



Universitat d'Alacant
Universidad de Alicante

SYNTHESIS OF 3,3-DISUBSTITUTED 2-OXINDOLES BY
DEACYLATIVE ALKYLATION AND PHOTOCATALYTIC
ALKYLATION OF OLEFINS BY ZINC-SULFINATES

Aitor Ortega Martínez



Tesis

Doctorales

www.eltallerdigital.com

UNIVERSIDAD de ALICANTE



Universitat d'Alacant
Universidad de Alicante



Instituto de Síntesis Orgánica (ISO)

SYNTHESIS OF 3,3-DISUBSTITUTED 2-OXINDOLES BY DEACYLATIVE ALKYLATION AND PHOTOCATALYTIC ALKYLATION OF OLEFINS BY ZINC-SULFINATES

Memoria para optar al Título de Doctor Internacional por la
Universidad de Alicante presentada por el Licenciado:

Aitor Ortega Martínez

Alicante, marzo de 2018

V.º B.º de la Directora y del Tutor

Fdo.: Carmen Nájera Domingo
Catedrática de Química Orgánica
Directora de la Tesis Doctoral

Fdo.: José Miguel Sansano Gil
Catedrático de Química Orgánica
Tutor de la Tesis Doctoral

Instituto de Síntesis Orgánica (ISO), Facultad de Ciencias, Fase I, Universidad de Alicante
Campus de Sant Vicent del Raspeig, Apdo. 99, E-03080 Alicante, España
Tel. +34 965903400, ext. 2121; +34 965903549; Fax +34 965903549
Web: <http://iso.ua.es>; E-mail: iso@ua.es

Agradecimientos

Hace 4 años, en febrero de 2014, empecé uno de mis mayores sueños por aquel entonces: empezar a formarme como investigador en Química Orgánica. Tras todo este tiempo, si hay una cosa completamente clara es que, sin Carmen y JM, esta etapa de mi vida no hubiera sido posible de la forma en la que la he vivido. Os doy las gracias de todo corazón por haberme brindado la oportunidad de aprender tantísimas cosas de vosotros, de desarrollarme profesionalmente y, además, por escucharme y tenerme en cuenta para todo. Me he sentido apoyado y respaldado siempre, cosa que no todo el mundo puede decir de su periodo de tesis doctoral; por todo ello, gracias de nuevo. Y aunque los resultados de las investigaciones no hayan acompañado siempre y junto al grandísimo esfuerzo, dedicación, trabajo, frustración, alegrías, columnas *crema*, pinchazos de HPLC racémicos, conversiones de ^1H RMN >99%... salgo de este doctorado con la sensación de que he adquirido una formación científica excelente. Sin duda eso no hubiera sido posible sin todo mi grupo de investigación y, por ello, extiendo mis agradecimientos a ellos también: a todas y cada una de las personas que lo forman o formaron parte en su día. Finalmente, Carmen, a ti te tengo que hacer una mención especial: el día a día contigo me ha hecho que te tome como un referente. Eres una persona digna de admirar, cercana y una excelente científica. Una persona con la que siempre he podido hablar, discutir y trabajar de la mejor forma posible. Muchas gracias, de verdad.

Otra parte vital de la tesis doctoral ha sido la gente con la que me he rodeado, mis amigos y compañeros. Sin ellos, nada hubiera sido igual, y creo que como persona he de agradecerles muchísimas cosas. Todo empezó con mis mentores, Luis y Pascuali, que además de ser los que me enseñaron una inmensidad de cosas, a los que les pregunté infinidad de dudas del laboratorio, son amigos que nunca voy a olvidar. Todas esas risas en el *cuartico*, tardes de cervezas, agobios, consejos, cenas... serán inolvidables, gracias. De aquella época también hay gente muy importante de la que no me voy a olvidar:

Abraham, Irene, Chus, Alberto Sirvent, Regina... gente con la que empecé la tesis e hicieron que me sintiera como en casa. Luego, tras el cambio generacional del laboratorio, han estado o siguen estando en mi día a día personas tan importantes como Alejandro, Marcos, Ana, Edu, Felipe, Guillermo, Fran, Luana, Josie, Giovanna, Rocco... gracias por haber estado ahí y por todos esos momentos juntos. Finalmente, el *cuartico*, Cristina y Cynthia... mil gracias por hacerme sentir como en casa, por la buena química, por el desahogo de nuestros problemas y por tantos ratos de risas, buenos momentos, consejos, reacciones *crema*, por el apoyo y por saber aguantarme. No se puede pedir amigas y compañeras mejores que vosotras.

Sin duda, una parte importantísima de este doctorado ha sido la terapia de la semana: el consejo de sabios. Javi, Naiara, Marcos, Cristina y Alejandro... gracias por todo el apoyo que me habéis dado durante estos 4 años. Sois amigos, prácticamente familia que, tras casi 10 años juntos, sé que siempre vais a estar a mi lado y yo al vuestro. Gracias de todo corazón por haber estado siempre ahí.

Casi para acabar, no me puedo olvidar de mis amigos de Benissa. También casi familia que, por muchos años que pasen, siempre me han apoyado y han estado para todo lo que necesite. Aitor, Xema, Sánchez, Fran y Dani... gracias, de verdad.

Por último, y podría decir que lo más importante, dar las gracias a mi familia. A mis padres y a mi hermano. Cristian, gracias por todos estos años de buena convivencia, por ser esa excelente persona que eres y por estar siempre a mi lado, nunca olvides que vales millones y que me tienes siempre aquí para lo que necesites. Mamá, papá... qué os voy a decir a vosotros dos. Si soy lo que soy hoy en día, es gracias a vosotros, a lo que os habéis esforzado en vuestra vida para darme todo lo que he necesitado para llegar hasta aquí. Sin vuestro apoyo, este doctorado hubiera sido imposible... así que nunca olvidéis que el Título de Doctor también es vuestro. Gracias familia, os quiero de todo corazón.

Table of contents

PREFACE	9
GENERAL INTRODUCTION	13
1. Oxindoles as prominent scaffolds	15
1.1. Natural products containing oxindole core. Structure & biological activities	17
1.2. Synthetic oxindoles with an extensive range of therapeutic benefits	22
1.2.1. Cancer	24
1.2.2. Diabetes.....	29
1.2.3. Human immuno deficiency virus (HIV)	30
1.2.4. Antioxidant	31
1.2.5. Progesterone antagonists.....	32
1.2.6. Stroke	34
1.2.7. Acetylcholinesterase inhibitors	34
1.2.8. Kinase inhibitors.....	36
1.2.9. Anti-bacterial	39
1.2.10. Anti-leishmanial	40
1.2.11. β_3 Adrenergic receptors agonists	41
1.2.12. Phosphatase inhibitors	42
1.2.13. <i>N</i> -Methyl-D-aspartate receptor blockers.....	42
1.2.14. Spermicidal	43
1.2.15. Vasopressin antagonists	44
1.2.16. Analgesic	45
2. Synthesis of 3,3-disubstituted 2-oxindoles	46
2.1. Nucleophilic addition to isatins	47
2.2. Intramolecular coupling reactions.....	54
2.3. Methyleneindolinones as substrates	59
2.4. Oxindoles as electrophiles	63
2.5. Reactions based on <i>O</i> -substituted oxindoles	63
2.6. Palladium-catalyzed decarboxylative allylation	66
2.7. Direct functionalization of 3-substituted 2-oxindoles.....	67
3. Deacylative alkylation as synthetic methodology	82

CHAPTER 1: <i>Synthesis of 3,3-disubstituted 2-oxindoles by deacylative alkylation of 3-acetyl-2-oxindoles</i>	89
Introduction	91
Objectives	93
Results and discussion.....	95
Conclusions	107
Experimental section.....	109
General methods	109
Experimental procedures	109
Experimental data.....	113
Annex 1	125
CHAPTER 2: <i>Palladium-catalyzed allylation and deacylative allylation of 3-acetyl-2-oxindoles with allylic alcohols</i>	127
Introduction	129
Objectives	131
Results and discussion.....	133
Conclusions	145
Experimental section.....	147
Experimental procedures	147
Experimental data.....	149
Annex 2	165

CHAPTER 3: <i>Synthesis of 3-substituted 3-fluoro-2-oxindoles by deacylative alkylation</i>	167
Introduction	169
Objectives.....	171
Results and discussion.....	173
Conclusions	179
Experimental section	181
General methods	181
Experimental procedures	181
Experimental data.....	183
CHAPTER 4: <i>Photocatalytic radical alkylation of electrophilic olefins by benzylic and alkylic zinc-sulfonates</i>	193
Introduction	195
Objectives.....	213
Results and discussion.....	215
Conclusions	229
Experimental section	231
General methods	231
Experimental procedures and data.....	233
Annex 3	267
REFERENCES	269
ABBREVIATIONS	287
RESUMEN EN CASTELLANO	293
BIOGRAPHY	331



PREFACE

Universitat d'Alacant
Universidad de Alicante

Preface

In this doctoral thesis, the research about the synthesis of 3,3-disubstituted 2-oxindoles by deacylative alkylation processes and the photocatalytic alkylation of alkenes developed during my Ph.D. are described. The projects concerning the oxindole derivatives have been carried out under the supervision of Prof. Carmen Nájera Domingo and Prof. José Miguel Sansano Gil and were developed in the Organic Chemistry Department and the Organic Synthesis Institute at the University of Alicante (Spain). Regarding the photocatalytic part of this doctoral thesis, it has been developed during my three months stay at the University of Bologna (Italy) under the supervision of Prof. Pier Giorgio Cozzi.

The thesis is divided into a general introduction and four chapters. In the general introduction, natural products and synthetic derivatives that contains an oxindole core are described, including comments about their biological activity. Furthermore, general methodologies for the synthesis of oxindole derivatives are included. In the last part of the introduction, deacylative alkylation process is described. Chapters were carried out with a short introduction, the propose of the objectives, the comments and discussion of the obtained results and finally the conclusions. Chapter 1 involves the synthesis of 3,3-disubstituted 2-oxindole derivatives by a deacylative alkylation process using alkyl halides. Chapter 2 describes the allylation and deacylative allylation catalyzed by palladium of 2-oxindoles using non-activated allylic alcohols. In the Chapter 3 is described the synthesis of 3-fluoro-2-oxindoles combining the methodologies described in both previous Chapters. Finally, in the Chapter 4, the photocatalytic alkylation of electrophilic olefins by benzylic and alkylic zinc sulfonates is surveyed.

These results have been supported by Spanish Ministerio de Economía y Competitividad (MINECO) (projects CTQ2013-43446-P and CTQ2014-51912-REDC), the Spanish Ministerio de Economía, Industria y Competitividad, Agencia Estatal de Investigación (AEI)

and Fondo Europeo de Desarrollo Regional (FEDER, EU) (projects CTQ2016-76782-P and CTQ2016-81797-REDC), the Generalitat Valenciana (PROMETEO2009/039 and PROMETEOII/2014/017) and the University of Alicante. I also thank Spanish Ministerio de Economía y Competitividad (MINECO) for a fellowship (BES-2014-069695).

Most of the results described in this doctoral thesis have been published in the following international peer reviewed journals:

“*Synthesis of 3,3-Disubstituted 2-Oxindoles by Deacylative Alkylation of 3-Acetyl-2-oxindoles*” A. Ortega-Martínez, C. Molina, C. Moreno-Cabrerizo, J. M. Sansano and C. Nájera, *Synthesis*, 2017, **49**, 5203–5210.

“*Palladium-catalyzed allylation and deacylative allylation of 3-acetyl-2-oxindoles with allylic alcohols*” A. Ortega-Martínez, R. de Lorenzo, J. M. Sansano and C. Nájera, *Tetrahedron*, 2018, **74**, 253–259.

“*Photocatalytic Radical Alkylation of Electrophilic Olefins by Benzylic and Alkyl Zinc-Sulfinates*” A. Gualandi, D. Mazzearella, A. Ortega-Martínez, L. Mengozzi, F. Calcinelli, E. Matteucci, F. Monti, N. Armaroli, L. Sambri and P. G. Cozzi, *ACS Catal.*, 2017, **7**, 5357–5362.



GENERAL

INTRODUCTION

Universitat d'Alacant

Universidad de Alicante

GENERAL INTRODUCTION

1. Oxindoles as prominent scaffolds

Oxindoles are a family of heterocyclic compounds that have attracted to the academia and industry for years ago, due to the large amount of bioactive natural products and pharmaceutical derivatives with extensive biological activities. The simplest molecular structure of a 2-oxindole **1** consists in a benzene ring fused with a pyrrole ring having a carbonyl group at the position 2 (Figure 1).

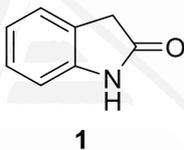


Figure 1. Simplest structure of 2-oxindole.

There are different names as 1,3-dihydro-2*H*-indol-2-one or indolin-2-one but the most common used in the academia and literature is 2-oxindole. The derivative framework bearing a tetrasubstituted carbon stereocenter at the 3 position is a privileged structure which forms a large family of natural and synthetic products with biological activity. There are many substituents that can be attached at the 3 position: alkyl, alkenyl, aryl, heteroatoms (oxygen, nitrogen, sulfur) and halogens (fluorine, chlorine, bromine) among others, through a broad range of synthetic methodologies.

Although the most variations have been done at the 3 position of the oxindole, there are also substitution in another parts of the molecule: in the aromatic ring, the totality of the positions have been studied to exchange the hydrogen atom for another moieties as hydroxy, methoxy, ethoxy, bromine, chlorine, fluorine, amides, nitro,

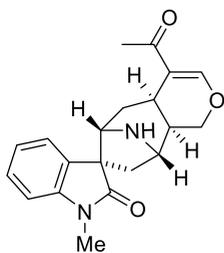
and pyrrole among others. Of course, another susceptible position that can be substituted is the hydrogen atom of the amide group. Albeit numerous natural products have the N-H moiety, others are methylated at the 1 position. However, many synthetic drugs have been prepared with different groups at the N as for example aryl, alkyl or benzyl groups. This fact shows the enormous variations and possibilities that the oxindole core can provide.

In this general introduction, different topics will be described for demonstrating that oxindoles are prominent scaffolds. In the first part, on one hand some products that can be found in the nature will be shown. Also, their chemical structure as well as their biological activities will be displayed. On the other hand, in the recent years, a broad range of synthetic oxindoles have emerged showing bioactivity against numerous diseases. This is a good reason to comment the oxindole derivative structures and their therapeutic benefits achieved. For this reason, the pharmaceutical industry is trying to find new leading compounds that could commercialize just in case to overcome the clinical. Accordingly, new synthetic methodologies of oxindoles are emerging to be more efficient and greener.

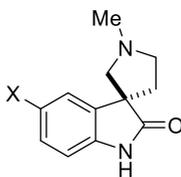
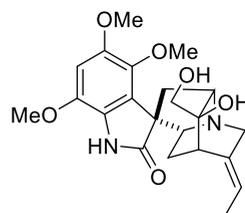
The second part will consist in a background focused on the synthesis of 3,3-disubstituted 2-oxindoles, describing the most important strategies available in the literature until now. At the end of this section an introduction of the deacylative alkylation process will be displayed with the aim of apply this synthetic methodology for the new synthesis of oxindole derivatives.

inhibitory activity of ganglionic transmission in vivo in rabbits and rats,⁵ strychnofoline (**8**) which produces the mitosis inhibition in cell lines as mouse melanoma B16, Ehrlich and Hepatom HW165⁶ and the alkaloid (+)-elacomine (**9**) was also isolated from these plant families. Finally, spirotryprostatins A and B (**10** and **11**, respectively) inhibit the G2/M progression of mammalian tsFT210 cells and were isolated from the fermentation broth of *Aspergillus fumigatus*⁷ (Figure 3).

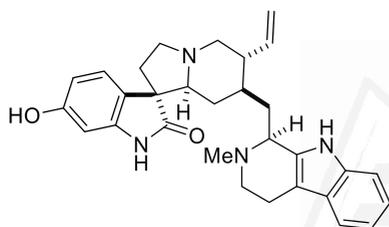
The non-spirocyclic quaternary stereocenter at the 3 position of oxindole derivatives are also present in the nature in a multiple molecular structures. One of the most typical alkaloids are the 3-substituted 3-hydroxy-2-oxindole and have been isolated from several sources. For example, maremycin A and B (**12** and **13**, respectively) have been isolated from the culture broth of marine *Streptomyces*⁸, and the natural brominated oxindole derivatives convolutamydines A, B, C, D, and E (**14**, **15**, **16**, **17** and **18**, respectively) isolated from marine bryozoan.⁸ Specifically, the convolutamydine A (**14**) has been isolated from *Amathiaconvoluta* with a potent activity in the differentiation of HL-60 human plomylocytic leukemia cells.⁹ Also, another 3-substituted 3-hydroxy-2-oxindole derivative isolated from *Uncariaattenuata* Korth in Thailand is compound **19**.¹⁰ Finally, oxindole derivative donaxaridine (**20**) was isolated from typical Mediterranean giant reed *Arundo donax*¹¹ (Figure 4).



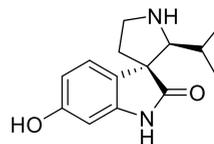
alstonisine (4)

horsifiline (5): X = MeO
coerulescine (6): X = H

chitosenine (7)



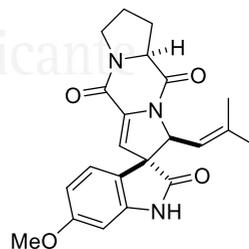
strychnofoline (8)



(+) -elacomine (9)



spirotryprostatin A (10)



spirotryprostatin B (11)

Figure 3. Natural spiro[pyrrolidine-3,3'-2-oxindole] alkaloids.

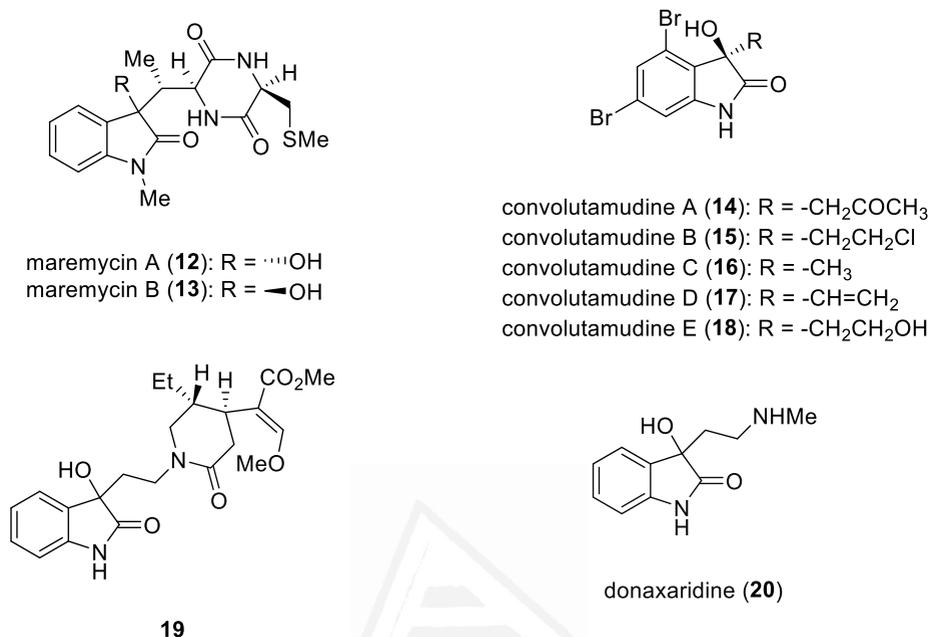


Figure 4. Natural 3-substituted 3-hydroxy-2-oxindole alkaloids.

There are other derivatives that could be potentially synthesized from 3,3-disubstituted oxindole family. They can be classified as pyrrolidinoindolines bearing a carbon substituent at C-3a of the hexahydropyrrolo[2,3-b]indole ring system. Again, there are numerous natural products containing this framework. The alkaloid physostigmine (**21**) belongs to this class of pyrrolidinoindolines. It was initially isolated from the seeds of the African Calabar bean *Physostigma venenosum* and it is a potent reversible inhibitor of butyryl- and acetylcholinesterase and is employed clinically for the treatment of glaucoma.¹² Also, for almost two decades, **21** was evaluated in clinical trials for the symptomatic treatment of Alzheimer's disease.¹³ Unfortunately, it showed short duration of action, low bioavailability and narrow therapeutic window. For this reason, a powerful synthetic derivate was synthesized which will be

discussed in the next section of the introduction (see section 1.2.7). Also it is possible to find compounds as flustramine B (**22**) which was found in marine bryozoan *Flustra foliacea*¹⁴ and (-)-pseudophrynaminol (**23**) in the skin of an Australian frog called *Pseudophryne coriacea*.¹⁵ Other natural derivatives as flustraminol (**24**), CPC-1 (**25**) and flustramine C (**26**) have been also described¹⁶ (Figure 5).

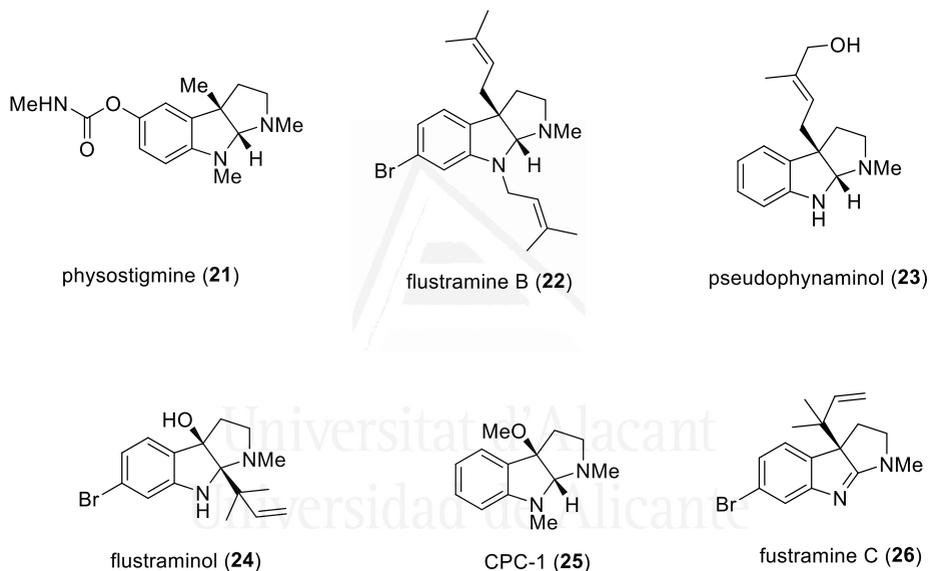


Figure 5. Natural pyrrolidinoindoline alkaloids derived from 2-oxindole.

Finally, other natural products can be found related with the oxindoles. For example the first oxindolephytoalexin (antimicrobial secondary metabolites produced by plants as a defense mechanism responding to a biological, physical or chemical stress) that was found in a cruciferous is the (-)-spirobrassinin (**27**),¹⁷ the *N*-methylwelwitindolinone C isothiocyanate (**28**), which is the major oxindole alkaloid in a specific blue-green algae (cyanobacteria)¹⁸ and

finally, to show the wide range of sources where oxindole derivatives can be found, the alkaloid (+)-alantrypinone (**29**) was isolated from the fungus *Penicillium thymicola* (Figure 6).¹⁹

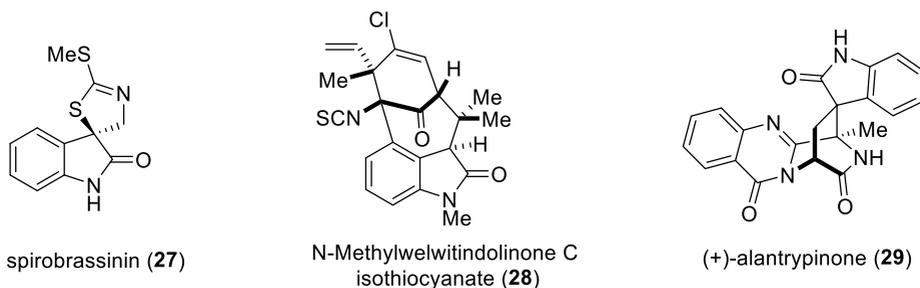


Figure 6. Different related oxindole alkaloids.

1.2. Synthetic oxindoles with an extensive range of therapeutic benefits

Due to the numerous natural products with interesting biological activities, synthetic oxindoles have attracted much attention to the pharmaceutical industry. Thanks to the synthetic existent methodologies and new ones that are emerging, this industry is developing new synthetic oxindoles with amazing bioactivities. For example, it has been developed a marketed anti-cancer agent sunitinib (**30**), which is implicated in the treatment of tumors in gastrointestinal stromal and metastatic cells in the renal cancer.²⁰ Also, a potent HIV-1 non-nucleoside reverse transcriptase inhibitor **31**^{21,22} was developed, a growth hormone secretagogue SM-130686 (**32**)²³ and an inductor of systemic cartilage hyperplasia in rats AG-041R (**33**) were discovered (Figure 7).²⁴ In this section, the wide variety of synthetic drugs and lead candidates that were or are being investigated will be shown, in order to know the biological activities of these oxindole derivatives. There is a huge list of diseases where these compounds are active: anti-cancer, anti-HIV, anti-diabetic, antibacterial, antioxidant, anti-leishmanial, β_3 adrenergic

receptor agonists, phosphatase inhibitors, *N*-methyl-D-aspartate receptor blockers, spermicidal, vasopressin antagonists, analgesic, progesterone antagonists, stroke, kinase and acetylcholinesterase inhibitors. It is worth to note that almost 100 compounds will be displayed only to demonstrate the big number of interesting compounds that can be obtained from the oxindole core and the importance of developing greener and more efficient synthetic methodologies. Some important brief comments will be displayed in each disease.

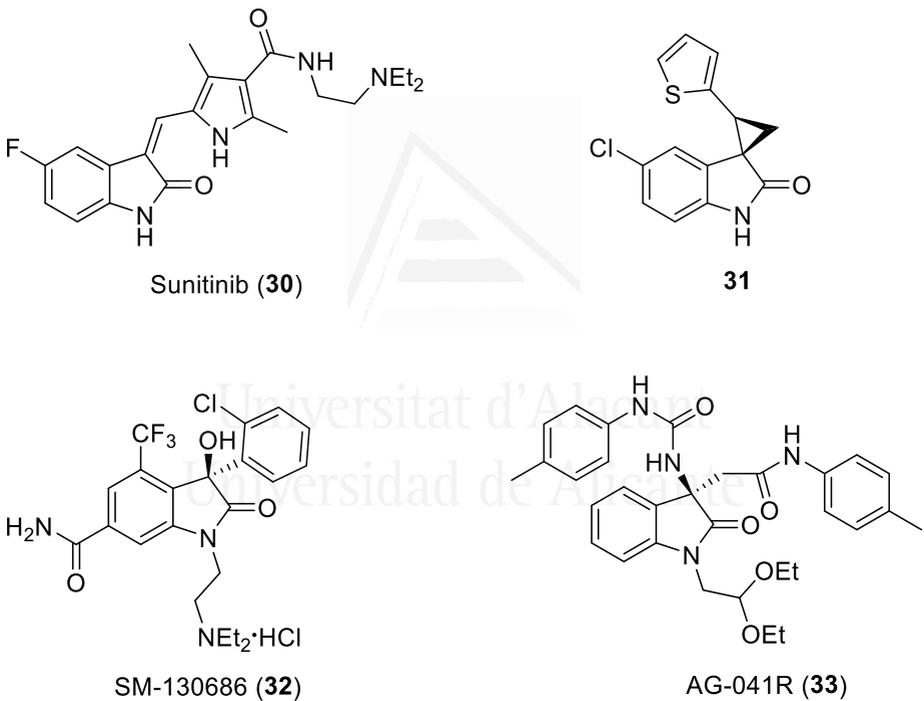


Figure 7. Some examples of oxindole derived drugs.

1.2.1. Cancer

The disease called as cancer or carcinogenesis is the leading cause of death worldwide causing around 8.2 million of deaths in 2012 and is expected to rise by 75% reaching near to 25 million in next to decades.²⁵ Cancer is distinguished by uncontrollable growth of cells leading to malignant tumors that invade the normal cells and can spread to distant parts of the body through different systems. Exist different treatments for this disease, but all the available anti-cancer drugs have side effects as nephrotoxicity, bone marrow depression and alopecia due to their non-selectivity. For this reason, new anti-cancer agents need to be developed to improve the efficacy and diminish the side-effects.

Numerous natural and synthetic oxindole derivatives have been evaluated as anti-cancer drugs. The molecules 5-hydroxyoxindole (**34**) and isatin (**35**) (Figure 8), that are present in mammalian body fluids and tissues, were found to have anti-proliferative activity because show inhibition of cell proliferation through interaction with extracellular signal-regulated kinases (ERKs) and promotion of apoptosis.²⁶

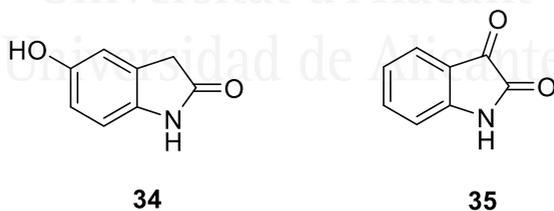
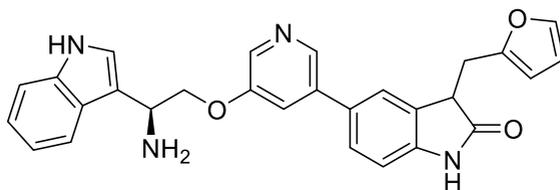


Figure 8. Molecules that show biological activity.

Later, several investigations have been done by research groups and pharmaceutical companies to synthesize a big number (more than 40) oxindole derivatives with different biological activities and potencies against cancer.^{27–42} One of the most relevant oxindole-pyridine derivative is **36**³¹ which is a very potent ($IC_{50} = 0.17$ nM) protein kinase B/Akt inhibitor with 100 fold selectivity over other Akt isoenzymes. This Akt kinase, plays crucial role in signal

transduction pathway that regulates many processes in the cancer (Figure 9).

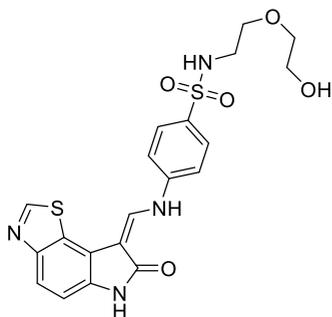


36

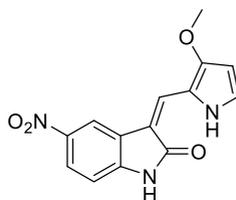
Figure 9. Very potent oxindole derivative Akt inhibitor.

In the following figure will be shown the oxindole derivatives **37-64** cited in the previous paragraph that have shown different activities against cancer (Figure 10). Among others, some of these compounds showed activity against human lung,³⁵ leukemia and breast cancer cell lines.⁴¹

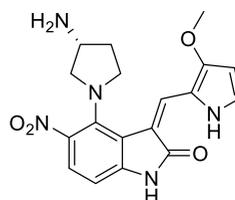
Universitat d'Alacant
Universidad de Alicante



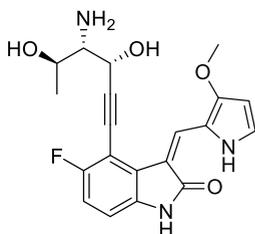
37



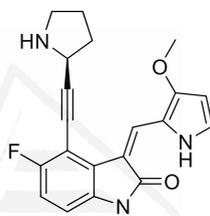
38



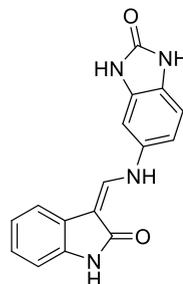
39



40



41



42

Figure 10. Anti-cancer oxindole derivative structures.

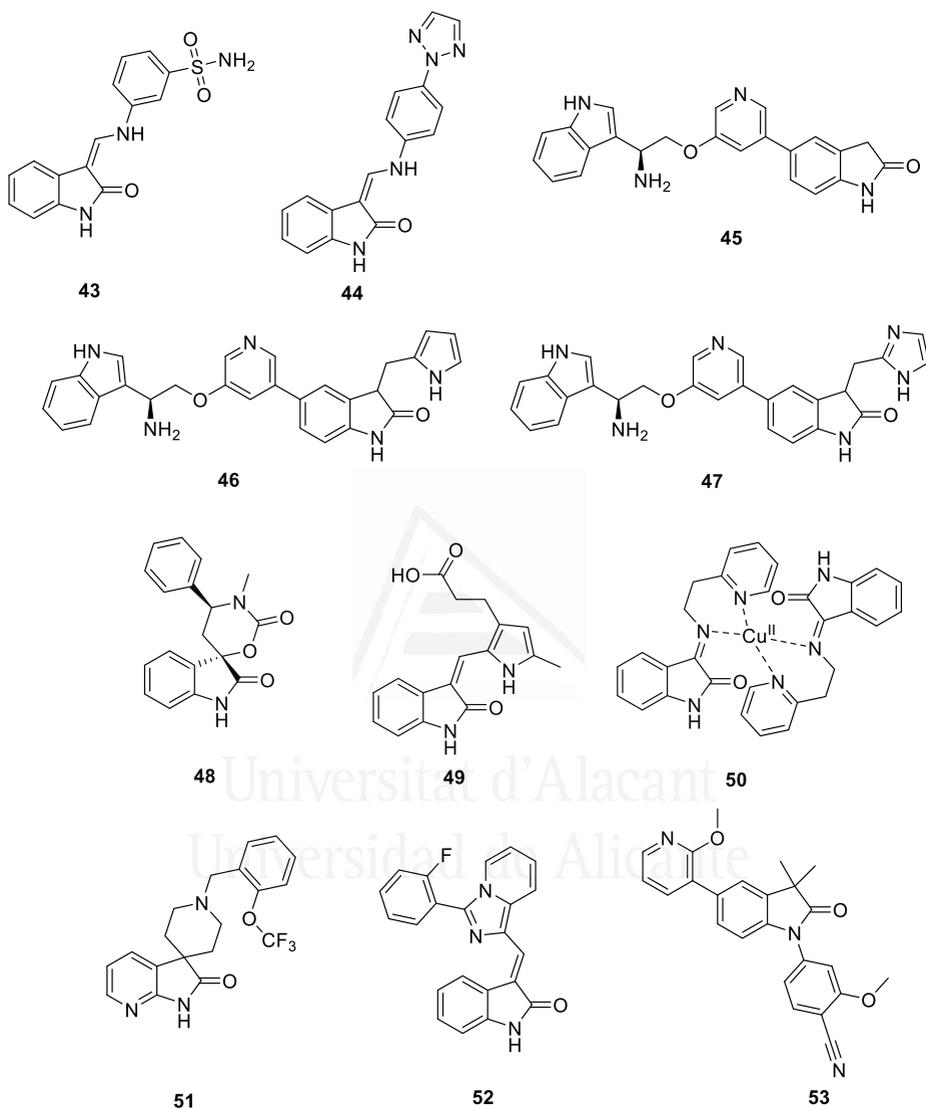


Figure 10. Anti-cancer oxindole derivative structures (cont.).

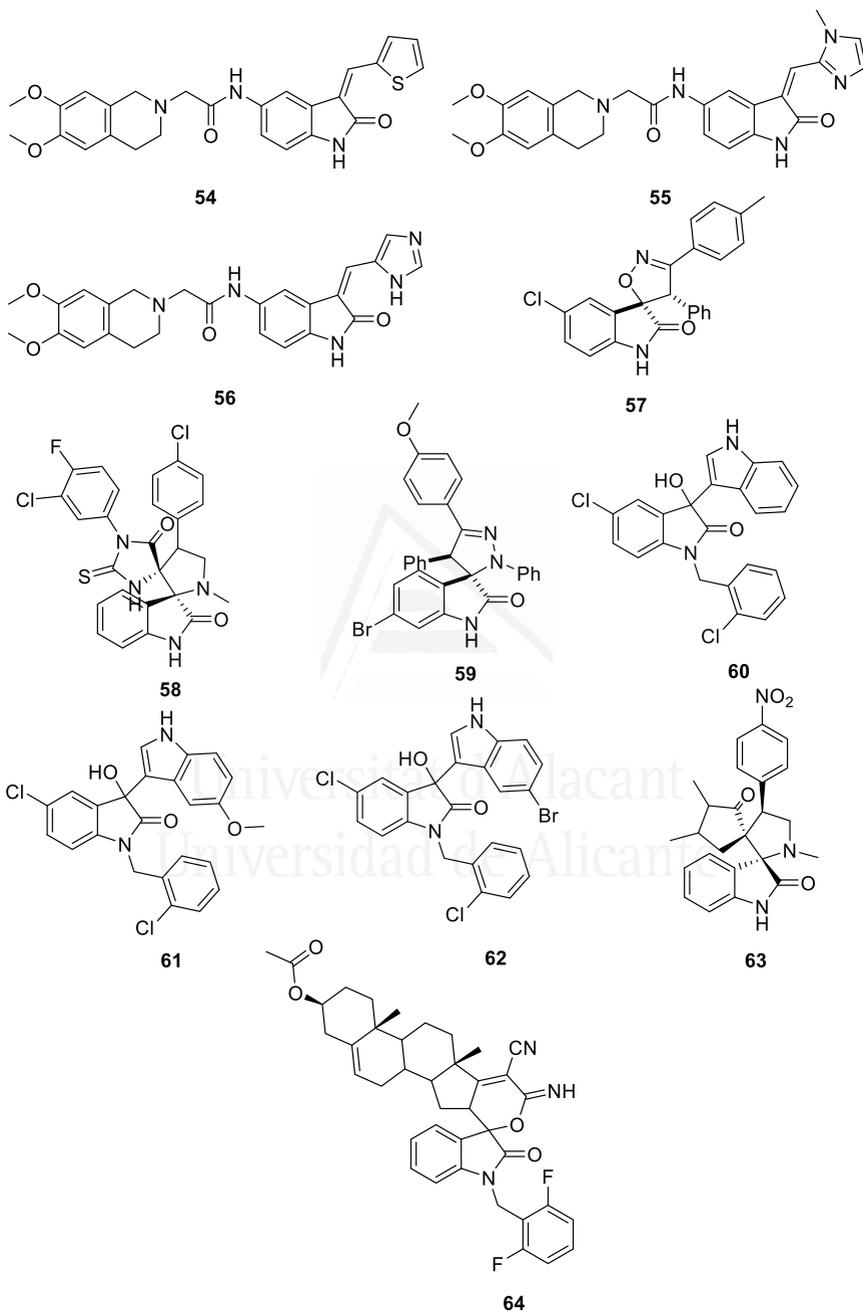


Figure 10. Anti-cancer oxindole derivative structures (cont.).

1.2.2. Diabetes

Diabetes is a metabolic disorder and in 2013 was estimated that over 382 million people throughout the world had this disease.⁴³ It is characterized by improper secretion of insulin and/or defective insulin function that results in elevated glucose level. Chronic hyperglycemia leads various complications, for example retinopathy, neuropathy, nephropathy and cardiovascular complications.⁴⁴ In 1992, a series of oxindole-1-acetic acids were investigated against aldose reductase enzyme, a key enzyme that causes diabetic complications. The synthesized oxindole derivatives showed potent *in-vitro* inhibitory activity against this enzyme, but poor *in-vivo* efficacy. Later, new promising series of oxindole analogues have been discovered as potent α -glucosidase (related with type II diabetes enzyme) inhibitors. Among them, different inhibitors **65-69** (Figure 11) were synthesized, with an IC_{50} between 2.71 μ M to 37.93 μ M. These biological activities are even greater than standard drug for type II diabetes acarbose with $IC_{50} = 38.25 \mu$ M.⁴⁵

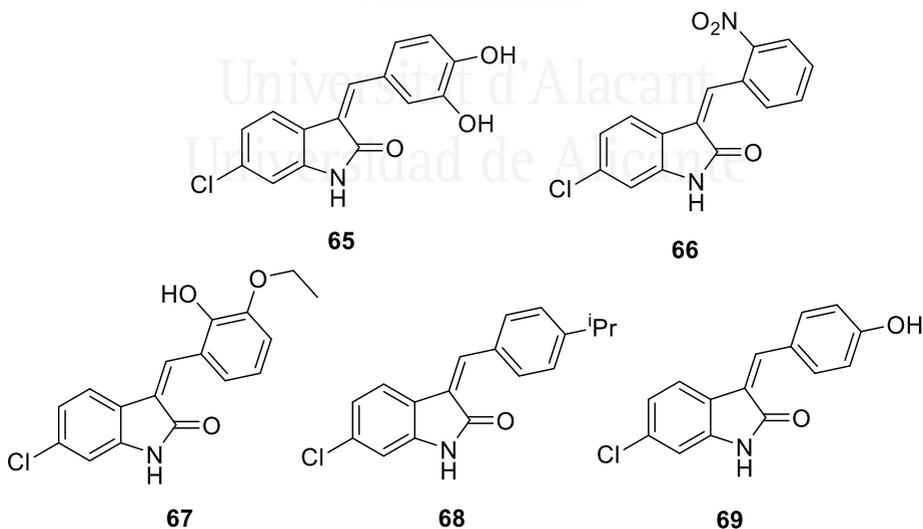


Figure 11. Anti-diabetic oxindole derivative structures.

