkenes as electrophiles

In 1998, Catellani and Del Rio described the first Pd-catalyzed annulation between *ortho*-nucleophile-bearing aryl halides and norbornene and norbornadiene, to afford indolines and 2,3-dihydrobenzofurans.<sup>[30]</sup> This method was later revisited and extended by Larock<sup>[31]</sup> in 2004 (Scheme 20).



Scheme 20. Pd-catalyzed annulation of cyclic alkenes with aryl iodides.

It should be noted that this method is expected to be successful only for alkenes unable to undergo dehydropalladation from the alkylpalladium intermediate (that would otherwise give the classical Heck-type product). This is the case of alkenes incorporated into small cycles, or lacking allylic hydrogens (Scheme 21).



Scheme 21. Bias of alkylpalladium complexes derived from conformationally rigid cyclic alkenes.

## Alkynes as electrophiles

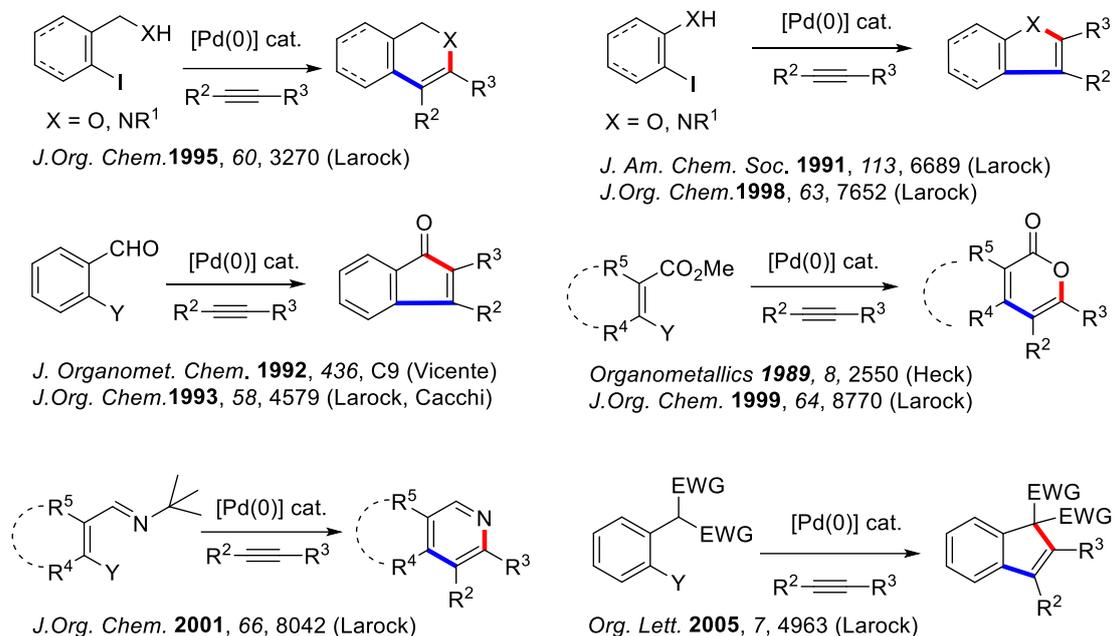
The palladium-catalyzed annulation reaction between alkynes and *ortho*-functionalized aryl or vinyl halides has proven very useful for the synthesis of a number of carbo- and heterocycles, including benzofuran, benzopyran, isocoumarin, isoquinoline, pyridine and indole derivatives (Scheme 22).<sup>[32,33,17]</sup>

<sup>30</sup> Catellani, M.; Del Rio, A. *Izv. Akad. Nauk, Ser. Khim.* **1998**, 957 [*Russ. Chem. Bull.* **1998**, *47*, 928-931. (Engl. Transl.)].

<sup>31</sup> Emrich, D. E.; Larock, R. C. *J. Organomet. Chem.* **2004**, *689*, 3756-3776.

<sup>32</sup> For a review, see : a) *Top Organomet Chem*, **2005**, *14*, 147-182, Larock, R. C. in *Palladium-Catalyzed Annulation of Alkynes*, Springer-Verlag Berlin Heidelberg.

Several *ortho*-located functional groups can be used with this chemistry, such as aldehydes, esters, carboxylic acids, imines, amines and some resonance stabilized acid carbons.

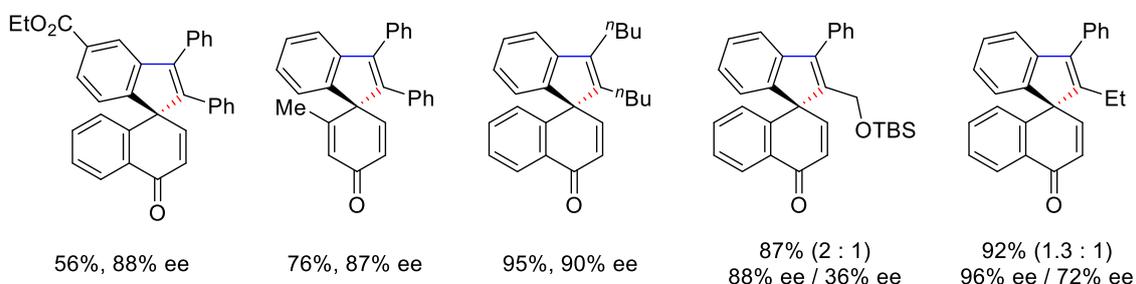
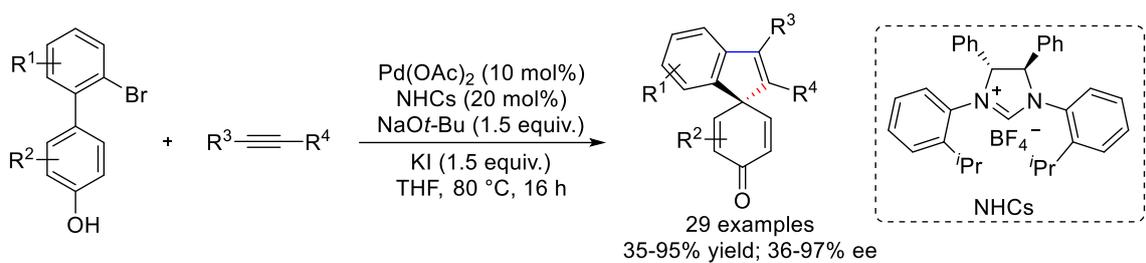


Scheme 22. Pd-catalyzed annulation between alkynes and *ortho*-functionalized aryl halides.

More recently, the group of Luan reported a Pd-catalyzed dynamic kinetic asymmetric annulation between tropos (racemic) biaryl bromides and alkynes in the presence of chiral Pd-NHC complexes to produce a series of enantioenriched spirocyclic (Scheme 23).<sup>[34]</sup>

<sup>33</sup> Selected examples: a) Wensbo, D.; Eriksson, A.; Jeschke, T.; Annby, U.; Gronowitz, S. *Tetrahedron Lett.* **1993**, *34*, 2823-2826. b) Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. K. C. *J. Org. Chem.* **1995**, *60*, 3270-3271. c) Zhang, H.-M.; Larock, R.C. *Org. Lett.* **2001**, *3*, 3083-3086. d) Dai, W.-M.; Lai, K. W. *Tetrahedron Lett.* **2002**, *43*, 9377-9380. e) Shen, M.; Li, G.-S.; Lu, B. Z.; Hossain, A.; Roschangar, F.; Farina, V.; Senanayake, C. H. *Org. Lett.* **2004**, *6*, 4129-4132. f) Pal, R.; Chatterjee, N.; Roy, M.; Nouh, E. S. A.; Sarkar, S.; Jaisankar, P.; Sarkar, S.; Sen, A. K. *Tetrahedron Lett.* **2016**, *57*, 43-47.

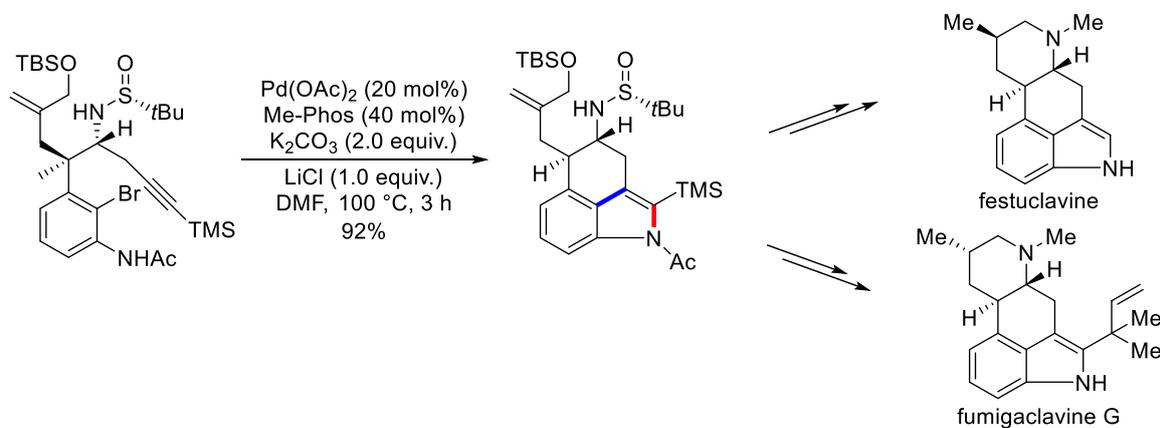
<sup>34</sup> Yang, L.; Zheng, H.-Y.; Luo, L.; Nan, J.; Liu, J.-J.; Wang, Y.-Y.; Luan, X.-J. *J. Am. Chem. Soc.* **2015**, *137*, 4876-4879.



Scheme 23. Pd-catalyzed dynamic kinetic asymmetric annulations between racemic biaryl bromides with alkynes.

This efficient and powerful strategy was applied for the key steps in the synthesis of some alkaloids or natural products.<sup>[35]</sup>

Recently, the Jia group used a Pd-catalyzed Larock indole annulation as the key step for the total synthesis of a range of the ergot alkaloids endowed of a broad spectrum of potent pharmacological activities, such as, festuclavine, pyroclavine, costaclavine, fumigaclavine G (Scheme 24).<sup>[36]</sup>



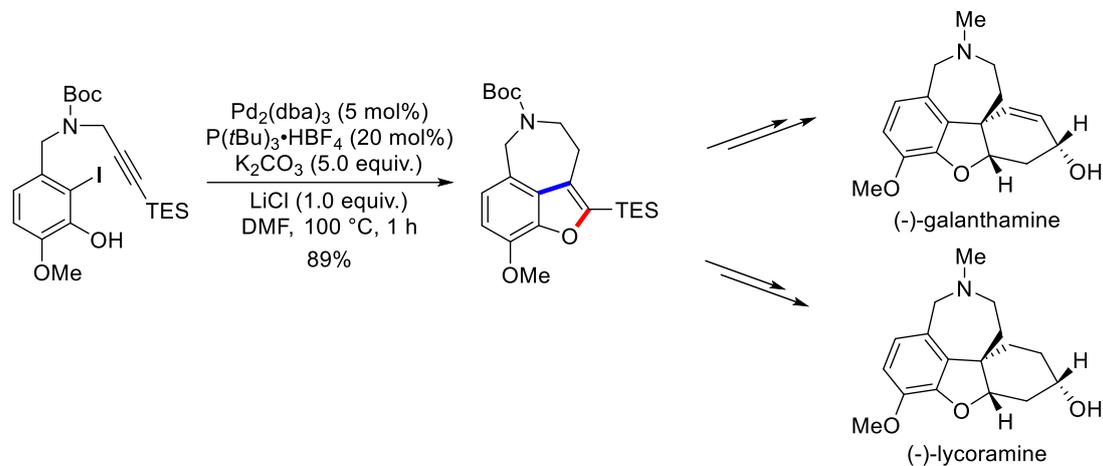
Scheme 24. Synthesis of ergot and alkaloids via Pd-catalyzed intramolecular Larock indole annulation.

Besides, the asymmetric total synthesis of (-)-galanthamine and (-)-lycoramine as the representative

<sup>35</sup> a) Jeffrey, J. L.; Sarpong, R. *Org. Lett.* **2009**, *11*, 5450-5453. b) Ma, J.; Yin, W.-Y.; Liao, X.-B.; Cook, J. M. *J. Org. Chem.* **2009**, *74*, 264-273. c) Wang, C.; Sperry, J.; *Org. Lett.* **2011**, *13*, 6444-6447. d) Jana, G. K.; Sinha, S. *Tetrahedron* **2012**, *68*, 7155-7165. e) Wang, C.; Sperry, J. *Tetrahedron* **2013**, *69*, 4563-4577. f) Li, Q.; Xia, T.-T.; Yao, L.-C.; Deng, H.-T.; Liao, X.-B. *Chem. Sci.* **2015**, *6*, 2599-2605.

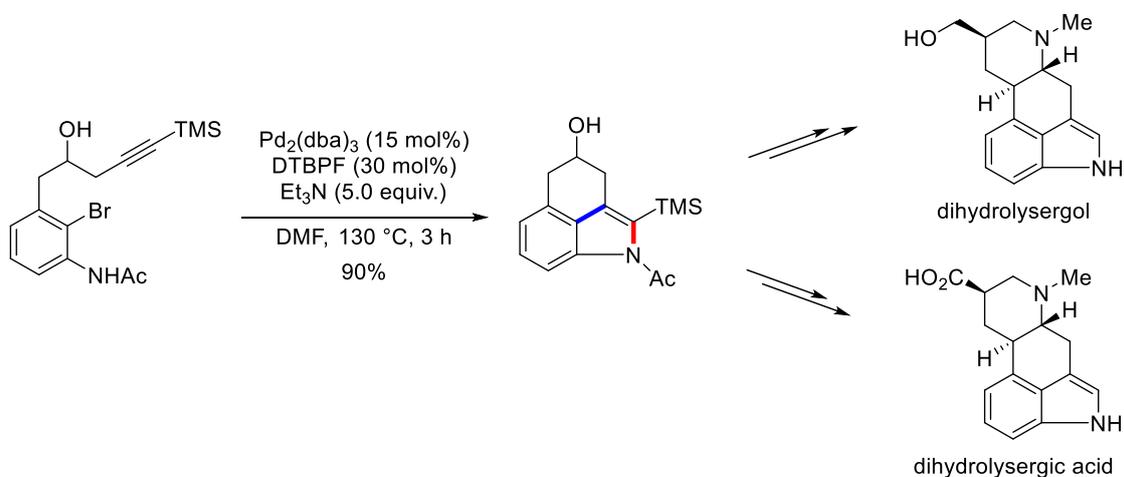
<sup>36</sup> a) Shan, D.; Gao, Y.; Jia, Y.-X. *Angew. Chem. Int. Ed.* **2013**, *52*, 4902-4905. b) Liu, H.-C.; Zhang, X.-W.; Shan, D.; Pitchakuntla, M.; Ma, Y.-F.; Jia, Y.-X. *Org. Lett.* **2017**, *19*, 3323-3326.

member of the Amaryllidaceae alkaloids was also achieved by using this annulation as the key step (Scheme 25).<sup>[37]</sup>



Scheme 25. Synthesis of amaryllidaceae alkaloids via Pd-catalyzed intramolecular Larock indole annulation.

The Boger group exploited this annulation as the key step for the total syntheses of dihydrolysergic acid and dihydrolysergol, which are alkaloids of interest in the treatment of a range of neurological diseases (Scheme 26).<sup>[38]</sup>

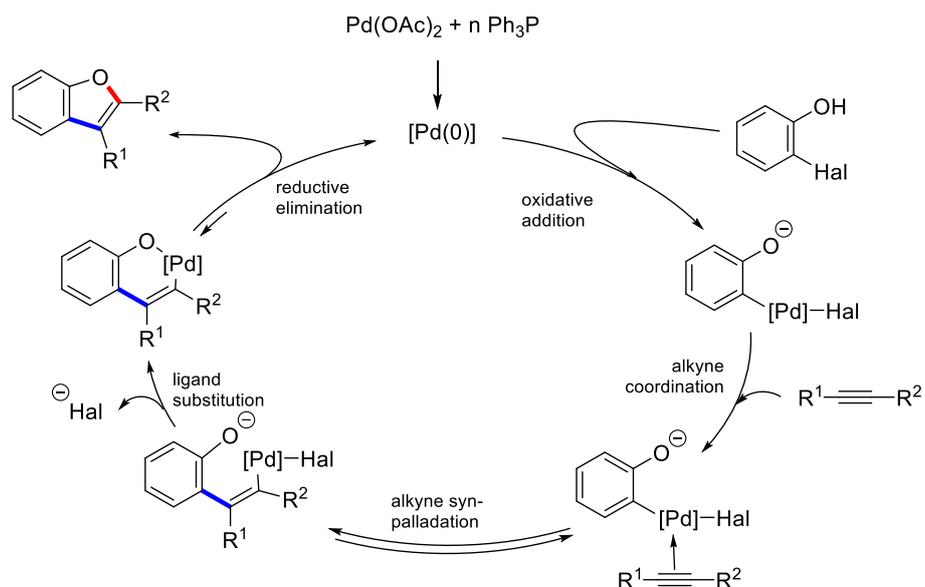


Scheme 26. Synthesis of dihydrolysergic acid and dihydrolysergol via Pd-catalyzed intramolecular Larock indole annulation.

The mechanism of these transformations is analogous to that previously described in the case of alkenes. However, in this case, palladation of the alkyne produces a  $\sigma$ -vinylpalladium intermediate (Scheme 27).

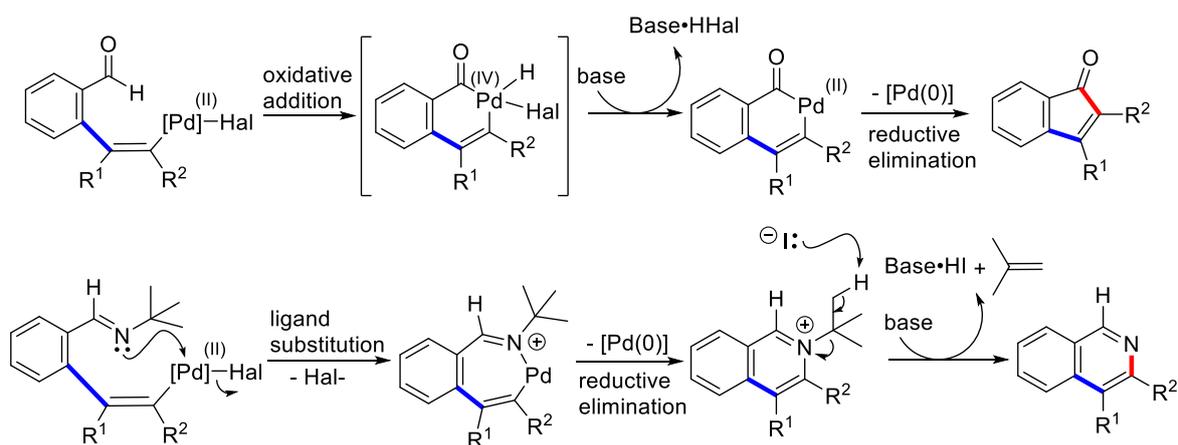
<sup>37</sup> Li, L.; Yang, Q.; Wang, Y.; Jia, Y.-X. *Angew. Chem. Int. Ed.* **2015**, *54*, 6255-6259.

<sup>38</sup> Lee, K.; Poudel, Y. B.; Glinkerman, C. M.; Boger, D. L. *Tetrahedron* **2015**, *71*, 5897-5905.



Scheme 27. Mechanism of the Pd-catalyzed annulation between an *ortho*-halo phenol and an alkyne.

The mechanism of the following cyclization step may depend on the nature of the *ortho*-located functional group. Thus, for example, in the case of an aldehyde, the authors proposed an oxidative addition to afford a Pd(IV) intermediate, which is then deprotonated by the base before undergoing reductive elimination to give the indenone product. In contrast, in the case of a *tert*-butyl imine, an initial ligand substitution is expected to produce an N-Pd-iminium complex, which then undergoes a base promoted elimination of isoprene to afford the final isoquinoline (Scheme 28).

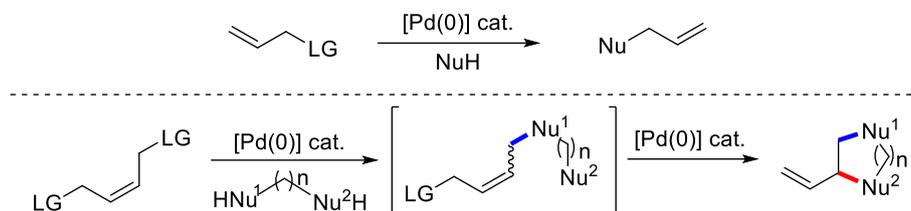


Scheme 28. Evolution of the vinylpalladium intermediate as a function of the aryl *ortho*-substituent.

## 2.2.2 Annulations between bis-nucleophiles and bis-allylic electrophiles

The palladium-catalyzed allylation of nucleophiles (Pd-AA) is one of the most useful transformations

for organic synthesis (Scheme 29, top).<sup>[39]</sup> Indeed, this key reaction has been used by chemists in a great number of syntheses, and developed in a number of variations, including X-C and C-C bond formations, as well as asymmetric variants (Pd-AAA). In particular, when the substrate is a bis-allylic system, its interaction with a bis-nucleophile may allow accomplishing an annulation reaction via a Pd-catalyzed cascade process (Scheme 29, bottom).

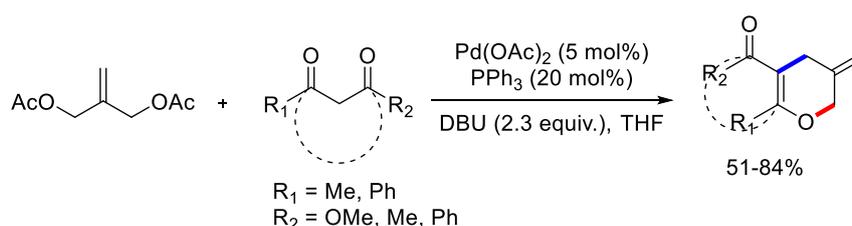


Scheme 29. Top: generic Pd-catalyzed allylation. Bottom: generic Pd-catalyzed cascade allylic alkylation using a bis-allylic system and a bis-nucleophile.

Various combinations of carbon, nitrogen and oxygen bis-nucleophiles have been used for the construction of a variety of vinyl substituted annulated systems. Although this chemistry can in principle lead to a number of regioisomeric products, the use of symmetric electrophiles and/or nucleophiles allowed to avoid of such issue, and to adopt this strategy in total syntheses.<sup>[40]</sup>

#### Acyclic bis-allylic electrophiles<sup>[41]</sup>

In 1987, the Lu group reported the Pd(0)-catalyzed annulation between 2-methylene propan-1,3-diol diacetate and  $\beta$ -diketones or  $\beta$ -ketoesters (Scheme 30),<sup>[42]</sup> which gave dihydropyran derivatives in a one pot reaction.



Scheme 30. Di-allylic alkylation of 2-methylene propan-1,3-diol diacetate with  $\beta$ -diketones or  $\beta$ -ketoesters.

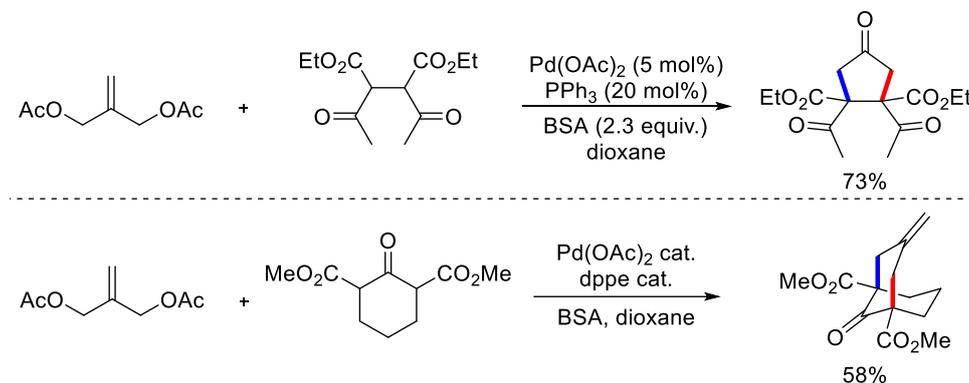
<sup>39</sup> a) Tsuji, J.; Takahashi, H.; Morikawa, M. *Tetrahedron Lett.* **1965**, *6*, 4387-4388. b) For reviews, see: a) Poli, G.; Prestat, G.; Liron, F.; Kammerer-Pentier C.; Kazmaier, U. *Top. Organomet. Chem.* **2012**, *38*, 1-63; b) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385-393. c) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921-2944.

<sup>40</sup> a) **Agelastatin A**: Trost, B. M.; Dong, G.-B. *Chem. Eur. J.* **2009**, *15*, 6910-6919. b) **Huperzine A**: He, X.-C.; Wang, B.; Yu, G.; Bai, D. *Tetrahedron: Asymmetry* **2001**, *12*, 3213-3216.

<sup>41</sup> a) Trost, B. M.; Vercauteren, J. *Tetrahedron Lett.* **1985**, *26*, 131-134. b) Trost, B. M.; Tometzki, G. B.; Hung, M.-H. *J. Am. Chem. Soc.* **1987**, *109*, 2176-2177. c) Shimizu, I.; Ohashi, Y.; Tsuji, J. *Tetrahedron Lett.* **1985**, *26*, 3825-3828. d) Hayashi, T.; Yamamoto, A.; Ito, Y. *Tetrahedron Lett.* **1988**, *29*, 669-672.

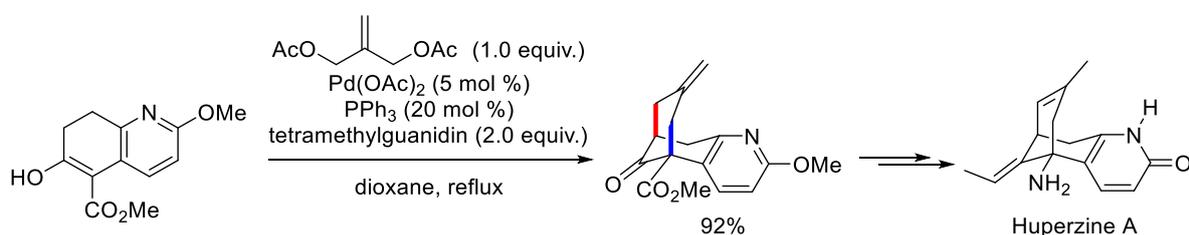
<sup>42</sup> Huang, Y.-J.; Lu, X.-Y. *Tetrahedron Lett.* **1987**, *28*, 6219-6210.

Furthermore, the analogous reaction of this 2-methylene propan-1,3-diol diacetate with various dicarbanionic nucleophiles allowed to generate five- or six-membered rings (Scheme 31).<sup>[43]</sup>



Scheme 31. Di-allylic alkylation of 2-methylene propan-1,3-diol diacetate with dicarbanions.

In 1992, the Sivaramakrishnan group achieved the synthesis of bicyclo[3,3,1]nonanes through a Pd-catalyzed AA between 2-methylene propan-1,3-diol diacetate and a variety of cyclic  $\beta$ -ketoesters.<sup>[44]</sup> This method was used by Kozikowski and Tückmantel in the synthesis of the Chinese nootropic agent Huperzine A and its analogs (Scheme 32).<sup>[45]</sup>



Scheme 32. Synthesis of Chinese Nootropic Agent Huperzine A and its analogs.

Morpholines, piperazines and 1,4-benzodioxanes are heterocyclic structures present in a large number of molecules of biological and/or therapeutic relevance. In 1990, Saegusa reported the palladium-catalyzed annulation reaction between allylic 1,4-diacetates (or dicarbonates) and 1,2-bifunctional nucleophiles such as 1,2-aminoalcohols or ethylenediamines (Scheme 33).<sup>[46]</sup> Analogous Pd-catalyzed diastereoselective syntheses of 2-vinyl-1,4-benzodioxanes, 2-vinylmorpholines and 2-vinylpiperazines were reported by

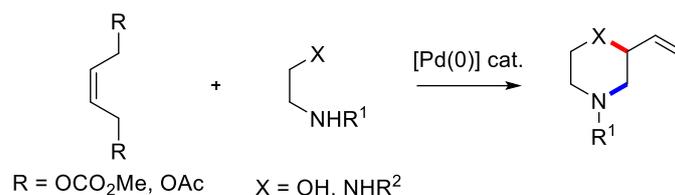
<sup>43</sup> Huang, Y.-J.; Lu, X.-Y. *Tetrahedron Lett.* **1988**, *29*, 5663-5664.

<sup>44</sup> Gravel, D.; Benoît, S.; Kumanovic, S.; Sivaramakrishnan, H. *Tetrahedron Lett.* **1992**, *33*, 1407-1410.

<sup>45</sup> a) Campiani, G.; Sun, L.-Q.; Kozikowski, A. P.; Aagaard, P.; McKinney, M. *J. Org. Chem.* **1993**, *58*, 7660-7669.; b) Kozikowski, A. P.; Tückmantel, W. *Acc. Chem. Res.* **1999**, *32*, 641-650.

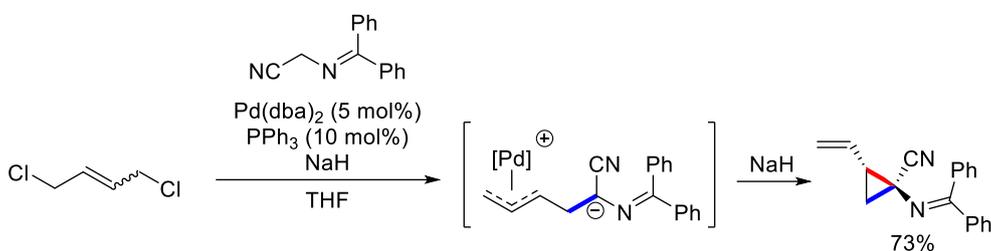
<sup>46</sup> Tsuda, T.; Kiyoi, T.; Saegusa, T. *J. Org. Chem.* **1990**, *55*, 3388-3390.

Hayashi,<sup>[47]</sup> Sinou,<sup>[48]</sup> Achiwa<sup>[49]</sup> and Muzart.<sup>[50]</sup>



Scheme 33. Synthesis of morpholines or piperazines.

In 1995, the Salaün group reported an approach to 1-aminocyclopropanecarboxylic acids through the Pd-catalyzed annulation between 1,4-dichlorobut-2-ene and *N*-(diphenylmethylene)aminoacetonitrile. The reaction occurs through two subsequent Pd-catalyzed allylations of the bis-nucleophile (Scheme 34).<sup>[51]</sup>



Scheme 34. Synthesis of 1-aminocyclopropanecarboxylic acid.

In 1999, the Sinou group developed a facile palladium-catalyzed annulation between various substituted benzene-1,2-diols, or *N,N*-bis(arylsulfonyl)-*o*-phenylenediamines, and 1,4-bis(methoxycarbonyloxy)but-2-ene to form substituted 2-vinyl-2,3 dihydro-benzo[1,4]dioxins<sup>[52]</sup> or 1,2,3,4-tetrahydro-2-vinylquinoxalines<sup>[53]</sup> in good yields (Scheme 35).

<sup>47</sup> Uozumi, Y.; Tanahashi, A.; Hayashi, T. *J. Org. Chem.* **1993**, *58*, 6826-6828.

<sup>48</sup> Massacret, M.; Goux, C.; Lhoste, P.; Sinou, D. *Tetrahedron Lett.* **1994**, *35*, 6093-6096.

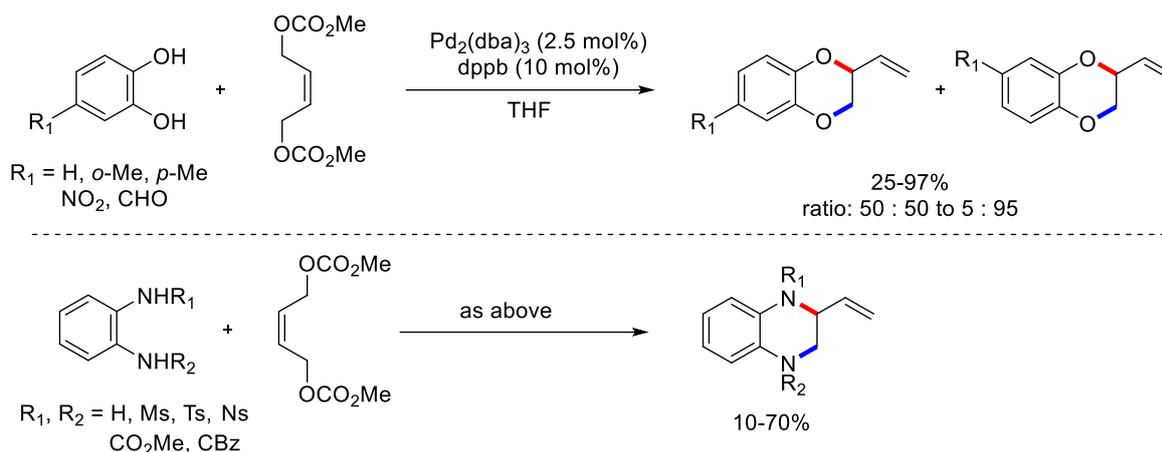
<sup>49</sup> Yamazaki, A.; Achiwa, K. *Tetrahedron: Asymmetry* **1995**, *6*, 1021-1024.

<sup>50</sup> Thorey, C.; Wilken, J.; Henin, F.; Martens, J.; Mehler, T.; Muzart, J. *Tetrahedron Lett.* **1995**, *36*, 5527-5530.

<sup>51</sup> Gaucher, A.; Dorizon, P.; Ollivier, J.; Salaün, J. *Tetrahedron Lett.* **1995**, *36*, 2979-2982.

<sup>52</sup> Massacret, M.; Lhoste, P.; Lakhmiri, R.; Parella, T.; Sinou, D. *Eur. J. Org. Chem.* **1999**, 2665-2673.

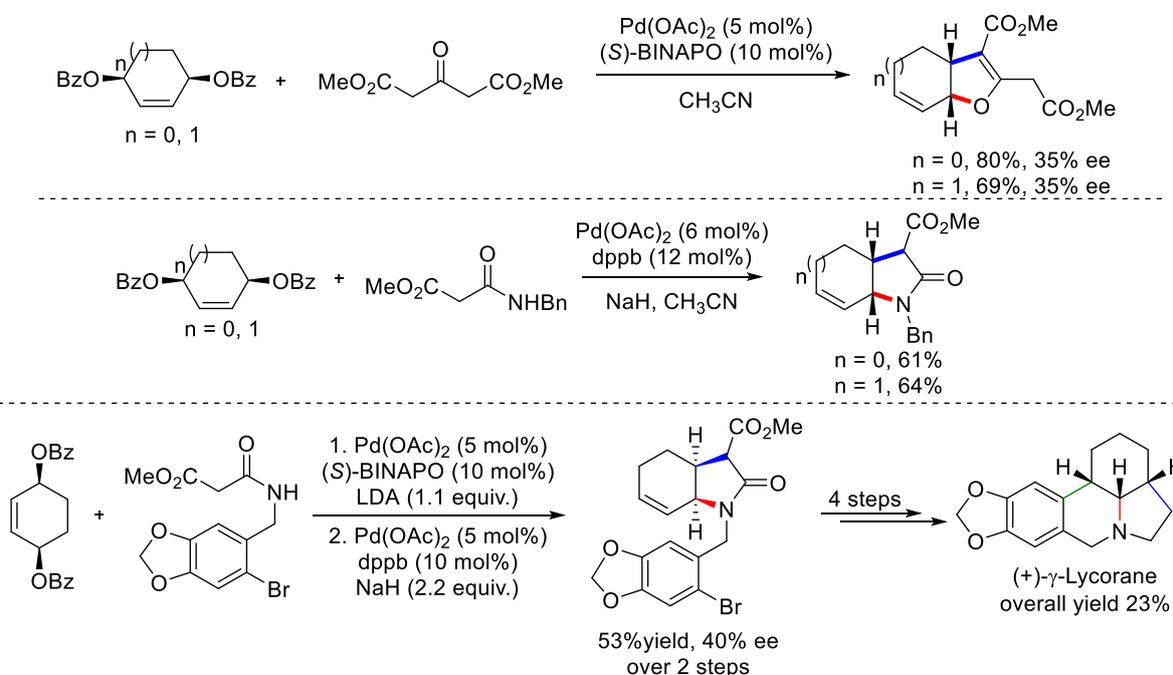
<sup>53</sup> Massacret, M.; Lhoste, P.; Sinou, D. *Eur. J. Org. Chem.* **1999**, 129-134.



Scheme 35. Synthesis of 2-vinyl-2,3 dihydro-benzo[1,4]dioxins and 1,2,3,4-tetrahydro-2-vinylquinoxalines.

### Cyclic allylic electrophiles

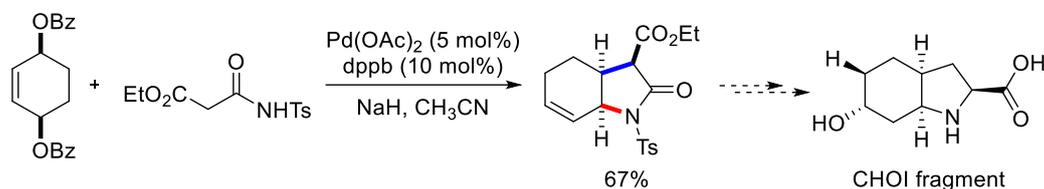
In 1995, the Mori group reported a smart strategy for the synthesis of tetrahydrobenzofurans and tetrahydroindolones through the Pd-catalyzed annulation reaction between 1,4-dibenzoyloxycyclohex-2-ene and 3-oxoglutarate, or monomalonamide. Use of the chiral enantiopure ligand BINAPO gave a mediocre (~50%) enantiodiscrimination. The same group exploited this method as the key steps for synthesis of the natural product (+)- $\gamma$ -lycorane (Scheme 36).<sup>[54]</sup>



Scheme 36. Pd-catalyzed annulation to give tetrahydrobenzofurans and tetrahydroindolones.

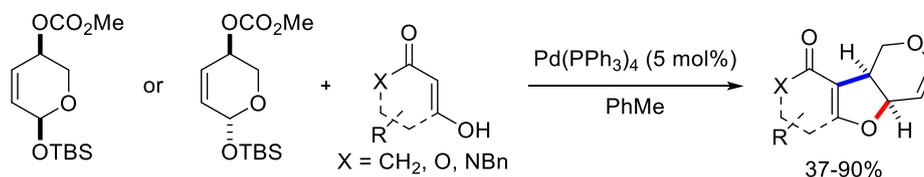
<sup>54</sup> Yochizaki, H.; Satoh, H.; Sato, Y.; Nukui, S.; Shibasaki, M.; Mori, M. *J. Org. Chem.* **1995**, *60*, 2016-2021.

More recently, our group reported an analogous Pd-catalyzed annulation strategy by the reaction between *N*-tosyl malonamide and 1,4-dibenzoyloxycyclohex-2-ene. Further functional group modifications of the annulation product gave analogs of the 2-carboxyl-6-hydroxyoctahydroindole (CHOI) unit, which in turn is a substructure of aeruginosins, a family of molecules found in cyanobacteria (Scheme 37).<sup>[2]</sup>



Scheme 37. Palladium-catalyzed annulation toward CHOI analogs.

In 2013, the Harvey group developed a Pd-catalyzed annulation between cyclic  $\beta$ -dicarbonyls and dihydropyrans that gave regioselectively furo[3,2-*c*]pyrans (Scheme 38). It should be noted that inherent steric and stereoelectronic factors in the pyran substrates favor a faster ionization at the allylic carbonate site than that at the anomeric OTBS group, which in turn determines the structure of the transient  $\pi$ -allyl-Pd species generated in the cascade, and thus the subsequent regioselective substitution by the nucleophile at C3 position. Interestingly, the *cis*-fused furopyrans were formed from either the *cis*- or the *trans*-substituted bis-electrophiles.<sup>[55]</sup>



Scheme 38. Palladium-catalyzed cascade allylic alkylation of dihydropyrans.

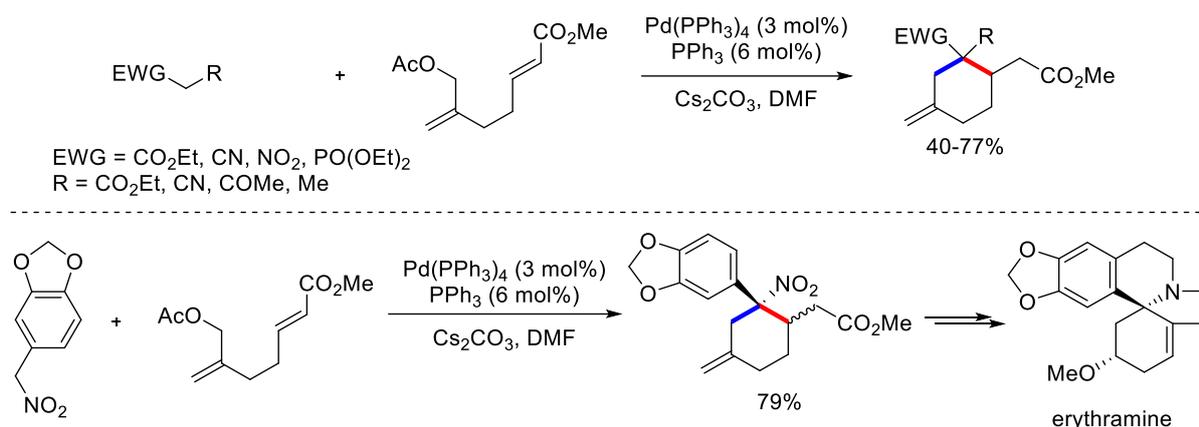
### Allylic / Michael acceptor electrophiles

Despite the number of palladium-catalyzed annulations reported, Pd-catalyzed allylation / Michael sequences are still rare. In 1998, the Desmaële group reported a palladium-catalyzed allylation followed by spontaneous intramolecular Michael addition to produce six-member rings. A variety of combinations between active methylene compounds and methyl 6-acetoxymethyl-hepta-2,6-dienoate were investigated, which provided a new access to cyclohexane derivatives.<sup>[56]</sup> The authors applied this strategy to the

<sup>55</sup> Bartlett, M. J.; Turner, C. A.; Harvey, J. E. *Org. Lett.* **2013**, *15*, 2430-2433.

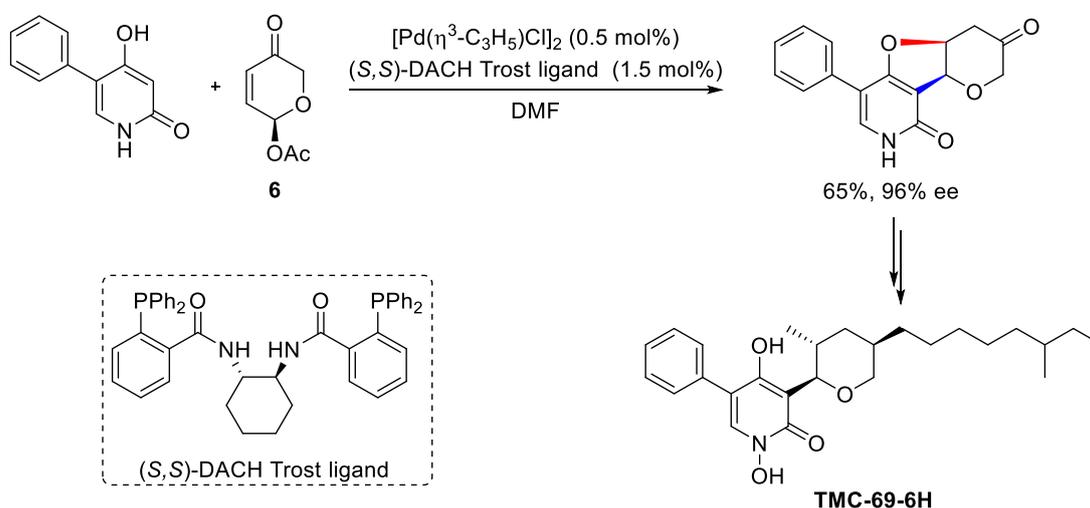
<sup>56</sup> a) Jousse, C.; Mainguy, D.; Desmaële, D. *Tetrahedron Lett.* **1998**, *39*, 1349-1352. b) Karinthi, J. C.; Riche, C.; Chiaroni, A.; Desmaële, D. *Eur. J. Org. Chem.* **2001**, 3631-3640. c) Karinthi, J. C.; Zouhiri, F.; Mahuteau, J.; Desmaële, D. *Tetrahedron* **2003**, *59*, 2093-2099.

synthesis of erythramine, an alkaloid of the family of erythrines (Scheme 39).



Scheme 39. Pd-catalyzed annulation of methyl 6-acetoxymethyl-hepta-2,6-dienoate with active methylene compounds.

In 2004, the Fürstner group achieved the total synthesis of the antitumor agent TMC-69-6H.<sup>[57]</sup> The key step of this synthesis was a Pd-catalyzed [3+2]-C-C/O-C bond-forming annulation between 4-hydroxy-2-pyridone and pyranil acetate, which involved a palladium-catalyzed allylic alkylation followed by a spontaneous oxa-Michael reaction. In the presence of the chiral ligand – (*S,S*)-Trosc DACH ligand – and allylpalladium chloride dimer, a key tricyclic product was obtained in 65% yield and excellent enantioselectivity (Scheme 40).

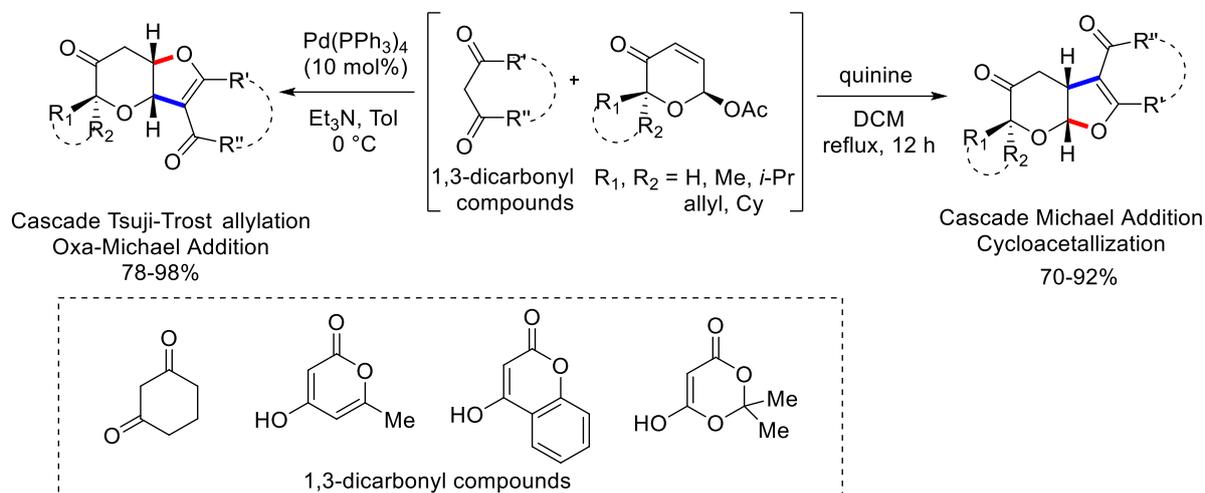


Scheme 40. Pd-catalyzed [3+2]-C-C/O-C bond-forming annulation for synthesis of TMC-69-6H x.

Similarly, in 2016 Tong reported the synthesis of furopyranones through Pd-catalyzed oxa-[3+2]-annulation between acetoxy-2-pyranones and 1,3-dicarbonyl compounds. Here again, the annulation

<sup>57</sup> Fürstner, A.; Feyen, F.; Prinz, H.; Waldmann, H. *Tetrahedron* **2004**, *60*, 9543-9558.

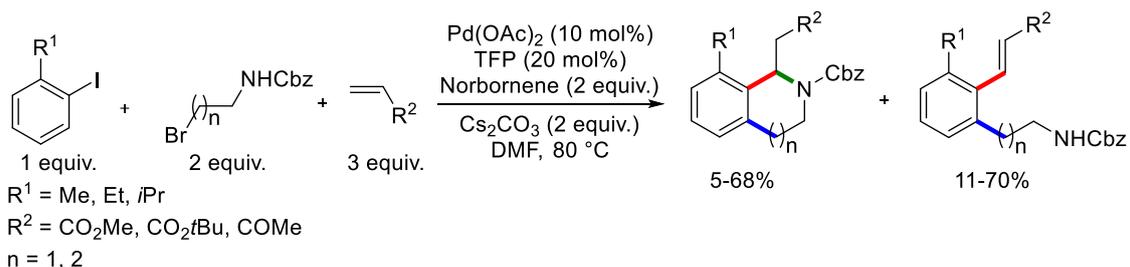
involves a palladium-catalyzed allylation followed by an intramolecular oxa-Michael reaction (Scheme 41, left).<sup>[58]</sup> The authors also found that using quinine as catalyst instead of the palladium system afforded another regioisomers of furopyranones, deriving from an intermolecular Michael addition followed by S<sub>N</sub>2-type cycloacetalization (Scheme 41, right).



Scheme 41. [3+2]-C-C/O-C bond-forming annulation for synthesis of furopyranones derivatives.

## Two, initially separated, electrophilic components

In 2004, the Catellani group presented the one-pot synthesis of tetrahydrobenzazepines and tetrahydroisoquinolines by the Pd-catalyzed reaction between an *o*-iodoalkylbenzene, an *N*-protected bromoalkylamine and an electron-poor olefin (Scheme 42).<sup>[59]</sup>



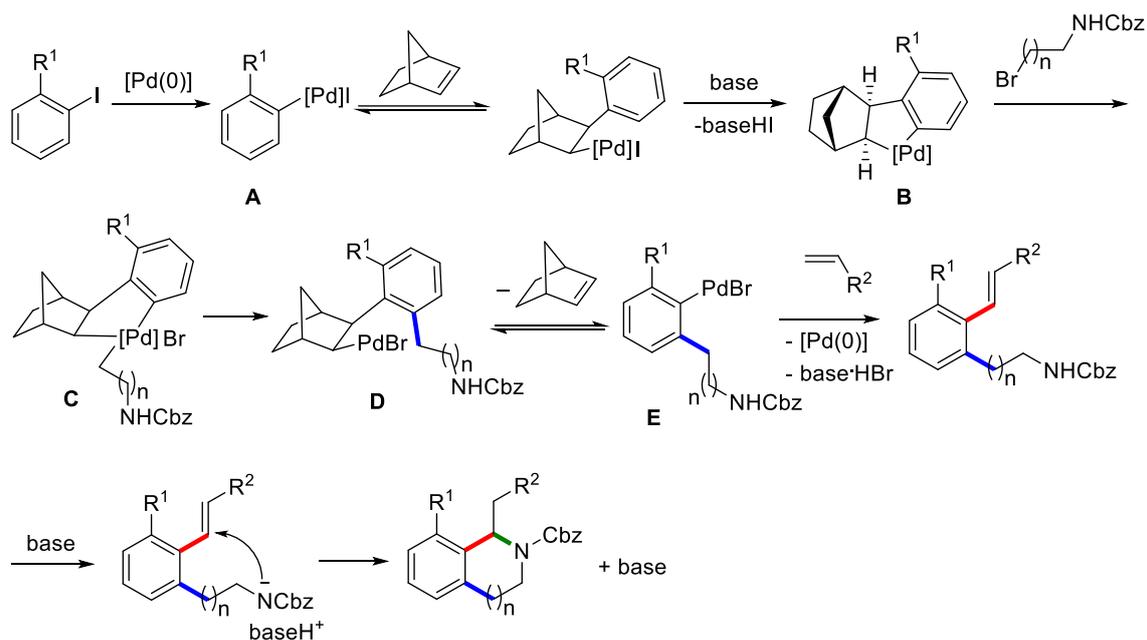
Scheme 42. [Pd-cat *o*-alkylation / Pd-cat alkenylation / aza-Michael] strategy to tetrahydrobenzazepines and tetrahydroisoquinolines.

A plausible mechanism of this transformation involves a Pd-catalyzed *ortho*-alkylation, followed by a Pd-catalyzed alkenylation and a final intramolecular aza-Michael reaction (Scheme 43). More precisely, i)

<sup>58</sup> Yu, J.-X.; Ma, H.-C.; Yao, H.-L.; Cheng, H.; Tong, R.-B. *Org. Chem. Front.* **2016**, *3*, 714-719.

<sup>59</sup> a) Ferraccioli, R.; Carezzi, D.; Catellani, M. *Tetrahedron Lett.* **2004**, *45*, 6903-6907. See also: b) Lautens, M.; Piguel S. *Angew. Chem. Int. Ed.* **2000**, *39*, 1045-1046. c) Lautens, M.; Paquin, J. F.; Piguel, S.; Dahlmann M. *J. Org. Chem.* **2001**, *66*, 8127-8134. c) Lautens, M.; Paquin, J.F.; Piguel S. *J. Org. Chem.* **2002**, *67*, 3972-3974.

oxidative addition of the aromatic iodide to Pd(0) gives the corresponding  $\sigma$ -arylpalladium iodide complex **A**; ii) norbornene insertion and subsequent intramolecular *ortho*-palladation forms palladacycle **B**; iii) oxidative addition of **B** to *N*-Cbz-bromoalkylamine leads to the palladium(IV) metallacycle **C**; iv) reductive elimination generates the  $\sigma$ -alkylpalladium intermediate **D**; v) decarbopalladation affords the corresponding  $\sigma$ -arylpalladium complex **E** and regenerates norbornene; vi) carbopalladation of the electron-poor olefin followed by dehydropalladation completes the catalytic cycle, generating the final alkene and Pd(0); vii) finally, intramolecular aza-Michael addition can furnish the final annulation bicyclic product.



Scheme 43. The Pd-catalyzed strategy to tetrahydroisoquinolines.

### 2.2.3 Annulation from Pd-TMM or cyclopropanes

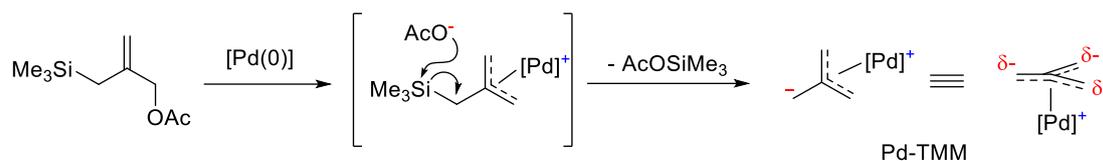
Pd-catalyzed [3+2]-annulation reactions from 3-acetoxy-2-trimethylsilylmethyl-1-propene are one of the most effective methods for synthesis of five-membered carbocycles and heterocycles.

#### Pd-catalyzed [3+2]-annulation from 3-acetoxy-2-trimethylsilylmethyl-1-propene

The interaction between 3-acetoxy-2-trimethylsilylmethyl-1-propene (ASMP) and a Pd(0) complex generates a zwitterionic complex (Pd-TMM) (Scheme 44).<sup>[60]</sup> The positive charge is stabilized by palladium, which prevents ring closing to methylenecyclopropane and Pd(0). This chemistry was discovered and

<sup>60</sup> a) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1979**, *101*, 6429-6432. b) Trost, B. M. *Angew. Chem. Int. Ed.* **1986**, *25*, 1-20. c) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49-92. d) Trost, B. M. *Pure Appl. Chem.* **1988**, *60*, 1615-1626. e) Yamago, S.; Nakamura, E. *Org. React.* **2003**, *61*, 1-217.

mainly developed by Prof. B. M. Trost.



Scheme 44. Generation of TMM-Pd.

This stable 1,3-dipole favors the singlet state, which has a nucleophilic nature and reacts with a number of electrophilic dipolarophiles to provide five-membered ring systems (Figure 1).

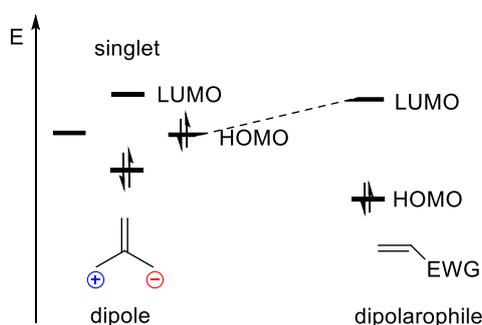
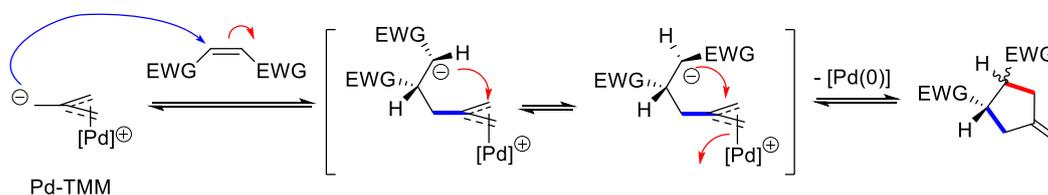


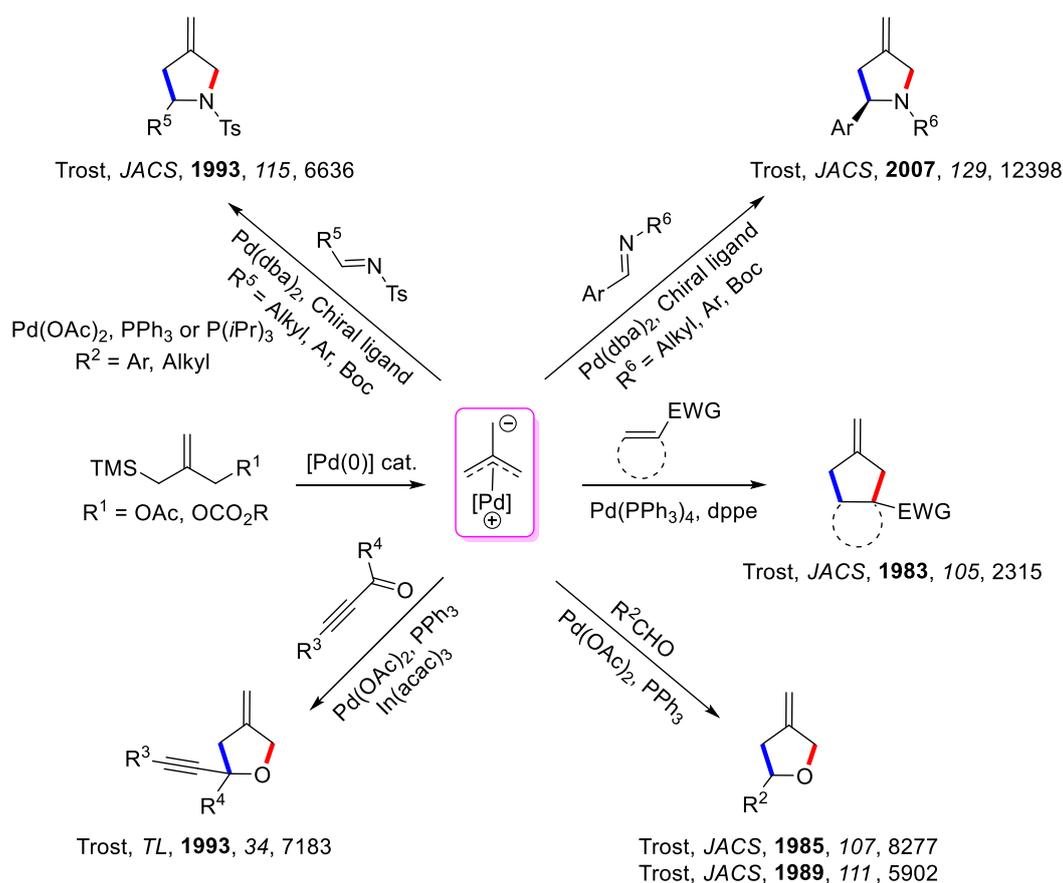
Figure 1. Qualitative molecular orbital interaction diagram between the  $\pi$ -system of Pd-TMM and that of a generic electrophilic dipolarophile.

Pd-TMM, generated *in-situ* from ASMP, gives  $[3_{2\sigma}+2_{2\pi}]$  cycloaddition with a number of electron-deficient olefins. For example, the reaction with dimethyl fumarate led to exclusively the *trans* cycloadduct, whereas with dimethyl maleate produced *cis/trans* mixtures of methylenecyclopentanes. This lack of stereospecificity suggests a stepwise, non-concerted mechanism (Scheme 45).



Scheme 45. Stepwise non-stereospecific mechanism in the cycloaddition of Pd-TMM.

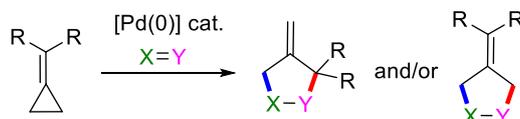
The *in-situ* generated Pd-TMM could be also react with  $\alpha,\beta$ -unsaturated-ketones, nitriles, esters, imines, aldehydes and ynones to form substituted 5-membered carbo- or heterocycles (Scheme 46).



Scheme 46. Overview of Pd-catalyzed [3+2]-annulations from Pd-TMMs.

### Pd-catalyzed [3+2]-annulation from methylenecyclopropanes

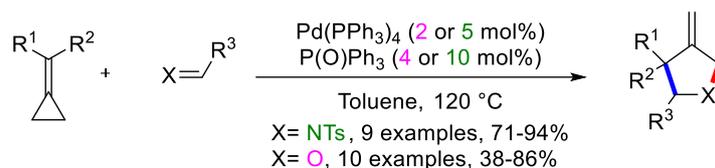
It is also possible to obtain Pd(0)-catalyzed cycloadditions by the reaction between methylenecyclopropanes and alkenes and carbonyl derivatives (Scheme 47).



Scheme 47. Pd-catalyzed cycloaddition between methylenecyclopropanes and alkenes or carbonyl derivatives.

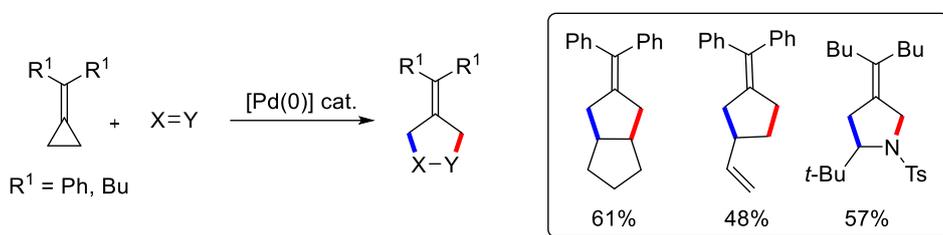
This chemistry was pioneered by Binger and co-workers,<sup>[61]</sup> who studied  $\alpha,\beta$ -unsaturated esters as electrophiles. Yamamoto later reported analogous Pd-catalyzed [3+2]-cycloadditions between methylenecyclopropanes and aldehydes or *N*-tosylimines (Scheme 48).<sup>[62]</sup>

<sup>61</sup> a) Binger, P.; Schuchardt, U. *Angew. Chem. Int. Ed.* **1977**, *16*, 249-250. b) Binger, P.; Schuchardt, U. *Chem. Ber.* **1981**, *114*, 3313-3324. For a review, see: c) Binger, P.; Büch, H. M. *Top. Curr. Chem.* **1987**, *135*, 77.



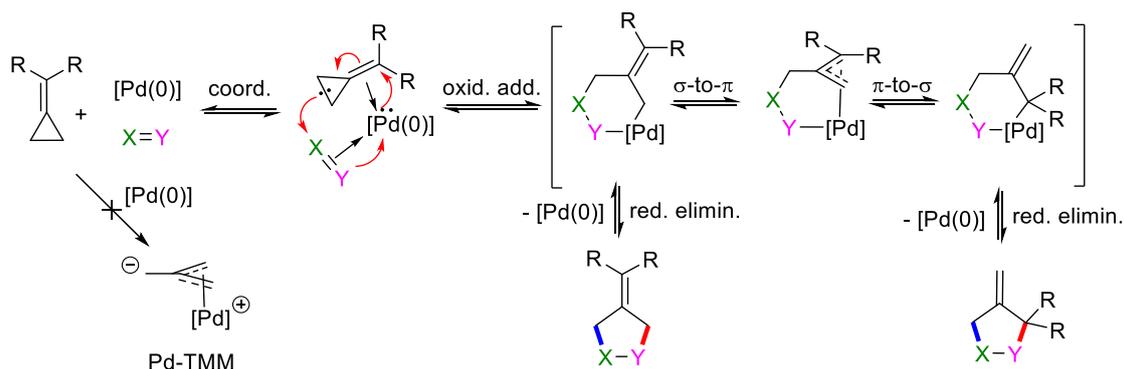
Scheme 48. Pd-catalyzed [3+2]-cycloaddition of methylenecyclopropanes.

Although, at a first glance, it is tempting to think at a mechanism involving the previously described zwitterionic Pd-TMM complexes, these two approaches show different selectivities. Thus, for example, methylenecyclopropanes substituted at the exo alkene led to the following regioisomerically pure products (Scheme 49).<sup>[62b,63]</sup>



Scheme 49. Pd-catalyzed [3+2]-cycloaddition of dibutyl- or diphenyl-methylenecyclopropanes.

These results suggest that the mechanism of this transformation involves a rapid  $\sigma$ - $\pi$ - $\sigma$  scrambling between the allylpalladium complexes, the most reactive one being a function of the substitution of the methylenecyclopropane (Scheme 50).



Scheme 50. The mechanism of the Pd-catalyzed cycloaddition between methylenecyclopropanes and alkenes.

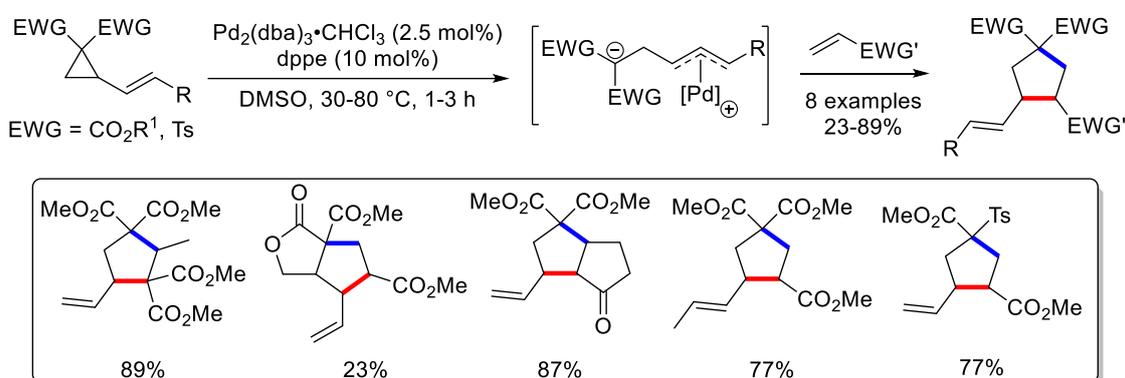
<sup>62</sup> a) Nakamura, I.; Oh, B. H.; Saito, S.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2001**, *40*, 1298-1230. b) Oh, B. H.; Nakamura, I.; Saito, S.; Yamamoto, Y. *Tetrahedron Lett.* **2001**, *42*, 6203-6205.

<sup>63</sup> Binger, P.; Bentz, P. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 622-623.

### Pd-catalyzed [3+2]-annulation from vinylcyclopropanes

In addition, the Pd-catalyzed [3+2]-annulation of 1,3-dipolar species generated from vinylcyclopropanes with dipolarophiles has become a highly efficient strategy for the synthesis of five membered ring compounds.

In 1985, the first Pd-catalyzed [3+2]-annulation of vinylcyclopropanes with  $\alpha,\beta$ -unsaturated ketones or esters was reported by Tsuji and co-workers.<sup>[64]</sup> Upon interaction with a Pd(0) complex, the doubly EWG-activated cyclopropanes generate through C-C bond cleavage a zwitterionic  $\pi$ -allylpalladium complex bearing a carbanion as its counteranion. Following annulation with an electron-deficient alkene generates the cyclopentane (Scheme 51).



Scheme 51. Pd-catalyzed [3+2]-annulation of vinylcyclopropanes.

This smart [3+2]-annulation strategy could be later extended to a variety of other vinyltricyclic 1,3-dipole precursors, such as vinyl-oxiranes or vinyl-aziridines, as well as to a number of 1,3-dipolarophiles, such as carbon dioxide,<sup>[65]</sup> benzaldehyde,<sup>[66]</sup> isocyanates,<sup>[67]</sup> carbodiimide<sup>[68]</sup> and activated olefins,<sup>[69]</sup> generating vinyl substituted- carbonates, dioxolanes, oxazolidinones, pyrrolidines<sup>[70]</sup> or other tetrahydrofurans. Some examples were shown in Scheme 52. This reaction normally proceeds under neutral conditions, and provides a convenient strategy for the synthesis of five-membered carbocycles and heterocycles.

<sup>64</sup> Shimizu, I.; Ohashi, Y.; Tsuji, J. *Tetrahedron Lett.* **1985**, *26*, 3825-3828.

<sup>65</sup> a) Fujinami, T.; Suzuki, T.; Kamiya, M.; Fukuzawa, S.; Sakai, S. *Chem. Lett.* **1985**, 199-200. b) Trost, M. B.; Angle, S. R. *J. Am. Chem. Soc.* **1985**, *107*, 6123-6124.

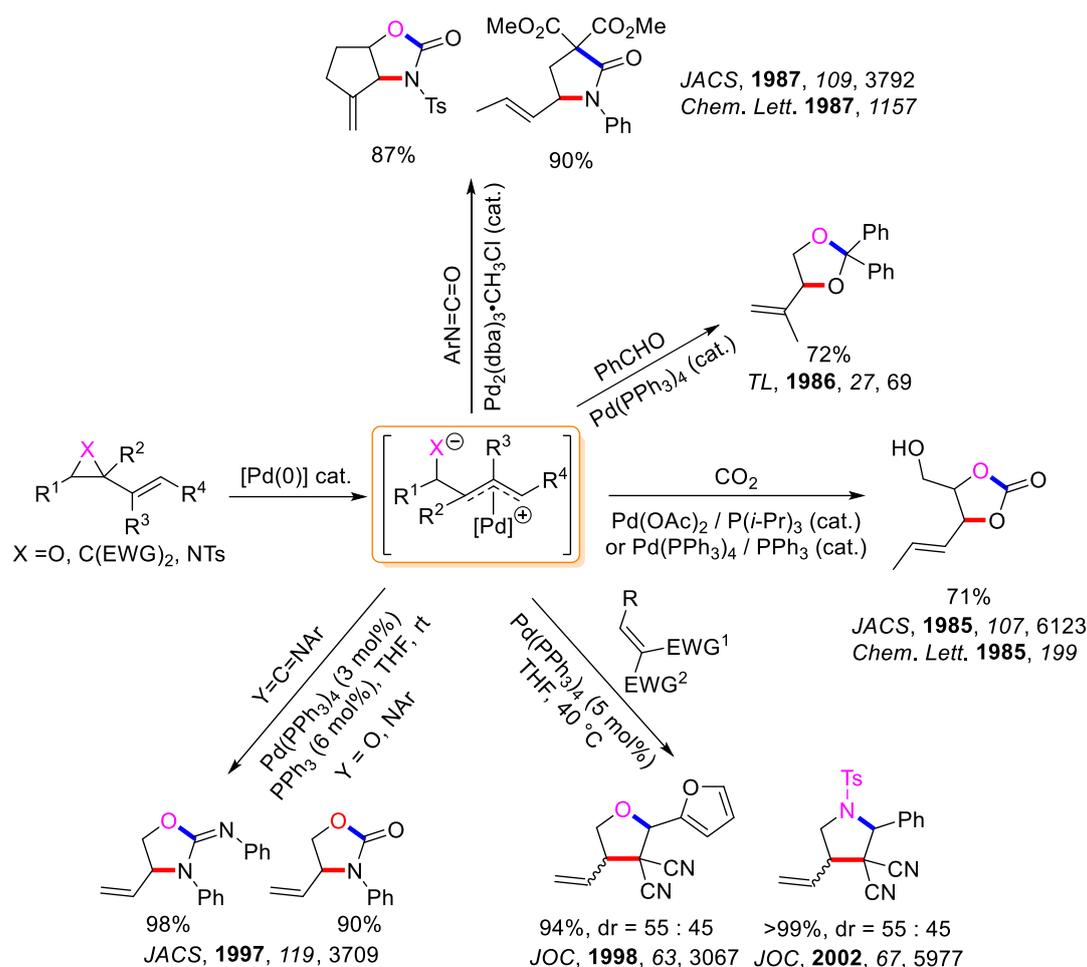
<sup>66</sup> Suzuki, S.; Fushiji, Y.; Kobayashi, Y.; Sato, F. *Tetrahedron Lett.*, **1986**, *27*, 69-70.

<sup>67</sup> a) Yamamoto, K.; Ishida, T.; Tsuji, J. *Chem. Lett.* **1987**, 1157-1158. b) Trost, M. B.; Anantha, R. S. *J. Am. Chem. Soc.* **1987**, *109*, 3792-3794.

<sup>68</sup> Larksarp, C.; Alper, H.; *J. Am. Chem. Soc.* **1997**, *119*, 3709-3715.

<sup>69</sup> Shim, J. G.; Yamamoto, Y.; *J. Org. Chem.* **1998**, *63*, 3067-3071.

<sup>70</sup> Aoyagi, K.; Nakamura, H.; Yamamo, Y. *J. Org. Chem.* **2002**, *67*, 5977-5980.



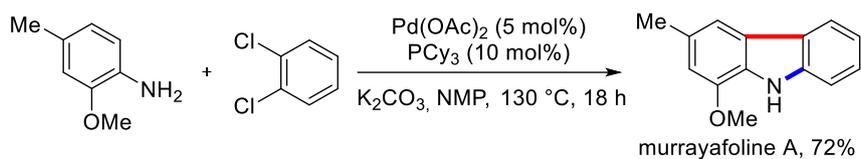
Scheme 52. Pd-catalyzed [3+2]-annulations of vinyl cyclopropanes, -oxiranes or -aziridines.

## 2.2.4 Pd-catalyzed [3+2]-C-C/N-C bond-forming annulations based on C-H activation

In contrast to the above-described annulation methods, Pd-catalyzed [3+2]-C-C/N-C bond-forming annulation reactions based on C-H bond activation have been less reported. A brief selection is presented herein.

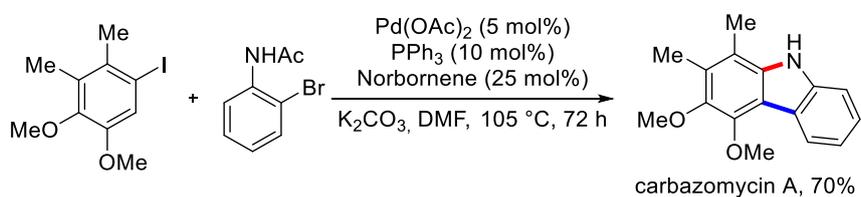
In 2007, the Ackermann group achieved an approach to carbazoles involving a new [3+2]-C-C/N-C bond-forming annulation. In the presence of the following catalytic mixture Pd(OAc)<sub>2</sub>/PPh<sub>3</sub>, 2-methoxy-4-methylaniline reacted with 1,2-dichlorobenzene at 130 °C, generating the annulated product murrayafoline A in 72% yield (Scheme 53). The process entailed the Buchwald-Hartwig Pd-catalyzed intermolecular arylation of the aniline with the *ortho*-dichlorobenzene, followed by an intramolecular direct C-H bond arylation.<sup>[71]</sup>

<sup>71</sup> Ackermann, L.; Althammer, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 1627-1629.



*Scheme 53. Synthesis of murrayafoline A.*

One year later, another one-pot palladium catalytic procedure for the synthesis of the carbazoles was reported by the Catellani group.<sup>[72]</sup> An aryl aryl iodide reacted with *o*-bromo-*N*-acetylaniline at 105 °C in the presence of Pd(OAc)<sub>2</sub> and PPh<sub>3</sub> to afford carbazomycin A in 70% yield (Scheme 54). In 2004, the same group used a similar strategy for a three components Pd-catalyzed annulation to benzazepines (Scheme 42).<sup>[59]</sup>



*Scheme 54. Synthesis of carbazomycin A.*

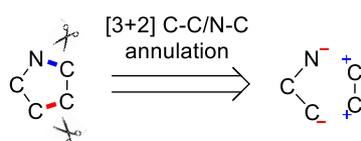
However, the Pd-catalyzed [3+2]-C-C/N-C bond-forming annulations still is an active field of research. The few examples reported encourage us develop new efficient strategies for synthesis of *N*-polyheterocycles.

<sup>72</sup> Ca, N. D.; Sassi, G.; Catellani, M. *Adv. Synth. Catal.* **2008**, *350*, 2179-2182.

## Chapter 2: Palladium-Catalyzed [3+2]-C-C/N-C Bond-Forming Annulation

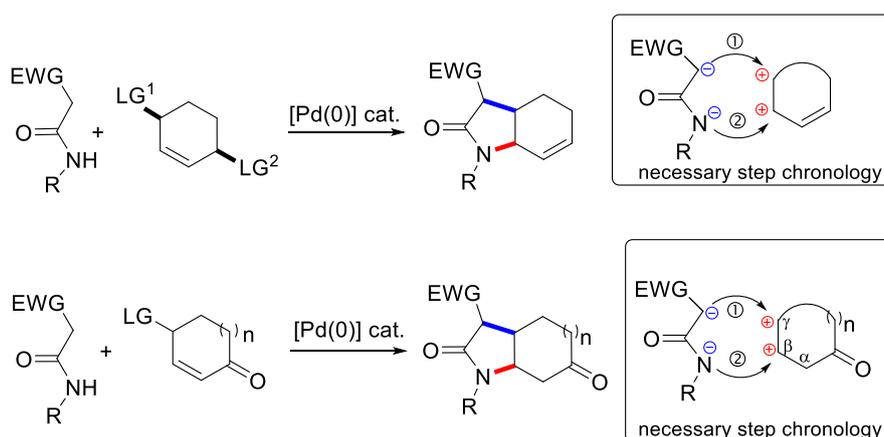
### 1. Conception of the new [3+2]-C-C/N-C annulation plan

As mentioned in chapter 1, our group has been working since a few years on the development of [3+2] C-C/N-C annulation sequences involving the reaction between a bis-(C/N)-nucleophiles and bis-(C/C)-electrophiles (Scheme 55).



Scheme 55. Concept of [3+2]-C-C/N-C bond-forming annulation between a bis-(C/N)-nucleophile and a bis-(C/C)-electrophile.

