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# Development of innovative methodologies in phosphine organocatalysis and enantioselective gold(I)-catalysis

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# Development of innovative methodologies in phosphine organocatalysis and enantioselective gold(I)-catalysis

Thèse de doctorat de l'Université Paris-Saclay  
préparée à l'Université Paris-Sud  
au sein de l'Institut de Chimie Moléculaire et des Matériaux d'Orsay  
et de l'Institut de Chimie des Substances Naturelles

École doctorale n°571 Sciences chimiques : molécules, matériaux,  
instrumentation et biosystèmes (2MIB)  
Spécialité de doctorat: Chimie

Thèse présentée et soutenue à Gif-sur-Yvette, le 12 décembre 2019, par

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## General introduction

Phosphines play a major role in modern organic chemistry. In the field of catalysis, organophosphorus-derivatives can be applied as catalysts in numerous transformations by itself, as an organocatalyst, or as ligand in organometallic catalysis.

Among the family of phosphine-promoted reactions, the most well-known transformations include the Wittig reaction, Mitsunobu reaction, Appel reaction and many others. The discovery of those transformations highlighted the development of phosphorus chemistry. However, the formation of corresponding phosphine oxides might hinder the isolation of pure target products and are low atom economy processes. Hence, phosphine-catalyzed reactions were carried out to solve those problems. One of the most widely used strategies is the *in situ* regeneration of trivalent phosphines via reduction of phosphine oxide.

On the other hand, progresses have been made in homogeneous gold catalysis. If this field was discovered last century, the research on this area increased explosively in the last decade. Organophosphines are commonly applied as ligands to coordinate the gold center. Among Au-catalyzed transformations, the cyclizations of 1,n-enynes provide simple and atom-economic approaches toward the isolation of complex cyclic structures. More interestingly, chiral phosphine ligand-gold catalyst system promotes asymmetric synthesis which is one of the hottest topics in organic chemistry for now.

This thesis includes four chapters. In **chapter I**, we have resumed our discoveries in the development of new phosphine-catalyzed reactions. We synthesized 1,2-dihydroquinolines via the development of a new catalytic Michael addition/Wittig process. We then serendipitously discovered a new phosphine-catalyzed olefination reaction.

We then focused on the general introduction of gold catalysis in **Chapter II**. Two methodologies of enantioselective gold(I)-catalyzed 1,n-enyne cyclizations will be reported in **Chapter III** and **IV**, independently. In **Chapter III**, an enantioselective 1,5-enyne cyclization/nucleophilic addition catalyzed by acyclic TADDOL-derived phosphoramidite mono-gold catalyst was carried out toward the synthesis of functionalized cyclopentenes. Finally, In **Chapter IV**, we reported a cyclization/cascade nucleophilic addition sequence of 1,6-enynes, toward the isolation of complex enantioenriched tetra- and penta-cycles. This transformation possesses potential in asymmetric synthesis of natural products.



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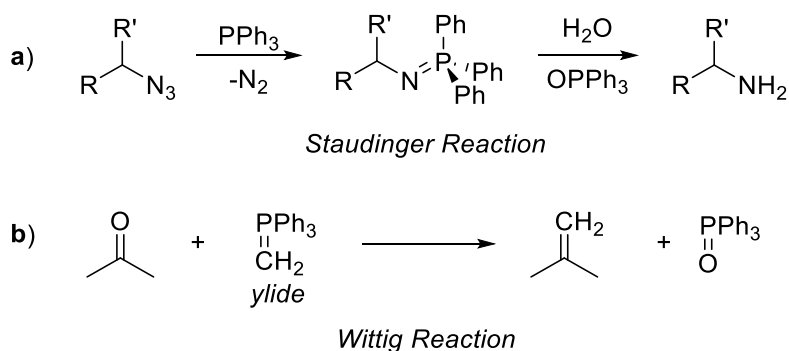
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## **Chapter 1:**

# **Development of new phosphine-catalyzed processes**

## 1.1 Brief introduction on the organophosphorus chemistry

Research on the use of organophosphorus compounds was developed as early as the start of last century. A reaction promoted by phosphine or phosphite, to transform azide derivatives to primary amines, was disclosed in 1919 (*Scheme I-1a*).<sup>1</sup> This reaction known as Staudinger reaction was one of the first to unlock the exploitation of phosphine-promoted transformations.



*Scheme I-1. Staudinger and Wittig reactions*

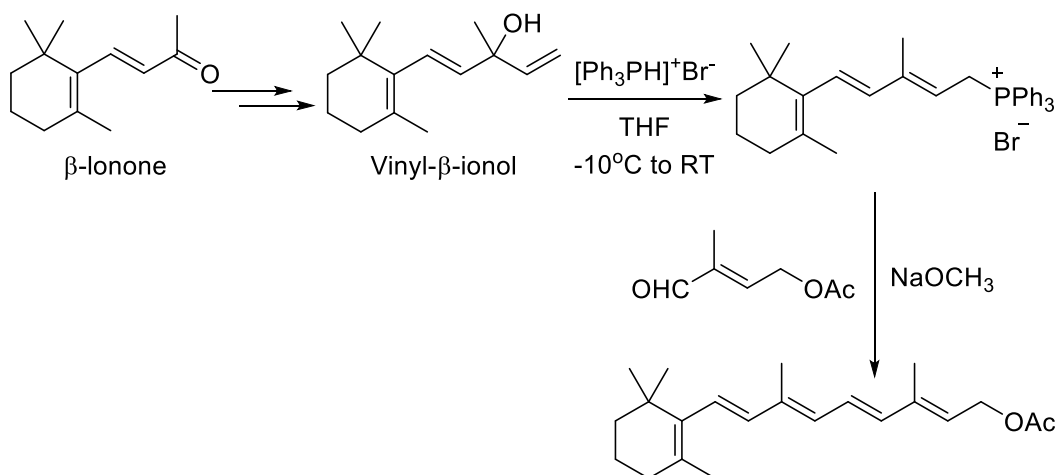
In 1953, an olefination reaction was discovered by Wittig *et al.*<sup>2</sup> This transformation, described in just six-line's text publication, was the reaction between a ketone or an aldehyde and a phosphorus ylide, to yield an alkene and the phosphine oxide (*Scheme I-1b*). The Wittig reaction was treated as one of the most important discoveries in organic chemistry at that time. This achievement was so pivotal that brought Wittig the Nobel Prize in chemistry in 1979, for "the development of the use of boron- and phosphorus-containing compounds, respectively, into important reagents in organic synthesis". Wittig olefination was applied in numerous methodologies and syntheses for the formation of alkenes and brought a huge influence in both academic and industrial area.<sup>3</sup> An important example was the development of industrial syntheses of vitamin A and carotenoid by BASF Group. A sophisticated process was accomplished to synthesize vitamin A acetate from vinyl- $\beta$ -ionol directly through a Wittig reaction, the corresponding producing plant came to stream in 1971. During their investigation, different phosphonium salt and aldehyde combinations were tested ( $C_{15}+C_5$ ,  $C_{13}+C_7$ , *etc.*, *Scheme I-2*).<sup>4</sup>

<sup>1</sup> Staudinger, H.; Meyer, J. *Helvetica*. **1919**, *2*, 635.

<sup>2</sup> a) Wittig, G.; Schöllkopf, U. *Chem. Ber.* **1954**, *87*, 1318. b) Wittig, G.; Geissler, G. *Liebigs Ann. Chem.* **1953**, *580*, 44.

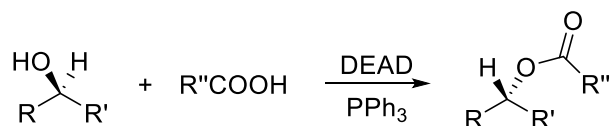
<sup>3</sup> Pommer, H. *Angew. Chem. Int. Edit.* **1977**, *16*, 423.

<sup>4</sup> Pommer, H. *Angew. Chem.* **1960**, *72*, 10.



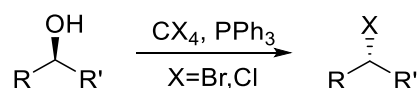
*Scheme I-2. BASF synthesis of Vitamin A acetate*

The renaissance of organophosphorus chemistry between the 60's and the 70's was marked by the discovery of different reactions promoted by trivalent phosphines. As a prime example, we can cite the Mitsunobu reaction, first reported in 1967 by Japanese chemists (*Scheme I-3*).<sup>5</sup> This reaction transforms primary or secondary alcohols to a variety of other functions (such as esters, phenyl ethers, thioethers and so on), using triphenylphosphine and diethyl azodicarboxylate (DEAD reagent). When chiral secondary alcohols are employed as starting material, the inversion of stereochemistry can be observed. Besides, the reaction condition being mild in most cases, Mitsunobu reaction is an intuitive choice for the inversion of stereogenic centers in the context of total synthesis of natural compounds.



*Scheme I-3. Mitsunobu reaction*

As a last representative example, we can cite the Appel reaction, to convert primary or secondary alcohols into their corresponding alkyl halides (*Scheme I-4*). The transformation was highlighted by its application in the synthesis of bradykinin (a pharmacologically active peptide widely used in dilating blood vessel).<sup>6</sup>



*Scheme I-4. Appel reaction*

<sup>5</sup> a) Mitsunobu, O. *Synthesis*. **1981**, 1. b) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, 40.

<sup>6</sup> Appel, R.; Willms, L. *Eur. J. Inorg. Chem.* **1979**, 112, 1064.

---

Considering the importance of such reactions in organic synthesis, we can only bow in the front of these pillars of organic chemistry. However, some negative sides of these venerable transformations could be noted.

## **1.2 Drawbacks of stoichiometric organophosphorus promoted reactions**

Even if numerous advantages were taken from phosphine-promoted reactions, we can also notice that classical organophosphorus promoted reactions possess several drawbacks.

### **1.2.1 Low atom economy**

As a stoichiometric process, at least one molar equivalent of phosphine reagent would be required along with the formation of stoichiometric quantity of corresponding phosphine oxide. Even though the strong phosphine-oxygen bond is the main driving force for the completion of those reactions, it brings the problem of low environmental sustainability.

In the past, the phosphorus reagents have been already widely applied in industry at a production scale, but we can argue that now it will be more difficult to achieve industrial applications, because of the use of huge quantity of organophosphorus compounds and the formation of large quantity of phosphine oxide waste.<sup>7</sup>

### **1.2.2 Purification problem**

Obstacles during the purification process are mainly caused by phosphine oxide. In many cases, the formation of byproduct phosphine oxide, such as triphenylphosphine oxide (TPPO), hampers to purify the target compound, and is very difficult to be removed from the crude reaction mixture.

Based on these drawbacks in the stoichiometric organophosphorus promoted reactions, it was become urgent to develop eco-friendlier versions of these reactions.

## **1.3 Development of alternatives to the phosphine-promoted reactions**

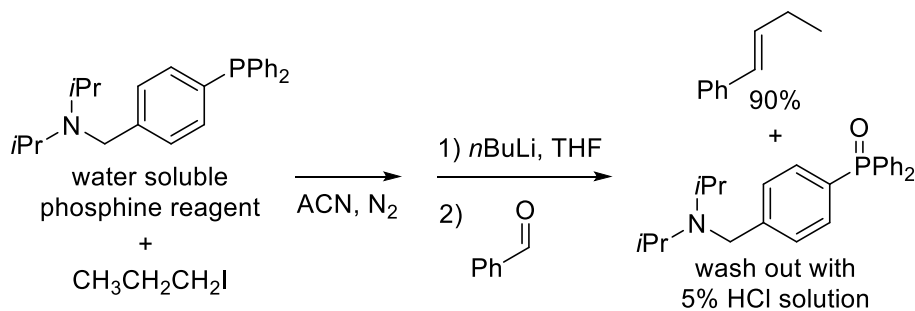
Different strategies were developed to simplify stoichiometric phosphine-promoted transformations based on various defaults in those transformations.

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<sup>7</sup> Kolodiaznyy, O. I. *Org. Process Res. Dev.* **1999**, *3*, 381.

### 1.3.1 Use of water soluble phosphines

Phosphine-promoted reactions such as a triphenylphosphine-promoted Wittig reaction faced the severe problem to separate the formed olefin from the triphenylphosphine oxide byproduct. The application of water soluble phosphine reagent could avoid this purification problem. This method was firstly used by Bottaro,<sup>8</sup> and a simple 4-diisopropylamino-methyltriphenylphosphine was prepared and proved to possess the same reactivity as triphenylphosphine in Wittig reaction (*Scheme I-5*).



*Scheme I-5. Water soluble phosphine*

Similar strategies taking advantage of the solubility of phosphine reagent were also discovered in Mitsunobu reaction. Normally Mitsunobu reaction faces stoichiometric utilization of both phosphine reagent and DEAD (diethyl azodicarboxylate) and their corresponding byproducts. A series of phosphines were used to replace TPP such as ferrocenyl tagged phosphine, phosphonium ion tagged phosphine reagent, *etc.*<sup>9</sup>

### 1.3.2 Immobilization of the phosphine reagent

Since an insoluble *polymer-supported phosphine* can be separated from reaction system by simple filtration, strategies that immobilize trivalent phosphine on polymer were developed. One of the earliest work to facilitate a stoichiometric phosphine-promoted reaction using polystyrene as the polymer support was applied in a Wittig reaction. With the use of a cross linked macroporous polymer, up to 93% yield of the target olefin could be obtained.<sup>10</sup>

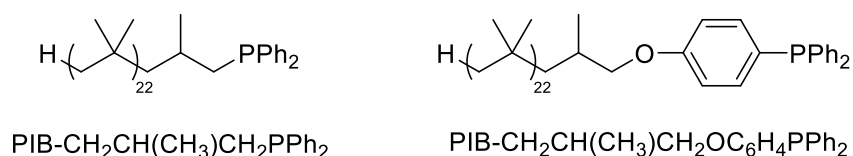
Some works were reported after following this idea, but otherwise studies that focus on a phosphine linked to soluble polymers are quite limited. In 2011, Hobbs and coworkers reported the use of terminally functionalized polyisobutylene (PIB), a nonpolar phase selective support. The PIB-phosphine derivative was used and the corresponding phosphine oxide could be removed in heptane phase and reused after reduction (*Scheme I-6*).

<sup>8</sup> Bottaro, J. C. *Synth. Commun.* **1985**, *15*, 195.

<sup>9</sup> But, T. Y. S.; Toy, P. H. *Chem. Asian. J.* **2007**, *2*, 1340.

<sup>10</sup> Bergbreiter, D. E.; Yang, Y. C.; Hobbs, C. E. *J. Org. Chem.* **2011**, *76*, 6912.

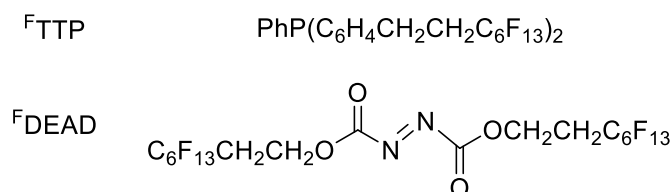
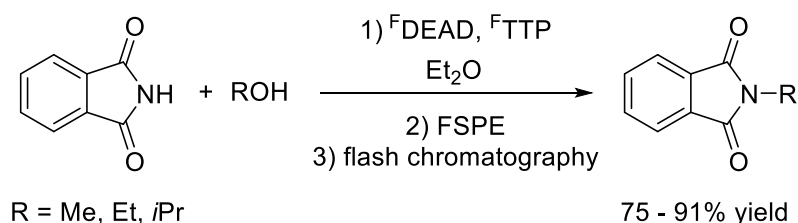




*Scheme I-6. Nonpolar phase selective polymer-phosphine*

### 1.3.3 Fluorous-containing phosphines

Fluorous-containing reagents were also applied to try to more easily isolate the product and facilitate the separation of the phosphine oxide. Fluorous phosphine and fluorous azodicarboxylate derivatives were employed in a Mitsunobu reaction (*Scheme I-7*).<sup>11</sup> With rapid solid phase extraction (spe) over fluorous silica, pure target compounds were isolated in excellent yields. The fluorous reagents have been recovered and reused.



*Scheme I-7. Fluorous containing reagents in Mitsunobu reaction*

All those strategies are only focused on avoiding difficult purification processes, but cannot solve the fundamental problem of the stoichiometric use of phosphine reagent and the formation of stoichiometric amounts of byproduct.

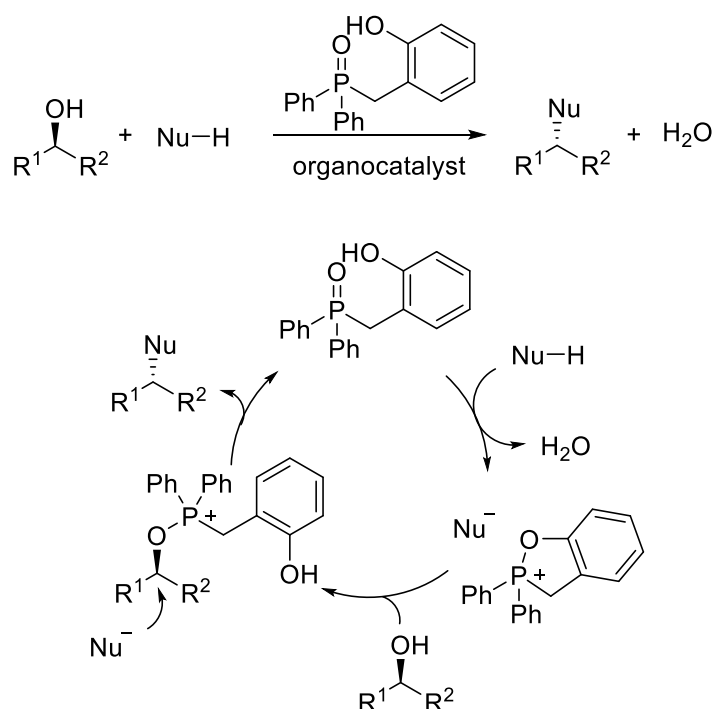
### 1.3.4 P(V) redox neutral method

More recently, the first catalytic nucleophilic substitution of alcohols, in other words an P(V)-catalyzed Mitsunobu reaction, was designed and reported.<sup>12</sup> The catalytic Mitsunobu reactions published before were mainly focused on modification of the original reaction conditions. In fact, the studies of *in situ* regeneration of trivalent phosphine and DEAD always applied respectively stoichiometric quantity of reducing agent and oxidant. The latest result inaugurated a new concept to only treat the substrate and an acidic nucleophile with a

<sup>11</sup> Dandapani, S.; P. Curran, D. *Tetrahedron* **2002**, *58*, 10.

<sup>12</sup> Beddoe, R. H.; Andrews, K. G.; Magné, V.; Cuthbertson, J. D.; Saska, J.; Shannon-Little, A. L.; Shanahan, S. E.; Sneddon, H. F.; Denton, R. M. *Science* **2019**, *365*, 6.

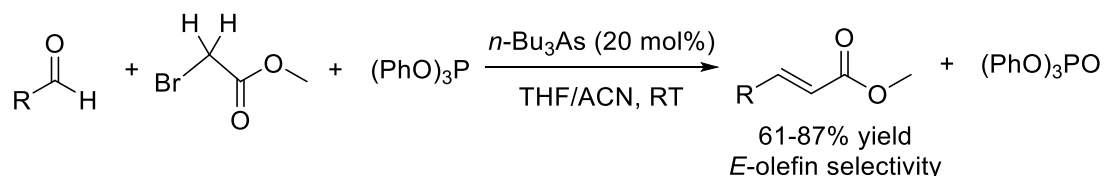
catalytic amount of well-designed P(V) molecule, to achieve high atom economy with only H<sub>2</sub>O as byproduct (*Scheme I-8*).



*Scheme I-8. P(V)-catalyzed Mitsunobu reaction*

### 1.3.5 Wittig-type catalytic reactions

In the past, some other strategies were applied. For example, a catalytic process was developed in a Wittig-type reaction by Huang *et al.*<sup>13</sup> A tributylarsine-catalyzed olefination methodology was disclosed with bromo-compounds and aldehydes as substrates, treated with potassium carbonate and triphenylphosphite (*Scheme I-9*). The high activity of the arsonium ylides promoted the olefination with high *E*-stereoselectivity of the double bond. The tributylarsine oxide formed during the reaction process could be easily reduced *in situ* by triphenylphosphite. This methodology was continued to be developed with antimony in this group in 1990.<sup>14</sup> Even if we note the catalytic use of *n*-Bu<sub>3</sub>As, we can also see the formation of the large amount of phosphite oxide waste, which reduces the beauty of the process.



*Scheme I-9. Catalytic Wittig-type reaction*

<sup>13</sup> Shi, L.; Wang, W.; Wang, Y.; Huang, Y. *J. Org. Chem.* **1989**, *54*, 2027.

<sup>14</sup> Liao, Y.; Huang, Y.-Z. *Tetrahedron Lett.* **1990**, *31*, 5897.

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In 2002, Tang's group found that another catalyst, PEG-telluride, whose quantity can be reduced to only 2 mol %, was a better choice for catalytic Wittig-type reactions.<sup>17</sup> Compared to the corresponding oxides of arsenic and antimony, tellurium oxide is easier to be reduced thanks to its weaker bond strength.

In those Wittig-type catalytic reactions, arsenic and tellurium were successfully applied to replace organophosphorus reagents.<sup>15</sup> Having said that, even if the corresponding oxides of these reagents are easier to reduce compared to the phosphine oxide, those compounds with arsenic, tellurium and antimony metalloids are recognized to be highly toxic and carcinogenic agents. When those compounds go into the ecosystem, serious problems such as underground water pollution, soil contamination and healthy injury of living species can be caused.<sup>16</sup> Of course, those methodologies could not be widely accepted or applied in industrial production.

In the framework of our work, we decided to focus our attention to the development of new P(III)/P(V) redox cycling processes, based on the *in situ* reduction of phosphine oxide. Before to detail our contribution in this field, we will introduce the first example of a catalytic Wittig reaction and the applications of the *in situ* reduction of phosphine oxide in important transformations. Finally, we will resume all necessary requirements to develop new catalytic processes.

## 1.4 Phosphine-catalyzed reactions *via in situ* phosphine oxide reduction

### 1.4.1 Catalytic Wittig reaction (CWR)

In 2009, O'Brien and co-workers reported the first Wittig reaction, catalytic in phosphine via *in situ* phosphine oxide reduction.<sup>17</sup> This is also the first example of this class of transformations.

A sub-stoichiometric quantity of carefully selected cyclic phosphine oxide precatalyst 3-methyl-1-phenyl phospholene-1-oxide (10 mol%) was used in this Wittig reaction. This phosphine oxide proved to be more easily reduced by the diphenylsilane than triphenylphosphine. Due to its peculiar chemoselectivity, diphenylsilane was chosen as reducing agent. It is very important to note that organic functions like an aldehyde or a

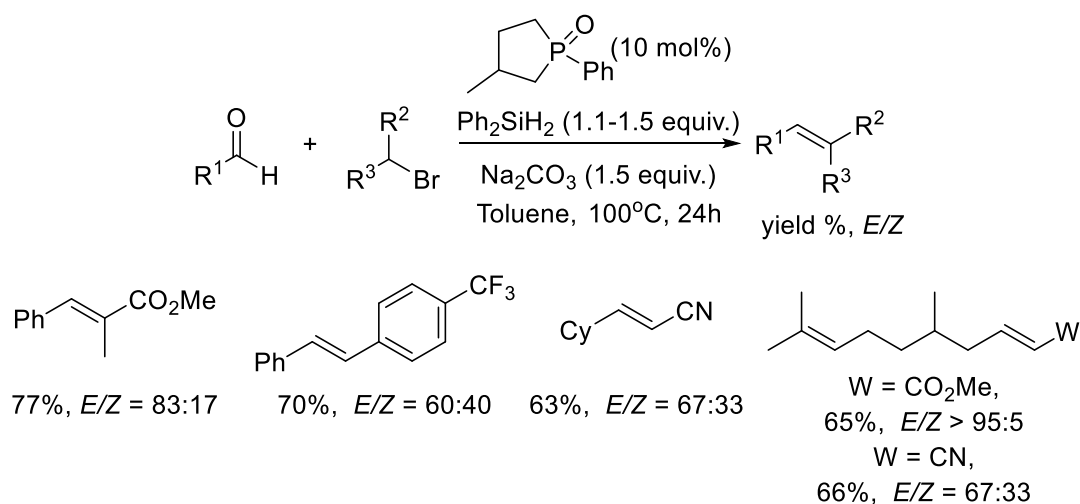
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<sup>15</sup> a) Shi, L.; Wang, W.; Wang, Y.; Huang, Y. *J. Org. Chem.* **1989**, *54*, 2027. b) Huang, Z. Z.; Tang, Y. *J. Org. Chem.* **2002**, *67*, 5320.

<sup>16</sup> a) Belzile, N.; Chen, Y.-W. *Appl. Geochem.* **2015**, *63*, 83. b) Singh, N.; Kumar, D.; Sahu, A. P. *J. Environ. Biol.* **2007**, *28*, 359.

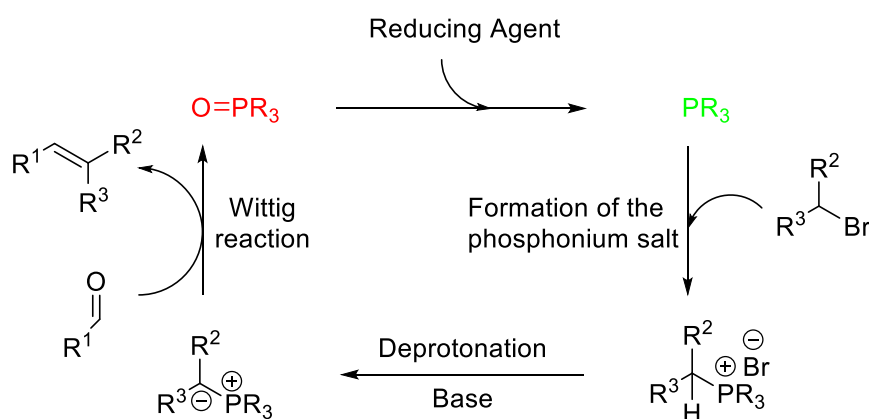
<sup>17</sup> O'Brien, C. J.; Tellez, J. L.; Nixon, Z. S.; Kang, L. J.; Carter, A. L.; Kunkel, S. R.; Przeworski, K. C.; Chass, G. A. *Angew. Chem. Int. Ed.* **2009**, *48*, 6836.

bromoalkyl could be sensitive to different reducing agents and the later have to be chosen consequently. Finally, sodium carbonate was chosen as the base to accomplish the deprotonation step. This work was applied to a broad scope of heteroaryl, aryl, and alkyl aldehydes to deliver alkenes efficiently and most examples showed very high selectivity in favor of the *E*-isomer (*Scheme I-10*).



*Scheme I-10. First catalytic Wittig reaction (CWR)*

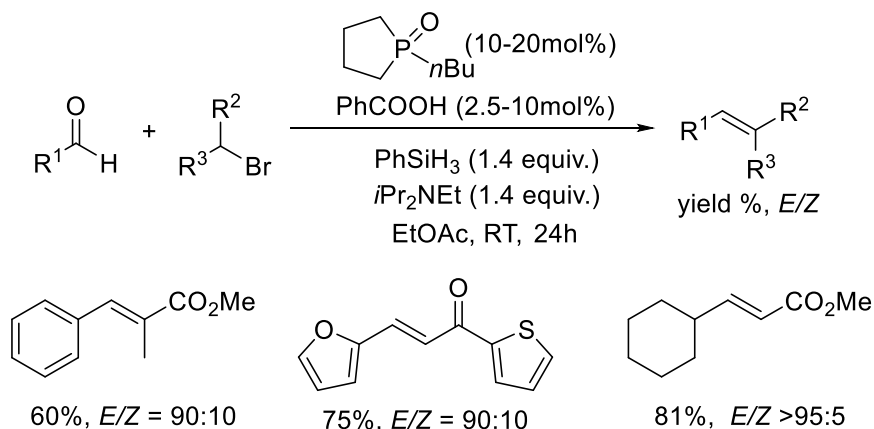
Concerning the mechanism, the catalytic cycle started with the reduction of the phosphine oxide by the silane. Then the trivalent phosphine reacted with the bromoalkyl derivative to furnish the corresponding phosphonium salt. By deprotonation with sodium carbonate, the phosphonium salt was then transformed into a phosphonium ylide. The final step delivered the olefination product and the concomitant formation of the phosphine oxide byproduct. After reduction once again of this phosphine oxide, another catalytic cycle could be started. In case of the direct use of trivalent phosphine as catalyst, the catalytic cycle starts directly from the second step (*Scheme I-11*).



*Scheme I-11. CWR mechanism*

Even though a highly user-friendly CWR was developed, there are still some drawbacks than can be noticed in this synthetic methodology.<sup>18</sup> We can highlight the harsh reaction condition (100°C, 24 h) and the lower isolated yields than in the corresponding stoichiometric reaction. There is also sometimes the problem of the low control of the stereoselectivity in the formation of two alkene isomers. To try to render this CWR more appealing, a series of improvements on these different points were studied in O'Brien's group.

At the first stage, they focused on obtaining milder reaction condition by decreasing the reaction temperature to 20°C. To achieve this goal, the structure of the phosphine oxide and the activity of the silane have been properly designed. Furthermore, one of the key points in the improvement of this catalytic reaction was to introduce an appropriate additive like a Brønsted acid to accelerate the reduction of the phosphine oxide. In this goal, an aromatic carboxylic acid was selected and added to the reaction mixture. The authors discovered the benefits of this additive serendipitously, by using an aged benzaldehyde as substrate, contaminated with ~5% of benzoic acid. With a catalytic amounts of 4-nitrobenzoic acid (2.5 to 10 mol%), the CWR can be achieved at room temperature with cyclic phosphine oxide (10 mol%) in up to quantitative yields and higher stereoselectivity, in favor of the *E*-isomer (Scheme I-12).<sup>19</sup>



*Scheme I-12. CWR reaction conditions improvement*

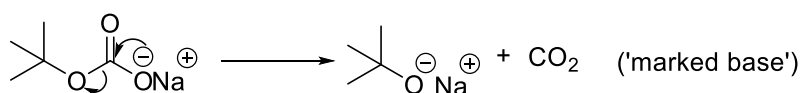
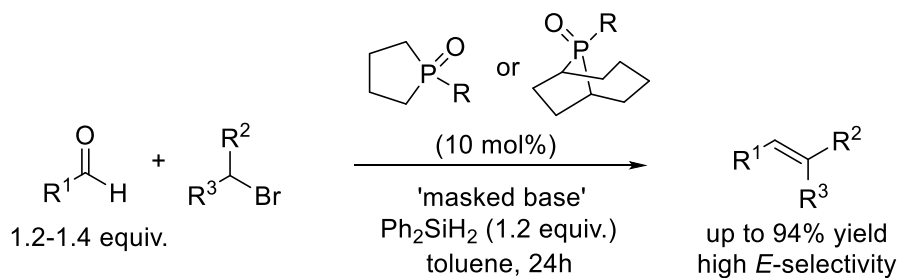
With the setup of these optimized reaction conditions (cyclic phosphine catalyst, appropriate silane, base and additive), O'Brien applied this catalytic methodology to a wide range of aldehydes, albeit with only stabilized ylides. So, the next challenge was to use semi-stabilized or unstabilized ylide in the CWR.

Compared to stabilized ylide, the ylide forming proton in phosphonium salt (the proton on the carbon atom bonded to phosphorus) for semi-stabilized ylide and non-stabilized ylide

<sup>18</sup> Marsden, S. P. *Nat. Chem.* **2009**, *1*, 685.

<sup>19</sup> O'Brien, C. J.; Lavigne, F.; Coyle, E. E.; Holohan, A. J.; Doonan, B. J. *Chem. Eur. J.* **2013**, *19*, 5854.

generation possesses higher pKa (in DMSO, semi-stabilized ylide is around 17-18, non-stabilized ylide is between 22-25). Based on the assumption in O'Brien group, to conquer this challenge, two main protocols were applied: (1) the use of a stronger base to deprotonate the ylide forming proton, and (2) modify the catalyst by changing the substituents of the phosphorus atom to tune the pKa of the ylide forming proton (*Scheme I-13*).<sup>20</sup>



*Scheme I-13. In situ generation of the base*

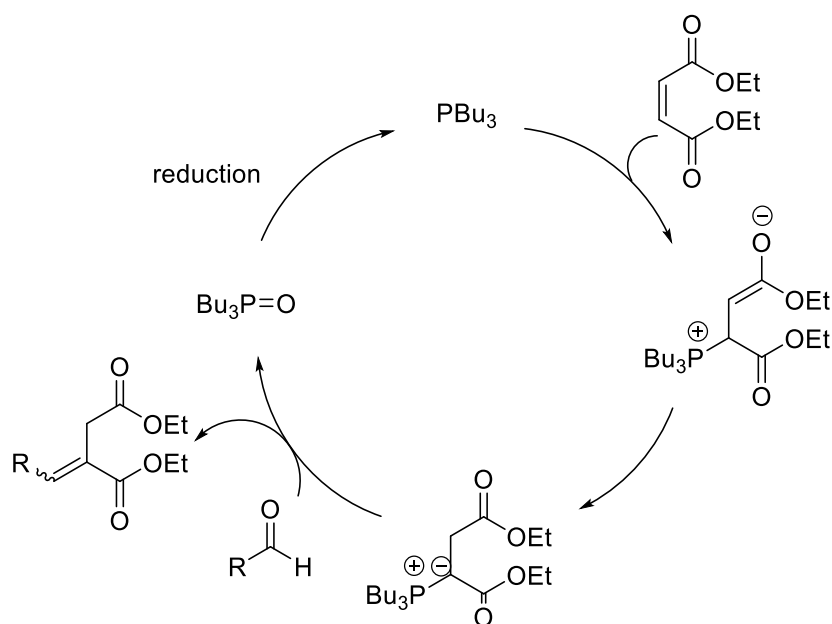
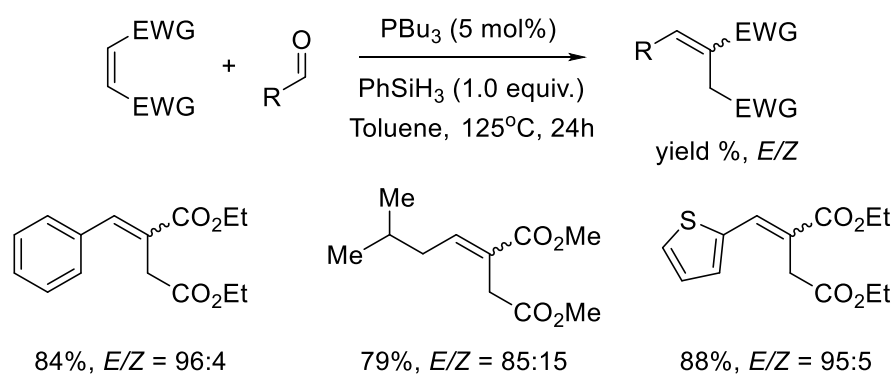
To choose a suitable base, on one hand it must be efficient enough to deprotonate the proton on the carbon atom bonded to the phosphonium salt, on the other hand, it has to achieve a selective deprotonation only of this proton. The researchers suggested and tested a masked base, sodium *tert*-butyl carbonate, which can release NaOtBu in the reaction system slowly. For the tuning of pKa of phosphonium salt, the researchers focused on the modification of the cyclic phosphines, by modifying the substituent on phosphorus center with electron-withdrawing group, to decrease the electron density of the phosphorus center. All those improvements brought a success in the use of semi-stabilized ylides in the CWR. The results showed a high *E*-selectivity (*E/Z*-selectivity up to 95/5). Non-stabilized ylides were also investigated, and because the formation rate of phosphonium salt became slower, organoiodides were used to replace organobromide substrates in these reactions. In this new methodology, organobromides also worked but brought 20% drop of isolated yield. The *E/Z* selectivity is around 75/25.

Recently, Werner developed a base-free CWR.<sup>21</sup> Tributylphosphine was used as the catalyst (5 mol %), with PhSiH<sub>3</sub> as reducing agent. Both aromatic, aliphatic and heteroaromatic aldehydes can be applied in this CWR, and the succinate products were isolated with up to 95% yield and up to 99/1 *E/Z* selectivity. Concerning the mechanism, the formation of the

<sup>20</sup> Coyle, E. E.; Doonan, B. J.; Holohan, A. J.; Walsh, K. A.; Lavigne, F.; Krenske, E. H.; O'Brien, C. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 12907.

<sup>21</sup> Schirmer, M. L.; Adomeit, S.; Werner, T. *Org. Lett.* **2015**, *17*, 3078.

phosphorus ylide was promoted first by the addition of  $\text{PBU}_3$  on well-selected substituted alkenes (maleates and fumarates), and then a proton shift leads to the phosphorous ylide. This ylide reacted with aldehyde consequently to give the corresponding succinate compounds. What is important to note in this work is that the base, which is normally used to deprotonate the phosphonium halide salt in “classical Wittig reaction” is not necessary with these reaction conditions and substrates (Scheme I-14).

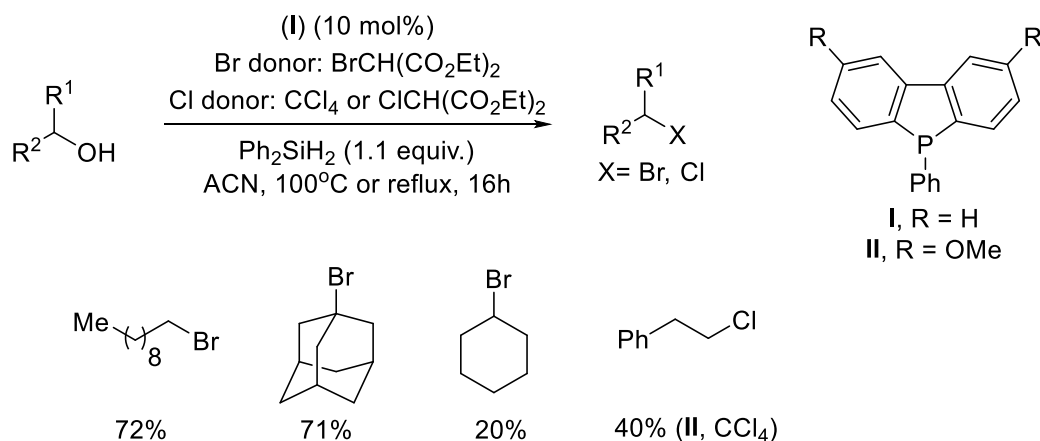


Scheme I-14. First base free CWR and the postulated mechanism

The success of the *in situ* mild reduction of phosphine oxide in CWR paved the way for a broader employment of this methodology to other phosphine-promoted reactions. In the following, applications of the P(III)/P(V) redox cycling strategy in various organophosphorus catalyzed reactions will be summarize.

## 1.4.2 Catalytic Appel reaction

Two years after the first CWR's publication, the *in situ* reduction protocol was used by van Delft and co-workers for the development of the catalytic Appel reaction (*Scheme I-15*). This transformation allowed the halogenation of differently functionalized alcohols, in moderate to good isolated yields.<sup>22</sup> Focused on five membered ring phosphine oxide as precatalyst, the authors readily synthesized and applied dibenzophosphole derivatives. Based on the reducing reagent diphenylsilane, a compatible bromine atom donor, diethyl bromomalonate, was selected for the investigation. This approach has led to the bromination of various alcohols. The chlorination reaction was also reported, promoted by  $\text{CCl}_4$ , and showed the full reaction potential although a lower conversion was detected which may be cause of the lower nucleophilicity of chloride.



*Scheme I-15. First catalytic Appel reaction*

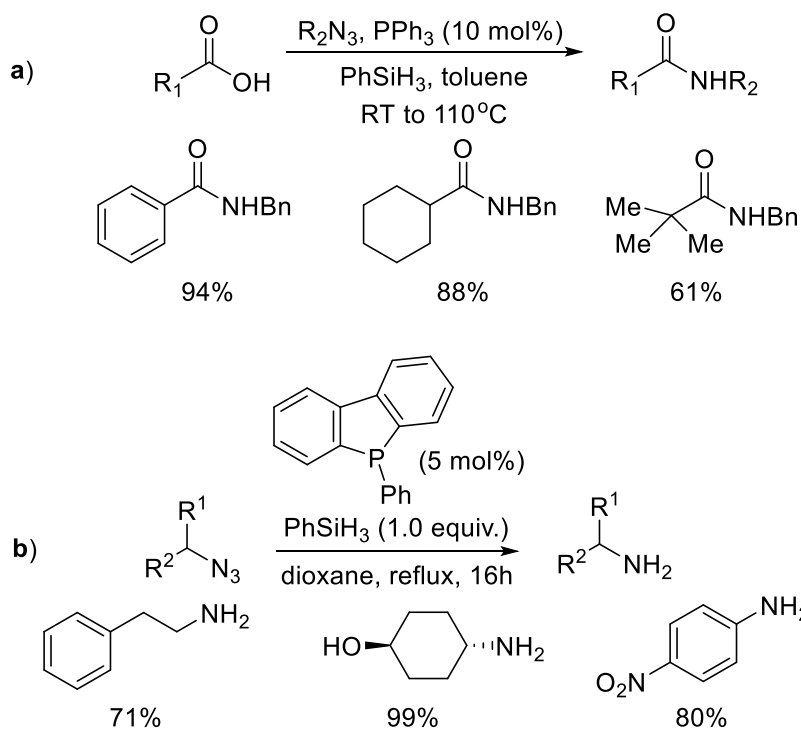
## 1.4.3 Catalytic Staudinger Reaction

A Staudinger ligation reaction was then developed (*Scheme I-16-a*).<sup>23</sup> To find a suitable phosphine oxide as precatalyst to form a compatible aza-ylide with silane, different precatalysts were tested, such as phospholane and dibenzophosphole. Given to a slower silylation rate of triphenylphosphine derived aza-ylide,  $\text{PPh}_3$  was found to be tolerant to  $\text{PhSiH}_3$ . Depending on those tests, a catalytic Staudinger ligation strategy was developed with carboxylic acid and both aliphatic and aromatic azides as coupling partners, catalyzed by  $\text{PPh}_3$  (10 mol %) and  $\text{PhSiH}_3$  as reductant, providing a sequence of amides converted from acids directly.

<sup>22</sup> van Kalker, H. A.; Leenders, S. H.; Hommersom, C. R.; Rutjes, F. P.; van Delft, F. L. *Chem. Eur. J.* **2011**, *17*, 11290.

<sup>23</sup> Kosal, A. D.; Wilson, E. E.; Ashfeld, B. L. *Angew. Chem. Int. Ed.* **2012**, *51*, 12036.





Scheme I-16. First catalytic Staudinger ligation and reduction reactions

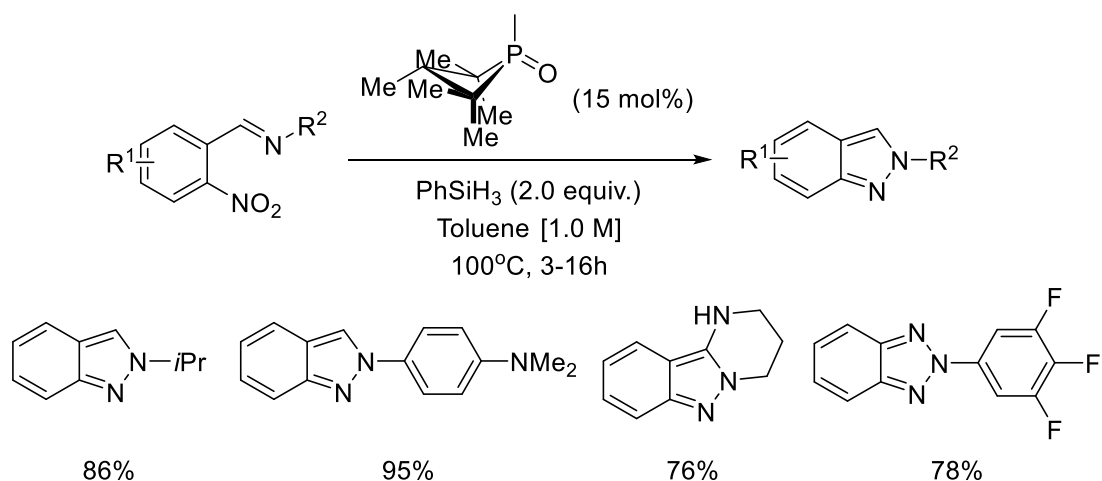
At the same time, with their work in the catalytic Appel reaction, van Delft's group developed a catalytic Staudinger reduction, with dibenzophosphole as catalyst (Scheme I-16-b). A series of azide compounds can be reduced to amines with catalytic quantity of phosphine.<sup>24</sup>

#### 1.4.4 Catalytic Cadogan reaction

More recently, the *in situ* reduction of phosphine oxide to form a P(III)/P(V) cycle was also applied in a Cadogan heterocyclization reaction.<sup>25</sup> Compared to original Cadogan reaction, which needs to perform the reaction in refluxing neat triethylphosphite (bp: 156°C), they utilized nontrigonal biphilic phosphine to facilitate the oxygen transfer from the nitro group. In their case, corresponding target compounds can be achieved in good to excellent yields at 100°C (Scheme I-17).

<sup>24</sup> van Kalker, H. A.; Bruins, J. J.; Rutjes, F. P. J. T.; van Delft, F. L. *Adv. Synth. Catal.* **2012**, *354*, 1417.

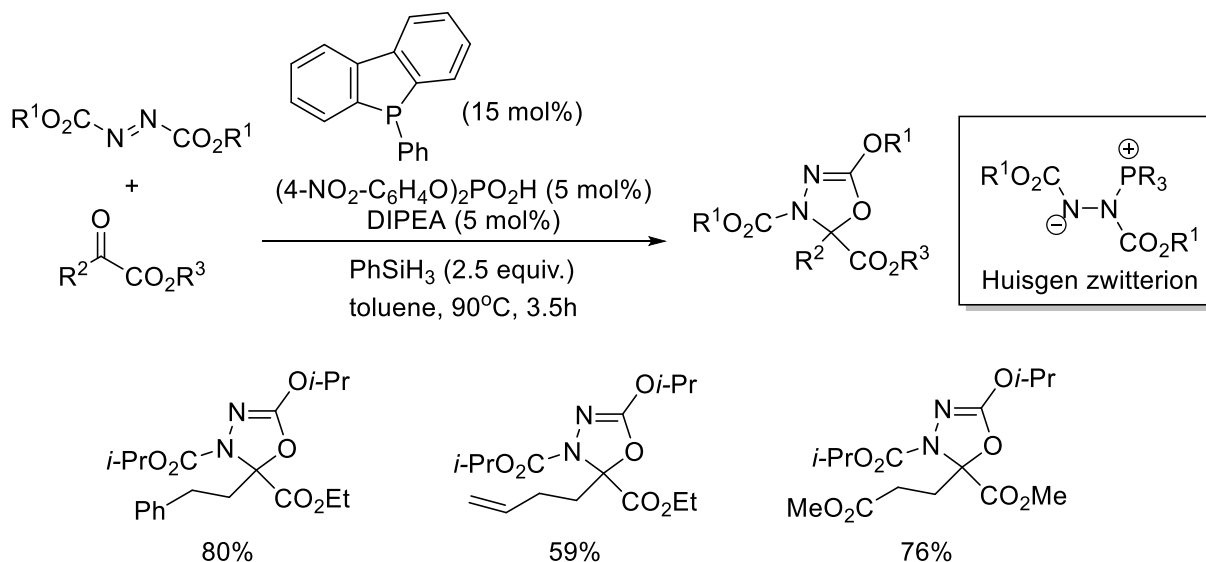
<sup>25</sup> Nykaza, T. V.; Harrison, T. S.; Ghosh, A.; Putnik, R. A.; Radosevich, A. T. *J. Am. Chem. Soc.* **2017**, *139*, 6839.



*Scheme I-17. Catalytic Cadogan reaction*

### 1.4.5 Phosphine-catalyzed tandem reactions developed in our group

Our research in redox organophosphorus catalysis started by developing the first catalytic cyclization between Huisgen zwitterion and  $\alpha$ -ketoester.<sup>26</sup> Dibenzophosphole (15 mol%) was chosen as catalyst, with phosphoric acid and DIPEA as additives. Two equivalents of azodicarboxylate substrate were used to ensure total conversion. The key intermediate to achieve this reactivity is the formation of Huisgen zwitterion from azodicarboxylate and phosphine (*Scheme I-18*).

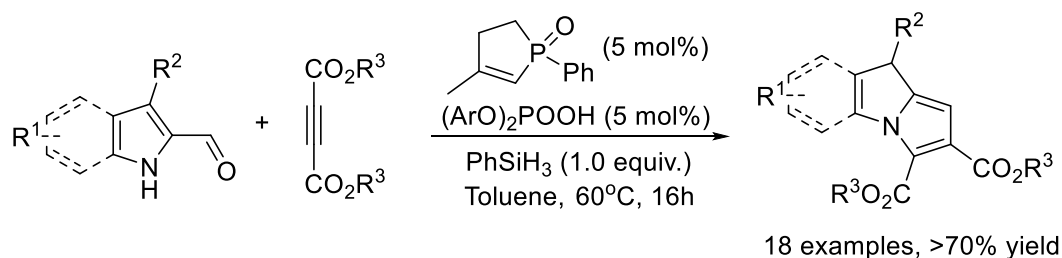


Our group also focused on new methodologies to synthesize heterocyclic compounds with the first Michael addition/intramolecular Wittig sequence.<sup>27</sup> With only 5 mol% of

<sup>26</sup> Fourmy, K.; Voituriez, A. *Org. Lett.* **2015**, *17*, 1537.

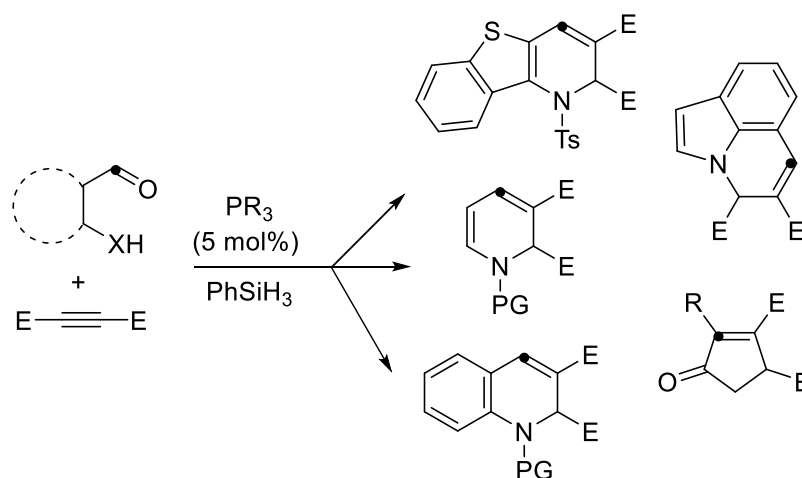
<sup>27</sup> Saleh, N.; Voituriez, A. *J. Org. Chem.* **2016**, *81*, 4371.

phospholene oxide precatalyst, *bis*(4-nitrophenyl)phosphate (5 mol%) as additive and PhSiH<sub>3</sub> in toluene at 60°C, excellent yields of pyrrolo[1,2-*α*]indole compounds can be achieved. Both electron-rich and electron-poor 1*H*-indole-2-carbaldehydes can be applied to introduce this protocol as a complement of the known methodologies for the synthesis of polycyclic nitrogen-containing heterocycles (*Scheme I-19*).



*Scheme I-19. First catalytic Michael addition/Wittig reaction*

A Michael addition/Wittig reaction to reach nitrogen-containing heterocycles and cyclopentenone derivatives was also reported in our group.<sup>28</sup> In this work, the scope was fully explored with different types of amino-aldehydes. Indeed, a library of different *N*-heterocyclic compounds possessing the core structure present in bioactive compounds can be built efficiently (*Scheme I-20*).



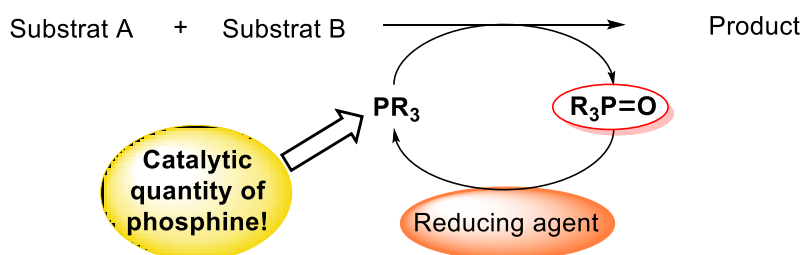
*Scheme I-20. Expanding the scope of the catalytic Michael addition/Wittig reaction*

## 1.5 Resume of the prerequisites to develop efficient phosphine-catalyzed processes *via* P(III)/P(V) redox cycling

To resume the last developments and the design of new organophosphorus-catalyzed methodologies, several fundamental elements must be considered: (1) the phosphine catalyst, (2) the reducing agent, (3) the additives and (4) the reaction conditions (*Scheme I-*

<sup>28</sup> Saleh, N.; Blanchard, F.; Voituriez, A. *Adv. Synth. Catal.* **2017**, 359, 2304.

21).



Scheme I-21. Concept to design a phosphine-catalyzed reaction

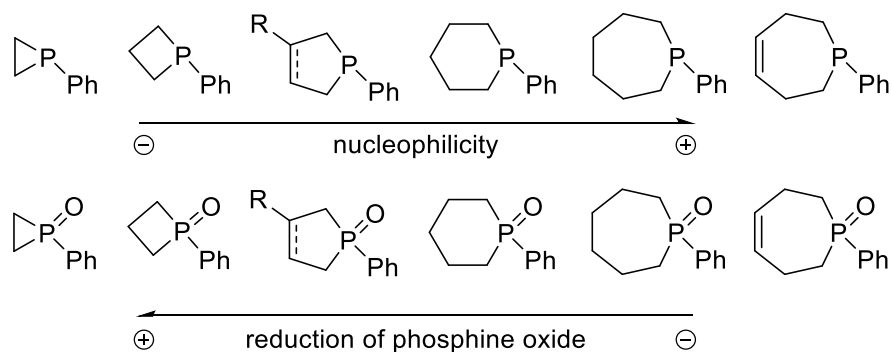
### 1.5.1 Phosphine catalyst

Activity of phosphine relies notably on its nucleophilicity. Compared to cyclic phosphines, acyclic phosphines possessing alkyl substituents are more electron-rich, and consequently showed a higher nucleophilicity. However, even if they are quite good nucleophiles, the corresponding oxides of acyclic phosphines are more difficult to reduce than cyclics (normally take longer time with same reaction condition). It is crucial to find the suitable balance between the activity and the facility to reduce the phosphine oxide.

During the development of the catalytic Appel reaction, the influence of the ring size of cyclic phosphine oxides on the reduction was investigated.<sup>29</sup> In former studies, five-membered ring cyclic phosphine oxides showed very often better activity in corresponding *in situ* reduction. We may ask ourselves why it is often this size of cycle that is always preferred, compared to smaller cycles [phosphirane (3-membered ring) and phosphetane (4)] or larger [phosphinane (6) or phosphhepane (7)].

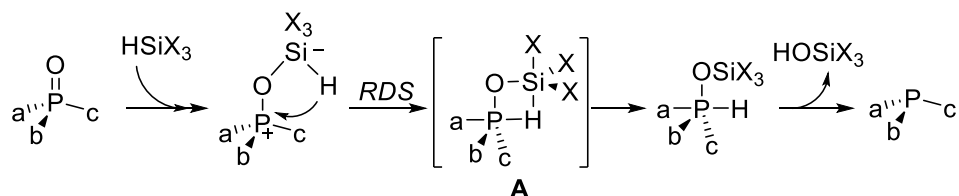
The experiments showed that five membered ring possesses a reasonable balance between nucleophilicity and workable reducing rate. With three or four membered rings, the phosphine oxide is easy to reduce, but they are weak nucleophiles to be applied as catalysts. This lower Lewis basicity was ascribed to the *s*-character in the valence lone pair. Six membered rings gave a much lower conversion compared to five membered rings with the same reaction condition. No activity was detected with both saturated and unsaturated seven membered rings. In the later cases, they possess a good nucleophilicity, but the corresponding phosphine oxide is more difficult to reduce (Scheme I-22).

<sup>29</sup> van Kalker, H. A.; Leenders, S. H.; Hommersom, C. R.; Rutjes, F. P.; van Delft, F. L. *Chem. Eur. J.* **2011**, *17*, 11290.



Scheme I-22. Influence of ring size of cyclic phosphines

The relation between the ring size of the cyclic phosphine and facility to reduce the corresponding phosphine oxide find its explanation in the bond angle imposed by the ring. In fact, the reduction of phosphine oxide by silane features a “P-O-Si-H” four-membered ring intermediate **A** (Scheme I-23). This intramolecular hydride shift from Si to P to form this four membered-ring **A** is the rate-determining step (RDS) of the reaction (Scheme I-23). The energetic barrier of this process is associated with bond angle contraction to “pseudo tetrahedral” phosphine oxide geometry to “trigonal bipyramidal” phosphorane.<sup>30</sup> Based on this mechanism, it’s understandable to speculate that the bond angle between P-C bonds on the phosphine center (a-P-b) could influence the reduction rate. When the a-P-b angle is close to 90° (which is the case in the cyclic intermediate), it should be more facile to reduce the corresponding phosphine oxide with silane. With this information, we can also easily understand why an acyclic phosphine such as triphenylphosphine oxide with [a-P-b = 110°] are more difficult to reduce.

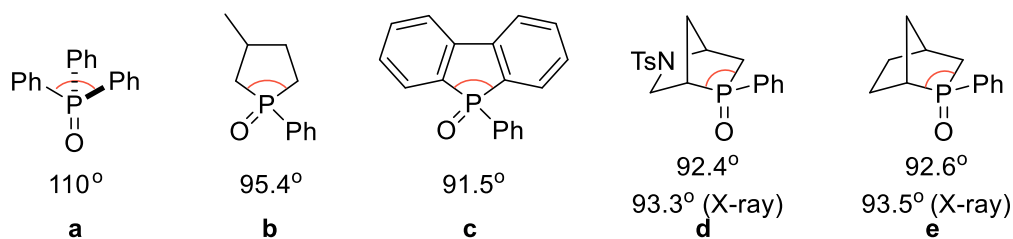


Scheme I-23. Postulated mechanism for the reduction of phosphine oxide

Recently, quite large numbers of transformations were realized with phospholane oxide and dibenzophosphole oxide precatalysts. In both structures, the a-P-b angles are close to 90°-95° (Scheme I-24). In Kwon’s group, a series of [2.2.1]bicyclic phosphine oxides were described with an (a-P-b) angle close to 90°. Experiments were designed to compare the silane-mediated reducing rate of phosphine oxides (diphenylsilane, 20 equiv.; CD<sub>3</sub>CN; 80°C). Phosphine **b** and **c** showed similar reactivity. Bicyclic phosphine oxide **d** and **e** could be totally reduced after 280 minutes, on the other side, **b** and **c** are totally reduced in 6 hours.<sup>31</sup>

<sup>30</sup> a) Fleischer, E. B.; Srivastava, T. S. *J. Am. Chem. Soc.* **1969**, *91*, 2403. b) Marsi, K. L. *J. Org. Chem.* **1974**, *39*, 3. c) Krenske, E. H. *J. Org. Chem.* **2012**, *77*, 3969.

<sup>31</sup> Zhang, K.; Cai, L.; Yang, Z.; Houk, K. N.; Kwon, O. *Chem. Sci.* **2018**, *9*, 1867.

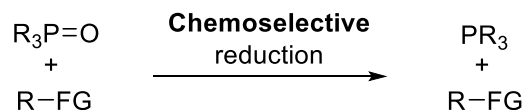


Scheme I-24. (*a-P-b*) Angles in acyclic and cyclic phosphine oxide

Besides, aryl and alkyl phosphines, cyclic or acyclic, will give different kind of phosphine ylides, which results for example in the CWR of different *E,Z*-stereoisomer *ratio* in the formation of the olefinic products.

### 1.5.2 Reducing agent

To achieve the *in situ* regeneration of the phosphine, a proper reducing agent is required. On one side, it must be active enough to reduce the phosphine oxide, on the other hand, through the existence of sensitive functions in the substrates and/or in the reaction intermediates or products (for example the aldehyde function in the CWR), the reduction reagent should be *chemoselective* to prevent those substrates from reduction (Scheme I-25). This is not an easy-achieving goal, because we can consider that the bond energy of a P-O bond [128 Kcal/mol] is quite important compared to other C-O bonds or C-X bonds present in the substrates. The choice of this reagent is one of the cornerstones in the development of new catalytic processes.



FG = ketone, aldehyde, olefin, nitrile, ester or amide groups

Scheme I-25. Selective reduction of phosphine oxide

In the literature, the reduction of phosphine oxide to trivalent phosphine can be achieved by using lithium aluminum hydride ( $\text{LiAlH}_4$ ) and a methylation reagent.<sup>32</sup> Silanes like phenylsilane ( $\text{PhSiH}_3$ ), a silane mixture ( $\text{PhSiH}_3 + \text{PhSiCl}_3$ ) and  $\text{PhSiHCl}_2$  are also empirically applied to reduce secondary phosphine oxides.<sup>33</sup> In some special cases of reduction by silane, the retention and inversion of the phosphine can be controlled by amine base as the additive reagent.<sup>35,b</sup> For deoxygenation of some acyclic phosphine oxides, hexachlorodisilane, along with an amine base in some cases were testified as an efficient method.<sup>34</sup> These examples are just some of the dozens of other methods described in the literature.<sup>35</sup>

<sup>32</sup> Imamoto, T.; Kikuchi, S.-i.; Miura, T.; Wada, Y. *Org. Lett.* **2001**, 3.

<sup>33</sup> a) Pilard, J.-F.; Baba, G.; Gaumont, A.-C.; Denis, J.-M. *Synlett* **1995**. b) L. Horner; W. D. Balzer *Tetrahedron Lett.* **1965**, 7, 1157.

<sup>34</sup> Naumann, K.; Zon, G.; Mislow, K. *J. Am. Chem. Soc.* **1969**, 91, 7012.

<sup>35</sup> Herault, D.; Nguyen, D. H.; Nuel, D.; Buono, G. *Chem. Soc. Rev.* **2015**, 44, 2508.

Among this plethora of proposed methodologies, for example, LiAlH<sub>4</sub> is a too harsh hydride source which may reduce sensitive functions in the reaction system. This is also the case of the chlorinated silane (such as Cl<sub>3</sub>SiH).

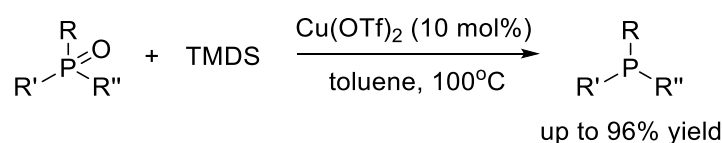
One of the other problems is the possible non desired hydrosilylation of aldehydes and ketones, because of the use of silanes in the reaction media. However, even in the case of the use of hydride sources such as phenylsilane or diphenylsilane, hydrosilylation reactions are not expected, since a metal source is needed to catalyze these reactions.<sup>36</sup>

The last very important point is related to the use of additives to promote selectively the reduction of phosphine oxide and this led us to look at few possibilities of selective activation.

### 1.5.3 Role of the additives

The additive should be carefully selected considering both: (1) the nature of the phosphine that we have to reduce and (2) the reaction which is considered. We can classify these additives in two classes: the organometallic and the organic compounds. Various reduction strategies were developed, among which the use of catalytic amount of additive possesses high potential to be applied and make improvement in organophosphorus catalysis.

Copper complex was treated to possess potential to achieve chemoselective catalytic reduction, with 3 equivalents of tetramethyldisiloxane (TMDS) and 10 mol% of Cu(OTf)<sub>2</sub>. Reduction of tertiary and secondary phosphine oxides can be achieved in good to excellent yields (*Scheme I-26*). Control experiments proved that the copper complex could not activate a hydrosilylation reaction. This transformation has high selectivity to P=O bond without touching the ketone, ether and olefin moieties in the compounds.<sup>37</sup>



*Scheme I-26. Copper-catalyzed reduction of phosphine oxide*

However, as a basic idea in green chemistry, it is better to avoid the use of metals in reaction systems when organic molecules can be used. In organophosphorus catalysis, it seems that it is also not necessary to introduce metal additives to promote this transformation. Beller's group tested various Brønsted acids in a reduction process and diaryl phosphoric acids proved to bring reasonable results in the phosphine oxide reduction, under mild conditions

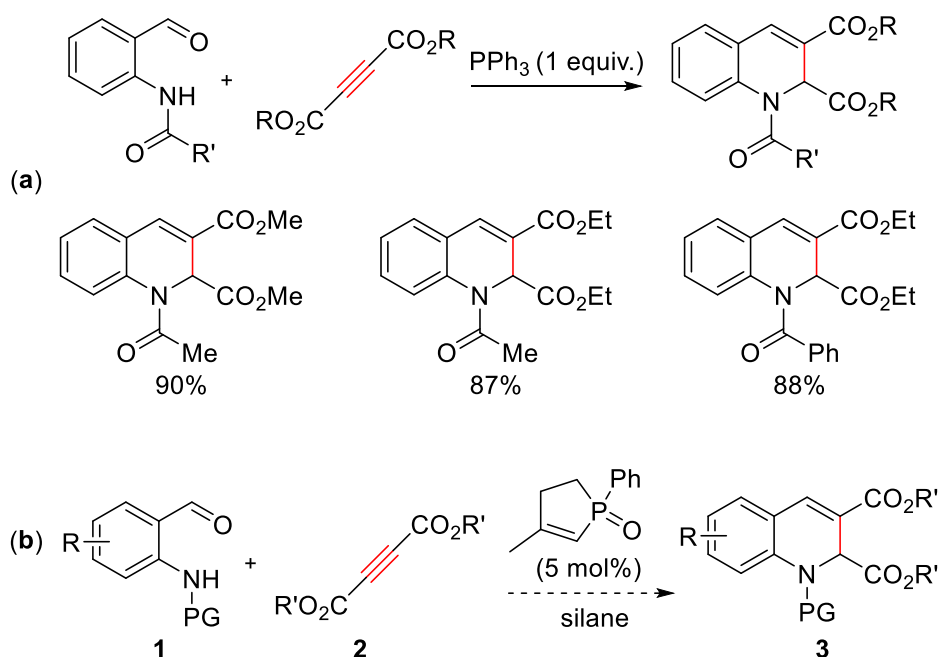
<sup>36</sup> a) Díez-González, S.; Nolan, S. P. *Org. Prep. Proced. Int.* **2007**, *39*, 523. b) Marciniec, B.; Maciejewski, H.; Pietraszuk, C.; Pawluc, P. *Hydrosilylation A Comprehensive Review on Recent Advances*, 2009.

<sup>37</sup> Li, Y.; Das, S.; Zhou, S.; Junge, K.; Beller, M. *J. Am. Chem. Soc.* **2012**, *134*, 9727.





developed a methodology using one equivalent of  $\text{PPh}_3$  to reach this goal (Scheme I-29-a).<sup>40</sup> Our initial target was to develop a catalytic Michael addition/Wittig transformation toward the synthesis of highly functionalized 1,2-dihydroquinolines (1,2-DHQ), starting from 2-aminobenzaldehydes and dialkyl acetylenedicarboxylates (DAAD) (Scheme I-29-b).

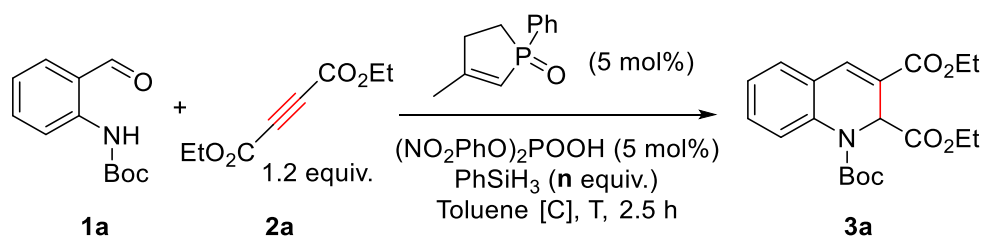


Scheme I-29. Our initial goal

Our study of this phosphine-catalyzed transformation started from the reaction between *tert*-butoxycarbonyl (Boc) protected 2-aminobenzaldehyde and diethyl acetylenedicarboxylate (1.2 equiv.). *p*-Phenylphospholene was applied as catalyst and  $[\text{PhSiH}_3/(\text{pNO}_2\text{PhO})_2\text{PO}_2\text{H}]$  as reducing system to selectively reduce *in situ* the phosphine oxide. The optimization of the reaction conditions was shown in Table I-1.

First, we verified the influence of the stoichiometry of phenylsilane to the reaction outcome (entries 1-3). By increasing the quantity of reducing reagent, a decrease of the yield of the target compound was observed: from 60 % isolated yield with 1.2 equivalent of phenylsilane, we obtained only 37% yield with 2 equivalents of phenylsilane. By increasing the quantity of silane, our goal was to have a faster phosphine oxide reduction rate, and possibly a better reactivity. Unfortunately (or not, see hereafter), another parallel reactivity seems to be taking place. Indeed, conversion was total in the case of the reaction described in entry 3, but not in the formation of the desired product. When replacing classical heating by microwave condition, the reaction time was decreased to only 2.5 hours instead of 20 hours (compare entries 3 and 4). With the use of microwave and a temperature of 100 °C, we reached 52% isolated yield (entry 5). Finally, with a more concentrated reaction mixture (0.5 mol/L), a better yield was obtained (entry 7, 67% isolated yield).

<sup>40</sup> Yavari, I.; Ramazani, A.; Esmaili, A. A. *J. Chem. Res. (S)* **1997**, 208.



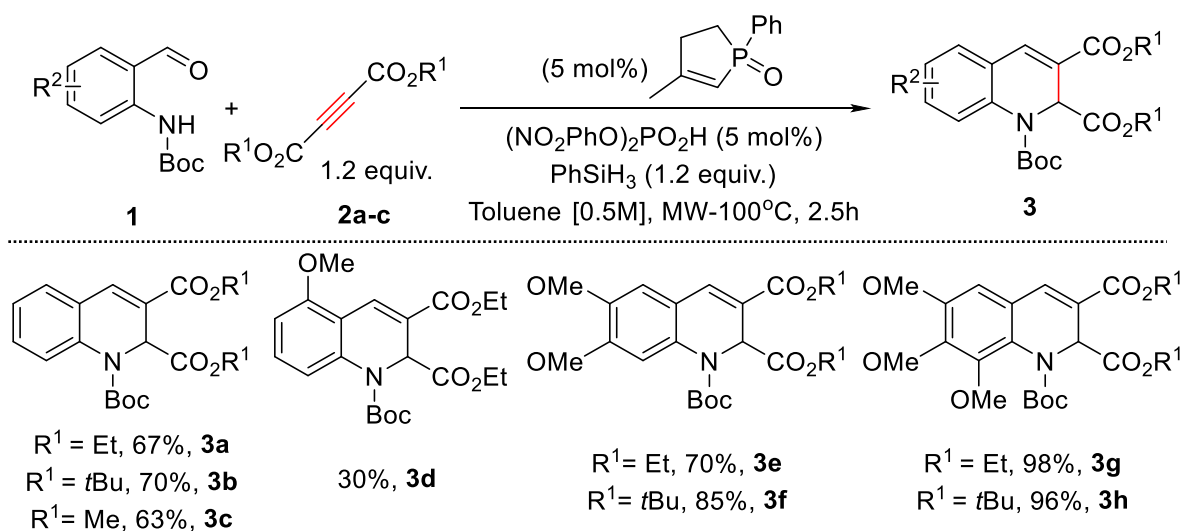
entry	n	[C]	T (h)	T (°C)	Yield <b>3a</b> (%) <sup>a</sup>
1	1.2	0.15	20	80	60
2	1.5	0.15	20	80	39
3	2.0	0.15	20	80	37
4	1.2	0.15	2.5	MW-80	39
5	1.2	0.15	2.5	MW-100	52
6	1.2	0.3	2.5	MW-100	59
7	1.2	0.5	2.5	MW-100	67

<sup>a</sup>Isolated yield at a 0.1 mmol scale.

Table I-1.

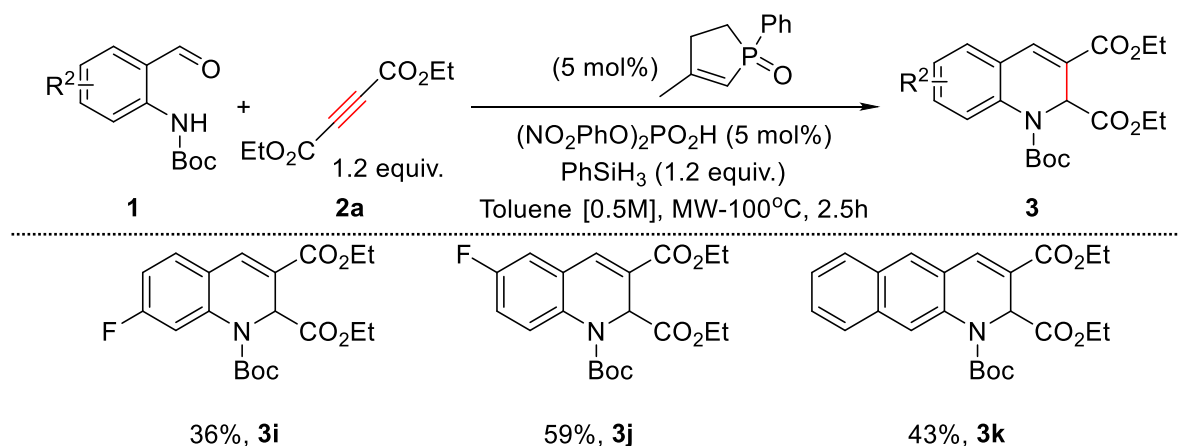
### 1.6.1.b Reaction scope

To explore the reaction scope of the formation of 1,2-dihydroquinoline-2,3-dicarboxylates, we carried out a series of tandem Michael addition/Wittig reactions using the optimized conditions (Scheme I-30). Without substituents on the amino benzaldehyde **1**, 1,2-DHQs **3a-c** could be obtained in 63-70% yields, by using ethyl, methyl and *tert*-butyl dialkyl acetylenedicarboxylates **2**. When electron-donating group like methoxy group was introduced in position 3, compound **3d** was isolated in only 30% yield. Two methoxy functions on amino benzaldehyde substrate could bring up to 85% yield (compounds **3e-3f**). When 2-amino-3,4,5-trimethoxybenzaldehyde was used as substrate, the electron-rich phenyl ring promotes the reactivity, with ethyl and *tert*-butyl dialkyl acetylenedicarboxylates, and the corresponding products (**3g, 3h**) can be obtained in 98% and 96% yield.



Scheme I-30. Reaction scope-Part 1

On the other hand, taking diethyl acetylenedicarboxylate **2a** as substrate, electron-withdrawing groups were investigated, such as fluorine group introduced in 5-position of **1**, and lower yield (36%) was acquired. When the fluorine was on 4-position, the result was a bit better (compound **3j**, 59%). 3-Amino-2-naphthaldehyde derivative reacted less well, and only 43% yield of compound **3k** could be isolated (*Scheme I-31*).

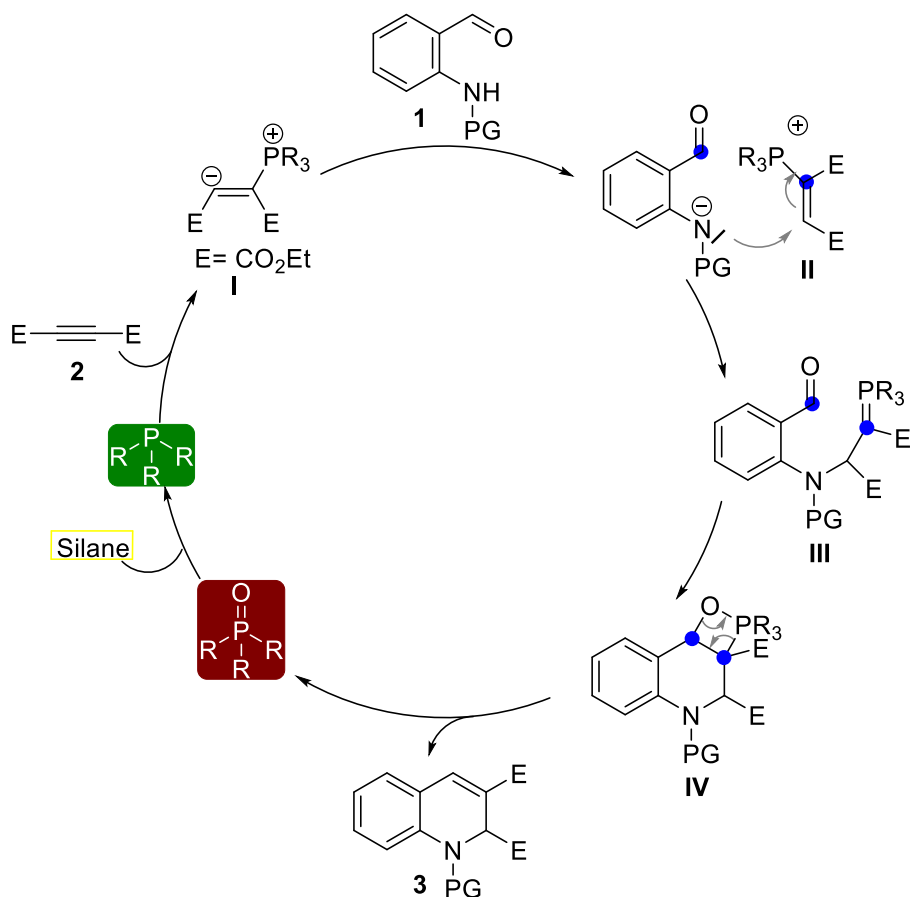


*Scheme I-31. Reaction scope-Part 2*

### 1.6.2 Postulated mechanism for the Michael addition/Wittig reaction

For the formation of the 1,2-dihydroquinoline-2,3-dicarboxylate (*Scheme I-32*) and according to the accepted mechanism,<sup>41</sup> the phosphine adds to DAAD **2**, and the zwitterionic species **I** is formed. The latter deprotonates the aniline **1** to obtain the vinylphosphonium salt **II**. After addition of the conjugate base of **1** to **II**, the phosphorus ylide **III** is formed and undergoes an intramolecular Wittig reaction to furnish the compound **3**. Finally, the phenylsilane reduces the phosphine oxide to the corresponding trivalent phosphine to close the catalytic cycle.

<sup>41</sup> Saleh, N.; Blanchard, F.; Voituriez, A. *Adv. Synth. Catal.* **2017**, *359*, 2304.



Scheme I-32. Postulated mechanism for the Michael addition/Wittig reaction

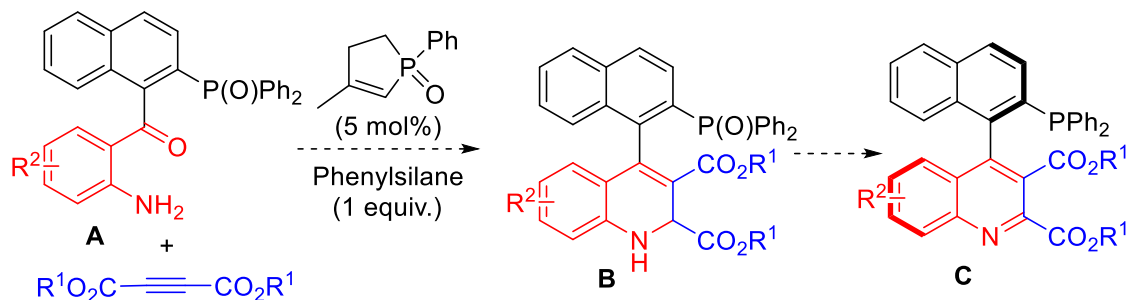
The postulated mechanism showed that the protecting groups of the 2-aminobenzaldehyde substrates could influence the reactivity and the reaction rate. In fact, both the deprotonation step and the Michael addition step could be modified by the nature of this functional group. In the same way, the electronic properties of the substituents of the aromatic part of the substrates could possibly change the reaction outcome.

In a final step, we wondered whether our methodology could not be applied to the synthesis of products of interest, and in particular to the synthesis of new chiral phosphines, possessing an axial chirality.

### 1.6.3 Toward the application of Michael addition/Wittig process in the preparation of chiral phosphine ligands

After the development of this catalytic protocol toward the synthesis of dihydroquinolines, we noticed that it could be a potential methodology to prepare chiral phosphine ligand in only few steps (Scheme I-33). Instead of using aldehyde as substrate, by applying a well-designed ketone **A**, if **A** could react under the corresponding reaction conditions, phosphine functionality could be introduced at a very early stage. Furthermore, if we utilize chiral phosphine in this process, the obtained compound **B** which possesses central chirality and axial chirality could be isolated in enantioenriched form. Continued to oxidize the

unsaturated dihydroquinolone **B** to quinolone derivative **C** and after reduction the phosphine oxide, axial chiral phosphines could be gained and used in organophosphorus catalysis or organometallic catalysis.