1.2.3. Human immuno deficiency virus (HIV)

The HIV is the leading cause of the deaths globally among the infectious diseases. The World Health Organization (WHO) says that over 35 million people worldwide were living with HIV in 2013.⁴⁶ Of these, 3.2 million being children (less than 15 years old). The mortality rate is increasing mostly in developing countries, probably due to high cost of the therapy for HIV, for side-effects and drug resistance associated with the therapy. For these reasons, it is necessary the development of new drugs that can be safer and more economic.

In this field, also exist oxindole derivatives that are bioactive against this disease.²¹ In the Figure 12 are described different of these compounds. Is worth to note that lead compound **70** ($IC_{50} = 0.066 \mu M$) was further optimized to establish structure-activity relationship (SAR) more potent active molecule. For describing an example of a common result of SAR in the field of Medicinal Chemistry, when the Br atom of **70** was replaced with larger **71**, smaller **72**, EDG and EWG, respectively, the inhibitory activity was reduced. For this reason, they can conclude that the Br atom was optimum for the inhibitory activity. Different modifications of the moieties in the molecules were performed to obtain oxindole derivatives **70-80** (Figure 12). Although, as is previously described, not every change provide a more potent molecule, finally they could synthesize a novel and potent anti-HIV compound **80** ($EC_{50} = 8 nM$).²² As is possible to see in the Figure 12, the cyclopropane ring at the 3 position is crucial for the biological activity against this disease.

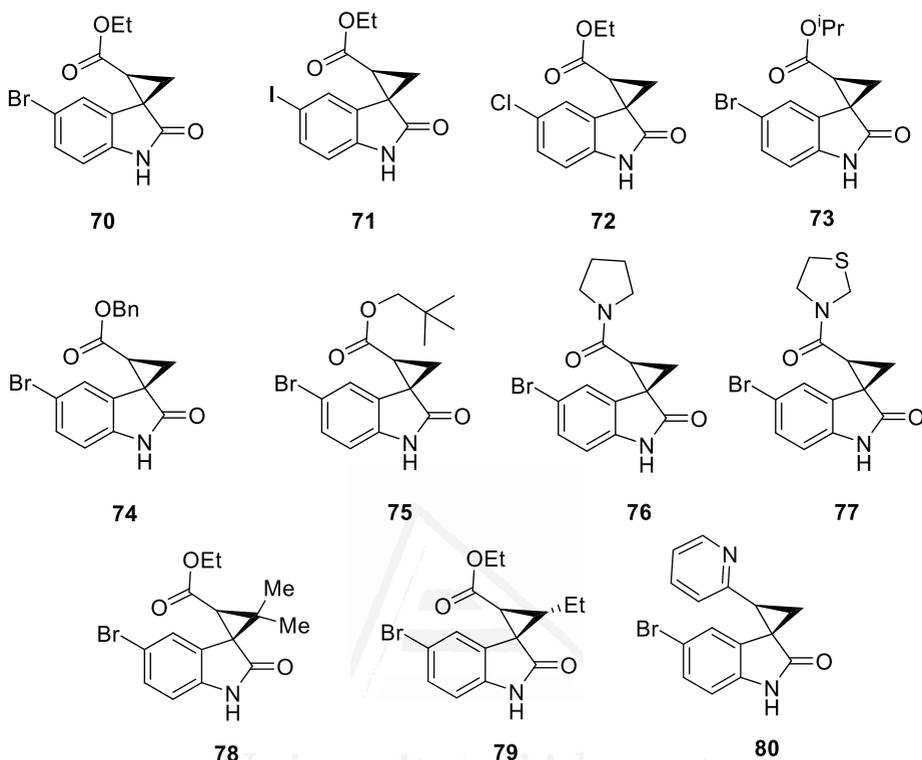


Figure 12. Anti-HIV oxindole derivatives structures.

1.2.4. Anti-oxidant

Several researchers have been working in the development of natural, synthetic and semi-synthetic antioxidants as therapeutics, because it is known that oxidative stress is implicated in the pathogenesis of several diseases such as cancer, neurodegenerative diseases, mitochondrial disorders, diabetes and cardiovascular diseases.

Again, oxindole derivatives can be included in this field. In 2010 it was explored the oxindole-3-acetic acid derivatives from corn powder used in soups and snacks, and it was concluded that these derivatives shown antioxidant activity against stable free-radical

molecule as 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical.⁴⁷ For this reason, in 2013 were synthesized 3-hydroxy oxindole derivatives **81** and **82** (Figure 13) and evaluated for lipid peroxidation inhibitory activity, DPPH radical scavenging activity, intracellular oxidative stress-suppressing effect and cytotoxicity.⁴⁸ In this work, it was compared the activity of oxindole **34** against compounds **81** and **82** and the 3-hydroxy oxindole derivative **81** showed stronger lipid peroxidation inhibitory activity than **34**, while compound **82** was worse than **34**. Is worth to note that all compounds **34**, **81** and **82** have a lower cytotoxicity on human leukemia HL60 cells than the widely used phenolic antioxidant 2,6-di-*tert*-butyl-4-methylphenol (BHT), which is widely employed as an antioxidant food additive in European Union and recognized as safe.⁴⁹

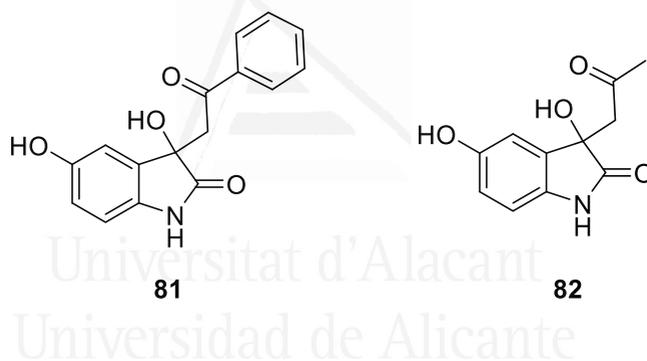


Figure 13. Antioxidant 3-hydroxy oxindole derivatives.

1.2.5. Progesterone antagonists

Progesterone receptor is a member of steroid receptor subfamily, which is involved in different physiological events like ovulation and maintenance of pregnancy through a ligand progesterone. Consequently, progesterone receptor antagonists are a target to use them as a potential contraceptive⁵⁰ and in the treatment of other diseases as uterine myoma, endometriosis and hormonal

dependent tumors. Nowadays, there is a need for the non-steroidal and more specific progesterone receptor antagonists.

In 2002, the 3,3-disubstituted-5-aryl oxindoles were studied as progesterone antagonists.⁵¹ In this case, the SAR was performed and analyzed at the 3 and 5 position of the oxindole core. The valuable 3 position of the oxindole core was substituted with different groups as alkyl, dialkyl or spirocyclic moieties and the 5 position with phenyl ring bearing different substitutions. On the other hand, when 3,3-dimethyl oxindole derivatives **83** were synthesized they had higher biological activity ($IC_{50} = 30.6$ nM) than mono-methylated molecules **84** ($IC_{50} = 102$ nM). When the ethyl group was the substituent, mono-ethylated derivatives were more potent than diethyl derivatives. 3,3-Spirocyclic compounds **85** and **86** were tested with good bioactivity (IC_{50} value of 85 nM and 32 nM, respectively). The substitution at the 5 position of the aromatic ring of the oxindole was performed and finally gave compound **87** with the highest potency observed, $IC_{50} = 13.2$ nM (Figure 14).

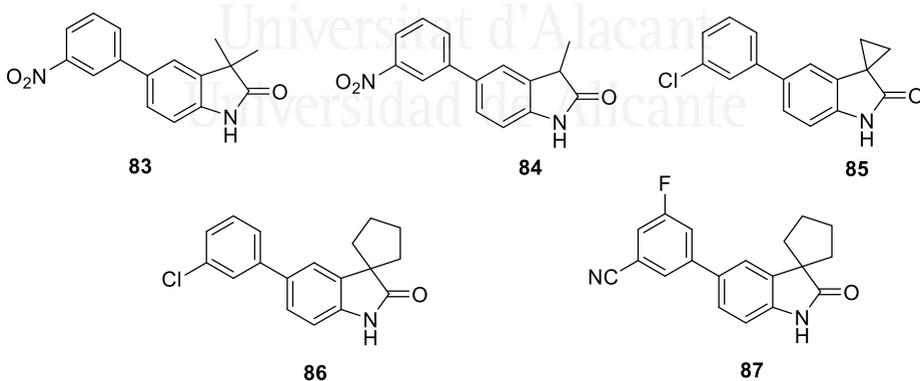


Figure 14. 3,3-Disubstituted oxindole progesterone antagonists with different bioactivities.

1.2.6. Stroke

The stroke, according to the WHO, causes 6.2 million deaths each year. This represents the second cause of death worldwide in 2015, with an 11% of the 56.4 million deaths worldwide in this year. Consequently, is a fact that there is a requirement to develop novel neuroprotective therapies for this disease. In 2002 Myers Squibb Pharmaceutical Research Institute recognized a novel fluorooxindole **88** (called as BMS-204352 or Maxipost™) as a potent maxi-K channel opener (Figure 15).⁵² In the SAR, they could demonstrate that unsubstituted phenyl analogues, exchanging F₃C group from the 6 to 5 position and replacing that group with EWG groups as nitrile and iodine moieties, every molecule resulted in loss of bioactivity. This drug showed satisfactory solid-state stability and excellent brain penetration, so it can be a good starting point for the development of new neuroprotective agents.

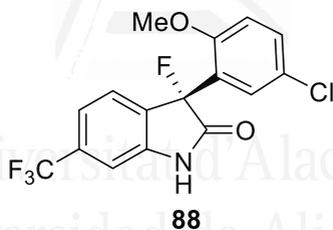


Figure 15. Maxipost™ a neuroprotective drug candidate.

1.2.7. Acetylcholinesterase inhibitors

Alzheimer's disease is the most common cause of dementia in the world. The most visible symptoms are the loss of memory and the cognitive impairment. According some reports of experts in this disease, 36 million of people were affected with Alzheimer's disease, and it has been estimated to increase up to 66 million in 2030. Knowing the pathogenesis of it, the treatment can be approached increasing the cholinergic transmission using cholinesterase

inhibitors.⁵³ There are not huge amounts of treatment options, so there is a need in the development of new drugs.

It is worth to note that phenserine, the synthetic derivate of natural product physostigmine (**21**), that can be obtained from an oxindole derivative (see section 1.1) and was a potent acetylcholinesterase (AChE) inhibitor showed, at least initially, better drug properties than physostigmine.^{53,54} This drug candidate reached the phase III of clinical trials but, unfortunately, at the 06 Phase III trial the development of this candidate drug was abandoned. There are some investigations about the methodologies and outcomes of these clinical trials of phenserine, and the conclusions were that the clinical trial of phenserine was abandoned, at least in part, due to the clinical trial was invalidated by relationships among the employed methods and outcomes.⁵⁵

In 2010 different oxindole derivatives as AChE inhibitors were explored and, among others, compound **89** showed high inhibitory bioactivity against AChE enzyme ($IC_{50} = 0.10 \mu M$). Other derivatives such as **90** ($IC_{50} = 0.11 \mu M$) were obtained and the authors justify that these compounds have same potency as AChE inhibitor drug donepezil but the synthesis is easier and cheaper.^{56,57} Posterior investigations of other research groups were done and they discovered a high bioactivity for the oxindole derivative **91** (Figure 16).⁵⁸

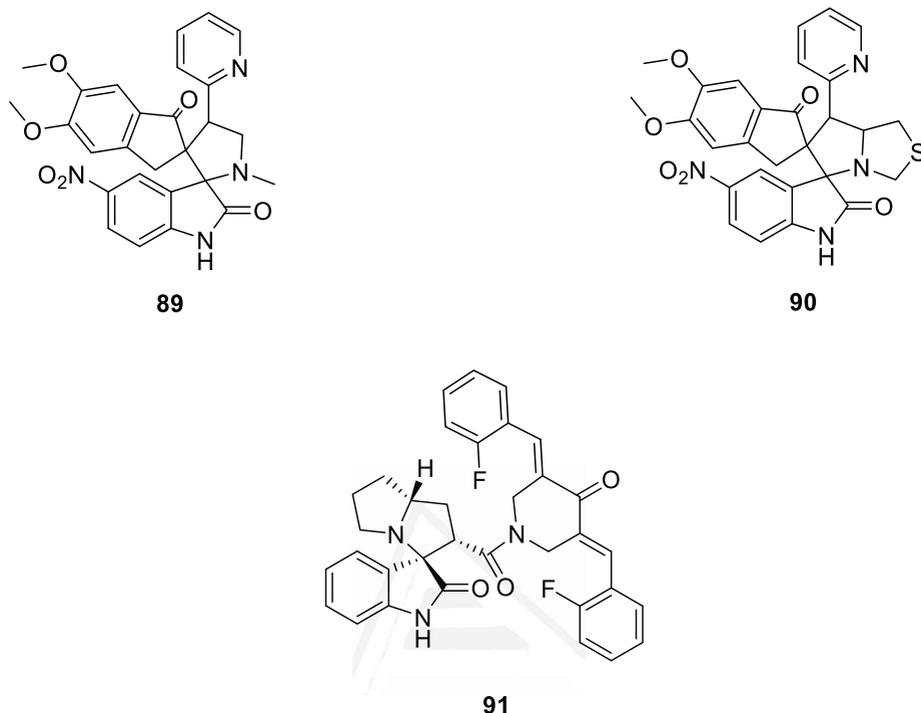


Figure 16. Oxindole derivatives as acetylcholinesterase inhibitors.

1.2.8. Kinase inhibitors

As it is well-known in biochemistry, a key step in almost all cellular processes is the protein phosphorylation. The transference of a phosphate group from ATP (called sometimes as “molecular unit of currency” of intracellular energy transfer) to substrate proteins is how kinases express their activity.⁵⁹ When the expression of various kinases does not work properly, it leads to a disease. Then, it is an important target in drug development and different oxindole derivatives have been synthesized and evaluated against a variety of kinases. For example, against cRaf1 kinase which play an important role of tumor formation. The compound **92** showed highest bioactivity

among the others synthesized molecules.⁶⁰ Later, a tyrosine kinase inhibitor with a sulfonamide group **93** was found with high IC₅₀ value (5 nM) but moderate cellular activity. This is because the high polar surface of the molecule. To solve this problem and improve the cellular activity, the sulfonamido group was replaced by a carboxamido group in **94**, which gave better results.⁶¹ More oxindole derivatives as **95**, **96**, **97**, **98**, **99** and **100** have been tested as kinase inhibitors (Figure 17).⁶²⁻⁶⁴

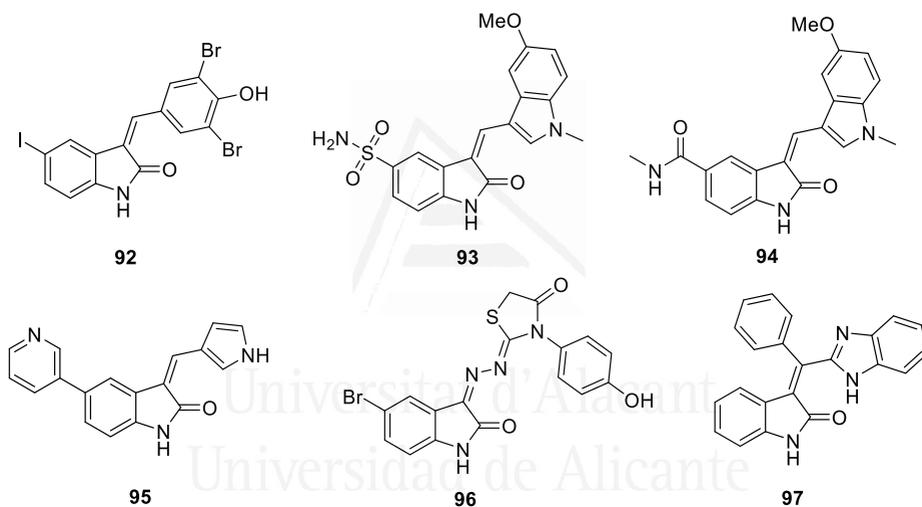


Figure 17. Kinase inhibitors with an oxindole core.

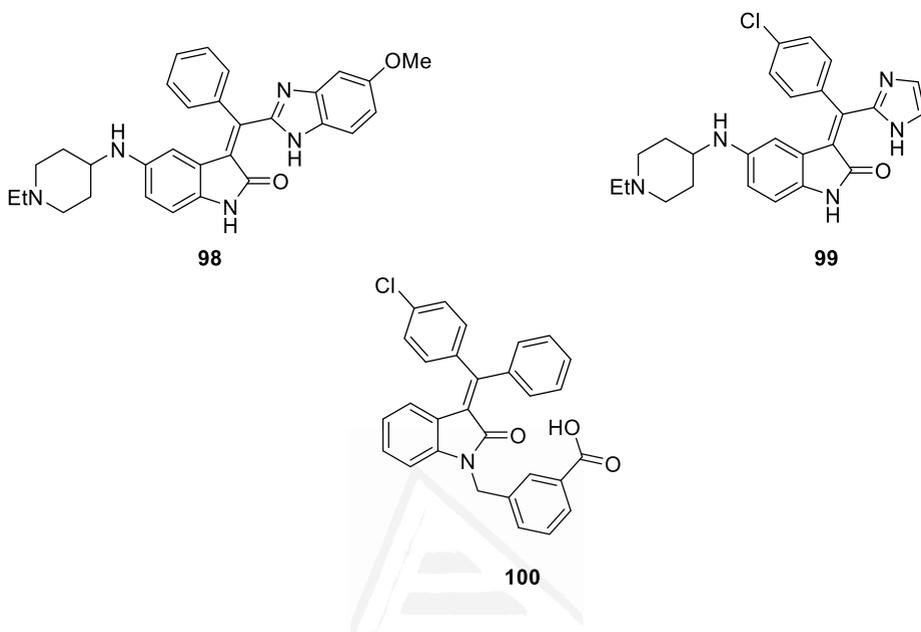


Figure 17. Kinase inhibitors with an oxindole core (cont.).

1.2.9. Anti-bacterial

The infectious diseases are caused by microbes like bacteria and fungi. The effects are ranging between minor skin infections to dangerous bubonic plague and tuberculosis, which are relevant causes of mortality. An enormous problem nowadays is the resistance developed by these microorganisms and probably will be one of the most important vital global problem in a not so far future. For this reason, novel anti-bacterials with different and new mode of action have received much attention for the treatment of bacterial infection. Oxindole derivatives are one of the most recent synthetic molecules of antibacterial studied for multiple resistant bacteria. Compound **101** showed excellent antibacterial activity against two bacterial strains *Escherichia coli* and *Staphylococcus aureus* equivalent to standard drug streptomycin.⁶⁵ The oxindole derivative **102**, among others, was the most active against Gram-positive bacteria *Staphylococcus aureus* and *Bacillus Subtilis* (Figure 18).⁶⁶

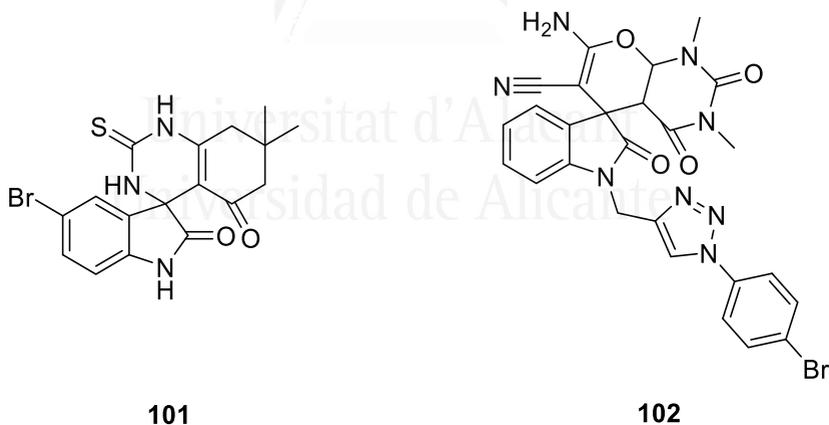


Figure 18. Oxindole derivatives with anti-bacterial activity.

1.2.10. Anti-leishmanial

The leishmaniasis is the ninth largest infectious disease that, according to WHO, it estimates that approximately 0.9 to 1.6 million of different leishmaniasis cases occur each year.⁶⁷ New oxindoles with anti-proliferative activity against this disease were reported. Molecules **103-106** presented leishmanicidal activity without any cytotoxic effects (Figure 19). Specifically compound **104** showed two times higher therapeutic index than commercial Amphotericin B.⁶⁸

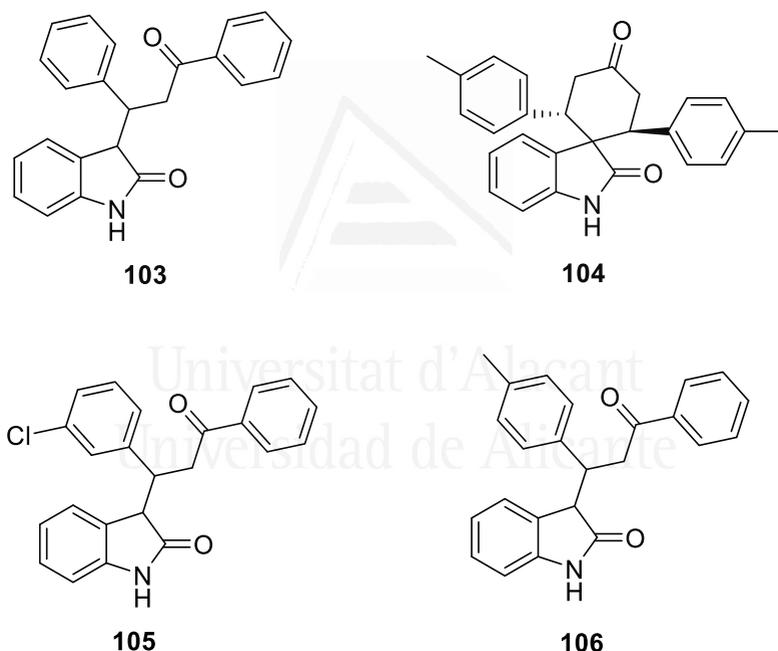


Figure 19. Anti-leishmanial oxindole bioactive derivatives.

1.2.11. β_3 Adrenergic receptor agonists

The β_3 adrenoreceptors play an important role in processes as lipolysis and thermogenesis in adipose tissues. It has been investigated that these receptors are expressed mainly in adipose tissues, brain, colon, urinary bladder small intestine and heart.⁶⁹ The β_3 adrenoreceptors agonists have shown increased fat oxidation and improved glucose uptake in obese and diabetic mice. Probably, it can also be used in gastrointestinal and urinary disease. In 2007 found an agonist of this receptor, replacing previous benzimidazole core for oxindole core **107**, although the last one was slightly less bioactive ($EC_{50} = 7.1$ nM versus $EC_{50} = 24.4$ nM). This encouraged the authors to optimize SAR with different substituents at the 3 position of the oxindole moiety. Methyl substituent of compound **108** ($EC_{50} = 12$ nM) and dimethyl substituted derivative **109** ($EC_{50} = 5.2$ nM) both at the 3 position, produced an increasing of the potency while a substituent as benzyl **110** ($EC_{50} = 268.1$ nM) lead to decrease it (Figure 20).⁷⁰

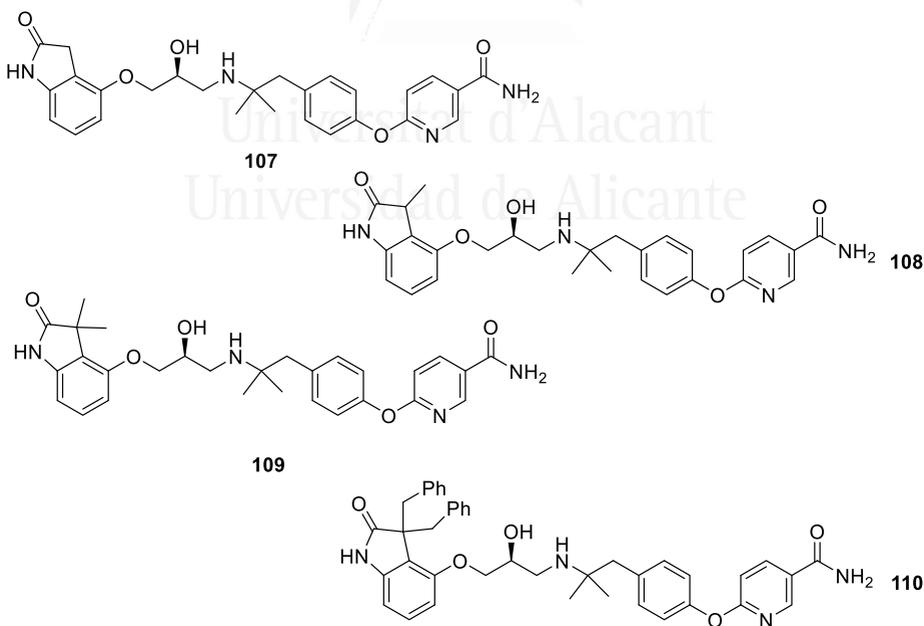


Figure 20. Oxindole derivatives β_3 adrenergic agonists.

1.2.12. Phosphatase inhibitors

A specific phosphatase, the tyrosine phosphatase-2, has been involved in various cell signaling, as for example cell proliferation, differentiation and migration. Also, it has been reported that it plays an important role in a oncogenic protein of *Helicobacter pylori* that causes gastric cancer.⁷¹ Accordingly, inhibitors of this protein can be employed as a therapy for this cancer. In 2008, it was found that oxindole derivative **111** showed moderate phosphatase inhibition ($IC_{50} = 47 \mu\text{M}$). After theoretical calculations that revealed that the introduction of carboxyl group at both terminal positions mimic a phosphate group, leading to a phosphatase inhibitor **112** that was 40 fold more potent than **111** (Figure 21).⁷²

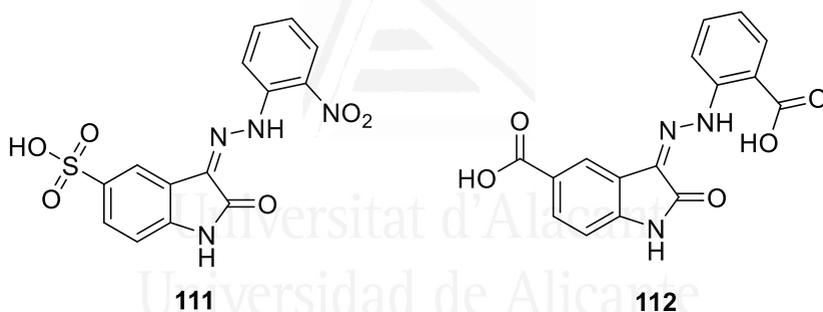


Figure 21. Phosphatase inhibitor with an oxindole core.

1.2.13. *N*-Methyl-D-aspartate receptor blockers

The *N*-methyl-D-aspartate (NMDA) receptor is identified as a critical neurotransmitter receptor in various important processes. For example, in rhythms for locomotion and breathing and also with processes that are associated with cognition and neuroplasticity.⁷³ Consequently, anomalous regulation of this receptor leads in numerous neurological disorders and diseases. The over-action of NMDA receptor results in neurodegenerative disorders like

Alzheimer's disease, stroke, vascular dementia and Parkinson's disease. Thus, NMDA antagonists are considered as promising drugs for the treatment of these neurodegenerative diseases. With the first NMDA blocker drug (Ifenprodil) structure in mind, some replacements were done to improve its activity. When oxindole core was introduced, a potent NMDA antagonist **113** was synthesized. After further modifications, compound **114** resulted in an improvement as an antagonist together with an improvement of selectivity (Figure 22).^{74,75}

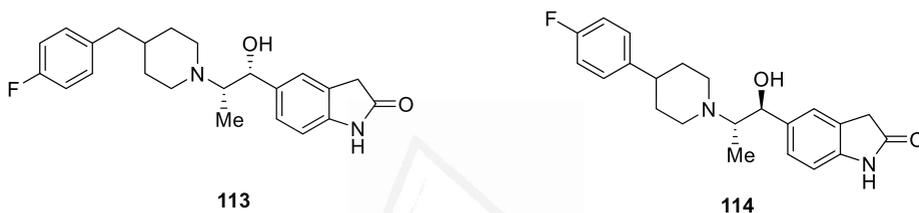


Figure 22. Oxindole derivatives NMDA receptor blockers.

1.2.14. Spermicidal

Additionally, oxindole structures have been investigated for dual contraception protection for women. A synthetic 3,3-diheteroaromatic oxindole derivatives were evaluated as spermicidal agents *in-vitro*. The structure **115** showed efficacy as a drug (Figure 23).⁷⁶

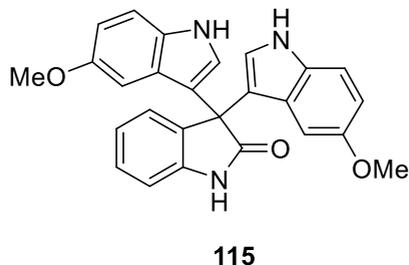


Figure 23. Spermicidal with an oxindole structure.

1.2.15. Vasopressin antagonists

The vasopressin is a nine amino acid member neuropeptide which is involved in various emotional processes and regulation of the stress. The compound **116** has been identified as an orally active, selective and potent V_{1b} receptor antagonists showing anti-anxiety and anti-depressant effects. Although it has good efficacy, poor pharmacokinetic profile was observed. Posterior modifications lead to compound **117**, that was equipotent anti-depressant compared with **116** but with an improvement of metabolic stability, oral bioavailability, brain penetration and half-life (Figure 24).⁷⁷

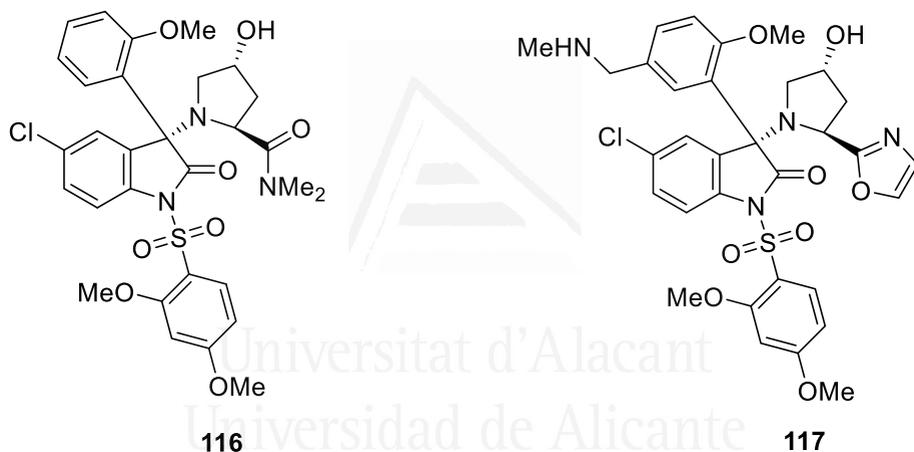


Figure 24. Oxindole derivatives as vasopressin antagonists.

1.2.16. Analgesic

A target for the treatment of chronic pain are voltage gated sodium channels, and in particular Na_v 1.7 channels. In 2011, 3-hydroxy and spirooxindoles were investigated as a Na_v 1.7 channel blockers in order to treat the chronic pain. After a wide screening, 3-hydroxy-2-oxindoles derivatives were identified as promising drug candidates. Specifically, 3-hydroxy-2-oxindole **118** ($\text{IC}_{50} = 0.3 \mu\text{M}$) was an interesting compound. After the replacement of the *N* substituent from *p*-chlorobenzyl to pentyl group and the moiety of the 3 position, they arrived to compound **119** with an $\text{IC}_{50} = 0.03 \mu\text{M}$. Finally, spiro compound **120** was synthesized increasing 10 fold the potency to $\text{IC}_{50} = 0.003 \mu\text{M}$ (Figure 25).⁷⁸

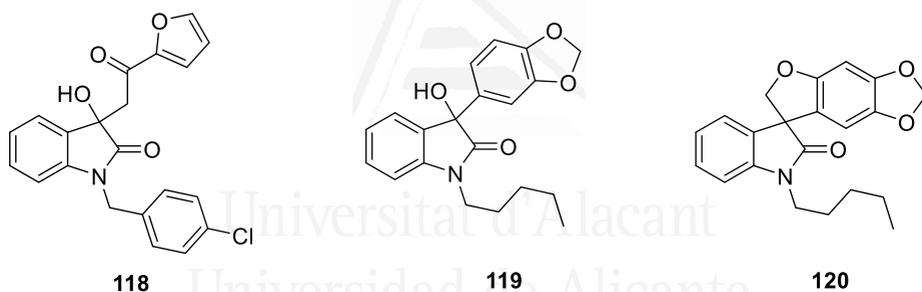


Figure 25. Analgesic oxindole derivatives that block Na_v 1.7 channel.

2. Synthesis of 3,3-disubstituted 2-oxindoles

Due to the enormous amount of pharmaceutical and natural products (see section 1.1 and 1.2), several research groups have been investigating diverse synthesis of the 3,3-disubstituted 2-oxindole framework. The development of new synthetic methodologies enables the synthesis of the target natural or pharmaceutical products for biological assays and SAR studies. Therefore, this topic can contribute to a benefit for the society: new therapeutic agents that could save lives.

It is worth to note that as most of the natural products shown above are chiral, the asymmetric synthesis of the 3,3-disubstituted 2-oxindoles is one of the most common research field. Despite that enantioselective synthesis of complex natural and pharmaceutical compounds is highly demanded, the formation of fully substituted stereocenters is one of the most challenges in organic synthesis, where are remarkable the catalytic processes.^{16,79} As it was described above, 3,3-disubstituted 2-oxindole unit include all kind of tetrasubstituted carbon stereocenters: all-carbon or containing an heteroatom, spirocyclic or not. Several metal catalyzed and organocatalyzed methods have been reported and in this part of the general introduction will be discussed the background about this topic.

Although many of synthesis for the formation of the tetrasubstituted carbon at the 3 position have been described, it is possible to classify them in the following seven main categories.

2.1. Nucleophilic addition to isatins

The nucleophilic addition to isatin **35** and derivatives as the keto imine **121**, is a useful method for the preparation of 3-amino or 3-hydroxy-2-oxindoles (Figure 26) due to the easy availability of them as starting materials.

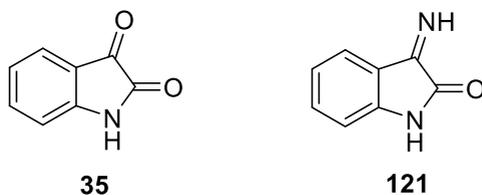
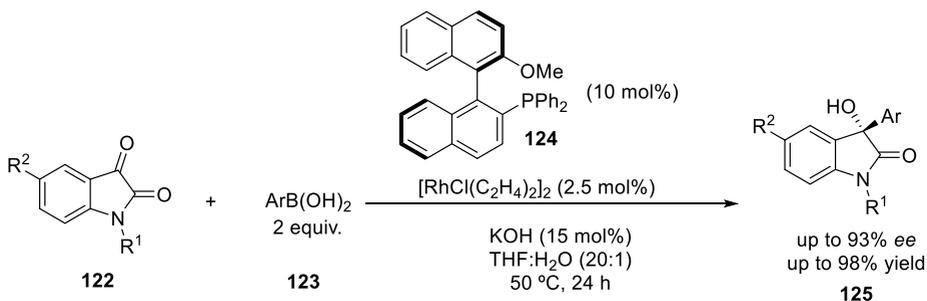


Figure 26. Isatin and its imino derivative.

In 2006, Hayashi and co-workers reported the first example of enantioselective reaction of isatins with alkenylboronic and arylboronic acids achieving up to 93% enantiomeric excess (*ee*) giving, in high yields, bioactive relevant 3-aryl-3-hydroxy-2-oxindoles.⁸⁰ They obtained these results using a rhodium-phosphine complex, a substoichiometric amounts of potassium hydroxide in a 20:1 mixture of THF:H₂O heating at 50 °C (Scheme 1). It is worth to note that the nitrogen substituent of isatins did not have high effects on the selectivity of the reaction. They could achieve high *ee* even with free N-H groups.



Scheme 1. Hayashi's arylation of isatins.

In the same year, it was found that chiral phosphoramidite **126**-rhodium complex catalyst (Figure 27) gave excellent yields but with a decrease of the enantiomeric excess, achieving only a 55% *ee*.⁸¹

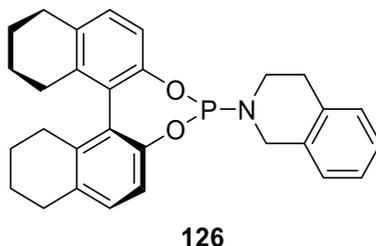
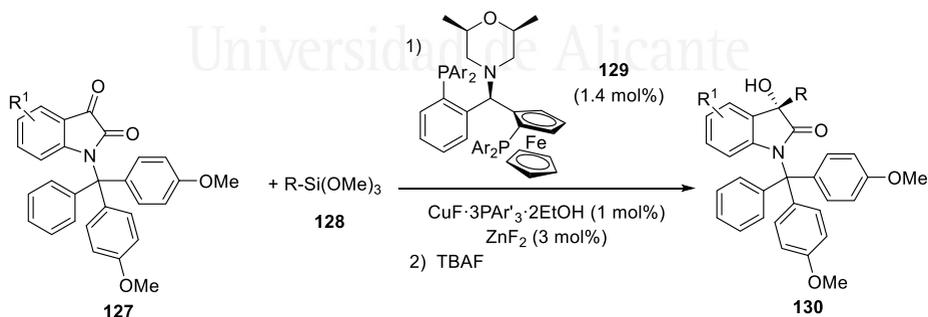


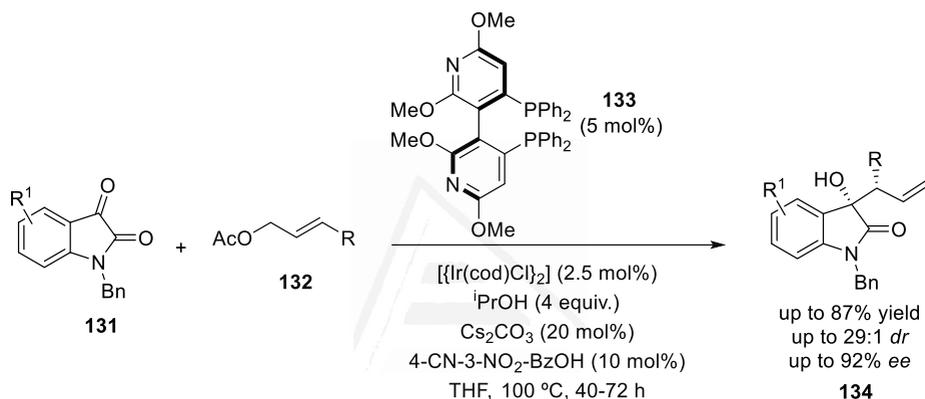
Figure 27. Chiral phosphoramidite ligand **126**.