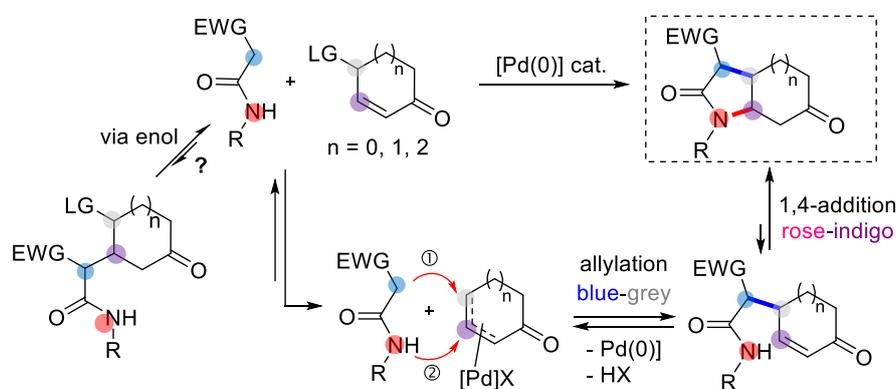
One of the two divergent approaches reported dealt with a chemoselective one-pot Pd-catalyzed [3+2]-C-C/N-C bond-forming annulation sequence involving the reaction between resonance-stabilized  $\beta$ -amido-esters and cyclic bis-allylic substrates (Scheme 56, top).<sup>[2]</sup> As a logical extension of this project, we next envisaged the study of new [3+2]-C-C/N-C bond forming annulation cascades using cyclic  $\alpha,\beta$ -unsaturated- $\gamma$ -oxy-carbonyls as the bis-electrophiles (Scheme 56, bottom).



Scheme 56. Conception of the new [3+2]-C-C/N-C annulation plan.

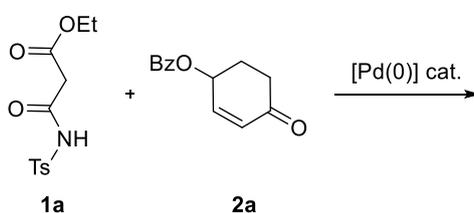
So, while the previous strategy was based on a double Pd-catalyzed allylation sequence (first an intermolecular C-allylation step, then an intramolecular N-allylation step), the new planned sequence is based on an initial Pd-catalyzed intermolecular C-allylation at the  $\gamma$  position of the carbonyl bis-electrophile

(unpoled position with respect to the carbonyl function), followed by an intramolecular aza-Michael reaction. Accordingly, allylation at the nucleophilic carbon atom should initially take place at the  $\gamma$ -position of the carbonyl derivative via the corresponding  $\eta^3$ -allylpalladium intermediate, and the thus formed  $\gamma$ -substituted carbonyl derivative should subsequently undergo a nitrogen-based intramolecular conjugate addition to afford the desired bicyclic structure. The challenge of the project resides in the fact that the desired bicyclic target can be successfully obtained only if the planned nucleophile/electrophile combinations ( $\text{Nu}_{\text{blue}}/\text{El}_{\text{grey}}$ ;  $\text{Nu}_{\text{rose}}/\text{El}_{\text{violet}}$ ) and in the desired chronology of events (*i.e.* first allylation, then 1,4 addition) match at the same time. This is not a trivial point, as the former step is a catalytic transformation, while the latter one is not. Therefore, an important requisite for the success of this annulation is that the kinetics of the intermolecular 1,4-addition has to be either intrinsically slower than the intermolecular allylation, and/or the potential intermolecular 1,4-addition has to be a reversible process (Scheme 57).



Scheme 57. General mechanism of the planned Pd(0)-catalyzed [3+2]-annulation.

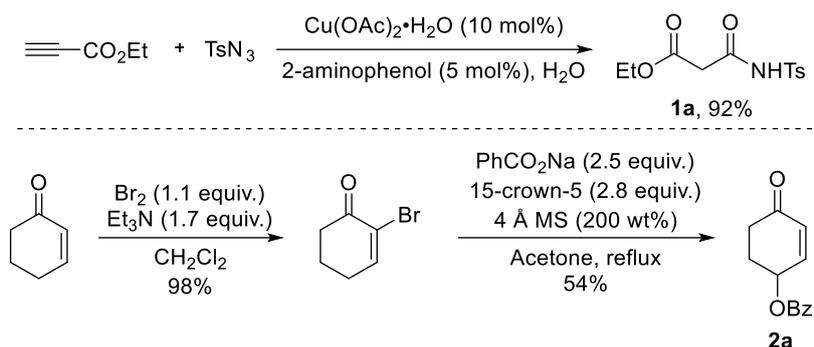
Accordingly, we considered for our first study the *N*-tosylamido-ester **1a** as our model bis-nucleophile, which is the same as used in the group for the C-allylation / N-allylation domino sequence,<sup>[2]</sup> and 2-cyclohexenone  $\gamma$ -benzoate **2a** as our model bis-electrophile (Scheme 58).



Scheme 58. Bis-nucleophile and bis-electrophile considered for our [3+2]-C-C/N-C annulation study.

Substrate **1a** was prepared in 92% yield by reaction between ethyl propiolate and tosyl azide (**GP1**, see experimental part) through copper(I)-catalyzed azide/alkyne cycloaddition followed by ring-opening

rearrangement and nucleophilic attack by H<sub>2</sub>O (Scheme 59, top).<sup>[73]</sup> Bis-electrophile **2a** was synthesized by a three-step sequence from 2-cyclohexen-1-one. Treatment of 2-cyclohexen-1-one with Br<sub>2</sub>/NEt<sub>3</sub> gave, after a dibromination / dehydrobromination sequence, 2-bromo-2-cyclohexen-1-one in 98% yield. This latter was transformed into 4-benzoyloxy-cyclohex-2-en-1-one **2a** by treatment with sodium benzoate in the presence of 15-crown-5. In this reaction, the benzoate anion acts first as a base to isomerize 2-bromo-2-cyclohexen-1-one into 2-bromo-3-cyclohexen-1-one, then performs a S<sub>N</sub>2' nucleophilic substitution (Scheme 59, bottom).<sup>[74]</sup>

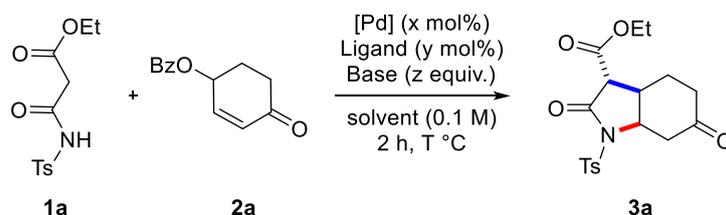


Scheme 59. Synthesis of substrates **1a** and **2a**.

## 2. First studies and optimization of the reaction conditions

We started the study of the reaction between *N*-tosylamido ester **1a** and 2-cyclohexenone 4-benzoate **2a** using the conditions previously developed by our group with cyclic bis-allylic substrates.<sup>[2]</sup> Accordingly, using the catalytic system [Pd(OAc)<sub>2</sub> (5 mol%), dppb (10 mol%)] and NaH (3 equiv.) as the base, in CH<sub>3</sub>CN at 50 °C, gave the desired fused pyrrolidone **3a** in 18% yield. A number of other catalytic systems, which varied the nature of the palladium source and/or the phosphine ligand, were subsequently screened. Solvent, concentration and temperature were also screened. The results of the tests are reported in Table 1.

Table 1. Optimization 1 of Pd-catalyzed [3+2]-annulation between **1a** and **2a**.

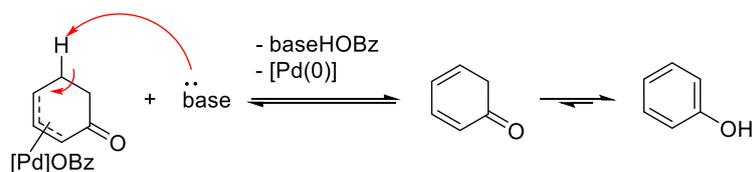


<sup>73</sup> Liu, Y.-T.; Wang, X.-Y.; Xu, J.-M.; Zhang, Q.; Zhao, Y.; Hu, Y.-F. *Tetrahedron* **2011**, *67*, 6294-6299.

<sup>74</sup> a) Jyothi, D.; Prasad, S. H. *Synlett* **2009**, 2309-2311. b) Hayashi, Y.; Shoji, M.; Kishida, S. *Tetrahedron Lett.* **2005**, *46*, 681-685.

Entry	1a (equiv.)	2a (equiv.)	[Pd] (x mol%)	Ligand (y mol%)	Base (z equiv.)	Solvent	T (°C)	Yield (%)
1	2	1	Pd(OAc) <sub>2</sub> (5)	dppb (10)	NaH (3)	CH <sub>3</sub> CN	50	18
2	2	1	Pd(OAc) <sub>2</sub> (5)	dppb (10)	Cs <sub>2</sub> CO <sub>3</sub> (1.5)	CH <sub>3</sub> CN	50	22
3	2	1	[Pd(η <sup>3</sup> -C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> (5)	PPh <sub>3</sub> (30)	Cs <sub>2</sub> CO <sub>3</sub> (1.5)	Toluene	rt	NR
4	2	1	[Pd(η <sup>3</sup> -C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> (5)	PPh <sub>3</sub> (30)	Cs <sub>2</sub> CO <sub>3</sub> (1.5)	THF	rt	13
5	2	1	[Pd(η <sup>3</sup> -C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> (5)	dppf (15)	-	THF	rt	43
6	1.2	1	[Pd(η <sup>3</sup> -C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> (5)	dppf (15)	-	THF	rt	70
7	1.2	1	[Pd(η <sup>3</sup> -C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> (5)	dppf (15)	-	THF (0.05 M)	rt	62
8	1.2	1	[Pd(η <sup>3</sup> -C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> (5)	dppe (15)	-	THF	rt	NR
9	1.2	1	[Pd(η <sup>3</sup> -C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> (5)	dppb (15)	-	THF	rt	32
10	1.2	1	[Pd(η <sup>3</sup> -C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> (5)	Xantphos (15)	-	THF	rt	24
11	1.2	1	[Pd(η <sup>3</sup> -C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> (5)	DEPPhos (15)	-	THF	rt	55

First of all, when we used a base (entries 1-4) with various Pd/ligand mixtures in presence of 2 equivalents of **1a** and one equivalent of **2a**, we obtained only very low amounts of the desired product **3a**, and significant amounts of phenol, probably deriving from base-promoted elimination of the benzoate from the η<sup>3</sup>-allylpalladium complex (Scheme 60).



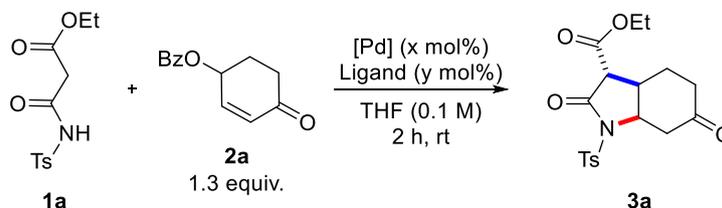
Scheme 60. Rationale for the formation of phenol.

To inhibit the formation of this by-product, we carried out further experiments in the absence of base in presence of [Pd(η<sup>3</sup>-C<sub>3</sub>H<sub>5</sub>)Cl]<sub>2</sub> as catalyst. Accordingly, working in THF at room temperature, we were able to observe product **3a** in significant amounts (entry 5), which was improved with a slight excess of bis-electrophile **1a** (1.2 equivalents of **1a** relative to **2a**) (entry 6). Otherwise, we found that using at 0.1 M dilution in THF gave a better yield than a more diluted concentration (compared entries 6 and 7). Different

phosphine ligands were also tested (entries 8-11) and the best result was obtained in presence of dppf.

As in the above reactions we found small amounts of phenol side product, we decided to continue our optimization using an excess of bis-electrophile **2a** (Table 1, entry 6). The results of the tests are reported in Table 2.

Table 2. Optimization 2 of Pd-catalyzed [3+2]-annulation between **1a** and **2a**.



Entry	[Pd] (x mol%)	Ligand (y mol%)	Yield (%)
1	$[\text{Pd}(\eta^3\text{-C}_3\text{H}_5\text{Cl})_2]$ (5)	dppf (15)	90
2	$\text{Pd}(\text{PPh}_3)_4$ (10)	-	67
3	$\text{Pd}(\text{OAc})_2$ (10)	$\text{PPh}_3$ (30)	73
4	$\text{Pd}(\text{OAc})_2$ (10)	dppf (15)	60
5	$\text{Pd}_2(\text{dba})_3$ (5)	$\text{PPh}_3$ (30)	81
6	$\text{Pd}_2(\text{dba})_3$ (5)	dppf (15)	82

We were glad to see that a slight excess of bis-electrophile **2a** (1.3 equivalents of **2a** relative to **1a**) allowed us to obtain **3a** with 90% yield (Table 1, entry 6 vs Table 2, entry 1). With this new stoichiometry various palladium catalyst precursors were also investigated in presence of different ligands, such as  $\text{Pd}(\text{PPh}_3)_4$  (entry 2),  $\text{Pd}(\text{OAc})_2$  (entries 3-4),  $\text{Pd}_2(\text{dba})_3$  (entries 5-6). All these tests allowed us to achieve the optimal conditions: (**GP7**, see experimental part) [ $\text{Pd}(\eta^3\text{-C}_3\text{H}_5\text{Cl})_2$  (5 mol%), dppf (15 mol%)] in THF at room temperature, leading to the desired bicyclic pyrrolidone **3a** in 90% yield (Table 2, entry 1).

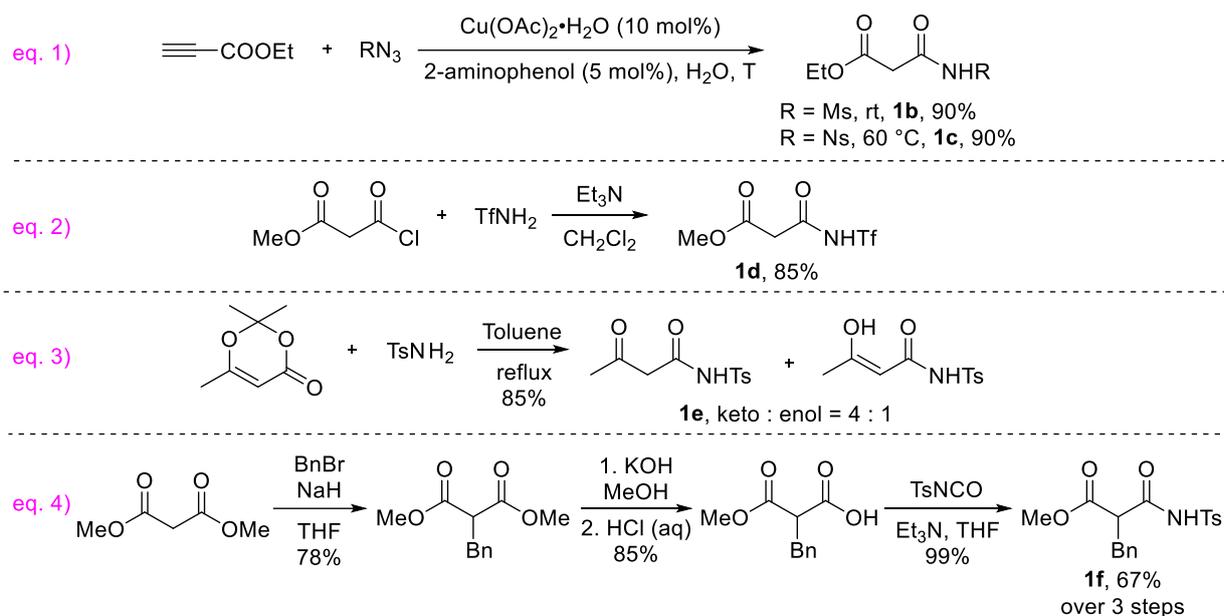
### 3. Scope and limitations of the Pd-catalyzed [3+2]-annulation

#### 3.1 From resonance-stabilized N-sulfonyl acetamides

With the optimized conditions in hand, the scope of this annulation between 2-cyclohexenone 4-benzoate **2a** and a series of resonance-stabilized N-sulfonyl acetamides was investigated.

Similarly to the synthesis of **1a**, the bis-nucleophiles **1b-1c** were prepared by copper-catalyzed reaction

between ethyl propiolate and methyl sulfonyl azide or 4-nitrobenzenesulfonyl azide, respectively, followed by treatment with water (Scheme 61, eq. 1). Bis-nucleophile **1d** was prepared from methyl malonyl chloride and trifluoromethanesulfonamide in dichloromethane in the presence of NEt<sub>3</sub> (Scheme 61, eq. 2) and **1e** was synthesized as a 4/1 ketone / enol mixture by the reaction between 2,2,6-trimethyl-1,3-dioxin-4-one and TsNH<sub>2</sub> (Scheme 61, eq. 3).<sup>[75]</sup> Benzylated bis-nucleophile **1f** was prepared by the decarboxylative coupling between 2-benzylmalooate monomethyl ester and tosyl isocyanate (Scheme 61, eq. 4).<sup>[76]</sup>

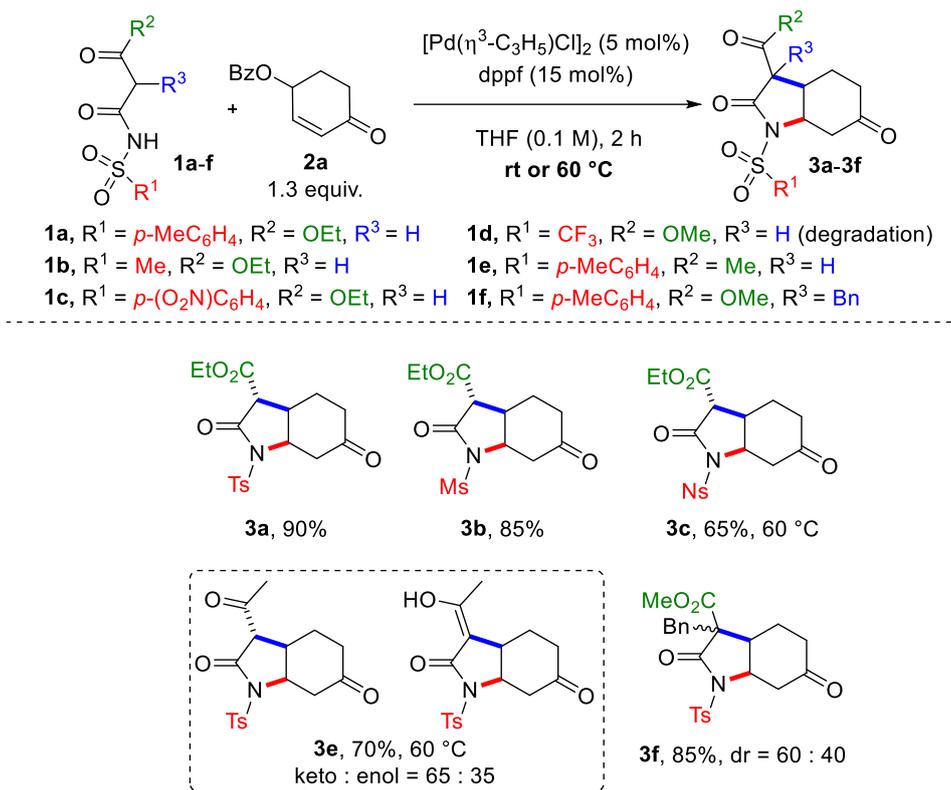


Scheme 61. Synthesis of resonance-stabilized N-sulfonyl acetamides **1a-1f**.

With the substrates in hand, the annulation between 2-cyclohexenone 4-benzoate **2a** and **1a-1f** was tested (Scheme 62).

<sup>75</sup> Clemens, R. J.; Hyatt, J. A. *J. Org. Chem.* **1985**, *50*, 2431-2435.

<sup>76</sup> Jalapa, N. A. E.; Ke, D.; Nebra, N.; Goanvic, L. L.; Ladeira, S. M.; Monot, J.; Vaca, B. M.; Bourissou, D. *ACS Catal.* **2014**, *4*, 3605-3611.



Scheme 62. Scope of the Pd-catalyzed [3+2]-annulation with **2a** and resonance-stabilized *N*-sulfonyl acetamides.

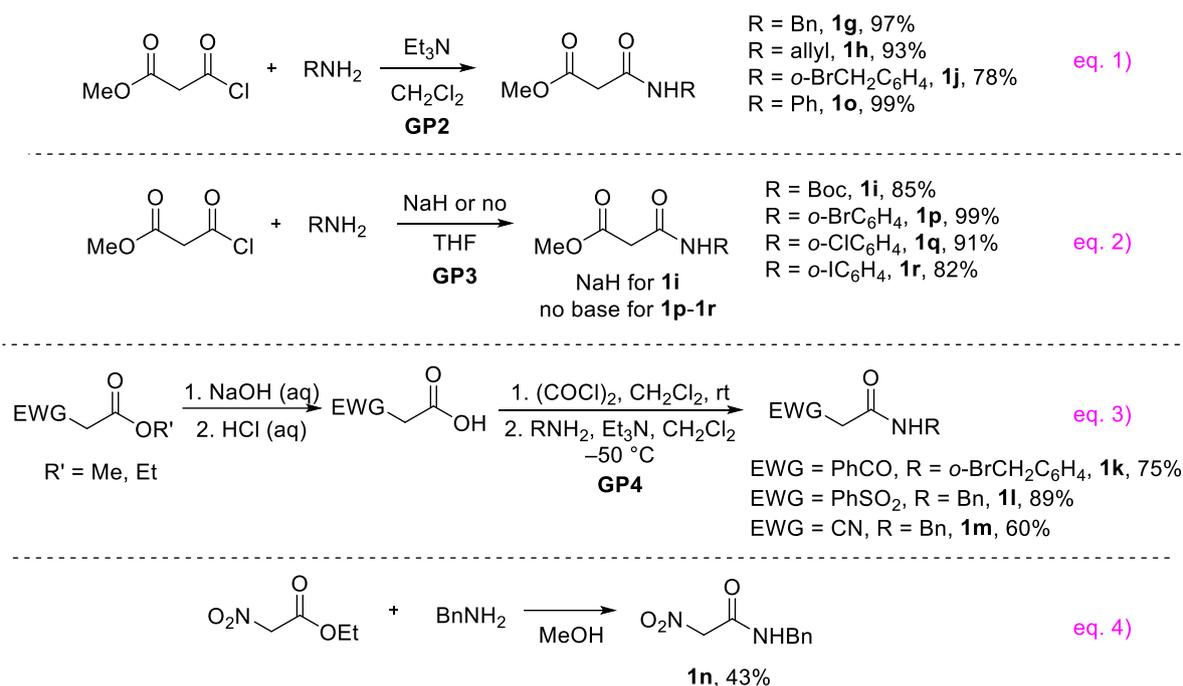
Most of the tested *N*-sulfonylacetamides showed good reactivity, giving the desired bicyclic pyrrolidones **3a-3c** in 65-90% yield. However, the *N*-triflyl derivative **1d** gave no reaction under the above conditions. The  $\beta$ -ketoamide bis-nucleophile **1e** also successfully afforded the expected annulated product as a 65 : 35 keto / enol mixture in 70% yield. Furthermore, in the case of the bis-nucleophiles **1c** and **1e**, we found that the reaction is better performed at 60 °C, due to the low reactivity of these bis-nucleophiles with respect to the other *N*-sulfonylacetamides. Besides, the annulation also worked satisfactorily when starting from the benzylated bis-nucleophile **1f**, affording the expected product as a mixture of diastereoisomers with excellent yield, which suggested that the annulation is highly tolerant of steric hindrance.

### 3.2 The influence of the substitution at the N-position of the *N*-amido-ester

Encouraged by the above results, we next turned our attention to investigate different *N*-protections at the resonance-stabilized acetamides.

First, the methyl ester-stabilized acetamides **1g-1j** were synthesized in good yields from methyl malonyl chloride using two different procedures (**GP2** and **GP3**, see experimental part). For example, *N*-benzyl **1g**, *N*-allyl **1h**, *N*-*tert*-butyloxycarbonyl **1i**, *N*-*o*-bromobenzyl **1j** were prepared by reacting methyl malonyl

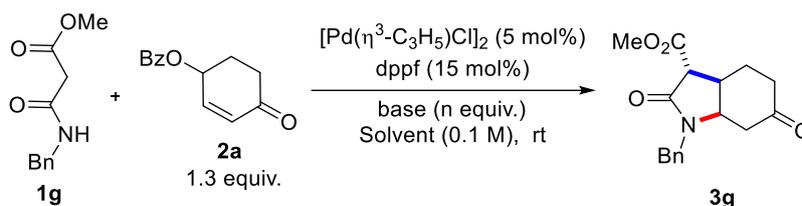
chloride with the corresponding amine in the presence of a base in dichloromethane or tetrahydrofuran (Scheme 63, equations 1 and 2). Next, acetamides bearing different electron-withdrawing groups **1k-1n** were synthesized by hydrolysis of the corresponding methyl or ethyl acetates followed by formation of the corresponding acid chloride, and subsequent amidation by treatment with the desired amine (**GP4**, see experimental part) (Scheme 63, equation 4). The nitroacetamide **1n** was directly prepared from ethyl nitroacetate by reaction with benzylamine in methanol (Scheme 63, equation 4). *N*-acetamides bearing differently substituted aromatic rings **1o-1r** were also prepared from methyl malonyl chloride by reaction with the corresponding aromatic anilines in tetrahydrofuran or dichloromethane (Scheme 63, equation 2).



Scheme 63. Synthesis of resonance-stabilized acetamides **1g-1r**.

With the new bis-nucleophiles in hand, this annulation between **2a** with **1g-1r** was investigated. Unfortunately, submission of the *N*-benzyl bis-nucleophile **1g** to the previously described optimized reaction conditions did not afford the expected annulated product. This result suggested that the new bis-nucleophile may possess an H-N that is not acidic enough to undergo the intramolecular step without the assistance of a base. It is important to highlight that Pd(0)-catalyzed allylation reactions or *N*-1,4-addition often need a base to carry out a preliminary deprotonation of the pro-nucleophile.<sup>[2]</sup> Consequently, the addition of a base was considered in different solvents (Table 3).

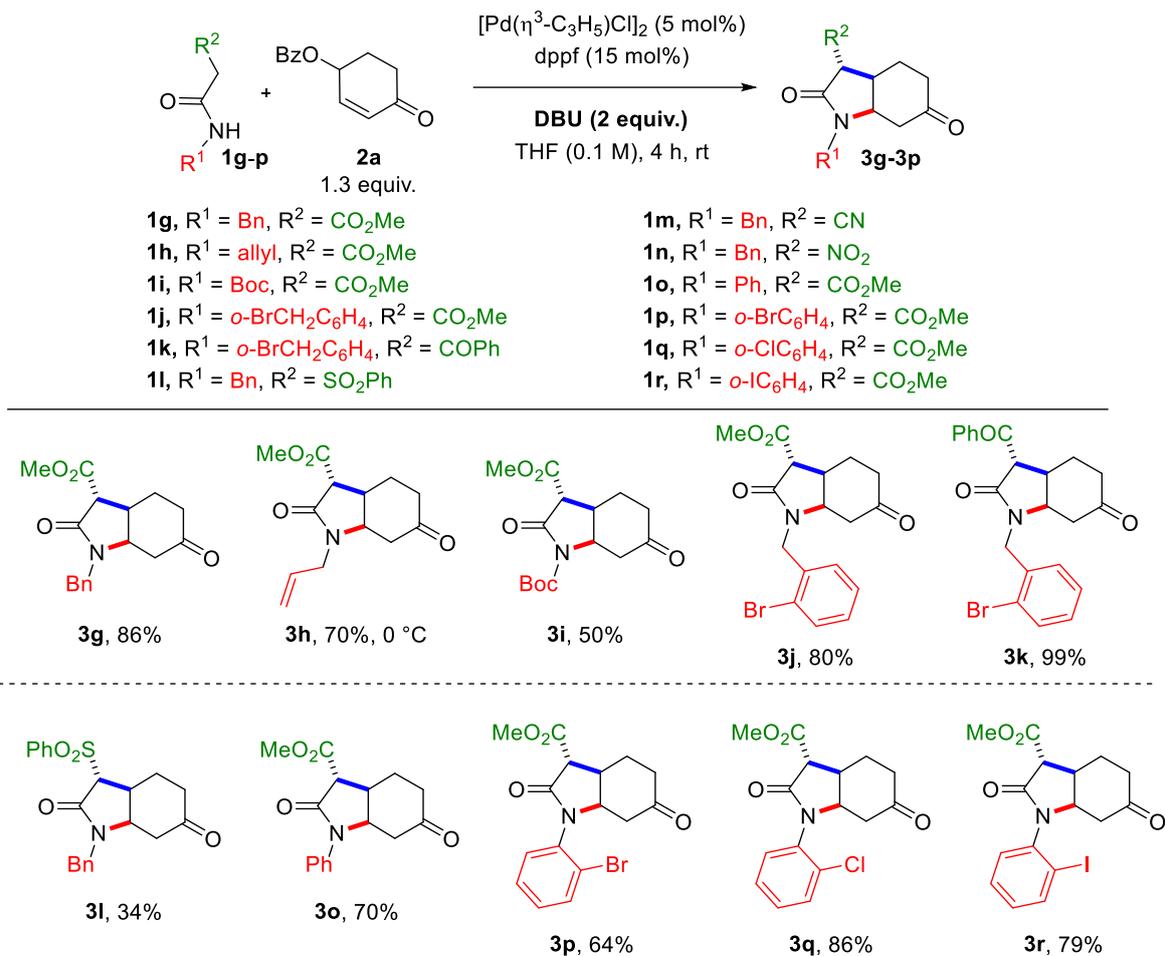
Table 3. Optimization studies between bis-nucleophile **1g** and bis-electrophile **2a**.



Entry	Base	Equiv.	Solvent	T (°C)	Yield (%)
1	NaH	0.5	THF	rt	No product
2	NaH	1.5	THF	rt	55
3	NaH	3	THF	rt	50
4	NaH	1.5	CH <sub>3</sub> CN	rt	30
5	NaH	1.2	THF	60	No product
6	DBU	2.0	THF	rt	86
7	DBU	1.0	THF	rt	20

Use of the previously optimized reaction conditions, no product was observed with 0.5 equivalent of NaH (entry 1), but with the addition of 1.5 equivalents of NaH, afforded the desired product **3g** in moderate yield (entry 2). Increasing the amount of NaH to 3.0 equivalents slightly reduce the yield (entry 3). Moreover, changing the solvent from THF to CH<sub>3</sub>CN did not allow any improvement (entry 4), and performing the reaction at higher temperature was disastrous (entry 5). Finally, after several trials, we found the new optimal conditions (**GP8**, see experimental part) for this less acidic bis-nucleophile were: ( $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$  (5 mol%), dppf (15 mol%), DBU (2.0 equiv.) in THF (0.1 M) at room temperature), which allowed to obtain the desired bicyclic pyrrolidone **3g** with an excellent yield of 86% (entry 6). The use of only one equivalent of DBU was not enough to attain a good result (entry 7).

With these new optimized conditions in hand, the scope of the *N*-substituted acetamides was then carried out (Scheme 64).



Scheme 64. Variations of the *N*-protection on the resonance-stabilized acetamide in the reaction with **2a**.

The *N*-allyl acetamide **1h** gave the desired annulated product **3h** in 70% yield. However, in this case, the reaction must be carried out at 0 °C for maximum yield. The *tert*-butyloxycarbonyl derivative **1i** afforded the desired product **3i** in 50% yield. Good yields of annulated pyrrolidones were also observed with *N*-*o*-bromobenzyl derivatives (**1j** and **1k**), carrying a methoxycarbonyl, or a benzoyl moiety as the resonance-stabilizing group for the acetamide. Moreover, application of the protocol to the *N*-benzyl acetamide bearing a phenylsulfonyl group gave also the desired annulated product **3l** in 34% yield. However, nitrile **1m** or nitro **1n** as resonance stabilizing group in the bis-nucleophile did not afford the expected products.

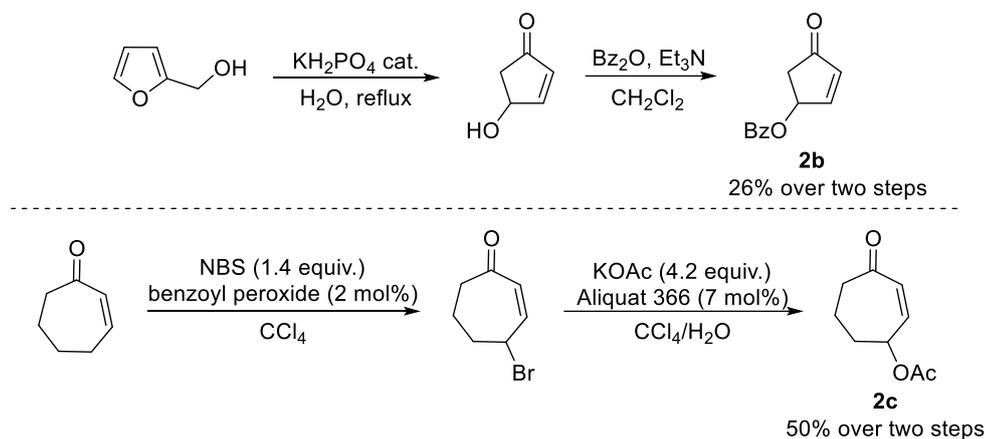
We also tested *N*-acetamides bearing differently substituted aromatic rings and carrying a methoxycarbonyl moiety as the resonance-stabilizing group (**1o-1r**). The reactions were successful, affording the desired products **3o-3r** in yields ranging from 64% (for **1p**), to 86% (for **1q**). Interestingly, the *o*-bromophenyl and *o*-chlorophenyl substituted *N*-acetamides **1p** and **1q** worked also in the absence of DBU, but not the *o*-iodo *N*-acetamides **1r**, though in lower yields. This different performance is very likely due to the enhancement of the H-N acidity of the nucleophile due to the high electronegativity of chlorine and bromine atoms, which activates the nitrogen atom to the aza-Michael step.

These above results suggest that the  $pK_a$ s of the two reacting positions in the bis-nucleophile (one at the active methylene, the other at N atom), must fit in an appropriate window to allow the annulations.

### 3.3 Scope of cyclic $\alpha,\beta$ -unsaturated- $\gamma$ -oxycarbonyl derivatives

Encouraged by the above results, we then turned our attention to explore the Pd-catalyzed [3+2]-annulation involving five- and seven-membered cyclic  $\alpha,\beta$ -unsaturated- $\gamma$ -oxycarbonyls.

Cyclopentenone 4-benzoate **2b** was synthesized from furfuryl alcohol by the Piancatelli reaction followed by a benzylation step (Scheme 65, top).<sup>[77]</sup> On the other hand, 4-acetoxy-2-cycloheptenone **2c** was prepared via a two-step sequence. Radical bromination of 2-cyclohepten-1-one with NBS in the presence of a catalytic amount of benzoyl peroxide gave the corresponding allylic bromide. Following treatment with potassium acetate under phase transfer catalysis led to **2c** (Scheme 65, bottom).<sup>[78]</sup>



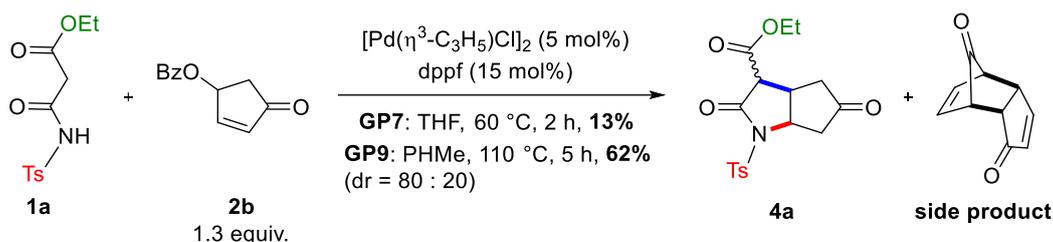
Scheme 65. Synthesis of bis-electrophiles **2b** and **2c**.

However, treatment of **2b** with bis-nucleophile **1a** under the first optimized conditions in THF at 60 °C without base (**GP7**) afforded the desired annulated compound **4a** only in a very low yield. The main product was dicyclopentadienone, generated through elimination of  $\eta^3$ -allylpalladium complex, followed by dimerizative Diels-Alder reaction of the transient dicyclopentadienone.<sup>[79]</sup> However, after much experimentation, we found that carrying out the reaction in toluene at 110 °C (**GP9**) gave the expected annulated product **4a** in 62% yield as a mixture of diastereoisomers (dr = 80 : 20) (Scheme 66).

<sup>77</sup> a) O'Byrne, A.; Murray, C.; Keegan, D.; Palacio, C.; Evans, P.; Morgan, B. S. *Org. Biomol. Chem.* **2010**, *8*, 539-545. b) Dols, P. P. M. A.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron* **1994**, *50*, 8515-8538.

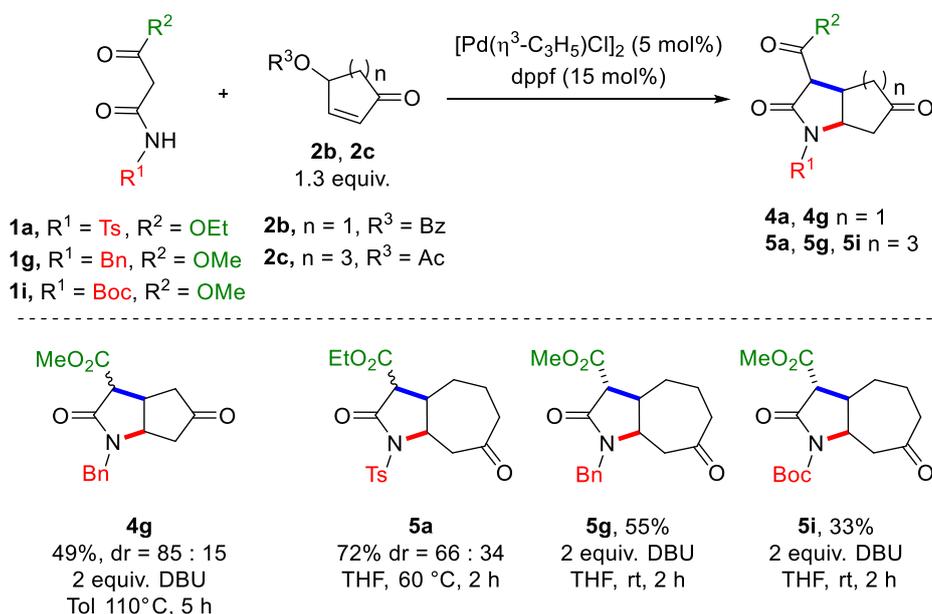
<sup>78</sup> Fujimoto, Y.; Xie, R.; Tully, S. E.; Berova, N.; Nakanishi, K. *Chirality*, **2002**, *14*, 340-346.

<sup>79</sup> Allen, C. F. H.; Vanllan, J. A. *J. Am. Chem. Soc.* **1950**, *72*, 5165-5167.



Scheme 66. Pd-catalyzed [3+2]-annulation between **1a** and **2b**.

Under these new optimized conditions, but in the presence of 2 equivalents of DBU (**GP10**), the cyclopentenone 4-benzoate **2b** reacted also with the *N*-benzyl bis-nucleophile **1g** affording the corresponding annulated product **4g** in 49% yield as a mixture of diastereoisomers (dr = 85 : 15) (Scheme 67). Furthermore, the reactions between the seven-membered acetate bis-electrophile **2c** and some bis-nucleophiles were carried out using the original optimized conditions in THF at rt or 60 °C (**GP7**). Thus, **2c** reacted smoothly with **1a** at 60 °C providing the desired annulated product **5a** as a mixture of diastereoisomers (dr = 66 : 34) in 72% yield. On the other hand, **2c** reacted with **1g** and **1i** in the presence of DBU at room temperature (**GP8**), affording the corresponding annulated compounds **5g** and **5i** as single diastereoisomers in 55% and 33% yield, respectively (Scheme 67).



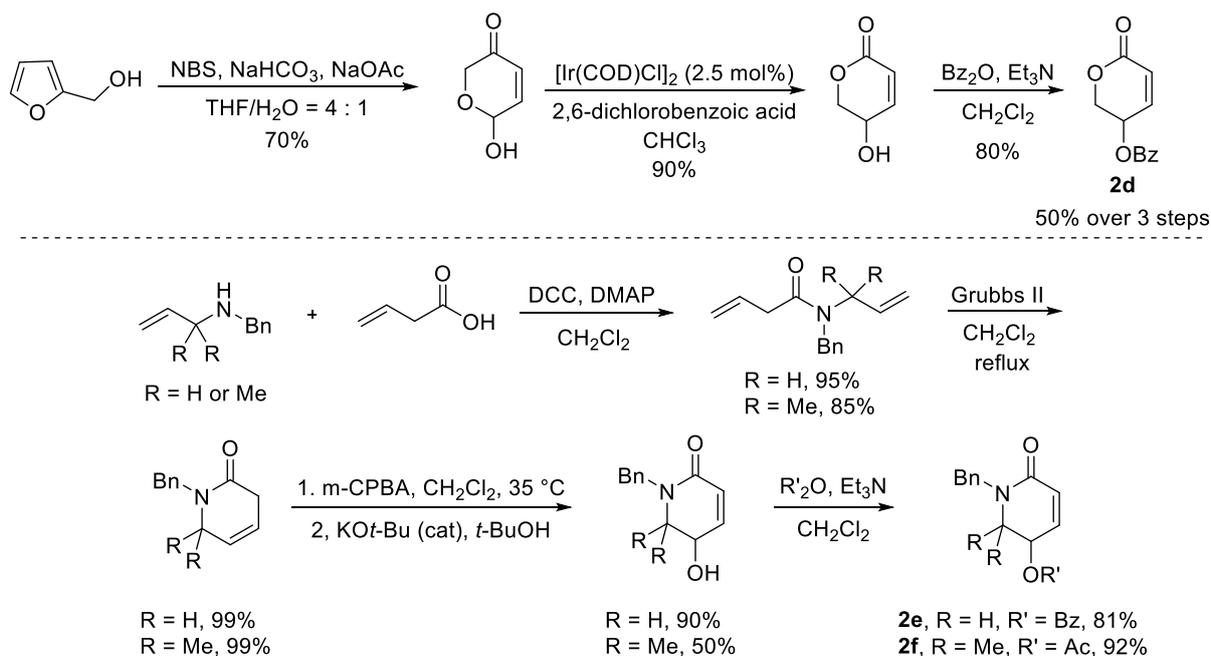
Scheme 67. Scope of the cyclic  $\alpha,\beta$ -unsaturated- $\gamma$ -oxycarbonyl.

The above results confirm the general validity of our new annulation plan, which allows to build up pyrrolidone structures fused at position 4,5 to five-, six- and seven-membered rings.

To gain further insights into the scope of annulation, we tested next the annulations using cyclic  $\alpha,\beta$ -

unsaturated- $\gamma$ -oxy-carbonyls bearing a heteroatom in the position close to the carbonyl **2d-2f**.

Bis-electrophile **2d** was prepared from furfuryl alcohol by the Achmatowicz reaction followed by Iridium-catalyzed dynamic kinetic isomerization and benzylation of the resulting pyranulose (Scheme 68, top).<sup>[80]</sup> Bis-electrophiles **2e-2f** were prepared in four steps from 3-butenic acid by amidation in the presence of the appropriate amine followed by ring-closing metathesis, *m*-CPBA epoxidation, KO*t*-Bu catalyzed elimination, and final benzylation of the resulting allylic alcohol (Scheme 68, bottom).

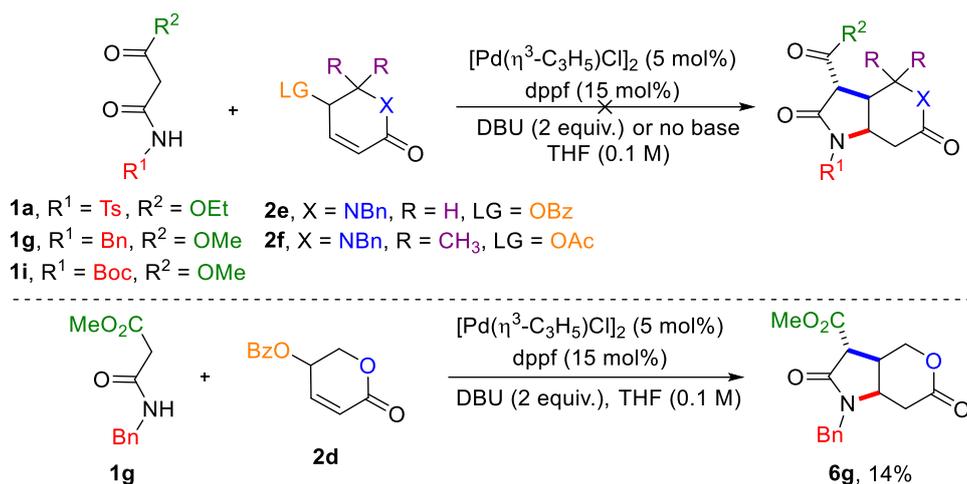


Scheme 68. Synthesis of bis-electrophiles **2d-2f**.

We first considered the formal incorporation of an oxygen **2d** or a nitrogen **2e** atom at position 6 of the parent cyclohexenone 4-benzoate (cyclohexenone numbering).

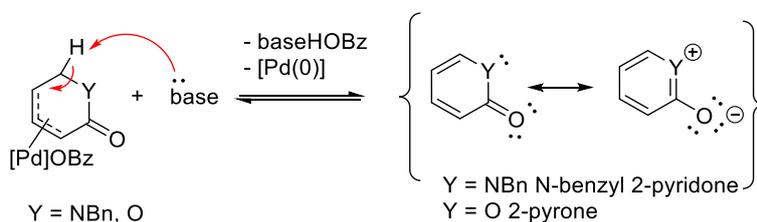
However, no desired annulated product was obtained from the amide derivative **2e** (Scheme 69, top), only a tiny amount of annulated product **6g** was detected from reaction of **2d** (Scheme 69, bottom).

<sup>80</sup> a) Takayama, H.; Jia, Z.-J.; Kremer, L.; Bauer, J. O.; Strohmman, C.; Ziegler, S.; Antonchick, A. P.; Waldmann, H. *Angew. Chem. Int. Ed.* **2013**, 52, 12404-12408. b) Wang, H.-Y.; Yang, K.; Bennett, S. R.; Guo, S.-R.; Tang, W.-P. *Angew. Chem. Int. Ed.* **2015**, 54, 8756-8759.



Scheme 69. Reactivity of cyclic  $\alpha,\beta$ -unsaturated- $\gamma$ -oxycarbonyls bearing a heteroatom at position 6.

The above preliminary experiments suggest that the  $\eta^3$ -allyl complexes deriving from this type of substrates have a very strong tendency to  $\beta$ -eliminate, leading to 2-pyrone or 2-pyridone, the driving force being very likely the aromatic character of these heterocycles. However, the reaction of bis-nucleophiles **1a** or **1g** with bis-electrophile **2f**, which was designed to avoid the  $\beta$ -elimination, turned out to be unsuccessful as well (Scheme 70).



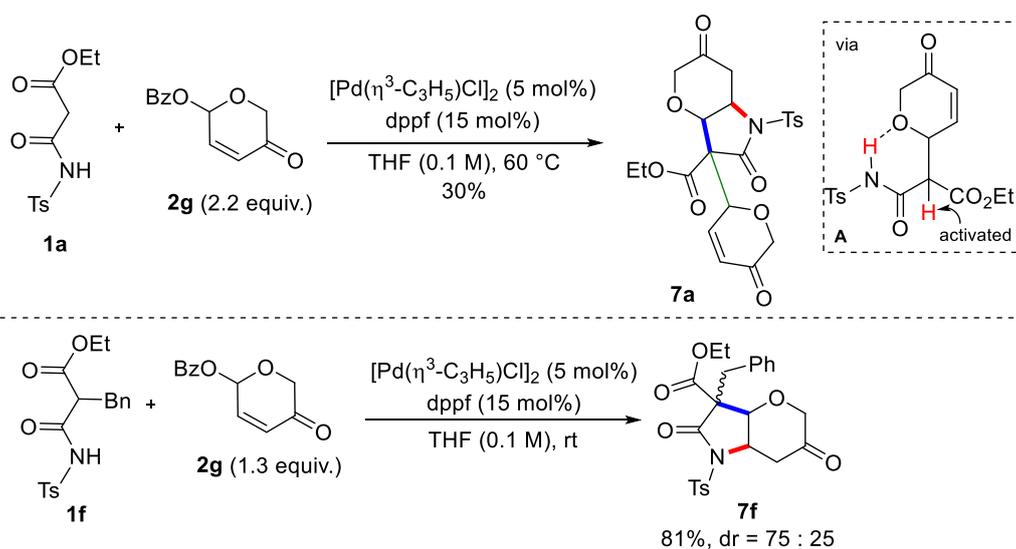
Scheme 70. Rational for the unsuccessful annulation when using **2d** and **2e**.

In view of the above disappointing results, we passed to consider the 5-oxo-5,6-dihydro-2H-pyran-2-yl benzoate **2g**, which bears the heteroatom at position 5. The bis-electrophile **2g** was synthesized following the same procedure reported by Waldmann and co-workers (Scheme 68, top).<sup>[80a,81]</sup>

In the event, treatment of **2g** with **1a** under the above optimized reaction conditions in THF without base (**GP7**) did not afford the expected adduct, but low amounts of product **7a**, resulting from double allylation of **1a** (with two equivalents of **2g**), with a single aza-Michael ring closure. After some relatively ineffective trials, annulation using 2.2 equivalents of **2g** provided the adduct **7a** in 30% yield (Scheme 71, top). This result suggested that, in this particular case, the initially formed annulated product is more

<sup>81</sup> van der Deen, H.; van Oeveren, A.; Kellogg, R. M.; Feringa B. L. *Tetrahedron Lett.* **1999**, *40*, 1755-1758.

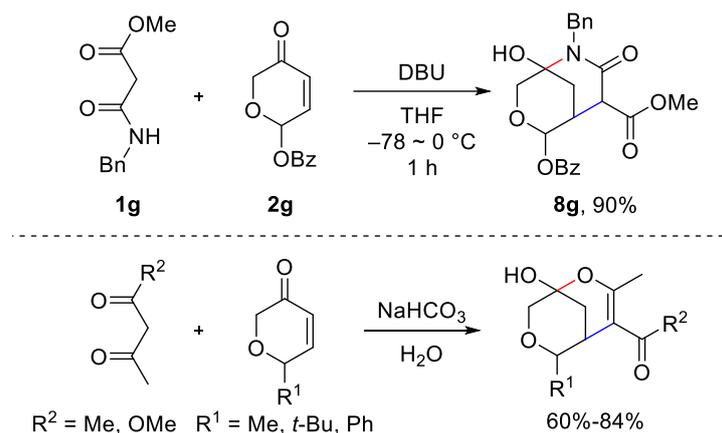
activated toward (a second) allylation than the starting substrate. We speculate that an intramolecular H-bond in the first generated intermediate **A** may be responsible of this unexpected behavior. Supposing that the use of a bis-nucleophile possessing a single carbon acid should reestablish the normal behavior, we used the mono-benzylated  $\beta$ -amido-ester **1f**. As expected, its reaction with **2g** under the optimized conditions (**GP7**) proceeded smoothly, affording the expected adduct **7f** as a mixture of diastereoisomers (dr = 75 : 25) in 81% yield (Scheme 71, bottom).



Scheme 71. Reactivity of cyclic  $\alpha,\beta$ -unsaturated- $\gamma$ -oxy-carbonyls bearing an oxygen at position 5.

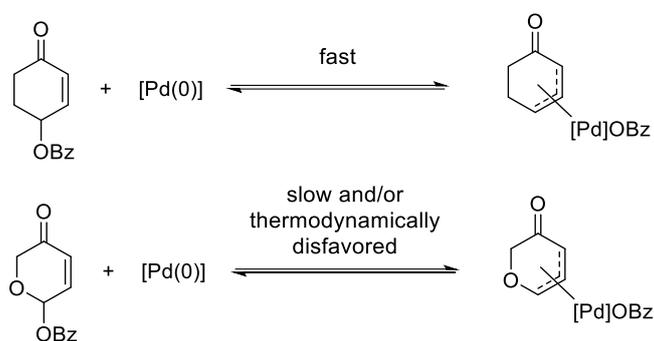
Reaction between bis-nucleophile **1g** and bis-electrophile **2g** provided another rather unexpected result, affording the bridged hemiaminal **8g** in excellent yield (Scheme 72, top), which results from an intermolecular Michael reaction followed by intramolecular acylaminohemiaminal formation between the amide and the keto functions. This result suggests that, in this case, the intermolecular Michael reaction wins against (is faster than the potential) Pd-catalyzed allylation. As expected, repetition of the reaction without the palladium catalytic system proceeds again without problems, affording **8g** in 90% yield. Ramasastry and co-workers observed an analogous reactivity that gave a bridged bicyclic acetal under aqueous basic conditions (Scheme 72, bottom).<sup>[82]</sup>

<sup>82</sup> Kasare, S.; Bankar, S. K.; Ramasastry, S. S. V. *Org. Lett.* **2014**, *16*, 4284-4287.



Scheme 72. Formation of bridged compound **8g**.

A number of other attempts to obtain the “regular” annulated product failed. The above results suggest that while generation of the  $\eta^3$ -allylpalladium intermediate from an 4-oxocyclohex-2-enone is a kinetically viable step, the corresponding ionization from a 6-oxy-2H-pyran-3(6H)-one (which incorporates an oxygen atom instead of a methylene group vicinal to the allylic position), is electronically disfavored (Scheme 73).

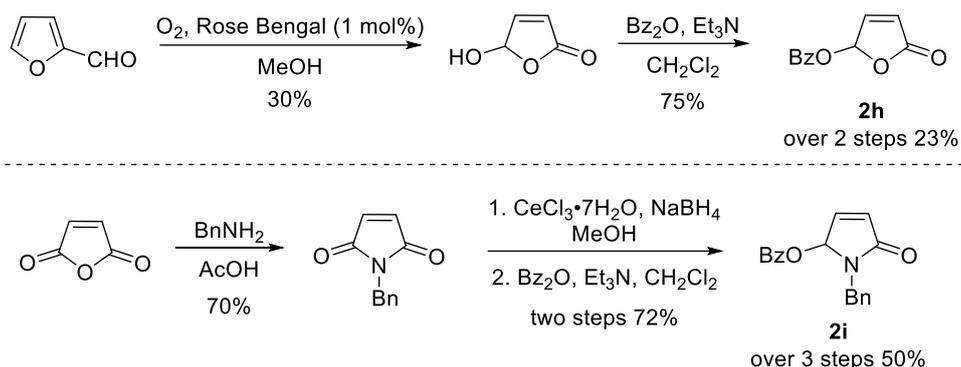


Scheme 73. Rational for the failure to observe ionization from 6-oxy-2H-pyran-3(6H)-one.

We next focused our attention on  $\gamma$ -benzoxybutenolide **2h** and the  $\gamma$ -lactam analog **2i**. The bis-electrophile **2h** was prepared in a two-step sequence from furfural. Reaction of furfural with singlet oxygen in presence of a photocatalyst (Rose Bengal) gave the  $\gamma$ -hydroxybutenolide, which was submitted to a benzylation step, leading to **2h** (Scheme 74, top).<sup>[83]</sup> On the other hand, **2i** was prepared in a three-step sequence from maleic anhydride. Reaction of maleic anhydride with benzylamine gave *N*-benzylmaleimide. Following chemoselective amide 1,2-reduction using  $\text{NaBH}_4/\text{CeCl}_3$  and subsequent benzylation according

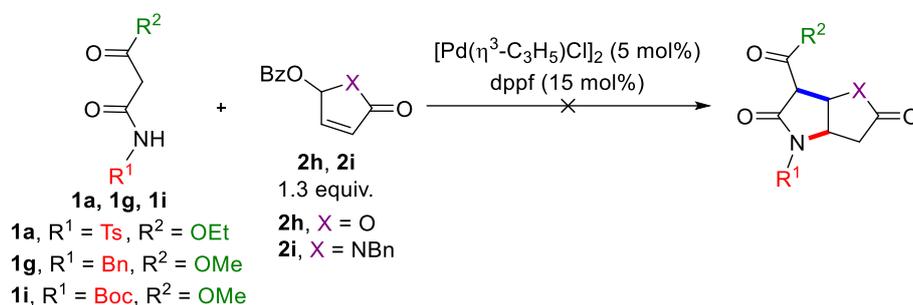
<sup>83</sup> Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 3090-3100.

to the procedure described by Takabe gave **2i** in 50% yield over 3 steps (Scheme 74, bottom).<sup>[84]</sup>



Scheme 74. Synthesis of the bis-electrophile **2h-2i**.

However, although Trost and Toste were able to engage **2h** in Pd-catalyzed allylations,<sup>[83]</sup> all attempts of annulation of these electrophiles under a wide variety of catalytic systems, met with failure (Scheme 75). These unsatisfactory results show that the kinetic preference for the Pd-catalyzed allylation over the conjugate addition, which is a key for the desired reaction enchainment, is very delicate and electronic variations on the cyclic bis-electrophile may easily jeopardize the final outcome.



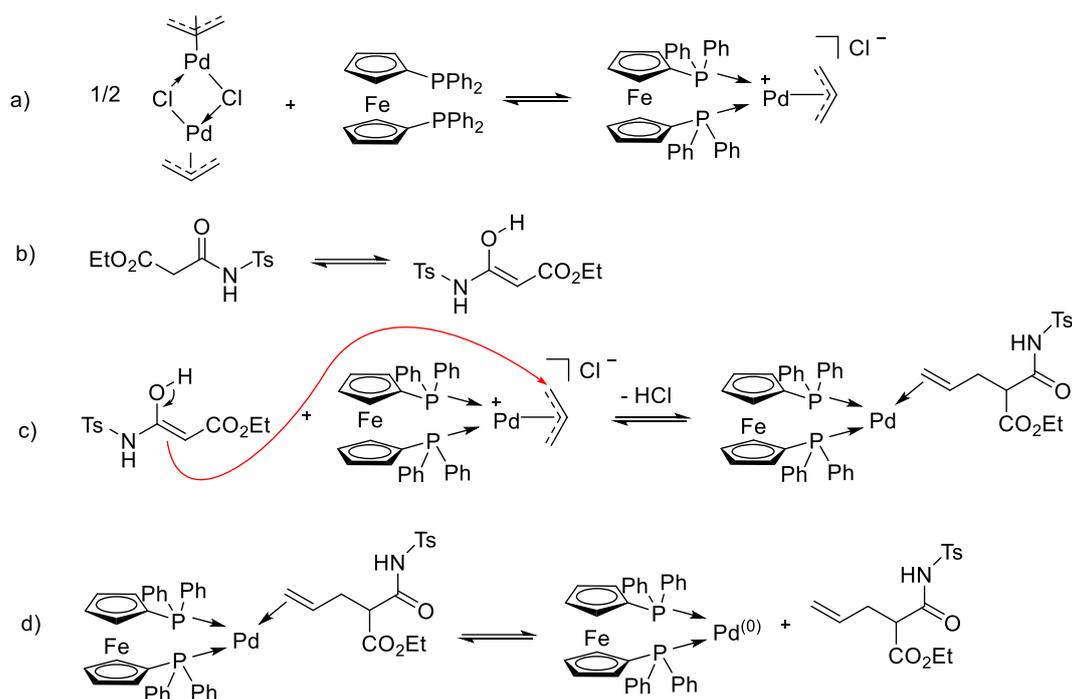
Scheme 75. Reactivity of cyclic  $\alpha,\beta$ -unsaturated- $\gamma$ -oxy-carbonyls lactone **2h** and lactam **2i**.

## 4. Mechanism

On the basis of our results, a plausible mechanism for the Pd-catalyzed [3+2]-C-C/N-C bond forming annulation between *N*-tosylamido ester **1a** and 2-cyclohexenone 4-benzoate **2a** is presented here below (Scheme 77). First, the bis-phosphine ligand (dppf) coordinates the dimeric pre-catalyst  $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$  generating the corresponding monomeric  $\eta^3$ -allylpalladium complex (Scheme 76, step a). Allylation of the

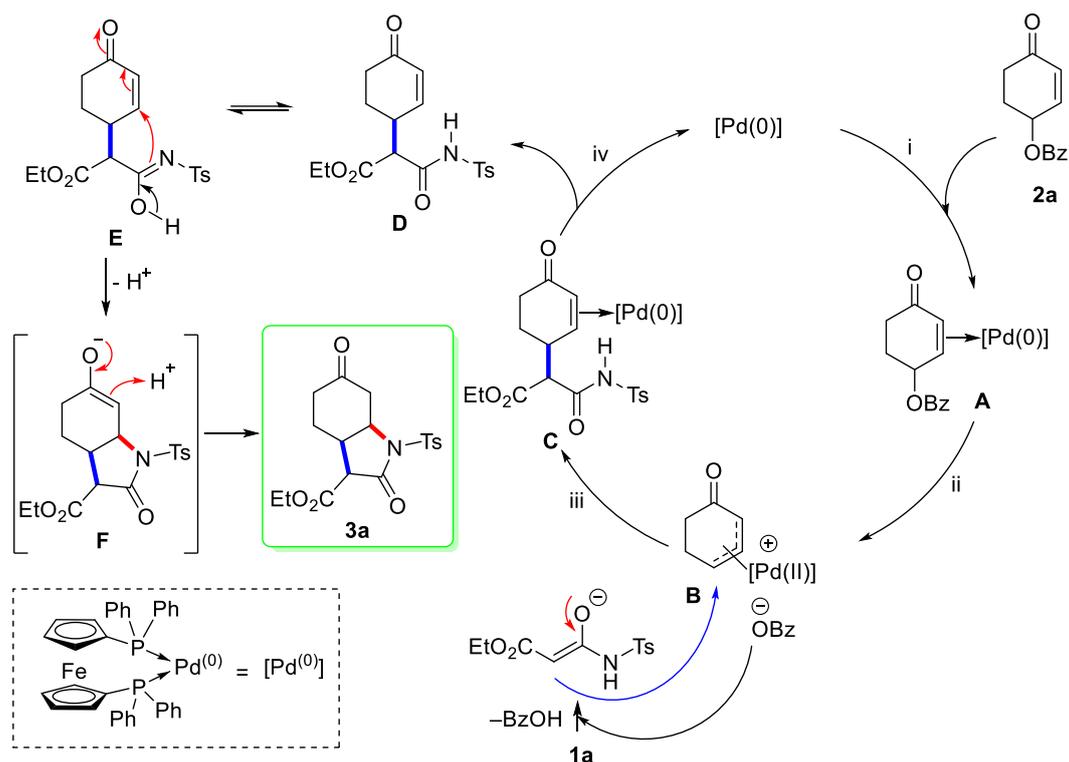
<sup>84</sup> a) Nöth, J.; Frankowski, K. J.; Neuenswander, B.; Aube, J.; Reiser, O. *J. Comb. Chem.* **2008**, *10*, 456-459. b) Mase, N.; Nishi, T.; Hiyoshi, M.; Ichihara, K.; Bessho, J.; Yoda, H.; Takabe, K. *J. Chem. Soc., Perkin Trans. 1*, **2002**, 707-709. c) Yamashita, S.; Mase, N.; Takabe, K. *Tetrahedron: Asymmetry* **2008**, *19*, 2115-2118.

enolic form of **1a** generates the Pd(0) catalyst (Scheme 76, steps b, c, and d).



Scheme 76. Generation of the Pd(0) catalyst from the pre-catalyst.

The catalytic cycle is supposed to proceed as follows: oxidative addition of the bis-electrophile **2a** to the [Pd(0)] complex affords the corresponding  $\eta^3$ -allyl-palladium(II) complex **B** through the  $\eta^2$ -alkene complex **A** (steps i and ii); C-allylation with the amidinium-enolate of the bis-nucleophile **1a**, formed in the meantime by deprotonation with the benzoate anion (counter-ion of the  $\eta^3$ -allylPd complex) gives the  $\eta^2$ -allyl-Pd(0) complex **C** (step iii); Decoordination of Pd(0) from **C** closes the catalytic cycle and releases the C-allylation product **D** (step iv). Then, the following part of the mechanism is expected to be non-catalyzed. Thus, intermediate **D**, very likely through the enol **E**, undergoes an intramolecular aza-Michael addition to provide **3a** through **F** (Scheme 77).



Scheme 77. Plausible mechanism of Pd-catalyzed [3+2]-C-C/N-C bond forming annulation.

## 5. Studies of enantioselectivity

During the last forty years, the request for fine-chemicals has substantially increased. For example, the development of new drugs is of major interest in our society. These expectations need the building of molecules with stereodefined stereogenic centers, which are frequently the basis of the activity of the drug. In this context, the palladium-catalyzed asymmetric allylic alkylation (Pd-AAA) is one of the most powerful strategies to construct carbon-carbon and carbon-heteroatom bonds in enantioselective way, which had extensive application in the synthesis of a number of pharmaceutical and natural products.<sup>[85]</sup> As a logical extension of our work, we next turned our attention to investigate an enantioselective version of our annulation process. Accordingly, we envisaged to test chiral enantiopure ligands for palladium, taking the annulation between **1a** and ( $\pm$ )-**2a** as our model reaction.

First of all, in the non-asymmetric version, the Pd-catalyzed part of the annulation is expected to take place via the following classical steps: 1) [Pd(0)] coordination; 2) ionization; 3) nucleophile allylation with concomitant reduction of the metal [Pd(II)→Pd(0)]; 4) [Pd(0)] decoordination from the alkene. Furthermore,

<sup>85</sup> a) Trost, B. M.; Crawley, M. L; *Chem. Rev.* **2003**, *103*, 2921-2943. b) Trost, B. M.; Machacek, M. R.; Aponick, A. *Acc. Chem. Res.* **2006**, *39*, 747-760. c) Trost, B. M.; Schultz, J. E. *Synthesis* **2019**, *51*, 1-30. d) Kazmaier, U. Editor: *Top. Organomet. Chem.* n. 38, *Transition Metal Catalyzed Enantioselective Allylic Substitution in Organic Synthesis*, Berlin / Heidelberg: Springer. **2012**.

provided that the reaction is under kinetic control, the use of a chiral enantiopure ligand for palladium can allow to obtain enantioenriched products, *i.e.* asymmetric catalysis. Indeed, in this case, the pathways leading to the two antipodal products may be energetically differentiated in the catalytic cycle due to of the diastereoisomeric relationships existing between each enantiomeric intermediate making part of the racemic mixture and the enantiopure catalytic system (Figure 2).

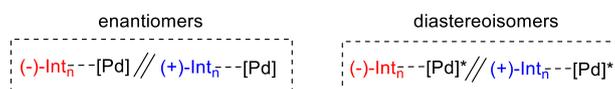


Figure 2. Concept of asymmetric catalysis: enantiomeric vs diastereoisomeric relationships between the intermediates of the catalytic cycle.

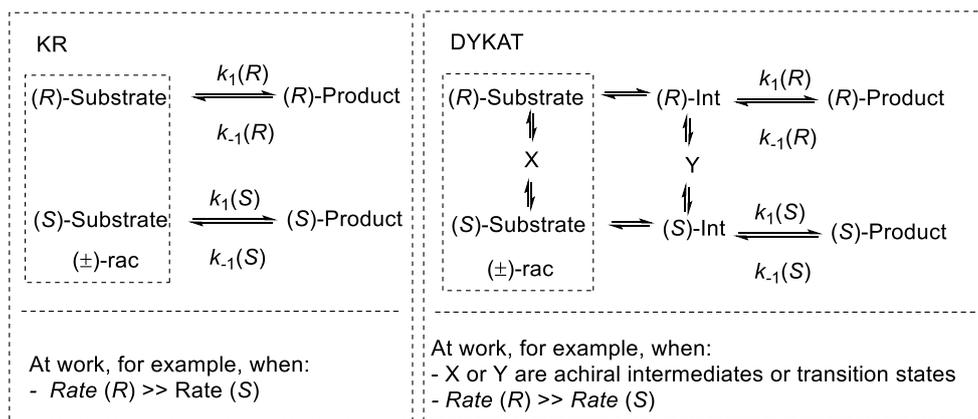
Before presenting our results, a brief introduction on asymmetric transformations starting from racemic substrates is presented.

## 5.1 Concepts in the asymmetric Pd-catalyzed allylation

An asymmetric transformations starting from a racemic substrate can proceed through either a (static) kinetic resolution (KR) or a dynamic kinetic resolution (DKR), better renamed by Trost dynamic kinetic asymmetric transformation (DYKAT).<sup>[86,87]</sup> A KR is at work when the enantiomers of a racemic substrate are converted to the chiral products with different kinetics, the ideal case being when only one enantiomeric substrate reacts giving a maximum theoretical yield of 50%. Of course, such a process is not efficient, as at least 50% of the substrate is left behind. On the other hand, in a DYKAT both the enantiomers of the racemic substrate can be channeled into the same enantiomeric product, thereby allowing for a theoretical 100% yield. This can happen because the enantiomeric substrates, or enantiomeric derivatives of them, located upstream of the enantio-discriminating step can rapidly interconvert through achiral intermediates or achiral transition states (Scheme 78).

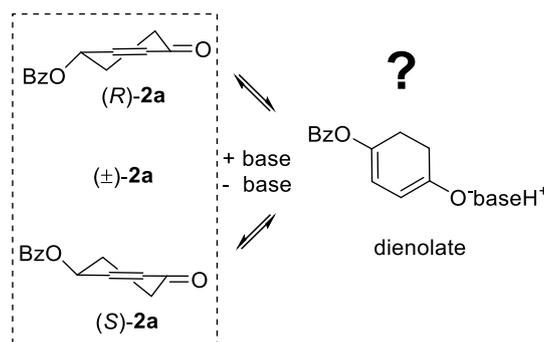
<sup>86</sup> a) Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 5968-5976. b) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 3543-3544. c) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 3090-3100. d) Boutier, A.; Kammerer-Pentier, C.; Krause, N. Prestat, G.; Poli, G. *Chem. Eur. J.*, **2012**, *18*, 3840-3844.

<sup>87</sup> Books and reviews: a) Walsh, P. J.; Kozlowski, M. C. *Fundamentals of Asymmetric Catalysis*; University Science Books, CA, 2009; p 272. b) Bhat, V.; Welin, E. R.; Guo, X.; Stoltz, B. M. *Chem. Rev.* **2017**, *117*, 4528-4561. c) Jenkins, K.; Caddick, S. *Chem. Soc. Rev.* **1996**, *25*, 447-456. d) Huerta, F. F.; Minidis, A. B. E.; Bäckvall, J.-E. *Chem. Soc. Rev.* **2001**, *30*, 321-331. e) Pellissier, H. *Tetrahedron*, **2003**, *59*, 8291-8327. f) Trost, B. M.; Fandrick, D. R. *Aldrichimica Acta* **2007**, *40*, 59. g) Rachwalski, M.; Vermuea N.; Rutjes F. P. J. T. *Chem. Soc. Rev.*, **2013**, *42*, 9268-9282.



Scheme 78. Concepts of KR and DYKAT.

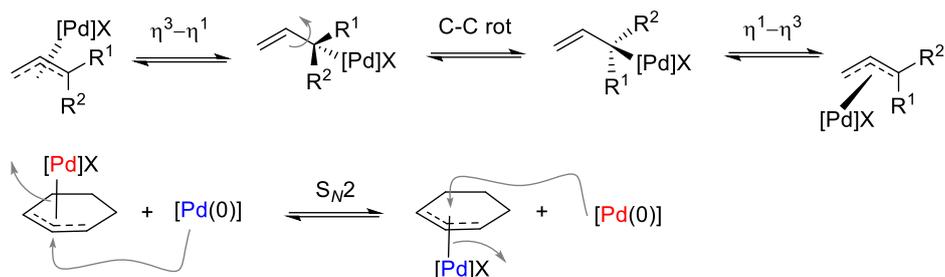
According to the above concepts, in our specific case, we first asked ourselves if it was possible to bring about a rapid racemization of the  $\gamma$ -oxy- $\alpha,\beta$ -unsaturated ketone ( $\pm$ )-**2a** through a base mediate enolization of the vinyllogous  $\gamma$ -position (Scheme 79).



Scheme 79. Conjectural enolization of ( $\pm$ )-**2a** through deprotonation at the  $\gamma$  vinyllogous position.

However, not so unexpectedly, a  $^1\text{H}$  NMR test wherein progressive amounts of DBU were added to a  $\text{CDCl}_3$  solution of ( $\pm$ )-**2a** did not show any acid character of the  $\gamma$ -H atom. We thus quickly ruled out this racemization hypothesis and focused our attention of the possible racemization at the level of the  $\eta^3$ -allylpalladium intermediate. This is possible indeed, as these complexes may be fluxional, and switch the allyl face coordinating the metal. Two mechanistic options are in principle possible. The former one involves exchange of the complexed allyl face of the  $\eta^3$ -allylpalladium complex through a  $\pi$ - $\sigma$ - $\pi$  equilibration (Scheme 80, top). Alternatively, switch of the coordinated face can be in principle obtained through  $\text{S}_{\text{N}}2$  displacement by Pd(0) (Scheme 80, bottom).<sup>[88]</sup>

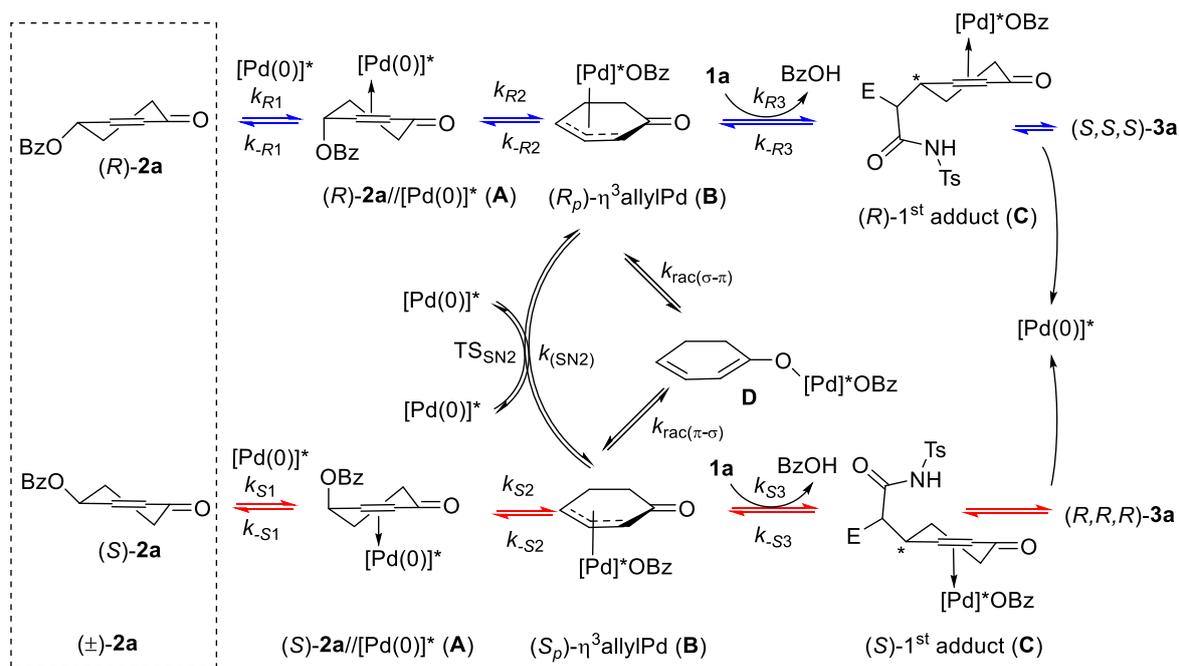
<sup>88</sup> a) Takahashi, T.; Jinbo, Y.; Kitamura, K.; Tsuji, J. *Tetrahedron Lett.* **1984**, *25*, 5921-5924. b) Granberg, K. L.; Bäckvall, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 6858-6863. c) Lemaire, S.; Giambastiani, G.; Prestat, G.; Poli, G. *Eur J. Org. Chem.* **2004**, 2840-2847.



Scheme 80. Possible pathways for the switch of the allyl face coordinated to the metal in  $\eta^3$ -allylpalladium complexes.

Top: [ $\eta^3$ - $\eta^1$  // C-C bond rotation //  $\eta^1$ - $\eta^3$ ] isomerization; bottom:  $S_N2$  displacement.

If we transpose the above two generic mechanisms to our specific case, a first racemization mechanism would correspond to a  $\pi$ - $\sigma$ / $\sigma$ - $\pi$  equilibration between ( $R_p$ )- and ( $S_p$ )- $\eta^3$ -allylPd intermediates **B** involving the 1,3-cyclohexadienyloxypalladium complex **D**. Alternatively, the equilibration between the same intermediates **B** may take place through an  $S_N2$  nucleophilic displacement of  $[Pd(0)]$ , which would in this case involve the achiral transition state  $TS_{SN2}$  (Scheme 81).



Scheme 81. Generic mechanistic path for a Pd-catalyzed annulation between **1a** and  $(\pm)$ -**2a** in the presence of a chiral ligand.

Step 1: Pd(0) coordination; step 2: ionization ( $\eta^3$ -allylpalladium formation); step 3: nucleophile allylation.

Now, as a function of the rates of the various steps involved in the process, which in turn may depend on the adopted reaction conditions, we can have KR or DYKAT at work, with the enantio-discriminating transition state being located at variable positions. As an example, the qualitative energetic profile depicted

in Figure 3 shows an arbitrarily chosen case where the kinetic constants favor the enantiomer (*R,R,R*)-**3a** via a KR. Here, the enantio-discriminating transition states appear to be the ones associated to the ionization (step 2), wherein the diastereoisomeric  $\eta^3$ -allylpalladium intermediates **B** are kinetically generated without any possible equilibration.

However, by appropriately changing the reaction conditions, the equilibration rates between the diastereoisomeric  $\eta^3$ -allylpalladium intermediates **B** (passing through either **D** or  $TS_{SN2}$ ) can be in principle enhanced to the point that become faster than their evolution to the products. This would correspond to Curtin-Hammett conditions wherein the enantiodiscriminating transition state becomes the nucleophile allylation (step 3) and a DYKAT is at work.