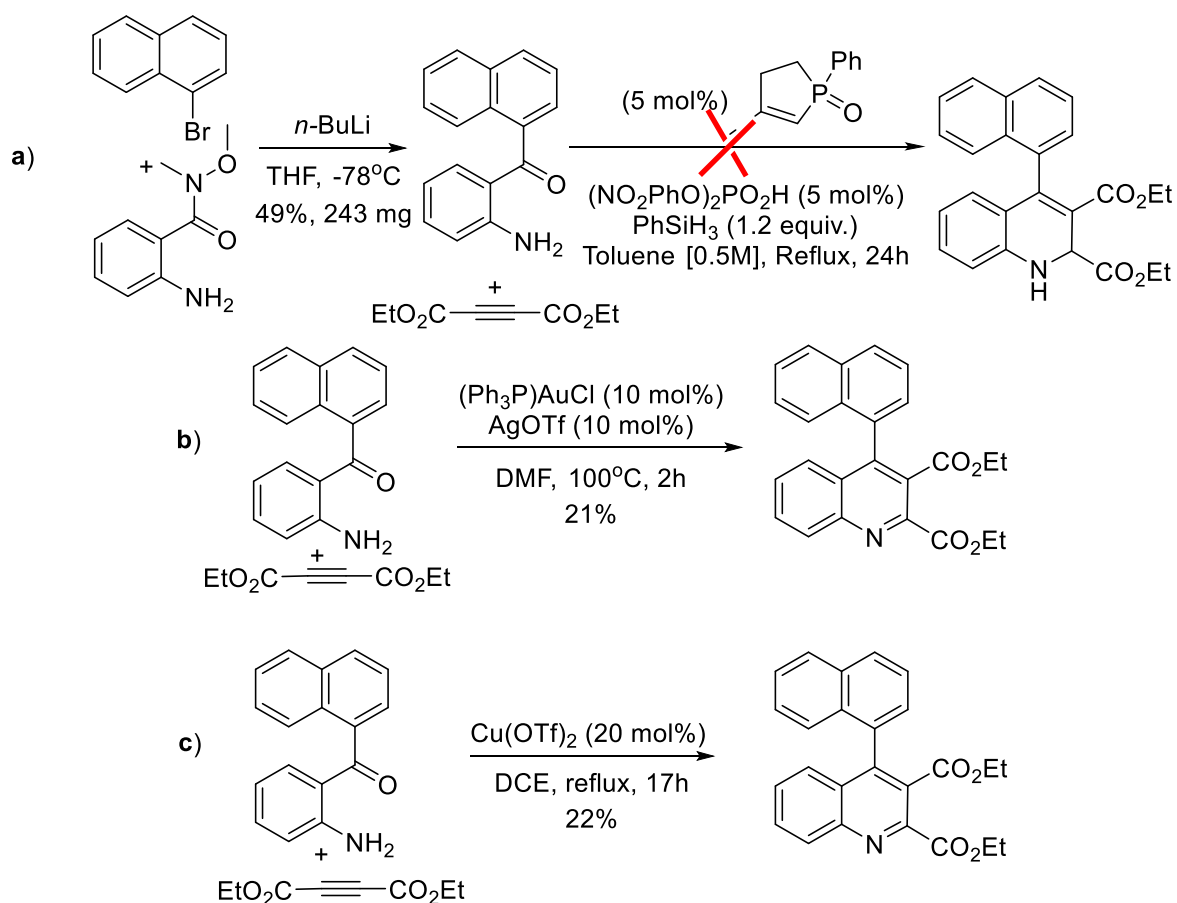
Scheme I-33. Simple preparation of chiral phosphine ligand

With this intriguing idea in mind, our first goal was to synthesize the ketone substrate. Based on the former research,<sup>42</sup> arylation of an amide can be achieved through addition of an aryllithium to a Weinreb amide. Shi's group also used this method for preparation of their substrates.<sup>43</sup> With *N,O*-dimethylhydroxylamine as a good leaving group, by treating with *n*BuLi, naphthalene moiety could be grafted to furnish the (2-aminophenyl)(naphthalen-1-yl)methanone compound in 49% yield at 243mg scale. This ketone substrate was tested under our optimal condition, however, no target dihydroquinolone compound could be observed (Scheme I-34-a). Two other protocols to prepare arylated quinolines were carried out, based on gold and copper catalyst. The corresponding target products could be accessed in 21% and 22% yield (Scheme I-34-b, c).<sup>44</sup> Even without high reactivity, this was still an exciting signal for our next goal.

<sup>42</sup> Frye, S. V.; Johnson, M. C.; Valvano, N. L. *J. Org. Chem.* **1991**, *56*, 3.

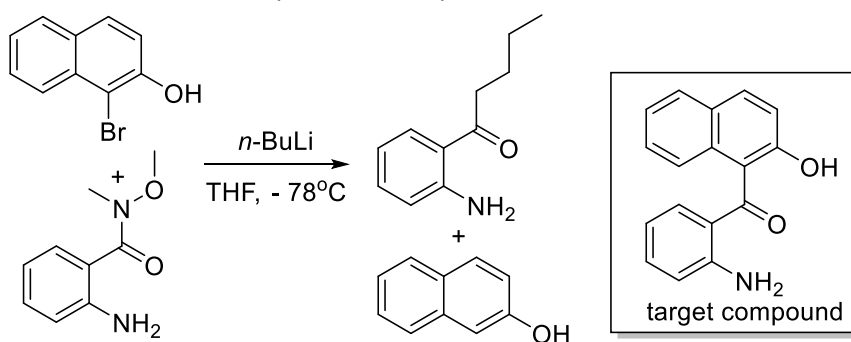
<sup>43</sup> Fan, X.; Yu, L. Z.; Wei, Y.; Shi, M. *Org. Lett.* **2017**, *19*, 4476.

<sup>44</sup> Pandit, R. P.; Lee, Y. R. *RSC Adv.* **2013**, *3*, 22039.



Scheme I-34. Toward the synthesis of dihydroquinoline derivative

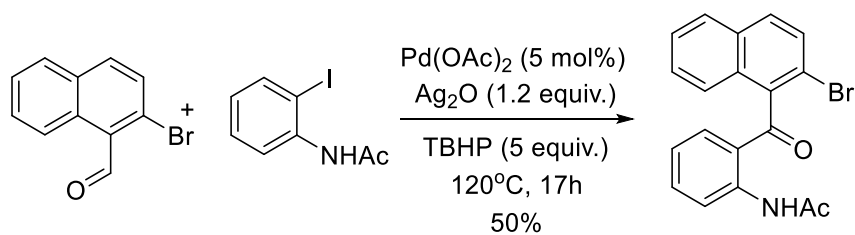
However when 2-bromo-2-naphthol was applied to introduce the aryl function, only byproducts (1-(2-aminophenyl)pentan-1-one and 2-naphthol) could be obtained, the target compound could not be detected (Scheme I-35).



Scheme I-35.

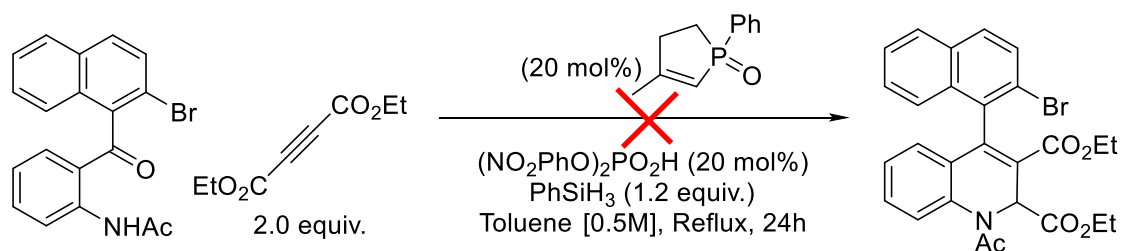
Then another group published a new palladium-catalyzed coupling reaction between 1-naphthaldehydes and *N*-(2-iodophenyl)acetamide.<sup>45</sup> With this method, target compound could be obtained in 50% yield (Scheme I-36).

<sup>45</sup> Basuli, S.; Satyanarayana, G. *Eur. J. Org. Chem.* **2018**, 2018, 957.



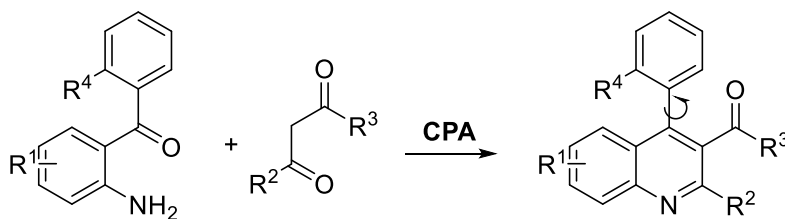
Scheme I-36.

However, when the new ketone substrate was tested in our protocol, no conversion could be detected and even we kept the reaction under reflux for 24 hours, the expected compound could not be isolated (Scheme I-37). The gold and copper-catalyzed methodologies will be tested with this substrate.



Scheme I-37.

More recently, an asymmetric synthesis of axial chiral 4-arylquinolines was reported,<sup>46</sup> by using chiral phosphoric acid (CPA) as catalyst. Rotation of the bond between quinolone and its 4-aryl moiety could be fixed, the target compounds were achieved as up to 97% *ee* with excellent yields. This could be a potential robust method toward our final goal (Scheme I-38).



Scheme I-38. Toward chiral 4-arylquinolines

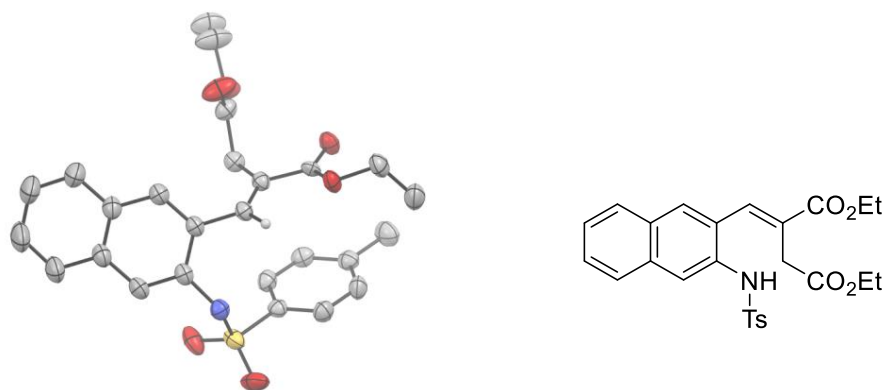
## 1.7 Toward the development of a new olefination reaction

### 1.7.1 Initial result and potential applications of a new olefination process

During the reaction scope studies for the synthesis of different 1,2-DHQs (Scheme I-31), in the case of the use of substrates possessing electron-withdrawing groups or with the use of *N*-Boc-3-amino-2-naphthaldehyde, besides the formation of the target dihydroquinoline compounds, a byproduct attracted our attention. The low yield of target product (such as **3k**) may not only be caused by low reactivity, but also it is also a clue to an unexpected activity which possesses valuable potential to be investigated. In the latter case, the byproduct was

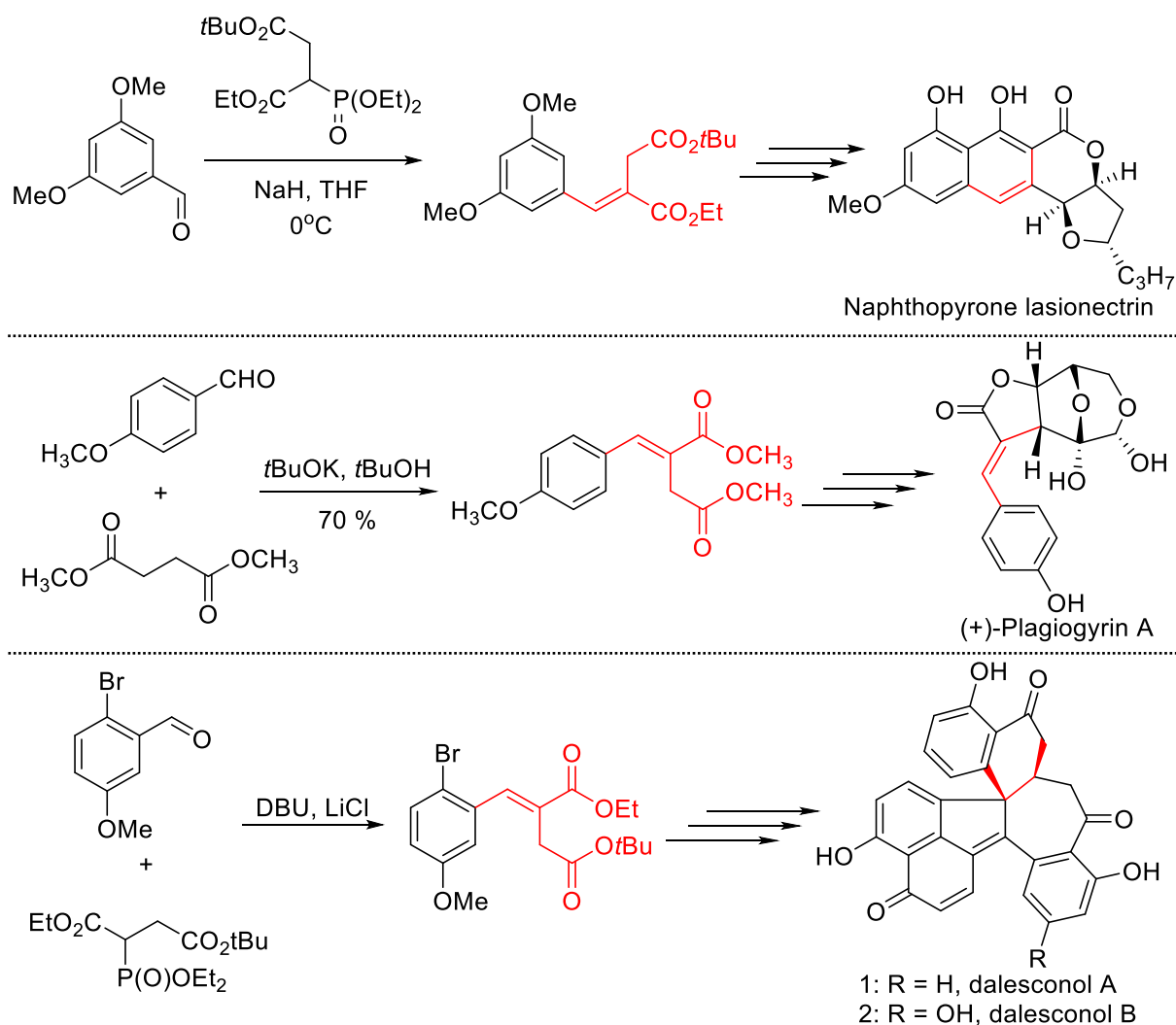
<sup>46</sup> Shao, Y. D.; Dong, M. M.; Wang, Y. A.; Cheng, P. M.; Wang, T.; Cheng, D. J. *Org. Lett.* **2019**, *21*, 4831.

isolated in 16% yield and analyzed by  $^1\text{H}$  NMR and X-ray crystallography analysis of the tosyl analogue confirmed the structure of a succinate derivative (*Scheme I-39*).



*Scheme I-39. X-ray structure of compound 4h*

Given the interest of the possible discovery of a new reactivity, we tried to optimize the reaction in order to obtain this new product as the major compound. There is also the question of the value of synthesizing such molecules.



*Scheme I-40. Succinates as building blocks in total synthesis*

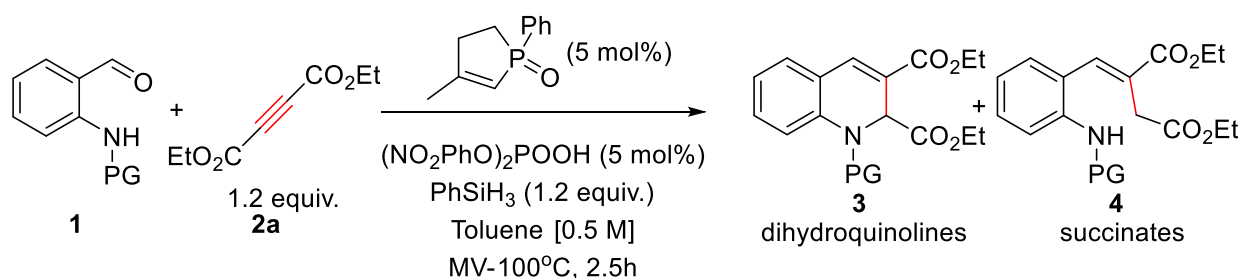


In former publications, succinate products were usually synthesized via a Stobbe condensation or a Horner–Wadsworth–Emmons reaction. The reaction conditions were normally quite harsh with notably the use of strong bases. At the same time, succinate moiety served as key building blocks in numerous total syntheses such as naphthopyrone lasionectrin, (+)-plagiogyrin A and dalesconol A and B (Scheme I-40).<sup>47</sup>

Considering the interest of succinate derivatives in organic synthesis, we thought that the discovery of new pathways for their synthesis was highly relevant.

### 1.7.2 Influence of the substrate substitution on the reaction outcome

To discover more about the new reactivity, we modified the functional group of aminobenzaldehyde (Table I-2).



entry	PG	ratio <sup>a</sup>	Yield <b>3</b> (%) <sup>b</sup>	Yield <b>4</b> (%) <sup>b</sup>
1	Boc	7.4/1	67, <b>3a</b>	9, <b>4a</b>
2	Cbz	1.3/1	47, <b>3l</b>	36, <b>4b</b>
3	H	4/1	16, <b>3m</b>	<5, <b>4c</b>
4	Bn	nd	<5, <b>3n</b>	<5, <b>4d</b>
5	Me	nd	<5, <b>3o</b>	<5, <b>4e</b>
6	Ns	1/3.1	23, <b>3p</b>	72, <b>4f</b>
7	Ts	1/3.0	23, <b>3q</b>	70, <b>4g</b>

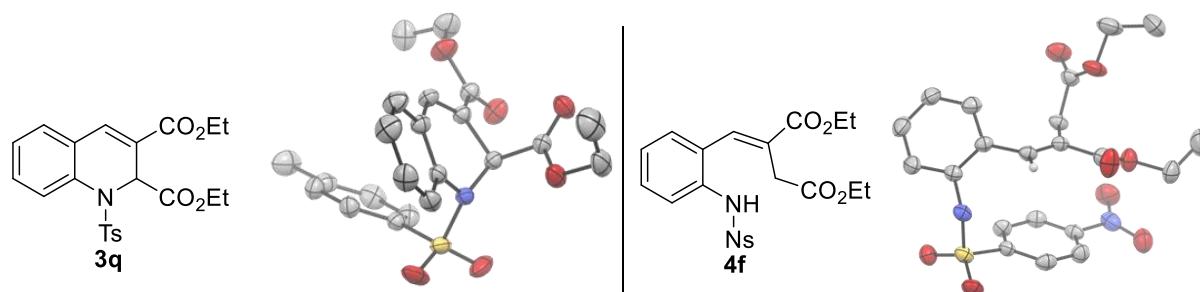
<sup>a</sup>Ratio were determined by <sup>1</sup>H NMR of the crude mixture. <sup>b</sup>Isolated yield at a 0.1 mmol scale.

Table I-2.

The starting point was the reactivity of the *N*-Boc-protected substrate **1a** (entry 1). The dihydroquinoline product was isolated in 67% yield, along with 9% isolated yield of the olefinic product. The use of the carboxybenzyl (Cbz) group gave a 1.3/1 mixture (entry 2, 36% yield of olefin). Unprotected aniline, benzyl-, or methyl-nitrogen substituted substrates gave disappointing results (entries 3-5). Finally, the use of nosyl- or tosyl-protecting groups furnished the succinates as the major products (entries 6-7, 70-72% isolated yields). We can

<sup>47</sup> a) Poral, V. L.; Furkert, D. P.; Brimble, M. A. *Org. Lett.* **2015**, *17*, 6214. b) Shi, Y.; Pierce, J. G. *Org. Lett.* **2016**, *18*, 5308. c) Snyder, S. A.; Sherwood, T. C.; Ross, A. G. *Angew. Chem. Int. Ed.* **2010**, *49*, 5146.

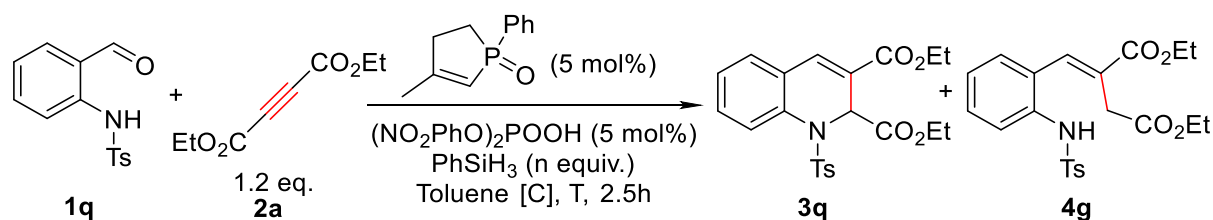
point out the huge influence of the aniline protecting group in the reaction outcome. The substrate **1a** (PG = Boc) gave mainly the cyclic product **3a**, whereas the substrates substituted with a more electron-withdrawing tosyl- or nosyl-group promoted the olefination reactivity. The molecular structures of compounds **3q** and **4f** were ascertained by X-ray crystallography studies (Scheme I-41).



Scheme I-41. X-ray structure of compounds **3q** and **4f**

### 1.7.3 Optimization of the reaction condition for the synthesis of succinate derivatives

Based on tosyl-protected aminobenzaldehyde substrate **1q**, we started to optimize the reaction conditions to obtain a better *ratio* of dihydroquinoline/succinate products and try to optimize the isolated yield of the newly desired compound (Table I-3).



entry	n	[C]	T (°C)	ratio <sup>a</sup>	Yield <b>3q</b> (%) <sup>b</sup>	Yield <b>4g</b> (%) <sup>b</sup>
1	1.2	0.5	MW-100	1/3.0	23	70
2	2.0	0.5	MW-100	1/3.8	19	73
3	2.0	0.15	MW-100	1/4.5	16	72
4	2.0	0.15	MW-80	1/7.9	11	87
5 <sup>c</sup>	2.0	0.15	MW-80	1/7.3	12	87
6 <sup>d</sup>	2.0	0.15	80	1/6.2	13	80
7 <sup>e</sup>	2.0	0.15	MW-100	nd	--	--
8 <sup>f</sup>	2.0	0.15	MW-100	nd	<5	<5

<sup>a</sup>Ratio were determined by <sup>1</sup>H NMR of the crude mixture. <sup>b</sup>Isolated yield at a 0.1 mmol scale. <sup>c</sup>2h reaction time. <sup>d</sup>40h reaction time. <sup>e</sup>Reaction conditions of entry 1, without phosphine catalyst. <sup>f</sup>Reaction conditions of entry 1, without phosphoric acid.

Table I-3.

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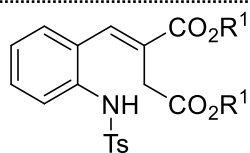
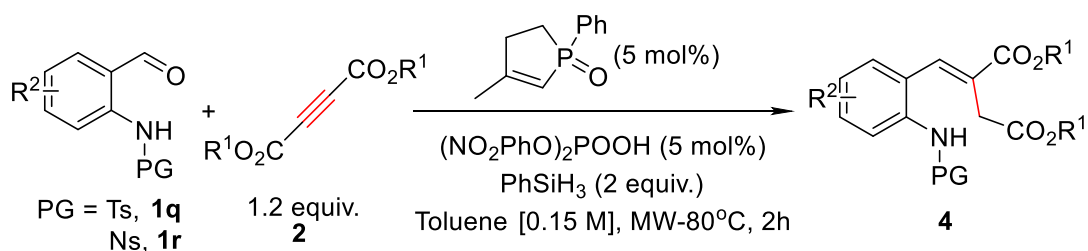
We started our optimization with the tosyl-protected substrate, in presence of 1.2 equivalent of diethyl but-2-ynedioate, using microwave heating at 100°C for 2.5 hours. We also kept the 4-methyl-1-phenyl-2,3-dihydrophosphole 1-oxide as phosphine catalyst (5 mol%) and *bis*(4-nitrophenyl)phosphinic acid (5 mol%) as additive, to facilitate the phosphine oxide reduction. Both increasing the quantity of silane and decreasing the reaction concentration had beneficial effect on the selectivity (entries 2 and 3). With 2 equivalents of PhSiH<sub>3</sub> at a 0.15 mol/L concentration, the product *ratio* increased to 1/4.5. Decreasing the reaction temperature to 80°C, under microwave heating during 2 hours, furnished the olefinic compound in 87% isolated yield, with only 12% of the dihydroquinoline derivative (entry 5). Classical heating could be employed, but with a lengthened reaction time (entry 6, 80% yield, 40h at 80°C). Finally, we verified that both the phosphine and the phosphoric acid catalysts were required for the reactivity (entries 7 and 8). Without phosphoric acid additive, dihydroquinoline could be detected in 4% <sup>1</sup>H NMR yield with only trace succinate, and reaction system with no phosphine brought no conversion of substrate.

In summary of this optimization, using microwave heating (2 h at 80°C) with 1.2 equivalents of DAAD, 2 equivalents of PhSiH<sub>3</sub> and catalytic amounts of both phosphine and phosphoric acid, it is now possible to isolate the desired product **4g** in 87% yield (entry 5). Therefore, we can begin to study the field of possibilities of this reaction.

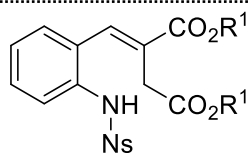
#### 1.7.4 Reaction scope of with 2-aminobenzaldehyde substrates

We extended the microwave-assisted catalytic olefination reaction between tosyl- and nosyl-protected aminobenzaldehydes and DAAD using 5 mol% of phospholene oxide precatalyst and phenylsilane, at 80°C (*Scheme I-42*).

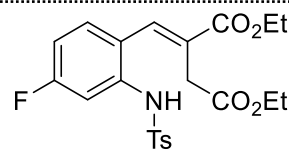
We first investigated the influence of the alkyl group of the DAAD substrate. Ethyl, *t*-butyl, or methyl groups gave the desired products **4g**, **4a** and **4b** in 64-87% yields. Next, with the nosyl functionalized aniline, diethyl (*E*)-2-((3-aminonaphthalen-2-yl)methylene)succinates **4c,4f** were isolated in good yields. Hence, tosyl- and nosyl-group on aniline are suitable to promote the new olefination process and achieved good to excellent yields of target compounds **4**. 2-Amino-4-fluorobenzaldehyde substrate furnished the corresponding olefinic product **4d** in 54% yield, as a mixture of both *Z*- and *E*-olefin. The 5-fluorobenzaldehyde derivative furnished product **4e** in 60% yield. When naphthaldehyde was used as substrate, with different DAAD up to 81% isolated yield was gained (**4h**, **4i**).



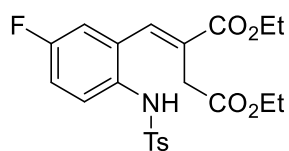
$\text{R}^1 = \text{Et}$ , 87%, **4g**  
 $\text{R}^1 = t\text{Bu}$ , 64%, **4a**  
 $\text{R}^1 = \text{Me}$ , 77%, **4b**



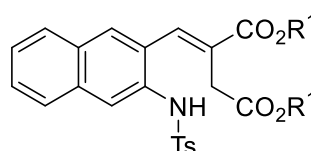
$\text{R}^1 = \text{Et}$ , 72%, **4f**  
 $\text{R}^1 = t\text{Bu}$ , 50%, **4c**



54%, **4d** ( $Z/E=7/3$ )



60%, **4e**



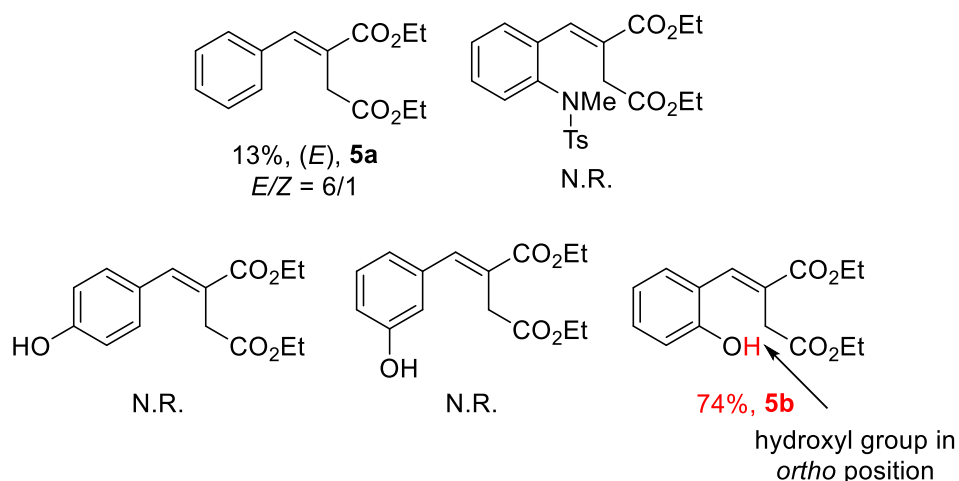
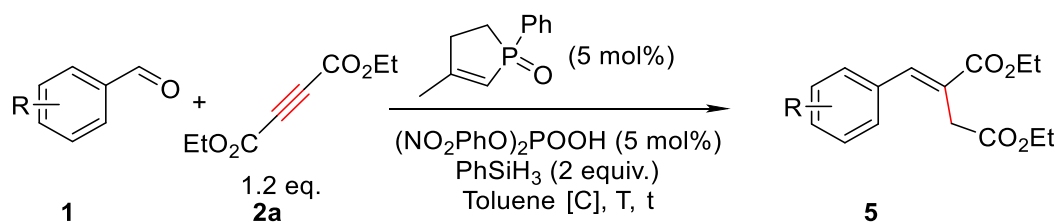
$\text{R}^1 = \text{Et}$ , 81%, **4h**  
 $\text{R}^1 = t\text{Bu}$ , 68%, **4i**

Scheme I-42. Reaction scope

### 1.7.5 Scope and limitations of the new olefination process

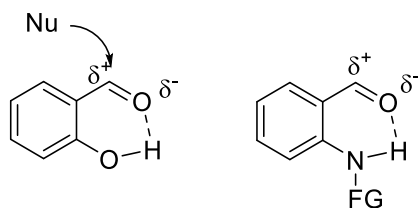
With the optimal olefination condition, we were wondering if this strategy can be expanded to unsubstituted benzaldehydes and not only 2-aminobenzaldehydes.

Benzaldehyde promoted 13% succinate compound **5a**, the *ratio* between *E* and *Z* structure was 6:1, and the two isomers could be easily separated through flash chromatography. With *para*- and *meta*-hydroxybenzaldehydes, also *ortho*-NMe(Ts) benzaldehyde, desired olefins could not be detected in none of the three examples. However, when the hydroxyl group was on *ortho*-position, we could obtain the target olefin **5b** in 74% yield (Scheme I-43).



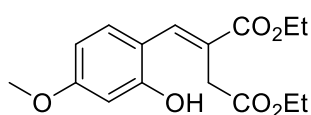
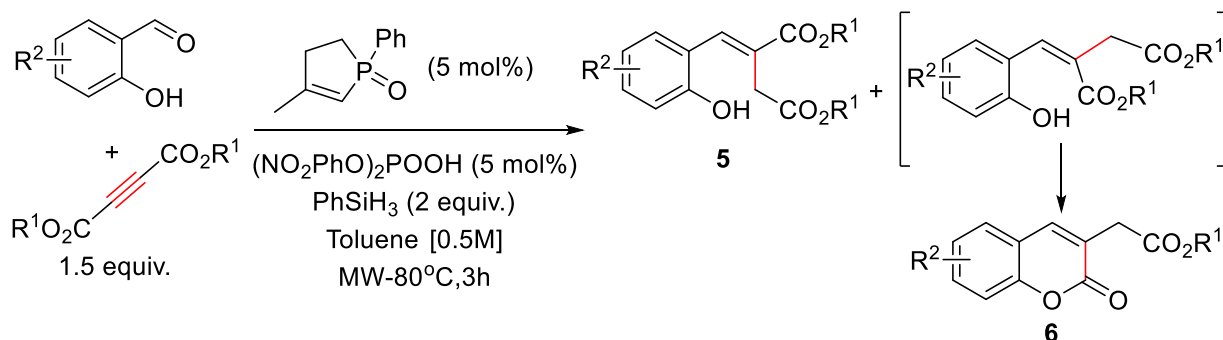
Scheme I-43. Scope and limitations of the reaction

Based on all those substrates we have tested for now, the aldehydes who could achieve good results in this olefination process all possessed a H-donor function on the *ortho*-position of the aldehyde, such as the aniline moiety and hydroxyl moiety. Possibly, we can postulate that this proton could activate the aldehyde in a possible six-member intermediate, thus promote the nucleophilic addition of the formed zwitterion. It's reasonable to speculate this acidic proton is necessary to promote the olefination reactivity (Scheme I-44).

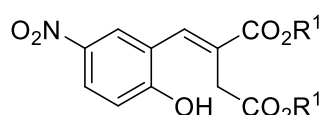


Scheme I-44. Activation of the aldehyde by H-bond

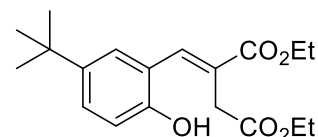
Considering the good result achieved by 2-hydroxybenzaldehyde, we decided to expand the scope of the family of 2-hydroxy-benzaldehyde substrates (Scheme I-45). The reaction condition was modified by increasing the reaction time to 3 hours and applying 1.5 equivalents of DAAD substrate, to attain the completion of aldehyde substrates.



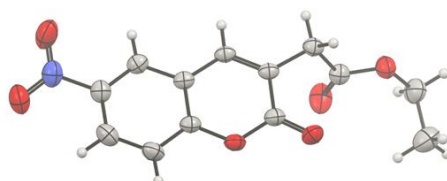
36% (*E*), **5e**; 13%, **6e**



$\text{R}^1 = \text{Et}$ , 67% (*E*), **5f**; 14%, **6f**  
 $\text{R}^1 = \text{Me}$ , 76% (*E*), **5g**; 15%, **6g**



66% (*E*), **5h**; 0%, **6h**



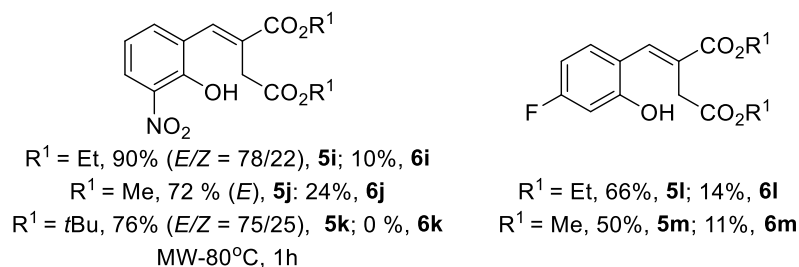
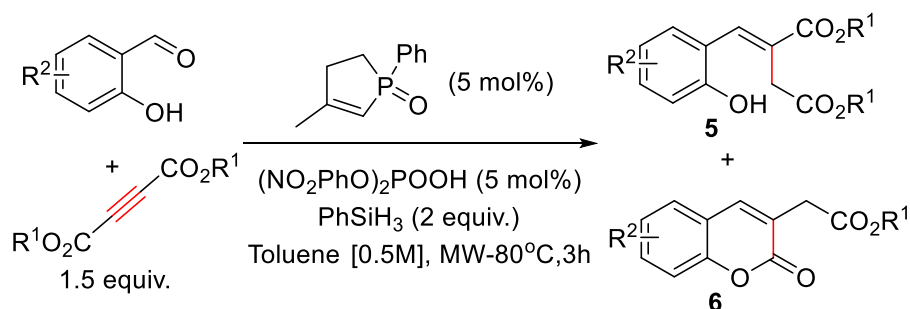
**6f**

*Scheme I-45. Reaction scope of 2-hydroxy-benzaldehyde substrates*

The first example of this series was the utilization of 5-methoxy-substrate. Besides 36% of pure *E*-olefinic compound **5b**, we did not find the formation of dihydrochromene derivative, which should be the resulting compound in classical Michael addition/Wittig reaction. However, a new 2*H*-chromen-2-one compound **6e** was detected. By introducing a strong electron-withdrawing nitro-group on position 4, up to 76% olefination compounds (**5f** and **5g**) could be obtained, and around 15% 2*H*-chromen-2-one products (**6f**, **6g**) could be isolated. The structure of **6f** was analyzed by X-ray single-crystal diffraction analysis, and the structure of this 2*H*-chromen-2-one compound has been confirmed. We speculated that intramolecular cyclization of *Z*-olefin formed the 2*H*-chromen-2-one compound (*Scheme I-45*).

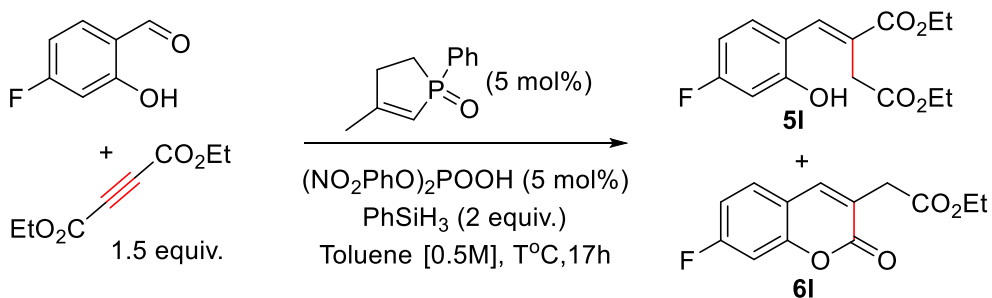
Several other 2-hydroxy-benzaldehyde substrates were tested, but more complex results were gained (*Scheme I-46*). 6-Nitro-2-hydroxybenzaldehyde brought higher activity reactions with ethyl-, *t*-butyl-, and methyl- DAAD, after reacted for only 1 hour under MW-80°C, no aldehyde substrate could be detected. Ethyl-DAAD gave 90% yield of **5i** but as a mixture of its *Z*- and *E*- isomer ( $E/Z = 78/22$ ); 10% yield of **6i** could be obtained at the same time. With methyl-DAAD, pure *E*-olefin **5j** was isolated in 72% yield, besides there was 24% yield of **6j**. *t*Bu-DAAD only produced olefinic molecule **5k** in 76% yield ( $E/Z = 75/25$  ratio). When fluorine was introduced on 5-position of 2-hydroxybenzaldehyde, both olefins (**5l**, **5m**) and 2*H*-

chromen-2-ones (**6l**, **6m**) are synthesized, however these compounds could not be separated on silica gel.



Scheme I-46. Reaction scope of 2-hydroxy-benzaldehyde substrates

Taking the reaction between 5-fluoro-2-hydroxybenzaldehyde and ethyl-DAAD under the optimal condition, but with classical heating for 17 hours, we investigated if the reaction temperature could bring any influence to the *ratio* between *E*- and *Z*- olefin. Three reactions were brought out at 60°C, 80°C and 100°C, and the *E/Z ratio* was respectively 80/20, 83/17 and 77/23. We would say there was almost no effect of reaction temperature on the stereoselectivity of the reaction (Table I-4).

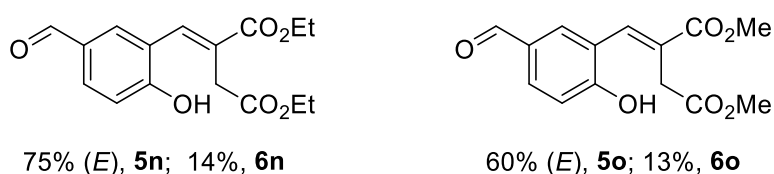
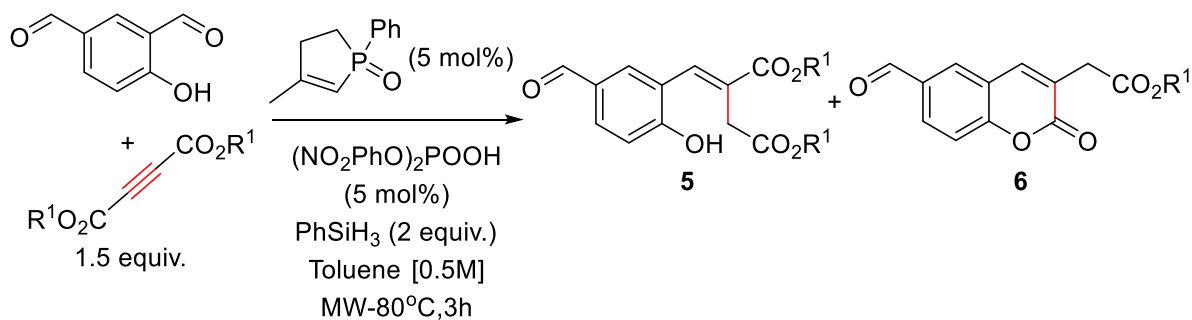


entry	T (°C)	Yield <b>5l</b> (%)	<i>E/Z ratio</i>
1	60	60	80/20
2	80	39	83/17
3	100	37	77/23

Table I-4. Temperature effects on *E/Z ratio*

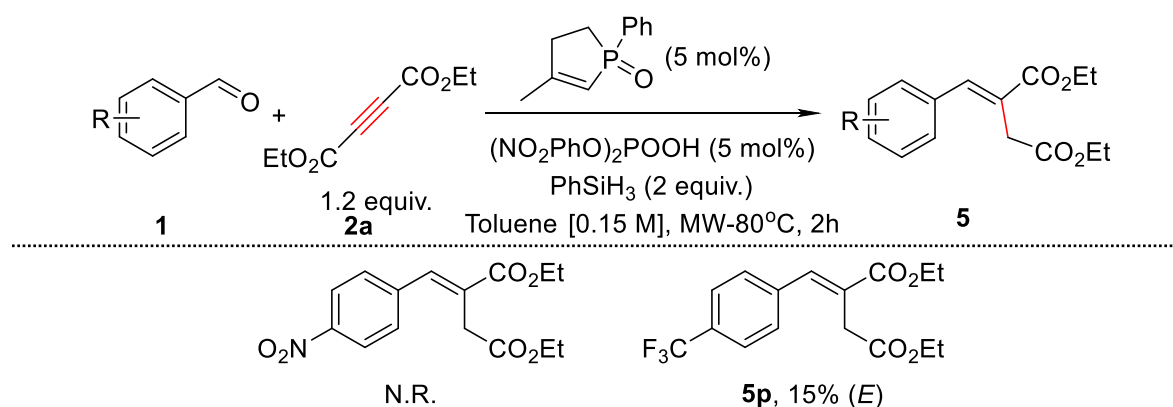
A *bis*-aldehyde compound was applied as substrate, to prove the high chemoselectivity of our methodology (Scheme I-47). In fact, only the aldehyde with *ortho*-hydroxyl moiety could be activated to form the olefin compound. That was confirmed by H-<sup>1</sup>H COSY NMR analysis. On one hand, this could be applied as a useful chemoselective olefination strategy. On the

other hand, the result helped to prove the important role of an H-donor on *ortho*-position of the benzaldehyde substrate. Compound **5n** and **5o** were isolated in 60-75% yields.



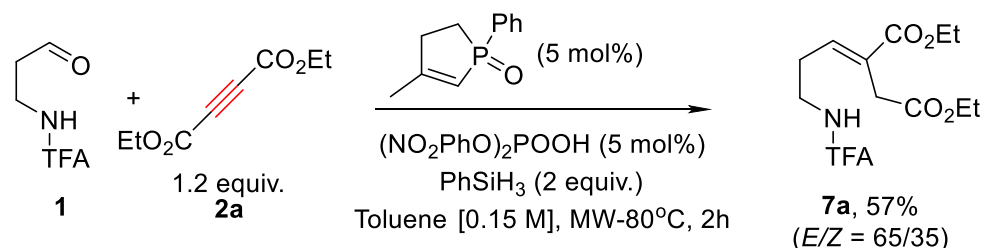
Scheme I-47. Reactivity of bis-aldehyde substrates

Besides, strong electron-withdrawing groups in *para*-position such as trifluoromethyl- and nitro- groups were applied under the optimal condition. With *para*-CF<sub>3</sub>, 15% of *E*-olefin compound **5p** could be isolated. The *para*-NO<sub>2</sub>-benzaldehyde substrate showed no activity under the same condition (Scheme I-48).



Scheme I-48. EWG-substituted-aldehydes

Finally, an example of aliphatic aldehyde was also succeeded. Target olefin **7a** was achieved in 57% isolated yield, with moderate selectivity in favor of the *E*-isomer (Scheme I-49).



Scheme I-49. Aliphatic aldehyde as substrate

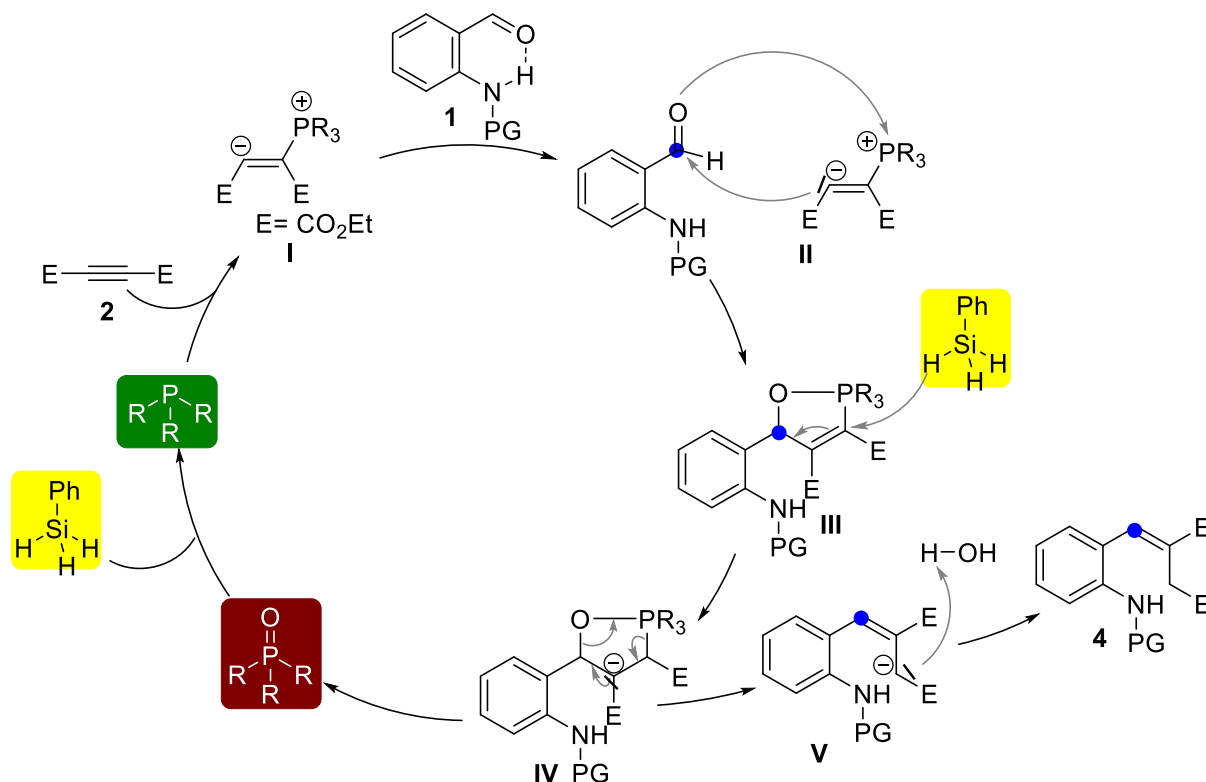


After demonstrating the full reaction scope of this new olefination process, it is now important to have a better understanding of the mechanism of formation of these products.

## 1.8 Proposed mechanism for the new olefination process

### 1.8.1 Postulated mechanism

We proposed a mechanism to explain the formation of the succinate derivatives (*Scheme I-50*).



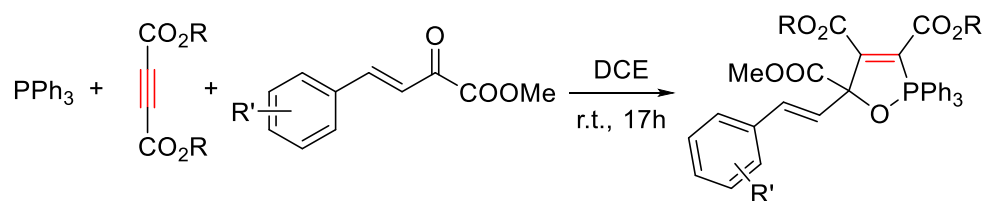
*Scheme I-50*. Proposed mechanism for the new olefination process

For the formation of the olefinic product, as in the mechanism proposed for the dihydroquinolines, the zwitterionic species **I** was first formed. This time, and contrary to the mechanism described in *Scheme I-31*, the zwitterion does not act as a base to deprotonate the nitrogen atom of the substrate, but could presumably do an addition on the aldehyde, to form the corresponding oxaphosphole **III**. At this stage, we do not have irrefutable proof of the formation of this cyclic intermediate but (1) many publications mention the formation of this kind of intermediates and (2) that could explain the formation of the olefinic product. Furthermore, the latter could then react in the presence of silane to form the intermediate **IV**. After opening of the oxaphosphole ring, intermediate **V** could be formed with the release of the phosphine oxide, which will be reduced by silane to complete the catalytic cycle. The desired succinate product might be subsequently formed via protonation with traces of water present in the solvent.

## 1.8.2 Formation of oxaphospholes in the literature

To prove the postulated mechanism, the first idea came to our mind was to isolate and characterize **III**, however, we miserably failed. Nevertheless, based on its structure, we assume that it would be unstable. Another possibility was to synthesize a compound possessing a similar oxaphosphole moiety, and then treated it with the same quantity of  $\text{PhSiH}_3$  and  $\text{H}_2\text{O}$ , as in our reaction condition. If with the use of silane as reducing agent, we can observe in the crude mixture the target olefinic compound, which can give us some insight in the reaction mechanism.

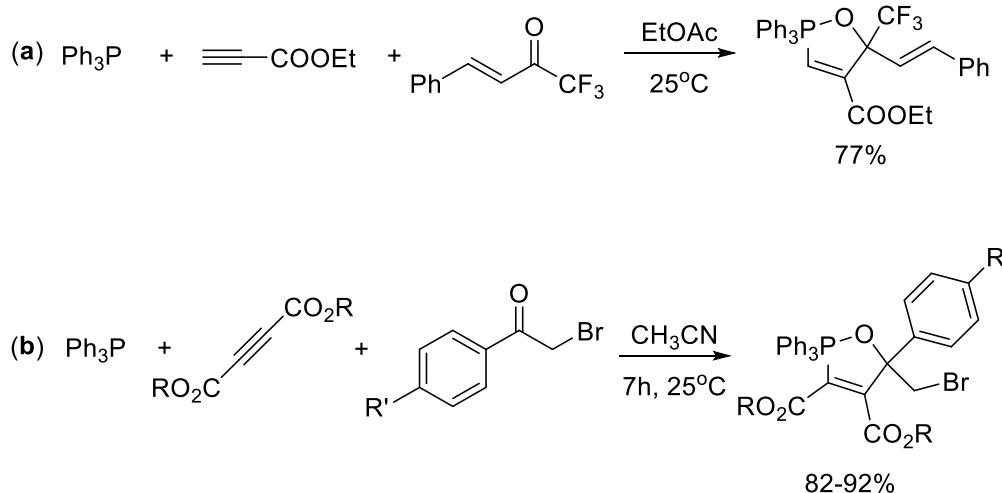
For the synthesis of oxaphosphole products, several methodologies were described with similar methods by developing multicomponent one-pot reaction in mild condition. The zwitterion intermediate formed between dialkylacetylenedicarboxylate and triphenylphosphine reacts with  $\alpha,\beta$ -unsaturated carbonyl compounds to furnish oxaphospholes.<sup>48</sup> For example, in the work reported by Balalaie and his coworkers, stable oxaphosphole compounds were isolated by reaction between dialkylacetylenedicarboxylates and methyl(arylmethylidene)pyruvates, in the presence of triphenylphosphine in dichloroethane at room temperature (Scheme I-51).<sup>50-e</sup>



Scheme I-51. Preparation of oxaphospholes

Zhu's group reported a multicomponent reaction system toward the synthesis of a series of trifluoromethyl-substituted 1,2 $\lambda$ -oxaphospholes under mild condition in EtOAc at room temperature (Scheme I-52).<sup>50-d</sup> Hosseini-Tabatabaei and co-workers developed a strategy for the isolation of 1,2-oxaphosphole derivatives from dialkyl acetylenedicarboxylates and phenacyl bromide in presence of triphenylphosphine.<sup>50-c</sup> Among all those methods oxaphospholes could be easily accessed under mild conditions. Those oxaphospholes could be obtained as stable compounds, mainly because they were stabilized by the quaternary carbon on the  $\alpha$ - position of oxygen, compared to our oxaphosphole intermediates (Scheme I-50-III), a tertiary carbon on the  $\alpha$ - position of oxygen gave the path to Scheme I-50-IV and Scheme I-50-V (Scheme I-52).

<sup>48</sup> a) Yavari, I.; Alizadeh, A.; Anary-Abbasinejad, M. *Tetrahedron Lett.* **2003**, *44*, 2877. b) Esmaeili, A.; Amini, S.; Bodaghi, A. *Synlett* **2007**, 2007, 1452. c) Charati, F. R.; Hossaini, Z.; Hosseini-Tabatabaei, M. R. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2011**, *186*, 1443. d) Zhu, S.-Z.; Gao, J.-M.; Fan, H.-F.; Wang, X.-W.; Zhao, J.-W.; Li, X.-J. *Synthesis* **2012**, *44*, 3315. e) Balalaie, S.; Baoosi, L.; Tahoori, F.; Rominger, F.; Bijanzadeh, H. R. *J. Iran. Chem. Soc.* **2015**, *12*, 101.

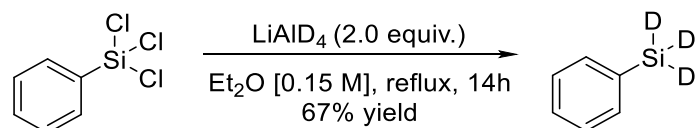


*Scheme I-52. Methods toward the isolation of oxaphospholes*

Unexpectedly, despite a large number of trials, we never succeed to isolate oxaphosphole compounds through those reported strategies. In most cases, no conversion of starting material was observed or the target compound was not isolated in sufficient amounts. In view of these unsatisfactory results, we have decided to start deuteration experiments in order to have some data that could help us to have a better understanding of our reaction.

### 1.8.3 H/D exchange experiments

Could not succeed in obtaining the oxaphosphole intermediate, we turned our attention toward the design of a series of deuterium labeling experiments to support our mechanistic hypothesis. With the introduction of deuterated phenylsilane and deuterium oxide ( $\text{D}_2\text{O}$ ) separately or together, corresponding deuterated target products should be isolated.

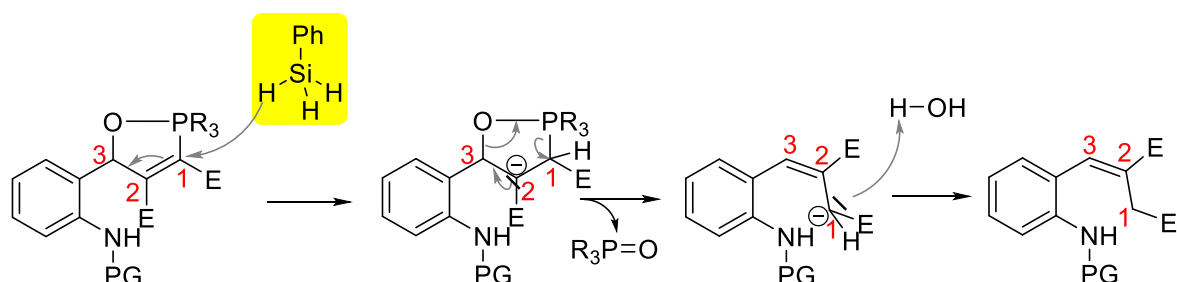


*Scheme I-53. Preparation of  $\text{PhSiD}_3$*

The preparation of deuterated phenylsilane followed reported procedure (*Scheme I-53*).<sup>49</sup> To the suspension of  $\text{LiAlD}_4$  in dry diethyl ether at  $0^\circ\text{C}$  under argon atmosphere, trichlorophenylsilane was added dropwise. The resulting mixture was refluxed for another 14 hours and then cooled to room temperature. After filtrating through celite, the solvent was removed at  $0^\circ\text{C}$  carefully. It is very important to prevent the reaction system from moisture during the synthesis procedure. The resulting colorless oil was checked by  $^1\text{H}$  NMR to certificate its deuterium content.

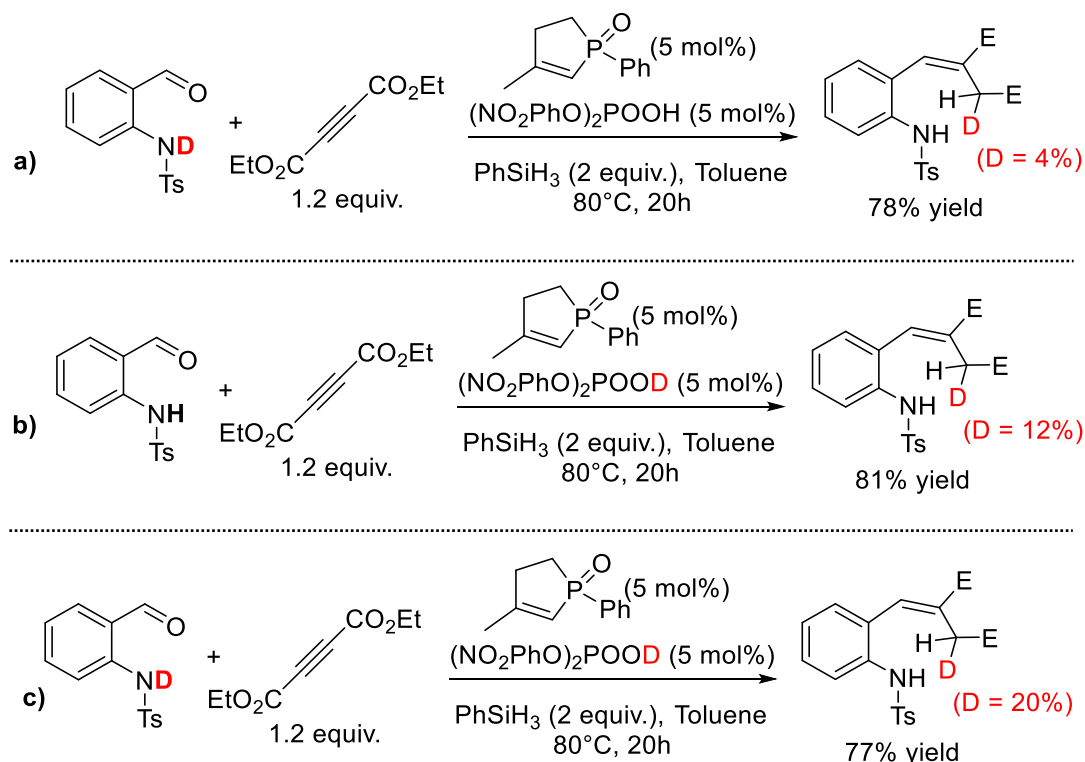
<sup>49</sup> Simmons, B. J.; Hoffmann, M.; Hwang, J.; Jackl, M. K.; Garg, N. K. *Org. Lett.* **2017**, *19*, 1910.

Turning back to the proposed mechanism, after the formation of oxaphosphole, phenylsilane reacts with the intermediate and provide a hydride. Electron transfer leads to remove the phosphine oxide. Trace water in the reaction system provides a proton in position **1** to finish the transformation to a new olefinic compound (*Scheme I-54*).



*Scheme I-54. Mechanism for the formation of succinates*

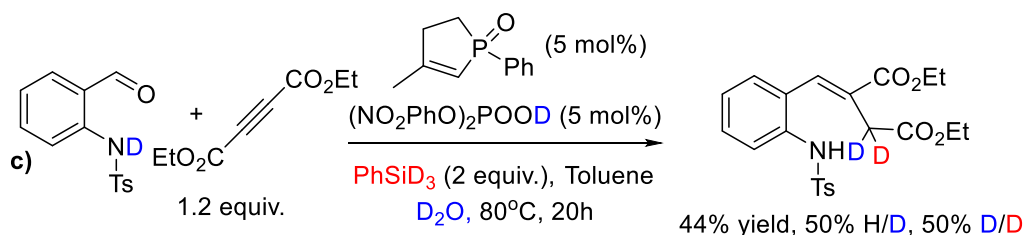
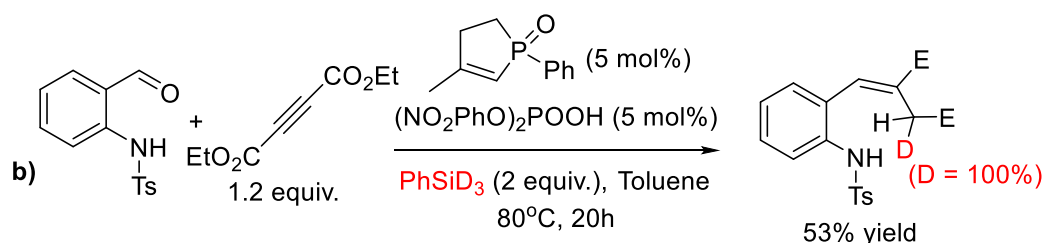
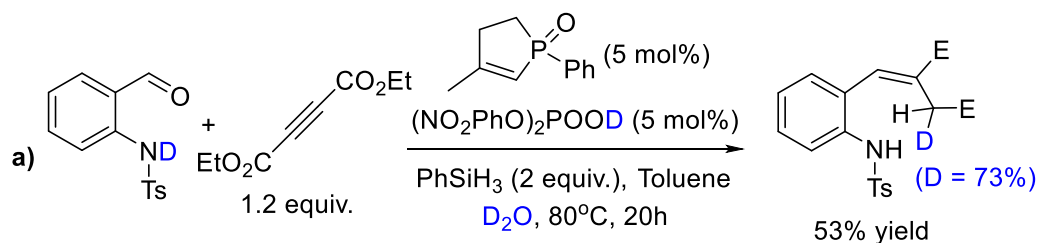
To design deuterium labeled experiments efficiently, at the first stage, we took care to consider all the active protons in the reaction system including  $\text{H}_2\text{O}$ , proton of the phosphoric acid additive and the proton provided by aniline, because of H/D exchange would happen easily among those protons. When deuterated aniline and deuterated phosphoric acid was introduced separately, the corresponding deuterium insertion was detected as 4% and 12%. (*Scheme I-55-a, I-55-b*) With both deuterium reagents, the deuterium insertion was about 20% (*Scheme I-55-c*).



*Scheme I-55. H/D exchange experiments*

By introducing  $\text{D}_2\text{O}$  instead of trace of  $\text{H}_2\text{O}$ , the deuteration in position one was partially observed in the corresponding  $^1\text{H}$  NMR spectrum (73% of deuterium was obtained, *Scheme I-56-a*). In this reaction, we tried our best to start with extremely dry solvent (distilled

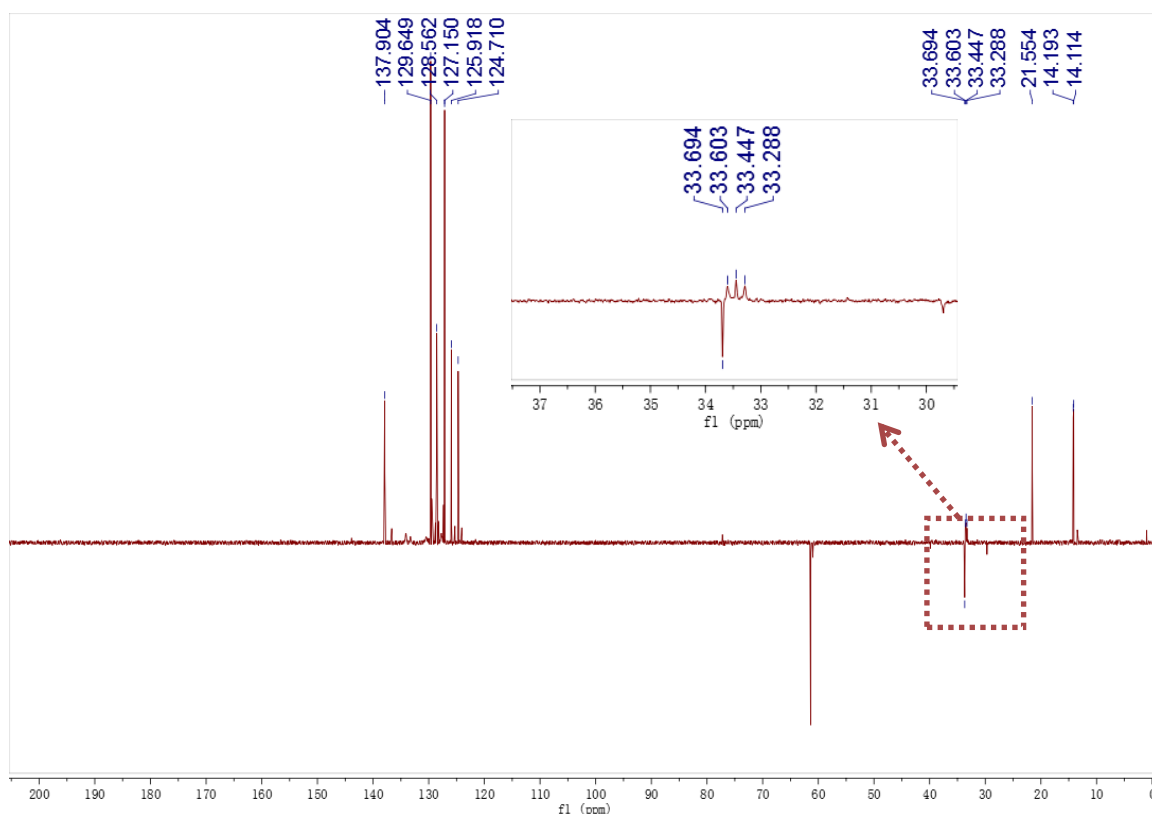
toluene treated with molecular sieve 4Å), and we have verified the quantity of non-deuterated water in the solvent by Karl-Fischer titration analysis (we found 12.0 ppm of H<sub>2</sub>O in the “dry” toluene compare to 109 ppm of H<sub>2</sub>O in the distilled toluene without being treated with molecular sieve 4Å). Furthermore, deuterated aniline substrate and phosphoric acid were also applied to avoid H/D exchange between D<sub>2</sub>O and other reagents in the reaction mixture.



Scheme I-56. Deuterium labeling experiments

When the system was treated with PhSiD<sub>3</sub>, 100% of a deuteration could be obtained (Scheme I-56-b). This test undoubtedly highlights the role of the silane in the reaction mechanism. Finally, if we combined the reaction conditions of the two former reactions, namely the concomitant use of both D<sub>2</sub>O and deuterated silane, a di-deuterated olefin compound was acquired (Scheme I-56-c). Like in the first test, some trace of water in the reaction mixture does not allow us to obtain the di-deuterated product in a completely pure form (Scheme I-56).

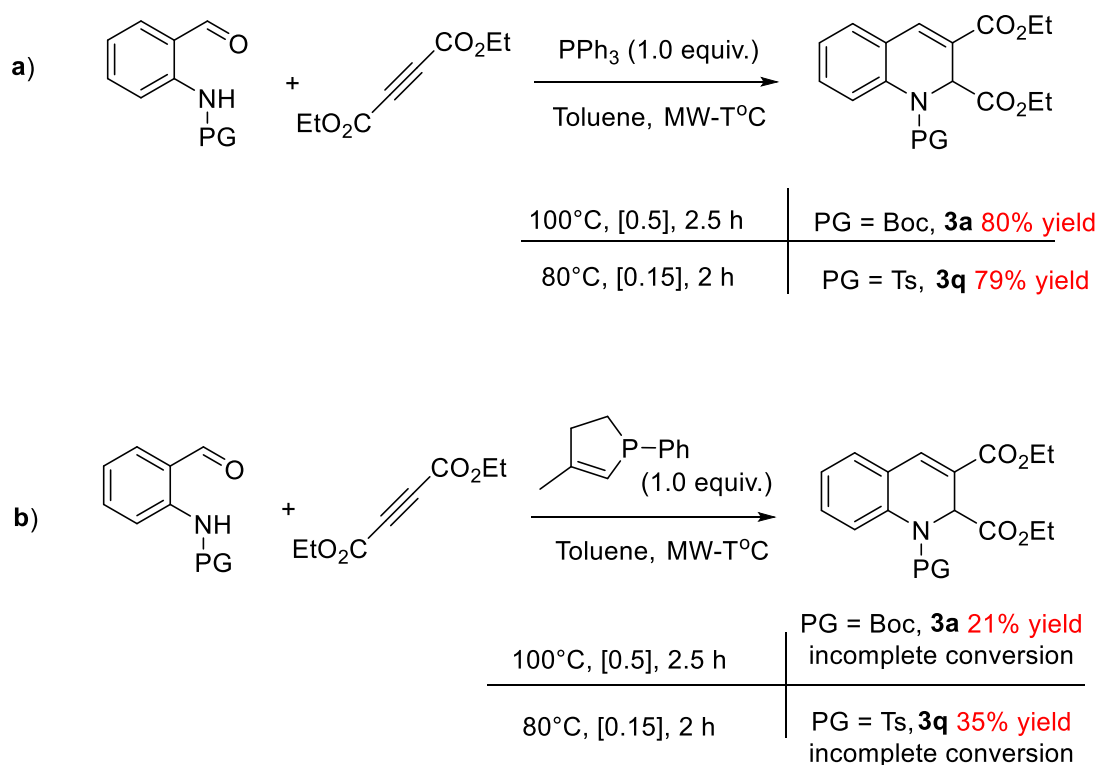
The <sup>13</sup>C NMR analysis showed a characteristic triplet peak at 33.5 ppm (see the zoom in the Scheme I-57 below) caused by deuterium atom, which was a singlet signal in the unlabeled NMR spectra. It also proved the successful deuterium labeling process.



Scheme I-57.  $^{13}\text{C}$  NMR spectra for reaction I-56-c

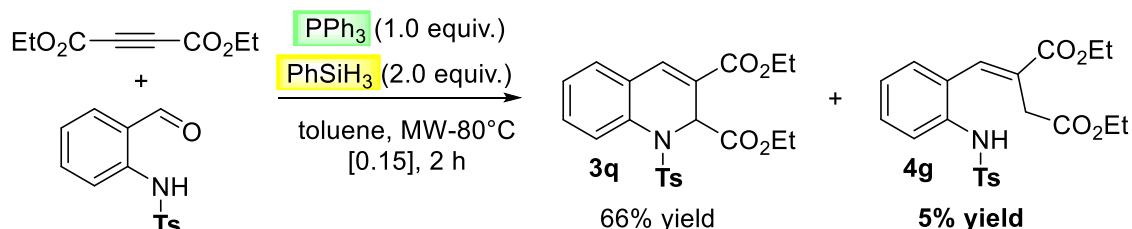
### 1.8.4 Additional control experiments

Some control experiments also provide subsidiary evidences for our postulated mechanism. (Scheme I-58) We took the best condition for the synthesis of either the dihydroquinolines and the succinate derivatives, and replacing [P-phenylphospholene/ $\text{PhSiH}_3$ / $(p\text{NO}_2\text{C}_6\text{H}_4\text{O})_2\text{PO}_2\text{H}$ ] catalytic system with stoichiometric quantity of triphenylphosphine (Scheme I-58-a), or trivalent 4-methyl-1-phenyl-2,3-dihydro-1H-phosphole (Scheme I-58-b). In both cases, only the formation of the 1,2-dihydroquinoline derivatives **3a** (PG = Boc) or **3q** (PG = Ts) was observed. By checking the crude  $^1\text{H}$  NMR spectra of the four reactions, not even traces of succinate derivative can be found.



Scheme I-58. Control experiments

Moreover, with the use of 1.0 equivalent of PPh<sub>3</sub> and stoichiometric amounts of phenylsilane, we observed the formation of product **3q** and the olefinic product **4g** (Scheme I-59). These results highlight the major role of the silane in the formation of product **4g**.



Scheme I-59. Control experiment

## 1.9 Conclusion

We have developed a catalytic Michael addition/Wittig reaction toward the synthesis of dihydroquinolines. During the development of this methodology, a new olefination reaction was observed and developed, which showed a good tolerance of both aromatic and aliphatic benzaldehyde substrates. The application of bi-aldehyde marked the chemoselectivity of our strategy. The formation of oxaphosphole as the key intermediate in our proposed mechanism was the main distinction from the oxaphosphetane intermediate in the classical Wittig reaction. The postulated mechanism was investigated and proved by a sequence of well-designed deuterium labeling experiments. This catalytic methodology toward the synthesis of 1,2-dihydroquinoline compounds can be applied in the future for the synthesis of chiral phosphine ligands.

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## **Chapter 1:**

### **Experimental Part**

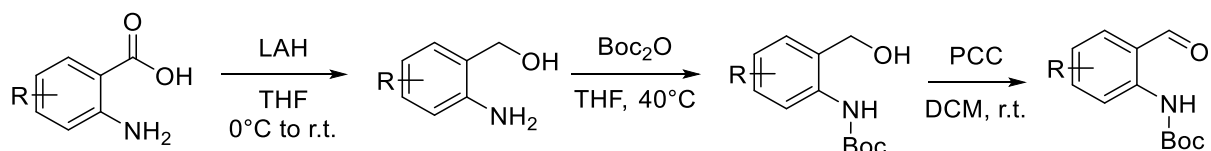


## 1.1 General information

### 1.1.1 General procedure for the synthesis of substrates 1

#### 1.1.1.a

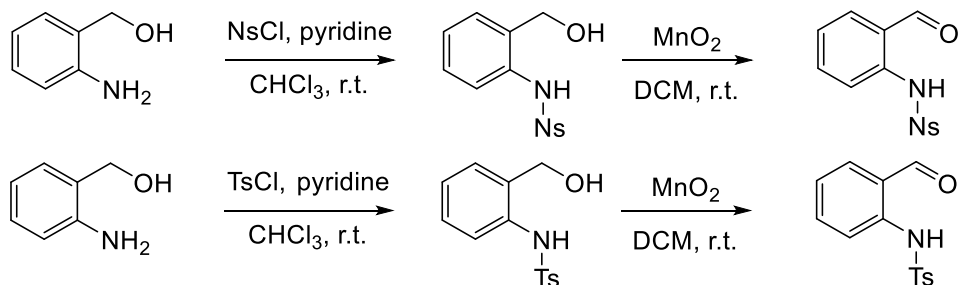
*Tert*-butyl (2-formylphenyl)carbamate derivatives **1a**<sup>50</sup> and **1h-m** (PG = Boc) were prepared according to the literature from commercially available 2-aminobenzoic acids or (2-aminophenyl)methanol.



To a solution of substituted 2-amino-benzoic acid (10 mmol) in dry THF (20 mL) was added dropwise a solution of  $\text{LiAlH}_4$  in THF (1M, 20 mL) while the temperature was maintained at 0 °C. The resulting mixture was allowed to warm to room temperature and was stirred for 2 h. The mixture was then hydrolyzed by addition of water (2 mL) and 5% NaOH (3.5 mL). The resulting suspension was filtered, and the precipitate was washed with ethyl acetate. Then the combined organic collection was evaporated. The residue was not purified and was used in the next step. The crude product and di-*tert*-butyl dicarbonate (1.2 equiv, 6 mmol) were dissolved in THF, the mixture was allowed to stir at 40 °C overnight. The organic layer was evaporated and the residue was dissolved in DCM, PCC (Pyridinium chlorochromate, 2eq, 10 mmol) was added and the mixture was stirred at r.t. for 5 h. The mixture was filtered through celite and the solvent was removed in vacuo. The residue was purified by flash chromatography on silica gel using Heptane/EA (4:1) as the eluent to yield the desired product.

#### 1.1.1.b Synthesis of substrates **1f** (PG = Ns) and **1g, 1n-p** (PG = Ts).

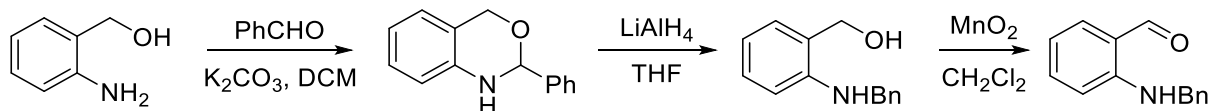
These substrates were prepared according to the literature procedure<sup>51</sup> from commercially available 2-aminobenzyl alcohol and corresponding arylsulfonyl chloride.



<sup>50</sup> Hovey, M. T.; Check, C. T.; Sipher, A. F.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2014**, *53*, 9603-9607.

<sup>51</sup> a) Bernárdez, R.; Suárez, J.; Fañanás-Mastral, M.; Varela, J. A.; Saá, C. *Org. Lett.* **2016**, *18*, 642-645. b) Chen, L.; Yang, G. M.; Wang, J.; Jia, Q. F.; Wei, J.; Du, Z. Y., *RSC Advances* **2015**, *5*, 76696-76699.

### 1.1.1.c Synthesis of substrate **1d** (PG = Bn).



**1d** was prepared according to the literature procedure.<sup>52</sup>

### 1.1.1.d Synthesis of substrate **1b** (PG = Cbz).

**1b** was prepared according to literature procedure.<sup>53</sup>

## 1.1.2 General procedure for the synthesis of products **3** and **4**

In a Standard Vial G10, amino-aldehydes **1** (0.1 mmol, 1 equiv), 4-methyl-1-phenyl-2,3-dihydrophosphole 1-oxide (5 mol %), *bis*(4-nitrophenyl)phosphate (5 mol %), and degassed toluene (0.5 M) were added. Dialkyl acetylenedicarboxylate **2** (0.12 mmol, 1.2 equiv) and phenylsilane (1.2 equiv) were then added using microsyringes (when di-*tert*-butyl acetylenedicarboxylate (0.12 mmol, 1.2 equiv) was used, add it before the toluene). The vial was sealed by reusable snap-cap with PTFE coated silicon septum and then the reaction mixture was heated at 100 °C for 2.5 h. The crude reaction mixture was concentrated and purified by flash chromatography using 12g GraceResolv<sup>TM</sup> silica gel pre-packed column and EtOAc/heptanes as eluent (0 to 20 % of EtOAc over 30 min, 18 mL/min)

## 1.1.3 General procedure for the synthesis of products **4**.

In a Standard Vial G10, amino-aldehydes **1** (0.1 mmol, 1 equiv), 4-methyl-1-phenyl-2,3-dihydrophosphole 1-oxide (5 mol %), *bis*(4-nitrophenyl)phosphate (5 mol %), and degassed toluene (0.15 M) were added. Dialkyl acetylenedicarboxylate **2** (0.12 mmol, 1.2 equiv) and phenylsilane (2.0 equiv) were then added using microsyringes (when di-*tert*-butyl acetylenedicarboxylate (0.12 mmol, 1.2 equiv) was used, add it before the toluene). The vial was sealed by reusable snap-cap with PTFE coated silicon septum and then the reaction mixture was heated at 80 °C for 2 h. The crude reaction mixture was concentrated and purified by flash chromatography using 12g GraceResolv<sup>TM</sup> silica gel pre-packed column and EtOAc/heptanes as eluent (0 to 20 % of EtOAc over 30 min, 18 mL/min)

<sup>52</sup> Yotphan, S.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2009**, *11*, 1511-1514.

<sup>53</sup> Wagner, A. M.; Knezevic, C. E.; Wall, J. L.; Sun, V. L.; Buss, J. A.; Allen, L. T.; Wenzel, A. G. *Tetrahedron Lett.* **2012**, *53*, 833-836.

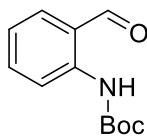
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**Tert-butyl 2-formylphenylcarbamate 1a**

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**Chemical Formula:** C<sub>12</sub>H<sub>15</sub>NO<sub>3</sub>

**Molecular Weight:** 221.2560

(431 mg, 79% yield). White solid; R<sub>f</sub> 0.64 (25% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 10.40 (bs, 1H), 9.90 (s, 1H), 8.46 (d, *J* = 8.4 Hz, 1H), 7.63 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.60-7.52 (m, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 1.54 (s, 9H)

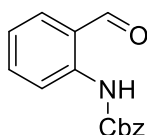
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**Benzyl (2-formylphenyl)carbamate 1l**

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**Chemical Formula:** C<sub>15</sub>H<sub>13</sub>NO<sub>3</sub>

**Molecular Weight:** 255.2730

(893 mg, 70% yield). Yellow solid; R<sub>f</sub> 0.5 (20% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 10.65 (bs, 1H), 9.90 (s, 1H), 8.48 (d, *J* = 8.5 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.47-7.29 (m, 5H), 7.18 (t, *J* = 7.5 Hz, 1H), 5.23 (s, 2H)

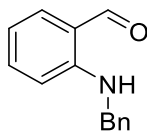
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**2-(benzylamino)benzaldehyde 1n**

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**Chemical Formula:** C<sub>14</sub>H<sub>13</sub>NO<sub>3</sub>

**Molecular Weight:** 211.2640

(516 mg, 49% yield). Yellow solid; R<sub>f</sub> 0.66 (10% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 9.87 (s, 1H), 8.75 (bs, 1H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.40-7.23 (m, 6H), 6.71 (t, *J* = 7.5 Hz, 1H), 6.65 (d, *J* = 8.4 Hz, 1H), 4.49 (s, 2H)

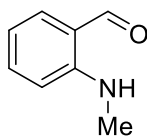
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**2-(methylamino)benzaldehyde 1o**

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**Chemical Formula:** C<sub>8</sub>H<sub>9</sub>NO

**Molecular Weight:** 135.1660

(130 mg, 56% yield). Yellow oil; R<sub>f</sub> 0.6 (30% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 9.82 (s, 1H), 8.24 (bs, 1H), 7.52-7.36 (m, 2H), 6.75-6.61 (m, 2H), 2.94 (s, 3H)

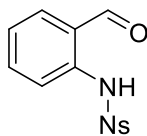
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***N*-(2-formylphenyl)-4-nitrobenzenesulfonamide 1p**

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**Chemical Formula:** C<sub>13</sub>H<sub>10</sub>N<sub>2</sub>O<sub>5</sub>S

**Molecular Weight:** 306.2920

(719 mg, 47% yield). White solid; R<sub>f</sub> 0.36 (30% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 10.92 (bs, 1H), 9.83 (s, 1H), 8.29 (d, *J* = 8.8 Hz, 2H), 8.06 (d, *J* = 8.8 Hz, 2H), 7.74 (d, *J* = 8.3 Hz, 1H), 7.69-7.52 (m, 2H), 7.30-7.21 (m, 1H)

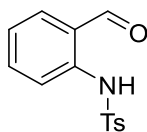
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***N*-(2-formylphenyl)-4-methylbenzenesulfonamide 1q**

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**Chemical Formula:** C<sub>14</sub>H<sub>13</sub>N<sub>2</sub>O<sub>3</sub>S

**Molecular Weight:** 275.3220

(449 mg, 33% yield). White solid; R<sub>f</sub> 0.58 (50% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 10.79 (bs, 1H), 9.83 (s, 1H), 7.78 (d, *J* = 8.2 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.62-7.56 (m, 1H), 7.51 (t, *J* = 7.9 Hz, 1H), 7.24 (d, *J* = 8.2 Hz, 2H), 7.16 (t, *J* = 7.5 Hz, 1H), 2.37 (s, 3H).