In 2009 it was also reported the alkenylation and arylation of isatins using the copper(I)/**129** chiral complex. In this example, the nitrogen of the isatin had to be protected with a bulky protecting group (PG) as di(*p*-methoxyphenyl)phenylmethyl to afford the product with excellent *ee*. Using this methodology they could synthesize the above commented growth hormone secretagogue SM-130686 (**32**) (see section 1.2) (Scheme 2).⁸²



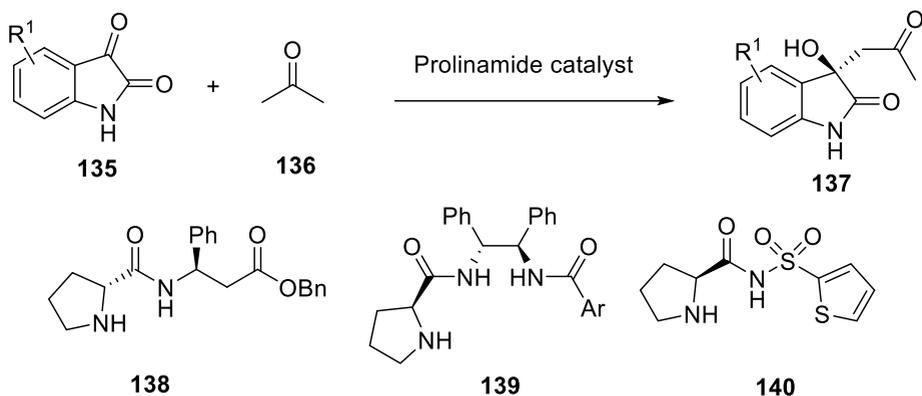
Scheme 2. Copper(I) mediated arylation of isatins.

Krische and co-workers, also in 2009, developed the first enantioselective allylation, prenylations and crotylations of isatins *via* ⁱPrOH-mediated transfer hydrogenation. This reaction was catalyzed by Ir that is forming a complex with (*R*)-(+)-2,2',6,6'-tetramethoxy-4,4'-bis(diphenylphosphino)-3,3'-bipyridine). These reactions also were the first examples of catalytic enantioselective ketone allylation without stoichiometric amounts of allylmetal reagents (Scheme 3).⁸³



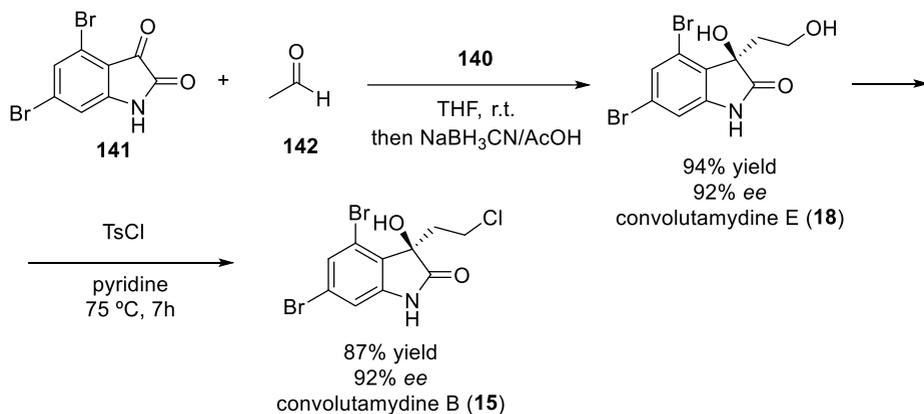
Scheme 3. Krische's allylation of isatin derivatives.

Besides, organocatalysis has been established as an efficient methodology for the synthesis of 3-hydroxy-2-oxindoles derivatives. In 2005 Tomasini and co-workers were the pioneers in the cross-aldol reaction of isatins and carbonyl compounds through an enamine catalysis.^{84,85} They found that, using a prolinamide **138** as catalyst, acetone and isatin reacted and obtaining up to 77% *ee* of the product, but with a reduced scope. Subsequent improvements of this method have been achieved by Xiao,⁸⁶ using **139** (up to 90% *ee*) and Toru with **140** (up to 97% *ee*) (Scheme 4).⁸⁷ These intermediates were suitable for the synthesis of the previously discussed natural alkaloid convolutamydin **14** (see section 1.1).



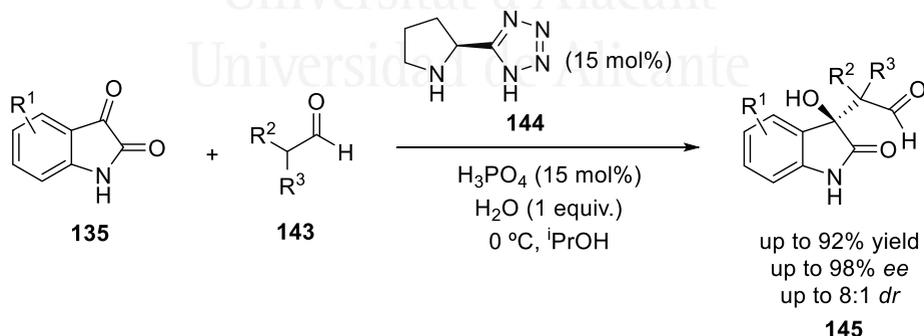
Scheme 4. Aldol reactions between isatins and acetone.

For the synthesis of convolutamydine E (**18**), Hara and co-workers reported in 2009 the aldol reaction between different aldehydes with 4,6-dibromoisatin **141** using the organocatalyst **140**. The results were satisfactory because the products were obtained in moderate to excellent diastereomeric ratios (*dr*) but with excellent *ee*. Specifically, the reaction between **141** and acetaldehyde and after reduction *in situ* with $\text{NaBH}_3\text{CN}/\text{AcOH}$ afforded convolutamydine E (**18**) in 94% yield and 92% *ee*. This product could be transformed into convolutamydine B (**15**) after treatment with *p*-toluenesulfonyl chloride in pyridine at 75 °C furnishing the natural alkaloid **15** in good yield without any loss of enantiomeric excess (Scheme 5). It is worth to note that when most simple isatin **35** was allowed to react with acetaldehyde, the yield decrease to 60% and the product was almost racemic (2% *ee*).⁸⁸



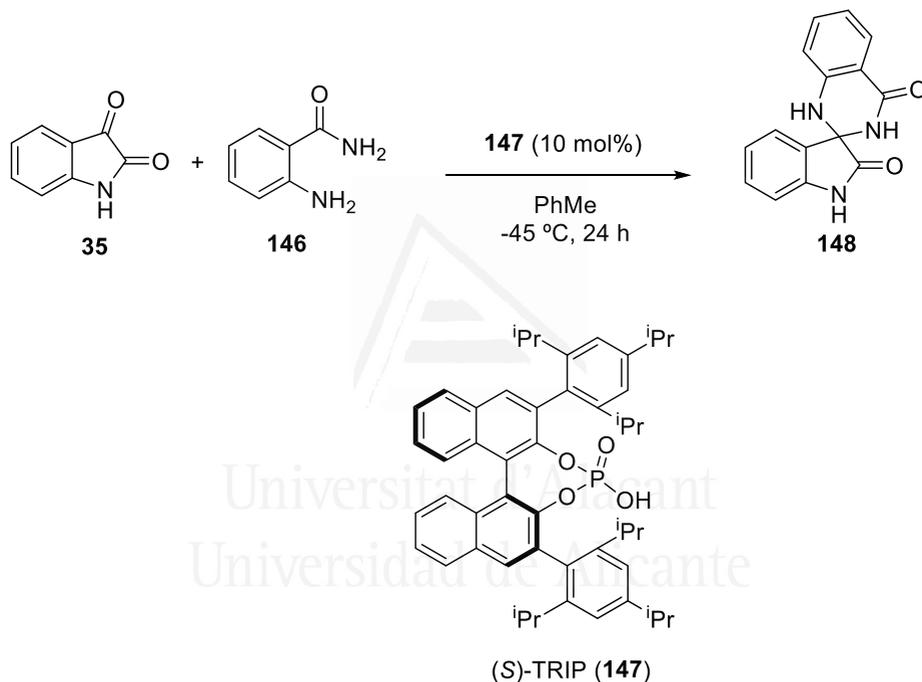
Scheme 5. Aldol reaction between isatin and acetaldehyde.

The reaction was also possible with α -branched aldehydes giving high enantiomeric excesses in products containing two contiguous quaternary stereocenters. This was reported by Wang and co-workers using chiral pyrrolidine **144** with a tetrazole moiety as organocatalyst. This procedure afforded good yield and good to excellent *ee* and *dr* (Scheme 6).⁸⁹



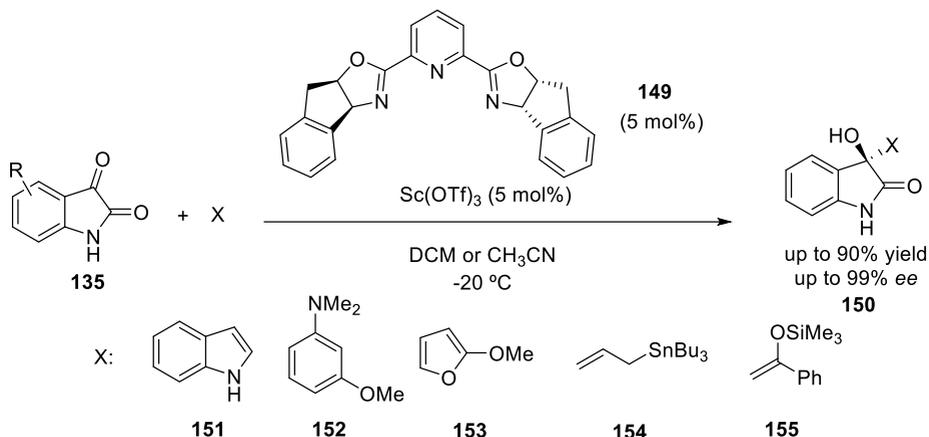
Scheme 6. Aldol reaction between isatin and α -branched aldehydes.

In the field of organocatalysis, the use of Brønsted acids as activators is a current practice. Isatin **35** and the nucleophile 2-aminobenzamide **146** reacted giving the spirocyclic product **148** in 84% *ee* and 85% of yield (Scheme 7).⁹⁰ The acid used (*S*)-3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diylhydrogenphosphate **147** is a very effective common chiral phosphoric acid in the field of organocatalysis, usually called as (*S*)-TRIP.



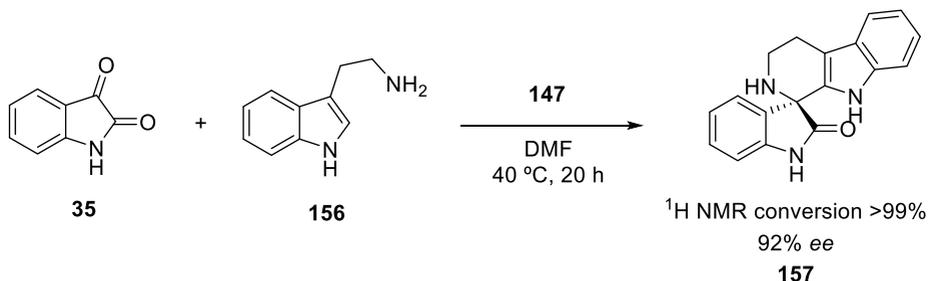
Scheme 7. Brønsted acid activation of isatin.

The research group of Franz developed a chiral complex formed by $\text{Sc}(\text{OTf})_3$ and a PyBox type bisoxazoline **149** which catalyze the addition of diverse type of nucleophile **151-155** (indoles, silane ethers, electron rich aryls and allyltributylstannane) to isatin derivatives (Scheme 8). Both *ee* and yield were excellent.⁹¹



Scheme 8. Chiral Sc(III)/PyBox-catalyzed reaction of isatins with different nucleophiles.

Also, an organocatalyzed Pictet-Spengler type reaction has been reported by Bencivenni and co-workers using tryptamine derivatives reacting with isatins obtaining up to 97% yield and up to 95% *ee*. These reactions were catalyzed by, again, phosphoric acid **147** and performed at 40 °C for 20 h in dimethylformamide (DMF) (Scheme 9).⁹²

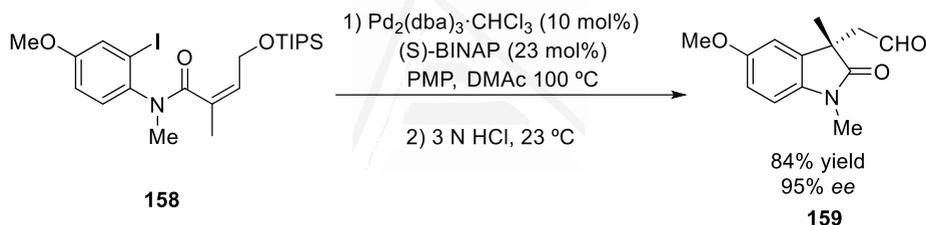


Scheme 9. Pictet-Spengler type reaction between tryptamine and isatin.

Many other methodologies based in nucleophilic addition to isatins have been widely reported.^{93–100}

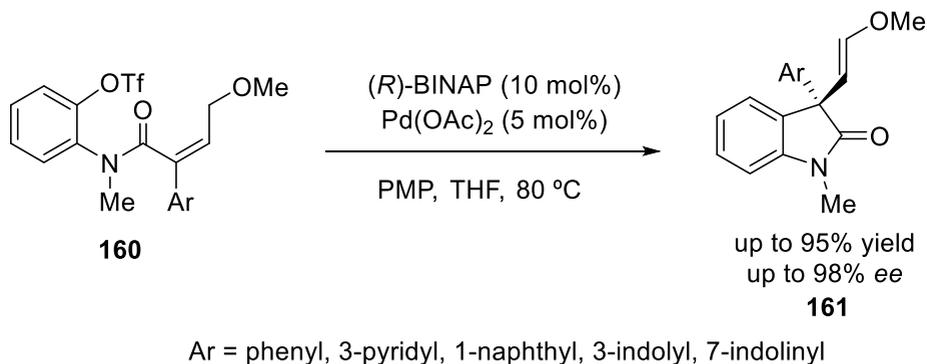
2.2. Intramolecular coupling reactions

In this area, we can find different types of intramolecular cyclizations of anilides based, for example, on Heck reactions, arylation reactions or cyanoamidation reactions. For the first type, namely Heck reactions, Overman's research group in 1993 performed the Pd-catalyzed intramolecular reaction of the anilide **158** in an enantioselective manner. With this methodology they could prepare the natural alkaloid (–)-physostigmine (**21**) (see section 1.1) with a 95% *ee* in the key step where an intramolecular cyclization took place (Scheme 10).¹⁰¹



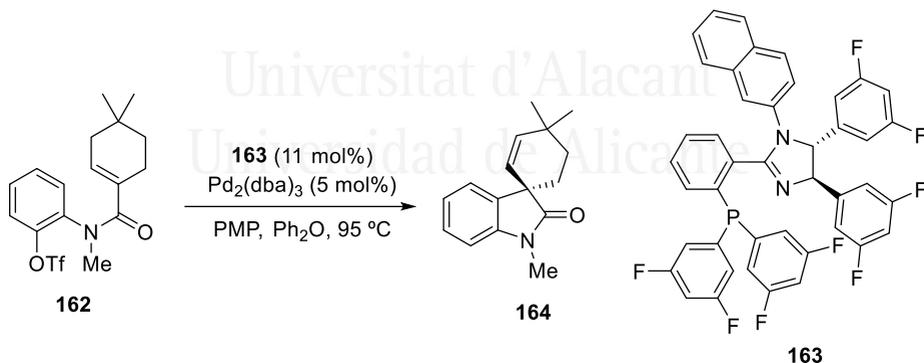
Scheme 10. Oxindole synthesis through an acetanilide cyclization.

Later, in 2003 the same strategy for the synthesis of 3-alkyl-3-aryl-2-oxindoles was applied. Now, the optimal palladium source was $\text{Pd}(\text{OAc})_2$ and (*R*)-BINAP was the source of chirality. In this case, a pseudohalide as triflate was used to perform the oxidative addition instead of iodine. Different aryl and heteroaryl groups at the 3 position of the oxindole were introduced (Scheme 11).¹⁰²



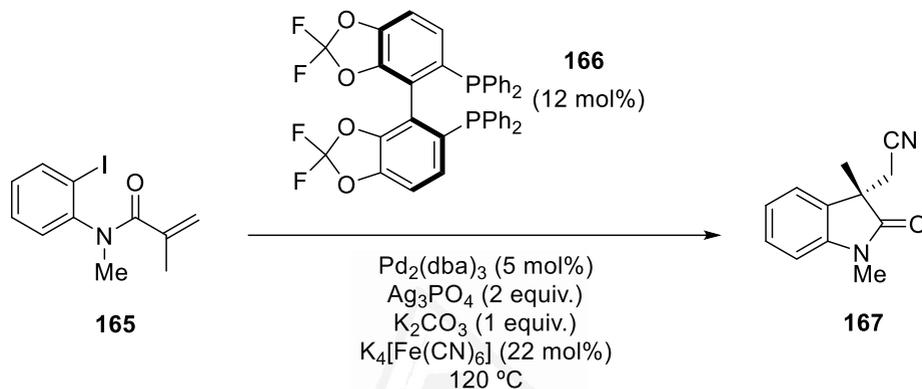
Scheme 11. 3-Aryl 2-oxindole synthesis through an acetanilide cyclization.

In the same year, Busacca and co-workers performed an intramolecular Heck reaction using again a pseudohalide and a new chiral phosphino-imidazoline ligand **163** with $\text{Pd}_2(\text{dba})_3$ giving a spirocyclic oxindole derivative **164** (Scheme 12).¹⁰³



Scheme 12. Spirocyclic oxindole synthesis through an intramolecular Heck reaction.

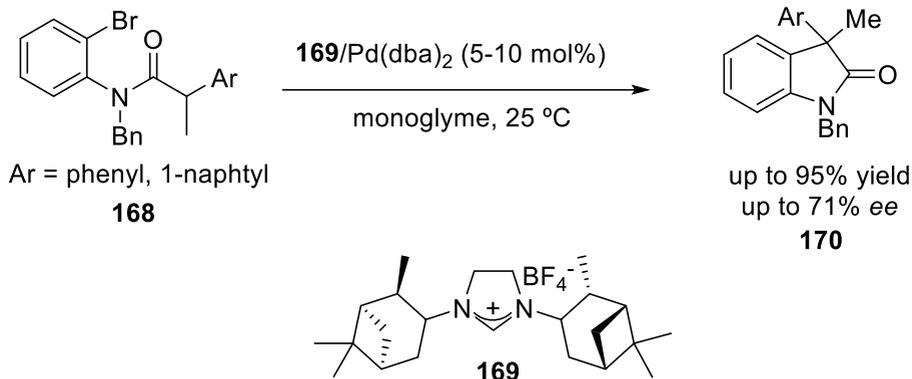
After few years, the research group of Zhu found a methodology involving a domino Heck-cyanation reaction in which they synthesized the intermediate **167**, that can be further transformed in physostigmine (**21**) natural alkaloid. This method provided moderate yield (54%) and *ee* (61%) (Scheme 13).¹⁰⁴



Scheme 13. Synthesis of **167**, an important precursor of natural product physostigmine

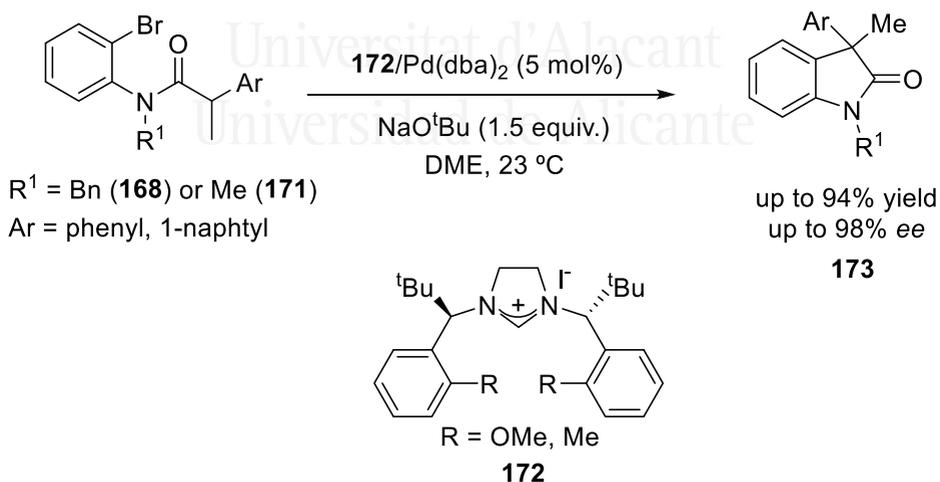
It is worth to note that the lowest temperature that was used with these methods was 80 °C. It means that heating conditions are probably needed in the most of cases to set up these experiments. Thus, higher economic resources must be invested to synthesize these prominent scaffolds.

On the other hand, there are some examples of intramolecular arylation reactions. For example, in the research group of Hartwig, the chiral derivative **169** was a good option as a ligand for the synthesis of 3,3-disubstituted oxindoles through amide α -arylation because it enhanced the reactivity of palladium catalyst. Compound **169** allowed to carry out the reaction at room temperature using less electrophilic aryl halides, as for example aryl bromides (Scheme 14).¹⁰⁵



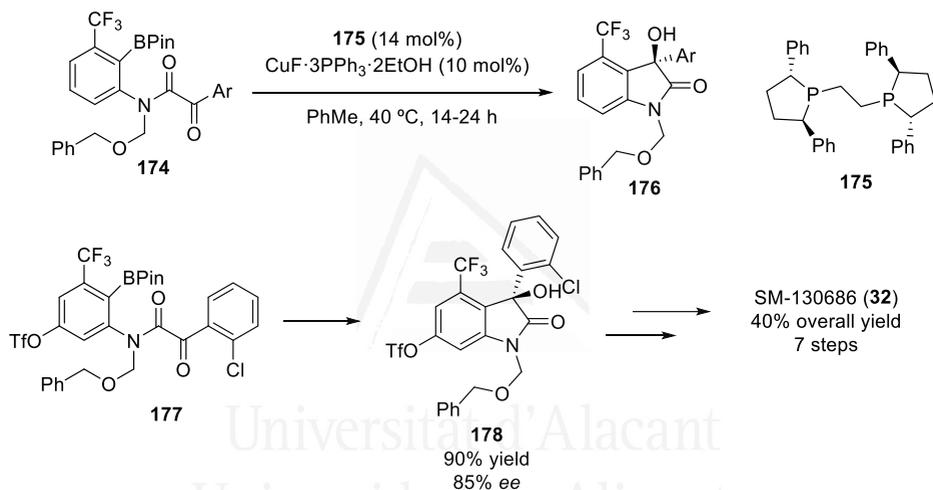
Scheme 14. Intramolecular arylation for the synthesis of 3,3-disubstituted 2-oxindoles.

It is important to note that, although the enantiomeric excess was not excellent, this was a starting point for the development of more efficient chiral carbenes as, for example, **172** developed by Kündig and co-workers (Scheme 15).¹⁰⁶



Scheme 15. Improvement of previously reported intramolecular cyclization.

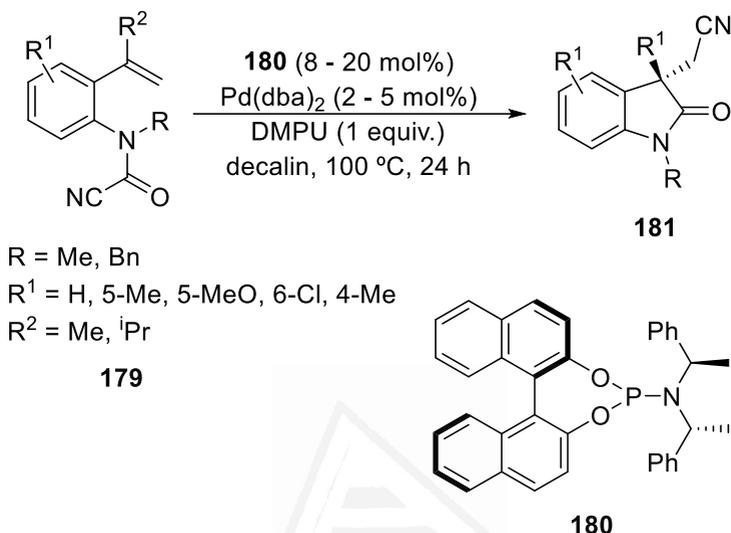
Also, intramolecular arylation reactions have emerged using copper(I) as catalyst in combination with the chiral diphosphine ligand **175** to carry out the same type of reaction. With this methodology, they could obtain up to 90% yield and up to 87% *ee*. With a specific substrate, they synthesized the compound **178** (Scheme 16) which is an intermediate of the growth hormone secretagogue SM-130686 (**32**) (see section 1.2).⁸²



Scheme 16. Copper(I) catalyzed intramolecular arylation and synthesis of SM-130686 (**32**).

Finally, an example of an intramolecular cyanoamidation reaction was also reported by Takemoto's research group. They could perform the enantioselective version catalyzed by Pd and in this case a phosphoramidite **180** provided the chiral information. It is worth to note that this reaction occurred under neutral conditions and tolerated several moieties on the aromatic ring with different nature using 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) as an additive and decalin as a solvent at 100 °C. In this interesting

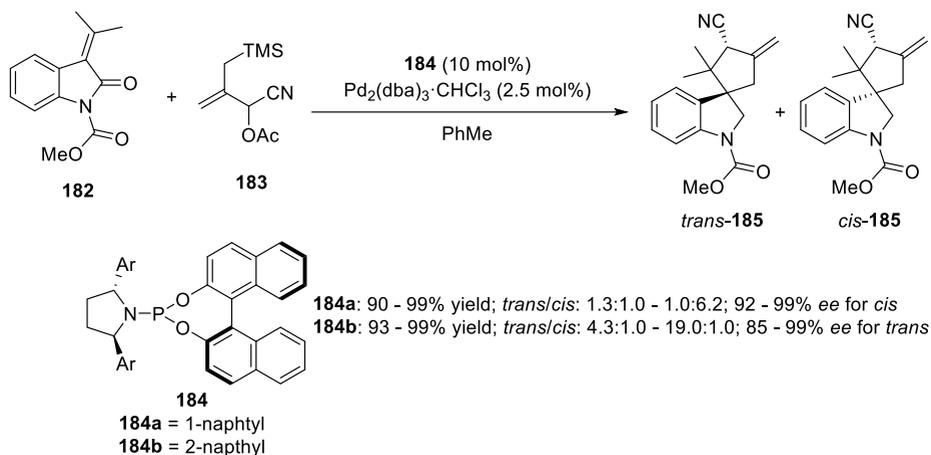
reaction, up to quantitative yields and up to 86% *ee* were obtained (Scheme 17).¹⁰⁷



Scheme 17. Enantioselective cyanoamidation as example of intramolecular arylation.

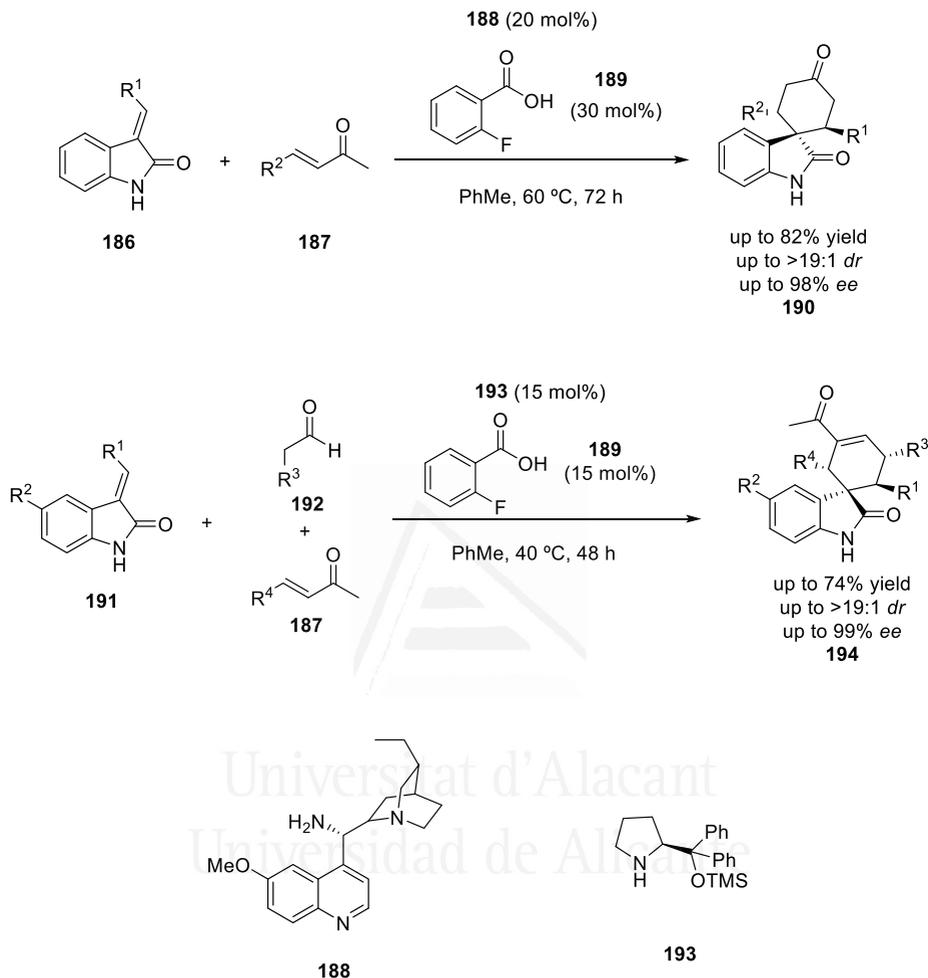
2.3. Methyleneindolinones as substrates

The methyleneindolinones are important substrates to synthesize different spirocyclic oxindole derivatives. For example, a [3+2]-cycloaddition of 3-alkylidene-2-oxindole and allyl acetate derivative, catalyzed by palladium complex, was reported by Trost and co-workers in 2007. In this methodology, the phosphoramidite **184** was employed as chiral ligand. Using the optimal conditions, they achieve excellent enantiomeric excess and yields. The diastereomeric ratio depends on the aryl substituents of the chiral ligand (Scheme 18).¹⁰⁸



Scheme 18. [3+2]-Cycloaddition of alkylidene 2-oxindoles

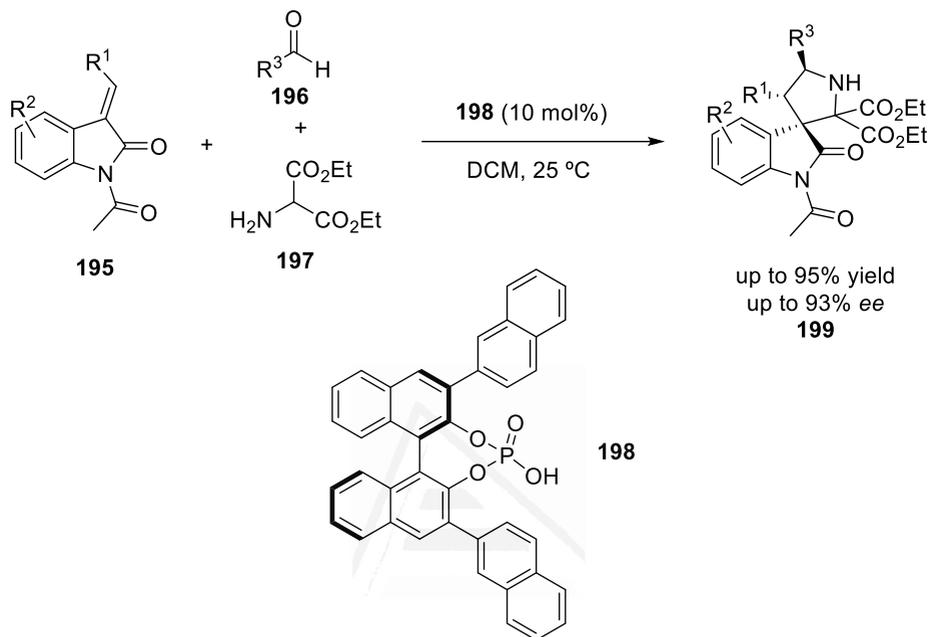
Also, the research group of Melchiorre reported a method for the synthesis of spirocyclic oxindoles catalyzed by different primary amine organocatalysts. When the catalyst **188** was used, a double Michael/Michael domino reaction was performed giving the spirocyclic oxindoles in moderate to good yields and excellent *ee*. On the other hand, using **193** a multicomponent cascade reaction between an α,β -unsaturated aldehyde and the methyleneindolinone proceed affording the final products with good yields and, again, excellent enantioselectivity through a Michael/Michael/aldol condensation procedure (Scheme 19).¹⁰⁹



Scheme 19. Organocatalyzed synthesis of spirocyclic 2-oxindoles.

Finally, Gong and co-workers developed a three-component 1,3-DC using different methyleneindolinones, aldehydes and amino esters catalyzed by, again, a chiral phosphoric acid organocatalysts **198** in dichloromethane at room temperature. This methodology afforded the spiro[pyrrolidine-3,3-oxindole]

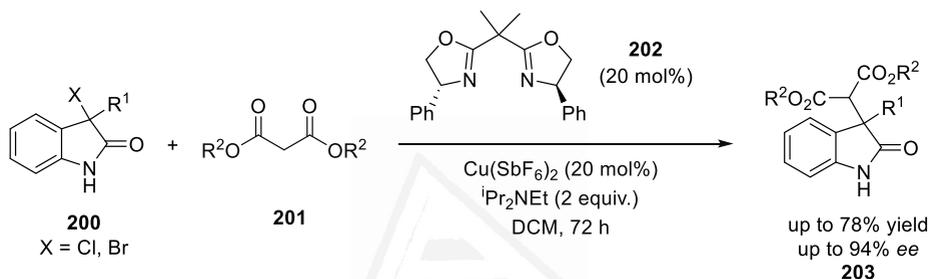
derivatives in excellent enantiomeric excesses and yields (Scheme 20).¹¹⁰



Scheme 20. Organocatalyzed 1,3-DC affording spiro derivatives.

2.4. Oxindoles as electrophiles

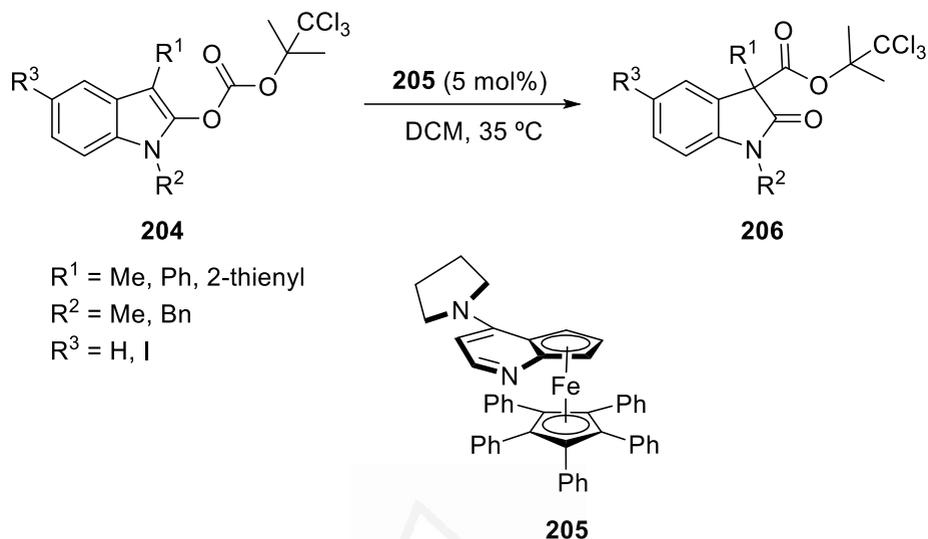
A less common methodology is the employment of oxindoles as electrophiles. In 2009 Stoltz reported an example where the oxindole structure was used as electrophile and using 1,3-dicarbonyl compounds as nucleophiles. In this case, a halooxindole reacted in presence of a base with activated malonate esters by chiral copper(II)-BOX complex to form a quaternary stereocenter. Good yields and excellent *ee* were achieved (Scheme 21).¹¹¹



Scheme 21. Example of the use of oxindoles as electrophiles.

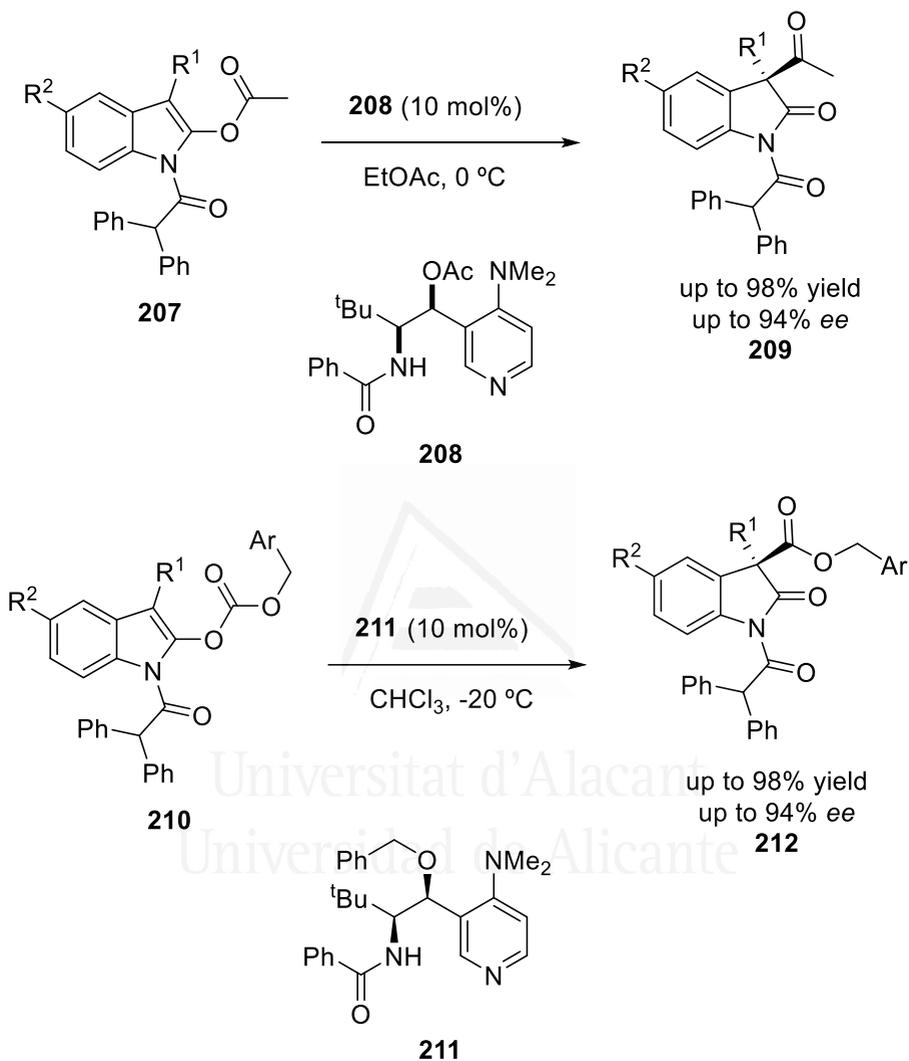
2.5. Reactions based on *O*-substituted oxindoles

The *O*-substituted 2-oxindole derivatives are important and versatile structures and have been used in many constructions of quaternary stereocenters at the 3 position. Indolyl acetates, carbonates and esters are adequate substrates for different intramolecular catalytic rearrangements. Also, indolyl silyl ethers have been used in the same way. This methodology has provided excellent results in yields and enantioselectivities. For example, Fu and co-workers reported in 2003 the first example of a catalytic enantioselective intramolecular reaction of *O*-acylated oxindole derivatives with yields between 72 to 94% and excellent enantiomeric excess ranging between 93 and 99% using a chiral 4-(pyrrolidino)pyridine derivative **205** as catalyst (Scheme 22).¹¹²



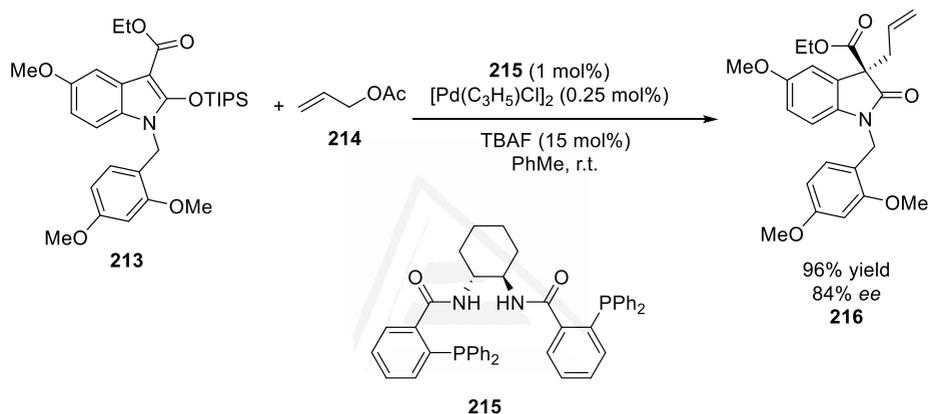
Scheme 22. *O*-Acylated oxindole intramolecular catalytic rearrangement.