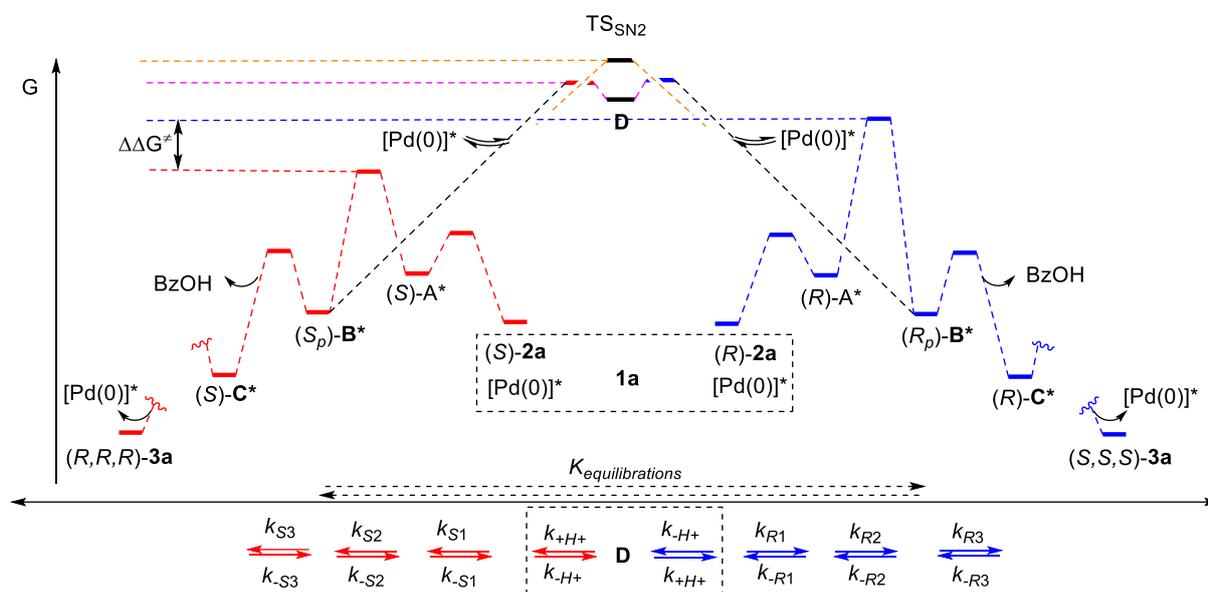


Figure 3. Qualitative energy profile for a generic annulation between **1a** and ( $\pm$ )-**2a** in the presence of a chiral ligand.

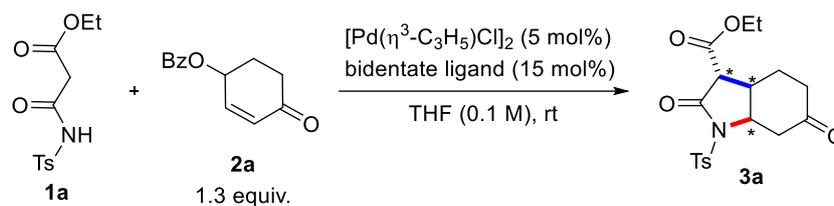
Color code: red path to (*R,R,R*)-**3a**; blue path to (*S,S,S*)-**3a**.

Furthermore, as step 3 is expected to be irreversible, and we never isolated or detected the open 1<sup>st</sup> adduct in the reaction crude, we can safely speculate that the aza-Michael step should not be rate determining.

## 5.2 Pd-catalyzed asymmetric [3+2]-annulations with chiral phosphine ligands

Since in the previous study, the bidentate phosphine ligand dppf was the ligand of choice, we settled to test a set of chiral enantiopure bidentate phosphine ligands using 5 mol%  $[Pd(\eta^3-C_3H_5)Cl]_2$ , 1.3 equiv. of **2a**, and working in THF at room temperature. The results are summarized in Table 4.

Table 4. Pd-catalyzed asymmetric [3+2]-annulation with chiral bidentate phosphine ligands.



Entry	Ligand <sup>a</sup>	Time (h)	Yield (%)	ee (%) <sup>b</sup>
1	( <i>R</i> )-BINAP	8	65	8
2	( <i>R</i> )-SynPhos	8	52	7
3	( <i>R</i> )-xylyl-P-Phos	8	65	18
4	SL-A101-1	18	74	2
5	(+)-DIOP	8	70	8
6	( <i>R,R</i> )-DACH Trost ligand	18	0	0
7	( <i>S<sub>C</sub>,R</i> )-TaniaPhos	8	82	23
8 <sup>c</sup>	( <i>S<sub>C</sub>,R</i> )-TaniaPhos	8	61	25
9	( <i>R<sub>C</sub>,R</i> )-TaniaPhos	8	85	10
10	( <i>S<sub>C</sub>,R</i> )-MandyPhos	18	85	2
11	SL-M001-1	18	85	2
12	SL-M004-1	18	58	26

<sup>a</sup>The structure of the phosphines is listed in Figure 4. The serial number of some ligands comes from *Solvias* company. <sup>b</sup>The enantiomeric purity of **3a** was determined by chiral HPLC : AD-H, 60 : 40 hexane : isopropanol, 1.0 mL/min, 220 nm, 13.78 min (*S* enantiomer), 23.25 min (*R* enantiomer). <sup>c</sup> Reaction was run at 0 °C.

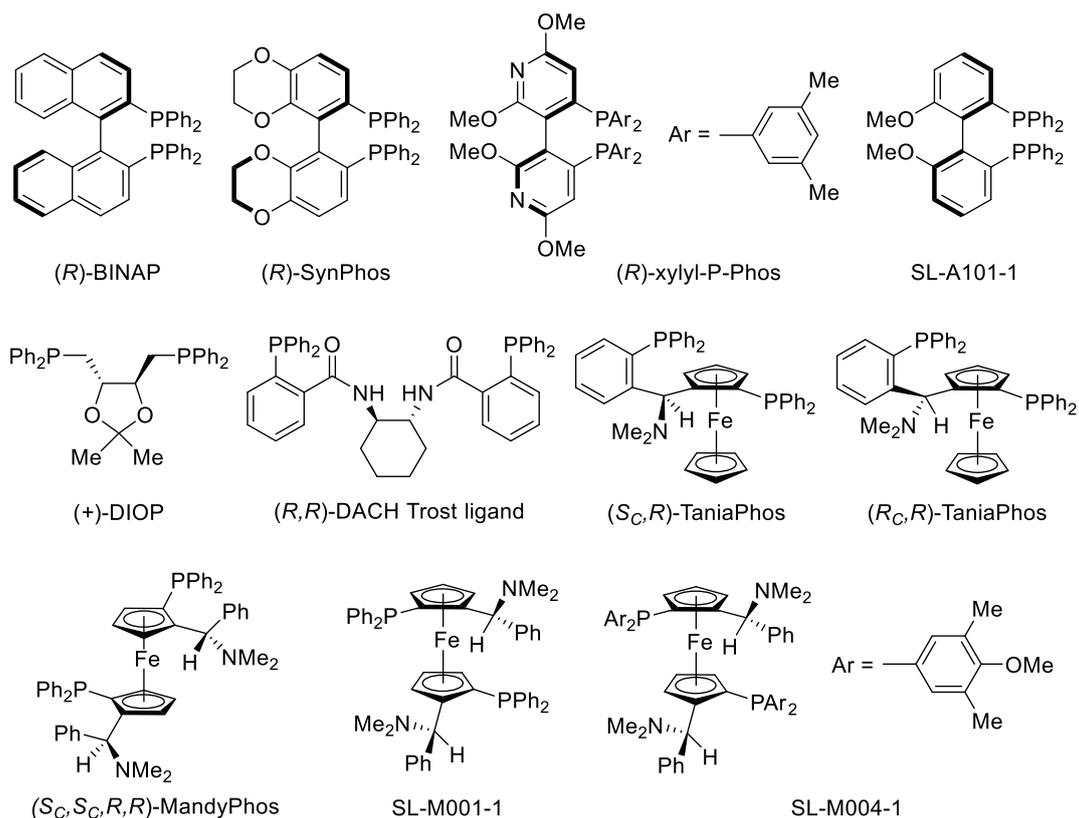


Figure 4. Chiral enantiopure bidentate phosphine ligands.

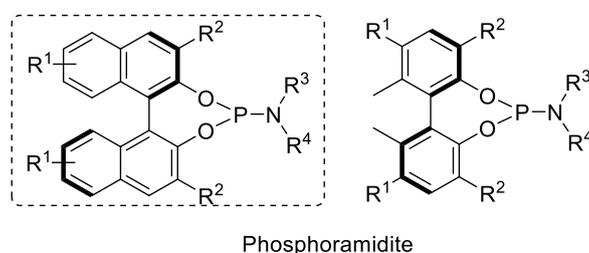
As Table 4 shows, the reaction with the axially chiral diphosphines such as (*R*)-BINAP and (*R*)-xylyl-P-Phos or C<sub>2</sub>-symmetric diphosphine ligands such as (+)-DIOP afforded the moderate to good yield, but low enantioselectivities (entries 1-5). To our surprise, no conversion of **1a** was observed with the (*R,R*)-DACH-phenyl Trost's ligand (entry 6). Ferrocenylphosphine (*S<sub>C</sub>,R*)-TaniaPhos gave an excellent yield (82%) but low enantioselectivity (23% ee), which prompted us to run the reaction at lower temperature (entry 7). Unfortunately, we were not able to improve the enantioselectivity (25% ee) without losing the reactivity by running the reaction at 0 °C (entry 8). Various of ferrocenylphosphines were also tested, but no improvement was observed in terms of enantioselectivity, despite the good yields (entries 9-12). It is noteworthy that the steric hindrance of the chiral ligands has an important influence on the reaction, the bigger steric hindrance, the lower the enantioselectivity.

### 5.3 Pd-catalyzed asymmetric [3+2]-annulations with chiral phosphoramidite ligands

A variety of chiral ligands have been designed, synthesized and employed in asymmetric catalysis, primarily with phosphorus or nitrogen donor atoms. Among them, bidentate ligands have traditionally been considered to be the most efficient ones, primarily due to the stability of their complexes and the

stereohomogeneous environment around the metal centers. However, the discovery of the remarkable catalytic properties of monodentate ligands such as Monophos and related analogues, has raised much interest toward this family of ligands. The application of chiral enantiopure monodentate phosphorus ligands in asymmetric reactions has been extensively described,<sup>[89]</sup> and phosphoramidites have attracted a great interest, due to the high catalytic activities and enantioselectivities associated to them.<sup>[90]</sup> In particular, it has been recently reported that axially chiral phosphoramidites allow Pd-catalyzed asymmetric allylic alkylation with excellent regio- and enantioselectivities.<sup>[91]</sup>

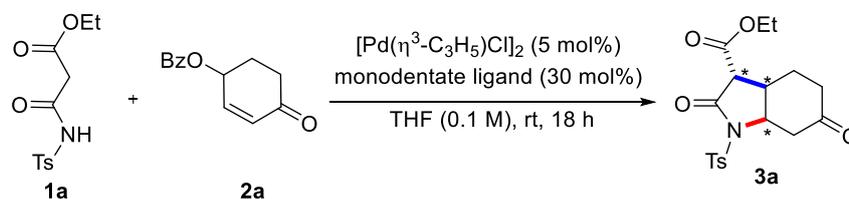
One of the distinguishing features of these chiral ligands is their modular nature as well as their easy fine-tuning through modification of the substituents on the aromatic ring and/or the nitrogen atom (Scheme 82). In particular, chiral phosphoramidite ligands based on the 1,1'-bi-2-naphthol (BINOL) backbone are stable and many of them are commercially available. For this reason, we decided to test them for our annulation reaction.



Scheme 82. Chiral phosphoramidite ligands.

On the basis of the above considerations, we next started to evaluate the influence of the chiral phosphoramidite ligands in our annulation reaction. The results were summarized in Table 5.

Table 5. Pd-catalyzed asymmetric [3+2]-annulation with chiral phosphoramidite ligands.



<sup>89</sup> See some examples : a) Uozumi, Y.; Tanahashi, A.; Lee, S.-Y.; Hayashi, T. *J. Org. Chem.* **1993**, *58*, 1945-1948. b) Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Stud, M. *Adv. Synth. Catal.* **2003**, *345*, 103-151. c) Eberhardt, L.; Armspach, D.; Matt, D.; Toupet, L.; Oswald, B. *Eur. J. Inorg. Chem.* **2007**, 4153-4161.

<sup>90</sup> a) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346-353. b) Minnaard, A. J.; Feringa, B. L.; Lefort, L.; Vries, J. J. D. *Acc. Chem. Res.* **2007**, *40*, 1267-1277. c) Trost, B. M.; Donckele, E. J.; Thaisrivongs, D. A.; Osipov, M.; Masters, J. T. *J. Am. Chem. Soc.* **2015**, *137*, 2776-2778. d) Huang, H.-Z.; Zhao, Y.-F.; Yang, Y.; Zhou, L.; Chang, M.-X. *Org. Lett.* **2017**, *19*, 1942-1945.

<sup>91</sup> a) Boele, M. D. K.; Kamer, P. C. J.; Lutz, M.; Spek, A. L.; Vries, J. G.; Leeuwen, P. W. N. M.; Strijdonck, G. P. *Chem. Eur. J.* **2004**, *10*, 6232-6246. b) Chapsal, B. D.; Ojima, I. *Org. Lett.* **2006**, *8*, 1395-1398. c) Lin, C.-F.; Chien, C.-W. Ojima, I. *Org. Chem. Front.* **2014**, *1*, 1062-1066. d) Balogh, S.; Farkas, G.; Toth, I.; Bakos, J. *Tetrahedron: Asymmetry* **2015**, *26*, 666-673.

Entry	2a (equiv.)	Ligand <sup>a</sup>	Yield (%)	ee (%) <sup>c</sup>
<b>1</b>	1.3	( <i>R</i> )-Monophos	53	66
<b>2</b>	1.3	( <i>S</i> )-Monophos	64	55
<b>3</b>	1.3	( <i>S</i> )-L1	69	18
<b>4</b>	1.3	( <i>S</i> )-L2	0	0
<b>5</b>	1.3	( <i>S</i> )-L3	53	30
<b>6</b>	1.3	( <i>S</i> )-L4	0	0
<b>7</b>	1.3	( <i>S</i> )-L5	55	18
<b>8</b>	1.3	( <i>S</i> )-L6	0	0
<b>9</b>	1.3	( <i>S</i> )-L7	Trace	-
<b>10</b>	1.3	( <i>S</i> )-L8	90	24
<b>11</b>	1.3	( <i>R</i> )-L9	66	8
<b>12</b>	1.3	( <i>R</i> )-L10	74	14
<b>13</b>	1.3	( <i>R</i> )-L11	0	0
<b>14</b>	1.3	( <i>S</i> )-L12	0	0
<b>15</b>	1.3	( <i>S</i> )-L13	0	0
<b>16</b>	2.0	( <i>R</i> )-Monophos	70	60
<b>17</b>	2.5	( <i>R</i> )-Monophos	66	64
<b>18</b>	3.0	( <i>R</i> )-Monophos	80	66
<b>19</b>	6.0	( <i>R</i> )-Monophos	80	66
<b>20<sup>b</sup></b>	3.0	( <i>R</i> )-Monophos	80	54

<sup>a</sup> The structure of above chiral phosphoramidite ligands is reported in Figure 5. All of these ligands were commercially available, except the ligands (*R*)-L9, (*R*)-L10, and (*R*)-L11, which were easily prepared from (*R*)-BINOL and the corresponding amine (Scheme 83). <sup>b</sup> Run reaction in DCM. <sup>c</sup> The enantiomeric purity of **3a** was determined by chiral HPLC : AD-H, 60 : 40 hexane : isopropanol, 1.0 mL/min, 220 nm, 13.78 min (S enantiomer), 23.25 min (R enantiomer).

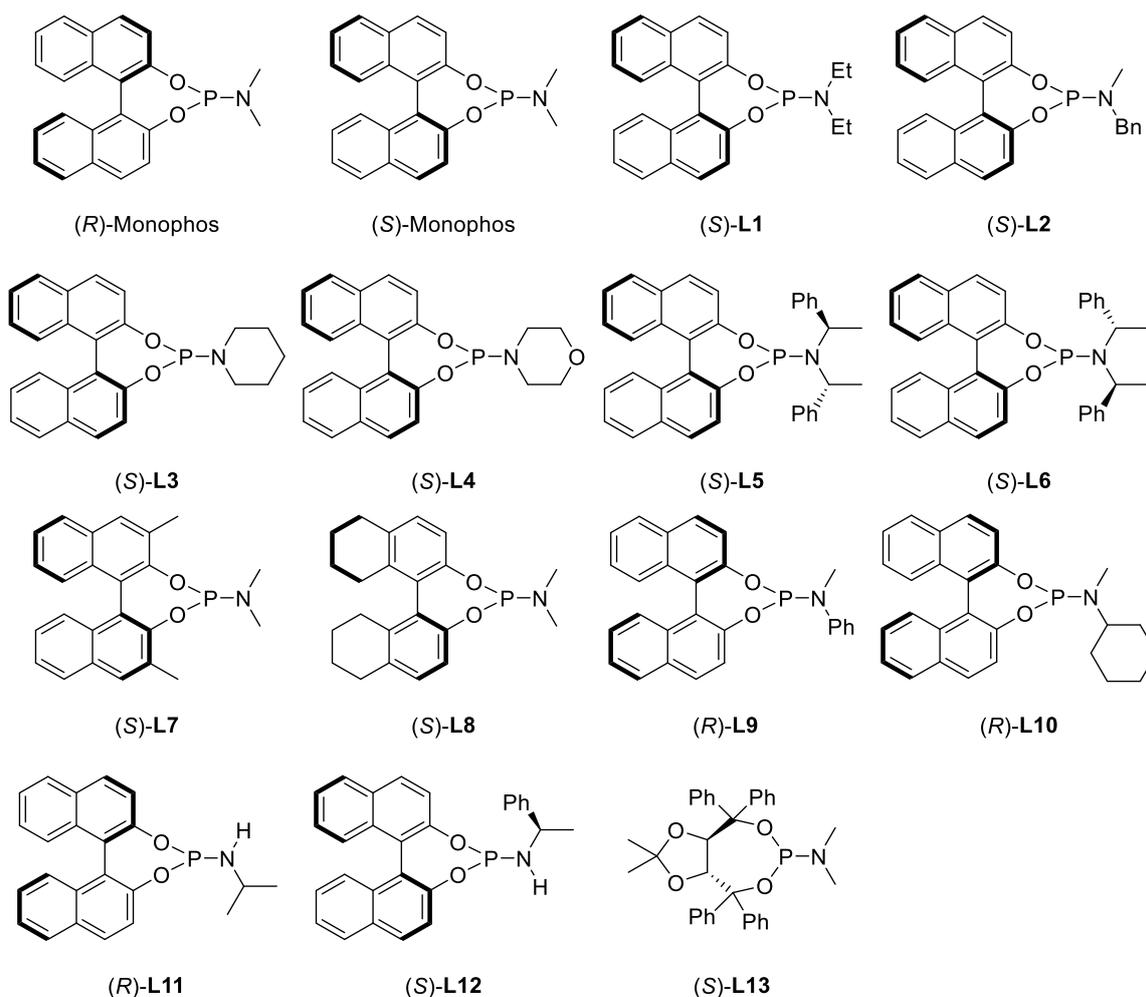
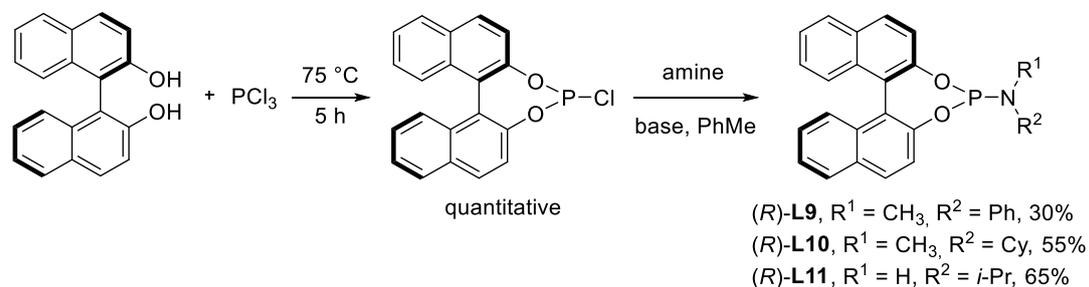


Figure 5. Chiral phosphoramidite ligands.

Phosphoramidites (*R*)-L9, (*R*)-L10, and (*R*)-L11 were synthesized by the reaction of 1,1'-bi-2-naphthol with  $\text{PCl}_3$  followed by treatment of the resulting chlorophosphite with methylphenylamine, cyclohexylmethylamine, and isopropylamine, respectively<sup>[92]</sup> (Scheme 83).



Scheme 83. The synthesis of the chiral phosphoramidites ligands (*R*)-L9 to (*R*)-L11.

<sup>92</sup> a) Lefort, L.; Boogers, J. A. F.; Vries, A. H. M.; Vries, J. G. *Org. Lett.* **2004**, *6*, 1733-1735. b) Breuil, P. A. R.; Patureau, F. W.; Reek, J. N. H. *Angew. Chem. Int. Ed.* **2009**, *48*, 2162-2165. c) Smith, S. M.; Takacs, M. J. *J. Am. Chem. Soc.* **2010**, *132*, 1740-1741.

As Table 5 clearly indicates, (*R*)-Monophos and (*S*)-Monophos gave the best enantioselectivities. Interestingly, (*R*)-Monophos gave 66% ee with 53% yield, while (*S*)-Monophos gave a somehow reversed 55% ee and 64% yield (entries 1-2).

Phosphoramidite (*S*)-**L1**, which carries a NEt<sub>2</sub> group instead of the NMe<sub>2</sub> of Monophos, afforded a higher yield, but lower enantioselectivity (entry 3), while the reaction with (*S*)-**L2**, which carries an NBnMe group, did not proceed (entry 4). This result clearly indicated that raising the steric hindrance of the substituents on the nitrogen atom inhibits catalysis. (*S*)-**L3** and (*S*)-**L4** ligands, carrying cyclo-substitution on the nitrogen atom, gave markedly contrasting results. Indeed, while phosphoramidite (*S*)-**L3** generated the product in 53% yield with 30% enantioselectivity, (*S*)-**L4** did not show any reactivity (entries 5-6).

Other phosphoramidites possessing two or one phenylmethyl groups of different configurations on nitrogen were also tested, but without obtaining good results in yield or enantioselectivity. In particular, comparison of the results of (*S*)-**L5** and (*S*)-**L6** confirms the crucial role of the steric hindrance in the proximity of nitrogen atom (entries 7 and 8).

The influence of the structure of the axially chiral diol was investigated next. (*S*)-**L7** gave no reaction (entry 9), which suggests that steric hindrance at position 2 and 4 of the naphthol is to be avoided. On the other hand, saturation of the two distal rings of 1,1'-bi-2-naphthol (*S*)-**L8** has a beneficial impact on the chemical yield (Entry 10), although at expenses of the enantioselection. However, it has to be recalled that with the adopted stoichiometry of **1a**: ( $\pm$ )-**2a** = 1 : 1.3, if **1a** is totally consumed, the maximum ee% of the product will be only 30%! This good result in yield seems to suggest that electronic enrichment of the oxygen atoms of the ligand brings about a more stable catalytic system.

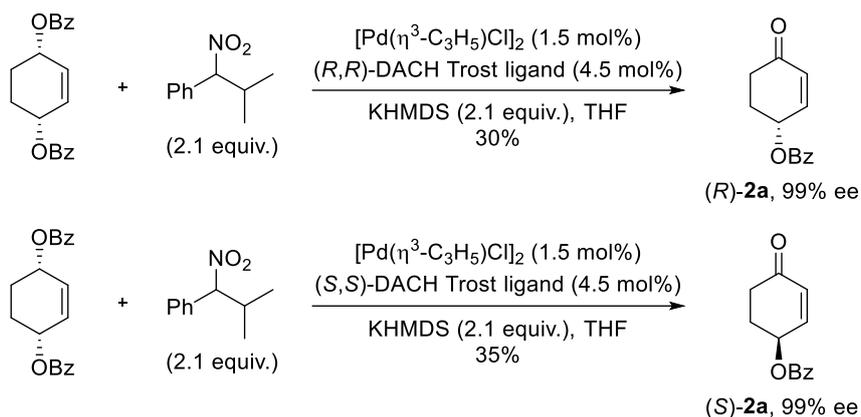
The reaction with (*R*)-**L9** and (*R*)-**L10** gave moderate yields (66% and 74%) but with low enantioselectivity (8% ee and 14% ee) (entries 11-12). Otherwise no conversion was observed under the (*R*)-**L11** or (*S*)-**L12** catalytic system. These last results confirm that a free N-H on the ligand bond is unsuitable (entries 13-14). Moreover, a phosphoramidite derived of TADDOL (*S*)-**L13** gave no reactivity (entry 15).

The influence of the stoichiometry of ( $\pm$ )-**2a** and solvent were also evaluated, but no sensible improvement was observed in terms of enantioselectivity, despite an improved yield (entries 16-20).

In order to better understand the mechanism of this catalytic process, we decided to also test the annulation on the separated enantiomers of the cyclic bis-electrophile. Accordingly, we prepared the enantiopure ketones (*R*)-**2a** and (*S*)-**2a** through the asymmetric, nitronate-promoted Pd-catalyzed oxidation of the *meso* cyclohex-2-ene-1,4-diyl dibenzoate, in the presence of the (*R,R*)- and (*S,S*)-DACH Trost ligands (Scheme 84).<sup>[93,94]</sup>

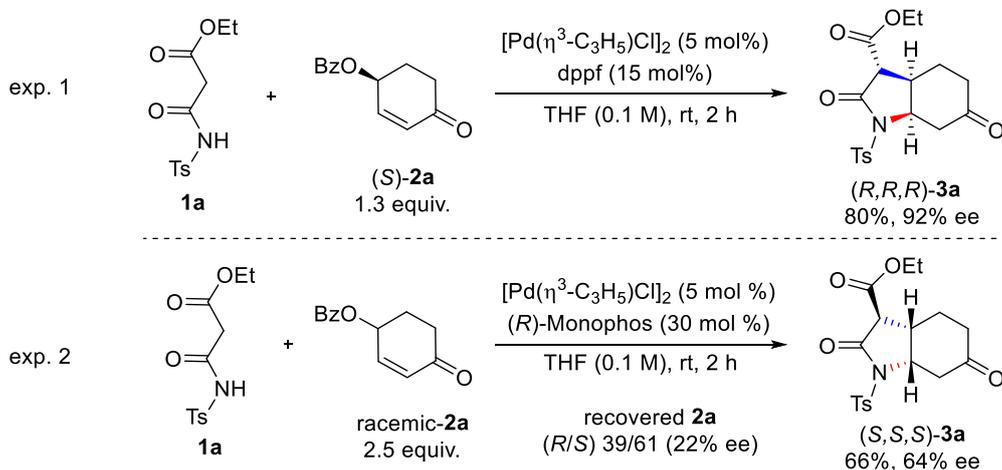
<sup>93</sup> Trost, B. M.; Masters, J. T.; Lumb, J. P.; Fateen, D. *Chem. Sci.*, **2014**, *5*, 1354-1360.

<sup>94</sup> The enantiopurity of the resulting ketones, as determined by chiral HPLC [OJ-H, 90 : 10 hexane : isopropanol, 0.5 mL/min, 220 nm, 33.39 min (*R* enantiomer), 36.73 min (*S* enantiomer)] is in agreement with the literature data.



Scheme 84. Synthesis of chiral substrate *(R)*-**2a** and *(S)*-**2a**.

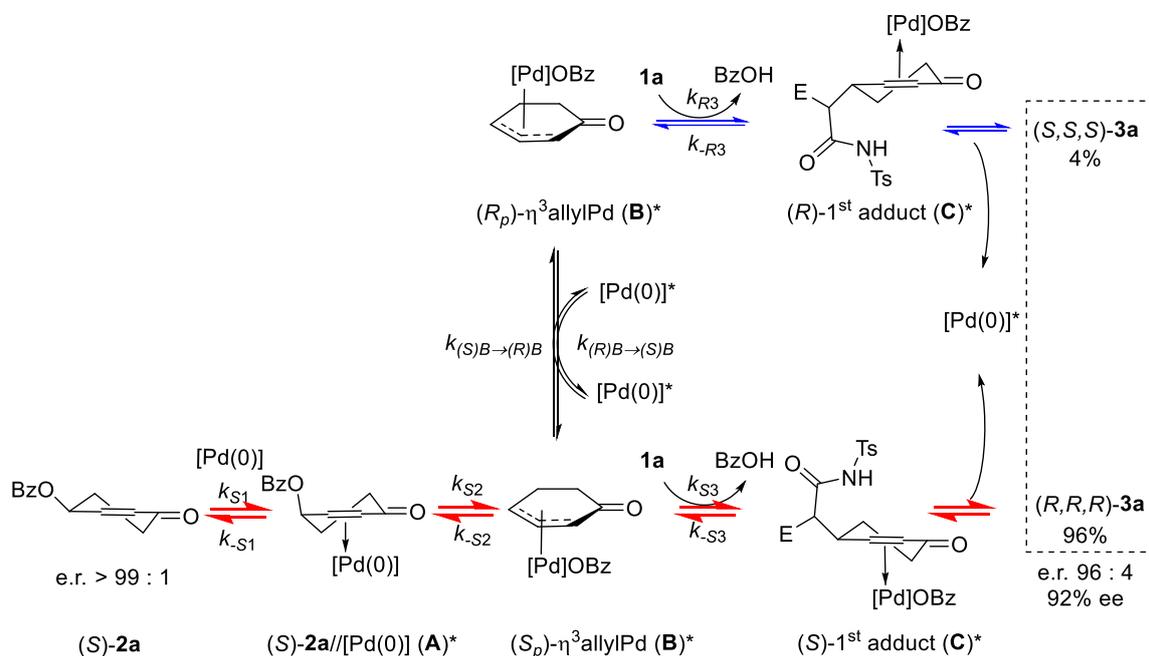
We then performed two experiments. In the former one, *(S)*-**2a** (1.3 equiv.) was submitted to the annulation with **1a**, using the achiral catalytic system  $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5\text{Cl})_2]$  (5 mol%), dppf 15 (mol%) (Scheme 85, top). In a second experiment, racemic ( $\pm$ )-**2a** (2.5 equiv.) was put it to react with **1a** in the presence of the chiral catalytic system of  $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5\text{Cl})_2]$  (5 mol%), *(R)*-Monophos (30 mol%) (Scheme 85, bottom). In the event, the first experiment afforded the annulated product **3a** in 80% yield and 92% ee, while the second one afforded, as expected, the annulated product in 66% yield and 64% ee. Furthermore, analysis of the recovered unreacted substrate **2a** initially present in excess (2.5 equiv. at the beginning of the reaction) showed an enantiomer ratio (e.r.) (*R/S*) of 39/61 (22% ee) (Scheme 85, bottom).



Scheme 85. Pd-catalyzed asymmetric [3+2]-annulation of *(S)*-**2a** and racemic-**2a**.

Experiment 1 reveals that starting from an enantiopure ketone, we end up with a highly enantioenriched (92% ee) product **3a**. So, a slight erosion of enantioselectivity of *(S)*-**2a** took place during the reaction, probably due to a minor equilibration via  $\text{S}_{\text{N}}2$  displacement at the level of the  $\eta^3$ -allylpalladium complex

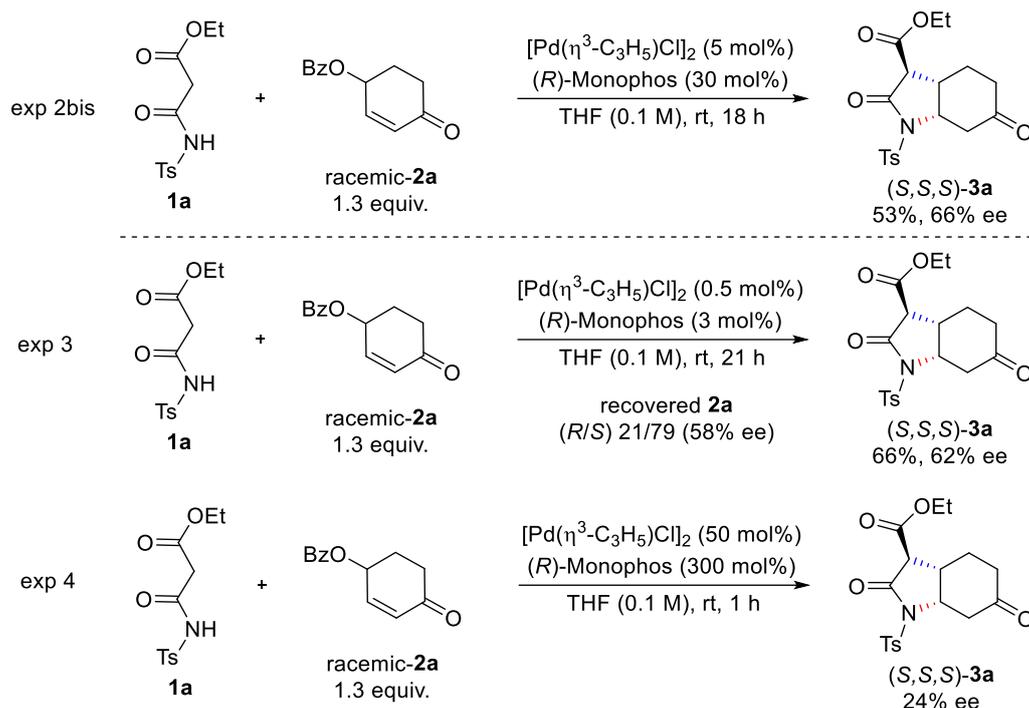
(Scheme 86). This means that  $k_{S3} \gg k_{(S)B \rightarrow (R)B}$ . The absolute configuration of the 1<sup>st</sup> adduct **C** and of **3a** are deduced on the basis of the classical double inversion mechanism in Pd-catalyzed allylations using resonance stabilized carbon-based nucleophiles.



Scheme 86. Proposed mechanism for experiment 1 of Scheme 85.

Experiment 2 reveals that the (*R*)-Monophos-based catalytic system has a  $\geq 82 : 18$  kinetic preference for enantiomer (*R*)-**2a** (matched pair: (*R*)-Monophos ligand / (*R*)-**2a** enantiomer), which is expected to give (*S,S,S*)-**3a**, leaving thus unreacted ketone enriched in the (*S*)-**2a** enantiomer. However, as we saw in experiment 1, under these reaction conditions only a very little extent of  $\eta^3$ -allylpalladium equilibration takes place.

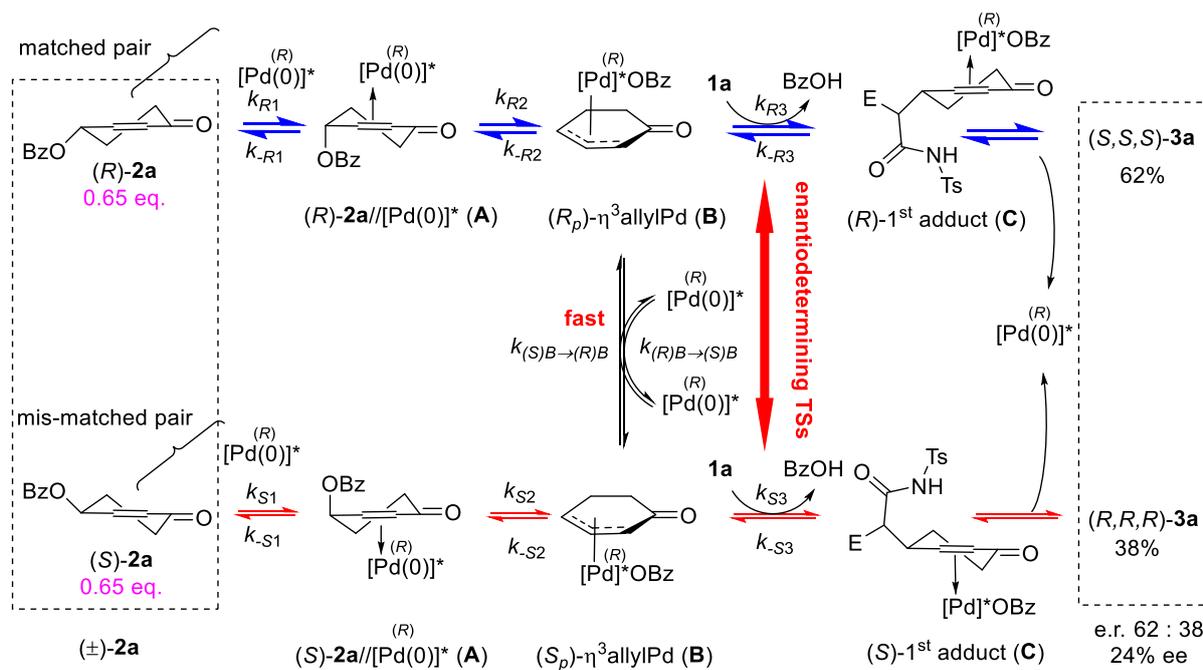
Two additional experiments were carried out next (Scheme 87). A 10-fold decrease in catalyst loading to 0.5 mol%  $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5\text{Cl})_2]$  and 3 mol% (*R*)-Monophos, increased the yield of the reaction (66%) without a significant effect on enantioselectivity (62%) (Scheme 87, exp 3). Alternatively, a 10-fold increase in catalyst loading to 50 mol%  $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5\text{Cl})_2]$  and 300 mol% (*R*)-Monophos, had a detrimental effect on the enantioselectivity (23%) but excellent yield, however, it was found that it is difficult to separate with the oxide of (*R*)-Monophos (Scheme 87, exp 4).



Scheme 87. Pd-catalyzed asymmetric [3+2]-annulation of **1a** and racemic-**2a** with different amounts of Palladium catalyst.

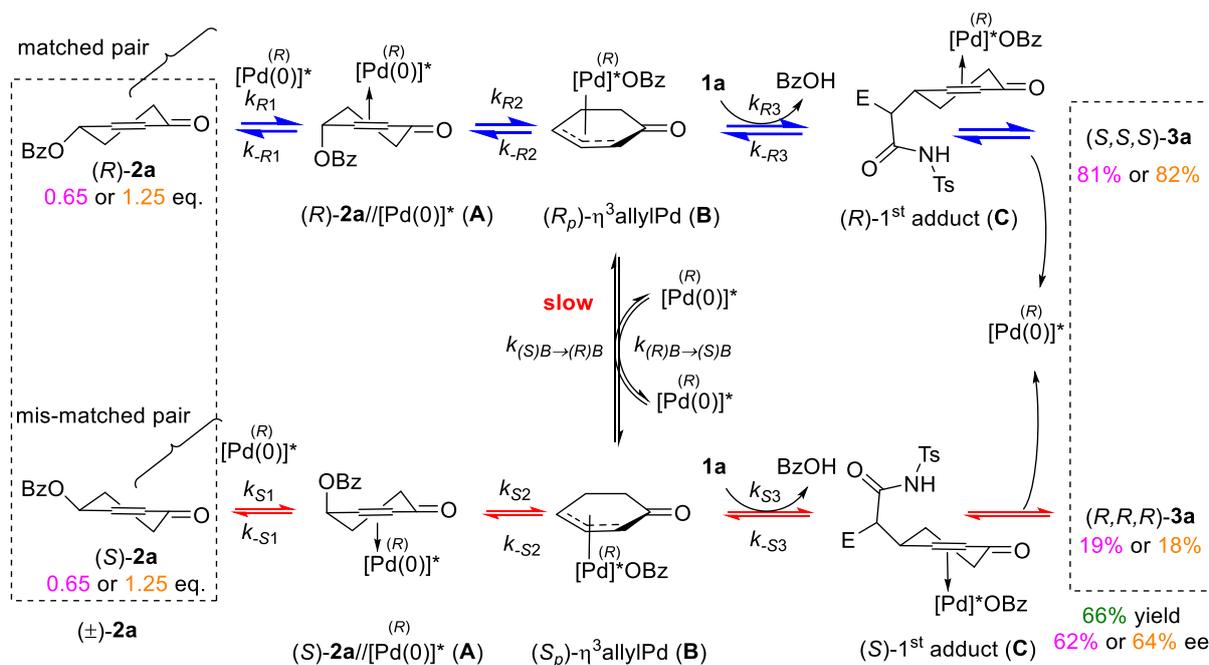
The high increase in the concentration of palladium in exp 4 is expected to increase the rate of racemization between the ( $R_p$ )- and ( $S_p$ )- $\eta^3$ -allylPd intermediates **B** through  $S_N2$  displacement to the point that the nucleophile addition (step 3) becomes the slow enantiodiscriminating step. Indeed, when passing to a tenfold amount of Pd (Scheme 87, exp 4), the enantiomeric ratio drastically changed, which suggests that the slow step shifts from step 1 or 2, to step 3. As this protocol gave 24 ee% in favor of product ( $S,S,S$ )-**3a**, by applying the Boltzmann distribution equation<sup>[95]</sup> to the observed enantiomeric ratio we deduce an energy difference between the diastereoisomeric transitions states of step 3  $\Delta G^\ddagger_{TS3} = \sim 1.2$  kJ/mol (in favor of the ( $S,S,S$ )-**3a** path) (Scheme 88).

<sup>95</sup> *Statistical Physics* (2nd Edition), F. Mandl, Manchester Physics, John Wiley & Sons, 2008, ISBN 9780471915331.



Scheme 88. Mechanistic scenario corresponding to experiment exp 4 of Scheme 87.

The results from experiment 2 of Scheme 85 and experiment 3 of Scheme 87 suggest that when using these protocols the starting material **2a** is not undergoing a racemization during the course of the reaction. Therefore, our Pd-catalyzed asymmetric [3+2] annulation shows essentially a static kinetic asymmetric transformation (KAT), with the [(*R*)-Monophos ligand / (*R*)-**2a** enantiomer] as the matched pair, associated to  $\geq$  a 82 : 18 selectivity. This facial selectivity may be due to enantiodifferentiation in step 1 (coordination) or step 2 (ionization) (Scheme 89).



Scheme 89. Proposed mechanism for experiment 2 of Scheme 85 and experiment 3 of Scheme 87.

Applying the Boltzmann distribution equation to the observed enantiomeric ratio, we deduce an energy difference between the involved diastereoisomeric transition states of  $\sim 3.8$  kJ/mol (again in favor of the  $(S,S,S)$ -**3a** path).

As to the enantiomeric ratios of the recovered starting substrate **2a**, assuming that these reactions take place via a simple KAT and without side products, their values can be calculated applying the following formula ( $X$  represents the mole fraction):

$$\frac{X(R)\text{-2a}_{\text{recov}}}{X(S)\text{-2a}_{\text{recov}}} = \frac{(R)\text{-2a}_{t=0} - X_{(S,S,S)\text{-3a}}}{(S)\text{-2a}_{t=0} - X_{(R,R,R)\text{-3a}}}$$

Scheme 90. General formula to estimate the enantiomeric ratio of recovered **2a**.

Accordingly, the enantiomeric ratios of the recovered **2a** from exp 3 of Scheme 87 and from exp 2 of Scheme 85 are as follows:

Exp 3 of Scheme 3:

(R,R,R)-3a/(S,S,S)-3a = 19/81;  
yield of 3a: 66%

$$\frac{(R)\text{-}2a_{\text{recov}}}{(S)\text{-}2a_{\text{recov}}} = 21/79$$

$$\frac{(R)\text{-}2a_{\text{recov}}}{(S)\text{-}2a_{\text{recov}}} = \frac{(0.65 - 0.53)}{(0.65 - 0.13)} = 0.23 \approx 21/79$$

Exp 2 of Scheme 1:

(R,R,R)-3a/(S,S,S)-3a = 18/82;  
yield of 3a: 66%

$$\frac{(R)\text{-}2a_{\text{recov}}}{(S)\text{-}2a_{\text{recov}}} = 39/61$$

$$\frac{(R)\text{-}2a_{\text{recov}}}{(S)\text{-}2a_{\text{recov}}} = \frac{(1.25 - 0.54)}{(1.25 - 0.12)} = 0.63 \approx 39/61$$

*Scheme 91. Estimation of the enantiomeric ratios of recovered 2a from experiment 2 of Scheme 85 and experiment 3 of Scheme 87, and.*

The calculated values correspond to the observed values, and are therefore consistent with a simple KAT.

It is important to note that the selectivity value is a value associated to the couple (chiral ligand / racemic substrate). Under static kinetic transformation conditions, this value is maximal at the beginning of the reaction, and decreases with the advancement of the reaction as the amount of matching enantiomer progressively diminishes. Of course, this decrease will also depend on the stoichiometry of the racemic substrate present at the outset of the reaction.

## 6. Conclusion

In summary, we have successfully developed a new domino transformation between cyclic  $\alpha,\beta$ -unsaturated- $\gamma$ -oxy-carbonyl derivatives as bis-electrophiles and resonance-stabilized acetamides as bis-nucleophiles, via an intermolecular Pd-catalyzed allylation and intramolecular aza-Michael reaction sequence, which allowed a rapid and efficient assembly of bicyclic pyrrolidin-2-ones. The key to the success of this [3+2]-C-C/N-C bond forming annulation is due to the total chemoselectivity of the former step (C-allylation) as well as to the well-defined chronology of the following steps.<sup>[96]</sup>

As the bicyclic 4,5-fused pyrrolidines are found incorporated in interesting alkaloids such as mesembrine-type alkaloids,<sup>[97]</sup> daphniphyllum alkaloids,<sup>[98]</sup> lycorine-type alkaloids,<sup>[99]</sup> and strychnine,<sup>[100]</sup> this annulation is expected to find wide application in organic synthesis. Furthermore, this Pd-catalyzed [3+2]-C-C/N-C bond forming annulation, taking place under neutral conditions, broadened the potential of

<sup>96</sup> Liu, Y.; Mao, Z.-Y.; Pradal, A.; Huang, P.-Q.; Oble, J.; Poli, G. *Org. Lett.* **2018**, *20*, 4057-4061.

<sup>97</sup> Smith, M. T.; Crouch, N. R.; Gericke, N.; Hirst, M. J. *Ethnopharmacol.* **1996**, *50*, 119-130.

<sup>98</sup> Kobayashi, J.; Kubota, T. *Nat. Prod. Rep.* **2009**, *26*, 936-962.

<sup>99</sup> Chen, Y.-J.; Cai, S.-L.; Wang, C.-C.; Cheng, J.-D.; Kramer, S.; Sun, X.-W. *Chem. Asian J.* **2017**, *12*, 1309-1313.

<sup>100</sup> Bonjoch, J.; Solé, D. *Chem. Rev.* **2000**, *100*, 3455-3482.

the palladium-catalyzed couplings and increased the synthetic potential of amides.

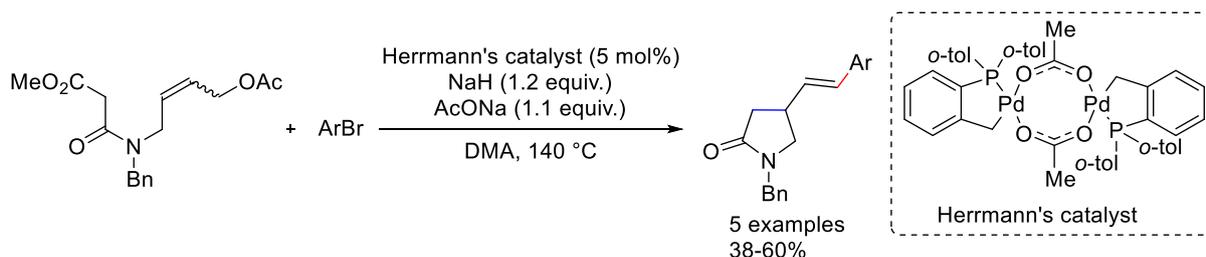
Finally, a Pd-catalyzed asymmetric [3+2]-annulation was also investigated. Under our best conditions [ $\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$  (5 mol%), (*R*)-Monophos (30 mol%), ( $\pm$ )-**2a** (2.5 equiv.), THF (0.1 M, rt 2 h), the annulated product (*S,S,S*)-**3a** was obtained in 64 % ee ( $\geq$  a 82 : 18 kinetic preference) and 66% yield, (matched pair: (*R*)-Monophos ligand / (*R*)-**2a** enantiomer).

# Chapter 3: Palladium-Catalyzed Triple Domino: “ALAMAR” Sequence

## 1. Introduction

A domino reaction has been defined by Tietze in 1990's as a process involving two or more consecutive reactions in which subsequent *in-situ* spontaneous reactions result as a consequence of the functionality formed by bond formation or fragmentation in the previous step.<sup>[101]</sup> Since domino reactions allow the efficient generation of complex molecular structures from simple substrates in a step-economic way, this strategy has attracted the attention of organic chemists.<sup>[102]</sup>

The ROCS team has been working on the study and the development of catalytic domino reactions for twenty years.<sup>[103]</sup> For example, in 2001, this group developed a Pd-catalyzed pseudo-domino<sup>[104]</sup> reaction for the synthesis  $\gamma$ -lactams via allylic alkylation / Heck reaction (Scheme 92).<sup>[105]</sup>



Scheme 92. Pd-catalyzed pseudo-domino reaction for the synthesis of the *trans*  $\gamma$ -lactams.

The plausible mechanism for this transformation is shown in Scheme 93: i) deprotonation by NaH and oxidative addition of the substrate to the Pd(0) complex to form the  $\pi$ -allyl intermediate **A**, which undergoes intramolecular nucleophilic attack by the enolate, generating the vinylpyrrolidone **B**; ii) then, an intermolecular Heck reaction between **B** and the aryl bromide followed by decarboxylation affords the final product.

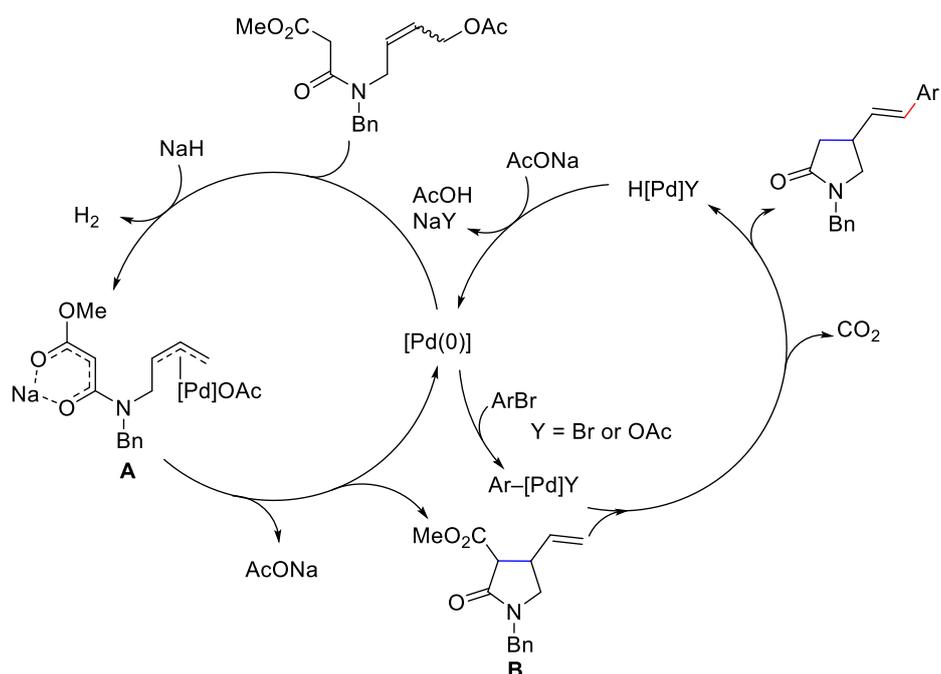
<sup>101</sup> a) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim **2006**. b) Tietze, L. F. *Domino Reactions: Concepts for Efficient Organic Synthesis*, Wiley-VCH, Weinheim **2014**. c) Tietze, L. F.; Beifuss, U. *Angew. Chem. Int. Ed.* **1993**, *32*, 131-163. b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115-136.

<sup>102</sup> a) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 7134-7186. b) Nicolaou, K. C.; Chen, J. S. *Chem. Soc. Rev.* **2009**, *38*, 2993-3009. c) Walsike, J.-C.; Obrey, J. O.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001-1020. d) Ajamian, A.; Gleason, J. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 3754-3760. (e) Lee, J. M.; Na, Y.; Han, H.; Chang, S. *Chem. Soc. Rev.* **2004**, *33*, 302-312. (f) Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365-2379.

<sup>103</sup> Kammerer, C.; Prestat, G.; Madec, D.; Poli, G. *Acc. Chem. Res.* **2014**, *47*, 3439-3447.

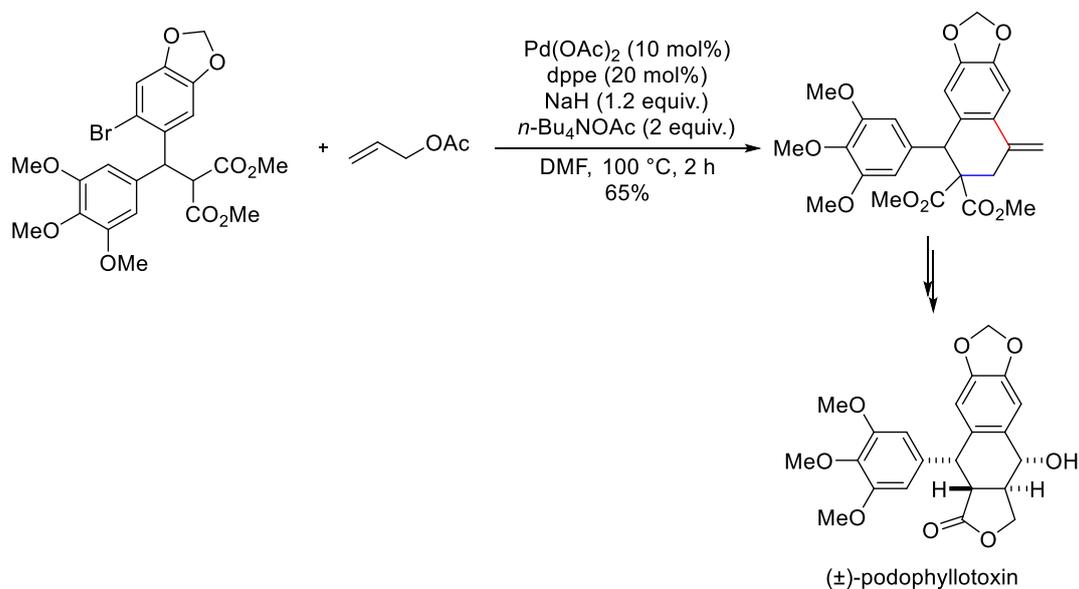
<sup>104</sup> Prestat, G.; Poli, G. *Chemtracts - Org. Chem.* **2004**, *17*, 97.

<sup>105</sup> a) Poli, G.; Giambastiani, G.; Pacini, B. *Tetrahedron Lett.* **2001**, *42*, 5179-5182. b) Poli, G.; Giambastiani, G. *J. Org. Chem.* **2002**, *67*, 9456-9459.



Scheme 93. The mechanism of Pd-catalyzed pseudo-domino reaction featuring allylic alkylation / Heck reaction.

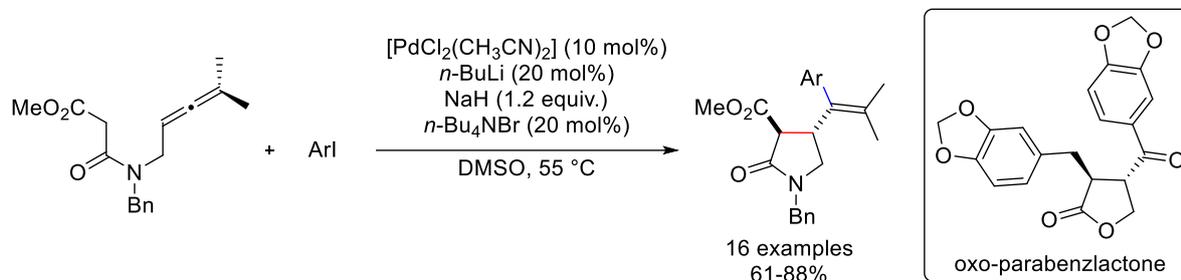
This strategy was subsequently applied in the formal synthesis of podophyllotoxin via an intermolecular allylic alkylation / intramolecular Heck sequence (Scheme 94).<sup>[106]</sup>



Scheme 94. Application for the formal synthesis of the (±)-podophyllotoxin.

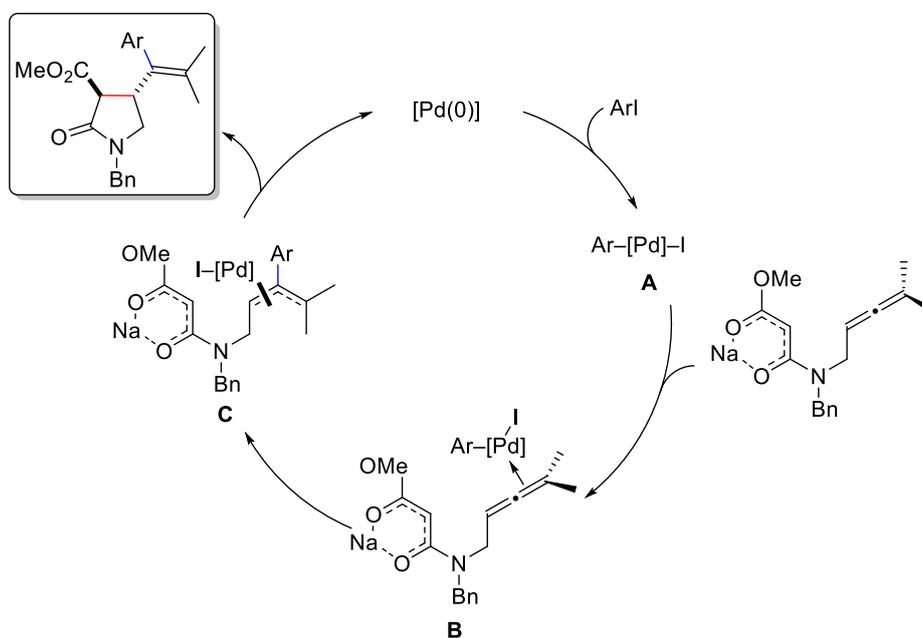
<sup>106</sup> Mingoia, F.; Vitale, M.; Madec, D.; Prestat, G.; Poli, G. *Tetrahedron Lett.* **2008**, *49*, 760-763.

In 2009, this strategy was extended to a Pd-catalyzed [carbopalladation / allylic alkylation] domino sequence for the synthesis of the *trans*  $\gamma$ -lactams starting from amidoallenes (Scheme 95).<sup>[107]</sup> The sequence could be applied to the synthesis of the new aza-analog of oxo-parabenzlactone.



Scheme 95. Pd-catalyzed domino reaction for the synthesis of the *trans*  $\gamma$ -lactams.

Mechanistically, this domino process starts with an oxidative addition of the aryl iodide to the Pd(0) complex, to form the aryl palladium species **A**. Coordination of the allene double bond to the aryl palladium species **A** and subsequent carbopalladation gives the  $\pi$ -allyl intermediate **C**. Subsequent intramolecular nucleophilic substitution of the malonamide enolate arm to the  $\pi$ -allyl moiety affords the *trans*  $\gamma$ -lactam (Scheme 96).



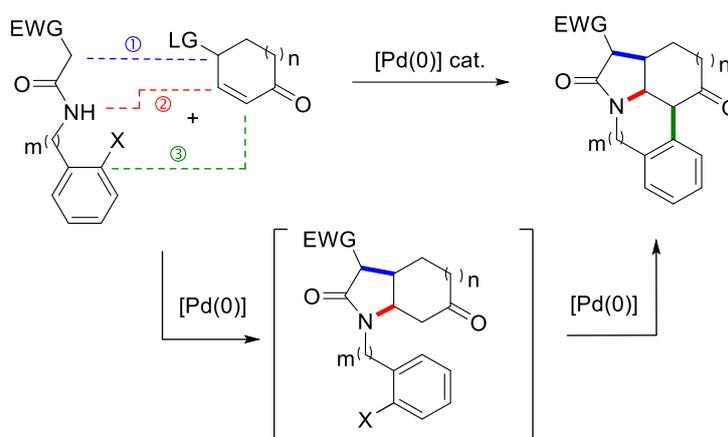
Scheme 96. Mechanism of the Pd-catalyzed domino reaction featuring carbopalladation/allylic alkylation.

<sup>107</sup> Kammerer, C.; Prestat, G.; Madec, D.; Poli, G. *Chem. Eur. J.* **2009**, *15*, 4224-4227.

## 2. Toward a multiple pseudo-domino

### 2.1 The concept

On the basis of my previous results on Pd-catalyzed annulation (see chapter 2), and as a logical extension of this exciting project, we envisioned to next develop more complex cascades so as to increase the complexity of the final target. In particular, we speculated that if we used a bis-nucleophile bearing a halo-aryl moiety, the allylation / conjugate addition sequence could be interfaced to a Buchwald-Hartwig Pd-catalyzed intramolecular keto  $\alpha$ -arylation (Scheme 97).



Scheme 97. Conceived multiple pseudo-domino sequence: Pd-catalyzed allylation / aza-Michael / Pd-catalyzed amine arylation.

Before describing my results on this part of project, the Buchwald-Hartwig ketone  $\alpha$ -arylation will be briefly reviewed.

### 2.2 The $\alpha$ -arylation of enolizable nucleophiles<sup>[108]</sup>

#### 2.2.1 Introduction and early studies

The alkylation of enolizable nucleophiles is traditionally one of the most studied C–C bond forming reactions in organic chemistry. Thus, a huge amount of studies on this transformation are available, focusing on the C–nucleophile, the C–electrophile, diastereo- or enantioselective variants. Surprisingly enough, investigations of the complementary arylation of enolizable nucleophiles started much later, and this,

<sup>108</sup> a) Culkin, D. A.; Hartwig J. F. *Acc. Chem. Res.* **2003**, *36*, 234-245. b) Burke, A. J.; Silva Marques, C. *Catalytic Arylation Methods: From the Academic Lab to Industrial Processes*, 1<sup>st</sup> Ed. **2015**, Chapter 8. Wiley-VCH Verlag GmbH & Co. c) Schlummer, B.; Scholz, U. Chapt. 3, *Palladium-Catalyzed Arylations of Amines and  $\alpha$ -C–H Acidic Compounds* in: *Modern Arylation Methods*, Ackermann, L. Ed., **2009** WILEY-VCH Verlag. d) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082-1146. e) Prim, D.; Marque, S.; Gaucher, A.; Campagne, J.-M. *Org. React.* **2012**, *76*, 49-279.

despite the fact that many natural products and important drugs incorporate the Ar–C–CO substructure (Figure 6).

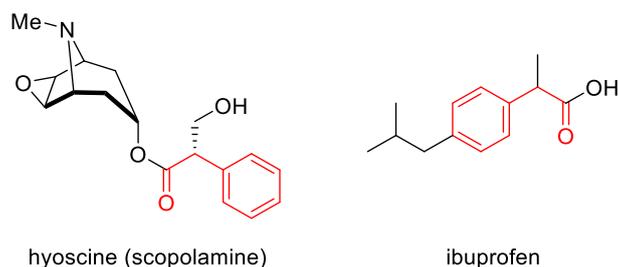
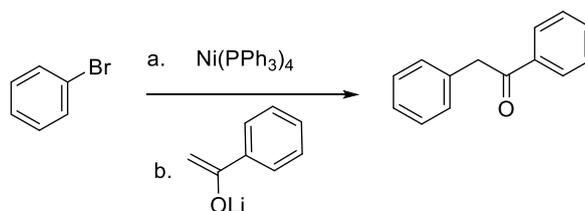


Figure 6. Examples of relevant molecules incorporating the Ar–C–CO substructure.

The first examples of inter- as well as intramolecular arylation of ketone enolates were reported in 1973 by Semmelhack using nickel as promoter.<sup>[109]</sup> The reaction was low yielding and almost stoichiometric in nickel (Scheme 98).



Scheme 98. First example of metal promoted  $\alpha$ -arylation of a carbonyl derivative.

## 2.2.2 The Pd-catalyzed intermolecular $\alpha$ -arylation of ketones

Subsequent studies revealed that palladium is the metal of choice to perform the arylation of enolizable carbon nucleophiles.<sup>[110]</sup>

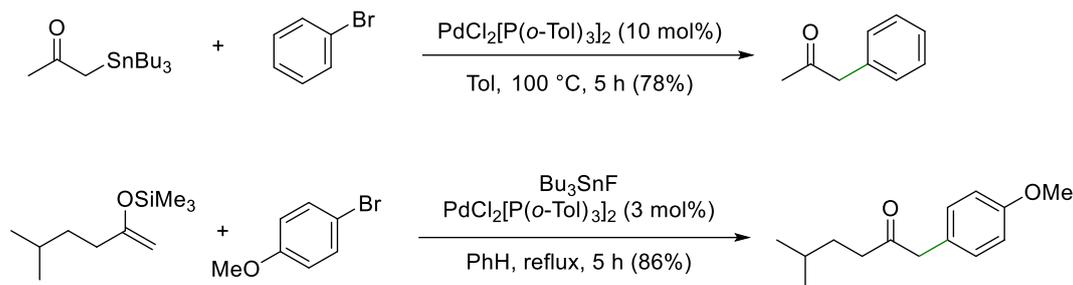
The first Pd-mediated arylations were reported independently in 1982 by the groups of Migita<sup>[111]</sup> and Kuwajima.<sup>[112]</sup> They were rather narrow in scope and involved the reaction between preformed, or *in-situ* generated, stannylated carbonyl compounds and aryl halides.

<sup>109</sup> Semmelhack, M. F.; Stauffer, R. D.; Rogerson, T. D. *Tetrahedron Lett.* **1973**, *14*, 4519-4522.

<sup>110</sup> Nickel- and copper-catalyzed arylations will not be covered in this brief survey.

<sup>111</sup> Kosugi, M.; Suzuki, M.; Hagiwara, I.; Goto, K.; Saitoh, K.; Migita, T. *Chem. Lett.* **1982**, 939-940.

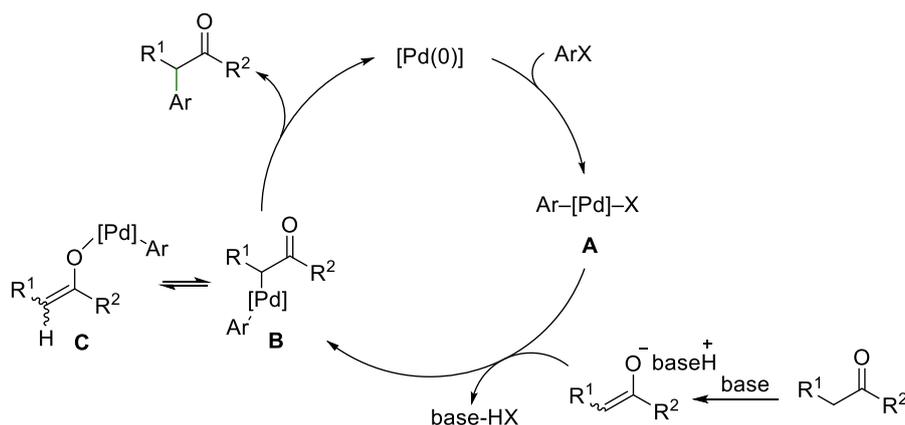
<sup>112</sup> Kuwajima, I.; Urabe, H. *J. Am. Chem. Soc.* **1982**, *104*, 6831-6833.



Scheme 99. Pioneering Pd-catalyzed arylation of carbonyl compounds.

In 1997, the groups of Buchwald,<sup>[113]</sup> Hartwig,<sup>[114]</sup> and Miura<sup>[115]</sup> independently reported the palladium-catalyzed  $\alpha$ -arylation of ketones with aryl halides. These reactions were carried out in the presence of a base and a catalyst system consisting of a combination of Pd(OAc)<sub>2</sub> (or a Pd(0) compound such as Pd(dba)<sub>2</sub> or Pd<sub>2</sub>(dba)<sub>3</sub>) with a suitable phosphine ligand. This method could be applied to the synthesis of organic structural units, pharmaceutical and agrochemical derivatives, and natural products.

The catalytic cycle of the palladium-catalyzed  $\alpha$ -arylation reaction involves three steps: i) oxidative addition of the aryl halide onto the Pd(0) species generating the corresponding Pd(II) complex **A**; ii) ligand substitution of the halide in **A** by the ketone enolate leading to the  $\sigma$ -alkylarylpalladium complex **B**, which may be equilibrium with the corresponding palladium-enolate complex **C**; iii) reductive elimination from the  $\sigma$ -alkylarylpalladium complex giving the final arylated product and regenerating the Pd(0) complex (Scheme 100). However, this simplified catalytic cycle does not take into account the crucial roles played by the ligand and the solvent.



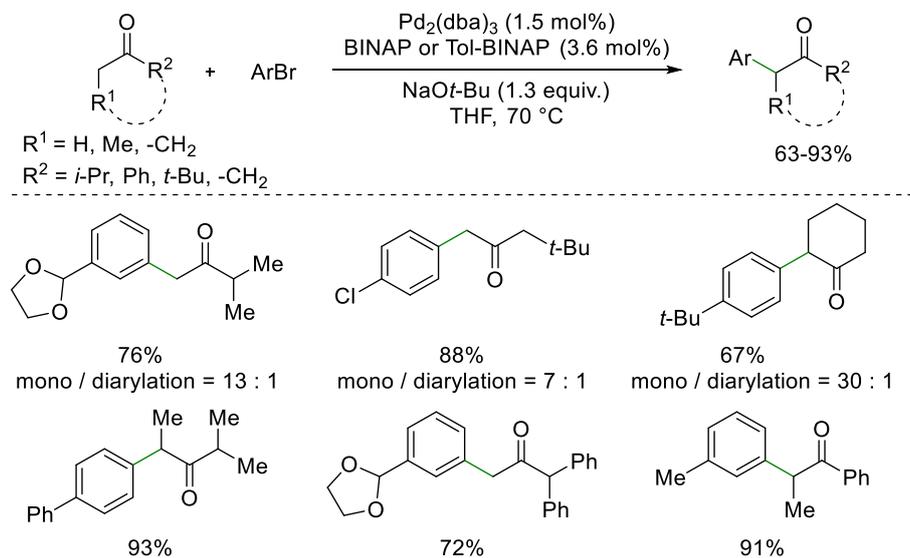
Scheme 100. The catalytic cycle of Pd-catalyzed  $\alpha$ -arylation of ketones with aryl halides.

<sup>113</sup> Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 11108-11109.

<sup>114</sup> Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382-12383.

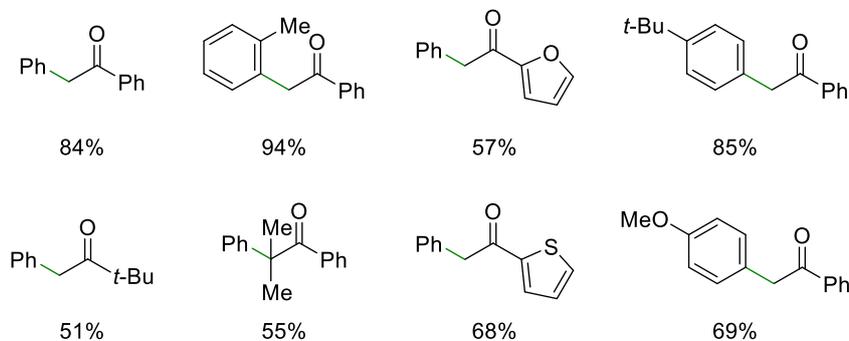
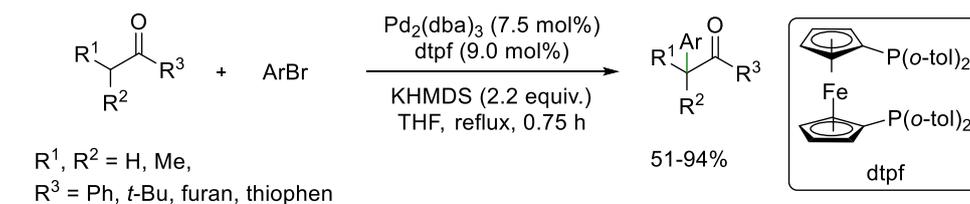
<sup>115</sup> Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem. Int. Ed.* **1997**, *36*, 1740-1742.

In his pioneering work, Buchwald reports the use of NaOt-Bu as the base, Pd<sub>2</sub>(dba)<sub>3</sub> as the palladium source, and BINAP or Tol-BINAP as the ligand, working in THF at reflux (Scheme 101). In particular, ketones containing α,α'-enolizable positions were preferentially arylated at the least hindered side (methyl > methylene), while the α-arylation of methinic groups was not noticed under above conditions. The diarylation was observed only for methyl ketones, at the relatively unhindered α'-position.<sup>[113]</sup>



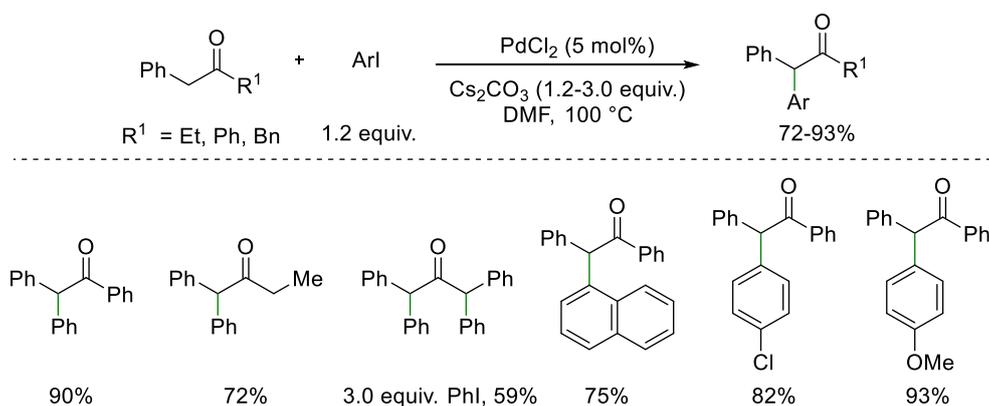
Scheme 101. Pd<sub>2</sub>(dba)<sub>3</sub>/BINAP or Tol-BINAP-catalyzed coupling of ketones with aryl bromides.

In the same year, Hartwig independently described a procedure for the α-arylation of ketones with aryl bromides in the presence of KHMDS or NaOt-Bu as the base, Pd(dba)<sub>2</sub> as the metal source, and dppf or dtbpf as ligand, working in THF at reflux.<sup>[114]</sup> We can notice that both the protocols of Hartwig and Buchwald call for a bidentate chelating ligand. This is crucial, as a chelating phosphine, creating a tetra-coordinate arylpalladium C-enolate, impedes undesirable β-hydrogen elimination. In particular, when KHMDS was used as the base, arylations involving electron-neutral or electron-rich aryl bromides were more selective for monoarylation. However, when NaOt-Bu was the base, good selectivity was noticed for arylations involving electron-poor aryl bromides. Some representative examples of Pd(dba)<sub>2</sub>/dtpf-catalyzed α-arylation reactions are presented in Scheme 102.



Scheme 102.  $\text{Pd}(\text{dba})_2/\text{dtpf}$ -catalyzed  $\alpha$ -arylation of ketones with aryl bromides.

In the same year, Miura reported the use of aryl iodides as electrophiles under ligandless conditions.<sup>[116]</sup> The reaction was performed by treatment of the benzyl ketone with aryl iodide in the presence of  $\text{Cs}_2\text{CO}_3$  and  $\text{PdCl}_2$ . Treatment of 1,3-diphenylpropane-2-one with 3 equivalents of iodobenzene gave selectively the corresponding  $\alpha, \alpha'$ -diarylated compound in 59% yield (Scheme 103). Interestingly, the authors demonstrated that a phosphine ligand should be used for the arylation of benzyl ketones if aryl bromides are.



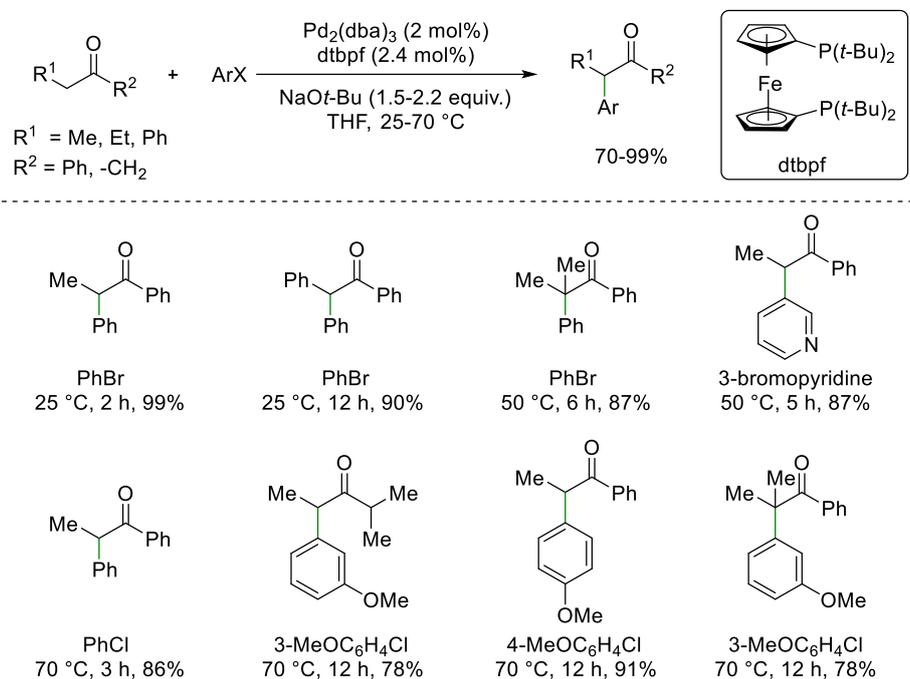
Scheme 103.  $\text{PdCl}_2$ -catalyzed  $\alpha$ -arylation of benzyl ketones with aryl iodides.

In 1999, Kawatsura and Hartwig<sup>[117]</sup> reported the  $\alpha$ -arylation of ketones in the presence of the sterically hindered catalytic system  $\text{Pd}(\text{dba})_2 / \text{dtbpf}$ . This catalyst system led to very rapid reaction rates for reactions

<sup>116</sup> Satoh, T.; Inoh, J.-I.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2239-2246.

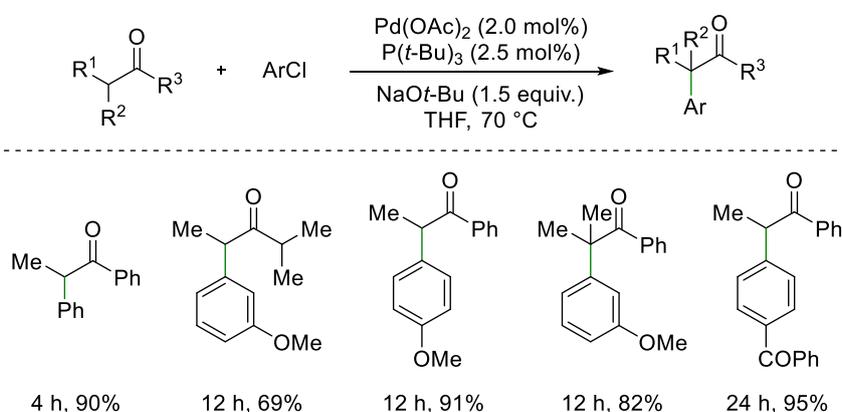
<sup>117</sup> Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473-1478.

of aryl bromides with ketones, even at room temperature. This catalyst gave also mild reactions with aryl chlorides with yields that were similar to those obtained with the corresponding aryl bromides (Scheme 104).