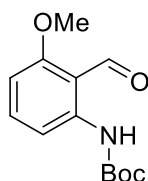
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**Tert-butyl (2-formyl-3-methoxyphenyl)carbamate 1d**

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**Chemical Formula:** C<sub>13</sub>H<sub>17</sub>N<sub>2</sub>O<sub>4</sub>

**Molecular Weight:** 251.2820

(254 mg, 84% yield). Yellow solid; R<sub>f</sub> 0.74 (25% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 10.97 (bs, 1H), 10.48 (s, 1H), 8.01 (d, *J* = 8.6 Hz, 1H), 7.47 (t, *J* = 8.5 Hz, 1H), 6.53 (d, *J* = 8.3 Hz, 1H), 3.90 (s, 3H), 1.52 (s, 9H)

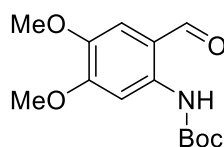
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**Tert-butyl 2-formyl-4,5-dimethoxyphenylcarbamate 1e**

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**Chemical Formula:** C<sub>14</sub>H<sub>19</sub>NO<sub>5</sub>

**Molecular Weight:** 281.3080

(510 mg, 72% yield). White solid; mp 132-133 °C; R<sub>f</sub> 0.4 (30% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 10.56 (bs, 1H), 9.72 (s, 1H), 8.14 (s, 1H), 6.99 (s, 1H), 3.99 (s, 3H), 3.89 (s, 3H), 1.52 (s, 9H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 192.8 (CH), 155.8 (C), 153.2 (C), 143.7 (C), 138.7 (C), 116.7 (CH), 114.1 (C), 101.5 (CH), 81.0 (C), 56.5 (CH<sub>3</sub>), 56.4 (CH<sub>3</sub>), 28.4 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 3327, 3058, 2846, 2761, 1720, 1683, 1589, 1485, 1455, 1392, 1340, 1239, 1156, 1089, 1014, 924, 859, 734 cm<sup>-1</sup>;

**HRMS** (ESI) Calcd. For C<sub>14</sub>H<sub>20</sub>NO<sub>5</sub> [M+H]<sup>+</sup>: 282.1341, found: 282.1343.

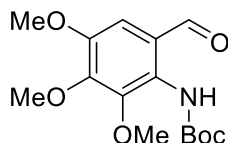
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**Tert-butyl 6-formyl-2,3,4-trimethoxyphenylcarbamate 1g**

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**Chemical Formula:** C<sub>15</sub>H<sub>21</sub>NO<sub>6</sub>

**Molecular Weight:** 311.3340

(297 mg, 81% yield). White solid; mp 115-116 °C; R<sub>f</sub> 0.17 (25% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 9.93 (s, 1H), 7.15 (s, 1H), 6.75 (s, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 1.45 (s, 9H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 189.1 (CH), 154.9 (C), 151.3 (C), 147.2 (C), 146.8 (C), 127.7 (C), 125.4 (C), 105.7 (CH), 81.4 (C), 61.2 (CH<sub>3</sub>), 61.1 (CH<sub>3</sub>), 56.2 (CH<sub>3</sub>), 28.2 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 3673, 3276, 2983, 2728, 1732, 1717, 1649, 1588, 1519, 1455, 1364, 1268, 1256, 1157, 1135, 1055, 1026, 853, 801, 781, 699 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>15</sub>H<sub>21</sub>NNaO<sub>6</sub> [M+Na]<sup>+</sup>: 334.1267, found: 334.1281

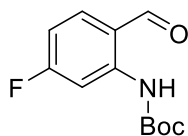
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**Tert-butyl 5-fluoro-2-formylphenylcarbamate 1i**

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**Chemical Formula:** C<sub>15</sub>H<sub>21</sub>NO<sub>6</sub>

**Molecular Weight:** 311.3340

(506 mg, 66 % yield). Yellow solid; mp 79-80 °C; R<sub>f</sub> 0.55 (20% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 10.56 (s, 1H), 9.83 (s, 1H), 8.23 (dd, *J* = 12.2, 2.5 Hz, 1H), 7.61 (dd, *J* = 8.6, 6.3 Hz, 1H), 6.80 (ddd, *J* = 8.6, 7.6, 2.5 Hz, 1H), 1.53 (s, 9H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 193.6 (CH), 167.6 (d, *J* = 254.3 Hz, C), 152.7 (C), 144.5 (d, *J* = 14.0 Hz, C), 138.7 (d, *J* = 14.0 Hz, CH), 118.3 (C), 109.3 (d, *J* = 92.4 Hz, CH), 105.8 (d, *J* = 28.7 Hz, CH), 81.6 (C), 28.4 (CH<sub>3</sub>)

**<sup>19</sup>F NMR** (282 MHz, CDCl<sub>3</sub>) δ -98.3

**IR:** ν<sub>max</sub> = 3286, 1732, 1676, 1612, 1592, 1530, 1450, 1369, 1326, 1289, 1265, 1247, 1197, 1149, 1115, 988, 886, 876, 829, 732, 703 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>12</sub>H<sub>13</sub>FNO<sub>3</sub> [M-H]<sup>-</sup>: 238.0879, found: 238.0885

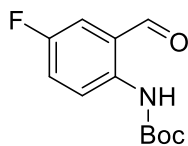
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**Tert-butyl (4-fluoro-2-formylphenyl)carbamate 1j**

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**Chemical Formula:** C<sub>12</sub>H<sub>14</sub>FNO<sub>3</sub>

**Molecular Weight:** 239.2464

(1.25 g, 81% yield). Yellow solid; R<sub>f</sub>0.3 (10% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 10.21 (s, 1H), 9.84 (s, 1H), 8.47 (dd, *J* = 8.9, 4.6 Hz, 1H), 7.36-7.26 (m, 2H), 1.53 (s, 9H)

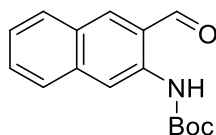
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**Tert-butyl 3-formylnaphthalen-2-ylcarbamate 1k**

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**Chemical Formula:** C<sub>16</sub>H<sub>17</sub>NO<sub>3</sub>

**Molecular Weight:** 271.3160

(874 mg, 60% yield). Yellow solid; mp 130-131 °C; R<sub>f</sub>0.32 (10% EtOAc/PE)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 10.18 (bs, 1H), 10.04 (s, 1H), 8.77 (s, 1H), 8.14 (s, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.57 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.41 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H), 1.58 (s, 9H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 195.1 (CH), 153.3 (C), 140.3 (CH), 137.4 (C), 136.5 (C), 130.4 (CH), 129.1 (CH), 128.2 (C), 127.7 (CH), 125.4 (CH), 122.8 (C), 115.1 (CH), 80.9 (C), 28.5 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 3314, 3058, 1726, 1671, 1634, 1538, 1486, 1440, 1365, 1264, 1249, 1228, 1146, 1119, 1046, 1019, 889, 837, 791, 744, 730 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>16</sub>H<sub>18</sub>NO<sub>3</sub> [M+H]<sup>+</sup>: 272.1287, found: 272.1277.



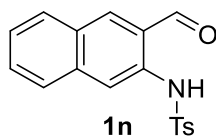
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***N*-(3-formylnaphthalen-2-yl)-4-methylbenzenesulfonamide 1x**

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**Chemical Formula:** C<sub>16</sub>H<sub>17</sub>NO<sub>3</sub>

**Molecular Weight:** 271.3160

(395 mg, 45% yield). Yellow solid; mp 237-238 °C; R<sub>f</sub> 0.22 (20% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 10.43 (s, 1H), 9.94 (s, 1H), 8.11 (s, 1H), 8.02 (s, 1H), 7.89-7.73 (m, 4H), 7.66-7.56 (m, 1H), 7.51-7.41 (m, 1H), 7.18 (d, *J* = 8.1 Hz, 2H), 2.31 (s, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 195.0 (CH), 144.1 (C), 140.3 (CH), 136.6 (C), 136.5 (C), 134.7 (C), 130.7 (CH), 129.8 (CH), 129.2 (CH), 128.9 (C), 127.7 (CH), 127.4 (CH), 126.2 (CH), 123.1 (C), 115.9 (CH), 21.6 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 3200, 3056, 1668, 1634, 1472, 1406, 1324, 1264, 1168, 1156, 1109, 1091, 898, 733, 703 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>18</sub>H<sub>16</sub>NO<sub>3</sub>S [M+H]<sup>+</sup>: 326.0851, found: 326.0870

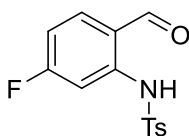
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***N*-(5-fluoro-2-formylphenyl)-4-methylbenzenesulfonamide 1v**

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**Chemical Formula:** C<sub>14</sub>H<sub>12</sub>FNO<sub>3</sub>S

**Molecular Weight:** 293.3124

(357 mg, 38% yield). Yellow solid; mp 125-126 °C; R<sub>f</sub> 0.24 (20% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 11.03 (s, 1H), 9.77 (s, 1H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.59 (dd, *J* = 8.6, 6.1 Hz, 1H), 7.41 (dd, *J* = 11.0, 2.1 Hz, 1H), 7.27 (d, *J* = 8.2 Hz, 2H), 6.86-6.77 (m, 1H), 2.38 (s, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 193.6 (CH), 167.1 (d, *J* = 256.6 Hz, C), 144.7 (C), 142.7 (d, *J* = 13.4 Hz, C), 138.8 (d, *J* = 11.9 Hz, CH), 136.2 (C), 130.1 (CH), 127.4 (CH), 118.7 (C), 110.5 (d, *J* = 22.8 Hz, CH), 105.2 (d, *J* = 27.7 Hz, CH), 21.7 (CH<sub>3</sub>)

**<sup>19</sup>F NMR** (282 MHz, CDCl<sub>3</sub>) δ -97.3

**IR:** ν<sub>max</sub> = 3138, 1675, 1614, 1588, 1506, 1435, 1398, 1343, 1287, 1320, 1265, 1197, 1188, 1174, 1154, 1106, 1189, 995, 888, 704, 658 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>14</sub>H<sub>13</sub>FNO<sub>3</sub>S [M+H]<sup>+</sup>: 294.0600, found: 294.0633

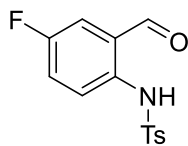
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***N*-(4-fluoro-2-formylphenyl)-4-methylbenzenesulfonamide 1w**

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**Chemical Formula:** C<sub>14</sub>H<sub>12</sub>FNO<sub>3</sub>S

**Molecular Weight:** 293.3124

(375 mg, 40% yield). White solid; mp 135-136 °C; R<sub>f</sub> 0.26 (20% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 10.41 (s, 1H), 9.72 (s, 1H), 7.75-7.62 (m, 3H), 7.30-7.17 (m, 4H), 2.34 (s, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 193.7 (CH), 158.3 (d, *J* = 244.3 Hz, C), 144.5 (C), 136.3 (C), 129.9 (CH), 127.4 (CH), 123.22 (d, *J* = 22.3 Hz, CH), 123.19 (d, *J* = 5.9 Hz, C), 121.3 (d, *J* = 22.5 Hz, CH), 120.8 (d, *J* = 6.8 Hz, CH), 21.7 (CH<sub>3</sub>)

**<sup>19</sup>F NMR** (282 MHz, CDCl<sub>3</sub>) δ -118.6

**IR:** ν<sub>max</sub> = 3196, 3067, 1674, 1589, 1493, 1402, 1386, 1340, 1307, 1264, 1163, 1143, 1089, 900, 813, 773, 734, 656 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>14</sub>H<sub>13</sub>FNO<sub>3</sub>S [M+H]<sup>+</sup>: 294.0600, found: 294.0648

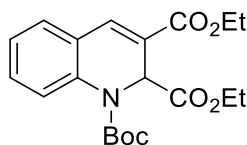
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**1-tert-butyl 2,3-diethyl quinoline-1,2,3(2*H*)-tricarboxylate 3a**

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**Chemical Formula:** C<sub>20</sub>H<sub>25</sub>NO<sub>6</sub>

**Molecular Weight:** 398.1577

(25mg, 67% yield). White solid; mp 132 °C; R<sub>f</sub> 0.48 (25% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.80 (d, *J* = 8.0 Hz, 1H), 7.54 (s, 1H), 7.37-7.29 (m, 1H), 7.28-7.21 (m, 1H), 7.08 (td, *J* = 7.5, 0.9 Hz, 1H), 6.28 (s, 1H), 4.44-4.24 (m, 2H), 4.18-3.92 (m, 2H), 1.55 (s, 9H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.13 (t, *J* = 7.1 Hz, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 169.4 (C), 164.9 (C), 152.5 (C), 136.9 (C), 134.2 (CH), 130.4 (CH), 128.8 (CH), 125.0 (C), 124.2 (CH), 123.9 (CH), 82.6 (C), 61.6 (CH<sub>2</sub>), 61.2 (CH<sub>2</sub>), 53.5 (CH), 28.3 (CH<sub>3</sub>), 14.4 (CH<sub>3</sub>), 14.1 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 2981, 1744, 1708, 1485, 1457, 1368, 1265, 1229, 1201, 1154, 1128, 1024, 945, 855, 720, 703

**HRMS** (ESI) Calcd. For C<sub>20</sub>H<sub>25</sub>NNaO<sub>6</sub> [M+Na]<sup>+</sup>: 398.1580, found: 398.1577

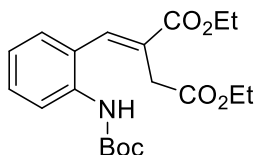
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**(E)-Diethyl-2-(2-((tert-butoxycarbonyl)amino)benzylidene)succinate 3a'**

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**Chemical Formula:** C<sub>20</sub>H<sub>27</sub>NO<sub>6</sub>

**Molecular Weight:** 377.4370

(3.5 mg, 9% yield, *E/Z* ratio = 90/10). Colorless oil; *R<sub>f</sub>* 0.48 (25% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.97 (d, *J* = 8.3 Hz, 1H), 7.79 (s, 1H), 7.36-7.29 (m, 1H), 7.20-7.00 (m, 2H), 6.48 (bs, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.34 (s, 2H), 1.52 (s, 9H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.24 (t, *J* = 7.1 Hz, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 170.9 (C), 166.7 (C), 152.8 (C), 138.2 (CH), 136.4 (C), 130.3 (C), 129.7 (CH), 128.7 (CH), 125.3 (C), 123.4 (CH), 120.9 (CH), 81.0 (C), 61.5 (CH<sub>2</sub>), 61.1 (CH<sub>2</sub>), 34.0 (CH<sub>2</sub>), 28.4 (CH<sub>3</sub>), 14.3 (CH<sub>3</sub>)

**IR:**  $\nu_{\max}$  = 2981, 2935, 1709, 1581, 1518, 1473, 1449, 1368, 1297, 1255, 1232, 1152, 1095, 1025, 948, 854, 774, 734, 702

**HRMS** (ESI) Calcd. For C<sub>20</sub>H<sub>27</sub>NNaO<sub>6</sub> [M+Na]<sup>+</sup>: 400.1736, found: 400.1757

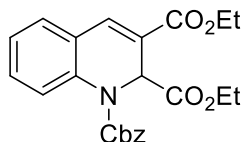
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**1-Benzyl 2,3-diethyl quinoline-1,2,3(2H)-tricarboxylate 3I**

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**Chemical Formula:** C<sub>23</sub>H<sub>23</sub>NO<sub>6</sub>

**Molecular Weight:** 409.4380

(19 mg, 47% yield). Colorless oil; *R<sub>f</sub>* 0.31 (20% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.83 (bs, 1H), 7.56 (s, 1H), 7.45-7.20 (m, 7H), 7.11 (td, *J* = 7.5, 1.0 Hz, 1H), 6.37 (s, 1H), 5.41-5.23 (m, 2H), 4.43-4.26 (m, 2H), 4.16-3.94 (m, 2H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.12 (t, *J* = 7.1 Hz, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 169.1 (C), 164.8 (C), 153.7 (C), 136.3 (C), 135.8 (C), 134.2 (CH), 130.7 (CH), 128.9 (CH), 128.7 (CH), 128.4 (CH), 128.1 (CH), 125.0 (C), 124.7 (CH), 123.9 (CH), 68.5 (CH<sub>2</sub>), 61.8 (CH<sub>2</sub>), 61.3 (CH<sub>2</sub>), 53.8 (CH), 14.4 (CH<sub>3</sub>), 14.0 (CH<sub>3</sub>)

**IR:**  $\nu_{\max}$  = 1713, 1572, 1487, 1457, 1392, 1315, 1264, 1232, 1129, 1048, 1028, 896, 732, 702 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>23</sub>H<sub>24</sub>NO<sub>6</sub> [M+H]<sup>+</sup>: 410.1604, found: 410.1644.

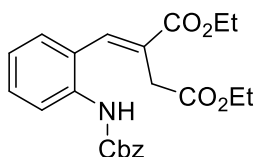
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**Diethyl (*E*)-2-(2-(((benzyloxy)carbonyl)amino)benzylidene)succinate 4b**

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**Chemical Formula:** C<sub>23</sub>H<sub>25</sub>NO<sub>6</sub>

**Molecular Weight:** 411.4540

(15mg, 36% yield, *E/Z* ratio = 95/5). Colorless oil; R<sub>f</sub> 0.27 (20% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.02 (d, *J* = 8.3 Hz, 1H), 7.77 (s, 1H), 7.45-7.31 (m, 6H), 7.15-7.05 (m, 2H), 6.85 (s, 1H), 5.21 (s, 2H), 4.28 (q, *J* = 7.1 Hz, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.31 (s, 2H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 171.0 (C), 166.4 (C), 153.5 (C), 138.1 (CH), 137.0 (C), 136.1 (CH), 135.8 (C), 130.8 (C), 129.7 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.3 (C), 123.8 (CH), 120.9 (CH), 67.3 (CH<sub>2</sub>), 61.5 (CH<sub>2</sub>), 61.2 (CH<sub>2</sub>), 33.9 (CH<sub>2</sub>), 14.3 (CH<sub>3</sub>), 14.2 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 2987, 1732, 1584, 1521, 1451, 1371, 1299, 1265, 1213, 1097, 1039, 1029, 732, 702 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>23</sub>H<sub>26</sub>NO<sub>6</sub> [M+H]<sup>+</sup>: 412.1760, found: 412.1765.

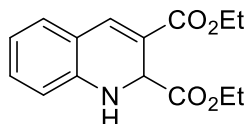
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**Diethyl 1,2-dihydroquinoline-2,3-dicarboxylate 3m**

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**Chemical Formula:** C<sub>15</sub>H<sub>17</sub>NO<sub>4</sub>

**Molecular Weight:** 275.3040

(27.5mg, 20% yield,). Yellow oil; R<sub>f</sub> 0.45 (30% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.52 (s, 1H), 7.10-7.02 (m, 2H), 6.68 (t, *J* = 7.1 Hz, 1H), 6.62 (d, *J* = 7.9 Hz, 1H), 5.07 (s, 1H), 4.89 (bs, 1H), 4.34-4.25 (m, 2H), 4.18-4.04 (m, 2H), 1.33 (t, *J* = 6.9 Hz, 3H), 1.18 (t, *J* = 6.9 Hz, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 172.1 (C), 165.7 (C), 144.2 (C), 135.5 (CH), 131.9 (CH), 129.8 (CH), 120.3 (C), 118.9 (CH), 118.6 (C), 114.0 (CH), 61.5 (CH<sub>2</sub>), 60.9 (CH<sub>2</sub>), 52.9 (CH), 14.4 (CH<sub>3</sub>), 14.1 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 3374, 2982, 1730, 1701, 1634, 1607, 1479, 1369, 1298, 1263, 1232, 1198, 1154, 1059, 1020, 858, 780, 736, 702 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>15</sub>H<sub>18</sub>NO<sub>4</sub> [M+H]<sup>+</sup>: 276.1236, found: 276.1237

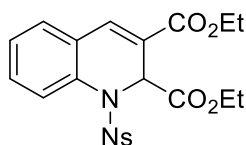
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**Diethyl 1-(4-nitrophenylsulfonyl)-1,2-dihydroquinoline-2,3-dicarboxylate 3p**

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**Chemical Formula:** C<sub>21</sub>H<sub>20</sub>N<sub>2</sub>O<sub>8</sub>S

**Molecular Weight:** 460.4570

(10.6 mg, 23% yield). White solid; mp 169-170 °C; R<sub>f</sub> 0.38 (20% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.15-8.07 (m, 2H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.62-7.55 (m, 2H), 7.47 (td, *J* = 7.8, 1.6 Hz, 1H), 7.29 (td, *J* = 7.5, 1.1 Hz, 1H), 7.18 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.06 (s, 1H), 6.15 (s, 1H), 4.28 (qd, *J* = 7.1, 0.7 Hz, 2H), 4.08 (m, 2H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 167.5 (C), 164.2 (C), 150.4 (C), 143.8 (C), 133.9 (C), 132.7 (CH), 131.5 (CH), 129.2 (CH), 128.4 (CH), 127.8 (CH), 127.0 (CH), 126.4 (C), 125.2 (C), 123.9 (CH), 62.5 (CH<sub>2</sub>), 61.7 (CH<sub>2</sub>), 55.7 (CH), 14.4 (CH<sub>3</sub>), 14.0 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 1738, 1709, 1533, 1349, 1311, 1265, 1228, 1175, 1088, 1069, 1023, 856, 732, 703 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>21</sub>H<sub>21</sub>N<sub>2</sub>O<sub>8</sub>S [M+H]<sup>+</sup>: 461.1019, found: 461.1017

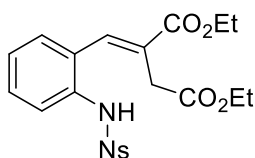
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**Diethyl (*E*)-2-(2-((4-nitrophenyl)sulfonamido)benzylidene)succinate 4f**

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**Chemical Formula:** C<sub>21</sub>H<sub>22</sub>N<sub>2</sub>O<sub>8</sub>S

**Molecular Weight:** 462.4730

(33 mg, 72% yield, *E/Z* ratio > 98/2). Colorless oil; R<sub>f</sub> 0.23 (20% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.26 (d, *J* = 8.9 Hz, 2H), 7.97-7.84 (m, 3H), 7.54 (dd, *J* = 8.1, 0.7 Hz, 1H), 7.40-7.31 (m, 1H), 7.22 (td, *J* = 7.5, 1.0 Hz, 1H), 7.07-6.96 (m, 2H), 4.30-4.05 (m, 4H), 3.10 (s, 2H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.24 (t, *J* = 7.2 Hz, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 171.8 (C), 165.8 (C), 150.2 (C), 145.8 (C), 138.0 (CH), 133.2 (C), 131.0 (C), 130.2 (C), 129.9 (CH), 128.8 (CH), 128.5 (CH), 127.1 (CH), 126.3 (CH), 124.3 (CH), 61.8 (CH<sub>2</sub>), 61.7 (CH<sub>2</sub>), 33.8 (CH<sub>2</sub>), 14.22 (CH<sub>3</sub>), 14.16 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 2985, 2922, 1712, 1533, 1350, 1265, 1196, 1170, 1092, 1027, 855, 735, 703 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>21</sub>H<sub>22</sub>N<sub>2</sub>NaO<sub>8</sub>S [M+Na]<sup>+</sup>: 485.0995, found: 485.1014

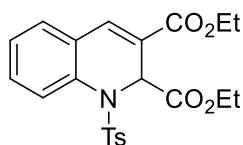
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**Diethyl 1-tosyl-1,2-dihydroquinoline-2,3-dicarboxylate 3q**

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**Chemical Formula:** C<sub>22</sub>H<sub>23</sub>N<sub>2</sub>O<sub>6</sub>S

**Molecular Weight:** 429.4870

(5 mg, 12% yield). White solid; mp 92-93 °C; R<sub>f</sub> 0.32 (30% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.86 (d, *J* = 8.2 Hz, 1H), 7.43 (td, *J* = 7.5, 1.5 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.24 (td, *J* = 7.5, 1.2 Hz, 1H), 7.15 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.09 (s, 1H), 7.06 (d, *J* = 8.4 Hz, 2H), 6.16 (s, 1H), 4.38- 4.21 (m, 2H), 4.15-4.00 (m, 2H), 2.33 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.15 (t, *J* = 7.1 Hz, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 168.2 (C), 164.4 (C), 135.5 (C), 134.8 (C), 133.1 (CH), 131.0 (CH), 129.3 (CH), 128.9 (CH), 127.12 (CH), 127.05 (CH), 127.0 (CH), 126.6 (C), 125.0 (C), 62.1 (CH<sub>2</sub>), 61.3 (CH<sub>2</sub>), 55.6 (CH), 21.7 (CH<sub>3</sub>), 14.5 (CH<sub>3</sub>), 14.1 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 2988, 1709, 1365, 1264, 1219, 1170, 1089, 1067, 896, 732, 703, 664 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>22</sub>H<sub>24</sub>NO<sub>6</sub>S [M+H]<sup>+</sup>: 430.1324, found: 430.1328

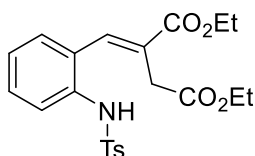
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**Diethyl (*E*)-2-(2-((4-methylphenyl)sulfonamido)benzylidene)succinate 4g**

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**Chemical Formula:** C<sub>22</sub>H<sub>25</sub>N<sub>2</sub>O<sub>6</sub>S

**Molecular Weight:** 431.5030

(36 mg, 87% yield, *E/Z* ratio > 98/2). Colorless oil; R<sub>f</sub> 0.24 (30% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.60-7.53 (m, 3H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.24-7.09 (m, 5H), 7.01 (d, *J* = 7.1 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.10 (s, 2H), 2.39 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 171.2 (C), 166.0 (C), 144.0 (C), 138.0 (CH), 136.9 (C), 134.3 (C), 130.8 (C), 129.8 (CH), 129.2 (C), 128.7 (CH), 127.2 (CH), 126.0 (CH), 124.9 (CH), 61.5 (CH<sub>2</sub>), 33.8 (CH<sub>2</sub>), 21.7 (CH<sub>3</sub>), 14.3 (CH<sub>3</sub>), 14.2 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 2987, 1712, 1489, 1371, 1326, 1265, 1393, 1165, 1092, 1028, 920, 815, 732, 703, 664 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>22</sub>H<sub>26</sub>NO<sub>6</sub>S [M+H]<sup>+</sup>: 432.1481, found: 432.1486

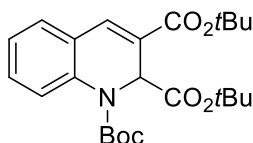
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**Tri-tert-butyl quinoline-1,2,3(2H)-tricarboxylate 3b**

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**Chemical Formula:** C<sub>24</sub>H<sub>33</sub>N<sub>2</sub>O<sub>6</sub>

**Molecular Weight:** 431.5290

(30 mg, 70% yield). White solid; mp 133-134 °C; R<sub>f</sub> 0.51 (30% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.85-7.76 (m, 1H), 7.41 (s, 1H), 7.34-7.27 (m, 1H), 7.22 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.05 (td, *J* = 7.5, 1.0 Hz, 1H), 6.11 (s, 1H), 1.57 (s, 9H), 1.55 (s, 9H), 1.30 (s, 9H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 168.6 (C), 164.2 (C), 152.6 (C), 137.0 (C), 133.0 (CH), 130.1 (CH), 128.6 (CH), 125.1 (C), 123.9 (CH), 123.6 (CH), 82.3 (C), 82.1 (C), 81.3 (C), 54.1 (CH), 28.4 (CH<sub>3</sub>), 28.3 (CH<sub>3</sub>), 28.0 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 2978, 2933, 1740, 1708, 1485, 1457, 1368, 1317, 1288, 1246, 1150, 1128, 1049, 1018, 949, 848, 736 cm<sup>-1</sup>; **HRMS** (ESI) Calcd. For C<sub>24</sub>H<sub>33</sub>NNaO<sub>6</sub> [M+Na]<sup>+</sup>: 454.2206, found: 454.2252

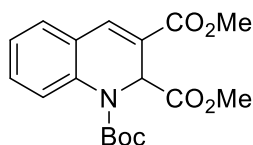
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**1-(Tert-butyl) 2,3-dimethyl quinoline-1,2,3(2H)-tricarboxylate 3c**

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**Chemical Formula:** C<sub>18</sub>H<sub>21</sub>N<sub>2</sub>O<sub>6</sub>

**Molecular Weight:** 347.3670

(22 mg, 63% yield). White solid; mp 126-127 °C; R<sub>f</sub> 0.25 (30% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.85-7.78 (m, 1H), 7.56 (s, 1H), 7.37-7.31 (m, 1H), 7.25 (d, *J* = 7.5 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.31 (s, 1H), 3.88 (s, 3H), 3.61 (s, 3H), 1.55 (s, 9H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 170.0 (C), 165.4 (C), 152.5 (C), 136.9 (C), 134.7 (CH), 130.6 (CH), 128.9 (CH), 124.9 (C), 124.3 (CH), 124.1 (CH), 82.8 (C), 53.3 (CH<sub>3</sub>), 52.8 (CH<sub>3</sub>), 52.4 (CH), 28.4 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 2981, 2955, 1747, 1713, 1639, 1485, 1436, 1370, 1336, 1292, 1265, 1235, 1155, 1128, 1080, 1022, 991, 858, 788, 705, 733, 702 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>20</sub>H<sub>24</sub>N<sub>2</sub>NaO<sub>6</sub> [M+CH<sub>3</sub>CN+Na]<sup>+</sup>: 411.1532, found: 411.1520

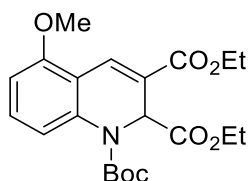
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**1-(tert-butyl) 2,3-diethyl 5-methoxyquinoline-1,2,3(2H)-tricarboxylate 3d**

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**Chemical Formula:** C<sub>21</sub>H<sub>27</sub>NO<sub>7</sub>

**Molecular Weight:** 405.4470

(12 mg, 30% yield). White solid; mp 84-87 °C; R<sub>f</sub> 0.42 (30% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.94 (s, 1H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.27 (t, *J* = 8.2 Hz, 1H), 6.60 (d, *J* = 8.3 Hz, 1H), 6.27 (s, 1H), 4.43-4.23 (m, 2H), 4.15-3.96 (m, 2H), 3.86 (s, 3H), 1.54 (s, 9H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 169.6 (C), 165.2 (C), 156.6 (C), 152.6 (C), 137.9 (C), 130.9 (CH), 129.1 (CH), 123.8 (C), 116.4 (CH), 114.9 (C), 105.7 (CH), 82.7 (C), 61.6 (CH<sub>2</sub>), 61.1 (CH<sub>2</sub>), 55.8 (CH<sub>3</sub>), 53.2 (CH), 28.4 (CH<sub>3</sub>), 14.5 (CH<sub>3</sub>), 14.1 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 3343, 2981, 2932, 1713, 1583, 1518, 1449, 1393, 1368, 1324, 1298, 1234, 1152, 1096, 1026, 770, 756 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>21</sub>H<sub>27</sub>NNaO<sub>7</sub> [M+Na]<sup>+</sup>: 428.1685, found: 428.1722

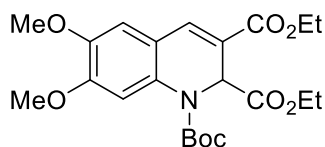
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**1-(Tert-butyl) 2,3-diethyl 6,7-dimethoxyquinoline-1,2,3(2H)-tricarboxylate 3e**

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**Chemical Formula:** C<sub>22</sub>H<sub>29</sub>NO<sub>8</sub>

**Molecular Weight:** 435.4730

(31 mg, 70% yield). White solid; mp 140-143 °C; R<sub>f</sub> 0.44 (30% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.48 (s, 1H), 7.50-7.40 (m, 1H), 6.71 (s, 1H), 6.27 (bs, 1H), 4.40-4.25 (m, 2H), 4.17-3.95 (m, 2H), 3.92 (s, 3H), 3.85 (s, 3H), 1.55 (s, 9H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 169.9 (C), 165.1 (C), 152.7 (C), 145.9 (C), 138.0 (C), 134.1 (CH), 131.6 (C), 117.7 (C), 110.5 (CH), 107.7 (CH), 82.6 (C), 61.6 (CH<sub>2</sub>), 61.1 (CH<sub>2</sub>), 56.19 (CH<sub>3</sub>), 56.13 (CH<sub>3</sub>), 53.5 (CH), 28.5 (CH<sub>3</sub>), 14.4 (CH<sub>3</sub>), 14.1 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 1740, 1706, 1509, 1338, 1297, 1230, 1157, 1132, 1020, 989, 856, 730, 702 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>22</sub>H<sub>29</sub>NNaO<sub>8</sub> [M+Na]<sup>+</sup>: 458.1791, found: 458.1802



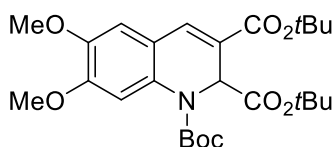
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**Tri-tert-butyl 6,7-dimethoxyquinoline-1,2,3(2H)-tricarboxylate 3f**

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**Chemical Formula:** C<sub>26</sub>H<sub>37</sub>NO<sub>8</sub>

**Molecular Weight:** 491.5810

(37 mg, 85% yield). White solid; mp 126-127 °C; R<sub>f</sub> 0.26 (30% EtOAc/*n*-Heptane)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.60-7.45 (bs, 1H), 7.34 (s, 1H), 6.70 (s, 1H), 6.10 (bs, 1H), 3.92 (s, 3H), 3.85 (s, 3H), 1.56 (s, 9H), 1.55 (s, 9H), 1.32 (s, 9H)

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 169.0 (C), 164.4 (C), 152.7 (C), 150.4 (C), 145.6 (C), 134.3 (CH), 132.8 (CH), 117.8 (C), 115.7 (C), 110.4 (CH), 107.4 (C), 82.2 (C), 82.1 (C), 81.0 (C), 56.2 (CH<sub>3</sub>), 56.1 (CH<sub>3</sub>), 54.1 (CH), 28.5 (CH<sub>3</sub>), 28.3 (CH<sub>3</sub>), 28.0 (CH<sub>3</sub>)

IR: ν<sub>max</sub> = 2977, 2934, 1738, 1702, 1612, 1569, 1508, 1455, 1367, 1338, 1243, 1227, 1139, 1128, 1026, 990, 951, 849, 763, 734, 700 cm<sup>-1</sup>

HRMS (ESI) Calcd. For C<sub>26</sub>H<sub>37</sub>NNaO<sub>8</sub> [M+Na]<sup>+</sup>: 514.2417, found: 514,2435

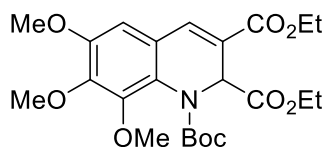
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**1-(Tert-butyl) 2,3-diethyl 6,7,8-trimethoxyquinoline-1,2,3(2H)-tricarboxylate 3g**

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**Chemical Formula:** C<sub>23</sub>H<sub>31</sub>NO<sub>9</sub>

**Molecular Weight:** 465.4990

(45.5 mg, 98% yield). White solid; mp 132-133 °C; R<sub>f</sub> 0.28 (30% EtOAc/*n*-Heptane)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.49 (s, 1H), 6.58 (s, 1H), 6.20 (s, 1H), 4.39-4.23 (m, 2H), 4.13-3.97 (m, 2H), 3.91 (s, 6H), 3.84 (s, 3H), 1.45 (s, 9H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H)

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 169.4 (C), 165.0 (C), 151.3 (C), 148.6 (C), 144.8 (C), 133.8 (CH), 126.7 (C), 124.6 (C), 121.6 (C), 106.3 (CH), 82.0 (C), 61.6 (CH<sub>3</sub>), 61.2 (CH<sub>3</sub>), 60.6 (CH<sub>3</sub>), 56.2 (CH<sub>2</sub>), 54.2 (CH), 28.1 (CH<sub>3</sub>), 14.4 (CH<sub>3</sub>), 14.1 (CH<sub>3</sub>)

IR: ν<sub>max</sub> = 2988, 2901, 1742, 1709, 1467, 1393, 1385, 1294, 1264, 1250, 1160, 1109, 1066, 894, 732, 702 cm<sup>-1</sup>

HRMS (ESI) Calcd. For C<sub>23</sub>H<sub>31</sub>NNaO<sub>9</sub> [M+Na]<sup>+</sup>: 488.1897, found: 488.1895

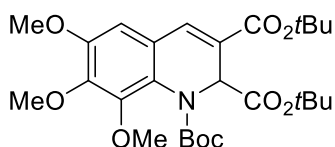
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**Tri-tert-butyl 6,7,8-trimethoxyquinoline-1,2,3(2H)-tricarboxylate 3h**

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**Chemical Formula:** C<sub>27</sub>H<sub>39</sub>NO<sub>9</sub>

**Molecular Weight:** 521.6070

(50 mg, 96% yield). White solid; mp 110-111 °C; R<sub>f</sub> 0.34 (30% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.35 (s, 1H), 6.55 (s, 1H), 6.00 (s, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 3.84 (s, 3H), 1.54 (s, 9H), 1.45 (s, 9H), 1.31 (s, 9H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 168.2 (C), 164.1 (C), 153.3 (C), 151.1 (C), 148.5 (C), 144.4 (C), 132.4 (CH), 128.9 (C), 124.5 (C), 122.0 (C), 105.9 (CH), 81.9 (C), 81.6 (C), 81.2 (C), 61.1 (CH<sub>3</sub>), 60.6 (CH<sub>3</sub>), 56.2 (CH<sub>3</sub>), 55.0 (CH), 28.3 (CH<sub>3</sub>), 28.1 (CH<sub>3</sub>), 28.0 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 2988, 2902, 1706, 1467, 1394, 1369, 1264, 1155, 1111, 1076, 1066, 934, 895, 732, 703 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>27</sub>H<sub>40</sub>NO<sub>9</sub> [M+H]<sup>+</sup>: 522.2703, found: 522.2715

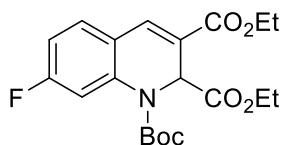
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**1-(Tert-butyl) 2,3-diethyl 7-fluoroquinoline-1,2,3(2H)-tricarboxylate 3i**

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**Chemical Formula:** C<sub>20</sub>H<sub>24</sub>FNO<sub>6</sub>

**Molecular Weight:** 393.4114

(14 mg, 36% yield). White solid; mp 119-120 °C; R<sub>f</sub> 0.64 (30% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.70-7.60 (m, 1H), 7.50 (s, 1H), 7.22 (dd, *J* = 8.5, 6.3 Hz, 1H), 6.80 (td, *J* = 8.2, 2.5 Hz, 1H), 6.26 (s, 1H), 4.39-4.28 (m, 2H), 4.14-3.99 (m, 2H), 1.56 (s, 9H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.15 (t, *J* = 7.1 Hz, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 169.3 (C), 164.9 (C), 163.8 (d, *J* = 247.6 Hz, C), 152.2 (C), 138.7 (d, *J* = 12.1 Hz, C), 133.5 (CH), 130.3 (d, *J* = 10.4 Hz, CH), 124.5 (C), 121.2 (C), 111.5 (d, *J* = 22.7 Hz, CH), 111.3 (d, *J* = 27.6 Hz, CH), 83.3 (C), 61.8 (CH<sub>2</sub>), 61.3 (CH<sub>2</sub>), 53.4 (CH), 28.3 (CH<sub>3</sub>), 14.4 (CH<sub>3</sub>), 14.1 (CH<sub>3</sub>)

**<sup>19</sup>F NMR** (282 MHz, CDCl<sub>3</sub>) δ -107.5

**IR:** ν<sub>max</sub> = 2982, 1743, 1709, 1489, 1369, 1290, 1265, 1231, 1154, 1121, 1026, 859, 732, 703

**HRMS** (ESI) Calcd. For C<sub>20</sub>H<sub>24</sub>FNNaO<sub>6</sub> [M+Na]<sup>+</sup>: 416.1485, found: 416.1485

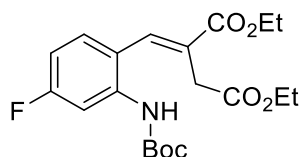
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**Diethyl (*E*)-2-(2-((*tert*-butoxycarbonyl)amino)-4-fluorobenzylidene)succinate 3i'**

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**Chemical Formula:** C<sub>20</sub>H<sub>26</sub>FNO<sub>6</sub>

**Molecular Weight:** 395.4274

(5 mg, 13% yield, *E/Z* ratio = 95/5). Colorless oil; R<sub>f</sub> 0.69 (20% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.88 (d, *J* = 11.0 Hz, 1H), 7.70 (s, 1H), 7.15-7.04 (m, 1H), 6.75 (t, *J* = 8.2 Hz, 1H), 6.55 (s, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.32 (s, 2H), 1.52 (s, 9H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.0 Hz, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 170.8 (C), 166.5 (C), 163.5 (d, *J* = 244.8 Hz, C), 152.4 (C), 138.2 (d, *J* = 11.6 Hz, C), 137.1 (CH), 130.8 (C), 130.0 (d, *J* = 10.1 Hz, CH), 120.0 (C), 110.0 (d, *J* = 22.1 Hz, CH), 107.5 (d, *J* = 27.7 Hz, CH), 81.5 (C), 61.6 (CH<sub>2</sub>), 61.2 (CH<sub>2</sub>), 34.0 (CH<sub>2</sub>), 28.4 (CH<sub>3</sub>), 14.3 (CH<sub>3</sub>); **<sup>19</sup>F NMR** (282 MHz, CDCl<sub>3</sub>) δ -109.9

**IR:** ν<sub>max</sub> = 2981, 2902, 1714, 1516, 1419, 1369, 1241, 1156, 1097, 1050, 1027, 871, 821, 736

**HRMS** (ESI) Calcd. For C<sub>20</sub>H<sub>27</sub>FNO<sub>6</sub> [M+H]<sup>+</sup>: 396.1822, found: 396.1823

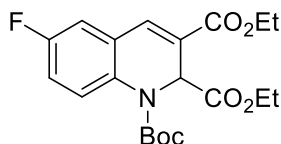
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**1-(*Tert*-butyl) 2,3-diethyl 6-fluoroquinoline-1,2,3(2*H*)-tricarboxylate 3j**

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**Chemical Formula:** C<sub>20</sub>H<sub>24</sub>FNO<sub>6</sub>

**Molecular Weight:** 393.4114

(23 mg, 59% yield). White solid; mp 126-127 °C; R<sub>f</sub> 0.68 (20% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.80-7.70 (m, 1H), 7.47 (s, 1H), 7.09-6.99 (m, 1H), 6.95 (dd, *J* = 8.3, 2.9 Hz, 1H), 6.28 (bs, 1H), 4.41-4.26 (m, 2H), 4.18-3.97 (m, 2H), 1.54 (s, 9H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 169.2 (C), 164.7 (C), 159.3 (d, *J* = 242.7 Hz, C), 152.5 (C), 133.1 (CH), 132.9 (C), 126.4 (d, *J* = 8.6 Hz, C), 125.8 (d, *J* = 8.6 Hz, CH), 117.2 (d, *J* = 22.7 Hz, CH), 114.5 (d, *J* = 23.0 Hz, CH), 82.9 (C), 61.8 (CH<sub>2</sub>), 61.5 (CH<sub>2</sub>), 53.5 (CH), 28.3 (CH<sub>3</sub>), 14.4 (CH<sub>3</sub>), 14.1(CH<sub>3</sub>)

**<sup>19</sup>F NMR** (282 MHz, CDCl<sub>3</sub>) δ -118.6

**IR:** ν<sub>max</sub> = 2981, 2921, 1745, 1716, 1489, 1369, 1331, 1292, 1240, 1157, 1122, 1028, 943, 859, 765 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>20</sub>H<sub>24</sub>FNNaO<sub>6</sub> [M+H]<sup>+</sup>: 416.1485, found: 416.1507

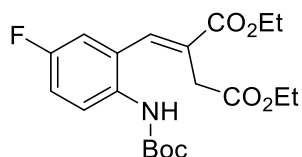
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**Diethyl (*E*)-2-(2-((*tert*-butoxycarbonyl)amino)-5-fluorobenzylidene)succinate 3j'**

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**Chemical Formula:** C<sub>20</sub>H<sub>26</sub>FNO<sub>6</sub>

**Molecular Weight:** 395.4274

(5 mg, 12% yield, *E/Z* ratio = 95/5). Colorless oil; R<sub>f</sub> 0.60 (30% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.90-7.80 (m, 1H), 7.72 (s, 1H), 7.11-6.96 (m, 1H), 6.88 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.43 (bs, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.33 (s, 2H), 1.51 (s, 9H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 170.7 (C), 166.4 (C), 158.7 (d, *J* = 241.9 Hz, C), 153.0 (C), 137.2 (CH), 135.8 (C), 132.4 (C), 131.0 (C), 123.3 (CH), 116.3 (d, *J* = 21.9 Hz, CH), 115.2 (d, *J* = 23.6 Hz, CH), 81.1 (C), 61.6 (CH<sub>2</sub>), 61.3 (CH<sub>2</sub>), 33.9 (CH<sub>2</sub>), 28.4 (CH<sub>3</sub>), 14.3 (CH<sub>3</sub>)

**<sup>19</sup>F NMR** (282 MHz, CDCl<sub>3</sub>) δ -118.8

**IR:** ν<sub>max</sub> = 3346, 2981, 2932, 1713, 1515, 1419, 1393, 1368, 1324, 1237, 1178, 1150, 1095, 1049, 1025, 819, 771, 735 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>20</sub>H<sub>26</sub>FNNaO<sub>6</sub> [M+Na]<sup>+</sup>: 418.1642, found: 418.1649

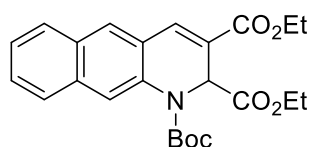
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**1-(*Tert*-butyl) 2,3-diethyl benzo[*g*]quinoline-1,2,3(2*H*)-tricarboxylate 3k**

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**Chemical Formula:** C<sub>24</sub>H<sub>27</sub>FNO<sub>6</sub>

**Molecular Weight:** 425.4810

(18 mg, 43% yield). Light yellow solid; mp 145-146 °C; R<sub>f</sub> 0.32 (20% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.25 (bs, 1H), 7.81-7.70 (m, 4H), 7.51-7.36 (m, 2H), 6.36 (s, 1H), 4.45-4.28 (m, 2H), 4.15-3.96 (m, 2H), 1.59 (s, 9H), 1.39 (t, *J* = 7.1 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 169.3 (C), 165.0 (C), 152.8 (C), 134.8 (CH), 134.7 (C), 133.4 (C), 130.3 (C), 129.1 (CH), 128.1 (CH), 128.0 (CH), 127.6 (CH), 127.2 (C), 125.8 (CH), 124.7 (C), 121.7 (CH), 82.6 (C), 61.7 (CH<sub>2</sub>), 61.3 (CH<sub>2</sub>), 53.9 (CH), 28.4 (CH<sub>3</sub>), 14.4 (CH<sub>3</sub>), 14.1 (CH<sub>3</sub>)

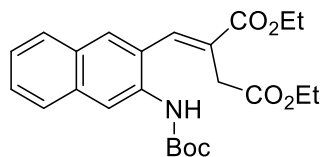
**IR:** ν<sub>max</sub> = 2981, 1741, 1708, 1632, 1369, 1348, 1297, 1265, 1248, 1231, 1157, 1080, 1020, 947, 730, 702 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>24</sub>H<sub>27</sub>NNaO<sub>6</sub> [M+Na]<sup>+</sup>: 448.1736, found: 448.1731

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**(E) and (Z)-Diethyl-2-((3-((tert-butoxycarbonyl)amino)naphthalen-2-yl)methylene)succinate**  
**3k'**

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**Chemical Formula:** C<sub>24</sub>H<sub>29</sub>FNO<sub>6</sub>

**Molecular Weight:** 427.4970

(7 mg, 16% yield, *E/Z* ratio = 55/45). Colorless oil; R<sub>f</sub> 0.27 (20% EtOAc /*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.44 (d, *J* = 10.0 Hz, 2H, *Z&E*), 7.92 (s, 1H, *E*), 7.83-7.75 (m, 2H, *Z&E*), 7.70 (t, *J* = 9.0 Hz, 2H, *Z&E*), 7.63 (s, 1H, *E*), 7.54 (s, 1H, *Z*), 7.50-7.30 (m, 4H, *Z&E*), 7.01 (d, *J* = 0.9 Hz, 1H, *Z*), 6.87 (s, 1H, *Z*), 6.60 (s, 1H, *E*), 4.33 (q, *J* = 7.1 Hz, 3H, *E*), 4.24 (q, *J* = 7.1 Hz, 2H, *Z*), 4.16 (q, *J* = 7.1 Hz, 2H, *E*), 3.95 (q, *J* = 7.1 Hz, 2H, *Z*), 3.54 (d, *J* = 0.9 Hz, 2H, *Z*), 3.42 (s, 2H, *E*), 1.56 (s, 18H, *Z&E*), 1.36 (t, *J* = 7.2 Hz, 3H), 1.32 (t, *J* = 7.2 Hz, 3H), 1.25 (t, *J* = 7.2 Hz, 3H, *E*), 0.82 (t, *J* = 7.2 Hz, 3H, *Z*)

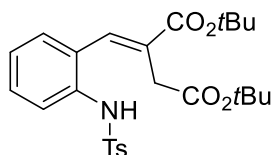
**IR:** ν<sub>max</sub> = 2982, 1725, 1715, 1528, 1486, 1368, 1265, 1156, 1097, 896, 854, 733, 703

**HRMS** (ESI) Calcd. For C<sub>24</sub>H<sub>29</sub>NNaO<sub>6</sub> [M+Na]<sup>+</sup>: 450.1893, found: 450.1898

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**Di-tert-butyl (E)-2-(2-((4-methylphenyl)sulfonamido)benzylidene)succinate 4a**

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**Chemical Formula:** C<sub>26</sub>H<sub>33</sub>FNO<sub>6</sub>S

**Molecular Weight:** 487.6110

(31 mg, 64% yield, *E/Z* ratio = 80/20). White solid; mp 131-132 °C; R<sub>f</sub> 0.17 (20% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.62-7.55 (m, 3H), 7.34-7.27 (m, 1H), 7.24-7.16 (m, 2H), 7.14-7.05 (m, 3H), 6.98 (d, *J* = 7.6 Hz, 1H), 2.98 (s, 2H), 2.38 (s, 3H), 1.53 (s, 9H), 1.43 (s, 9H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 170.5 (C), 165.2 (C), 143.9 (C), 136.4 (CH), 133.0 (C), 129.8 (CH), 129.50 (C), 129.48 (CH), 128.8 (CH), 127.3 (C), 127.2 (CH), 125.7 (CH), 124.2 (CH), 81.74 (C), 81.66 (C), 35.1 (CH<sub>2</sub>), 28.2 (CH<sub>3</sub>), 28.1 (CH<sub>3</sub>), 21.7 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 2988, 2902, 1709, 1265, 1165, 1091, 1066, 1057, 896, 732, 703 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>26</sub>H<sub>33</sub>NNaO<sub>6</sub>S [M+Na]<sup>+</sup>: 510.1926, found: 510.1926

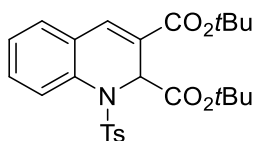
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**Di-tert-butyl 1-tosyl-1,2-dihydroquinoline-2,3-dicarboxylate 4a'**

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**Chemical Formula:** C<sub>26</sub>H<sub>31</sub>FNO<sub>6</sub>S

**Molecular Weight:** 485.5950

(13.6 mg, 29% yield). White solid; mp 123-126 °C; R<sub>f</sub> 0.27 (30% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.84 (d, *J* = 8.1 Hz, 1H), 7.40 (td, *J* = 7.8, 1.6 Hz, 1H), 7.27 (d, *J* = 8.1 Hz, 2H), 7.21 (td, *J* = 7.5, 1.1 Hz, 1H), 7.12 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.04 (d, *J* = 8.1 Hz, 2H), 6.92 (s, 1H), 5.98 (s, 1H), 2.32 (s, 3H), 1.53 (s, 9H), 1.30 (s, 9H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 167.0 (C), 163.6 (C), 143.9 (C), 135.8 (C), 135.0 (C), 131.6 (CH), 130.7 (CH), 129.3 (CH), 128.6 (CH), 127.1 (CH), 126.8 (CH), 82.7 (C), 81.5 (C), 56.2 (CH), 28.2 (CH<sub>3</sub>), 27.9 (CH<sub>3</sub>), 21.6 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 2979, 2926, 1745, 1702, 1456, 1394, 1368, 1315, 1242, 1154, 1087, 1067, 902, 834, 813, 735, 707, 661 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>26</sub>H<sub>31</sub>NNaO<sub>6</sub>S [M+Na]<sup>+</sup>: 508.1770, found: 508.1811

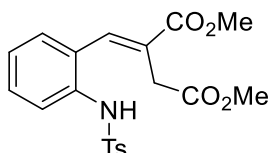
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**Dimethyl (*E*)-2-(2-((4-methylphenyl)sulfonamido)benzylidene)succinate 4b**

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**Chemical Formula:** C<sub>20</sub>H<sub>21</sub>NO<sub>6</sub>S

**Molecular Weight:** 403.4490

(31 mg, 77 % yield, *E/Z* ratio > 98/2). Colorless oil; R<sub>f</sub> 0.17 (30% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.61 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 7.5 Hz, 1H), 7.32 (dt, *J* = 7.5, 1.5 Hz, 1H), 7.25-7.12 (m, 3H), 7.16 (dt, *J* = 7.5, 0.9 Hz, 1H), 7.09 (bs, 1H), 7.01 (d, *J* = 7.8 Hz, 1H), 3.81 (s, 3H), 3.70 (s, 3H), 3.13 (s, 2H), 2.40 (s, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 171.6 (C), 166.5 (C), 159.0 (C), 144.1 (C), 138.5 (CH), 136.9 (C), 134.3 (C), 130.3 (C), 129.9 (CH), 129.8 (CH), 128.7 (CH), 127.3 (CH), 126.1 (CH), 124.9 (CH), 52.6 (CH<sub>3</sub>), 52.5 (CH<sub>3</sub>), 33.0 (CH<sub>2</sub>), 21.7 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 2988, 2902, 1394, 1264, 1166, 1066, 1057, 896, 814, 730, 703 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>20</sub>H<sub>22</sub>NO<sub>6</sub>S [M+H]<sup>+</sup>: 404.1168, found: 404.1186

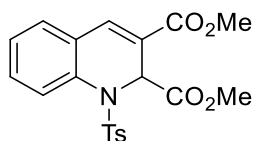
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**Dimethyl 1-tosyl-1,2-dihydroquinoline-2,3-dicarboxylate 4b'**

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**Chemical Formula:** C<sub>20</sub>H<sub>19</sub>FNO<sub>6</sub>S

**Molecular Weight:** 401.4330

(5 mg, 13 % yield). White solid; mp 133-134°C; R<sub>f</sub> 0.24 (30% EtOAc/*n*-Heptane)

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.86 (d, *J* = 8.1 Hz, 1H), 7.46-7.39 (m, 1H), 7.36-7.27 (m, 2H), 7.22 (dd, *J* = 7.4, 1.1 Hz, 1H), 7.14 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.11 (s, 1H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.18 (s, 1H), 3.82 (s, 3H), 3.64 (s, 3H), 2.33 (s, 3H)

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 168.8 (C), 164.8 (C), 144.3 (C), 135.5 (C), 134.7 (C), 133.6 (CH), 131.2 (CH), 129.3 (CH), 129.1 (CH), 127.2 (CH), 127.0 (CH), 126.4 (C), 124.4 (C), 55.5 (CH), 53.2 (CH<sub>3</sub>), 52.4, 21.7 (CH<sub>3</sub>)

IR: ν<sub>max</sub> = 2973, 2902, 1437, 1407, 1394, 1264, 1171, 1075, 1066, 1067, 896, 730, 702 cm<sup>-1</sup>

HRMS (ESI) Calcd. For C<sub>20</sub>H<sub>20</sub>NO<sub>6</sub>S [M+H]<sup>+</sup>: 402.1011, found: 402.1018

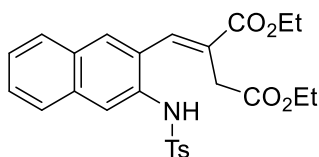
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**(*E*)-diethyl 2-((3-(4-methylphenylsulfonamido)naphthalen-2-yl)methylene)succinate 4h**

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**Chemical Formula:** C<sub>26</sub>H<sub>27</sub>FNO<sub>6</sub>S

**Molecular Weight:** 481.5630

(39 mg, 81% yield, *E/Z* ratio = 85/15). Crystal slowly; mp 92-93 °C; R<sub>f</sub> 0.37 (30% EtOAc/*n*-Heptane)

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 8.03 (s, 1H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.54-7.38 (m, 3H), 7.32 (bs, 1H), 7.22-7.16 (m, 3H), 4.29 (q, *J* = 7.1 Hz, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.16 (s, 2H), 2.37 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H)

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 171.2 (C), 166.1 (C), 144.0 (C), 138.2 (CH), 136.9 (C), 133.7 (C), 131.7 (C), 131.1 (C), 131.0 (C), 129.8 (CH), 129.6 (C), 128.4 (CH), 128.0 (CH), 127.8 (CH), 127.3 (CH), 126.5 (CH), 122.7 (CH), 61.6 (CH<sub>2</sub>), 33.8 (CH<sub>2</sub>), 21.7 (CH<sub>3</sub>), 14.34 (CH<sub>3</sub>), 14.26 (CH<sub>3</sub>)

IR: ν<sub>max</sub> = 2988, 1713, 1501, 1448, 1324, 1265, 1187, 1167, 1090, 896, 815, 733, 703 cm<sup>-1</sup>

HRMS (ESI) Calcd. For C<sub>26</sub>H<sub>27</sub>NNaO<sub>6</sub>S [M+Na]<sup>+</sup>: 504.1457, found: 504.1451

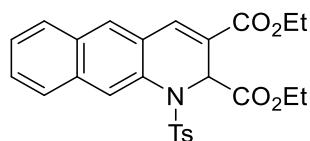
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**Diethyl 1-tosyl-1,2-dihydrobenzo[g]quinoline-2,3-dicarboxylate 4h'**

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**Chemical Formula:** C<sub>26</sub>H<sub>25</sub>NO<sub>6</sub>S

**Molecular Weight:** 479.5470

(8 mg, 17% yield). White solid; mp 145-146 °C; R<sub>f</sub> 0.29 (30% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.29 (s, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.63 (s, 1H), 7.55-7.45 (m, 2H), 7.30-7.20 (m, 3H), 7.01 (d, *J* = 8.0 Hz, 2H), 6.20 (s, 1H), 4.37-4.24 (m, 2H), 4.14-4.00 (m, 2H), 2.31 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.15 (t, *J* = 7.1 Hz, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 144.2 (C), 135.6 (C), 134.5 (C), 133.9 (CH), 131.2 (C), 129.4 (CH), 129.3 (CH), 128.7 (CH), 128.3 (CH), 128.0 (CH), 127.2 (CH), 126.9 (CH), 126.2 (C), 125.8 (CH), 125.0 (C), 62.2 (CH<sub>2</sub>), 61.3 (CH<sub>2</sub>), 55.9 (CH), 21.7 (CH<sub>3</sub>), 14.5 (CH<sub>3</sub>), 14.1 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 2982, 2926, 2845, 1740, 1705, 1634, 1598, 1447, 1364, 1327, 1264, 1248, 1222, 1167, 1131, 1090, 1068, 1020, 914, 840, 814, 733, 702, 663 cm<sup>-1</sup>

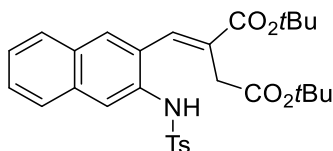
**HRMS** (ESI) Calcd. For C<sub>26</sub>H<sub>26</sub>NO<sub>6</sub>S [M+H]<sup>+</sup>: 480.1481, found: 480.1516

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**(*E*)-di-tert-butyl-2-((3-(4-methylphenylsulfonamido)naphthalen-2-yl)methylene)succinate**

**4i**

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**Chemical Formula:** C<sub>30</sub>H<sub>35</sub>NO<sub>6</sub>S

**Molecular Weight:** 537.6710

(37 mg, 68% yield, *E/Z* ratio = 77/23). Colorless oil; R<sub>f</sub> 0.19 (30% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.02 (bs, 1H), 7.81 (d, *J* = 7.9 Hz, 1H), 7.70-7.59 (m, 3H), 7.53-7.37 (m, 3H), 7.32-7.22 (m, 2H), 7.16 (d, *J* = 8.1 Hz, 2H), 3.04 (bs, 2H), 2.35 (s, 3H), 1.55 (s, 9H), 1.44 (s, 9H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 170.4 (C), 165.2 (C), 143.8 (C), 136.4 (CH), 133.5 (C), 132.9 (C), 131.8 (C), 130.8 (C), 129.7 (CH), 128.44 (C), 128.35 (CH), 127.8 (CH), 127.6 (CH), 127.2 (CH), 127.1 (CH), 126.2 (CH), 121.9 (CH), 81.6 (C), 81.6 (C), 35.0 (CH<sub>2</sub>), 28.1 (CH<sub>3</sub>), 28.0 (CH<sub>3</sub>), 21.5 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 3258, 2979, 1706, 1598, 1500, 1468, 1411, 1393, 1368, 1339, 1326, 1289, 1265, 1149, 1090, 909, 843, 814, 737, 733, 703 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>30</sub>H<sub>35</sub>NNaO<sub>6</sub>S [M+Na]<sup>+</sup>: 560.2083, found: 560.2125



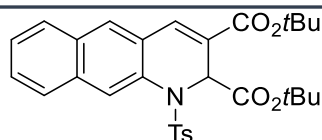
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**Di-tert-butyl 1-tosyl-1,2-dihydrobenzo[g]quinoline-2,3-dicarboxylate 4i'**

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**Chemical Formula:** C<sub>30</sub>H<sub>33</sub>NO<sub>6</sub>S

**Molecular Weight:** 535.6550

(9 mg, 17% yield); Light yellow solid; mp 141-143 °C; R<sub>f</sub>0.27 (30% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.28 (s, 1H), 7.91 (d, *J* = 7.9 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.60 (s, 1H), 7.57-7.44 (m, 2H), 7.30-7.22 (m, 2H), 7.12 (s, 1H), 7.00 (d, *J* = 8.1 Hz, 2H), 6.04 (s, 1H), 2.30 (s, 3H), 1.55 (s, 9H), 1.30 (s, 9H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 166.9 (C), 163.6 (C), 143.9 (C), 135.9 (C), 134.4 (C), 132.4 (CH), 131.8 (C), 131.6 (C), 129.3 (CH), 128.9 (CH), 128.7 (CH), 128.2 (CH), 127.7 (CH), 127.2 (CH), 126.7 (CH), 125.7 (CH), 125.2 (C), 82.8 (C), 81.6 (C), 56.5 (CH), 28.3 (CH<sub>3</sub>), 28.0 (CH<sub>3</sub>), 21.6 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 1744, 1703, 1368, 1325, 1265, 1155, 1131, 1067, 959, 914, 898, 841, 732, 703 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>30</sub>H<sub>33</sub>NNaO<sub>6</sub>S [M+Na]<sup>+</sup>: 558.1926, found: 558.1955

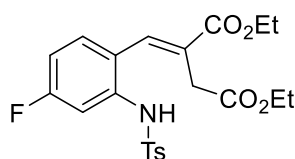
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**Diethyl (*E*)-2-(4-fluoro-2-((4-methylphenyl)sulfonamido)benzylidene)succinate 4d**

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**Chemical Formula:** C<sub>22</sub>H<sub>24</sub>FNO<sub>6</sub>S

**Molecular Weight:** 449.4934

(24 mg, 54% yield, *E/Z* ratio = 88/12). Colorless oil; R<sub>f</sub>0.22 (20% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.65 (d, *J* = 8.2 Hz, 2H), 7.34 (dd, *J* = 10.1, 2.3 Hz, 1H), 7.26-7.15 (m, 4H), 7.03-6.96 (m, 1H), 6.84 (td, *J* = 8.2, 2.3 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.11 (s, 2H), 2.40 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 4H), 1.25 (t, *J* = 7.1 Hz, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 171.2 (C), 165.9 (C), 163.1 (d, *J* = 247.5 Hz, C), 144.4 (C), 137.0 (CH), 136.6 (C), 131.6 (C), 129.9 (CH), 127.4 (C), 127.3 (CH), 123.9 (C), 112.7 (d, *J* = 21.7 Hz, CH), 110.9 (d, *J* = 25.5 Hz, CH), 61.6 (CH<sub>2</sub>), 33.8 (CH<sub>2</sub>), 21.7 (CH<sub>3</sub>), 14.3 (CH<sub>3</sub>), 14.2 (CH<sub>3</sub>)

**<sup>19</sup>F NMR** (282 MHz, CDCl<sub>3</sub>) δ -109.8 (*E*), -111.3 (*Z*)

**IR:** ν<sub>max</sub> = 3251, 2987, 1710, 1607, 1499, 1408, 1371, 1326, 1265, 1169, 1154, 1090, 1028, 985, 894, 814, 732, 705, 664 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>22</sub>H<sub>25</sub>FNO<sub>6</sub>S [M+H]<sup>+</sup>: 450.1387, found: 450.1387

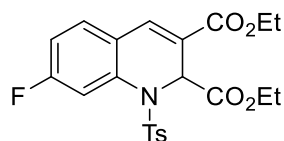
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**Diethyl 7-fluoro-1-tosyl-1,2-dihydroquinoline-2,3-dicarboxylate 4d'**

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**Chemical Formula:** C<sub>22</sub>H<sub>27</sub>FNO<sub>6</sub>S

**Molecular Weight:** 447.4774

(11 mg, 25% yield). White solid; mp 118-119 °C; R<sub>f</sub> 0.22 (30% EtOAc /*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.63 (dd, *J* = 9.9, 2.4 Hz, 1H), 7.37-7.32 (m, 2H), 7.17-7.04 (m, 4H), 6.93 (td, *J* = 8.2, 2.5 Hz, 1H), 6.16 (s, 1H), 4.38-4.20 (m, 2H), 4.17-4.01 (m, 2H), 2.33 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.16 (t, *J* = 7.1 Hz, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 168.1 (C), 164.8 (d, *J* = 82.6 Hz, C), 144.5 (C), 135.5 (CH), 132.3 (CH), 130.4 (d, *J* = 9.9 Hz, CH), 129.5 (CH), 127.1 (CH), 124.1 (C), 122.8 (C), 114.3 (d, *J* = 24.1 Hz, CH), 62.3 (CH<sub>2</sub>), 61.4 (CH<sub>2</sub>), 55.4 (CH), 21.7 (CH<sub>3</sub>), 14.5 (CH<sub>3</sub>), 14.1 (CH<sub>3</sub>)

**<sup>19</sup>F NMR** (282 MHz, CDCl<sub>3</sub>) δ -106.1

**IR:** ν<sub>max</sub> = 2988, 2901, 1710, 1421, 1394, 1264, 1227, 1171, 1067, 1055, 896, 731, 703 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>22</sub>H<sub>23</sub>FNO<sub>6</sub>S [M+H]<sup>+</sup>: 448.1230, found: 448.1259

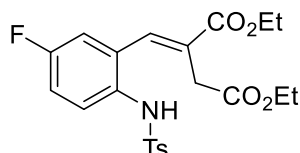
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**Diethyl (*E*)-2-(5-fluoro-2-((4-methylphenyl)sulfonamido)benzylidene)succinate 4e**

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**Chemical Formula:** C<sub>22</sub>H<sub>24</sub>FNO<sub>6</sub>S

**Molecular Weight:** 449.4934

(27 mg, 60% yield, *E/Z* ratio > 98/2). Colorless oil; R<sub>f</sub> 0.18 (30% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.57-7.52 (m, 3H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.17 (bs, 1H), 7.04 (td, *J* = 8.4, 2.9 Hz, 1H), 6.96 (bs, 1H), 6.74 (dd, *J* = 8.6, 2.9 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.07 (s, 2H), 2.41 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 171.2 (C), 165.7 (C), 160.6 (d, *J* = 245.9 Hz, C), 144.1 (C), 137.1 (CH), 136.7 (C), 132.2 (C), 132.1 (d, *J* = 8.5 Hz, C), 129.8 (CH), 128.4 (d, *J* = 9.1 Hz, CH), 127.3 (CH), 116.6 (d, *J* = 22.3 Hz, CH), 115.4 (d, *J* = 23.6 Hz, CH), 61.8 (CH<sub>2</sub>), 61.6 (CH<sub>2</sub>), 33.8 (CH<sub>2</sub>), 21.7 (CH<sub>3</sub>), 14.3 (CH<sub>3</sub>), 14.2 (CH<sub>3</sub>)

**<sup>19</sup>F NMR** (282 MHz, CDCl<sub>3</sub>) δ -117.8

**IR:** ν<sub>max</sub> = 2988, 2902, 1714, 1394, 1265, 1165, 1091, 1028, 896, 731, 702 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>22</sub>H<sub>25</sub>FNO<sub>6</sub>S [M+H]<sup>+</sup>: 450.1387, found: 450.1403

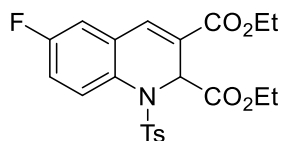
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**Diethyl 6-fluoro-1-tosyl-1,2-dihydroquinoline-2,3-dicarboxylate 4e'**

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**Chemical Formula:** C<sub>22</sub>H<sub>22</sub>FNO<sub>6</sub>S

**Molecular Weight:** 447.4774

(12 mg, 27% yield). White solid; mp 142-144 °C; R<sub>f</sub> 0.27 (30% EtOAc /*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.83 (dd, *J* = 8.9, 5.0 Hz, 1H), 7.30-7.20 (m, 2H), 7.16-7.04 (m, 3H), 6.98 (s, 1H), 6.84 (dd, *J* = 8.2, 2.9 Hz, 1H), 6.13 (s, 1H), 4.37-4.22 (m, 2H), 4.18-4.01 (m, 2H), 2.33 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.15 (t, *J* = 7.1 Hz, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 167.9 (C), 163.3 (d, *J* = 106.9 Hz, C), 144.4 (C), 135.2 (C), 131.9 (CH), 129.4 (CH), 129.2 (d, *J* = 8.3 Hz, CH), 127.1 (CH), 126.6 (C), 117.8 (d, *J* = 22.9 Hz, CH), 114.9 (d, *J* = 23.3 Hz, CH), 62.3 (CH<sub>2</sub>), 61.5 (CH<sub>2</sub>), 55.7 (CH), 21.7 (CH<sub>3</sub>), 14.5 (CH<sub>3</sub>), 14.1 (CH<sub>3</sub>)

**<sup>19</sup>F NMR** (282 MHz, CDCl<sub>3</sub>) δ -114.2

**IR:** ν<sub>max</sub> = 1736, 1713, 1486, 1367, 1265, 1235, 1170, 1089, 1071, 1024, 732, 703, 665 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>22</sub>H<sub>23</sub>FNO<sub>6</sub>S [M+H]<sup>+</sup>: 448.1230, found: 448.1259

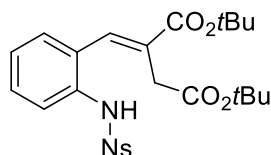
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**Di-tert-butyl (E)-2-(2-((4-nitrophenyl)sulfonamido)benzylidene)succinate 4c**

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**Chemical Formula:** C<sub>25</sub>H<sub>30</sub>FNO<sub>8</sub>S

**Molecular Weight:** 518.5810

(26 mg, 50% yield, *E/Z* ratio = 95/5). Colorless oil; R<sub>f</sub> 0.19 (30% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.27 (d, *J* = 8.7 Hz, 2H), 7.95-7.85 (m, 3H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.18 (td, *J* = 7.5, 1.0 Hz, 1H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.92 (s, 1H), 2.99 (s, 2H), 1.51 (s, 9H), 1.45 (s, 9H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 171.3 (C), 164.9 (C), 146.0 (C), 136.7 (CH), 133.2 (C), 130.2 (C), 129.6 (CH), 128.8 (CH), 128.5 (CH), 126.8 (CH), 125.8 (CH), 124.4 (CH), 82.4 (C), 82.0 (C), 35.1 (CH<sub>2</sub>), 28.2 (CH<sub>3</sub>), 28.1 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 1707, 1534, 1501, 1340, 1265, 1158, 1110, 1092, 854, 733, 703 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>25</sub>H<sub>30</sub>N<sub>2</sub>NaO<sub>8</sub>S [M+Na]<sup>+</sup>: 541.1621, found: 541.1600

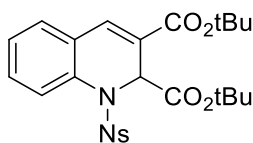
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**Di-tert-butyl 1-((4-nitrophenyl)sulfonyl)-1,2-dihydroquinoline-2,3-dicarboxylate 4c'**

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**Chemical Formula:** C<sub>25</sub>H<sub>28</sub>NO<sub>6</sub>S

**Molecular Weight:** 516.5650

(11 mg, 20% yield). Light yellow solid; mp 171-173 °C; R<sub>f</sub> 0.34 (30% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.14-8.05 (m, 2H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.61-7.55 (m, 2H), 7.46 (td, *J* = 7.8, 1.6 Hz, 1H), 7.31-7.24 (m, 1H), 7.16 (dd, *J* = 7.6, 1.5 Hz, 1H), 6.88 (s, 1H), 6.00 (s, 1H), 1.51 (s, 9H), 1.30 (s, 9H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 166.3 (C), 150.3 (C), 144.0 (C), 134.0 (C), 132.2 (C), 131.2 (CH), 128.9 (CH), 128.4 (CH), 127.6 (CH), 127.3 (C), 127.2 (CH), 126.6 (C), 123.8 (CH), 83.3 (C), 82.1 (C), 56.2 (CH), 28.2 (CH<sub>3</sub>), 27.9 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 2980, 2932, 1747, 1703, 1533, 1456, 1370, 1349, 1315, 1257, 1176, 1157, 1088, 1069, 854, 738, 700 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>27</sub>H<sub>31</sub>N<sub>3</sub>NaO<sub>8</sub>S [M+Na+ACN]<sup>+</sup>: 580.1730, found: 580.1717

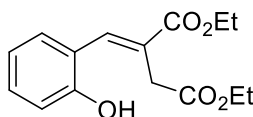
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**Diethyl (*E*)-2-(2-hydroxybenzylidene)succinate 5b**

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**Chemical Formula:** C<sub>15</sub>H<sub>18</sub>O<sub>5</sub>

**Molecular Weight:** 278.3040

(21 mg, 74% yield, *E/Z* ratio = 88/12). Colorless oil; R<sub>f</sub> 0.26 (30% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.92 (s, 1H), 7.21 (td, *J* = 7.7, 1.5 Hz, 1H), 7.14 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.96- 6.86 (m, 2H), 6.63 (bs, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.41 (s, 2H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 172.3 (C), 167.2 (C), 154.1 (C), 138.4 (CH), 130.5 (CH), 129.6 (CH), 121.9 (C), 120.5 (CH), 116.6 (CH), 61.5 (CH<sub>2</sub>), 61.4 (CH<sub>2</sub>), 34.3 (CH<sub>2</sub>), 14.3 (CH<sub>3</sub>), 14.2 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 3380, 2986, 1705, 1455, 1371, 1328, 1265, 1189, 1100, 1028, 732, 703 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>15</sub>H<sub>19</sub>O<sub>5</sub> [M+H]<sup>+</sup>: 279.1232, found: 279.1211

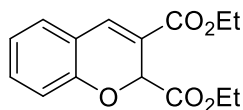
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**Diethyl 2*H*-chromene-2,3-dicarboxylate 5e'**

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**Chemical Formula:** C<sub>15</sub>H<sub>16</sub>O<sub>5</sub>

**Molecular Weight:** 276.2880

(4 mg, 15% yield). White solid; R<sub>f</sub> 0.29 (30% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.49 (s, 1H), 7.25 (t, *J* = 7.7 Hz, 1H), 7.15 (d, *J* = 7.5 Hz, 1H), 7.04-6.86 (m, 2H), 5.76 (s, 1H), 4.38-4.21 (m, 2H), 4.19-4.01 (m, 2H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.16 (t, *J* = 7.1 Hz, 3H)

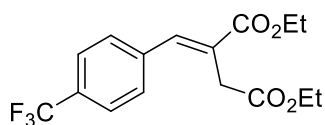
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**Diethyl (*E*)-2-(4-(trifluoromethyl)benzylidene)succinate 5p**

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**Chemical Formula:** C<sub>16</sub>H<sub>17</sub>F<sub>3</sub>O<sub>4</sub>

**Molecular Weight:** 330.3032

(10 mg, 8% yield). Colorless oil; R<sub>f</sub> 0.4 (20% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.89 (s, 1H), 7.65 (d, *J* = 8.2 Hz, 2H), 7.46 (d, *J* = 8.1 Hz, 2H), 4.29 (q, *J* = 7.1 Hz, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.47 (s, 2H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H)

**HRMS** (ESI) Calcd. For C<sub>16</sub>H<sub>18</sub>F<sub>3</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 331.1157, found: 331.1174

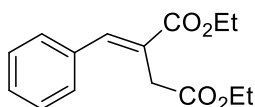
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**Diethyl (*E*)-2-benzylidenesuccinate 5a**

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**Chemical Formula:** C<sub>16</sub>H<sub>17</sub>F<sub>3</sub>O<sub>4</sub>

**Molecular Weight:** 330.3032

(3.5 mg, 13% yield). Colorless oil; R<sub>f</sub> 0.25 (10% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.89 (s, 1H), 7.42-7.31 (m, 5H), 4.28 (q, *J* = 7.1 Hz, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.52 (s, 2H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 171.3 (C), 167.5 (C), 141.8 (CH), 135.2 (C), 129.1 (CH), 128.9 (CH), 128.7 (CH), 126.5 (C), 61.3 (CH<sub>2</sub>), 61.1 (CH<sub>2</sub>), 33.9 (CH<sub>2</sub>), 14.4 (CH<sub>3</sub>), 14.3 (CH<sub>3</sub>)

**HRMS** (ESI) Calcd. For C<sub>15</sub>H<sub>19</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 263.1283, found: 263.1299

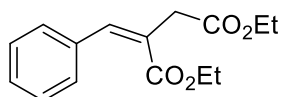
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**Diethyl (*Z*)-2-benzylidenesuccinate 5a'**

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**Chemical Formula:** C<sub>15</sub>H<sub>18</sub>O<sub>4</sub>

**Molecular Weight:** 262.3050

Colorless oil; R<sub>f</sub> 0.20 (10% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.35-7.25 (m, 5H), 6.88 bs, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.46 (bs, 2H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.09 (t, *J* = 7.1 Hz, 3H)

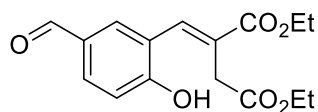
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**Diethyl (E)-2-(5-formyl-2-hydroxybenzylidene)succinate 5n**

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**Chemical Formula:** C<sub>16</sub>H<sub>18</sub>O<sub>6</sub>

**Molecular Weight:** 306.3140

(75% yield). Colorless oil; R<sub>f</sub> 0.33 (35% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 9.83 (s, 1H), 8.01 (bs, 1OH), 7.90 (s, 1H), 7.78 (d, *J* = 8.1 Hz, 1H), 7.72 (s, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 4.28 (dd, *J* = 14.2, 7.0 Hz, 2H), 4.21 (dd, *J* = 14.1, 7.0 Hz, 2H), 3.40 (s, 2H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 190.8 (CH), 172.3 (C), 166.9 (C), 160.0 (C), 137.1 (CH), 132.5 (CH), 132.3 (CH), 129.5 (C), 129.4 (C), 122.5 (C), 117.3 (CH), 61.8 (CH<sub>2</sub>), 61.7 (CH<sub>2</sub>), 34.3 (CH<sub>2</sub>), 14.3 (CH<sub>3</sub>), 14.2 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 3310, 2983, 2001, 1691, 1594, 1436, 1371, 1265, 1183, 1097, 1025, 830, 734, 702 cm<sup>-1</sup>

**HRMS(ESI)** Calcd. For C<sub>16</sub>H<sub>19</sub>O<sub>6</sub> [M+H]<sup>+</sup>: 307.1182, found: 307.1182.

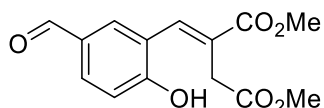
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**Dimethyl (E)-2-(5-formyl-2-hydroxybenzylidene)succinate 5o**

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**Chemical Formula:** C<sub>14</sub>H<sub>14</sub>O<sub>6</sub>

**Molecular Weight:** 278.2600

(33.4mg, 60% yield). Colorless oil; R<sub>f</sub> 0.10 (40% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 9.83 (s, 1H), 7.91 (s, 1H), 7.82 (bs, 1H), 7.78 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.70 (d, *J* = 1.4 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 3.84 (s, 3H), 3.75 (s, 3H), 3.42 (s, 2H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 190.8 (CH), 179.9 (C), 172.7 (C), 167.3 (C), 159.8 (C), 137.3 (CH), 132.4 (CH), 129.6 (C), 122.5 (C), 117.3 (CH), 52.8 (CH<sub>3</sub>), 52.7 (CH<sub>3</sub>), 34.0 (CH<sub>2</sub>)

**IR:** ν<sub>max</sub> = 3312, 2955, 1690, 1593, 1506, 1437, 1377, 1333, 1265, 1200, 1175, 1098, 1008, 896, 831, 732, 703 cm<sup>-1</sup>. **HRMS(ESI)** Calcd. For C<sub>14</sub>H<sub>14</sub>O<sub>6</sub> [M+H]<sup>+</sup>: 279.0869, found: 279.0880.