Vedejs and co-workers applied this methodology with 4-(dimethylamino)pyridine (DMAP) derivatives as catalysts. They found that excellent yields and *ee* could be achieved with specific *O*-indoyl acetates and carbonates. They carried out the reactions with *O*-acyl substrates in EtOAc at 0 °C using **208** as catalyst, and the reaction with carbonates were performed in CHCl_3 at -20 °C with catalyst **211** (Scheme 23).¹¹³



Scheme 23. *O*-Acyated and *O*-carbonated oxindole rearrangements.

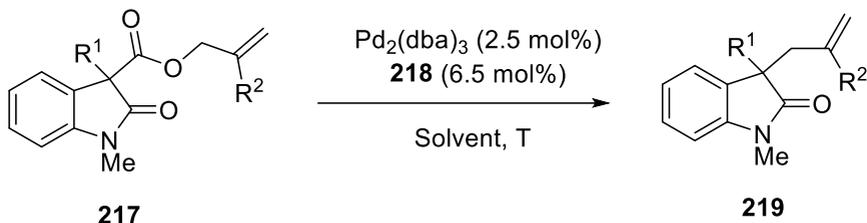
In 2006, Trost *et al.* developed the asymmetric synthesis of an oxindole derivative through a palladium-catalyzed asymmetric allylic alkylation (AAA). With this methodology they synthesized the natural alkaloid (–)-horsfiline (**5**) (see, section 1.1) through an enantiomerically enriched intermediate **216** using only 0.25 mol% of $[\text{Pd}(\text{C}_3\text{H}_5)\text{Cl}]_2$ and 1 mol% of Trost's ligand **215**. The overall yield of the total synthesis was 11.1% starting from the available *p*-anisidine (Scheme 24).¹¹⁴



Scheme 24. Indoyl silane as precursor of a natural alkaloid.

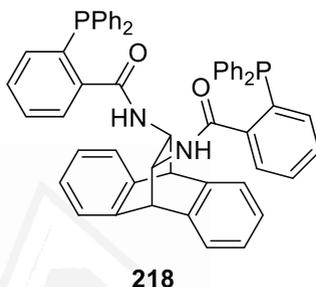
2.6. Palladium-catalyzed decarboxylative allylation

This recently-emerged methodology is also useful for the formation of quaternary stereocenters in the oxindole framework. In 2011 Taylor and co-workers developed an asymmetric decarboxylative allylation of alkyl- and aryl-substituted oxindoles catalyzed by Pd. In this contribution, excellent yields and good to excellent enantioselectivities were achieved. It is worth to note that for different oxindole substrates, different optimal conditions were needed. These reaction conditions involved solvents as tetrahydrofuran (THF), dimethoxyethane (DME), toluene and also reaction times between 24 to 48 h. They could obtain different allylated products in yields up to >99% and *ee* up to 95% using the chiral ligand **218** (Scheme 25).¹¹⁵



R¹ = Me, CH₂CN, CH(CH₃)₂, Cy, Ph

R² = H, Me, Ph



Scheme 25. Taylor's decarboxylative allylation methodology.

2.7. Direct functionalization of 3-substituted 2-oxindoles

The direct functionalization of 3-substituted 2-oxindoles is the most versatile and useful methodology for the formation of quaternary stereocenter in the oxindole core. This method is based on the nucleophilic reactivity of the prochiral 3 position of the oxindole. For the synthesis of starting materials (the 3 substituted 2-oxindole derivatives), exist some methods as condensation of 2-oxindole **1** or its derivatives with an aldehyde and posterior reduction, through a Wittig reaction from isatin and triphenylphosphorane and reduction and also from Grignard reagents and isatins and posterior reductive deoxygenation. It is remarkable that these methodologies, although efficient, require different steps (posterior reduction, reductive deoxygenation) and could be that it is not possible to access to a specific ylide or require multiple steps. In the next chapter will be discussed an alternative synthesis for these important 3-substituted 2-oxindole derivatives.

As a general information about the chemistry of 3-substituted 2-oxindoles, it has been studied that pK_a value of hydrogens at the 3 position of the oxindole **1** is 18.2 and this value is altered by the substituents bonded to nitrogen atom. For example, the pK_a of *N*-methyloxindole **220** is slightly less acidic, but when nitrogen is substituted with an acetyl group, these hydrogens are 100000 more acidic ($pK_a = 13.0$) in the oxindole structure **221** (Figure 28).¹¹⁶

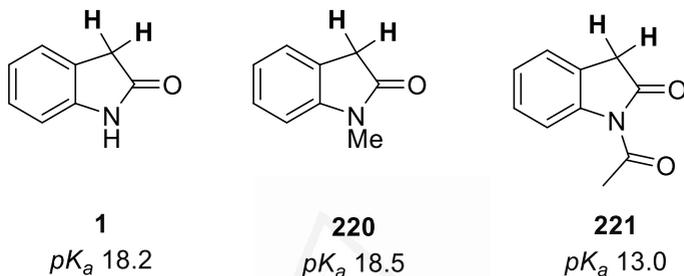


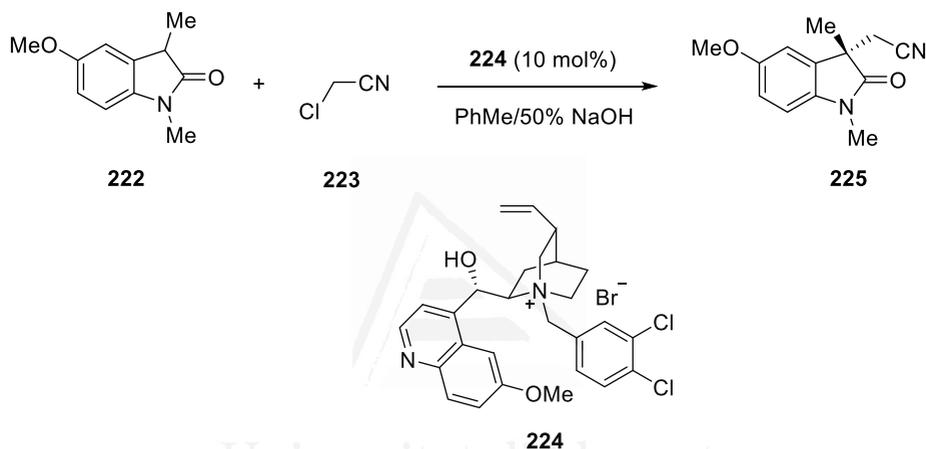
Figure 28. pK_a Values of oxindole derivatives.

Consequently, many methodologies utilize *N*-Boc-3-substituted oxindoles as starting materials because the acidity of the hydrogen is higher and softer bases can be used to deprotonate and form the enolate. Unfortunately, the direct synthesis of *N*-Boc substituted oxindoles from unprotected 3-substituted 2-oxindoles is a challenging task, due to the concomitant parallel reactions at O and N atom. Furthermore, the enantioselective functionalization at the 3 position of unprotected 3-substituted 2-oxindole is still a challenge.

As a background concerning what have been reported in the literature, some methodologies of direct functionalization of 3-substituted 2-oxindoles will be discussed. There are a lot of examples but some representative examples of alkylation, fluorination, hydroxylation, Mannich, Michael, amination, arylation and aldol reactions will be presented.

Wong and co-workers, in 1991, reported one of the first examples of catalytic asymmetric alkylation using 3-prochiral oxindoles under chiral phase-transfer catalysis (PTC).¹¹⁷ Using a

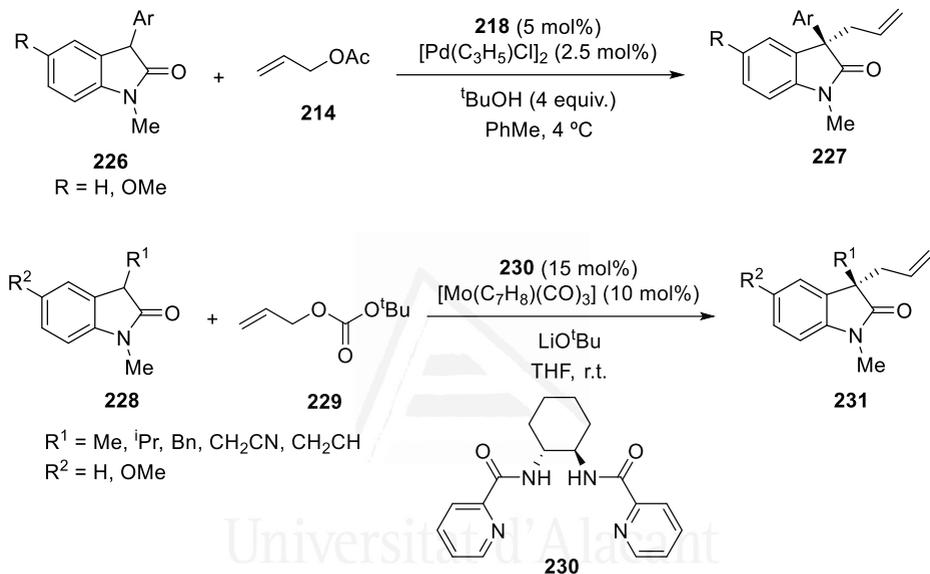
chiral ammonium bromide salt **224** as phase-transfer catalyst, 5-methoxy-1,3-dimethylindolin-2-one **222** and chloroacetonitrile as alkylating agent in a mixture of toluene and 50% NaOH water solution they achieved compound **225** in a 83% yield and 77% of *ee* (Scheme 26). This compound **225** is the key precursor of (-)-physostigmine **21** (see section 1.1).



Scheme 26. One of the first examples of catalytic asymmetric alkylation of oxindole.

In 2005, Trost developed a very efficient enantioselective synthesis of 3-allyl-3-aryloxindoles through an asymmetric allylic alkylation (AAA) reaction catalyzed by Pd. This methodology allowed to allylate 3-aryl-1-methyloxindole derivatives with high enantioselectivity (70 to 97% *ee*) and high yields (72 to 96%). In this case, also chiral ligand **218** was used and π -allylpalladium(II) chloride dimer as palladium source, using allyl acetate as allylating agent.¹¹⁸ It is worth to note that, for these type of reactions, allylating reagents must be previously activated as a carbonates or acetates, among others, because the direct use of allyl alcohol is not enough reactive due to the poor ability of hydroxy moiety as a leaving group. One year later, again Trost and co-workers provided a similar methodology for the asymmetric synthesis of 3-alkyloxindoles, but in

this situation molybdenum catalyst and tuned chiral ligand **230** were used for achieving excellent results (up to 93% *ee* and 99% yield). In this last work, also an allyl carbonate was used instead of allyl acetate (Scheme 27).¹¹⁹

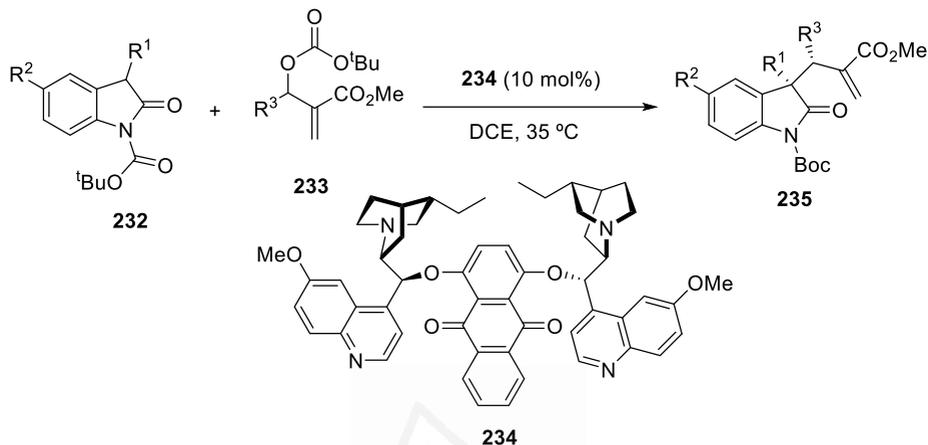


Scheme 27. Alkylation of 3-substituted 2-oxindole derivatives catalyzed by metals.

The molybdenum methodology was also applied by Trost and co-workers for posterior alkylations using different allyl carbonate derivatives for the synthesis of vicinal tertiary and quaternary stereocenters.¹²⁰

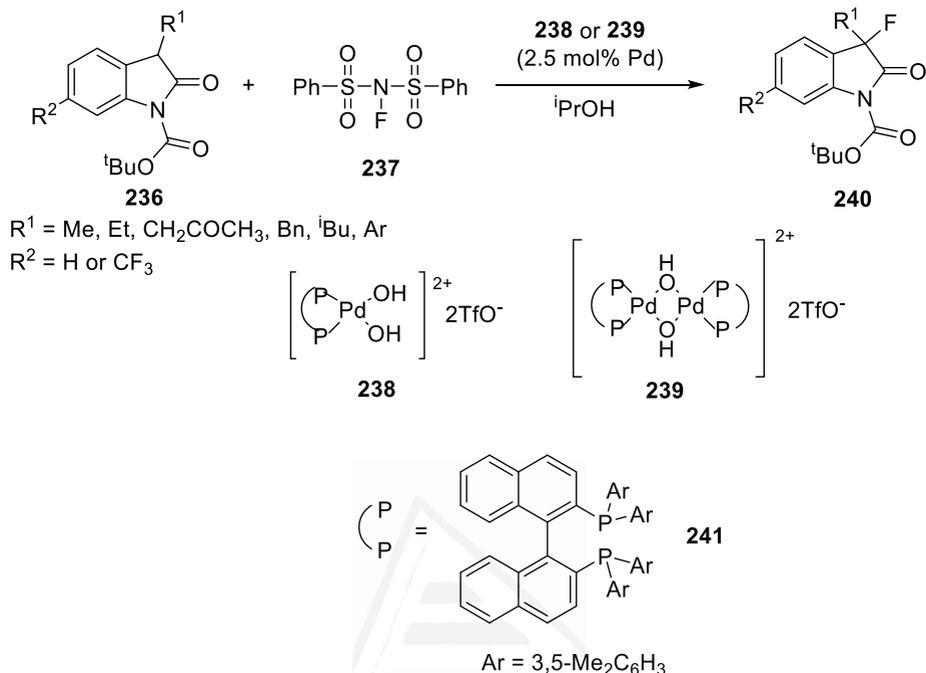
Next, Chen developed in 2008 an asymmetric allylic alkylation catalyzed by a Lewis base (DHQD)₂AQN **234** *Cinchona* alkaloid derivative. In this method, *N*-Boc-3-substituted oxindole derivatives must be used providing the corresponding products in up

to 98% yield, 96% *ee* and 92:8 of *dr* through a Morita-Baylis-Hillman reaction (Scheme 28).¹²¹



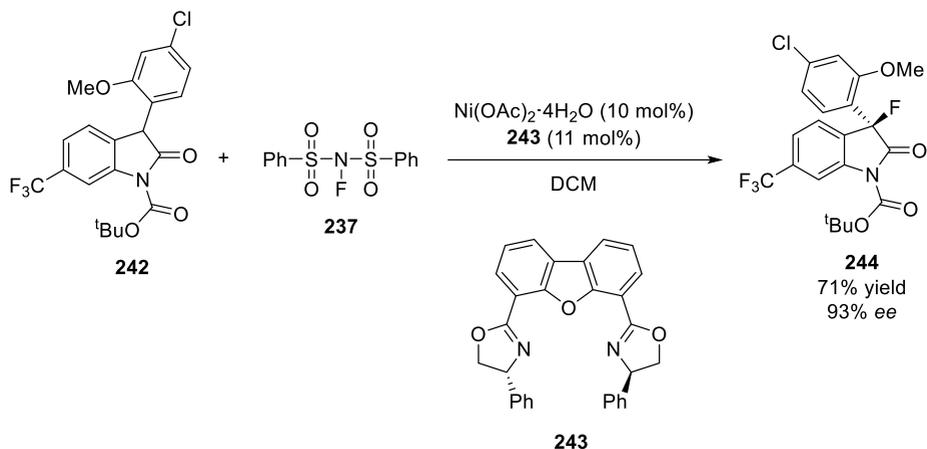
Scheme 28. Morita-Baylis-Hillman reaction for alkylated 3-substituted 2-oxindoles.

Fluorination at the 3 position is an important strategy for developing (see section 1.2.6) synthetic fluorinated drugs and important structures for the synthesis of bioactive oxindole derivatives. Some methodologies have been published in this field. For example, Sodeoka *et al.* in 2005 reported a very efficient asymmetric method for the fluorination at the 3 position of oxindole core. Using a modified BINAP chiral ligand, the (*S*)-DM-BINAP **241** and the palladium source, palladium complexes **238** and **239** were generated. Using these catalysts, different 3-substituted *N*-Boc-2-oxindoles were fluorinated obtaining up to 96% *ee* and 97% yield. It is important to note that the *N*-Boc group is required for obtaining high enantioselectivities in the process, because when free nitrogen atom derivative was used, 5% *ee* was obtained. The fluorinating agent employed was *N*-fluorobenzenesulfonimide (NFSI) (Scheme 29).¹²²



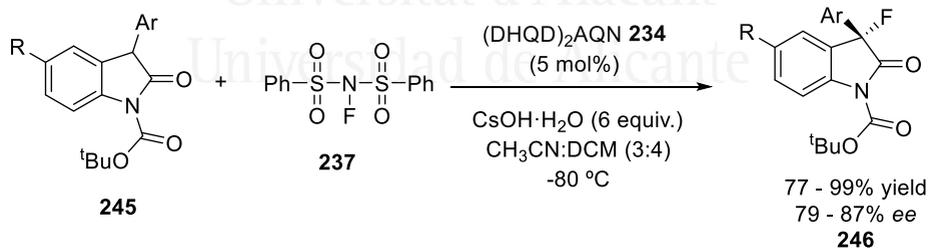
Scheme 29. Methodology for the fluorination of oxindole derivatives.

In the same year, Shibata and Toru developed a fluorination of *N*-Boc-3-methyl and 3-aryl oxindoles using Ni(II) salts and chiral ligand **243**. With this method, they could synthesize the bioactive fluorinated synthetic drug MaxipostTM (**88**) (see section 1.2.6) through the intermediate **244** (71% yield, 93% *ee*) (Scheme 30).¹²³



Scheme 30. Synthesis of an intermediate of Maxipost™ synthetic drug.

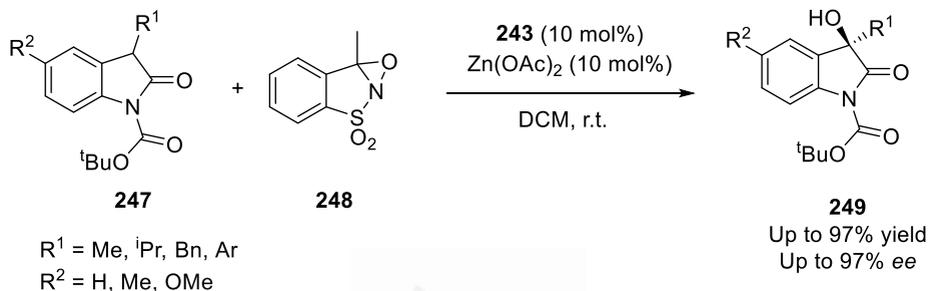
Three years later, the same research group, reported that $(\text{DHQD})_2\text{AQN}$ **234** was able to promote the fluorination reaction of, again, *N*-Boc protected 3-aryl oxindoles giving up to 87% *ee* with 6 equiv. of cesium hydroxide monohydrate (Scheme 31).¹²⁴



Scheme 31. Fluorination reaction of *N*-Boc-2-oxindole derivatives.

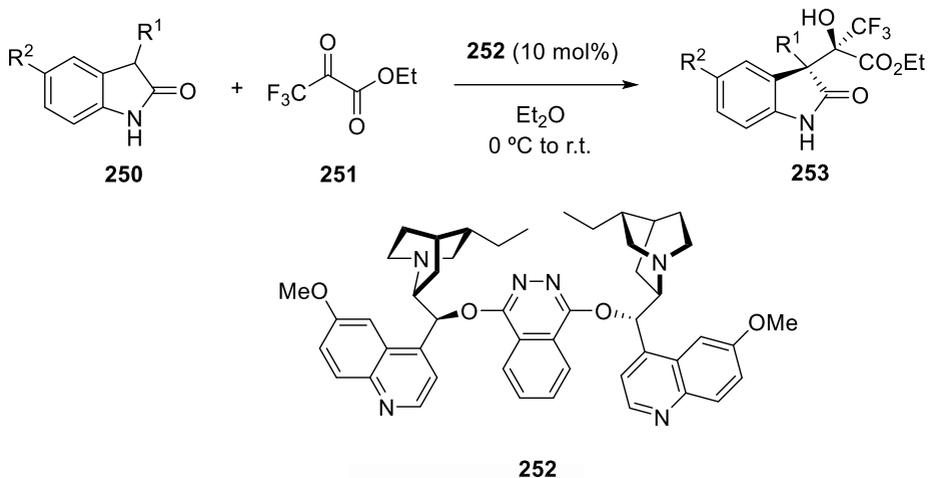
Other important reactions are the hydroxylation of 2-oxindoles at the 3 position. The simplest methodology is the nucleophilic attack to isatins, but starting from 3-substituted 2-oxindole is an alternative with multiple possibilities. Again, Shibata and Toru reported the

first example of catalytic hydroxylation of 3-alkyl and 3-aryl *N*-Boc protected 2-oxindoles. In this reaction conditions, they used the chiral ligand **243** but now using Zn(II) as a metal for form the complex. They achieved up to 97% yield and 97% *ee* using the racemic oxaziridine **248** as oxygen source (Scheme 32).



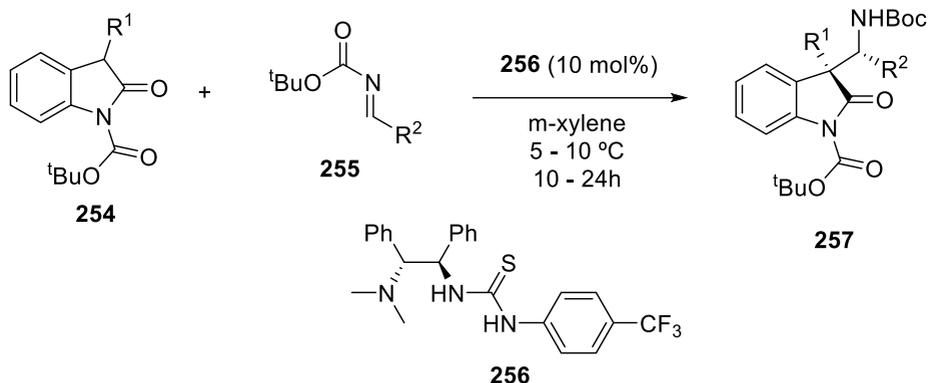
Scheme 32. Hydroxylation of 2-oxindole derivatives catalyzed by Zn(II) chiral complex.

Other type of chemistry ready to perform with 3-prochiral 2-oxindoles is the aldol reaction. Toru and Shibata developed an organocatalyzed reaction in which two adjacent stereocenters were formed. Now, (DHQD)₂PHAL **252** promoted the reaction of trifluoropyruvate derivate **251** and unprotected 3-alkyloxindole to afford the aldol product up to 99% yield, 94:6 *dr* and 99% *ee* (Scheme 33).¹²⁵



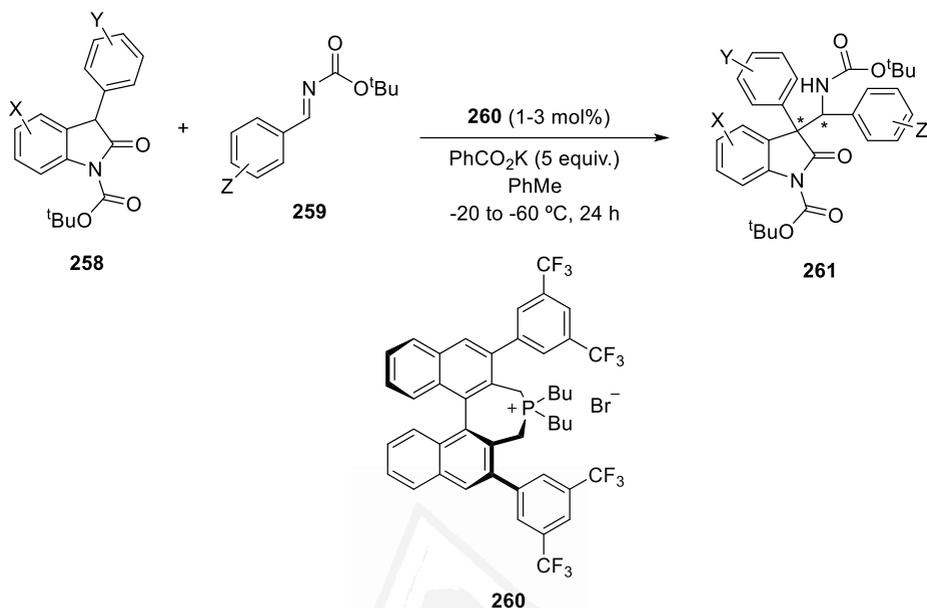
Scheme 33. Aldol reaction from 3-substituted unprotected 2-oxindoles.

Mannich reactions are also possible to be performed using 3-substituted 2-oxindole derivatives. Also in this case, two contiguous stereocenters are formed and these intermediates could be useful for the total synthesis of natural alkaloids as (–)-horsfiline (**5**), coerule-scine (**6**) and elacomine (**9**) (see section 1.1). Some years ago, in 2008, Chen reported the first example of enantioselective Mannich reaction of 3-alkyl and 3-aryl *N*-Boc substituted 2-oxindoles. The electrophiles were *N*-Boc imines and the reaction was catalyzed by the thiourea **256**, obtaining the corresponding products in good yields (40 – 95%), low to excellent enantioselectivities (5 – 93%) and *dr* up to 19:1 (Scheme 34).¹²⁶ Again, the *N*-Boc was very important for the reactivity and selectivity.



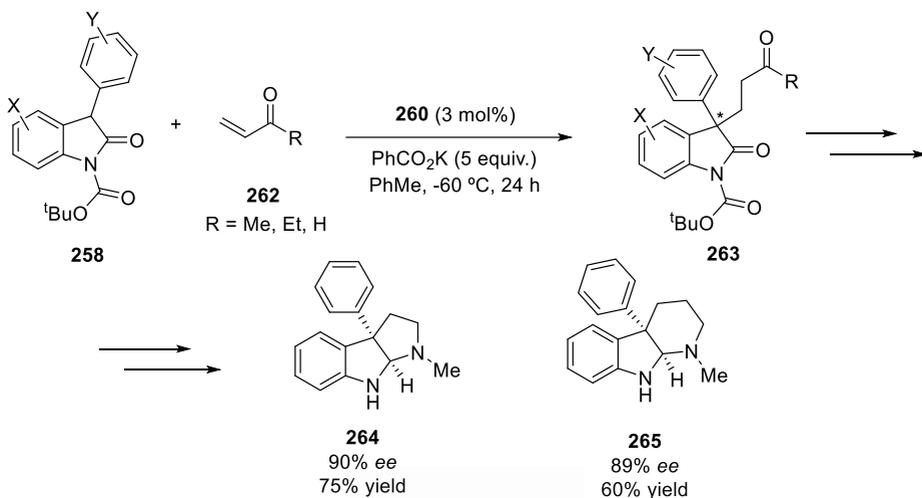
Scheme 34. Mannich reaction of *N*-Boc 3-substituted 2-oxindoles.

In 2009, Maruoka *et al.* developed a method for the asymmetric Mannich reaction of 3-aryl-2-oxindoles under PTC using quaternary tetraalkylphosphonium salt **260**. In this work, yields and diastereomeric ratios were excellent 95 – 99% and 96:4 – >99:1, respectively. The *ee* were good in a range of 56 to 88%. In this method, also *N*-Boc-2-oxindoles and *N*-Boc imines were used as starting materials (Scheme 35).¹²⁷



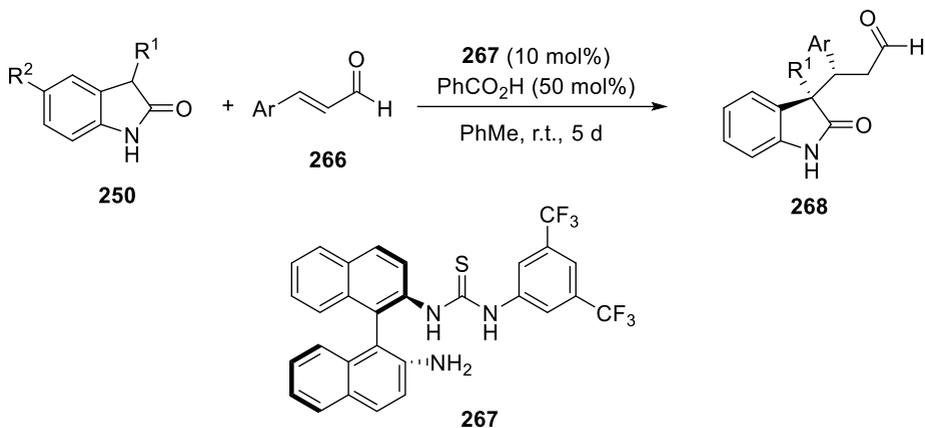
Scheme 35. Efficient method for the asymmetric Mannich reaction of 3-aryl-2-oxindoles.

Also, the Maruoka's research group, reported the application of the same methodology¹²⁷ in Michael additions. Here, the phase-transfer catalyst **260** at $-60\text{ }^\circ\text{C}$ provided excellent yields (91 – 99%) and excellent enantioselectivities (96 – >99% *ee*) for a scope of 20 oxindole derivatives. With these products, they could synthesize compounds **264** and **265**, which are synthetic derivatives of natural alkaloids (see section 1.1.) (–)-pseudophrynaminol (**23**), flustramine B and C (**22** and **26**, respectively), flustraminol (**24**), physostigmine (**21**) and CPC-1 (**25**) (Scheme 36). Such as it was described in section 1.2, these synthetic methodologies are very important for medicinal chemistry.



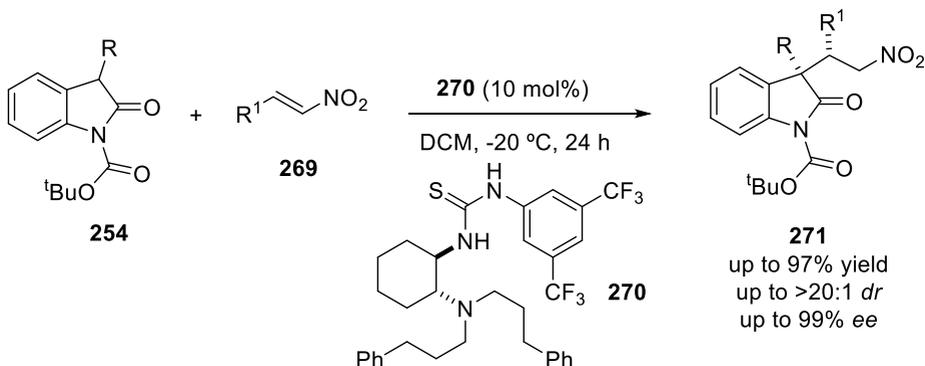
Scheme 36. Maruoka's methodology for asymmetric Michel addition of 3-aryl-2-oxindoles.

Melchiorre developed a Michael addition of unprotected oxindoles to α,β -unsaturated aldehydes using an organocatalyst based in a bifunctional primary amine-thiourea **267** affording the desired products in a range of 47 to 85% yield, 5:1 to 19:1 *dr* and *ee* from 73 to 93% (Scheme 37).¹²⁸



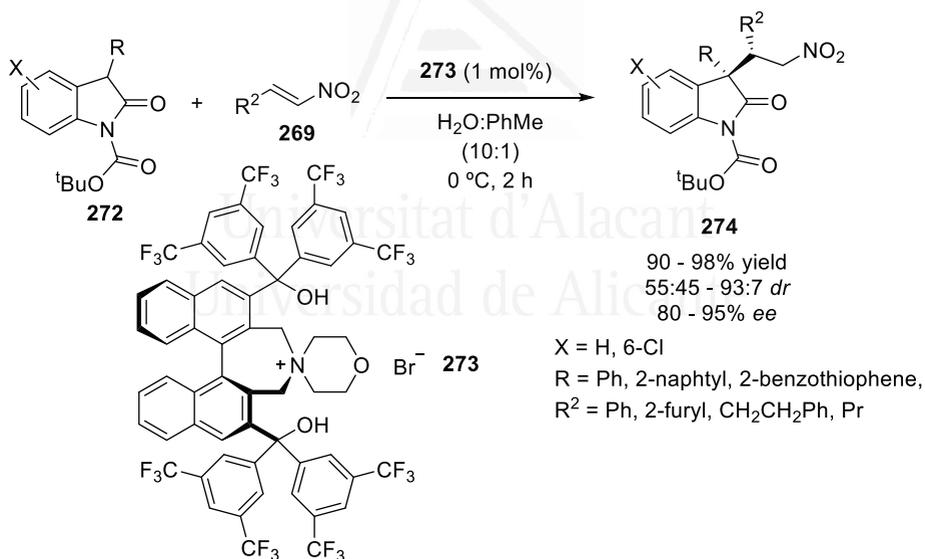
Scheme 37. Organocatalytic Michael addition of unprotected 3-substituted 2-oxindoles.

Barbas III *et al.* also reported the catalytic enantioselective Michael addition of *N*-Boc oxindole derivatives to nitroalkenes. The resultant products allowed to synthesize esermethole, an intermediate for the synthesis of (+)-physostigmine, the enantiomer of alkaloid **21**. The method consisted in the use of organocatalyst **270** (10 mol%) affording the Michael products in up to 97% yield, >20:1 *dr* and up to 99% *ee* (Scheme 38).¹²⁹



Scheme 38. Organocatalytic nitroalkane Michael addition of 2-oxindoles.

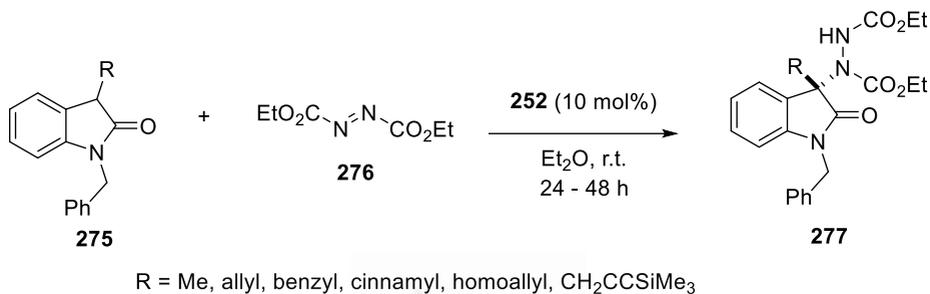
Finally, for Michael additions, Maruoka and coworkers reported a singular enantioselective base-free phase transfer reaction. Although, it was believed that quaternary ammonium salts as PTC needed bases and additives, they demonstrated that without them, enantioselective phase-transfer Michael addition of 3-aryloxindole to nitroalkenes was promoted using catalyst **273** (only 1 mol%) in a water-rich solvent. The reaction proceeded almost quantitatively (90 to 98% of yield), from 55:45 to 93:7 *dr* and 80 to 95% of *ee* in 8 examples (Scheme 39).¹³⁰ Only when the oxindole core has a methyl group at 3 position the reaction with β -nitrostyrene produced a decrease of both the yield and the *ee*, 34% yield and 25% *ee*, respectively, maintaining a 70:30 *dr*. Probably, this disappointed result is due to the less reactivity exhibited by the methyl derivative in comparison with the aryl substituted.



Scheme 39. Enantioselective base-free PTC Michael reaction.

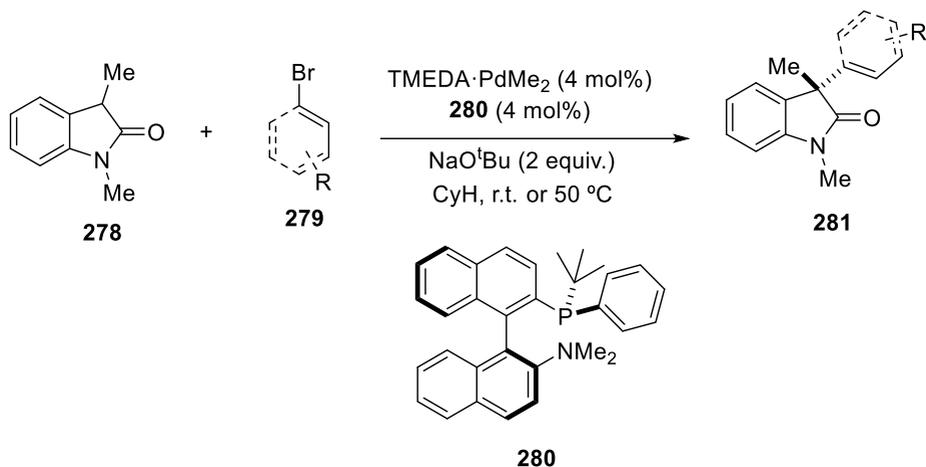
One of the last reaction types are the amination reaction at the 3 position of the oxindole derivative being possible to synthesize, for example, the synthetic drug AG-041R (**33**) (see section 1.2). In this

field, Barbas III *et al.* reported a method for the amination of *N*-benzyl 3-alkyloxindoles using (DHQD)₂PHAL **252** as catalyst and diethyl azodicarboxylate DEAD as aminating agent (Scheme 40). They obtained excellent yields and enantioselectivities (up to 98% yield and 99% *ee*, respectively).



Scheme 40. Asymmetric α -amination of 3-substituted 2-oxindoles.

Finally, an enantioselective arylation reaction of 1,3-dimethyloxindole derivatives was developed by Buchwald *et al.* in 2009. The process was catalyzed by palladium complex formed by dimethyl(*N,N,N',N'*-tetramethylethylenediamine)palladium(II) TMEDA·PdMe₂ and an axially chiral P-stereogenic ligand **280** affording the arylated products in a range from 62 – 87% yield and 54 – 99% enantiomeric excess in cyclohexane as a solvent at room temperature or heating at 50 °C. Also vinylations were suitable under these reaction conditions (Scheme 41).¹³¹

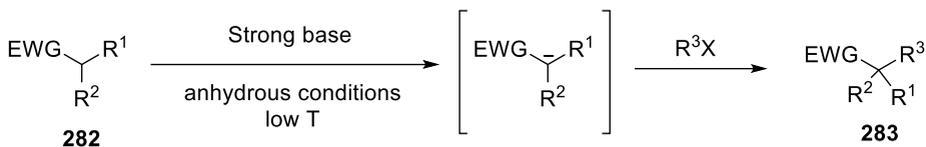


Scheme 41. Enantioselective arylation or vinylation of 1,3-dimethyl-2-oxindoles.

3. Deacylative alkylation as a synthetic methodology

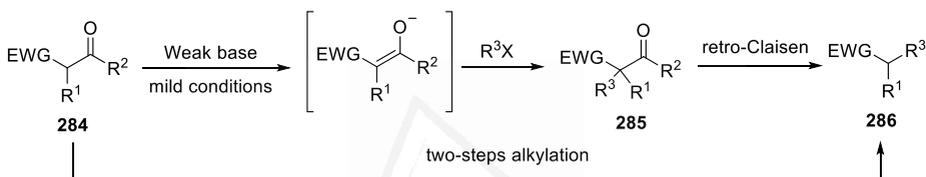
As it was demonstrated above, several synthetic strategies for the synthesis of 3,3-disubstituted 2-oxindoles have been carried out recently. Our research group envisaged that a non-developed strategy for the unsymmetrical synthesis of oxindoles derivatives could be carried out using a Deacylative Alkylation (DaA) methodology. In this last part of general introduction, this procedure will be explained in order to know how it works.

The most common alkylation at the α -position of a carbonyl derivative is carried out by the deprotonation and then the alkylation with an electrophilic compound. This methodology must be performed under strict reaction conditions: the use of strong bases, low temperature and anhydrous media are usually employed (Scheme 42).



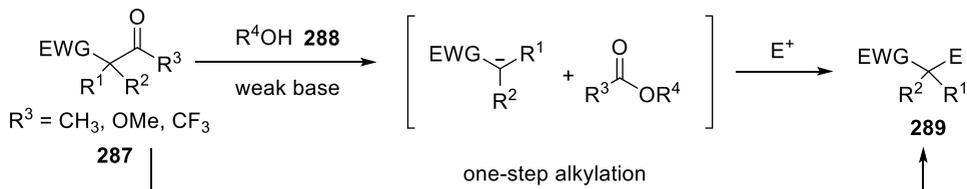
Scheme 42. Classical alkylation of enolates.