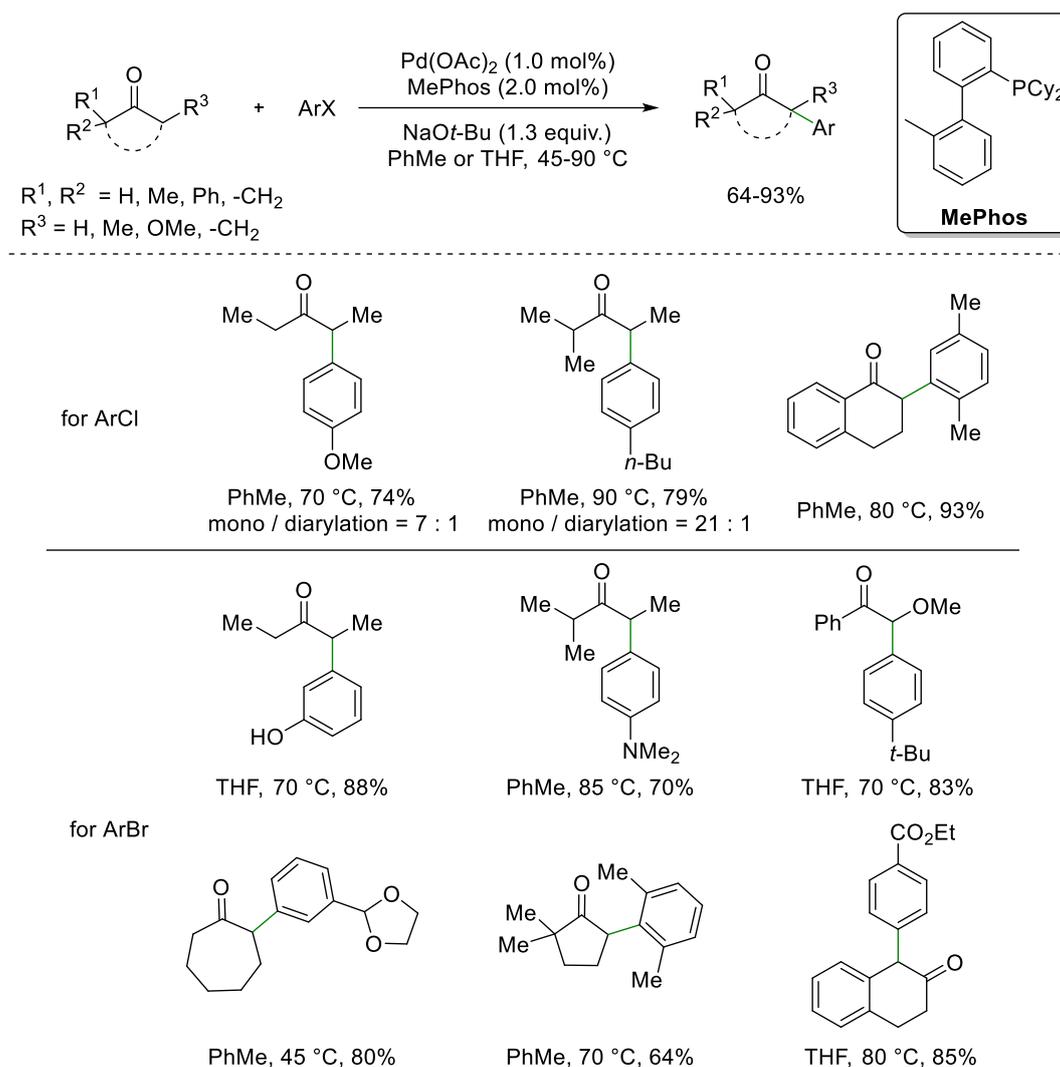
Scheme 104.  $Pd(dba)_2/dtbpf$ -catalyzed  $\alpha$ -arylation of ketones with aryl chlorides and bromides.

Additionally, the authors found that the sterically hindered monophosphine  $P(t-Bu)_3$  gives also exceptionally fast rates and high turnover numbers of  $\alpha$ -arylation of ketones with aryl chlorides (Scheme 105).<sup>[117]</sup> These results demonstrated that palladium complexes of bulky monophosphine ligands could allow oxidative addition of aryl chlorides under mild conditions, and palladium enolates coordinated by certain monophosphines underwent a rapid C–C bond-forming reductive elimination, thus demonstrating that the use of a chelating phosphine to impede  $\beta$ -H elimination was not compulsory.



Scheme 105.  $Pd(dba)_2/P(t-Bu)_3$ -catalyzed  $\alpha$ -arylation of ketones with aryl chlorides.

In 2000, Buchwald reported a highly efficient  $\alpha$ -arylation of ketones with aryl halides in the presence of NaOt-Bu using a catalyst system composed of a combination of Pd(OAc)<sub>2</sub> and commercial monophosphine ligand, such as 2-(dicyclohexylphosphino)-2'-isopropylbiphenyl, MePhos, or JohnPhos in toluene or THF.<sup>[118]</sup> A various range of ketones and functionalized aryl bromides or chlorides were shown to high selectivity and reactive efficiently. Some chosen examples are shown in Scheme 106.



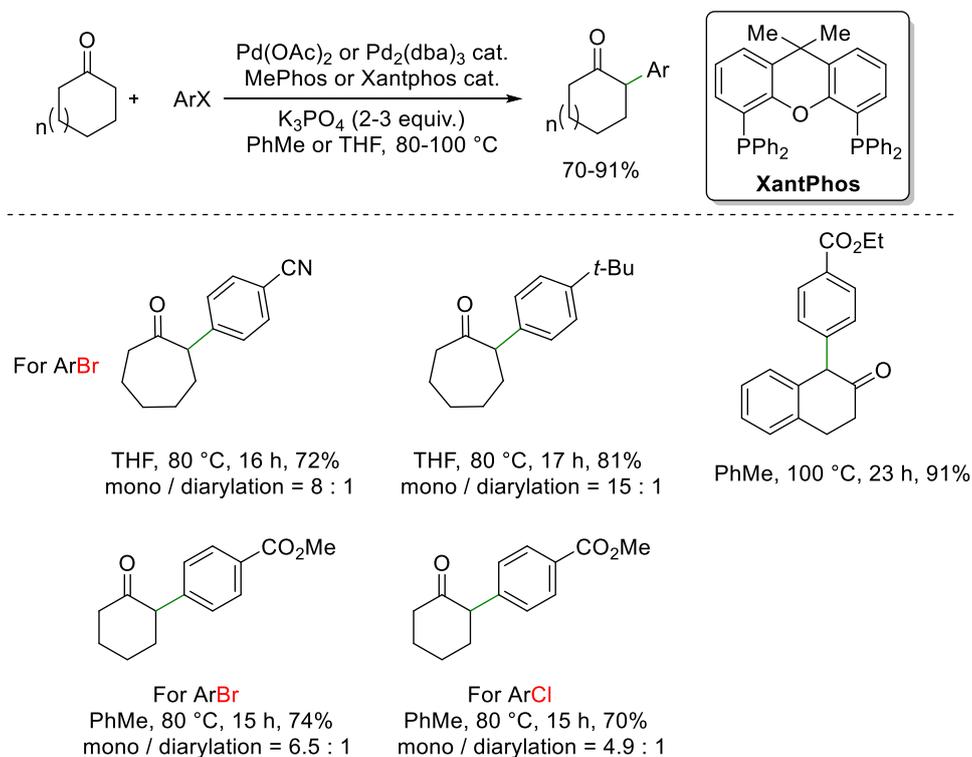
Scheme 106. Pd(OAc)<sub>2</sub>/MePhos-catalyzed  $\alpha$ -arylation of ketones with aryl chlorides and bromides.

Both cyclic or acyclic and aromatic ketones could be used, with the exception of cyclopentanone, which gave a self-aldol condensation instead of the  $\alpha$ -arylation. Several aryl halides could be reacted, including those substituted with alkyl, methoxy, 1,3-dioxolane, hydroxy, dimethylamino, nitrile, and ester functions. Aryl halides substituted with ester or nitrile functions could be coupled with aromatic, but aliphatic ketones.

<sup>118</sup> Fox, J. M.; Huang, X.-H.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360-1370.

This  $\alpha$ -arylation could also be successfully carried out with the catalyst system consisting of  $\text{Pd}_2(\text{dba})_3$  or  $\text{Pd}(\text{OAc})_2$  and the bidentate ligand XantPhos, in combination with NaHMDS or NaOt-Bu.

Noteworthy,  $\text{K}_3\text{PO}_4$  could also be used as the base instead of NaOt-Bu or NaHMDS<sup>[119]</sup> in the  $\alpha$ -arylation of cycloalkanones featuring base-sensitive functional groups, using MePhos or Xantphos as the ligands (Scheme 107).<sup>[118]</sup>



Scheme 107. Pd-catalyzed  $\alpha$ -arylation of cycloalkanones use  $\text{K}_3\text{PO}_4$  as the base.

This major protocol advancement boosted the use of the intermolecular Pd-catalyzed  $\alpha$ -arylation of ketones in organic synthesis, and this type of coupling could be applied, *inter alia*, in the synthesis of some natural products.<sup>[120]</sup>

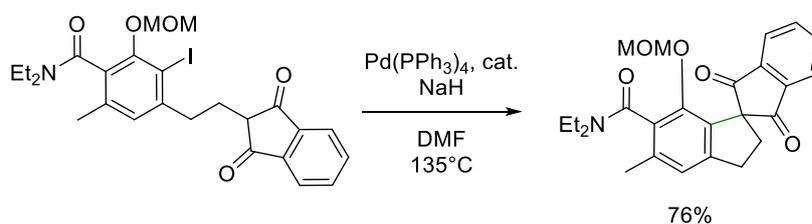
<sup>119</sup>  $\text{K}_3\text{PO}_4$  ( $pK_a$  of the conjugated acid = 12.3); NaOt-Bu ( $pK_a$  of the conjugated acid = 19) or NaHMDS ( $pK_a$  of the conjugated acid = 26 (in THF), 30 (in DMSO)).

<sup>120</sup> For a selection of examples, see: a) Ehrentraut, A.; Zapf, A.; Beller, M. *Adv. Synth. Catal.* **2002**, *344*, 209-217. b) Viciu, M. S.; Germaneau, R. F.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 4053-4056. c) Carril, M.; SanMartin, R.; Churrucua, F.; Tellitu, I.; Dominguez, E. *Org. Lett.* **2005**, *7*, 4787-4789. d) Limbeck, M.; Wamhoff, H.; Rölle, T.; Griebenow, N. *Tetrahedron Lett.* **2006**, *47*, 2945-2948. e) Wills, M. C.; Taylor, D.; Gillmore, A. T. *Tetrahedron* **2006**, *62*, 11513-11520. f) Ackermann, L.; Spatz, J. H.; Gschrei, C. J.; Born, R.; Althammer, A. *Angew. Chem. Int. Ed.* **2006**, *45*, 7627-7630. g) Grasa, G. A.; Colacot, T. J. *Org. Lett.* **2007**, *9*, 5489-5492.

### 2.2.3 The Pd-catalyzed intramolecular $\alpha$ -arylation of ketones

The intramolecular version of the Pd-catalyzed arylation of carbonyls is a very useful strategy to build up cyclic structures. This variant involves the regioselective ( $\alpha$  vs.  $\alpha'$ ) issue, and has been extensively applied in several syntheses, including those of natural products.

As a matter of fact, the first Pd-catalyzed arylation was an intramolecular version, reported by Ciufolini in 1988,<sup>[121]</sup> and discovered while working on the synthesis of Fredericamycin. The authors reported that treatment of an iododiketone with NaH, followed by addition of Pd(PPh<sub>3</sub>)<sub>4</sub> in DMF afforded, after 30 min at 135 °C, a spirocyclic product in 76% yield (Scheme 108).

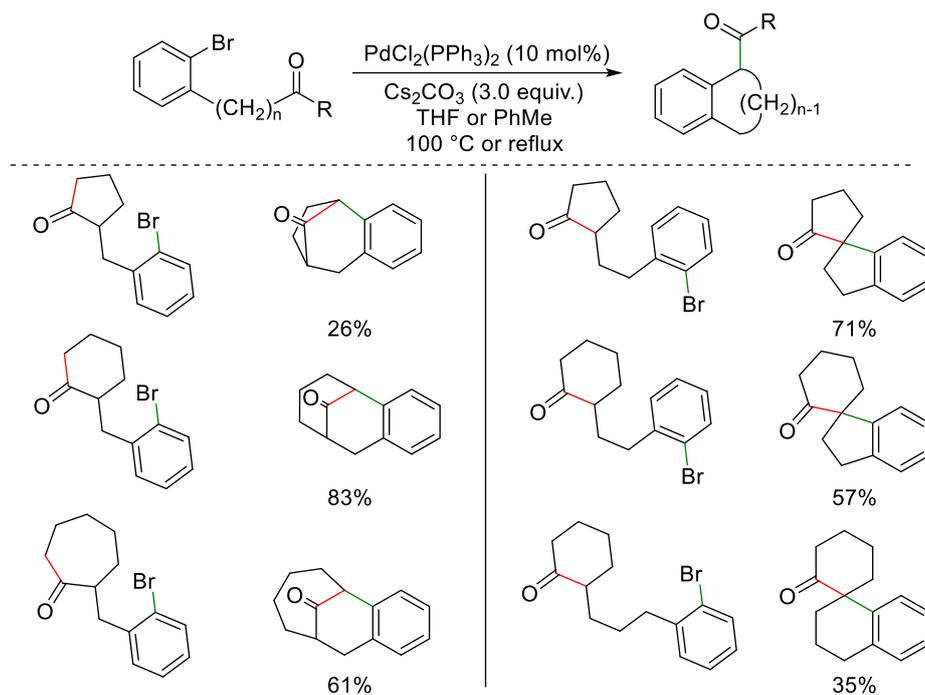


Scheme 108. Pioneering Pd-catalyzed  $\alpha$ -arylation of ketones.

Almost 10 years later, the Muratake group<sup>[122]</sup> reported that in the presence of the system [PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>4</sub> / Cs<sub>2</sub>CO<sub>3</sub>] in THF or PhMe, 2-bromobenzyl substituted cycloalkanones afforded the corresponding bridged 2-tetralones in 26-83% yield, while spiro-compounds were formed in 35-71% yield from 2-(3-(2-bromophenyl)propyl)cycloalkanones (Scheme 109).

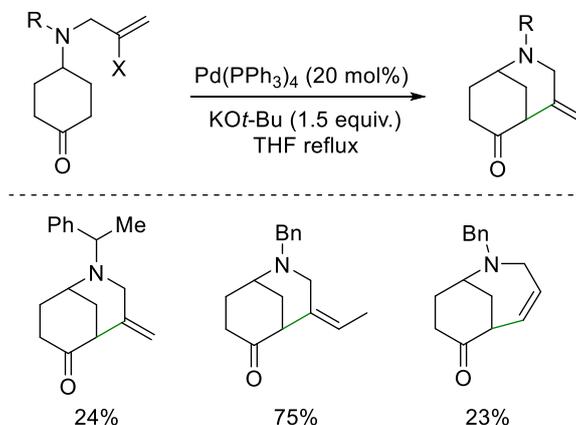
<sup>121</sup> Ciufolini, M. A.; Qi, H.-B.; Browne, M. E. *J. Org. Chem.* **1988**, *53*, 4149-4151.

<sup>122</sup> a) Muratake, H.; Natsume, M. *Tetrahedron Lett.* **1997**, *38*, 7581-7582. b) Muratake, H.; Nakai, H. *Tetrahedron Lett.* **1999**, *40*, 2355-2358. c) Muratake, H.; Natsume, M.; Nakai, H. *Tetrahedron* **2004**, *60*, 11783-11803.



*Scheme 109. Pd-catalyzed intramolecular  $\alpha$ -arylation of ketones.*

In 2000, Solé and Bonjoch described an intramolecular  $\alpha$ -arylation of amino-tethered vinyl halides and ketone enolates in the presence of KO<sup>t</sup>-Bu and Pd(PPh<sub>3</sub>)<sub>4</sub> in refluxing THF.<sup>[123]</sup> In some cases, the system of Muratake [PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> / Cs<sub>2</sub>CO<sub>3</sub>] in toluene at 110 °C was also effective (Scheme 110).



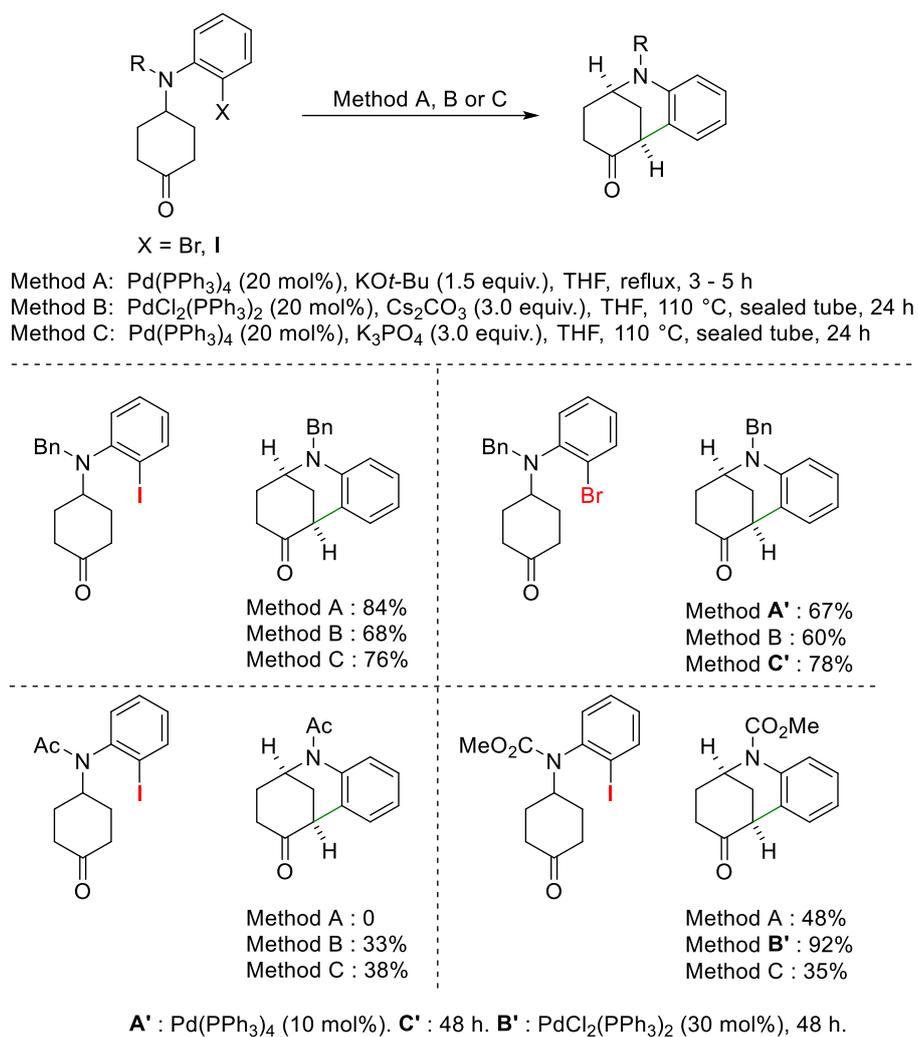
*Scheme 110. Pd-catalyzed intramolecular  $\alpha$ -arylation of vinyl halides and ketone enolates.*

Further studies by the same group found that 4-(2-iodophenyl)amino)cyclohexanones undergo Pd-catalyzed arylation to afford the corresponding bridged heterocycles in moderate to good yields<sup>[124]</sup>

<sup>123</sup> Solé, D.; Peidró, E.; Bonjoch, J. *Org. Lett.* **2000**, *2*, 2225-2258.

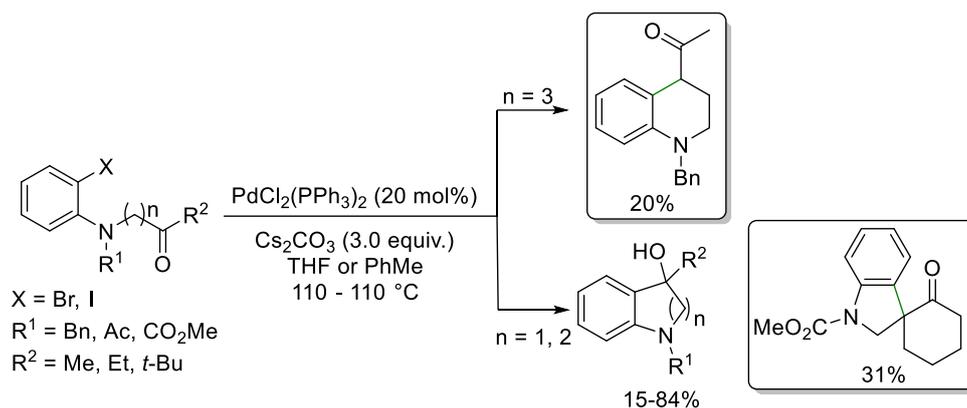
<sup>124</sup> a) Solé, D.; Vallverdú, L.; Solans, X.; Font-Bardía, M.; Bonjoch, J. *J. Am. Chem. Soc.* **2003**, *125*, 1587-1594. b) Solé, D.; Vallverdú, L.; Peidró, E.; Bonjoch, J. *Chem. Commun.* **2001**, 1888-1889. c) Solé, D.; Vallverdú, L.; Bonjoch, J. *Adv. Synth. Catal.* **2001**, *343*, 439-442.

(Scheme 111).



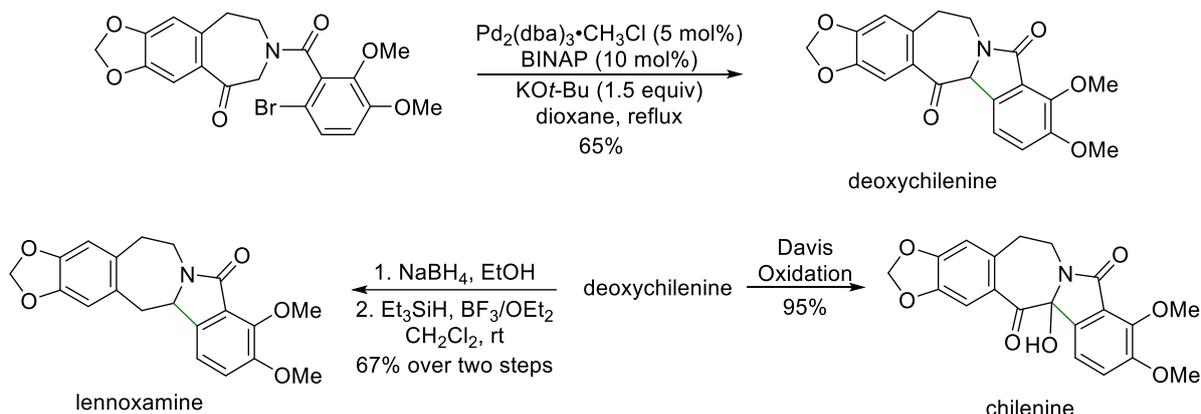
Scheme 111. Pd-catalyzed intramolecular  $\alpha$ -arylation of 2-haloanilino cyclohexanones.

On the other hand, under the above conditions, only  $\omega$ -(2-haloanilino) linear alkanones could generate the corresponding  $\alpha$ -arylation products, the other shorter 2-haloanilino alkanones gave cyclic Friedel-Crafts type products, except for a carbamate (Scheme 112).



Scheme 112. Pd-catalyzed intramolecular  $\alpha$ -arylation of 2-haloanilino alkanones.

In 2005, Honda reported the Pd-catalyzed intramolecular  $\alpha$ -arylation of *o*-bromobenzamides using the system  $[\text{Pd}_2(\text{dba})_3 / \text{BINAP} / \text{KO}t\text{-Bu}]$ , which was successfully applied to the synthesis of natural products, such as lennoxamine, 1,3-deoxychilenine, and chilenine (Scheme 113).<sup>[125]</sup>

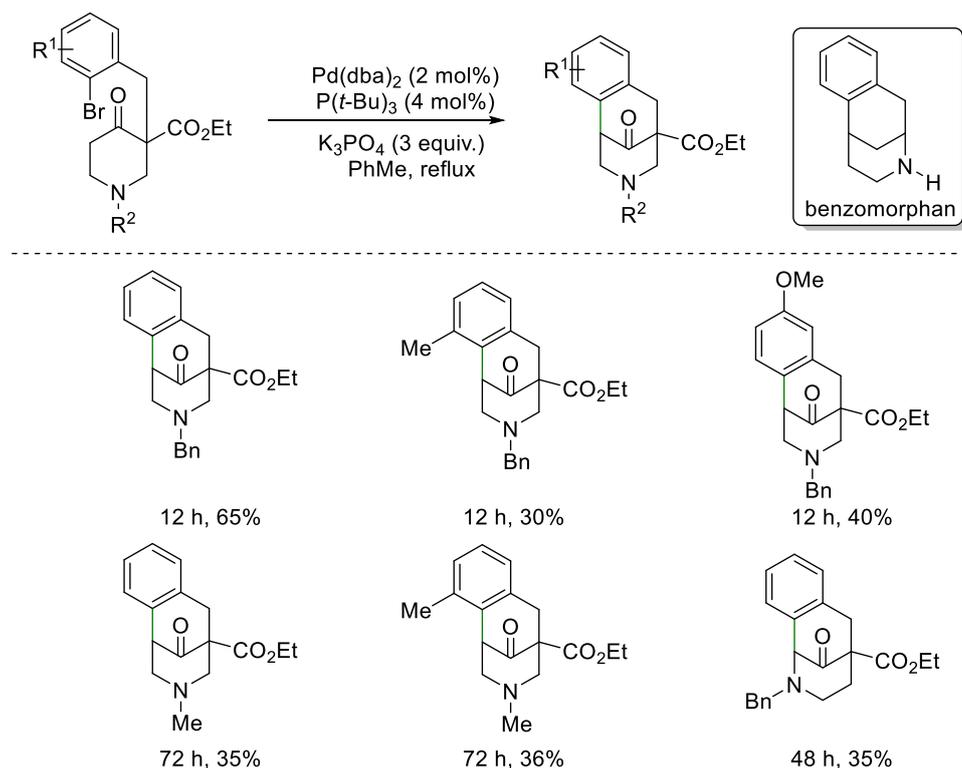


Scheme 113. Pd-catalyzed intramolecular  $\alpha$ -arylations for the synthesis of lennoxamine, 1,3-deoxychilenine, and chilenine.

In 2007, Khartulyari and Maier achieved the intramolecular Pd-catalyzed  $\alpha$ -arylation of 3-(2-bromophenethyl)-4-oxopiperidines using the system  $[\text{Pd}(\text{dba})_2 / \text{P}(t\text{-Bu})_3 / \text{K}_3\text{PO}_4]$ . The resulting bridged polycyclic structures could be further processed for the synthesis of benzomorphan analogues (Scheme 114).<sup>[126]</sup> It was found that *N*-methylated substrates were less reactive than the corresponding *N*-benzylated ones. Change of the location of the nitrogen atom on the substrate was also possible (Scheme 114).

<sup>125</sup> Honda, T.; Sakamaki, Y. *Tetrahedron Lett.* **2005**, *46*, 6823-6825.

<sup>126</sup> Khartulyari, A. S.; Maier, M. E. *Eur. J. Org. Chem.* **2007**, 317-324.

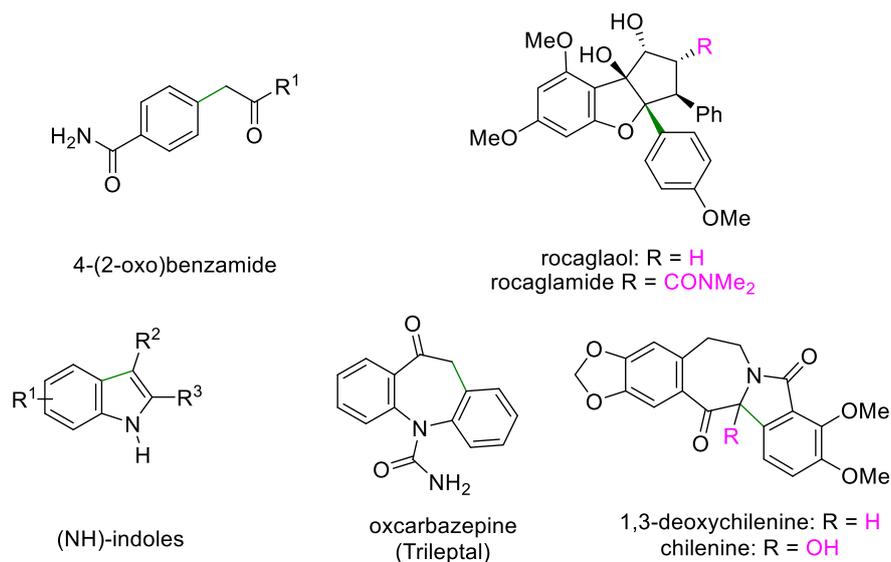


Scheme 114. Synthesis of the benzomorphan analogues.

The Pd-catalyzed  $\alpha$ -arylation of enolizable carbonyl derivatives proved to be a general and robust tool in organic synthesis to achieve inter- as well as intramolecular arylations. This is, *inter alia*, demonstrated by the syntheses of the many target molecules and drugs that exploited this reaction as the key step, such as 4-(2-oxo)benzamides,<sup>[120d]</sup> Rocaglamide and Rocaglaos,<sup>[127]</sup> *N*-substituted indoles<sup>[128]</sup>, Oxcarbazepine (Trileptal)<sup>[120c]</sup>, and the isoindolo benzazepine alkaloids such as 1,3-deoxychilenine, and chilenine<sup>[125]</sup> (Scheme 115).

<sup>127</sup> Sido, A. S. S.; Boulanger, L.; Désaubry, L. *Tetrahedron Lett.* **2005**, *46*, 8017-8018. b) Diedrichs, N.; Ragot, J. P.; Thede, K. *Eur. J. Org. Chem.* **2005**, 1731-1735.

<sup>128</sup> a) Rutherford, J. L.; Rainka, M. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 15168-15169. b) Willis, M. C.; Brace, G. N.; Holmes, J. P. *Angew. Chem. Int. Ed.* **2005**, *44*, 403-406.



Scheme 115. A selection of structures whose synthesis exploited the Pd-catalyzed  $\alpha$ -arylation reaction.

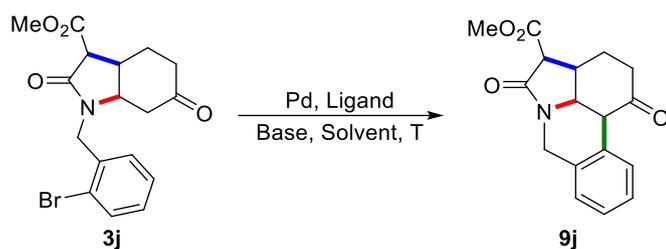
### 3. Study of the [Allylation / Aza-Michael / Arylation] (ALAMAR) Domino sequence

#### 3.1 Preliminary studies

As briefly mentioned in paragraph 2, in the frame of a logical continuation of our studies on the Pd-catalyzed [3+2] annulation described in chapter 2, we next decided to extend the domino sequence of one step by using a bis-nucleophile bearing a halo-aryl moiety. In this manner, we hoped to be able to end up with an overall [allylation / aza-Michael / arylation] (ALAMAR) domino sequence. We were aware that the accomplishment of such an ambitious plan depended, among other things, on the possibility of intramolecularly trapping the enolate issued from the nitrogen 1,4-addition with the catalytically generated arylpalladium(II) moiety, avoiding a premature enolate internal quench from the acid carbon atom of the bis-nucleophile.

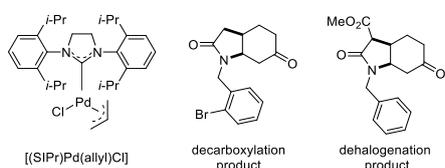
Accordingly, the cyclization of bicyclic structure **3j**, already isolated in the previous study, was chosen as the model to reaction to validate the ALAMAR concept, and hopefully, to optimize this multiple domino sequence. Different sources of palladium, ligands, bases and reaction conditions (solvents and temperatures) were screened, without obtaining any success in our first trials (Table 6).

Table 6. First attempts of Pd-catalyzed intramolecular  $\alpha$ -arylation of **3j**.



Entry	Pd (x mol%)	Ligand (y mol%)	Base (equiv.)	Solvent	T (°C)	Yield	
1	Pd <sub>2</sub> (dba) <sub>3</sub> (10)	BINAP (20)	NaOt-Bu (2.0)	PhMe	100	0 <sup>a</sup>	
2	Pd <sub>2</sub> (dba) <sub>3</sub> (5)	dppf (10)	NaOt-Bu (2.5)	THF	100	0 <sup>a</sup>	
3	Pd <sub>2</sub> (dba) <sub>3</sub> (5)	dtbpf (10)	NaOt-Bu (2.5)	THF	100	0 <sup>a</sup>	
4	[(SIPr)Pd(allyl)Cl] (5)		NaOt-Bu (2.5)	THF	100	0 <sup>a</sup>	
5	Pd <sub>2</sub> (dba) <sub>3</sub> (5)	dtbpf (10)	NaOt-Bu (2.5)	THF	60	0 <sup>a</sup>	
6	Pd <sub>2</sub> (dba) <sub>3</sub> (5)	dtbpf (10)	NaOt-Bu (2.5)	THF	rt	0	
7	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> (10)		Cs <sub>2</sub> CO <sub>3</sub> (3.0)	THF	100	0 <sup>b</sup>	
8	Pd <sub>2</sub> (dba) <sub>3</sub> (5)	Xantphos (15)	K <sub>3</sub> PO <sub>4</sub> (2.5)	THF	60	0 <sup>c</sup>	
9	[Pd( $\eta^3$ -C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> (5)		dppf (15)	DBU (2.0)	THF	100	0 <sup>d</sup>

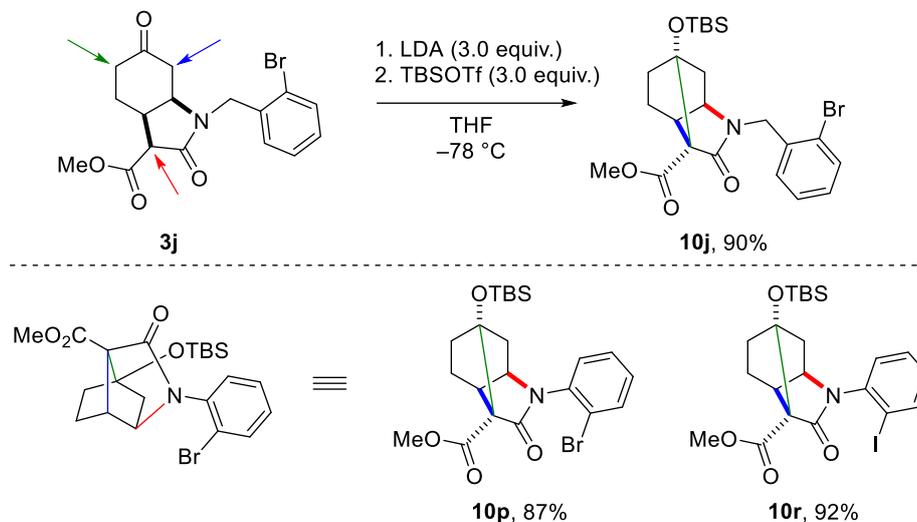
<sup>a</sup> Degradation. <sup>b</sup> A tiny amount of the decarboxylation product was obtained. <sup>c</sup> The dehalogenation product was obtained in 34% yield. <sup>d</sup> No reaction and slow degradation.



The bicyclic starting material **3j** was found to be unstable at high temperature in the presence of NaOt-Bu (entries 1-5), while no intramolecular  $\alpha$ -arylation could be observed working at room temperature (entry 6). In the presence of Cs<sub>2</sub>CO<sub>3</sub> as the base, the demethoxycarbonylation product was exclusively observed for a reaction at 100 °C with PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> as catalyst (entry 7). Surprisingly, with the system [Pd<sub>2</sub>(dba)<sub>3</sub> / Xantphos / K<sub>3</sub>PO<sub>4</sub>], the dehalogenation product was obtained in 34% yield (entry 8). This result suggested that the oxidative addition of the aryl halide to Pd(0) did take place, although the subsequent reaction with the enolate failed. Also, our previously optimized annulation reaction conditions using the system [Pd( $\eta^3$ -C<sub>3</sub>H<sub>5</sub>)Cl]<sub>2</sub> / dppf / DBU] at 100 °C in THF gave substrate degradation.

In the above described protocols, we always paid attention to use 2.0 or more equivalents of base in the hope to obtain a virtually complete deprotonation of the ketone function (at  $\alpha$  or  $\alpha'$  position), besides that of the, clearly more acidic, malonamide moiety. Since this point is crucial for the success of the desired reaction, we made a test on **3j**, by treating it with LDA (3.0 equiv.) in THF at -78 °C, followed by addition of *t*-butyldimethylsilyl triflate (3.0 equiv.). In the event, the bridged product **10j** was obtained in 90% yield

(Scheme 116). Applying the same protocol to the other substrates **3p** and **3r**, analogously afforded in high yield the corresponding bridged polycyclic products **10p** and **10r**.



Scheme 116. Synthesis of the tricycle compounds **10**.

The 3D structure of compound **10p** was confirmed by X-ray crystallographic analysis (Figure 7).

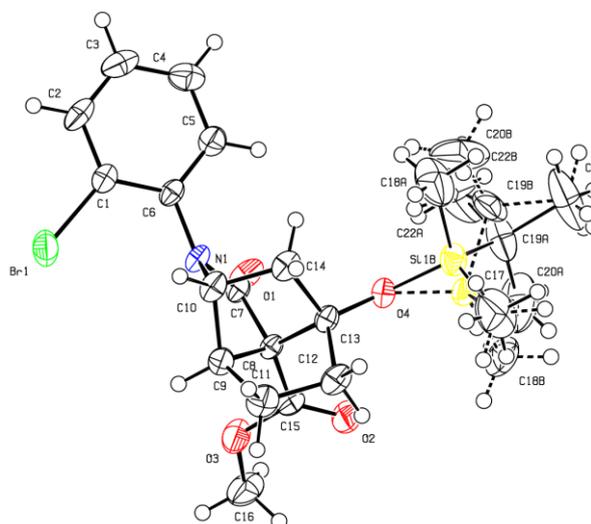
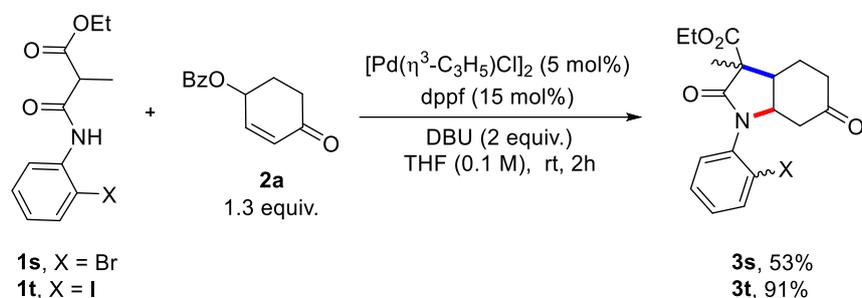


Figure 7. ORTEP X-ray structure of a monocrystal of compound **10p** (CCDC 1826879).

### 3.2 Study of the sequential Pd-catalyzed [3+2] annulation / arylation from **1s** and **2a**

This result suggests that as soon as the first equivalent of base deprotonates the malonamide H atom, the resulting enolate undergoes an immediate intramolecular aldol reaction with the keto function, which prevents the second, desired, deprotonation. To avoid this situation, we prepared the new methylated

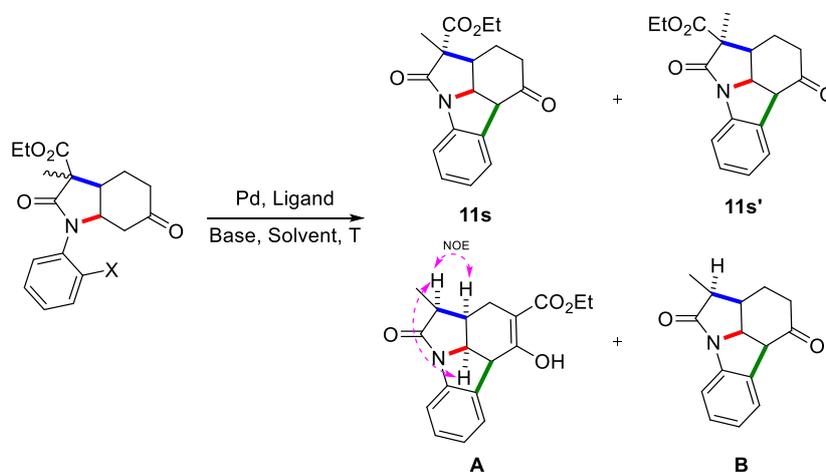
bicyclic malonamides **1s** and **1t** by standard methylation and submitted them to our optimized annulation protocol (**GP7**, see experiment part), obtaining **3s** and **3t** in 53% and 91% yield respectively (Scheme 117). Although the annulation worked satisfactorily, it has to be noted that the spectra of these two bicycles are fuzzy due to the presence of the two epimers at the methylated malonamide center as well as to the known atropisomerism of the amide N-C<sub>Ar</sub> bond.<sup>[129]</sup>



Scheme 117. Synthesis of the bicyclic compounds **3q** and **3r**.

Some Pd-catalyzed intramolecular arylation tests were submitted to the two new substrates **3s** and **3t**. These results were shown in the Table 7.

Table 7. Pd-catalyzed intramolecular α-arylation of **3q** / **3r**.



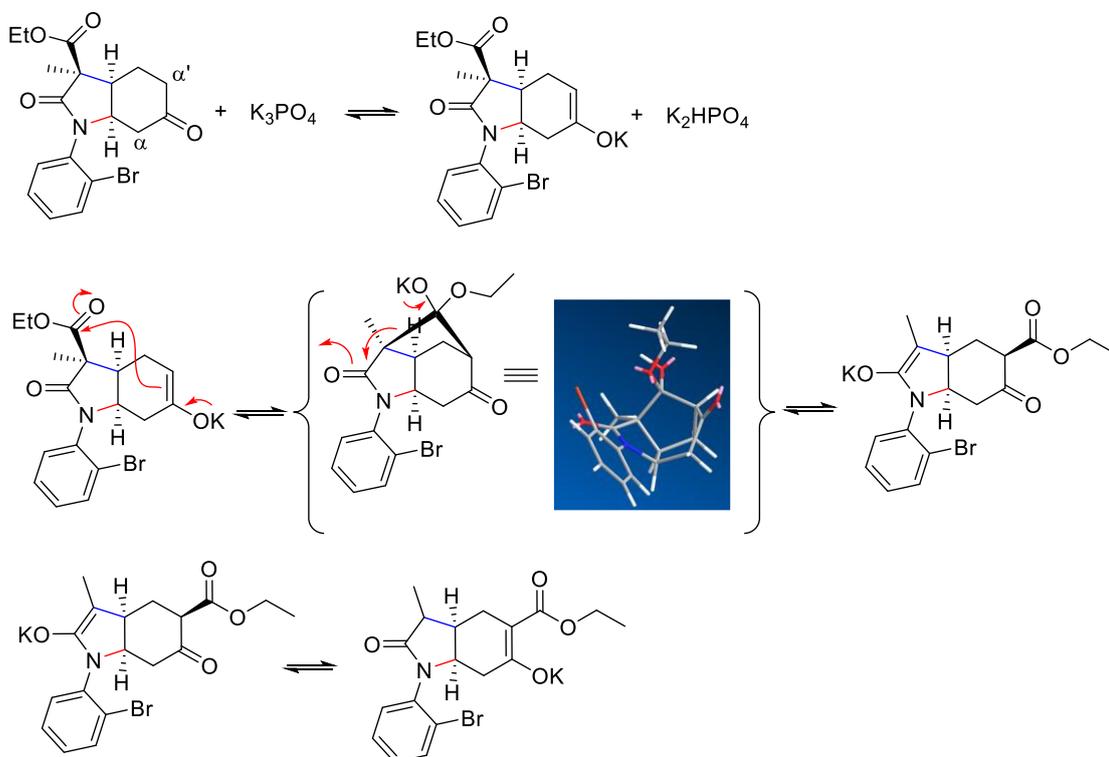
Entry	X	Pd (x mol%)	Ligand (y mol%)	Base (equiv.)	Solvent	T (°C)	<b>11s</b> (%)	<b>11s'</b> (%)	<b>A</b> (%)	<b>B</b> (%)
<b>1</b>	Br	Pd <sub>2</sub> (dba) <sub>3</sub> (5)	Xantphos (15)	K <sub>3</sub> PO <sub>4</sub> (2.5)	THF	60				
<b>2<sup>a</sup></b>	Br	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> (20)		Cs <sub>2</sub> CO <sub>3</sub> (3.0)	THF	100	39	Trace	10	
<b>3</b>	Br	Pd(PPh <sub>3</sub> ) <sub>4</sub> (20)		K <sub>3</sub> PO <sub>4</sub> (3.0)	THF	100	40		12	Trace

<sup>129</sup> See for example: Lapiere, A.; Geib, S.; Curran D. *J. Am. Chem. Soc.* **2007**, *129*, 494-495.

<b>4<sup>a</sup></b>	Br	Pd(PPh <sub>3</sub> ) <sub>4</sub> (20)		K <sub>3</sub> PO <sub>4</sub> (3.0)	PhMe	145	45	Trace	10
<b>5</b>	I	Pd(PPh <sub>3</sub> ) <sub>4</sub> (20)		K <sub>3</sub> PO <sub>4</sub> (3.0)	PhMe	145	35	8	Trace
<b>6</b>	I	Pd(OAc) <sub>2</sub> (20)	Xantphos (30)	K <sub>3</sub> PO <sub>4</sub> (3.0)	PhMe	145	20	Trace	Trace
<b>7</b>	I	Pd(OAc) <sub>2</sub> (20)	PPh <sub>3</sub> (60)	K <sub>3</sub> PO <sub>4</sub> (3.0)	PhMe	145	28	9	Trace

<sup>a</sup> NMR yield. The spatial structure of the tricycle compound **11s** and **11s'** were confirmed in NOE.

As can be seen from the table, the desired intramolecular arylation product **11s** could be finally observed for the first time, although with moderate yields. Heating, in THF at 100°C, or in Toluene at 145°C was necessary. The best conditions for the bromide as well as for the iodide called for the system [Pd(PPh<sub>3</sub>)<sub>4</sub> / K<sub>3</sub>PO<sub>4</sub> / in PhMe at 145°C] (entries 2 and 3). Interestingly, the cyclized product **11s** is mainly present as a major epimer. Furthermore, long reaction times favor the formation of the decarboxylated product **B** as a byproduct (entries 4 and 6). Also, when working in THF, the minor byproduct **A** was observed, which visibly stems from an internal trans-acylation (Claisen-type) reaction from the α'-enolate, as described here below (Scheme 118).

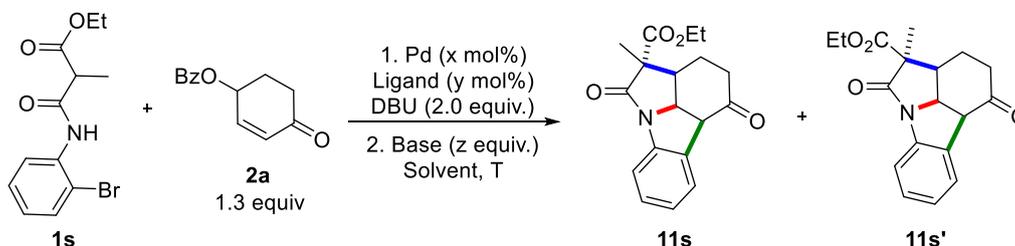


Scheme 118. Proposed mechanism for the formation of compound **A**.

### 3.3 Study of the ALAMAR domino sequence from **1s** and **2a**

At this stage of our study, we investigated the direct reaction between the bis-nucleophile **1s**, bearing a methyl group on the  $\alpha$ -position, and bis-electrophile **2a**. The results were presented in Table 8.

Table 8. Pd-catalyzed one-pot domino reaction of **1s** with **2a**.



Entry	Pd (x mol%)	Ligand (y mol%)	Base (z equiv.)	Solvent	T (°C)	11s Yield (%)	11s' Yield (%)
1	Pd(PPh <sub>3</sub> ) <sub>4</sub> (10)		K <sub>3</sub> PO <sub>4</sub> (3)	THF	100	30	8
2	[Pd( $\eta^3$ -C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> (5)	dppf (15)	DBU (2)	THF	100	degradation	
3	Pd <sub>2</sub> (dba) <sub>3</sub> (5)	dppf (15)	NaOt-Bu (3)	THF	100	degradation	
4	[Pd( $\eta^3$ -C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub> (5)	dppf (15)	K <sub>3</sub> PO <sub>4</sub> (3)	PhMe	145	55	18
5	Pd(OAc) <sub>2</sub> (10)	dppb (15)	DBU (2) + K <sub>3</sub> PO <sub>4</sub> (3) <sup>a</sup>	PhMe	145	70	29

<sup>a</sup> this base was added after 10 min.

Interestingly, when we investigated the one-pot domino reaction between **1s** with **2a** using the system [Pd(PPh<sub>3</sub>)<sub>4</sub> / K<sub>3</sub>PO<sub>4</sub>], the desired products **11s** and **11s'** were respectively obtained in 30% and 8% yield (entry 1), which is sensibly better than the sequential yield.<sup>[130]</sup> This fact is not surprising. Indeed, while the domino process involves the exclusive formation of the desired  $\alpha$ -enolate that can directly react with the  $\sigma$ -arylpalladium complex, in the two-step protocol the undesired  $\alpha'$ -enolate can be competitively formed, and is irreversibly lost in the *trans*-acylation step, as we did observe.

Further experiments showed that using DBU or NaOt-Bu as bases, at 100 °C gave only degradation (entries 2 and 3). On the other hand, using the system [[Pd( $\eta^3$ -C<sub>3</sub>H<sub>5</sub>)Cl]<sub>2</sub> / dppf / K<sub>3</sub>PO<sub>4</sub>] in toluene at 145 °C afforded the desired tricyclic diastereoisomeric compound **11s** / **11s'** in 55% and 18% yield, respectively (entry 4). Finally, we were very glad to find that treatment of **1s** with **2a** using the catalyst system consisting of [Pd(OAc)<sub>2</sub> (10 mol%), dppb (15 mol%) and DBU (2 equiv.)] in toluene at room temperature for 10 min, followed by addition of dry K<sub>3</sub>PO<sub>4</sub> and toluene in a sealed tube, and heating at 145 °C for further 2 h, gave the desired tricyclic compounds **11s** / **11s'** in an isolated yield of 70% and 29%

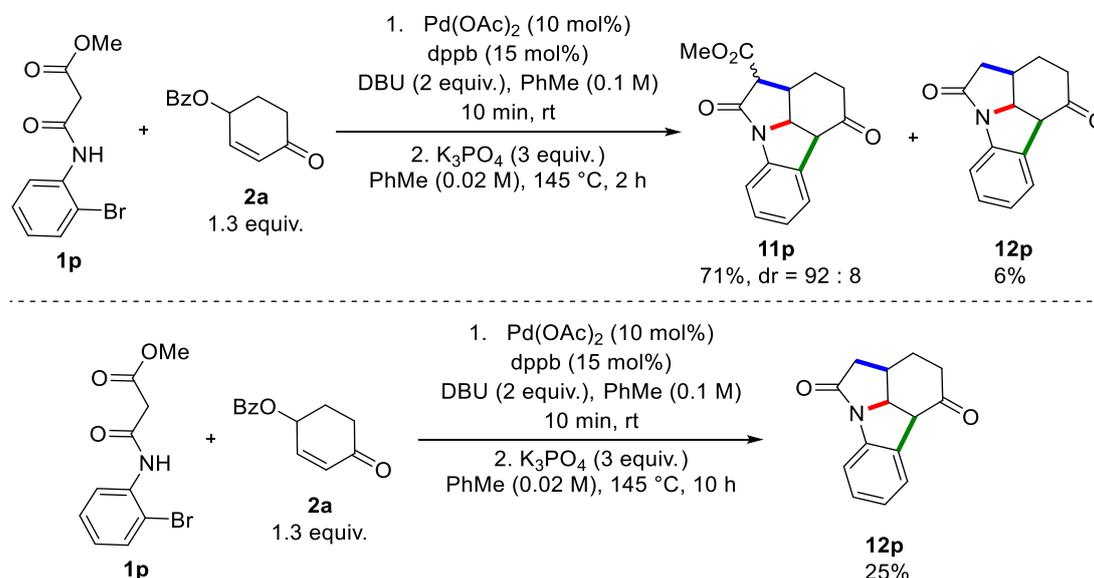
<sup>130</sup> The yield of the single [3+2] annulation was 53%, and that of the intramolecular  $\alpha$ -arylation was 40%.

yields, respectively (entry 5).

This satisfactory result validated our hypothesis that the  $\alpha$ -enolate generated by the aza-Michael addition could be immediately captured by the transiently generated  $\sigma$ -arylpalladium(II) complex to form the *cis/cis* fused tricyclic compound, rather than suffering premature proton transfer from the bis-nucleophile component. This positive result encouraged us to continue the investigation of the one-pot domino reaction between the bis-electrophile **2a** and some other amides bis-nucleophiles.

### 3.4 Scope of the one-pot domino sequence

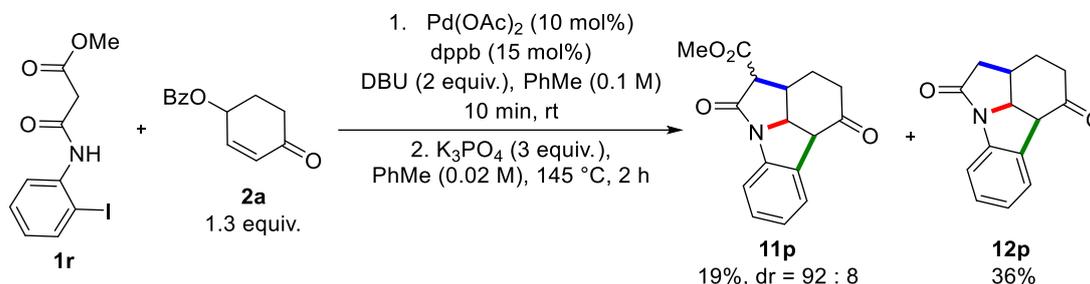
With the previously optimized reaction conditions in hand (Table 8, entry 5), the scope of the one-pot domino tricyclic reaction was next evaluated. The domino reaction between methyl 3-((2-bromophenyl)amino)-3-oxopropanoate **1p** and bis-electrophile **2a** was first tested. Under the above optimized conditions (GP13, see experiment part), the desired tricyclic compound **11p** was obtained in 71% yield with a 92 : 8 ratio of diastereoisomers. The demethoxycarbonylated product **12p** was also found in 6% yield (Scheme 119, top). On the other hand, attempts to exclusively obtain compound **12p** by rising the reaction temperature and/or using longer reaction times where only partially satisfactory, allowing to obtain **12p** in only 25% yield after 10 h at 145 °C (Scheme 119, bottom).



Scheme 119. Pd-catalyzed ALAMAR domino reaction of **1p** with **2a**.

Treatment of the iodoamide bis-nucleophile **1r** with **2a** under the optimized conditions gave the “normal” and decarboxylated tricyclic products **11p** and **12p** in 19% and 36% yield, respectively. (Scheme 120). In this case, the reaction needed longer time than then when starting from the corresponding

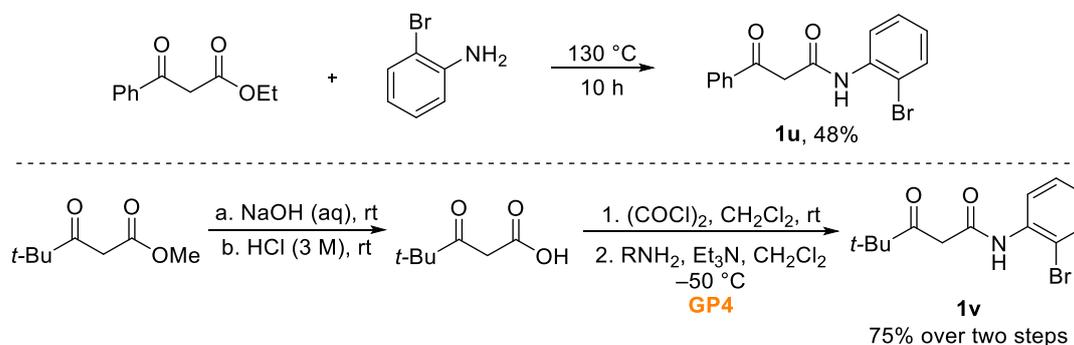
bromoamide bis-nucleophile **1p**, which brought about a considerable proportion of decarboxylated product. It has to be noted that the aryl bromide bis-nucleophile **1p** was more reactive than aryl iodide bis-nucleophile **1r** in this domino reaction.



Scheme 120. Pd-catalyzed one-pot domino reaction of **1r** with **2a**.

These results suggest that under our reaction conditions the demethoxycarbonylative reaction can hardly be avoided. Nonetheless, we thought that we could get around this drawback by using resonance stabilizing groups for the acetamide-based bis-nucleophiles different from the ester function.

Accordingly, bis-nucleophile **1u** was prepared by reacting ethyl benzoylacetate with 2-bromoaniline neat at 135 °C for 10 h under N<sub>2</sub>, following the procedure described by Jia<sup>[131]</sup> (Scheme 121, top). Substrate **1v** was synthesized from pivaloylacetate via basic hydrolysis to give the corresponding β-keto acid, which was then transformed into the acid chloride and next reacted with 2-bromoaniline (Scheme 121, bottom).

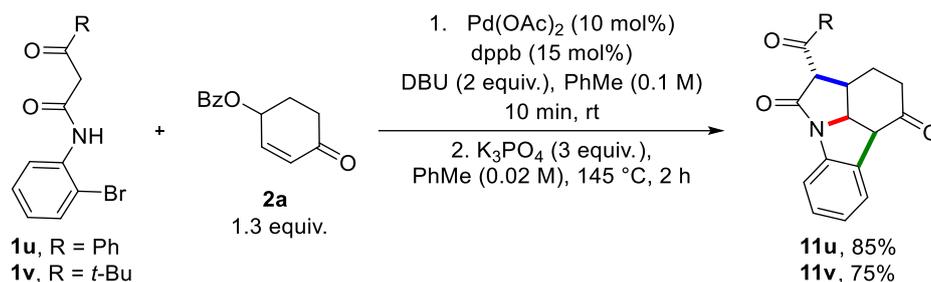


Scheme 121. Synthesis of bis-nucleophile **1u** and **1v**.

To our delight, submission of the β-ketoamide bis-nucleophile **1u** and **1v** to the one-pot domino reaction generated smoothly the desired 6/5/5 tricyclic compounds **11u** and **11v** in excellent yields and as a single diastereomers (Scheme 122). This unequivocal improvement may be attributed to the higher acidity of the active methylenes of β-ketoamides with respect to malonamides and to the absence of

<sup>131</sup> Jia, Y.-X.; He, J.-Q.; Chen, C.; Yu, W.-B.; Liu, R.-R.; Xu, L.-M.; Li, Y.-J.; Gao, J.-R. *Tetrahedron Lett.* **2014**, *55*, 2805-2808.

demethoxycarbonylative side reaction.



Scheme 122. Pd-catalyzed one-pot domino reaction of **1u** / **1v** with **2a**.

The spatial structure of the compound **11v** was confirmed by X-ray crystallographic analysis (Figure 8).

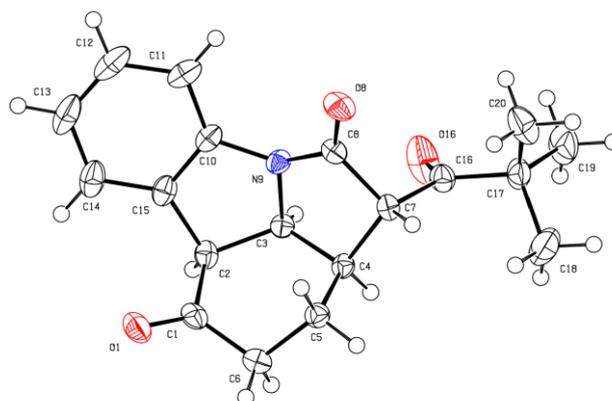
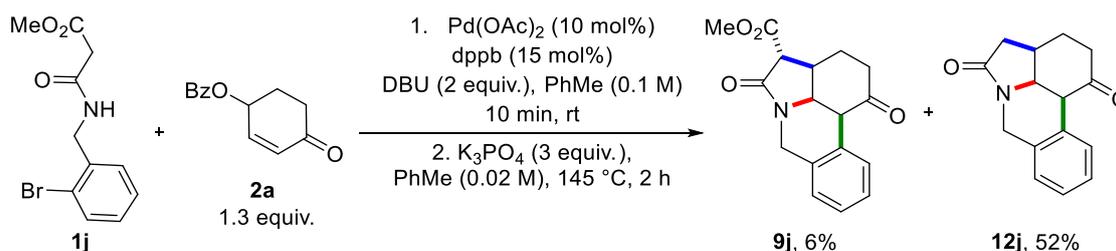


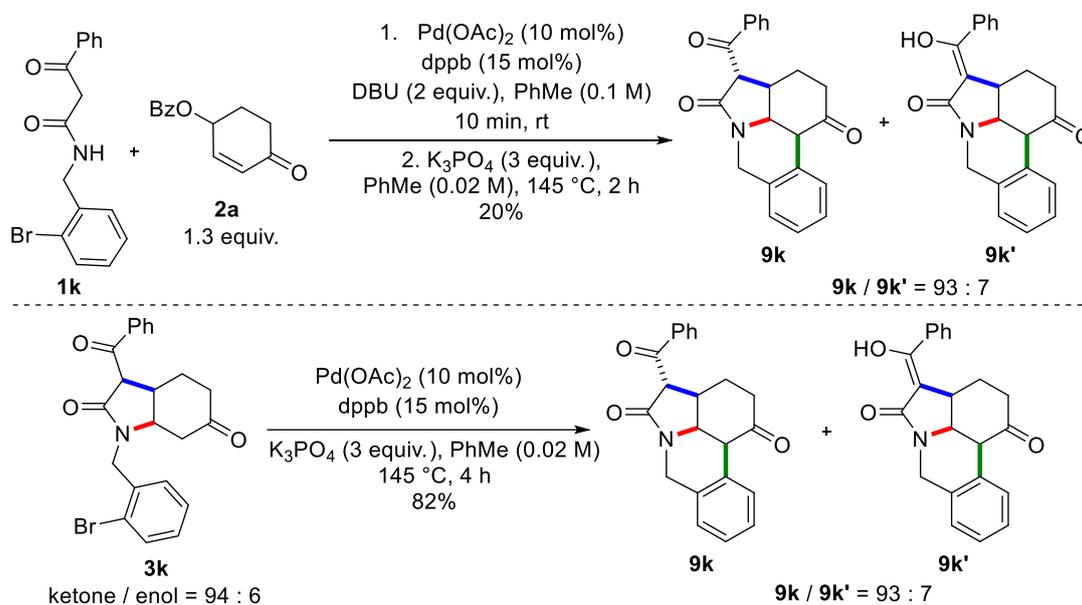
Figure 8. X-ray crystal structure of a monocrystal of compound **11v** (CCDC 1824090).

Encouraged by these positive results, we next turned our attention to the one-pot domino reaction for synthesis 6/5/6 fused tricyclic compounds. Accordingly, under the above optimized reaction conditions, methyl 3-((2-bromobenzyl)amino)-3-oxopropanoate **1j** gave the desired triple domino product, too. However, due to the prolonged reaction time required (12 h), the demethoxycarbonylated compound **12j** was the major product (52% yield), while the intact tricycle adduct **9j** being obtained in 6% yield (Scheme 123).



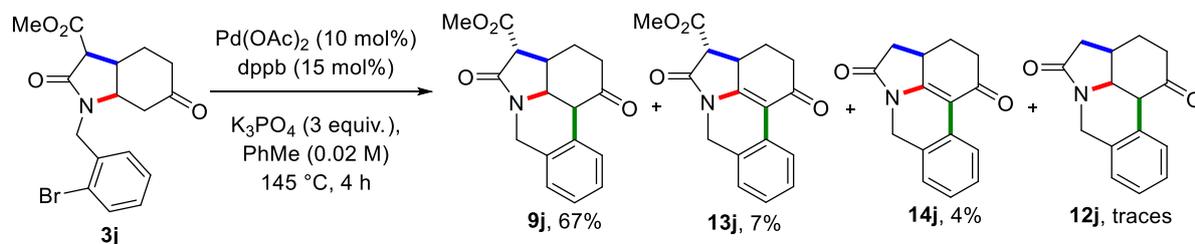
Scheme 123. Pd-catalyzed one-pot domino reaction of **1j** with **2a**.

We next envisioned using  $\beta$ -ketoamide *N*-benzyl bis-nucleophiles in the domino reaction, hoping to avoid in this case the demethoxycarbonylation. As it was, use of the above reaction conditions with  $\beta$ -phenylketoamide **1k** gave the desired tricyclic product **9k** in rather low yield (20%), as a 93/7 keto/enol mixture (Scheme 124, top). However, submitting the intermediate **3k** to system [Pd(OAc)<sub>2</sub> / dppb / K<sub>3</sub>PO<sub>4</sub>] in toluene at 145 °C gave **9k/9k'** in 82% yield (Scheme 124, bottom).



Scheme 124. Pd-catalyzed generation of the 6/5/6 tricyclic structures of **9k** and **9k'**. Top: ALAMAR domino reaction. Bottom: simple  $\alpha$ -keto arylation starting from the intermediate **3k**.

Intrigued by the different results afforded by the two above reaction condition, we decided to revisit the Pd-catalyzed intermolecular  $\alpha$ -keto arylation of **3j** using the new catalytic system [Pd(OAc)<sub>2</sub> / dppb / K<sub>3</sub>PO<sub>4</sub>]. In the event, the reaction gave the desired tricycle **9j** in 67% yield, with the demethoxycarbonylated product **12j** now almost absent. However, under these conditions we could isolate minor amounts of the tricyclic compound **13j** and the demethoxycarbonylated compound **14j** in 7% yield and 4% yield, respectively, likely deriving from a Saegusa-Ito type<sup>[132]</sup> oxidation reaction (Scheme 125).



Scheme 125. Pd-catalyzed intramolecular  $\alpha$ -keto arylation of **3j** using the catalytic system [Pd(OAc)<sub>2</sub> / dppb / K<sub>3</sub>PO<sub>4</sub>].

<sup>132</sup> Diao, T. N.; Stahl, S. S. *J. Am. Chem. Soc.* **2011**, *133*, 14566-14569.

We can conclude that access to 6/5/6 fused tricycles with this domino strategy appears to be significantly more difficult than access to the 6/5/5 manifold. This different behavior may be due to the fact that a 7-membered palladacycle (*vide infra*) is more difficult to generate than a corresponding 6-membered one.

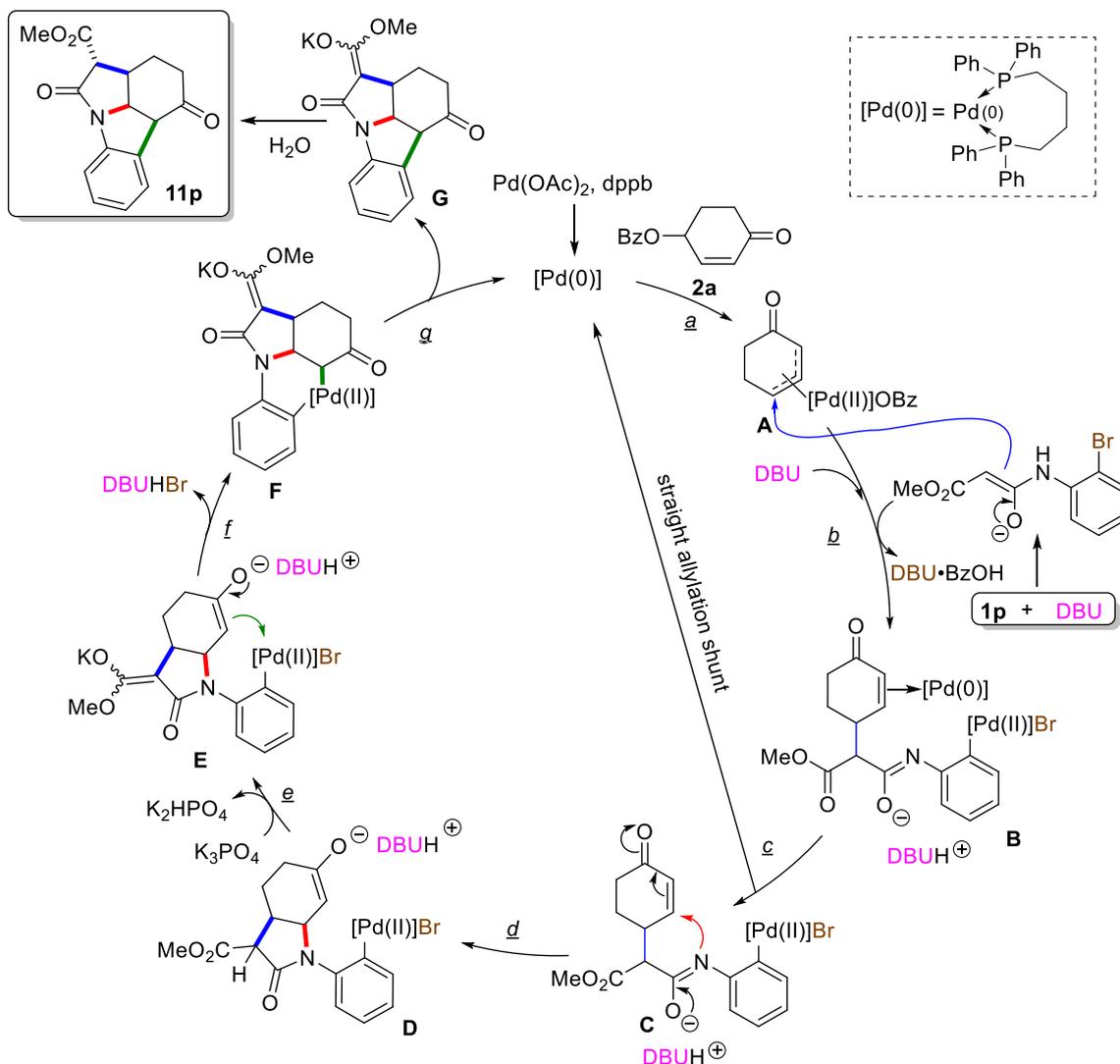
### 3.5 Mechanism

On the basis of the reported results and of ours, we propose for the ALAMAR domino sequence the following mechanism (Scheme 126). Oxidative addition of the bis-electrophile **2a** to the [Pd(0)] complex affords the corresponding transient  $\eta^3$ -allyl-palladium(II) complex **A** (*step a*), which undergoes nucleophilic attack by the amidinium enolate of the bis-nucleophile **1p** in the meantime formed in the presence of DBU. After a new deprotonation by DBU and a new oxidative addition of the aryl halide function to the [Pd(0)] complex, amidate **B** is formed (*step b*). Pd(0) decoordination closes the allylative cycle, affording intermediate **C** (*step c*) that undergoes an intramolecular aza-Michael addition to give the bicyclic enolate **D** (*step d*). Deprotonation of the remaining malonamide C-H position by  $K_3PO_4$  takes place,<sup>[133]</sup> impeding its otherwise catastrophic intramolecular transfer to the very basic newly formed transient enolate, generating the dienolate **E** (*step e*). Then, enolate-palladation generates the corresponding alkylaryl-palladium (II) complex **F** (*step f*), which, after reductive elimination, affords the resonance-stabilized K-enolate **G**<sup>[134]</sup> of the newly formed tricyclic structure and regenerates the [Pd(0)] complex, thereby closing the arylative cycle (*step g*). Finally, hydrolytic quenching stereoselectively protonates the resonance-stabilized enolate **G**, generating the final tricyclic product **11p** as a single diastereoisomer.

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<sup>133</sup> We cannot rule out a possible deprotonation at the malonamide C-H position in an earlier stage.

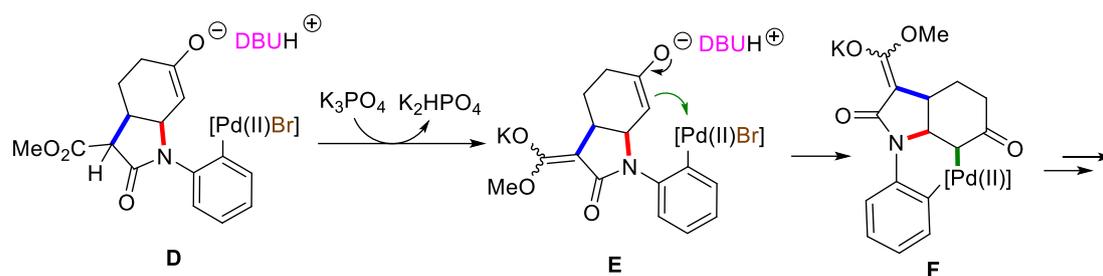
<sup>134</sup> The respective location of the two enolate counterions (DBUH<sup>+</sup> and K<sup>+</sup>) is tentative.



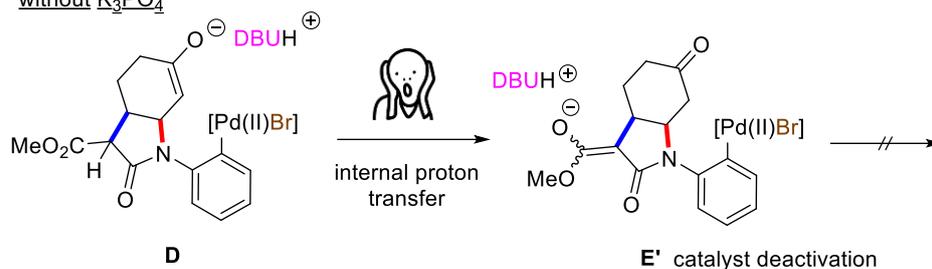
Scheme 126. Proposed mechanism for the Pd-catalyzed ALAMAR domino sequence.

The crucial role of  $K_3PO_4$  is key in the enolate palladation step (Scheme 127, top). Indeed, running the reaction in the absence of this inorganic base, internal proton transfer quenches the enolate giving the unproductive intermediate **E'** that sequesters the catalytic palladium (Scheme 127, bottom). Since the allylation catalytic cycle is likely to run much faster than the arylation catalytic cycle, the former cycle can still work to a great extent before palladium is totally and irreversibly sequestered by intermediate **E'**. The net result in this case is production of the annulated product **3n** through a straight allylation shunt, from the molecules that escaped undergoing oxidative addition at the C-Br bond.

with  $K_3PO_4$



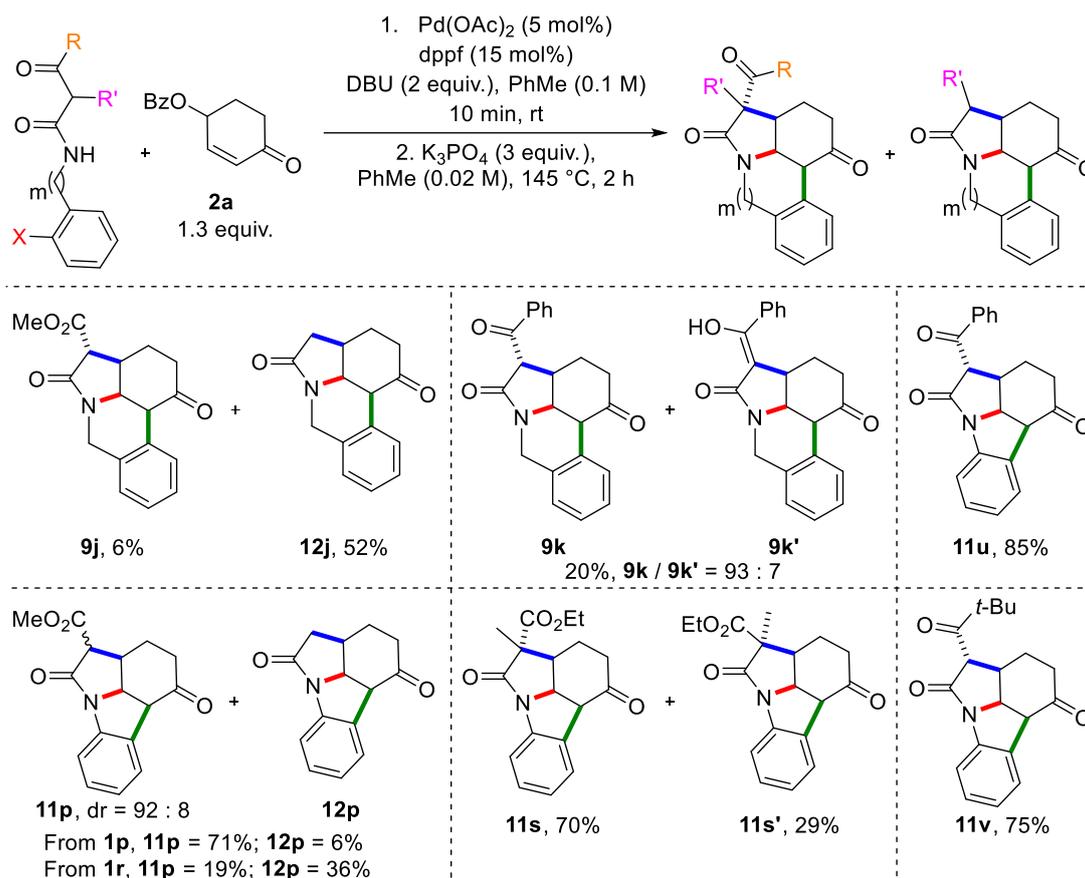
without  $K_3PO_4$



Scheme 127. Comparison of the domino process with and w/out  $K_3PO_4$ .

### 3.6 Conclusion and Perspectives

In summary, we have successfully developed a new Pd-catalyzed [allylation / aza-Michael / keto  $\alpha$ -arylation] (ALAMAR) domino sequence that allows the selective formation of fused tricyclic systems through the generation of two new cycles and three new bonds in the same synthetic operation. A range of bis-nucleophiles bearing various substitutions at the nitrogen atom could be used (Scheme 128). In particular, the generation of 6/5/5 fused tricyclic structures proved easier than that of 6/5/6 frameworks.<sup>[96]</sup>



Scheme 128. The scope of the Pd-catalyzed one-pot domino reaction.

We have proposed a plausible mechanism for this domino process, which involves a first intermolecular Pd-catalyzed allylation reaction (Tsuji-Trost), followed by an intramolecular aza-Michael addition and finally by an intramolecular Pd-catalyzed keto  $\alpha$ -arylation.