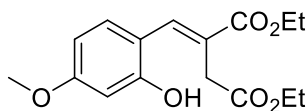
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**Diethyl (E)-2-(2-hydroxy-4-methoxybenzylidene)succinate 5e**

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**Chemical Formula:** C<sub>16</sub>H<sub>20</sub>O<sub>6</sub>

**Molecular Weight:** 308.3300

(23.4 mg, 38% yield ). Colorless oil; R<sub>f</sub> 0.31 (30% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.88 (s, 1H), 7.08 (d, *J* = 8.4 Hz, 1H), 6.59 (bs, 1OH), 6.48 (m, 2H), 4.26 (q, *J* = 7.1 Hz, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.77 (s, 3H), 3.41 (s, 2H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 172.6 (C), 167.4 (C), 161.7 (C), 155.5 (C), 138.2 (CH), 130.7 (CH), 126.5 (C), 114.5 (C), 106.9 (CH), 102.0 (CH), 61.5 (CH<sub>2</sub>), 61.3 (CH<sub>2</sub>), 55.4 (CH<sub>3</sub>), 34.4 (CH<sub>2</sub>), 14.3 (CH<sub>3</sub>), 14.2 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 3375, 2983, 2175, 1698, 1611, 1518, 1369, 1269, 1180, 1166, 1098, 1028, 831, 734, 701 cm<sup>-1</sup>

**HRMS(ESI)** Calcd. For C<sub>16</sub>H<sub>21</sub>O<sub>6</sub> [M+H]<sup>+</sup>: 309.1338, found: 309.1348.

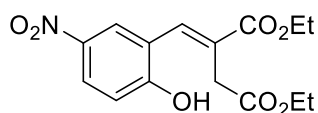
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**Diethyl (E)-2-(2-hydroxy-5-nitrobenzylidene)succinate 5f**

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**Chemical Formula:** C<sub>15</sub>H<sub>17</sub>NO<sub>7</sub>

**Molecular Weight:** 323.3010

(43 mg, 67 % yield ). Colorless oil; R<sub>f</sub> 0.17 (40 % EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.16- 8.08 (m, 2H), 7.83 (s, 1H), 7.35 (bs, 1H), 7.01 (d, *J* = 8.7 Hz, 1H), 4.31 (dd, *J* = 14.2, 7.1 Hz, 2H), 4.23 (dd, *J* = 14.2, 7.1 Hz, 2H), 3.38 (s, 2H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.30 (t, *J* = 7.2 Hz, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 172.4 (C), 166.6 (C), 159.8 (C), 141.2 (C), 136.2 (CH), 130.5 (C), 126.3 (CH), 125.9 (CH), 122.1 (C), 117.2 (CH), 62.1 (CH<sub>2</sub>), 62.0 (CH<sub>2</sub>), 34.3 (CH<sub>2</sub>), 14.3 (CH<sub>3</sub>), 14.2 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 3331, 2986, 2928, 1710, 1526, 1342, 1296, 1265, 1087, 1027, 732, 703 cm<sup>-1</sup>

**HRMS(ESI)** Calcd. For C<sub>15</sub>H<sub>18</sub>NO<sub>7</sub> [M+H]<sup>+</sup>: 324.1083, found: 324.1085



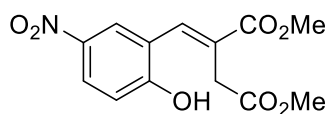
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**Dimethyl (E)-2-(2-hydroxy-5-nitrobenzylidene)succinate 5g**

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**Chemical Formula:** C<sub>13</sub>H<sub>17</sub>NO<sub>7</sub>

**Molecular Weight:** 295.2470

(mg, 60 % yield). Colorless oil; R<sub>f</sub> 0.17 (40 % EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.18- 8.07 (m, 2H), 7.84 (s, 1H), 7.74 (s, 1H), 7.01 (d, *J* = 8.9 Hz, 1H), 3.86 (s, 3H), 3.78 (s, 3H), 3.41 (s, 2H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 172.8 (C), 167.0 (C), 159.6 (C), 136.5 (CH), 130.1 (C), 126.4 (CH), 125.8 (CH), 122.1 (C), 117.2 (CH), 53.0 (CH<sub>3</sub>), 52.9 (CH<sub>3</sub>), 34.0 (CH<sub>2</sub>)

**IR:** ν<sub>max</sub> = 3317, 2956, 1710, 1618, 1587, 1525, 1497, 1437, 1339, 1288, 1204, 1087, 832, 778, 751 cm<sup>-1</sup>

**HRMS(ESI)** Calcd. For C<sub>13</sub>H<sub>14</sub>NO<sub>7</sub> [M+H]<sup>+</sup>: 296.0770, found: 296.0761

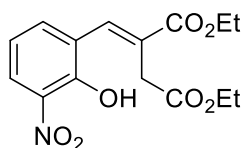
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**(E) and (Z) Diethyl-2-(2-hydroxy-3-nitrobenzylidene)succinate 5i**

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**Chemical Formula:** C<sub>15</sub>H<sub>17</sub>NO<sub>7</sub>

**Molecular Weight:** 323.3010

(58 mg, 90 % yield, E/Z ratio = 72/28). Colorless oil; R<sub>f</sub> 0.65 (40 % EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 11.00 (s, 1H, *E*), 10.96 (s, 1H, *Z*), 8.13 (dd, *J* = 8.6, 1.5 Hz, 1H, *E*), 8.07 (dd, *J* = 8.5, 1.5 Hz, 1H, *Z*), 7.94 (s, 1H, *E*), 7.64 (d, *J* = 7.2 Hz, 1H, *E*), 7.59 (d, *J* = 8.1 Hz, 1H, *Z*), 7.05- 6.98 (m, 1H, *E*), 6.94 (m, 2H, *Z*), 4.29 (q, *J* = 7.1 Hz, 2H, *E*), 4.18 (q, *J* = 7.1, 2H, *E*), 4.10 (m, 1H), 3.51 (s, 2H, *Z*), 3.41 (s, 2H, *E*), 1.34 (t, *J* = 7.1 Hz, 3H, *E*), 1.27 (t, *J*=7.1, 5H), 1.09 (t, *J*=7.1, 1H)

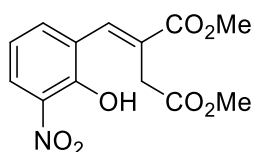
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**Dimethyl (E)-2-(2-hydroxy-3-nitrobenzylidene)succinate 5j**

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**Chemical Formula:** C<sub>13</sub>H<sub>13</sub>NO<sub>7</sub>

**Molecular Weight:** 295,2470

(42 mg, 72 % yield). Colorless oil; R<sub>f</sub> 0.65 (40 % EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 11.00 (s, 1H), 8.14 (dd, *J* = 8.6, 1.3 Hz, 1H), 7.97 (s, 1H), 7.66-7.60 (m, 1H), 7.07- 6.99 (m, 1H), 3.85 (s, 3H), 3.74 (s, 3H), 3.44 (s, 2H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 171.5 (C), 167.2 (C), 153.4 (C), 137.4 (CH), 135.6 (CH), 128.6 (C), 126.8 (C), 125.8 (CH), 119.9 (CH), 52.6 (CH<sub>3</sub>), 52.5 (CH<sub>3</sub>), 34.0 (CH<sub>2</sub>)

**IR:** ν<sub>max</sub> = 3231, 2955, 1713, 1608, 1539, 1446, 1313, 1265, 1198, 1099, 1011, 909, 851, 773, 733, 702 cm<sup>-1</sup>

**HRMS(ESI)** Calcd. For C<sub>13</sub>H<sub>14</sub>NO<sub>7</sub> [M+H]<sup>+</sup>: 296.0770, found: 296.0772

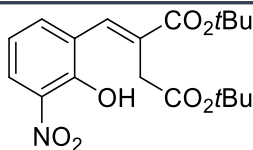
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**(E) and (Z) Di-tert-butyl-2-(2-hydroxy-3-nitrobenzylidene)succinate 5k**

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**Chemical Formula:** C<sub>19</sub>H<sub>25</sub>NO<sub>7</sub>

**Molecular Weight:** 379.4090

(57.3 mg, 76 % yield, *E/Z* ratio = 75/25). Colorless oil; R<sub>f</sub> 0.62 (40 % EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 10.99 (s, 1H, *E*), 10.94 (s, 1H, *Z*), 8.12 (dd, *J*=8.5, 1.5, 1H, *E*), 8.06 (dd, *J*=8.6, 1.4, 1H, *Z*), 7.83 (s, 1H, *E*), 7.64 (d, *J*=7.5, 1H, *E*), 7.58 (d, *J*=7.5, 1H, *Z*), 7.06- 6.98 (m, 1H, *E*), 6.97- 6.91 (m, 1H, *Z*), 6.83 (s, 1H, *Z*), 3.38 (d, *J*=1.1, 2H, *Z*), 3.30 (s, 2H, *E*), 1.55 (s, 9H, *E*), 1.47 (s, 9H, *Z*), 1.47 (s, 9H, *E*), 1.32 (s, 9H, *Z*)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 170.0 (C, *E*), 169.8 (C, *Z*), 165.7 (C, *E*), 165.6 (C, *Z*), 153.3 (C, *E*), 152.7 (C, *Z*), 137.9 (CH, *Z*), 137.3 (CH, *E*), 133.7 (CH, *E*), 131.7 (CH, *Z*), 130.8 (C, *E*), 128.3 (C, *Z*), 127.3 (C, *Z*), 125.2 (CH, *E*), 124.5 (CH, *Z*), 119.6 (CH, *E*), 119.0 (CH, *Z*), 81.4 (C, *E*), 81.1 (C, *Z*), 41.9 (CH<sub>2</sub>, *Z*), 35.4 (CH<sub>2</sub>, *E*), 28.0 (3CH<sub>3</sub>, *E*), 27.8 (3CH<sub>3</sub>, *Z*)

**IR:** ν<sub>max</sub> = 3676, 2980, 1709, 1608, 1540, 1446, 1368, 1314, 1255, 1149, 11101, 969, 910, 845, 739, 702 cm<sup>-1</sup>.

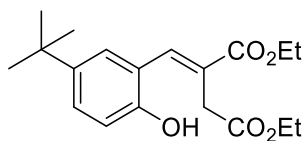
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**Diethyl (E)-2-(5-(tert-butyl)-2-hydroxybenzylidene)succinate 5h**

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**Chemical Formula:** C<sub>19</sub>H<sub>26</sub>O<sub>5</sub>

**Molecular Weight:** 334.4120

(44 mg, 66 % yield). Colorless oil; R<sub>f</sub> 0.45 (40 % EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.91 (s, 1H), 7.25 (dd, *J* = 8.8, 2.1 Hz, 1H), 7.14 (d, *J* = 2.3 Hz, 1H), 6.84 (d, *J* = 8.5 Hz, 1H), 6.15- 5.98 (m, 1H), 4.28 (q, *J* = 7.2 Hz, 2H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.40 (s, 2H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.30-1.24 (m, 12H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 172.4 (C), 167.1 (C), 151.5 (C), 143.3 (C), 138.8 (CH), 128.2 (C), 127.6 (CH), 126.5 (CH), 121.1 (C), 116.2 (CH), 61.5 (CH<sub>2</sub>), 61.4 (CH<sub>2</sub>), 34.5 (CH<sub>2</sub>), 31.5 (3CH<sub>3</sub>), 14.3 (CH<sub>3</sub>), 14.3 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 3396, 2963, 1703, 1505, 1369, 1287, 1265, 1182, 1127, 1097, 1027, 896, 822, 737, 703 cm<sup>-1</sup>.

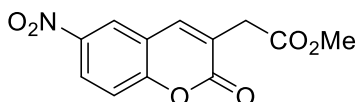
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**Methyl 2-(6-nitro-2-oxo-2H-chromen-3-yl)acetate 6g**

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**Chemical Formula:** C<sub>12</sub>H<sub>9</sub>NO<sub>6</sub>

**Molecular Weight:** 263.2050

(9 mg, 10 % yield). Colorless oil; R<sub>f</sub> 0.64 (40 % EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.47- 8.33 (m, 2H), 7.77 (s, 1H), 7.47 (d, *J* = 9.0, 1H), 3.76 (s, 3H), 3.65 (s, 2H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 179.9 (C), 169.9 (C), 157.0 (C), 140.3 (CH), 126.3 (CH), 123.6 (CH), 118.0 (CH), 52.7 (CH<sub>3</sub>), 35.8 (CH<sub>2</sub>)

**IR:** ν<sub>max</sub> = 3334, 2974, 2888, 1419, 1381, 1268, 1087, 1047, 880, 804, 736, 703 cm<sup>-1</sup>

**HRMS(ESI)** Calcd. For C<sub>12</sub>H<sub>10</sub>NO<sub>6</sub> [M+H]<sup>+</sup>: 264.0508, found: 264.0507

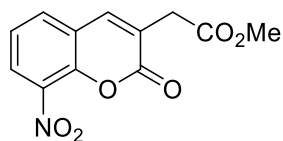
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**Methyl 2-(8-nitro-2-oxochroman-3-yl)acetate 6j**

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**Chemical Formula:** C<sub>12</sub>H<sub>9</sub>NO<sub>6</sub>

**Molecular Weight:** 263,2050

(7.5 mg, 15 % yield). Colorless oil; R<sub>f</sub> 0.62 (40 % EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.10 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.77- 7.70 (m, 2H), 7.40 (t, *J* = 8.0 Hz, 1H), 3.75 (s, 3H), 3.64 (s, 2H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 169.8 (C), 158.6 (C), 151.4 (C), 145.9 (C), 140.4 (CH), 132.5 (CH), 126.9 (CH), 123.9 (CH), 121.0 (C), 52.5 (CH<sub>3</sub>), 35.6 (CH<sub>2</sub>)

**IR:** ν<sub>max</sub> = 2955, 1732, 1610, 1534, 1343, 1265, 1184, 1056, 905, 828, 786, 733, 702 cm<sup>-1</sup>

**HRMS(ESI)** Calcd. For C<sub>12</sub>H<sub>9</sub>NO<sub>6</sub> [M+H]<sup>+</sup>:264.0508, found: 264.0507

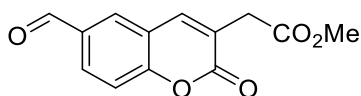
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**Methyl 2-(6-formyl-2-oxo-2H-chromen-3-yl)acetate 6o**

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**Chemical Formula:** C<sub>13</sub>H<sub>10</sub>O<sub>5</sub>

**Molecular Weight:** 246.2180

(6.3 mg, 13% yield). White solid; R<sub>f</sub> 0.12 (40 % EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 10.04 (s, 1H), 8.12- 7.98 (m, 2H), 7.77 (s, 1H), 7.48 (d, *J* = 8.3 Hz, 1H), 3.76 (s, 3H), 3.64 (s, 2H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 190.2 (CH), 179.9 (C), 141.0 (CH), 132.2 (CH), 130.0 (CH), 119.6 (C), 117.9 (CH), 52.6 (CH<sub>3</sub>), 35.9 (CH<sub>2</sub>)

**IR:** ν<sub>max</sub> = 2956, 1729, 1698, 1638, 1605, 1438, 1340, 1264, 1210, 1152, 818, 787, 732, 703 cm<sup>-1</sup>

**HRMS(ESI)** Calcd. For C<sub>13</sub>H<sub>10</sub>O<sub>5</sub> [M+H]<sup>+</sup>:247.0606, found: 247.0605

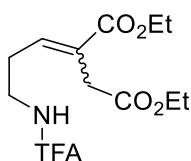
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**Diethyl 2-(3-(2,2,2-trifluoroacetamido)propylidene)succinate 7a**

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**Chemical Formula:** C<sub>13</sub>H<sub>18</sub>FNO<sub>5</sub>

**Molecular Weight:** 325.2842

(37 mg, 57% yield, *E/Z* ratio = 65/35). Colorless oil; R<sub>f</sub> 0.44 (60% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.73 (bs, 0.35H, *Z*), 7.45 (bs, 0.65H, *E*), 6.90 (t, *J* = 7.5 Hz, 0.65H, *E*), 6.01 (t, *J* = 7.5 Hz, 0.35H, *Z*), 4.30-4.10 (m, 4H, *E&Z*), 3.60-3.44 (m, 2H, *E&Z*), 3.36 (bs, 1.3H, *E*), 3.29 (bs, 0.7H, *Z*), 2.80-2.73 (m, 0.7H, *Z*), 2.60-2.47 (m, 1.3H, *E*), 1.35-1.20 (m, 6H, *E&Z*)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 171.7 (C, *E*), 170.8 (C, *Z*), 167.2 (C, *Z*), 166.4 (C, *E*), 158.0 (C, *E&Z*), 141.3 (CH, *E*), 141.1 (CH, *Z*), 129.6 (C, *Z*), 128.7 (C, *E*), 116.0 (C, q, *J* = 286 Hz, *E&Z*), 61.6 (CH<sub>2</sub>, *E*), 61.4 (CH<sub>2</sub>, *Z*), 61.3 (CH<sub>2</sub>, *E*), 61.2 (CH<sub>2</sub>, *Z*), 40.3 (CH<sub>2</sub>, *Z*), 39.2 (CH<sub>2</sub>, *Z*), 38.9 (CH<sub>2</sub>, *E*), 32.2 (CH<sub>2</sub>, *E*), 28.1 (CH<sub>2</sub>, *E*), 27.8 (CH<sub>2</sub>, *Z*), 14.25 (CH<sub>3</sub>, *E*), 14.19 (CH<sub>3</sub>, *E&Z*), 14.1 (CH<sub>3</sub>, *Z*)

**IR:** ν<sub>max</sub> = 3325, 2925, 1709, 1556, 1371, 1180, 1031, 724 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>13</sub>H<sub>19</sub>F<sub>3</sub>NO<sub>5</sub> [M+H]<sup>+</sup>: 326.1215, found: 326.1219

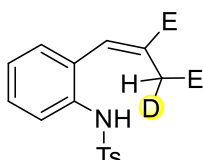
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**Deuterated (*E*)-diethyl 2-(2-(4-methylphenylsulfonamido)benzylidene)succinate**

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**Chemical Formula:** C<sub>16</sub>H<sub>14</sub>DNO<sub>2</sub>S

**Molecular Weight:** 286.3671

(18.5 mg, 43% yield). Colorless oil; R<sub>f</sub> 0.24 (30% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.59 (d, *J* = 8.2 Hz, 2H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.18-7.13 (m, 2H), 7.09 (bs, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.09 (d, *J* = 8.5 Hz, 1H), 2.39 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H)

**<sup>13</sup>C NMR** (126 MHz, CDCl<sub>3</sub>) δ 171.2 (C), 166.0 (C), 144.0 (C), 138.0 (CH), 136.9 (C), 134.3 (C), 131.0 (C), 129.8 (CH), 129.2 (C), 128.7 (CH), 127.3 (CH), 126.1 (CH), 124.8 (CH), 61.6 (CH<sub>2</sub>), 61.5 (CH<sub>2</sub>), 33.6 (t, *J* = 19.9 Hz, CHD), 21.7 (CH<sub>3</sub>), 14.33 (CH<sub>3</sub>), 14.25 (CH<sub>3</sub>)

**HRMS** (ESI) Calcd. For C<sub>22</sub>H<sub>24</sub>DNNaO<sub>6</sub>S [M+Na]<sup>+</sup>: 455.1363, found: 455.1378

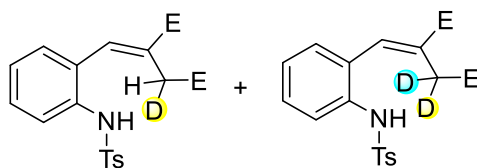
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### Deuterated products

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(19 mg, 44% yield). Colorless oil;  $R_f$  0.24 (30% EtOAc/n-Heptane)

$^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.59 (d,  $J = 8.0$  Hz, 2H), 7.57 (d,  $J = 8.0$  Hz, 1H), 7.32 (t,  $J = 8.2$  Hz, 1H), 7.22 (d,  $J = 8.0$  Hz, 2H), 7.18-7.13 (m, 2H), 7.09 (bs, 1H), 7.01 (d,  $J = 7.7$  Hz, 1H), 4.26 (q,  $J = 7.1$  Hz, 2H), 4.17 (q,  $J = 7.1$  Hz, 2H), 3.09 (d,  $J = 8.5$  Hz, 0.5H), 2.40 (s, 3H), 1.34 (t,  $J = 7.1$  Hz, 3H), 1.25 (t,  $J = 7.1$  Hz, 3H)

**HRMS** (ESI) Calcd. For  $\text{C}_{22}\text{H}_{23}\text{D}_2\text{NNaO}_6\text{S}$   $[\text{M}+\text{Na}]^+$ : 456.1426, found: 456.1434.

- (1) Saget, T.; Cramer, N. *Angewandte Chemie International Edition* **2013**, *52*, 7865.
- (2) Albicker, M. Ä.; Cramer, N. *Angewandte Chemie International Edition* **2009**, *48*, 9139.
- (3) Moteki, S. A.; Wu, D.; Chandra, K. L.; Reddy, D. S.; Takacs, J. M. *Org. Lett.* **2006**, *8*, 4.
- (4) Perotti, J.; Cravero, R.; Luna, L.; Grau, R.; Vaillard, S. *Arkivoc* **2011**, 2011, 92.



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**Chapter 2:**  
**General introduction to homogeneous gold(I)  
catalysis**



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## 2.1 Brief history of gold

Gold was discovered in the Middle East before 6000 B.C. Archeological discoveries manifested its existence in four major ancient civilizations in the world, by the proof of delicate handicrafts. Gold also showed its economic importance as soon as it started to combine with human society. It was used as the hard currency for thousands years, and it has never lost its value, even during the various financial crises.

Gold is a naturally stable metal and it is widely dispersed throughout the world, so it could be used easily by our ancestors. However, the same character of stability covered its importance in chemical applications for a long time.

Gold played an important role in the core concept of alchemy, which was treated as the origin of modern chemistry. Alchemists trusted that all metals, especially lead, can be transferred into gold through the 'philosopher's stone', which was also believed to bring immortal life. The idea attracted numerous alchemists who dedicated their whole lives to find the 'philosopher's stone'. Now we all know that the 'philosopher's stone' was only a cryptic concept which can never come true.

In fact, the development of gold in chemistry today proved that gold complex should be treated as a real 'philosopher's stone' in transition metal catalysis, transforming simple substrates to complex (polycyclic) compounds. Furthermore, it is possible to achieve the synthesis of enantiopure compounds via enantioselective Au-catalysis, to activate many different molecular bonds including carbon-hydrogen bonds, and so on. As an important transition/precious metal, gold started to shine in transition metal catalysis area in the past decades.

## 2.2 Development of homogeneous gold catalysis

Entering the 20th century, gold complexes started to emerge in transition metal catalyzed reactions as efficient catalysts.<sup>54</sup> In 1935, Schwemberger first reported an AuCl or AuCl<sub>3</sub> catalyzed chlorination of naphthalene (*Scheme II-1-a*).<sup>55</sup> In 1972, Gassman found that AuI<sub>3</sub> promoted rearrangement of bicyclo[1.1.0]butane into diene (*Scheme II-1-b*).<sup>56</sup> Several years later, in 1976, Thomas disclosed the first example of gold(III) catalyzed hydration of alkynes to form ketones (*Scheme II-1-c*).<sup>57</sup>

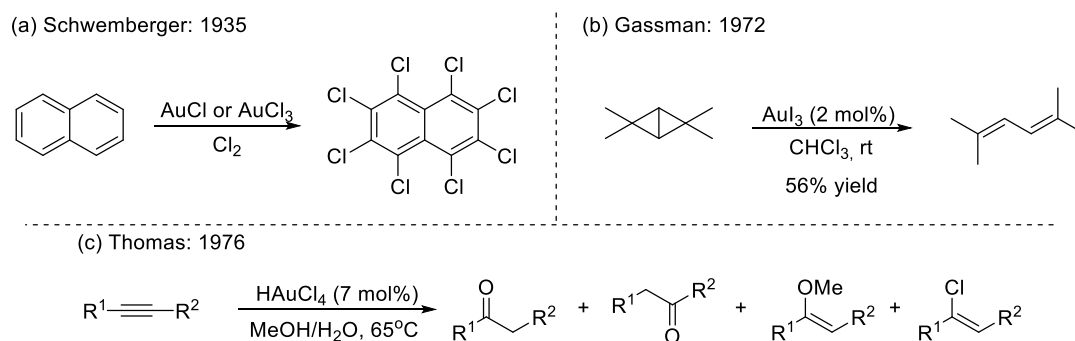
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<sup>54</sup> a) Stephen, A.; Hashmi, K. *Gold Bull.* **2004**, *37*, 51. b) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180.

<sup>55</sup> Schwemberger, W.; Gordon, W. *Chem. Zentralbl.* **1935**, *106*, 514

<sup>56</sup> Gassman, P.; Meyer, G.; Williams, F. J. *Am. Chem. Soc.* **1972**, *94*, 7741.

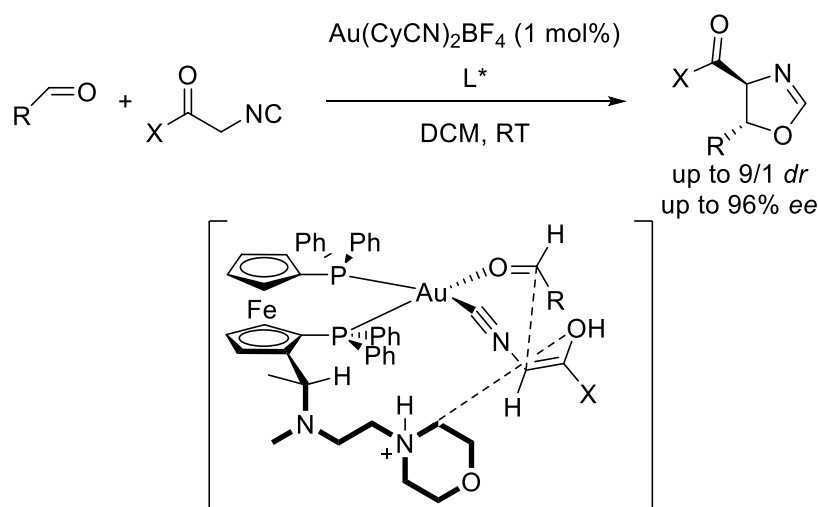
<sup>57</sup> Norman, R.; Parr, W.; Thomas C. J. *Chem. Soc., Perkin Trans. 1*, **1976**, 1983.



*Scheme II-1. Initial work in homogeneous gold catalysis*

In the continuation of this introduction, we wanted to present some relevant examples that we considered important in the development of homogeneous gold catalysis.

In the field of asymmetric Au-catalysis, the cornerstone study was developed by Ito and co-workers in 1986.<sup>58</sup> This work was achieved long time before the “golden rush” of homogeneous gold catalysis, especially asymmetric gold catalysis. They reported the first asymmetric reaction of aldehydes with isocyanoacetate, catalyzed by  $[\text{Au}(\text{CyCN})_2]\text{BF}_4$  in presence of chiral ferrocenylphosphine ligand. The *trans*-oxazoline compounds were obtained as the major product. This catalytic system promoted high enantioselectivity, with up to 96% *ee* (*Scheme II-2*).

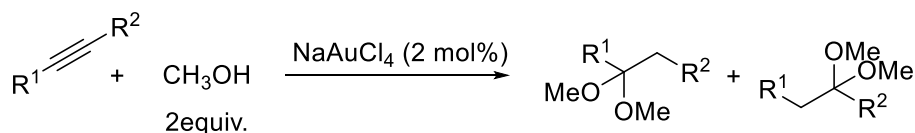


*Scheme II-2. The first example in asymmetric Au-catalysis*

A gold(III)-catalyzed hydration of alkyne was discovered in Utimoto's team in 1991 (*Scheme II-3*).<sup>59</sup> Before this protocol, those kind of reactions were mainly achieved by highly toxic mercury(II) catalyst. This methodology relied on efficient activation of Au(III) complexes. The corresponding dimethoxyalkyl compounds were obtained in excellent yields. It was mentioned that when gold(I) complex was tested, no hydration of alkyne substrate was nevertheless observed.

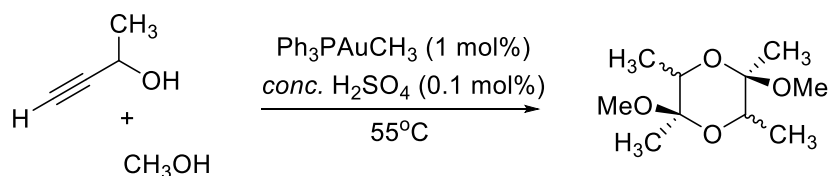
<sup>58</sup> Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405.

<sup>59</sup> Fukuda, Y.; Utimoto, K. *J. Org. Chem.* **1991**, *56*, 3729.



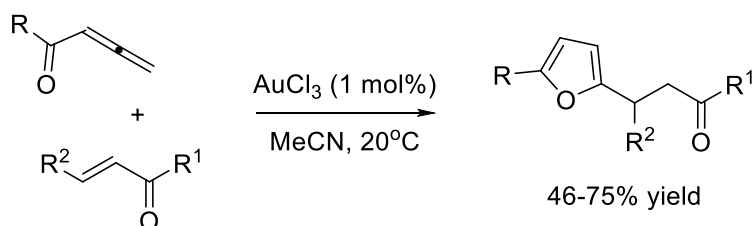
Scheme II-3. Gold(III)-catalyzed hydration of alkynes

Another milestone in the development of homogeneous gold-catalyzed reactions was raised by Teles and co-workers, from BASF, in 1998.<sup>60</sup> They discovered that cationic gold(I) complexes are highly efficient to catalyze the addition of alcohol to alkynes under mild conditions. This study showed that cationic phosphine-gold(I) complex prepared *in situ* from the precatalyst  $\text{Ph}_3\text{PAuMe}$  and sulfuric acid, is one of the most efficient catalyst for these addition reactions. In some cases, the turnover frequency could reach  $1.5 \text{ s}^{-1}$  (Scheme II-4). The effect of counterion of the gold complex was also studied with respect to the catalytic activity. This study had greatly contributed to further development in homogeneous gold catalysis.



Scheme II-4. Homogeneous gold-catalyzed addition of alcohol to alkyne

In 2000, Hashmi reported an  $\text{AuCl}_3$ -catalyzed cross isomerization between terminal allenylketones and  $\alpha,\beta$ -unsaturated ketones, to form furan products. In this transformation, both the formation of C-C and C-O bonds could be promoted. With certain substrates, compared to Pd(II) or Ag(I) catalysts,  $\text{AuCl}_3$  showed much higher activity. In some cases, even only 0.1 mol% of  $\text{AuCl}_3$  gave complete conversion of substrates (Scheme II-5).



Scheme II-5. Cross-dimerization of allenyl ketones and Michael acceptors

In fact, before 2000, the publications about homogeneous gold catalysis were quite sparse. For too long this metal has been considered inert with low catalytic activity. However, based on those initial researches, more and more attention was attracted to this area, especially because of the gold catalysts can promote formation of various bonds, including carbon-carbon bond and carbon-heteroatom bonds. The quantity of publications about homogeneous gold catalysis has flourished in the past decade.<sup>61</sup>

<sup>60</sup> Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 1415.

<sup>61</sup> a) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. b) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. c) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395.

## 2.3 General features of gold catalysis

From a general point of view, homogeneous Au(I)-catalysis exhibits several features:

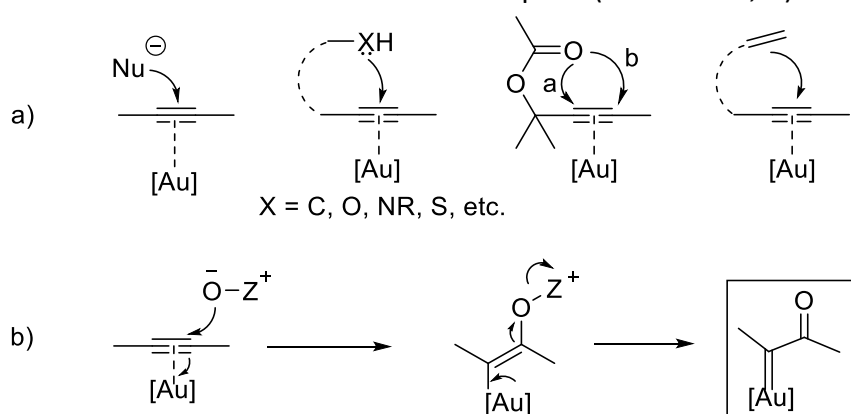
- 1) air stability of the complexes (the high oxidation potential of Au(I) to Au(III) complexes allows most of gold(I)-catalyzed reactions to proceed without the rigorous exclusion of air);
- 2) most of the catalysts tolerate the presence of water;
- 3) high chemoselectivity: among others, organogold species prefer protodeauration over  $\beta$ -hydride elimination, thereby increasing the product selectivity;
- 4) high catalytic activity, mild reaction conditions and relative non-toxicity.

We will now detail various points that are very important in gold catalysis, namely the different activation modes, the choice of the counteranion and the possible structures of the ligand coordinated to the metal center.

### 2.3.1 Activation modes in Au-catalysis

As a carbophilic, soft Lewis acid, cationic gold complexes could activate different unsaturated bonds toward the addition of nucleophiles, via a  $\pi$ -complex. A number of different unsaturated substrates have been designed to develop intra- or inter-molecular reactions. Among all the possible functionalities which could be activated by gold complexes, we can cite alkynes, allenes, alkenes, dienes, carbonyls and so on.

In the same way, different nucleophiles could be engaged in these transformations. Most of the research work focused on (1) the formation of C-C or C-heteroatom bonds by addition of external or internal nucleophiles on activated substrates; (2) the cycloisomerizations involving migration of propargyl esters (among others); and (3) the cycloisomerization of 1,*n*-enynes in which the alkene acts as an internal nucleophile (*Scheme II-6, a*).

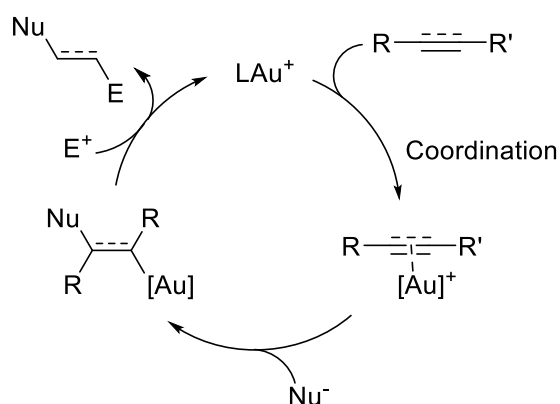


*Scheme II-6. Activation modes in Au-catalysis*

Recently, some work was also developed in the field of gold catalyzed oxidative cyclizations, which could expand even more the reaction scope of the gold-catalyzed transformations

(Scheme II-6, b).<sup>62</sup>

In the framework of this PhD work, we will be more involved in the use of cationic gold(I) catalysts to activate alkyne derivatives. In gold catalysis, activation of carbon-carbon multiple bond is the most common reactivity pattern. For example, the general mechanism for activation of alkynes is outlined in *Scheme II-7*. The reaction started with the  $\pi$ -complexation of the alkyne by the cationic gold(I) complex. After that, addition of nucleophile to the ( $\eta^2$ -alkyne)[Au]<sup>+</sup> complex occurred. The corresponding *trans*-vinyl-gold complex was postulated to be an intermediate (and was confirmed in several publications later). Finally, the vinylgold complex undergoes the protodeauration step or is captured by an electrophile, to form the desired product and regenerate the active catalyst (*Scheme II-7*).



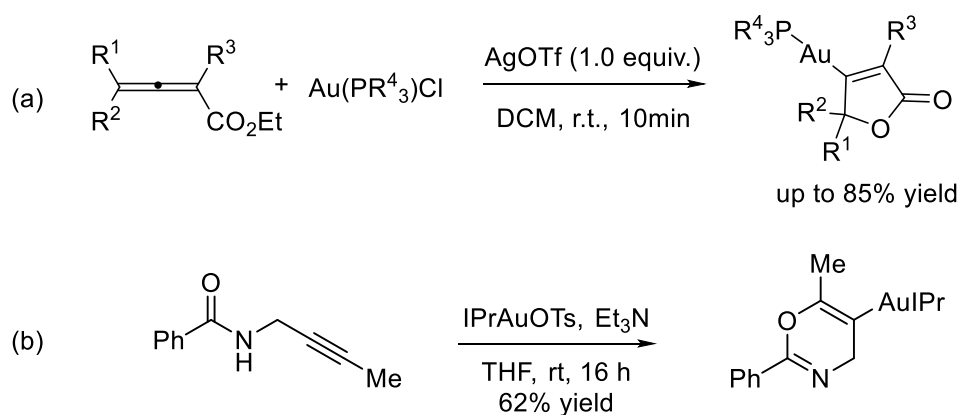
*Scheme II-7. Activation of C-C multiple bond by cationic gold complexes*

Hence cationic gold complex can be treated as a soft Lewis acid. If we took into account these kinds of mechanisms, a large quantity of compounds possessing unsaturated bond can be used in Au-catalyzed reactions. If we also considered the countless nucleophiles that could be used, these processes can be applied in the construction of numerous complex (polycyclic) molecules.

To confirm the proposed mechanism, series of work were focused on the search on different steps of the mechanism. For example, Hammond *et al.*, isolated stable alkenyl gold compounds during their research on a gold-catalyzed cyclization reaction of allenates (*Scheme II-8, a*).<sup>63</sup> The structures of these vinyl-gold complexes were determined by <sup>1</sup>H, <sup>13</sup>C, and <sup>31</sup>P NMR spectroscopy and X-ray crystallography. Control experiments showed that the alkenyl gold should be the real intermediate of Au-catalyzed reactions.

<sup>62</sup> Zhang, L. *Acc. Chem. Res.* **2014**, *47*, 877.

<sup>63</sup> Liu, L. P.; Hammond, G. B. *Chem. Asian. J.* **2009**, *4*, 1230.



*Scheme II-8. Preparation of stable alkenyl gold compounds*

The Hashmi's group also prepared a stable vinylgold complex via cyclization of *N*-propargyl carboxamide, which displays a Me-substituted alkynyl group, using a stoichiometric amount of a cationic NHC-gold complex (*Scheme II-8, b*).<sup>64</sup>

In addition to the intrinsic reactivity in gold-catalysis which depends on the considered substrates, one of the most important features is the structure of the active catalyst. Until today, amounts of gold(I) and gold(III) catalysts were developed, from the simplest AuCl and AuCl<sub>3</sub> to specially designed ligands applied in gold catalysis. It mainly depends on two factors: the structure of the coordinated ligand and the nature of the counteranion.

## 2.3.2 Structure of gold catalysts

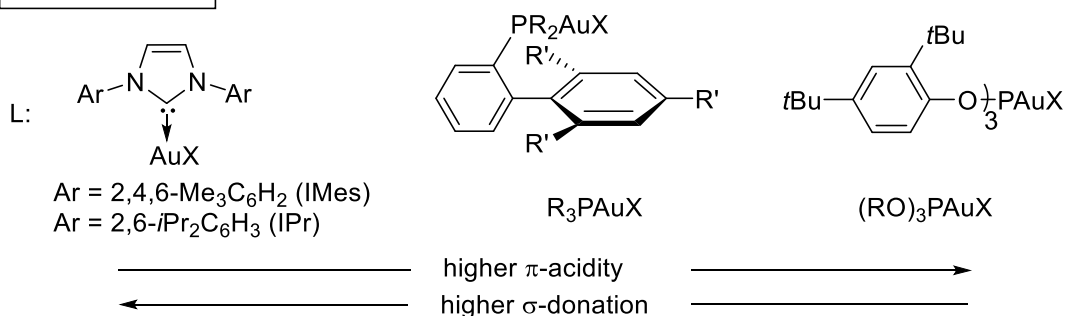
### 2.3.2.1 Ligands design in gold(I)-catalysis

The nature and the structure of the ligand play a major role in gold catalysis, by tuning both the reactivity and the selectivity of gold catalysts in the desired transformation. Some research groups undertook fine studies focus on the relation between the structure of the ligand and the reaction outcome.

Trivalent phosphines or phosphites as well as *N*-heterocyclic carbenes (NHC) are the most commonly used ligands for the synthesis of gold(I) complexes (*Scheme II-9*).

<sup>64</sup> Hashmi, A. S.; Schuster, A. M.; Rominger, F. *Angew. Chem. Int. Ed.* **2009**, *48*, 8247.

LAuX catalysts:



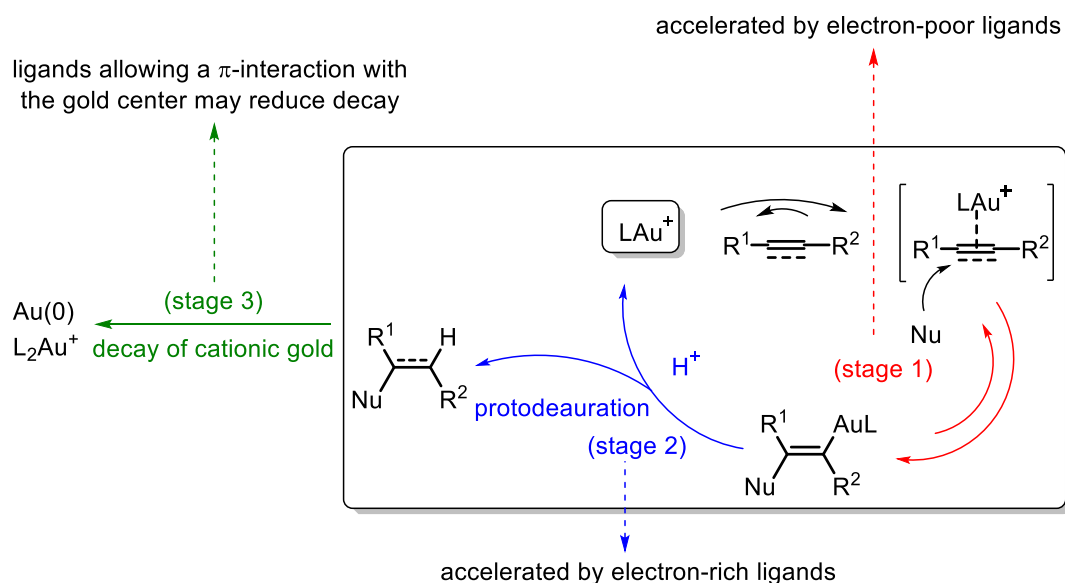
X<sup>-</sup>: NTf<sub>2</sub><sup>-</sup>, SbF<sub>6</sub><sup>-</sup>, BF<sub>4</sub><sup>-</sup>, PF<sub>6</sub><sup>-</sup>, OTs<sup>-</sup>, OMs<sup>-</sup>, OTf<sup>-</sup>

Scheme II-9. Ligand's influence in gold catalysis

NHC ligands are strong  $\sigma$ -donors but relatively weak  $\pi$ -acceptors. With respect to these latter, the phosphine and phosphite ligands are weaker  $\sigma$ -donors but stronger  $\pi$ -acceptors (Scheme II-9). Moreover, the substitution patterns of the ligands also modulate their electronic properties. Thus, if the ligands are substituted with electron-withdrawing groups, the  $\sigma$ -donating capacity of the ligands tends to decrease. At the same time, their  $\pi$ -backbonding ability increased because the  $\pi$ -accepting orbitals on the ligands are lowered in energy. Generally speaking, ligands can exhibit a wide range of  $\sigma$ -donor and  $\pi$ -acceptor properties, and the steric and electronic features of gold catalyst can be tuned by modifications of the ligands.

We can link directly the properties of the ligand and the reaction outcomes. Xu and Hammond studied specifically the ligand effects for applications in homogeneous gold(I)-catalysis.<sup>65</sup> Most of the gold(I)-catalyzed reactions followed three main stages. In *stage 1*, the nucleophiles do an addition on the [LAu]<sup>+</sup>-activated unsaturated bond, to form for example a *trans*-alkenyl gold intermediate (Scheme II-10). In *stage 2*, the vinyl-gold complex is trapped by an electrophile to give the final product (called protodeauration step if the electrophile is a proton). In this step, regeneration of the cationic gold catalyst also occurs. However, deactivation of the gold(I) catalyst can happen via reduction of gold(I) to gold(0) species and via ligand exchanges leading to inactive [L<sub>2</sub>Au]<sup>+</sup> derivatives (*stage 3*, Scheme II-10).

<sup>65</sup> Wang, W.; Hammond, G. B.; Xu, B. *J. Am. Chem. Soc.* **2012**, *134*, 5697.

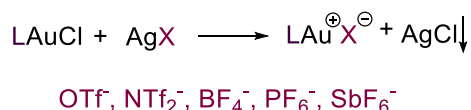


*Scheme II-10.*

It was proved that electron-deficient ligands could accelerate the stage 1 and that electron-rich ligands could promote the stage 2. For stage 3, when the substrate was present in the reaction mixture, both electron-rich and electron-poor ligands led to faster catalyst decay, compared to triphenylphosphine. However, all ligands with arene moieties allowing a  $\pi$ -interaction with the gold center, i.e. *o*-biarylphosphines, may stabilize the cationic gold complexes. These theoretical and experimental investigations highlighted how the electronic properties of the ligand affect the reaction kinetic and provide guidelines for the design of novel ligands for gold catalysis.

### 2.3.2.2 Influence of counterions in gold(I) catalysis

The statistics data of gold catalyzed reactions, mainly including Au(I)-catalysis, from 2000 to 2015 showed that the most widely used counterion was chloride ( $\text{Cl}^-$ , 25%), followed by hexafluoroantimonate ( $\text{SbF}_6^-$ ), triflate ( $\text{OTf}^-$ ) and *bis*trifluoromethanesulfonamide ( $\text{NTf}_2^-$ ). It is necessary to mention that before 2005, most of the publications mentioned the application of only AuCl and AuCl<sub>3</sub>. However after 2005, silver halide scavengers were more and more utilized.<sup>66</sup> In fact, in most instances, the gold halide pre-catalyst can be activated by halide scavengers based on silver salt with weak counterion (such as  $\text{NTf}_2^-$ ,  $\text{OTf}^-$ ,  $\text{SbF}_6^-$ , etc., *Scheme II-11*).



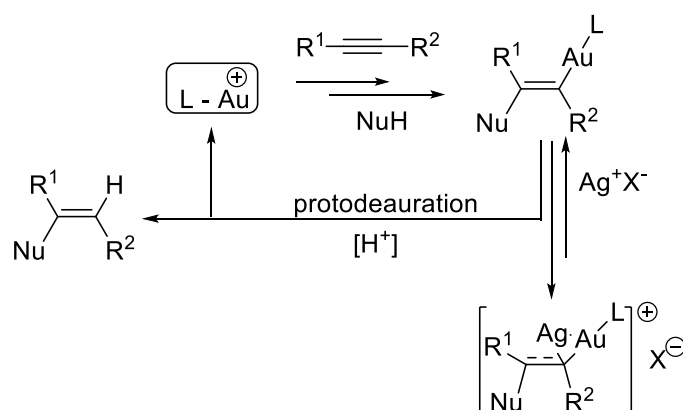
*Scheme II-11. Activation by silver salt*

Some sodium salts, gallium salts and copper salts were also used to activate gold pre-

<sup>66</sup> Jia, M.; Bandini, M. *ACS Catal.* **2015**, *5*, 1638.



catalyst.<sup>67</sup> The use of sodium salts were suggested to be applied because of the Na<sup>+</sup> brings no influence in gold-catalyzed processes, however, the operation must be carried out in glove box. With the treatment of AgX, corresponding [LAuX] was formed with AgCl as residue, which was considered for many years to be inert in the reaction system. However, this widely accepted idea has been strongly questioned by different research groups.<sup>68</sup> Problems caused by silver salts are often observed due to its chemical property as a Lewis acid metal. Even though this problem was overlooked for a long time, silver salt can generate similar activity than gold complex in some cases.<sup>69</sup> Very often, it is difficult to say if the [L-Au]<sup>+</sup> is the real  $\pi$ -acid which participated in reaction system solely. Some research reported the formation of different intermediates with Ag<sup>+</sup> in reaction sequence.<sup>15</sup> In some cases the silver can even react with gold to form bimetallic complexes (*Scheme II-12*).<sup>70</sup>



*Scheme II-12. Silver/gold bimetallic intermediate*

Some solutions were mentioned such as the use of a bit lower quantity of silver salt applying in reaction system, compared to [LAuCl].<sup>71</sup> It is also possible to react the gold pre-catalyst with silver salt separately and then filtrate the formed AgCl residue before to transfer this solution to the reaction flask. The order of the introduction of reagents is very important. Echavarren observed different results based on the introduction order of the substrate, the gold precatalyst and/or the silver salt.<sup>72</sup> Indeed, the followed reaction conditions were used: (A) *in situ* generation of the catalyst in the presence of the substrate(s), (B) *in situ* generation of the catalyst followed by the addition of the substrate(s), and (C) filtration of the catalyst through celite after its generation *in situ*, followed by the addition of the substrate(s). These studies inform us a lot about the possible pitfalls we may encounter in gold(I) catalysis.

To finish this introduction part, we will now detail different methodologies used for the development of enantioselective gold(I) transformations.

<sup>67</sup> Guerinot, A.; Fang, W.; Sircoglou, M.; Bour, C.; Bezzenine-Lafolle, S.; Gandon, V. *Angew. Chem. Int. Ed.* **2013**, *52*, 5848.

<sup>68</sup> Wang, D.; Cai, R.; Sharma, S.; Jirak, J.; Thummanapelli, S. K.; Akhmedov, N. G.; Zhang, H.; Liu, X.; Petersen, J. L.; Shi, X. *J. Am. Chem. Soc.* **2012**, *134*, 9012.

<sup>69</sup> a) Briones, J. F.; Davies, H. M. *J. Am. Chem. Soc.* **2012**, *134*, 11916. b) Briones, J. F.; Davies, H. M. *J. Am. Chem. Soc.* **2013**, *135*, 13314. c) Lo, V. K.; Chan, A. O.; Che, C. M. *Org. Biomol. Chem.* **2015**, *13*, 6667

<sup>70</sup> a) Zhdanko, A.; Maier, M. E. *ACS Catal.* **2015**, *5*, 5994. b) Lu, Z.; Han, J.; Hammond, G. B.; Xu, B. *Org. Lett.* **2015**, *17*, 4534.

<sup>71</sup> Teller, H.; Corbet, M.; Mantilli, L.; Gopakumar, G.; Goddard, R.; Thiel, W.; Furstner, A. *J. Am. Chem. Soc.* **2012**, *134*, 15331.

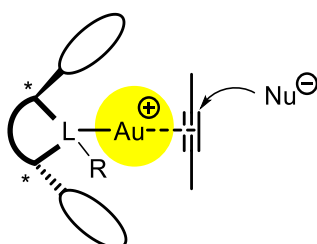
<sup>72</sup> Escofet, A. H.; Echavarren, A. M. *Org. Lett.* **2013**, *15*, 5782.

## 2.4 Strategies used for the development of asymmetric gold(I)-catalysis

The preparation of enantiopure compounds from achiral substrate had been one of the most important topics in organic synthesis. It continued to challenge organic chemists for a long time. In fact after the first example published by Ito in 1986, the area of asymmetric gold catalysis has remain for a long time a deserted area.<sup>73</sup> Fortunately, it came back into the game since the beginning of 21<sup>st</sup> century.

### 2.4.1 Chiral ligands controlled asymmetric transfer

For a long time, the achievement of efficient asymmetric reactions with chiral gold complexes has been a challenging task. This relates to the linear-coordination geometry of gold(I) complexes, where the substrate and the chiral ancillary ligand (L\*) are placed on opposite sides of the gold center (*Scheme II-13*).



*Scheme II-13. Strategy in asymmetric gold catalysis*

Therefore, chiral ligands must be specifically designed to create a chiral pocket surrounding both the metal and the remote substrate. In order to develop asymmetric gold catalysis, various types of ligands with central, axial, planar and helical chirality have been designed and prepared by many research groups in recent years, all over the world. Various asymmetric transformations and impressive levels of enantioselectivity have been achieved. We present hereafter selected examples representing the different strategies.

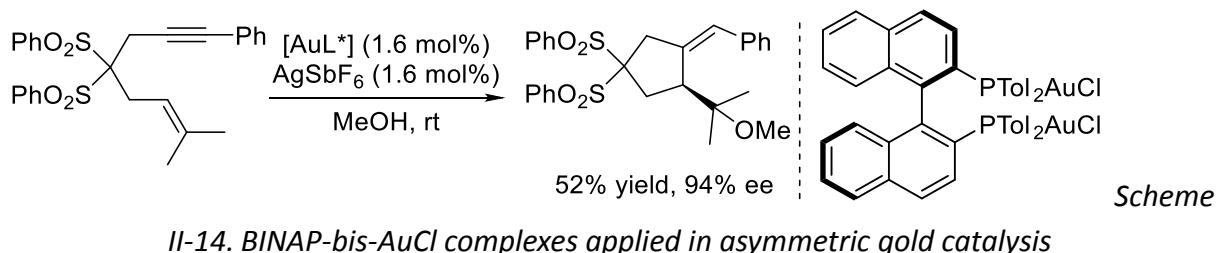
#### 2.4.1.1 Chiral bidentate diphosphine ligands

The first asymmetric gold-catalyzed reaction was reported in 1986 by Ito. The aldol reaction of methyl  $\alpha$ -isocyanocarboxylates with aldehydes was achieved with high enantioselectivity.<sup>20</sup> A ferrocene-derived planar chiral phosphine ligand was applied (*Scheme II-2*). This work has shown the great potential of chiral diphosphines as ligands for applications in asymmetric gold-catalyzed reactions.

However, it took nearly twenty years to see another enantioselective Au(I)-catalyzed process. In 2005, the alkoxy cyclization of enynes was published in Echavarren's group, using BINAP-*bis*-AuCl complexes (*Scheme II-14*).<sup>74</sup>

<sup>73</sup> Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405.

<sup>74</sup> Muñoz, M. P.; Adrio, J.; Carretero, J. C.; Echavarren, A. M. *Organometallics* **2005**, *24*, 1293.



II-14. BINAP-bis-AuCl complexes applied in asymmetric gold catalysis

Among all the asymmetric Au(I)-catalyzed systems, bidentate phosphine ligands show great ability in chirality induction, based notably on their bulky or large substituents on their phosphorus atoms. A vast number of transformations with bidentate chiral ligands were raised out, and chiral ligands based on three different backbones are quite often applied:

- 1) SEGPLHOS backbone: a representative example was developed by Toste's group of an asymmetric Rautenstrauch rearrangement (Scheme II-15-a).<sup>75</sup>
- 2) BINAP backbone: the enantioselective cycloisomerization of ene-allenes into vinylcyclohexenes was reported catalyzed with [3,5-xylyl-BINAP(AuCl)<sub>2</sub>]/AgOTf catalytic system (Scheme II-15-b).<sup>76</sup>
- 3) BIPHEP backbone: benzopyrans were synthesized *via* rearrangement of allylic oxonium intermediates. (*R*)-MeO-DTBM-BIPHEP(AuCl)<sub>2</sub> was used to achieve its asymmetric synthesis (Scheme II-15-c).<sup>77</sup>

The improvement in chiral information transfer caused by diphosphine ligands is mainly ascribed to their very bulky substituents on the phosphorus atom. In many cases, with *mono*-cationic *bis*-gold complexes, the reaction outcome showed both better reactivity and enantioselectivity.<sup>78</sup> The opposite tendency also exists, by increasing the loading of silver salt, the enantioselectivity could be increased.<sup>79</sup> The aurophilic interaction between the two metal centers possibly influences the enantioselectivity of the transformations, even though it is quite difficult to clarify the mechanism. The main disadvantage of those bimetallic Au(I) catalysts is their complicated preparation procedure and their relatively higher price.

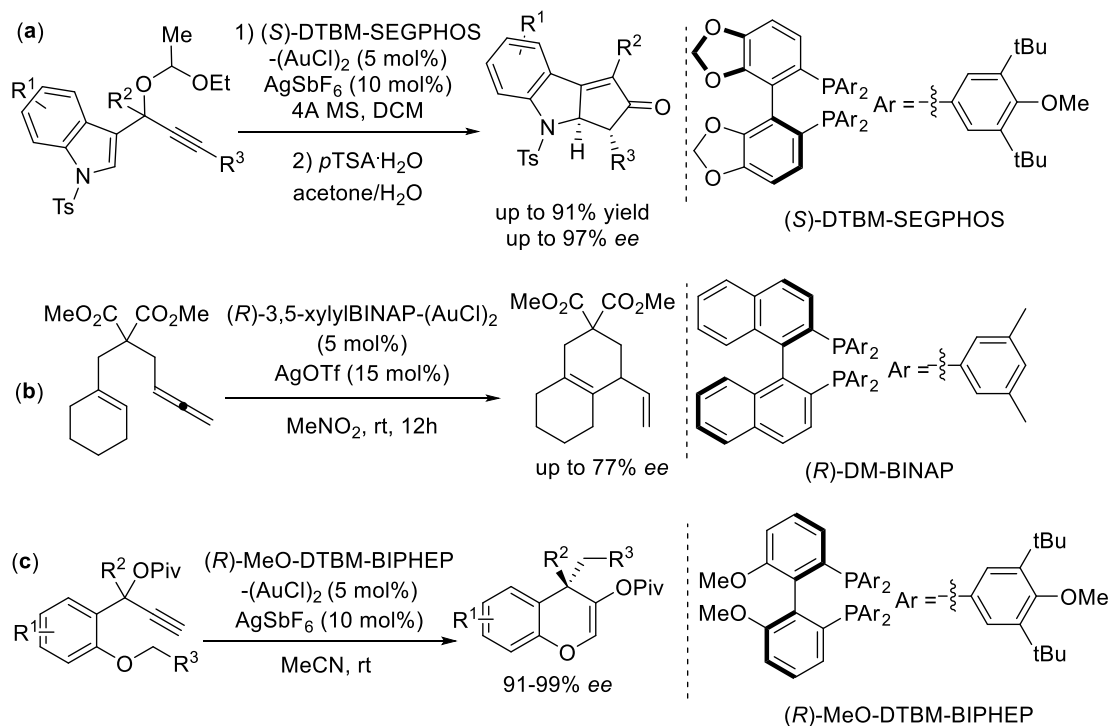
<sup>75</sup> Zi, W.; Wu, H.; Toste, F. D. *J. Am. Chem. Soc.* **2015**, *137*, 3225.

<sup>76</sup> Tarselli, M. A.; Chianese, A. R.; Lee, S. J.; Gagné, M. R. *Angew. Chem.* **2007**, *119*, 6790.

<sup>77</sup> Uemura, M.; Watson, I. D. G.; Katsukawa, M.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 3464.

<sup>78</sup> a) Gawade, S. A.; Bhunia, S.; Liu, R. S. *Angew. Chem. Int. Ed.* **2012**, *51*, 7835. b) Cao, Z. Y.; Wang, X.; Tan, C.; Zhao, X. L.; Zhou, J.; Ding, K. *J. Am. Chem. Soc.* **2013**, *135*, 8197. c) Cheon, C. H.; Kanno, O.; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 13248.

<sup>79</sup> Wu, H.; Zi, W.; Li, G.; Lu, H.; Toste, F. D. *Angew. Chem. Int. Ed.* **2015**, *54*, 8529.



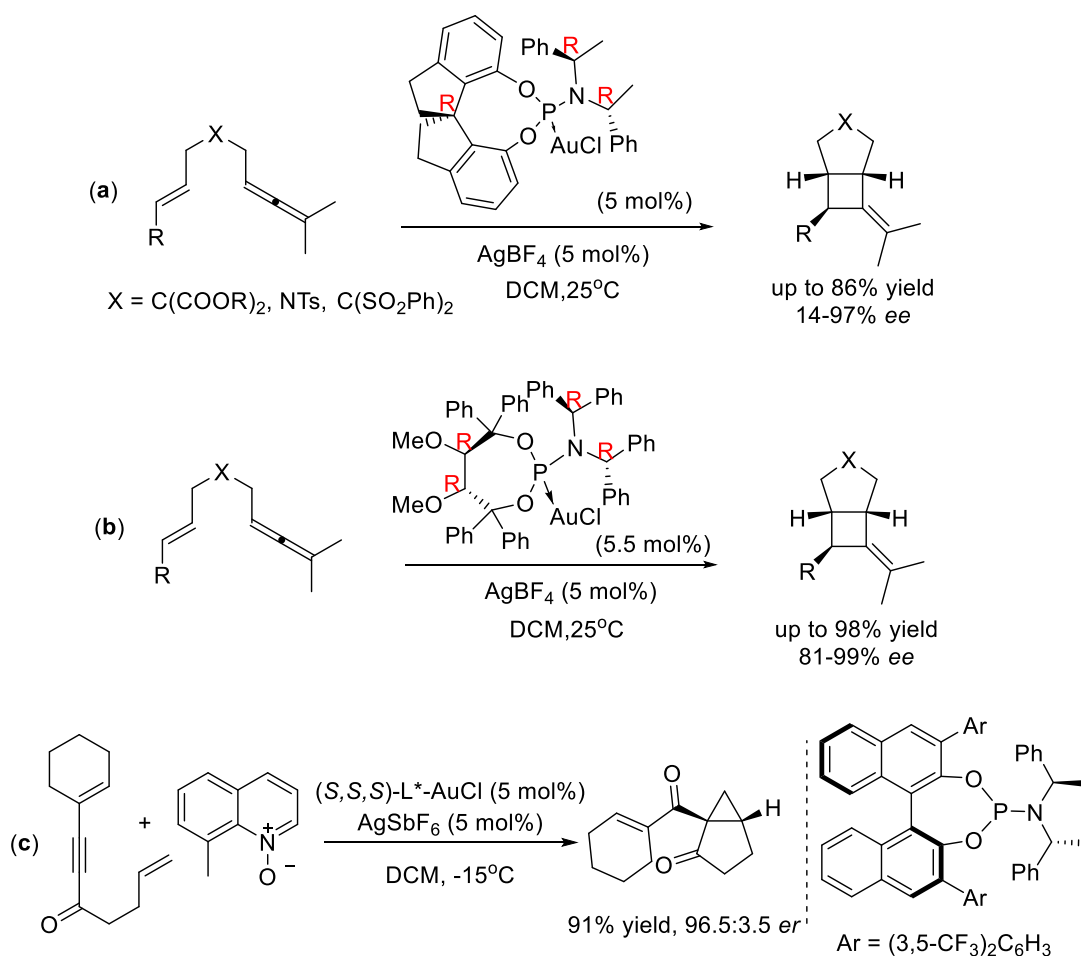
Scheme II-15. Bidentate chiral phosphine ligands

#### 2.4.1.2 Chiral monodentate phosphoramidite ligands

Compared to chiral bimetallic gold complex, the chiral monodentate phosphoramidite Au-complex possess a more facile synthesis procedure. A large number of asymmetric cycloisomerization/cycloaddition processes were reported promoted by chiral monodentate phosphoramidite-Au(I) complex. Such in the gold-catalyzed asymmetric synthesis of bicyclic products reported in Toste's group, different chiral monodentate phosphoramidite-Au(I) complexes were screened (Scheme II-16-a).<sup>80</sup> Another seminal work came from Fürstner's group (Scheme II-16, b). Acyclic TADDOL backbone was utilized and proved to be efficient in several asymmetric cycloisomerizations. We can make a direct comparison between two different kinds of monodentate phosphoramidite chiral gold catalysts. With the same cycloisomerization of allenene as model reaction, the well-designed acyclic TADDOL-backbone catalyst brought slight increase in the ees than traditional SIPHOS-derived-catalyst. More recently, a highly enantioselective oxidative cyclopropanation of 1,6-enynes was reported in Zhang's group (Scheme II-16-c).<sup>81</sup> Cationic Au(I)/chiral phosphoramidite complexes was used to introduce chirality information.

<sup>80</sup> Gonzalez, A. Z.; Benitez, D.; Tkatchouk, E.; Goddard, W. A. III; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 5500.

<sup>81</sup> Qian, D.; Hu, H.; Liu, F.; Tang, B.; Ye, W.; Wang, Y.; Zhang, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 13751.



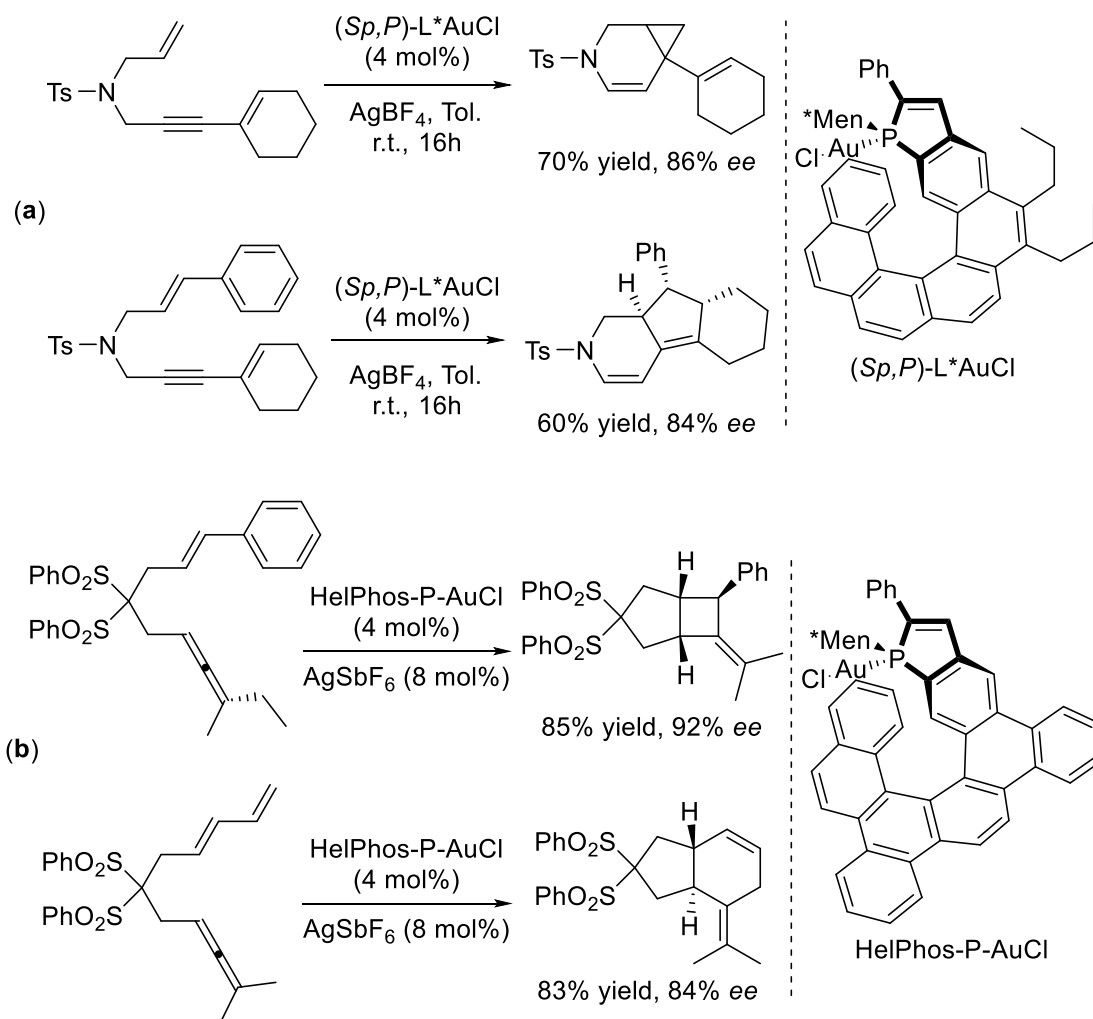
Scheme II-16. Monodentate phosphoramidite chiral ligands

### 2.4.1.3 Chiral phosphahelicene ligands

Our group developed series of phosphahelicene ligands and the corresponding gold-complexes, for uses in asymmetric catalysis. The most unique feature of the chiral phosphahelicene was that the phosphorus function was embedded in the helicene structure directly, achieved excellent enantioselectivity in asymmetric cycloisomerizations of *N*-tethered 1,6-enynes and dien-yne (*Scheme II-17-a*).<sup>82</sup> With this exciting result in hand, several new chiral phosphahelicene ligands were obtained through [2+2+2] cyclotrimerization, and the corresponding chiral Au(I)-catalysts showed both high reactivity and enantioselectivity in asymmetric [2+2] and [4+2] cycloaddition reactions (*Scheme II-17-b*).<sup>83</sup>

<sup>82</sup> Yavari, K.; Aillard, P.; Zhang, Y.; Nuter, F.; Retailleau, P.; Voiturez, A.; Marinetti, A. *Angew. Chem. Int. Ed.* **2014**, *53*, 861.

<sup>83</sup> Aillard, P.; Retailleau, P.; Voiturez, A.; Marinetti, A. *Chem. Eur. J.* **2015**, *21*, 11989.



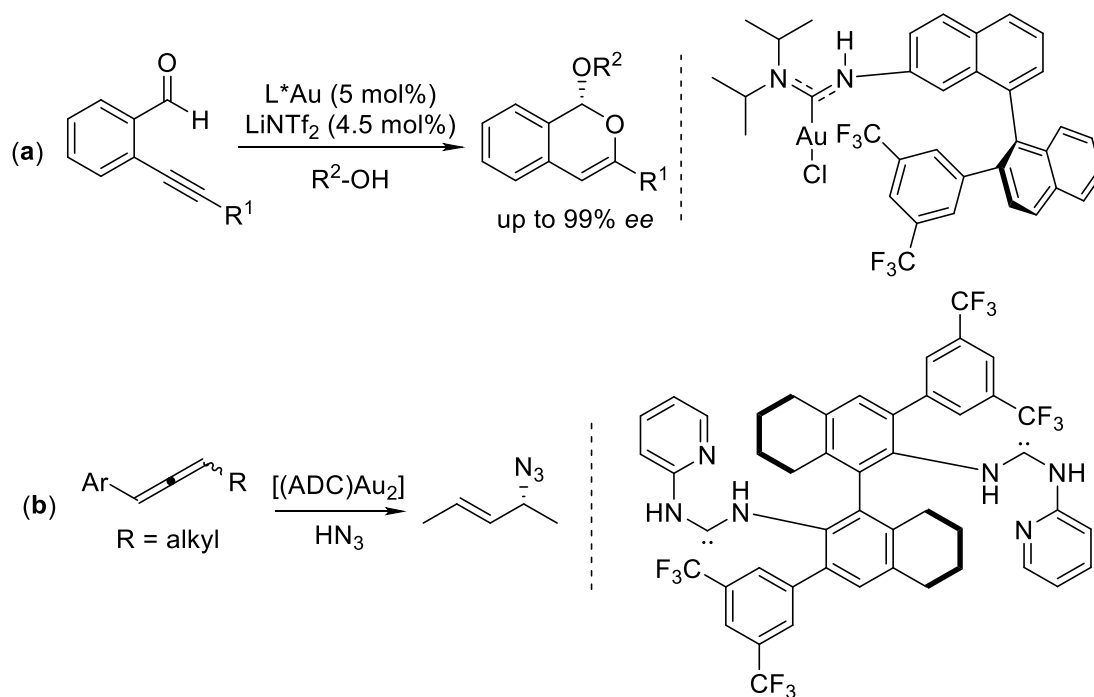
Scheme II-17. Chiral phosphahelicene ligands

#### 2.4.1.4 Chiral carbene ligands

Chiral nitroheterocarbenes are another class of chiral ligands which are quite used in chiral information transfer. The main idea is always to build a bulky environment around the Au(I)-metal center. In 2012, Slaughter and coworkers reported a monodentate acyclic diaminecarbene (ADC) which promoted asymmetric Au(I)-catalyzed alkynylbenzaldehyde cyclizations (Scheme II-18-a).<sup>84</sup> A recent work reported in Toste's group in 2016 disclosed the utilization of BINAM-derived-ADC in the development of enantioselective hydroazidation process (Scheme II-18-b).<sup>85</sup> ADC ligands take advantage of the wide N-C-N angle ( $116^\circ$  to  $121^\circ$ ) to place the chiral moiety closer to the gold center.

<sup>84</sup> Handa, S.; Slaughter, L. M. *Angew. Chem. Int. Ed.* **2012**, *51*, 2912.

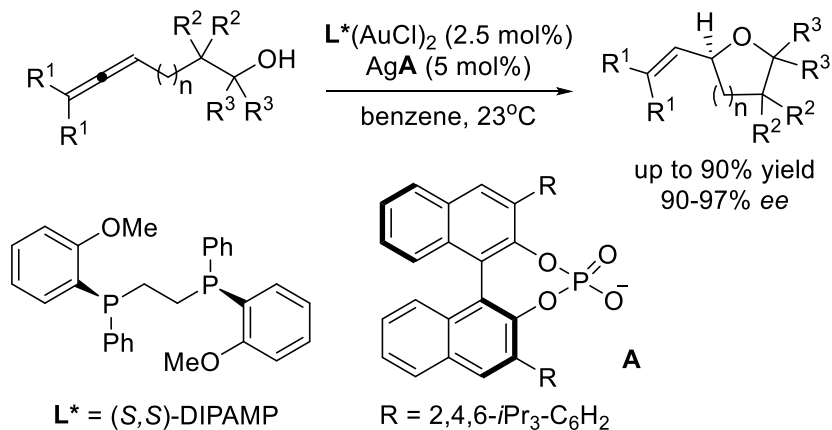
<sup>85</sup> Khrakovsky, D. A.; Tao, C.; Johnson, M. W.; Thornbury, R. T.; Shevick, S. L.; Toste, F. D. *Angew. Chem. Int. Ed.* **2016**, *55*, 6079.



Scheme II-18. Chiral nitroheterocarbene ligands

#### 2.4.2 Chiral counteranion controlled asymmetric transfer

Toste's group reported in 2007 the first gold-catalyzed reactions with the strategy using a chiral counteranion.<sup>86</sup> Chiral binaphthol-derived phosphate anion was used successfully in asymmetric hydroalkoxylation process. Combining both chiral ligand and chiral counteranion in Au(I)-catalysis system showed a high efficiency, such excellent results could not be obtained with either chiral ligand or chiral counteranion separately (Scheme II-19).



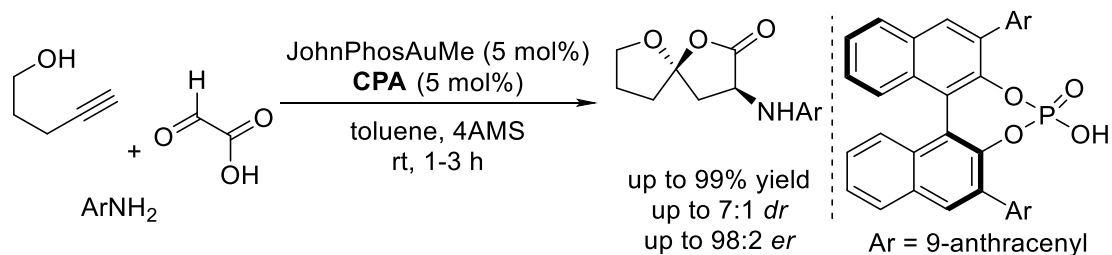
Scheme II-19. Chiral counteranion strategy in Au-catalyzed asymmetric transformations

More recently, Cala and co-workers discovered the first multicomponent catalytic asymmetric synthesis of spiroacetals through chiral phosphoric acid/(JohnPhos)AuMe catalyst system (Scheme II-20).<sup>87</sup> Alkynol derivatives, arylamines and glyoxylic acid were applied as substrates. This synthetic protocol brought high to excellent enantioselectivities to

<sup>86</sup> Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007**, *317*, 496.

<sup>87</sup> Cala, L.; Mendoza, A.; Fananas, F. J.; Rodriguez, F. *Chem. Commun.* **2013**, *49*, 2715.

target spiroacetals with only H<sub>2</sub>O as the byproduct. This strategy also brought other prominent success.<sup>88</sup>



*Scheme II-20. CPA applied in asymmetric synthesis of spiroacetals*

## 2.5 Conclusion

As we have seen in this introduction chapter, in gold(I)-catalysis, the ligand coordinated to the gold center and the nature of the counteranion proved to be fundamental to successfully developed new transformations.

In the field of enantioselective Au-catalyzed processes, the application of bimetallic gold complexes based on BINAP, BIPHEP and SEGPHOS backbones showed excellent asymmetric induction in many reactions. Chiral monodentate phosphoramidite Au-complexes brought also very interesting results in catalysis. Another solution aims at the counteranion part of gold(I) catalyst, and chiral counteranions were used successfully to control the asymmetric induction in some reactions.

Despite the huge number of recent studies, the discovery of new reactions and the development of enantioselective transformations is always a very big area of interest. In this context, the two next chapters will focus on the development of new gold-catalyzed enantioselective cyclization reactions.

<sup>88</sup> a) Michelet, V.; Pradal, A.; Toullec, P. *Synthesis* **2011**, 2011, 1501. b) Sengupta, S.; Shi, X. *ChemCatChem* **2010**, 2, 609. c) Widenhoefer, R. A. *Chem. Eur. J.* **2008**, 14, 5382. d) Shinde, V. S.; Mane, M. V.; Vanka, K.; Mallick, A.; Patil, N. T. *Chem. Eur. J.* **2015**, 21, 975. e) Patil, N. T. *Chem. Asian. J.* **2012**, 7, 2186.





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## **Chapter 3:**

### **Gold(I)-catalyzed enantioselective 1,5-enyne cyclization/nucleophilic addition reaction**

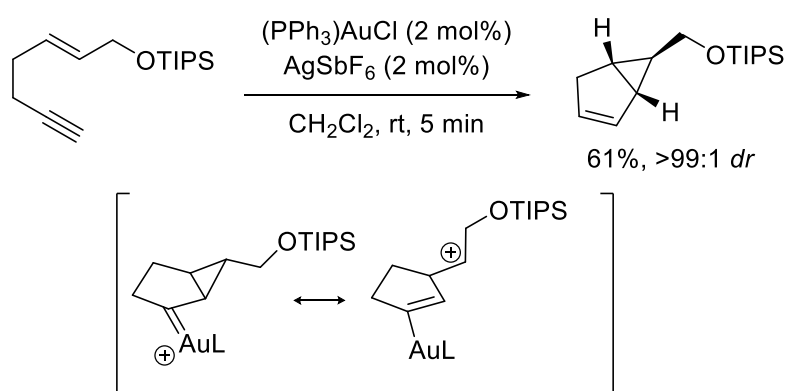
### 3.1 Introduction on gold(I)-catalyzed enyne cyclizations

During the last decade, the use of gold(I) in organic synthesis has grown considerably, due to the design of new catalysts and the development of innovative methodologies.<sup>89</sup> Among others, notable advancements in gold catalysis are related to the Au-catalyzed cycloisomerization reactions. Indeed, among the possible transition metal complexes that could catalyze enyne cycloisomerization processes, gold(I) complexes proved to be among the most efficient. As part of the work of this thesis, we decided to focus first on the development of 1,5-enyne cycloisomerization processes. These substrates have been much less studied than their 1,6-enyne congeners, and no asymmetric version of intermolecular nucleophilic addition/cyclization of 1,5-enynes was known.

The racemic gold-catalyzed cycloisomerization of 1,5-enynes was explored simultaneously by several research groups in 2004. In the bibliographic part developed just after, we decided to classify the known transformations as: i) simple 1,5-enyne cycloisomerizations, ii) cyclizations involving an internal nucleophilic addition, and iii) cyclizations involving an external nucleophilic addition.