Furthermore, other methodologies as acetyl acetic and malonic ester synthesis exist as possibilities for the alkylation process but two steps are needed (Scheme 43).



Scheme 43. Acetyl acetic and malonic ester methodologies.

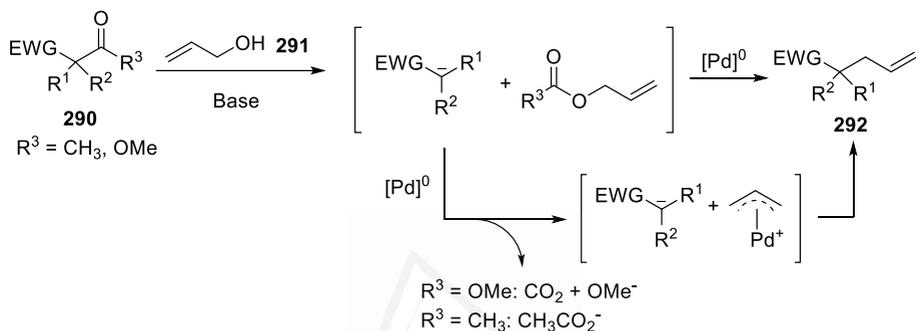
On the other hand, DaA methodology, based on carbon-carbon cleavage, can be performed under mild reactions conditions and the formed byproducts are usually innocuous and easy to treat. This methodology performs an *in situ* retro-Claisen/alkylation, generating a quaternary stereocenter using a carbonyl traceless directing group (Scheme 44).



Scheme 44. Deacylative alkylation.

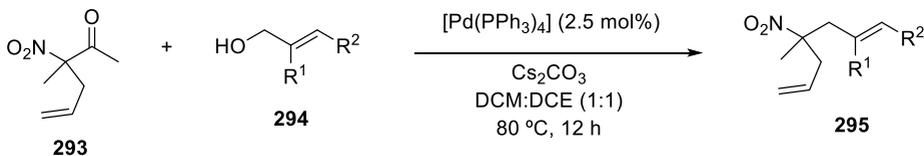
Besides, an advantage of this methodology, is that it is possible to carry out under metal-catalysis where new C-C bonds are formed,

as for example the palladium-catalyzed allylation reaction. This DaA also provides the generation of quaternary stereocenters at the α -position of diverse carbonyl compounds in a regioselective manner forming, *in situ*, the reactive enolate species. This is possible because the retro-Claisen process activates the nucleophile and the electrophile at the same time (Scheme 45).



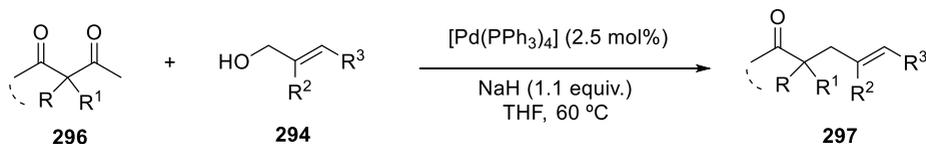
Scheme 45. Palladium-catalyzed DaA.

Pd-catalyzed deacylative allylations of carbonyl derivatives with allylic alcohols is a useful methodology. Greening and Tunge described firstly this methodology in 2011 and it occurs through a retro-Claisen condensation. They performed the catalytic allylation through the *in-situ* generation of the nucleophile species and allyl acetate from the allylic alcohol, which is not active in palladium catalytic cycle. It is an efficient method for allylation of nitroalkanes at the α -position giving products **295** in a range yields for primary alcohols from 79 to 92% heating at 80 °C for 12 h (Scheme 46).¹³²



Scheme 46. First example of palladium-catalyzed deacylative allylation.

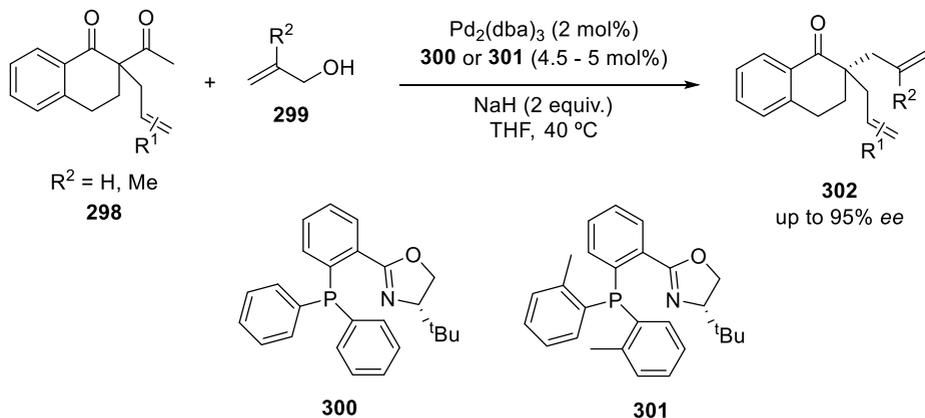
The same researchers developed this DaA using 1,3-dicarbonyl derivatives. In this case, sodium hydride was used as base and the optimal solvent was THF heating at 60 °C. They could perform the reaction also using α - or β -tetralones, phenyl-1,3-butadiones, acetylacetone and alkyl acetoacetates (Scheme 47). Other carbon nucleophiles as cyanoacetone derivatives were allowed to react under these conditions.¹³³



Scheme 47. Tunge's DaA of 1,3-dicarbonyl derivatives.

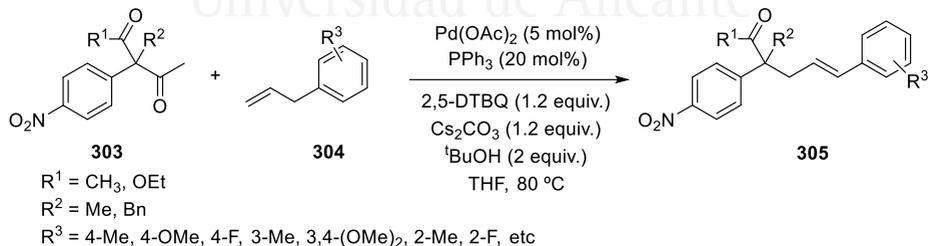
The authors conclude that using the deacylative alkylation method by allylic alkoxides ($pK_a \approx 30$) leads to a retro-Claisen activation producing nitronates ($pK_a \approx 17$), enolates ($pK_a \approx 18 - 25$) and nitrile stabilized anions ($pK_a \approx 23$).

Also, for the asymmetric DaA studies were set up obtaining good to excellent enantiomeric excesses. In this work published in 2013, α -tetralones were used as pronucleophiles and allylic alcohols as electrophilic species. PHOX type chiral ligands **300** and **301** were used as chirality inductors forming a complex with $\text{Pd}_2(\text{dba})_3$. The authors, applied this methodology for the synthesis of natural products such as the biologically active natural product (+)-hamigeran B, an antiviral compound (Scheme 48).¹³⁴



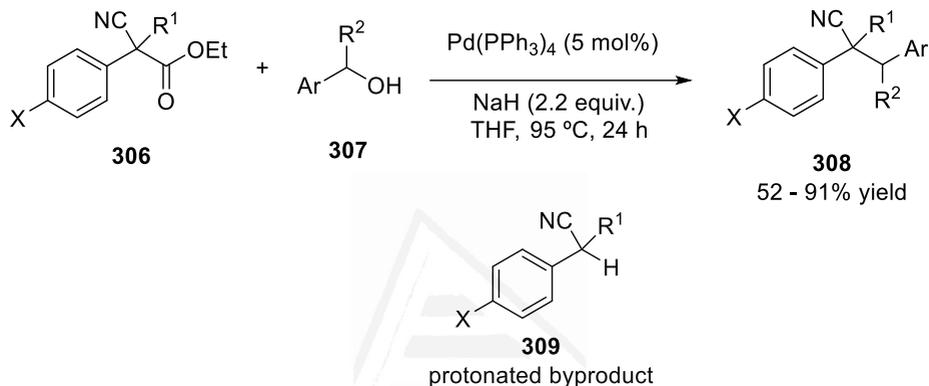
Scheme 48. Asymmetric version of DaA of tetralones.

Recently, a palladium-catalyzed C-H activation of allyl compounds has been emerged as a new methodology for the DaA. In 2017, Wang and co-workers reported the formation of a quaternary stereocenter using this strategy. Prop-1-ene derivatives forms the π -allylpalladium intermediate using 2,5-di-*tert*-butylbenzoquinone (2,5-DTBQ) as oxidant under basic conditions (Scheme 49).¹³⁵



Scheme 49. Pd-catalyzed deaclyative allylic C-H alkylation.

Deacylative benzylation was also reported, again, by Tunge *et al.* In this procedure, benzylic alcohols and cyanoacetates gave the benzylated β -arylpropionitriles **308** through a η^3 -benzylpalladium intermediate. In this procedure, similar conditions were used but higher temperatures were required for optimal results. The solvent, palladium and ligands choices were critical for avoid the protonated byproducts **309** (Scheme 50).¹³⁶



Scheme 50. DaA benzylation of cyanoacetates.

It can be concluded that DaA is a useful synthetic methodology for the generation of quaternary stereocenters under mild reaction conditions avoiding the classical employment of very low temperatures and very strong bases. The high tolerance of functional groups and the high chemo and regioselectivity increase its usefulness.

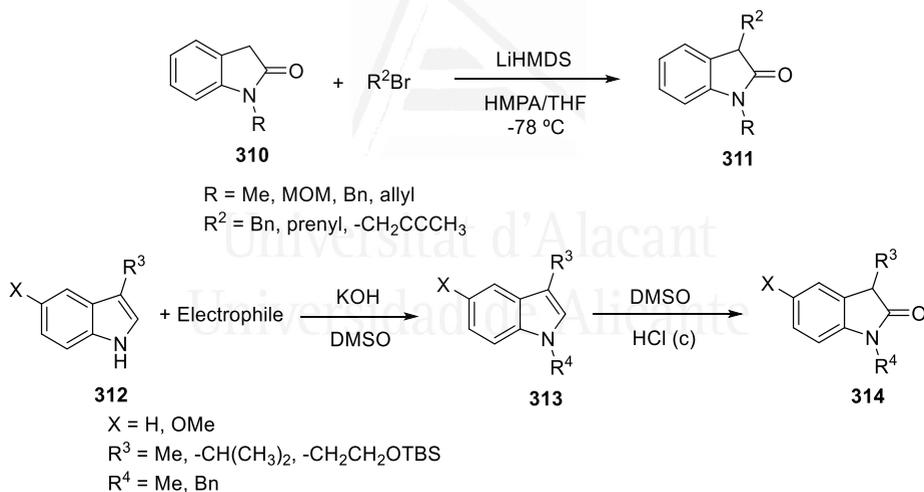
CHAPTER 1:
SYNTHESIS OF
3,3-DISUBSTITUTED
2-OXINDOLES BY
DEACYLATIVE ALKYLATION
OF 3-ACETYL-2-OXINDOLES

Universitat d'Alacant
Universidad de Alicante

CHAPTER 1

Introduction

Knowing the big interest of academy and industry for the oxindole derivatives, our research group thought about new methodologies that could allow the synthesis of diverse structural 3,3-disubstituted 2-oxindoles in an efficient manner. The first information found was the synthesis of starting materials. Such as it was described in the literature,¹¹⁹ the preparation of 3,3-disubstituted 2-oxindoles started from the synthesis of 3-alkyl 2-oxindoles, which were generated in two main ways (Scheme 51):



Scheme 51. Synthesis of 3-substituted oxindoles as starting materials.

The first method, consisted in the cryogenic deprotonation of *N*-alkylated 2-oxindole **310**. The reaction was carried out in a 5:1 THF:hexamethylphosphoramide (HMPA) at -78 °C under inert atmosphere. As deprotonating agent, very strong base as lithium bis(trimethylsilyl)amide (LiHMDS) was used. After column

chromatography, the corresponding 3-substituted 2-oxindoles **311** were isolated in a 50 – 65% yield. Sometimes, the starting material *N*-alkylated 2-oxindole is commercially available but, in many occasions, they have to be prepared. It is worth to note that HMPA is considerate as hazardous solvent because is reasonably anticipated to be a human carcinogen based on studies in animals.¹³⁷ In the second method, starting from commercially available indole derivatives **312**, first a *N*-alkylation using potassium hydroxide in DMSO (Heaney's method) gave **313** and then, in a second step, it was oxidized to the corresponding oxindole **314** using DMSO and concentrated HCl.

These methods, although effective, were not very efficient and could not be used in general, depending on that the starting materials were available and which alkyl groups were desired to be coupled. Also, as it was described above, numerous methodologies for direct functionalization of 3,3-disubstituted 2-oxindoles from 3-substituted 2-oxindoles were described (see section 2.7 of General Introduction).

Objectives

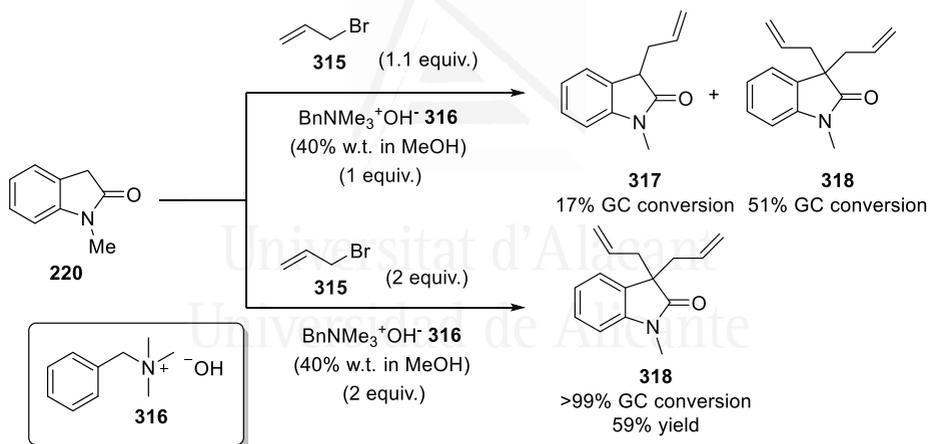
- The study in search of an easier methodology for the synthesis of 3-substituted 3-acetyl-2-oxindoles under the mildest possible conditions. After a retro-claisen methodology, synthesize the monoalkylated 3-substituted 2-oxindoles.
- Develop the DaA of 3-substituted 3-acetyl-2-oxindoles for the synthesis of different 3,3-disubstituted 2-oxindoles and prepare the important intermediates for the synthesis of natural and/or pharmaceutical synthetic derivatives.



Universitat d'Alacant
Universidad de Alicante

Results and discussion

Initial studies were focused on the attempt of the simplest synthesis of 3-substituted 2-oxindole starting from 3 unsubstituted *N*-methyl-2-oxindole **220**. This compound is commercially available and it was used as starting model for the monoalkylation. After the treatment of **220** with 1.1 equiv. of allyl bromide **315** as electrophile, and 1 equiv. of the base benzyltrimethylammonium hydroxide **316** (40% weight in methanol solution), also called Triton B, gas chromatography (GC) analysis revealed: 17% of desired monoalkylated product **317**, 51% of diallylated product **318** and a 32% of the unreacted starting material **220** (Scheme 52).



Scheme 52. Attempt for the synthesis of 3-substituted 2-oxindole.

Surprisingly, using no excess of base the product **318** was considerably more abundant in the reaction mixture. Trying to take advantage of this results, even not being the targeting compound, 3,3-diallyl-2-oxindole **318** was attempted to synthesize using 2 equiv. of both **315** and **316**. GC conversions were excellent, but when was purified by flash chromatography, a moderate 59% yield was obtained.

With these results in hand, it can be concluded that the simplest monoalkylation of 2-oxindoles was not possible in these conditions. These results support that the target 3-monosubstituted 2-oxindoles are not easy to synthesize and need specific conditions to achieve them.

At this point, and after a deep literature revision, our research group envisaged that first monoalkylation step and posterior deacylative alkylation of compounds 3-acetyl-2-oxindole derivatives **319** (Figure 29) would be an excellent strategy for the synthesis of target unsymmetrical 3,3-disubstituted 2-oxindole derivatives and also for the 3-monoalkylated 2-oxindole.

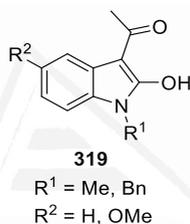
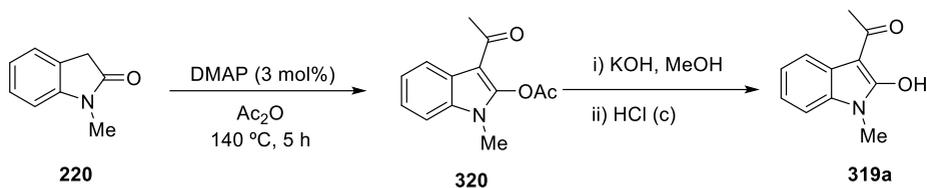


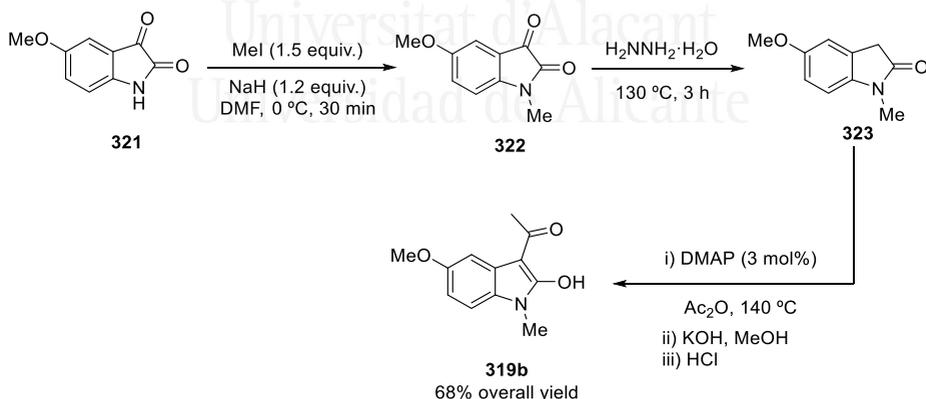
Figure 29. 3-Acetyl-1-methyl-2-oxindoles.

To perform the study, starting material **319a** was prepared from **220** by reaction with acetic anhydride in the presence of catalytic amounts of 4-(*N,N*-dimethylamino)pyridine (DMAP) at 140 °C for 5 h.¹³⁸ Afterwards, a hydrolysis with KOH in MeOH and posterior acidification with concentrated HCl were required to prepare **319a**, due to the concomitant acylation at oxygen atom in addition to the 3 position of the oxindole, which gave product **320** (Scheme 53). After purification by flash chromatography, the target product was obtained in an 88% yield.



Scheme 53. Synthesis of *N*-methyl-3-acetyl-2-oxindole **319a**.

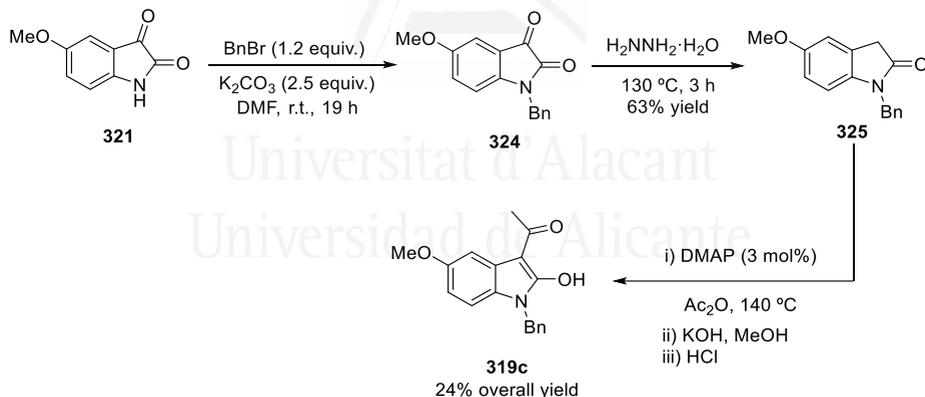
Due to some synthetic intermediates and/or natural products, such as physostigmine and horsfiline, have a methoxy moiety at the 5 position of the oxindole core, it was decided that it would be interesting the same synthesis for **319b** and **319c** derivatives, which include this functional group in the structure. The starting material was 5-methoxyisatin **321**, because 5-methoxy-1-methyl-2-oxindole **323** was not commercially available. Starting from isatin **321**, it was methylated at the 1 position using sodium hydride as base and iodomethane as alkylating agent in dimethylformamide (DMF) at 0 °C for 30 min, giving intermediate **322** (Scheme 54).



Scheme 54. Synthesis of *N*-methyl-3-acetyl-2-oxindole **319b**.

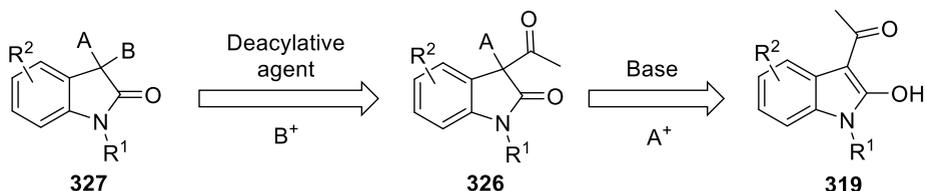
At this point, a Wolff-Kishner reduction was performed in order to obtain the 2-oxindole **323** heating at 130 °C for 3 hours.¹³⁹ Now, the same hydrolysis procedure for **319a** was carried out, giving the desired product **319b** in 68% overall yield.

A similar synthetic pathway was accomplished for the 1-benzyl-5-methoxy derivative **319c**. In this case, *N*-alkylation of the isatin was the only difference according to the procedure employed to obtain **319b**. Now, compound **321** was benzylated using benzyl bromide as electrophile and potassium carbonate as a base in DMF.¹⁴⁰ After the same Wolff-Kishner reduction, 1-benzyl-5-methoxy-2-oxindole **325** was obtained in 63% yield after these previous two steps.¹⁴¹ Using the standard acetylation conditions, target product **319c** was obtained in overall yield of 24% (Scheme 55). The decrease in the overall yield was originated by the use of a weaker base (K_2CO_3) in the alkylation step.



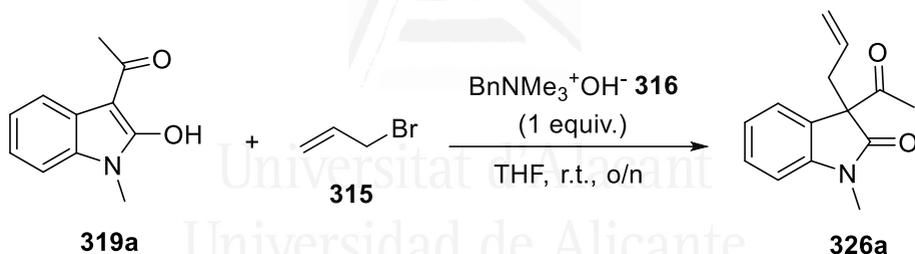
Scheme 55. Synthesis of *N*-methyl-3-acetyl-2-oxindole **319c**.

With the starting materials **319a-c** in hand, the proposed retrosynthetic pathway for the synthesis of 3,3-disubstituted target oxindoles **327** is shown in Scheme 56.



Scheme 56. Retrosynthetic analysis for 3,3-disubstituted-2-oxindoles by DaA.

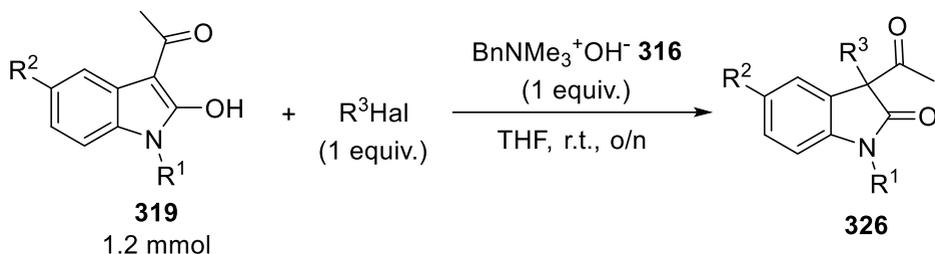
For the first monoalkylation, the optimal condition found was the use of 1 equiv. of **319a**, 1 equiv. of commercial available Triton B **316** as base, 1 equiv. of the electrophile allyl bromide **315**, in THF at room temperature overnight. The 3-acetylated 3-allylated product **326a** was obtained with >99% of GC conversion and in 84% of isolated yield (Scheme 57):



Scheme 57. Alkylation of **319a**.

There are some important considerations to set up successfully these experiments. One of them is that the base must be added dropwise. When the addition of the base was assayed in one portion, different amounts of deacylated product, dialkylated product and unreacted starting materials were identified from the reaction crude. These results encouraged us to continue with this research line, because understanding properly them it will be possible to exploit the chemistry of these 3-acetyl-2-oxindoles.

The reaction scope of the alkylation of 3-acetyl-2-oxindoles was performed using different alkyl halides and different 3-acetyl-3-alkyl-2-oxindoles (Table 1). Entries 1, 3, 4, 5 and 7 of Table 1 were carried out in a 1.2 mmol scale but entries 6, 8 and 9 of Table 1 were carried out in 0.3, 4.6 and 0.6 mmol scale, respectively. The entry 2 of Table 1 could be scaled up to 7.2 mmol (1.4 g) obtaining 1.3 g of final product in an 88% yield after flash chromatography. It is important to note that only entries 2, 8 and 9 of Table 1, in which the starting materials **319** were methylated, good to excellent yields (between 85 – 92%) were obtained. In addition, the deacylated byproduct was not observed after the flash chromatography. Moderate to good yields (between 50 – 84%) were achieved in entries 1, 3, 4, 5, 6 and 7 of Table 1, despite the inevitable presence of deacylated byproduct (between 4 – 10% amount) during the flash chromatography. Different alkyl halides were suitable as electrophiles at room temperature. Only when pentyl bromide was employed (Table 1, entry 6) reflux was needed due to its lower electrophilicity.

Table 1. Synthesis of 3-acetyl-3-alkyl 2-oxindoles.

Entry	319	R ¹	R ²	R ³ Hal	326	Yield ^a
1	319a	Me	H		326a	84% ^b
2	319a^c	Me	H	MeI	326b	88%
3	319a	Me	H		326c	54% ^d
4	319a	Me	H		326d	68% ^d
5	319a	Me	H		326e	84% ^e
6	319a^f	Me	H		326f	50% ^b
7	319a	Me	H		326g	69% ^g
8	319b^h	Me	OMe	MeI	326h	85%
9	319cⁱ	Bn	OMe	MeI	326i	92%

^a Isolated yield after flash chromatography.

^b 6% deacylated product was also obtained.

^c 2 equiv. of MeI was used on a 7.2 mmol scale.

^d 4% deacylated product was also obtained.

^e 5% deacylated product was also obtained on a 1.8 mmol scale.

^f Under reflux on a 0.3 mmol scale.

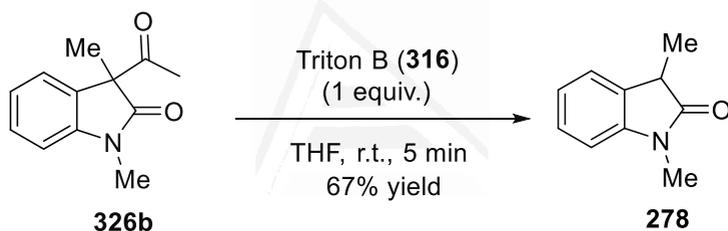
^g 10% deacylated product was also obtained.

^h 2 equiv. of MeI was used on a 4.6 mmol scale.

ⁱ 2 equiv. of MeI was used on a 0.6 mmol scale.

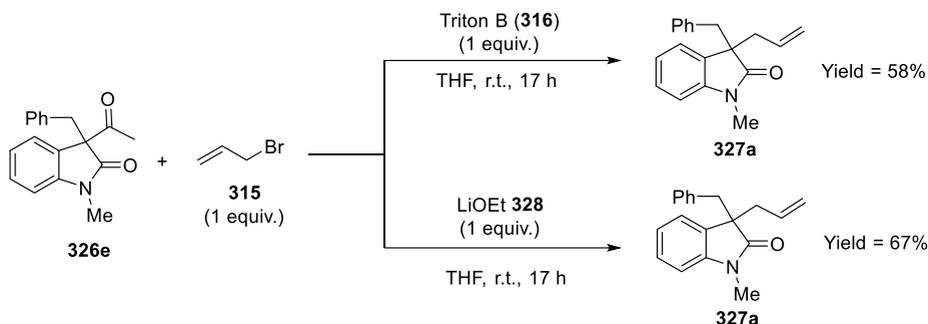
Analyzing the deacetylation byproducts, it was concluded that these products have not a high stability. This reactivity will be advantageous in the synthesis of target 3-substituted 2-oxindole and 3,3-disubstituted 2-oxindole through a Deacylative Alkylation (DaA) process and under mild conditions.

Monosubstituted 2-oxindole derivative **278**, was important starting compound for alkaloid preparations (see section 2.7 of General Introduction). This compound was synthesized fastly and under mild conditions treating compound **326b** with 1 equiv. of Triton B in THF at room temperature for 5 minutes. After quenching the reaction with acetic acid and purify by flash chromatography, **278** was obtained in 67% yield (Scheme 58).



Scheme 58. Synthesis of 1,3-dimethyl-2-oxindole.

To accomplish the next goal, DaA process was carried out for the preparation of unsymmetrically 3,3-disubstituted 2-oxindoles using alkyl halides. Starting from compound **326e** and allyl bromide to form **327a**, it was compared Triton B (**316**) and lithium ethoxide **328** as deacylative agents to find the optimal deacylative agent (Scheme 59):



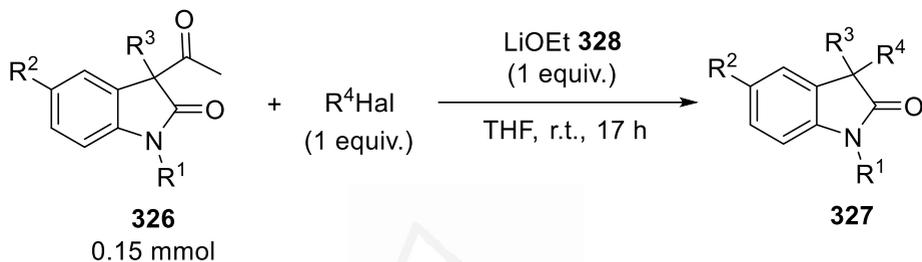
Scheme 59. Different conditions for DaA of **326e**.

After flash chromatography of both reactions, the isolated yield was higher when lithium ethoxide **328** was used as deacylative agent compared with Triton B **316**.

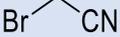
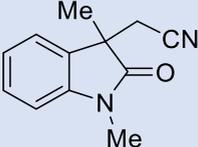
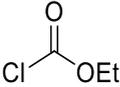
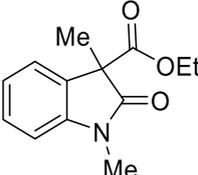
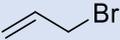
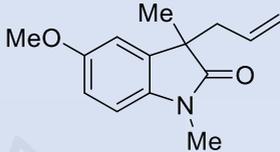
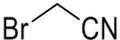
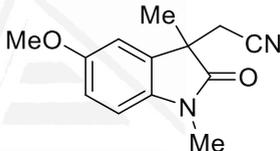
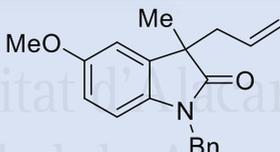
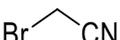
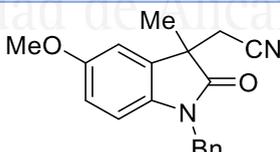
At this point, different alkyl halides were used in the scope of the reaction using a solution of LiOEt **328** 1M in THF. Good to excellent yields were achieved in all cases (Table 2). Compound **326b** was used as a model compound and was allowed to react with allyl bromide, propargyl bromide, benzyl bromide, cinnamyl bromide and bromoacetonitrile (Table 2, entries 1, 2, 3, 4 and 5, respectively) to give products **327b-f**. In all cases, good isolated yields were achieved (69 – 88%) and the products were completely stable after purification. Also, an interesting electrophile, ethyl chloroformate was used for synthesizing the corresponding ethyl ester derivative **327g**. Finally, 5-methoxy derivatives **327h-k** were synthesized using the same procedure. Compound **327h** was isolated in 75% yield. This is the key intermediate of racemic natural product esermethole,¹¹⁹ which is precursor of natural alkaloid physostigmine **21** and the pharmaceutical derivative phenserine an acetylcholinesterase inhibitor (see sections 1.1, 1.2 and 2.7 of General Introduction). Besides, the derivative **327i** was synthesized in excellent yield in a 2 mmol scale, is also precursor of racemic esermethole and physostigmine, but through a shorter synthetic pathway than **327h**.¹⁰⁴ 5-Methoxy compounds **327j** and **327k** are derivatives that

can be deprotected at the N- position giving the corresponding N-unprotected compounds.

Table 2. Synthesis of 3,3-disubstituted 2-oxindoles by DaA.



	326	R⁴Hal	Product	327	Yield^a
1	326b			327b	72
2	326b			327c	69
3	326b			327d	87
4	326b^b			327e	75

5	326b			327f	88
6	326b			327g	65
7	326h			327h	75
8	326h ^c			327i	93
9	326i			327j	70
10	326i			327k	74

^a Isolated yield after flash chromatography.

^b 1.5 equiv. of cinnamyl bromide were used.

^c 2 mmol scale.

Conclusions

The acetylation of 2-oxindoles allows their monoalkylation under mild conditions using Triton B as base. By subsequent deacetylation it is possible to prepare the corresponding 3-alkylated 2-oxindoles. The 3-substituted 3-acetyl-2-oxindoles can undergo deacylative alkylation with alkyl halides in the presence of LiOEt, affording the corresponding 3,3-disubstituted 2-oxindoles under very mild conditions. This methodology is suitable for the preparation of unsymmetrical 3,3-disubstituted oxindoles, which cannot be easily prepared by other strategies.



Universitat d'Alacant
Universidad de Alicante

Experimental Section

1. General methods

Melting points were determined with a Marienfeld melting point meter (MPM-H2) apparatus and are uncorrected. For flash chromatography, silica gel 60 (40-60 μm) was employed. ^1H NMR (300, 400 MHz or 500 MHz) and ^{13}C NMR (75, 101 or 126 MHz) spectra were recorded using Bruker AV300, Bruker AV400 and Bruker ADVANCE DRX500, respectively, with CDCl_3 as solvent and TMS as internal standard and chemical shifts are given in ppm. Low-resolution electron impact (GC-EI) mass spectra were obtained at 70 eV using an Agilent 6890N Network GC system and Agilent 5973 Network Mass Selective Detector. High-resolution mass spectra (GC-EI) were recorded using a QTOF Agilent 7200 instrument for the exact mass and Agilent 7890B for the GC. Analytical TLC was performed using ALUGRAM® Xtra SIL G/UV₂₅₄ silica gel plates, and the spots were determined under UV light ($\lambda=254$ nm).

2. Experimental procedures

2.1. Synthesis of 1-(2-hydroxy-1-methyl-1*H*-indol-3-yl)ethanone (**319a**)

To a round-bottom flask containing a solution of *N*-methyl-2-oxindole (4.85 g, 33 mmol) in acetic anhydride (36 mL, 381 mmol), DMAP (118 mg, 0.96 mmol) was added. The mixture was heated at 140 °C for 5 h. The mixture was evaporated under reduced pressure, the crude residue was dissolved in MeOH (80 mL) and a solution of KOH (18 g, 321 mmol) in MeOH (120 mL) at 0 °C was added. The solution was stirred at r.t. for 22 h then cooled in an ice-bath at 0 °C and 12 M aqueous HCl was added until pH 3. At this point, H₂O (140 mL) was added and the solution was extracted with EtOAc (3 \times 140 mL). The organic phases were dried over MgSO_4 , filtered, and concentrated. The residue was purified by flash chromatography (hexane/EtOAc) to give pure **319a**.

Yield: 5.5 g (88%); purple solid; mp 109–110 °C (hexane/EtOAc) (Lit.¹³⁸110–111 °C).

The spectral data are consistent with reported data.¹³⁸

2.2. Synthesis of 1-(2-hydroxy-1-methyl-5-methoxy-1*H*-indol-3-yl)ethanone (**319b**)

A round-bottom flask containing a solution of 5-methoxyisatin (3.54 g, 20 mmol) in anhydrous DMF (40 mL) was cooled to 0 °C, then sodium hydride (606 mg, 24 mmol) was added in one portion and the mixture was stirred for 5 min. Iodomethane was added (1.84 mL, 30 mmol) and the mixture was stirred at 0 °C for 30 min. The mixture was poured in saturated aqueous NH₄Cl (20 mL) and extracted with dichloromethane (3 × 40 mL). The organic phase was washed with H₂O (3 × 15 mL) and brine (20 mL), dried over MgSO₄, and evaporated under vacuum. The dark-red solid was dissolved in hydrazine monohydrate (12 mL, 247 mmol) and heated at 130 °C for 3 h. After cooling the solution to r.t., H₂O (50 mL) was added and the mixture was extracted with EtOAc (3 × 50 mL). The organic phase was washed with saturated aqueous NaHCO₃ (50 mL), brine (50 mL), and dried over MgSO₄, filtered and concentrated.¹³ To the resulting residue, acetic anhydride (22.5 mL, 238 mmol) was added. Then, DMAP (73.3 mg, 0.6 mmol) was added and the mixture was heated at reflux (140 °C) for 5 h and then evaporated under reduced pressure. The residue was dissolved in MeOH (50 mL), then a solution of KOH (11 g, 196 mmol) in MeOH (70 mL) at 0 °C was added. The solution was stirred at r.t. for 22 h and then cooled in an ice-bath at 0 °C. A solution of 12 M aqueous HCl was added until pH 3. The organic solvent was evaporated and the residue was extracted with EtOAc (3 × 100 mL), washed with H₂O (100 mL), dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (hexane/EtOAc) to give pure **319b**.

Overall yield: 2.97 g (68%); purple solid; mp 83–84 °C (hexane/EtOAc) (Lit.¹⁴²83 °C).

The spectral data are consistent with reported data.¹⁴²

2.3. Synthesis of 1-(1-benzyl-2-hydroxy-5-methoxy-1*H*-indol-3-yl)ethanone (**319c**)

A mixture of 5-methoxyisatin (2.84 g, 16 mmol) and K_2CO_3 (5.53 g, 40 mmol) was dissolved in anhydrous DMF (12 mL) under Ar. Benzyl bromide (5.71 mL, 48 mmol) was added dropwise and the mixture was stirred at r.t. for 19 h. The mixture was extracted with dichloromethane (3×20 mL) and the organic phase was washed with H_2O (20 mL) and brine (20 mL), dried with $MgSO_4$, filtered, and concentrated to obtain a red solid.¹⁴⁰ The crude material was dissolved in DMSO (12 mL), hydrazine hydrate (1.81 mL, 32 mmol) was added dropwise and the mixture was heated at 150 °C for 5 h. The mixture was cooled to r.t., extracted with EtOAc (2×100 mL), and the organic phase was washed with H_2O (100 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (hexane/EtOAc) to give pure 1-benzyl-5-methoxy-2-oxindole (2.55 g, 63%) as a brown oil.¹⁴¹

The above product was dissolved in acetic anhydride (11.5 mL, 121 mmol) and DMAP (37 mg, 0.3 mmol) was added. The mixture was heated at reflux (140 °C) for 6 h and then cooled to r.t. and evaporated under reduced pressure. The residue was dissolved in MeOH (40 mL) cooled at 0 °C and then a solution of KOH (8.5 g, 151 mmol) in MeOH (60 mL) was added. The solution was stirred at r.t. for 18 h then the solution was cooled in an ice-bath at 0 °C and 12 M aqueous HCl was added until pH 3. The organic solvent was evaporated under reduced pressure, H_2O (50 mL) was added and the mixture was extracted with EtOAc (3×50 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (hexane/EtOAc) to give pure **319c**.

Overall yield: 1.15 g (24%); brown solid; mp 145–146 °C (hexane/EtOAc) (Lit.¹⁴³ 150–151 °C).