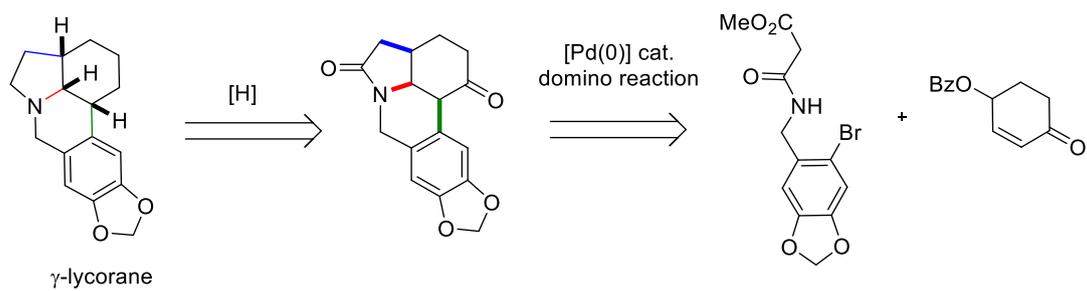
In addition, the discovery of the new tricyclic  $\alpha,\beta$ -unsaturated ketones byproducts **13j** and **14j** may be a hint for the future development of an oxidative variant of this method.

The extension to a four-stage domino sequence was also achieved when the demethocarbonylation step added to the sequence, as described for the formation of **12j** and **12p**.

Overall, the strategy enables an impressive increase of structure complexity starting from simple substrates, through a single multi-catalytic one-pot operation and may lend itself as key reaction in the synthesis of relevant target molecules such as natural products or molecules of biological or pharmacological relevance.  $\gamma$ -Lycorane,<sup>[135]</sup> a member of the pharmacologically interesting lycorine alkaloids

<sup>135</sup> a) Kotera, K. *Tetrahedron* **1961**, *12*, 248-261. b) Yochizaki, H.; Satoh, H.; Sato, Y.; Nukui, S.; Shibasaki, M.; Mori, M. *J. Org. Chem.* **1995**, *60*, 2016-2021. c) Chapsal, B. D.; Ojima, I. *Org. Lett.* **2006**, *8*, 1395-1398. d) Yu, W.-L.; Nunns, T.; Richardson, J.; Milburn, K. I. *Org. Lett.* **2018**, *20*, 1272-1274.

family,<sup>[136]</sup> of the *amaryllidaceae*, is just an example (Scheme 129).



Scheme 129. Retrosynthetic analysis of  $\gamma$ -lycorane using our domino strategy.

<sup>136</sup> Nair, J. J.; van Staden J. *Nat. Prod. Commun.* **2014**, 9, 1193-1210.

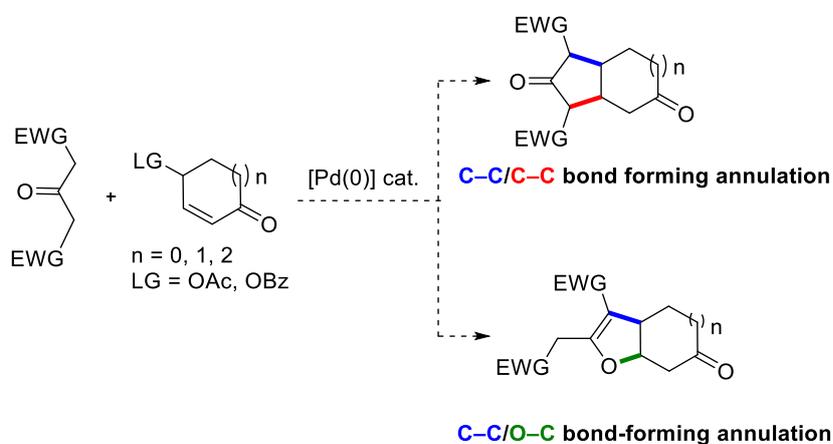


# Chapter 4: Palladium-Catalyzed [3+2]-C-C/O-C and C-C/C-C Bond-Forming Annulation

## 1. Introduction and Objectives

As previously introduced, the palladium-catalyzed domino reactions allow for the rapid establishment of molecular complexity through sequential and mechanistically independent bond-forming steps, which is crucial in multistep syntheses of complex target molecules.

In the chapters 2 and 3, we have successfully developed a new palladium-catalyzed [3+2]-C-C/N-C bond-forming annulation strategy for the synthesis of hexahydroindoles and the related "ALAMAR" triple domino strategy that allows the construction of the fused tetracyclic structures octahydropyrrolocarbazoles and hexahydropyrrolophenanthridines. As an extension of the above project, we reasoned that exchange of the activated malonamide for a 1,3-activated 1,3-propanone as the bis-nucleophilic partner might have allowed the achievement of novel [3+2]-C-C/C-C and/or [3+2]-C-C/O-C bond-forming annulations according to a first Pd-catalyzed C-allylation followed by an intramolecular C- and/or O-Michael reaction, respectively (Scheme 130).



Scheme 130. Predicted reactivity of the couple [3-oxoglutarate /  $\gamma$ -acyloxy- $\alpha,\beta$ -unsaturated ketone] under Pd-catalysis.

This variation was judged of high interest, as, if successful, it could have enabled the formation of fused bicyclic cyclopentanic (pentalene-, indene-, or azulene-type) and/or annulated furan-based structures, and both these substructures are incorporated into biologically relevant pharmaceuticals and/or natural

products (Figure 9).<sup>[137]</sup>

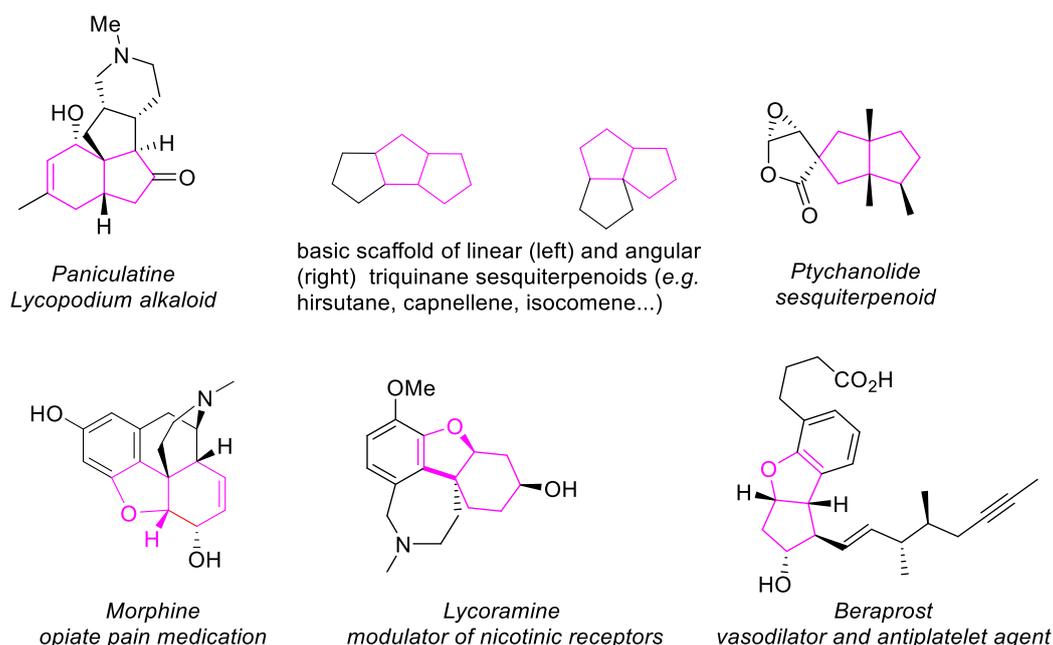


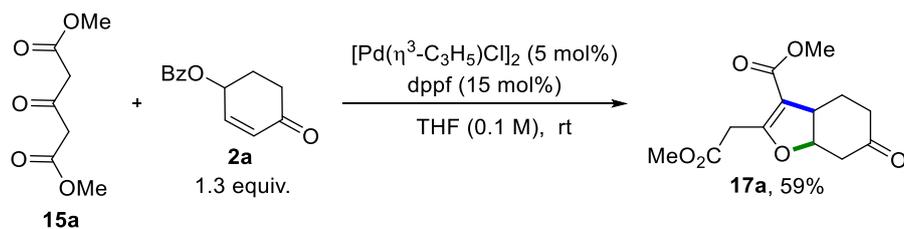
Figure 9. Examples of annulated cyclopentanic (top) and furan-based (bottom) substructures in natural products.

## 2. Studies of Pd-catalyzed [3+2] annulation between 3-oxoglutarate and 2-cyclohexenone 4-benzoate

### 2.1 Optimization of the [3+2]-C-C/O-C annulation

We started our study using dimethyl-3-oxoglutarate **15a** and 2-cyclohexenone 4-benzoate **2a** as bis-nucleophile and bis-electrophile model substrates, respectively. The first test was performed using the conditions previously developed for the [3+2]-C-C/N-C bond-forming annulation {[Pd( $\eta^3$ -C<sub>3</sub>H<sub>5</sub>)Cl]<sub>2</sub> (5 mol%), dppf (15 mol%)} in THF (0.1 M) at room temperature, which generated the annulated bicycle **17a** in 59% yield, resulting from a C-allylation and subsequent intramolecular O-Michael reaction (Scheme 131). Noteworthy, this [3+2]-C-C/O-C bond-forming annulation could be carried out in the absence of base.

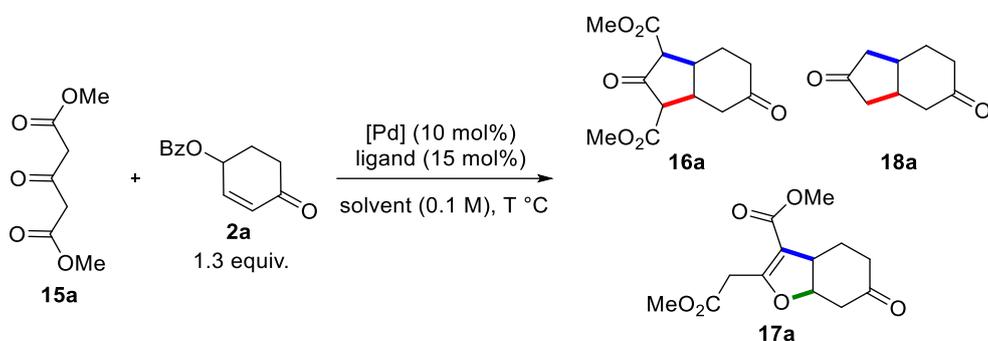
<sup>137</sup> For C-C bond: from left, a) Mehta, G.; Reddy, M. S.; Thomas, A. *Tetrahedron* **1998**, *54*, 7865-7882. b) Qiu, Y.; Lan, W.-J.; Li, H.-J.; Chen, L.-P. *Molecules* **2018**, *23*, 2095. c) Kutateladze, A. G.; Kuznetsov, D. M. *J. Org. Chem.* **2017**, *82*, 10795-10802. d) Takeda, R.; Naoki, H.; Iwashita, T.; Hirose, Y. *Tetrahedron Lett.* **1981**, *22*, 5307-5310. For O-C bond: from left, a) Trost, B. M.; Tang, W.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 14785-14803. b) Reddy, N. K.; Vijaykumar, B. V. D.; Chandrasekhar, S. *Org. Lett.* **2012**, *14*, 299-301.



Scheme 131. Pd-catalyzed [3+2] annulation between **15a** and **2a**.

With the annulated compound **17a** in hand, we next started to investigate the influence of each reaction parameter, such as palladium catalyst, ligand, temperature and time. The results were collected in Table 9.

Table 9. Optimization of Pd-catalyzed [3+2] annulation between **15a** and **2a**.



Entry	[Pd]	Ligand	solvent	T (°C), Time	Product	Yield (%)
1	[Pd( $\eta^3$ -C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub>	dppf	THF	rt, 1 h	<b>17a</b>	59
2	[Pd( $\eta^3$ -C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub>	dppf	THF	0, 2 h	<b>17a</b>	55
3	[Pd( $\eta^3$ -C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub>	dppf	THF	70, 1 h	<b>17a</b>	19
4	Pd(OAc) <sub>2</sub>	dppb	THF	rt, 1 h	<b>17a</b>	35
5	Pd(OAc) <sub>2</sub>	dppb	CH <sub>3</sub> CN	rt, 1 h	No reaction	
6	Pd(OAc) <sub>2</sub>	dppb	DMF	rt, 1 h	<b>17a</b>	66
7	Pd(OAc) <sub>2</sub>	dppb	DMSO	rt, 1 h	<b>17a</b>	75
8	Pd(OAc) <sub>2</sub>	dppe	DMSO	rt, 1 h	<b>17a</b>	traces
9	Pd(OAc) <sub>2</sub>	dppb	DMSO	75, 1 h	<b>17a</b>	73
10	Pd(OAc) <sub>2</sub>	dppb	DMSO	100, 6 h	<b>18a</b>	50
11	Pd(OAc) <sub>2</sub>	dppb	DMSO	130, 6 h	<b>18a</b>	69
12	[Pd( $\eta^3$ -C <sub>3</sub> H <sub>5</sub> )Cl] <sub>2</sub>	dppf	DMSO	130, 6 h	<b>18a</b>	33

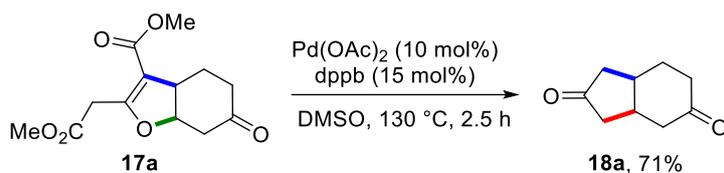
<b>13</b>	Pd(OAc) <sub>2</sub>	dppb	DMF	130, 6 h	<b>18a</b>	Trace
<b>14</b>	Pd(OAc) <sub>2</sub>	dppb	DMA	130, 6 h	<b>18a</b>	69
<b>15</b>	Pd(OAc) <sub>2</sub>	dppb	DMSO	130, MW-20 min	<b>18a</b>	35
<b>16</b>	Pd(OAc) <sub>2</sub>	dppb	DMSO	130, MW-1 h	<b>18a</b>	69
<b>17</b>	Pd(OAc) <sub>2</sub>	dppb	DMSO	160, MW-30 min	<b>18a</b>	60
<b>18</b>	Pd(OAc) <sub>2</sub>	dppb	DMSO	160, MW-1 h	<b>18a</b>	40

The effect of the reaction temperature was first evaluated. No improvement was observed at 0 or 70 °C, using the catalytic system {[Pd( $\eta^3$ -C<sub>3</sub>H<sub>5</sub>)Cl]<sub>2</sub> / dppf} (entries 1-3). Purification of the crude reaction turned out to be easier using the catalytic system [Pd(OAc)<sub>2</sub> / dppb], which gave **17a** in 35% yield (entry 4). This catalytic system which was thus selected to continue the optimization. Then, the influence of the solvent was investigated. No annulated product was observed in CH<sub>3</sub>CN, but **17a** was generated in 66% and 75%, respectively, when working in DMF and DMSO (entries 5-7). The bidentate phosphine ligands dppe gave only traces of **17a** (entry 8). Next, the effect of the reaction temperature in DMSO was examined. The product **17a** was obtained in similar yield at 75 °C (entry 9). However, working at 100 °C or 130 °C during 6 hours gave the new annulated product **18a** in 50% and 69% yield, respectively (entries 10, and 11). This new annulated product is plausibly generated by C-allylation followed by intramolecular C-Michael addition and subsequent decarboxylation, although the supposed intermediate **16a** was never observed the reaction crude.

Comparatively, use of the system {[Pd( $\eta^3$ -C<sub>3</sub>H<sub>5</sub>)Cl]<sub>2</sub> / dppf} in DMSO at 130 °C during 6 hours **18a** gave a lower yield (33%) (entry 12). With the system [Pd(OAc)<sub>2</sub> / dppb], use of DMF as solvent during 6 hours at 130 °C gave only in trace amounts of product (entry 13), while switching to DMA allowed to obtain the decarboxylated product **18a** in 69% yield (entry 14).

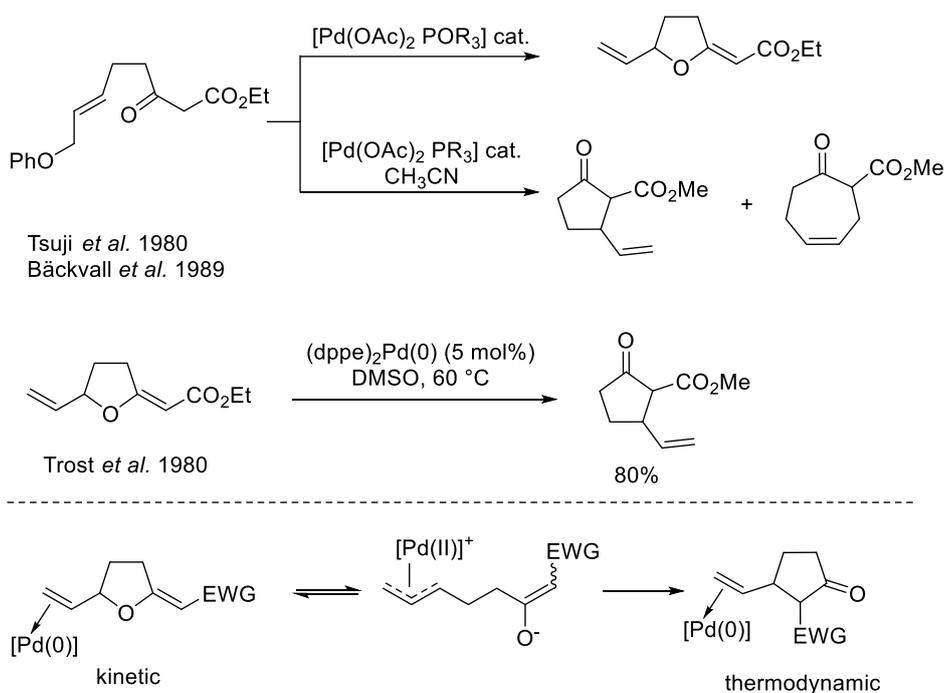
Microwave irradiation tests were also performed (entries 15-18). The best conditions, which required irradiation for 1 h at 130 °C, gave **18a** in 69% yield (entry 16).

We next passed to investigate the conversion of the *O*-annulated product **17a** into the *C*-annulated product **18a** (Scheme 132). Using the system [Pd(OAc)<sub>2</sub> / dppb] in DMSO no transformation was observed either at room temperature or at 75 °C. However, heating at 130 °C during 2.5 h gave the expected compound **18a** in 71% yield. It is noteworthy that no transformation of **17a** to **18a** occurred in other solvents, such as THF, CH<sub>3</sub>CN, DMF or Toluene.



Scheme 132. Conversion of **17a** to **18a**.

Tsuji,<sup>[138]</sup> and Trost,<sup>[139]</sup> pioneered the Pd-catalyzed *O*-allylation-to-*C*-allylation shift in the early 80's, and other groups<sup>[140]</sup> performed more recently further studies (Scheme 133). In particular,  $\beta$ -ketoesters having an allylic system at appropriate distance to undergo a Pd-catalyzed cyclization, undergo intramolecular allylation via oxygen or carbon in proportions highly dependent on the substrate and the reaction conditions. While *O*-allylation is usually kinetically controlled, *C*-allylation affords the thermodynamically more stable isomer.



Scheme 133. Precedents of Pd-catalyzed 1,3-Oxygen-to-Carbon allyl shifts.

<sup>138</sup> Tsuji, J.; Kobayashi, Y.; Kataoka, H.; Takahashi, T. *Tetrahedron Lett.* **1980**, *21*, 1475-1478.

<sup>139</sup> a) Trost, B. M.; Runge, T. A.; Jungheim, L. N. *J. Am. Chem. Soc.* **1980**, *102*, 2840-2841. b) Trost, B. M.; Runge, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 2485-2487. d) Trost, B. M.; Runge, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 7550-7559. e) Trost, B. M.; Runge, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 7559-7572. k) Trost, B. M.; Huang, Z.; Murhade G. M. *Science*, **2018**, *362*, 564-568.

<sup>140</sup> a) Yamamoto, K.; Tsuji, J. *Tetrahedron Lett.* **1982**, *23*, 3089-3092. b) Bäckvall, J. E.; Vågberg, J. O.; Granberg, K. L. *Tetrahedron Lett.* **1989**, *30*, 617-620. c) Koch, G.; Pfaltz, A. *Tetrahedron: Asymmetry* **1996**, *7*, 2213-2216. d) Nasveschuk, C. G.; Rovis, T. *Org. Biomol. Chem.* **2008**, *6*, 240-254. e) Brioché, J. C. R.; Barker, T. A.; Whatrup, D. J.; Barker, M. D.; Harrity, J. P. A. *Org. Lett.* **2010**, *12*, 4832-4835.

In accord with the above body of knowledge, our results suggest that the C–C/O–C annulated compound **17a** is the kinetic product, while the C–C/C–C annulated compound **18a** is the thermodynamic product.

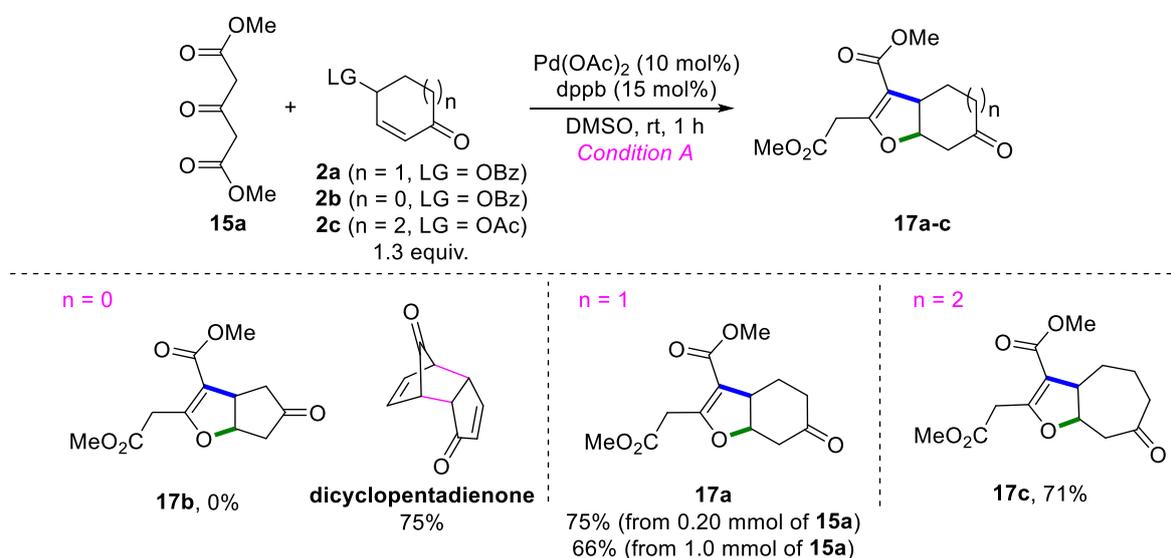
In conclusion, this study allowed to obtain the optimal reaction conditions for the synthesis of the furan derivatives **17a** [Pd(OAc)<sub>2</sub> (10 mol%), dppb (15 mol%)] in DMSO, 1 h at room temperature (conditions **A**, entry 7)], as well as for the formation of the bicyclo[4.3.0]nonane-dione **18a** [Pd(OAc)<sub>2</sub> (10 mol%), dppb (15 mol%)] in DMSO at 130 °C, 6 h (conditions **B**, entry 11), or 1 h under microwave irradiation (conditions **C**, entry 16)].

## 2.2 Scope and limitations of the Pd-catalyzed [3+2] annulation

With the best reaction conditions in hand, we next turned our attention to assessing the scope of these Pd-catalyzed [3+2]-C–C/O–C and C–C/C–C bond-forming annulation reactions.

### 2.2.1 Pd-catalyzed [3+2]-C–C/O–C annulations between **15a** and bis-electrophiles **2a-2c**

First, we tested the Pd-catalyzed [3+2]-C–C/O–C annulation between dimethyl-3-oxoglutarate **15a** and five- and seven-member ring bis-electrophile (**2b-2c**) (Scheme 134).



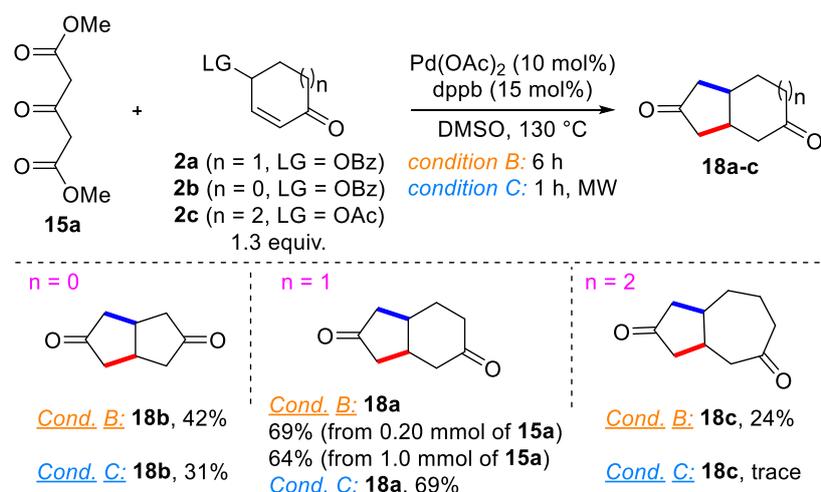
Scheme 134. Pd-catalyzed [3+2]-C–C/O–C bond-forming annulation between **15a** and **2a-2c**.

Under the optimized reaction conditions **A**, at room temperature in DMSO, the six- (**2a**) as well as the seven-membered (**2c**) bis-electrophiles reacted efficiently, affording the furo-cycloalkanones **17a** and **17c** in

good yields. Additionally, we managed to scale up the protocol to 1 mmol without a significant yield loss. On the other hand, treatment of cyclopentenone 4-benzoate **2b** under *conditions A* (even in THF or Toluene) did not allow the generation of the corresponding C–C/O–C annulated product. Indeed, elimination of the benzoate anion, probably from the  $\eta^3$ -allylpalladium complex, produced cyclopentadienone, which in turn underwent an immediate self Diels-Alder cycloaddition to form the corresponding endo dimer dicyclopentadienone.

## 2.2.2 Pd-catalyzed [3+2]-C–C/C–C annulations between **15a** and bis-electrophiles **2a-2c**

Then, the Pd-catalyzed [3+2]-C–C/C–C bond-forming annulation between dimethyl-3-oxoglutarate **15a** and the five- and seven-member ring bis-electrophile was examined (Scheme 135). As shown in Table 9, 2-cyclohexenone 4-benzoate **2a** gave the desired bicyclo[4.3.0]nonane-dione **18a** in 69% yield under either condition **B** or the microwave irradiation (condition **C**). Dione **18a** was also obtained in 64% yield starting from 1.0 mmol of **15a** without a substantial yield drop. Interestingly, the five-membered ring bis-electrophile **2b** gave the bicyclo[3.3.0]octane-dione **18b** in 42% and 31% yield, under the reaction conditions **B** and **C**, respectively. The moderate yield was due to the competitive formation of the dicyclopentadienone byproduct, as in the previous case. This result indicates that the undesired Pd-catalyzed elimination from a  $\gamma$ -acyloxycyclopentenone can be partially skipped by running the reaction at high temperature. However, the desired bicyclo[3.3.0]octane-3,7-dione structure can be also obtained under basic conditions and in the absence of Pd catalysis, as reported by Winterfeldt and Osterthun in the seventies.<sup>[141]</sup> The seven-member ring bis-electrophile **2c** gave the desired bicyclo[5.3.0]docane-dione **18c** in 24% yield under condition **B**, while no desired product was observed under microwave irradiation.



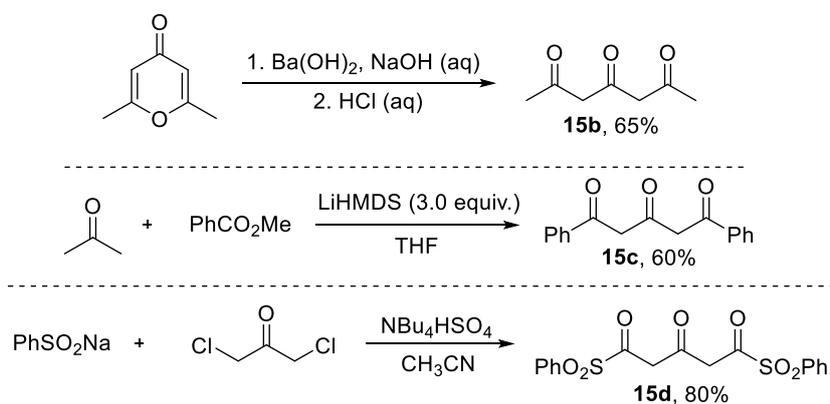
Scheme 135. Pd-catalyzed [3+2]-C–C/C–C bond-forming annulation of **15a** with **2a-2c**.

<sup>141</sup> Winterfeldt, E.; Osterthun, V. *Chem. Ber.* **1977**, *110*, 146-153. With this protocol, the mechanism is expected to involve a [conjugate addition/trans-enolization/ $\beta$ -elimination/conjugate addition] sequence.

### 2.2.3 Pd-catalyzed [3+2] annulation between **2a** and 1,3-activated propan-2-ones bis-nucleophiles other than **15a**

The reaction between the 1,3-activated 1,3-propanones bis-nucleophiles other than **15a** was then considered in the reaction with 2-cyclohexenone 4-benzoate (**2a**).

Our choice went on ketone-based activating groups at positions 1 and 3 of propan-2-one, so as to avoid the decarboxylation issues previously encountered using esters as activating groups. Accordingly, 1,3-diacetylacetone **15b**,<sup>[142]</sup> 1,3-dibenzoylacetone **15c**<sup>[143]</sup> and 1,3-bis-benzenesulfonylacetone **15d**<sup>[144]</sup> were smoothly synthesized according to reported protocols (Scheme 136).



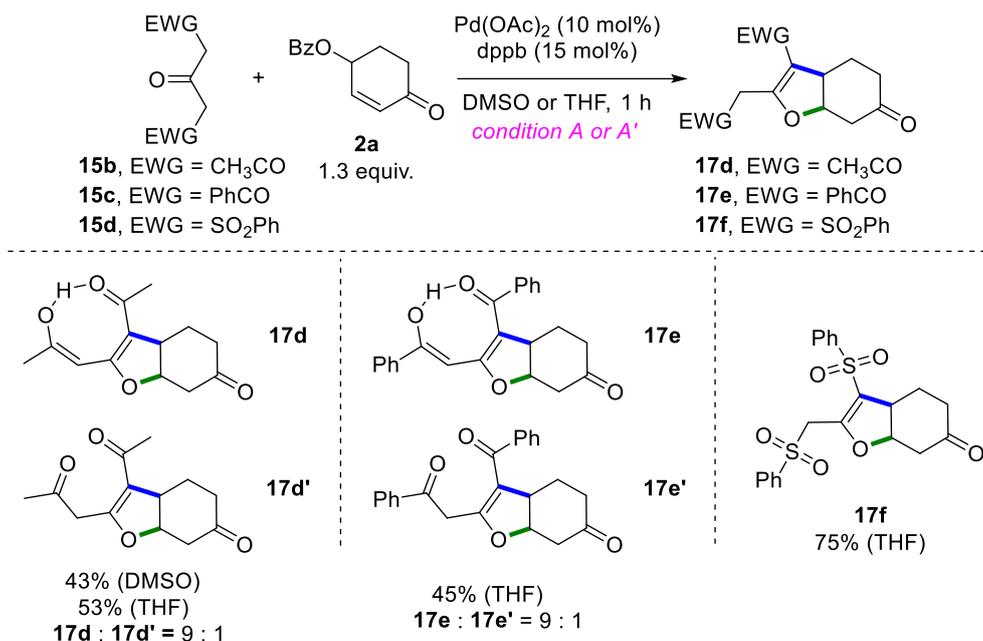
Scheme 136. Synthesis of bis-nucleophiles **15b-15d**.

With these new bis-nucleophiles in hand, the [3+2] annulation of **2a** with them was tested next. Thus, using the optimized conditions **A**, diacetylacetone **15b** gave the desired product **17d/17d'** in 43% yield as a 9:1 enol/ketone mixture. A slight yield improvement (53%) changing from DMSO to THF as solvent (condition **A'**), which also eased the work up. Similarly, starting from dibenzoylacetone **15c** and under conditions **A'**, the expected annulated product **17e/17e'** was obtained in 45% yield, again as a 9:1 enol/ketone mixture. Finally, under condition **A'**, the 1,3-bis-benzenesulfonylacetone **15d** afforded smoothly the annulated product **17f** in 75% yield (Scheme 137).

<sup>142</sup> Schwolow, S.; Kunz, H.; Rheinheimer, J.; Opatz, T. *Eur. J. Org. Chem.* **2013**, 6519-6524.

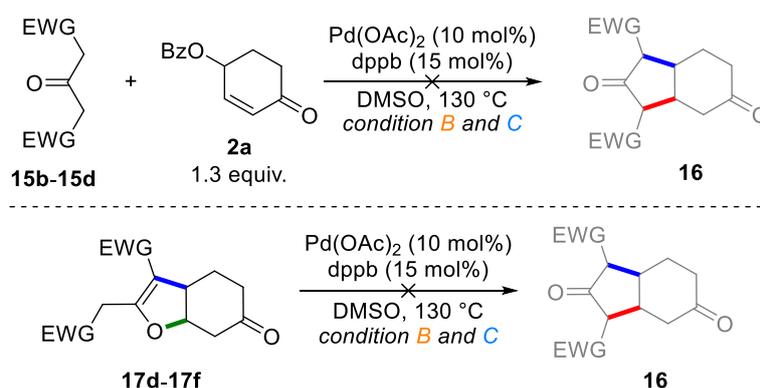
<sup>143</sup> Knigth, J. D.; Metz, C. R.; Beam, C. F.; Pennington, W. T.; VanDerveer, D. G. *Synth. Commun.* **2008**, *38*, 2465-2482.

<sup>144</sup> Chen, Y.; Lam, Y.; Lai, Y.-H. *Org. Lett.* **2002**, *4*, 3935-3937.



Scheme 137. Pd-catalyzed [3+2]-C-C/O-C bond-forming annulation between **2a** with **15b-15d**.

Unfortunately, the bis-nucleophiles **15b-15d** were unable to generate the annulated C-C/C-C products **16** under condition **B** or **C**. Despite several trials were attempted, such as change of time, temperature, solvent, catalytic system or base, all of them failed (Scheme 138, top). Furthermore, attempted conversion of the bicyclic C-C/O-C type products **17** into the corresponding C-C/C-C **16** ones failed too (Scheme 138, bottom).



Scheme 138. Attempted Pd-catalyzed [3+2]-C-C/C-C bond-forming annulations from **15b-15d** and from **17d-17f**.

## 2.2.4 Pd-catalyzed [3+2] annulation of **2a** and bis-nucleophiles **19**

Our studies clearly show that in the frame of the [3+2] Pd-catalyzed annulations between 1,3-bis-nucleophiles and  $\gamma$ -acyloxy  $\alpha,\beta$ -unsaturated cyclic ketones, the C-C/O-C bond forming type is intrinsically

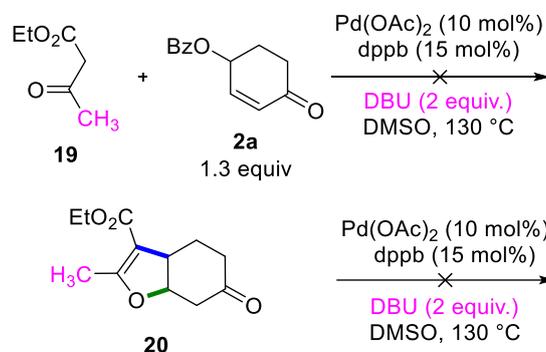
easier and more efficient than the corresponding C–C/C–C one. We thus thought that a simple  $\beta$ -ketoester might also have performed well as 1,3 C,O-nucleophile. Accordingly, we chose ethyl acetoacetate **19** for this test.

Using conditions **A** or **A'**, the first attempt of annulation between **19** and **2a** gave no observable product. However, when the reaction was repeated in the presence of 2.0 equivalents of DBU, the expected tetrahydrobenzofuranone **20** was obtained in quantitative yield (Scheme 139). A control test performed in the absence of the palladium catalytic system gave no product, confirming the need of the palladium catalysis. An analogous reactivity was observed by Tong on acetylated pyranuloses.<sup>[58,145]</sup>



Scheme 139. Pd-catalyzed [3+2]-C–C/O–C bond-forming annulation between **2a** and bis-nucleophile **19**.

Not so unexpectedly, attempts to obtain the C–C/C–C type of annulation under condition **B** or **C** with added DBU, either starting from the reaction components **19** + **2a** or from the tetrahydrobenzofuranone **20** met with failure (no reaction with some degradation) (Scheme 140).



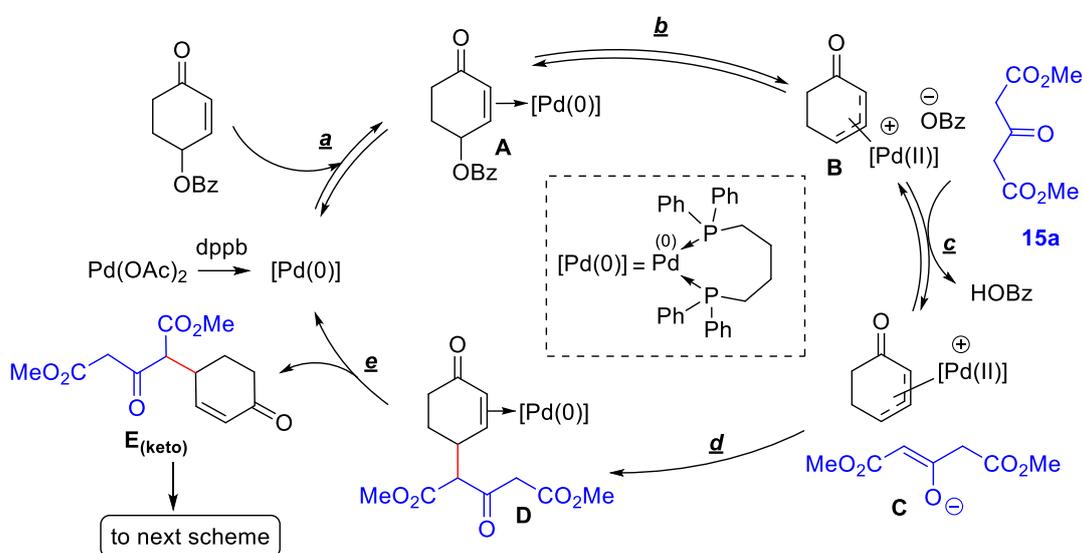
Scheme 140. Attempted Pd-catalyzed [3+2]-C–C/C–C bond-forming annulation between **2a** and ethyl acetoacetate **19**.

We believe that the impracticality of the O-to-C shift in the case of the triketones, 1,3-bis-benzenesulfonylacetone and ethyl acetoacetate is likely due to the high activation barrier of the corresponding retro-Michael reaction and to the intrinsic irreversible character of the conjugate addition with these bis-nucleophiles.

<sup>145</sup> For an old non catalytic example of intramolecular Michael reaction to afford an oxabicyclo[3.3.0]octane, see: Knolker H.-J.; Winterfeldt, E. *Liebigs Ann. Chem.* **1986**, 465-478.

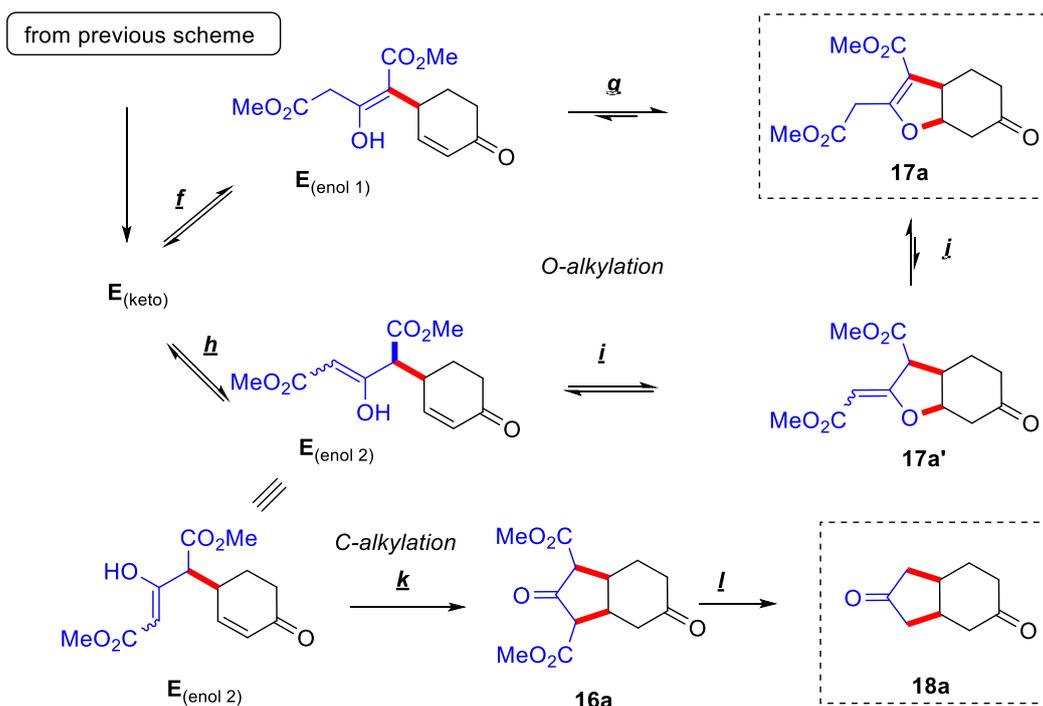
## 2.3 Mechanism

On the basis of the above results, a plausible mechanism for the Pd-catalyzed [3+2]-C-C/O-C and C-C/C-C bond-forming annulations is proposed for the reaction between dimethyl-3-oxoglutarate **15a** and 2-cyclohexenone 4-benzoate **2a**. Oxidative addition of the bis-electrophile **2a** onto the Pd(0) complex to form  $\eta^3$ -allyl-complex **B** from  $\eta^2$ -alkene complex **A** (steps **a** and **b**) starts the reaction. Deprotonation of the pro-nucleophile **15a** by the counter-anion of the  $\eta^3$ -allyl-Pd complex brings about the enolate counterion exchange (step **c**), and the subsequent C-allylation from the resulting complex **C** leads to the Pd(0) complex **D** (step **d**). Pd(0) decoordination ends the catalytic cycle, which generates intermediate  $E_{(keto)}$  (step **e**) (Scheme 141).



Scheme 141. Proposed mechanism for the Pd-catalyzed part of the [3+2] annulation reaction between **2a** and **15a**.

The ensuing intramolecular *O*-conjugate addition of an enol tautomer of  $E_{(keto)}$  affords the kinetic C-C/O-C adduct **17a** through steps (**f, g**), or (**h, i, j**) (Scheme 142, top and middle lines). At room temperature and typical reaction times, the reaction halts at this stage. However, at 130 °C the reversibility of the sequence leading to **17a** becomes significant and the system acquires enough energy to undergo the irreversible intramolecular *C*-conjugate addition of enol  $E_{(enol)}$  followed by double demethoxycarbonylation to give the final bicyclo[4.3.0]nonane-dione **18a** (steps **k, l**) (Scheme 142, bottom line).



Scheme 142. Proposed mechanism for the temperature dependent cyclization part of the [3+2] annulation reaction between **2a** and **15a**.

### 3. Conclusion and Perspectives

In summary, we have successfully developed two chemoselective and complementary methods of Pd-catalyzed [3+2]-annulation between cyclic  $\alpha,\beta$ -unsaturated- $\gamma$ -oxy-carbonyl derivatives and dialkyl-3-oxoglutarates involving an intermolecular Pd-catalyzed *C*-allylation followed by a subsequent intramolecular *O*-Michael addition or *C*-Michael addition. Noteworthy, the *O*-Michael addition step becomes reversible at high temperature, which allows the conversion from the kinetic *O*-alkylated to the thermodynamic *C*-alkylated product. The key to the success of this [3+2] annulation is attributed to the total chemoselectivity of the former step (*C*-allylation) as well as to the well-defined chronology of the following steps.<sup>[146]</sup>

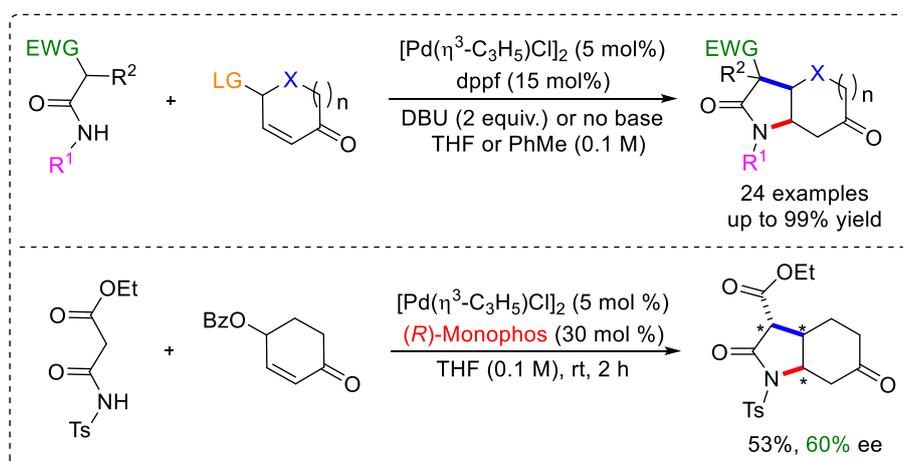
The strategy allows a straightforward synthesis of bicyclic cyclopentanic and annulated furan-based structures whose substructures are found incorporated into a number of natural products or molecules of synthetic interest. We thus think that this method may be of great synthetic value.

<sup>146</sup> Liu, Y.; Oble, J.; Poli, G. *Beilstein J. Org. Chem.* **2019**, *15*, 1107-1115.

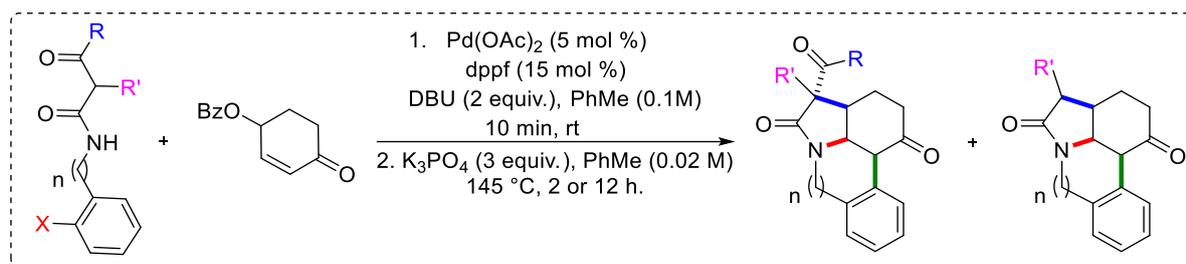
## General Conclusion

The synthesis of complex carbocyclic and heterocyclic structures remains an important subject for the synthetic chemists. In the past decades, palladium chemistry has gained an important place in the toolbox of chemists, and its use became a privileged strategy for the selective formation of carbon-carbon and carbon-heteroatom bonds. Among the different types of palladium-catalyzed transformations, annulation reactions occupy a special place as they facilitate the synthesis of a diversity of complex cycles in a single synthetic operation, through sequential bond-forming steps. In this context, the Pd-catalyzed [3+2]-annulations represent an actively investigated field, and the reported examples encourage us to develop newer and more efficient strategies for synthesis of carbo- and heterocycles. This thesis research was thus dedicated to the development of new palladium-catalyzed [3+2] annulations.

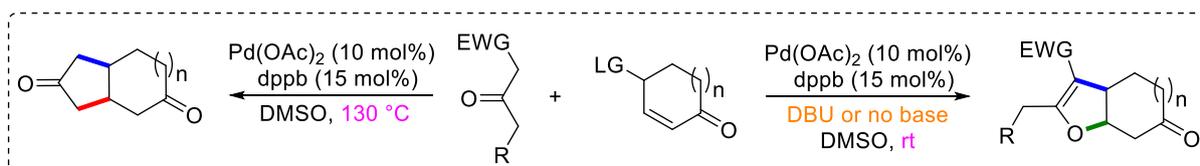
I first tackled and developed a new [3+2]-C-C/N-C bond forming annulation between resonance-stabilized acetamides and cyclic  $\alpha,\beta$ -unsaturated- $\gamma$ -oxy-carbonyl derivatives, which enables the synthesis of bicyclic pyrrolidin-2-ones via an [intermolecular Tsuji-Trost allylation / intramolecular aza-Michael] domino sequence. Then, I investigated an asymmetric version of this annulation. In particular, the use of the catalytic system  $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$  Monophos allowed to obtain the annulated product in 53% yield and 60% ee.



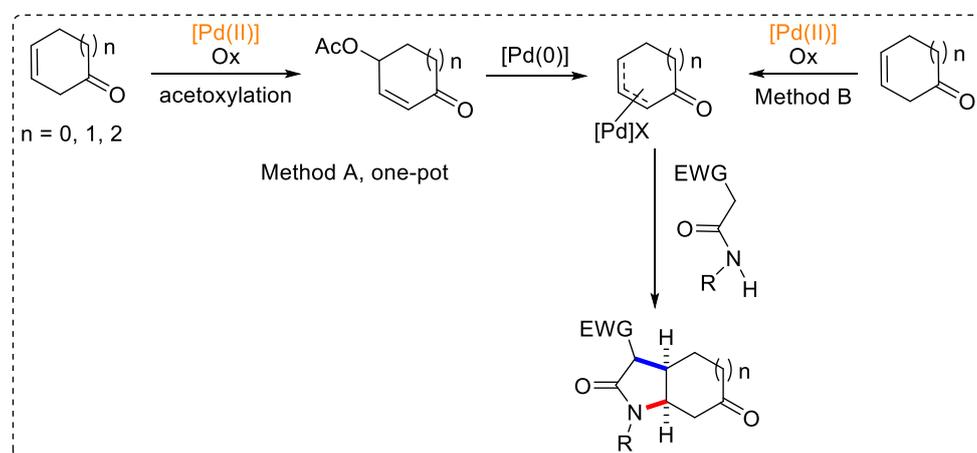
I subsequently developed a Pd-catalyzed [allylation / aza-Michael / keto  $\alpha$ -arylation] (ALAMAR) triple domino sequence, which enabled the selective formation of fused tricyclic systems. This sequence allows the generation of two new cycles and three new bonds in the same synthetic operation. It should be noted that although, if separately considered, each transformation may appear classical, the field of domino reactions is deceptively trivial. Indeed, the great difficulty of this type of one-pot studies consists in the fine tuning of substrates, reagents and reaction conditions to obtain full compatibility of all the programmed transformations, achieve the desired enchainment of bond breaking and forming actions, and minimize interferences among the reaction actors.



Finally, I investigated the reaction between 3-oxoglutarates and cyclic  $\gamma$ -oxy-2-cycloalkenones, which allowed to develop two complementary [3+2]-annulations protocols. These domino transformations allow to perform C-C/O-C or C-C/C-C [3+2]-annulations at will, via an intermolecular Pd-catalyzed C-allylation / intramolecular O- or C-1,4-addition sequence, respectively. In particular, exploitation of the reversibility of the O-1,4-addition step, and of the irreversibility of the C-1,4-addition / demethoxycarboxylation path, the intramolecular conjugate addition step could be diverted from the kinetic (O-alkylation) to the thermodynamic path (C-alkylation) by a simple temperature change.



As the previous study showed that the bicyclic product was generated from  $\pi$ -allyl Pd complex with bis-nucleophiles, so for the future we plan to generate this acetate bis-electrophiles via Pd-catalyzed acetoxylation of this  $\beta,\gamma$ -unsaturated ketone to achieve this annulation in one-pot. Besides, we also plan to generate this  $\pi$ -allyl Pd complexes via allylic C-H activation, so as to achieve the [3+2] annulation directly from simple alkenes. This C-H activation-based modification would hold a great advantages over the traditional strategy in terms of atom- and step-economy.



## Experimental Section

### 1. General remarks

All annulation reactions were carried out under an argon atmosphere by standard syringe and septa techniques and all domino reactions were carried out in a sealed tube. Glassware was flame-dried under vacuum or taken directly from the oven (100 °C) and let cool under vacuum prior to every use. Reagents and solvents were purchased from commercial sources and generally used as received. Dichloromethane, THF and *N,N*-dimethylformamide were dried on a Braun purification system MB SPS-800. Toluene was dried on a Braun purification system MB SPS-800. Where necessary, other organic compounds were dried and/or distilled. TLC were performed on Merck 60 F254 silica gel and revealed with either a ultra-violet lamp ( $\lambda = 254$  nm) or a specific color reagent (potassium permanganate, *p*-anisaldehyde, etc.). A silica gel Merck Geduran® SI 60 (40-63  $\mu\text{m}$ ) was used for flash column chromatography.

NMR spectra ( $^1\text{H}$ ,  $^{13}\text{C}$ ,  $^{19}\text{F}$ ) were recorded on a Bruker AM 300 MHz or on a Bruker AVANCE 400 MHz or 600 MHz spectrophotometer. NMR experiments were carried out at room temperature in deuteriochloroform ( $\text{CDCl}_3$ ), deuteromethanol ( $\text{CD}_3\text{OD}$ ), deuterioacetone ( $(\text{CD}_3)_2\text{CO}$ ) and **deuterodimethylsulfoxide** ( $(\text{CD}_3)_2\text{SO}$ ). Chemical shifts are given in parts per million (ppm) using the residual non-deuterated signals as ( $\text{CDCl}_3$ :  $\delta$  7.26 ppm for  $^1\text{H}$ , 77.0 ppm for  $^{13}\text{C}$ ;  $\text{CD}_3\text{OD}$ :  $\delta$  3.31 ppm for  $^1\text{H}$ , 49.0 ppm for  $^{13}\text{C}$ ;  $(\text{CD}_3)_2\text{CO}$ :  $\delta$  2.05 ppm for  $^1\text{H}$ , 29.8 ppm for  $^{13}\text{C}$ ;  $\text{DMSO-}d_6$ :  $\delta$  2.50 ppm for  $^1\text{H}$ , 39.5 ppm for  $^{13}\text{C}$ ). The terms s, d, t, q and m represent singulet, doublet, triplet, quartet and multiplet, respectively. The term (br) is used when the peak is broad, and the correct multiplicity cannot be surely assigned. Coupling constants ( $J$ ) are given in Hertz (Hz). For previously unknown compounds, a combination of  $^{13}\text{C}$  DEPT and 2D experiments (COSY, HSQC and HMBC) were often used to complete assignment of  $^1\text{H}$  and  $^{13}\text{C}$  signals.

IR spectra were recorded with a Tensor 27 (ATR diamond) Bruker spectrometer. IR was reported as characteristic bands ( $\text{cm}^{-1}$ ). Melting points were measured in capillary tubes on Stuart Scientific SMP3 apparatus and are uncorrected. High-resolution mass spectra (HRMS) were recorded using a mass spectrometer MicroTOF from Bruker with an electron spray ion source (ESI) and a TOF detector or using a mass spectrometer from Thermo Fisher Scientific with an electron spray ion source (ESI) and a LTQ Orbitrap as detector at Institut Parisien de Chimie Moléculaire.

## 2. General procedures

### 2.1 Synthesis of starting materials

#### 2.1.1 Synthesis of bis-nucleophiles 1

##### **General procedure: synthesis of 1a-1c (GP1).**

Following a slightly modified version of a reported procedure:<sup>[73]</sup> to a stirred solution of sulfonyl azide (1 equiv), ethyl propynoate (1.1 equiv), and 2-aminophenol (5 mol %) in H<sub>2</sub>O (0.5 M) was added Cu(OAc)<sub>2</sub>•H<sub>2</sub>O (10 mol %) slowly at room temperature. After consumption of the azide which was monitored by TLC, then the reaction was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with brine and dried over anhydrous MgSO<sub>4</sub>, then filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to afford the corresponding product.

##### **General procedure: synthesis of bis-nucleophiles 1d, 1g-1h, 1j, 1o (GP2).**

Methyl malonyl chloride (1.0 equiv) and Et<sub>3</sub>N (1.2 equiv) were added to a solution of the corresponding amine (1.0 equiv) in dry CH<sub>2</sub>Cl<sub>2</sub> (0.5 M) at 0 °C. After stirred for 5 hours at room temperature, then the reaction was quenched with a saturated aqueous NaHCO<sub>3</sub> solution and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with brine, dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to afford the corresponding product.

##### **General procedure: synthesis of bis-nucleophiles 1p-1r (GP3).**

Methyl malonyl chloride (1 equiv) was added to a solution of the corresponding amine (1 equiv) in dry THF (0.5 M) at 0 °C. After stirred for 12 hours at room temperature, then the reaction was diluted with EtOAc, washed with 5% aqueous NaHCO<sub>3</sub> solution and brine, dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to afford the corresponding product.

##### **General procedure for synthesis of bis-nucleophiles 1k-1m, 1v (GP4).**

Following the procedure described by Maulide:<sup>[147]</sup> the corresponding β-ester (5.0 mmol, 1.0 equiv) was added into an aqueous solution (5 mL) of NaOH (200 mg, 5.0 mmol, 1.0 equiv). The mixture was stirred under air atmosphere at room temperature over 12 h then Et<sub>2</sub>O (5 mL) was added. The layers were separated, and the aqueous one was washed with Et<sub>2</sub>O (2 x 5 mL) before being acidified with a concentrated solution of HCl (37% w/w in H<sub>2</sub>O) till to pH = 1. Then the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were dried with anhydrous MgSO<sub>4</sub>, filtered, and concentrated under reduced

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<sup>147</sup> Merad, J.; Maier, T.; Rodrigues, C. A. B.; Maulide, N. *Monatsh Chem*, **2017**, *148*, 57-62.

pressure, to give the desired corresponding crude  $\beta$ -acid.

To a solution of crude  $\beta$ -acid (5.0 mmol, 1 equiv) in anhydrous  $\text{CH}_2\text{Cl}_2$  (5 mL), oxalyl chloride (0.58 mL, 6.5 mmol, 1.3 equiv) and two drops of DMF were added dropwise. After stirred for 1 h at room temperature, then the excess oxalyl chloride was removed under vacuum. The crude acid chloride was dissolved in anhydrous  $\text{CH}_2\text{Cl}_2$  (15 mL). Then,  $\text{Et}_3\text{N}$  (0.7 mL, 5.0 mmol, 1.0 equiv) and appropriate amine (5.0 mmol, 1.0 equiv) were added slowly at  $-50\text{ }^\circ\text{C}$ . The mixture was stirred for 2 hours at the same temperature, and then quenched with a saturated aqueous  $\text{NH}_4\text{Cl}$  solution. The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic layers were washed with brine, dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to afford the corresponding product.

#### **General procedure for synthesis of bis-nucleophiles 1s-1t (GP5).**

Following the procedure described by Kirsch:<sup>[148]</sup> to a solution of diethylmethylmalonate (2.5 g, 14.7 mmol, 1 equiv) in EtOH (25 mL) was added potassium hydroxide (968 mg, 14.7 mmol, techn. 85%, 1 equiv). The reaction mixture was allowed to heat to reflux at  $110\text{ }^\circ\text{C}$  for 4 hours. Then after solvent evaporation under reduced pressure, the resulting oily residue was diluted in water (20 mL) and extracted with  $\text{Et}_2\text{O}$ . The aqueous layer was acidified with 5 M aqueous HCl-solution (2.5 mL) and extracted with EtOAc. The combined organic layers were dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure to give 3-ethoxy-2-methyl-3-oxopropanoic acid as colorless oil (1.8 g, 12.3 mmol, 84%).

Following the procedure described by Helmchen:<sup>[149]</sup> to a solution of 2-haloaniline (2.0 mmol, 1 equiv), DMAP (0.24 mmol, 0.12 equiv) and 3-ethoxy-2-methyl-3-oxopropanoic acid (2.0 mmol, 1 equiv) in  $\text{CH}_2\text{Cl}_2$  (0.2 M) at  $0\text{ }^\circ\text{C}$  was added DCC (2.4 mmol, 1.2 equiv). The resulting mixture was stirred at room temperature until completion of the amidation, which was monitored by TLC. The reaction mixture was diluted with EtOAc, then the resulting suspension was filtered through a pad of Celite and aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to afford the corresponding product.

### **2.1.2 Synthesis of bis-electrophiles 2**

#### **General procedure for synthesis of compounds 2e-2f (GP6).**

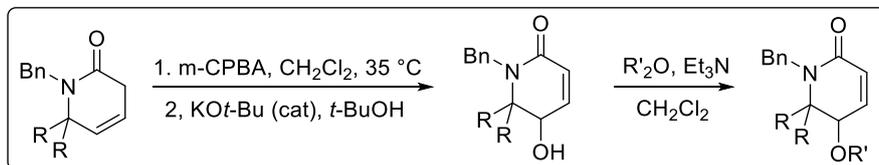
To a solution of the allylic alcohol (1.0 equiv) in dry  $\text{CH}_2\text{Cl}_2$  (0.5 M) at  $0\text{ }^\circ\text{C}$  were successively added the corresponding acidic anhydride (1.1 equiv) and  $\text{Et}_3\text{N}$  (1.2 equiv). After 10 hours at  $35\text{ }^\circ\text{C}$ , the reaction was

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<sup>148</sup> Klahn, P.; Erhardt, H.; Kotthaus, A.; Kirsch, S. F. *Angew. Chem. Int. Ed.* **2014**, *53*, 7913-7917.

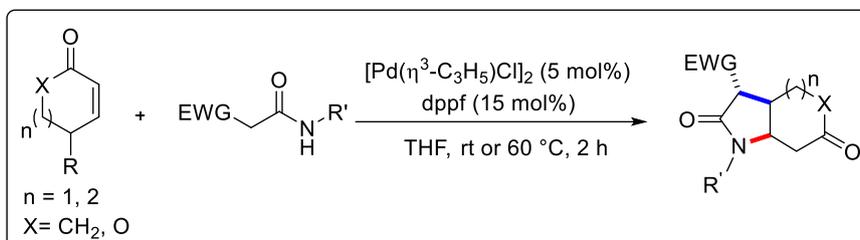
<sup>149</sup> Hoecker, J.; Rudolf, G. C.; Bächle, F.; Fleischer, S.; Lindner, B. D.; Helmchen, G. *Eur. J. Org. Chem.* **2013**, *23*, 5149-5159.

quenched with a saturated aqueous  $\text{NH}_4\text{Cl}$  solution and the aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$ . The combined organic layers were washed with brine, dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. Purification by column chromatography on silica gel to afford the corresponding product. Detailed steps are shown below.



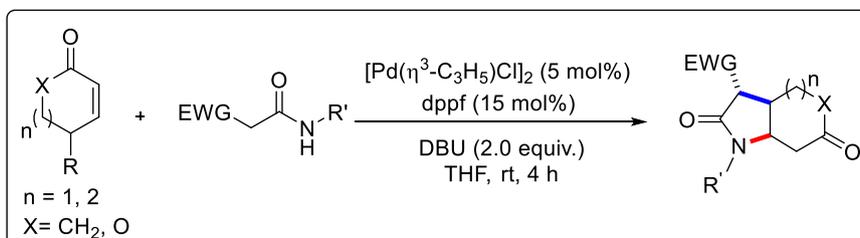
## 2.2 Procedures of Pd(0)-catalyzed [3 + 2]-C-C/N-C bond-forming annulation

**General procedure 7 (GP7): conditions A without base in THF**



In a Schlenk tube,  $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$  (0.05 equiv) and dppf (0.15 equiv) were dissolved in anhydrous THF (0.1 M) under an argon atmosphere. After 10 minutes, the bis-nucleophile **1** (1.0 equiv) and the bis-electrophile **2** (1.3 equiv) were added to reaction. After 2h stirring at room temperature (or at 60 °C), the mixture was filtered on a plug of silica and washed with EtOAc. The filtrate was washed with 5% aqueous  $\text{NaHCO}_3$  solution and brine, and then dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to afford the corresponding 4,5-fused bicyclic pyrrolidin-2-one.

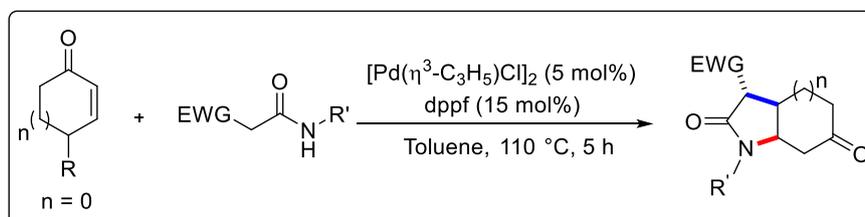
**General procedures 8 (GP8): conditions B with base in THF**



In a Schlenk tube,  $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$  (0.05 equiv) and dppf (0.15 equiv) were dissolved in anhydrous THF (0.1 M) under an argon atmosphere. After 10 minutes, the bis-nucleophile **1** (1.0 equiv), the bis-electrophile **2** (1.3 equiv) and DBU (2.0 equiv) were added. After 4 h stirring, the reaction mixture was filtered on a plug

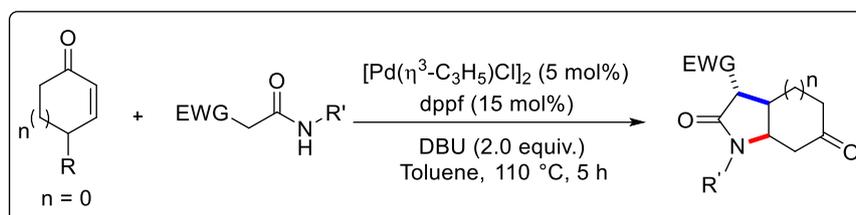
of silica and washed with EtOAc. The filtrate was washed with 5% aqueous NaHCO<sub>3</sub> solution and brine, and then dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to afford the corresponding 4, 5-fused bicyclic pyrrolidin-2-one.

**General procedure 9 (GP9): conditions C without base in Toluene**



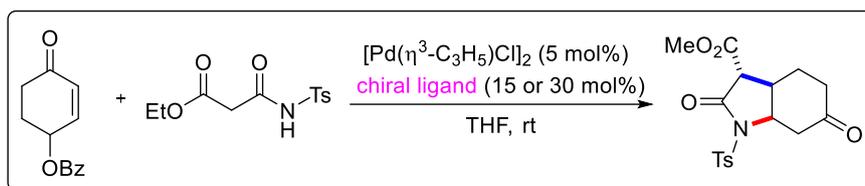
In a Schlenk tube, [Pd(η<sup>3</sup>-C<sub>3</sub>H<sub>5</sub>)Cl]<sub>2</sub> (0.05 equiv) and dppf (0.15 equiv) were dissolved in anhydrous toluene (0.1 M) under an argon atmosphere. After 10 minutes, the bis-nucleophile **1** (1.0 equiv) and bis-electrophile **2** (1.3 equiv) were added to reaction. After stirring at 110 °C for 5 h, the mixture was filtered on a plug of silica and washed with EtOAc. The filtrate was washed with 10% aqueous NaHCO<sub>3</sub> solution and brine, and then dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to afford the corresponding 4, 5-fused bicyclic pyrrolidin-2-one.

**General procedure 10 (GP10): conditions D with base in Toluene**



In a Schlenk tube, [Pd(η<sup>3</sup>-C<sub>3</sub>H<sub>5</sub>)Cl]<sub>2</sub> (0.05 equiv) and dppf (0.15 equiv) were dissolved in anhydrous toluene (0.1 M) under an argon atmosphere. After 10 minutes, the bis-nucleophile **1** (1.0 equiv), the bis-electrophile **2** (1.3 equiv) and DBU (2.0 equiv) were added to reaction. After stirring at 110 °C for 5 h, the mixture was filtered on a plug of silica and washed with EtOAc. The filtrate was washed with 10% aqueous NaHCO<sub>3</sub> solution and brine, and then dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to afford the corresponding 4, 5-fused bicyclic pyrrolidin-2-one.

**General procedures 11 (GP11): Pd-catalyzed asymmetric [3+2]-C-C/N-C bond-forming annulation**

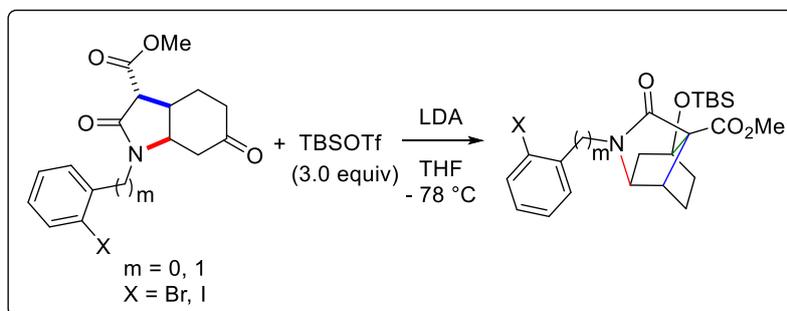


In a Schlenk tube,  $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$  (0.05 equiv) and chiral ligand (0.15 or 0.3 equiv) were dissolved in anhydrous THF (0.1 M) under an argon atmosphere. After 10 minutes, the 3-oxo-3-(toluene-4-sulfonylamino)-propionic acid ethyl ester **1a** (1.0 equiv) and the 4-oxocyclohex-2-en-1-yl benzoate **2a** (1.3 equiv) were added to reaction. After 12-18 h stirring at room temperature, the mixture was filtered on a plug of silica and washed with EtOAc. The filtrate was washed with 5% aqueous  $\text{NaHCO}_3$  solution and brine, and then dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to afford the corresponding ethyl 2,6-dioxo-1-tosyloctahydro-1*H*-indole-3-carboxylate **3a**. The enantioselectivity of **3a** was determined by chiral HPLC : AD-H, 60 : 40 hexane : isopropanol, 1.0 mL/min, 220 nm, 13.78 min (*S* enantiomer), 23.25 min (*R* enantiomer).

## 2.3 Procedures of Pd(0)-catalyzed triple domino reactions

### 2.3.1 Synthesis of tricyclic silyl ether products

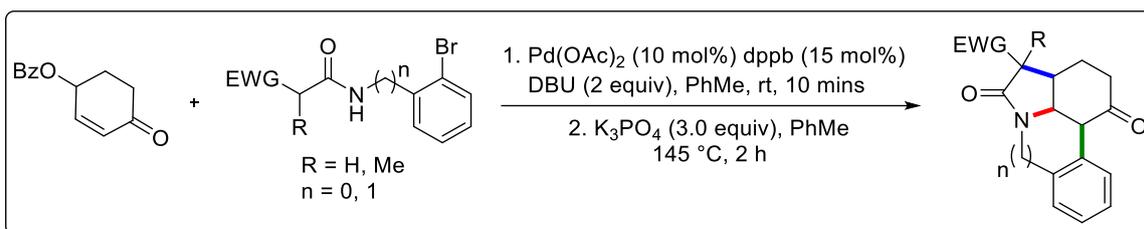
General procedures 12 (GP12):



To a solution of the bicyclic ketoamidoester **3** (1 equiv) in anhydrous THF (0.1 M) were added LDA (3.0 equiv) and TBSOTf (3.0 equiv) dropwise at  $-78\text{ }^\circ\text{C}$ . After stirred for 1 h at  $-20\text{ }^\circ\text{C}$ , the reaction was quenched with a saturated aqueous  $\text{NH}_4\text{Cl}$  solution and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to afford the corresponding product **10**.

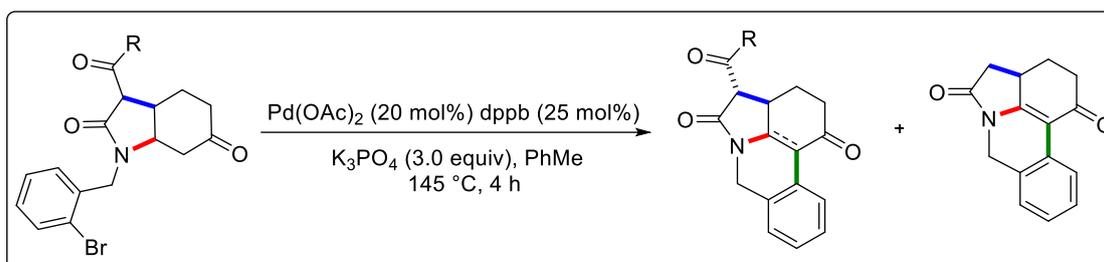
### 2.3.2 Synthesis of tricyclic products

General procedures 13 (GP13)



In a sealed tube,  $\text{Pd}(\text{OAc})_2$  (0.10 equiv), dppb (0.15 equiv) and anhydrous PhMe (0.1 M) were introduced under an argon atmosphere. After stirred for 10 minutes, the bis-electrophile (1.3 equiv), the bis-nucleophile (1.0 equiv) and DBU (2.0 equiv) were added at  $0\text{ }^\circ\text{C}$ . The reaction was allowed to stir for 10 mins at room temperature, then  $\text{K}_3\text{PO}_4$  (3.0 equiv) and PhMe (0.02 M) were added. After stirred for 2 hours at  $145\text{ }^\circ\text{C}$ , the reaction was filtered on a plug of Celite, washed with EtOAc and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to afford the corresponding product **10** and/or **11**.

#### General procedures 14 (GP14)

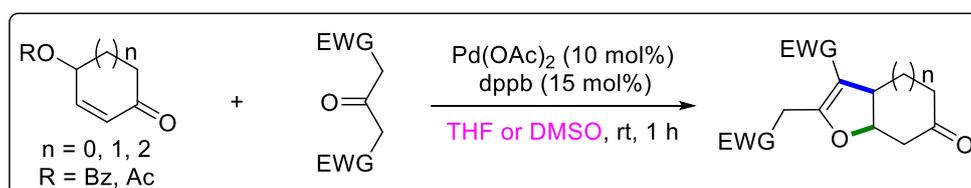


In a sealed tube, under an argon atmosphere, to a solution of  $\text{Pd}(\text{OAc})_2$  (0.20 equiv), dppb (0.25 equiv), and  $\text{K}_3\text{PO}_4$  (3.0 equiv) in anhydrous PhMe (0.02 M) at room temperature, after 10 mins, was added the bicycle compound (1.0 equiv). After the reaction was stirred at  $145\text{ }^\circ\text{C}$  for 4 h, the reaction mixture was filtered on a plug of celite and washed with EtOAc, concentrated under reduced pressure. Purification by column chromatography on silica gel to afford the corresponding product **9**, **12-14**.

## 2.4 Procedures of Pd(0)-catalyzed [3+2]-C-C/O-C or C-C/C-C bond-forming annulation

### 2.4.1 Procedures of Pd(0)-catalyzed [3+2]-C-C/O-C bond-forming annulation

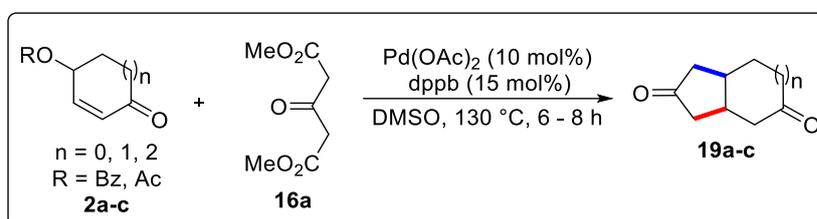
General procedures 15 (GP15): conditions E in THF or DMSO at rt



In a schlenk tube, under an argon atmosphere, were added Pd(OAc)<sub>2</sub> (0.10 equiv), dppb (0.15 equiv) and anhydrous THF or DMSO (0.1 M). After 10 mins, the cyclic electrophilic **2a-c** (1.3 equiv) and the bis-nucleophile **15a** or **1u-1w** (1.0 equiv) were added. The reaction was allowed to stir at room temperature. After 1 hour, the reaction mixture was filtered on a plug of silica and washed with EtOAc. The filtrate was washed with a 10% aqueous solution of NaHCO<sub>3</sub>. The aqueous phase was extracted with EtOAc, and the combined organic phases were washed with brine, dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by column chromatography on silica gel to afford the corresponding product **18**.

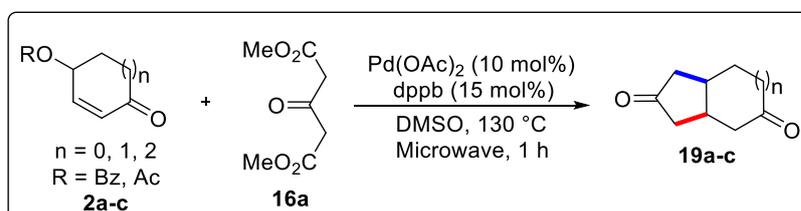
#### 2.4.2 Procedures of Pd(0)-catalyzed [3+2]-C-C/C-C bond-forming annulation

**General procedure 16 (GP16): conditions F in DMSO at 130 °C**



In a sealed tube, under an argon atmosphere, were added Pd(OAc)<sub>2</sub> (0.10 equiv), dppb (0.15 equiv) and anhydrous DMSO (0.1 M). After 10 mins, the cyclic electrophilic **2a-c** (1.3 equiv) and dimethyl-3-oxoglutarate **15a** (1.0 equiv) were added. The reaction was allowed to stir at 130 °C. After 6 hours or 8 hours, the reaction mixture was filtered on a plug of silica and washed with EtOAc. The filtrate was washed with a 10% aqueous solution of NaHCO<sub>3</sub>. The aqueous phase was extracted with EtOAc, and the combined organic phases were washed with brine, dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by column chromatography on silica gel to afford the corresponding product **19a-c**.

**General procedure 17 (GP17): conditions G in DMSO at 130 °C with microwave**

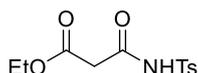


In a sealed microwave tube, under an argon atmosphere, were added Pd(OAc)<sub>2</sub> (0.10 equiv), dppb (0.15 equiv) and anhydrous THF (0.1 M). After 10 mins, the cyclic electrophilic **2a-c** (1.3 equiv) and dimethyl-3-oxoglutarate **15a** (1.0 equiv) were added. The reaction was allowed to stir at 130 °C under microwave irradiation conditions. After 1 hour, the reaction mixture was filtered on a plug of silica and washed with EtOAc. The filtrate was washed with a 10% aqueous solution of NaHCO<sub>3</sub>. The aqueous phase was extracted with EtOAc, and the combined organic phases were washed with brine, dried over anhydrous MgSO<sub>4</sub>,

filtered and concentrated under reduced pressure. Purification by column chromatography on silica gel to afford the corresponding product **19a-c**.