#### 3.1.1 Au-catalyzed cycloisomerization of 1,5-enyne substrates

Toste and co-workers reported a first result in 2004,<sup>90</sup> applying non-substituted 1,5-enyne substrates in gold catalysis. Bicyclo[3.1.0]hexene compounds can be prepared rapidly in only 5 minutes, with 1-3 mol% of the  $(\text{PPh}_3)\text{AuCl}/\text{AgSbF}_6$  catalytic system at room temperature. Palladium(II) or platinum(II) give almost no target compound. Gold(III) chloride has been tested, but it led to a lower yield. The mechanism of gold-promoted 1,5-enyne cyclization was proposed, and the key step was the formation of a cationic gold intermediate, which could be trapped by nucleophiles to furnish the target cyclopropane compounds (*Scheme III-1*).

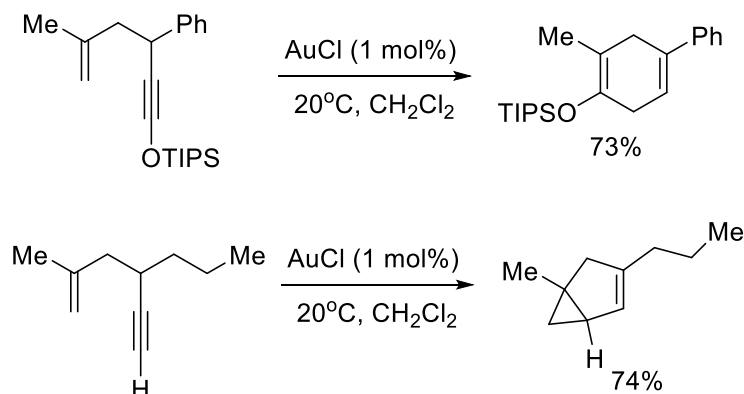


*Scheme III-1. Gold-catalyzed 1,5-enyne cycloisomerization reaction*

<sup>89</sup> a) Marin-Luna, M.; Nieto Faza, O.; Silva Lopez, C. *Front. Chem.* **2019**, *7*, 296. b) Lu, Z.; Hammond, G. B.; Xu, B. *Acc. Chem. Res.* **2019**, *52*, 1275. c) Mato, M.; García-Morales, C.; Echavarren, A. M. *ChemCatChem* **2018**, *11*, 53. d) Wei, Y.; Shi, M. *ACS Catal.* **2016**, *6*, 2515. e) Dorel, R.; Echavarren, A. M. *Chem. Rev.* **2015**, *115*, 9028. f) Asiri, A. M.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2016**, *45*, 4471.

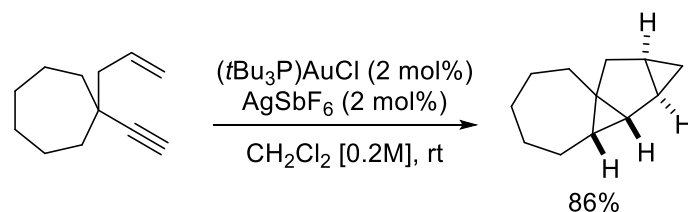
<sup>90</sup> Luzung, M.; Markham, J.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 10858.

The same year, Kozmin also investigated the reactivity of AuCl-catalyzed transformation of 1,5-enynes (*Scheme III-2*).<sup>91</sup> In the case of the use of siloxy-substituted alkyne, the selectivity toward the formation of the diene product, instead of the standard cyclization product, was observed. That could be explained in the mechanism by the presence of the siloxyl group. Indeed, a control experiment using alkyl-substituted-enyne substrate achieved the cyclopropane product in 74% yield. We can notice that the different reactivity could also be attributed to the nature itself of the substrate backbone.



*Scheme III-2. Au(I)-catalyzed 1,5-enyne transformations*

Toste's group revisited their former developed gold-catalyzed cycloisomerization of 1,5-enynes,<sup>92</sup> by the use of substrates possessing a cycloheptyl backbone. With the use of an achiral cationic gold complex, the synthesis of a series of tetracyclododecanes could be achieved in high yields (*Scheme III-3*).



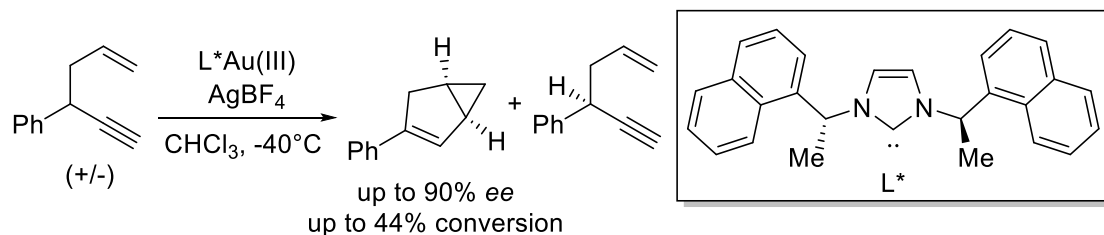
*Scheme III-3. Synthesis of tetracyclododecane products*

In 2017, to acquire an enantioselective variant of 1,5-enyne cycloisomerization, Toste's group established an enantioconvergent kinetic resolution system using a chiral gold(III) catalyst to gain enantiopure bicyclo[3.1.0]hexane.<sup>93</sup> Applying a chiral gold(III) catalyst can avoid an inherent drawback of chiral gold(I) complexes in asymmetric synthesis, namely their linear structure which places the chiral ligand and the substrate pretty far away. Up to 90% enantiomeric excess was achieved, albeit the yield could at best be 50% (*Scheme III-4*).

<sup>91</sup> Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 11806.

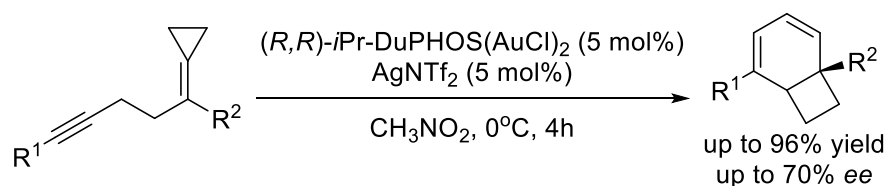
<sup>92</sup> Horino, Y.; Yamamoto, T.; Ueda, K.; Kuroda, S.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 2809.

<sup>93</sup> Bohan, P. T.; Toste, F. D. *J. Am. Chem. Soc.* **2017**, *139*, 11016.



Scheme III-4. Enantioconvergent kinetic resolution of 1,5-enyne with Au(III) catalyst

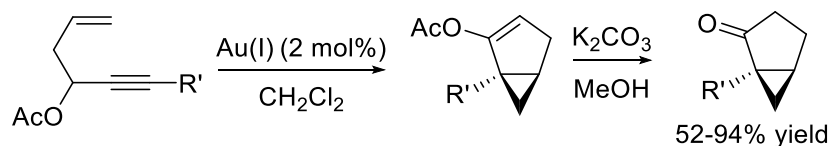
An enantioselective transformation was carried out with cyclopropylidene 1,5-enyne substrates.<sup>94</sup> Gold(I) catalyst promoted the ring-expansion of cyclopropylidenes. This protocol provided a high efficient pathway toward [4.2.0]bicycle compounds. DuPhos was introduced to transfer chirality to corresponding target products. This strategy showed very high reactivity with moderate to good enantioselectivity (Scheme III-5).



Scheme III-5.

### 3.1.2 Au-catalyzed cycloisomerization of hydroxylated and acetoxyated 1,5-enynes

The first gold-catalyzed cycloisomerization of acetoxyated 1,5-enynes was developed in Fürstner's group in 2004, with either PtCl<sub>2</sub> or (Ph<sub>3</sub>P)AuCl/AgSbF<sub>6</sub> catalytic system. 1,5-Enyne substrates can be transformed into bicyclo[3.1.0]hexanone structures efficiently.<sup>95</sup> The ester function participates to the Au-catalyzed rearrangement process, and the enol ester group can be easily transformed into the corresponding ketone (Scheme III-6). It should be noted that at the same time, Malacria developed a similar transformation, using PtCl<sub>2</sub>-catalyzed cycloisomerization of 5-en-1-yn-3-ol substrates.<sup>96</sup>



Scheme III-6. Au-catalyzed cycloisomerization of acetoxyated 1,5-enynes

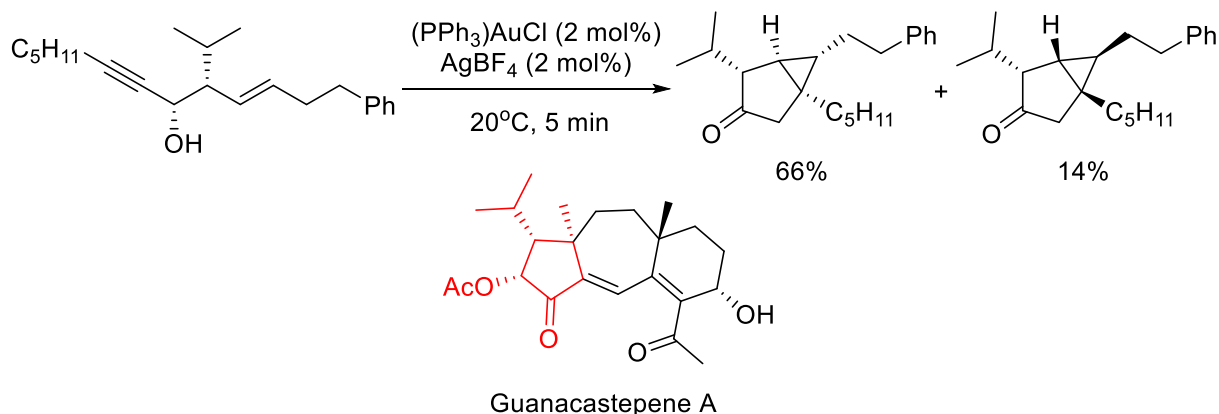
Based on the reactivity brought by the gold catalyst, a protocol toward the synthesis of a key building block of Guanacastepene A was developed by Gagosz<sup>97</sup> (Scheme III-7). The diastereoselective cyclization of 3-hydroxylated 1,5-enyne occurred, in favor of the *syn*-isomer.

<sup>94</sup> Zheng, H.; Felix, R. J.; Gagne, M. R. *Org. Lett.* **2014**, *16*, 2272.

<sup>95</sup> Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654.

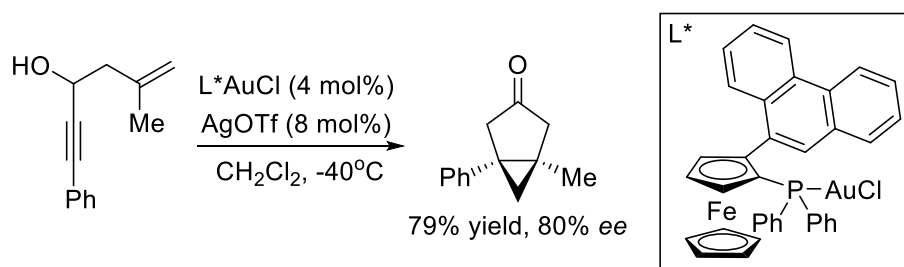
<sup>96</sup> Harrak, Y.; Blaszykowski, C.; Bernard, M.; Cariou, K.; Mainetti, E.; Mouriès, V.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2004**, *126*, 8656.

<sup>97</sup> Gagosz, F. *Org. Lett.* **2005**, *7*, 4129.



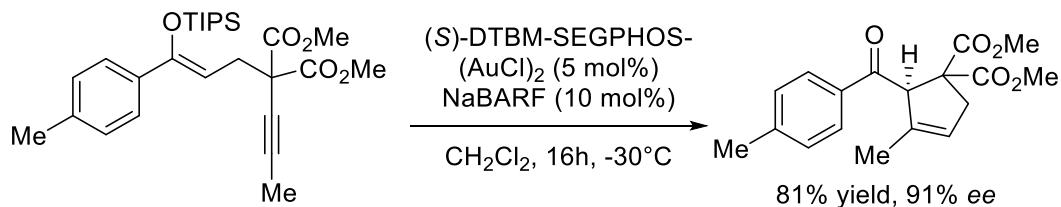
*Scheme III-7. Potential building block toward the synthesis of Guanacastepene A*

Our group developed the first enantioselective version of the hydroxylated 1,5-enyne cyclization, with the use of a chiral gold complex.<sup>98</sup> In spite of the established synthetic utility of this reaction, asymmetric variant had only been made with platinum catalysts,<sup>99</sup> but as far as we are aware, it had not been explored with chiral gold catalysts. By utilizing a well-designed planar chiral ferrocenylphosphine ligand, up to 80% *ee* could be achieved at low reaction temperature (*Scheme III-8*).



*Scheme III-8. Planar chiral ligand promoted 1,5-enyne enantioselective cycloisomerization*

Another asymmetric Au(I)-catalyzed 1,5-enyne transformation was carried out with silyloxy-1,5-enyne substrates.<sup>100</sup> The vinyl-silyloxy group was transferred into a ketone and with chiral gold complex, such as (*S*)-DTBM-SEGPHOS-(AuCl)<sub>2</sub> as *bis*-gold chiral precatalyst. Excellent enantiomeric excesses in the cyclized products could be obtained (*Scheme III-9*).



*Scheme III-9. Asymmetric catalysis with silyloxy 1,5-enynes*

### 3.1.3 Au-catalyzed 1,5-enyne cyclization/intramolecular nucleophilic addition

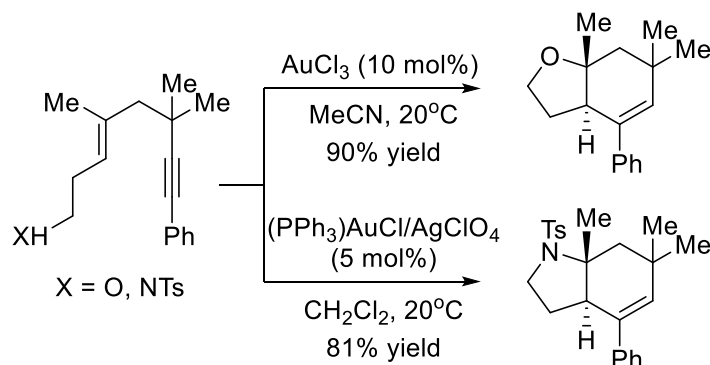
To develop other 1,5-enyne cyclization transformations, a tandem cyclization/intramolecular

<sup>98</sup> Wu, Z.; Retailleau, P.; Gandon, V.; Voituriez, A.; Marinetti, A. *Eur. J. Org. Chem.* **2016**, 2016, 70.

<sup>99</sup> Zhang, Y.; Jullien, H.; Brissy, D.; Retailleau, P.; Voituriez, A.; Marinetti, A. *ChemCatChem* **2013**, 5, 2051.

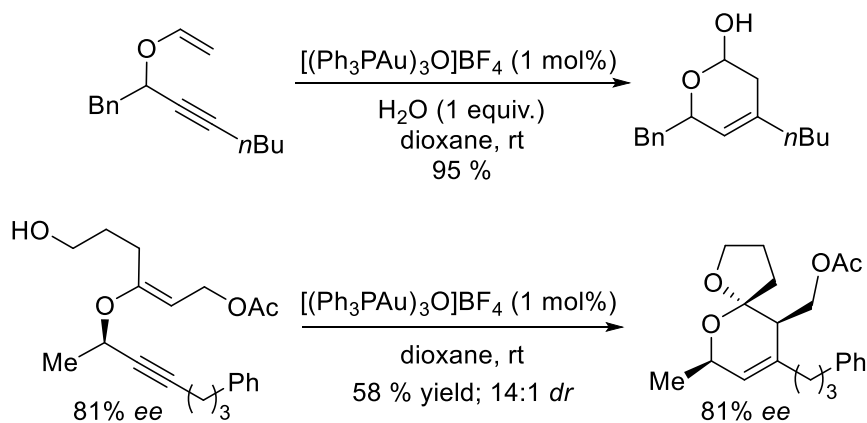
<sup>100</sup> Brazeau, J. F.; Zhang, S.; Colomer, I.; Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2012**, 134, 2742.

nucleophilic addition process could be imagined, toward the synthesis of more structurally complex compounds. It is reasonable to postulate that the carbocation intermediate could be trapped by suitable nucleophiles. This hypothesis was firstly demonstrated in Kozmin's group in 2005, utilizing the nucleophilic intramolecular addition of hydroxyl or aniline moieties (*Scheme III-10*). After the 6-*endo* cyclization, a concomitant cyclization could be observed with the intramolecular formation of C-N or C-O bonds.<sup>101</sup>



*Scheme III-10. 1,5-Enyne cyclization/intramolecular nucleophilic addition*

Another similar reactivity was used to synthesize pyrans from acyclic 1,5-enyne (propargyl vinyl ether) precursors, after treatment with a cationic gold complex.<sup>102</sup> The nucleophilic addition of H<sub>2</sub>O could trap the oxocarbenium intermediate, and produce the corresponding pyrans. Based on this result, water was replaced by a pendant alcohol functionality in the substrate, which gave the spiroketal derivative successfully. The process also showed complete chirality transfer (*Scheme III-11*).



*Scheme III-11. Preparation of pyrans from acyclic 1,5-enynes*

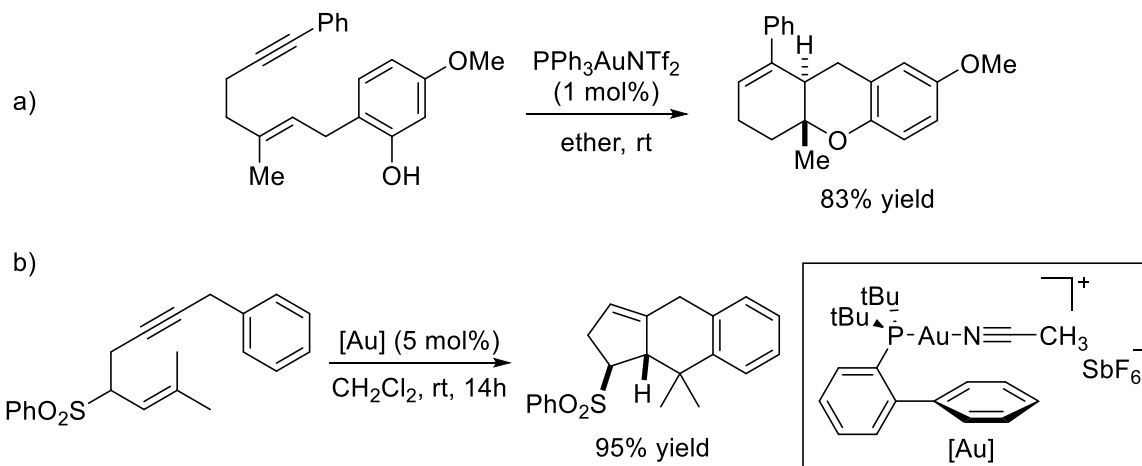
With the use of phenol as intramolecular nucleophile, Michelet's team carried out a similar transformation (*Scheme III-12a*).<sup>103</sup> The phenoxycyclization occurred in good yields on different substrates. Echavarren's group investigated the introduction of a terminal phenyl group to the 1,5-enyne substrate, to achieve an intramolecular arylation process, catalyzed

<sup>101</sup> Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 6962.

<sup>102</sup> Sherry, B. D.; Maus, L.; Laforteza, B. N.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 8132.

<sup>103</sup> Toullec, P. Y.; Blarre, T.; Michelet, V. *Org. Lett.* **2009**, *11*, 2888.

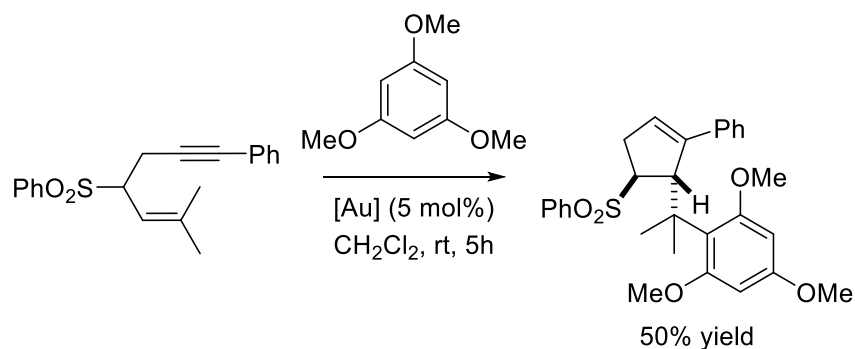
by different achiral gold catalysts. Tricyclic or more complex structures could be achieved in moderate to good yields (*Scheme III-12b*).<sup>104</sup>



*Scheme III-12. Cyclizations with intramolecular nucleophile additions*

### 3.1.4 Au-catalyzed 1,5-enyne cyclization involving intermolecular nucleophilic addition

Electron-rich aromatic and heteroaromatic compounds could be applied as nucleophiles in this transformation, such as 1,3,5-trimethoxybenzene and indoles. Echavarren's group reported a C-nucleophile addition to the carbocation intermediate formed during the Au(I)-catalyzed 1,5-enyne process.<sup>105</sup> Different carbon nucleophiles were tested with various substituted enyne substrates (*Scheme III-13*).



*Scheme III-13. 1,5-Enyne cyclization/carbon nucleophile addition*

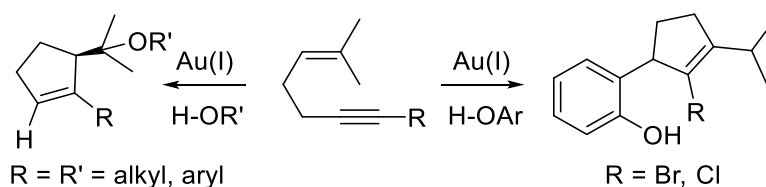
Another example was developed by Magauer, with the use of 1-bromo-1,5-enyne substrate.<sup>106</sup> Compared to former studies of Au(I)-catalyzed 1,5-enyne cyclization where external oxygen nucleophiles does an addition on the carbocation intermediate (*Scheme III-13, left*), this work showed a new reactivity which promoted a sequential OH/CH bond insertion of phenols (*Scheme III-14, right*).

<sup>104</sup> Lopez-Carrillo, V.; Huguet, N.; Mosquera, A.; Echavarren, A. M. *Chem. Eur. J.* **2011**, *17*, 10972.

<sup>105</sup> Amijs, C. H. M.; López-Carrillo, V.; Raducan, M.; Pérez-Galán, P.; Ferrer, C.; Echavarren, A. M. *J. Org. Chem.* **2008**, *73*, 7721.

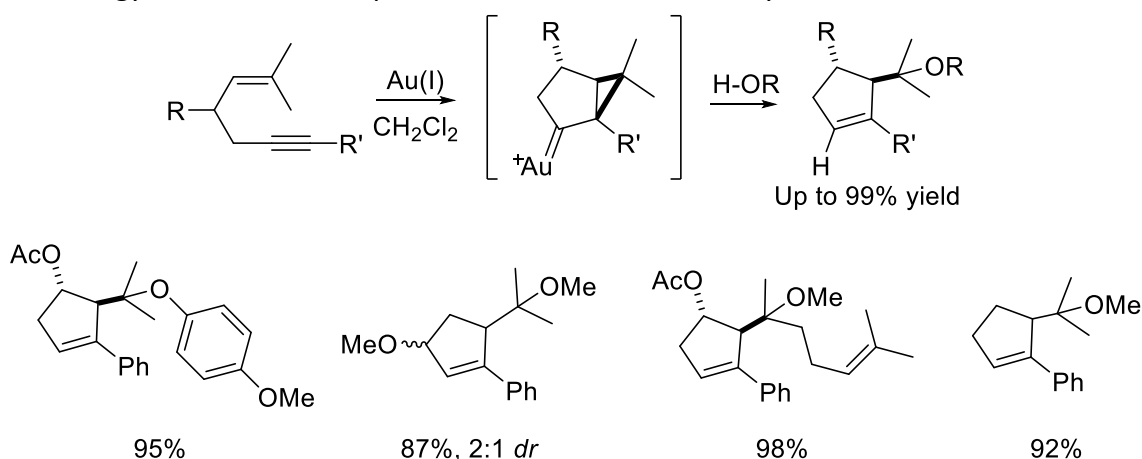
<sup>106</sup> Speck, K.; Karaghiosoff, K.; Magauer, T. *Org. Lett.* **2015**, *17*, 1982.





*Scheme III-14. New reactivity observed with 1-bromo-1,5-enyne substrates*

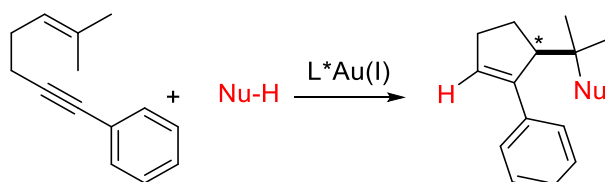
When alcohol was introduced as solvent in gold(I)-catalyzed 1,5-enyne reaction, cyclopentene compounds were isolated through a 5-*endo* alkoxy cyclization process (*Scheme III-15*). In Gagosz's work,<sup>107</sup> aryl- and alkyl-substituted alkynes were all tolerated in this methodology and the reaction proved to be sometimes totally diastereoselective.



*Scheme III-15. Gold-catalyzed 5-endo hydroxy- and alkoxy cyclization process*

On one hand, cyclization reaction of enyne is highlighted by its efficiency in building complex cyclic molecules from simple acyclic substrates; on the other hand, asymmetric catalysis keeps being a challenge and possesses tremendous potential in chemical applications such as the development of valuable methodologies and the applications in total synthesis.

In all those methodologies, cationic gold(I) complexes produced from LAuCl/AgX systems possess a high value in cycloisomerization/cyclization of 1,5-enynes, those transformations undergo mild reaction conditions with low quantity of gold catalysts. All in all, it would be relevant to develop an enantioselective 1,5-enyne cyclization transformation, which has high potential for developing valuable complex structures (*Scheme III-16*).



*Scheme III-16. Toward asymmetric 1,5-enyne cyclization/external nucleophile addition*

Even though the first Au-catalyzed hydroxylated 1,5-enyne cyclization was discovered fifteen

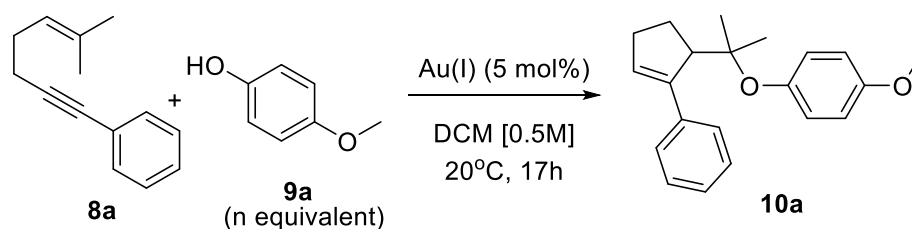
<sup>107</sup> Buzas, A. K.; Istrate, F. M.; Gagosz, F. *Angew. Chem. Int. Ed.* **2007**, *46*, 1141.

years ago,<sup>108</sup> to the best of our knowledge, enantioselective Au(I)-catalyzed 1,5-enyne cyclization/external nucleophilic addition has never been achieved. The main reason not only includes the difficulty to find a suitable chiral catalyst, but may also be due to the reaction mechanism itself. We will now detail our study in order to achieve this goal.

## 3.2 Development of the racemic 1,5-enyne cyclization/nucleophilic addition

### 3.2.1 Optimization of the reaction conditions

At the first stage, we screened different achiral gold(I) catalysts to optimize the racemic cyclization/nucleophilic addition transformation. We started the optimization with (6-methylhept-5-en-1-yn-1-yl)benzene (**8a**) and *p*-methoxyphenol (**9a**) as substrates. All the reactions were carried out at 0.1 mmol scale, in the presence of 3 to 5 mol% of achiral gold(I) catalyst in CH<sub>2</sub>Cl<sub>2</sub> at 20°C for 2 hours.



entry	[Au]	[Au]/mol%	n	Yield (%) <sup>a</sup>
1	JohnPhosAu(MeCN)SbF <sub>6</sub>	3	1.2	45
2	JohnPhosAu(MeCN)SbF <sub>6</sub>	5	1.2	54
3	JohnPhosAu(MeCN)SbF <sub>6</sub>	5	2.0	73
4	Ph <sub>3</sub> PAuNTf <sub>2</sub>	5	2.0	15
5	Ph <sub>3</sub> PAuOTf	5	2.0	<5
6	Ph <sub>3</sub> PAuSbF <sub>6</sub>	5	2.0	60
7	Ph <sub>3</sub> PAuBF <sub>4</sub>	5	2.0	80
8	Ph <sub>3</sub> PAuBF <sub>4</sub>	3	2.0	72
9	Ph <sub>3</sub> PAuBF <sub>4</sub>	3	1.2	64

<sup>a</sup>Isolated yield at a 0.1 mmol scale.

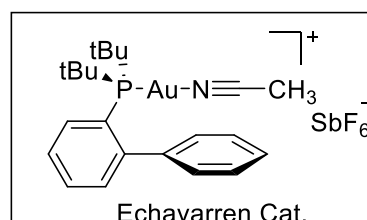


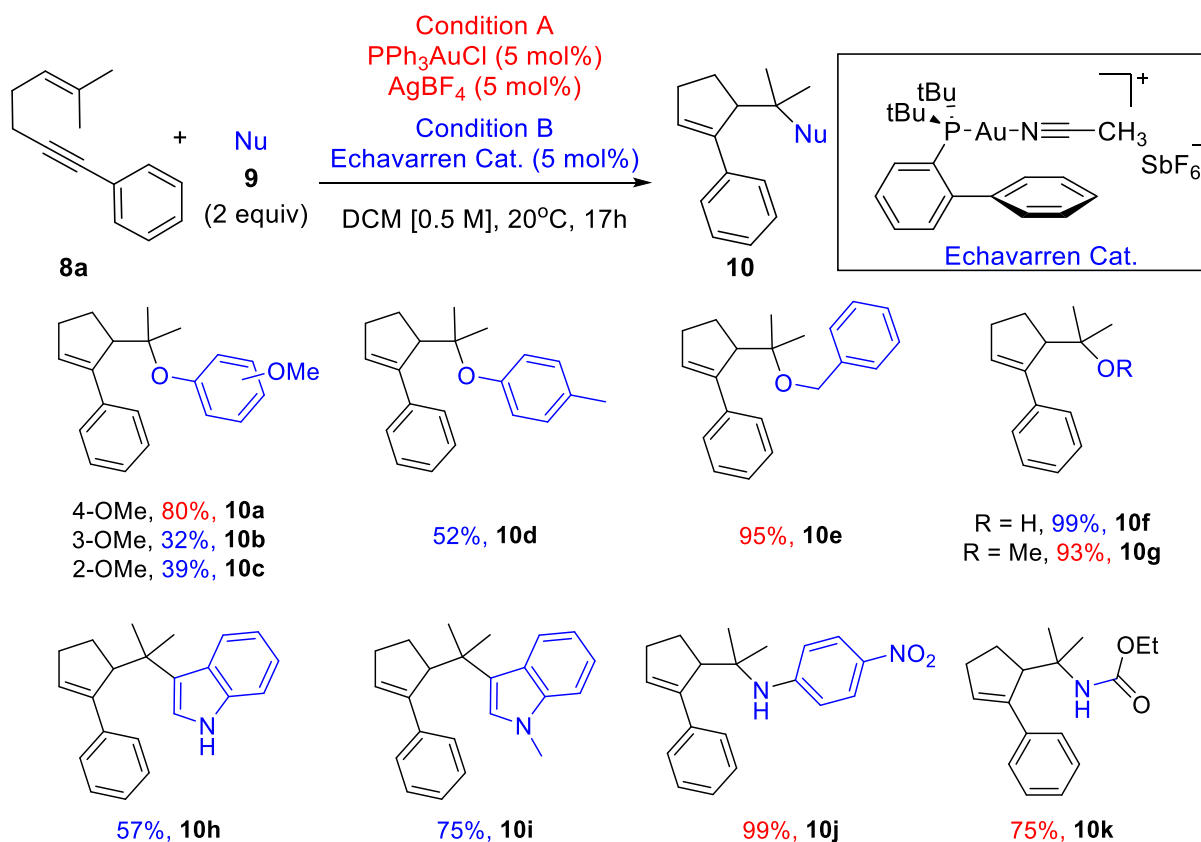
Table III-1. Optimization of the racemic transformation

<sup>108</sup> Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654.

Echavarren catalyst [(acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate] (3 mol%) was firstly tested to give moderate yield of **10a** (entry 1, 45% yield). By increasing the catalyst loading to 5 mol% and the quantity of nucleophile to two equivalents, the yield of **10a** was increased to 73% (entries 2-3). Then, we have tested  $\text{Ph}_3\text{PAuCl}$  as precatalyst, activated by different silver salts (entries 4-7). Among all the silver salt screened ( $\text{AgNTf}_2$ ,  $\text{AgOTf}$ ,  $\text{AgSbF}_6$ ,  $\text{AgBF}_4$ ), the best conversion was obtained with the catalytic system  $\text{Ph}_3\text{PAuCl}/\text{AgBF}_4$ , which gives the desired compound **10a** in 80% isolated yield (entry 7). Decreasing either the catalytic loading to 3 mol% and/or the stoichiometry of the nucleophile compared to the 1,5-enyne substrate proved to be detrimental to the conversion (entries 8-9, *Table III-1*).

### 3.2.2 Racemic reaction scope

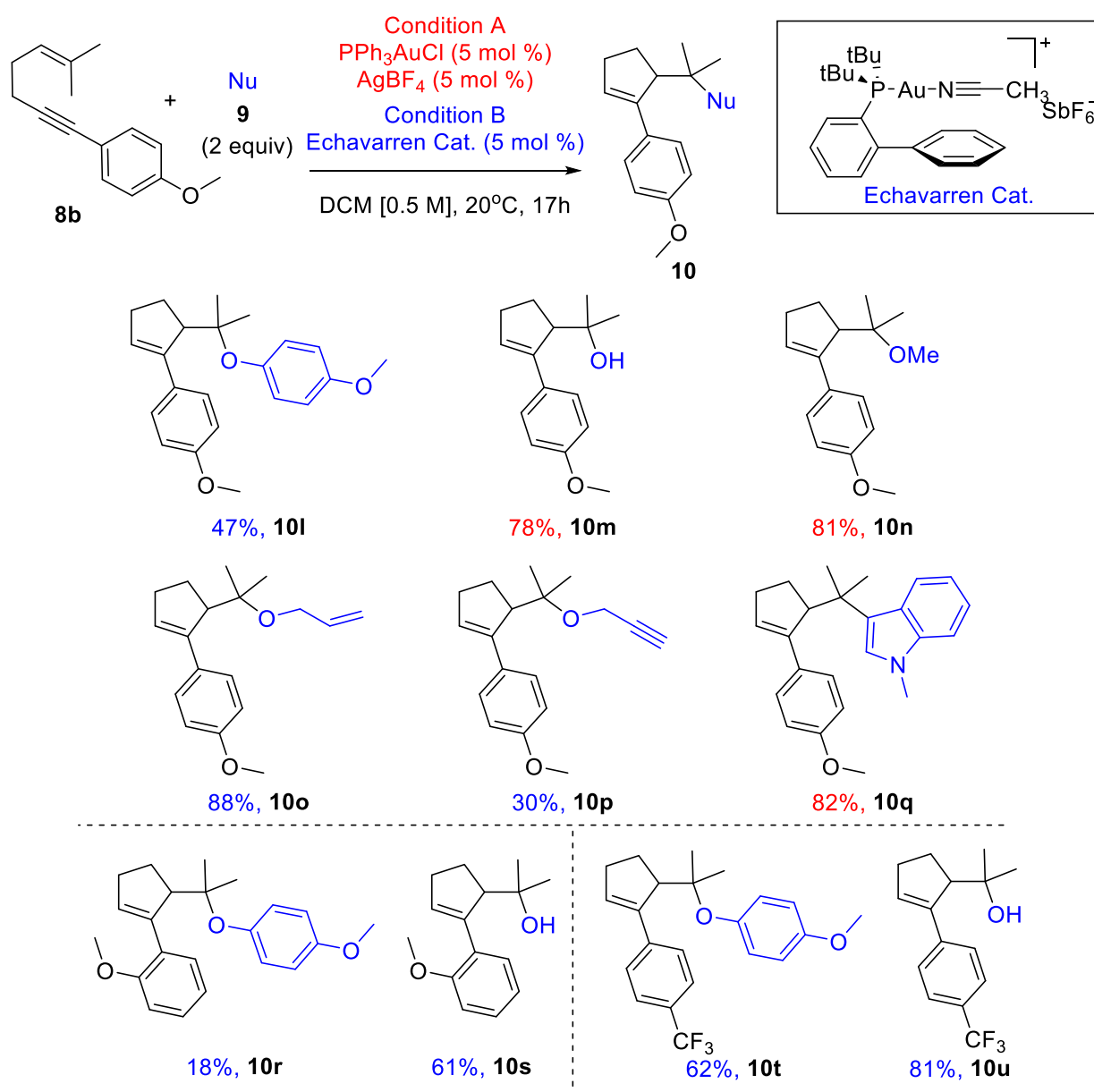
With the two best conditions in hand, a series of nucleophiles were tested with substrate **8a**. In *Scheme III-17*, the two reaction conditions were specified as condition **A** and condition **B**. For condition **A**, the reactions were performed with  $\text{Ph}_3\text{PAuCl}/\text{AgBF}_4$  (5 mol%) catalyst system in  $\text{CH}_2\text{Cl}_2$  [0.5 M] at  $20^\circ\text{C}$  for 17 hours. For condition **B**, the catalyst system was replaced by the  $\text{JohnPhosAu}(\text{MeCN})\text{SbF}_6$  catalyst with the same loading than condition **A**. The reaction scope was tested under both conditions, and only the best results were retained in the following (*Scheme III-17*).



*Scheme III-17. Reaction scope in the synthesis of racemic compounds – Part 1*

Different aromatic alcohols were used as nucleophiles, giving the corresponding

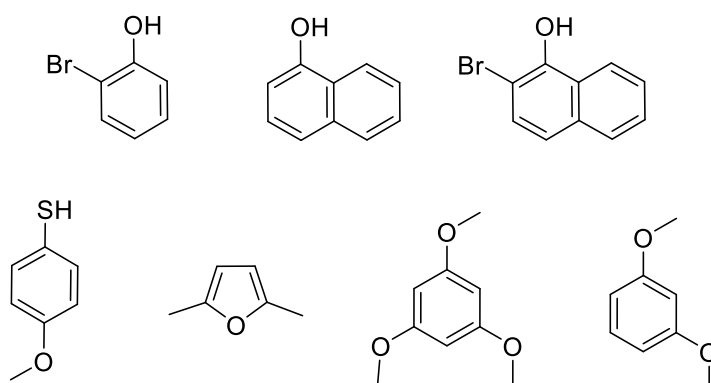
cyclization/nucleophile addition products in moderate to excellent yields (compounds **10a-10d**, 32-80% yields). The addition of benzyl alcohol furnished the product **10e** in 95% yield. Water and methanol were tested as nucleophiles and gave excellent results (compounds **10f** and **10g**, 93-99% yields). They were actually introduced as 9/1 mixtures of CH<sub>2</sub>Cl<sub>2</sub>/H<sub>2</sub>O or CH<sub>2</sub>Cl<sub>2</sub>/MeOH. Interestingly, carbon nucleophile could be used in our methodology. With simple indole and 1-methylindole, the addition occurred at position 3 of the indole in 57-75% yield (compounds **10h**, **10i**). Amine derivatives could be also used and the corresponding compounds were isolated in good to excellent yields. The addition of *p*-NO<sub>2</sub>-aniline furnished the corresponding product **10j** in quantitative yield. Interestingly, when ethyl carbamate was used, the (2-phenylcyclopent-2-en-1-yl)methanamine **10k** derivative was isolated in 75% yield.



Scheme III-18. Reaction scope in the synthesis of racemic compounds – Part 2

After these initial results, we then modified the substituent on the phenyl ring of substrate **8a** (Scheme III-18). Starting with 1-methoxy-4-(6-methylhept-5-en-1-yn-1-yl)benzene **8b**, both 4-methoxyphenol, water and methanol proved to be good nucleophiles and gave the corresponding products in 47-81% yields (products **10l-10n**). The cyclopentene derivatives were obtained in moderate to good yields with the use of allyl alcohol, propargyl alcohol and *N*-methylindole as nucleophiles (compounds **10o-10q**). The 2-methoxybenzene-substituted substrate gave in this transformation disappointing results, especially with the use of 4-methoxyphenol as nucleophile (18% yield). The steric hindrance imposed in the cyclized product could be one of the explanations of this low reactivity. However, the introduction of water allowed the isolation of product **10s** in higher yield. Finally, the 4-trifluoromethylbenzene-enyne substrate was also suitable for this transformation, furnishing the desired compounds **10t** and **10u** in 62% and 81% yields, respectively (Scheme III-18).

Some other nucleophiles such as bulky phenol derivatives (2-bromophenol, 1-naphthol, 2-bromonaphthalen-1-ol) were not compatible with this transformation. Unexpectedly, 4-methoxythiophenol caused degradation of enyne substrate and/or the reaction product. Indeed, in the crude  $^1\text{H}$  NMR of this reaction, no enyne substrate was observed and after purification on silica gel, no major compound could be isolated. One hypothesis lies on the fact that sulfur-containing compounds are common poisons of metal catalyst,<sup>109</sup> that may cause unanticipated side-reactions (although many examples of efficient gold-catalyzed transformations with sulfur-containing compounds have been described). Lastly, bulky heteroaromatic and aromatic substrates such as 2,5-dimethylfuran, 1,3,5-trimethoxybenzene and 1,3-dimethoxybenzene did not produce the desired result (Scheme III-19).



Scheme III-19. Incompatible substrates in this reaction

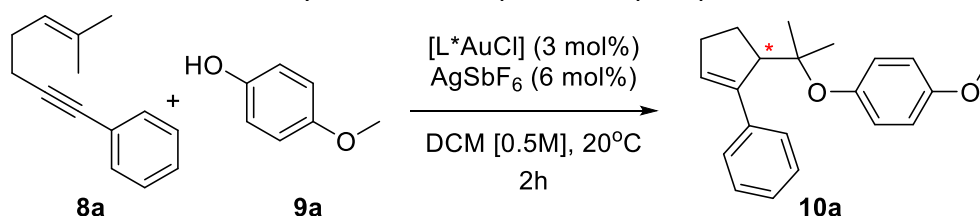
Having demonstrated the possible substrate scope in this transformation, we will now detail the development of the asymmetric version of this reaction.

<sup>109</sup> Oudar, J. *Catal. Rev. - Sci. Eng.* **2006**, *22*, 171.

### 3.3 Development of the asymmetric 1,5-enyne cyclization/nucleophilic addition

#### 3.3.1 Optimization of the reaction conditions

Subsequently, we focused our attention on the development of an enantioselective variant of this reaction. We started with (6-methylhept-5-en-1-yn-1-yl)benzene (**8a**) and *p*-methoxyphenol (**9a**, 1.2 equiv.) as substrates, in dichloromethane at room temperature. In a first tests campaign, AgSbF<sub>6</sub> was chosen as the chlorine atom abstraction agent. Concerning the introduction and the formation of the active catalyst, our strategy was to premix digold(I) precatalyst (3 mol%) and silver salt (6 mol%) in solvent for 10-15 minutes. The mixture was then filtrated and added to the substrates. We propose that procedure to try to avoid the possible negative influence of the silver salt (see Chapter 2). We can add that this procedure was also applied with achiral gold catalyst, described in *Scheme III-17* and *18*. At this stage, eight different chiral bimetallic gold(I) precatalysts [L\*(AuCl)<sub>2</sub>] were tested. They were easily prepared from the commercially available atropochiral diphosphines.



entry	[L*AuCl]	yield (%) <sup>a</sup>	ee (%) <sup>b</sup>
1	(I)	33	16
2	(II)	11	4
3	(III)	10	36
4	(IV)	6	20
5	(V)	33	16
6	(VI)	41	40
7	(VII)	42	50
8	(VIII)	10	23

<sup>a</sup>Isolated yield at a 0.05 mmol scale. <sup>b</sup>Determined by SFC on a chiral stationary phase.

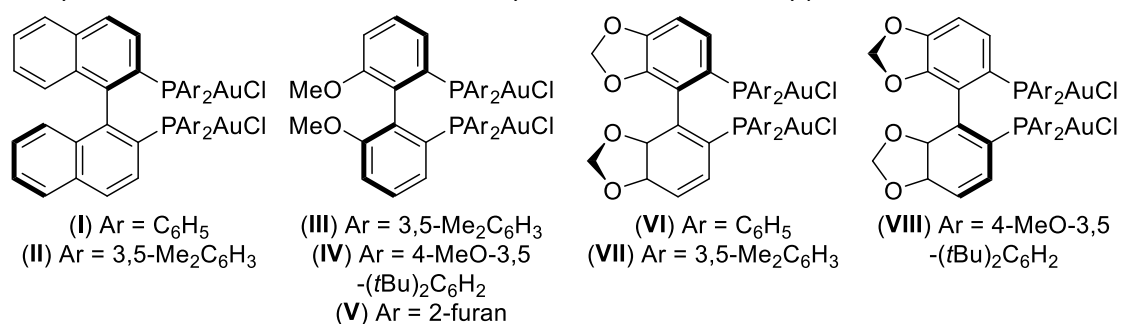
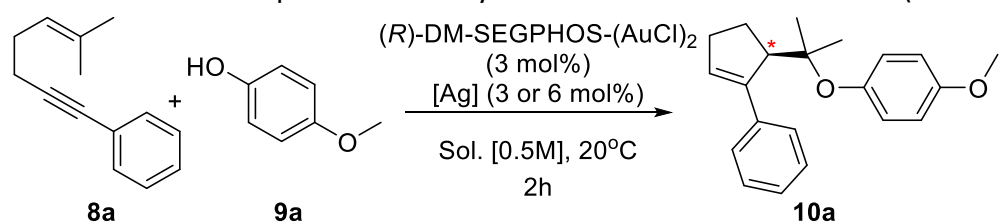


Table III-2. Optimization of the asymmetric transformation

In this alkoxylation/5-*endo*-trig cyclization of the 1,5-enyne substrate **8a**, the digold complexes, which usually furnish a good level of enantioselectivities in asymmetric cyclization reactions, provided in the present study quite disappointing results (*Table III-2*). Indeed, either the (*R*)-BINAP- or the (*R*)-MeO-BIPHEP-*bis*gold(I) precatalyst (**I-II**) and (**III-V**), after activation with AgSbF<sub>6</sub>, afforded low isolated yields and enantiomeric excesses (6-33% yields and up to 36% *ee*, entries 1-5). Other digold(I) complexes of atropochiral SEGPHOS-diphosphines (**VI-VIII**), triggered slightly better enantioselectivities (entries 6-8, up to 50% *ee*). The difference between the SEGPHOS-gold catalysts **VII** (Ar = 3,5-Me<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, 42% yield, 50% *ee*) and **VIII** (Ar = 4-OMe-3,5-*t*Bu<sub>2</sub>C<sub>6</sub>H<sub>2</sub>, 10% yield, 23% *ee*) show the huge impact of the phosphorus substituents of the diphosphine on the reaction outcome. With our best result in hand (*Table III-2*, entry 7), we kept the SEGPHOS-(AuCl)<sub>2</sub> derivative (**VII**), and tried to optimize the reaction conditions to improve both the yield and the enantiomeric *ratio* (*Table III-3*).



entry	[AgX]	[Au]/[Ag]	solvent	yield (%) <sup>a</sup>	<i>ee</i> (%) <sup>b</sup>
1	AgSbF <sub>6</sub>	1/2	CH <sub>2</sub> Cl <sub>2</sub>	42	50
2	AgSbF <sub>6</sub>	1/1	CH <sub>2</sub> Cl <sub>2</sub>	99	55
3	AgBF <sub>4</sub>	1/1	CH <sub>2</sub> Cl <sub>2</sub>	76	51
4	AgNTf <sub>2</sub>	1/1	CH <sub>2</sub> Cl <sub>2</sub>	72	40
5	AgOTf	1/1	CH <sub>2</sub> Cl <sub>2</sub>	59	54
6	AgPF <sub>6</sub>	1/1	CH <sub>2</sub> Cl <sub>2</sub>	43	43
7	AgSbF <sub>6</sub>	1/1	DCE	62	55
8	AgSbF <sub>6</sub>	1/1	Toluene	66	25
9	AgSbF <sub>6</sub>	1/1	THF	<5	--
10	AgSbF <sub>6</sub>	1/1	MeNO <sub>2</sub>	--	--
11 <sup>c</sup>	AgSbF <sub>6</sub>	1/1	CH <sub>2</sub> Cl <sub>2</sub>	99	68
12 <sup>d</sup>	AgSbF <sub>6</sub>	1/1	CH <sub>2</sub> Cl <sub>2</sub>	20	73

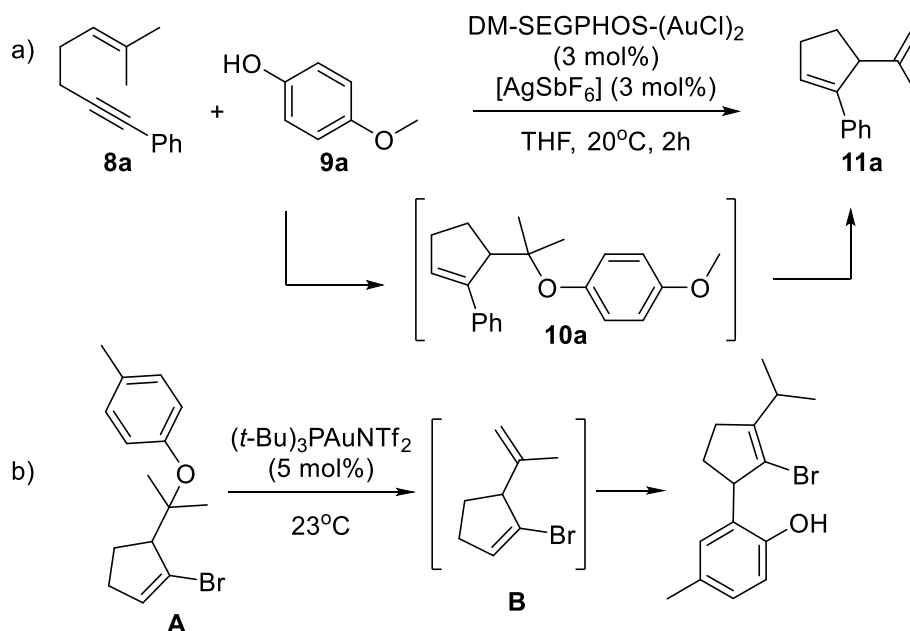
<sup>a</sup>Isolated yield at a 0.05 mmol scale. <sup>b</sup>Determined by SFC on a chiral stationary phase. <sup>c</sup>-40°C. <sup>d</sup>-60°C

*Table III-3. Optimization of silver salts and solvents*

We first verified the influence of the [Au]/[Ag] *ratio* on the reaction outcome. Starting with bimetallic gold(I) complexes, we have added two equivalents of chloride abstractor silver hexafluoroantimonate [AgSbF<sub>6</sub>]. We obtained product **10a** in 42% isolated yield and 50% *ee* (entry 1). In comparison, when only one equivalent of silver salt was added, the yield considerably increased to 99%, with 55% *ee* (entry 2). This effect was already observed by

Echavarren, which proved that gold(I)-catalyzed enantioselective alkoxy cyclization of 1,6-enyne substrates was sensitive to the Au/Ag ratio.<sup>110</sup> In the present transformation, our results showed that monocationic *bis*(gold) complex is also the most active and a slightly more selective catalyst. Careful optimization of silver salts revealed that AgSbF<sub>6</sub> gave the best results in terms of yield and enantiomeric excess, among all the silver salts tested (AgBF<sub>4</sub>, AgNTf<sub>2</sub>, AgOTf and AgPF<sub>6</sub>; entries 2-6). Finally, a quick solvent screening revealed that dichloromethane was the best solvent for this reaction, giving the enantioenriched 1-methoxy-4-((2-(2-phenylcyclopent-2-en-1-yl)propan-2-yl)oxy)benzene **10a** in 99% isolated yield and 55% *ee* (entries 7-10, *Table III-3*).

We have to point out that when THF was used as solvent (entry 9), different activity can be observed, with the formation of (5-(prop-1-en-2-yl)cyclopent-1-en-1-yl)benzene (**11a**, 99% isolated yield, *Scheme III-20-a*). The formation of **11a** from 1,5-enyne substrate had been reported in former publications,<sup>111</sup> as a degradation of compound **10a** based on a postulated mechanism *Scheme III-20-b*). In this publication, a sequential O-H/C-H bond functionalization gold(I)-catalyzed cyclization of 1-bromo-1,5-enynes was developed. Control experiments showed that the reactivity of isolated compound *III-20-b-A* with gold catalyst furnished the elimination product *III-20-b-B*. This is probably what we have observed with the use as THF as solvent. However, when we treated compound **10a** with DM-SEGPHOS-(AuCl)<sub>2</sub>/AgSbF<sub>6</sub> (5 mol%) at room temperature in DCM, no compound **11a** could be detected.



*Scheme III-20. Proposed formation of the byproduct 11a*

The optimization was finished with decreasing the reaction temperature to -40°C and -60°C for 24h, with two equivalents of nucleophile (*Table III-3*, entries 11-12). The desired 1-

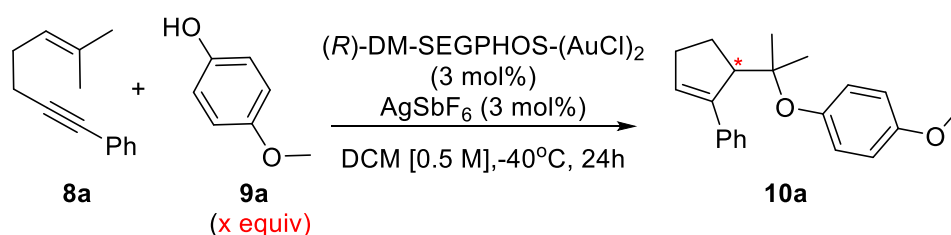
<sup>110</sup> Muñoz, M. P.; Adrio, J.; Carretero, J. C.; Echavarren, A. M. *Organometallics* **2005**, *24*, 1293.

<sup>111</sup> Speck, K.; Karaghiosoff, K.; Magauer, T. *Org. Lett.* **2015**, *17*, 1982.



methoxy-4-((2-(2-phenylcyclopent-2-en-1-yl)propan-2-yl)oxy)benzene product **10a** was isolated at  $-40^{\circ}\text{C}$  in quantitative yield and 68% *ee* (entry 11). In our best condition, no compound **11a** was detected. The enantioselectivity was increased slightly to 73% *ee* at  $-60^{\circ}\text{C}$ , but we could only get 20% yield of compound **10a** (entry 12).

Several control experiments were performed to be sure that the quantity of nucleophile compared to the enyne substrate would not influence the enantioselectivity of the reaction. Increasing the proportion of nucleophile to ten equivalents caused a slight decrease in enantioselectivity (Table III-4, compare entries 1 and 4). Between one and three equivalents, the results are the same in term of *ees*, with a higher isolated yield with two equivalents of nucleophile (Table III-4, entry 2). This is why two equivalents of nucleophile were retained in the optimized reaction conditions.

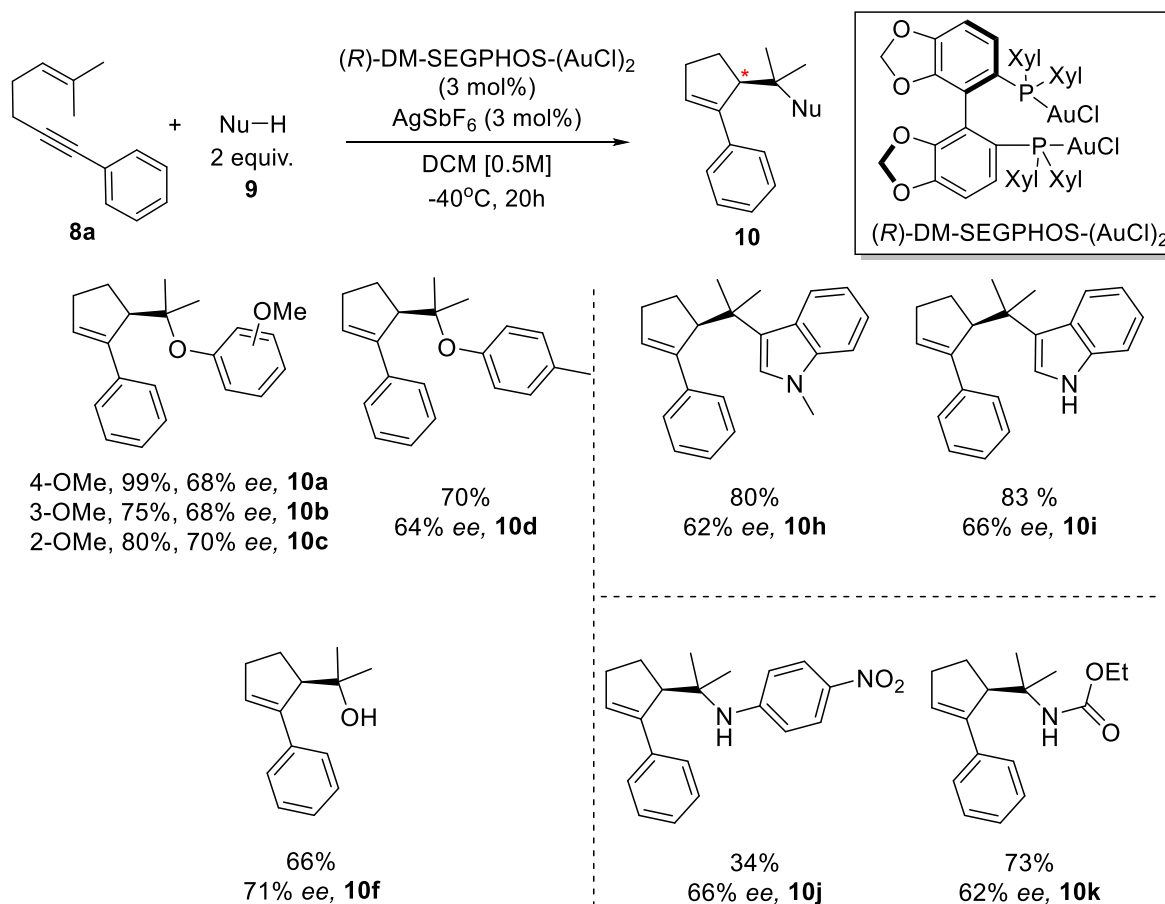


entry	9a/x equiv	10a /Isolated Yield (%)	ee (%)
1	1 equiv	81	68
2	2 equiv	99	69
3	3 equiv	95	68
4	10 equiv	99	64

Table III-4. Influence of the quantity of nucleophiles

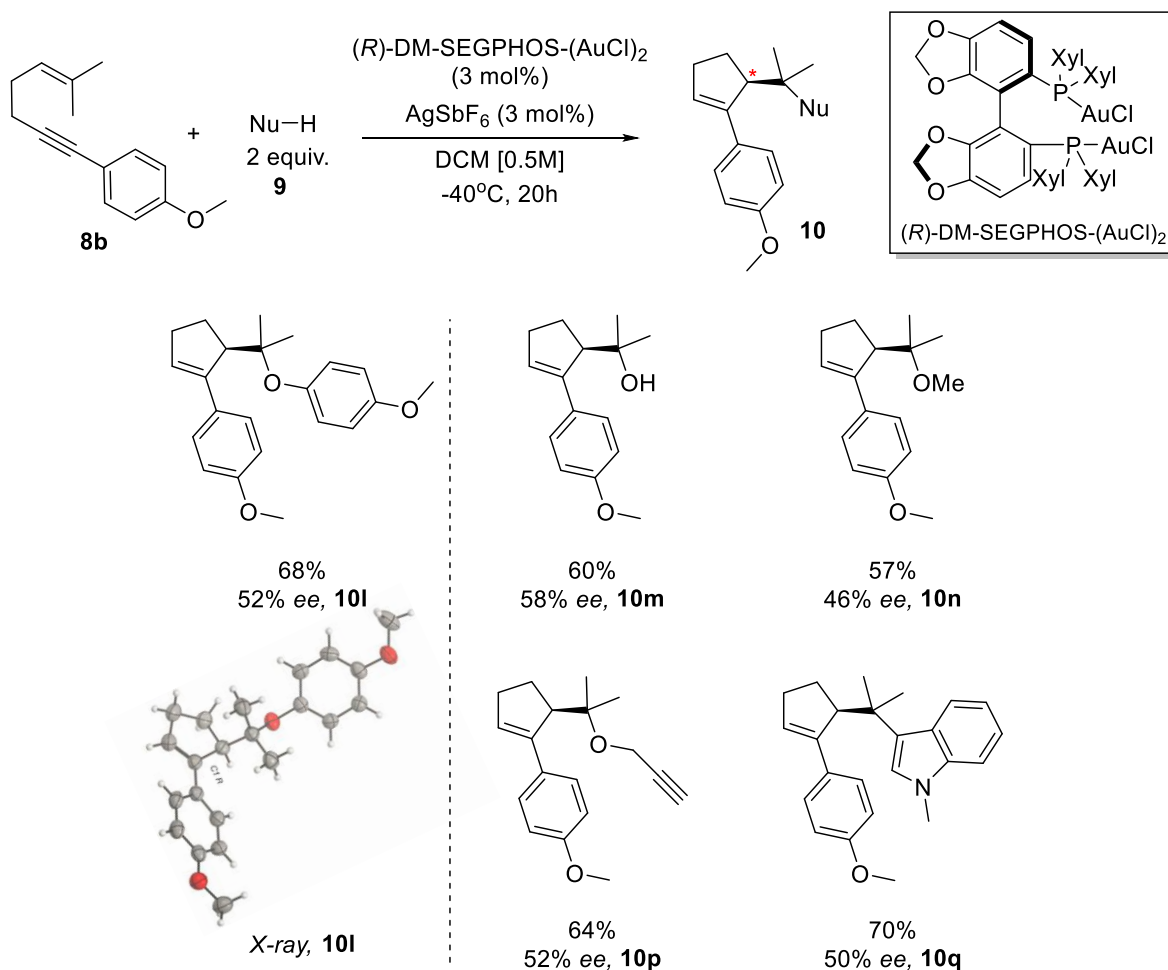
### 3.3.2 Reaction scope with DM-SEGPHOS-(AuCl)<sub>2</sub> precatalyst

Starting with the optimal reaction conditions, a range of nucleophiles was tested with substrate **8a**, in presence of 3 mol% (*R*)-DM-SEGPHOS-(AuCl)<sub>2</sub> and AgSbF<sub>6</sub> in dichloromethane at  $-40^{\circ}\text{C}$  for 20 hours. The results are showed below in the scheme III-21. With methoxy-phenols, the position of methoxy group did not bring difference to their corresponding *ees* (**10a-10c**, around 70% *ee*). The *p*-methylphenol caused a decrease of the enantioselectivity (**10d**). With H<sub>2</sub>O as nucleophile, 71% *ee* could be obtained, in 60% yield (**10f**). Both indole and 1-methylindole were used and verified an efficient carbon-carbon bond formation. If quite good yields around 80% were obtained, lower *ees* were detected (62-66% *ee*, compounds **10h** and **10i**). Amines reacted well but also brought lower enantiomeric excess than phenol nucleophiles (**10j**, **10k**, Scheme III-21).



Scheme III-21. Reaction scope - Part 1

Next we tested *p*-methoxy-1,5-enyne substrate **8b** with various nucleophiles. The results are quite different when we focus on enantiomeric excesses. The best result was brought by H<sub>2</sub>O with 58% *ee* (**10m**). With methoxyphenol and propargyl alcohol the outcomes were slightly lower (**10l** and **10p**, 52% *ee*). Compared to other aliphatic alcohol, MeOH gave the lowest enantioselectivity (**10n**, 46% *ee*). 1-Methylindole showed good reactivity but gave only 50% *ee* (**10q**, Scheme III-22). The absolute configuration of target chiral compound **10l** could be confirmed as *R*-isomer by X-ray crystallography analysis.



Scheme III-22. Reaction scope - Part 2

Interested, and at the same time intrigued by these different results obtained in terms of enantioselectivity using various nucleophiles, we tried to have a better understanding of the reaction mechanism.

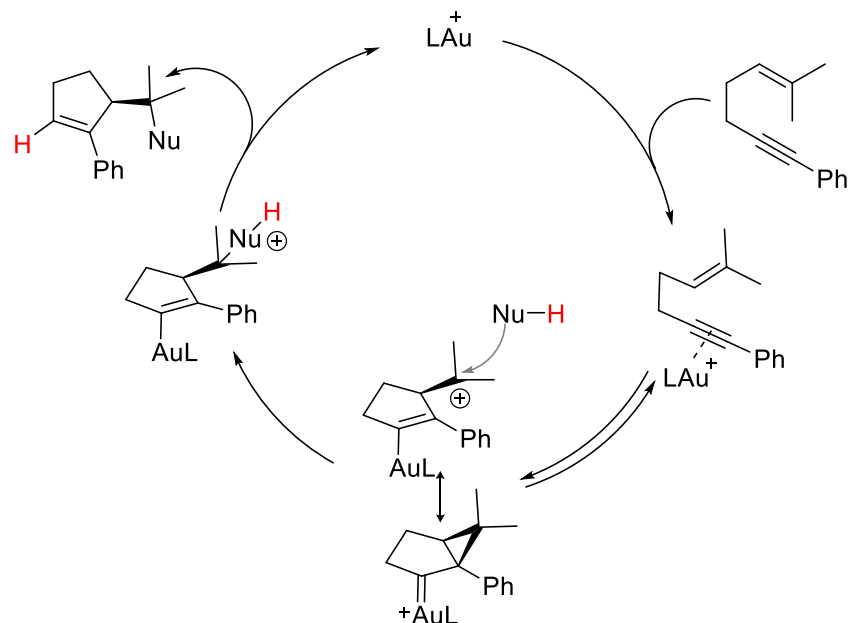
### 3.4 Reaction mechanism - studies of the influence brought by the nucleophile

#### 3.4.1 Mechanism of Au(I)-catalyzed 1,5-enyne cyclization/nucleophilic addition reaction

The mechanism of gold-catalyzed 1,5-enyne cycloisomerization reaction has been well studied in different publications (Scheme III-23).<sup>112</sup> Gold catalysts can activate the alkyne, and that promotes the nucleophilic addition of the pendant olefin to form the cationic intermediate. This cationic intermediate can be considered as a hybrid resonance between

<sup>112</sup> a) Luzung, M.; Markham, J.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 10858. b) Bohan, P. T.; Toste, F. D. *J. Am. Chem. Soc.* **2017**, *139*, 11016. c) Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654. d) Buzas, A. K.; Istrate, F. M.; Gagosz, F. *Angew. Chem. Int. Ed. Engl.* **2007**, *46*, 1141. e) Ariafard, A.; Asadollah, E.; Ostadebrahim, M.; Rajabi, N. A.; Yates, B. F. *J. Am. Chem. Soc.* **2012**, *134*, 16882.

carbenoid and carbocation, which was analyzed by DFT calculations in former studies.<sup>113</sup> The intermediate can be trapped in the presence of a nucleophile. At the end, protodeauration produces the target compound.



Scheme III-23. Proposed mechanism

With the proposed mechanism, to achieve an enantioselective 1,5-ene-yne cyclization/nucleophilic addition sequence, the challenge mainly comes from the control of the cationic intermediate formation step. An acceptable hypothesis could be that the nucleophilic addition step should not influence the final enantiomeric excess of the product.

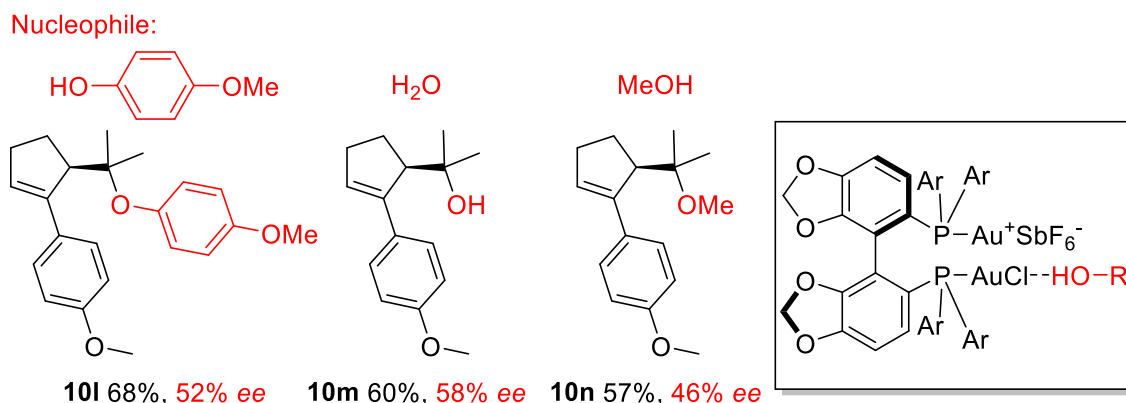
Indeed, based on the postulated mechanism, if the enantioselectivity of this transformation is already fixed when the carbocation intermediate is formed, the addition of different nucleophiles should not cause much influence on the outcome and on the enantioselectivity. However, with all the results we have just given, this is clearly not the case. Our results show an obvious effect of the nature of the nucleophile on the reaction outcome. Also, a slight decrease of the *ees* was observed when an excess of nucleophile was involved in the reaction (Table III-4).

### 3.4.2 Studies on the influence brought by the nucleophile in this transformation

Based on those results, we propose a potential hypothesis. In our condition, the *bis*-gold catalyst is activated by only one equivalent of silver salt, which means that one equivalent of gold remains under the form of a gold chloride [AuCl]. It is known that the chloride may form hydrogen bonds in the presence of nucleophiles such as alcohols. The cooperation

<sup>113</sup> a) Ariaifard, A.; Asadollah, E.; Ostadebrahim, M.; Rajabi, N. A.; Yates, B. F. *J. Am. Chem. Soc.* **2012**, *134*, 16882. b) Benitez, D.; Shapiro, N. D.; Tkatchouk, E.; Wang, Y.; Goddard, W. A., 3rd; Toste, F. D. *Nat. Chem.* **2009**, *1*, 482. c) Echavarren, A. M. *Nat. Chem.* **2009**, *1*, 431.

between the “spectator” [AuCl] and nucleophiles able to form hydrogen bond could be treated as a modification of the chiral ligand. This may have an effect on the outcome and on the enantiomeric excess of the products (*Scheme III-24*).

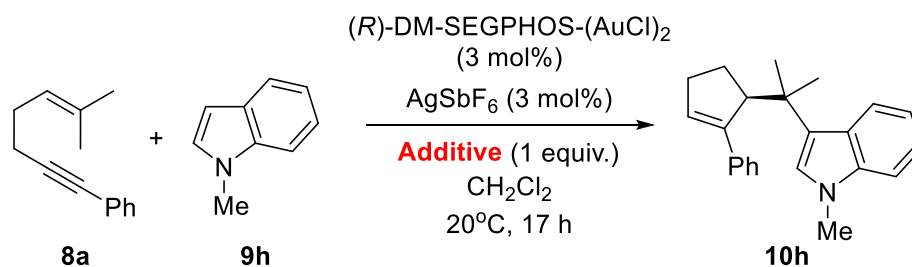


*Scheme III-24. Possible hydrogen bond influence on chiral bis-gold catalyst*

Potentially, one might even imagine that we could add in the reaction mixture an additive which could interact with the catalyst, and possibly have an impact on the enantioselectivity of the reaction. To clarify this point, we decided to screen different achiral and enantiopure alcohols in the reaction between 1,5-enyne substrate **8a** and 1-methyl-indole **9h**, which is a nucleophile which could not form H-bond. Furthermore, we chose bulky alcohols to avoid the formation of the corresponding addition product.

We started our investigation with (*R*)-DM-SEGPPOS-AuCl<sub>2</sub> (3 mol%) as catalyst, treated with 3 mol% of AgSbF<sub>6</sub> in dichloromethane at 20°C for 17 hours. Besides, one equivalent of different additives was introduced (*Table III-5*).

The first two examples were designed to compare the influence of the quantity of silver salt. Activating only one Au-Cl bond in the chiral *bis*-gold catalyst (entry 2) resulted in a slightly better result than when both Au-Cl were activated by the silver salt (entry 1). Introduction of an achiral alcohol *t*BuOH did not bring any change on the enantioselectivity, but a decrease in activity. With both *D*-menthol and *L*-menthol, the enantiomeric excess could be increased by about 5% (entry 4-5). Achiral and chiral alcohols with much bulkier structures were applied as additives. The influence was not obvious, with less than 4% *ee* difference (entry 6-8). Among all the results, *L*-menthol caused the most obvious enhancement (entry 5). Next, we tested two reactions with and without *L*-menthol at -40°C, the one with *L*-menthol brought 65% *ee* compare to the control experiment with 62% *ee* (entries 9-10). These few tests at least showed us a possible effect of nucleophiles on the results we obtained. That can explain partially why the *ees* are different with different nucleophiles, whereas it was at the beginning rather counterintuitive.



entry	[Au/Ag] ratio	Additive	Yield <b>10h</b> (%) <sup>a</sup>	ee (%) <sup>b</sup>
1	1/2	-	62	+49
2	1/1	-	90	+52
3	1/1	<i>t</i> -BuOH	78	+52
4	1/1	<i>D</i> -menthol	50	+56
5	1/1	<i>L</i> -menthol	50	+57
6	1/1	1-adamantanol	95	+55
7	1/1	(-)-isopinocampheol	35	+51
8	1/1	( <i>R</i> )-BINOL	88	+52
9 <sup>c</sup>	1/1	-	80	+62
10 <sup>c</sup>	1/1	<i>L</i> -menthol	57	+65

<sup>a</sup>Isolated yield. <sup>b</sup>Determined by SFC on a chiral stationary phase. <sup>c</sup>-40°C.

Table III-5. Addition of different alcohol additives

Another explanation of this phenomenon was highlighted by Toste in 2011.<sup>114</sup> In the case of bicationic gold complex, the alcohol such as *L*-menthol can be treated like a co-catalyst, which also acts as Brønsted acid by coordination with gold catalyst.

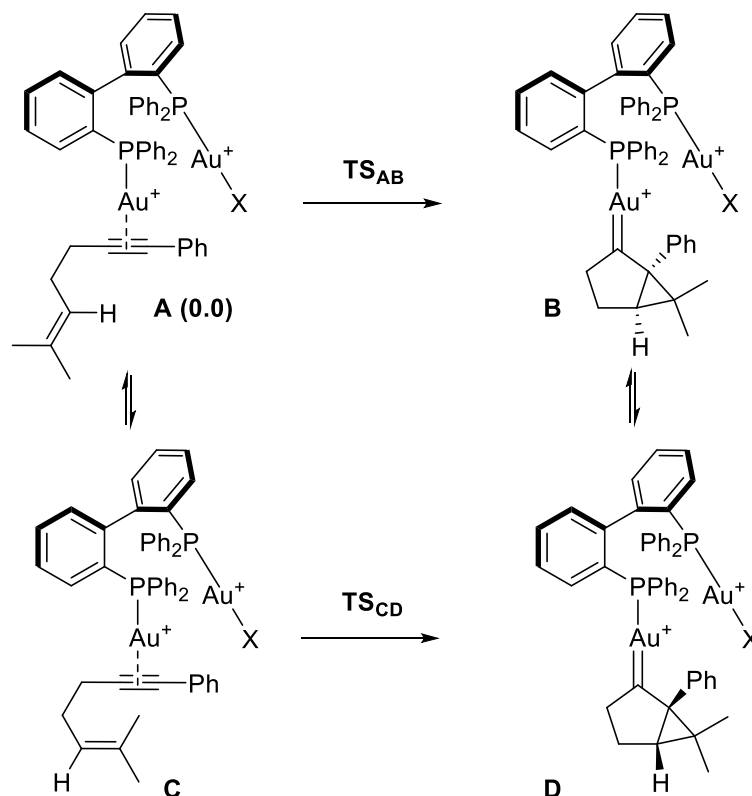
### 3.4.3 DFT calculations

To shed light on the reaction mechanism, DFT computations were carried out. The simplified model ligand used is 2,2'-bis(diphenylphosphaneyl)-1,1'-biphenyl and the model substrate is enyne **8a**. All structures were optimized using the Gaussian 09 software package at the B3LYP level of density functional theory (DFT). The effective-core potential of Hay and Wadt with a double- $\xi$  valence basis set (LANL2DZ) was used to describe Au. The other atoms were described by the 6-31G(d,p) basis set. Thermal corrections to the Gibbs free energy were obtained at the same level of theory. Single-point energy calculations were carried out at the M06 level with the quadruple- $\zeta$  valence def2-QZVP basis set on Au and the 6-311+G(2d,p) basis set on other elements. This level was also chosen to obtain the solvation energy in toluene using the CPCM model. The value presented herein are Gibbs free energies (kcal/mol) obtained from the M06/def2-QZVP(Au)-6-311+G(2d,p)//B3LYP/LANL2DZ(Au)-6-

<sup>114</sup> Kanno, O.; Kuriyama, W.; Wang, Z. J.; Toste, F. D. *Angew. Chem. Int. Ed.* **2011**, *50*, 9919.

31G(d,p) calculations in CH<sub>2</sub>Cl<sub>2</sub> ( $\Delta G_{298}$ , kcal/mol).

The computed steps are shown in *Scheme III-25* (see also *Table III-7* for selected structures). The structure differs from the nature of X which can be a simple chloride, a chloride H-bonded to methanol, or a chloride H-bonded to L-menthol.



*Scheme III-25. Calculated steps*

The Gibbs free energies of the computed species relatively to the gold alkyne complex **A** are given in *Table III-6*. From the  $\Delta\Delta G$  of activation, the *ee* has been estimated (Hammond postulate). All cyclopropylcarbene formations are reversible, which makes the results more difficult to interpret. Thus, only trends can be derived from these calculations. Clearly the presence of an additive (*L*-menthol) or the nucleophile itself (MeOH) influences the cyclization barriers and therefore the *ees*. The computations in the presence of an additive predict the experimentally observed absolute configuration of the carbons, but further work is ongoing to fully rationalize this effect.

Entry	X	TS <sub>AB</sub>	B	C	TS <sub>CD</sub>	D	<i>ee</i> (%)
1	Cl <sup>-</sup>	12.9	1.8	1.0	13.4	2.5	50
2	Cl <sup>-</sup> ...HOMe	13.4	3.0	-1.8	12.8	2.4	58
3	Cl <sup>-</sup> ...L-menthol	14.3	1.9	-4.3	13.0	2.2	64

*Table III-6. Gibbs free energies (kcal/mol) relatively to A.*

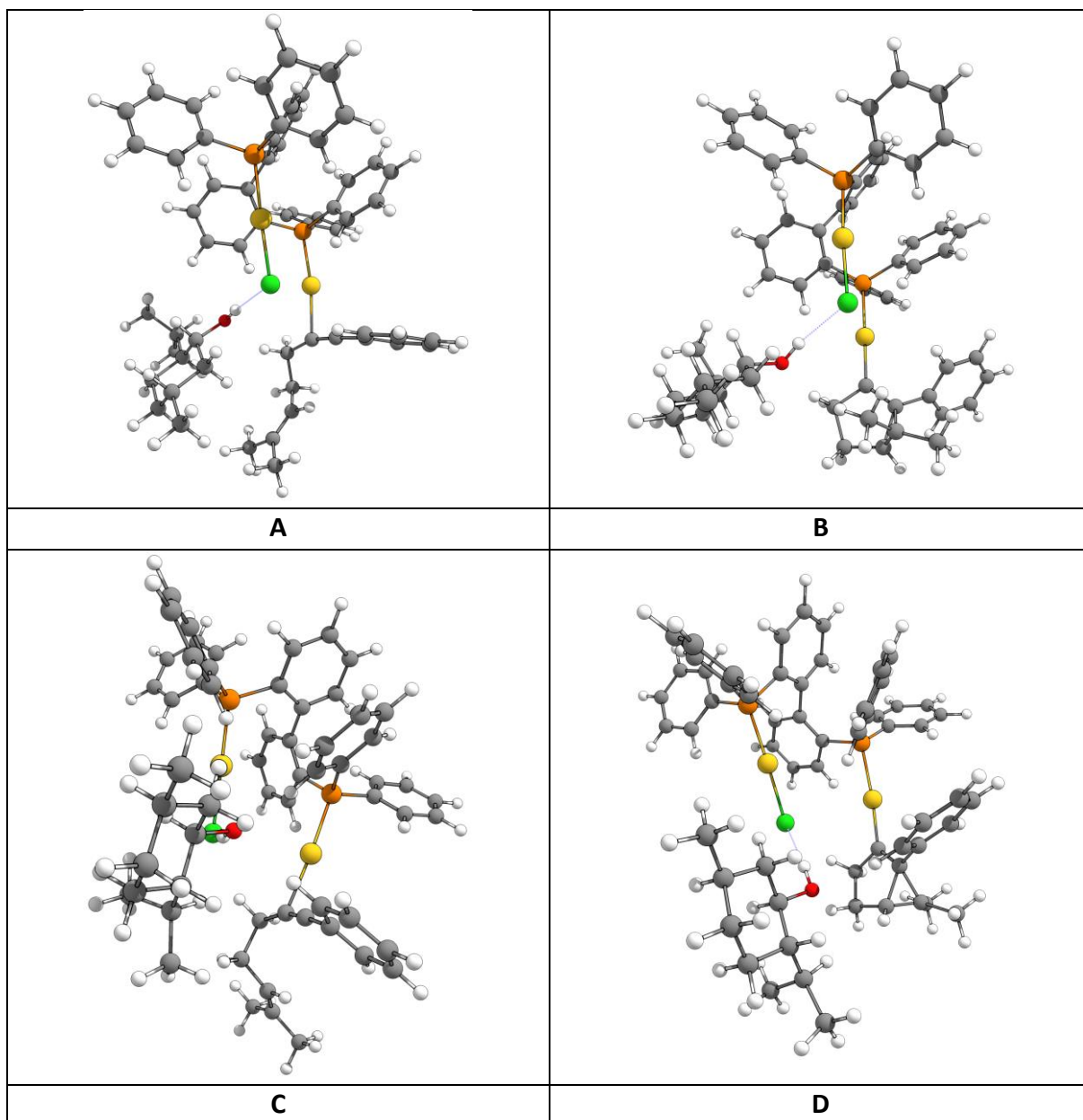


Table III-7. Calculated minima with  $X = Cl \cdots L$ -menthol

In conclusion of this study, even if the most common commercially available bimetallic chiral gold catalysts (with atropisomeric BINAP, BIPHEP and SEGPHOS diphosphines) were all tested, and if we tried our best to optimize the reaction conditions (silver salt, reaction temperature, concentration, stoichiometry), only moderate enantiomeric excesses were achieved in this reaction (up to 71% *ee*). In a last burst of pride and being very interested by the work of Fürstner on the development of a new chiral phosphoramidite-gold(I) catalyst, we decided to focus our attention on the synthesis of this complex.