The spectral data are consistent with reported data.¹⁴³

2.4. General procedure for monoalkylation of 3-acetyl-2-oxindoles **319**

To a solution of 3-acetyl-2-oxindole **319** (227 mg, 1.2 mmol) and alkyl halide (1.2 mmol) in THF (7 mL) was added benzyltrimethylammonium hydroxide (Triton B) in MeOH (40wt%, 0.545 mL, 1.2 mmol). The reaction was stirred at r.t. overnight, H₂O (20 mL) was added, the mixture was extracted with EtOAc (3 × 20 mL) and the combined organic layers were dried over MgSO₄, filtered and evaporated. The correspondent residue was purified by flash chromatography (EtOAc/hexane) to afford the corresponding product **326** (see, Table 1).

2.5. General procedure for deacylative alkylation of 3-monoalkylated 3-acetyl-2-oxindoles **326** with alkyl halides.

Oxindole **326** (0.15 mmol) and alkyl halide (0.165 mmol) were dissolved under an argon atmosphere in anhydrous THF (1.5 mL). A 1 M solution of LiOEt (0.15 mL, 0.15 mmol) was added dropwise and the reaction mixture was stirred at r.t. overnight. Afterwards, 10 mL of H₂O were added and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried over MgSO₄, filtered and concentrated. After flash chromatography, pure 3,3-dialkylated 2-oxindole **327** was obtained (see, Table 2).

2.6. General procedure for deacylative alkylation of 3-monoalkylated 3-acetyl-2-oxindoles **326** with alkenes.

Oxindole **326b** (30.5 mg, 0.15 mmol) and electrophilic alkene (0.21 mmol) were dissolved in THF (1.5 mL). After three cycles of freezing-pump-thaw and filling the flask with Ar, benzyltrimethylammonium hydroxide (Triton B) in MeOH (40wt%, 0.068 mL, 0.15 mmol) was added. The mixture was stirred overnight at r.t. and extractive workup was performed with EtOAc (3 × 10 mL) and H₂O (10 mL). The organic phases were dried with MgSO₄, filtered and concentrated, and the resulting crude product was purified by flash chromatography (EtOAc/hexane) to give **329**.

3. Experimental data

Compounds **326b**, **326f**, **326h**, **326i**, **327a**, **327b**, **327d**, **327e**, **327f**, **327g**, **327h**, **327i**, and **327k** are known compounds and experimental data are consistent with reported data:

326b: 3-Acetyl-1,3-dimethylindolin-2-one (1.36 g, 88% yield)¹⁴⁴

326f: 3-Acetyl-3-benzyl-1-methylindolin-2-one (341 mg, 84% yield)¹⁴⁴

326h: 3-Acetyl-5-methoxy-1,3-dimethylindolin-2-one (899 mg, 85% yield)¹⁴⁵

326i: 3-Acetyl-1-benzyl-5-methoxy-3-methylindolin-2-one (171 mg, 92% yield)¹⁴⁴

327a: 3-Allyl-3-benzyl-1-methylindolin-2-one (28 mg, 67% yield)¹⁴⁶

327b: 3-Allyl-1,3-dimethylindolin-2-one (22mg, 72% yield)¹⁴⁷

327d: 3-Benzyl-1,3-dimethylindolin-2-one (33 mg, 87% yield)¹⁴⁸

327e: 3-Cinnamyl-1,3-dimethylindolin-2-one (31 mg, 75% yield)¹⁴⁸

327f: 2-(1,3-Dimethyl-2-oxoindolin-3-yl)acetonitrile (27 mg, 88%)¹⁰⁴

327g: Ethyl 1,3-dimethyl-2-oxoindoline-3-carboxylate (23 mg, 65% yield)¹⁴⁴

327h: 3-Allyl-5-methoxy-1,3-dimethylindolin-2-one (26 mg, 75%)¹⁴⁶

327i: 2-(5-Methoxy-1,3-dimethyl-2-oxoindolin-3-yl)acetonitrile (429 mg, 93%)¹⁰⁴

327k: 2-(1-Benzyl-5-methoxy-3-methyl-2-oxoindolin-3-yl)acetonitrile (34 mg, 74%)¹⁰⁷

Following, characterization data of new compounds **326a**, **326c**, **326d**, **326f**, **326g**, **327c**, **327j**, **329c**, **329f**, **329g** and **329h** will be displayed:

3-Acetyl-3-allyl-1-methylindolin-2-one (326a)

Yield: 192 mg (84%); pale-yellow oil.

^1H NMR (300 MHz): δ = 7.36 (td, J = 7.7, 1.4 Hz, 1 H), 7.18 (dd, J = 7.4, 1.0 Hz, 1 H), 7.10 (td, J = 7.5, 1.0 Hz, 1 H), 6.90 (d, J = 7.8 Hz, 1 H), 5.30 (dddd, J = 16.8, 10.0, 7.8, 6.7 Hz, 1 H), 5.00 (m, 1 H), 4.88 (m, 1 H), 3.28 (s, 3 H), 2.91 (m, 2 H), 1.99 (s, 3 H).

^{13}C NMR (101 MHz): δ = 200.7, 174.5, 144.3, 131.5, 129.3, 127.0, 124.2, 123.3, 119.5, 108.6, 66.4, 37.5, 26.6.

LRMS (EI): m/z (%) = 229 (9) $[\text{M}]^+$, 188 (13), 187 (100), 186 (22), 172 (12), 160 (22), 158 (14), 144 (10), 143 (10).

HRMS (EI): m/z calcd. for $\text{C}_{14}\text{H}_{15}\text{NO}_2$: 229.1103; found: 229.1107.

(E)-3-Acetyl-3-(3,7-dimethylocta-2,6-dien-1-yl)-1-methylindolin-2-one (326c)

Yield: 210 mg (54%); brown oil.

^1H NMR (300 MHz): δ = 7.34 (td, J = 7.7, 1.3 Hz, 1 H), 7.19 (dd, J = 7.5, 1.2 Hz, 1 H), 7.07 (td, J = 7.5, 1.0 Hz, 1 H), 6.88 (d, J = 7.8 Hz, 1 H), 4.89 (m, 1 H), 4.73–4.60 (m, 1 H), 3.26 (s, 3 H), 2.89 (m, 2 H), 2.01 (s, 3 H), 1.80 (m, 4 H), 1.62 (s, 3 H), 1.51 (s, 3 H), 1.49 (s, 3 H).

^{13}C NMR (101 MHz): δ = 201.4, 175.0, 144.3, 139.9, 131.4, 129.2, 127.6, 124.3, 124.1, 123.1, 116.7, 108.3, 66.6, 39.9, 32.2, 26.8, 26.8, 26.6, 25.8, 17.7, 16.5.

LRMS (EI): m/z = 325 (8) $[\text{M}]^+$, 214 (14), 198 (12), 190 (15), 189 (100), 171 (10), 160 (36), 159 (35), 69 (24).

HRMS (EI): m/z calcd. for $\text{C}_{21}\text{H}_{27}\text{NO}_2$: 325.2042; found: 325.2044.

3-Acetyl-1-methyl-3-(prop-2-yn-1-yl)indolin-2-one (326d)

Yield: 186 mg (68%); brown solid; mp 84–86 °C (hexane/EtOAc).

^1H NMR (300 MHz): δ = 7.41 (td, J = 7.7, 1.3 Hz, 1 H), 7.24 (dd, J = 7.4, 0.9 Hz, 1 H), 7.13 (td, J = 7.5, 0.9 Hz, 1 H), 6.95 (d, J = 7.8 Hz, 1 H), 3.32 (s, 3 H), 3.13 (dd, J = 16.8, 2.7 Hz, 1 H), 2.93 (dd, J = 16.9, 2.6 Hz, 1 H), 1.97 (s, 3 H), 1.76 (t, J = 2.6 Hz, 1 H).

^{13}C NMR (101 MHz): δ = 199.5, 173.6, 144.7, 129.8, 126.7, 124.0, 123.5, 108.7, 78.6, 70.5, 65.1, 26.8, 26.3, 23.0.

LRMS (EI): m/z = 227 (8) $[\text{M}]^+$, 186 (13), 185 (100), 184 (60), 157 (12), 156 (14), 128 (13).

HRMS (EI): m/z calcd. for $\text{C}_{14}\text{H}_{13}\text{NO}_2$: 225.0946; found: 227.0945.

3-Acetyl-1-methyl-3-pentylindolin-2-one (326f)

Yield: 39 mg (50%); colorless oil.

^1H NMR (300 MHz): δ = 7.35 (td, J = 7.6, 1.5 Hz, 1 H), 7.22–7.04 (m, 2 H), 6.91 (d, J = 7.8 Hz, 1 H), 3.29 (s, 3 H), 2.27–2.04 (m, 2 H), 2.00 (s, 3 H), 1.23–1.14 (m, 5 H), 0.83–0.72 (m, 4 H).

^{13}C NMR (101 MHz): δ = 201.5, 175.3, 144.3, 129.1, 127.7, 124.0, 123.3, 108.5, 66.9, 33.4, 31.9, 26.6, 26.6, 23.4, 22.4, 14.0

LRMS (EI): m/z = 259 (7) $[\text{M}]^+$, 218 (10), 217 (64), 161 (12), 160 (100), 147 (10).

HRMS (EI): m/z calcd. for $\text{C}_{16}\text{H}_{21}\text{NO}_2$: 259.1572; found: 259.1576.

Methyl 2-(3-Acetyl-1-methyl-2-oxoindolin-3-yl)acetate (326g)

Yield: 215 mg (69%); purple oil.

^1H NMR (300 MHz): δ = 7.38 (td, J = 7.7, 1.3 Hz, 1 H), 7.20 (d, J = 7.3 Hz, 1 H), 7.08 (td, J = 7.5, 1.0 Hz, 1 H), 6.95 (d, J = 7.8 Hz, 1 H), 3.50 (s, 3 H), 3.34 (s, 3 H), 3.40–3.19 (m, 2 H), 1.93 (s, 3 H).

^{13}C NMR (101 MHz): δ = 199.2, 174.3, 170.3, 145.0, 129.7, 126.9, 123.8, 123.3, 108.8, 63.5, 51.9, 37.2, 27.0, 25.7.

LRMS (EI): m/z = 261 (2) $[\text{M}]^+$, 219 (50), 160 (31), 159 (100), 130 (21).

HRMS (EI): m/z calcd. for $\text{C}_{14}\text{H}_{15}\text{NO}_4$: 261.1001; found: 261.1005.

1,3-Dimethyl-3-(prop-2-yn-1-yl)indolin-2-one (327c)

Yield: 21 mg (69%); yellow oil.

^1H NMR (400 MHz): δ = 7.46–7.43 (m, 1 H), 7.30 (td, J = 7.7, 1.2 Hz, 1 H), 7.09 (td, J = 7.6, 1.0 Hz, 1 H), 6.86 (d, J = 7.8 Hz, 1 H), 3.23 (s, 3 H), 2.70 (dd, J = 16.5, 2.7 Hz, 1 H), 2.49 (dd, J = 16.6, 2.7 Hz, 1 H), 1.96 (t, J = 2.7 Hz, 1 H), 1.46 (s, 3 H).

^{13}C NMR (101 MHz): δ = 179.5, 143.1, 133.1, 128.3, 123.3, 122.7, 108.1, 79.8, 70.8, 46.7, 27.8, 26.4, 21.9.

LRMS (EI): m/z = 199 (28) $[\text{M}]^+$, 161 (11), 160 (100), 132 (9), 130 (8), 117 (10).

HRMS (EI): m/z calcd. for $\text{C}_{13}\text{H}_{13}\text{NO}$: 199.0997; found: 199.0996.

3-Allyl-1-benzyl-5-methoxy-3-methylindolin-2-one (327j)

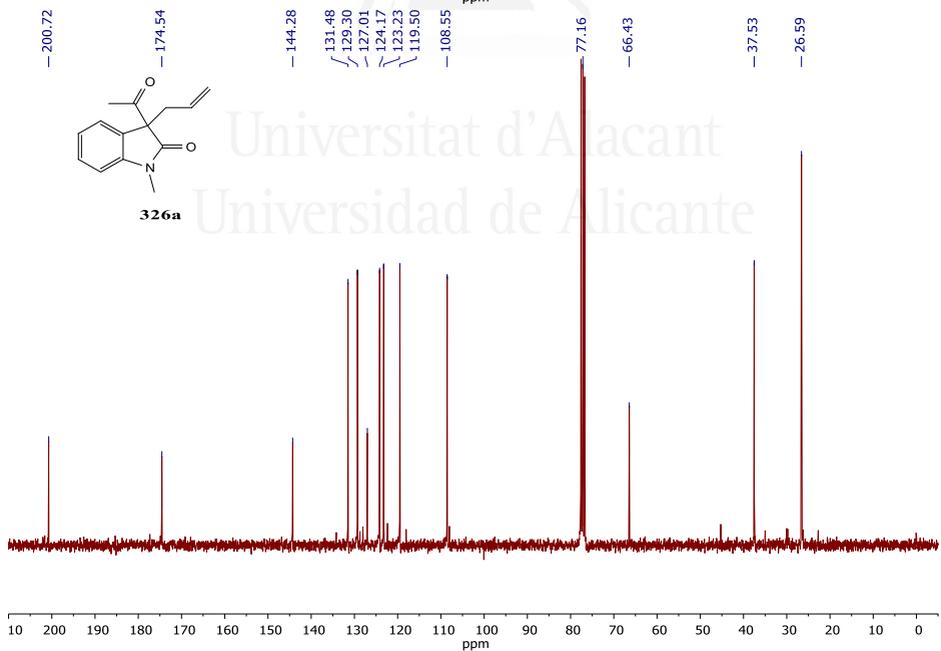
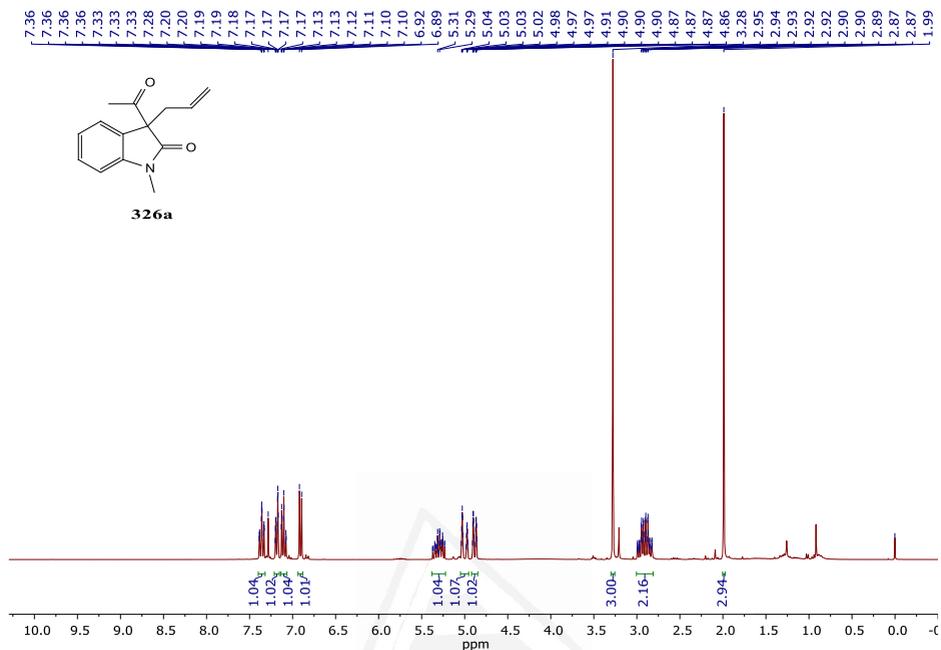
Yield: 32 mg (70%); pale-yellow solid; mp 74–76 °C(hexane/EtOAc).

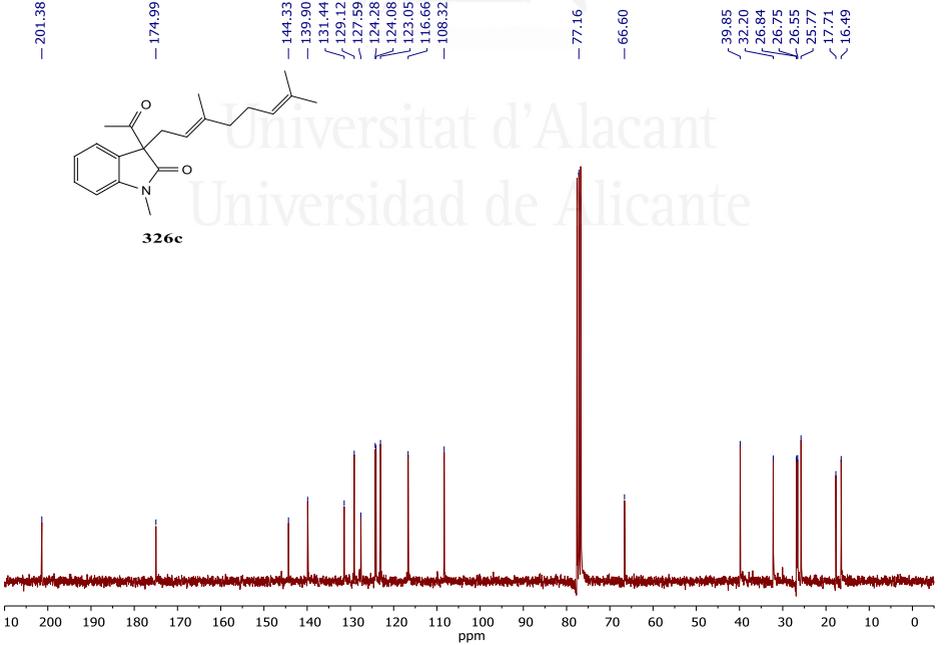
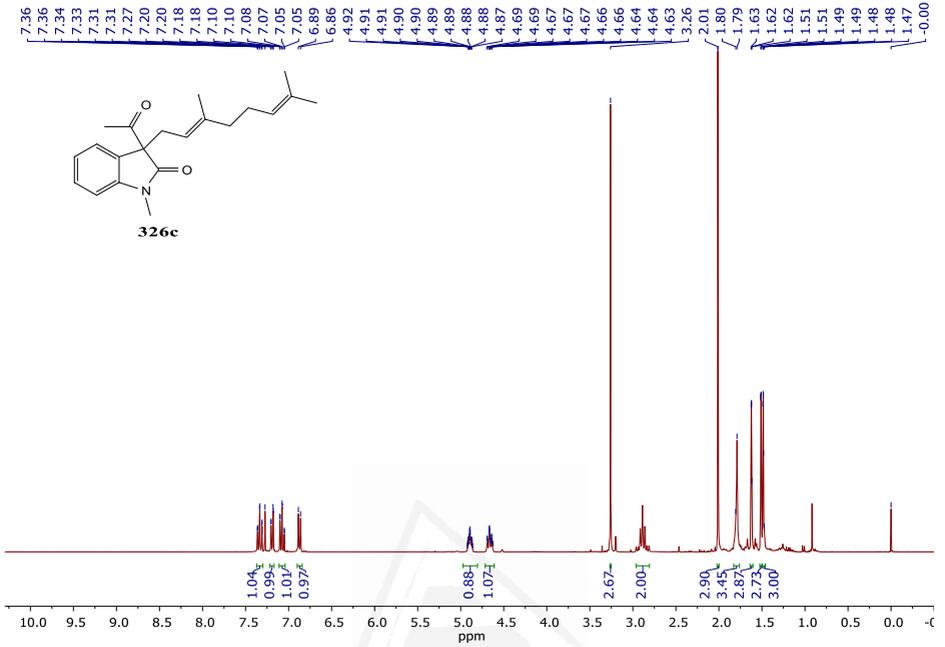
^1H NMR (300 MHz): δ 7.33–7.20 (m, 5H), 6.82 (d, J = 2.5 Hz, 1H), 6.65 (dd, J = 8.5, 2.5 Hz, 1H), 6.57 (d, J = 8.4 Hz, 1H), 5.48 (dddd, J = 16.9, 10.0, 7.9, 6.7 Hz, 1H), 5.08–4.93 (m, 3H), 4.77 (d, J = 15.7 Hz, 1H), 3.75 (s, 3H), 2.62 (dd, J = 13.5, 7.9 Hz, 1H), 2.54 (dd, J = 13.5, 6.7 Hz, 1H), 1.42 (s, 3H).

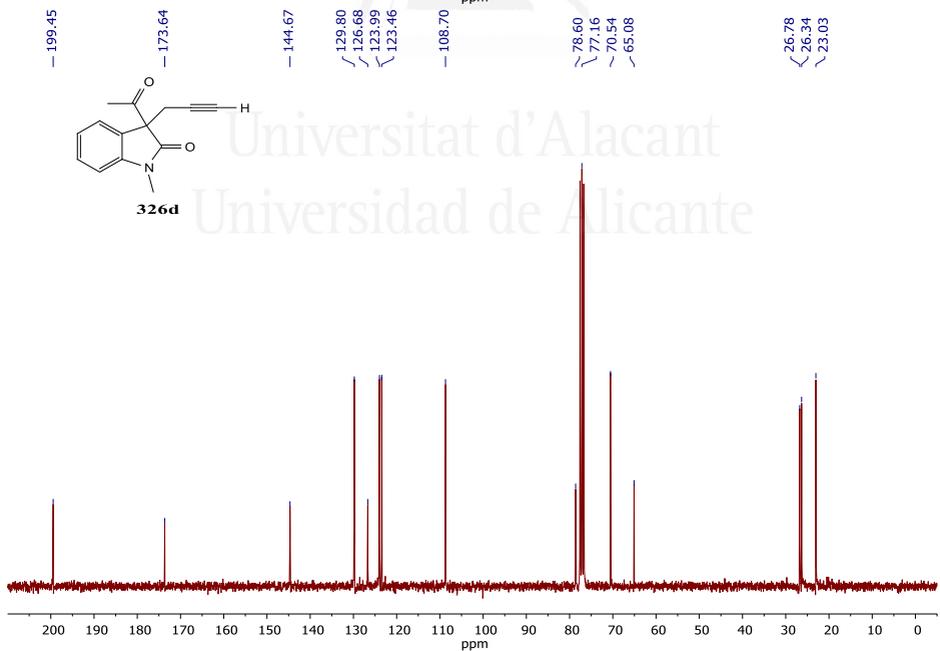
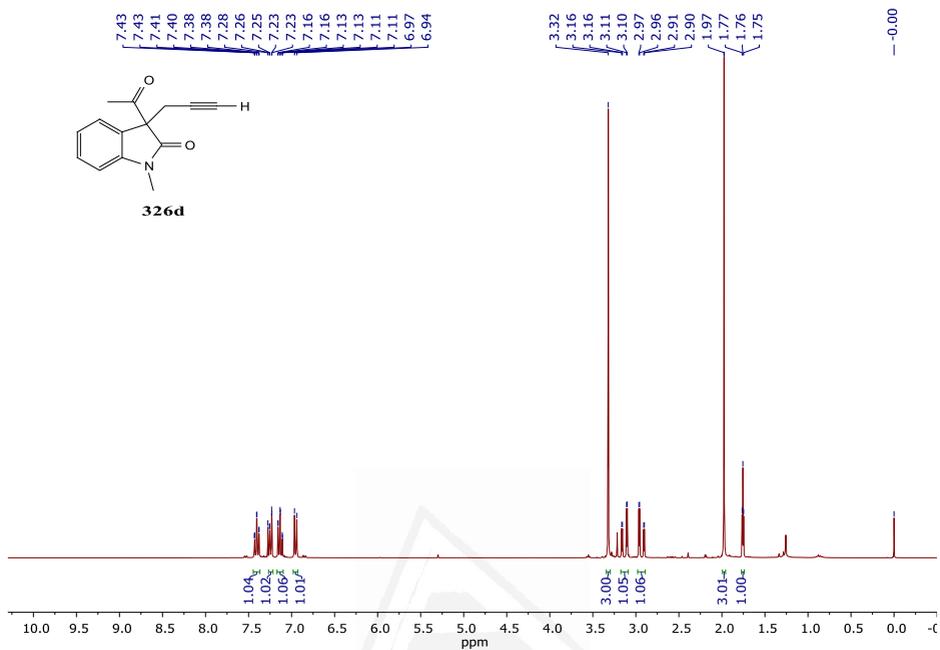
^{13}C NMR (75 MHz): δ = 180.0, 156.0, 136.2, 135.8, 135.1, 132.8, 128.8, 127.6, 127.4, 119.0, 111.7, 110.8, 109.4, 55.9, 48.9, 43.8, 42.6, 23.4.

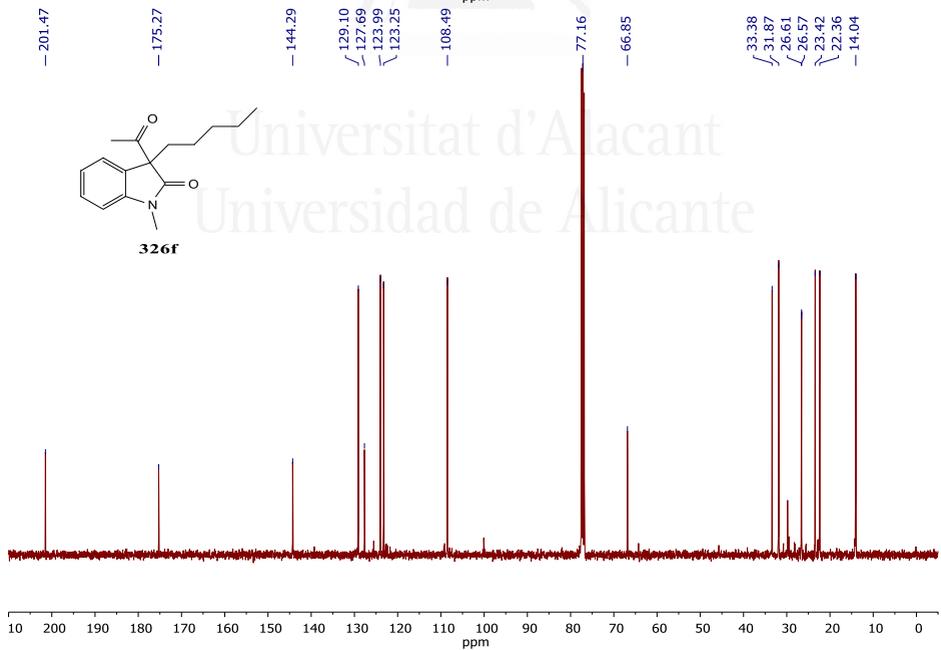
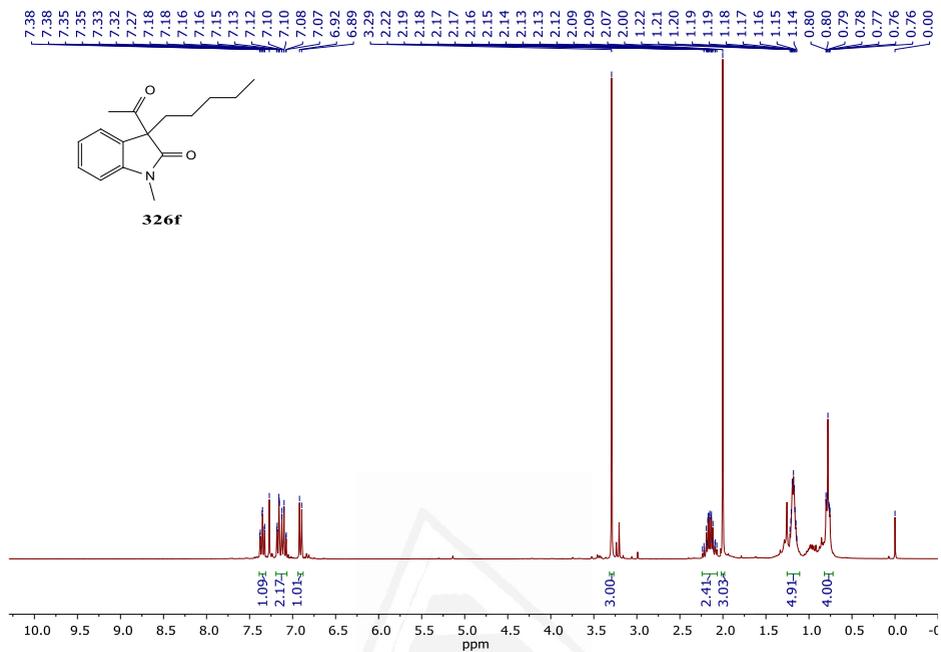
LRMS (EI): m/z = 308 (13), 307 (58) $[\text{M}]^+$, 267 (20), 266 (100), 91 (67).

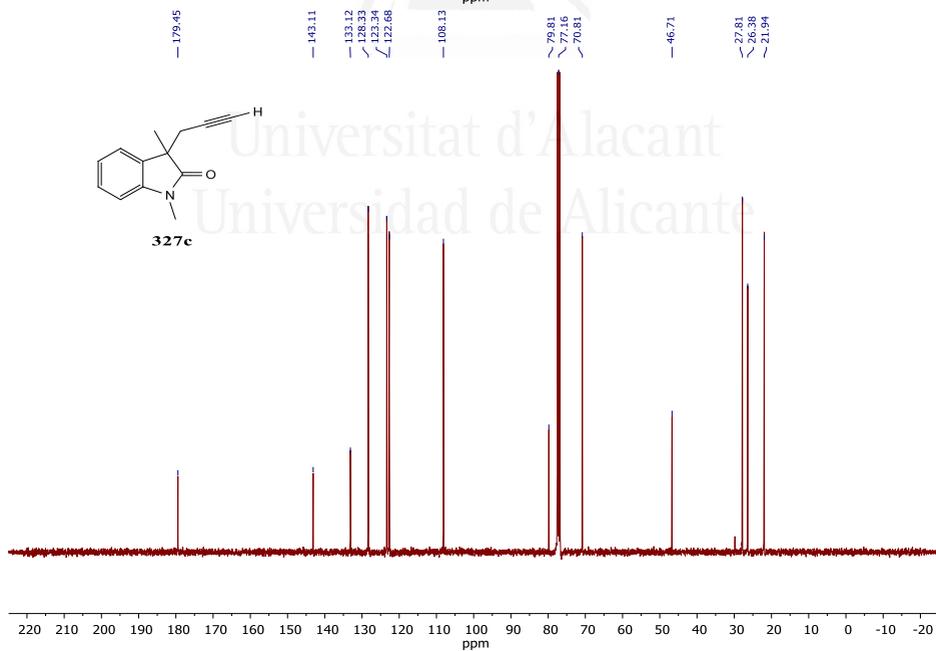
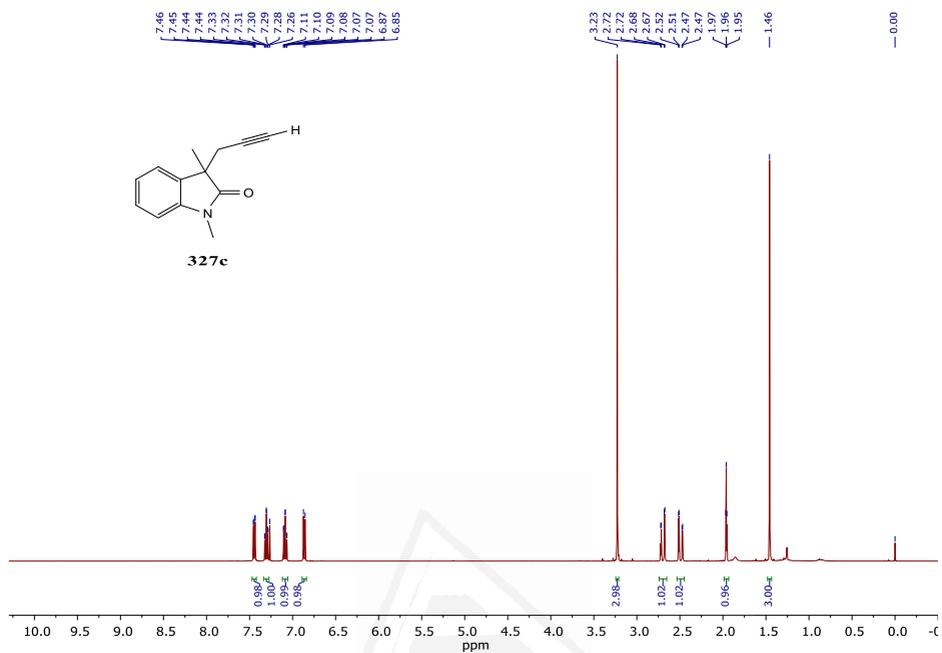
HRMS (EI): m/z calcd. for $\text{C}_{20}\text{H}_{21}\text{NO}_2$: 307.1572; found: 307.1570.

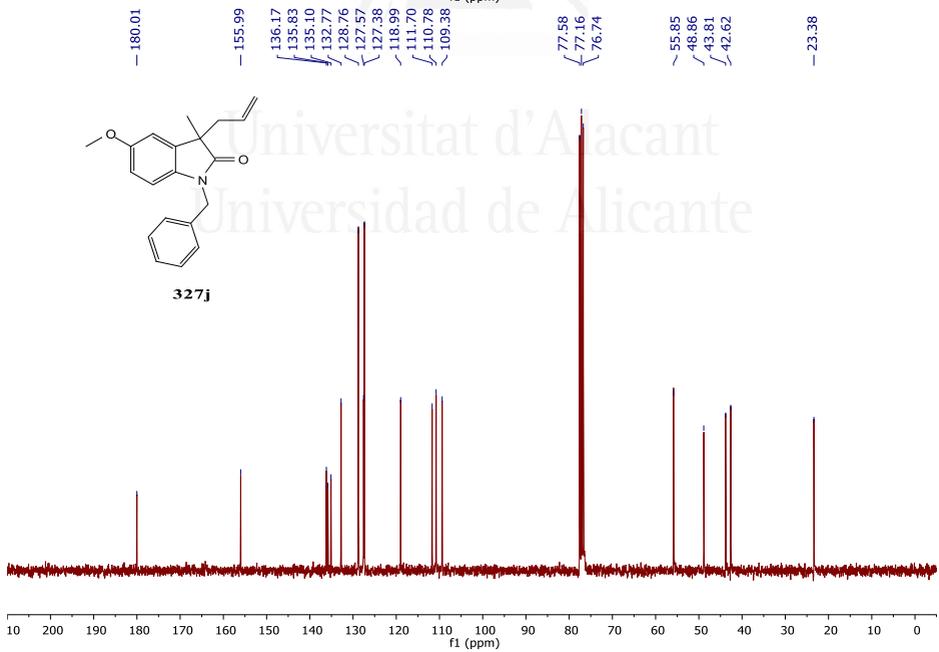
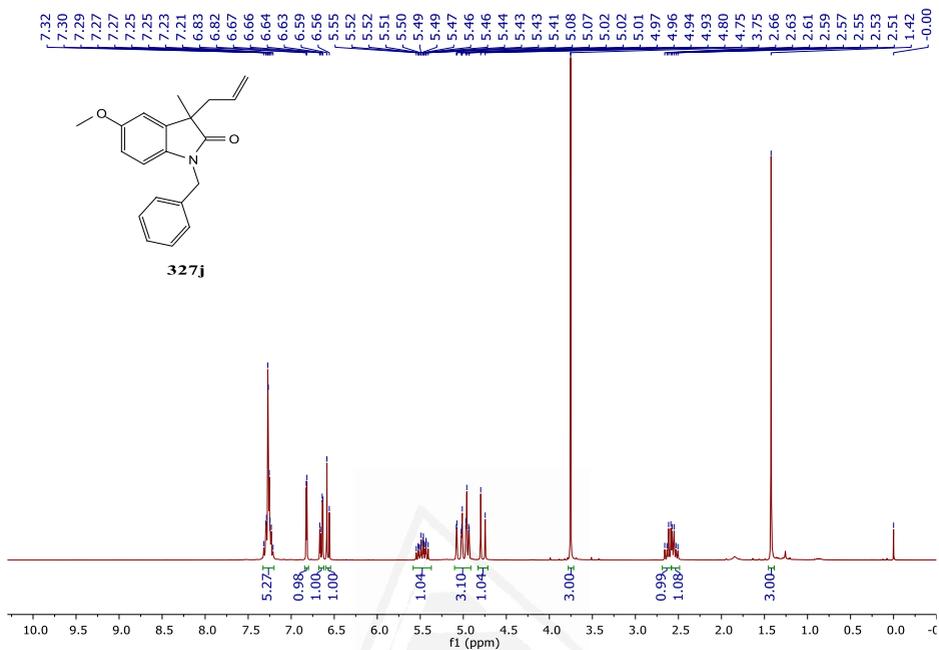












The corresponding paper of this research can be found with the following reference:

A. Ortega-Martínez, C. Molina, C. Moreno-Cabrerizo, J. M. Sansano and C. Nájera, *Synthesis*, 2017, **49**, 5203–5210.

DOI: 10.1055/s-0036-1590880



Universitat d'Alacant
Universidad de Alicante

CHAPTER 2:
PALLADIUM-CATALYZED
ALLYLATION AND
DEACYLATIVE ALLYLATION
OF 3-ACETYL-2-OXINDOLES
WITH ALLYLIC ALCOHOLS

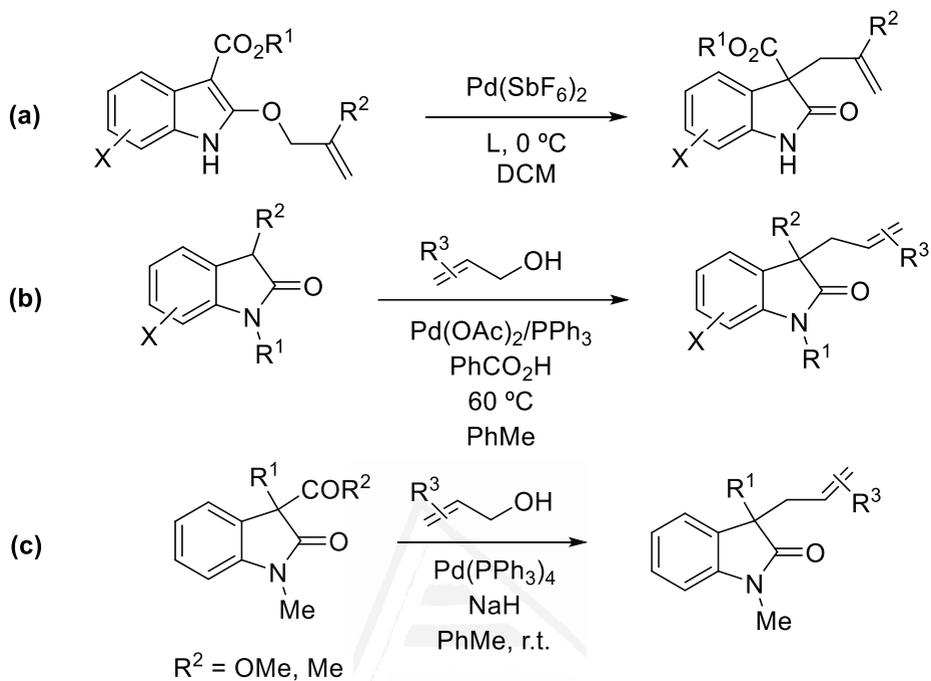
Universitat d'Alacant
Universidad de Alicante

CHAPTER 2

Introduction

As it has shown in General Introduction (see sections 2.6, 2.7 and 3), palladium has an important role for the C–C bond formation at 3 position of 2-oxindoles. Specifically, for the allylation, the most common species for the formation of π -allyl Pd electrophilic intermediates are the acetates, carbonates and phosphates derived from allylic alcohols. They are used due to the poor leaving group ability of the OH group. However, the direct use of commercially available allyl alcohols is desirable because avoids the preparation of their derivatives saving costs and synthetic steps.

For the synthesis of 3-allyl-2-oxindoles catalyzed by palladium, different methodologies have been reported (Scheme 60). The methodology **(a)** was reported by Kozłowski *et al.* and it is an intramolecular process mediated on the Meerwein–Eschenmoser Claisen rearrangement of 2-allyloxindoles.¹⁴⁹ The methodology **(b)** is a direct allylic alkylation of oxindoles using non-activated allylic alcohols catalyzed by Pd and co-catalyzed by PhCO₂H.¹⁵⁰ When we were studying the Pd-catalyzed DaA of 3-acetyl-2-oxindoles, Bisai and co-workers published a palladium catalyzed allylation DaA of 3-acyl-2-oxindoles with allylic alcohols using the ester and the ketone derivatives **(c)**.¹⁵¹



Scheme 60. Reported synthesis of 3-allyl-2-oxindoles.