### 3. Analytical data

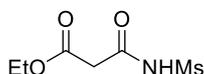
#### 3.1 Analytical data of bis-nucleophiles



##### 3-oxo-3-(toluene-4-sulfonylamino)-propionic acid ethyl ester **1a**

Prepared according to **GP1** from 4-methylbenzenesulfonyl azide (987 mg, 5.0 mmol) and ethyl propynoate (0.56 mL, 5.5 mmol). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/1; Rf 0.19 in EtOAc/Cyclohexane = 1/1) to give desired product **1a** as a white solid (1.3 g, 92%). These data are in good agreement with those reported in the literature.<sup>[73]</sup>

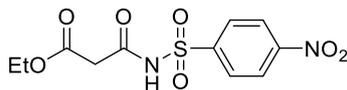
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  10.01 (s, 1H), 7.97 (d,  $J$  = 8.3 Hz, 2H), 7.33 (d,  $J$  = 8.3 Hz, 2H), 4.22 (q,  $J$  = 7.2 Hz, 2H), 3.33 (s, 2H), 2.44 (s, 3H), 1.28 (t,  $J$  = 7.2 Hz, 3H).



##### 3-methanesulfonylamino-3-oxo-propionic acid ethyl ester **1b**

Prepared according to **GP1** from methylsulfonyl azide (605 mg, 5.0 mmol) and ethyl propynoate (0.56 mL, 5.5 mmol). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/1; Rf 0.28 in EtOAc/Cyclohexane = 2/1) to give desired product **1b** as a white solid (940 mg, 90%). These data are in good agreement with those reported in the literature.<sup>[73]</sup>

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  9.92 (s, 1H), 4.25 (q,  $J$  = 7.2 Hz, 2H), 3.46 (s, 2H), 3.31 (s, 3H), 1.31 (t,  $J$  = 7.2 Hz, 3H).



##### 3-nitrobenzenesulfonylamino-3-oxo-propionic acid ethyl ester **1c**

Prepared according to **GP1** from 4-nitrobenzenesulfonyl azide (1.14 g, 5.0 mmol) and ethyl propynoate (0.56 mL, 5.5 mmol). The reaction was stirred for 3 hours at 60 °C. The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/1; Rf 0.27 in EtOAc/Cyclohexane = 2/1) to give desired product **1c** as a yellow solid (1.42 g, 90%).

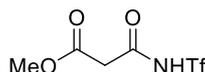
**Mp:** 103 °C.

**IR (cm<sup>-1</sup>):** 3249, 2987, 2873, 1726, 1526, 1448, 1343, 1311, 1163, 1127, 1082, 1014.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ (ppm) 10.30 (s, 1H), 8.38 (d, *J* = 8.9 Hz, 2H), 8.32 (d, *J* = 8.9 Hz, 2H), 4.24 (q, *J* = 7.2 Hz, 2H), 3.37 (s, 2H), 1.29 (t, *J* = 7.2 Hz, 3H).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ (ppm) 168.4, 163.4, 150.8, 143.8, 130.0, 124.1, 62.6, 41.1, 13.9.

**HRMS (ESI)** calcd for C<sub>11</sub>H<sub>12</sub>N<sub>2</sub>O<sub>7</sub>SNa [M+Na]<sup>+</sup>: 339.0257; found: 339.0278.



**methyl 3-oxo-3-(trifluoromethylsulfonamido)propanoate 1d**

Prepared according to **GP2** from methyl malonyl chloride (0.11 mL, 1.0 mmol), and trifluoromethanesulfonate (149 mg, 1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc; R<sub>f</sub> 0.25 in EtOAc) to give desired product **1d** as a white solid (212 mg, 85%).

**Mp:** 156 °C.

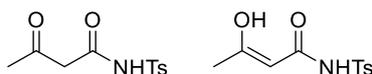
**IR (cm<sup>-1</sup>):** 2985, 1709, 1623, 1575, 1448, 1355, 1297, 1208, 1180, 1137, 1023.

**<sup>1</sup>H NMR (400 MHz, (CD<sub>3</sub>)<sub>2</sub>CO):** δ 3.64 (s, 3H), 3.25 (s, 2H).

**<sup>13</sup>C NMR (100 MHz, (CD<sub>3</sub>)<sub>2</sub>CO):** δ 175.3, 169.9, 121.4 (*J* = 322.3 Hz), 52.0, 46.6.

**<sup>19</sup>F NMR (282 MHz, (CD<sub>3</sub>)<sub>2</sub>CO):** δ -80.05.

**HRMS (ESI)** calcd for C<sub>5</sub>H<sub>5</sub>F<sub>3</sub>NO<sub>5</sub>SNa<sub>2</sub> [(M-H)+2Na]<sup>+</sup>: 293.9630; found: 293.9621.



**3-oxo-N-tosylbutanamide 1e and 3-Hydroxy-N-tosylbut-2-enamide 1e'**

To a solution of 4-methyl benzenesulfonamide (171 mg, 1.0 mmol, 1.0 equiv) in anhydrous toluene (10 mL) at room temperature was added 2,2,6-trimethyl-1,3-dioxin-4-one (185 mg, 1.3 mmol, 1.3 equiv). The reaction was allowed to heat to reflux for 3 hours, and then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1:1; R<sub>f</sub> 0.16 in EtOAc/Cyclohexane = 1/1) to give compound **1e** and **1e'** as a 80/20 ketone/enol (217 mg, 85%,) as a white solid.

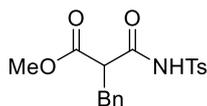
**Mp:** 78 °C.

**IR (cm<sup>-1</sup>):** 3102, 2900, 1726, 1678, 1593, 1480, 1418, 1352, 1304, 1175, 1138, 1085, 1024.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 12.8 (br s, 1H, enol), 9.92 (br s, 1H, ketone), 7.94 (d, *J* = 8.3 Hz, 4H, 2H ketone + 2H enol), 7.32 (d, *J* = 8.3 Hz, 4H, 2H ketone + 2H enol), 5.07(s, 1H, enol), 3.48 (s, 2H, ketone), 2.43 (s, 6H, 3H ketone + 3H enol), 2.22 (s, 3H, ketone), 1.92 (s, 3H, enol).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** for ketone: δ 203.1, 164.3, 145.1, 135.3, 129.5 (2C), 128.3 (2C), 49.5, 30.7, 21.6.; for enol: δ 178.8, 169.3, 144.9, 135.9, 129.5 (2C), 128.0 (2C), 89.9, 30.7, 21.6.

**HRMS (ESI)** calcd for C<sub>11</sub>H<sub>13</sub>NO<sub>4</sub>SK [M+K]<sup>+</sup>: 294.0197; found: 294.0196.



### **methyl 2-benzyl-3-(4-methylphenylsulfonamido)-3-oxopropanoate 1f**

Following the procedure described by Kirsch:<sup>[148]</sup> Sodium hydride (440 mg, 11.0 mmol, 60% in paraffin, 1.1 equiv) was suspended in anhydrous THF (15 mL) at 0 °C and then treated dropwise with a solution of dimethyl malonate (1.26 mL, 11.0 mmol, 1.1 equiv) in anhydrous THF (10 mL). After stirred for 30 min at room temperature, a solution of benzyl bromide (1.20 mL, 10.0 mmol, 1 equiv) in anhydrous THF (15 mL) was added slowly, and stirring was continued for further 2 hours. After treatment with a saturated aqueous NH<sub>4</sub>Cl solution and extracted with Et<sub>2</sub>O, the combined organic layers were washed with brine, dried over anhydrous MgSO<sub>4</sub>, then filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/6; R<sub>f</sub> 0.33 in EtOAc/Cyclohexane = 1/6) to give dimethyl 2-benzylmalonate (1.9 g, 78%).

To a solution of dimethyl-2-benzylmalonate (1.1 g, 5.0 mmol, 1 equiv) in MeOH (10 mL) was added Solid KOH (330 mg, 5.0 mmol, techn. 85%, 1 equiv). After stirred for 4 hours at room temperature, the solvent was removed under reduced pressure. The resulting oily residue was diluted in water (10 mL) and extracted with Et<sub>2</sub>O. The aqueous layer was acidified with 5 M aqueous HCl-solution (1.5 mL) till to pH = 1 and then extracted with EtOAc. The combined organic layers were dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to give 2-Benzyl-3-methoxy-3-oxopropanoic acid as colorless oil (884 mg, 4.25 mmol, 85%).

Following the procedure described by Bourissou:<sup>[76]</sup> to a solution of 2-benzyl-3-methoxy-3-oxopropanoic acid (460 mg, 2.2 mmol, 1 equiv) in anhydrous THF (5 mL), was added tosyl isocyanate (0.34 ml, 2.2 mmol, 1 equiv) under argon. After stirred for 10 min at room temperature the inert atmosphere was disconnected and Et<sub>3</sub>N (0.31 mL, 2.2 mmol, 1 equiv) was added dropwise to the open flask, allowing the release of the formed CO<sub>2</sub>. After stirred for 1 hour at room temperature, the solution was diluted with an equal volume of EtOAc, then washed with 2M HCl solution and brine. The solution was dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/1; R<sub>f</sub> 0.22 in EtOAc/Cyclohexane = 1/1) to give

compound **1f** as a white solid (800 mg, 99%).

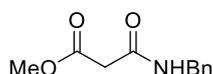
**Mp:** 90 °C.

**IR (cm<sup>-1</sup>):** 2972, 2879, 1747, 1711, 1597, 1490, 1442, 1345, 1279, 1167, 1084, 1043.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 9.58 (br s, 1H), 7.88 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 7.21-7.10 (m, 3H), 7.04-6.93 (m, 2H), 3.62 (s, 3H), 3.57 (t, *J* = 7.4 Hz, 1H), 3.14 (d, *J* = 7.1 Hz, 2H), 2.45 (s, 3H).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ 170.0, 165.8, 145.0, 136.3, 135.1, 129.4, 128.6, 128.5, 128.4, 126.9, 54.3, 52.8, 35.6, 21.6.

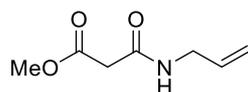
**HRMS (ESI)** calcd for C<sub>18</sub>H<sub>19</sub>NO<sub>5</sub>Na [M+Na]<sup>+</sup>: 384.0876; found: 384.0882.



#### methyl 3-(benzylamino)-3-oxopropanoate **1g**

Prepared according to **GP2** from methyl malonyl chloride (1.1 mL, 10 mmol) and benzylamine (1.1 mL, 10 mmol). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/1; R<sub>f</sub> 0.37 in EtOAc/Cyclohexane = 2/1) to give desired product **1g** as a white solid (2.0 g, 97%). These data are in good agreement with those reported in the literature.<sup>[150]</sup>

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.36-7.27 (m, 5H), 4.48 (d, *J* = 5.7 Hz, 2H), 3.74 (s, 3H), 3.36 (s, 2H).



#### methyl 3-(allylamino)-3-oxopropanoate **1h**

Prepared according to **GP2** from methyl malonyl chloride (0.21 mL, 2.0 mmol) and allyl amine (0.15 mL, 2.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 2/1; R<sub>f</sub> 0.29 in EtOAc/Cyclohexane = 2/1) to give desired product **1h** as a colorless oil (290 mg, 93%).

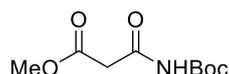
**IR (cm<sup>-1</sup>):** 3283, 3082, 2953, 1739, 1647, 1547, 1428, 1335, 1206, 1156, 1023.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 7.15 (br s, 1H), 5.86 (ddd, *J* = 17.2, 10.2, 5.6 Hz, 1H), 5.26-5.13 (m, 2H), 3.93 (tt, *J* = 5.7, 1.6 Hz, 2H), 3.76 (s, 3H), 3.35 (s, 2H).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ 169.6, 164.7, 133.6, 116.2, 52.3, 41.8, 41.0.

**HRMS (ESI)** calcd for C<sub>7</sub>H<sub>11</sub>NO<sub>3</sub>Na [M+Na]<sup>+</sup>: 180.0631; found: 180.0634.

<sup>150</sup> Tolomelli, A.; Cardillo, G.; Gentiluoci, L.; Juris, R.; Viola, A.; Juaristi, E. *ARKIVOC*. **2012**, 196-209.



**methyl 3-((*tert*-butoxycarbonyl)amino)-3-oxopropanoate 1i**

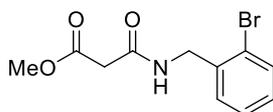
To a solution of NaH (24 mg, 1.0 mmol, 2.0 equiv) in anhydrous THF (1 mL) at 0 °C was added the solution of *tert*-butylcarbamate (60 mg, 0.5 mmol, 1.0 equiv) in anhydrous THF (1 mL). After stirred for 10 min at the same temperature, methyl malonyl chloride (0.07 mL, 0.6 mmol, 1.2 equiv) was added. The reaction was allowed to warm to room temperature and stirred for 5 hours. Then the reaction was quenched with H<sub>2</sub>O (2 mL) and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine, dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/2; R<sub>f</sub> 0.54 in EtOAc/Cyclohexane = 1/1) to give compound **1i** as a colorless oil (90 mg, 85%).

**IR (cm<sup>-1</sup>):** 3199, 3148, 2982, 2942, 1746, 1684, 1501, 1445, 1374, 1297, 1224, 1142, 1074 1008.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.13 (br s, 1H), 3.72 (s, 2H), 3.69 (s, 3H), 1.43 (s, 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 167.6, 167.1, 150.3, 82.9, 52.3, 43.0, 27.8.

**HRMS (ESI)** calcd for C<sub>9</sub>H<sub>15</sub>NO<sub>5</sub>Na [M+Na]<sup>+</sup>: 240.0842; found: 240.0841.



**methyl 3-((2-bromobenzyl)amino)-3-oxopropanoate 1j**

Prepared according to **GP2** from methyl malonyl chloride (0.21 mL, 2.0 mmol) and 2-bromobenzylamine hydrochloride (446 mg, 2.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/1; R<sub>f</sub> 0.34 in EtOAc/Cyclohexane = 1/1) to give desired product **1j** as a white solid (440 mg, 78%).

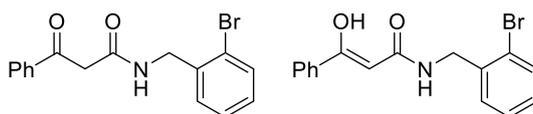
**Mp:** 86 °C.

**IR (cm<sup>-1</sup>):** 3256, 3093, 2993, 2832, 1748, 1670, 1632, 1567, 1489, 1430, 1339, 1158.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 8.13 (br s, 1H), 7.55 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.38 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.28 (td, *J* = 7.5, 1.2 Hz, 1H), 7.14 (td, *J* = 7.7, 1.8 Hz, 1H), 4.55 (d, *J* = 6.0 Hz, 2H), 3.74 (s, 3H), 3.36 (s, 2H).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ 169.9, 164.7, 136.9, 132.8, 130.2, 129.2, 127.7, 123.7, 52.5, 43.8, 40.8.

**HRMS (ESI)** calcd for C<sub>11</sub>H<sub>12</sub>BrNO<sub>3</sub>Na [M+Na]<sup>+</sup>: 307.9893; found: 307.9897.



***N*-(2-bromobenzyl)-3-oxo-3-phenylpropanamide **1k** and *N*-(2-bromobenzyl)-3-hydroxy-3-phenylacrylamide **1k'****

Following **GP4** with ethyl benzoylacetate (0.86 mL, 5.0 mmol), 2-bromobenzylamine hydrochloride (1.11 g, 5.0 mmol) and Et<sub>3</sub>N (1.67 mL, 11.0 mmol, 2.2 equiv). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/2; R<sub>f</sub> 0.42 in EtOAc/Cyclohexane = 1/2) to give compounds **1k** and **1k'** as a 83/17 ketone/enol mixture as a white solid (1.24 g, 75%).

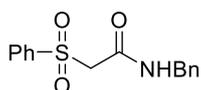
**Mp:** 127 °C.

**IR (cm<sup>-1</sup>):** 3353, 3280, 2920, 1684, 1642, 1527, 1439, 1340, 1272, 1210, 1167, 1028.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 14.09 (br s, 1H<sub>enol</sub>), 8.01-7.96 (m, 2H<sub>ketone</sub>), 7.75-7.72 (m, 2H<sub>enol</sub>), 7.66-7.36 (m, 11H, 6H<sub>ketone</sub>+5H<sub>enol</sub>), 7.32-7.23 (m, 2H, 1H<sub>ketone</sub>+1H<sub>enol</sub>), 7.17-7.10 (m, 2H, 1H<sub>ketone</sub>+1H<sub>enol</sub>), 5.98 (brs, 1H<sub>enol</sub>, -NH), 5.54 (s, 1H<sub>enol</sub>), 4.61 (d, *J* = 6.1 Hz, 2H<sub>enol</sub>), 4.57 (d, *J* = 6.0 Hz, 2H<sub>ketone</sub>), 3.98 (s, 2H<sub>ketone</sub>).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** only ketone: δ 195.9, 165.7, 137.0, 136.1, 134.0, 132.8, 130.0, 129.1, 128.8 (2C), 128.5 (2C), 127.6, 123.7, 45.2, 43.9.

**HRMS (ESI)** calcd for C<sub>16</sub>H<sub>14</sub>BrNO<sub>2</sub>Na [M+Na]<sup>+</sup>: 354.0100; found: 354.0095.



***N*-benzyl-2-(phenylsulfonyl)acetamide **1l****

Prepared according to **GP4** from commercially available methyl 2-(phenylsulfonyl)acetate (1.02 g, 4.76 mmol), Et<sub>3</sub>N (0.09 mL, 0.6 mmol) and benzylamine (0.06 mL, 0.5 mmol). The residue was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/1; R<sub>f</sub> 0.59 in EtOAc/Cyclohexane = 2/1) to give compound **1l** as a white solid (130 mg, 89%).

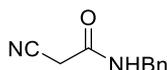
**Mp:** 152 °C.

**IR (cm<sup>-1</sup>):** 3351, 3000, 2932, 1887, 1661, 1524, 1441, 1330, 1246, 1144, 1080.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 7.80 (dd, *J* = 8.4, 1.2 Hz, 2H), 7.70-7.64 (m, 1H), 7.55-7.48 (m, 2H), 7.39-7.26 (m, 5H), 4.45 (d, *J* = 5.9 Hz, 2H), 4.04 (s, 2H).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ 160.3, 138.0, 137.2, 134.4, 129.4, 128.8, 128.1, 128.0, 127.8, 61.8, 44.1.

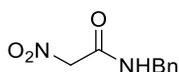
**HRMS (ESI)** calcd for  $C_{15}H_{15}NO_3SNa$   $[M+Na]^+$ : 312.0665; found: 312.0668.



**N-benzyl-2-cyanoacetamide 1m**

Prepared according to **GP4** from commercially available cyanoacetic acid (170 mg, 2.0 mmol) and benzylamine (0.22 mL, 2.0 mmol). The residue was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 2/1; Rf 0.34 in EtOAc/Cyclohexane = 2/1) to give compound **1m** as a white solid (214 mg, 60%). These data are in good agreement with those reported in the literature.<sup>[151]</sup>

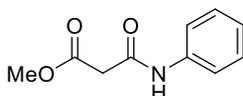
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  7.39-7.21 (m, 5H), 6.56 (br s, 1H), 4.44 (d,  $J$  = 5.7 Hz, 2H), 3.36 (s, 2H).



**N-benzyl-2-nitroacetamide 1n**

To a solution of ethyl nitroacetate (400 mg, 3.0 mmol, 1.0 equiv) in MeOH (5 mL) at room temperature was added dropwise benzylamine (1.6 mg, 15.0 mmol, 5.0 equiv). After stirred for 3 d at the same temperature, the mixture was concentrated in vacuo, and the residue was acidified with 1 N HCl (pH = 4) and extracted with EtOAc (3  $\times$  10 mL). The combined organic layers were washed with brine, dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 2/1; Rf 0.35 in EtOAc/Cyclohexane = 2/1) to give compound **1n** a white solid (214 mg, 60%). These data are in good agreement with those reported in the literature.<sup>[152]</sup>

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  7.39-7.27 (m, 5H), 7.28-7.26 (m, 2H), 6.71 (br s, 1H), 5.13 (s, 2H), 4.52 (d,  $J$  = 5.7 Hz, 2H).



**methyl 3-oxo-3-(phenylamino)propanoate 1o**

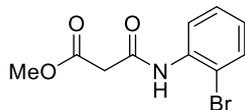
Prepared according to **GP2** from methyl malonyl chloride (0.21 mL, 2.0 mmol) and aniline (0.18 mL, 2.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/2; Rf 0.30 in EtOAc/Cyclohexane = 2/3) to give desired product **1o** as a white solid (380 mg, 99%). These data are in good agreement with those reported in the literature.<sup>[153]</sup>

<sup>151</sup> Jöst, C.; Nitsche, C.; Scholz, T.; Roux, L.; Klein, C. D. *J. Med. Chem.* **2014**, *57*, 7590-7599.

<sup>152</sup> He, L.-W.; Srikanth, G. S. C.; Castle, S. L. *J. Org. Chem.* **2005**, *70*, 8140-8147.

<sup>153</sup> Abas, H.; Frampton, C. S.; Spivey, A. C. *J. Org. Chem.* **2016**, *81*, 9947-9956.

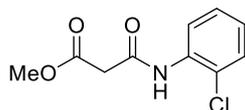
**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 9.19 (br s, 1H), 7.54 (d, *J* = 7.7 Hz, 2H), 7.31 (t, *J* = 7.8 Hz, 2H), 7.11 (t, *J* = 7.4 Hz, 1H), 3.78 (s, 3H), 3.47 (s, 2H).



**methyl 3-((2-bromophenyl)amino)-3-oxopropanoate 1p**

Prepared according to **GP3** from methyl malonyl chloride (0.21 mL, 2.0 mmol) and 2-bromoaniline (345 mg, 2.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/2; R<sub>f</sub> 0.40 in EtOAc/Cyclohexane = 1/2) to give desired product **1p** as a white solid (540 mg, 99%). These data are in good agreement with those reported in the literature.<sup>[154]</sup>

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 9.57 (br s, 1H), 8.33 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.55 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.33-7.29 (m, 1H), 6.99 (ddd, *J* = 8.0, 7.4, 1.5 Hz, 1H), 3.83 (s, 3H), 3.55 (s, 2H).



**methyl 3-((2-chlorophenyl)amino)-3-oxopropanoate 1q**

Prepared according to **GP3** from methyl malonyl chloride (0.21 mL, 2.0 mmol) and 2-chloroaniline (0.21 mL, 2.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/2; R<sub>f</sub> 0.54 in EtOAc/Cyclohexane = 1/2) to give desired product **1q** as a white solid (410 mg, 91%).

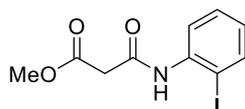
**Mp:** 81 °C.

**IR (cm<sup>-1</sup>):** 3258, 3049, 3001, 2953, 1735, 1654, 1587, 1538, 1474, 1435, 1400, 1339, 1262, 1198, 1150, 1021.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 9.67 (br s, 1H), 8.37 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.38 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.29-7.24 (m, 1H), 7.05 (td, *J* = 7.8, 1.6 Hz, 1H), 3.83 (s, 3H), 3.54 (s, 2H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 169.9, 162.8, 134.5, 129.1, 127.6, 124.9, 123.3, 121.8, 52.7, 41.6.

**HRMS (ESI)** calcd for C<sub>10</sub>H<sub>10</sub>ClNO<sub>3</sub>Na [M+Na]<sup>+</sup>: 250.0241; found: 250.0238.



**methyl 3-((2-iodophenyl)amino)-3-oxopropanoate 1r**

<sup>154</sup> Evindar, G.; Batey, R. A. *J. Org. Chem.* **2006**, *71*, 1802-1808.

Prepared according to **GP3** from methyl malonyl chloride (0.21 mL, 2.0 mmol) and 2-iodoaniline (438 mg, 2.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/2; Rf 0.48 in EtOAc/Cyclohexane = 1/2) to give desired product **1r** as a white solid (520 mg, 82%).

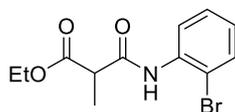
**Mp:** 87 °C.

**IR (cm<sup>-1</sup>):** 3239, 3031, 2953, 1739, 1651, 1576, 1528, 1443, 1427, 1346, 1302, 1267, 1199, 1150, 1017.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 9.19 (br s, 1H), 8.67 (d, *J* = 8.2 Hz, 1H), 7.81 (d, *J* = 7.8 Hz, 1H), 7.34 (t, *J* = 7.7 Hz, 1H), 6.86 (t, *J* = 7.7 Hz, 1H), 3.83 (s, 3H), 3.54 (s, 2H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 169.5, 163.0, 139.1, 138.3, 129.0, 126.3, 122.7, 89.8, 52.8, 41.9.

**HRMS (ESI)** calcd for C<sub>10</sub>H<sub>10</sub>INO<sub>3</sub>Na [M+Na]<sup>+</sup>: 341.9598; found: 341.9610.



#### ethyl 3-((2-bromophenyl)amino)-2-methyl-3-oxopropanoate **1s**

Prepared according to **GP5** from 2-bromoaniline (350 mg, 2.0 mmol) and 3-ethoxy-2-methyl-3-oxopropanoic acid (292 mg, 2.0 mmol). The resulting crude product was purified by column chromatography on silica gel (hexane/EtOAc 1/4; Rf 0.46 in EtOAc/Cyclohexane = 1/4) to give compound **1s** as a white solid (540 mg, 90%).

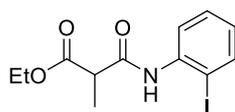
**Mp:** 82 °C.

**IR (cm<sup>-1</sup>):** 3264, 2989, 1738, 1655, 1584, 1534, 1438, 1309, 1280, 1215, 1174, 1094.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.94 (brs, 1H), 8.32 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.54 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.33-7.28 (m, 1H), 6.95-7.00 (m, 1H), 4.27 (qd, *J* = 7.1, 1.5 Hz, 2H), 3.51 (q, *J* = 7.3 Hz, 1H), 1.56 (d, *J* = 7.3 Hz, 3H), 1.32 (t, *J* = 7.1 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 172.0, 167.0, 135.6, 132.3, 128.2, 125.3, 122.0, 113.6, 62.0, 47.8, 15.2, 14.1.

**HRMS (ESI)** calcd for C<sub>12</sub>H<sub>14</sub>BrNO<sub>3</sub>Na [M+Na]<sup>+</sup>: 322.0049; found: 322.0055.



#### ethyl 3-((2-iodophenyl)amino)-2-methyl-3-oxopropanoate **1t**

Prepared according to **GP5** from 2-iodoaniline (300 mg, 1.37 mmol) and 3-ethoxy-2-methyl-3-

oxopropanoic acid (200 mg, 1.37 mmol). The resulting crude product was purified by column chromatography on silica gel (hexane/EtOAc 1/4; Rf 0.35 in EtOAc/Cyclohexane = 1/4) to give compound **1t** as a white solid (430 mg, 90%).

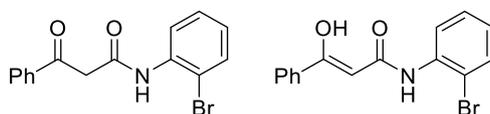
**Mp:** 95 °C.

**IR (cm<sup>-1</sup>):** 3233, 2983, 2934, 1742, 1654, 1530, 1462, 1434, 1370, 1344, 1239, 1213, 1177, 1039.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.61 (brs, 1H), 8.18 (d, *J* = 8.3 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.33 (t, *J* = 7.8 Hz, 1H), 6.85 (m, t, *J* = 7.7 Hz, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 3.51 (q, *J* = 7.3 Hz, 1H), 1.57 (d, *J* = 7.2 Hz, 3H), 1.33 (t, *J* = 7.1 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 171.9, 167.1, 139.0, 138.2, 129.1, 126.2, 123.3, 89.9, 61.9, 47.9, 15.2, 14.1.

**HRMS (ESI)** calcd for C<sub>12</sub>H<sub>14</sub>INO<sub>3</sub>Na [M+Na]<sup>+</sup>: 369.9911; found: 369.9919.



***N*-(2-bromophenyl)-3-oxo-3-phenylpropanamide **1u** and *N*-(2-bromophenyl)-3-hydroxy-3-phenylacrylamide **1u'****

Following the procedure described by Jia:<sup>[131]</sup> A mixture of β-ketoester (0.9 mL, 5 mmol, 1.0 equiv) and 2-bromoaniline (1.03 g, 6 mmol, 1.2 equiv) was stirred at 145 °C for 20 hours under argon. After cooling to room temperature, purification by column chromatography on silica gel (hexane/EtOAc = 1/8; Rf 0.23 in EtOAc/Cyclohexane = 1/8) afforded **1u** and **1u'** as a 86/14 ketone/enol as a white solid (380 mg, 48%).

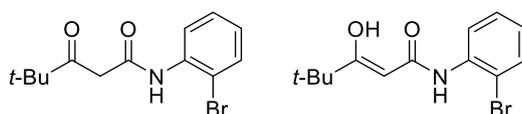
**Mp:** 130 °C.

**IR (cm<sup>-1</sup>):** 3177, 2936, 1688, 1658, 1581, 1528, 1435, 1368, 1294, 1207, 1015.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 13.85 (s, 1H enol), 9.58 (s, 1H, NH), 8.27 (dd, *J* = 8.2, 1.6 Hz, 1H-ketone), 8.01-7.95 (m, 2H-ketone), 7.76-7.72 (m, 2H-enol), 7.59-7.54 (m, 1H-ketone), 7.51-7.33 (m, 8H, 3H-ketone+5H-enol), 7.29-7.26 (m, 1H-enol), 7.26-7.21 (m, 1H-ketone), 6.95-6.89 (m, 2H, 1H-ketone+1H-enol), 5.65 (s, 1H enol), 4.09 (s, 2H ketone).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** only ketone, δ 195.8, 163.9, 136.1, 135.8, 134.3, 132.5, 129.0 (2C), 128.6 (2C), 128.2, 126.0, 125.4, 122.4, 45.8.

**HRMS (ESI)** calcd for C<sub>15</sub>H<sub>12</sub>BrNO<sub>2</sub>Na [M+Na]<sup>+</sup>: 339.9944; found: 339.9942.



***N*-(2-bromophenyl)-4,4-dimethyl-3-oxopentanamide **1v** and *N*-(2-bromophenyl)-3-hydroxy-4,4-dimethylpent-2-enamide **1v'****

Following **GP4** with methyl pivaloylacetate (0.80 mL, 5.0 mmol) and 2-bromoaniline (860 mg, 5.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/5; R<sub>f</sub> 0.35 in EtOAc/Cyclohexane = 1/5) to give compounds **1v** and **1v'** as a 93/7 ketone/enol as a colorless oil (1.1 g, 75%).

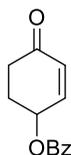
**IR (cm<sup>-1</sup>):** 3259, 2969, 1696, 1585, 1525, 1433, 1295, 1201, 1063, 1018.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 13.66 (s, 1H-enol), 9.56 (brs, 1H), 8.31 (dd, *J* = 8.3, 1.6 Hz, 1H-ketone), 8.26 (d, *J* = 8.8 Hz, 1H-enol), 7.54 (dd, *J* = 8.0, 1.5 Hz, 1H-ketone), 7.53-7.51 (m, 1H-enol), 7.31-7.26 (m, 1H-ketone+1H-enol), 6.99-6.94 (m, 1H-ketone+1H-enol), 5.08 (s, 1H-enol), 3.68 (s, 2H-ketone), 1.22 (s, 9H-ketone), 1.19 (s, 9H-enol).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** only ketone: δ 212.1, 164.0, 135.9, 132.4, 128.3, 125.3, 122.2, 113.7, 45.3, 44.2, 25.8 (3C).

**HRMS (ESI)** calcd for C<sub>13</sub>H<sub>16</sub>BrNO<sub>2</sub>Na [M+Na]<sup>+</sup>: 320.0257; found: 320.0251.

### 3.2 Analytical data of bis-electrophiles



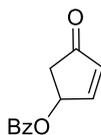
#### 4-oxocyclohex-2-en-1-yl benzoate **2a**

Following the procedure described by Hayashi:<sup>[74]</sup> to a stirred solution of 2-cyclohexen-1-one (0.6 mL, 6.2 mmol, 1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (16 mL) at 0 °C was added a solution of bromine (0.33 mL, 6.32 mmol, 1.02 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (16 mL) over 1 h. Et<sub>3</sub>N (1.44 mL, 10.35 mmol, 1.7 equiv) was added dropwise and the resulting mixture was allowed to warm to room temperature and stirred for 1.5 h. The reaction was quenched with HCl solution (1.0 M aq., 10 mL). The layers were separated and the organic layer was washed with brine (10 mL), dried (MgSO<sub>4</sub>) and concentrated in vacuum to obtain 2-bromo-2-cyclohexen-1-one (1.07 g, 98%).

To a solution of 2-bromo-2-cyclohexen-1-one (174 mg, 1.0 mmol, 1.0 equiv) in anhydrous acetone (5 mL), PhCO<sub>2</sub>Na (360 mg, 2.5 mmol, 2.5 equiv), 4Å MS (348 mg, 200 wt %) and 15-crown-5 (0.56 mL, 2.8 mmol, 2.8 equiv) were added. Then, the reaction was heated to reflux for 12 hours. The mixture was filtered and

the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: Et<sub>2</sub>O/Pentane = 1/5; R<sub>f</sub> 0.30 in Et<sub>2</sub>O/Pentane = 1/4) to give compound **2a** as a white solid (117 mg, 54%). These data are in good agreement with those reported in the literature.<sup>[74]</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.06 (dd, *J* = 8.5, 1.3 Hz, 2H), 7.62-7.57 (m, 1H), 7.49-7.44 (m, 2H), 6.98 (ddd, *J* = 10.2, 2.8, 1.4 Hz, 1H), 6.12 (ddd, *J* = 10.2, 1.8, 0.8 Hz, 1H), 5.86-5.80 (m, 1H), 2.74-2.66 (m, 1H), 2.58-2.45 (m, 2H), 2.31-2.21 (m, 1H).

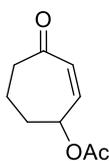


#### 4-benzoyloxy-2-cyclopentenone **2b**

Following the procedure described by Evans:<sup>[77]</sup> furfuryl alcohol (7.35 mL, 85.0 mmol, 1 equiv) and potassium dihydrogen orthophosphate (2.1 g, 15.5 mmol, 0.18 equiv) were dissolved in water (0.5 L). The resulting solution was degassed with a stream of argon during 1 h stirring. The reaction was heated to reflux for 48 h and then cooled to room temperature. The aqueous layer was washed with EtOAc (2 x 100 mL), and then the combined organic layers were discarded. The aqueous layer was concentrated almost to dryness (ca. 25 mL) under reduced pressure and the residue was then thoroughly extracted with EtOAc (5 x 20 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered and the solvent removed under reduced pressure to give 4-hydroxycyclopent-2-enone as brown oil (2.943 g, 30%).

To a solution of the 4-hydroxycyclopent-2-enone (98 mg, 1.0 mmol, 1.0 equiv) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (0.5 M) at 0 °C were added Et<sub>3</sub>N (0.168 mL, 1.2 mmol, 1.2 equiv) and benzoic anhydride (249 mg, 1.1 mmol, 1.1 equiv). After stirred for 10 hours at room temperature, the reaction was treated with a saturated aqueous NaHCO<sub>3</sub> solution, and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with brine, dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/10; R<sub>f</sub> 0.49 in EtOAc/Cyclohexane = 1/2) to give desired product **2b** as a white solid (172 mg, 85%). These data are in good agreement with those reported in the literature.<sup>[77b]</sup>

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.06-8.00 (m, 2H), 7.70 (dd, *J* = 5.7, 2.4 Hz, 1H), 7.62-7.55 (m, 1H), 7.49-7.42 (m, 2H), 6.40 (d, *J* = 5.7, 1.3 Hz, 1H), 6.14-6.08 (m, 1H), 2.95 (dd, *J* = 18.8, 6.4 Hz, 1H), 2.49 (dd, *J* = 18.8, 2.2 Hz, 1H).

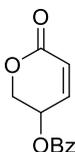


#### 4-acetoxy-2-cycloheptenone **2c**

Following the procedure described by Nakanishi:<sup>[78]</sup> to a solution of 2-cyclohepten-1-one (80%, 275 mg, 2 mmol, 1 equiv) in carbon tetrachloride (4 mL) were added *N*-bromosuccinimide (500 mg, 2.8 mmol, 2.8 equiv) and benzoyl peroxide (1 mg). After 3 hours heating at reflux, the resulting dark brown solution was cooled to room temperature and then petroleum ether (10 mL) was added to precipitate the succinimide, which was removed by filtration with additional washing with petroleum ether (5 mL). The filtrate was concentrated under reduced pressure to give a solution of crude 4-bromo-2-cycloheptenone in CCl<sub>4</sub> with a final volume of ca. 1 mL.

To a solution of potassium acetate (820 mg, 8.4 mmol, 4.2 equiv) and the phase transfer catalyst Aliquat 336 (55 mg, 0.14 mmol, 0.07 equiv) in H<sub>2</sub>O (2 mL) was mixed with the previous CCl<sub>4</sub> solution. After stirred overnight at room temperature, the mixture was diluted with 20 mL Et<sub>2</sub>O and washed with water (2 x 5 mL) and brine. The organic layer was dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/8; R<sub>f</sub> 0.22 in EtOAc/Cyclohexane = 1/8) to give compound **2c** as a colorless oil (168 mg, 50%). These data are in good agreement with those reported in the literature.<sup>[78]</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 6.42 (dd, *J* = 12.6, 3.3 Hz, 1H), 6.01 (dd, *J* = 12.6, 2.2 Hz, 1H), 5.61-5.55 (m, 1H), 2.67-2.58 (m, 2H), 2.22-2.15 (m, 1H), 2.19 (s, 3H), 1.92-1.83 (m, 3H).



#### 6-oxo-3,6-dihydro-2H-pyran-3-yl benzoate **2d**

Following the procedure described by Tang:<sup>[80]</sup> to an oven-dried flask was added 6-hydroxy-2H-pyran-3(6H)-one (114 mg, 1.0 mmol, 1.0 equiv), [Ir(COD)Cl]<sub>2</sub> (17 mg, 0.025 mmol, 0.025 equiv), 2,6-dichlorobenzoic acid (96 mg, 0.5 mmol, 0.5 equiv) and anhydrous CHCl<sub>3</sub> (10 mL) under argon. After stirred for 2 hours, the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 3/1) to give 5-hydroxy-5,6-dihydro-2H-pyran-2-one as a yellow oil (103 mg, 90%).

Et<sub>3</sub>N (0.335 mL, 2.4 mmol, 1.2 equiv) and benzoyl anhydride (498 mg, 2.2 mmol, 1.1 equiv) were added to a solution of 5-hydroxy-5,6-dihydro-2H-pyran-2-one (228 mg, 2.0 mmol, 1.0 equiv) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (0.5 M) at 0 °C. After stirred 2 hours at 35 °C, the reaction was treated with a saturated aqueous NH<sub>4</sub>Cl solution and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with brine, dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/2; R<sub>f</sub> 0.33 in

EtOAc/Cyclohexane = 1/2) to give desired product **2d** as a white solid (349 mg, 80%).

**Mp:** 80 °C.

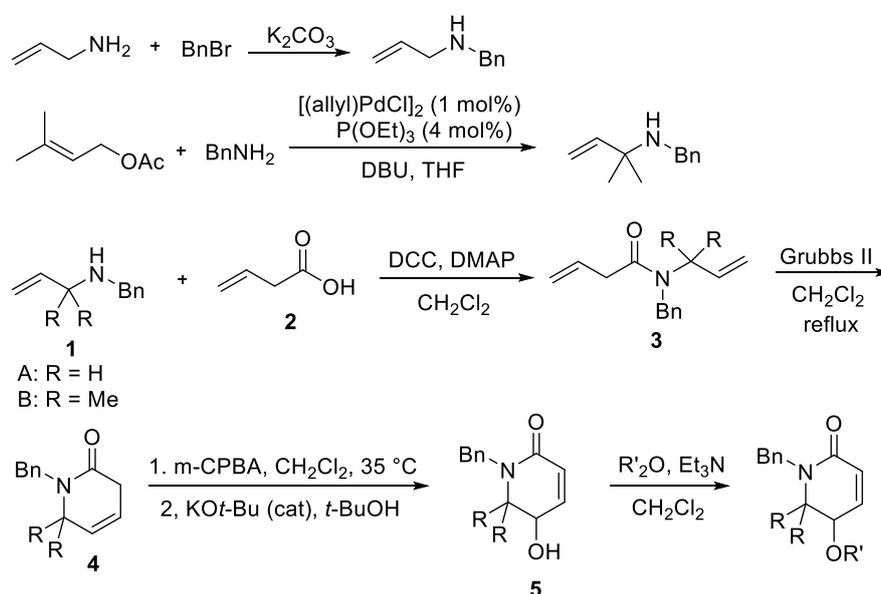
**IR (cm<sup>-1</sup>):** 3064, 2954, 1711, 1594, 1452, 1412, 1345, 1265, 1234, 1100, 1060.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 8.07-8.00 (m, 2H), 7.64-7.57 (m, 1H), 7.49-7.43 (m, 2H), 7.05 (ddt, *J* = 9.8, 5.0, 0.7 Hz, 1H), 6.26 (dd, *J* = 9.8, 0.7 Hz, 1H), 5.59 (dddd, *J* = 8.5, 5.0, 3.6, 0.7 Hz, 1H), 4.66 (dd, *J* = 3.6, 0.7 Hz, 2H).

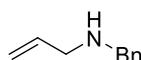
**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ 165.6, 161.0, 140.9, 133.8, 129.9, 128.8, 128.6, 124.8, 69.2, 62.4.

**HRMS (ESI)** calcd for C<sub>12</sub>H<sub>10</sub>O<sub>4</sub>Na [M+Na]<sup>+</sup>: 241.0471; found: 214.0476.

### General procedure for synthesis of compounds **2e-2f** (GP6).



Following the procedure described by List:<sup>[155]</sup> To a suspension of K<sub>2</sub>CO<sub>3</sub> (1.66 g, 12.0 mmol) in allylamine (6.0 mL, 80.0 mmol), was added benzyl bromide (1.2 mL, 10.0 mmol) slowly via syringe addition over a period of 15 mins. The resulting suspension was stirred at room temperature for 24 hours. K<sub>2</sub>CO<sub>3</sub> was filtered off over a Celite pad and washed with dichloromethane. Filtrate was concentrated under reduced pressure. Purification by column chromatography on silica gel (EtOAc; R<sub>f</sub> 0.16 in EtOAc/Cyclohexane = 1/1) afforded *N*-benzyl allylamine **1A** as a clear oil (1.32 g, 90%). These data are in good agreement with those reported in the literature.<sup>[155]</sup>

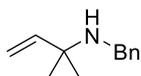


<sup>155</sup> Mukherjee, S.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 11336-11337.

### ***N*-allyl-benzyl-amine 1A**

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.35-7.23 (m, 5H), 6.00-5.89 (m, 1H), 5.21 (ddd, *J* = 17.2, 3.4, 1.7 Hz, 1H), 5.15-5.10 (m, 1H), 3.80 (s, 2H), 3.29 (dt, *J* = 6.0, 1.4 Hz, 2H), 1.45 (s, 1H).

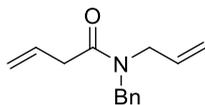
Following the procedure described by Yudin:<sup>[156]</sup> To a solution of [Pd(η<sup>3</sup>-C<sub>3</sub>H<sub>5</sub>)Cl]<sub>2</sub> (3.7 mg, 0.01 mmol) in dry THF (1 mL) were added P(OEt)<sub>3</sub> (14 μL, 0.04 mmol), DBU (0.16 mL, 1.05 mmol), prenyl acetate (0.14 mL, 1.0 mmol) and benzyl amine (0.11 mL, 1.0 mmol) via syringe. The solution was stirred at room temperature for 20 hours. Water (3 mL) was added, the organic layer was separated and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with brine, dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by column chromatography on silica gel (EtOAc/Cyclohexane = 5/1; R<sub>f</sub> 0.48 in EtOAc) afforded *N*-benzyl-2-methylbut-3-en-2-amine **1B** as a clear oil (158 mg, 90%). These data are in good agreement with those reported in the literature.<sup>[156]</sup>



### ***N*-benzyl-2-methylbut-3-en-2-amine 1B**

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 7.37-7.20 (m, 5H), 5.86 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.16-5.06 (m, 2H), 3.66 (s, 2H), 1.26 (s, 6H).

Following the procedure described by Helmchen:<sup>[149]</sup> To a solution of allylamine **1** (10.0 mmol), DMAP (159 mg, 1.3 mmol) and 3-butenic acid (1.1 mL, 13.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL, 0.5 M) at 0 °C, DCC (2.68 g, 13.0 mmol) was added. The resulting mixture was stirred at room temperature until completion monitored by TLC. The reaction mixture was diluted with EtOAc, and the suspension was filtered through a pad of Celite. Water was added, and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried with MgSO<sub>4</sub> and concentrated under reduced pressure. Purification by column chromatography on silica gel (EtOAc/Cyclohexane = 1/4; R<sub>f</sub> 0.5 in EtOAc/Cyclohexane = 1/2) afforded *N*-allyl-*N*-benzylbut-3-enamide **3A** (2.04 g, 95%) or (EtOAc/Cyclohexane = 1/5; R<sub>f</sub> 0.5 in EtOAc/Cyclohexane = 1/4) afforded *N*-benzyl-*N*-(2-methylbut-3-en-2-yl)but-3-enamide **3B** (2.07 g, 85%) as a yellow oil.



### ***N*-allyl-*N*-benzylbut-3-enamide 3A**

**IR (cm<sup>-1</sup>):** 3076, 3024, 2979, 2928, 2856, 1710, 1454, 1410, 1357, 1029, 1170, 1031.

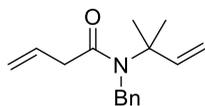
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 7.40-7.14 (m, 5H), 6.10-5.91 (m, 1H), 5.86-5.66 (m, 1H), 5.28-5.05 (m, 4H),

<sup>156</sup> Dubovyk, I.; Watsion, I. D. G.; Yudin, A. K. *J. Org. Chem.* **2013**, *78*, 1559-1575.

4.61-4.48 (m, 2H), 4.03-3.79 (m, 2H), 3.22-3.12 (m, 2H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 171.2, 171.1, 137.5, 136.6, 132.9, 132.6, 131.7, 131.6, 128.8, 128.5, 127.5, 127.3, 126.3, 117.7, 117.5, 116.9, 50.1, 49.0, 48.1, 47.9, 38.6, 38.4.

HRMS (ESI) calcd for C<sub>14</sub>H<sub>17</sub>NONa [M+Na]<sup>+</sup>: 238.1202; found: 238.1209.



**N-benzyl-N-(2-methylbut-3-en-2-yl)but-3-enamide 3B**

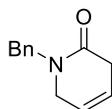
IR (cm<sup>-1</sup>): 3079, 2976, 2929, 1727, 1651, 1492, 1456, 1394, 1299, 1261, 1160, 1077.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.39-7.19 (m, 5H), 6.09 (dd, *J* = 17.5, 10.8 Hz, 1H), 6.02-5.90 (m, 1H), 5.11 (dq, *J* = 10.2, 1.4 Hz, 1H), 5.07-4.98 (m, 2H), 4.96 (dd, *J* = 10.8, 0.7 Hz, 1H), 4.60 (s, 2H), 3.07 (s, dt, *J* = 6.5, 1.5 Hz, 2H), 1.51 (s, 6H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 172.3, 145.2, 139.2, 132.3, 128.7, 127.0, 126.6, 117.2, 110.9, 61.0, 49.0, 41.0, 26.1.

HRMS (ESI) calcd for C<sub>16</sub>H<sub>21</sub>NONa [M+Na]<sup>+</sup>: 266.1515; found: 266.1505.

In a dry Schlenk flask under argon, a solution of diene **3** (1.0 mmol) and Grubbs II catalyst (8.5 mg, 0.01 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (33 mL, 0.03 M) was heated at reflux until TLC indicated complete conversion. The mixture was concentrated under reduced pressure. Purification by column chromatography on silica gel (EtOAc/Cyclohexane = 2/1; R<sub>f</sub> 0.16 in EtOAc/Cyclohexane = 1/2) afforded 1-benzyl-1, 6-dihydropyridin-2(3*H*)-one **4A** (185 mg, 99%) as a colorless oil or (EtOAc/Cyclohexane = 2/1; R<sub>f</sub> 0.21 in EtOAc/Cyclohexane = 1/1) afforded 1-benzyl-6, 6-dimethyl-1, 6-dihydropyridin-2(3*H*)-one **4B** (213 mg, 99%) as a white solid.



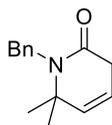
**1-benzyl-1,6-dihydropyridin-2(3H)-one 4A**

IR (cm<sup>-1</sup>): 3034, 2914, 2853, 1734, 1640, 1491, 1447, 1324, 1240, 1041.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.34-7.23 (m, 5H), 5.78-5.72 (m, 1H), 5.70-5.63 (m, 1H), 4.66 (s, 2H), 3.83-3.78 (m, 2H), 3.06-3.01 (m, 2H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 167.0, 136.6, 128.5, 128.0, 127.4, 122.4, 120.7, 49.6, 48.2, 32.1.

HRMS (ESI) calcd for C<sub>12</sub>H<sub>13</sub>NONa [M+Na]<sup>+</sup>: 210.0889; found: 210.0894.



**1-Benzyl-6,6-dimethyl-1,6-dihydropyridin-2(3H)-one 4B**

**IR (cm<sup>-1</sup>):** 2969, 2923, 1728, 1628, 1495, 1433, 1397, 1355, 1245, 1198, 1150, 1076.

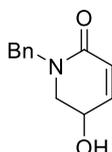
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 7.31-7.15 (m, 5H), 5.70 (dt, *J* = 10.1, 3.4 Hz, 1H), 5.59 (dt, *J* = 10.1, 1.9 Hz, 1H), 4.73 (s, 2H), 3.07 (dd, *J* = 3.4, 1.9 Hz, 2H), 1.29 (s, 6H).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ 168.6, 139.2, 133.4, 128.2, 126.6, 126.4, 119.1, 59.3, 45.0, 31.8, 28.6.

**HRMS (ESI)** calcd for C<sub>14</sub>H<sub>17</sub>NONa [M+Na]<sup>+</sup>: 238.1202; found: 238.1198.

Following the procedure described by Liebeskind:<sup>[157]</sup> To a solution of compound **4** (1.0 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL, 0.2 M) at 0 °C was added m-CPBA (for **4A** 2 mmol or for **4B** 3 mmol). The mixture was stirred at 35 °C for 20 h until completion monitored by TLC. Then, the mixture was cooled to 0 °C and saturated aqueous Na<sub>2</sub>SO<sub>3</sub> solution (0.5 mL) and saturated aqueous NaHCO<sub>3</sub> solution (25 mL) were successively added. The organic layer was separated, washed with saturated aqueous NaHCO<sub>3</sub> (2 x 10 mL), dried with MgSO<sub>4</sub> and concentrated under reduced pressure to give the crude.

To a solution of crude in *t*-BuOH (10 mL, 0.1 M) was added KO<sup>*t*</sup>-Bu (6 mg, 0.05 mmol). The mixture was stirred at room temperature for 30 seconds (for **4B** 10 min) and then water (1 mL) was added. Then, *t*-BuOH was evaporated under reduced pressure and EtOAc (10 mL) and water (2 mL) were added. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by column chromatography on silica gel (MeOH/EtOAc = 1/20; R<sub>f</sub> 0.47 in MeOH/EtOAc = 1/20) afforded 1-benzyl-5-hydroxy-5,6-dihydropyridin-2(1H)-one **5A** (183 mg, 90%) as a white solid or (EtOAc; R<sub>f</sub> 0.27 in EtOAc/Cyclohexane = 2/1) afforded 1-benzyl-5-hydroxy-6,6-dimethyl-5,6-dihydropyridin-2(1H)-one **5B** (116 mg, 50%) as a white solid.



**1-benzyl-5-hydroxy-5,6-dihydropyridin-2(1H)-one 5A**

**Mp:** 52 °C.

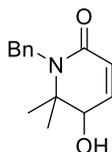
<sup>157</sup> Arrayas, R. G.; Alcudia, A.; Liebeskind, L. S. *Org. Lett.* **2001**, *3*, 3381-3383.

**IR (cm<sup>-1</sup>):** 3344, 1652, 1592, 1489, 1443, 1363, 1325, 1259, 1144, 1109, 1050.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.34-7.24 (m, 5H), 6.59 (dd, *J* = 9.8 4.4 Hz, 1H), 5.99 (d, *J* = 9.8 Hz, 1H), 4.76 (d, *J* = 14.8 Hz, 1H), 4.46 (d, *J* = 14.8 Hz, 1H), 4.28 (dd, *J* = 9.6, 4.8 Hz, 1H), 3.45 (dd, *J* = 13.3, 5.0 Hz, 1H), 3.37 (dd, *J* = 13.3, 5.0 Hz, 1H), 3.26 (br s, 1H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 163.3, 140.4, 136.6, 128.7, 128.1, 127.6, 126.1, 62.1, 52.2, 50.0.

**HRMS (ESI)** calcd for C<sub>12</sub>H<sub>13</sub>NO<sub>2</sub>Na [M+Na]<sup>+</sup>: 226.0838; found: 226.0832.



**1-benzyl-5-hydroxy-6,6-dimethyl-5,6-dihydropyridin-2(1H)-one 5B**

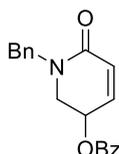
**Mp:** 95 °C.

**IR (cm<sup>-1</sup>):** 3375, 2984, 2930, 1661, 1601, 1436, 1401, 1357, 1289, 1196, 1114, 1074..

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 7.33-7.18 (m, 5H), 6.53 (dd, *J* = 9.8 3.9 Hz, 1H), 6.01 (d, *J* = 9.8 Hz, 1H), 4.82 (d, *J* = 15.8 Hz, 1H), 4.53 (d, *J* = 15.8 Hz, 1H), 4.03-3.95 (m, 1H), 3.76 (d, *J* = 6.4 Hz, 1H), 1.26 (s, 3H), 1.17 (s, 3H).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ 164.5, 140.8, 139.3, 128.4, 127.1, 126.8, 124.8, 71.4, 61.2, 44.4, 25.5, 20.8.

**HRMS (ESI)** calcd for C<sub>14</sub>H<sub>17</sub>NO<sub>2</sub>Na [M+Na]<sup>+</sup>: 254.1151; found: 254.1143.



**1-Benzyl-6-oxo-1,2,3,6-tetrahydropyridin-3-yl benzoate 2e**

Prepared according to **GP6** from 1-benzyl-5-hydroxy-5,6-dihydropyridin-2(1H)-one **5A** (203 mg, 1.0 mmol), and benzoyl anhydride (249 mg, 1.1 mmol). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/1; R<sub>f</sub> 0.4 in EtOAc/Cyclohexane = 1/1) to give desired product **2e** (249 mg, 81%) as a colorless oil.

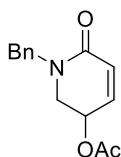
**IR (cm<sup>-1</sup>):** 1716, 1667, 1610, 1484, 1444, 1328, 1258, 1173, 1104, 1063, 1017.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 7.92-7.84 (m, 2H), 7.60-7.53 (m, 1H), 7.44-7.38 (m, 2H), 7.33-7.17 (m, 5H), 6.71 (ddd, *J* = 9.8, 5.0, 1.1 Hz, 1H), 6.27 (d, *J* = 9.8 Hz, 1H), 5.49 (dt, *J* = 4.6, 3.6 Hz, 1H), 5.07 (d, *J* = 14.9 Hz, 1H), 4.30 (d, *J* = 14.9 Hz, 1H), 3.73 (dd, *J* = 14.1, 4.6 Hz, 1H), 3.57 (ddd, *J* = 14.1, 3.6 1.1 Hz, 1H).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ 165.5, 162.6, 136.5, 134.9, 122.4, 129.7, 129.3, 128.6, 128.3, 128.0, 127.5, 63.9,

49.4, 48.8.

**HRMS (ESI)** calcd for  $C_{19}H_{17}NO_3Na$   $[M+Na]^+$ : 330.1101; found: 330.1112.



**1-benzyl-6-oxo-1,2,3,6-tetrahydropyridin-3-yl acetate 2e'**

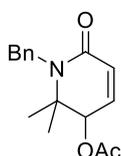
Prepared according to **GP6** from 5-hydroxy-5,6-dihydro-2H-pyran-2-one **5A** (203 mg, 1.0 mmol), and acetic anhydride (0.11 mL, 1.1 mmol). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 3/1; Rf 0.62 in EtOAc) to give desired product **2e'** (220 mg, 90%) as a colorless oil.

**IR (cm<sup>-1</sup>):** 1735, 1667, 1610, 1485, 1440, 1427, 1370, 1227, 1029.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  7.36-7.23 (m, 5H), 6.55 (ddd,  $J = 9.8, 4.7, 1.1$  Hz, 1H), 6.19 (d,  $J = 9.8$  Hz, 1H), 5.25 (dt,  $J = 4.5, 4.5$  Hz, 1H), 4.87 (d,  $J = 14.9$  Hz, 1H), 4.41 (d,  $J = 14.9$  Hz, 1H), 3.58 (dd,  $J = 14.0, 4.7$  Hz, 1H), 3.38 (ddd,  $J = 14.0, 4.0, 1.1$  Hz, 1H), 1.94 (s, 3H).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  170.0, 162.6, 136.4, 135.0, 129.0, 128.6, 128.0, 127.5, 63.5, 49.4, 48.7, 20.7.

**HRMS (ESI)** calcd for  $C_{14}H_{15}NO_3Na$   $[M+Na]^+$ : 268.0944; found: 268.0941.



**1-benzyl-2,2-dimethyl-6-oxo-1,2,3,6-tetrahydropyridin-3-yl acetate 2f**

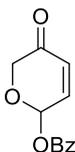
Prepared according to **GP6** from 1-benzyl-5-hydroxy-6,6-dimethyl-5,6-dihydropyridin-2(1H)-one **5B** (102 mg, 0.5 mmol), and acetic anhydride (0.05 mL, 0.55 mmol). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 2/1; Rf 0.56 in EtOAc/Cyclohexane = 2/1) to give desired product **2f** (126 mg, 92%) as a colorless oil.

**IR (cm<sup>-1</sup>):** 2983, 2929, 1738, 1668, 1615, 1418, 1406, 1229, 1140, 1021.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  7.34-7.18 (m, 5H), 6.53 (dd,  $J = 9.8, 4.8$  Hz, 1H), 6.22 (d,  $J = 9.8$  Hz, 1H), 5.13 (d,  $J = 4.8$  Hz, 1H), 4.84 (d,  $J = 16.1$  Hz, 2H), 4.61 (d,  $J = 16.1$  Hz, 1H), 2.06 (s, 3H), 1.24 (s, 6H).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):**  $\delta$  170.1, 163.7, 139.1, 134.8, 128.4, 128.0, 126.8 (2C), 59.2, 44.0, 25.4, 22.1, 20.7.

**HRMS (ESI)** calcd for  $C_{16}H_{19}NO_3Na$   $[M+Na]^+$ : 296.1257; found: 296.1257.

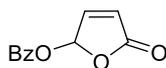


### 5-oxo-5,6-dihydro-2H-pyran-2-yl benzoate **2g**

Following the procedure described by Waldmann:<sup>[80]</sup> to a solution of furfuryl alcohol (0.53 mL, 6.12 mmol, 1.0 equiv), NaHCO<sub>3</sub> (1.03 g, 12.24 mmol, 2.0 equiv) and NaOAc (1.09 g, 6.12 mmol, 1.0 equiv) in THF/H<sub>2</sub>O (4/1, 10 ml) was added NBS (1.14 g, 6.42 mmol, 1.05 equiv) at 0 °C. After stirred for 10 min, the reaction mixture was extracted with ethyl acetate (3×40 ml). The combined organic phase was dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/1; Rf 0.31 in EtOAc/Cyclohexane = 1/1) to give 6-hydroxy-2H-pyran-3(6H)-one as a white solid (490 mg, 70%).

Et<sub>3</sub>N (0.335 mL, 2.4 mmol, 1.2 equiv) and benzoyl anhydride (498 mg, 2.2 mmol, 1.1 equiv) were added to a solution of the 6-hydroxy-2H-pyran-3(6H)-one (228 mg, 2.0 mmol, 1.0 equiv) in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (0.5 M) at 0 °C. After stirred for 1 hour, the reaction was treated with saturated aqueous NH<sub>4</sub>Cl and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with brine, dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/10; Rf 0.51 in EtOAc/Cyclohexane = 1/3) to give desired product **2g** as a white solid (305 mg, 70%). These data are in good agreement with those reported in the literature.<sup>[80]</sup>

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.10-8.00 (m, 2H), 7.66-7.57 (m, 1H), 7.52-7.42 (m, 2H), 7.06 (dd, *J* = 10.4, 3.6 Hz, 1H), 6.75 (dd, *J* = 3.6, 0.8 Hz, 1H), 6.34 (d, *J* = 10.4 Hz, 1H), 4.62 (d, *J* = 17.1 Hz, 1H), 4.29 (d, *J* = 17.1 Hz, 1H).



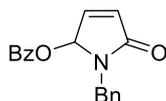
### 5-oxo-2,5-dihydrofuran-2-yl benzoate **2h**

Following the modified procedure described by Trost:<sup>[83]</sup> Into a solution of furfural (1.7 mL, 20 mmol) and rose bengal (20 mg, 0.02 mmol) in MeOH (20 ml) was bubbled oxygen gas and the pink/orange solution irradiated by sunlight. After 12 hours, the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/1; Rf 0.26 in EtOAc/Cyclohexane = 1/1) to give 5-hydroxy-2(5H)-furanone as a light yellow oil (600 mg, yield: 30%).

To a solution of the 5-hydroxy-2(5H)-furanone (200 mg, 2.0 mmol, 1.0 equiv) in dry CH<sub>2</sub>Cl<sub>2</sub> (0.5 M) at 0 °C was added benzoyl anhydride (452 mg, 2.0 mmol, 1.0 equiv), after 5 min then was added Et<sub>3</sub>N (0.31 mL, 2.2 mmol, 1.1 equiv). After 4 hours at room temperature, the reaction was quenched with a saturated

aqueous NH<sub>4</sub>Cl solution and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with brine, dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1:3; R<sub>f</sub> 0.42 in EtOAc/Cyclohexane = 1/2) to give desired product **2h** as a white solid (306 mg, 75%). These data are in good agreement with those reported in the literature.<sup>[83]</sup>

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.06 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.63 (tt, *J* = 7.4, 1.3 Hz, 1H), 7.51-7.45 (m, 3H), 7.26 (t, *J* = 1.2 Hz, 1H), 6.39 (dd, *J* = 5.6, 1.2 Hz, 1H).



### 1-benzyl-5-oxo-2,5-dihydro-1H-pyrrol-2-yl benzoate **2i**

Following the procedure described by Takabe:<sup>[84]</sup> To a solution of maleic anhydride (2.16 g, 22 mmol) in AcOH (20 ml) was added benzylamine (2.18 mL, 20 mmol). The reaction mixture was stirred at reflux for 3 hours and then the acetic acid was removed under reduced pressure. The residue was dissolved in EtOAc (20 ml) and washed with aqueous NaHCO<sub>3</sub> solution (2 x 20 ml), 1 M HCl (2 x 20 ml) solution and saturated aqueous NaCl solution (20 ml). The combined organic layers were dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under reduced pressure to afford the *N*-benzylmaleimide (2.62 g, yield: 70%) in sufficient purity for further elaboration.

To a solution of *N*-benzylmaleimide (1.87 g, 10 mmol) in MeOH (10 ml) was added cerium (III) chloride heptahydrate (4.47 g, 12 mmol), and the mixture was stirred for 5 min. After the solution was cooled to 0 °C, sodium borohydride (454 mg, 12 mmol) was added portion wise, and the mixture was stirred for 1 h. The reaction mixture was quenched with ice water, and methanol removed under reduced pressure. The residue was extracted with EtOAc (3 times). The combined organic layers were washed with brine, dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification by column chromatography on silica gel (eluent: EtOAc/Cyclohexane = 2/1; R<sub>f</sub> 0.19 in EtOAc/Cyclohexane = 1/1) afforded the 1-benzyl-5-hydroxy-1H-pyrrol-2(5H)-one (2.04 g, 90%).

To a solution of the 1-benzyl-5-hydroxy-1H-pyrrol-2(5H)-one (95 mg, 0.5 mmol, 1.0 equiv) in dry CH<sub>2</sub>Cl<sub>2</sub> (2 mL, 0.25 M) at 0 °C was added benzoyl anhydride (113 mg, 0.5 mmol, 1.0 equiv), after 5 min then was added Et<sub>3</sub>N (0.08 mL, 0.55 mmol, 1.1 equiv). After 12 hours at room temperature, the reaction was quenched with a saturated aqueous NH<sub>4</sub>Cl solution and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with brine, dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/3; R<sub>f</sub> 0.31 in EtOAc/Cyclohexane = 1/3) to give desired product **2i** (117 mg, 80%) as a white solid.

**Mp:** 106 °C.

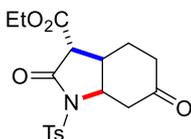
**IR (cm<sup>-1</sup>):** 2930, 1700, 1594, 1450, 1405, 1319, 1259, 1220, 1168, 1099.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 7.91-7.83 (m, 2H), 7.58 (tt, *J* = 7.4, 1.3 Hz, 1H), 7.45-7.38 (m, 2H), 7.30-7.17 (m, 5H), 7.08 (dd, *J* = 6.0, 1.8 Hz, 1H), 6.66 (d, *J* = 1.8 Hz, 1H), 6.35 (d, *J* = 6.0 Hz, 1H), 4.82 (d, *J* = 15.1 Hz, 1H), 4.45 (d, *J* = 15.1 Hz, 1H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 169.7, 165.6, 142.4, 136.7, 133.6, 129.8, 129.7, 128.7, 128.6, 128.4, 128.1, 127.5, 83.3, 44.0.

**HRMS (ESI)** calcd for C<sub>18</sub>H<sub>15</sub>NO<sub>3</sub>Na [M+Na]<sup>+</sup>: 316.0944; found: 316.0945.

### 3.3 Analytical data of compounds relating to Chapter 2



#### ethyl 2,6-dioxo-1-tosyloctahydro-1H-indole-3-carboxylate **3a**

Following **GP7** with **2a** (84 mg, 0.39 mmol) and **1a** (86 mg, 0.30 mmol). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/1; R<sub>f</sub> 0.38 in EtOAc/Cyclohexane = 1/1) to give compound **3a** as a pale yellow solid (102 mg, 90%).

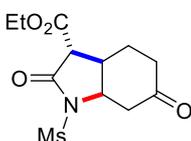
**Mp:** 131 °C.

**IR (cm<sup>-1</sup>):** 2982, 2927, 1711, 1595, 1459, 1355, 1274, 1168, 1120, 1084, 1012.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.85 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.3 Hz, 2H), 4.68 (ddd, *J* = 10.0, 8.5, 5.7 Hz, 1H), 4.21-4.09 (m, 2H), 3.46 (d, *J* = 10.5 Hz, 1H), 3.15-3.06 (m, 2H), 2.52 (dd, *J* = 15.5, 10.0 Hz, 1H), 2.38 (s, 3H), 2.41-2.32 (m, 1H), 2.25 (ddd, *J* = 13.0, 8.2, 4.8 Hz, 1H), 2.09-2.18 (m, 1H), 1.90-1.80 (m, 1H), 1.20 (t, *J* = 7.1 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 206.7, 167.2, 166.8, 145.6, 134.7, 129.6, 128.2, 62.1, 56.5, 52.9, 43.6, 35.8, 34.1, 23.8, 21.5, 13.9.

**HRMS (ESI)** calcd for C<sub>18</sub>H<sub>21</sub>NO<sub>6</sub>SNa [M+Na]<sup>+</sup>: 402.0982; found: 402.0987.



### ethyl 1-(methylsulfonyl)-2,6-dioxooctahydro-1H-indole-3-carboxylate **3b**

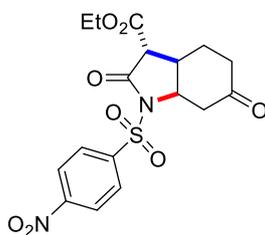
Following **GP7** with **2a** (84 mg, 0.39 mmol) and **1b** (63 mg, 0.30 mmol). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/1; Rf 0.40 in EtOAc/Cyclohexane = 2/1) to give compound **3b** as a colorless oil (77 mg, 85%).

**IR (cm<sup>-1</sup>):** 2982, 2935, 1754, 1716, 1462, 1353, 1270, 1165, 1122, 1101, 1029.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 4.64 (ddd, *J* = 9.5, 8.5, 5.7 Hz, 1H), 4.33-4.19 (m, 2H), 3.60 (d, *J* = 10.0 Hz, 1H), 3.27 (s, 3H), 3.29-3.14 (m, 1H), 3.06 (dd, *J* = 15.6, 5.7 Hz, 1H), 2.65 (dd, *J* = 15.6, 9.5 Hz, 1H), 2.46 (ddd, *J* = 13.5, 8.5, 4.8 Hz, 1H), 2.37-2.16 (m, 2H), 2.02-1.87 (m, 1H), 1.31 (t, *J* = 7.1 Hz, 3H).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ 206.7, 168.7, 167.1, 62.4, 56.3, 53.1, 43.5, 41.5, 35.9, 34.2, 24.0, 14.0.

**HRMS (ESI)** calcd for C<sub>12</sub>H<sub>17</sub>NO<sub>6</sub>SNa [M+Na]<sup>+</sup>: 326.0669; found: 326.0649



### ethyl 1-((4-nitrophenyl)sulfonyl)-2,6-dioxooctahydro-1H-indole-3-carboxylate **3c**

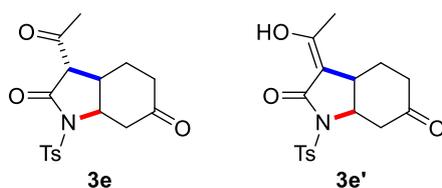
Following **GP7** with **2a** (84 mg, 0.39 mmol) and **1c** (95 mg, 0.30 mmol) at 60 °C. The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/1; Rf 0.38 in EtOAc/Cyclohexane = 1/1) to give compound **3c** as a colorless oil (80 mg, 65%).

**IR (cm<sup>-1</sup>):** 3110, 2985, 2934, 2257, 1758, 1719, 1606, 1531, 1467, 1359, 1305, 1272, 1169, 1120, 1091, 1028.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 8.38 (d, *J* = 9.0 Hz, 2H), 8.24 (d, *J* = 9.0 Hz, 2H), 4.78 (ddd, *J* = 9.5, 8.5, 5.7 Hz, 1H), 4.28-4.17 (m, 2H), 3.48 (d, *J* = 10.0 Hz, 1H), 3.23-3.12 (m, 2H), 2.63 (dd, *J* = 15.5, 9.5 Hz, 1H), 2.48-2.31 (m, 2H), 2.26-2.15 (m, 1H), 1.98-1.85 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ 206.2, 167.7, 166.6, 151.0, 143.0, 129.9, 124.2, 62.5, 57.0, 52.8, 43.6, 35.9, 34.3, 24.0, 14.0.

**HRMS (ESI)** calcd for C<sub>17</sub>H<sub>18</sub>N<sub>2</sub>O<sub>8</sub>SNa [M+MeOH+Na]<sup>+</sup>: 465.0938; found: 465.0928.



**3e : 3e' = 65 / 35**

**3-acetyl-1-tosylhexahydro-1H-indole-2,6-dione 3e and 3-(1-Hydroxyethylidene)-1-tosylhexahydro-1H-indole-2,6-dione 3e'**

Following **GP7** with **2a** (84 mg, 0.39 mmol) and **1e** (77 mg, 0.30 mmol) at 60 °C. The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/1; Rf 0.35 in EtOAc/Cyclohexane = 1/1) to give compound **3e** and **3e'** as a 65/35 ketone: enol as a waxy solid (73 mg, 70%).

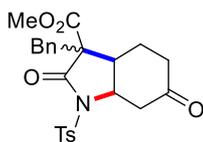
**Mp:** 60 °C.

**IR (cm<sup>-1</sup>):** 2922, 1713, 1667, 1630, 1593, 1497, 1356, 1228, 1163, 1121, 1085.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ketone and enol):** δ 11.71 (s, 1H, enol), 7.96-7.86 (m, 4H, 2H ketone + 2Henol), 7.38-7.30 (m, 4H, 2H-ketone + 2H-enol), 4.76 (ddd, *J* = 11.0, 6.0, 4.9 Hz, 1Henol), 4.67 (ddd, *J* = 14.4, 8.9, 5.5 Hz, 1Hketone), 3.50 (d, *J* = 9.6 Hz, 1H, ketone), 3.41-3.34 (m, 1H, enol), 3.29-3.20 (m, 1H, ketone), 3.17 (dd, *J* = 15.7, 5.5 Hz, 1H, ketone), 3.09 (dd, *J* = 16.0, 6.0 Hz, 1H, enol), 2.99 (dd, *J* = 16.0, 4.9 Hz, 1H, enol), 2.57 (dd, *J* = 15.7, 9.8 Hz, 1H, ketone), 2.47-2.41 (m, 6H, 3H ketone + 3H enol), 2.41-2.24 (m, 7H, 5H ketone + 2H enol), 2.20-2.12 (m, 2H, 1H ketone + 1H enol), 1.97 (s, 3Henol), 1.91-1.83 (m, 1H, enol), 3.41-3.34 (m, 1H, ketone).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ketone and enol):** δ for ketone, 207.1, 199.7, 167.8, 145.7, 134.8, 129.7(2C), 128.3(2C), 59.9, 55.9, 43.6, 36.3, 31.3, 30.0, 24.2, 21.6.; for enol 208.6, 172.0, 170.8, 145.2, 135.5, 129.6(2C), 128.1(2C), 101.3, 56.1, 42.6, 35.9, 32.4, 25.5, 21.6, 19.0.

**HRMS (ESI)** calcd for C<sub>17</sub>H<sub>19</sub>NO<sub>5</sub>SNa [M+Na]<sup>+</sup>: 372.0876; found: 372.0886.



**methyl 3-benzyl-2,6-dioxo-1-tosyl-1,2,3,4,5,6-hexahydroindole-3-carboxylate 3f**

Following **GP7** with **2a** (84 mg, 0.39 mmol) and **1f** (108 mg, 0.30 mmol). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/2; Rf 0.60 in EtOAc/Cyclohexane = 1/1) to give compound **3f** as a waxy solid as a 60/40 diastereomeric mixture (116 mg, 85%).

**Mp:** 68 °C.

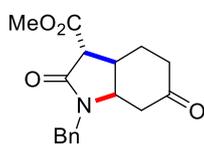
**IR (cm<sup>-1</sup>):** 2921, 2854, 1718, 1595, 1495, 1360, 1224, 1171, 1084.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, diastereomeric mixture):** δ 7.94-7.84 (m, 4H, 2H major + 2H minor diast.), 7.39-7.31 (m, 4H, 2H major + 2H minor diast.), 7.22-6.90 (m, 10H, 5H major + 5H minor diast.), 4.68 (q, *J* = 6.6 Hz, 1H, minor diast.), 4.21 (ddd, *J* = 14.7, 9.6, 5.0 Hz, 1H, major diast.), 3.70 (s, 3H, major diast.), 3.50-3.40 (m,

5H, 1H major + 4H minor diast.), 3.22-2.97 (m, 5H, 2H major + 3H minor diast.), 2.86-2.67 (m, 3H, 2H major + 1H minor diast.), 2.49 (s, 3H, major diast.), 2.45 (s, 3H, minor diast.), 2.43-2.24 (m, 3H, 2H major + 1H minor diast.), 2.17-2.11 (m, 1H, minor diast.), 2.06-1.98 (m, 2H, 1H major + 1H minor diast.), 1.91-1.84 (m, 1H, minor diast.), 1.66-1.58 (m, 1H, major diast.).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, diastereomeric mixture):** δ 207.5 (minor), 207.4 (major), 170.8 (major), 170.3 (minor), 170.2 (major), 168.5 (minor), 145.4 (minor), 145.3 (major), 135.3 (minor), 135.0 (major), 134.6 (2C, major + minor), 130.2 (2C, major), 129.5 (4C, 2Cmajor + 2Cminor), 128.7 (4C, 2Cmajor + 2Cminor), 128.6 (2C, minor), 128.4 (4C, 2Cmajor + 2Cminor), 127.2 (major), 127.0 (minor), 61.2 (major), 60.8 (minor), 56.8 (minor), 54.8 (major), 53.1 (minor), 52.9 (major), 43.4 (minor), 42.6 (major), 38.0 (minor), 37.7 (major), 37.6 (minor), 37.0 (major), 35.0 (minor), 34.7 (major), 21.6 (2C, major + minor), 20.8 (minor), 20.6 (major).

**HRMS (ESI)** calcd for C<sub>24</sub>H<sub>25</sub>NO<sub>6</sub>Na [M+Na]<sup>+</sup>: 478.1295; found: 478.1287.



**methyl 1-benzyl-2,6-dioxooctahydro-1H-indole-3-carboxylate 3g**

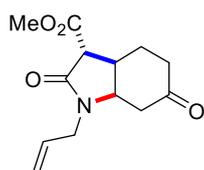
Following **GP8** with **2a** (84 mg, 0.39 mmol), **1g** (62 mg, 0.30 mmol) and DBU (0.09 mL, 0.6 mmol). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 2/1; Rf 0.30 in EtOAc/Cyclohexane = 2/1) to give compound **3i** as a colorless oil (78 mg, 86%).

**IR (cm<sup>-1</sup>):** 2953, 1738, 1683, 1497, 1426, 1362, 1335, 1265, 1163, 1081, 1025.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.35-7.28 (m, 3H), 7.24-7.20 (m, 2H), 5.05 (d, *J* = 15.1 Hz, 1H), 3.97 (ddd, *J* = 12.8, 7.3, 5.2 Hz, 1H), 3.90 (d, *J* = 15.1 Hz, 1H), 3.81 (s, 3H), 3.38 (d, *J* = 5.2 Hz, 1H), 3.00-2.92 (m, 1H), 2.60 (dd, *J* = 15.5, 5.2 Hz, 1H), 2.46 (dd, *J* = 15.5, 7.3 Hz, 1H), 2.37 (ddd, *J* = 18.2, 8.0, 4.7 Hz, 1H), 2.27 (ddd, *J* = 18.2, 8.6, 4.7 Hz, 1H), 2.20-2.12 (m, 1H), 1.94-1.85 (m, 1H).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ 208.2, 170.0, 169.0, 135.0, 128.8, 128.0, 127.9, 54.2, 54.1, 52.9, 44.5, 41.2, 36.6, 33.8, 25.7.

**HRMS (ESI)** calcd for C<sub>17</sub>H<sub>19</sub>NO<sub>4</sub>Na [M+Na]<sup>+</sup>: 324.1206; found: 324.1203.



**methyl 1-allyl-2,6-dioxooctahydro-1H-indole-3-carboxylate 3h**

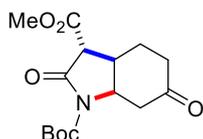
Following **GP8** with **2a** (96 mg, 0.45 mmol, 1.5 equiv), **1h** (47 mg, 0.30 mmol) and DBU (0.09 mL, 0.6 mmol) at 0 °C. The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 3/1; Rf 0.26 in EtOAc/Cyclohexane = 3/1) to give compound **3h** as a colorless oil (53 mg, 70%).