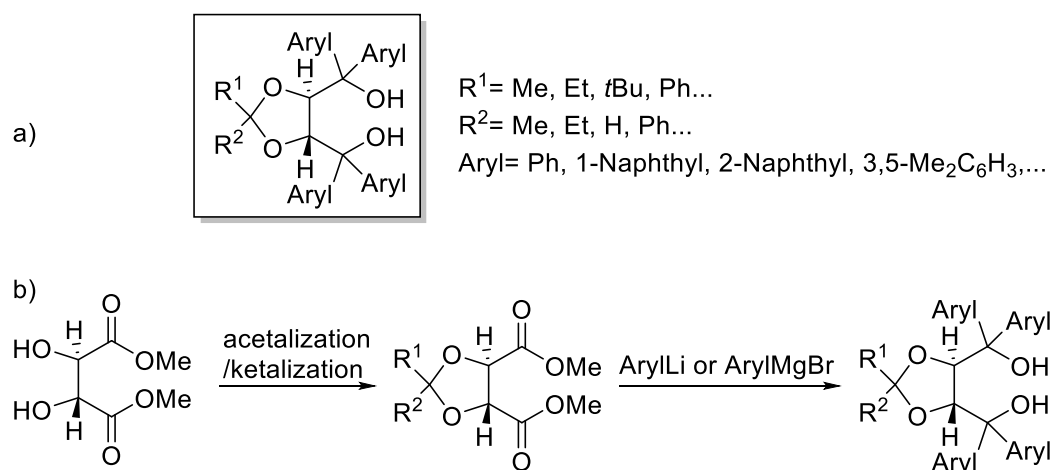
## 3.5 Use of the Taddol-phosphoramidite-gold(I) catalyst in the enantioselective 1,5-enyne cyclization/nucleophilic addition

### 3.5.1 Synthesis and applications of Taddol-derived metal catalysts and chiral auxiliaries

#### 3.5.1.1 Introduction

TADDOLs and their analogue compounds are derived from tartaric acid and were firstly prepared by Frankland in 1904 and then developed par Seebach.<sup>115</sup> This chiral molecule of interest found many applications as chiral ligand in asymmetric transition metal catalysis and more generally as chiral auxiliary in asymmetric synthesis. The most common TADDOLs were shown in the *Scheme III-26a*. Based on various starting materials, such as different diol-protecting groups ( $R^1$ ,  $R^2$ ) and aromatic groups (Ar) which can be introduced to synthesize TADDOLs, large numbers of TADDOL auxiliaries and ligands have been reported. Several advantages should be also mentioned:

- (1) The synthesis of this chiral backbone is very simple and amenable to *multi-gram scales*.
- (2) The chiral backbone comes from an enantiopure natural compound (tartaric acid). As a consequence, it is not necessary to construct a complex chiral structure, which avoids difficulties in chiral compounds separation.
- (3) They are mostly solids, possess high thermal stability, and are easy to handle.
- (4) Taddol derivatives possess relatively low molecular weight, it is more atom economic if we compare it to some complex ligands with high molecular weight.



*Scheme III-26. General information on TADDOLs*

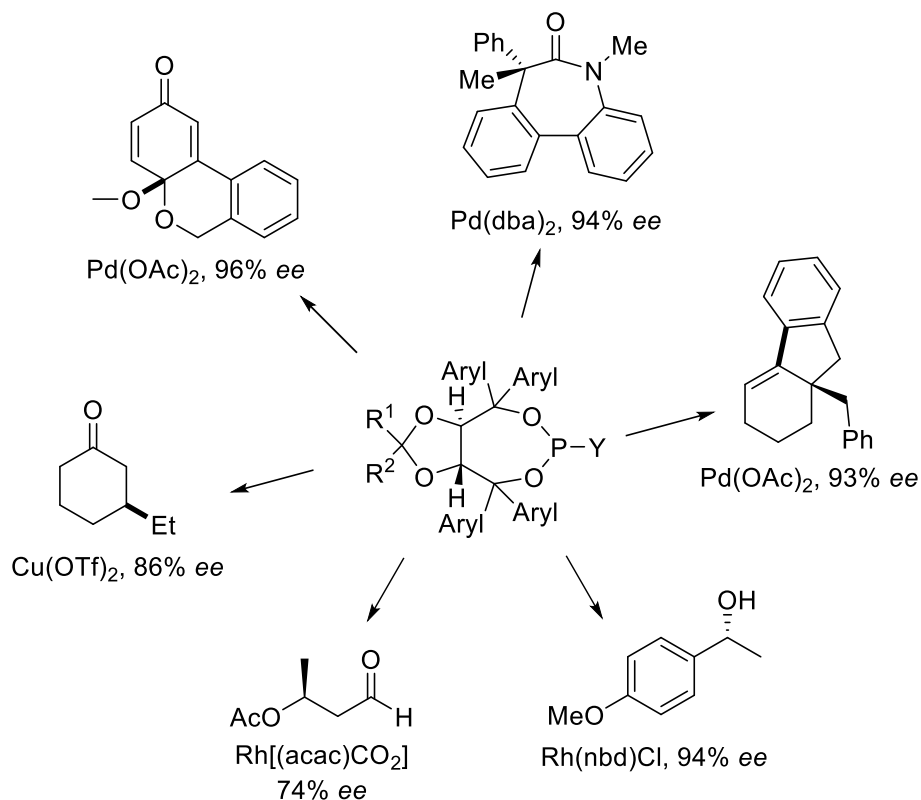
The synthetic procedure of preparation of TADDOLs<sup>116</sup> started from the enantiopure dimethyl (*2R,3R*)-2,3-dihydroxysuccinate backbone. After acetalization/ketalization reactions, the corresponding protected diol is treated with aryl lithium salts or Grignard reagents to

<sup>115</sup> Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 92.

<sup>116</sup> Seebach, D.; Beck, A. K.; Imwinkelried, R.; Roggo, S.; Wonnacott, A. *Helv. Chim. Acta.* **1987**, *70*, 954.

introduce the aryl moieties (*Scheme III-26b*).

In general, we can apply the TADDOL analogues in three major classes of reactions. At the first stage, stoichiometric quantity of TADDOL auxiliary with main group metals such as Na, Mg, Li and Al can be used in asymmetric synthesis. This chiral molecule also emerged in TADDOL-titanium mediated asymmetric synthesis. As a chelating ligand, it is possible to use TADDOL derivatives complex with metallic centers for enantioselective transformations. Some research results with TADDOLates chelating to transition metals includes rhodium, palladium, iridium and copper-catalyzed processes (*Scheme III-27*)<sup>1171-4</sup>.



*Scheme III-27. TADDOLs applied in asymmetric catalysis*

### 3.5.1.2 Application of TADDOL derivatives in gold(I) catalysis

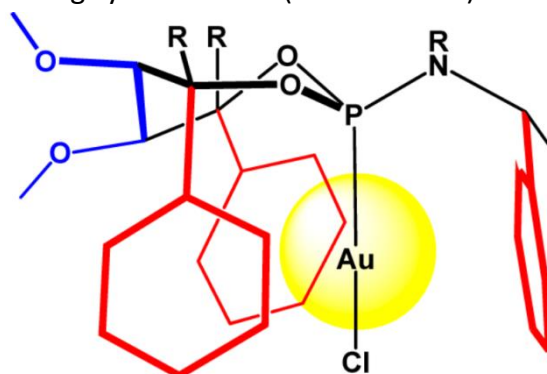
Up to now, to the best of our knowledge, there is only few examples of TADDOL-derived ligands applied in Au(I) enantioselective reactions. In 2010, Fürstner used an acyclic TADDOL backbone ligand as building block for the synthesis of phosphoramidite ligands.<sup>118</sup> This chiral monophosphine ligand was used in gold(I) catalysis and was successfully applied in several different methodologies to give generally excellent enantioselectivities. Their initial idea came from the research of the default of chiral gold(I) complex, which possess linear structure which hinders the transfer of chiral information. To solve this problem, one of the

<sup>117</sup> (a) Saget, T.; Cramer, N. *Angew. Chem. Inter. Ed.* **2013**, *52*, 7865. (b) Albicker, M. Ä.; Cramer, N. *Angew. Chem. Inter. Ed.* **2009**, *48*, 9139. (c) Moteki, S. A.; Wu, D.; Chandra, K. L.; Reddy, D. S.; Takacs, J. M. *Org. Lett.* **2006**, *8*, 4. (d) Perotti, J.; Cravero, R.; Luna, L.; Grau, R.; Vaillard, S. *Arkivoc* **2011**, 2011, 92.

<sup>118</sup> Teller, H.; Flugge, S.; Goddard, R.; Fürstner, A. *Angew. Chem. Int. Ed.* **2010**, *49*, 1949.

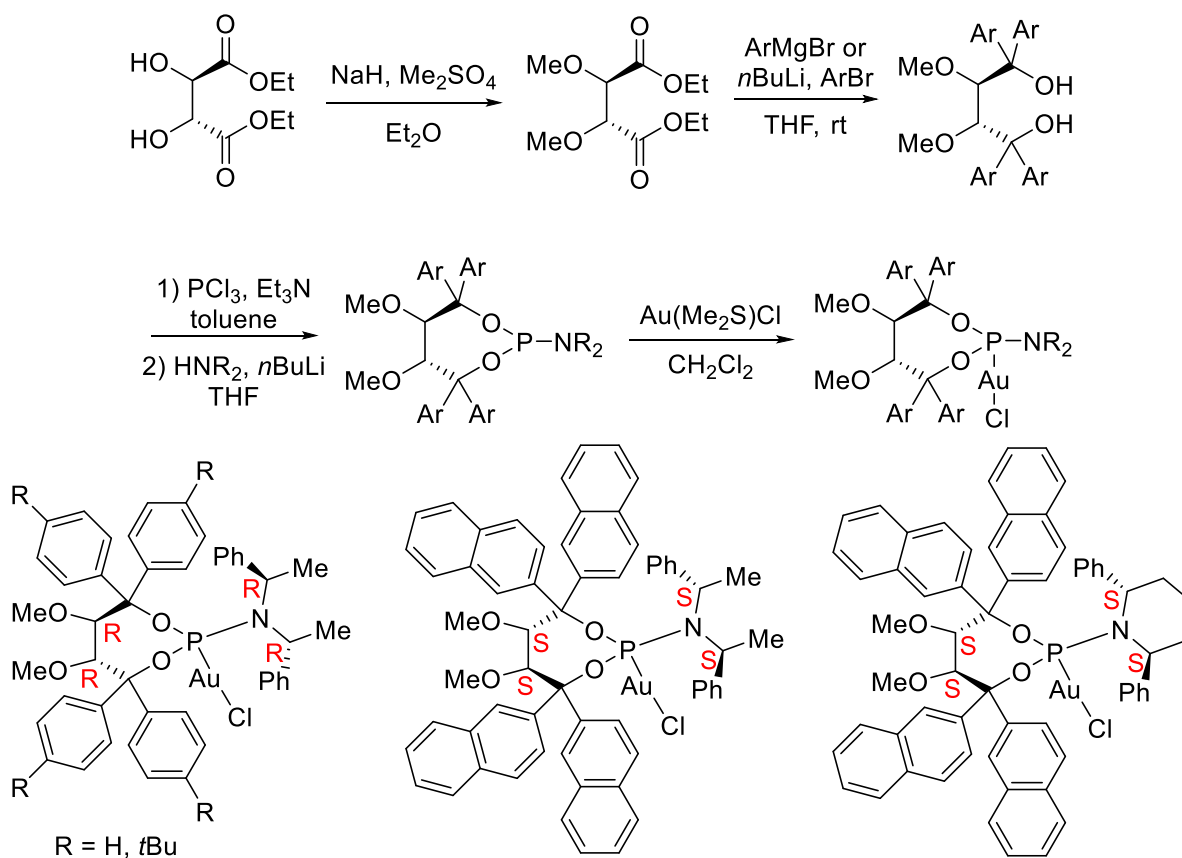
methods that can be utilized, is the use of bulkier ligand to remedy the loss of the chirality transfer caused by gold(I) complex's linear geometry.

The structure of the acyclic TADDOL was designed to construct a binding pocket around the rotatable L\*-Au bond. The structure analysis showed that the seven membered ring in acyclic TADDOL was more puckered, and one of the aryl ring was placed closer to the metal center compared to the corresponding cyclic TADDOL (*Scheme III-28*).



*Scheme III-28. Chiral pocket around the gold atom*

The synthetic pathway proposed by Fürstner for the synthesis of this new chiral gold catalyst is described in *Scheme III-29*. The procedure required four steps and it seems simple and efficient.



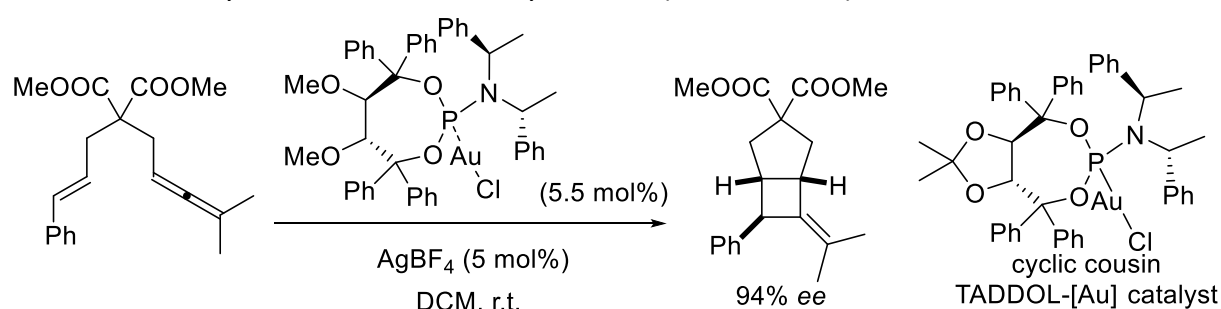
*Scheme III-29. Synthesis of acyclic TADDOLs developed in Fürstner's group*

During their research, different acyclic TADDOL backbones were prepared from very cheap

enantiopure diethyl tartrate. Aromatic substituents on acyclic TADDOL could be modified easily by introducing the corresponding Grignard reagent. Starting with the TADDOL alcohol, and treated with  $\text{PCl}_3$ , then the chiral amine was introduced in presence of a base to furnish the phosphoramidate. The gold(I) precatalyst complex could be obtained easily by introducing  $\text{DMS}\cdot\text{AuCl}$ . With this new synthetic procedure, four acyclic TADDOLs-based gold(I) catalysts were synthesized (*Scheme III-29*).

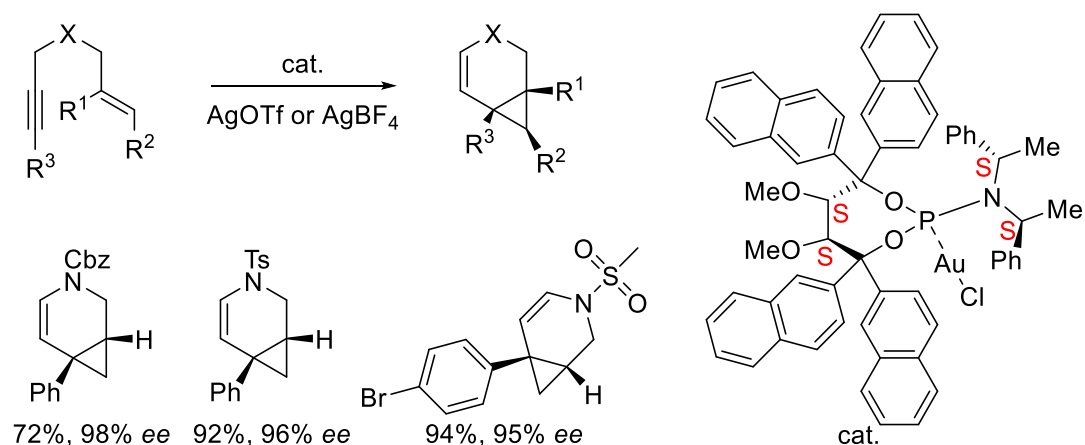
These new gold complexes were then tested in large range of enantioselective reactions including cycloisomerization of 1,6-enyne, [2+2] and [4+2] cycloaddition of ene-allenes, hydroarylation of indole derivatives, intramolecular hydroamination and also hydroalkoxylation of allenes. They made comparison between *bis*-metallic gold catalysts derived from BIPHEP diphosphines and their new acyclic TADDOL catalyst system, the acyclic TADDOL gold(I) catalyst showed similar or better enantioselectivities in different reactions.

For example, in the benchmark reaction of the [2+2] cycloaddition of ene-allenes, the acyclic TADDOL-[Au] catalyst furnished the target compound with 94% *ee* and 91% yield. The same product was obtained with up to 95% *ee* using SEGPHOS-derived digold catalyst, and only 84% *ee* with its cyclic TADDOL-[Au] catalyst cousin (*Scheme III-30*).



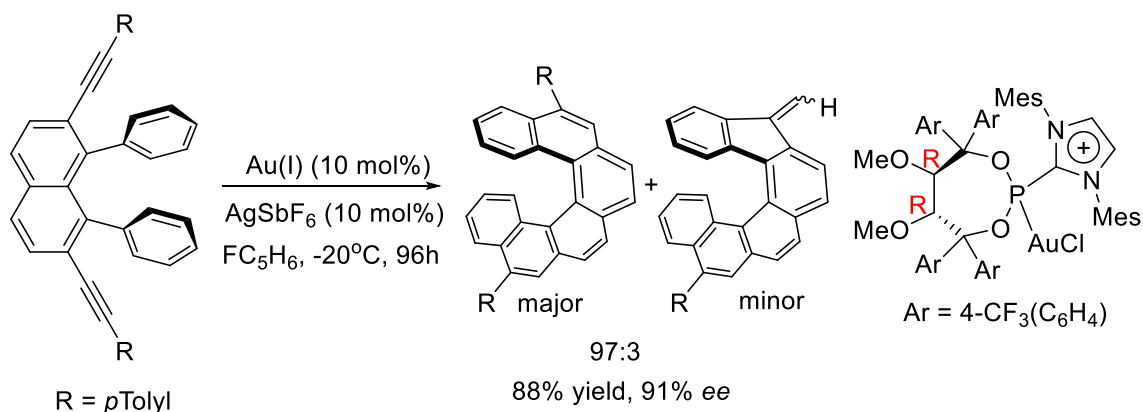
*Scheme III-30. Application in [2+2] cycloaddition of ene-allenes*

On the other hand, impressive results were also obtained in terms of enantioselectivity in the 1,6-enyne cycloisomerization reaction, which is a classical catalytic test in asymmetric platinum- and gold-catalysis field. Acyclic TADDOL gold catalyst substituted by 2-naphthyl aromatic groups proved to be efficient in a series of asymmetric isomerization processes (*Scheme III-31*).



Scheme III-31. Application in 1,6-enyne cycloisomerization

The only other example of applying TADDOL ligand into gold catalysis was carried out in Alcarazo's group.<sup>119</sup> With an acyclic TADDOL backbone chiral phosphoramidate ligand, a highly efficient synthesis toward the synthesis of [6]carbohelicenes was achieved (Scheme III-32).



Scheme III-32. Asymmetric synthesis of [6]carbohelicenes

### 3.5.1.3 Synthesis of acyclic TADDOLs ligand

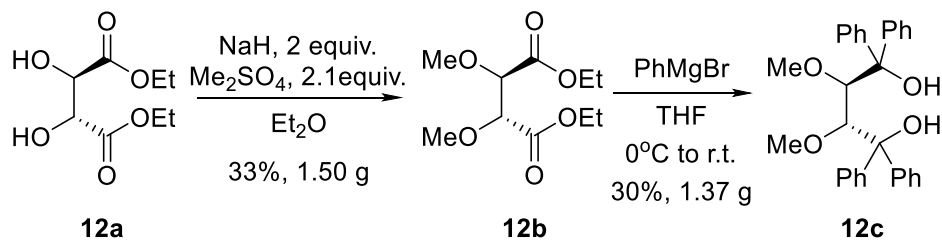
The amazing results acquired in Fürstner's group encouraged us to test the 1,5-enyne cyclization reaction with one of their acyclic TADDOL catalysts. We followed the procedure described in the two publications, however, very low isolated yields were obtained, even when we tried to enhance the reaction conditions by distilling the solvent and purifying the reagents. Thus, we developed our own strategy by modifying the procedure described in former publications.

Diethyl (2*R*, 3*R*)-2,3-dimethoxysuccinate (**12c**) was prepared from commercial available *L*-(+)-diethyl tartrate (**12a**) according to the known procedures as shown in Scheme III-33.<sup>120</sup> Sodium hydride was dispersed in anhydrous diethyl ether and cooled to 0°C, then diethyl tartrate and dimethyl sulfate were added consecutively. The resulting mixture was allowed

<sup>119</sup> Gonzalez-Fernandez, E.; Nicholls, L. D.; Schaaf, L. D.; Fares, C.; Lehmann, C. W.; Alcarazo, M. *J. Am. Chem. Soc.* **2017**, *139*, 1428.

<sup>120</sup> Seebach, D.; Kalinowski, H. O.; Bastani, B.; Crass, G.; Daum, H.; Dörr, H.; Dupreez, N. P.; Ehrig, V.; Langer, W.; Nüssler, C.; Oei, H. A.; Schmidt, M. *Helv. Chim. Acta.* **1977**, *60*, 301.

to warm to room temperature and was stirred overnight. The reaction was quenched by *sat.* NaHCO<sub>3</sub>, and the title compound diethyl (2*R*,3*R*)-2,3-dimethoxysuccinate **12b** was obtained in 33% isolated yield as colorless to light yellow liquid, at 1.5 grams scale (*Scheme III-33*).

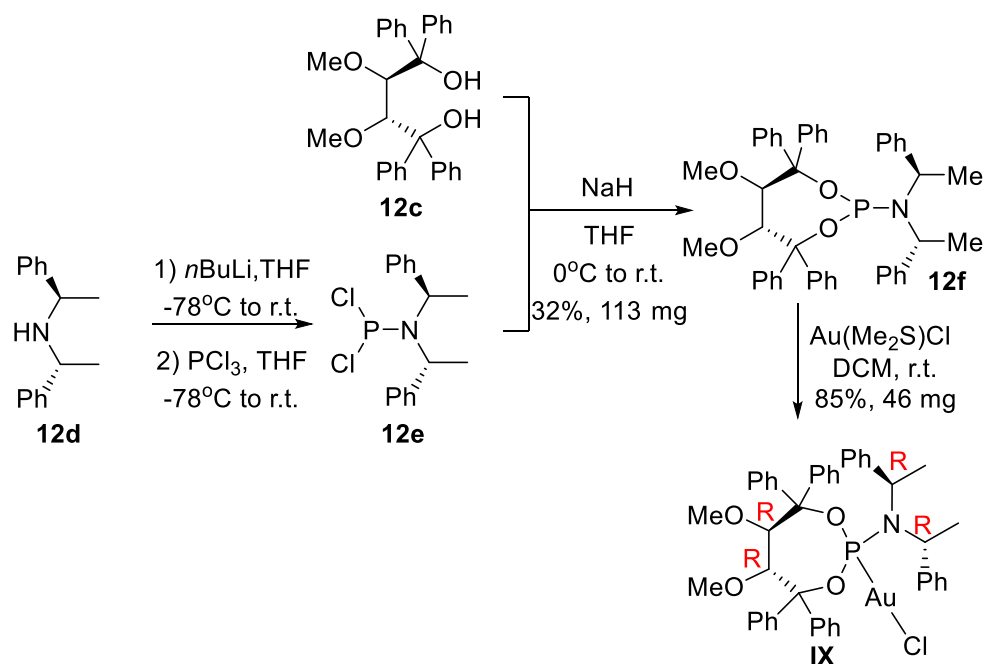


*Scheme III-33. Synthesis of an acyclic TADDOL*

The synthesis of (2*R*,3*R*)-2,3-dimethoxy-1,1,4,4-tetraphenylbutane-1,4-diol **12c** was reported firstly in Toda's group.<sup>121</sup> Grignard reagent was readily prepared and the diester derivative was dissolved in dry THF and was added slowly at 0°C, then the reaction system was kept reacting for another 2 hours at room temperature (*ie* 38°C in Gif this summer), until quenched by *sat.* NH<sub>4</sub>Cl. The title diol compound (acyclic TADDOL) was obtained in 30% isolated yield (1.37 grams) as white foam (*Scheme III-33*).

The phosphoramidite **12e** was prepared through our own strategy. In the first step, the chiral amine **12d** was dissolved in dry THF and cooled to -78°C, treated with *n*BuLi slowly and warmed to room temperature, stirred for 30 minutes to form the corresponding amine-lithium salt. Then PCl<sub>3</sub> in THF was cooled to -78°C, the former amine-lithium THF solution was added dropwise. The mixture was warmed up and kept at room temperature overnight. Phosphorus NMR can confirm the formation of the phosphorus compound **12e**. In this step, it is crucial to make sure the purity of all chemicals applied, especially for PCl<sub>3</sub>, it is necessary to use lately distilled reagent (*Scheme III-34*).

<sup>121</sup> FumioToda; KoichiTanaka *Tetrahedron Lett.* **1988**, 29, 551.



Scheme III-34. Synthesis of acyclic TADDOL-Au(I) catalyst

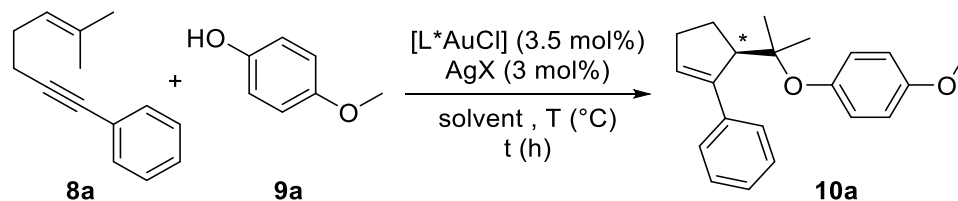
In the second stage, already prepared (2*R*,3*R*)-2,3-dimethoxy-1,1,4,4-tetraphenylbutane-1,4-diol (acyclic TADDOL backbone, **12c**) was dissolved in dry THF, treated with sodium hydride at  $0^\circ\text{C}$ . After stirring at r.t. for 30 minutes, the mixture from the first batch was introduced. The target phosphoramidite **12f** was achieved in 32% yield as light yellow foam (113 mg), 50% diol substrate can be recycled. With the precatalyst in hand, the target TADDOL-[Au] can be obtained easily by treating with chloro(dimethylsulfide)gold(I), in 85% yield at 46 mg scale (Scheme III-34).

### 3.5.2 Application of the acyclic TADDOL-Au(I) complex in enantioselective 1,5-ene yne cyclization/nucleophilic addition process

#### 3.5.2.1 Optimization with acyclic TADDOL-Au(I) complex

We next turned our attention to the use of the TADDOL phosphoramidite-AuCl monogold catalyst (**IX**), synthesized by ourselves, in the 1,5-ene yne cyclization reaction. As a reminder, up to now, the best result was obtained with the (*R*)-DM-SEGPPOS-(AuCl)<sub>2</sub>/AgSbF<sub>6</sub> catalytic system, with quantitative yield and up to 55% *ee* (Table III-7, entry 1). With the acyclic TADDOL-Au(I) complex in hand, we directly increased the enantioselectivity to 75% *ee*, albeit with a lower yield (entry 2). In order to find the best compromise between yields and *ees*, we next screened different silver salts (entries 2-6). The reaction reached 84% isolated yield and 77% *ee* using silver hexafluorophosphate (entry 4), among all the silver salts tested (AgSbF<sub>6</sub>, AgBF<sub>4</sub>, AgPF<sub>6</sub>, AgNTf<sub>2</sub>, and AgOTf). Lower reaction temperatures were tried and the best condition were achieved at  $-20^\circ\text{C}$  (entry 7). The decrease of the reaction temperature to  $-40^\circ\text{C}$  (entry 8) did not improve this result. When decreasing the quantity of Au(I) catalyst to 2 mol%, an excellent 81% yield and 86% *ee* can be achieved (entry 9). *Ratio* of [Au] to [Ag] did

not influence the reaction outcome. As a control experiment, we treated the starting materials with only 3 mol% of AgPF<sub>6</sub>, and all the substrates can be recycled with no degradation and no new product was formed based on <sup>1</sup>H NMR data.



entry	[L*AuCl]	X	[Au] / [Ag] ratio	solvent	T (°C) /t (h)	Yield <b>10a</b> (%) <sup>a</sup>	ee (%) <sup>b</sup>
1	(VIII)	SbF <sub>6</sub>	1/1	DCM	25/2	99	+55
2	(IX)	SbF <sub>6</sub>	1.2/1	DCM	25/2	33	+75
3	(IX)	BF <sub>4</sub>	1.2/1	DCM	25/2	60	+76
4	(IX)	PF <sub>6</sub>	1.2/1	DCM	25/2	84	+77
5	(IX)	NTf <sub>2</sub>	1.2/1	DCM	25/2	80	+65
6	(IX)	OTf	1.2/1	DCM	25/2	53	+62
7	(IX)	PF <sub>6</sub>	1.2/1	DCE	-20/24	80	+86
8	(IX)	PF <sub>6</sub>	1.2/1	DCE	-40/24	72	+85
9 <sup>c</sup>	(IX)	PF <sub>6</sub>	1/1	DCE	-20/24	81	+86

<sup>a</sup>Isolated yield at a 0.05 mmol scale. <sup>b</sup>Determined by SFC on a chiral stationary phase. <sup>c</sup>2 mol% of (IX) and AgPF<sub>6</sub>.

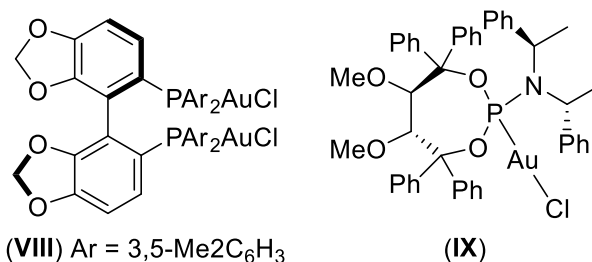


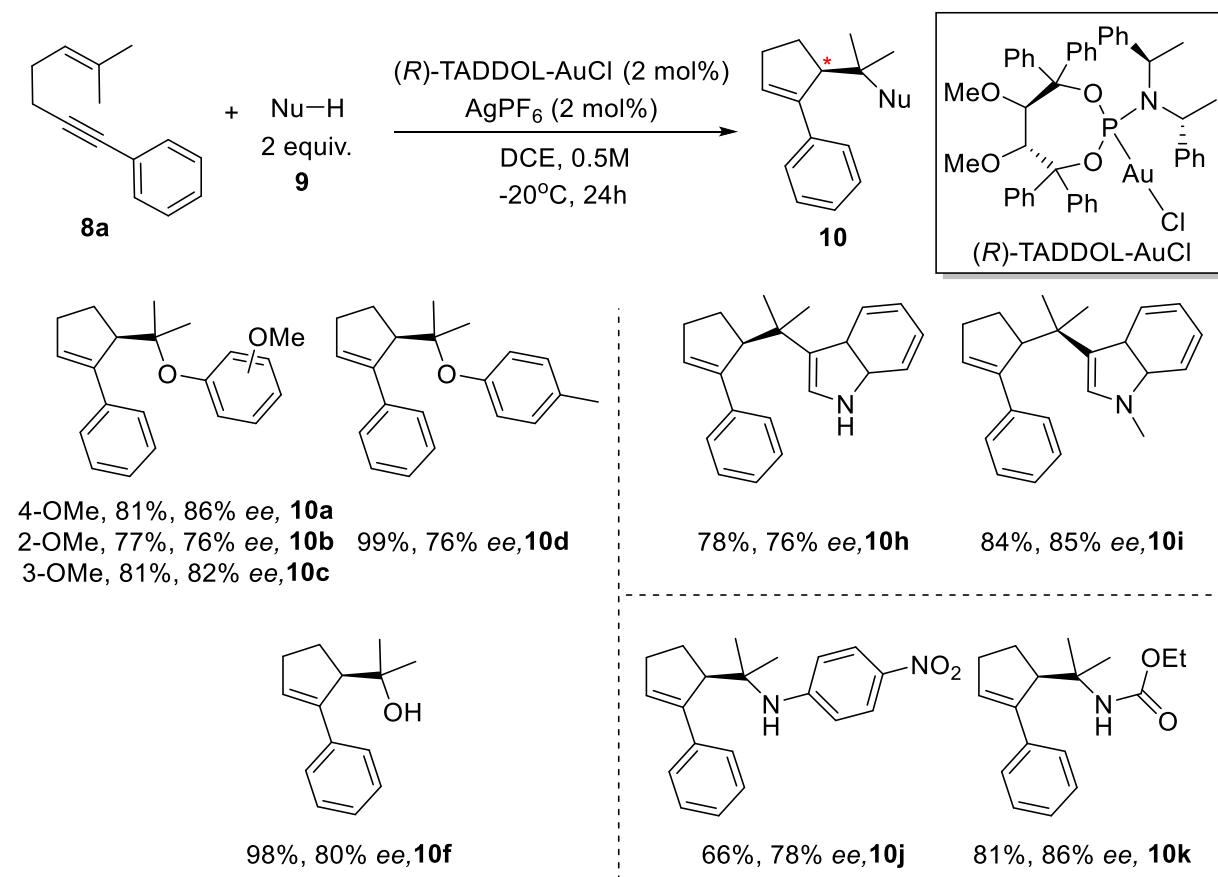
Table III-7. Optimization of the reaction with catalyst (IX)

### 3.5.2.2 Reaction scope with acyclic TADDOLs Au(I) complex

With the optimized reaction conditions in hand, various nucleophiles were tested. Starting with unfunctionalized (6-methylhept-5-en-1-yn-1-yl)benzene substrate **8a**, when methoxyphenol with methoxy group on *ortho*-, *meta*- and *para*-position were used as nucleophiles, target products were isolated in 77-81% isolated yields and up to 86% *ee*. A *para*-methylphenol gave 99% yield, with a bit lower *ee*. The methodology also succeeded in carbon-carbon bond formation when indoles were applied as nucleophiles, excellent results can be obtained. Water was tested as nucleophile and promoted the formation of the desired compound in 98% isolated yield and 80% *ee*. Amides were also suitable in this

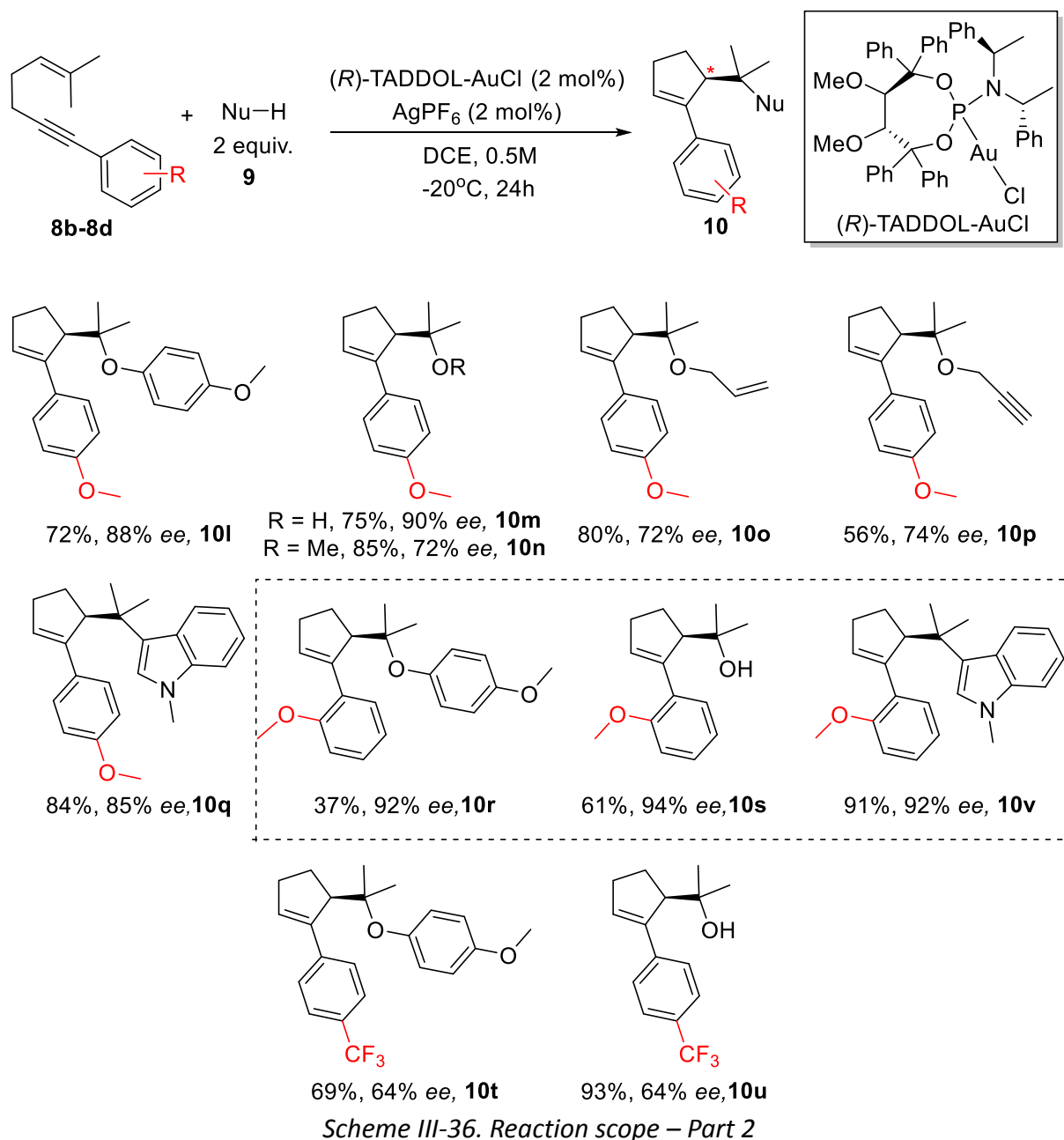


transformation, the aliphatic amide (ethyl carbamate, 81% yield, 86% *ee*) showing better activity and enantioselectivity than aromatic 4-nitroaniline (66% yield, 78% *ee*, Scheme III-35).



Scheme III-35. Reaction scope – Part 1

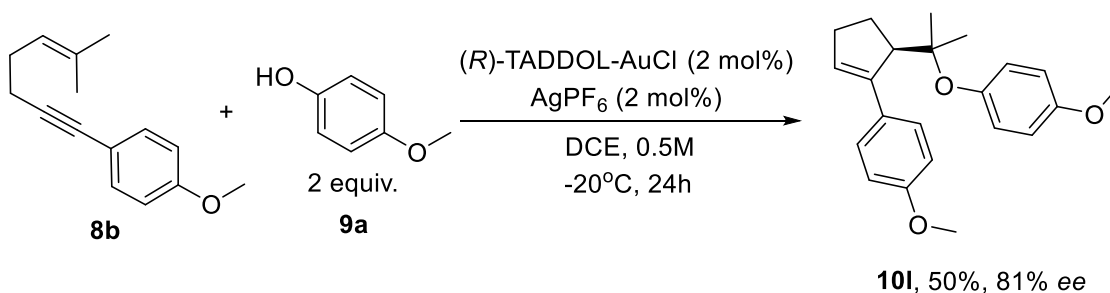
Different substituents on the phenyl ring of 1,5-enyne substrate were tested. With substrate **8b**, with electron-donating methoxy group on *para* position, *ee* values were increased with aromatic alcohol like *para*-methoxyphenol (**10l**, 88% *ee*). Excellent result could also be gained when H<sub>2</sub>O was introduced as nucleophile (**10m**, 90% *ee*). But with simple aliphatic alcohol such as methanol (**10o**), propargyl alcohol (**10n**) and allyl alcohol (**10p**), obvious loss of enantioselectivity was observed, enantiomeric excesses decreased to only 72-74% in these three examples (Scheme III-36).



2-Methoxy substituted enyne substrate (**8c**) showed the best results, in all three examples, corresponding products (**10r-10v**) could be achieved with 92-94% ee in moderate to excellent yields. We postulated that those results had taken the advantage of the 'suitable' steric hindrance brought by the methoxyl group. The introduction of strong electron-withdrawing trifluoromethyl group could not improve the enantioselectivity, much lower ee value were obtained in both cases (**10t**, **10u**, 64% ee, *Scheme III-36*).

The methodology was tested at a 1 mmol scale, starting with 1-methoxy-4-(6-methylhept-5-en-1-yn-1-yl)benzene **8b** as substrate (1 mmol, 214 mg) and 4-methoxyphenol **9a** as nucleophile, in presence of Taddol-phosphoramidite-AuCl/AgPF<sub>6</sub> catalytic system. A slightly

decrease in both the yield and the enantioselectivity was observed (81% *ee*), compared to the result at 0.05 mmol scale (72% yield, 88% *ee*, Scheme III-37).



Scheme III-37. 1 mmol scale reaction

### 3.6 Conclusion

Hence, we have developed the first asymmetric gold(I)-catalyzed 1,5-enyne cyclization/nucleophilic addition sequence. An acyclic TADDOL backbone was applied as the chiral ligand, which is also a quite rare example for the utilization of TADDOL-derivative chiral ligand in enantioselective gold catalysis. Twenty examples were carried out with good to excellent yields and up to 94% enantiomeric excess. A 1 mmol scale reaction was tested with good yield and a slightly decrease of enantioselectivity.

The interaction between nucleophile and *bis*-gold catalyst was investigated. A hypothesis was raised that a possible hydrogen bond between proton from nucleophiles and chlorine in unactivated AuCl moiety may influence the reaction outcome, both on reactivity and enantioselectivity. The corresponding DFT calculations supported our suggestion.

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## **Chapter 3:**

### **Experimental Part**

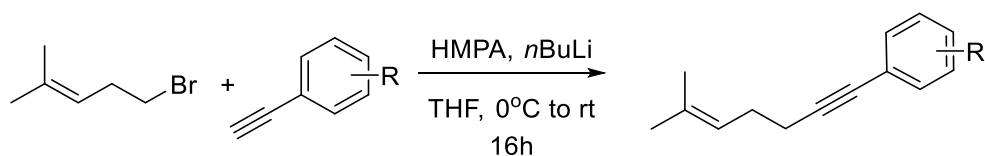
### 3.1 General information

Reactions were performed using oven dried glasswares under an atmosphere of argon. All separations were carried out under flash-chromatographic conditions on silica gel (Redi Sep prepacked column, 230–400 mesh) at medium pressure (20 psi) with use of a CombiFlash Companion. Reactions were monitored by thin-layer chromatography on Merck silica gel plates (60 F254 aluminum sheets) which were rendered visible by ultraviolet and spraying with vanillin (15%) + sulfuric acid (2.5%) in EtOH followed by heating. Reagent-grade chemicals were obtained from diverse commercial suppliers and used as received.  $^1\text{H}$  NMR (500 or 300 MHz) and  $^{13}\text{C}$  NMR (125 or 75 MHz) spectra were recorded on Brüker Avance spectrometers at 298 K unless otherwise stated. Chemical shifts are given in ppm ( $\delta$ ) and are referenced to the internal solvent signal. Multiplicities are declared as follow: s (singlet), brs (broad singlet), d (doublet), t (triplet), q (quadruplet), dd (doublet of doublet), ddd (doublet of doublet of doublet), dt (doublet of triplet), m (multiplet). Coupling constants  $J$  are given in Hz. Carbon multiplicities were determined by DEPT135 experiment. Infrared spectra (IR) were recorded on a Perkin-Elmer FT-IR system using diamond window Dura SamplIR II and the data are reported in reciprocal centimeters ( $\text{cm}^{-1}$ ). Melting points were recorded in open capillary tubes on a Büchi B-540 apparatus and are uncorrected. High-resolution mass spectrometry (HRMS) was performed using electrospray ionization (ESI) and time-of-flight (TOF) analyzer, in positive-ion or negative-ion detection mode. Supercritical fluid chromatography (SFC) separation was performed on a Investigator SFC System (Waters) equipped with a diode array UV detector. Data are reported as follows: column type, temperature, eluent, flow rate, pressure in column, retention time (tr).

#### 3.1.1 General procedure

##### 3.1.1.a Synthesis of substrates

Procedure I: for the synthesis of substrates **8a-8d**



To a solution of phenylacetylene compounds (1.0 eq.) in THF was added *n*BuLi (1.6 M, 1.2 eq.) dropwise at 0°C, keep the mixture stir for 1 hour. Then HMPA (2.0 eq.) and 5-bromo-2-methyl-2-pentene (1.1 eq.) was added in order at 0°C. Warm the reaction mixture to atmosphere temperature and stir overnight. Quenched at 0°C by saturated  $\text{NH}_4\text{Cl}$  aq., extracted with PE, evaporated and purified by flash chromatography on silica gel using PE/EA (from 0% to 2%) as the eluent to yield the target product.

##### 3.1.1.b Synthesis of cyclopentene compounds

**Procedure II:** For synthesis of racemic mixture of compounds **10a-10u**

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In a Schlenk tube, substrates **8a-8d** (0.1 mmol, 1.0 equiv), nucleophile (0.2 mmol, 2.0 equiv.), gold catalyst (5 mol %) and distilled DCM (0.5 M) were added. The reaction mixture was then reacted at 20 °C for 17h (2h for several cases). The crude reaction mixture was concentrated and purified by automatic flash chromatography using 4g silica gel pre-packed column and EtOAc/heptane as eluent (5-10% EtOAc/heptane). Alternatively, prepared TLC (5-10% EtOAc/heptane) could be used for the purification. For condition A, Echavarren catalyst (**I**) was used as catalyst; For condition B, Ph<sub>3</sub>PAuBF<sub>4</sub> was used as gold catalyst.

**Procedure III: For asymmetric synthesis of compounds 10a-10d**

In a Schlenk tube, substrates **10a-10d** (0.05 mmol, 1.0 equiv), nucleophile (0.1 mmol, 2.0 equiv.) were added. Chiral gold catalyst (**X**) (2 mol %), AgPF<sub>6</sub> (2 mol %) and distilled DCE (0.5 M) were added to another reactions tube, kept the mixture stir for 15 minutes at 20°C, filtrated and injected to the former Schlenk tube. The reaction mixture was then reacted at 20 °C for 24h. The crude reaction mixture was concentrated and purified by automatic flash chromatography using 4g silica gel pre-packed column and EtOAc/heptane as eluent (5-10% EtOAc/heptane). Alternatively, prepared TLC (5-10% EtOAc/heptane) could be used for the purification.

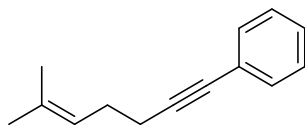
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(6-methylhept-5-en-1-yn-1-yl)benzene 8a

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**Chemical Formula:** C<sub>14</sub>H<sub>16</sub>

**Molecular Weight:** 184.2820

(207 mg, 61 % yield). Colorless oil; R<sub>f</sub> 0.35 (n-heptane)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.39 (d, *J* = 6.1 Hz, 2H), 7.33- 7.23 (m, 3H), 5.24 (t, *J* = 6.6 Hz, 1H), 2.42 (t, *J* = 7.3 Hz, 2H), 2.30 (q, *J* = 7.2 Hz, 2H), 1.73 (s, 3H), 1.67 (s, 3H)

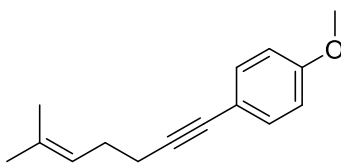
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(6-methylhept-5-en-1-yn-1-yl)benzene 8b

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**Chemical Formula:** C<sub>15</sub>H<sub>18</sub>O

**Molecular Weight:** 214.3080

(224 mg, 27 % yield). Colorless oil; R<sub>f</sub> 0.7 (n-heptane)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.35- 7.30 (m, 2H), 6.83- 6.78 (m, 2H), 5.27- 5.20 (m, 1H), 3.80 (s, 3H), 2.40 (dd, *J* = 11.1, 3.9 Hz, 2H), 2.29 (q, *J* = 7.2 Hz, 2H), 1.73 (d, *J* = 0.5 Hz, 3H), 1.66 (s, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 133.0 (CH), 123.1 (CH), 116.4 (C), 114.0 (CH), 88.6 (C), 80.4 (C), 55.4 (CH<sub>3</sub>), 27.8 (CH<sub>2</sub>), 25.9 (CH<sub>3</sub>), 20.1 (CH<sub>2</sub>), 17.9 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 2966, 2913, 2837, 1607, 1508, 1442, 1377, 1289, 1265, 1246, 1172, 1106, 1034, 830, 796, 737, 704 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>15</sub>H<sub>19</sub>O [M+H]<sup>+</sup>: 215.1436, found: 215.1430.

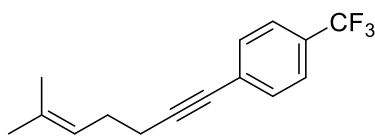
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**1-(6-methylhept-5-en-1-yn-1-yl)-4-(trifluoromethyl)benzene 8c**

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**Chemical Formula:** C<sub>15</sub>H<sub>15</sub>F<sub>3</sub>

**Molecular Weight:** 252.2802

(526 mg, 52 % yield). Colorless oil; R<sub>f</sub> 0.6 (n-heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.51 (q, *J* = 8.4 Hz, 4H), 5.22 (dddd, *J* = 7.0, 5.6, 2.8, 1.4 Hz, 1H), 2.44 (dd, *J* = 10.9, 3.9 Hz, 2H), 2.31 (dd, *J* = 14.3, 7.2 Hz, 2H), 1.73 (s, 3H), 1.67 (s, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 133.5 (C), 131.9 (CH), 128.1 (C), 126.0 (C), 125.3 (CH), 122.7 (CH), 93.3 (C), 79.7 (C), 27.5 (CH<sub>2</sub>), 25.9 (CH<sub>3</sub>), 20.1 (CH<sub>2</sub>), 18.0 (CH<sub>3</sub>)

**<sup>19</sup>F NMR** (282 MHz, CDCl<sub>3</sub>) δ -62.8

**IR:** ν<sub>max</sub> = 2971, 2918, 2232, 1617, 1406, 1378, 1324, 1267, 1167, 1127, 1105, 1068, 1018, 842, 741 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>15</sub>H<sub>16</sub>F<sub>3</sub> [M+H]<sup>+</sup>: 253.1204, found: 253.1215.

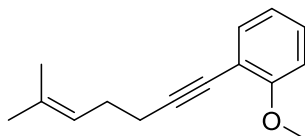
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**1-methoxy-2-(6-methylhept-5-en-1-yn-1-yl)benzene 8d**

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**Chemical Formula:** C<sub>15</sub>H<sub>18</sub>O

**Molecular Weight:** 214.3080

(240 mg, 37 % yield). Colorless oil; R<sub>f</sub> 0.63 (5 % EtOAc /n-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.30 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.21- 7.13 (m, 1H), 6.80 (ddd, *J* = 8.3, 6.3, 2.6 Hz, 2H), 5.18 (dddd, *J* = 7.0, 5.7, 2.8, 1.4 Hz, 1H), 3.80 (s, 3H), 2.45- 2.36 (m, 2H), 2.25 (q, *J* = 7.2 Hz, 2H), 1.65 (d, *J* = 0.8 Hz, 3H), 1.58 (s, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 160.0 (C), 133.8 (CH), 133.0 (C), 129.0 (CH), 123.1 (CH), 120.5 (CH), 113.3 (C), 110.7 (CH), 94.6 (C), 55.9 (CH<sub>3</sub>), 27.8 (CH<sub>2</sub>), 25.9 (CH<sub>3</sub>), 20.5 (CH<sub>2</sub>), 16.0 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 2967, 2914, 1596, 1492, 1464, 1434, 1292, 1262, 1237, 1117, 1049, 1026, 793, 748, 735, 703 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>15</sub>H<sub>19</sub>O [M+H]<sup>+</sup>: 215.1436, found: 215.1430.



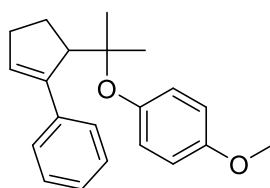
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**1-methoxy-4-((2-(2-phenylcyclopent-2-en-1-yl)propan-2-yl)oxy)benzene 10a**

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**Chemical Formula:** C<sub>21</sub>H<sub>24</sub>O<sub>2</sub>

**Molecular Weight:** 308.4210

(24.6 mg, 80% yield). Colorless oil; R<sub>f</sub> 0.27 (5% EtOAc/n-Heptane)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.38-7.34 (m, 2H), 7.27 (t, *J* = 7.5 Hz, 2H), 7.19 (t, *J* = 7.3 Hz, 1H), 6.79-6.72 (m, 4H), 6.02 (bs, 1H), 3.76 (s, 3H), 3.55 (d, *J* = 9.3 Hz, 1H), 2.58-2.40 (m, 3H), 2.29-2.22 (m, 1H), 1.19 (s, 3H), 0.91 (s, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 155.7 (C), 148.5 (C), 145.6 (C), 139.6 (C), 132.3 (CH), 128.1 (CH), 127.1 (CH), 126.7 (CH), 125.3 (CH), 113.9 (CH), 84.1 (C), 55.6 (CH<sub>3</sub>), 55.4 (CH), 32.4 (CH<sub>2</sub>), 27.9 (CH<sub>2</sub>), 26.2 (CH<sub>3</sub>), 23.5 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 3669, 2977, 2935, 1873, 1598, 1503, 1442, 1366, 1265, 1216, 1180, 1136, 1121, 1035, 911, 886, 840, 763, 697 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>21</sub>H<sub>25</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 309.1855, found: 309.1862.

For asymmetric synthesis of compound **10a** (12.2 mg, 81% yield)

**SFC Analysis:** 93:7 e.r. [CHIRALPAK<sup>®</sup> IC, 30°C, 5% *i*PrOH, 4.0 mL/min, 100 bar, retention times: 6.0 min (major) and 8.9 min (minor)]

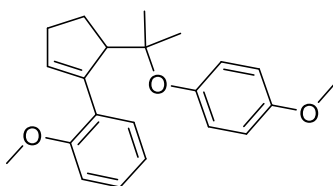
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**1-methoxy-2-(5-(2-(4-methoxyphenoxy)propan-2-yl)cyclopent-1-en-1-yl)benzene 10r**

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**Chemical Formula:** C<sub>22</sub>H<sub>26</sub>O<sub>3</sub>

**Molecular Weight:** 338.4470

(6 mg, 18% yield). Colorless oil; R<sub>f</sub> 0.5 (5% EtOAc /n-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.24-7.16 (m, 2H), 6.89 (t, *J* = 7.4 Hz, 1H), 6.83-6.69 (m, 5H), 5.92 (d, *J* = 1.9 Hz, 1H), 3.83-3.78 (m, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 2.52-2.45 (m, 2H), 2.40-2.25 (m, 2H), 1.11 (s, 3H), 0.87 (s, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 156.9 (C), 155.4 (C), 148.7 (C), 143.4 (C), 133.4 (CH), 129.9 (CH), 129.4 (C), 127.9 (CH), 125.0 (CH), 120.4 (CH), 113.7 (CH), 110.6 (CH), 83.6 (C), 55.8 (CH<sub>3</sub>), 55.5 (CH), 55.2 (CH<sub>3</sub>), 31.6 (CH<sub>2</sub>), 26.9 (CH<sub>2</sub>), 25.0 (CH<sub>3</sub>), 22.9 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 3669, 2972, 2836, 1596, 1578, 1505, 1464, 1265, 1240, 1219, 1124, 1032, 842, 738, 704 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>22</sub>H<sub>26</sub>O<sub>3</sub>Na [M+Na]<sup>+</sup>: 361.1780, found: 361.1766;

For asymmetric synthesis of compound **10r** (6.2 mg, 37% yield)

**SFC Analysis:** 96:4 e.r. [CHIRALPAK® IC, 30°C, 5% *i*PrOH, 4.0 mL/min, 100 bar, retention times: 7.3 min (major) and 11.3 min (minor)]

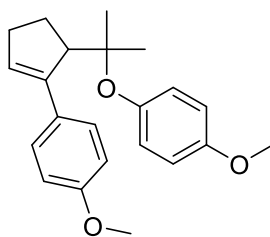
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**1-methoxy-4-(5-(2-(4-methoxyphenoxy)propan-2-yl)cyclopent-1-en-1-yl)benzene 10I**

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**Chemical Formula:** C<sub>22</sub>H<sub>26</sub>O<sub>3</sub>

**Molecular Weight:** 338.4470

(15 mg, 45% yield). Colorless oil, crystal forms at 4°C, mp: 53.8- 54.7 °C; R<sub>f</sub> 0.29 (5 % EtOAc /n-Heptane)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.27 (d, *J* = 6.9 Hz, 2H), 6.80- 6.72 (m, 4H), 5.94 (s, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 3.49 (d, *J* = 9.3 Hz, 1H), 2.56 – 2.39 (m, 3H), 2.25- 2.21 (m, 1H), 1.17 (s, 3H), 0.91 (s, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 158.6 (C), 155.7 (C), 148.6 (C), 145.0 (C), 132.2 (C), 130.8 (CH), 128.1 (2CH), 125.4 (2CH), 113.9 (2CH), 113.5 (2CH), 84.2 (C), 55.6 (CH), 55.3 (CH<sub>3</sub>), 32.4 (CH<sub>2</sub>), 27.9 (CH<sub>2</sub>), 26.4 (CH<sub>3</sub>), 23.4 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub>= 3038, 2975, 2836, 1606, 1502, 1464, 1366, 1292, 1247, 1217, 1177, 1121, 1035, 887, 833, 811, 742, 705 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>22</sub>H<sub>27</sub>O<sub>3</sub>[M+H]<sup>+</sup>: 339.1960, found: 339.1944.

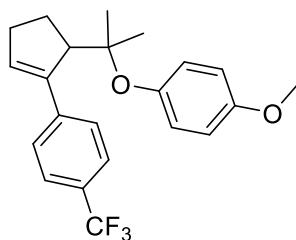
For asymmetric synthesis of compound **10I** (12.1 mg, 72% yield)

**SFC Analysis:** 94:6 e.r. [CHIRALPAK<sup>®</sup> IC, 30°C, 5% *i*PrOH, 4.0 mL/min, 100 bar, retention times: 11.0 min (major) and 16.0 min (minor)]

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**1-methoxy-4-((2-(2-(4-(trifluoromethyl)phenyl)cyclopent-2-en-1-yl)propan-2-yl)oxy)benzene**  
**10t**

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**Chemical Formula:** C<sub>22</sub>H<sub>23</sub>F<sub>3</sub>O<sub>2</sub>

**Molecular Weight:** 376.4192

( mg, % yield). Colorless oil; R<sub>f</sub> 0.55 (5 % EtOAc /n-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.52 (d, *J* = 8.7 Hz, 2H), 7.47 (d, *J* = 8.7 Hz, 2H), 6.78-6.63 (m, 4H), 6.12 (bs, 1H), 3.75 (s, 3H), 3.61-3.53 (m, 1H), 2.63-2.42 (m, 2H), 2.42-2.22 (m, 2H), 1.20 (s, 3H), 0.91 (s, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 155.6 (C), 148.2 (C), 144.5 (C), 143.1 (C), 134.3 (CH), 127.2 (CH), 125.0 (CH), 124.9 (CH), 124.9 (CH), 113.8 (CH), 83.7 (C), 55.5 (CH&CH<sub>3</sub>), 32.4 (CH<sub>2</sub>), 27.7 (CH<sub>2</sub>), 25.1 (CH<sub>3</sub>), 23.9 (CH<sub>3</sub>); **<sup>19</sup>F NMR** (282 MHz, CDCl<sub>3</sub>) δ -62.358

**IR:** ν<sub>max</sub> = 2983, 2934, 1615, 1505, 1466, 1367, 1328, 1265, 1218, 1164, 1123, 1109, 1069, 1038, 840, 737, 704 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>22</sub>H<sub>24</sub>O<sub>2</sub>F<sub>3</sub> [M+H]<sup>+</sup>: 377.1728, found: 377.1745.

For asymmetric synthesis of compound **10t** (12.9 mg, 69% yield)

**SFC Analysis:** 82:18 e.r. [CHIRALPAK<sup>®</sup> IC, 30°C, 5% *i*PrOH, 4.0 mL/min, 100 bar, retention times: 3.0 min (major) and 3.8 min (minor)]

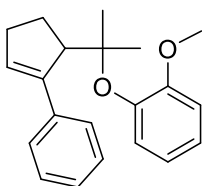
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**1-methoxy-2-((2-(2-phenylcyclopent-2-en-1-yl)propan-2-yl)oxy)benzene 10c**

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**Chemical Formula:** C<sub>22</sub>H<sub>23</sub>F<sub>3</sub>O<sub>2</sub>

**Molecular Weight:** 376.4192

(12.0 mg, 39% yield). Colorless oil; R<sub>f</sub> 0.33 (5% EtOAc /n-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.38-7.32 (m, 2H), 7.28-7.21 (m, 2H), 7.20-7.12 (m, 1H), 7.00 (dt, J = 7.8, 1.8 Hz, 1H), 6.91 (dd, J = 7.9, 1.7 Hz, 1H), 6.84 (dd, J = 8.0, 1.7 Hz, 1H), 6.79 (dt, J = 8.1, 1.7 Hz, 1H), 6.01 (bs, 1H), 3.76 (s, 3H), 3.64 (d, J = 9.4 Hz, 1H), 2.69-2.37 (m, 3H), 2.232-2.17 (m, 1H), 1.15 (s, 3H), 0.91 (s, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 154.5 (C), 145.6 (C), 144.5 (C), 139.6 (C), 132.6 (CH), 128.2 (CH), 127.0 (CH), 125.9 (CH), 124.1 (CH), 120.4 (CH), 112.4 (CH), 85.8 (C), 55.9 (CH), 55.7 (CH<sub>3</sub>), 32.6 (CH<sub>2</sub>), 27.7 (CH<sub>2</sub>), 26.8 (CH<sub>3</sub>), 22.6 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 2977, 2935, 1871, 1745, 1598, 1505, 1464, 1442, 1382, 1366, 1217, 1136, 1121, 1035, 911, 886, 840, 763, 739, 697 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>21</sub>H<sub>24</sub>O<sub>2</sub>Na [M+ Na]<sup>+</sup>: 331.1661, found: 331.1674.

For asymmetric synthesis of compound **10c** (11.6 mg, 77% yield)

**SFC Analysis:** 91:9 e.r. [CHIRALPAK<sup>®</sup> IC, 30°C, 5% *i*PrOH, 4.0 mL/min, 100 bar, retention times: 4.7 min (major) and 5.7 min (minor)]

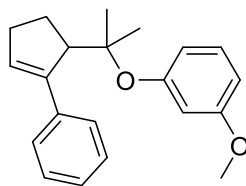
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**1-methoxy-3-((2-(2-phenylcyclopent-2-en-1-yl)propan-2-yl)oxy)benzene 10b**

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**Chemical Formula:** C<sub>21</sub>H<sub>24</sub>O<sub>2</sub>

**Molecular Weight:** 308.4210

(11.3 mg, 31% yield). Colorless oil; R<sub>f</sub> 0.46 (5% EtOAc/n-Heptane)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.37 (d, *J* = 7.5 Hz, 2H), 7.27 (t, *J* = 7.5 Hz, 2H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.10 (t, *J* = 8.2 Hz, 1H), 6.58 (dd, *J* = 8.2, 1.5 Hz, 1H), 6.46 (d, *J* = 8.0 Hz, 1H), 6.30 (bs, 1H), 6.02 (bs, 1H), 3.72 (s, 3H), 3.62 (d, *J* = 9.3 Hz, 1H), 2.58-2.43 (m, 2H), 2.39-2.34 (m, 1H), 2.28-2.20 (m, 1H), 1.26 (s, 3H), 0.99 (s, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 160.2 (C), 156.6 (C), 145.6 (C), 139.6 (C), 132.3 (CH), 129.1 (CH), 128.1 (CH), 127.1 (CH), 126.7 (CH), 116.2 (CH), 109.9 (CH), 108.8 (CH), 84.6 (C), 55.7 (CH), 55.4 (CH<sub>3</sub>), 32.4 (CH<sub>2</sub>), 27.8 (CH<sub>2</sub>), 25.7 (CH<sub>3</sub>), 24.1 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 2978, 2938, 1597, 1587, 1279, 1263, 1195, 1143, 1135, 1119, 1041, 959, 762, 732, 698 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>24</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub>SNa [M+Na]<sup>+</sup>: 331.1661, found: 331.1674;

For asymmetric synthesis of compound **10b** (12.5 mg, 81% yield)

**SFC Analysis:** 88.5:12.5 e.r. [CHIRALPAK<sup>®</sup> AD-H, 30°C, 3% *i*PrOH, 4.0 mL/min, 100 bar, retention times: 6.8 min (major) and 9.1 min (minor)]

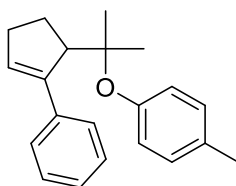
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**1-methyl-4-((2-(2-phenylcyclopent-2-en-1-yl)propan-2-yl)oxy)benzene 10d**

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**Chemical Formula:** C<sub>21</sub>H<sub>24</sub>O

**Molecular Weight:** 292.4220

(18.0 mg, 62% yield). Colorless oil; R<sub>f</sub> 0.45 (5% EtOAc /n-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.36-7.31 (m, 2H), 7.29-7.22 (m, 3H), 6.98 (d, *J* = 8.1 Hz, 2H), 6.68 (d, *J* = 8.1 Hz, 2H), 6.00 (bs, 1H), 3.56 (d, *J* = 9.1 Hz, 1H), 2.60-2.35 (m, 3H), 2.34-2.20 (m, 1H), 2.26 (s, 3H), 1.19 (s, 3H), 0.92 (s, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 152.8 (C), 145.6 (C), 139.6 (C), 132.6 (C), 132.3 (CH), 129.4 (CH), 128.1 (CH), 127.1 (CH), 126.7 (CH), 124.1 (CH), 84.1 (C), 55.52 (CH), 32.5 (CH<sub>2</sub>), 27.8 (CH<sub>2</sub>), 26.2 (CH<sub>3</sub>), 23.6 (CH<sub>3</sub>), 20.9 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 3027, 2978, 1887, 1610, 1506, 1445, 1382, 1366, 1265, 1224, 1136, 1122, 1032, 949, 885, 836, 762, 736, 698 cm<sup>-1</sup>

**HRMS(ESI)** Calcd. For C<sub>14</sub>H<sub>17</sub> [M-OR]<sup>+</sup>: 185.1330, found: 185.1320

For asymmetric synthesis of compound **10d** (14.6 mg, 99% yield)

**SFC Analysis:** 88:12 e.r. [CHIRALPAK<sup>®</sup> IC, 30°C, 5% *i*PrOH, 4.0 mL/min, 100 bar, retention times: 3.4 min (major) and 5.2 min (minor)]

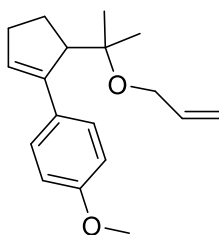
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**1-(5-(2-(allyloxy)propan-2-yl)cyclopent-1-en-1-yl)-4-methoxybenzene 10o**

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**Chemical Formula:** C<sub>18</sub>H<sub>24</sub>O<sub>2</sub>

**Molecular Weight:** 272.3880

(24.0 mg, 88% yield). Colorless oil; R<sub>f</sub> 0.4 (5 % EtOAc /n-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.30-7.20 (m, 2H), 6.87-6.74 (m, 2H), 5.90-5.71 (m, 2H), 5.19 (dq, J = 17.1, 1.5 Hz, 1H), 5.06 (dq, J = 10.2, 1.5 Hz, 1H), 3.90-3.84 (m, 2H), 3.80 (s, 3H), 3.40 (d, J = 9.3 Hz, 1H), 2.48-2.33 (m, 2H), 2.30-2.04 (m, 2H), 1.07 (s, 3H), 0.92 (s, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 158.6 (C), 145.2 (C), 136.4 (CH), 132.3 (C), 130.5 (CH), 128.1 (CH), 115.5 (CH<sub>2</sub>), 113.5 (CH), 78.9 (C), 62.6 (CH<sub>2</sub>), 55.4 (CH<sub>3</sub>), 54.3 (CH), 32.4 (CH<sub>2</sub>), 26.9 (CH<sub>2</sub>), 25.4 (CH<sub>3</sub>), 22.6 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 3452, 2972, 2936, 1728, 1668, 1600, 1510, 1463, 1367, 1246, 1174, 1031, 829, 736, 702 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>15</sub>H<sub>19</sub>O<sub>2</sub> [M-OAllyl]<sup>+</sup>: 231.1385, found: 231.1392

For asymmetric synthesis of compound **10o** (10.9 mg, 80% yield)

**SFC Analysis:** 86:14 e.r. [CHIRALPAK<sup>®</sup> AD-H, 30°C, 2% *i*PrOH, 4.0 mL/min, 100 bar, retention times: 3.9 min (minor) and 4.7 min (major)]



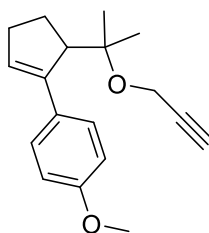
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**1-methoxy-4-(5-(2-(prop-2-yn-1-yloxy)propan-2-yl)cyclopent-1-en-1-yl)benzene 10p**

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**Chemical Formula:** C<sub>18</sub>H<sub>22</sub>O<sub>2</sub>

**Molecular Weight:** 270.3720

(8.0 mg, 30% yield). Colorless oil; R<sub>f</sub> 0.2 (5 % EtOAc /n-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.25 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 5.89-5.83 (m, 1H), 4.04 (d, *J* = 2.4 Hz, 2H), 3.80 (s, 3H), 3.38 (bd, *J* = 9.3 Hz, 1H), 2.46-2.38 (m, 2H), 2.34 (t, *J* = 2.4 Hz, 1H), 2.31-2.02 (m, 2H), 1.09 (s, 3H), 0.93 (s, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 158.6, 144.9, 132.0, 130.7, 128.1, 113.6, 81.9 (C), 80.2 (C), 72.9 (CH), 55.4 (CH), 54.2 (CH), 50.0 (CH<sub>2</sub>), 32.4 (CH<sub>2</sub>), 27.0 (CH<sub>2</sub>), 25.5 (CH<sub>3</sub>), 22.5 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 3286, 2972, 2937, 1729, 1668, 1599, 1510, 1463, 1368, 1244, 1173, 1059, 1031, 831, 735 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>15</sub>H<sub>19</sub>O<sub>2</sub>[M-OPropargyl]<sup>+</sup>: 231.1385, found: 231.1382.

For asymmetric synthesis of compound **10p** (8.0 mg, 59% yield)

**SFC Analysis:** 87:13 e.r. [CHIRALPAK<sup>®</sup> AD-H, 30°C, 3% *i*PrOH, 4.0 mL/min, 100 bar, retention times: 4.2 min (minor) and 5.0 min (major)]

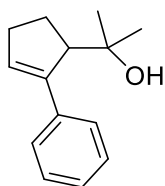
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**2-(2-phenylcyclopent-2-en-1-yl)propan-2-ol 10f**

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**Chemical Formula:** C<sub>14</sub>H<sub>18</sub>O

**Molecular Weight:** 202.2970

(20.0 mg, 99% yield). Colorless oil; R<sub>f</sub> 0.32 (20 % EtOAc /n-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.45-7.36 (m, 2H), 7.35-7.27 (m, 2H), 7.26-7.17 (m, 1H), 6.06-6.01 (m, 1H), 3.36 (bd, *J* = 9.4 Hz, 1H), 2.49-2.42 (m, 2H), 2.27-2.15 (m, 1H), 2.08-1.94 (m, 1H), 1.30 (bs, OH), 1.15 (s, 3H), 1.08 (s, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 145.0 (C), 139.1 (C), 131.9 (CH), 128.5 (CH), 127.2 (CH), 127.0 (CH), 75.2 (C), 56.8 (CH), 32.36 (CH<sub>2</sub>), 28.3 (CH<sub>3</sub>), 27.9 (CH<sub>2</sub>), 27.1 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 3424, 2971, 2931, 1676, 1598, 1493, 1466, 1444, 1371, 1143, 1120, 1031, 951, 917, 865, 843, 809, 762, 696 cm<sup>-1</sup>

**HRMS(ESI)** Calcd. For C<sub>14</sub>H<sub>17</sub> [M-OH]<sup>+</sup>: 185.1330, found: 185.1322.

For asymmetric synthesis of compound **10f** (9.9 mg, 98% yield)

**SFC Analysis:** 90:10 e.r. [CHIRALPAK<sup>®</sup> IA, 30°C, 5% *i*PrOH, 4.0 mL/min, 100 bar, retention times: 4.6 min (major) and 7.1 min (minor)]

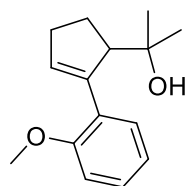
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**2-(2-(2-methoxyphenyl)cyclopent-2-en-1-yl)propan-2-ol 10s**

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**Chemical Formula:** C<sub>15</sub>H<sub>20</sub>O<sub>2</sub>

**Molecular Weight:** 232.3230

(14 mg, 61% yield). Light yellow oil

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.26-7.16 (m, 1H), 7.20 (d, *J* = 7.5 Hz, 1H), 6.92 (td, *J* = 7.5, 0.9 Hz, 1H), 6.85 (d, *J* = 8.1 Hz, 1H), 5.90 (dd, *J* = 4.0, 2.4 Hz, 1H), 3.84 (s, 3H), 3.52-3.46 (m, 1H), 2.53-2.33 (m, 2H), 2.26-2.11 (m, 1H), 2.02-1.88 (m, 1H), 1.63 (s, OH), 1.07 (s, 3H), 1.03 (s, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 156.5 (C), 142.7 (C), 133.5 (CH), 129.8 (CH), 129.1 (C), 128.3 (CH), 120.8 (CH), 110.9 (CH), 74.2 (C), 57.8 (CH), 55.4, 31.6 (CH<sub>3</sub>), 29.7 (CH<sub>2</sub>), 27.8 (CH<sub>3</sub>), 27.0 (CH<sub>2</sub>), 26.5 (CH<sub>3</sub>)

**IR:**  $\nu_{\max}$  = 3442, 2933, 1596, 1578, 1488, 1463, 1435, 1266, 1237, 1179, 1152, 1115, 1027, 948, 920, 785, 749, 740, 703 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>15</sub>H<sub>19</sub>O<sub>3</sub> [M-OH]<sup>+</sup>: 215.1436, found: 215.1430.

For asymmetric synthesis of compound **10s** (7.1 mg, 61% yield)

**SFC Analysis:** 97:3 e.r. [CHIRALPAK<sup>®</sup> IB, 30°C, 2% *i*PrOH, 4.0 mL/min, 100 bar, retention times: 5.0 min (major) and 5.5 min (minor)]

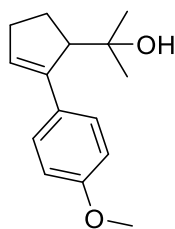
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**2-(2-(4-methoxyphenyl)cyclopent-2-en-1-yl)propan-2-ol 10m**

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**Chemical Formula:** C<sub>15</sub>H<sub>20</sub>O<sub>2</sub>

**Molecular Weight:** 232.3230

(18.0 mg, 78% yield). Colorless oil; R<sub>f</sub> 0.34 (25 % EtOAc /n-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.34 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 5.95 (bs, 1H), 3.80 (s, 3H), 3.30 (d, *J* = 9.4 Hz, 1H), 2.48-2.38 (m, 2H), 2.21-2.14 (m, 1H), 2.07-1.89 (m, 1H), 1.59 (bs, OH), 1.16 (s, 3H), 1.07 (s, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 144.4 (C), 131.6 (C), 130.3 (CH), 128.2 (CH), 114.0 (CH), 75.2 (C), 56.8 (CH), 55.4 (CH<sub>3</sub>), 32.3 (CH<sub>2</sub>), 28.4 (CH<sub>3</sub>), 28.0 (CH<sub>2</sub>), 26.9 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 3419, 2969, 1739, 1605, 1510, 1464, 1293, 1250, 1178, 1034, 952, 847, 830, 805, 736 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>15</sub>H<sub>19</sub>O [M-OH]<sup>+</sup>: 215.1436, found: 215.1434.

For asymmetric synthesis of compound **10m** (9.5 mg, 75% yield)

**SFC Analysis:** 95:5 e.r. [CHIRALPAK<sup>®</sup> IC, 30°C, 2% *i*PrOH, 4.0 mL/min, 100 bar, retention times: 23.8 min (minor) and 25.7 min (major)]

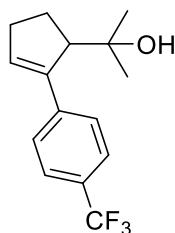
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**2-(2-(4-(trifluoromethyl)phenyl)cyclopent-2-en-1-yl)propan-2-ol 10u**

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**Chemical Formula:** C<sub>15</sub>H<sub>17</sub>F<sub>3</sub>O

**Molecular Weight:** 270.2952

(22 mg, 81% yield). White solid, crystal slowly, mp: 67.2- 69.8 °C; R<sub>f</sub> 0.12 (5% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.57 (d, *J* = 8.0 Hz, 2H), 7.52 (d, *J* = 8.2 Hz, 2H), 6.14 (s, 1H), 3.35 (d, *J* = 9.5 Hz, 1H), 2.56-2.39 (m, 2H), 2.25-2.18 (m, 1H), 2.11-1.98 (m, 1H), 1.15 (s, 3H), 1.07 (s, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 134.3 (CH), 127.2 (CH), 125.4 (CH), 75.1 (C), 56.8 (CH), 32.5 (CH<sub>2</sub>), 28.5 (CH<sub>3</sub>), 28.0 (CH<sub>2</sub>), 27.4 (CH<sub>3</sub>); **<sup>19</sup>F NMR** (282 MHz, CDCl<sub>3</sub>) δ -62.479

**IR:** ν<sub>max</sub> = 3050, 2964, 2930, 1598, 1544, 1485, 1464, 1362, 1329, 1265, 1224, 1152, 1106, 1019, 993, 816, 760, 735, 698 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>15</sub>H<sub>16</sub>F<sub>3</sub> [M-OH]<sup>+</sup>: 253.1204, found: 253.1203.

For asymmetric synthesis of compound **10u** (12.6 mg, 93% yield)

**SFC Analysis:** 82:18 e.r. [CHIRALPAK<sup>®</sup> IA, 30°C, 5% *i*PrOH, 4.0 mL/min, 100 bar, retention times: 3.2 min (major) and 5.1 min (minor)].