Objectives

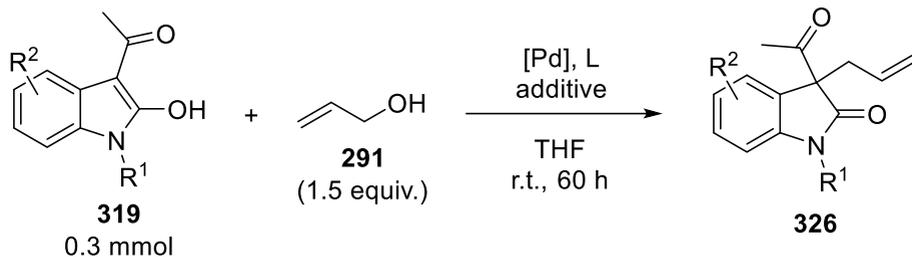
- To study the Pd-catalyzed direct allylation and deacylative allylation of oxindole derivatives obtained in Chapter 1 to synthesize 3,3-disubstituted 2-oxindoles.
- To study the synthesis of 3-substituted 3-hydroxy-2-oxindoles due to the formation of these derivatives as byproducts after a deacylative oxidation process.



Universitat d'Alacant
Universidad de Alicante

Results and discussion

Initially, studies for the direct allylation of compounds **319** were performed using non-activated allyl alcohol **291** as electrophile, employing different Pd sources, ligands and additives for the synthesis of 3-acetyl-3-allyl-2-oxindoles **326** (Table 3). First, using the reaction conditions of Tamaru *et al.* for the allylation of active methylene compounds,¹⁵² 60 mol% of triethylborane and 3 mol% of both Pd(OAc)₂ and 1,3-bis(diphenylphosphino)propane (dppp) the corresponding 3-acetyl-3-allyl-1-methyl-2-oxindole **326a** was formed in 99% isolated crude yield (Table 3, entry 1). In order to decrease the amount of the additive, instead of 60 mol% of Et₃B, 3 mol% of *p*-toluenesulfonic acid (TsOH) was employed affording only 3% of **326a** (Table 3, entry 2). Afterwards, Pd(dba)₂ was used instead of Pd(OAc)₂ but the reaction failed (Table 3, entry 3). However, when *rac*-BINAP was used as ligand, product **326a** was formed in 66% isolated crude yield (Table 3, entry 4). At this point, *rac*-BINOL phosphoric acid was used instead of TsOH and the allylated product **326a** was formed in 96% isolated yield (Table 3, entry 5). Using the optimal reaction conditions of entry 5 of Table 3, allylated 5-methoxy derivatives **326j** and **326k** were obtained in 61% and 89% isolated yield, respectively, after chromatographic purification (Table 3, entries 6 and 7). To the best of our knowledge, this is the first palladium-catalyzed allylation of 3-acetyl-1-methyl-2-oxindoles with allyl alcohol.

Table 3. Pd catalyzed allylation of 3-acetyl-2-oxindoles with allyl alcohol.

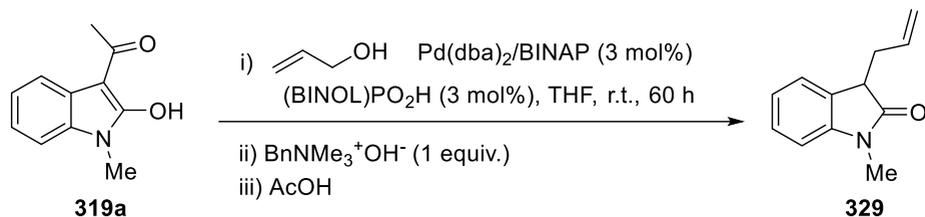
	319	[Pd] (3 mol%)	Ligand (3 mol%)	Additive (mol%)	326	Yield (%) ^a
1	319a	Pd(OAc) ₂	dppp	Et ₃ B (60)	326a	99%
2	319a	Pd(OAc) ₂	dppp	TsOH (3)	326a	3%
3	319a	Pd(dba) ₂	dppp	TsOH (3)	326a	—
4	319a	Pd(dba) ₂	<i>rac</i> -BINAP	TsOH (3)	326a	66%
5	319a	Pd(dba) ₂	<i>rac</i> -BINAP	(BINOL)PO ₂ H (3) ^b	326a	98 (96)
6	319b	Pd(dba) ₂	<i>rac</i> -BINAP	(BINOL)PO ₂ H (3) ^b	326j	91 (61)
7	319c	Pd(dba) ₂	<i>rac</i> -BINAP	(BINOL)PO ₂ H (3) ^b	326k	99 (89)

^a Isolated crude yield. In parenthesis, yield after flash chromatography.

^b Racemic (BINOL)PO₂H was employed.

Again, we demonstrated that this is an interesting methodology for the synthesis of 3-substituted 2-oxindoles, under very mild conditions, because when 3-allyl-1-methyl-2-oxindole **326** was treated in situ with Triton B once allylation process was finished and after final addition of acetic acid, compound **329** was isolated in 61% yield. This process avoids the use of cryogenic conditions (-78 °C) and

strong bases necessary for the allylation of *N*-methyl-2-oxindole (Scheme 61).

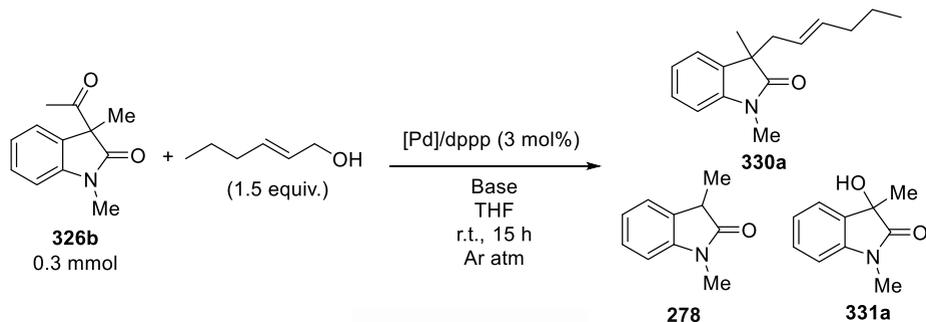


Scheme 61. Synthesis of 3-allyl-1-methyl-2-oxindole.

Then, the Pd-catalyzed deacylative allylation of 3-acetyl-1,3-dimethyl-2-oxindole **326b** was tried. In order to find the optimal reaction conditions, the study was carried out using *trans*-hex-2-en-1-ol as electrophile with different catalysts and bases (Table 4). When Pd(OAc)₂ and dppp (3 mol%) as catalyst and potassium *tert*-butoxide as base in THF under Ar atmosphere at r.t. were used after 15 hours, a 3:1 mixture of desired compound **330a** and the oxidized 3-hydroxy-1,3-dimethyl-2-oxindole **331a** were obtained. After flash chromatography, **330a** was isolated in 54% yield (Table 4, entry 1). Because no added oxidizing agent was present in the media, it was thought that oxygen should have to be the reason of the obtained byproduct. In order to perform the reaction in absence of oxygen a freezing-pump-thaw was performed to the reaction mixture before the addition of the base. In the presence of LiO^tBu as base not only a 95:5 mixture of **330a**:**331a** was obtained, but also a 17% of deacylated product **278** were observed. After flash chromatography a 66% isolated yield was obtained (Table 4, entry 2). When the amount of phosphine ligand was increased to 6 mol%, worse results were obtained because a 61:39 mixture of **330a**:**278** was observed (Table 4, entry 3). In the attempt for improving the conversion of the desired product, Pd₂(dba)₃ was used instead of Pd(OAc)₂ but higher amounts of deacylated product **278** were formed (Table 4, entry 4). Finally, when the amount of the base was increased to 1.5 equiv. best results were achieved obtaining 86% of **330a** and only 10% and 3% of **278**

and **331a**, respectively. When **330a** was isolated by flash chromatography a 70% yield was obtained (Table 4, entry 5).

Table 4. Pd-catalyzed DaA of 3-acetyl-2-oxindoles.



	[Pd]/dppp (3 mol%)	Base (equiv.)	Products ratio (%) ^a	Yield 331a (%) ^b
1^c	Pd(OAc) ₂	KO ^t Bu (1.1 equiv.)	330a (76) 331a (24)	54
2^d	Pd(OAc) ₂	LiO ^t Bu (1.1 equiv.)	330a (79) 278 (17) 331a (4)	66
3^d	Pd(OAc) ₂ ^e	LiO ^t Bu (1.1 equiv.)	330a (61) 278 (39)	—
4^d	Pd ₂ (dba) ₃ ^f	LiO ^t Bu (1.1 equiv.)	330a (49) 278 (51)	—
5^d	Pd(OAc) ₂	LiO ^t Bu (1.5 equiv.)	330a (86) 278 (10) 331a (3)	70

^a Determined by 300 MHz ¹H NMR on the crude product.

^b Isolated yield after flash chromatography.

^c Without using freezing-pump-thaw.

^d Using freezing-pump-thaw.

^e 6 mol% of dppp was used.

^f 1.5 mol% of Pd₂(dba)₃ was used.

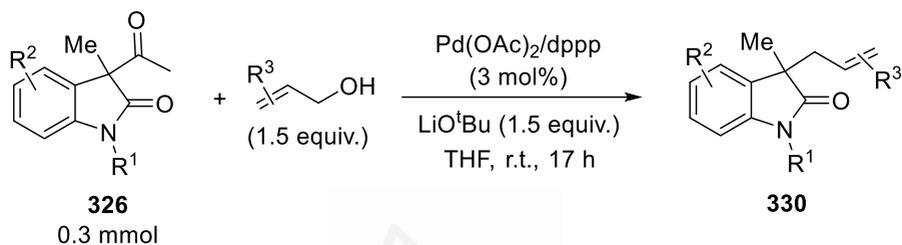
For studies about the scope of the reaction, different assays were performed with a variety of substituted allylic alcohols and oxindoles **326** using the optimal conditions found (Table 5). Generally, in these examples 17 h instead of 15 h were used as reaction time depending on the nature of the allylic alcohol. The reaction of 3-acetyl-1,3-dimethyl-2-oxindole **326a** with primary allylic alcohols such as allyl alcohol and methallyl alcohol gave the corresponding products **327b** and **330b** in good yields (Table 5, entries 2 and 3). When geraniol was used as electrophile, despite being also a primary alcohol, moderate 45% yield of product **330e** was obtained (Table 5, entry 6). However, a *ca.* 2:1 inseparable mixture of products **330c** and **330c'** were obtained when 1-methylallyl alcohol was used as electrophile, due to the γ - and α -allylation processes affording a moderate 45% overall yield (Table 5, entry 4). Comparable results were obtained using prenyl alcohol which afforded, in this case, a separable mixture of α - and γ -isomers **330d** and **330d'** in 51% and 16% yields, respectively (Table 5, entry 5).

In the case of secondary pent-1,4-dien-3-ol, a 8:1 mixture of inseparable γ - and α -products **330f** and **330f'** was obtained in 62% overall yield (Table 5, entry 7). When cyclohexen-2-ol was used to continue the scope, **330g** was obtained in good yield (75%) as a *ca.* 1:1 mixture of diastereoisomers (Table 5, entry 8). Other primary alcohols as (-)-myrtenol and cinnamyl alcohol provided the corresponding products **330h** and **330i** in moderate 56% and 51% yield, respectively (Table 5, entries 9 and 10). It is worth to note that both diastereoisomers of **330h** were not separable and the reaction involving cinnamyl alcohol needed longer reaction times (24 h) to be completed.

Different oxindole derivatives **326g** and **326i** were coupled with allyl alcohol providing the expected allylated products **327h**, which is an intermediate of racemic natural product esermethole (see Chapter 1), and **327j** in 72% and 74% yield, respectively (Table 5, entries 11 and 12). In all cases depicted in Table 6 that included the possibility of obtaining mixtures of (*E*)- and (*Z*)-stereoisomers

(products **330a**, **330c**, **330e**, **330f** and **330i**), no (*Z*)-derivatives were observed in any case after the analysis of ^1H NMR of the crude mixture. The coupling constants of the double bond protons always corresponded to the (*E*)-stereoisomer.

Table 5. Pd catalyzed DaA of 3-acetyl-2-oxindoles.

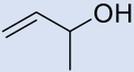
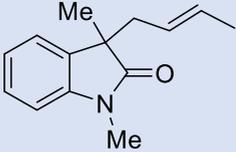
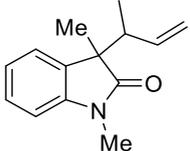
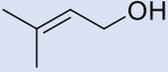
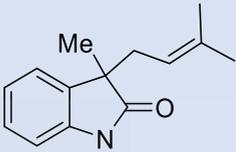
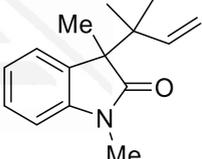
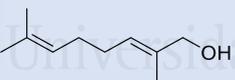
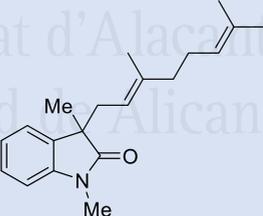


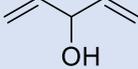
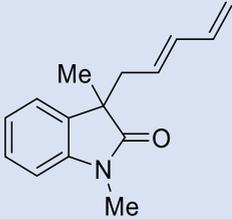
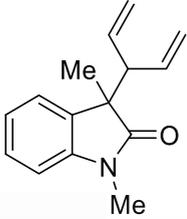
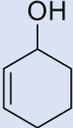
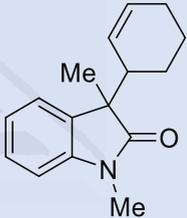
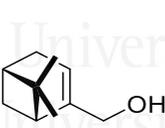
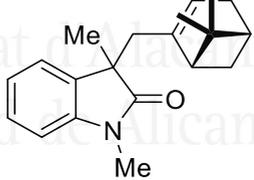
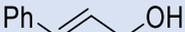
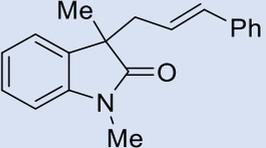
326b: $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{H}$

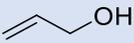
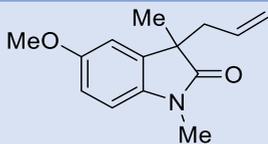
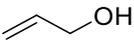
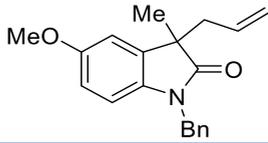
326h: $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{OMe}$

326i: $\text{R}^1 = \text{Bn}$, $\text{R}^2 = \text{OMe}$

	326	Allylic alcohol	Product	330	Yield (%) ^a
1	326a			330a	70
2	326a			327b	80
3	326a			330b	74

4	326a			330c	45 ^b
				330c'	
5	326a			330d	51
				330d'	16
6	326a			330e	45

7	326a			330f	55 ^c
				330f	7
8	326a			330g ^d	75
9	326a			330h	56 ^e
10	326a			330i ^f	51

11	326h			327h	72
12	326i			327j ^g	77

^a Isolated yield after flash chromatography.

^b An inseparable mixture of compounds **331c**(68%) and **331c'** (32%) was obtained.

^c A 8:1 mixture of compounds **331f**and **331f'** was obtained.

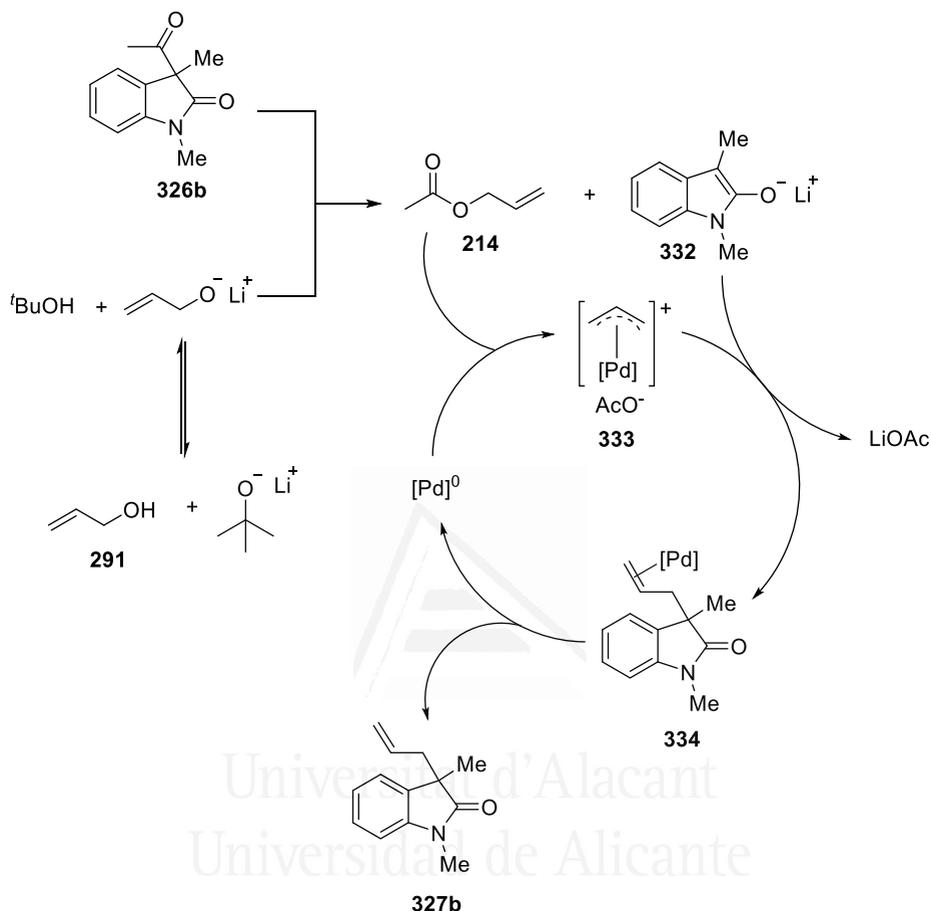
^d A *ca.* 1:1 mixture of diastereoisomers was obtained.

^e A 5.5:1 mixture of diastereoisomers was obtained.

^f 24 h reaction time.

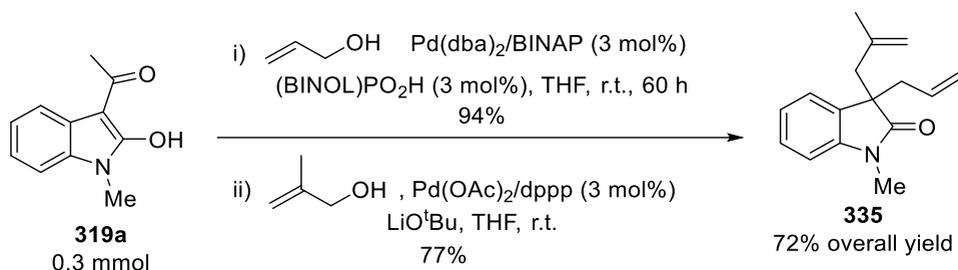
^g 0.22 mmol scale

The proposed mechanism for the Pd-catalyzed DaA reaction, based in Tsuji-Trost reaction, is shown in Scheme 62. At the beginning, an acid-base equilibrium between allyl alcohol **291** and lithium *tert*-butoxide occurred. When the allyl alkoxide is formed, the attack as a nucleophile to the 3-acetyl oxindole derivative **326** afforded the activated allyl acetate **214** and the corresponding stabilized anion **332**. At this point, the palladium catalytic cycle starts by the oxidative addition of Pd(0) with allyl acetate giving the π -allylpalladium intermediate **333**. Now, a nucleophilic substitution occurs to afford lithium acetate and the intermediate **334** that is ready to regenerate the active Pd(0) specie affording the final product **327b**.



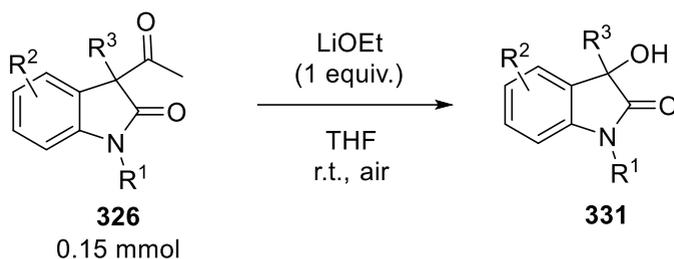
Scheme 62. Proposed mechanism for Pd-catalyzed DaA of 3-acetyl-1,3-dimethyl-2-oxindole with allylic alcohol.

In order to apply both mentioned methodologies in Chapter 2, a combined double allylation for the synthesis of unsymmetrically disubstituted 3,3-diallylated oxindole derivative **335** was carried out. First allylation of **319a** gave after flash chromatography the intermediate **326a** in 94% yield. The following step was the Pd-catalyzed deacylative allylation using methallyl alcohol affording the corresponding product **335** in 72% overall yield after flash chromatography (Scheme 63).



Scheme 63. Synthesis of unsymmetrically 3,3-diallylated oxindole.

The evitable formation of 3-hydroxy-1,3-dimethyl-2-oxindole byproducts using freezing-pump-thaw procedure prompt us to be interested in the optimal reaction conditions for the synthesis of these oxidized derivatives. 3-Substituted 3-hydroxy-2-oxindoles are important structures for pharmaceutical derivatives and natural alkaloids (see sections 1.1. and 1.2. of General Introduction). Although different methodologies have been described for their syntheses,^{151,153} we performed the deacylative hydroxylation of 3-acetyl-3-alkyl-2-oxindoles **326** under mild conditions using 1 equiv. of LiOEt in THF at r.t. under air atmosphere giving the corresponding 3-alkyl-3-hydroxy-2-oxindoles **331** in good yields (Table 6). When 3-acetyl-1,3-dimethyl-2-oxindole is assayed in air atmosphere using LiOEt, corresponding **331a** product is obtained in 70% isolated yield (Table 6, entry 1). When different 3-substituted 3-acyl-2-oxindoles, such as benzylated, allylated and propargylated derivatives were used, 68%, 68% and 70% yields of **331b**, **331c** and **331d** were respectively obtained (Table 6, entries 2, 3 and 4). 5-Methoxy oxindole derivatives **326h** and **326i** were also assayed and 57% and 58% yields were obtained for **331e** and **331f**, respectively (Table 6, entries 5 and 6).

Table 6. Synthesis of 3-alkyl-3-hydroxy-2-oxindoles.

	326	R¹	R²	R³	332	Yield (%)^a
1	326a	Me	H	Me	332a	70
2	326a	Me	H	Bn	331b	68
3	326a	Me	H	Allyl	331c	68
4	326a	Me	H	Propargyl	331d^b	70
5	326h	Me	OMe	Me	331e	57
6	326i	Be	OMe	Me	331f	58

^a Isolated yield after flash chromatography.

^b 0.13 mmol scale

Conclusions

The Pd-catalyzed allylation of 3-acetyl-2-oxindoles with allyl alcohol can be performed under BINOL-derived phosphoric acid as co-catalyst in THF at r.t. in good yields. This methodology allows the synthesis of monoallylated 2-oxindoles by *in situ* deacetylation with Triton B. For the deacylative allylation of 3-acetyl-3-methyl-2-oxindoles with allylic alcohols, Pd(OAc)₂/dppp and LiO^tBu as base gave the best results affording the corresponding 3,3-disubstituted 2-oxindoles in moderate to good yields. The mildness of both transformations allows to prepare no-easily accessible unsymmetrical 3,3-diallylated-1-methyl-2-oxindoles. By treatment of 3-alkyl-3-acetyl-2-oxindoles with LiOEt under air the corresponding 3-alkyl-3-hydroxy-2-oxindoles can be easily prepared. These reaction conditions are very mild, the selective substitution and the high tolerance of the reagents to many functional groups convert this process in an *a priori* useful tool for the synthesis of natural products.

Experimental Section

1. Experimental procedures

1.1. General procedure for the Pd-catalyzed synthesis of 3-acetyl-3-allyl-2-oxindoles **326**.

To a round-bottom flask was added Pd(dba)₂ (5.2 mg, 0.009 mmol), *rac*-BINAP (5.6 mg, 0.009 mmol), and dry THF (1.5 mL) and the mixture stirred for 30 min. Then, the oxindole **319** (0.3 mmol), the BINOL derived phosphoric acid (3.1 mg, 0.009 mmol) and allyl alcohol **291** (31 μ L, 0.45 mmol) were added. The resulting mixture was stirred at rt for 60 h, and afterwards, 10 mL of H₂O were added and the mixture was extracted with EtOAc (3 \times 10 mL). The combined organic phases were dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography (EtOAc/hexane) affording pure products **326**.

1.2. Typical procedure for the synthesis of 3-allyl-1-methylindolin-2-one **329**.

After performing the Pd-catalyzed allylation of compound **319a** (see, Section 2.1), a solution of benzyltrimethylammonium hydroxide (Triton B) in MeOH (40 wt%, 136 μ L, 0.3 mmol) was added and, immediately, acetic acid (0.85 mL, 15 mmol). Afterwards, the extractive work-up was performed with EtOAc (3 \times 10 mL), the organic phases were washed with H₂O (10 mL), dried with MgSO₄, filtered and concentrated. The resulting crude was purified by flash chromatography (hexane/EtOAc) to afford pure compound **329** in 61% yield.

1.3. General procedure for the Pd-catalyzed deacylative allylation of compounds **326**. Synthesis of 3-allylated 3-methyl-2-oxindoles **330**.

To a mixture of Pd(OAc)₂ (2.0 mg, 0.009 mmol) and 1,3-bis(diphenylphosphino)propane (3.7 mg, 0.009 mmol), was added dry

THF (1 mL) under Ar and stirring continued for 30 min. This mixture was added to a solution of oxindole **326** (0.3 mmol) in dry THF (0.5 mL). Finally, the allylic alcohol (0.45 mmol) was added and the mixture was degassed by three cycles of freeze-pump-thaw and filled with Ar before the addition of LiO^tBu (36 mg, 0.45 mmol). The solution was stirred at r.t. for 14 h and then extracted with EtOAc (3 × 10 mL). The organic phases were washed with water (10 mL), dried over MgSO₄, and evaporated under vacuum. The pure compounds **330** were obtained after flash chromatography (hexane/EtOAc).

1.4. General procedure for the deacylative oxidation of compounds **326**. Synthesis of 3-alkyl-3-hydroxy-2-oxindoles **331**.

To a solution of oxindole **326** (0.15 mmol) in dry THF (1.5 mL) was added dropwise a solution of LiOEt (0.1 M in THF, 150 μL, 0.15 mmol) and the mixture was stirred at rt for 12 h. Afterwards, the extractive work-up was performed with EtOAc (3 × 10 mL), the organic phases were washed with H₂O (10 mL), dried with MgSO₄, filtered and concentrated. The pure compounds **331** were obtained after flash chromatography (hexane/EtOAc).

1.5. General procedure for the combined double allylation of **319a**. Synthesis of 3-allyl-3-methallyl-1-methyl-2-oxindole **335**.

The first step was carried out following the description of section 2.1. for the synthesis of intermediate **326a**. The second step was run according to section 2.3. and, after purification, product **335** was isolated in 72% yield.

2. Experimental data

Compounds **329**, **330b**, **330d**, **330d'**, **330h**, **330i**, **331a**, **331b**, **331c**, **331d**, **331e** and **335** are known compounds and experimental data are consistent with reported data:

329: 3-Allyl-1-methylindolin-2-one (36 mg, 61% yield)¹⁵⁴

330b: 1,3-Dimethyl-3-(2-methylallyl)indolin-2-one (48 mg, 74% yield)¹⁵¹

330d: 1,3-Dimethyl-3-(3-methylbut-2-en-1-yl)indolin-2-one (35 mg, 51% yield)¹⁴⁸

330d': 1,3-Dimethyl-3-(2-methylbut-3-en-2-yl)indolin-2-one (11 mg, 16% yield)¹⁴⁸

330h: 3-(((1S,5R)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl)-1,3-dimethylindolin-2-one (49 mg, 56% yield)¹⁵¹

330i: 3-Cinnamyl-1,3-dimethylindolin-2-one (42 mg, 51% yield)¹⁴⁷

331a: 3-Hydroxy-1,3-dimethylindolin-2-one (19 mg, 70% yield)¹⁵⁵

331b: 3-Benzyl-3-hydroxy-1-methylindolin-2-one (26 mg, 68% yield)¹⁵⁶

331c: 3-Allyl-3-hydroxy-1-methylindolin-2-one (21 mg, 68% yield)¹⁵⁷

331d: 3-Hydroxy-1-methyl-3-(prop-2-yn-1-yl)indolin-2-one (19 mg, 70% yield)¹⁵⁸

331e: 3-Hydroxy-5-methoxy-1,3-dimethylindolin-2-one (18 mg, 57% yield)¹⁵⁹

335: 3-Allyl-1-methyl-3-(2-methylallyl)indolin-2-one (52 mg, 77% overall yield)¹⁶⁰

Following, characterization data of new compounds **326j**, **326k**, **331a**, **331c**, **331e**, **331f**, **331f**, **331g** and **332f** will be displayed:

3-Acetyl-3-allyl-5-methoxy-1-methylindolin-2-one (326j)

Yield: 47 mg (61%); Orange oil.

^1H NMR (400 MHz): δ = 6.88 (dd, J = 8.5, 2.5 Hz, 1H), 6.82–6.79 (m, 2H), 5.31 (dddd, J = 16.9, 10.1, 7.8, 6.7 Hz, 1H), 5.04–4.99 (m, 1H), 4.91–4.88 (m, 1H), 3.79 (s, 3H), 3.25 (s, 3H), 2.96–2.83 (m, 2H), 2.00 (s, 3H).

^{13}C NMR (101 MHz): δ = 200.8, 174.2, 156.4, 137.8, 131.5, 128.2, 119.5, 113.8, 111.2, 108.9, 66.8, 55.9, 37.6, 26.7, 26.6.

LRMS (EI) m/z (%) = 259 (28) $[\text{M}]^+$, 218 (15), 217 (100), 216 (21), 202 (37), 190 (12), 188 (16), 176 (10), 174 (29), 173 (11), 144 (18), 115 (21), 77 (11).

HRMS (ESI): calcd. for $\text{C}_{15}\text{H}_{17}\text{NO}_3$ 259.1208; found 259.1206.

3-Acetyl-3-allyl-1-benzyl-5-methoxyindolin-2-one (326k)

Yield: 89 mg (89%); Pale orange oil.

^1H NMR (300 MHz): δ = 7.33–7.27 (m, 5H), 6.78–6.74 (m, 2H), 6.69 (dd, J = 8.3, 0.6 Hz, 1H), 5.33 (dddd, J = 16.6, 10.0, 8.0, 6.5 Hz, 1H), 5.07 (ddd, J = 17.0, 3.1, 1.2 Hz, 1H), 5.01–4.86 (m, 3H), 3.75 (s, 3H), 3.03–2.88 (m, 2H), 2.01 (s, 3H).

^{13}C NMR (75 MHz): δ = 200.7, 174.3, 156.4, 136.9, 135.7, 131.6, 128.9, 128.2, 127.9, 127.6, 119.8, 113.8, 111.1, 110.1, 66.8, 55.9, 44.3, 37.6, 26.7.

LRMS (EI) m/z (%): 335 (10) $[\text{M}]^+$, 294 (11), 293 (47), 91 (100).

HRMS (ESI): calcd. for $\text{C}_{21}\text{H}_{21}\text{NO}_3$ 335.1521; found 335.1521.

(E)-3-(Hex-2-en-1-yl)-1,3-dimethylindolin-2-one (330a)

Yield: 51 mg (70%); Yellow oil.

^1H NMR (400 MHz): δ = 7.27–7.23 (m, 1H), 7.19–7.16 (m, 1H), 7.05 (td, J = 7.5, 0.9 Hz, 1H), 6.81 (d, J = 7.7 Hz, 1H), 5.40–5.32 (m, 1H), 5.08–4.99 (m, 1H), 3.18 (s, 3H), 2.50–2.39 (m, 2H), 1.81 (q, J = 7.0 Hz, 2H), 1.35 (s, 3H), 1.20 (q, J = 7.3 Hz, 2H), 0.73 (t, J = 7.4 Hz, 3H).

^{13}C NMR (101 MHz): δ = 180.5, 143.3, 134.9, 134.0, 127.7, 123.9, 123.0, 122.3, 107.9, 48.7, 41.5, 34.5, 26.1, 22.6, 22.5, 13.5.

LRMS (EI) m/z (%): 243 (8) $[\text{M}]^+$, 162 (9), 161 (80), 160 (100), 130 (8), 117 (9).

HRMS (ESI): calcd. for $\text{C}_{16}\text{H}_{21}\text{NO}$ 243.1623; found 243.1621.

(E)-3-(But-2-en-1-yl)-1,3-dimethylindolin-2-one (330c) and isomers:

Yield: 33 mg (45%); Brown oil.

^1H NMR (400 MHz): δ = 7.29–7.24 (m, 1.7H), 7.21 (d, J = 7.3 Hz, 0.3H), 7.17 (d, J = 7.3 Hz, 1H), 7.05 (t, J = 7.5 Hz, 1.5H), 6.83 (d, J = 7.7 Hz, 1.4H), 5.87 (dt, J = 17.3, 9.4 Hz, 0.2H), 5.67–5.54 (m, 0.3H), 5.42 (dq, J = 12.8, 6.3 Hz, 1H), 5.16–4.99 (m, 1.4H), 4.90 (d, J = 10.1 Hz, 0.1H), 3.24 (s, 0.4H), 3.22 (s, 0.7H), 3.20 (s, 3H), 3.18 (s, 0.3H), 2.70–2.47 (m, 0.7H), 2.43 (d, J = 7.2 Hz, 1.6H), 1.66 (d, J = 6.7 Hz, 0.3H), 1.52 (d, J = 6.3 Hz, 3H), 1.45 (s, 0.3H), 1.39 (s, 0.6H), 1.35 (s, 3H), 0.99 (d, J = 6.9 Hz, 0.3H), 0.68 (d, J = 6.7 Hz, 0.5H).

^{13}C NMR (101 MHz): δ = 180.6, 143.3, 143.2, 139.2, 138.6, 134.0, 134.0, 129.4, 127.9, 127.8, 127.8, 127.7, 127.4, 124.9, 124.2, 123.9, 123.2, 123.2, 123.0, 122.9, 122.4, 122.3, 122.3, 121.1, 117.0, 115.8, 108.1, 107.9, 107.9, 107.8, 51.3, 51.2, 48.6, 48.4, 45.9, 44.9, 41.4, 35.5, 26.2, 22.8, 22.6, 22.2, 21.6, 18.0, 15.3, 15.0, 13.1.

LRMS (EI) m/z (%): 215 (10) $[\text{M}]^+$, 161 (32), 161 (100), 160 (100), 132 (11), 130 (14), 117 (16) 77 (11), 55 (13).

HRMS (ESI): calcd. for C₁₄H₁₇NO 215.1310; found 215.1309.

(E)-3-(3,7-Dimethylocta-2,6-dien-1-yl)-1,3-dimethylindolin-2-one (330e):

Yield: 61 mg (45%); Pale yellow oil.

¹H NMR (400 MHz): δ = 7.27–7.22 (m, 1H), 7.21–7.17 (m, 1H), 7.03 (td, J = 7.5, 0.9 Hz, 1H), 6.81 (d, J = 7.7 Hz, 1H), 5.00–4.93 (m, 1H), 4.89–4.82 (m, 1H), 3.19 (s, 3H), 2.47 (d, J = 7.6 Hz, 2H), 1.95–1.82 (m, 4H), 1.64 (s, 3H), 1.54 (s, 3H), 1.50 (s, 3H), 1.37 (s, 3H)

¹³C NMR (101 MHz): δ = 180.8, 143.3, 138.9, 134.2, 131.5, 127.7, 124.3, 123.1, 122.3, 118.3, 107.8, 48.7, 39.9, 36.8, 26.8, 26.2, 25.8, 22.4, 17.8, 16.4.

LRMS (EI) *m/z* (%): 297 (1) [M]⁺, 162 (11), 161 (100), 160 (30), 130 (8), 117 (8), 69 (27).

HRMS (ESI): calcd. for C₂₀H₂₇NO 297.2093; found 297.2093.

**(E)-1,3-Dimethyl-3-(penta-2,4-dien-1-yl)indolin-2-one (330f):
Mixture of isomers (major *trans* isomer);**

Yield: 38 mg (55%); Pale yellow wax.

¹H NMR (300 MHz): δ = 7.26 (td, J = 7.9, 1.3 Hz, 1H), 7.21–7.16 (m, 1H), 7.06 (td, J = 7.5, 1.0 Hz, 1H), 6.83 (d, J = 7.8 Hz, 1H), 6.21–5.96 (m, 2H), 5.36 (dt, J = 15.0, 7.7 Hz, 1H), 5.09–5.02 (m, 1H), 4.96–4.92 (m, 1H), 3.19 (s, 3H), 2.53 (d, J = 7.7 Hz, 2H), 1.37 (s, 3H).

¹³C NMR (75 MHz): δ = 180.2, 143.2, 136.7, 134.8, 133.7, 128.3, 127.9, 123.0, 122.5, 116.3, 108.0, 48.5, 41.3, 26.2, 22.7.

LRMS (EI) *m/z* (%): 227 (5) [M]⁺, 174 (9), 161 (13), 160 (100), 132 (11), 130 (13), 117 (15), 77 (10), 67 (10).

HRMS (ESI): calcd. for C₁₅H₁₇NO 227.1310; found 227.1305.

1,3-Dimethyl-3-(penta-1,4-dien-3-yl)indolin-2-one (330f):

Yield: 5 mg (7%); Colorless oil.

^1H NMR (300 MHz): δ = 7.31–7.25 (m, 1H), 7.22–7.20 (m, 1H), 7.05 (td, J = 7.5, 1.0 Hz, 1H), 6.82 (d, J = 7.8 Hz, 1H), 5.86 (ddd, J = 17.0, 10.4, 8.3 Hz, 1H), 5.39 (ddd, J = 17.1, 10.2, 8.7 Hz, 1H), 5.19–5.01 (m, 3H), 4.93 (dd, J = 10.1, 1.9 Hz, 1H), 3.22–3.14 (m, 4H), 1.36 (s, 3H).

^{13}C NMR (75 MHz): δ = 179.9, 143.7, 135.7, 135.6, 132.4, 128.0, 123.7, 122.3, 118.2, 117.4, 107.9, 55.6, 51.2, 26.2, 21.8.

LRMS (EI) m/z (%): 227 (5) $[\text{M}]^+$, 161 (11), 160 (100), 132 (10), 130 (11), 117 (13), 77 (7), 67 (5), 65 (5).

HRMS (ESI): calcd. for $\text{C}_{15}\text{H}_{17}\text{NO}$ 227.1310; found 227.1309.

**3-(Cyclohex-2-en-1-yl)-1,3-dimethylindolin-2-one (330g):
Mixture of diastereoisomers.**

Yield: 55 mg (75%); Pale yellow oil.

^1H NMR (major diastereoisomer, 300 MHz): δ = 7.29–7.23 (m, 1H), 7.21–7.18 (m, 1H), 7.02 (td, J = 7.5, 1.0 Hz, 1H), 6.82 (d, J = 7.8 Hz, 1H), 5.88–5.74 (m, 2H), 3.21 (s, 3H), 2.72–2.63 (m, 1H), 1.95–1.72 (m, 2H), 1.64–1.33 (m, 6H), 0.95–0.83 (m, 1H).

^{13}C NMR (major diastereoisomer, 75 MHz): δ = 180.5, 143.7, 133.1, 130.8, 127.7, 126.0, 123.8, 122.3, 107.7, 51.0, 43.0, 26.2, 25.1, 24.5, 21.8, 21.5.

LRMS (EI) m/z (%): 241 (8) $[\text{M}]^+$, 162 (20), 161 (100), 160 (73), 130 (11), 117 (11), 81 (22).

HRMS (ESI): calcd. for $\text{C}_{16}\text{H}_{19}\text{NO}$ 241.1467; found 241.1464.

1-Benzyl-3-hydroxy-5-methoxy-3-methylindolin-2-one (331f):

Yield: 25 mg (58%); Orange solid; m.p. 135–137 °C (hexane/EtOAc).