**IR (cm<sup>-1</sup>):** 2953, 1737, 1683, 1442, 1418, 1267, 1199, 1163, 1027 cm<sup>-1</sup>.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 5.66 (dddd, *J* = 17.4, 10.1, 7.5, 4.7 Hz, 1H), 5.25-5.18 (m, 2H), 4.31 (ddt, *J* = 15.5, 4.7, 1.8 Hz, 1H), 4.15 (ddd, *J* = 12.5, 7.3, 5.2 Hz, 1H), 3.78 (s, 3H), 3.45 (ddd, *J* = 15.5, 7.5, 1.1 Hz, 1H), 3.31 (d, *J* = 5.5 Hz, 1H), 3.07-2.97 (m, 1H), 2.69 (dd, *J* = 15.5, 5.2 Hz, 1H), 2.47 (dd, *J* = 15.5, 7.3 Hz, 1H), 2.40-2.25 (m, 2H), 2.21-2.13 (m, 1H), 1.92-1.83 (m, 1H).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ 208.3, 169.9, 168.5, 131.3, 118.8, 54.6, 54.1, 52.9, 43.4, 41.4, 36.6, 33.8, 25.6.

**HRMS (ESI)** calcd for C<sub>13</sub>H<sub>17</sub>NO<sub>4</sub>Na [M+Na]<sup>+</sup>: 274.1050; found: 274.1047.



#### **1-tert-butyl 3-methyl 2,6-dioxooctahydro-1H-indole-1,3-dicarboxylate 3i**

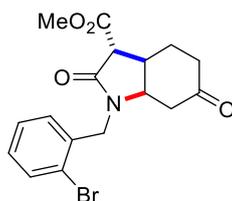
Following **GP8** with **2a** (57 mg, 0.26 mmol), **1i** (44 mg, 0.20 mmol) and DBU (0.06 mL, 0.4 mmol). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/1; Rf 0.33 in EtOAc/Cyclohexane = 1/1) to give compound **3g** as a colorless oil (31 mg, 50%).

**IR (cm<sup>-1</sup>):** 2976, 2914, 1782, 1721, 1447, 1356, 1285, 1244, 1153, 1107, 1033, 1015.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 4.51 (ddd, *J* = 14.4, 8.6, 5.7 Hz, 1H), 3.82 (s, 3H), 3.54 (d, *J* = 10.4 Hz, 1H), 3.14-3.05 (m, 1H), 3.00 (dd, *J* = 16.0, 5.7 Hz, 1H), 2.49-2.39 (m, 2H), 2.31 (ddd, *J* = 17.0, 8.4, 4.8 Hz, 1H), 2.23-2.14 (m, 1H), 1.96-1.86 (m, 1H), 1.52 (s, 9H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 207.4, 168.2, 167.4, 148.9, 84.1, 55.0, 53.7, 53.0, 42.7, 36.1, 32.9, 27.8, 24.0.

**HRMS (ESI)** calcd for C<sub>15</sub>H<sub>21</sub>NO<sub>6</sub>Na [M+Na]<sup>+</sup>: 334.1261; found: 334.1255.



#### **methyl 1-(2-bromobenzyl)-2,6-dioxooctahydro-1H-indole-3-carboxylate 3j**

Following **GP8** with **2a** (114 mg, 0.52 mmol), **1j** (114 mg, 0.40 mmol) and DBU (0.12 mL, 0.8 mmol).

The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 2/1; Rf 0.26 in EtOAc/Cyclohexane = 1/1) to give compound **3j** as a white solid (120 mg, 80%).

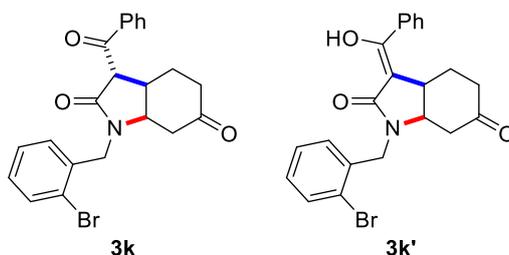
**Mp:** 115 °C.

**IR (cm<sup>-1</sup>):** 2952, 1686, 1429, 1360, 1274, 1161, 1118, 1023.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 7.53 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.31-7.22 (m, 2H), 7.17-7.11 (m, 1H), 4.95 (d, *J* = 15.7 Hz, 1H), 4.25 (d, *J* = 15.7 Hz, 1H), 3.98 (td, *J* = 8.1, 5.3 Hz, 1H), 3.80 (s, 3H), 3.40 (d, *J* = 6.1 Hz, 1H), 3.07-2.97 (m, 1H), 2.66 (dd, *J* = 15.5, 5.3 Hz, 1H), 2.48 (dd, *J* = 15.5, 7.8 Hz, 1H), 2.42-2.11 (m, 3H), 1.96-1.84 (m, 1H).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ 208.0, 169.8, 168.9, 134.3, 133.0, 129.5, 129.4, 127.9, 123.3, 54.4, 53.7, 52.8, 44.3, 41.5, 36.5, 33.8, 25.3.

**HRMS (ESI)** calcd for C<sub>17</sub>H<sub>18</sub>BrNO<sub>4</sub>Na [M+Na]<sup>+</sup>: 402.0311; found: 402.0323.



**3-benzoyl-1-(2-bromobenzyl)hexahydro-1H-indole-2,6-dione **3k** and 1-(2-bromobenzyl)-3-(hydroxy(phenyl)methylene)hexahydro-1H-indole-2,6-dione **3k'****

Following **GP8** with **2a** (281 mg, 1.3 mmol), **1k** (331 mg, 1.0 mmol) and DBU (0.3 mL, 2.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 2/1; Rf 0.47 in EtOAc/Cyclohexane = 2/1) to give compound **3k/3k'** as a 94/6 ketone:enol as colorless oil (420 mg, 99%).

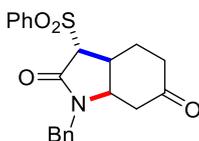
**IR (cm<sup>-1</sup>):** 2947, 1708, 1666, 1586, 1437, 1412, 1359, 1271, 1225, 1175, 1019.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 12.96 (brs, 1H enol), 8.22-7.97 (m, 4H, 2Hketone+2Henol), 7.62-7.57 (m, 2H, 1Hketone+1Henol), 7.53-7.47 (m, 3Hketone), 7.42-7.38 (m, 3Henol), 7.30-7.20 (m, 4H, 2Hketone+2Henol), 7.16-7.08 (m, 2H, 1Hketone+1Henol), 4.95 (d, *J* = 15.7 Hz, 1Henol), 4.93 (d, *J* = 15.7 Hz, 1Hketone), 4.41 (d, *J* = 4.6 Hz, 1Hketone), 4.30 (d, *J* = 15.7 Hz, 1Henol), 4.23 (d, *J* = 15.7 Hz, 1Hketone), 4.12-4.01 (m, 2H, 1Hketone+1Henol), 3.81-3.71 (m, 1Henol), 3.27-3.18 (m, 1Hketone), 2.68 (dd, *J* = 15.5, 5.2 Hz, 1Hketone), 2.62 (dd, *J* = 5.0, 1.8 Hz, 2Henol), 2.55 (dd, *J* = 15.5, 7.1 Hz, 1Hketone), 2.40 (ddd, *J* = 18.3, 7.8, 4.8 Hz, 2H, 1Hketone+1Henol), 2.29 (ddd, *J* = 18.3, 8.8, 4.8 Hz, 2H, 1Hketone+1Henol), 2.18-2.09 (m, 2H, 1Hketone+1Henol), 1.96-1.86 (m, 2H, 1Hketone+1Henol).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** only ketone, δ 208.4, 195.3, 169.5, 136.0, 134.2, 133.7, 132.9, 129.5, 129.4,

129.3, 128.6, 127.9, 123.2, 56.6, 54.4, 44.1, 41.4, 36.8, 33.3, 25.6.

**HRMS (ESI)** calcd for  $C_{22}H_{20}BrNO_3Na$   $[M+Na]^+$ : 448.0519; found: 448.0531.



**1-Benzyl-3-(phenylsulfonyl)hexahydro-1H-indole-2,6-dione 3I**

Following **GP8** with **2a** (57 mg, 0.26 mmol), **1I** (58 mg, 0.20 mmol) and DBU (0.06 mL, 0.4 mmol). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 2/1; Rf 0.50 in EtOAc/Cyclohexane = 2/1) to give compound **3I** as a white solid (13 mg, 34%).

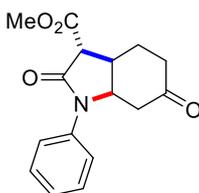
**Mp:** 200 °C.

**IR (cm<sup>-1</sup>):** 2976, 2914, 1782, 1721, 1447, 1356, 1285, 1244, 1153, 1107, 1033, 1015.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 8.00 (d, *J* = 7.2 Hz, 2H), 7.76-7.69 (m, 1H), 7.61 (t, *J* = 7.6 Hz, 2H), 7.37-7.28 (m, 3H), 7.22-7.14 (m, 2H), 5.04 (d, *J* = 15.2 Hz, 1H), 4.01 (ddd, *J* = 11.5, 6.6, 5.0 Hz, 1H), 3.84 (d, *J* = 15.2 Hz, 1H), 3.84 (d, *J* = 4.1 Hz, 1H), 3.45-3.35 (m, 1H), 2.62 (dd, *J* = 15.6, 5.0 Hz, 1H), 2.48 (dd, *J* = 15.6, 6.6 Hz, 1H), 2.38-2.27 (m, 3H), 2.03-1.92 (m, 1H).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ 207.6, 164.9, 137.4, 134.4, 134.2, 129.5, 129.1, 128.9, 128.0, 127.8, 53.2, 44.5, 40.9, 36.4, 30.9, 26.3.

**HRMS (ESI)** calcd for  $C_{21}H_{21}NO_4SNa$   $[M+Na]^+$ : 406.1083; found: 406.1097.



**methyl 2,6-dioxo-1-phenyloctahydro-1H-indole-3-carboxylate 3o**

Following **GP8** with **2a** (85 mg, 0.39 mmol), **1o** (58 mg, 0.30 mmol) and DBU (0.09 mL, 0.6 mmol). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 2/1; Rf 0.31 in EtOAc/Cyclohexane = 2/1) to give compound **3o** (60 mg, 70%) as a white solid.

**Mp:** 96 °C.

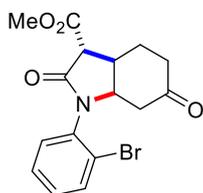
**IR (cm<sup>-1</sup>):** 3056, 2953, 1741, 1698, 1596, 1496, 1398, 1264, 1166.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.39-7.34 (m, 2H), 7.29-7.25 (m, 2H), 7.25-7.20 (m, 1H), 4.73 (ddd, *J* = 12.3, 6.9, 5.4 Hz, 1H), 3.78 (s, 3H), 3.49 (d, *J* = 5.6 Hz, 1H), 3.21-3.14 (m, 1H), 2.65 (dd, *J* = 15.8, 5.4 Hz, 1H), 2.48-

2.39 (m, 2H), 2.34 (ddd,  $J = 17.8, 8.4, 4.9$  Hz, 1H), 2.25-2.16 (m, 1H), 2.02-1.92 (m, 1H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  208.0, 169.5, 168.0, 136.1, 129.3, 126.9, 124.3, 57.2, 54.7, 52.9, 41.6, 36.7, 33.7, 25.5.

HRMS (ESI) calcd for  $\text{C}_{16}\text{H}_{17}\text{NO}_4\text{Na}$   $[\text{M}+\text{Na}]^+$ : 310.1050; found: 310.1046.



### methyl 1-(2-bromophenyl)-2,6-dioxooctahydro-1H-indole-3-carboxylate **3p**

Following **GP8** with **2a** (85 mg, 0.39 mmol), **1p** (82 mg, 0.30 mmol) and DBU (0.09 mL, 0.60 mmol). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 2/1;  $R_f$  0.29 in EtOAc/Cyclohexane = 2/1) to give compound **3p** as a white solid (70 mg, 64%).

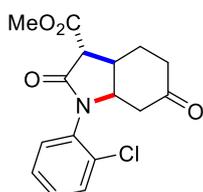
**Mp**: 129 °C.

**IR** ( $\text{cm}^{-1}$ ): 3057, 2953, 1708, 1477, 1264, 1165.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.63 (dd,  $J = 8.0, 1.4$  Hz, 1H), 7.35 (td,  $J = 7.6, 1.4$  Hz, 1H), 7.22 (td,  $J = 7.9, 1.6$  Hz, 1H), 7.12 (dd,  $J = 7.9, 1.4$  Hz, 1H), 4.69 (td,  $J = 7.9, 5.8$  Hz, 1H), 3.80 (s, 3H), 3.45 (d,  $J = 5.0$  Hz, 1H), 3.33-3.20 (m, 1H), 2.53-2.41 (m, 3H), 3.45 (ddd,  $J = 17.7, 9.2, 4.8$  Hz, 1H), 2.27-2.18 (m, 1H), 2.07-1.97 (m, 1H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  208.1, 169.2, 168.1, 134.9, 133.8, 130.1 (2C), 128.5, 122.9, 57.7, 54.1, 52.9, 41.3, 37.0, 34.3, 25.7.

HRMS (ESI) calcd for  $\text{C}_{16}\text{H}_{16}\text{BrNO}_4\text{Na}$   $[\text{M}+\text{Na}]^+$ : 388.0155; found: 388.0139.



### methyl 1-(2-chlorophenyl)-2,6-dioxooctahydro-1H-indole-3-carboxylate **3q**

Following **GP8** with **2a** (57 mg, 0.26 mmol), **1q** (56 mg, 0.20 mmol) and DBU (0.06 mL, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 2/1;  $R_f$  0.25 in EtOAc/Cyclohexane = 2/3) to give compound **3q** as a white solid (55 mg, 86%).

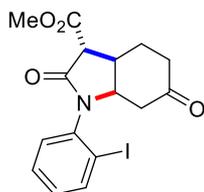
**Mp**: 123 °C.

**IR** ( $\text{cm}^{-1}$ ): 2953, 1743, 1699, 1480, 1441, 1400, 1287, 1266, 1199, 1163, 1061, 1028.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.43-7.38 (m, 1H), 7.28-7.23 (m, 2H), 7.12-7.05 (m, 1H), 4.69-4.61 (m, 1H), 3.76 (s, 3H), 3.40 (d, *J* = 4.8 Hz, 1H), 3.25-3.18 (m, 1H), 2.48-2.29 (m, 4H), 2.23-2.14 (m, 1H), 2.02-1.92 (m, 1H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 208.1, 169.3, 168.3, 133.4, 132.9, 130.7, 130.0, 129.9, 127.9, 57.8, 54.2, 53.0, 41.3, 37.0, 34.4, 25.8.

**HRMS (ESI)** calcd for C<sub>16</sub>H<sub>16</sub>ClNO<sub>4</sub>Na [M+Na]<sup>+</sup>: 344.0660; found: 344.0669.



**methyl 1-(2-iodophenyl)-2,6-dioxooctahydro-1H-indole-3-carboxylate 3r**

Following **GP8** with **2a** (57 mg, 0.26 mmol), **1r** (64 mg, 0.20 mmol) and DBU (0.06 mL, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 2/1; R<sub>f</sub> 0.25 in EtOAc/Cyclohexane = 2/3) to give compound **3r** as a white solid (65 mg, 79%).

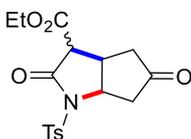
**Mp:** 125 °C.

**IR (cm<sup>-1</sup>):** 2952, 1742, 1699, 1469, 1400, 1267, 1199, 1164, 1095, 1022.

**<sup>1</sup>H NMR (600 MHz, DMSO-d<sub>6</sub>, 375K):** δ 7.95 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.48 (td, *J* = 7.6, 1.4 Hz, 1H), 7.19 (d, *J* = 7.7 Hz, 1H), 7.15 (td, *J* = 7.7, 1.4 Hz, 1H), 4.64-4.59 (m, 1H), 3.75 (s, 3H), 3.63 (d, *J* = 6.8 Hz, 1H), 3.27-3.22 (m, 1H), 2.54-2.49 (m, 1H), 2.46-2.43 (m, 1H), 2.43-2.40 (m, 1H), 2.34 (ddd, *J* = 17.2, 9.4, 4.9 Hz, 1H), 2.23-2.17 (m, 1H), 2.04-1.97 (m, 1H).

**<sup>13</sup>C NMR (175 MHz, DMSO-d<sub>6</sub>, 375K):** δ 207.4, 168.8, 167.3, 139.2, 138.8, 129.5 (2C), 128.7, 98.2, 57.0, 53.1, 51.7, 40.9, 36.2, 34.0, 24.2.

**HRMS (ESI)** calcd for C<sub>16</sub>H<sub>16</sub>I<sup>16</sup>NO<sub>4</sub>Na [M+Na]<sup>+</sup>: 436.0016; found: 436.0031.



**ethyl 2,5-dioxo-1-tosylcyclopenta[b]pyrrole-3-carboxylate 4a**

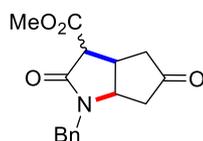
Following **GP9** with **2b** (79 mg, 0.39 mmol) and **1a** (86 mg, 0.30 mmol). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/1; R<sub>f</sub> 0.15 in Et<sub>2</sub>O/Petane = 2/1) to give compound **4a** as a 80/20 diastereomeric mixture as a colorless oil (68mg, 62%).

**IR (cm<sup>-1</sup>):** 3062, 2983, 2923, 1922, 1735, 1595, 1453, 1406, 1361, 1309, 1267, 1221, 1166, 1130, 1085, 1024.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, diastereomeric mixture):** δ 7.90 (d, *J* = 8.3 Hz, 4H, 2H major + 2H minor diast.), 7.34 (d, *J* = 8.3 Hz, 4H, 2H major + 2H minor diast.), 4.95 (dt, *J* = 7.6, 5.0 Hz, 2H, 1H major + 1H minor diast.), 4.19-4.00 (m, 4H, 2H major + 2H minor diast.), 3.68 (d, *J* = 9.9 Hz, 1H, minor diast.), 3.47-3.34 (m, 2H, 1H major + 1H minor diast.), 3.30 (d, *J* = 6.8 Hz, 1H, major), 2.98-2.83 (m, 2H, 1H major + 1H minor diast.), 2.83-2.53 (m, 4H, 2H major + 2H minor diast.), 2.44 (s, 6H, 3H major + 3H minor diast.), 2.39 (d, *J* = 4.7 Hz, 1H, minor diast.), 2.31-2.21 (m, 1H, major), 1.20 (t, *J* = 7.1 Hz, 3H, major), 1.13 (t, *J* = 7.1 Hz, 3H, minor diast.).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, diastereomeric mixture):** δ 212.9 (minor), 212.8 (major), 168.0 (minor), 167.5 (major), 166.6 (2C, major + minor), 145.6 (2C, major + minor), 134.7 (minor), 134.4 (major), 129.6 (2C, minor), 129.6(2C, major), 128.2 (2C, major), 128.1 (2C, minor), 62.1 (major), 62.0 (minor), 59.1 (minor), 58.8 (major), 54.6 (major), 52.8 (minor), 44.1 (major), 43.5 (minor), 41.7 (major), 39.1 (minor), 36.3 (major), 34.5 (minor), 21.5 (2C, major + minor), 13.7 (major), 13.5 (minor).

**HRMS (ESI)** calcd for C<sub>17</sub>H<sub>19</sub>NO<sub>6</sub>SNa [M+Na]<sup>+</sup>: 388.0825; found: 388.0823.



**methyl 1-benzyl-2,5-dioxooctahydrocyclopenta[*b*]pyrrole-3-carboxylate **4g****

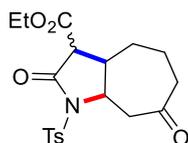
Following **GP10** with **2b** (53 mg, 0.26 mmol), **1g** (42 mg, 0.20 mmol) and DBU (0.06 mL, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 2/1; R<sub>f</sub> 0.44 in EtOAc/Cyclohexane = 2/1) to give compound **4g** as a 85/15 diastereomeric mixture as a colorless oil (28 mg, 49%).

**IR (cm<sup>-1</sup>):** 2956, 2919, 1737, 1684, 1540, 1495, 1437, 1402, 1250, 1159, 1080, 1022.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, diastereomeric mixture):** δ 7.37-7.28 (m, 6H, 3H major + 3H minor diast.), 7.25-7.18 (m, 4H, 2H major + 2H minor diast.), 4.96 (d, *J* = 15.0 Hz, 1H, major diast.), 4.96 (d, *J* = 15.0 Hz, 1H, minor diast.), 4.30-4.21 (m, 1H, major), 4.14-3.99 (d, *J* = 15.0 Hz, 3H, 1H major + 2H minor diast.), 3.80 (s, 3H, major diast.), 3.75 (s, 3H, minor diast.), 3.39 (d, *J* = 3.4 Hz, 1H, major), 3.32-3.32 (m, 2H, 1H major + 1H minor diast.), 2.66 (dd, *J* = 19.3, 9.7 Hz, 2H, 1H major + 1H minor diast.), 2.44-2.28 (m, 5H, 2H major + 3H minor diast.), 2.17 (dd, *J* = 19.3, 6.8 Hz, 2H, 1H major + 1H minor diast.).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, diastereomeric mixture):** δ 213.7 (2C, major + minor), 169.4 (major), 169.3 (minor), 169.0 (major), 168.8 (minor), 135.4 (minor), 135.1 (major), 128.9 (2C, minor), 128.8 (2C, major), 128.2 (2C, minor), 128.0 (2C, major), 127.9 (2C, major + minor), 57.6 (2C, major + minor), 55.1 (major), 52.8 (major), 52.5 (minor), 52.0 (minor), 45.7 (minor), 45.3 (major), 42.1 (major), 41.6 (minor), 41.5 (major), 39.1 (minor), 36.4 (major), 35.1 (minor).

**HRMS (ESI)** calcd for  $C_{16}H_{17}NO_4Na$   $[M+Na]^+$ : 310.1050; found: 310.1046.



**ethyl 2,7-dioxo-1-tosyldecahydrocyclohepta[b]pyrrole-3-carboxylate 5a**

Following **GP7** with **2c** (65 mg, 0.39 mmol) and **1a** (86 mg, 0.30 mmol) at 60 °C. The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/2;  $R_f$  0.24 in EtOAc/Cyclohexane = 2/3) to give compound **5a** as a 66/34 diastereomeric mixture as a waxy solid (85 mg, 72%).

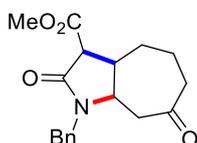
**Mp:** 55 °C.

**IR (cm<sup>-1</sup>):** 2929, 2862, 1754, 1738, 1595, 1284, 1165, 1095, 1023.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, diastereomeric mixture):**  $\delta$  7.96-7.86 (m, 4H, 2H major + 2H minor), 7.36-7.29 (m, 4H, 2H major + 2H minor), 4.80-4.68 (m, 1H, major), 4.44 (ddd,  $J$  = 13.8, 9.0, 4.9 Hz, 1H, minor), 4.25-4.09 (m, 4H, 2H major + 2H minor), 3.77 (dd,  $J$  = 17.3, 4.9 Hz, 1H, minor), 3.37 (d,  $J$  = 12.2 Hz, 1H, major), 3.28 (d,  $J$  = 12.2 Hz, 1H, minor), 3.18-3.05 (m, 2H, major), 2.74-2.45 (m, 6H, 3H major + 3H minor), 2.43 (s, 6H, 3H major + 3H minor), 2.36-2.26 (m, 1H, minor), 2.08-1.86 (m, 4H, 2H major + 2H minor), 1.83-1.52 (m, 4H, 2H major + 2H minor), 1.29-1.22 (m, 6H, 3H major + 3H minor).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, diastereomeric mixture):**  $\delta$  208.5 (minor), 207.2 (major), 167.9 (minor), 166.9 (3C, 2Cmajor + minor), 145.6 (2C, major + minor), 135.5 (minor), 135.0 (major), 129.8 (2C, minor), 129.7 (2C, major), 128.5 (2C, major), 128.1 (2C, minor), 62.2 (major), 59.7 (minor), 56.7 (major), 54.7 (minor), 53.2 (major), 49.2 (minor), 44.5 (major), 43.9 (minor), 43.2 (minor), 42.3 (major), 39.8 (major), 32.8 (minor), 26.9 (minor), 26.8 (major), 24.9 (minor), 21.7 (2C, major + minor), 19.4 (major), 14.1 (minor), 14.0 (major).

**HRMS (ESI)** calcd for  $C_{19}H_{23}NO_6SNa$   $[M+Na]^+$ : 416.1138; found: 416.1140.



**methyl 1-benzyl-2,7-dioxodecahydrocyclohepta[b]pyrrole-3-carboxylate 5g**

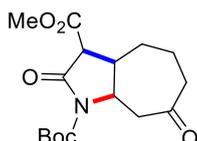
Following **GP8** with **2c** (44 mg, 0.26 mmol), **1g** (86 mg, 0.20 mmol) and DBU (0.06 mL, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/1;  $R_f$  0.45 in EtOAc/Cyclohexane = 2/1) to give compound **5g** as a colorless oil (35 mg, 55%).

**IR (cm<sup>-1</sup>):** 2924, 2859, 1740, 1688, 1435, 1363, 1275, 1203, 1163.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 7.37-7.27 (m, 3H), 7.26-7.20 (m, 2H), 4.98 (d, *J* = 15.2 Hz, 1H), 4.01 (d, *J* = 15.2 Hz, 1H), 3.81 (s, 3H), 3.72 (ddd, *J* = 13.1, 8.1, 4.8 Hz, 1H), 3.37 (d, *J* = 9.1 Hz, 1H), 3.00-2.88 (m, 1H), 2.65-2.53 (m, 2H), 2.49-2.38 (m, 2H), 1.98-1.85 (m, 2H), 1.80-1.69 (m, 1H), 1.64-1.53 (m, 1H).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ 208.3, 169.8, 168.7, 135.5, 128.9, 127.9 (2C), 55.0, 53.6, 52.8, 44.7, 44.2, 42.7, 40.0, 28.3, 20.5.

**HRMS (ESI)** calcd for C<sub>18</sub>H<sub>21</sub>NO<sub>4</sub>Na [M+Na]<sup>+</sup>: 338.1363; found: 338.1371.



### 1-*tert*-butyl 3-methyl 2,7-dioxooctahydrocyclohepta[*b*]pyrrole-1,3(2*H*)-dicarboxylate **5i**

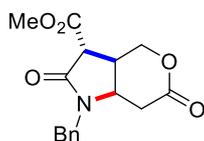
Following **GP8** with **2c** (44 mg, 0.26 mmol), **1i** (44 mg, 0.20 mmol) and DBU (0.06 mL, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/1; R<sub>f</sub> 0.33 in EtOAc/Cyclohexane = 1/1) to give compound **5i** as a colorless oil (21 mg, 33%).

**IR (cm<sup>-1</sup>):** 2927, 2863, 1789, 1733, 1707, 1360, 1298, 1251, 1154, 1095.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 4.45 (ddd, *J* = 11.8, 8.2, 3.2 Hz, 1H), 3.81 (s, 3H), 3.46 (d, *J* = 12.2 Hz, 1H), 3.12-3.00 (m, 1H), 2.87 (dd, *J* = 14.1, 3.3 Hz, 1H), 2.71-2.64 (m, 1H), 2.63-2.57 (m, 1H), 2.52-2.43 (m, 1H), 2.02-1.90 (m, 2H), 1.76-1.68 (m, 1H), 1.67-1.62 (m, 1H), 1.53 (s, 9H).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ 207.7, 168.3, 167.1, 149.0, 84.2, 55.2, 54.2, 53.0, 43.5, 43.2, 38.4, 27.9, 27.1, 19.5.

**HRMS (ESI)** calcd for C<sub>16</sub>H<sub>23</sub>NO<sub>6</sub>Na [M+Na]<sup>+</sup>: 348.1418; found: 348.1431.



### methyl 1-benzyl-2,6-dioxooctahydropyrano[4,3-*b*]pyrrole-3-carboxylate **6g**

Following **GP8** with **2d** (85 mg, 0.39 mmol), **1g** (62 mg, 0.30 mmol) and DBU (0.09 mL, 0.6 mmol). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 3/1; R<sub>f</sub> 0.31 in EtOAc/Cyclohexane = 3/1) to give compound **6g** (13 mg, 14%) as a white solid.

**Mp:** 132 °C.

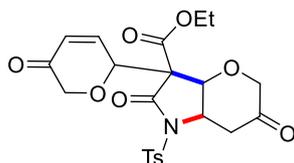
**IR (cm<sup>-1</sup>):** 2952, 2929, 1735, 1680, 1427, 1359, 1238, 1164, 1080.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 7.39-7.31 (m, 3H), 7.23-7.19 (m, 2H), 5.10 (d, *J* = 15.2 Hz, 1H), 4.37 (dd, *J* = 12.2,

4.1 Hz, 1H), 4.23 (dd,  $J = 12.2, 4.4$  Hz, 1H), 4.13-4.06 (m, 1H), 3.95 (d,  $J = 15.2$  Hz, 1H), 3.84 (s, 3H), 3.57 (d,  $J = 5.4$  Hz, 1H), 3.24-3.14 (m, 1H), 2.75-2.60 (m, 2H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  169.5, 169.2, 167.9, 134.5, 129.1, 128.2, 128.0, 68.0, 53.2, 52.1, 50.7, 44.7, 33.8, 32.7.

HRMS (ESI) calcd for  $\text{C}_{16}\text{H}_{17}\text{NO}_5\text{Na}$   $[\text{M}+\text{Na}]^+$ : 326.0999; found: 326.0989.



**ethyl 2,6-Dioxo-3-(5-oxo-5,6-dihydro-2H-pyran-2-yl)-1-tosylpyrrole-3-carboxylate 7a**

Following **GP7** with **2g** (144 mg, 0.66 mmol) and **1a** (86 mg, 0.30 mmol) at 60 °C. The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 2/3;  $R_f$  0.25 in EtOAc/Cyclohexane = 1/1) to give compound **7a** as a white solid (43 mg, 30%, only one diastereomer).

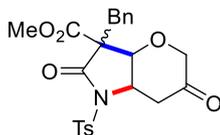
**Mp**: 212 °C.

**IR** ( $\text{cm}^{-1}$ ): 2987, 2929, 1736, 1694, 1366, 1266, 1176, 1104, 1072, 1018.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.82 (d,  $J = 8.3$  Hz, 2H), 7.25 (d,  $J = 8.3$  Hz, 2H), 6.98 (dd,  $J = 10.7, 1.5$  Hz, 1H), 5.98 (dd,  $J = 10.7, 2.4$  Hz, 1H), 4.88 (dd,  $J = 3.9, 2.2$  Hz, 1H), 4.54-4.50 (m, 1H), 4.50-4.42 (m, 1H), 4.33-4.22 (m, 3H), 3.88 (dd,  $J = 16.1, 2.1$  Hz, 1H), 3.86 (d,  $J = 18.2$  Hz, 1H), 3.65 (d,  $J = 16.1$  Hz, 1H), 3.40 (dd,  $J = 15.0, 5.8$  Hz, 1H), 3.11 (dd,  $J = 15.0, 9.1$  Hz, 1H), 2.42 (s, 3H), 1.24 (t,  $J = 7.1$  Hz, 3H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  206.2, 191.8, 167.3, 164.8, 146.9, 146.4, 134.0, 129.4, 128.6, 127.1, 76.4, 74.6, 73.3, 71.6, 64.2, 62.7, 56.8, 42.6, 21.6, 13.9.

HRMS (ESI) calcd for  $\text{C}_{22}\text{H}_{23}\text{NO}_9\text{SNa}$   $[\text{M}+\text{Na}]^+$ : 500.0986; found: 500.0977.



**methyl 3-benzyl-2,6-dioxo-1-tosylpyrrole-3-carboxylate 7f**

Following **GP7** with **2g** (57 mg, 0.26 mmol) and **1f** (73 mg, 0.20 mmol). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/2;  $R_f$  0.60 in EtOAc/Cyclohexane = 1/1) to give compound **7f** as a 75/25 diastereomeric mixture as a white solid (74 mg, 81%).

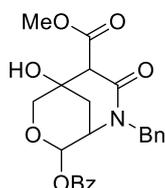
**Mp:** 160 °C.

**IR (cm<sup>-1</sup>):** 2921, 2852, 1732, 1594, 1496, 1360, 1168, 1117, 1079, 1032.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>, diastereomeric mixture):** δ 7.93-7.85 (m, 4H, 2H major + 2H minor diast.), 7.39-7.33 (m, 4H, 2H major + 2H minor diast.), 7.23-6.90 (m, 10H, 5H major + 5H minor diast.), 4.64 (ddd, *J* = 17.3, 6.5, 4.9 Hz, 1H, minor diast.), 4.38 (d, *J* = 4.9 Hz, 1H, minor diast.), 4.30-4.23 (m, 2H, 1H major + 1H minor diast.), 4.16 (d, *J* = 18.1 Hz, 1H, major diast.), 3.99-3.90 (m, 2H, 1H major + 1H minor diast.), 3.73 (d, *J* = 18.1 Hz, 1H, major diast.), 3.73 (s, 3H, major diast.), 3.49-3.43 (m, 4H, 1H major + 3H minor diast.), 3.38-3.21 (m, 5H, 2H major + 3H minor diast.), 3.03 (dd, *J* = 14.8, 10.7 Hz, 1H, major diast.), 2.90 (dd, *J* = 15.9, 6.4 Hz, 1H, minor diast.), 2.50 (s, 3H, major diast.), 2.45 (s, 3H, minor diast.).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, diastereomeric mixture):** δ 206.2 (minor), 206.1 (major), 169.6 (major), 168.2 (minor), 167.5 (major), 166.4 (minor), 145.7 (2C, major + minor), 135.3 (minor), 134.9 (major), 134.6 (minor), 134.0 (major), 130.1 (2C, major), 129.7 (2C, major), 129.6 (2C, minor), 129.5 (2C, minor), 128.9 (2C, major), 128.6 (2C, major), 128.5 (2C, minor), 128.4 (2C, minor), 127.5 (major), 127.2 (minor), 73.7 (minor), 73.2 (2C, major + minor), 72.6 (major), 62.8 (minor), 61.8 (major), 56.8 (minor), 55.0 (major), 53.1 (2C, major + minor), 42.5 (minor), 41.1 (major), 37.8 (major), 33.2 (minor), 21.7 (2C, major + minor).

**HRMS (ESI)** calcd for C<sub>23</sub>H<sub>23</sub>NO<sub>7</sub>SNa [M+Na]<sup>+</sup>: 480.1087; found: 480.1071.



**methyl 8-(benzoyloxy)-2-benzyl-5-hydroxy-3-oxo-7-oxa-2-azabicyclo[3.3.1]nonane-4-carboxylate **8g****

To a solution of **2g** (66 mg, 0.3 mmol, 1.5 equiv) in THF (3 mL) were added **1g** (42 mg, 0.2 mmol, 1 equiv) and DBU (0.09 mL, 0.6 mmol, 3 equiv) at -78 °C. Then the reaction was slowly allowed to warm to 0 °C. After stirred for 1 h, the solution was diluted with an equal volume of EtOAc and then washed with 1M HCl solution and brine. The mixture was dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/1; R<sub>f</sub> 0.38 in EtOAc/Cyclohexane = 1/1) to give compound **8g** as a white solid (115 mg, 90%).

**Mp:** 156 °C.

**IR (cm<sup>-1</sup>):** 3301, 2933, 1735, 1628, 1444, 1265, 1124, 1080, 1056.

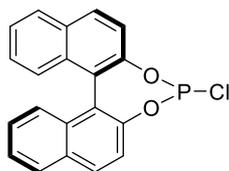
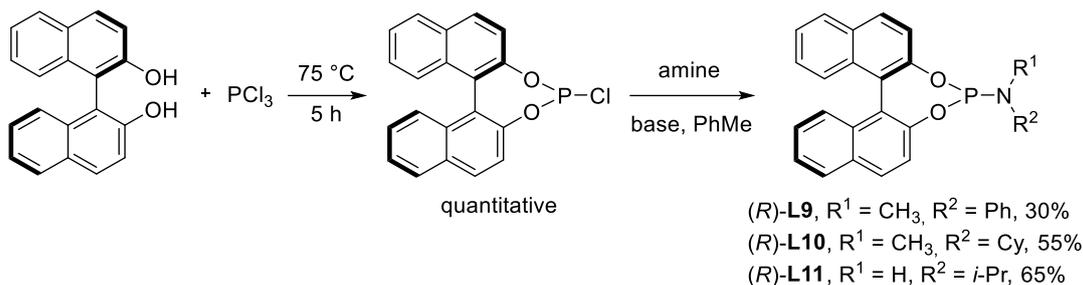
**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 8.11-8.07 (m, 2H), 7.68-7.62 (m, 1H), 7.54-7.48 (m, 2H), 7.38-7.34 (m, 2H), 7.30-7.23 (m, 2H), 7.21-7.14 (m, 1H), 6.25 (d, *J* = 1.6 Hz, 1H), 5.05 (d, *J* = 15.0 Hz, 1H), 4.41 (d, *J* = 15.0 Hz, 1H), 3.84-3.78 (m, 2H), 3.71 (s, 3H), 3.61 (br s, 1H), 3.56 (d, *J* = 11.4 Hz, 1H), 2.62-2.57 (m, 1H), 2.49-2.42 (m,

2H).

$^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  170.7, 166.0, 164.5, 139.2, 133.8, 129.8, 129.2, 128.6, 128.4, 127.2, 126.8, 92.8, 81.2, 65.2, 53.0, 50.8, 43.6, 35.3, 31.0.

HRMS (ESI) calcd for  $\text{C}_{23}\text{H}_{23}\text{NO}_7\text{Na}$   $[\text{M}+\text{Na}]^+$ : 448.1367; found: 448.1379.

### 3.4 Chiral HPLC Chromatograms of compounds relating to Chapter 2

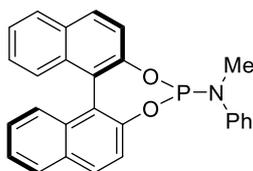


#### (*R*)-(+)-1,1'-binaphthyl-2,2'-dioxychlorophosphine

A mixture of (*R*)-BINOL (286 mg, 1.0 mmol) and phosphorus trichloride (1.8 mL, 20 mmol) was stirred for 5 h at 75 °C. Then, the reaction mixture was concentrated in vacuo to remove the excess of phosphorus trichloride. The residue was twice coevaporated with anhydrous toluene. A white precipitate was virtually pure product, the yield was quantitative. These data are in good agreement with those reported in the literature.<sup>[158]</sup>

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.01 (dd,  $J = 8.8, 6.1$  Hz, 2H), 7.98-7.93 (m, 2H), 7.53 (dd,  $J = 8.8, 1.0$  Hz, 1H), 7.51-7.44 (m, 3H), 7.41-7.36 (m, 2H), 7.34-7.27 (m, 2H).

$^{31}\text{P}$  NMR (162MHz,  $\text{CDCl}_3$ ):  $\delta$  178.3.



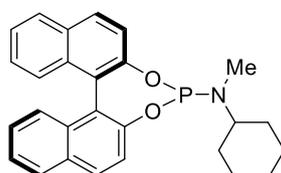
#### (BINOL)PN(Me)Ph

<sup>158</sup> Smith, C. R.; RajanBabu, T. V. *Org. Lett.*, **2008**, *10*, 1657-1659.

Following a slightly modified procedure described by Takacs:<sup>[92]</sup> To a solution of *N*-methylaniline (22  $\mu$ L, 0.2 mmol) and (*R*)-(+)-1,1'-binaphthyl-2,2'-dioxchlorophosphine (70 mg, 0.2 mmol) in dry THF (2 mL) at -78  $^{\circ}$ C was added triethylamine (31  $\mu$ L, 0.22 mmol) dropwise. The reaction was allowed to warm to room temperature and stirred for overnight. Then filtered under nitrogen through a pad of celite, the celite was further washed with dry THF and the solvents were under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: DCM/Cyclohexane = 1/4; Rf 0.48 in DCM/Cyclohexane = 1/3) to give compound (**R**)-**L9** as a white solid (25 mg, 30%). These data are in good agreement with those reported in the literature.<sup>[92c]</sup>

**H NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  8.01 (d, *J* = 8.8 Hz, 1H), 7.99-7.89 (m, 3H), 7.57 (dd, *J* = 8.8, 1.0 Hz, 1H), 7.48-7.26 (m, 11H), 7.16-7.09 (m, 1H), 2.67 (d, *J* = 2.5 Hz, 3H).

**<sup>31</sup>P NMR (162MHz, CDCl<sub>3</sub>):**  $\delta$  143.71.



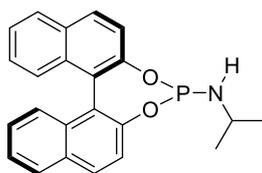
**(BINOL)PN(Me)Cy**

Following the procedure described by Lefort:<sup>[159]</sup> To a solution of *N*-methylcyclohexylamine (39  $\mu$ L, 0.3 mmol) and (*R*)-(+)-1,1'-binaphthyl-2,2'-dioxchlorophosphine (105 mg, 0.3 mmol) in dry toluene (3 mL) at -78  $^{\circ}$ C was added triethylamine (46  $\mu$ L, 0.33 mmol) dropwise. The reaction was allowed to warm to room temperature and stirred for 2 h. Then filtered under nitrogen through a pad of celite, the celite was further washed with dry toluene and the solvents were under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: DCM/Cyclohexane = 1/5; Rf 0.41 in DCM/Cyclohexane = 1/5) to give compound (**R**)-**L10** as a white solid (70 mg, 55%). These data are in good agreement with those reported in the literature.

**H NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  7.96 (d, *J* = 8.8 Hz, 1H), 7.94-7.86 (m, 3H), 7.52 (dd, *J* = 8.7, 0.9 Hz, 1H), 7.45-7.38 (m, 4H), 7.36-7.33 (m, 1H), 7.30-7.21 (m, 2H), 3.25 (qt, *J* = 11.8, 3.5 Hz, 1H), 2.67 (d, *J* = 5.4 Hz, 3H), 1.90-1.48 (m, 7H), 1.37-1.18 (m, 2H), 1.13-1.00 (m, 1H).

**<sup>31</sup>P NMR (162MHz, CDCl<sub>3</sub>):**  $\delta$  149.68.

<sup>159</sup> Lefort, L.; Boogers, J. A. F.; Kuilman, T.; Vijn, R. J.; Janssen, J.; Straatman, H.; de Vries, J. G.; de Vries, A. H. *Org. Process Res. Dev.* **2010**, *14*, 568-573.



**(R)-O,O'-(1,1'-Dinaphthyl-2,2'-diyl)-N-i-propylphosphorus amidite**

Following the procedure described by Lefort:<sup>[160]</sup> To a solution of isopropylamine (29  $\mu$ L, 0.33 mmol) and (*R*)-(+)-1,1'-binaphthyl-2,2'-dioxylphosphine (105 mg, 0.3 mmol) in dry toluene (3 mL) at -78 °C was added triethylamine (88  $\mu$ L, 0.33 mmol) dropwise. The reaction was allowed to warm to room temperature and stirred for 2 h. Then filtered under nitrogen through a pad of celite, the celite was further washed with dry toluene and the solvents were under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent: Et<sub>3</sub>N/DCM = 1/9; R<sub>f</sub> 0.35 in Et<sub>3</sub>N/DCM = 1/9) to give compound (**R**)-**L11** as a white solid (70 mg, 55%). It was noteworthy that this ligand is easily oxidized in the air. These data are in good agreement with those reported in the literature.<sup>[160]</sup>

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):**  $\delta$  8.03-7.89 (m, 4H), 7.54 (d, *J* = 8.7 Hz, 1H), 7.49-7.17 (m, 7H), 3.68-3.40 (m, 1H), 3.00 (d, *J* = 9.4 Hz, 1H, NH), 1.25 (d, *J* = 6.5 Hz, 3H), 1.18 (d, *J* = 6.5 Hz, 3H)

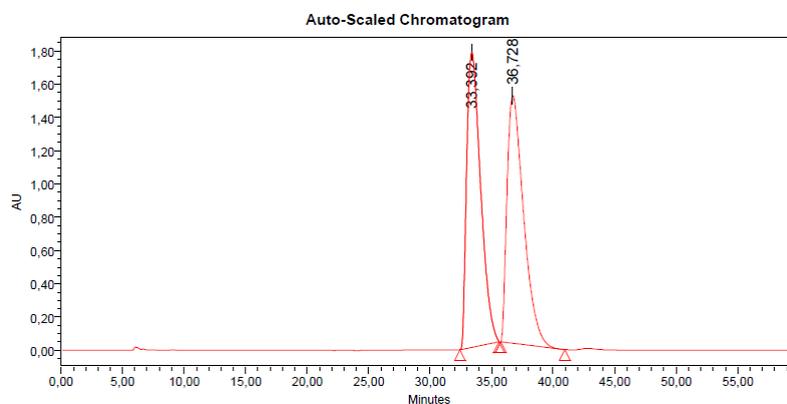
**<sup>31</sup>P NMR (121.5 MHz, CDCl<sub>3</sub>):**  $\delta$  152.19.

The enantioselectivity of substrate **2a** was determined by chiral HPLC : OJ-H, 90 : 10 hexane : isopropanol, 0.5 mL/min, 220 nm, 33.39 min (*R* enantiomer), 36.73 min (*S* enantiomer).

The enantioselectivity of compound **3a** was determined by chiral HPLC : AD-H, 60 : 40 hexane : isopropanol, 1.0 mL/min, 220 nm, 13.78 min (*S* enantiomer), 23.25 min (*R* enantiomer). Notably, it was found that the peak of retention time has a slight amount of migration under the sensitive and unstable measurement condition. For example, the compound **3a** gave a lightly different spectrum under the same condition in different high performance liquid chromatography machine (More details see Page 172 and 173).

<sup>160</sup> Lefort, L.; Boogers, J. A. F.; de Vries, A. H.; de Vries, J. G. *Org. Lett.* **2004**, *6*, 1733-1735.

SAMPLE INFORMATION			
Sample Name:	LY-A12 OJH 0.5ml/min 90/10	Acquired By:	malacia
Sample Type:	Unknown	Date Acquired:	02/06/2017 12:29:54
Vial:	1	Acq. Method Set:	HPLC Malacia Grad
Injection #:	4	Date Processed:	02/06/2017 13:35:37
Injection Volume:	20,00 ul	Processing Method:	Default
Run Time:	60,0 Minutes	Channel Name:	2487Channel 1
Sample Set Name:		Proc. Chnl. Descr.:	

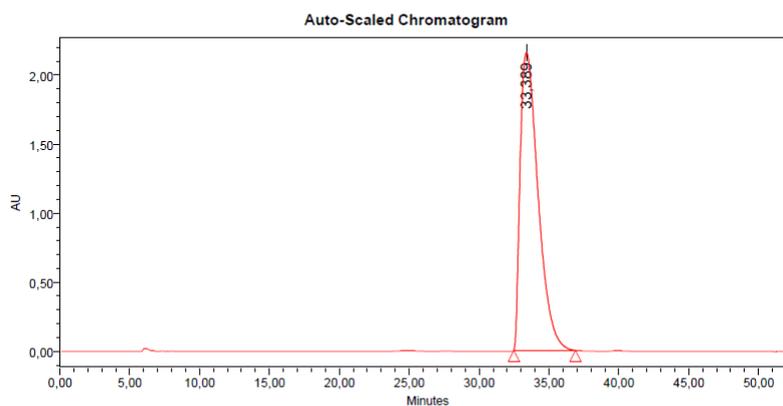


**Peak Results**

Name	RT	Area	Height	% Area
1	33,392	139666049	1773418	50,06
2	36,728	139330515	1488685	49,94

The starting material of racemic **2a**.

SAMPLE INFORMATION			
Sample Name:	LY-B94 OJH 0.5ml/min 90/10	Acquired By:	malacia
Sample Type:	Unknown	Date Acquired:	02/06/2017 13:33:49
Vial:	1	Acq. Method Set:	HPLC Malacia Grad
Injection #:	5	Date Processed:	02/06/2017 14:28:58
Injection Volume:	20,00 ul	Processing Method:	Default
Run Time:	60,0 Minutes	Channel Name:	2487Channel 1
Sample Set Name:		Proc. Chnl. Descr.:	

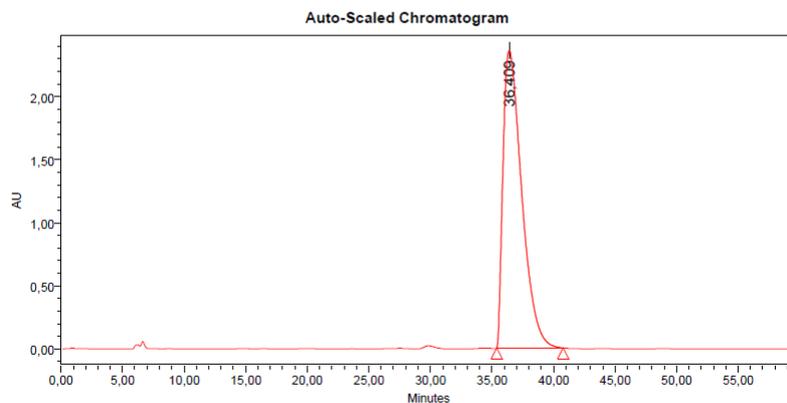


**Peak Results**

Name	RT	Area	Height	% Area
1	33,389	191805115	2153338	100,00

The starting material of (*R*)-**2a** (Scheme 84, top).

SAMPLE INFORMATION			
Sample Name:	LY-B88 OJH 0.5ml/min 90/10	Acquired By:	malacia
Sample Type:	Unknown	Date Acquired:	02/06/2017 15:27:55
Vial:	1	Acq. Method Set:	HPLC Malacia Grad
Injection #:	7	Date Processed:	02/06/2017 16:29:00
Injection Volume:	20,00 ul	Processing Method:	Default
Run Time:	60,0 Minutes	Channel Name:	2487Channel 1
Sample Set Name:		Proc. Chnl. Descr.:	

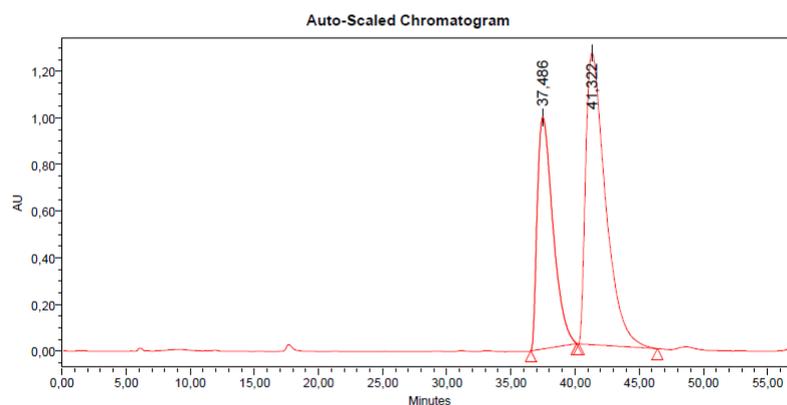


**Peak Results**

Name	RT	Area	Height	% Area
1	36,409	248570140	2357755	100,00

The starting material of (S)-2a (Scheme 84, bottom).

SAMPLE INFORMATION			
Sample Name:	LY-B69-Rc-S OJH 90/10 0.5ml/min	Acquired By:	malacia
Sample Type:	Unknown	Date Acquired:	21/04/2017 13:17:30
Vial:	1	Acq. Method Set:	HPLC Malacia Grad
Injection #:	3	Date Processed:	21/04/2017 14:17:14
Injection Volume:	20,00 ul	Processing Method:	Default
Run Time:	70,0 Minutes	Channel Name:	2487Channel 2
Sample Set Name:		Proc. Chnl. Descr.:	

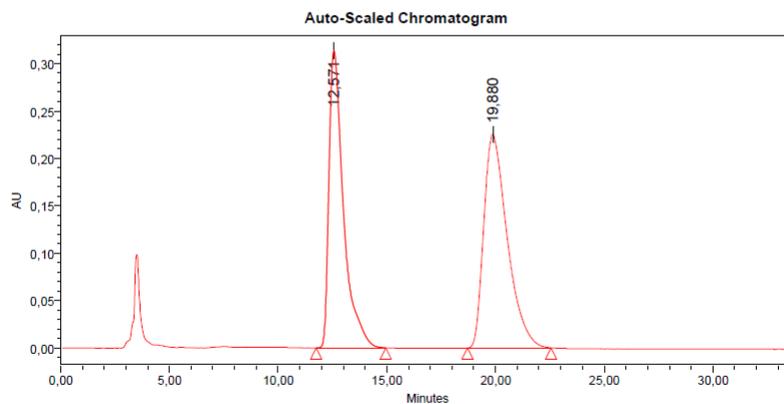


**Peak Results**

Name	RT	Area	Height	% Area
1	37,486	84677565	993107	38,70
2	41,322	134141711	1249979	61,30

The recovery starting material of 2a (Scheme 87, bottom).

SAMPLE INFORMATION			
Sample Name:	LY-B55 ADH 60/40 254nm 220nm	Acquired By:	malacia
Sample Type:	Unknown	Date Acquired:	04/04/2017 12:02:23
Vial:	1	Acq. Method Set:	HPLC Malacia Grad
Injection #:	4	Date Processed:	04/04/2017 12:42:26
Injection Volume:	20,00 ul	Processing Method:	Default
Run Time:	40,0 Minutes	Channel Name:	2487Channel 2
Sample Set Name:		Proc. Chnl. Descr.:	

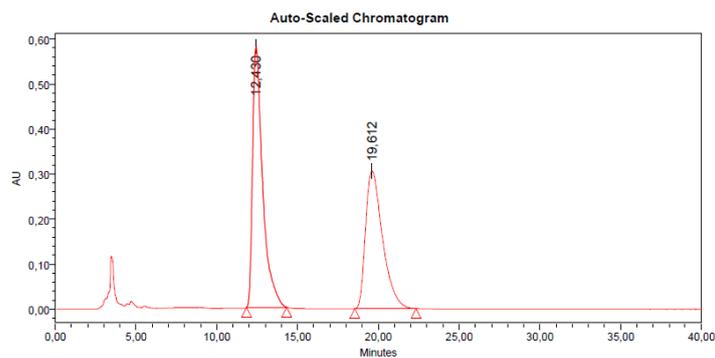


**Peak Results**

Name	RT	Area	Height	% Area
1	12,571	14424004	313509	46,03
2	19,880	16912158	225655	53,97

Compound **3a** (under (*R*)-BINAP, Table 4, entry 1, yield = 65%; ee = 8%).

SAMPLE INFORMATION			
Sample Name:	LY-B57-Syn ADH 60/40 254nm	Acquired By:	malacia
Sample Type:	Unknown	Date Acquired:	04/04/2017 14:47:43
Vial:	1	Acq. Method Set:	HPLC Malacia Grad
Injection #:	8	Date Processed:	04/04/2017 16:04:21
Injection Volume:	20,00 ul	Processing Method:	Default
Run Time:	40,0 Minutes	Channel Name:	2487Channel 2
Sample Set Name:		Proc. Chnl. Descr.:	

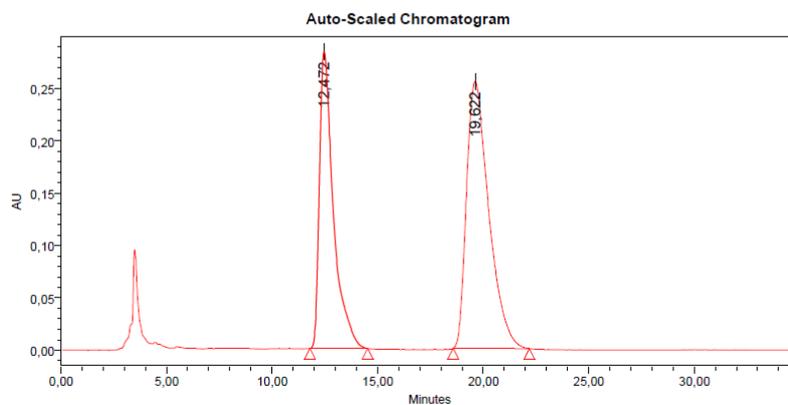


**Peak Results**

Name	RT	Area	Height	% Area
1	12,430	25107960	578645	52,92
2	19,612	22340585	305399	47,08

Compound **3a** (under (*R*)-SynPhos, Table 4, entry 2, yield = 52%; ee = 7%).

SAMPLE INFORMATION			
Sample Name:	LY-B57-Xyl ADH 60/40 254nm	Acquired By:	malacia
Sample Type:	Unknown	Date Acquired:	04/04/2017 14:11:24
Vial:	1	Acq. Method Set:	HPLC Malacia Grad
Injection #:	7	Date Processed:	04/04/2017 14:50:28
Injection Volume:	20,00 ul	Processing Method:	Default
Run Time:	40,0 Minutes	Channel Name:	2487Channel 2
Sample Set Name:		Proc. Chnl. Descr.:	

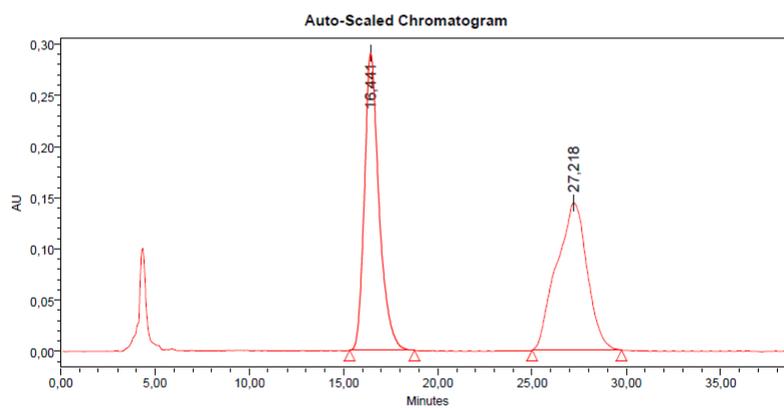


**Peak Results**

Name	RT	Area	Height	% Area
1	12,472	13028931	283662	41,09
2	19,622	18679345	255252	58,91

Compound **3a** (under (*R*)-xylyl-P-Phos, Table 4, entry 3, yield = 65%; ee = 18%).

SAMPLE INFORMATION			
Sample Name:	LY-B63 ADH 60/40 254nm 220nm	Acquired By:	malacia
Sample Type:	Unknown	Date Acquired:	13/04/2017 12:08:17
Vial:	1	Acq. Method Set:	HPLC Malacia Grad
Injection #:	3	Date Processed:	13/04/2017 12:50:15
Injection Volume:	20,00 ul	Processing Method:	Default
Run Time:	40,0 Minutes	Channel Name:	2487Channel 2
Sample Set Name:		Proc. Chnl. Descr.:	

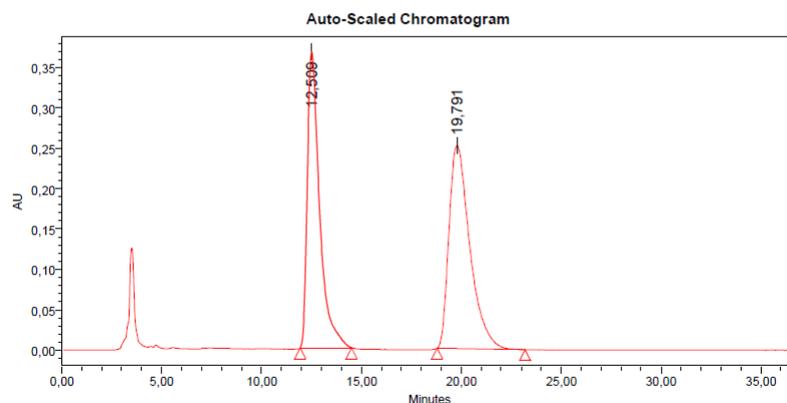


**Peak Results**

Name	RT	Area	Height	% Area
1	16,441	15663887	290038	49,11
2	27,218	16232258	143718	50,89

Compound **3a** (under SL-A101-1, Table 4, entry 4, yield = 74%; ee = 2%).

SAMPLE INFORMATION			
Sample Name:	LY-B56 ADH 60/40 254nm 220nm	Acquired By:	malacia
Sample Type:	Unknown	Date Acquired:	04/04/2017 12:51:14
Vial:	1	Acq. Method Set:	HPLC Malacia Grad
Injection #:	5	Date Processed:	04/04/2017 13:36:26
Injection Volume:	20,00 ul	Processing Method:	Default
Run Time:	40,0 Minutes	Channel Name:	2487Channel 2
Sample Set Name:		Proc. Chnl. Descr.:	

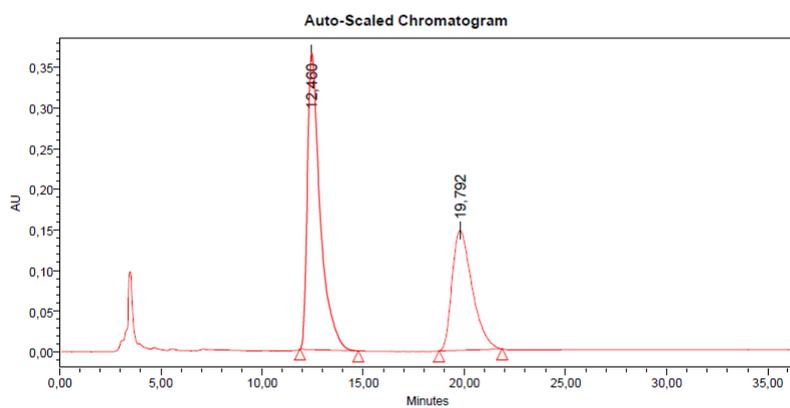


**Peak Results**

Name	RT	Area	Height	% Area
1	12,509	15657511	367379	46,27
2	19,791	18184603	251683	53,73

Compound **3a** (under (+)-DIOP, Table 4, entry 5, yield = 70%; ee = 8%).

SAMPLE INFORMATION			
Sample Name:	LY-B57-Tan ADH 60/40 254nm	Acquired By:	malacia
Sample Type:	Unknown	Date Acquired:	04/04/2017 13:33:43
Vial:	1	Acq. Method Set:	HPLC Malacia Grad
Injection #:	6	Date Processed:	04/04/2017 14:13:27
Injection Volume:	20,00 ul	Processing Method:	Default
Run Time:	40,0 Minutes	Channel Name:	2487Channel 2
Sample Set Name:		Proc. Chnl. Descr.:	

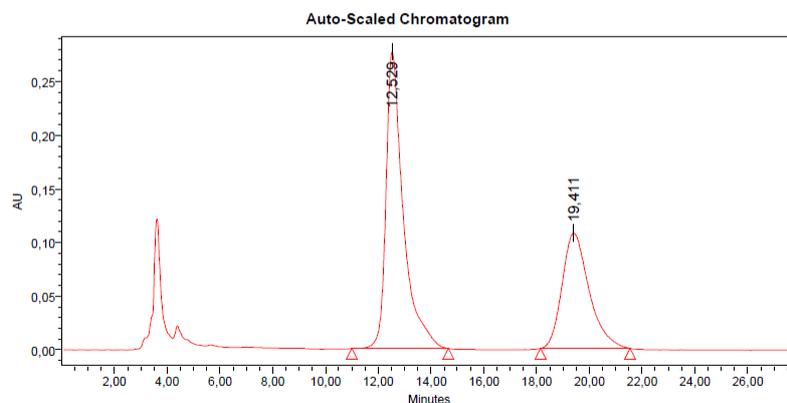


**Peak Results**

Name	RT	Area	Height	% Area
1	12,460	15988647	364598	61,10
2	19,792	10180310	147085	38,90

Compound **3a** (under (Sc,R)-TaniaPhos, Table 4, entry 7, yield = 82%; ee = 23%).

SAMPLE INFORMATION			
Sample Name:	LY-B58-New ADH 60/40 220 nm	Acquired By:	malacia
Sample Type:	Unknown	Date Acquired:	20/04/2017 14:55:26
Vial:	1	Acq. Method Set:	HPLC Malacia Grad
Injection #:	7	Date Processed:	20/04/2017 15:23:57
Injection Volume:	20,00 ul	Processing Method:	Default
Run Time:	40,0 Minutes	Channel Name:	2487Channel 2
Sample Set Name:		Proc. Chnl. Descr.:	

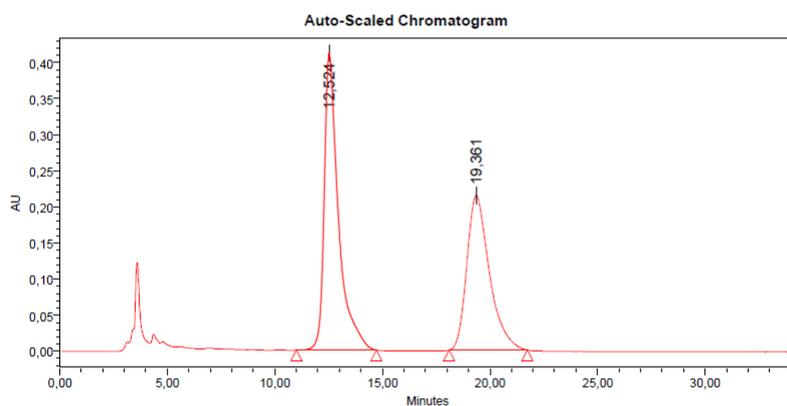


**Peak Results**

Name	RT	Area	Height	% Area
1	12,529	12542056	276370	62,18
2	19,411	7629369	107401	37,82

Compound **3a** (under(*Sc,R*)-TaniaPhos at 0 °C, Table 4, entry 8, yield = 61%; ee = 25%).

SAMPLE INFORMATION			
Sample Name:	LY-B62-New ADH 60/40 220 nm	Acquired By:	malacia
Sample Type:	Unknown	Date Acquired:	20/04/2017 14:20:09
Vial:	1	Acq. Method Set:	HPLC Malacia Grad
Injection #:	6	Date Processed:	20/04/2017 14:58:35
Injection Volume:	20,00 ul	Processing Method:	Default
Run Time:	40,0 Minutes	Channel Name:	2487Channel 2
Sample Set Name:		Proc. Chnl. Descr.:	

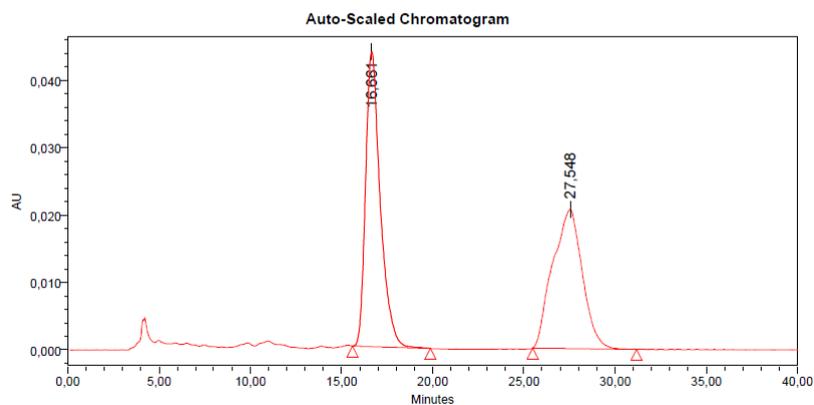


**Peak Results**

Name	RT	Area	Height	% Area
1	12,524	18826664	411051	54,73
2	19,361	15572946	214043	45,27

Compound **3a** (under (*Rc,R*)-TaniaPhos, Table 4, entry 9, yield = 85%; ee = 10%).

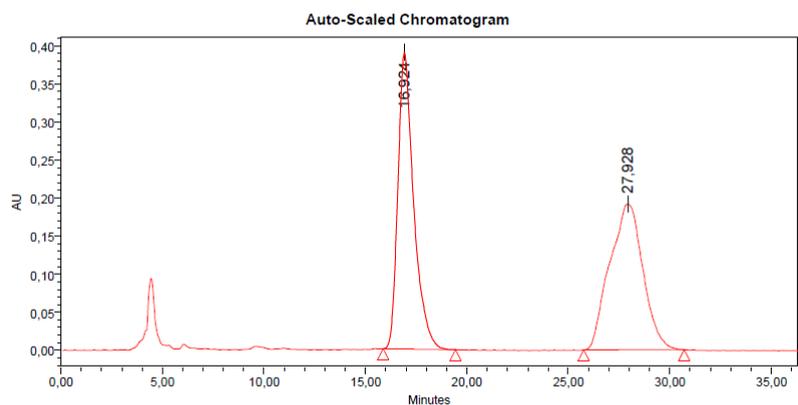
SAMPLE INFORMATION			
Sample Name:	LY-B61 ADH 60/40 254nm 220nm	Acquired By:	malacia
Sample Type:	Unknown	Date Acquired:	11/04/2017 14:13:04
Vial:	1	Acq. Method Set:	HPLC Malacia Grad
Injection #:	5	Date Processed:	11/04/2017 15:08:18
Injection Volume:	20,00 ul	Processing Method:	Default
Run Time:	40,0 Minutes	Channel Name:	2487Channel 1
Sample Set Name:		Proc. Chnl. Descr.:	



Peak Results				
Name	RT	Area	Height	% Area
1	16,661	2443493	43754	51,21
2	27,548	2328355	20636	48,79

Compound **3a** (under (*Sc,R*)-MandyPhos, Table 4, entry 10, yield = 85%; ee = 2%).

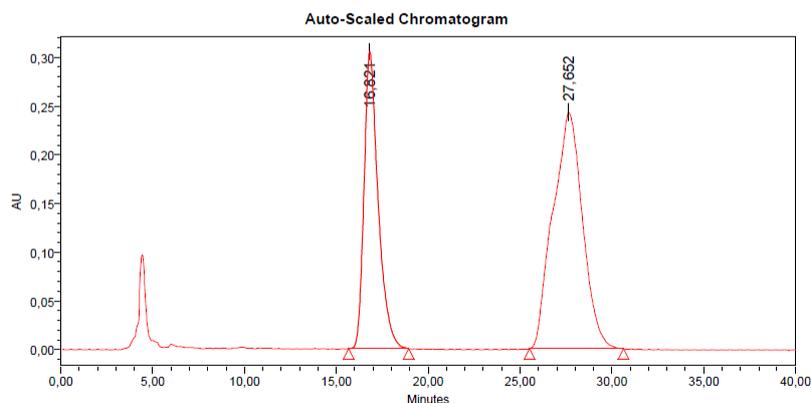
SAMPLE INFORMATION			
Sample Name:	LY-B59 ADH 60/40 254nm 220nm	Acquired By:	malacia
Sample Type:	Unknown	Date Acquired:	11/04/2017 12:25:43
Vial:	1	Acq. Method Set:	HPLC Malacia Grad
Injection #:	3	Date Processed:	11/04/2017 14:01:27
Injection Volume:	20,00 ul	Processing Method:	Default
Run Time:	40,0 Minutes	Channel Name:	2487Channel 2
Sample Set Name:		Proc. Chnl. Descr.:	



Peak Results				
Name	RT	Area	Height	% Area
1	16,924	21028772	389837	49,15
2	27,928	21757375	191323	50,85

Compound **3a** (under SL-M001-1, Table 4, entry 11, yield = 85%; ee = 2%).

SAMPLE INFORMATION			
Sample Name:	LY-B60 ADH 60/40 254nm 220nm	Acquired By:	malacia
Sample Type:	Unknown	Date Acquired:	11/04/2017 13:03:15
Vial:	1	Acq. Method Set:	HPLC Malacia Grad
Injection #:	4	Date Processed:	11/04/2017 14:04:41
Injection Volume:	20,00 ul	Processing Method:	Default
Run Time:	40,0 Minutes	Channel Name:	2487Channel 2
Sample Set Name:		Proc. Chnl. Descr.:	

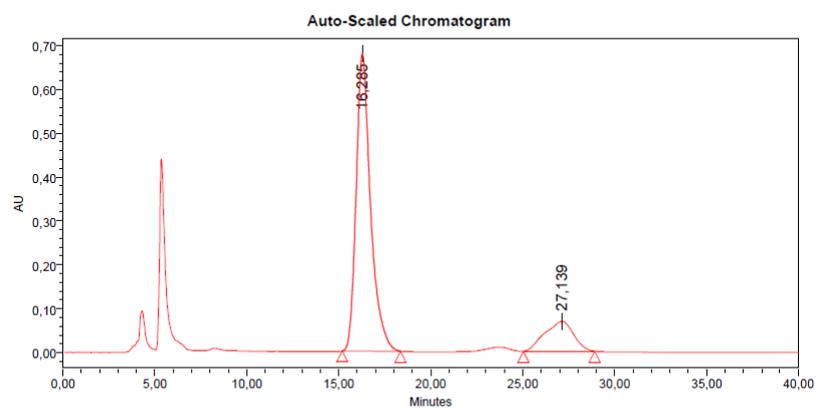


Peak Results

Name	RT	Area	Height	% Area
1	16,821	16261249	304962	37,41
2	27,652	27207851	242635	62,59

Compound **3a** (under SL-M004-1, Table 4, entry 12, yield = 85%; ee = 2%).

SAMPLE INFORMATION			
Sample Name:	LY-B64 ADH 60/40 254nm 220nm	Acquired By:	malacia
Sample Type:	Unknown	Date Acquired:	13/04/2017 12:48:20
Vial:	1	Acq. Method Set:	HPLC Malacia Grad
Injection #:	4	Date Processed:	13/04/2017 13:36:05
Injection Volume:	20,00 ul	Processing Method:	Default
Run Time:	40,0 Minutes	Channel Name:	2487Channel 2
Sample Set Name:		Proc. Chnl. Descr.:	

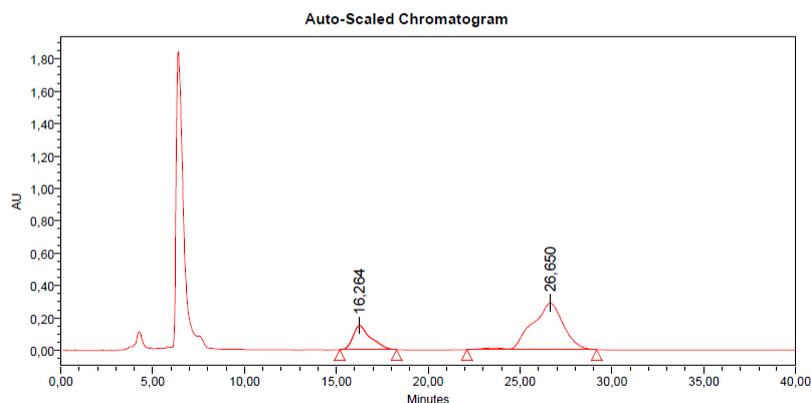


Peak Results

Name	RT	Area	Height	% Area
1	16,285	36836472	678237	83,36
2	27,139	7350800	67910	16,64

Compound **3a** (under *(R)*-MonoPhos, Table 5, entry 1, yield = 53%; ee = 66%).

SAMPLE INFORMATION			
Sample Name:	LY-B65 ADH 60/40 254nm 220nm	Acquired By:	malacia
Sample Type:	Unknown	Date Acquired:	13/04/2017 13:31:36
Vial:	1	Acq. Method Set:	HPLC Malacia Grad
Injection #:	5	Date Processed:	13/04/2017 14:14:52
Injection Volume:	20,00 ul	Processing Method:	Default
Run Time:	40,0 Minutes	Channel Name:	2487Channel 2
Sample Set Name:		Proc. Chnl. Descr.:	



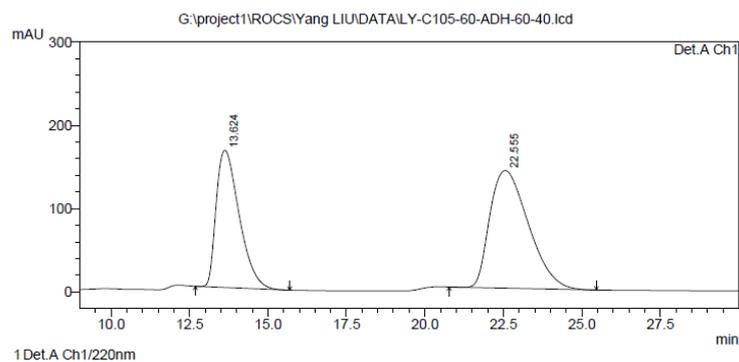
Peak Results

Name	RT	Area	Height	% Area
1	16,264	9988362	150168	22,60
2	26,650	34213125	286942	77,40

Compound **3a** (under (*S*)-MonoPhos, Table 5, entry 2, yield = 64%; ee = 55%).

Acquired by : Admin  
Sample Name : LY-C105  
Injection Volume : 20 uL  
Data File Name : LY-C105-60-ADH-60-40.lcd  
Method File Name : LY-C115-C66-ADH-60-40.lcm  
Batch File Name : LY-C115-B60-ADH-60-40.lcb  
Report File Name : Default.lcr  
Data Acquired : 03/09/2018 17:35:23  
Data Processed : 03/09/2018 18:31:26

<Chromatogram>



Results>

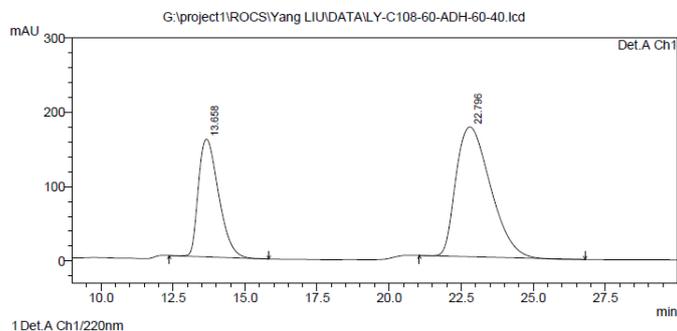
PeakTable

Ret. Time	Area	Height	Area %
13.624	8402908	164753	40.995
22.555	12094630	141251	59.005
	20497539	306004	100.000

Compound **3a** (under (*S*)-L1, Table 5, entry 3, yield = 69%; ee = 18%).