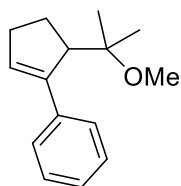
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(5-(2-methoxypropan-2-yl)cyclopent-1-en-1-yl)benzene 10g

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**Chemical Formula:** C<sub>15</sub>H<sub>20</sub>O

**Molecular Weight:** 216.3240

(20.0 mg, 93% yield). Colorless oil; R<sub>f</sub> 0.36 (5% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.36- 7.32 (m, 2H), 7.29 (dd, *J* = 10.3, 4.8 Hz, 2H), 7.21 (dd, *J* = 10.2, 4.3 Hz, 1H), 5.94 (s, 1H), 3.44 (d, *J* = 9.4 Hz, 1H), 3.16 (s, 3H), 2.45 (ddd, *J* = 7.6, 6.2, 2.4 Hz, 2H), 2.26- 2.19 (m, 1H), 2.13 (dq, *J* = 13.5, 9.3 Hz, 1H), 1.05 (s, 3H), 0.88 (s, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 145.8 (C), 139.6 (C), 131.9 (CH), 128.1 (CH), 127.0 (CH), 126.7 (CH), 78.4 (C), 53.8 (CH), 49.0 (CH<sub>3</sub>), 32.5 (CH<sub>2</sub>), 26.7 (CH<sub>2</sub>), 24.8 (CH<sub>3</sub>), 22.1 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 2975, 2939, 1469, 1444, 1381, 1365, 1265, 1129, 1075, 909, 825, 797, 762, 735, 698 cm<sup>-1</sup>

**HRMS(ESI)** Calcd. For C<sub>14</sub>H<sub>17</sub> [M-OMe]<sup>+</sup>:185.1330, found: 185.1369

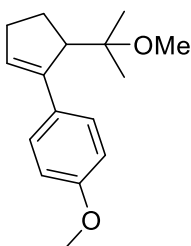
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**1-methoxy-4-(5-(2-methoxypropan-2-yl)cyclopent-1-en-1-yl)benzene 10n**

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**Chemical Formula:** C<sub>16</sub>H<sub>22</sub>O<sub>2</sub>

**Molecular Weight:** 246.3500

(20.0 mg, 99% yield). Colorless oil; R<sub>f</sub> 0.32 (20 % EtOAc /n-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.25 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 5.85 (bs, 1H), 3.80 (s, 3H), 3.37 (d, *J* = 9.0 Hz, 1H), 3.16 (s, 3H), 2.44-2.37 (m, 2H), 2.26-2.01 (m, 2H), 1.03 (s, 3H), 0.88 (s, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 145.0 (C), 139.1 (C), 131.9 (CH), 128.5 (CH), 127.2 (CH), 127.0 (CH), 75.2 (C), 56.8 (CH), 32.36 (CH<sub>2</sub>), 28.3 (CH<sub>3</sub>), 27.9 (CH<sub>2</sub>), 27.1 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 3424, 2971, 2931, 1676, 1598, 1493, 1466, 1444, 1371, 1143, 1120, 1031, 951, 917, 865, 843, 809, 762, 696 cm<sup>-1</sup>

**HRMS(ESI)** Calcd. For C<sub>14</sub>H<sub>17</sub> [M-OH]<sup>+</sup>: 185.1330, found: 185.1322.

For asymmetric synthesis of compound **10f** (9.9 mg, 98% yield)

**SFC Analysis:** 90:10 e.r. [CHIRALPAK<sup>®</sup> IA, 30°C, 5% *i*PrOH, 4.0 mL/min, 100 bar, retention times: 4.6 min (major) and 7.1 min (minor)]

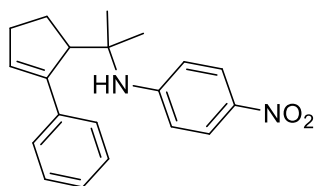
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**4-nitro-N-(2-(5-phenylcyclopent-1-en-1-yl)propan-2-yl)aniline 10j**

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**Chemical Formula:** C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub>

**Molecular Weight:** 322.4080

(32 mg, 99% yield). Yellow oil; R<sub>f</sub> 0.27 (15% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.95 (d, *J* = 9.3 Hz, 2H), 7.26-7.15 (m, 5H), 6.28 (d, *J* = 9.3 Hz, 2H), 6.04-5.91 (m, 1H), 4.37 (bs, NH), 3.77 (d, *J* = 9.6 Hz, 1H), 2.53-2.42 (m, 2H), 2.36-2.14 (m, 1H), 2.04-1.93 (m, 1H), 1.42 (s, 3H), 1.22 (s, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 179.8 (C), 152.2 (C), 145.2 (C), 139.3 (C), 132.8 (CH), 128.5 (CH), 127.2 (CH), 126.8 (CH), 126.2 (CH), 113.0 (CH), 58.5 (C), 54.2 (CH), 32.3 (CH<sub>2</sub>), 27.3 (CH<sub>2</sub>), 26.4 (CH<sub>3</sub>), 25.2 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 3409, 3379, 2981, 2850, 1595, 1504, 1474, 1317, 1304, 1266, 1184, 1110, 831, 734, 698, 673 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>20</sub>H<sub>23</sub>N<sub>2</sub>O<sub>2</sub>[M+H]<sup>+</sup>: 323.1760, found: 323.1738

For asymmetric synthesis of compound **10j** (10.7 mg, 66% yield)

**SFC Analysis:** 89:11 e.r. [CHIRALPAK<sup>®</sup> IB, 30°C, 10% MeOH, 4.0 mL/min, 100 bar, retention times: 6.9 min (major) and 7.8 min (minor)]



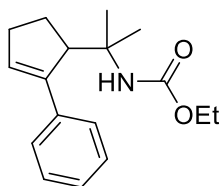
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**Ethyl (2-(2-phenylcyclopent-2-en-1-yl)propan-2-yl)carbamate 10k**

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**Chemical Formula:** C<sub>17</sub>H<sub>23</sub>NO<sub>2</sub>

**Molecular Weight:** 273.3760

(20.5 mg, 75% yield). Yellow oil; R<sub>f</sub> 0.3 (5% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.26-7.06 (m, 5H), 5.87-5.80 (m, 1H), 4.25 (bs, NH), 3.93-3.70 (m, 3H), 2.34-2.16 (m, 2H), 2.19-2.01 (m, 1H), 1.91-1.79 (m, 1H), 1.19 (s, 3H), 1.03 (t, *J* = 7.0 Hz, 3H), 0.98 (s, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 145.8 (C), 139.7 (C), 132.2 (CH), 128.3 (CH), 126.8 (CH), 126.7 (CH), 56.0 (CH<sub>2</sub>), 56.8 (C), 52.9 (CH), 32.3 (CH<sub>2</sub>), 27.6 (CH<sub>2</sub>), 25.4 (CH<sub>3</sub>), 14.7 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 3430, 3345, 2978, 2931, 1711, 1506, 1386, 1366, 1263, 1241, 1215, 1165, 1088, 1034, 764, 736, 701 cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>17</sub>H<sub>24</sub>NO<sub>2</sub>[M+H]<sup>+</sup>: 274.1807, found: 274.1804

For asymmetric synthesis of compound **10k** (11 mg, 81% yield)

**SFC Analysis:** 93:7 e.r. [CHIRALPAK<sup>®</sup> AD-H, 30°C, 2% *i*PrOH, 4.0 mL/min, 100 bar, retention times: 6.0 min (major) and 7.0 min (minor)]

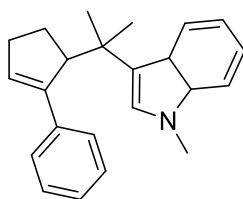
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**1-methyl-3-(2-(2-phenylcyclopent-2-en-1-yl)propan-2-yl)-3a,7a-dihydro-1H-indole 10i**

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**Chemical Formula:** C<sub>23</sub>H<sub>27</sub>N

**Molecular Weight:** 317.4760

(25.0 mg, 79% yield). Colorless oil; R<sub>f</sub> 0.26 (5% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.90 (d, *J* = 7.9 Hz, 1H), 7.24-7.18 (m, 2H), 7.15-7.02 (m, 6H), 6.45 (s, 1H), 5.92-5.87 (m, 1H), 4.02 (dd, *J* = 9.3, 1.3 Hz, 1H), 3.54 (s, 3H), 2.41-2.32 (m, 2H), 2.12-1.88 (m, 2H), 1.43 (s, 3H), 1.19 (s, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 146.9 (C), 140.2 (C), 137.8 (C), 131.2 (CH), 127.5 (CH), 126.6 (CH), 125.9 (CH), 125.8 (CH), 125.8 (C), 124.5 (C), 121.6 (CH), 120.9 (CH), 118.2 (CH), 109.3 (CH), 54.1 (CH), 39.7 (C), 32.5 (CH<sub>2</sub>), 32.4 (CH<sub>3</sub>), 28.3 (CH<sub>2</sub>), 27.2 (CH<sub>3</sub>), 25.3 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub>=3050, 2964, 2932, 2847, 2302, 1872, 1687, 1485, 1362, 1329, 1265, 1152, 1106, 1019, 993, 816, 760, 733, 697, 733, 697, 662cm<sup>-1</sup>

**HRMS** (ESI) Calcd. For C<sub>22</sub>H<sub>24</sub>N[M+H]<sup>+</sup>: 302.1909, found: 302.1911

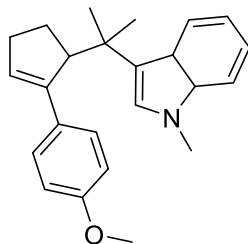
For asymmetric synthesis of compound **10i** (12.7 mg, 84% yield)

**SFC Analysis:** 92.5:7.5 e.r. [CHIRALPAK<sup>®</sup> AD-H, 30°C, 3% *i*PrOH, 4.0 mL/min, 100 bar, retention times: 7.0 min (major) and 8.1 min (minor)]

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**3-(2-(2-(4-methoxyphenyl)cyclopent-2-en-1-yl)propan-2-yl)-1-methyl-3a,7a-dihydro-1H-indole 10q**

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**Chemical Formula:** C<sub>24</sub>H<sub>29</sub>NO

**Molecular Weight:** 347.5020

(26.0 mg, 82% yield). Yellow oil; R<sub>f</sub> 0.4 (5% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.89 (d, *J* = 7.8 Hz, 1H), 7.23-7.18 (m, 2H), 7.15-7.08 (m, 1H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.61 (d, *J* = 8.0 Hz, 2H), 6.47 (s, 1H), 5.82 (bs, 1H), 3.95 (d, *J* = 8.9 Hz, 1H), 3.77 (s, 3H), 3.56 (s, 3H), 2.44-2.25 (m, 2H), 2.10-1.87 (m, 2H), 1.41 (s, 3H), 1.18 (s, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 129.8 (CH), 129.2 (C), 127.7 (CH), 125.9 (CH), 121.6 (CH), 121.0 (CH), 118.2 (CH), 112.9 (CH), 109.3 (CH), 55.4 (CH<sub>3</sub>), 54.1 (CH), 32.4 (CH<sub>3</sub>, CH<sub>2</sub>), 29.9 (C), 28.3 (CH<sub>2</sub>), 27.3(CH<sub>3</sub>), 25.4(CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 2962, 2932, 2253, 1685, 1606, 1509, 1465, 1328, 1292, 1248, 1177, 1152, 1106, 1036, 906, 832, 810, 732 cm<sup>-1</sup>

**HRMS(ESI) Calcd.** HRMS(ESI) Calcd. For C<sub>24</sub>H<sub>26</sub>NO [M-H]<sup>+</sup>: 344.2014, found: 344.2007

For asymmetric synthesis of compound **10q** (14.6 mg, 84% yield)

**SFC Analysis:** 92.5:7.5 e.r. [CHIRALPAK<sup>®</sup> IA, 30°C, 5% *i*PrOH, 4.0 mL/min, 100 bar, retention times: 8.6 min (minor) and 10.5 min (major)]

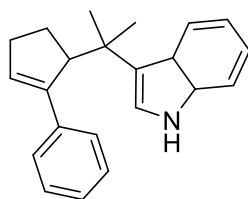
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**3-(2-(2-phenylcyclopent-2-en-1-yl)propan-2-yl)-3a,7a-dihydro-1H-indole 10h**

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**Chemical Formula:** C<sub>22</sub>H<sub>25</sub>N

**Molecular Weight:** 303.4490

(20.0 mg, 93% yield). Colorless oil; R<sub>f</sub> 0.5 (20% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.98 (d, *J* = 7.6 Hz, 1H), 7.73 (bs, NH), 7.35 (dd, *J* = 6.9, 1.2 Hz, 1H), 7.29-7.16 (m, 7H), 6.77 (d, *J* = 2.4 Hz, 1H), 5.97 (bs, 1H), 4.09 (d, *J* = 9.2 Hz, 1H), 2.42-2.35 (m, 2H), 2.17-1.88 (m, 2H), 1.44 (s, 3H), 1.24 (s, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 146.7 (C), 140.3 (C), 137.3 (C), 131.5 (CH), 127.8 (CH<sub>2</sub>), 126.7 (CH<sub>2</sub>), 126.2 (CH), 121.6 (CH), 121.5 (CH), 120.7 (CH), 118.9 (CH), 111.4 (CH), 53.7 (CH), 34.0 (C), 32.5 (CH<sub>2</sub>), 32.0 (C), 28.5 (CH<sub>2</sub>), 28.0 (CH<sub>2</sub>), 24.8 (CH<sub>3</sub>), 22.8 (CH<sub>3</sub>), 14.3 (C)

**IR:** ν<sub>max</sub> = 3424, 3054, 2966, 2849, 1619, 1459, 1416, 1383, 1363, 1335, 1265, 1103, 1017, 896, 815, 737, 700 cm<sup>-1</sup>

**HRMS(ESI)** Calcd. For C<sub>22</sub>H<sub>24</sub>N[M+H]<sup>+</sup>: 302.1909, found: 302.1907

For asymmetric synthesis of compound **10h** (11.5 mg, 78% yield)

**SFC Analysis:** 88:12 e.r. [CHIRALPAK<sup>®</sup> IA, 30°C, 10% *i*PrOH, 4.0 mL/min, 100 bar, retention times: 10.5 min (minor) and 13.0 min (major)]

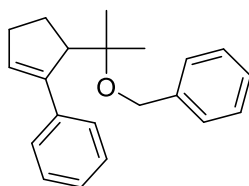
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**(5-(2-(benzyloxy)propan-2-yl)cyclopent-1-en-1-yl)benzene 10e**

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**Chemical Formula:** C<sub>21</sub>H<sub>24</sub>O

**Molecular Weight:** 292.4220

(29.0 mg, 99% yield). Colorless oil; R<sub>f</sub> 0.5 (5% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.37-7.31 (m, 2H), 7.31-7.14 (m, 8H), 5.94 (bs, 1H), 4.39 (s, 2H), 3.53 (d, *J* = 8.7 Hz, 1H), 2.51-2.40 (m, 2H), 2.39-2.25 (m, 1H), 2.16 (dq, *J* = 13.5, 9.3 Hz, 1H), 1.14 (s, 3H), 1.00 (s, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 145.8 (C), 134.0 (C), 139.7 (C), 132.0 (CH), 128.3 (CH), 128.2 (CH), 127.4 (CH), 127.1 (CH), 126.7 (CH), 79.2 (C), 63.6 (CH<sub>2</sub>), 54.6 (CH), 32.6 (CH<sub>2</sub>), 27.1 (CH<sub>2</sub>), 25.0 (CH<sub>3</sub>), 22.8 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 3342, 2975, 2898, 1706, 1599, 1494, 1452, 1385, 1365, 1265, 1145, 1062, 1027, 910, 733, 696 cm<sup>-1</sup>

**HRMS(ESI)** Calcd. For C<sub>21</sub>H<sub>24</sub>ONa[M+Na]<sup>+</sup>: 315.1721, found: 315.1725

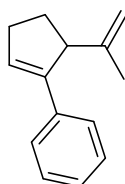
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**(5-(prop-1-en-2-yl)cyclopent-1-en-1-yl)benzene 11a**

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**Chemical Formula:** C<sub>14</sub>H<sub>16</sub>

**Molecular Weight:** 184.2820

Colorless oil; R<sub>f</sub> 0.74 (5% EtOAc/*n*-Heptane)

**<sup>1</sup>H NMR**<sup>122</sup> (300 MHz, CDCl<sub>3</sub>) δ 7.46 (d, *J* = 7.4 Hz, 2H), 7.26 (dt, *J* = 26.3, 6.9 Hz, 3H), 6.30 (s, 1H), 4.81 (s, 1H), 4.75 (s, 1H), 3.81 (d, *J* = 8.8 Hz, 1H), 2.61- 2.42 (m, 2H), 2.37- 2.24 (m, 1H), 1.92- 1.86 (m, 1H), 1.67 (s, 3H).

<sup>122</sup> Speck, K.; Karaghiosoff, K.; Magauer, K. *Org. Lett.*, **2015**, *17*, 1982.

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## **Chapter 4:**

# **Gold(I)-catalyzed enantioselective 1,6-enyne cyclization/intramolecular nucleophilic addition process**

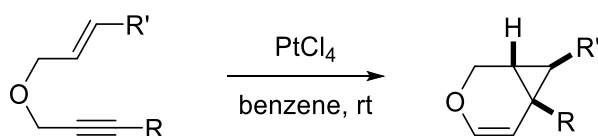
## 4.1 Transition metal catalyzed cyclization of 1,6-enyne substrates

### 4.1.1 Preliminary studies in 1,6-enyne cyclization process

The cyclization of 1,6-enyne derivatives can be achieved through a wide range of transition metal catalysts, such as palladium, rhodium, platinum, iridium or gold.<sup>123</sup>

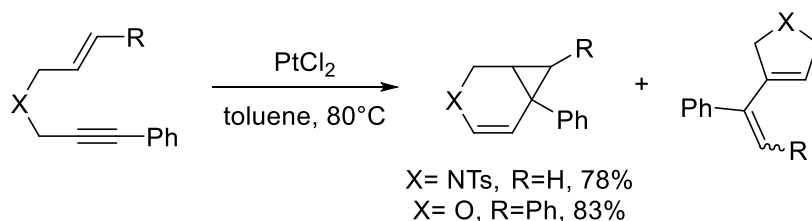
This introduction will include some model examples of transition metal catalyzed 1,6-enyne cyclization reactions, including asymmetric versions, catalyzed by platinum and gold.

In 1995, Blum reported the formation of bicycloheptene derivatives via cycloisomerization of 1,6-enynes.<sup>124</sup> This kind of transformations are intended as rearrangements of polyunsaturated substrates by which carbon-carbon bonds are formed and at least one degree of unsaturation is consumed to make a cyclic product. Normally in such process, no loss or gain of any atom should take place. In this pioneer work, it was observed that allylic propargylic ethers could be transformed into 3-oxabicyclo[4.1.0]hept-4-enes by cycloisomerization, in presence of  $\text{PtCl}_4$  (Scheme IV-1).



Scheme IV-1. Initial Pt-catalyzed 1,6-enyne cycloisomerization

Related study was reported by Fürstner in 2000.<sup>125</sup> This work can be treated as the advanced version of the original work, by improving the reaction conditions and detailing more about the possible different reactivities in this transformation. They noticed that the  $\text{PtCl}_2$ -catalyzed cycloisomerization of 1,6-enynes displaying heteroelements (O, NTs) in the chain tethering the alkene and the alkyne moieties leads to bicyclo[4.1.0] heptene derivatives in good yields. Another product can also be formed, such as the vinylcyclopentene shown in Scheme IV-2. At the same time, Echavarren described additional examples of enynes cycloisomerizations promoted by platinum chloride.<sup>126</sup>



Scheme IV-2.  $\text{Pt}_2\text{Cl}$ -catalyzed 1,6-enyne cycloisomerization

To have a better understanding of the mechanism of this transformation, several groups

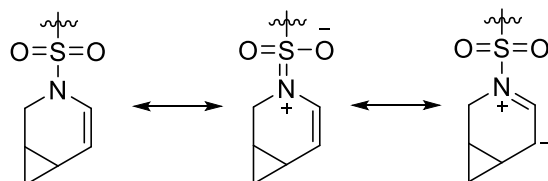
<sup>123</sup> Marinetti, A.; Jullien, H.; Voituriez, A. *Chem. Soc. Rev.* **2012**, *41*, 4884.

<sup>124</sup> Blum, J.; Beer-Kraft, H.; Badrieh, Y. *J. Org. Chem.* **1995**, *60*, 5567.

<sup>125</sup> Fürstner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2000**, *122*, 6785.

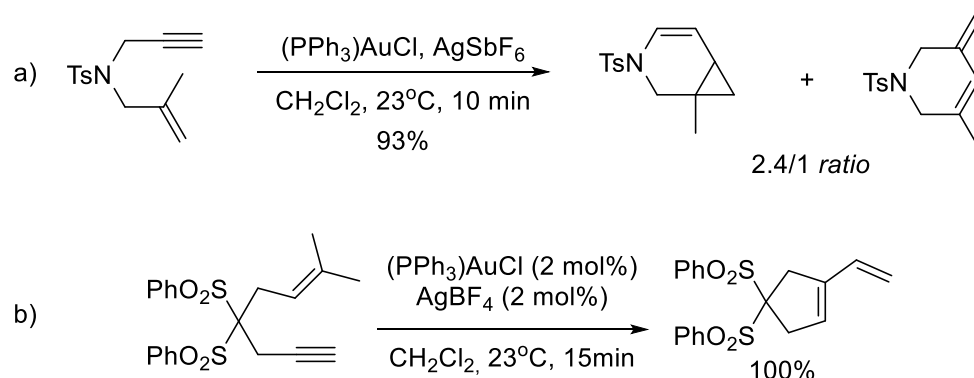
<sup>126</sup> Méndez, M.; Muñoz, M. P.; Echavarren, A. M. *J. Am. Chem. Soc.* **2000**, *122*, 11549.

including Soriano, Gandon and Fensterbank carried out independently the corresponding DFT calculation.<sup>127</sup> Interestingly, the presence of heteroatoms, such as the *N*-tosyl group, could induce stabilization of the final product by delocalization of the lone ion pair (*Scheme IV-3*).



*Scheme IV-3. Stabilization of the product with the N-tosyl group*

Even more interestingly in the framework of my PhD work, Echavarren and coworkers investigated in 2004 the first gold-catalyzed cycloisomerization of 1,6-enynes, bearing an *N*-tosyl group in the tethered chain, by using cationic gold catalyst, formed *in situ* from  $(\text{PPh}_3)\text{AuCl}$  and  $\text{AgSbF}_6$ .<sup>128</sup> These reactions gave aza-bicycloheptene derivatives *via 6-endo-dig* pathway (*Scheme IV-4-a*). The concomitant formation of a 1,3-diene was observed, coming from a different skeletal rearrangement (*Scheme IV-4-a* and *b*). DFT calculation showed that, compared to [Pt], [Pd] and  $\text{AuCl}_3$  catalysts, cationic Au(I)-catalyst furnished the highest activity in the endocyclic rearrangement process of 1,6-enyne substrates.



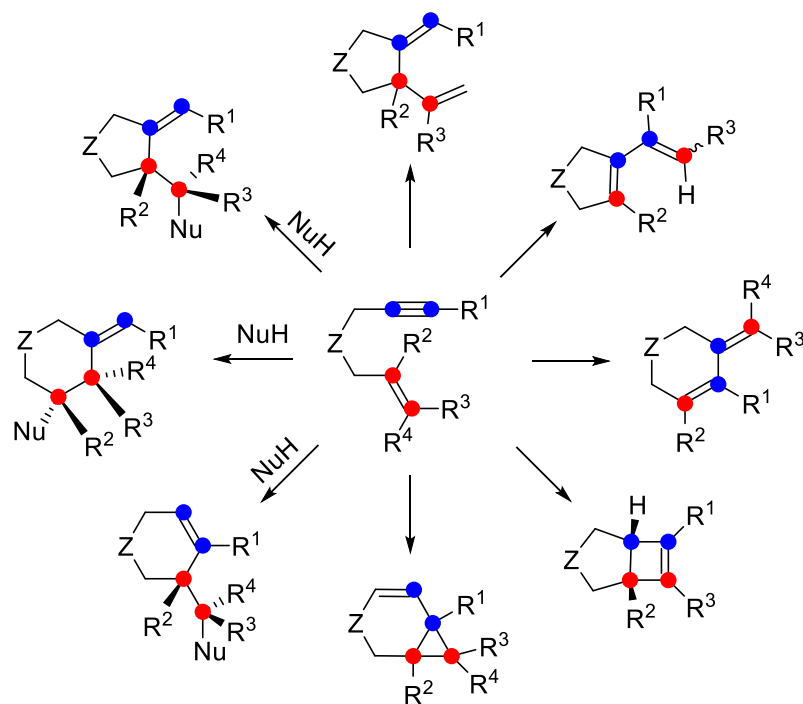
*Scheme IV-4. First Au(I)-catalyzed 1,6-enyne cycloisomerization*

Since then, transition metal promoted 1,6-enyne cyclizations have been widely developed. Those transformations provide a variety of reactivity toward the synthesis of a library of valuable molecules. As a general scheme, we can see hereafter the structural possibilities which are available from simple 1,6-enyne substrates (*Scheme IV-4*).

<sup>127</sup> a) Soriano, E.; Ballesteros, P.; Marco-Contelles, J. *J. Org. Chem.* **2004**, *69*, 8018. b) Gimbert, Y.; Fensterbank, L.; Gandon, V.; Goddard, J.-P.; Lesage, D. *Organometallics* **2013**, *32*, 374. c) Baumgarten, S.; Lesage, D.; Gandon, V.; Goddard, J.-P.; Malacria, M.; Tabet, J.-C.; Gimbert, Y.; Fensterbank, L. *ChemCatChem* **2009**, *1*, 138.

<sup>128</sup> Nieto-Oberhuber, C.; Munoz, M. P.; Bunuel, E.; Nevado, C.; Cardenas, D. J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2402.





Scheme IV-4. Possible transformations from 1,6-enyne substrates

Among enyne cycloisomerization transformations, 1,6-enyne has been the most studied substrate.<sup>129</sup> Cyclopentyl-, cyclohexyl- and bicyclic cyclopropyl derivatives, especially nitrogen-containing ones, formed in those reactions are widely present in alkaloids. Alkaloids are natural products and many possess valuable bioactivity and pharmaceutical activity.<sup>130</sup> Therefore, it is quite understandable to develop asymmetric catalysis methodologies, by manipulating chiral transition metal catalysts, for the synthesis of enantioenriched nitrogen-containing polycycles.<sup>131</sup> These transformations have been carried out under Ir, Pt, Au and Rh catalysis, by using bidentate as well as monodentate chiral phosphines as ligands. In the next few examples, we will focus on the asymmetric gold(I)-catalyzed 1,6-enyne cycloisomerizations.

#### 4.1.2 Enantioselective Au(I)-catalyzed 1,6-enyne cycloisomerisations

Several groups developed the enantioselective version of the cycloisomerization of *N*-tosyl and oxygen-tethered 1,6-enynes. In 2009, Michelet used a bidentate chiral phosphine ligand, with a BIPHEP backbone, for these enantioselective transformations.<sup>132</sup> The corresponding products were obtained in good yields and up to 98% *ee* (Scheme IV-5-a). For the same reaction, Fürstner's team developed new phosphoramidite-gold(I) complexes to promote the formation of the products in good yields and excellent *ees* (Scheme IV-5-b).<sup>133</sup>

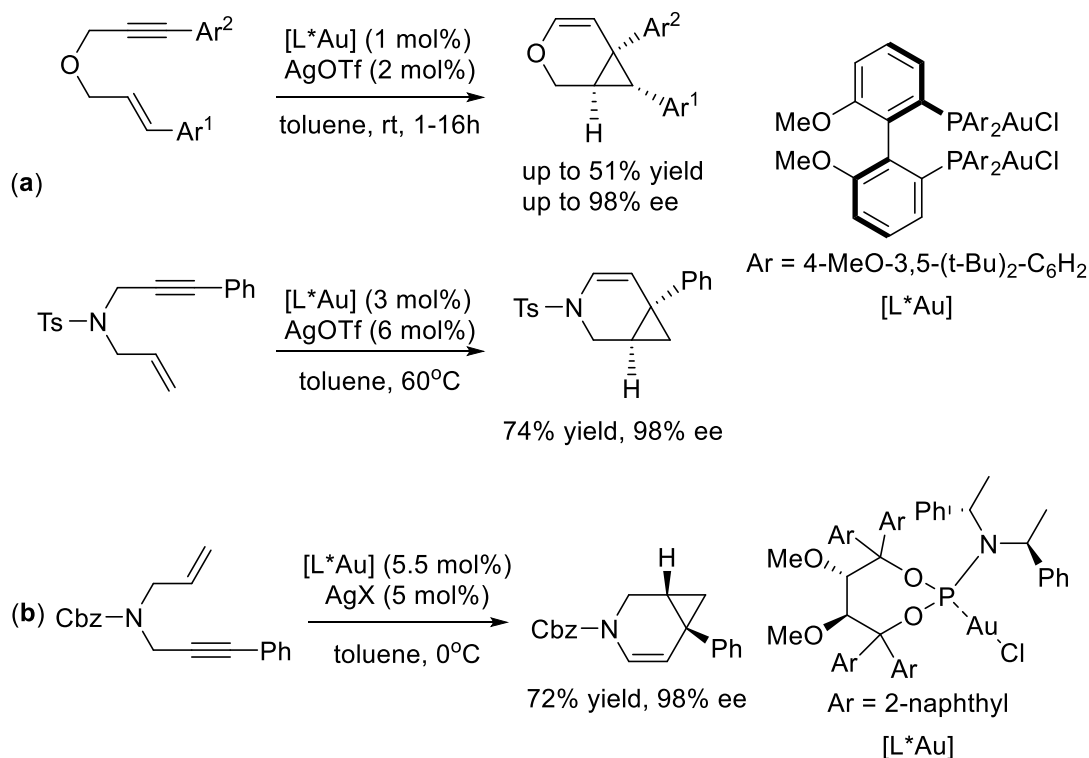
<sup>129</sup> a) Marinetti, A.; Jullien, H.; Voituriez, A. *Chem. Soc. Rev.* **2012**, *41*, 4884. b) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813.

<sup>130</sup> a) Michael, J. P. *Nat. Prod. Rep.* **2003**, *20*, 458. b) Gul, W.; Hamann, M. T. *Life Sci.* **2005**, *78*, 442.

<sup>131</sup> Chao, C. M.; Beltrami, D.; Toullec, P. Y.; Michelet, V. *Chem. Commun.* **2009**, 6988.

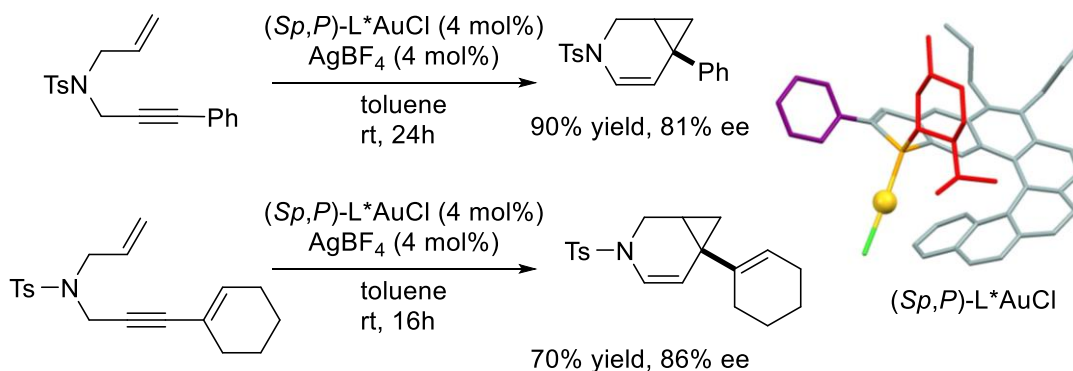
<sup>132</sup> Pradal, A.; Chao, C. M.; Toullec, P. Y.; Michelet, V. *Beilstein J. Org. Chem.* **2011**, *7*, 1021.

<sup>133</sup> Teller, H.; Corbet, M.; Mantilli, L.; Gopakumar, G.; Goddard, R.; Thiel, W.; Fürstner, A. *J. Am. Chem. Soc.* **2012**, *134*, 15331.



Scheme IV-5. Asymmetric 1,6-enyne cycloisomerizations

More recently, our group designed a series of phosphahelicenes, which afforded highly efficient gold(I) catalysts for cycloisomerization reactions. High catalytic activity and good enantiomeric excesses were obtained in the enantioselective cycloisomerization of, notably, *N*-tethered 1,6-enynes (Scheme IV-6).<sup>134</sup>

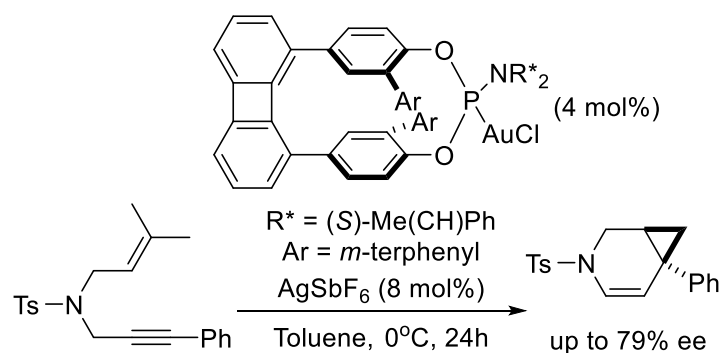


Scheme IV-6. Phosphahelicenes applied in 1,6-enyne cycloisomerization

Besides, our group also developed a new family of paracyclophane-phosphoramidite ligands, possessing planar chirality, and they used them in 1,6-enyne cycloisomerizations.<sup>135</sup> The corresponding 3-tosyl-3-azabicyclo[4.1.0]heptene derivative have been obtained in excellent yields and up to 79% ee (Scheme IV-7).

<sup>134</sup> Aillard, P.; Voituriez, A.; Dova, D.; Caeteruccio, S.; Licandro, E.; Marinetti, A. *Chem. Eur. J.* **2014**, *20*, 12373.

<sup>135</sup> Wu, Z.; Isaac, K.; Retailleau, P.; Betzer, J. F.; Voituriez, A.; Marinetti, A. *Chem. Eur. J.* **2016**, *22*, 3278.

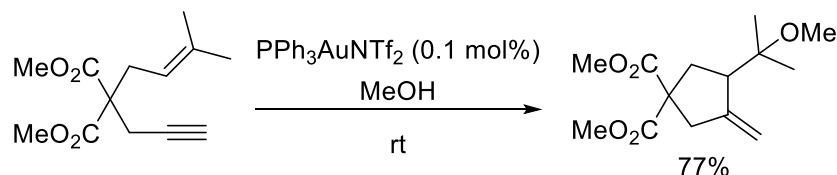


*Scheme IV-7. Planar chiral ligands in enantioselective reaction of 1,6-enyne*

Beside the reactions involving simple skeletal rearrangement of 1,6-enyne substrates in presence of gold catalysts, other transformations were developed thanks to the presence of other nucleophiles. In this case, we do not continue to call these reactions “cycloisomerization” but more simply “cyclization”, with addition of either an external or an internal nucleophile.

#### 4.1.3 Au(I)-catalyzed 1,6-enyne cyclization/external nucleophilic addition process

In the 1,6-enyne cyclization process, when an external nucleophile is introduced in the reaction flask, the carbocation intermediate could be trapped. For example, in Gagosz’s team, by using methanol as solvent in presence of polyunsaturated substrate, the reaction could lead to the methoxycyclization of the substrate, in presence of the cationic gold(I) complex. Even treated with only 0.1 mol% [ $\text{PPh}_3\text{AuNTf}_2$ ] (also call as the “Gagosz’s catalyst), quite good reactivity could be obtained (*Scheme-IV-8*).<sup>136</sup> The same reactivity was also highlighted by Echavarren.<sup>137</sup>



*Scheme IV-8. Cyclization in the presence of methanol*

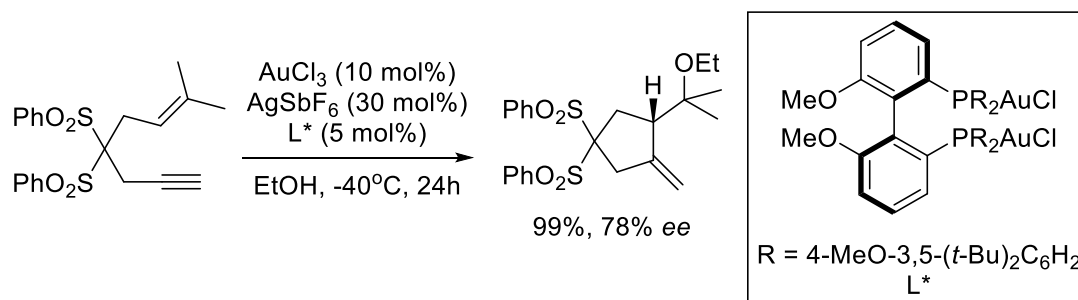
Besides, the addition of carbonated nucleophiles could be achieved in this transformation. In 2006, Michelet’s team published the addition of electron-rich aromatic compounds as nucleophiles in gold(I)-catalyzed 1,6-enyne cycloisomerizations (*Scheme-IV-9-a*).<sup>138</sup> It is noteworthy that the addition of the nucleophile (1,3-dimethoxybenzene, trimethoxybenzene, *N*-methylindole, pyrrole) to the alkene proved to be chemoselective.

<sup>136</sup> Mézailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133.

<sup>137</sup> Nieto-Oberhuber, C.; López, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178.

<sup>138</sup> Toullec, P. Y.; Genin, E.; Leseurre, L.; Genet, J. P.; Michelet, V. *Angew. Chem. Int. Ed.* **2006**, *45*, 7427.

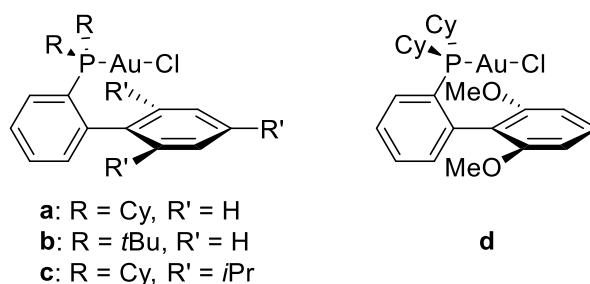




Scheme IV-10.

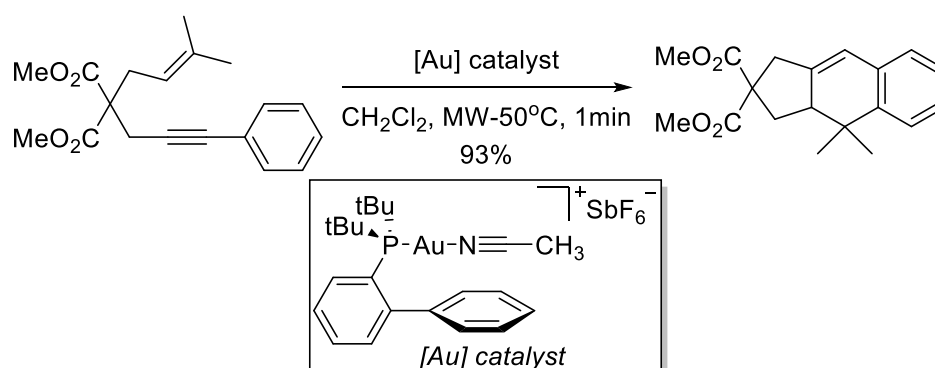
#### 4.1.4 Au(I)-catalyzed 1,6-enyne cyclization/internal nucleophilic addition process

In 2005, Echavarren's group synthesized several new biphenyl-based phosphine gold complexes, which were more bulky and were considered to bring higher activity and stability to gold catalyst (Scheme-IV-11).<sup>142</sup>



Scheme IV-11. Biaryl-based phosphine gold complexes

With those new catalysts, tricyclic compounds were obtained through cyclization of aryl-substituted 1,6-enynes, under mild condition. They showed very high reactivity, in some cases the completion of reaction could be achieved in 1 minute (Scheme-IV-12). Those catalysts, due to stabilization by acetonitrile ligand, can be isolated directly as the cationic form. This well-known catalyst, also called the "Echavarren's catalyst", was applied in numerous gold-catalyzed reactions. Based on the new catalysts, more examples and mechanistic investigation were then carried out by the same group.<sup>143</sup>



Scheme IV-12. Intramolecular nucleophilic addition

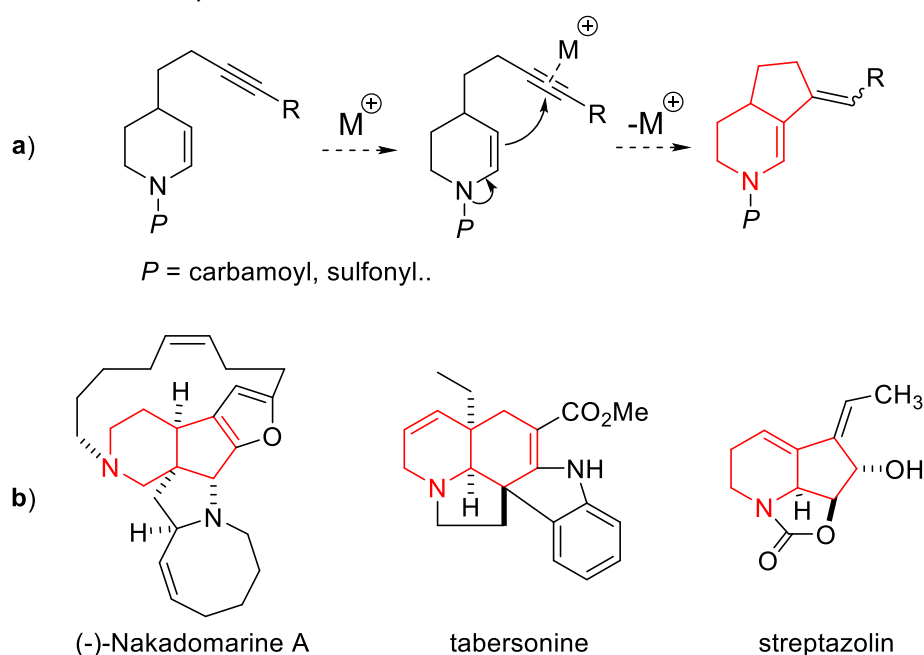
<sup>142</sup> Nieto-Oberhuber, C.; López, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178.

<sup>143</sup> Nieto-Oberhuber, C.; Pérez-Galán, P.; Herrero-Gómez, E.; Lauterbach, T.; Rodríguez, C.; López, S.; Bour, C.; Rosellón, A.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 269.

Later on, asymmetric version of this transformation was developed independently by Echavarren, Michelet and our team.<sup>144</sup>

## 4.2 Enamides as nucleophiles in transition metal catalysis and its application in synthesis

After this brief introduction on 1,6-enyne substrates and their reactivity in presence of gold complexes, we will look at with more details the substrates and reactivity that inspired us for the work detailed in this chapter. Indeed, the substrates such as enesulfonamide tethered with alkyne could undergo very interesting products, in presence of Lewis acids. The initial idea of applying *N*-sulfonyl- and *N*-carbamoyl-enamides moiety as nucleophiles in transition metal catalysis was carried out in Dake's group in 2004 (*Scheme IV-13-a*).<sup>145</sup> Enamide moiety's ability to capture the electrophiles formed in transition metal catalysis process had not been extensively studied. The potential value of this reactivity was the formation of heterocyclic systems that could be then manipulated for the synthesis of structural complex alkaloids (*Scheme IV-13-b*).



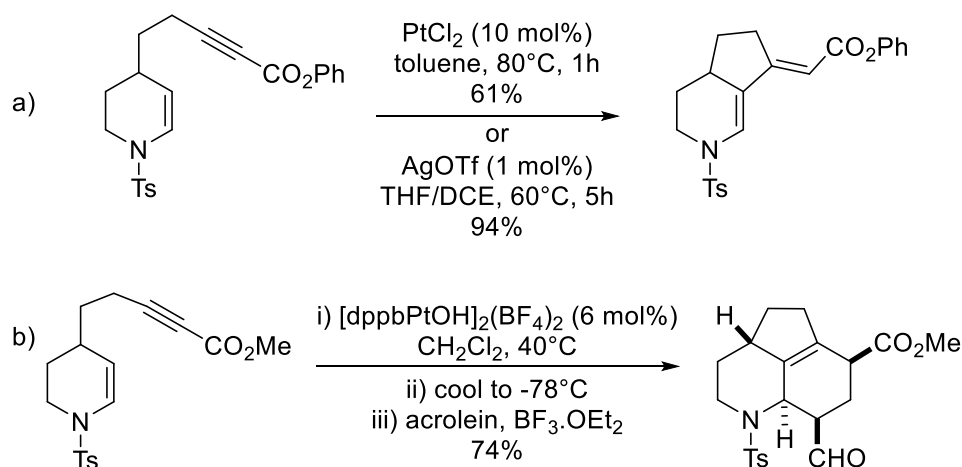
*Scheme IV-13. N-sulfonyl and N-carbamoyl moiety as  $\pi$ -nucleophiles for the synthesis of complex heterocycles*

The reaction of *N*-Ts-enamide substrates, substituted with ynoate functionality afforded the desired bicyclic product in 61% yield with  $\text{PtCl}_2$  as catalyst and in 94% yield with a silver salt. Reaction with  $\text{AgOTf}$  proceeds with only 1 mol% catalyst loading (*Scheme IV-14-a*).

<sup>144</sup> a) Chao, C. M.; Vitale, M. R.; Toullec, P. Y.; Genet, J. P.; Michelet, V. *Chem. Eur. J.* **2009**, *15*, 1319. b) Aillard, P.; Dova, D.; Magne, V.; Retailleau, P.; Cauteruccio, S.; Licandro, E.; Voituriez, A.; Marinetti, A. *Chem. Commun.* **2016**, *52*, 10984. c) Delpont, N.; Escofet, I.; Perez-Galan, P.; Spiegel, D.; Raducan, M.; Bour, C.; Sinisi, R.; Echavarren, A. M. *Catal. Sci. Technol.* **2013**, *3*, 3007.

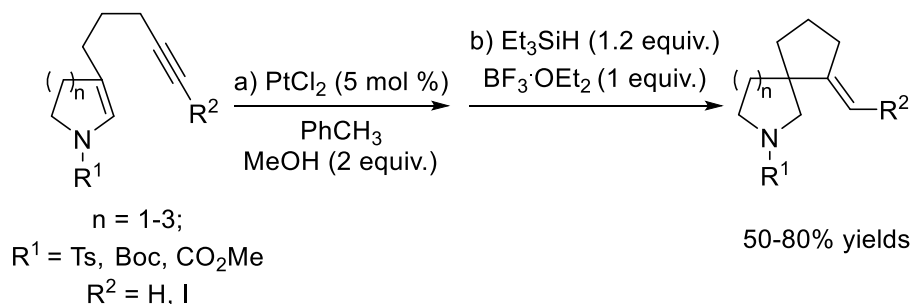
<sup>145</sup> Harrison, T. J.; Dake, G. R. *Org. Lett.* **2004**, *6*, 5023.

Furthermore, an additional Diels-Alder reaction could occur on these substrates with acrolein. After reaction with  $[\text{dppbPtOH}]_2(\text{BF}_4)_2$  catalyst at  $40^\circ\text{C}$ , the reaction was carried out at  $-78^\circ\text{C}$ , to obtain the corresponding tricyclic compound, in 74% yield. The reaction proved to be totally diastereoselective (*Scheme IV-14-b*).



*Scheme IV-14. Enesulfonamides as nucleophiles*

Dake continued to study the application of enesulfonamides, enecarbamates or enamides functional groups as  $\pi$ -nucleophiles in transition metal catalysis, especially with platinum(II) catalysis, for the formation of spirocyclic molecules.<sup>146</sup> Their hypothesis was realized by treating the reaction system with catalytic amount of platinum(II) salts like  $\text{PtCl}_2$ ,  $[\text{dppbPt}\mu\text{-OH}]_2(\text{BF}_4)_2$  or silver salt  $\text{AgOTf}$ . The corresponding spirocyclic compounds were obtained in 50% to 80% yields (*Scheme IV-15*). Interestingly, methanol was used to trap the azacarbenium ion intermediate, and after that the addition of silane and  $\text{BF}_3\cdot\text{OEt}_2$  afforded the product after reduction of the hemiaminal functionality.

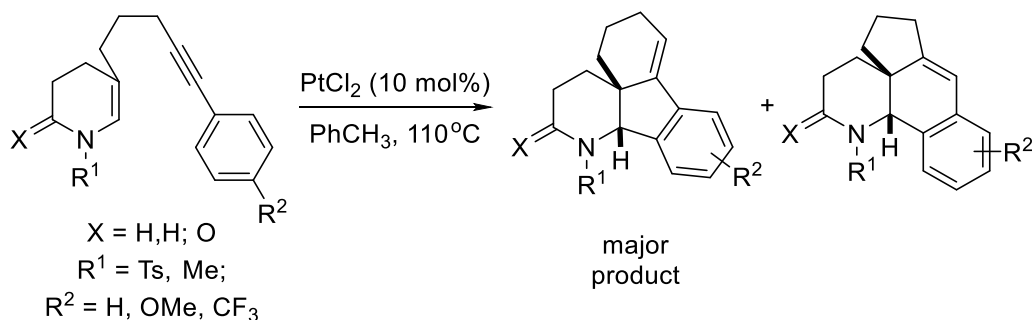


*Scheme IV-15. Synthesis of spirocyclic compounds*

By changing the alkyne substitution, this azacarbenium intermediate could be possibly be trapped intramolecularly by an aryl moiety, to give the corresponding tetracyclic core. They developed this idea through the synthesis of substrates described in *Scheme IV-16*. The functional groups on the 1-aryl-substituent on the alkyne showed higher influence to the activity and regioselectivity than the *N*-sulfonyl segment. This Pt(II)-catalyzed tandem cyclization/Friedel-Crafts ring closure process was fully developed later and 6-*endo* process

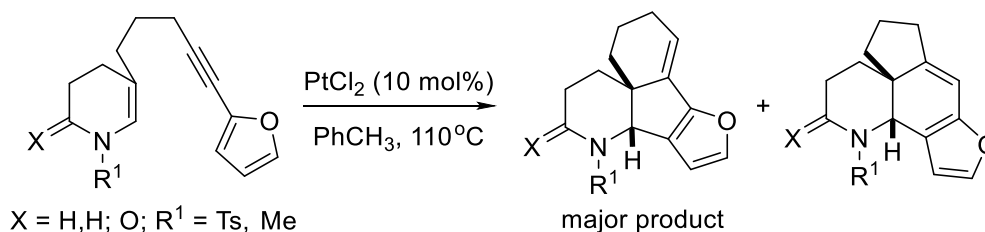
<sup>146</sup> Harrison, T. J.; Patrick, B. O.; Dake, G. R. *Org. Lett.* **2007**, *9*, 367.

was proved to be the main pathway in this methodology.<sup>147</sup>



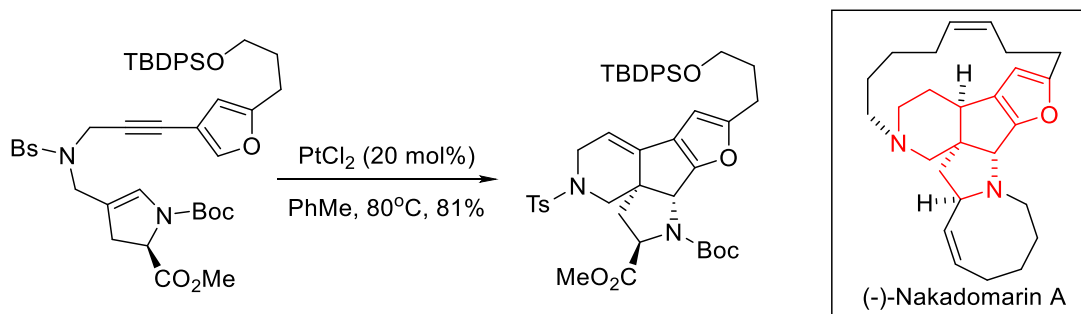
Scheme IV-16.

Furthermore, this methodology has been extended to the use of 2-furyl-alkyne derivatives. The results showed high regioselectivity (up to 25:1) but lower reactivity compared to aryl-alkyne derivatives (Scheme IV-17).



Scheme IV-17.

In 2011, Zhai's group finished the total synthesis of Nakadomarin A, which was extracted from an ocean sponge in 1997 by Kobayashi and colleagues and proved to possess prominent biological activity. Inspired by the efficient Pt(II)-catalysis developed by Dake, a novel synthetic pathway was developed toward the synthesis of the tetracyclic core of this complex alkaloid.<sup>148</sup> The enantiopure starting material was modified from Dake's method, using *N*-brosyl (*N*-SO<sub>2</sub>-4-Br-C<sub>6</sub>H<sub>4</sub>) as the enesulfonamide  $\pi$ -nucleophile. An alkyne moiety with an alkyl-substituted furan was used to obtain the required functionalities. Treated with 20 mol% of PtCl<sub>2</sub>, the target compound was isolated in 81% yield, as a single diastereoisomer (Scheme IV-18).



Scheme IV-18.

<sup>147</sup> Kozak, J. A.; Dodd, J. M.; Harrison, T. J.; Jardine, K. J.; Patrick, B. O.; Dake, G. R. *J. Org. Chem.* **2009**, *74*, 6929.

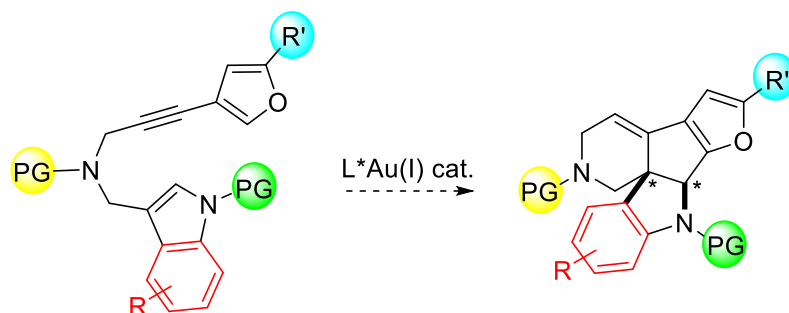
<sup>148</sup> Cheng, B.; Wu, F.; Yang, X.; Zhou, Y.; Wan, X.; Zhai, H. *Chem. Eur. J.* **2011**, *17*, 12569.



On one hand, this diastereoselective Pt(II)-catalyzed cascade reaction was consequently applied as a key step in the total synthesis of Nakadomarin A, hence an enantioselective transformation toward this core structure could be very valuable. On the other hand, as one of the hottest topics in organic chemistry, asymmetric catalysis is always one of the final goal which can be interesting to develop. Hence we attempted to develop and generalize the enantioselective version of this transformation.

### 4.3 Development of enantioselective 1,6-enyne polycyclization

Gold-catalyzed 1,6-enyne cycloisomerizations have already been very well studied. A vast quantity of corresponding works was published. However, asymmetric transformations remain a big challenge for the chemists and the applications possesses huge potential toward the synthesis of numerous valuable natural compounds. Hence we decided to develop an enantioselective gold(I)-catalyzed 1,6-enyne cyclization/intramolecular nucleophilic addition sequence (*Scheme-IV-19*).

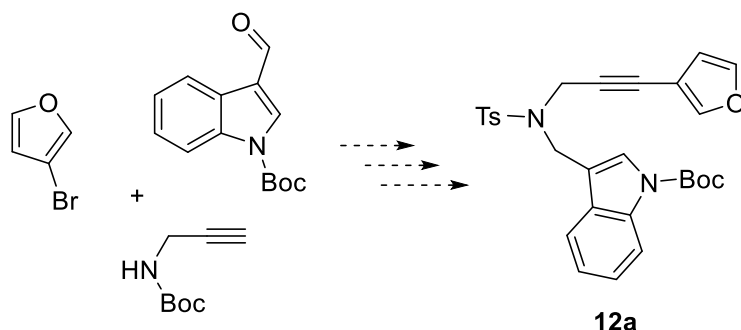


*Scheme IV-19. Toward Au(I)-catalyzed asymmetric 1,6-enyne reaction*

#### 4.3.1 Synthesis of 1,6-enyne substrates and optimization of the reaction conditions

##### 4.3.1.1 Preparation of substrate **12a** and initial result

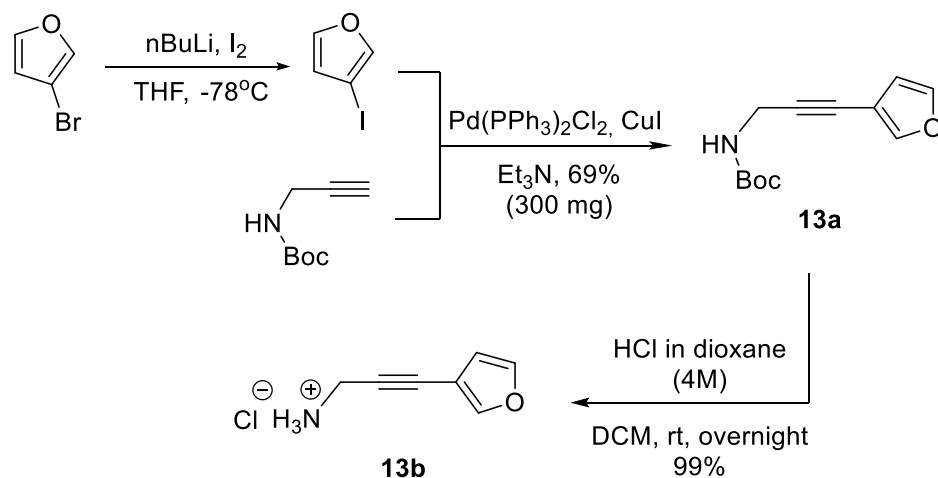
The first model substrate **12a** was prepared starting from building blocks described below (*Scheme IV-20*). We will next summarize the preparation of each of these products.



*Scheme IV-20. Preparation of the first model substrate **12a***

Firstly, the commercially available 3-bromofuran was treated with *n*BuLi at -78°C in dry THF, and then quenched with iodine. The corresponding 3-iodofuran was obtained as a solution in

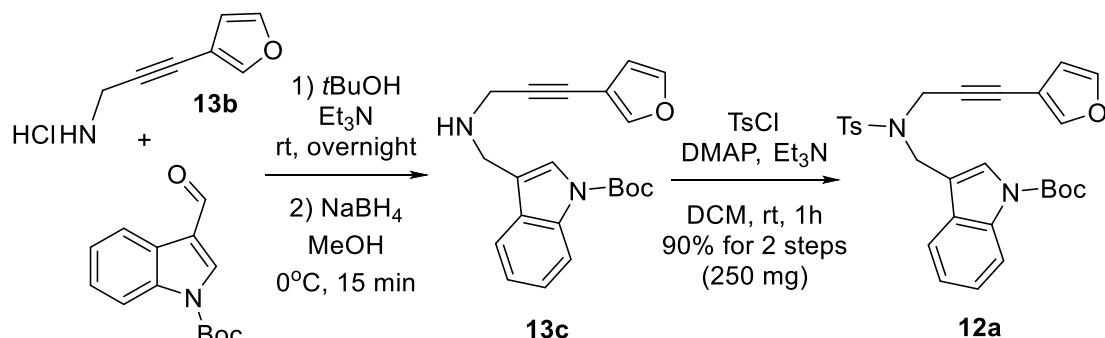
THF and utilized directly (*Scheme IV-21*). The Sonogashira coupling was then achieved from 3-iodofuran and *tert*-butyl-prop-2-yn-1-yl-carbamate, with a Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>/CuI mixture as catalytic system, in triethylamine. The desired *tert*-butyl (3-(furan-3-yl)prop-2-yn-1-yl)carbamate **13a** was isolated in 69% yield (300 mg) as light yellow solid.



*Scheme IV-21. Synthesis of 13b*

The formed amine **13a** was next treated with hydrochloric acid (4M, in dioxane) in dichloromethane. After reacted for overnight, the solvent was removed and the target (3-(furan-3-yl)prop-2-yn-1-yl)-1,2-azane hydrochloride **13b** was obtained as grey solid in quantitative yield.

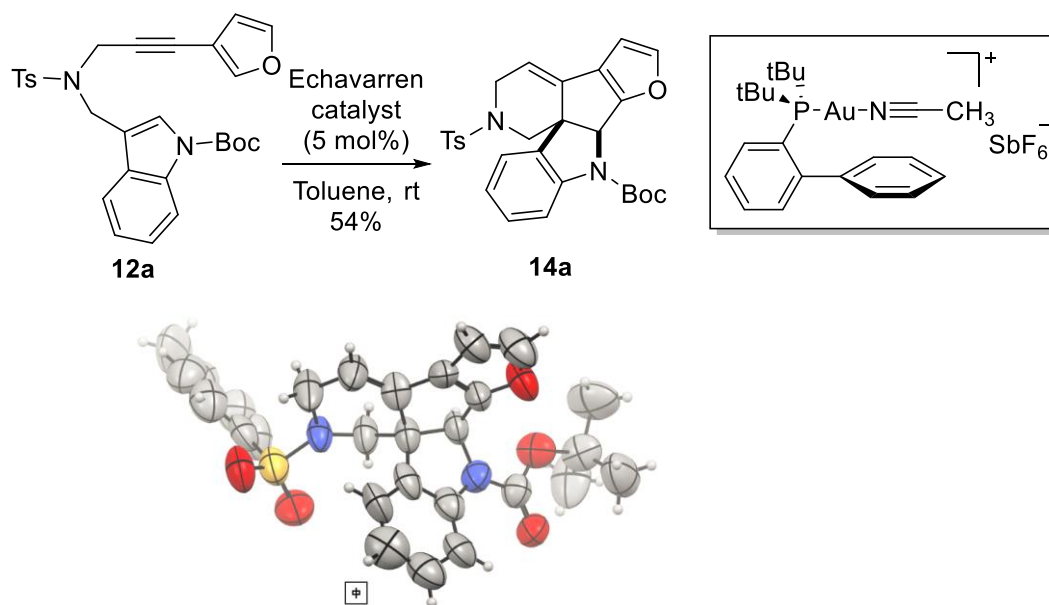
Subsequently, the hydrochloric acid salt **13b** and *N*-Boc-3-formyl-1*H*-indole underwent a reductive amination in presence of *t*BuOH and triethylamine. In the second step, sodium borohydride was used to reduce the newly formed imine. The corresponding amine compound **13c** was not isolated. After protection, the desired sulfonamide-tethered 1,6-enyne compound **12a** was obtained in pure form in two steps at 250 mg scale (90% yield, *Scheme IV-22*).



*Scheme IV-22. Synthesis of substrate 12a*

With the desired substrate in hand, we decided to test it in the cyclization/nucleophilic addition process. With the use of catalytic amount of Echavarren's catalyst [JohnPhosAu(MeCN)SbF<sub>6</sub>], at room temperature, the racemic product **14a** was isolated in

54% yield (*Scheme IV-23*). The structure of this pentacyclic backbone was confirmed by NMR analysis and X-ray diffraction studies.



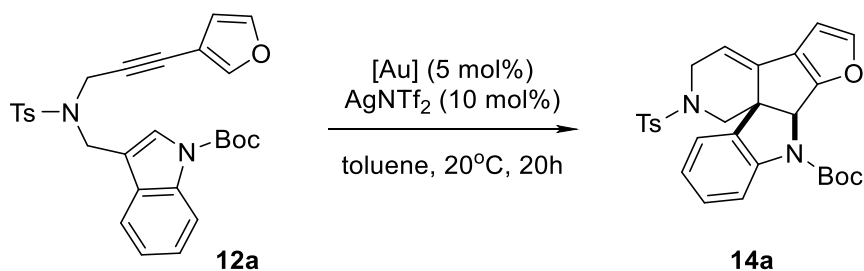
*Scheme IV-23. Synthesis of a new pentacyclic product and X-ray crystallography*

After the synthesis of the functionalized 1,6-enyne derivative **12a** and the related chiral polycyclic compound **14a**, we decided to screen different chiral gold(I) complexes with the hope of developing an enantioselective version of this reaction.

#### 4.3.1.2 Optimization of the asymmetric reaction

With the 1,6-enyne substrate **12a** in hand, an enantioselective cascade cyclization reaction was studied in presence of chiral gold catalysts. AgNTf<sub>2</sub> (5 mol%) served as chlorine atom scavenger, and the reaction was launched in toluene (0.125 M), at room temperature for 20 hours (*Table IV-1*). Like in the previous studies with 1,5-enyne substrates (see Chapter 3), we decided to mix together the chiral *bis*-gold chloride and the silver salt in toluene during 10 minutes. After filtration of the mixture, the active catalyst was added to the substrate.

Several commercially available chiral gold catalysts were tested in this transformation, especially the chiral *bis*-gold(I) catalysts who were often efficient in enyne cyclization reactions. However, all the tested catalysts could only gave moderate yields with unsatisfactory enantiomeric excesses. The atropochiral *bis*(phosphine)digold(I) **I** with BINAP backbone brought an interesting 50% yield, albeit with no enantioselectivity (*Table IV-1*, entry 1). Different BIPHEPs catalysts **II-IV** gave very low *ees* and the target compound could only be isolated in less than 51% yield (entries 2-4). With SEGPHOS *bis*gold(I) complexes **V** and **VII**, the yields reached 48%, but with low *ees* (entries 5 and 7).



entry	[L*AuCl]	yield (%) <sup>a</sup>	ee (%) <sup>b</sup>
1	(I)	50	0
2	(II)	51	0
3	(III)	24	28
4	(IV)	49	8
5	(V)	48	20
6	(VI)	38	38
7	(VII)	48	7

<sup>a</sup>Isolated yield at a 0.05 mmol scale. <sup>b</sup>Determined by SFC on a chiral stationary phase.

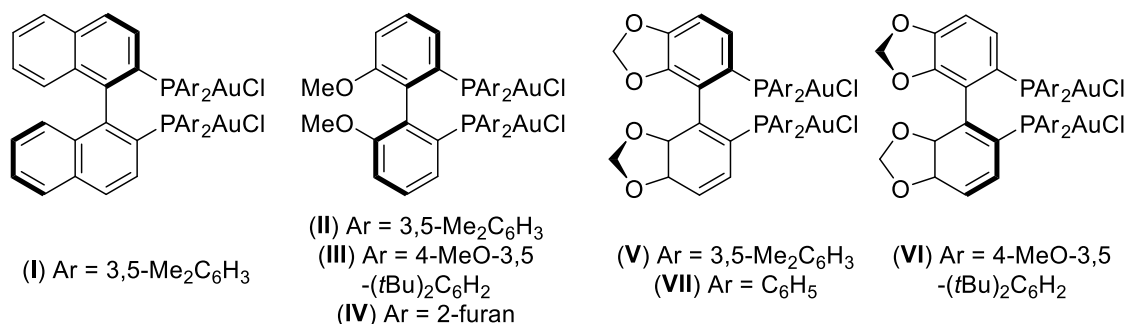
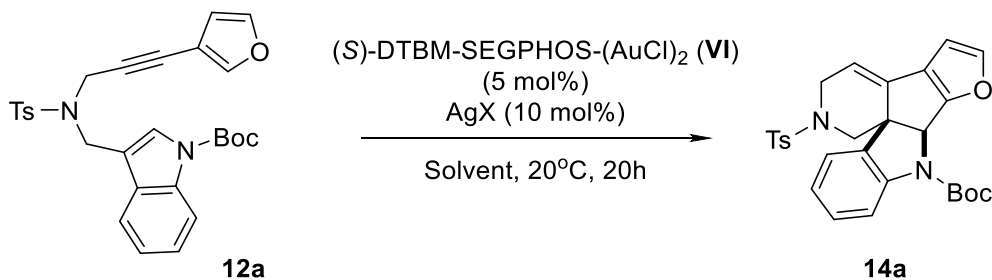


Table IV-1. Screening of chiral gold(I) catalysts

The “best” result was obtained with the use of (*S*)-DTBM-SEGPHOS-(AuCl)<sub>2</sub> as precatalyst, in 38% yield and 38% *ee* (entry 6). **VI** was kept as the optimal catalyst and we continued to optimize both the reaction activity and the enantioselectivity by screening different silver salts (Table IV-2).

It is commonly recognized that the *ratio* between silver salt and chiral *bis*-gold catalyst could cause noticeable influence on the reaction outcome (see chapter II, 2.3.2.2). However, in this protocol, changing the [Au]/[Ag] *ratio* from 1:1 to 1:2 brought almost no difference to the result (Table IV-2, entries 1-2). By keeping a [Au]/[Ag] = 1:2 *ratio*, several common halogen scavengers were tested. By introducing SbF<sub>6</sub><sup>-</sup>, BF<sub>4</sub><sup>-</sup> or PF<sub>6</sub><sup>-</sup> counteranions, the *ee* value could not be enhanced, the *ee* did not exceed 26% (entries 3-5). Even though with SbF<sub>6</sub><sup>-</sup> the yield could reach 63%, the enantioselectivity decreased to 24%. BF<sub>4</sub><sup>-</sup> and PF<sub>6</sub><sup>-</sup> reduced severely the reactivity of the catalytic system (respectively 20% and 10% yield). The triflate counteranion gave disappointing results (entry 6). When dichloromethane was applied as solvent, in combination with AgNTf<sub>2</sub>, only 7% *ee* could be obtained (entry 7). In conclusion of these first

trials, AgNTf<sub>2</sub> would be continuously applied in the next stage with [Au]/[Ag] = 1:1.



entry	AgX	solvent	yield (%) <sup>a</sup>	ee (%) <sup>b</sup>
1	AgNTf <sub>2</sub>	toluene	38	38
2 <sup>c</sup>	AgNTf <sub>2</sub>	toluene	40	38
3	AgSbF <sub>6</sub>	toluene	63	24
4	AgBF <sub>4</sub>	toluene	20	20
5	AgPF <sub>6</sub>	toluene	10	26
6	AgOTf	toluene	10	1
7	AgNTf <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub>	45	7

<sup>a</sup>Isolated yield at a 0.05 mmol scale. <sup>b</sup>Determined by SFC on a chiral stationary phase. <sup>c</sup>[Au]/[Ag]: 1/1 ratio.

*Table IV-2. Optimization of silver salts and solvent*

In view of these unsatisfactory results, we wondered whether there was not a great interest to synthesize different 1,6-enyne substrates, with various indole-protecting groups. Indeed, the reactivity of this enamine functionality should be drastically changed, depending on the protecting groups. In consequence, the enantioselectivity could be also impacted. The substrate was modified with few selected protecting groups on the indole moiety (NH, NAc, NMe), which were supposed to affect both the activity and the selectivity of this reaction.

### 4.3.2 Influence of the functional groups on *N*-indole

Different functional groups were introduced on the nitrogen atom of the indole backbone, to examine both the reactivity and the enantioselectivity obtained in this catalytic process with these new substrates. With the procedure described in scheme IV-21 and 22, the *tert*butyloxycarbonyl group was deprotected to furnish the compound **12b**. This compound could be easily acetylated (substrate **12c**) or *N*-methylated (**12d**) (Scheme-IV-24). As soon as we obtained these new substrates **12b-d**, several tests were carried out.

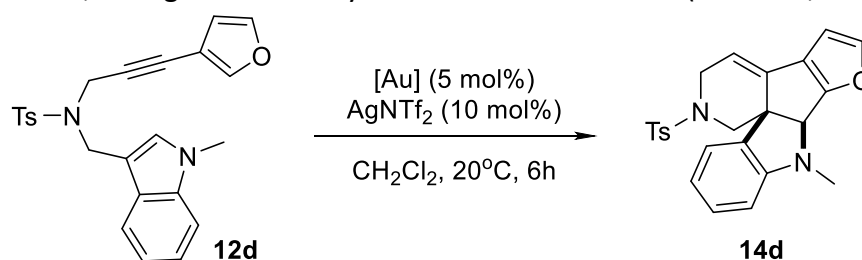


conditions with the *N*-Methylindole derivative **12d**, to try to increase the enantiomeric excesses.

### 4.3.3 Optimization of the cyclization with substrate **12d**

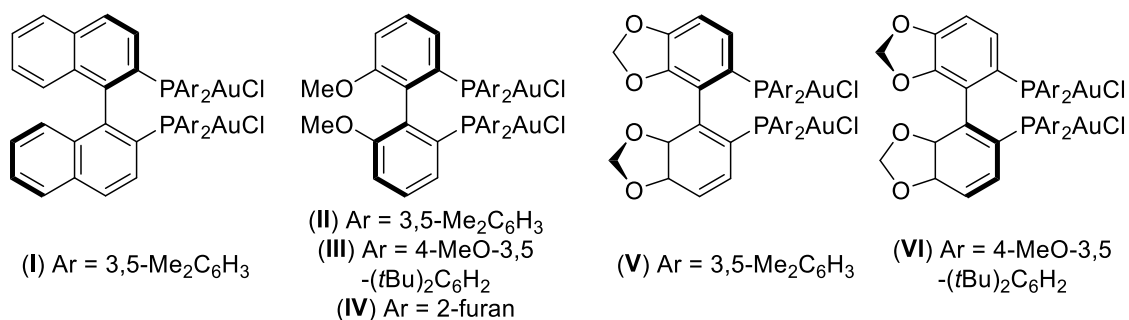
#### 4.3.3.1 Screening of chiral gold catalysts

With this exciting result with the substrate **12d**, we screened again different chiral Au(I)-catalysts (*Table IV-3*). The chiral digold(I) catalysts **I-V** (5 mol%) were tested with AgNTf<sub>2</sub> (10 mol%) in dichloromethane at 20°C. Three MeO-BIPHEP-(AuCl)<sub>2</sub> precatalysts brought lower enantioselectivities (*Table IV-3, entry 2-4*). Among all the results, the catalysts **I**, **V** and **VI** gave similar results, with good isolated yields and around 60% *ee* (entries 1, 5 and 6).



entry	[L*AuCl]	[Au]/[Ag]	yield (%) <sup>a</sup>	<i>ee</i> (%) <sup>b</sup>
1	(I)	1/2	78	59
2	(II)	1/2	70	20
3	(III)	1/2	35	41
4	(IV)	1/2	96	19
5	(V)	1/2	87	61
6	(VI)	1/2	62	60
7 <sup>c</sup>	(I)	1/1	95	46
8 <sup>c</sup>	(V)	1/1	96	65
9 <sup>c</sup>	(VI)	1/1	90	67

<sup>a</sup>Isolated yield at a 0.05 mmol scale. <sup>b</sup>Determined by SFC on a chiral stationary phase. <sup>c</sup>17h reaction time at 20°C.



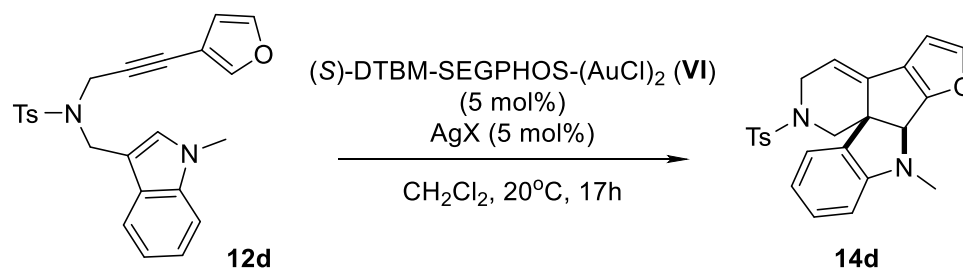
*Table IV-3. Test of different chiral gold(I) catalysts*

To verify the influence of the [Au]/[Ag] *ratio* in this reaction, we take the three best catalysts

and try to decrease the stoichiometry of the silver salt to a 1/1 *ratio* to gold (entries 7-9). Among these three new results (*S*)-DTBM-SEGPHOS-(AuCl)<sub>2</sub> was confirmed to be the optimal choice as chiral catalyst, after monocationisation of the *bis*-gold(I) complex with AgNTf<sub>2</sub>. Product **14d** was isolated in 90% yield and 67% *ee* (entry 9). We next verified the influence of the counteranion in the reaction.

#### 4.3.3.2 Optimization of the silver salts

Keeping the best catalytic system, we tested different silver salts to activate the chiral gold catalyst (Table IV-4). AgPF<sub>6</sub> and AgSbF<sub>6</sub> could only bring 40% conversion and 40-52% *ee* (entries 2-3). AgBF<sub>4</sub> gave very low reactivity and enantioselectivity (16% *ee*, entry 4). High reactivity could be obtained with AgOTf, but with moderate *ee* value (47% *ee*, entry 5). Hence, AgNTf<sub>2</sub> (entry 1) was kept to be the most suitable silver salt for this transformation, with an equimolar *ratio* of gold and silver salts.



entry	AgX	yield (%) <sup>a</sup>	<i>ee</i> (%) <sup>b</sup>
1	AgNTf <sub>2</sub>	90	67
2	AgPF <sub>6</sub>	40	40
3	AgSbF <sub>6</sub>	40	52
4	AgBF <sub>4</sub>	<10	16
5	AgOTf	83	47

<sup>a</sup>Isolated yield at a 0.05 mmol scale. <sup>b</sup>Determined by SFC on a chiral stationary phase.

Table IV-4. Optimization of silver salts

Two control experiments verified the effect of silver salt and acid. Treated with acetic acid, no conversion of starting material was detected. With only 5 mol% AgNTf<sub>2</sub>, no target product could be observed in the crude <sup>1</sup>H NMR.

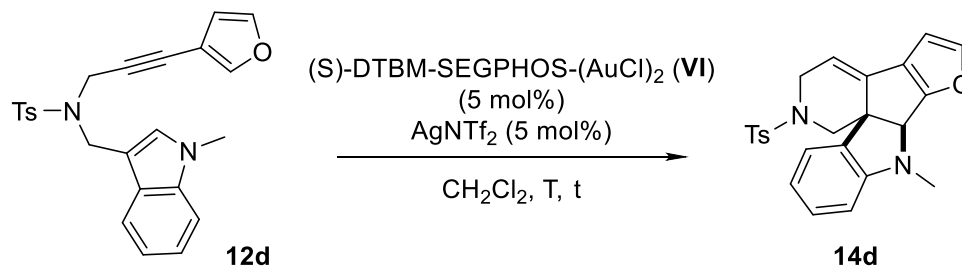
#### 4.3.3.3 Optimization of reaction temperature and kinetic experiments

We next studied the influence of the reaction temperature and the reaction time on the reaction outcome (Table IV-5).

When the reaction temperature was decreased to 0°C, even after 72 hours, the conversion was not total, and the *ee* value did not increase (70% *ee*, entry 2). At 10°C, the reaction results were independently checked after 20 hours, 26 hours and 40 hours (entries 3-5). Interestingly, with increase in reaction time, not only the conversion was better, but also the



enantiomeric excesses. After 40h at 10°C, the yield was quantitative and the enantioselectivity reached 90% ee (entry 5).

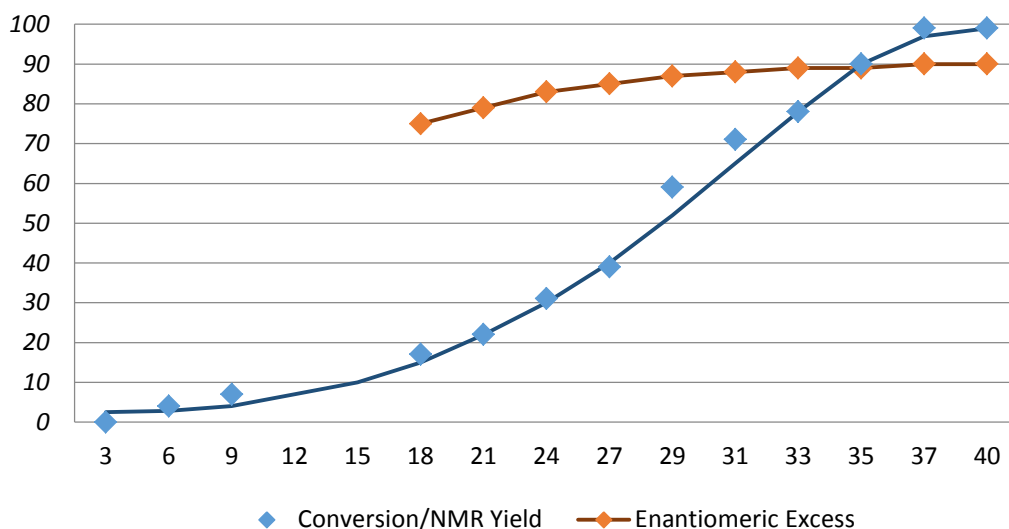
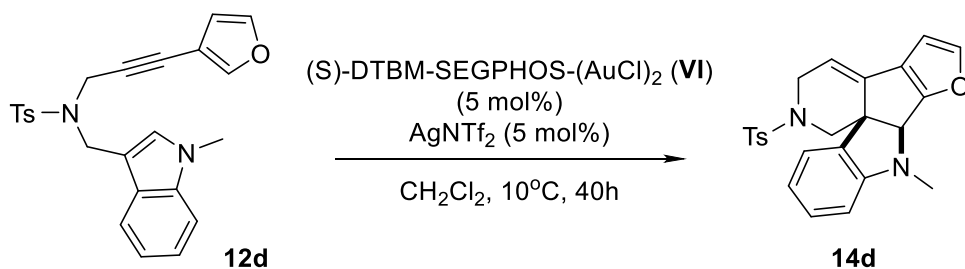


entry	T(°C)/t(h)	yield (%) <sup>a</sup>	ee (%) <sup>b</sup>
1	20°C/17h	90	67
2	0°C/72h	77	70
3	10°C/20h	43	72
4	10°C/26h	57	79
5	10°C/40h	99	90

<sup>a</sup>Isolated yield at a 0.05 mmol scale. <sup>b</sup>Determined by SFC on a chiral stationary phase.

*Table IV-5. Influence of the reaction temperature and time*

Interested by this phenomenon, we decided to study the relation between the conversion of starting material and the corresponding enantioselectivity of the product **14d**. Kinetic experiment was designed using 0.1 mmol of 1,6-enyne substrate, with 5 mol% of Au(I) catalyst **VI** and AgNTf<sub>2</sub> (5 mol%), in 0.8 mL dichloromethane at 10°C (*Scheme IV-27*). As we said, the reaction was expected to last 40 hours. For technical purpose, we decided to run two reactions under exactly the same reaction conditions, but timely interlaced. We took 0.1 mL of the reaction mixture every 3 hours and checked the conversion by <sup>1</sup>H NMR and the enantiomeric excess by chiral SFC. The ee value was started to be traced after 18 hours because the low conversion limited the separation of the target compound. We could observe gradually increase of both ees and the substrate conversion with time. The yield of the target compound **14d** increased from 17% to 90% between 18h and 35h reaction time. During this period, the enantiomeric excess increased from 75% to 90% ee. The enantioselectivity was then stabilized around 90% after 30 hours, until the total conversion of the substrate.