Acquired by : Admin  
 Sample Name : LY-C108  
 Injection Volume : 20  $\mu$ L  
 Data File Name : LY-C108-60-ADH-60-40.lcd  
 Method File Name : LY-C115-C66-ADH-60-40.lcm  
 Batch File Name : LY-C115-B60-ADH-60-40.lcb  
 Report File Name : Default.lcr  
 Data Acquired : 03/09/2018 16:13:46  
 Data Processed : 03/09/2018 17:29:06

<Chromatogram>



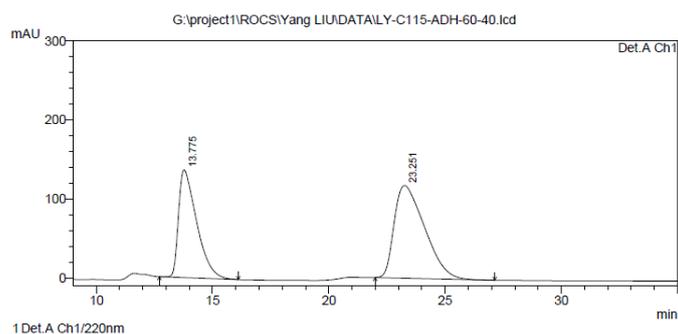
Results>

PeakTable			
Ret. Time	Area	Height	Area %
13.658	7716633	158380	34.680
22.796	14534461	174667	65.320
	22251094	333047	100.000

Compound **3a** (under (S)-L3, Table 5, entry 5, yield = 53%; ee = 30%).

Acquired by : Admin  
 Sample Name : LY-C115  
 Injection Volume : 20  $\mu$ L  
 Data File Name : LY-C115-ADH-60-40.lcd  
 Method File Name : LY-C115-C66-ADH-60-40.lcm  
 Batch File Name : LY-C115-B60-ADH-60-40.lcb  
 Report File Name : Default.lcr  
 Data Acquired : 03/09/2018 14:52:12  
 Data Processed : 03/09/2018 16:03:15

<Chromatogram>



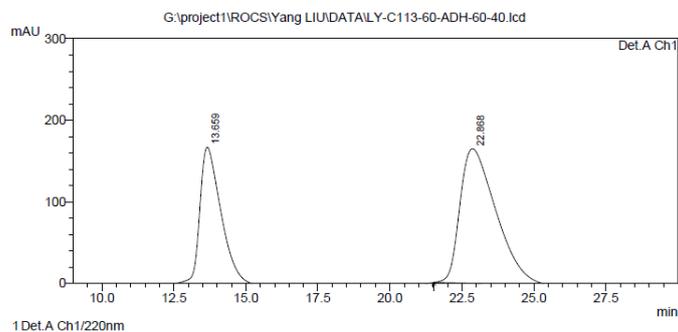
Results>

PeakTable			
Ret. Time	Area	Height	Area %
13.775	7396343	136402	40.095
23.251	10645820	117290	59.005
	18042163	253692	100.000

Compound **3a** (under (S)-L5, Table 5, entry 7, yield = 55%; ee = 18%).

Acquired by : Admin  
 Sample Name : LY-C113  
 Injection Volume : 20  $\mu$ L  
 Data File Name : LY-C113-60-ADH-60-40.lcd  
 Method File Name : LY-C113-ADH-60-40.lcm  
 Batch File Name : LY-C113-ADH-60-40.lcb  
 Report File Name : Default.lcr  
 Data Acquired : 28/08/2018 14:46:33  
 Data Processed : 28/08/2018 16:59:05

<Chromatogram>



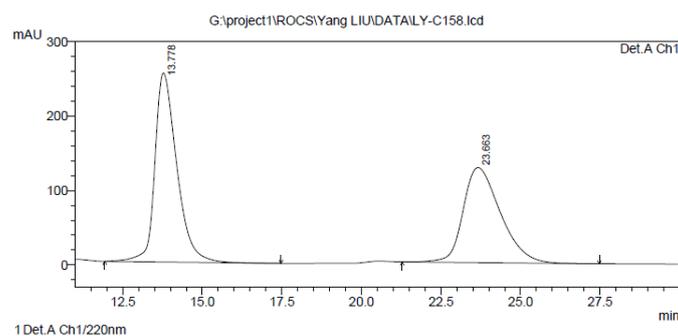
Results>

Detector A Ch1 220nm			
Ret. Time	Area	Height	Area %
13.659	8775390	168983	37.907
22.868	14374559	164848	62.093
	23149949	333831	100.000

Compound **3a** (under (S)-L8, Table 5, entry 10, yield = 90%; ee = 24%).

Acquired by : Admin  
 Sample Name : LY-C158  
 Injection Volume : 20  $\mu$ L  
 Data File Name : LY-C158.lcd  
 Method File Name : LY-ADH-60-40-220nm.lcm  
 Batch File Name : LY-ADH-60-40.lcb  
 Report File Name : Default.lcr  
 Data Acquired : 18/10/2018 12:02:26  
 Data Processed : 18/10/2018 12:44:25

<Chromatogram>



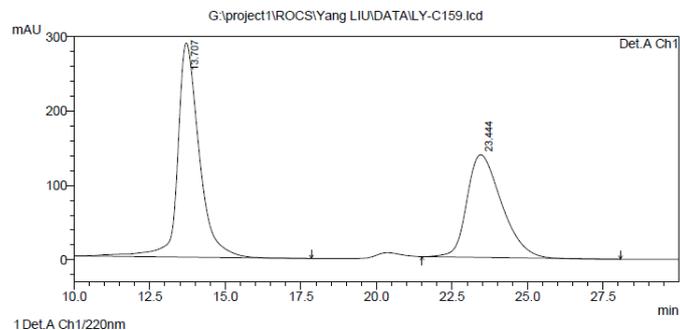
Results>

Detector A Ch1 220nm			
Ret. Time	Area	Height	Area %
13.778	12219915	254230	53.995
23.663	10411798	127785	46.005
	22631713	382015	100.000

Compound **3a** (under (R)-L9, Table 5, entry 11, yield = 66%; ee = 8%).

Acquired by : Admin  
 Sample Name : LY-C159  
 Injection Volume : 20 uL  
 Data File Name : LY-C159.Icd  
 Method File Name : LY-ADH-60-40-220nm.lcm  
 Batch File Name : LY-ADH-60-40.lcb  
 Report File Name : Default.lcr  
 Data Acquired : 18/10/2018 12:37:58  
 Data Processed : 18/10/2018 13:20:56

<Chromatogram>



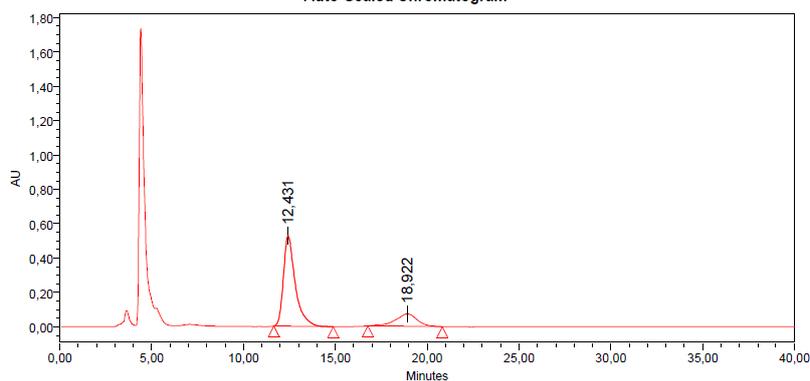
Results>

PeakTable			
Ret. Time	Area	Height	Area %
13.707	14360761	288207	56.697
23.444	10968157	138135	43.303
	25328918	426342	100.000

Compound **3a** (under (R)-L10, Table 5, entry 12, yield = 74%; ee = 14%).

SAMPLE INFORMATION			
Sample Name:	LY-B66 ADH 60/40 254nm 20nm	Acquired By:	malacia
Sample Type:	Unknown	Date Acquired:	18/04/2017 11:54:52
Vial:	1	Acq. Method Set:	HPLC Malacia Grad
Injection #:	3	Date Processed:	18/04/2017 12:38:07
Injection Volume:	20.00 ul	Processing Method:	Default
Run Time:	40,0 Minutes	Channel Name:	2487Channel 2
Sample Set Name:		Proc. Chnl. Descr.:	

Auto-Scaled Chromatogram



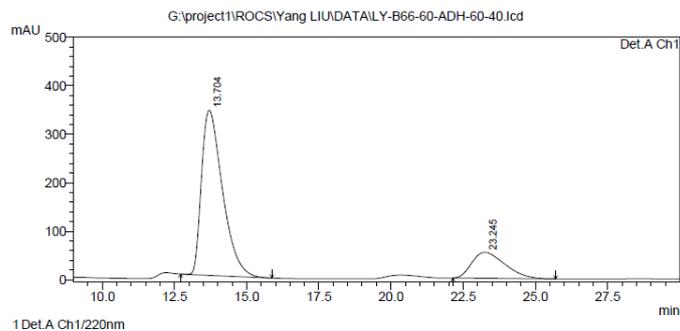
Peak Results

Name	RT	Area	Height	% Area
1	12,431	23497512	526216	79,61
2	18,922	6019794	72371	20,39

Compound **3a** (under (R)-MonoPhos with **2a** (2 equiv.), Table 5, entry 16, yield = 70%; ee = 60%).

Acquired by : Admin  
 Sample Name : LY-C66  
 Injection Volume : 20 uL  
 Data File Name : LY-B66-60-ADH-60-40.Icd  
 Method File Name : LY-C115-C66-ADH-60-40.Icm  
 Batch File Name : LY-C115-B60-ADH-60-40.Icb  
 Report File Name : Default Icr  
 Data Acquired : 03/09/2018 18:56:55  
 Data Processed : 03/09/2018 20:07:10

<Chromatogram>

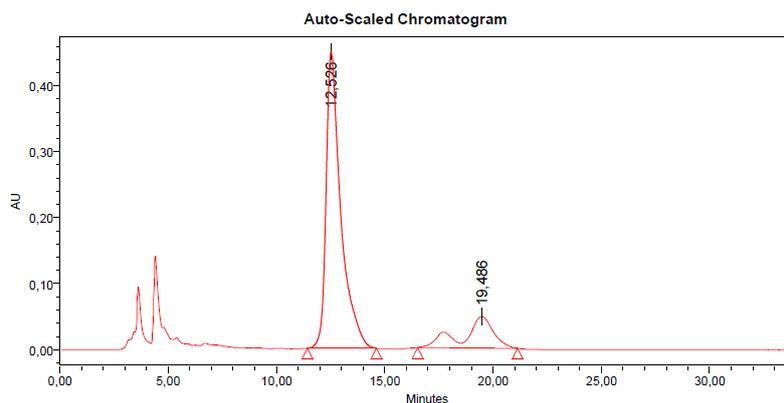


Results>

PeakTable			
Ret. Time	Area	Height	Area %
13.704	17251469	340285	80.205
23.245	4257772	53280	19.795
	21509241	393564	100.000

Compound **3a** (same with the above: ee = 60%, but a little of different retention time).

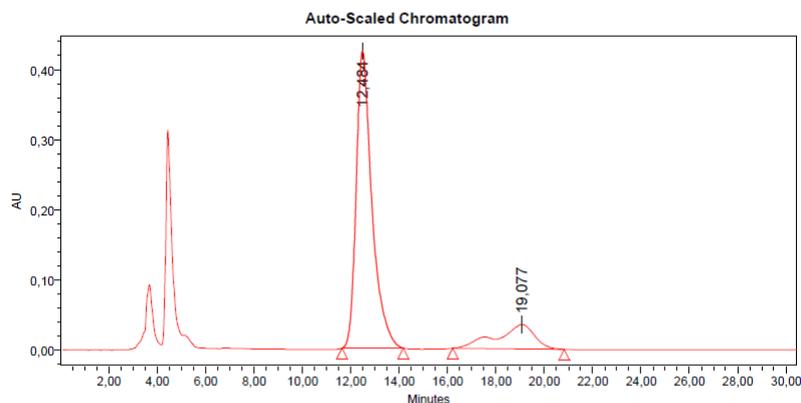
SAMPLE INFORMATION			
Sample Name:	LY-B69 ADH 60/40 254nm 220 nm	Acquired By:	malacia
Sample Type:	Unknown	Date Acquired:	20/04/2017 12:11:54
Vial:	1	Acq. Method Set:	HPLC Malacia Grad
Injection #:	3	Date Processed:	20/04/2017 12:52:27
Injection Volume:	20,00 ul	Processing Method:	Default
Run Time:	40,0 Minutes	Channel Name:	2487Channel 2
Sample Set Name:		Proc. Chnl. Descr.:	



Peak Results				
Name	RT	Area	Height	% Area
1	12.526	21214801	449255	82.14
2	19.486	4612626	47779	17.86

Compound **3a** (under (*R*)-MonoPhos with **2a** (2.5 equiv.), Table 5, entry 17, yield = 66%; ee = 64%).

SAMPLE INFORMATION			
Sample Name:	LY-B68-1 ADH 60/40 254nm 20nm	Acquired By:	malacia
Sample Type:	Unknown	Date Acquired:	18/04/2017 12:36:20
Vial:	1	Acq. Method Set:	HPLC Malacia Grad
Injection #:	4	Date Processed:	18/04/2017 14:06:15
Injection Volume:	20,00 ul	Processing Method:	Default
Run Time:	40,0 Minutes	Channel Name:	2487Channel 2
Sample Set Name:		Proc. Chnl. Descr.:	

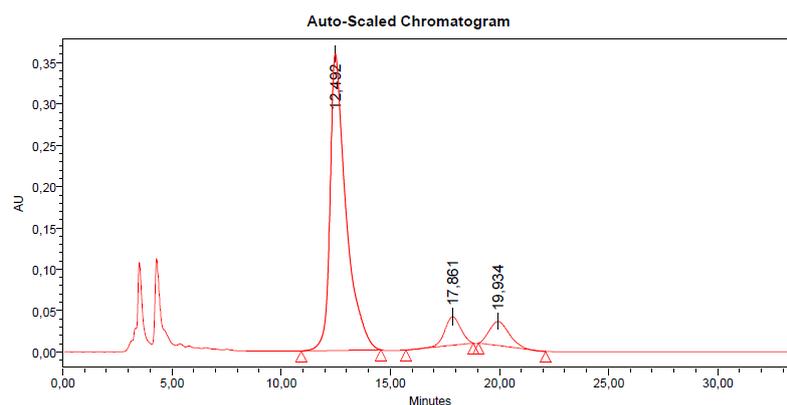


**Peak Results**

Name	RT	Area	Height	% Area
1	12,484	19138608	423644	83,42
2	19,077	3802987	34976	16,58

Compound **3a** (under (*R*)-MonoPhos with **2a** (3 equiv.), Table 5, entry 18, yield = 80%; ee = 66%).

SAMPLE INFORMATION			
Sample Name:	LY-B76 ADH 60/40 254nm 220nm	Acquired By:	malacia
Sample Type:	Unknown	Date Acquired:	27/04/2017 12:43:55
Vial:	1	Acq. Method Set:	HPLC Malacia Grad
Injection #:	3	Date Processed:	27/04/2017 14:03:27
Injection Volume:	20,00 ul	Processing Method:	Default
Run Time:	40,0 Minutes	Channel Name:	2487Channel 2
Sample Set Name:		Proc. Chnl. Descr.:	

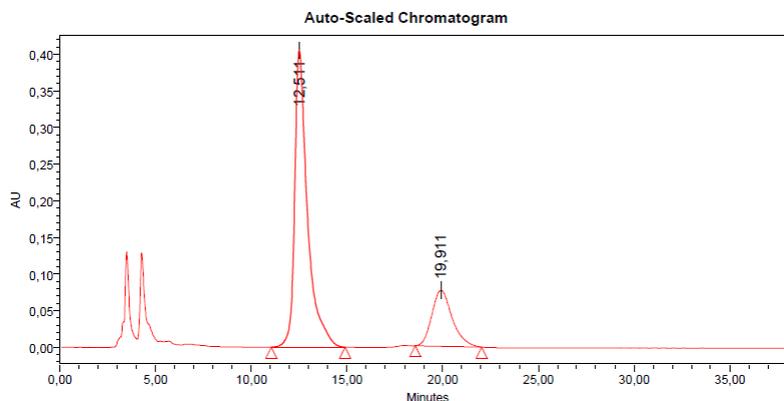


**Peak Results**

Name	RT	Area	Height	% Area
1	12,492	18273766	358614	83,50
2	17,861	1760311	34571	8,04
3	19,934	1849385	29069	8,45

Compound **3a** (under (*R*)-MonoPhos with **2a** (6 equiv.), Table 5, entry 19, yield = 80%; ee = 66%).

SAMPLE INFORMATION			
Sample Name:	LY-B75 ADH 60/40 254nm 220nm	Acquired By:	malacia
Sample Type:	Unknown	Date Acquired:	27/04/2017 12:04:43
Vial:	1	Acq. Method Set:	HPLC Malacia Grad
Injection #:	2	Date Processed:	27/04/2017 12:46:40
Injection Volume:	20,00 ul	Processing Method:	Default
Run Time:	40,0 Minutes	Channel Name:	2487Channel 2
Sample Set Name:		Proc. Chnl. Descr.:	



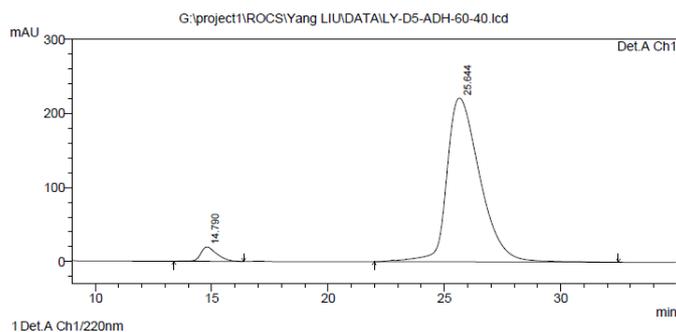
Peak Results

Name	RT	Area	Height	% Area
1	12,511	18911105	405432	76,95
2	19,911	5666122	76510	23,05

Compound **3a** (under (*R*)-MonoPhos with **2a** (3 equiv.) in DCM, Table 5, entry 20, yield = 80%; ee = 54%).

Acquired by : Admin  
Sample Name : LY-D5  
Injection Volume : 20 uL  
Data File Name : LY-D5-ADH-60-40.lcd  
Method File Name : LY-ADH-60-40- 220nm.lcm  
Batch File Name : LY-D5-ADH-60-40.lcb  
Report File Name : Default.lcr  
Data Acquired : 05/11/2018 10:26:40  
Data Processed : 05/11/2018 11:30:02

<Chromatogram>



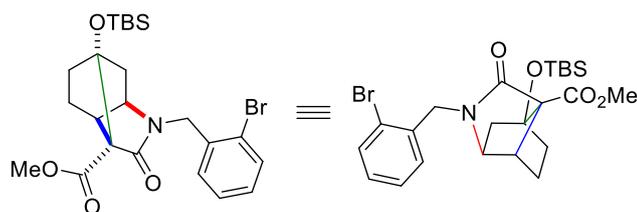
Results>

PeakTable

Detector A Ch1 220nm			
Ret. Time	Area	Height	Area %
14.790	938116	19424	4.119
25.644	21837028	221322	95.881
	22775145	240746	100.000

Compound **3a** (under dpfp from (*S*)-**2a** (1.3 equiv.), Scheme 87, yield = 80%; ee = 92%).

### 3.5 Analytical data of compounds relating to Chapter 3



**methyl 2-(2-bromobenzyl)-4-((*tert*-butyldimethylsilyl)oxy)-3-oxooctahydro-1,4-methanocyclopenta[*c*] pyrrole-3a-carboxylate 10j.**

Following **GP12** with **3j** (76 mg, 0.20 mmol). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/4; Rf 0.40 in EtOAc/Cyclohexane = 1/4) to give compound **10j** as a white solid (89 mg, 90%).

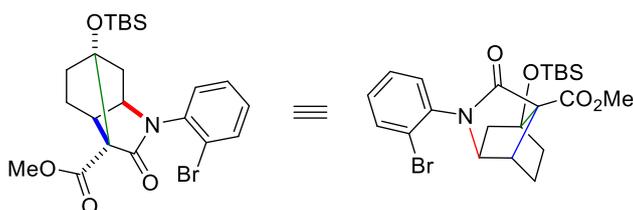
**Mp:** 96 °C.

**IR (cm<sup>-1</sup>):** 2955, 2854, 1744, 1693, 1468, 1435, 1395, 1305, 1249, 1208, 1021.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.54 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.38 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.27 (td, *J* = 7.5, 1.3 Hz, 1H), 7.13 (td, *J* = 7.7, 1.8 Hz, 1H), 4.76 (d, *J* = 15.4 Hz, 1H), 4.25 (d, *J* = 15.4 Hz, 1H), 3.82 (s, 3H), 3.51-3.47 (m, 1H), 2.74 (dt, *J* = 5.1, 2.4 Hz, 1H), 2.03-1.85 (m, 3H), 1.81-1.75 (m, 1H), 1.53 (dt, *J* = 12.2, 2.5 Hz, 1H), 1.44-1.37 (m, 1H), 0.88 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 171.1, 168.7, 136.1, 132.8, 130.5, 129.2, 127.8, 123.7, 85.5, 68.4, 58.8, 52.0, 51.5, 44.2, 43.1, 37.1, 25.6, 20.1, 17.9, -2.8 (2C).

**HRMS (ESI)** calcd for C<sub>23</sub>H<sub>32</sub>BrNO<sub>4</sub>SiNa [M+Na]<sup>+</sup>: 516.1176; found: 516.1170.



**methyl 2-(2-bromophenyl)-4-((*tert*-butyldimethylsilyl)oxy)-3-oxooctahydro-1,4-methanocyclopenta[*c*] pyrrole-3a-carboxylate 10p**

Following **GP12** with **3p** (150 mg, 0.41 mmol). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/4; Rf 0.45 in EtOAc/Cyclohexane = 1/4) to give compound **10p** as a white solid (170 mg, 87%).

**Mp:** 185 °C.

IR (cm<sup>-1</sup>): 2953, 2854, 1748, 1708, 1476, 1433, 1387, 1309, 1259, 1205, 1159, 1034.

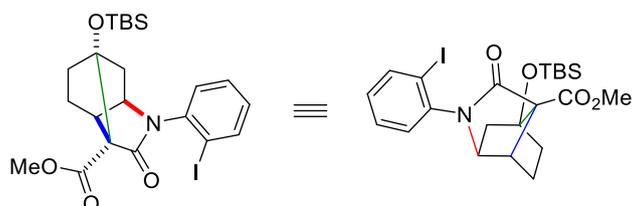
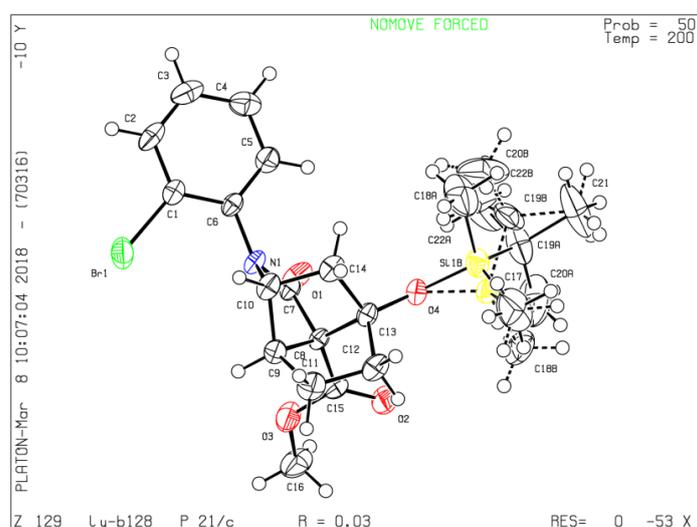
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.65-7.57 (m, 1H), 7.36-7.29 (m, 2H), 7.18-7.10 (m, 1H), 4.13-4.07 (m, 1H), 3.83 (s, 3H), 3.12-3.04 (m, 1H), 2.10-1.96 (m, 2H), 1.93 (dd, *J* = 12.3, 3.7 Hz, 1H), 1.87-1.78 (m, 2H), 1.58-1.47 (m, 1H), 0.93 (s, 8H), 0.11 (s, 3H), 0.10 (s, 3H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 169.9, 168.3, 135.5, 133.8, 128.9, 128.5, 128.1, 121.3, 85.5, 68.8, 62.0, 52.0, 50.7, 43.0, 36.8, 25.5, 20.4, 17.9, -2.8, -2.9.

HRMS (ESI) calcd for C<sub>22</sub>H<sub>30</sub>BrNO<sub>4</sub>SiNa [M+Na]<sup>+</sup>: 502.1020; found: 502.1012.

#### Crystallographic Data and structure refinement for **10p**

A single crystal was selected, mounted and transferred into a cold nitrogen gas stream. Intensity data was collected with a Bruker Kappa-APEX2 system using Mo-Kα fine-focus sealed tube radiation. Unit-cell parameters determination, data collection strategy and integration were carried out with the Bruker APEX2 suite of programs. Multi-scan absorption correction was applied.<sup>[161]</sup> The structures were solved using SHELXT-2014<sup>[162]</sup> and refined anisotropically by full-matrix least-squares methods with SHELXL-2014[C2] using the WinGX suite.<sup>[163]</sup> Crystallographic data was deposited at the Cambridge Crystallographic Data Centre with number CCDC 1826879. Data can be obtained free of charge via [www.ccdc.cam.ac.uk](http://www.ccdc.cam.ac.uk).



<sup>161</sup> Blessing, R.H. *Acta Cryst. A*, **1995**, *51*, 33.

<sup>162</sup> Sheldrick, G.M. *Acta Cryst. A*, **2008**, *64*, 112.

<sup>163</sup> Farrugia, L. J. *J. Appl. Cryst.* **1999**, *32*, 837.

**Methyl 2-(2-bromobenzyl)-4-((*tert*-butyldimethylsilyl)oxy)-3-oxooctahydro-1,4-methanocyclopenta[*c*] pyrrole-3a-carboxylate 10r**

Following **GP12** with **3r** (120 mg, 0.29 mmol). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/4; Rf 0.45 in EtOAc/Cyclohexane = 1/4 ) to give compound **10r** as a white solid (146 mg, 92%).

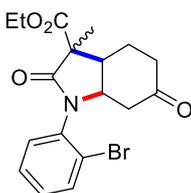
**Mp:** 176 °C.

**IR (cm<sup>-1</sup>):** 2933, 2853, 1748, 1709, 1470, 1431, 1384, 1308, 1259, 1203, 1158, 1094.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.88 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.37 (ddd, *J* = 7.9, 7.3, 1.4 Hz, 1H), 7.26 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.99 (ddd, *J* = 8.0, 7.4, 1.6 Hz, 1H), 4.08 (dd, *J* = 3.7, 2.9 Hz, 1H), 3.83 (s, 3H), 3.17-3.12 (m, 1H), 2.09-1.96 (m, 2H), 1.91 (dd, *J* = 12.4, 3.8 Hz, 1H), 1.87-1.79 (m, 2H), 1.58-1.50 (m, 1H), 0.93 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 169.9, 168.3, 135.5, 133.8, 128.9, 128.5, 128.1, 121.3, 85.5, 68.8, 62.0, 52.0, 50.7, 43.0, 36.8, 25.5, 20.4, 17.9, -2.8, -2.9.

**HRMS (ESI)** calcd for C<sub>22</sub>H<sub>30</sub>INO<sub>4</sub>SiNa [M+Na]<sup>+</sup>: 550.0881; found: 550.0880.



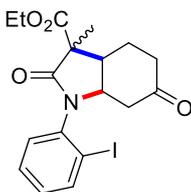
**ethyl 1-(2-bromophenyl)-3-methyl-2,6-dioxooctahydro-1H-indole-3-carboxylate 3s**

Following **GP8** with **2a** (57 mg, 0.26 mmol), **1s** (60 mg, 0.20 mmol) and DBU (0.06 mL, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/1; Rf 0.34 in EtOAc/Cyclohexane = 1/1) to give compound **3s** as a colorless oil (40 mg, 53%).

**IR (cm<sup>-1</sup>):** 2923, 1703, 1630, 1584, 1478, 1389, 1296, 1180, 1112, 1016.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.69-7.49 (m, 1H), 7.37-7.24 (m, 1H), 7.24-6.98 (m, 2H), 4.92-4.11 (m, 3H), 2.83-1.41 (m, 10H), 1.31-1.21 (m, 3H).

**HRMS (ESI)** calcd for C<sub>18</sub>H<sub>20</sub>BrNO<sub>4</sub>Na [M+Na]<sup>+</sup>: 416.0468; found: 416.0479.



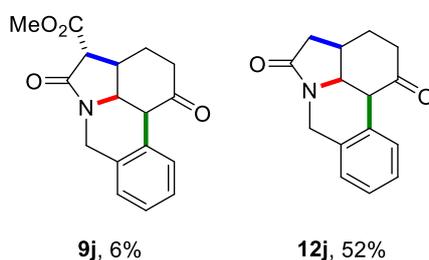
**ethyl 1-(2-iodophenyl)-3-methyl-2,6-dioxooctahydro-1H-indole-3-carboxylate 3t**

Following **GP8** with **2a** (57 mg, 0.26 mmol), **1t** (70 mg, 0.20 mmol) and DBU (0.06 mL, 0.40 mmol). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/1; Rf 0.33 in EtOAc/Cyclohexane = 1/1) to give compound **3t** as a colorless oil (80 mg, 91%).

**IR (cm<sup>-1</sup>):** 2917, 1699, 1627, 1579, 1470, 1390, 1298, 1235, 1177, 1108, 1018.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.06-7.80 (m, 1H), 7.47-7.35 (m, 1H), 7.22-6.96 (m, 2H), 4.71-4.20 (m, 3H), 2.91-1.39 (m, 10H), 1.38-1.28 (m, 3H).

**HRMS (ESI)** calcd for C<sub>18</sub>H<sub>20</sub>INO<sub>4</sub>Na [M+Na]<sup>+</sup>: 464.0329; found: 464.0348.



**methyl 1,5-dioxo-2,3,3a,3a<sup>1</sup>,4,5,7,11b-octahydro-1H-pyrrolo[3,2,1-*de*] phenanthridine-4-carboxylate 9j.**

**2,3,3a,4,7,11b-Hexahydro-1H-pyrrolo[3,2,1-*de*]phenanthridine-1,5(3a<sup>1</sup>H)-dione 12j**

Following **GP13** with **2a** (84 mg, 0.39 mmol) and **1j** (86 mg, 0.30 mmol) for 12 hours. The crude product was purified by flash chromatography on silica gel (eluent: EtOAc) to give **9j** (6 mg, 7%; Rf 0.53 in EtOAc/Cyclohexane = 3/1) as a colorless oil and compound **12j** as a grey solid (47 mg, 52%; Rf 0.27 in EtOAc/Cyclohexane = 3/1).

**9j:**

**IR (cm<sup>-1</sup>):** 2924, 2855, 1727, 1676, 1495, 1441, 1355, 1260, 1201, 1164, 1073, 1001.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 7.35-7.23 (m, 2H), 7.21-7.16 (m, 1H), 7.13-7.07 (m, 1H), 4.79 (d, *J* = 17.7 Hz, 1H), 4.53 (dd, *J* = 8.0, 4.9 Hz, 1H), 4.34 (d, *J* = 17.7 Hz, 1H), 3.85 (d, *J* = 4.9 Hz, 1H), 3.80 (s, 3H), 3.42-3.33 (m, 2H), 2.70-2.54 (m, 1H), 2.50-2.34 (m, 2H), 2.06-1.91 (m, 1H).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ 206.8, 169.8, 168.1, 131.3, 130.7, 129.7, 128.1, 126.7, 57.1, 53.9, 53.0, 51.4, 43.1, 35.7, 33.8, 25.5.

**HRMS (ESI)** calcd for C<sub>17</sub>H<sub>17</sub>NO<sub>4</sub>Na [M+Na]<sup>+</sup>: 322.1050; found: 322.1058.

**12j:**

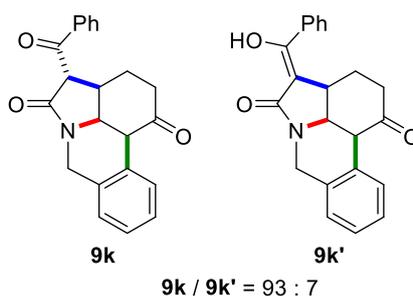
**Mp:** 122 °C.

**IR (cm<sup>-1</sup>):** 2932, 2856, 1719, 1651, 1494, 1450, 1409, 1362, 1271, 1113, 1066.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 7.33-7.22 (m, 2H), 7.20-7.15 (m, 1H), 7.13-7.07 (m, 1H), 4.77 (d, *J* = 17.7 Hz, 1H), 4.34 (dd, *J* = 8.0, 4.7 Hz, 1H), 4.28 (d, *J* = 17.7 Hz, 1H), 3.82 (d, *J* = 4.7 Hz, 1H), 3.11-2.99 (m, 1H), 2.79 (dd, *J* = 17.5, 9.8 Hz, 1H), 2.65-2.54 (m, 1H), 2.49-2.23 (m, 3H), 1.95-1.86 (m, 1H).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ 207.5, 173.5, 131.3, 131.0, 130.1, 127.9, 126.8, 126.5, 58.1, 51.7, 42.7, 36.5, 35.6, 28.8, 26.2.

**HRMS (ESI)** calcd for C<sub>15</sub>H<sub>15</sub>NO<sub>2</sub>Na [M+Na]<sup>+</sup>: 264.0995; found: 264.1004.



Following **GP13** with **2a** (57 mg, 0.26 mmol) and **1k** (66 mg, 0.20 mmol) for 12 hours or following **GP14** with **2k** (60 mg, 0.14 mmol) for 4 hours. The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 4/1; R<sub>f</sub> 0.27 in EtOAc/Cyclohexane = 4/1) to give the compounds **9k** and **9k'** as a 93/7 ketone: enol as a waxy solid (14 mg, 20%) or (40 mg, 82%).

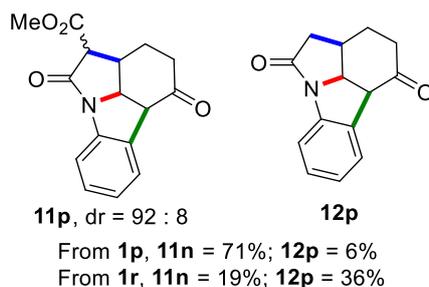
**Mp:** 182 °C.

**IR (cm<sup>-1</sup>):** 2926, 2879, 1693, 1670, 1595, 1580, 1446, 1322, 1270, 1220, 1077, 1061.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ketone and enol):** δ 12.83 (s, 1H, enol), 8.18-8.13 (m, 4H, 2H ketone + 2H enol), 7.65-7.60 (m, 2H, 1H ketone + 1H enol), 7.55-7.50 (m, 4H, 2H ketone + 2H enol), 7.33-7.27 (m, 4H, 2H ketone + 2H enol), 7.19-7.12 (m, 4H, 2H ketone + 2H enol), 4.76 (dd, *J* = 17.6 Hz, 2H, 1H ketone + 1H enol), 4.62 (dd, *J* = 7.7, 4.8 Hz, 2H, 1H ketone + 1H enol), 4.37-4.30 (m, 3H, 2H ketone + 1H enol), 3.90 (d, *J* = 4.8 Hz, 2H, 1H ketone + 1H enol), 3.63-3.54 (m, 2H, 1H ketone + 1H enol), 2.72-2.64 (m, 2H, 1H ketone + 1H enol), 2.54-2.39 (m, 4H, 2H ketone + 2H enol), 2.02-1.94 (m, 2H, 1H ketone + 1H enol).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, only ketone):** δ 207.1, 195.0, 168.7, 135.9, 133.8, 131.2, 130.8, 130.0, 129.7(2C), 128.6(2C), 128.0, 126.8, 126.7, 57.5, 57.4, 51.8, 43.2, 36.3, 33.8, 26.1.

**HRMS (ESI)** calcd for C<sub>22</sub>H<sub>19</sub>NO<sub>3</sub>Na [M+Na]<sup>+</sup>: 368.1257; found: 368.1255.



**methyl 1,5-dioxo-1,2,3,3a,3a1,4,5,10b-octahydropyrrolo[3,2,1-*jk*] carbazole-4-carboxylate **11p****

**and 2,3,3a,4-tetrahydropyrrolo[3,2,1-*jk*]carbazole-1,5(3a<sup>1</sup>H,10bH)-dione **12p****

Following **GP13** with **2a** (84 mg, 0.39 mmol) and **1p** (81 mg, 0.30 mmol) or **1r** (96 mg, 0.30 mmol). The crude product was purified by flash chromatography on silica gel to give the compounds **11p** (60 mg, 71%, or 16 mg, 19%, *dr* 92 : 8, eluent: EtOAc/Cyclohexane = 2/1; Rf 0.38 in EtOAc/Cyclohexane = 2/1) and **12p** (4 mg, 6%, or 24 mg, 36%, eluent: EtOAc/Cyclohexane = 4/1; Rf 0.27 in EtOAc/Cyclohexane = 4/1) or as colorless oil.

**11p:**

**IR (cm<sup>-1</sup>):** 2954, 1741, 1698, 1589, 1478, 1399, 1329, 1221, 1145, 1105.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, diastereomeric mixture):** δ 7.66-7.60 (m, 2H, 1H-major+1H-minor), 7.54-7.49 (m, 2H, 1H-major+1H-minor), 7.31-7.26 (m, 2H, 1H-major+1H-minor), 7.12 (td, *J* = 7.7, 1.2 Hz, 2H, 1H-major+1H-minor), 5.29 (ddd, *J* = 9.6, 5.6, 1.1 Hz, 1H-major), 4.96 (ddd, *J* = 9.7, 5.3, 1.1 Hz, 1H-minor), 4.14-4.11 (m, 1H-minor), 3.82 (s, 3H-major), 3.79 (s, 3H-minor), 3.75 (d, *J* = 9.6 Hz, 2H, 1H-major+1H-minor), 3.40 (s, 1H-major), 3.11 (dt, *J* = 12.7, 5.4 Hz, 2H, 1H-major+1H-minor), 2.53-2.46 (m, 2H, 1H-major+1H-minor), 2.39 (ddd, *J* = 16.1, 14.2, 4.2 Hz, 2H, 1H-major+1H-minor), 2.13-2.05 (m, 2H, 1H-major+1H-minor), 1.71-1.60 (m, 2H, 1H-major+1H-minor).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, diastereomeric mixture):** δ 205.7 (2C, major + minor), 168.4 (2C, major + minor), 167.3 (minor), 165.2 (major), 138.7 (minor), 138.5 (major), 131.0 (2C, major + minor), 128.9 (2C, major + minor), 127.2 (major), 127.0 (minor), 125.2 (major), 124.8 (minor), 114.8 (major), 114.5 (minor), 63.9 (major), 62.7 (minor), 60.3 (major), 56.0 (minor), 52.9 (major), 52.3 (minor), 49.7 (minor), 49.5 (major), 38.7 (major), 38.4 (minor), 38.3 (minor), 37.8 (major), 24.4 (major), 20.8 (minor).

**HRMS (ESI)** calcd for C<sub>16</sub>H<sub>15</sub>NO<sub>4</sub>Na [M+Na]<sup>+</sup>: 308.0893; found: 308.0899.

**12p:**

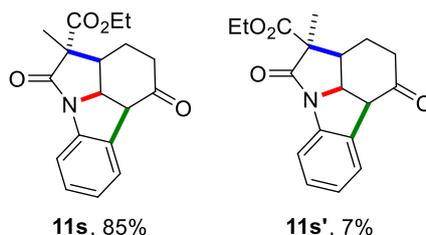
**Mp:** 170 °C.

**IR (cm<sup>-1</sup>):** 2958, 2910, 1699, 1474, 1395, 1296, 1106.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.62 (d, *J* = 7.8 Hz, 1H), 7.54-7.48 (m, 1H), 7.31-7.24 (m, 1H), 7.13-7.05 (m, 1H), 5.03 (ddd, *J* = 9.6, 5.5, 1.1 Hz, 1H), 3.74 (d, *J* = 9.6 Hz, 1H), 3.14 (dd, *J* = 16.4, 6.4 Hz, 1H), 2.84-2.74 (m, 1H), 2.53-2.44 (m, 1H), 2.41-2.29 (m, 2H), 2.06-1.96 (m, 1H), 1.71-1.55 (m, 1H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 206.5, 170.8, 139.1, 130.8, 128.8, 127.1, 124.5, 114.5, 64.7, 49.8, 42.8, 39.0, 34.1, 25.0.

**HRMS (ESI)** calcd for C<sub>14</sub>H<sub>13</sub>NO<sub>2</sub>Na [M+Na]<sup>+</sup>: 250.0838; found: 250.0834.



**ethyl 4-methyl-1,5-dioxo-1,2,3,3a,3a1,4,5,10b-octahydropyrrolo[3,2,1-*jk*]carbazole-4-carboxylate **11s** and **11s'**.**

Following **GP13** with **2a** (84 mg, 0.39 mmol) and **1s** (90 mg, 0.30 mmol). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/2) and (eluent: EtOAc/Cyclohexane = 1:1) to give compound **11s** (65 mg, yield: 70%; R<sub>f</sub> 0.53 in EtOAc/Cyclohexane = 1/1 and **11s'** (27 mg, yield: 29%; R<sub>f</sub> 0.40 in EtOAc/Cyclohexane = 1/1) as a white solid.

**11s:**

**MP:** 93 °C.

**IR (cm<sup>-1</sup>):** 2980, 1722, 1681, 1598, 1489, 1414, 1211, 1147, 1101.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.69-7.58 (m, 1H), 7.53-7.45 (m, 1H), 7.31-7.24 (m, 1H), 7.09 (td, *J* = 7.6, 1.2 Hz, 1H), 5.08 (ddd, *J* = 9.8, 5.1, 1.3 Hz, 1H), 4.26 (qd, *J* = 7.1, 3.9 Hz, 2H), 3.78 (d, *J* = 9.8 Hz, 1H), 3.12 (dt, *J* = 13.1, 5.1 Hz, 1H), 2.56-2.46 (m, 1H), 2.34 (ddd, *J* = 16.3, 14.4, 4.0 Hz, 1H), 2.05-1.95 (m, 1H), 1.38-1.50 (m, 1H), 1.43 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 206.1, 171.3, 168.7, 138.8, 130.6, 128.8, 126.9, 124.8, 114.7, 62.1, 61.7, 60.8, 49.6, 42.5, 38.5, 20.4, 15.3, 14.1.

**HRMS (ESI)** calcd for C<sub>18</sub>H<sub>19</sub>NO<sub>4</sub>Na [M+Na]<sup>+</sup>: 336.1206; found: 336.1198.

**11s':**

**MP:** 147 °C.

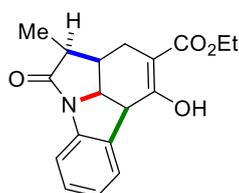
**IR (cm<sup>-1</sup>):** 2979, 2939, 1733, 1685, 1600, 1487, 1453, 1371, 1264, 1226, 1119.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.69-7.59 (m, 1H), 7.55-7.47 (m, 1H), 7.32-7.25 (m, 1H), 7.10 (td, *J* = 7.6, 1.2 Hz, 1H), 5.07 (dd, *J* = 9.5, 5.7 Hz, 1H), 4.33-4.15 (m, 2H), 3.77 (d, *J* = 9.5 Hz, 1H), 2.72-2.63 (m, 1H), 2.54-2.42 (m, 1H), 2.38-2.23 (m, 1H), 1.89-1.78 (m, 2H), 1.73 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 205.8, 169.9, 168.8, 138.6, 130.5, 128.9, 127.2, 124.7, 114.4, 61.5, 61.4, 60.7, 49.7, 44.4, 38.5, 22.1, 19.4, 14.2.

**HRMS (ESI)** calcd for C<sub>18</sub>H<sub>19</sub>NO<sub>4</sub>Na [M+Na]<sup>+</sup>: 336.1206; found: 336.1218.

As the Table 7 shown, compound **A** and **B** was observed during reaction in THF. The information was shown as follows:



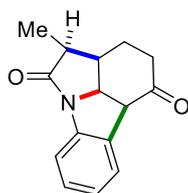
**ethyl 1-hydroxy-4-methyl-5-oxo-3,3a,3a1,4,5,10b-hexahydropyrrolo[3,2,1-*jk*]carbazole-2-carboxylate A**

**IR (cm<sup>-1</sup>):** 2975, 2934, 1703, 1651, 1616, 1598, 1480, 1462, 1382, 1277, 1212, 1034.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 12.4 (brs, 1H), 7.61-7.57 (m, 1H), 7.47-7.43 (m, 1H), 7.29-7.22 (m, 1H), 7.02 (td, *J* = 7.6, 1.1 Hz, 1H), 4.90-4.82 (m, 1H), 4.20 (qd, *J* = 7.1, 1.2 Hz, 2H), 4.05 (d, *J* = 9.7 Hz, 1H), 3.15 (qd, *J* = 7.2, 4.8 Hz, 1H), 2.62-2.52 (m, 2H), 1.69-1.57 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.21 (d, *J* = 7.2 Hz, 3H).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** δ 175.0, 171.7, 169.4, 140.0, 132.6, 128.9, 125.9, 124.1, 114.6, 96.2, 62.4, 60.8, 45.6, 42.1, 39.3, 18.6, 14.2, 9.5.

**HRMS (ESI)** calcd for C<sub>18</sub>H<sub>19</sub>NO<sub>4</sub>Na [M+Na]<sup>+</sup>: 336.1206; found: 336.1198.



**4-methyl-2,3,3a,3a1,4-tetrahydropyrrolo[3,2,1-*jk*]carbazole-1,5(3a<sup>1</sup>H, 10bH)-dione B**

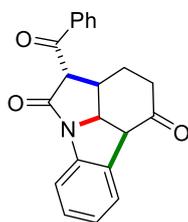
**IR (cm<sup>-1</sup>):** 2983, 1725, 1680, 1598, 1486, 1295, 1261, 1126, 1028.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.63 (dt, *J* = 7.9, 0.7 Hz, 1H), 7.52-7.49 (m, 1H), 7.30-7.27 (m, 1H), 7.07 (td, *J* = 7.6, 1.1 Hz, 1H), 4.93 (ddd, *J* = 9.7, 5.2, 1.3 Hz, 1H), 3.79 (d, *J* = 9.6 Hz, 1H), 3.26-3.18 (m, 1H), 2.81-2.73 (m, 1H), 2.56-2.49 (m, 1H), 2.35-2.24 (m, 1H), 2.00-1.92 (m, 1H), 1.42-1.37 (m, 1H), 1.20 (d, *J* = 7.3 Hz, 3H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 206.8, 173.3, 139.3, 130.5, 128.8, 126.8, 124.3, 114.4, 62.6, 49.9, 45.3, 39.8,

38.6, 19.7, 9.6.

**HRMS (ESI)** calcd for  $C_{15}H_{15}NO_2Na$   $[M+Na]^+$ : 264.0995; found: 264.1005.



**4-benzoyl-2,3,3a,4-tetrahydropyrrolo[3,2,1-jk]carbazole-1,5(3a<sup>1</sup>H,10bH)-dione 11u**

Following **GP13** with **2a** (84 mg, 0.39 mmol) and **1u** (95 mg, 0.30 mmol). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/1; R<sub>f</sub> 0.45 in EtOAc/Cyclohexane = 1/1) to give compound **11u** as a white solid (84 mg, 85%).

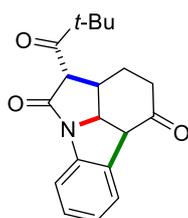
**Mp:** 224 °C.

**IR (cm<sup>-1</sup>):** 2935, 2858, 1709, 1668, 1593, 1478, 1401, 1281, 1145, 1104, 1040.

**<sup>1</sup>H NMR (300 MHz, DMSO):** δ 8.20-8.13 (m, 2H), 7.76-7.69 (m, 1H), 7.64-7.57 (m, 2H), 7.48-7.41 (m, 2H), 7.31-7.24 (m, 1H), 7.12 (td, *J* = 7.5, 1.2 Hz, 1H), 5.22 (dd, *J* = 9.7, 5.7 Hz, 1H), 4.73 (s, 1H), 3.98 (d, *J* = 9.7 Hz, 1H), 3.23-3.13 (m, 1H), 2.69-2.56 (m, 1H), 2.34-2.17 (m, 2H), 1.60-1.44 (m, 1H).

**<sup>13</sup>C NMR (100 MHz, DMSO):** δ 207.1, 194.5, 166.5, 138.5, 135.1, 134.0, 132.0, 129.4 (2C), 128.8 (2C), 128.2, 127.3, 124.4, 113.8, 63.9, 63.2, 49.2, 38.4, 37.2, 24.3.

**HRMS (ESI)** calcd for  $C_{21}H_{17}NO_3Na$   $[M+Na]^+$ : 354.1101; found: 354.1094.



**4-pivaloyl-2,3,3a,4-tetrahydropyrrolo[3,2,1-jk]carbazole-1,5(3a<sup>1</sup>H,10bH)-dione 11v**

Following **GP13** with **2a** (84 mg, 0.39 mmol) and **1v** (89 mg, 0.30 mmol). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/1; R<sub>f</sub> 0.52 in EtOAc/Cyclohexane = 1/1) to give compound **11v** as a white solid (70 mg, 75%).

**Mp:** 187 °C.

**IR (cm<sup>-1</sup>):** 2964, 1718, 1681, 1600, 1477, 1409, 1363, 1326, 1232, 1119, 1064.

**<sup>1</sup>H NMR (300 MHz, DMSO):** δ 7.47-7.40 (m, 2H), 7.31-7.24 (m, 1H), 7.11 (td, *J* = 7.5, 1.2 Hz, 1H), 5.18 (dd, *J*

= 9.7, 5.9 Hz, 1H), 4.11 (s, 1H), 3.94 (d,  $J = 9.7$  Hz, 1H), 2.87 (dt,  $J = 11.7, 5.6$  Hz, 1H), 2.59 (dd,  $J = 15.1, 4.0$  Hz, 1H), 2.25 (dt,  $J = 15.3, 3.2$  Hz, 1H), 2.14 (dt,  $J = 14.1, 4.4$  Hz, 1H), 1.49-1.34 (m, 1H), 1.20 (s, 9H).

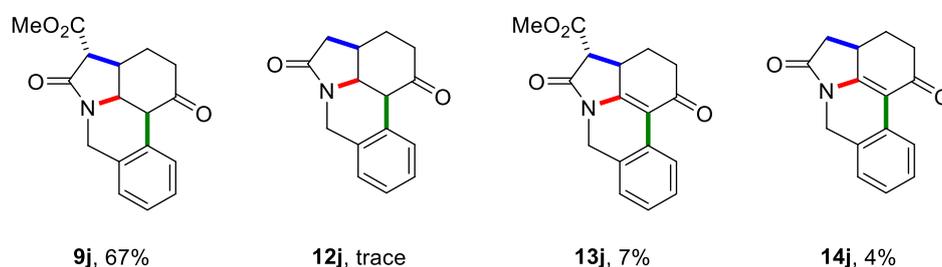
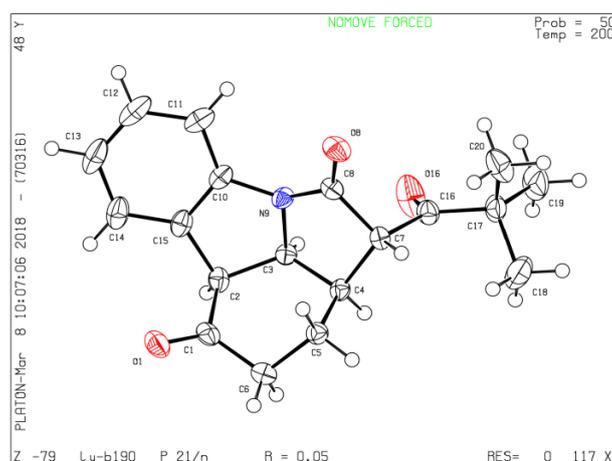
$^{13}\text{C}$  NMR (100 MHz, DMSO):  $\delta$  210.8, 207.0, 167.4, 138.4, 131.9, 128.2, 127.4, 124.3, 113.6, 63.9, 61.4, 49.1, 44.7, 38.3, 37.8, 25.4, 24.8.

HRMS (ESI) calcd for  $\text{C}_{19}\text{H}_{21}\text{NO}_3\text{Na}$   $[\text{M}+\text{Na}]^+$ : 334.1414; found: 334.1409.

#### Crystallographic Data for **11v**

A single crystal was selected, mounted and transferred into a cold nitrogen gas stream. Intensity data was collected with a Bruker Kappa-APEX2 system using Mo-K $\alpha$  fine-focus sealed tube radiation. Unit-cell parameters determination, data collection strategy and integration were carried out with the Bruker APEX2 suite of programs. Multi-scan absorption correction was applied.<sup>[161]</sup> The structures were solved using SHELXT-2014<sup>[162]</sup> and refined anisotropically by full-matrix least-squares methods with SHELXL-2014[C2] using the WinGX suite.<sup>[163]</sup> Crystallographic data was deposited at the Cambridge Crystallographic Data Centre with number CCDC 1824090. Data can be obtained free of charge via [www.ccdc.cam.ac.uk](http://www.ccdc.cam.ac.uk).

#### Crystal data and structure refinement for **11v**



**methyl 1,5-dioxo-2,3,3a,4,5,7-hexahydro-1H-pyrrolo[3,2,1-de]phenanthridine-4-carboxylate 13j and 2,3,3a,4-tetrahydro-1H-pyrrolo[3,2,1-de]phenanthridine-1,5(7H)-dione 14j.**

Following **GP14** with **3j** (76 mg, 0.20 mmol). The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/2 to 5/1) to give the compounds **9j** (40 mg, 67%), **13j** (4 mg, 7%) and **14j** (2 mg, yield: 4%) as a white solid.

**9j** was shown in page 179.

**13j:**

**Mp:** 137 °C.

**IR (cm<sup>-1</sup>):** 2922, 2850, 1732, 1615, 1496, 1437, 1420, 1279, 1234, 1171, 1084, 1043.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.74-8.68 (m, 1H), 7.30-7.25 (m, 1H), 7.20 (td, *J* = 7.5, 1.4 Hz, 1H), 7.08-7.04 (m, 1H), 5.09 (d, *J* = 16.5 Hz, 1H), 4.72 (d, *J* = 16.5 Hz, 1H), 3.89 (s, 2.77H), 3.74 (s, 0.23H), 3.68 (ddd, *J* = 12.9, 8.5, 4.9 Hz, 1H), 3.41 (d, *J* = 8.5 Hz, 1H), 2.73 (ddd, *J* = 17.5, 4.6, 2.4 Hz, 1H), 2.61 (ddd, *J* = 17.5, 13.5, 4.8 Hz, 1H), 2.38-2.32 (dtd, *J* = 12.3, 4.9, 2.4 Hz, 1H), 1.97-1.85 (m, 1H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 193.6, 169.4, 168.0, 157.4, 128.2, 127.6, 127.6, 126.2, 126.1(2C), 108.7, 53.3, 52.5, 43.7, 39.1, 38.7, 26.5. HRMS (ESI) calcd for C<sub>17</sub>H<sub>15</sub>NO<sub>4</sub>Na [M+Na]<sup>+</sup>: 320.0893; found: 320.0887.

**14j:**

**Mp:** 128 °C.

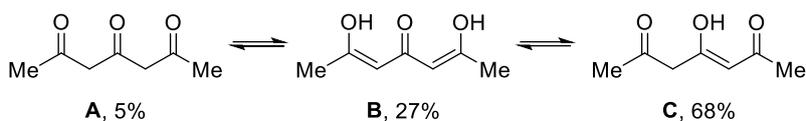
**IR (cm<sup>-1</sup>):** 2945, 1735, 1602, 1498, 1420, 1278, 1217, 1163, 1068.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 8.77-8.66 (m, 1H), 7.29-7.21 (m, 1H), 7.17 (td, *J* = 7.4, 1.5 Hz, 1H), 7.08-6.99 (m, 1H), 5.05 (d, *J* = 16.5 Hz, 1H), 4.68 (d, *J* = 16.5 Hz, 1H), 3.31-3.17 (m, 1H), 2.83 (dd, *J* = 17.2, 8.8 Hz, 1H), 2.69 (ddd, *J* = 17.5, 4.6, 2.3 Hz, 1H), 2.54 (ddd, *J* = 17.7, 13.3, 4.8 Hz, 1H), 2.40-2.25 (m, 2H), 1.94-1.79 (m, 1H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 193.9, 174.7, 161.3, 128.0 (2C), 127.2, 126.2, 126.1, 125.8, 107.8, 43.3, 39.0, 35.3, 35.2, 27.3.

**HRMS (ESI) calcd for C<sub>15</sub>H<sub>13</sub>NO<sub>2</sub>Na [M+Na]<sup>+</sup>: 262.0838; found: 262.0848.**

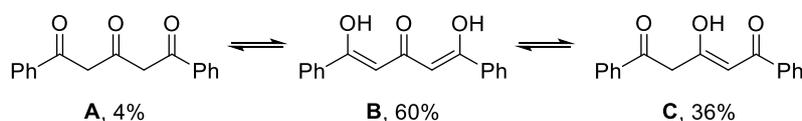
### 3.6 Analytical data of compounds relating to Chapter 4



#### diacetylacetone **15b**

Following the procedure described by Opatz:<sup>[142]</sup> Ba(OH)<sub>2</sub>·8H<sub>2</sub>O (10.0 g, 31.7 mmol, 2.0 equiv) was dissolved almost completely in boiling water (130 mL) under an argon atmosphere. The resulting suspension was added directly to a 50 °C warm solution of 2,6-dimethyl-γ-pyrone (1.97 g, 15.9 mmol, 1.0 equiv) in aqueous NaOH solution (8 wt.%, 4 mL). A yellow precipitate formed immediately. The solution was cooled slowly to 0 °C, the crystals were filtered off, washed with aqueous NaOH solution (4 wt.%), and then dissolved under ice cooling in aqueous HCl solution (15 wt.%, 20 mL). The resulting solution was stirred for 1 h, and extracted with Et<sub>2</sub>O. The combined organic layers were dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The product was recrystallized from petroleum ether to afford **15b** (1.35 g, 60%) as a white solid. These data are in good agreement with those reported in the literature.<sup>[142]</sup>

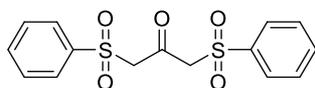
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 15.20 (s, 1H, C), 14.17 (s, 2H, B), 5.55 (s, 1H, C), 5.13 (s, 2H, B), 3.69 (s, 4H, A), 3.39 (s, 2H, C), 2.25 (s, 3H, C), 2.23 (s, 6H, A), 2.07 (s, 3H, C), 1.97 (s, 6H, B).



#### dibenzoylacetone **15c**

Following the procedure described by VanDerveer:<sup>[143]</sup> To a solution of distilled acetone (117 mg, 2.0 mmol, 1.0 equiv) in anhydrous THF (5 mL) at -78 °C was added LiHMDS (6.0 mL 6.0 mmol, 3.0 equiv, 1 mol/mL in THF) dropwise. After 15 mins, a solution of methyl benzoate (0.5 mL, 4.0 mmol, 2.0 equiv) in anhydrous THF (5 mL) was added. The mixture was allowed to stir overnight at room temperature, and then quenched with 3 M HCl aqueous solution and extracted with Et<sub>2</sub>O. The combined organic layers were washed with brine, dried over anhydrous MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The product was recrystallized from ethanol to afford **15c** (320 mg, 60%) as a yellow solid. These data are in good agreement with those reported in the literature.<sup>[143]</sup>

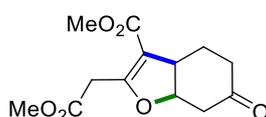
<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 15.83 (s, 1H, C), 14.76 (s, 2H, B), 8.07-7.41 (m, 30H, 10H A + 10H B + 10H C), 6.32 (s, 1H, C), 6.02 (s, 2H, B), 4.12 (s, 2H, C), 3.93 (s, 4H, A).



### 1,3-bis-benzenesulfonylpropan-2-one 15d

Following a slightly modified version of the procedure described by Lai:<sup>[144]</sup> To a solution of sodium benzenesulfinate (1.64 g, 10.0 mmol) in CH<sub>3</sub>CN (50mL) were added NBu<sub>4</sub>HSO<sub>4</sub> (340 mg, 1.0 mmol) and 1,3-dichloropropan-2-one (635 mg, 5.0 mmol) at room temperature. The mixture was stirred at 45 °C for 24 h and then concentrated under reduced pressure. The yellow oil obtained was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/1; R<sub>f</sub> 0.35 in EtOAc/Cyclohexane = 1/1) to give compound **15d** (1.35 g, 80%) as a white solid. These data are in good agreement with those reported in the literature.<sup>[144]</sup>

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.88-7.82 (m, 4H), 7.73-7.68 (m, 2H), 7.60-7.55 (m, 4H), 4.51 (s, 4H).



### methyl 2-(2-methoxy-2-oxoethyl)-6-oxo-3a,4,5,6,7,7a-hexahydrobenzofuran-3-carboxylate 17a

Following **GP15** with **2a** (57 mg, 0.26 mmol) and dimethyl-3-oxoglutarate (29 μL, 0.20 mmol) in DMSO. The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/1; R<sub>f</sub> 0.31 in EtOAc/Cyclohexane = 1/1) to give compound **17a** (40 mg, 75%) as a white solid (or 178 mg, 66% from 1 mmol of dimethyl-3-oxoglutarate).

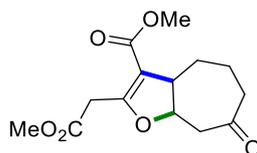
**Mp:** 83 °C

**IR (cm<sup>-1</sup>):** 2940, 1742, 1693, 1656, 1439, 1398, 1238, 1195, 1165, 1141, 1085.

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 5.15 (dt, *J* = 10.0, 3.5 Hz, 1H), 3.85 (d, *J* = 16.5 Hz, 1H), 3.71 (s, 3H), 3.68 (s, 3H), 3.60 - 3.51 (m, 2H), 2.80 (dd, *J* = 17.1, 3.5 Hz, 1H), 2.68 (dd, *J* = 17.1, 3.5 Hz, 1H), 2.41-2.27 (m, 2H), 2.15-2.06 (m, 1H), 2.04-1.90 (m, 1H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 209.0, 168.3, 165.2, 164.2, 107.3, 81.0, 52.3, 51.1, 41.1, 39.2, 35.5, 33.8, 23.5.

**HRMS (ESI)** calcd for C<sub>13</sub>H<sub>16</sub>O<sub>6</sub>Na [M+Na]<sup>+</sup>: 291.0839; found: 291.0831.



### methyl 2-(2-methoxy-2-oxoethyl)-7-oxo-4,5,6,7,8a-hexahydro-3aH-cyclohepta[b]furan-3-carboxylate 17c

Following **GP15** with **2c** (66 mg, 0.39 mmol) and dimethyl-3-oxoglutarate (44 μL, 0.30 mmol) in THF. The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/1; R<sub>f</sub>

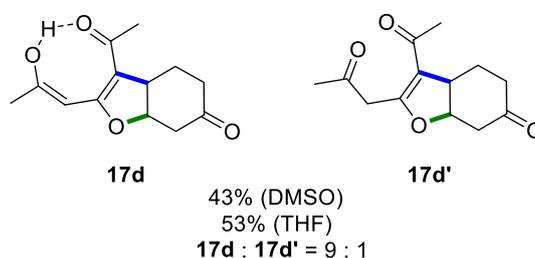
0.46 in EtOAc/Cyclohexane = 1/1) to give compound **17c** (60 mg, 71%) as a colorless oil.

**IR (cm<sup>-1</sup>):** 2953, 2923, 1852, 1743, 1693, 1647, 1437, 1331, 1228, 1191, 1169, 1115, 1061.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 4.90 (ddd, *J* = 10.1, 8.7, 4.1 Hz, 1H), 3.74-3.67 (m, 8H), 3.40-3.33 (m, 1H), 2.99 (dd, *J* = 13.4, 8.7 Hz, 1H), 2.84 (ddd, *J* = 13.5, 4.2, 1.1 Hz, 1H), 2.59 (dddd, *J* = 12.8, 8.9, 6.3, 0.8 Hz, 1H), 2.46-2.38 (m, 1H), 2.07-1.99 (m, 1H), 1.97-1.88 (m, 1H), 1.83-1.73 (m, 1H), 1.61-1.50 (m, 1H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 207.8, 168.4, 165.3, 162.8, 108.3, 80.8, 52.3, 51.0, 45.3, 44.7, 44.6, 34.0, 26.7, 20.7.

**HRMS (ESI)** calcd for C<sub>14</sub>H<sub>18</sub>O<sub>6</sub>Na [M+Na]<sup>+</sup>: 305.0996; found: 305.0996.



**3-acetyl-2-(2-hydroxyprop-1-en-1-yl)-4,5,7,7a-tetrahydrobenzofuran-6(3aH)-one 17d**

**and 3-acetyl-2-(2-oxopropyl)-4,5,7,7a-tetrahydrobenzofuran-6(3aH)-one 17d'**

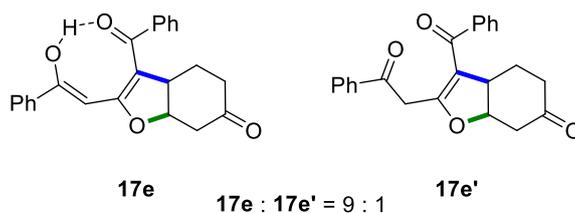
Following **GP15** with **2a** (57 mg, 0.26 mmol) and **15b** (29 mg, 0.20 mmol) in DMSO. The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/1; R<sub>f</sub> 0.25 in EtOAc/Cyclohexane = 1/1) to give compound **17d** and **17d'** as a 9/1 enol/ketone (25 mg, 53%) as a colorless oil.

**IR (cm<sup>-1</sup>):** 2925, 1718, 1585, 1381, 1237, 1223, 1135, 1067, 1043.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 16.36 (s, 1H, enol), 5.41 (s, 1H, enol), 5.09 (dt, *J* = 9.7, 3.6 Hz, 2H, 1H enol + 1H ketone), 3.71 (d, *J* = 2.2 Hz, 2H, ketone), 3.63-3.54 (m, 1H, ketone), 3.49-3.40 (m, 1H, enol), 2.83 (dd, *J* = 17.1, 3.6 Hz, 2H, 1H enol + 1H ketone), 2.70 (dd, *J* = 17.1, 3.6 Hz, 2H, 1H enol + 1H ketone), 2.39-2.28 (m, 2H, 1H enol + 1H ketone), 2.27-2.14 (m, 11H, 4H enol + 7H ketone), 2.07 (s, 3H, enol), 2.04-1.96 (m, 4H, 2H enol + 2H ketone).

**<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):** only enol δ 208.8, 191.7, 181.4, 167.7, 109.6, 97.4, 80.2, 41.2, 39.0, 35.7, 25.4, 23.8, 15.0.

**HRMS (ESI)** calcd for C<sub>13</sub>H<sub>17</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 237.1121; found: 237.1121.



**3-benzoyl-2-(-2-hydroxy-2-phenylvinyl)-4,5,7,7a-tetrahydrobenzofuran-6(3aH)-one 17e**

**and 3-benzoyl-2-(2-oxo-2-phenylethyl)-4,5,7,7a-tetrahydrobenzofuran-6(3aH)-one 17e'**

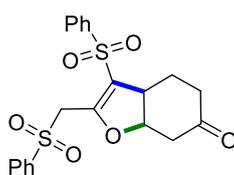
Following **GP15** with **2a** (57 mg, 0.26 mmol) and **15c** (53 mg, 0.20 mmol) in THF. The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/3; R<sub>f</sub> 0.35 in EtOAc/Cyclohexane = 1/2) to give compound **17e** and **17e'** as a 90/10 enol/ketone (32 mg, 45%) as a yellow oil.

**IR (cm<sup>-1</sup>):** 2926, 1723, 1592, 1571, 1492, 1357, 1250, 1132, 1054.

**<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):** δ 16.41 (s, 1H, enol), 7.66-7.60 (m, 4H, 2H enol + 2H ketone), 7.55-7.50 (m, 6H, 3H enol + 3H ketone), 7.48-7.40 (m, 6H, 3H enol + 3H ketone), 7.37-7.30 (m, 4H, 2H enol + 2H ketone), 6.02 (s, 1H, enol), 5.30 (dt, *J* = 9.7, 3.6 Hz, 2H, 1H enol + 1H ketone), 3.89-3.83 (m, 2H, 1H enol + 1H ketone), 2.94 (dd, *J* = 17.1, 3.6 Hz, 2H, 1H enol + 1H ketone), 2.81 (dd, *J* = 17.1, 3.6 Hz, 2H, 1H enol + 1H ketone), 2.88-2.76 (m, 2H, ketone), 2.50-2.31 (m, 6H, 3H enol + 3H ketone), 2.23-2.13 (m, 2H, 1H enol + 1H ketone).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ only enol 208.9, 186.2, 179.1, 165.4, 134.9, 131.6, 131.0, 130.2, 129.5 (2C), 128.4 (4C), 126.4 (2C), 113.5, 95.6, 80.5, 41.4, 41.1, 36.0, 24.0.

**HRMS (ESI)** calcd for C<sub>23</sub>H<sub>20</sub>O<sub>4</sub>Na [M+Na]<sup>+</sup>: 383.1254; found: 383.1252.



**3-(phenylsulfonyl)-2-((phenylsulfonyl)methyl)-4,5,7,7a-tetrahydrobenzofuran-6(3aH)-one 17f**

Following **GP15** with **2a** (57 mg, 0.26 mmol) and **15d** (68 mg, 0.20 mmol) in THF. The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 3/2; R<sub>f</sub> 0.38 in EtOAc/Cyclohexane = 2/1) to give compound **17f** (63 mg, 73%) as a yellow oil.

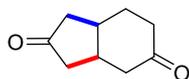
**IR (cm<sup>-1</sup>):** 2942, 1721, 1632, 1447, 1307, 1252, 1155, 1084.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.03 - 7.99 (m, 2H), 7.93 - 7.88 (m, 2H), 7.70 - 7.62 (m, 2H), 7.60 - 7.54 (m, 4H), 5.03 (dt, *J* = 10.3, 3.7 Hz, 1H), 4.78 (d, *J* = 14.0 Hz, 1H), 4.71 (dd, *J* = 14.0, 1.3 Hz, 1H), 3.31 - 3.25 (m, 1H), 2.64 (dd, *J* = 17.1, 3.6 Hz, 1H), 2.56 (dd, *J* = 17.1, 4.0 Hz, 1H), 2.24 - 2.17 (m, 2H), 2.08 - 2.01 (m, 1H), 1.88 -

1.78 (m, 1H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 207.3, 156.6, 140.6, 139.4, 134.2, 133.7, 129.3 (4C), 128.2 (2C), 127.6 (2C), 117.1, 81.7, 54.0, 40.8, 40.3, 35.2, 22.8.

HRMS (ESI) calcd for C<sub>21</sub>H<sub>20</sub>O<sub>6</sub>Na [M+Na]<sup>+</sup>: 455.0594; found: 455.0592.



**tetrahydro-1H-indene-2,5(3H,6H)-dione 18a**

Following **GP16** with **2a** (57 mg, 0.26 mmol) and dimethyl-3-oxoglutarate (29 μL, 0.20 mmol) during 6 h. The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 2/1) to give compound **18a** (21 mg, 69%) as a colorless oil (or 97 mg, 64% from 1 mmol of dimethyl-3-oxoglutarate).

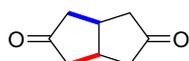
Following **GP17** with **2a** (57 mg, 0.26 mmol) and dimethyl-3-oxoglutarate (29 μL, 0.20 mmol) during 1 h. The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 2/1; R<sub>f</sub> 0.39 in EtOAc/Cyclohexane = 2/1) to give compound **18a** (21 mg, 69%) as a colorless oil.

IR (cm<sup>-1</sup>): 2929, 1738, 1706, 1405, 1303, 1230, 1205, 1158, 1137, 1072.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 2.88-2.76 (m, 1H), 2.68-2.59 (m, 1H), 2.53 (dd, J = 14.7, 6.5 Hz, 1H), 2.43-2.32 (m, 4H), 2.28 (dd, J = 15.1, 6.2 Hz, 1H), 2.18 (dd, J = 18.6, 5.1 Hz, 1H), 2.10-1.97 (m, 2H), 1.81-1.68 (m, 1H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 216.9, 210.3, 43.6, 42.8, 42.6, 38.4, 37.9, 34.2, 28.0.

HRMS (ESI) calcd for C<sub>9</sub>H<sub>12</sub>O<sub>2</sub>Na [M+Na]<sup>+</sup>: 175.0730; found: 175.0723.



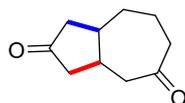
**cis-bicyclo[3.3.0]octane-3,7-dione 18b**

Following **GP16** with **2b** (315 mg, 1.56 mmol) and dimethyl-3-oxoglutarate (0.18 mL, 1.20 mmol) during 6 h. The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 3/2; R<sub>f</sub> 0.31 in EtOAc/Cyclohexane = 3/2) to give compound **18b** (70 mg, 42%) as a colorless oil.

Following **GP17** with **2b** (79 mg, 0.39 mmol) and dimethyl-3-oxoglutarate (43 μL, 0.30 mmol) during 1 h. The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 3/2) to give compound **18b** (13 mg, 31%) as a colorless oil.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 3.09 - 2.97 (m, 2H), 2.62 - 2.51 (m, 4H), 2.14 (dd, J = 19.5, 5.3 Hz, 4H). These

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



**hexahydroazulene-2,5(1H,3H)-dione 18c.**

Following **GP16** with **2c** (328 mg, 1.95 mmol) and dimethyl-3-oxoglutarate (0.22 mL, 1.50 mmol) during 8 hours. The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/1; Rf 0.34 in EtOAc/Cyclohexane = 1/1) to give compound **18c** (60 mg, 24%) as a colorless oil.

**IR (cm<sup>-1</sup>):** 3463, 2929, 1739, 1697, 1456, 1406, 1280, 1235, 1161.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 2.67-2.51 (m, 5H), 2.48-2.36 (m, 3H), 2.17-2.09 (m, 1H), 2.07-2.00 (m, 1H), 1.96-1.89 (m, 1H), 1.84-1.71 (m, 2H), 1.56-1.45 (m, 1H).

**<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):** δ 217.2, 211.8, 44.4, 44.3, 44.2, 43.4, 39.7, 35.7, 30.1, 20.4.

**HRMS (ESI)** calcd for C<sub>10</sub>H<sub>14</sub>O<sub>2</sub>Na [M+Na]<sup>+</sup>: 189.0886; found: 189.0885.



**ethyl 2-methyl-6-oxo-3a,4,5,6,7,7a-hexahydrobenzofuran-3-carboxylate 20**

Following **GP15** with **2a** (57 mg, 0.26 mmol), ethyl acetoacetate (26 μL, 0.20 mmol, 1.0 equiv) and DBU (0.06 mL, 0.40 mmol, 2.0 equiv) during 30 min. The crude product was purified by flash chromatography on silica gel (eluent: EtOAc/Cyclohexane = 1/2; Rf 0.25 in EtOAc/Cyclohexane = 1/2) to give compound **20** (45 mg, 99%) as a colorless oil.

**<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 5.06 (dt, *J* = 10.0, 3.7 Hz, 1H), 4.23 - 4.14 (m, 2H), 3.53 - 3.46 (m, 1H), 2.78 (dd, *J* = 17.0, 3.6 Hz, 1H), 2.68 (dd, *J* = 17.0, 3.8 Hz, 1H), 2.35 - 2.27 (m, 1H), 2.24 - 2.15 (m, 4H), 2.11 - 2.04 (m, 1H), 2.01 - 1.92 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H). These data are in good agreement with those reported in the literature.<sup>[165]</sup>

<sup>164</sup> Piers, E.; Karunaratne, V. *Can. J. Chem.* **1989**, *67*, 160-164.

<sup>165</sup> Chen, X.-H.; Liu, X.-G.; M. J. T. *J. Am. Chem. Soc.* **2016**, *138*, 6364-6367.

The publication based on this research:

**1. Palladium-Catalyzed [3+2]-C-C/N-C Bond Forming Annulation.**

Liu, Y.; Mao, Z.-Y.; Pradal, A.; Huang, P.-Q.; Oble, J.;\* Poli, G.\* *Org. Lett.* **2018**, *20*, 4057-4061.

**2. Switchable selectivity in Pd-Catalyzed [3+2]-annulations of  $\gamma$ -oxy-2-cycloalkenones with 3-oxoglutarates: C-C/C-C vs C-C/O-C bond formation.**

Liu, Y.; Oble, J.;\* Poli, G.\* *Beilstein J. Org. Chem.* **2019**, *15*, 1107-1115.

**3. Palladium-Catalyzed [3+2]-C-C/N-C Bond Forming Annulation via C-H activation.**

Liu, Y.; Oble, J.;\* Poli, G.\* in process.





## Studies on Palladium-Catalyzed [3+2]-Annulation / Domino Reactions

This thesis work is consecrated to the study of palladium-catalyzed [3+2]-annulation and domino reactions. First, a new domino sequence was developed, which involves the reaction between cyclic  $\alpha,\beta$ -unsaturated- $\gamma$ -oxy-carbonyl derivatives and resonance-stabilized acetamides. The resulting bicyclic pyrrolidin-2-ones were generated through an intermolecular Pd-catalyzed allylation followed by an intramolecular aza-Michael reaction sequence. An asymmetric version was also achieved, obtaining up to 60% ee.

A new Pd-catalyzed [allylation / aza-Michael / keto  $\alpha$ -arylation] (ALAMAR) triple domino sequence was also accomplished, which allows the selective one-pot formation of fused tricyclic systems.

Lastly, two selective and complementary domino transformations have been achieved, which allow to perform C-C/O-C or C-C/C-C [3+2]-annulations at will. These transformations occur through an intermolecular Pd-catalyzed C-allylation / intramolecular O- or C-1,4-addition sequence, respectively.

**Keywords:** Palladium; Catalysis; [3+2]-Annulation; Allylation; Michael reaction; Domino; Cascade.

## Études des Réactions Domino d'Annélation [3+2] Palladocatalysées

Ce travail de thèse est consacré à l'étude des réactions d'annélation [3+2] domino catalysées au palladium. Tout d'abord, une nouvelle séquence domino a été développée, qui implique la réaction entre les dérivés cycliques  $\alpha,\beta$ -insaturés- $\gamma$ -oxy-carbonylés et les acétamides stabilisés par résonance. Les pyrrolidine-2-ones bicycliques obtenues ont été générées par une allylation intermoléculaire catalysée au Pd, suivie d'une réaction d'aza-Michael intramoléculaire. Une version asymétrique a également été réalisée, obtenant jusqu'à 60% d'excès énantiomérique.

Ensuite, une nouvelle séquence domino triple catalysée au Pd [allylation / aza-Michael / keto  $\alpha$ -arylation] (ALAMAR) a également été réalisée, ce qui permet la formation sélective de systèmes tricycliques fusionnés en un seul pot.

Enfin, deux transformations domino sélectives et complémentaires ont été réalisées, permettant d'effectuer au choix des annulations de type C-C/O-C ou C-C/C-C [3+2]. Ces transformations se produisent par le biais d'une séquence de [C-allylation intermoléculaire / O- ou C-1,4-addition conjuguée intramoléculaire].

**Mots-clés:** Palladium; Catalyse; Annélation-[3+2]; Allylation; Réaction de Michael; Domino; Cascades.