Scheme IV-27. Kinetic experiments

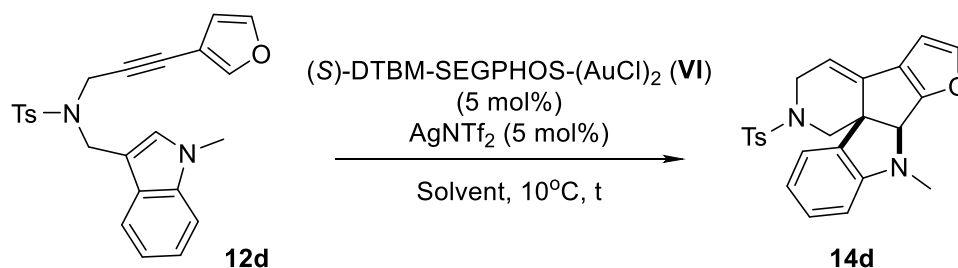
Some explanations of this phenomenon can be found in the mechanistic part (*Chapter 4.3.5*). As partial conclusion, in this catalytic process, it is very important to be sure that total conversion of the substrate was attained before to stop the reaction, to obtain high enantiomeric excesses of the target product. Before to explore the reaction scope, we had to be sure that dichloromethane was the best solvent in this transformation.

#### 4.3.3.4 Optimization of solvents

Different solvents were tested in this reaction (*Table IV-6*). All these catalytic tests have been monitored by TLC. The reactions were stopped when the substrate was fully consumed. With halogenated solvents, dichloroethane gave similar reactivity than dichloromethane, with 95% yield and 88% *ee* (entries 1-2). Chloroform kept high reactivity but only 8% *ee* (entry 3). When 1,4-dichlorobutane was used as solvent, it also kept high activity but low enantioselectivity (entry 4). Aromatic solvents proved to be not suitable in our protocol. All three aromatic solvents showed low reactivity (50-65% yield, entry 5-7).

Unusual results were obtained in entries 5 and 7, with the use of chlorobenzene and toluene. In those cases, opposite enantiomer was isolated, albeit in low *ees*. In the literature, some related examples in asymmetric gold(I) catalysis showed the isolation of different

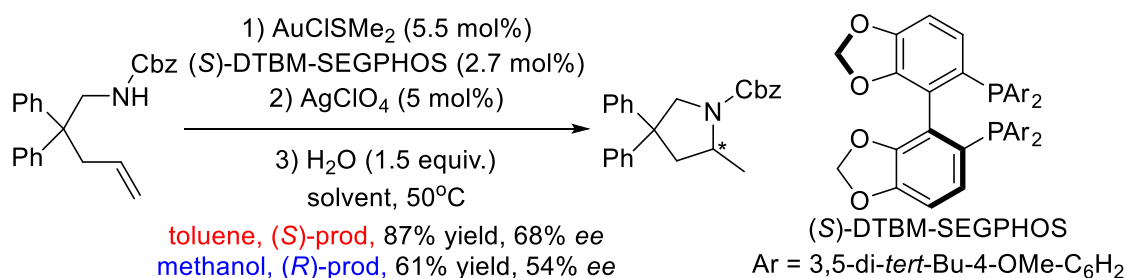
enantiomers, depending on the solvents used.<sup>149</sup>



entry	Solvent	t	yield (%)	ee (%)
1	CH <sub>2</sub> Cl <sub>2</sub>	40h	99	90
2	DCE	40h	95	88
3	CHCl <sub>3</sub>	18h	78	8
4	1,4-DCB	26h	80	52
5	PhCl	26h	65	-11
6	PhCF <sub>3</sub>	26h	63	8
7	toluene	26h	50	-3

Table IV-6. Optimization of solvents

For example, in the gold(I)-catalyzed asymmetric hydroamination of alkenes, Agbossou-Niedercorn *et al.* observed enantiodivergent reactions, with the use of methanol or toluene (Scheme IV-28).<sup>112-c</sup> This enantio-inversion proved to be controlled by gold-silver chloride adducts which occur only in methanol and allow a dual activation of the reagent.

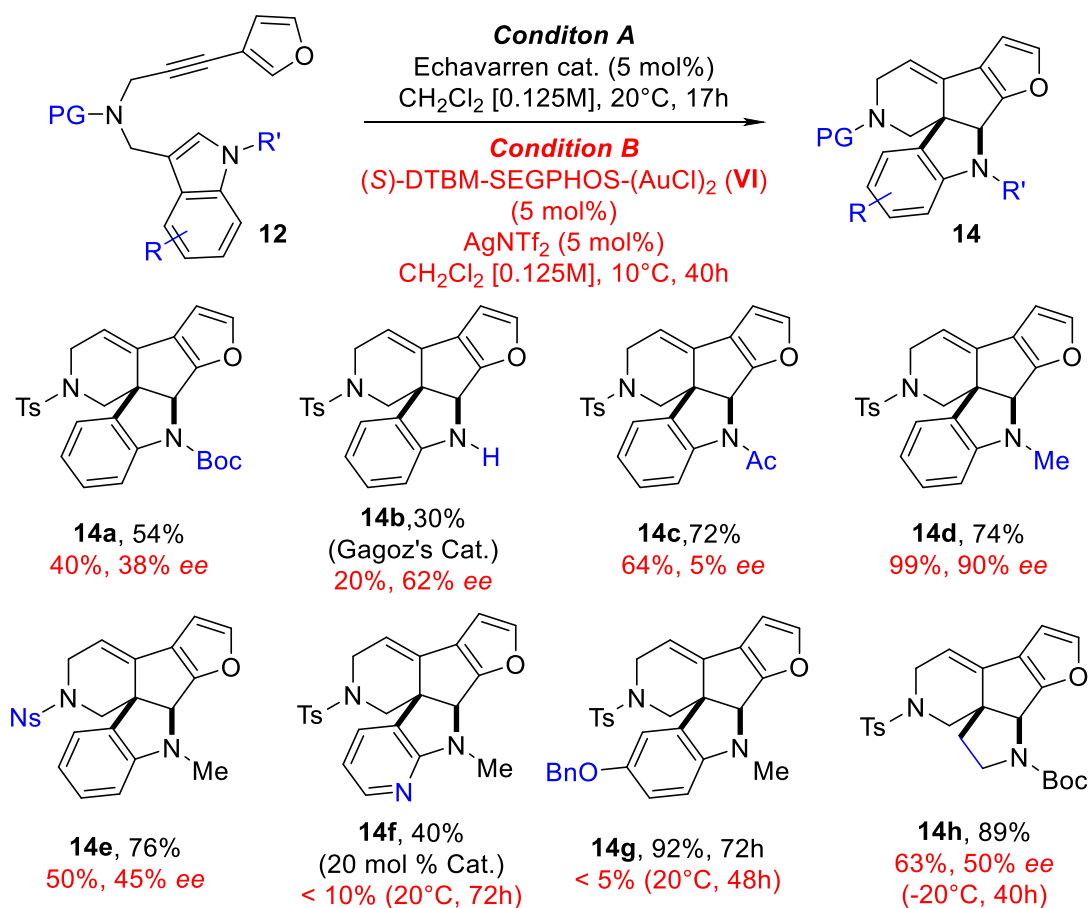


Scheme IV-28.

#### 4.3.4 Reaction scope

At this stage, we tested differently functionalized substrates in both racemic and asymmetric versions. Racemic reactions were carried out with 5 mol% Echavarren's catalyst in dichloromethane at 20°C for 17 hours. The racemic condition was labeled as *condition A*. The optimal condition toward asymmetric transformation was labeled as *condition B* (Scheme IV-29).

<sup>149</sup> a) Wu, H.; Zi, W.; Li, G.; Lu, H.; Toste, F. D. *Angew. Chem. Int. Ed.* **2015**, *54*, 8529. b) Ilg, M. K.; Wolf, L. M.; Mantilli, L.; Fares, C.; Thiel, W.; Furstner, A. *Chem. Eur. J.* **2015**, *21*, 12279. c) Abadie, M. A.; Trivelli, X.; Medina, F.; Duhal, N.; Kouach, M.; Linden, B.; Genin, E.; Vandewalle, M.; Capet, F.; Roussel, P.; Del Rosal, I.; Maron, L.; Agbossou-Niedercorn, F.; Michon, C. *Chem. Eur. J.* **2017**, *23*, 10777.



*Scheme IV-29. Reaction scope- Part 1*

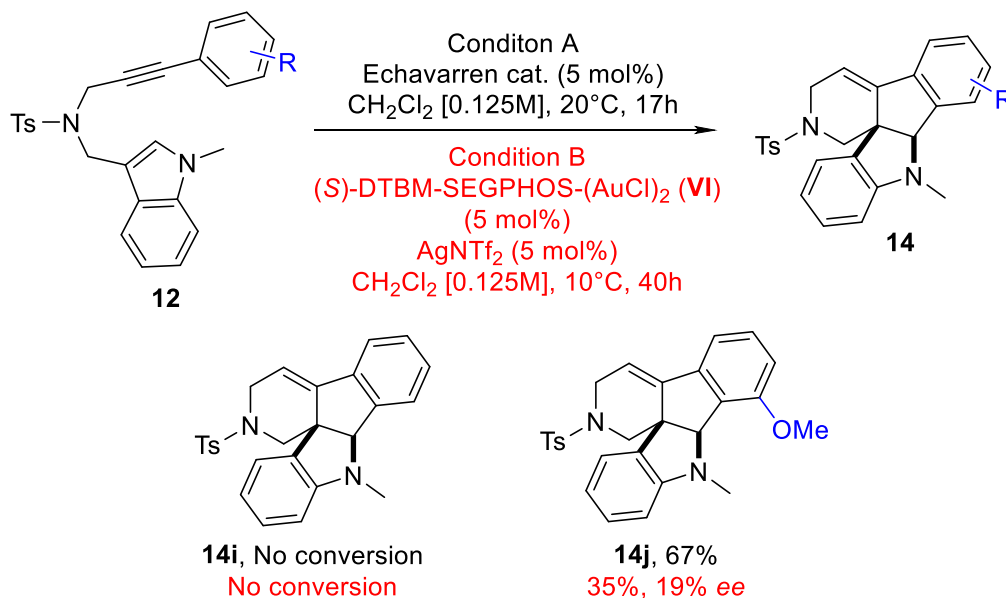
For the reaction scope, we first try various protecting groups of the indole moiety that we were able to test during this thesis. Corresponding products **14a-d** were obtained in moderate to excellent yields, and up to 90% ee, when *N*-methylindole **12d** was employed. By comparing the four results, we could notice the severe influence brought by different functional groups on indole moiety. Fully understanding these results remains not so obvious. The outcomes of racemic mixture of **14a-14d** were more acceptable, those compounds could be obtained in 30-74% isolated yields.

Keeping *N*-methylindole, we then modified the substitution of the *N*-propargyl moiety. The replacement of tosyl group (*p*Me-C<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>-) by nosyl group (*p*NO<sub>2</sub>-C<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>) had a huge impact on both conversion and enantioselectivity of the reaction (compound **14e**, 50% yield, 45% ee). Continuously, we modified the indole moiety. However, to our surprise, the functional groups on the indole influence severely the activity and the enantioselectivity in our transformation.

Replacing indole part with 7-azaindole, unfortunately, the substrate **12f** could not be activated under the best reaction condition. Even if the reaction temperature was increased to 20°C for 72 hours, less than 10% yield of **14f** could be observed by <sup>1</sup>H NMR analysis. When electron-donating benzyl alcohol group was introduced on 5-position of indole segment, we

had to enhance both reaction temperature and catalyst amount to promote the transformation. However, even after 48h reaction time, only trace amounts of **14g** could be detected. Using dihydropyrrole moiety to replace indole, the substrate was not stable enough at room temperature. However, catalytic activity was quite high under the optimal condition. Furthermore, at  $-20^{\circ}\text{C}$ , 63% isolated yield of compound **14h** could be obtained, with 50% *ee*. For the racemic version, compounds **14e-14h** were isolated in up to 92% isolated yield.

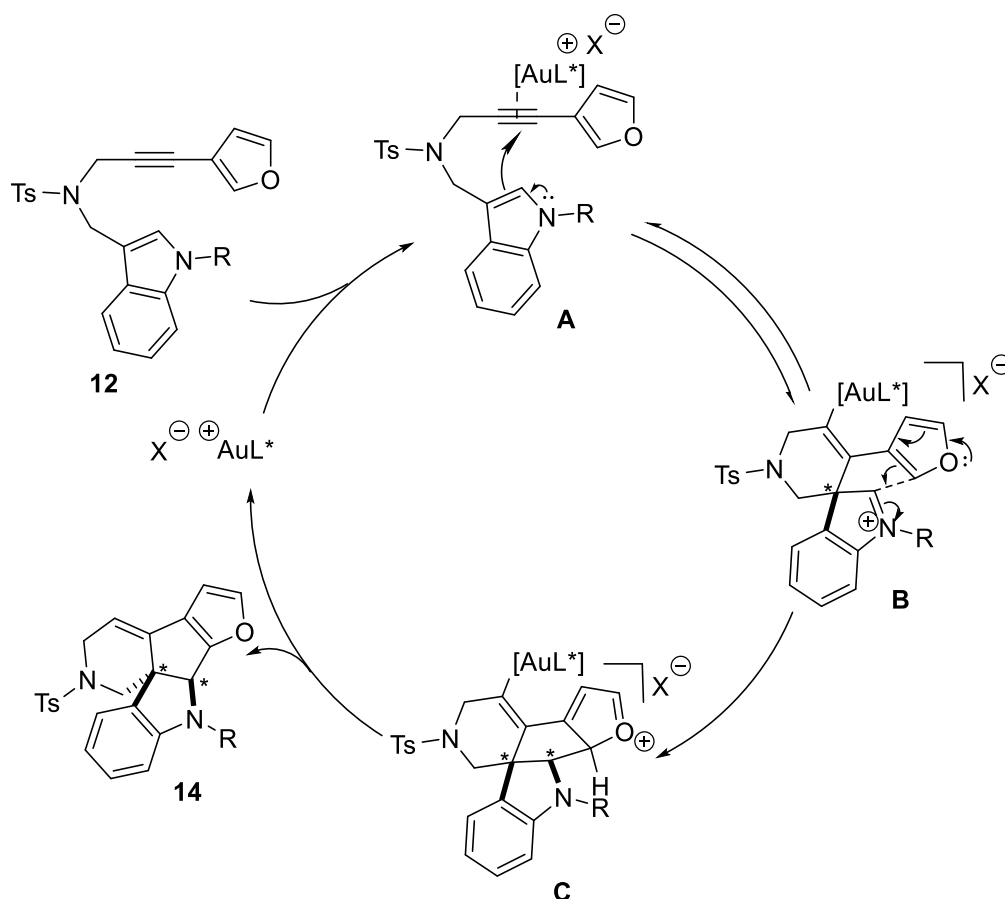
Replacing furan moiety with phenyl group decreased the electron density of aromatic ring (*Scheme-IV-30*). Toward the synthesis of compound **14i**, no conversion of substrate could be observed with either achiral gold(I) catalyst or the chiral gold(I) catalysis system. Introducing electron-donating methoxy group on the phenyl ring could promote the reactivity, especially with Echavarren's catalyst (compound **14j**, 67% yield). This molecule could be obtained in 35% yield and 19% *ee* with the use of chiral catalyst.



*Scheme IV-30. Reaction scope- Part 2*

#### 4.3.5 Proposed mechanism

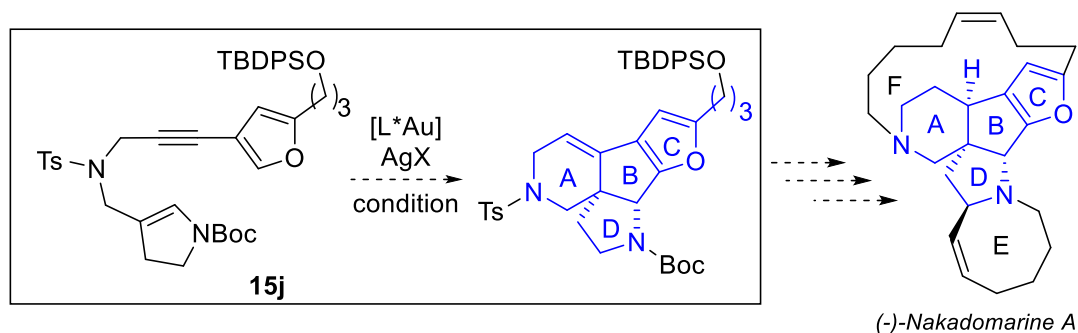
Based on former publications, we postulated the mechanism of this Au(I)-catalyzed cascade cyclization reaction (*Scheme IV-31*). Alkyne moiety of substrate **12** was activated by Au(I) complex (intermediate **A**) and then the electron transfers on indole segment promoted the nucleophilic addition, and the formation of the alkenyl gold complex intermediate **B**. This should be the enantio-determining step of the reaction. Continuously, electron-rich furan moiety promoted a cascade nucleophilic addition on the iminium moiety to form intermediate **C**. The final product **14** was delivered through the protodeauration step. The kinetic experiments and the variation of the *ees* over time could be supported by reversible process between intermediates **A** and **B**. DFT calculations should highlight such possible equilibrium.



#### 4.3.6 Toward the asymmetric synthesis of the tetracycle core of Nakadomarin

##### A

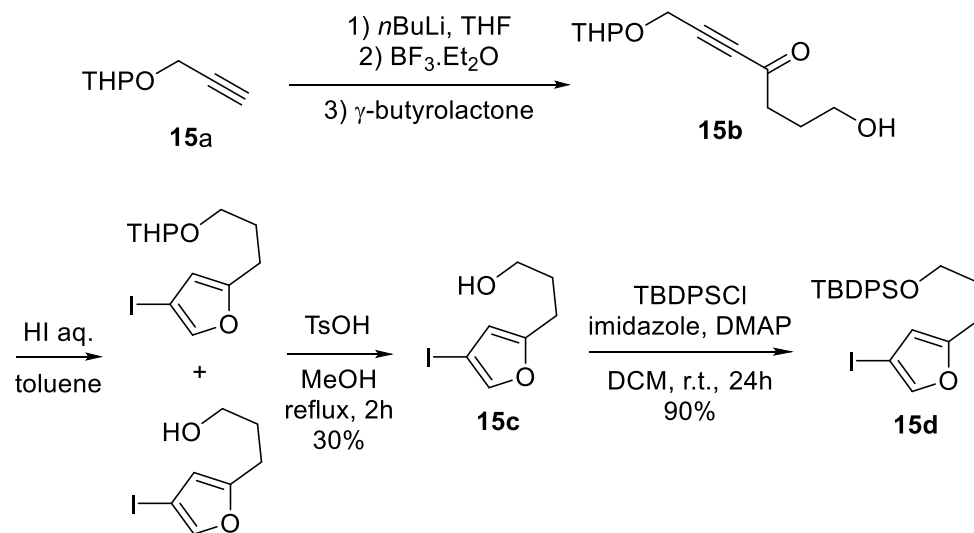
The main objective of this work was to use our newly developed gold-catalyzed methodology for the synthesis of the tetracyclic core structure of Nakadomarin A (Scheme IV-32).



For the synthesis of compound **15j**, the main goal was to synthesize the furan moiety and the propargylamine segment separately, and then connect the two parts through a Sonogashira coupling process.

The synthesis started from commercially available 2-(prop-2-yn-1-yloxy)tetrahydro-2H-pyran

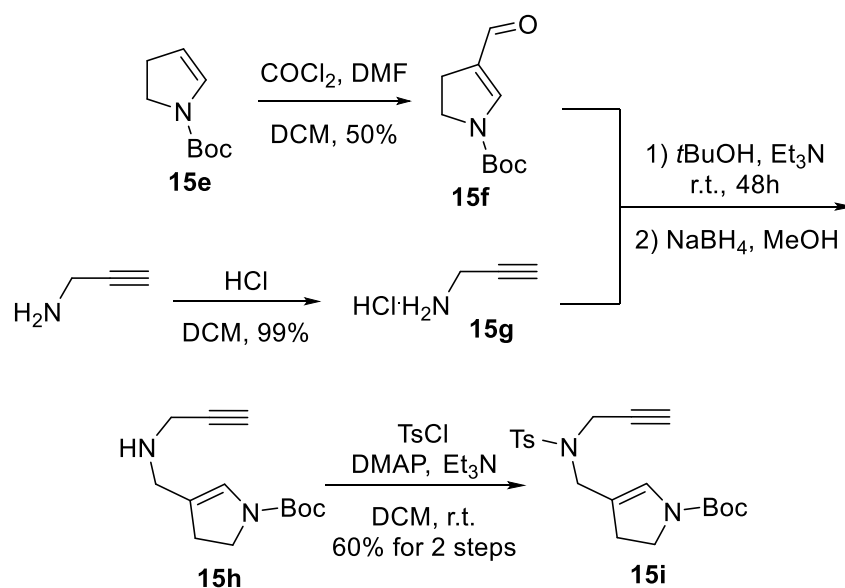
(**15a**), treated with *n*BuLi in dry THF. Boron trifluoride diethyl etherate was added dropwise and then treated with  $\gamma$ -butyrolactone, to give the ynone **15b**. The crude mixture was evaporated as light yellow oil, which was used immediately in the next step (*Scheme IV-33*).



*Scheme IV-33. Synthesis of furan moiety 15d*

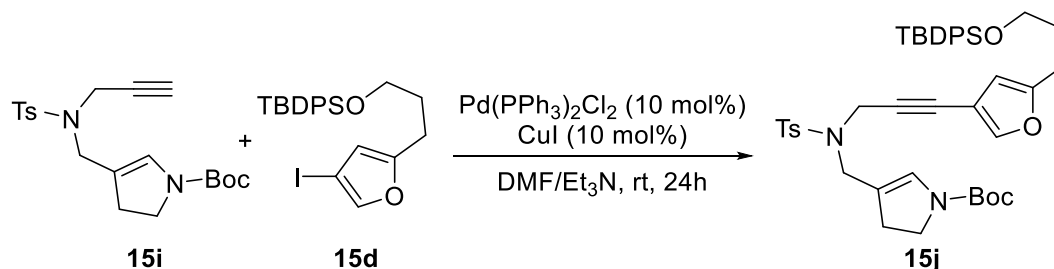
The former mixture was treated with hydroiodic acid (57 wt. % in H<sub>2</sub>O, distilled, stabilized) at 0°C, to achieve the cyclization and iodination with the formation of furan **15c** and its THP ether. The crude mixture was treated by *p*-toluenesulfonic acid to convert all the THP ether to the alcohol. Overall, furan derivative **15c** was obtained in 30% yield, starting from **15a**. The hydroxyl group of **15c** was protected by introducing *t*-butyldiphenylsilane group, in 90% yield (*Scheme IV-33*).

The unsaturated aldehyde **15f** was then prepared from *tert*-butyl 2,3-dihydro-1*H*-pyrrole-1-carboxylate **15e** by treatment with oxalyl chloride. Continuously, the reductive amination step was achieved with the hydrochloric acid salt of propargylamine **15g**, to obtain the terminal alkyne **15h** with sodium borohydride as reducing reagent. The amine was protected with a tosyl group, and the fragment **15i** was gained as white solid in 60% yield after 2 steps (*Scheme IV-34*).



Scheme IV-34. Synthesis of terminal alkyne moiety

With 1.2 equivalents of the product **15i** and 1.0 equivalent of furan fragment **15d**, the Sonogashira coupling reaction was carried out with *bis*(triphenylphosphine)Pd(II) chloride (10 mol%) and copper(I) iodide (20 mol%) as catalysts, in a solvent mixture DMF:Et<sub>3</sub>N (1:1) for 24 hours. The first catalytic test gave only 27% yield of compound **15j** (Table IV-7).



entry	additive	Solvent	yield (%)
1	--	Et <sub>3</sub> N:DMF=1:1	27
2	PPh <sub>3</sub> (20 mol%)	Et <sub>3</sub> N:DMF=1:1	33
3	PPh <sub>3</sub> (20 mol%)	Et <sub>3</sub> N	62

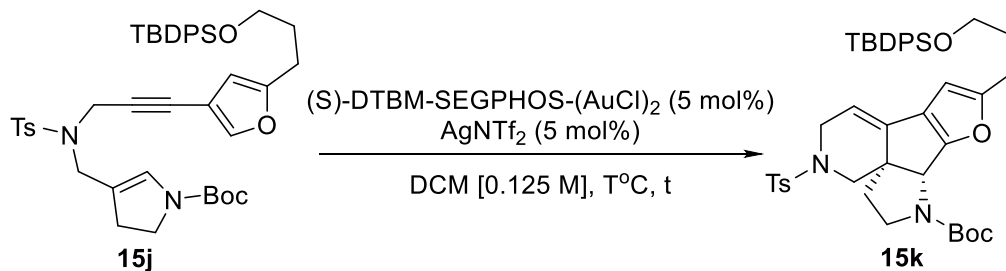
Table IV-7.

By introducing triphenylphosphine (20 mol%) as additional ligand, slight increase of the yield was observed. When the solvent was replaced by Et<sub>3</sub>N, compound **15j** could be isolated in 62% yield as light brown oil.

With this highly functionalized substrate **15j** in hand, we tested the efficiency of our methodology. Because of the alkyl chain on the furan moiety could improve the activity of the substrate, we started the test with lower reaction temperature than our former best condition (10°C). In the presence of 5 mol% of (*S*)-DTBM-SEGPHOS-(AuCl)<sub>2</sub> and 5 mol% of AgNTf<sub>2</sub> in dichloromethane at 0°C, 55% isolated yield and 42% *ee* was obtained (entry 1).



When the reaction temperature was decreased to  $-20^{\circ}\text{C}$ , the result was enhanced to 75% yield and 43% *ee* (entry 2). Start the reaction at  $-78^{\circ}\text{C}$ , did not allow to obtain better results (entry 3, Table IV-8).



entry	T/ $^{\circ}\text{C}$	t/h	yield (%) <sup>a</sup>	<i>ee</i> (%)
1	0	17	55	42
2	-20	17	75	43
3	-78	24	64	41

Table IV-8.

With those exciting preliminary results (43% *ee* for the tetracycle), we could see the potential of applying this methodology toward the total synthesis of Nakadomarin A. Here, we did the retrosynthesis analysis and we will introduce the main steps toward the asymmetric synthesis of Nakadomarin A, after the construction of the ABCD tetracycle (Scheme IV-35).

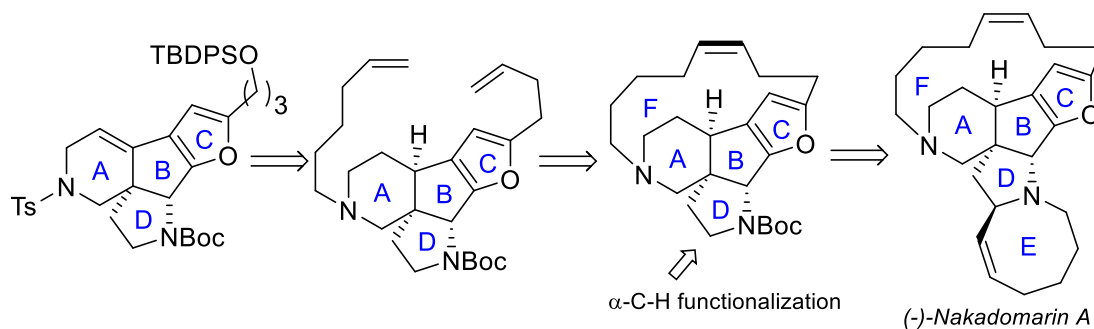
Starting with the polycyclic structure, deprotection and alkylation of the amine could permit to introduce the *N*-hexene moiety. The TBDPS group can be easily removed and the corresponding alcohol could be oxidized and transformed into olefin. Ring closing metathesis with transition metal catalysts will achieve the formation of the **F**-ring.<sup>150</sup>

At this stage, structure–activity relationship (SAR) studies could be conducted at the ICSN to highlight the influence of this **E**-ring in the cytotoxic activity.<sup>151</sup> In the longer term, C-H bond activation strategy could bring a very nice solution for the completion of the total synthesis of the Nakadomarin A.<sup>152</sup>

<sup>150</sup> a) Marx, V. M.; Herbert, M. B.; Keitz, B. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **2013**, *135*, 94. b) Meek, S. J.; O'Brien, R. V.; Lloveria, J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *471*, 461. c) Ogba, O. M.; Warner, N. C.; O'Leary, D. J.; Grubbs, R. H. *Chem. Soc. Rev.* **2018**, *47*, 4510.

<sup>151</sup> a) Sakai, R.; Higa, T.; Jefford, C. W.; Bernardinelli, G. *J. Am. Chem. Soc.* **1986**, *108*, 6404. b) J.E.Baldwin; R.C.Whitehead *Tetrahedron Lett.* **1992**, *33*, 2059. c) Kondo, K.; Shigemori, H.; Kikuchi, Y.; Ishibashi, M.; Sasaki, T.; Kobayashi, J. *J. Org. Chem.* **1992**, *57*, 2480.

<sup>152</sup> Chen, W.; Ma, L.; Paul, A.; Seidel, D. *Nat. Chem.* **2018**, *10*, 165.



*Scheme IV-35. Retrosynthesis of Nakadomarin A*

#### 4.4 Conclusion

Hence, we have developed an enantioselective 1,6-enyne cyclization/intramolecular nucleophilic addition sequence. Gold(I) catalysts showed high efficiency in this process, to promote the formation of the corresponding tetracyclic compounds. In asymmetric catalysis, we achieved to isolate a highly functionalized pentacyclic product in 90% yield and up to 90% ee. Even though not enough suitable substrates were obtained for this protocol, we are still working on the reaction scope. The application of our catalytic methodology in the asymmetric preparation of the core structure of Nakadomarin A is in process.



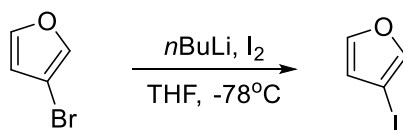
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## **Chapter 4**

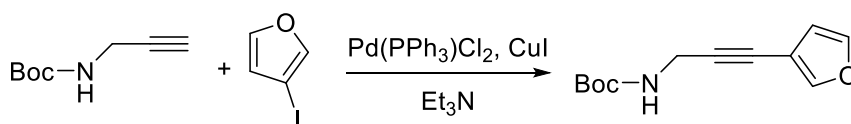
### **Experimental Part**

## 4.1 General information

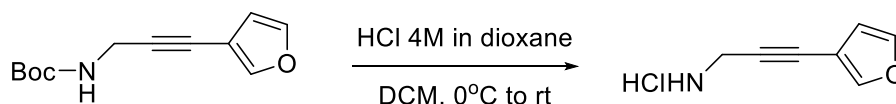
### 4.1.1 Synthesis of substrates 12a-12h



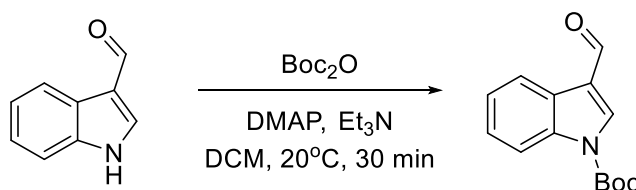
To a solution of 3-bromofuran (882  $\mu\text{L}$ , 10 mmol) in dry THF (8 mL) was added  $n\text{-BuLi}$  (1.3 M in hexane, 8.0 mL, 10.8 mmol) at  $-78^\circ\text{C}$ . After the mixture was stirred at this temperature for 1 h, a solution of  $\text{I}_2$  (3.74 g, 10.8 mmol) in THF (12 mL) was added dropwise. The mixture was stirred at  $-78^\circ\text{C}$  for another 1 h and warmed to rt to afford a solution of 3-iodofuran (ca 0.52 M) in THF, which was used into the next step.



To a mixture of tert-butyl prop-2-yn-1-ylcarbamate (1.242 g, 10 mmol),  $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$  (160 mg, 0.4 mmol), and  $\text{CuI}$  (152 mg, 0.8 mmol) were added a solution of the above 3-iodofuran in THF (0.52 M, 10 mmol) and  $\text{Et}_3\text{N}$  (20 mL, 144 mmol) sequentially at  $-78^\circ\text{C}$ . After the flask was flushed 3 times with  $\text{N}_2$ , the mixture was warmed to rt, stirred for about 48 h, and filtered through silica. The solid mass was washed with  $\text{EtOAc}$ . The combined filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography to give target product (607 mg, 69%) as an orange solid,  $R_f$  0.4 (25 % EA/heptane);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.57 (s, 1H), 7.34 (s, 1H), 6.40 (s, 1H), 4.78 (bs, 1H), 4.10 (s, 2H), 1.45 (s, 9H).

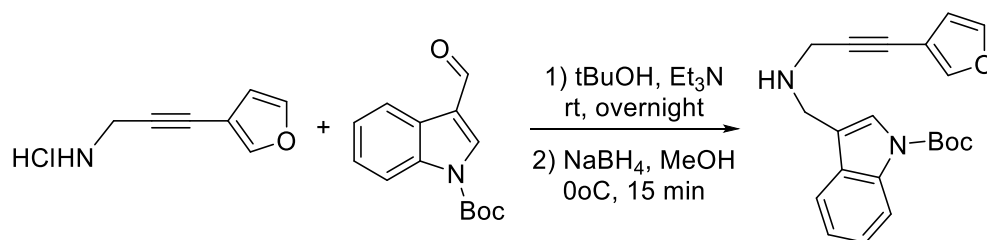


To a solution of St (607 mg, 2.74 mmol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) was added a solution of HCl in Dioxane (4 M, 2.1 mL, 3.27 mmol) at  $0^\circ\text{C}$ . The mixture was stirred at rt overnight. The solvents and excess HCl were removed under reduced pressure and the residue was crystallized from  $\text{MeOH}$ /ether to give target HCl salt (561.3 mg, %) as a grey solid, which was used into the next step.



To a solution of indole-3-carboxaldehyde, triethylamine (1.3 equiv.), and 10 mol%  $\text{DMAP}$  in  $\text{CH}_2\text{Cl}_2$  was added  $\text{Boc}_2\text{O}$  (1.2 equiv.). The reaction was stirred at room temperature until the

starting material was completely consumed. The reaction was diluted with  $\text{CH}_2\text{Cl}_2$ , worked up with water. The organic layer was washed with brine, dried over  $\text{MgSO}_4$ , filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography to give the target compound (421.3 mg, 86 %).

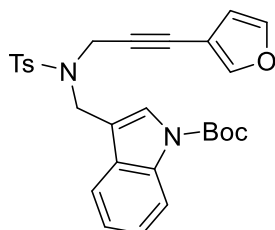


The above HCl salt (561.3 mg, 3.58 mmol) was dissolved in  $t\text{BuOH}$  (13 mL) and aldehyde (628 mg, 2.56 mmol) and  $\text{Et}_3\text{N}$  (364  $\mu\text{L}$ , 2.61 mmol) were added successively. The resultant mixture was stirred at rt overnight, concentrated under reduced pressure, and diluted with  $\text{MeOH}$  (13 mL).  $\text{NaBH}_4$  (135 mg, 3.58 mmol) was added at  $0^\circ\text{C}$  and the stirring was continued for 15 min. Then the mixture was quenched with saturated aqueous  $\text{NaHCO}_3$  solution and extracted with ether. The combined organic layers were washed with brine, dried ( $\text{MgSO}_4$ ), filtered, and concentrated to give a crude secondary amine, which was directly used into next step without purification.

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**tert-butyl 3-(((N-(3-(furan-3-yl)prop-2-yn-1-yl)-4-methylphenyl)sulfonamido)methyl)-1H-indole-1-carboxylate 12a**

---



**Chemical Formula:** C<sub>28</sub>H<sub>28</sub>N<sub>2</sub>O<sub>5</sub>S

**Molecular Weight:** 504.6010

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.10 (d, *J* = 8.1 Hz, 1H), 7.86 (dd, *J* = 8.3, 2.2 Hz, 3H), 7.57 (s, 1H), 7.39- 7.23 (m, 7H), 6.14 (s, 1H), 4.54 (s, 2H), 4.14 (s, 2H), 2.42 (s, 3H), 1.67 (s, 9H)

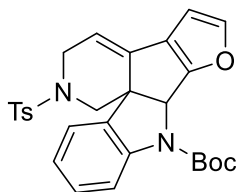
**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 145.8 (CH), 143.7 (C), 142.8 (CH), 135.9 (C), 135.8 (C), 129.7 (CH), 128.2 (CH), 125.9 (CH), 125.0 (CH), 123.1 (CH), 120.2 (CH), 115.3 (CH), 114.2 (C), 112.4 (CH), 84.2 (C), 83.6 (C), 41.9 (CH<sub>2</sub>), 36.6 (CH<sub>2</sub>), 28.3 (CH<sub>3</sub>), 21.6 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 2984, 2254, 1732, 1454, 1371, 1450, 1259, 1230, 1160, 1087, 1004, 904, 872, 725, 665. **HRMS(ESI)** Calcd. For C<sub>28</sub>H<sub>28</sub>N<sub>2</sub>O<sub>5</sub>SNa [M+Na]<sup>+</sup>: 527.1617, found: 527.1606.

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**tert-butyl 3-tosyl-2,3,4,9a-tetrahydro-9H-furo[3',2':4,5]pyrido[3',4':2,3]cyclopenta [1,2-b]indole-9-carboxylate 14a**

---



**Chemical Formula:** C<sub>28</sub>H<sub>28</sub>N<sub>2</sub>O<sub>5</sub>S

**Molecular Weight:** 504.6010

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.85 (s, 1H), 7.65 (d, *J* = 8.3 Hz, 2H), 7.43 (s, 1H), 7.37- 7.34 (m, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.28- 7.20 (m, 1H), 6.97 (s, 1H), 6.27 (d, *J* = 1.9 Hz, 1H), 5.63 (t, *J* = 3.3 Hz, 1H), 5.37 (d, *J* = 45.4 Hz, 1H), 4.48 (dd, *J* = 17.1, 2.8 Hz, 1H), 4.00 (d, *J* = 10.5 Hz, 1H), 3.52 (d, *J* = 15.2 Hz, 1H), 2.86 (s, 1H), 2.42 (s, 3H), 1.64 (s, 9H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 159.6 (C), 149.1 (C), 143.9 (C), 134.4 (C), 129.8 (CH), 129.5 (CH), 127.7 (CH), 125.7 (CH), 122.9 (CH), 115.0 (CH), 110.4 (CH), 105.1 (CH), 63.4 (CH), 50.4 (CH<sub>2</sub>), 44.8 (CH<sub>2</sub>), 32.0 (CH), 29.1 (CH), 28.5 (CH<sub>3</sub>), 22.8 (CH), 21.6 (CH<sub>3</sub>), 14.2 (C).

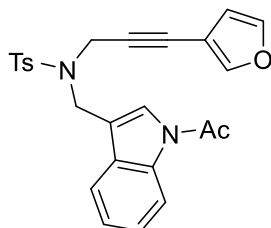
**IR:** ν<sub>max</sub> = 2980, 2255, 1705, 1480, 1463, 1388, 1370, 1316, 1261, 1161, 1151, 1047, 1021, 907, 730, 678.

**HRMS(ESI)** Calcd. For C<sub>28</sub>H<sub>28</sub>N<sub>2</sub>O<sub>5</sub>SNa [M+Na+CH<sub>3</sub>CN]<sup>+</sup>: 568.1882, found: 568.1855.

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**N-((1-acetyl-1H-indol-3-yl)methyl)-N-(3-(furan-3-yl)prop-2-yn-1-yl)-4-methylbenzenesulfonamide 12c**

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**Chemical Formula:** C<sub>25</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub>S

**Molecular Weight:** 446.5210

White solid; R<sub>f</sub> 0.46 (40% EtOAc/n-Heptane)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 8.39 (s, 1H), 7.91 - 7.77 (m, 3H), 7.45- 7.28 (m, 7H), 6.13 (s, 1H), 4.55 (s, 2H), 4.17 (s, 2H), 2.60 (s, 3H), 2.42 (s, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 168.5 (C), 145.8 (CH), 143.8 (C), 142.9 (CH), 136.2 (C), 135.8 (C), 130.0 (C), 129.7 (CH), 128.1 (CH), 127.5 (C), 125.9 (CH), 125.0 (CH), 124.1 (CH), 119.9 (CH), 116.6 (CH), 116.3 (C), 112.3 (CH), 106.7 (C), 83.6 (C), 41.9 (CH<sub>2</sub>), 36.9 (CH<sub>2</sub>), 24.1 (CH<sub>3</sub>), 21.6 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub>= 3055, 2922, 2236, 1706, 1598, 1453, 1388, 1343, 1328, 1265, 1221, 1159, 892, 733, 703, 662

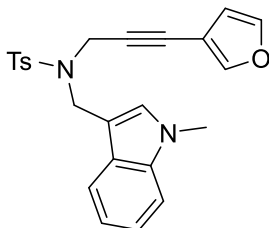
**HRMS(ESI)** Calcd. For C<sub>25</sub>H<sub>23</sub>N<sub>2</sub>O<sub>4</sub>S [M+H]<sup>+</sup>: 447.1379, found: 447.1392



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**N-(3-(furan-3-yl)prop-2-yn-1-yl)-4-methyl-N-((1-methyl-1H-indol-3-yl)methyl)benzenesulfon amide 12d**

---



**Chemical Formula:** C<sub>24</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub>S

**Molecular Weight:** 418.5110

White solid; R<sub>f</sub> 0.5 (30% EtOAc/n-Heptane)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.77 (dd, *J* = 13.1, 8.1 Hz, 3H), 7.28- 7.21 (m, 5H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.07 (t, *J* = 7.3 Hz, 1H), 6.96 (s, 1H), 6.08 (s, 1H), 4.51 (s, 2H), 4.05 (s, 2H), 3.69 (s, 3H), 2.33 (s, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 179.9 (C), 145.7 (CH), 143.4 (C), 142.8 (CH), 129.6 (CH), 129.3 (CH), 128.2 (CH), 127.6 (CH), 122.3 (CH), 119.8 (CH), 112.4 (CH), 109.4 (C), 107.9 (C), 84.2 (C), 41.9 (CH<sub>2</sub>), 36.2 (CH<sub>2</sub>), 33.0 (CH<sub>3</sub>), 21.6 (CH<sub>3</sub>)

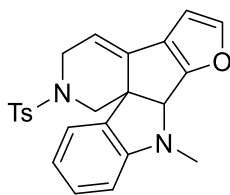
**IR:** ν<sub>max</sub> = 3055, 2987, 1556, 1475, 1344, 1330, 1264, 1158, 1092, 1003, 890, 789, 733, 704, 662

**HRMS(ESI)** Calcd. For C<sub>24</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub>NaS [M+Na]<sup>+</sup>: 441.1249, found: 441.1229

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**9-methyl-3-tosyl-3,4,9,9a-tetrahydro-2H-furo[3',2':4,5]pyrido[3',4':2,3]cyclopenta [1,2-b]indole 14d**

---



**Chemical Formula:** C<sub>24</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub>S

**Molecular Weight:** 418.5110

White solid; R<sub>f</sub> 0.65 (DCM 100%)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.65 (d, *J* = 8.2 Hz, 2H), 7.35- 7.27 (m, 4H), 7.15 (t, *J* = 7.6 Hz, 1H), 6.68 (t, *J* = 7.4 Hz, 1H), 6.45 (d, *J* = 7.8 Hz, 1H), 6.26 (d, *J* = 1.7 Hz, 1H), 5.58 (t, *J* = 3.2 Hz, 1H), 4.65 (s, 1H), 4.44 (dd, *J* = 16.9, 3.1 Hz, 1H), 4.04 (d, *J* = 10.4 Hz, 1H), 3.49 (dd, *J* = 16.9, 3.3 Hz, 1H), 3.05 (s, 3H), 2.85 (d, *J* = 10.4 Hz, 1H), 2.42 (s, 3H)

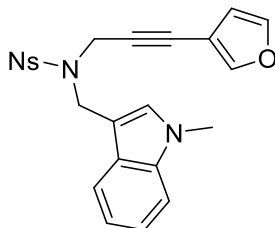
**IR:** ν<sub>max</sub> = 2947, 2889, 1603, 1483, 1351, 1222, 1165, 1116, 963, 909, 733, 719, 655 cm<sup>-1</sup>

**HRMS(ESI)** Calcd. For C<sub>18</sub>H<sub>16</sub>NO<sub>3</sub>S [M+H]<sup>+</sup>: 419.1429, found: 419.1429

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**N-(3-(furan-3-yl)prop-2-yn-1-yl)-N-((1-methyl-1H-indol-3-yl)methyl)-4-nitrobenzenesulfonamide 12e**

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**Chemical Formula:** C<sub>23</sub>H<sub>19</sub>N<sub>3</sub>O<sub>5</sub>S

**Molecular Weight:** 449.4810

Yellow solid;

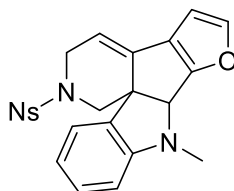
**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.32- 8.27 (m, 2H), 8.17- 8.09 (m, 2H), 7.82 (d, *J* = 7.9 Hz, 1H), 7.36 (s, 1H), 7.34- 7.24 (m, 4H), 7.16 (ddd, *J* = 8.0, 6.7, 1.4 Hz, 1H), 7.07 (s, 1H), 6.12 (d, *J* = 1.4 Hz, 1H), 4.63 (s, 2H), 4.18 (s, 2H), 3.78 (s, 3H)

**HRMS** (ESI) Calcd. For C<sub>23</sub>H<sub>20</sub>N<sub>3</sub>O<sub>5</sub>S [M+H]<sup>+</sup>: 450.1124, found: 450.1140.

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**9-methyl-3-((4-nitrophenyl)sulfonyl)-3,4,9,9a-tetrahydro-2H-furo[3',2':4,5]pyrido[3',4':2,3]cyclopenta[1,2-b]indole 14e**

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**Chemical Formula:** C<sub>23</sub>H<sub>19</sub>N<sub>3</sub>O<sub>5</sub>S

**Molecular Weight:** 449.4810

Yellow solid; R<sub>f</sub> 0.6 (DCM 100%)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.37- 8.28 (m, 2H), 7.98- 7.90 (m, 2H), 7.34 (d, *J* = 1.8 Hz, 1H), 7.12 (ddd, *J* = 11.0, 8.7, 4.3 Hz, 2H), 6.63- 6.53 (m, 1H), 6.45 (d, *J* = 7.8 Hz, 1H), 6.28 (d, *J* = 1.9 Hz, 1H), 5.60 (t, *J* = 3.2 Hz, 1H), 4.68 (s, 1H), 4.50 (dd, *J* = 16.9, 3.1 Hz, 1H), 4.08 (d, *J* = 10.7 Hz, 1H), 3.63 (dd, *J* = 16.9, 3.4 Hz, 1H), 3.05 (s, 3H), 3.01 (d, *J* = 10.7 Hz, 1H)

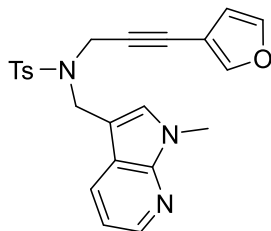
**IR:** ν<sub>max</sub> = 3051, 2892, 2256, 1604, 1530, 1483, 1350, 1312, 1265, 1170, 1116, 965, 906, 737, 708

**HRMS** (ESI) Calcd. For C<sub>23</sub>H<sub>20</sub>N<sub>3</sub>O<sub>5</sub>S [M+H]<sup>+</sup>: 450.1124, found: 450.1131

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**N-(3-(furan-3-yl)prop-2-yn-1-yl)-4-methyl-N-((1-methyl-1H-pyrrolo[2,3-b]pyridine-3-yl)methyl)benzenesulfonamide 12f**

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**Chemical Formula:** C<sub>23</sub>H<sub>21</sub>N<sub>3</sub>O<sub>3</sub>S

**Molecular Weight:** 419.4990

(320 mg, 29 %). White solid;

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 8.34 (dd, *J* = 4.7, 1.3 Hz, 1H), 8.15 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.83 (d, *J* = 8.2 Hz, 2H), 7.29 (dd, *J* = 13.2, 3.5 Hz, 4H), 7.14 (s, 1H), 7.07 (dd, *J* = 7.9, 4.7 Hz, 1H), 6.13 (d, *J* = 0.8 Hz, 1H), 4.54 (s, 2H), 4.10 (s, 2H), 3.84 (s, 3H), 2.39 (s, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 148.3 (C), 145.7 (CH), 143.6 (CH), 143.5 (C), 142.8 (CH), 136.1 (C), 129.6 (CH), 129.1 (CH), 128.2 (CH), 128.0 (CH), 119.9 (C), 115.9 (CH), 112.3 (CH), 106.6 (C), 83.8 (C), 42.0 (CH<sub>2</sub>), 36.3 (CH<sub>2</sub>), 31.3 (CH<sub>3</sub>), 21.6 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 3055, 2923, 2234, 1600, 1544, 1461, 1409, 1341, 1297, 1265, 1158, 1092, 1003, 889, 871, 736, 704, 660 cm<sup>-1</sup>

**HRMS(ESI)** Calcd. For C<sub>23</sub>H<sub>22</sub>N<sub>3</sub>O<sub>3</sub>S [M+H]<sup>+</sup>: 420.1382, found: 420.1381

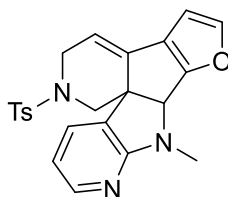
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**Compound 14f**

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**Chemical Formula:** C<sub>23</sub>H<sub>21</sub>N<sub>3</sub>O<sub>3</sub>S

**Molecular Weight:** 419.4990

(20 mg, 40%). White solid; R<sub>f</sub> 0.33 (10% EtOAc/DCM)

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.97 (dd, *J* = 5.3, 1.6 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 2H), 7.46 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.35 (d, *J* = 1.7 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 6.52 (dd, *J* = 7.2, 5.3 Hz, 1H), 6.29 (d, *J* = 1.9 Hz, 1H), 5.59 (t, *J* = 3.2 Hz, 1H), 4.67 (s, 1H), 4.44 (dd, *J* = 17.0, 3.1 Hz, 1H), 4.00 (d, *J* = 10.5 Hz, 1H), 3.46 (dd, *J* = 17.0, 3.3 Hz, 1H), 3.22 (s, 3H), 2.81 (d, *J* = 10.5 Hz, 1H), 2.42 (s, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 149.0 (CH), 148.2 (CH), 143.9 (C), 134.8 (C), 133.8 (C), 132.8 (CH), 129.9 (CH), 129.6 (C), 129.3 (C), 128.1 (C), 127.7 (CH), 125.6 (C), 113.5 (CH), 109.9 (CH), 105.1 (CH), 65.4 (CH), 58.9 (C), 50.0 (CH<sub>2</sub>), 44.9 (CH<sub>2</sub>), 30.6 (CH<sub>3</sub>), 21.6 (CH<sub>3</sub>)

**IR:** ν<sub>max</sub> = 3058, 2850, 2149, 1603, 1486, 1406, 1351, 1247, 1163, 1122, 1095, 1001, 964, 920, 893, 816, 773, 735, 718, 656 cm<sup>-1</sup>

**HRMS**(ESI) Calcd. For C<sub>23</sub>H<sub>22</sub>N<sub>3</sub>O<sub>3</sub>S [M+H]<sup>+</sup>: 420.1382, found: 420.1381

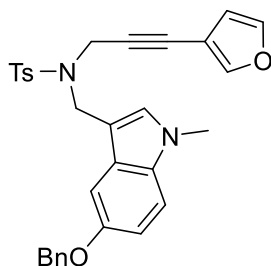
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**N-((5-(benzyloxy)-1-methyl-1H-indol-3-yl)methyl)-N-(3-(furan-3-yl)prop-2-yn-1-yl)-4-methylbenzenesulfonamide 12g**

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**Chemical Formula:** C<sub>31</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub>S

**Molecular Weight:** 524.6350

(300 mg, 11 %). Light yellow solid

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>) δ 7.87 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 7.4 Hz, 2H), 7.42 (d, *J* = 1.8 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.31 (dd, *J* = 8.2, 6.8 Hz, 5H), 7.20 (d, *J* = 8.8 Hz, 1H), 7.02- 6.96 (m, 2H), 6.16 (d, *J* = 1.5 Hz, 1H), 5.09 (s, 2H), 4.55 (s, 2H), 4.13 (s, 2H), 3.73 (s, 3H), 2.40 (s, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 153.5 (C), 145.7 (CH), 143.4 (C), 142.8 (CH), 137.7 (C), 136.4 (C), 132.8 (C), 129.8 (CH), 129.6 (CH), 128.6 (CH), 128.2 (CH), 128.0 (CH), 127.9 (CH), 127.6 (CH), 113.4 (CH), 112.5 (CH), 110.2 (CH), 107.3 (C), 102.6 (CH), 84.4 (C), 70.8 (CH<sub>2</sub>), 41.9 (CH<sub>2</sub>), 36.2 (CH<sub>2</sub>), 33.1 (CH<sub>3</sub>), 21.6 (CH<sub>3</sub>)

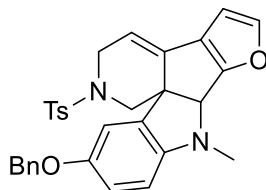
**IR:** ν<sub>max</sub> = 2922, 2236, 1623, 1579, 1490, 1344, 1327, 1264, 1206, 1158, 1091, 1003, 888, 872, 794, 737, 698, 662 m<sup>-1</sup>

**HRMS(ESI)** Calcd. For C<sub>31</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub>SNa [M+Na]<sup>+</sup>: 547.1667, found: 547.1654

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**6-(benzyloxy)-9-methyl-3-tosyl-3,4,9 $\alpha$ -tetrahydro-2H-furo[3',2':4,5]pyrido[3',4':2,3]cyclopenta[1,2-b]indole 14g**

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**Chemical Formula:** C<sub>31</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub>S

**Molecular Weight:** 524.6350

(24 mg, 92%). White solid; R<sub>f</sub> 0.30 (DCM)

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.69 (d, *J* = 8.1 Hz, 2H), 7.48 (d, *J* = 7.4 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.36 (s, 1H), 7.34- 7.28 (m, 3H), 7.06 (d, *J* = 2.3 Hz, 1H), 6.81 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.39 (d, *J* = 8.4 Hz, 1H), 6.29 (d, *J* = 1.6 Hz, 1H), 5.59 (s, 1H), 5.05- 4.96 (m, 2H), 4.67 (s, 1H), 4.42 (dd, *J* = 16.9, 3.1 Hz, 1H), 4.11 (d, *J* = 10.5 Hz, 1H), 3.51 (dd, *J* = 16.9, 3.1 Hz, 1H), 3.03 (s, 3H), 2.90 (d, *J* = 10.5 Hz, 1H), 2.40 (s, 3H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  148.8 (CH), 143.7 (C), 137.9 (C), 136.6 (C), 134.0 (C), 133.6 (C), 129.8 (CH), 128.6 (CH), 127.9 (CH), 127.8 (CH), 115.9 (CH), 113.9 (CH), 109.5 (CH), 108.0 (CH), 105.1 (CH), 71.4 (CH<sub>2</sub>), 69.3 (CH), 49.8 (CH<sub>2</sub>), 44.8 (CH<sub>2</sub>), 34.2 (CH<sub>3</sub>), 21.6 (CH<sub>3</sub>)

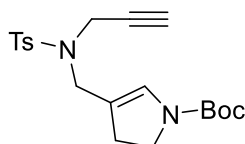
**IR:**  $\nu_{\max}$  = 2919, 2853, 2212, 1677, 1597, 1489, 1455, 1350, 1251, 1184, 1166, 1096, 1020, 965, 922, 815, 735, 714, 698, 656 cm<sup>-1</sup>

**HRMS**(ESI) Calcd. For C<sub>31</sub>H<sub>29</sub>N<sub>2</sub>O<sub>4</sub>S [M+H]<sup>+</sup>: 525.1848, found: 525.1838

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**tert-butyl4-(((4-methyl-N-(prop-2-yn-1-yl)phenyl)sulfonamido)methyl)-2,3-dihydro-1H-pyrrole-1-carboxylate 15i**

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**Chemical Formula:** C<sub>20</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>S

**Molecular Weight:** 390.4980

(264 mg, 60%). Colorless oil

**<sup>1</sup>H NMR** (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.73 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 6.50 (d, *J* = 87.2 Hz, 1H), 4.05 (s, 2H), 3.87 (s, 2H), 3.74 (d, *J* = 8.7 Hz, 2H), 3.48 (s, 1H), 2.59 (dd, *J* = 31.7, 7.5 Hz, 2H), 2.42 (s, 3H), 1.46 (s, 9H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  129.6 (CH), 127.9 (CH), 45.7 (CH<sub>2</sub>), 44.7 (CH<sub>2</sub>), 35.6 (CH<sub>2</sub>), 29.7 (CH<sub>2</sub>), 28.5 (CH<sub>3</sub>), 21.7 (CH<sub>3</sub>)

**IR:**  $\nu_{\max}$  = 3302, 2980, 2254, 1693, 1420, 1393, 1366, 1349, 1265, 1160, 1092, 1041, 895, 815, 733, 703, 661 m<sup>-1</sup>

**HRMS**(ESI) Calcd. For C<sub>20</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>SNa [M+Na]<sup>+</sup>: 413.1511, found: 413.1515.

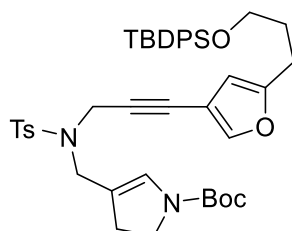
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**tert-butyl4-(((N-(3-(5-(3-((tert-butylidiphenylsilyl)oxy)propyl)furan-3-yl)prop-2-yn-1-yl)-4-methylphenyl)sulfonamido)methyl)-2,3-dihydro-1H-pyrrole-1-carboxylate 15j**

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**Chemical Formula:** C<sub>43</sub>H<sub>52</sub>N<sub>2</sub>O<sub>6</sub>SSi

**Molecular Weight:** 753.0420

(20 mg, 27%). Light yellow oil

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>) δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.70- 7.61 (m, 4H), 7.49- 7.32 (m, 6H), 7.26 (dd, *J* = 4.9, 3.3 Hz, 2H), 7.17 (s, 1H), 6.52 (d, *J* = 50.0 Hz, 1H), 5.70 (s, 1H), 4.22 (s, 2H), 3.90 (s, 2H), 3.75 (s, 2H), 3.69 (t, *J* = 6.1 Hz, 2H), 2.66 (m, 4H), 2.37 (s, 3H), 1.85 (dt, *J* = 13.4, 6.9 Hz, 2H), 1.47 (s, 9H), 1.06 (s, 9H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>) δ 144.3 (CH), 143.5 (C), 136.3 (C), 135.7 (CH), 134.0 (C), 129.8 (CH), 129.6 (CH), 128.0 (CH), 127.8 (CH), 115.5 (C), 107.6 (CH), 62.9 (CH<sub>2</sub>), 45.7 (CH<sub>2</sub>), 44.9 (CH<sub>2</sub>), 36.6 (CH<sub>2</sub>), 30.8 (CH<sub>2</sub>), 29.8 (CH<sub>2</sub>), 28.5 (CH<sub>3</sub>), 27.0 (CH<sub>3</sub>), 24.4 (CH<sub>2</sub>), 21.6 (CH<sub>3</sub>)

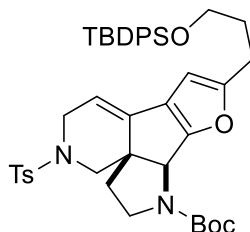
**IR:** ν<sub>max</sub>= 3053, 2931, 2860, 1698, 1427, 1394, 1368, 1264, 1163, 1091, 896, 817, 735, 703cm<sup>-1</sup>

**HRMS(ESI)** Calcd. For C<sub>43</sub>H<sub>52</sub>N<sub>2</sub>O<sub>6</sub>NaSi [M+Na]<sup>+</sup>: 775.3213, found: 775.3210

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**tert-butyl(3 $\alpha$ S,10 $\beta$ S)-9-(3-((tert-butyl)diphenylsilyl)oxy)propyl)-5-tosyl-2,3,4,5,6,10b-hexahydro-1H-furo[3',2':3,4]pyrrolo[3',2':1,5]cyclopenta[1,2-c]pyridine-1-carboxylate 15k**

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**Chemical Formula:** C<sub>43</sub>H<sub>52</sub>N<sub>2</sub>O<sub>6</sub>SSi

**Molecular Weight:** 753.0420

(10 mg, 50%). Colorless oil

**<sup>1</sup>H NMR** (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.72- 7.59 (m, 6H), 7.44- 7.28 (m, 8H), 5.85 (s, 1H), 5.33 (s, 1H), 4.72 (d,  $J$  = 58.4 Hz, 1H), 4.26 (dd,  $J$  = 16.7, 3.0 Hz, 1H), 3.93 (d,  $J$  = 10.7 Hz, 1H), 3.68 (t,  $J$  = 5.7 Hz, 2H), 3.56 (dd,  $J$  = 23.7, 8.4 Hz, 2H), 3.31 (t,  $J$  = 17.7 Hz, 1H), 2.72 (t,  $J$  = 7.3 Hz, 2H), 2.62 (d,  $J$  = 10.8 Hz, 1H), 2.43 (s, 3H), 2.35 (s, 1H), 1.97 (d,  $J$  = 9.9 Hz, 1H), 1.93- 1.81 (m, 2H), 1.52 (s, 9H), 1.04 (s, 9H)

**<sup>13</sup>C NMR** (75 MHz, CDCl<sub>3</sub>)  $\delta$  143.8 (C), 135.7 (CH), 134.0 (C), 129.9 (CH), 129.7 (CH), 127.8 (CH), 127.6 (CH), 108.7 (CH), 100.4 (CH), 80.1 (C), 63.0 (CH<sub>2</sub>), 61.6 (CH), 48.7 (CH<sub>2</sub>), 45.7 (CH<sub>2</sub>), 44.7 (CH<sub>2</sub>), 33.7 (CH<sub>2</sub>), 32.0 (CH<sub>2</sub>), 28.6 (CH<sub>3</sub>), 27.0 (CH<sub>3</sub>), 25.5 (CH<sub>2</sub>), 21.7 (CH<sub>3</sub>)

**IR:**  $\nu_{\max}$  = 3052, 2931, 2859, 1694, 1598, 1457, 1428, 1392, 1365, 1265, 1165, 1104, 1020, 977, 920, 816, 734, 701, 660 cm<sup>-1</sup>

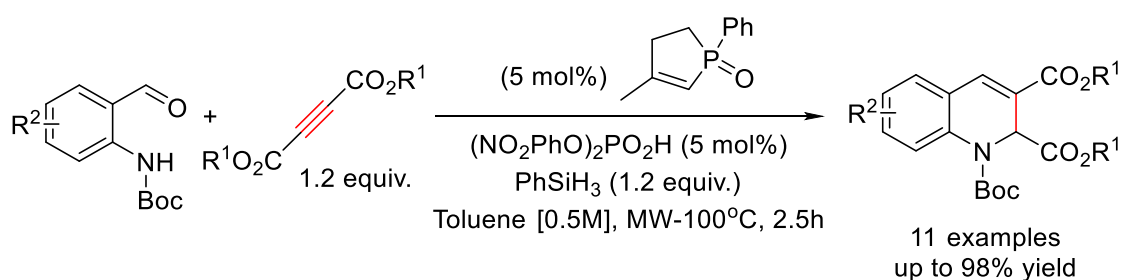
**HRMS(ESI)** Calcd. For C<sub>43</sub>H<sub>52</sub>N<sub>2</sub>O<sub>6</sub>NaSSiNa [M+Na]<sup>+</sup>: 775.3213, found: 775.3221



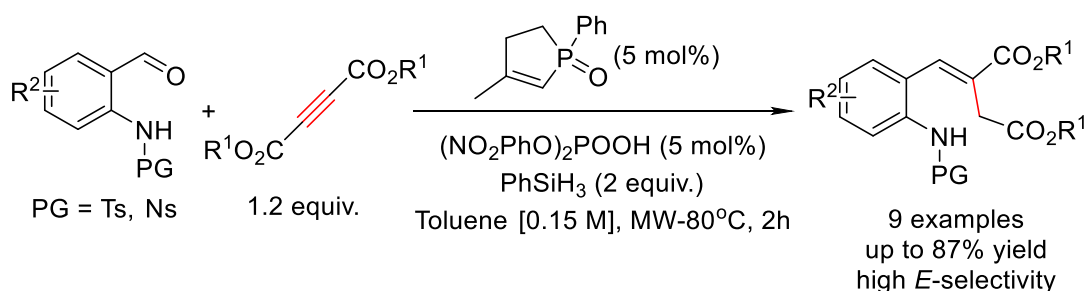
## General conclusions

In this manuscript, my research focused on two main applications of phosphine in organic chemistry: (1) new reactions in organocatalysis; and (2) development of new asymmetric gold(I)-catalysis processes.

In the first chapter, we first focused our work to the development of a catalytic Michael addition/Wittig reaction toward the synthesis of 1,2-dihydroquinolines. A well-chosen cyclic phosphine oxide was used as precatalyst. The *in situ* reduction of formed phosphine oxide was promoted by the quantitative use of phenylsilane and catalytic amount of  $(\text{NO}_2\text{PhO})_2\text{PO}_2\text{H}$ . The use of microwave heating allowed us to isolate eleven highly functionalized products, in up to 98% yield.<sup>153</sup>



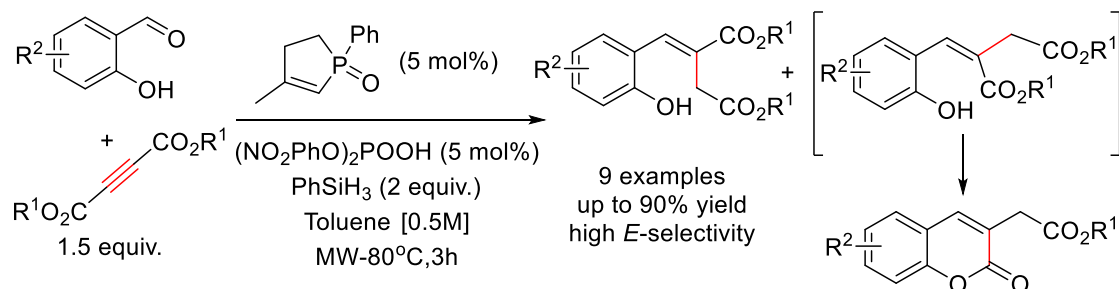
Beside 1,2-dihydroquinolines, an olefin byproduct was discovered. We noticed that these new molecules were valuable building blocks, possibly useful in the synthesis of different bioactive natural compounds. Hence, we decided to optimize this olefination reaction. After optimization, nine new products were synthesized, in up to 87% yield, and with generally good stereoselectivities, in favor of the *E*-isomer. Corresponding mechanism study was carried out. Phenylsilane behaves as a bifunctional reagent, both as reducing reagent for the phosphine oxide and also as a hydride donor. Trace water in the reaction system is also essential in the formation of olefins.<sup>152</sup>



2-hydroxylated benzaldehydes extended the reaction scope (nine examples, up to 95% yield). At the same time, 2*H*-chromen-2-ones were observed as byproducts. We postulated that they came from intramolecular condensation of *Z*-olefin. An alkyl-aldehyde was also tested and showed high reactivity. Unsubstituted benzaldehydes were not good candidates for this transformation. This last result confirmed the importance of proton-donor on the *ortho*-

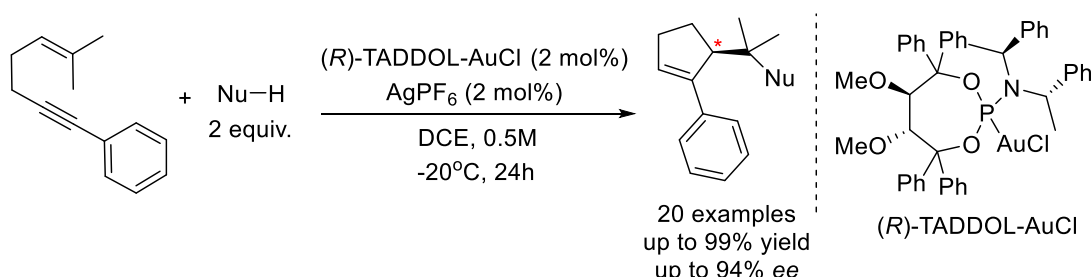
<sup>153</sup> Han, X.; Saleh, N.; Retailleau, P.; Voituriez, A. *Org. Lett.* **2018**, *20*, 4584.

position of aldehyde substrate in this transformation.

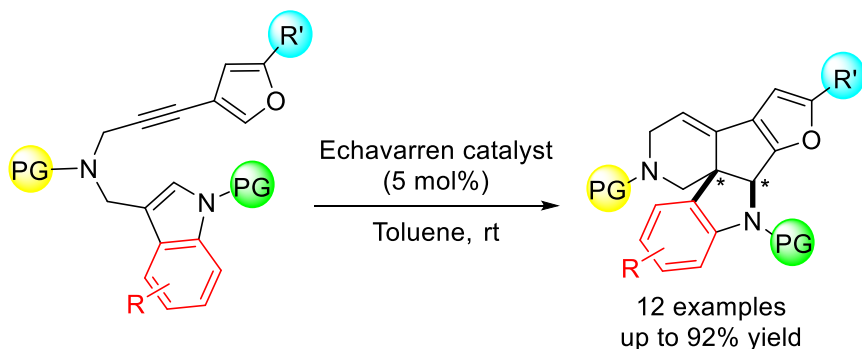


In the second part of this work, we developed two gold(I)-catalyzed asymmetric transformations of enyne substrates. Besides commercial available BIPHEP-, BINAP- and SEGPHOS-diphosphine ligands, we prepared an acyclic TADDOL-derived phosphoramidite to promote chirality induction.

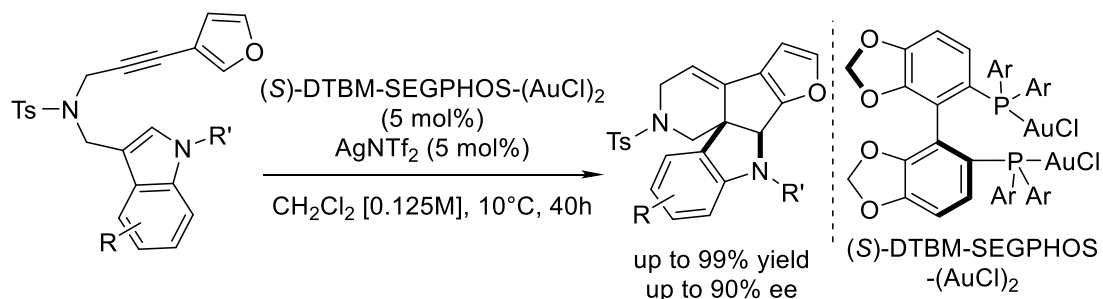
We developed the first gold(I)-catalyzed enantioselective 1,5-enyne cyclization/intermolecular nucleophilic addition sequence. All the diphosphine *bis*-gold complexes available in our laboratory were tested and were not so much efficient in this asymmetric transformation. We decided to prepare an acyclic TADDOL-derived phosphoramidite which could possess a good potential for this transformation. With this phosphoramidite *mono*-gold catalyst, the desired cyclopentene compounds were isolated in high yields and enantioselectivities (20 examples, up to 94% *ee*).



For the last part of our work, we developed an 1,6-enyne cyclization/cascade nucleophilic addition process. Based on a indole substituted 1,6-enyne substrate, we modified different part of this molecule toward a sequence of highly functionalized substrates. Cationic gold(I) complex promoted twelve racemic examples with up to 92% yield.



We continued to develop the asymmetric version of this transformation. After screening well-known axial chiral diphosphine *bis*-gold catalysts, (*S*)-DTBM-SEGPHOS-(AuCl)<sub>2</sub> proved to be the optimal choice. Moderate to excellent activity and enantioselectivity could be achieved for the target pentacyclic compounds. In the future, this asymmetric variant has the potential to be used in the synthesis of the tetracycle core of Nakadomarin A.



In conclusion, a new olefination process catalyzed by cyclic phosphine was carried out with good tolerance of different aldehyde substrates. On the other hand, new methodologies were developed for enantioselective cyclization of 1,5- and 1,6-enynes. Moderate to excellent reactivity and enantioselectivity could be obtained.

## Résumé étendu en français

Les phosphines jouent un rôle majeur dans la chimie organique moderne. Dans le domaine de la catalyse, les dérivés organophosphorés peuvent être appliqués comme catalyseurs dans de nombreuses transformations par lui-même, comme organocatalyseur, ou comme ligand dans la catalyse organométallique.

Parmi la famille des réactions phosphine-favorisées, les transformations les plus connues incluent la réaction de Wittig, la réaction de Mitsunobu, la réaction d'appel et beaucoup d'autres. La découverte de ces transformations a mis en évidence le développement de la chimie du phosphore. Cependant, la formation d'oxydes de phosphine correspondants pourrait entraver l'isolement des produits cibles purs et sont des processus d'économie atome faible. Par conséquent, des réactions phosphine-catalysées ont été effectuées pour résoudre ces problèmes. L'une des stratégies les plus largement utilisées est la régénération in situ des phosphines trivalentes par la réduction de l'oxyde de phosphine.

D'autre part, des progrès ont été réalisés dans la catalyse homogène de l'or. Si ce champ a été découvert le siècle dernier, la recherche sur ce domaine a augmenté de façon explosive au cours de la dernière décennie. Organophosphines sont couramment appliqués comme ligands pour coordonner le centre d'or. Parmi les transformations au-catalysées, les cyclisations de 1,n-enynes offrent des approches simples et atomes-économiques vers l'isolement de structures cycliques complexes. Plus intéressant encore, chiral phosphine ligand-or système catalyseur favorise la synthèse asymétrique qui est l'un des sujets les plus chauds dans la chimie organique pour l'instant.

Dans ce manuscrit, mes recherches ont porté sur deux applications principales de la phosphine en chimie organique : (1) de nouvelles réactions en organocatalyse; et (2) le développement de nouveaux processus asymétriques de catalyse de l'or (I).

Dans le premier chapitre, nous avons d'abord concentré notre travail sur le développement d'une réaction catalytique Michael addition/Wittig vers la synthèse de 1,2-dihydroquinolines. Un oxyde de phosphine cyclique bien choisi a été utilisé comme précatalyseur. La réduction in situ de l'oxyde de phosphine formé a été favorisée par l'utilisation quantitative de la phénylsilane et de la quantité catalytique de  $(\text{NO}_2\text{PhO})_2\text{PO}_2\text{H}$ . L'utilisation du chauffage par micro-ondes nous a permis d'isoler onze produits hautement fonctionnalisés, dans un rendement allant jusqu'à 98 %.

À côté de 1,2-dihydroquinolines, un sous-produit d'olefin a été découvert. Nous avons remarqué que ces nouvelles molécules étaient des blocs de construction précieux, peut-être utiles dans la synthèse de différents composés naturels bioactifs. Nous avons donc décidé d'optimiser cette réaction d'olefination. Après l'optimisation, neuf nouveaux produits ont été synthétisés, dans un rendement allant jusqu'à 87%, et avec des stéréotypes généralement bons, en faveur de l'E-isomer. L'étude correspondante de mécanisme a été effectuée. Phénylsilane se comporte comme un réactif bifonctionnel, à la fois comme réagent de réduction pour l'oxyde de phosphine et aussi comme un donneur d'hydride. L'eau de trace dans le système de réaction est également essentielle dans la formation des olefins.

Les benzaldéhydes hydroxylés ont étendu la portée de réaction (neuf exemples, jusqu'à 95 % de rendement). Dans le même temps, 2*H*-chromen-2-ones ont été observés comme sous-produits. Nous avons postulé qu'ils provenaient de condensation intramoléculaire de Z-olefin. Un alkyl-aldéhyde a également été testé et a montré une forte réactivité. Les benzaldéhydes non substitués n'étaient pas de bons candidats pour cette transformation. Ce dernier résultat a confirmé l'importance du proton-donneur sur l'orthoposition du substrat d'aldéhyde dans cette transformation.

Dans la deuxième partie de ce travail, nous avons développé deux transformations asymétriques aurifères (I)-catalysées de substrats enynes. Outre les ligands BIPHEP-, BINAP- et SEGPHOS-diphosphine disponibles, nous avons préparé une phosphoramidite acyclique dérivée de TADDOL pour favoriser l'induction de la chiralité.

Nous avons développé la première séquence d'addition nucléophile énantioselective d'or (I)-catalysé 1,5-enyne de cyclization/intermoléculaire nucléophilic. Tous les complexes diphosphine bis-or disponibles dans notre laboratoire ont été testés et n'ont pas été très efficaces dans cette transformation asymétrique. Nous avons décidé de préparer une phosphoramidite acyclique dérivée de TADDOL qui pourrait posséder un bon potentiel pour cette transformation. Avec ce catalyseur mono-or phosphoramidite, les composés cyclopentène désirés ont été isolés dans des rendements élevés et des énantioselectivités (20 exemples, jusqu'à 94% ee).

Nous avons continué à développer la version asymétrique de cette transformation. Après le dépistage bien connu des catalyseurs chiral de diphosphine *bis*- or, (*S*)-DTBM-SEGPHOS-(AuCl)<sub>2</sub> s'est avéré être le choix optimal. Une activité modérée à excellente et une énantiosélectivité pourraient être obtenues pour les composés pentacyclic cibles. A l'avenir, cette variante asymétrique a le potentiel d'être utilisée dans la synthèse du noyau tétracycle de Nakadomarin A.

En conclusion, un nouveau processus d'olefination catalysé par la phosphine cyclique a été réalisé avec une bonne tolérance de différents substrats d'aldéhyde. D'autre part, de nouvelles méthodologies ont été développées pour la cyclisation énantioselective de 1,5- et 1,6-enynes. Une réactivité et une énantiosélectivité modérées à excellentes pourraient être obtenues

**Titre :** Développement de méthodologies innovantes en organocatalyse par les phosphines et en catalyse énantiosélective à l'or(I)

**Mots clés :** phosphine, catalyse asymétrique, organométallique, organocatalysis, catalyse à l'Or

**Résumé :** Les phosphines jouent un rôle central dans la chimie organique moderne. Dans le domaine de la catalyse, les composés organophosphorés peuvent être appliqués soit en tant qu'organocatalyseurs dans de nombreuses transformations, soit en tant que ligands en catalyse organométallique.

Au cours de cette thèse, nous avons utilisé les phosphines dans ces deux applications : en organocatalyse et en catalyse asymétrique à l'or(I). Dans la première partie, nous avons développé une réaction d'addition de Michael/réaction de Wittig intramoléculaire. Nous avons judicieusement choisi la phosphine utilisée ainsi que l'agent réducteur afin de permettre la réduction in situ de l'oxyde de phosphine correspondant. Une nouvelle réaction d'oléfination a pu être découverte, donnant accès à des dérivés succinates. Un mécanisme réactionnel a pu être proposé, en se basant notamment sur des expériences de deutération.

Dans un deuxième temps, nous nous sommes intéressés au développement de réactions énantiosélectives catalysées par des complexes chiraux d'or(I), et utilisant des substrats énynes. Une première réaction de cyclisation d'énynes-1,5, suivie d'une addition nucléophile a été développée en utilisant des complexes d'or de structure TADDOL-phosphoramidite-AuCl. Ce catalyseur a permis l'obtention de vingt dérivés cyclopentènes avec de bons rendements et des excès énantiomériques atteignant 94% ee. Finalement, des substrats énynes-1,6 correctement substitués ont été utilisés dans une réaction de cyclisation, suivie d'un piégeage intramoléculaire, afin de donner accès à des composés tétracycliques et pentacycliques complexes. Les composés racémiques ont été isolés avec de bons rendements et la version asymétrique a également été développée, par l'utilisation de complexes chiraux d'or(I).

**Title :** Development of innovative methodologies in phosphine organocatalysis and enantioselective gold(I)-catalysis

**Keywords :** phosphine, asymmetric catalysis, organometallic, organocatalysis, Gold-catalysis

**Abstract :** Phosphines play a major role in modern organic chemistry. In the field of catalysis, organophosphorus derivatives can be applied as catalysts in numerous transformations by itself, as organocatalysts, or as ligands in organometallic catalysis.

This thesis focused on the application of phosphines both in phosphine organocatalysis and in asymmetric gold(I) catalysis. In the organophosphorus catalysis part, we have developed a phosphine-catalyzed Michael addition/Wittig reaction by using a well-chosen cyclic phosphine catalyst. In this process, silane was used as reducing agent to selectively reduce in situ the phosphine oxide. A new olefination process was discovered for the synthesis of succinate derivatives. Detailed mechanism research was carried out with H/D

exchange experiments.

In the asymmetric gold(I) catalysis part, we have developed two new methodologies based on cyclization reactions of 1,n-enyne substrates. A 1,5-enyne cyclization/nucleophilic addition reaction was first developed with an acyclic TADDOL-derived phosphoramidite-Au(I) complex. Twenty examples were carried out with good to excellent yields and up to 94% enantiomeric excess. For the 1,6-enyne cyclization/intramolecular nucleophilic addition sequence, we have synthesized a range of racemic tetracyclic and pentacyclic compounds in high yields. The enantioselective version of this transformation was carried out successfully with both high reactivity and enantioselectivity.