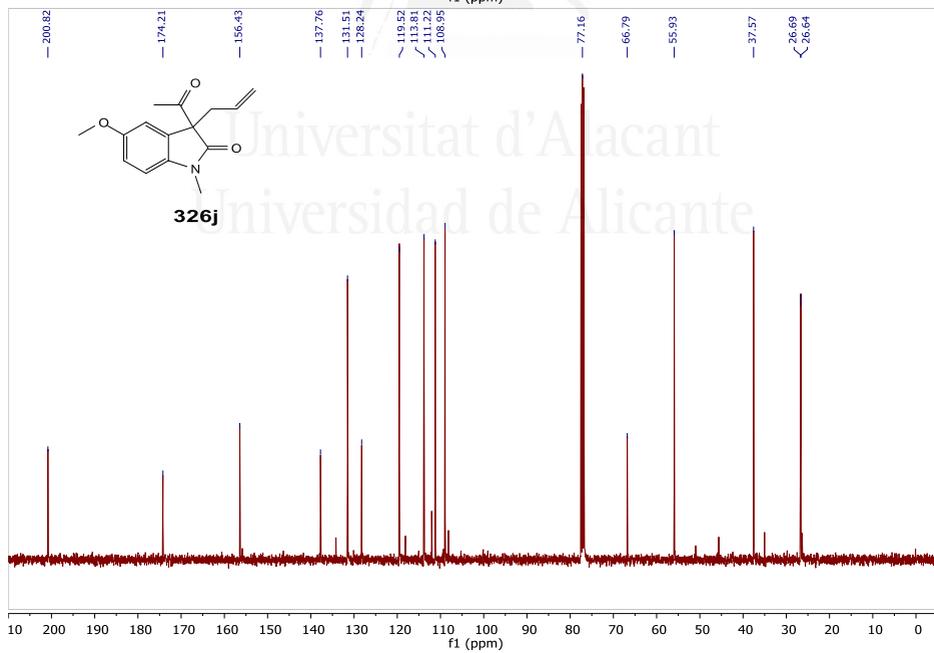
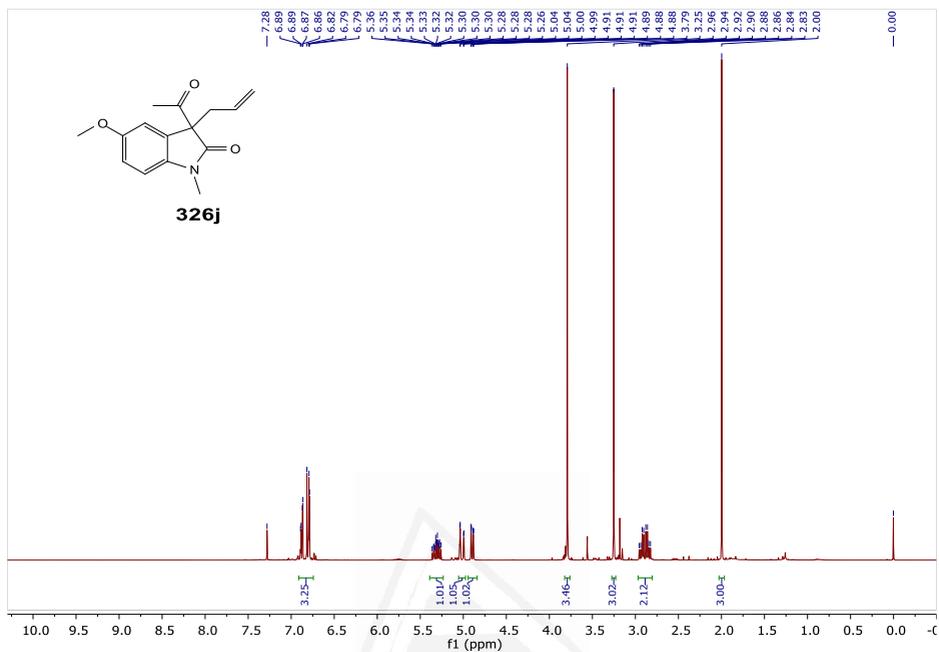
^1H NMR (400 MHz): δ = 7.32–7.23 (m, 5H), 7.04 (d, J = 2.6 Hz, 1H), 6.70 (dd, J = 8.5, 2.6 Hz, 1H), 6.60 (d, J = 8.5 Hz, 1H), 4.93 (d, J = 15.7 Hz, 1H), 4.78 (d, J = 15.7 Hz, 1H), 3.75 (s, 3H), 3.17 (br s, 1H), 1.67 (s, 3H).

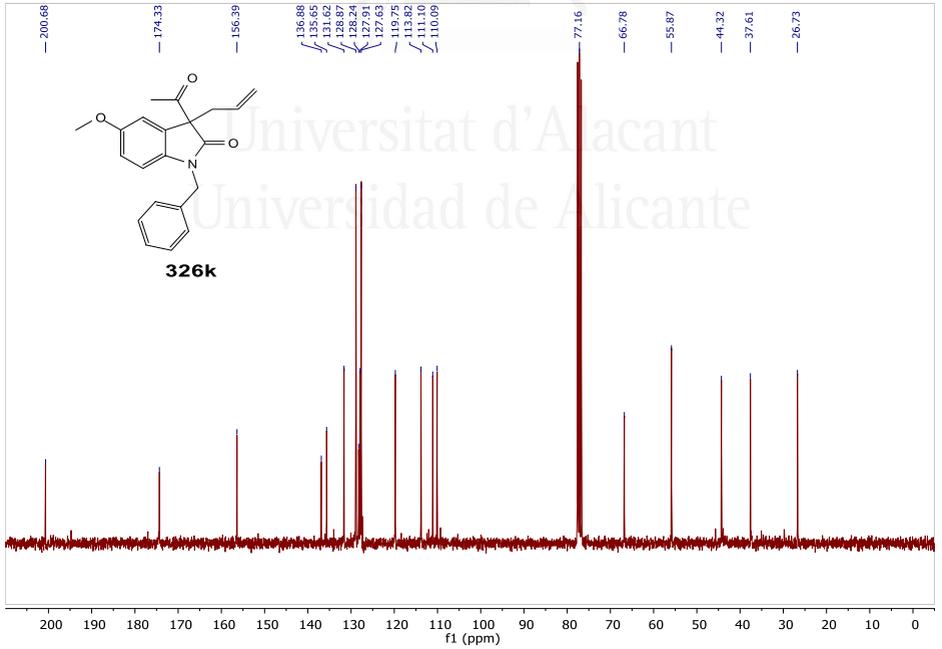
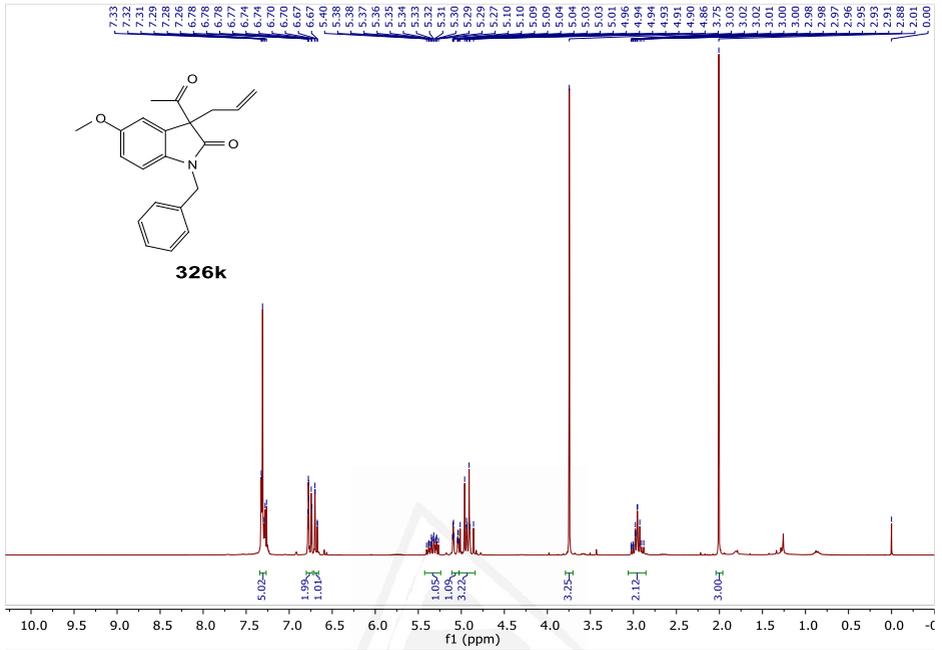
^{13}C NMR (101 MHz): δ = 178.8, 156.6, 135.6, 135.1, 132.9, 128.9, 127.8, 127.3, 114.2, 110.6, 110.3, 74.3, 55.9, 43.9, 25.3.

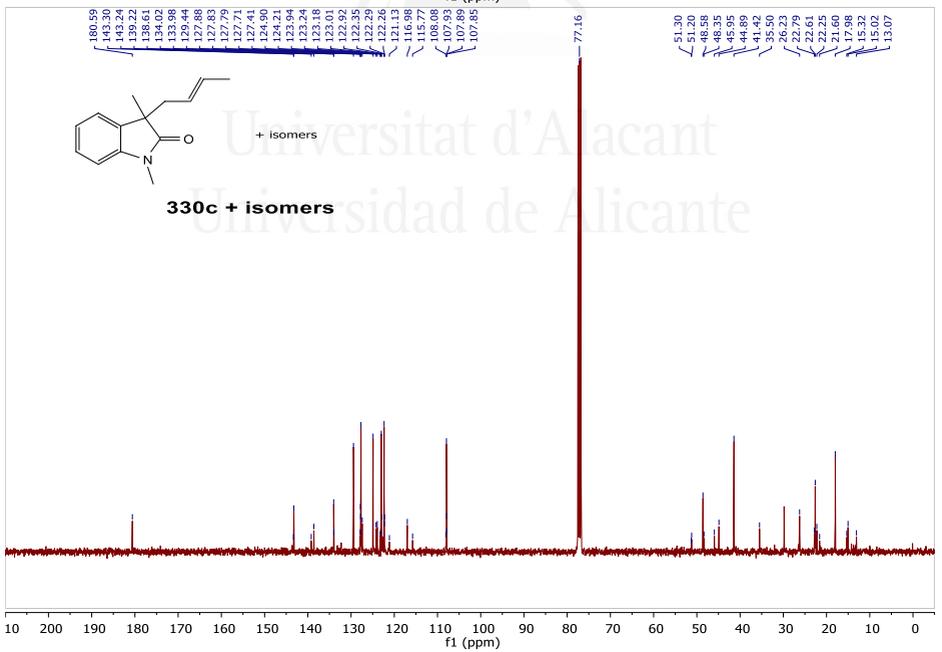
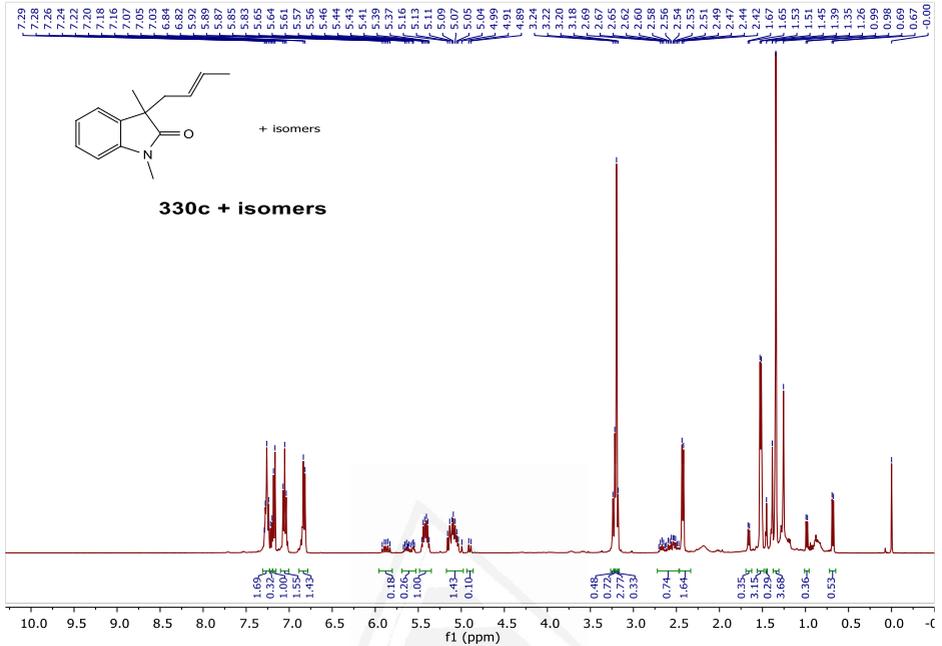
LRMS (EI) m/z (%): 283 (39) $[\text{M}]^+$, 267 (8), 192 (7), 174 (5), 146 (8), 106 (7), 92 (10), 91 (100), 89 (6), 77 (7), 65 (19) 63 (5), 51 (5).

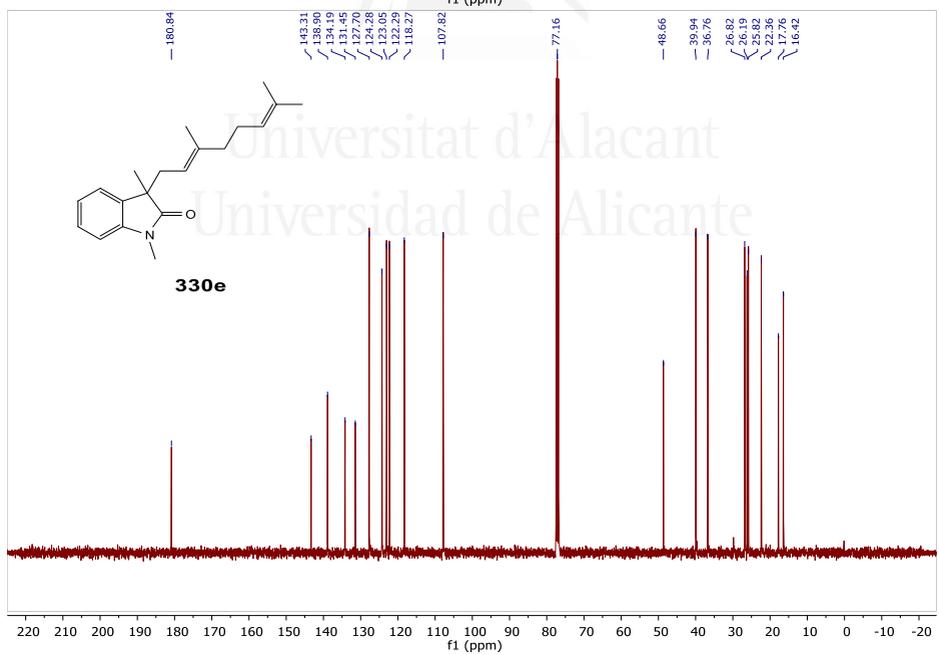
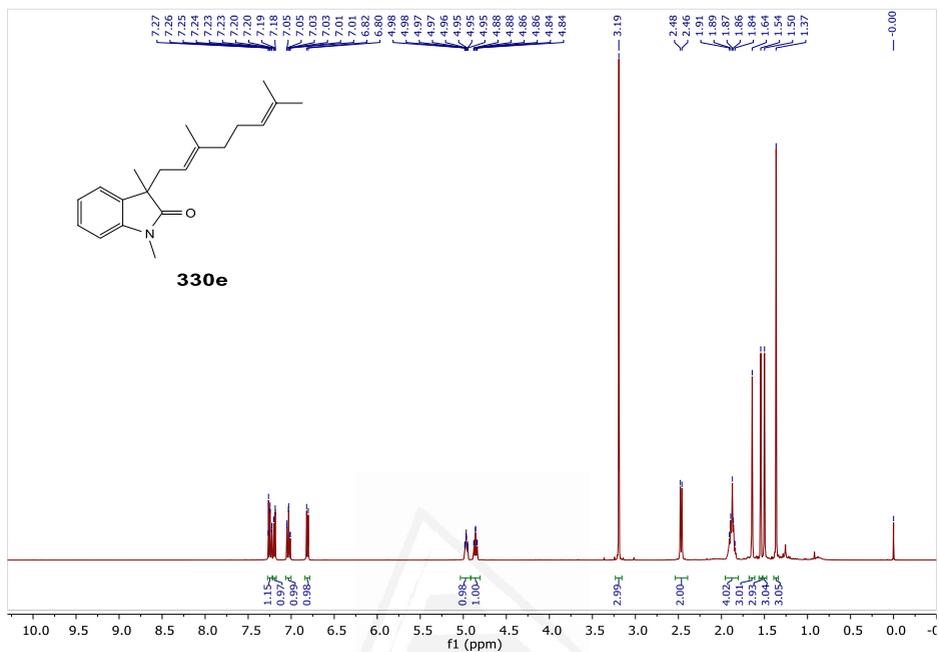
HRMS (ESI): calcd. for $\text{C}_{17}\text{H}_{17}\text{NO}_3$ 283.1208; found 283.1203.

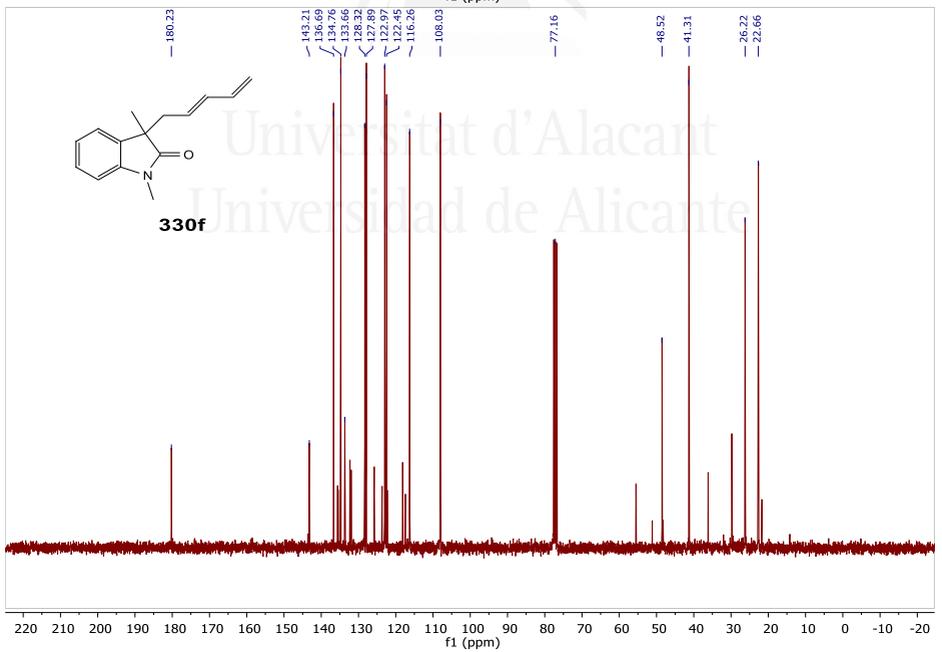
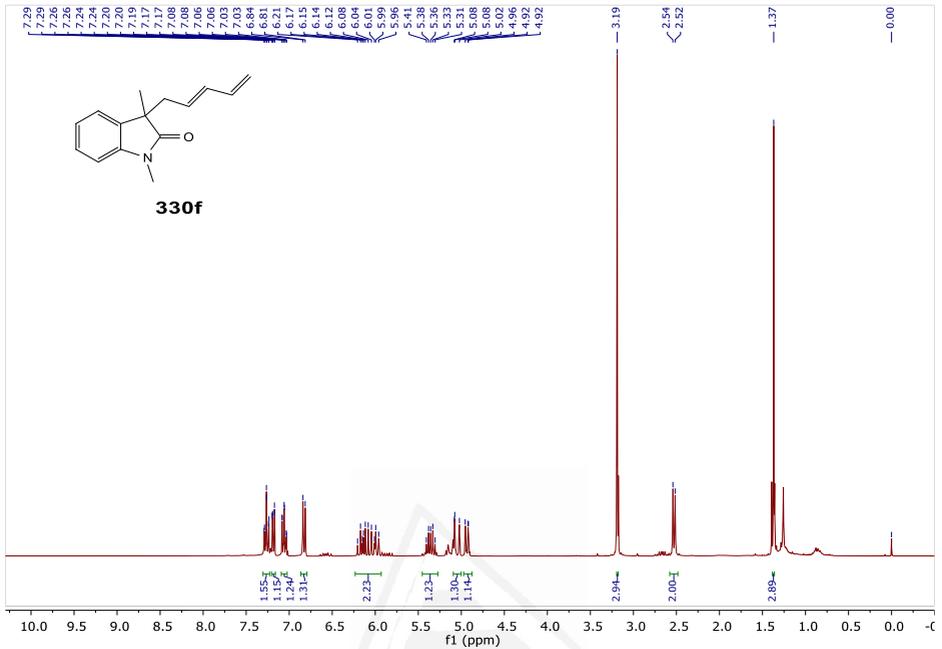


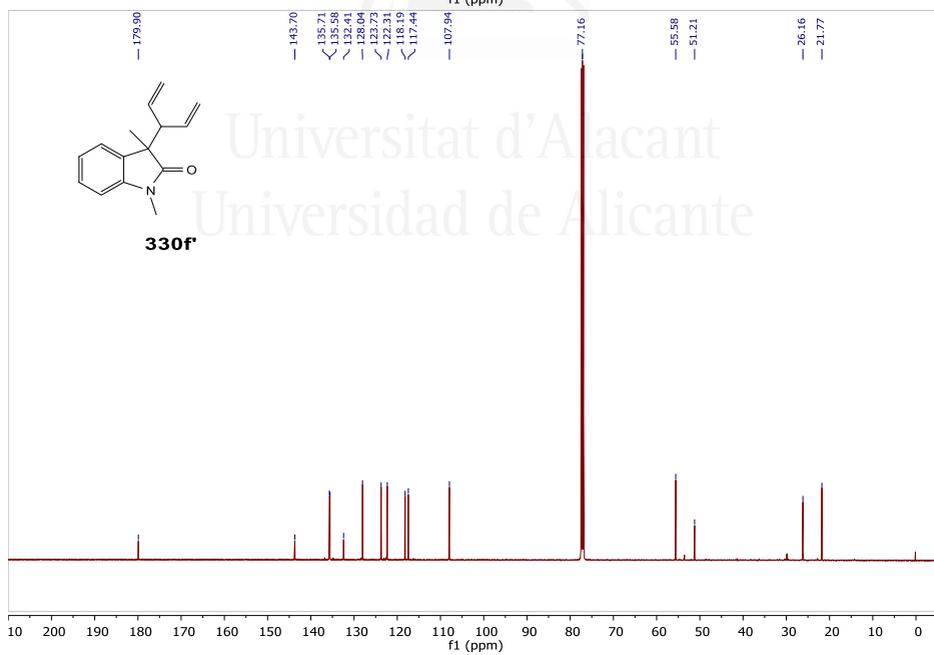
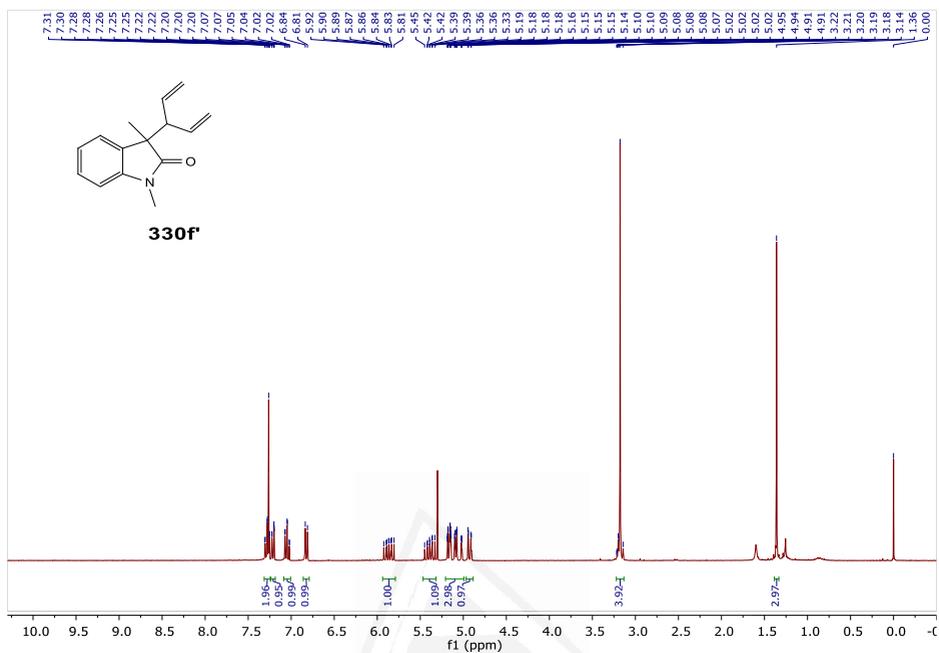


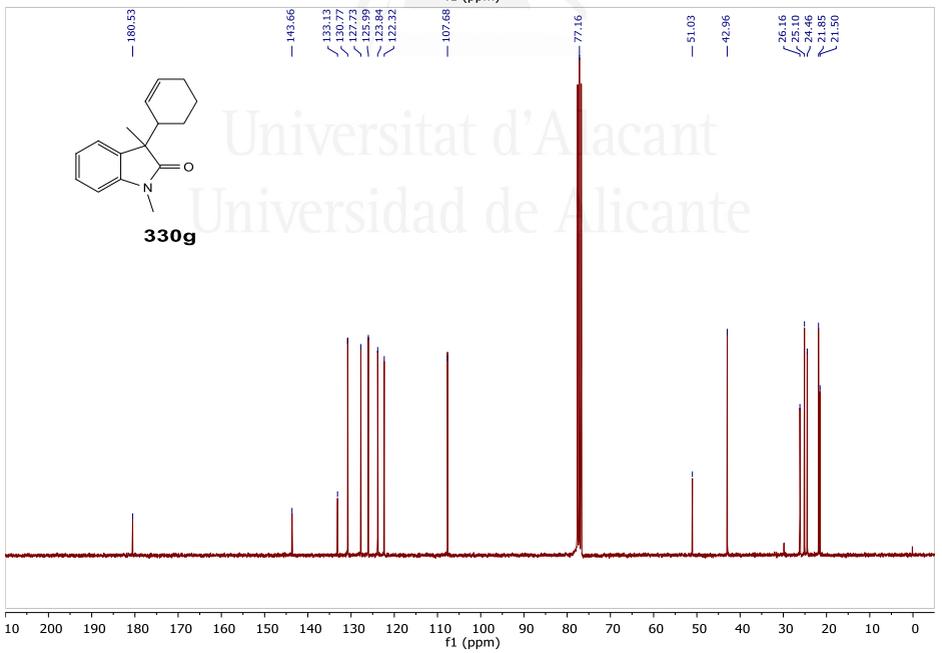
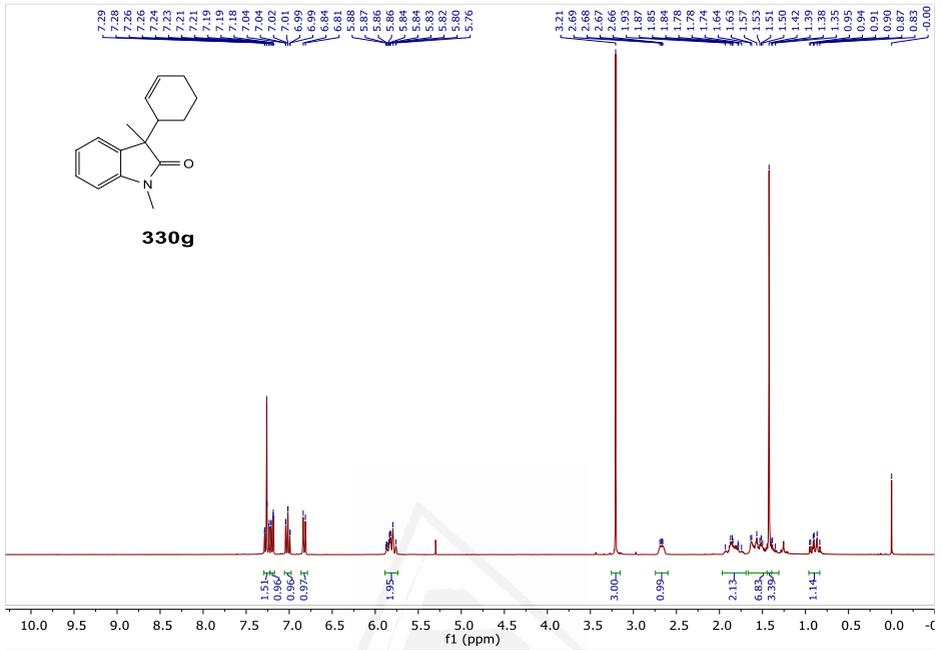


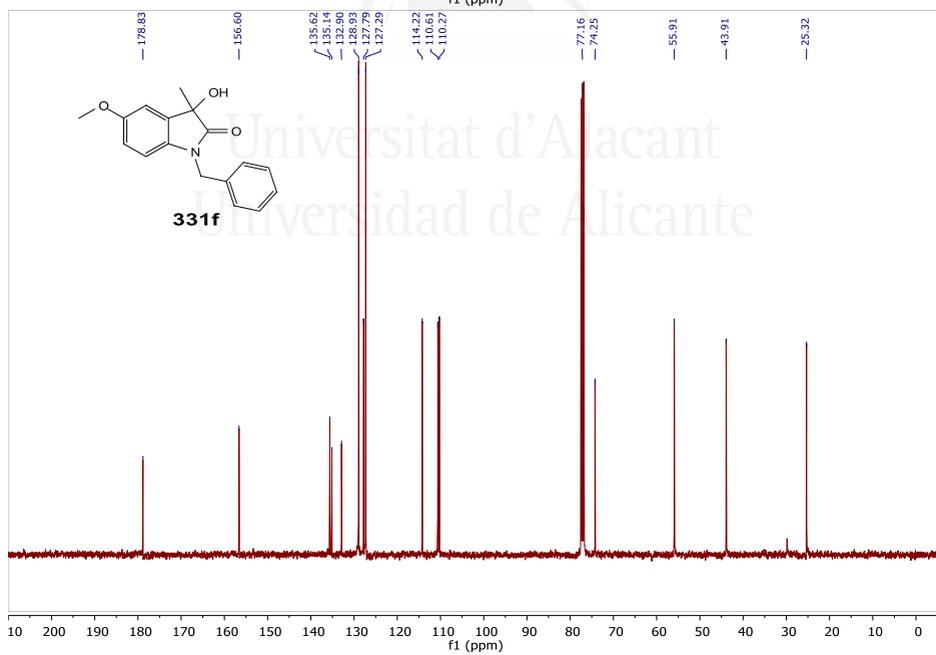
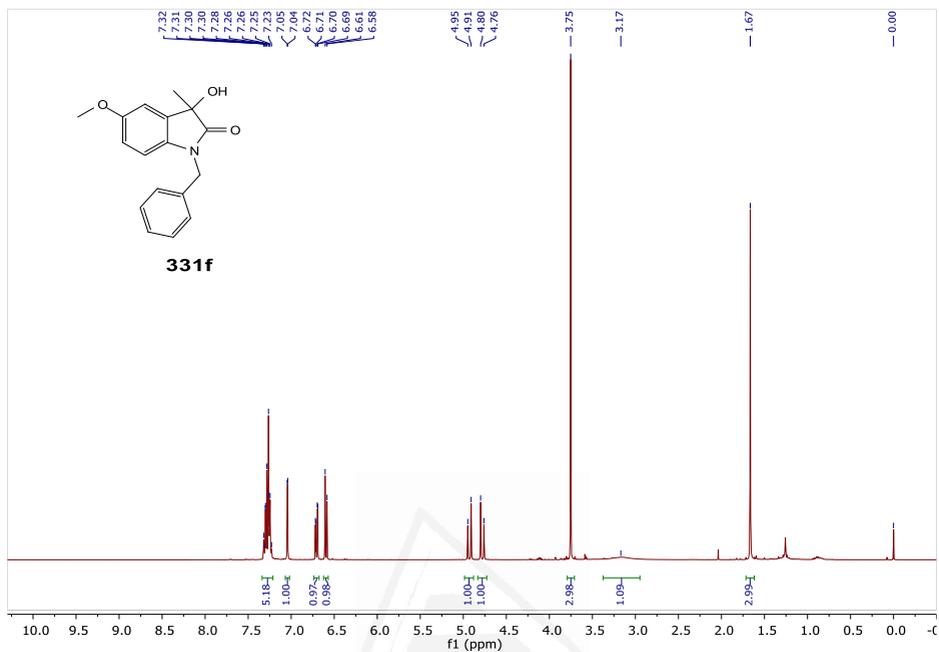












The corresponding paper of this research can be found with the following reference:

A. Ortega-Martínez, R. de Lorenzo, J. M. Sansano and C. Nájera, *Tetrahedron*, 2018, **74**, 253–259.

DOI: 10.1016/j.tet.2017.11.041



Universitat d'Alacant
Universidad de Alicante

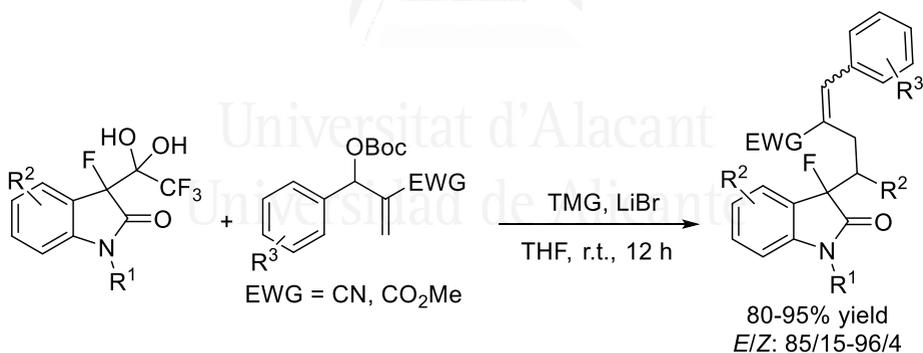
CHAPTER 3:
SYNTHESIS OF
3-SUBSTITUTED
3-FLUORO-2-OXINDOLES BY
DEACYLATIVE ALKYLATION

Universitat d'Alacant
Universidad de Alicante

CHAPTER 3

Introduction

Such as it was described in the General Introduction, fluorinated oxindole derivatives became also important scaffolds in organic synthesis. Many research groups have been investigating in the field for introducing fluorine atoms in a more efficient way. As it is possible to see in the literature, some fluorinations at the 3 position of oxindole (Scheme 29, 30, 31) have been developed. Recently, a detrifluoroacylative alkylation has been reported by Soloshonok and co-workers where a S_N2' of 3-fluorinated 2-oxindole derivatives was carried out with Morita-Baylis-Hillman carbonates using LiBr, tetramethylguanidine in THF at r.t. The *E/Z* ratio of the products is between 85/15 and 96/4 and the yields up to 95% (Scheme 64).¹⁶¹



Scheme 64. Detrifluoroacylative S_N2' allylation of 2-oxindole derivatives.

Most of the previously commented reactions are catalyzed by metals as Pd(II) and Ni(II) salts (Scheme 29, 30, 64) and few examples are organocatalyzed, in this case under basic conditions (Scheme 31).



Universitat d'Alacant
Universidad de Alicante

Objectives

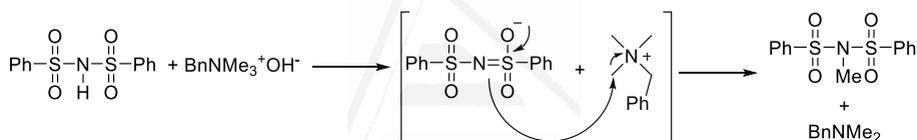
- To study the fluorination at the 3 position of 3-acetyl-2-oxindole derivative using an electrophilic fluorine source.
- The preparation of 3-alkyl 3-fluoro-2-oxindoles by deacylative alkylation of 3-acetyl-3-fluoro-2-oxindoles using alkyl halides.
- The synthesis of 3-allylated 3-fluoro-2-oxindole through Pd-catalyzed deacylative allylation of 3-acetyl-3-fluoro-2-oxindole.



Universitat d'Alacant
Universidad de Alicante

Results and discussion

Initially, studies for the fluorination at the 3 position of **319a** were assayed using *N*-fluorobenzenesulfonimide (NFSI) **237** used as source of electrophilic fluorine under different reaction conditions (Table 7). When 1 equiv. of Triton B was used (Table 7, entry 1), a complex crude mixture was obtained. Target compound **339**, deacylated product **340**, difluorinated derivative **341** and starting material **319a** were observed at the end of the process. Also, it was difficult to analyze the mixture of compounds **342**, because benzenesulfonimide and *N*-methylbenzenesulfonimide were obtained as byproducts of NFSI. Probably the last one proceeded from the nucleophilic attack of sulfonimide to the ammonium cation of Triton B, also giving benzyldimethylamine (Scheme 65):

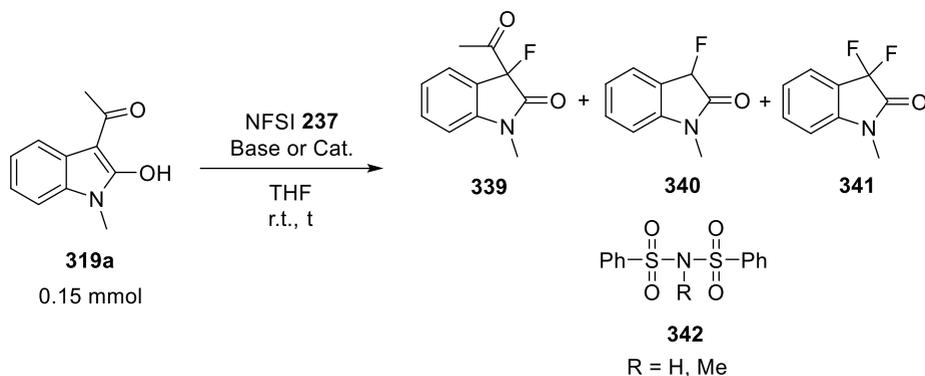


Scheme 65. Formation of *N*-methylbenzenesulfonimide byproduct through a S_N2 attack.

The amount of NFSI **237** was increased in order to improve the conversion of the final product **339** (Table 7, entry 2). With these reaction conditions in hands, the amount of difluorinated product was higher than the previous one but starting material **319a** was not observed. Anyway, the crude was attempted to purify by flash chromatography to characterize the final compound. Using hexane and ethyl acetate as eluents, only product **341** was cleanly separated but, unfortunately, benzenesulfonimide derivatives **341** did not. So, the desired 3-acetyl-3-fluoro-2-oxindole **339** could not be isolated as pure compound. Also, it was observed that **339** was not very stable under this purification conditions, giving also a 16% of deacylated product **340** after flash chromatography. At this point, it was decided

that Triton B was not the best option for fluorination of **319a** due to the side reactions detected, providing undesirable byproducts **341** and **342**.

The fluorination reaction of **319a** using *rac*-BINOL phosphoric acid as organocatalyst at room temperature for 18 h was not complete giving moderate conversion of **339** (62%) (Table 7, entry 3). But in this example, the reaction crude was completely clean, neither the deacylated nor the difluorinated product were observed and only benzenesulfonimide was obtained as byproduct without suffering any *N*-alkylation itself. Finally, *p*-toluenesulfonic acid was found to be the best catalyst to carry out the reaction (Table 7, entry 4). After 48 hours of reaction time with the possibility of scaling the reaction up to 2 mmol, the conversion was complete (>99 %) and, again, no oxindole byproducts were obtained. After testing different purifications conditions, it was found that the use of a 9.5:0.5 (PhMe:AcOEt) mixture as eluent and a fast elution of **339** were the most appropriate conditions, allowing the separation of benzenesulfonimide and the final product, providing **339** in a good 85% yield. In this reaction, only 15 mol% of catalyst was necessary, avoiding the use of stoichiometric amounts of base.

Table 7. Synthesis of 3-acetyl-3-fluoro-2-oxindole

	eq 237	Base (1 eq)	Cat.	t (h)	Cnv (%)	Yield (%) ^a
1	1	Triton B	–	18	339+341 (59) 340 (19) 319a (18)	–
2	1.4	Triton B	–	18	339 (60) 341 (40)	340 (61) 341 (16) 343 (23)
3	1.1	–	(BINOL)PO ₂ H (15 mol%)	18	339 (62) 319a (38)	–
4^b	1.1	–	TsOH (15 mol%)	48	339 (>99)	340 (85)

^a Isolated yield after flash chromatography.

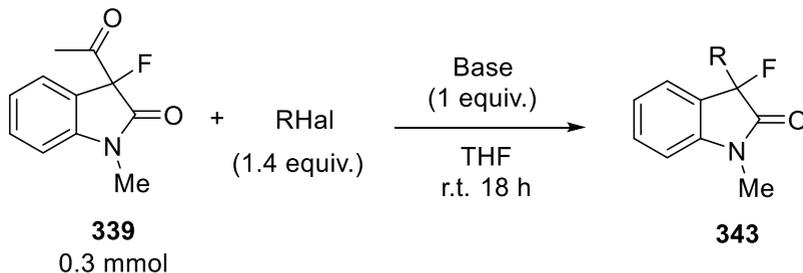
^b 2 mmol scale

At this point, deacylative alkylation process of **339** was performed for the synthesis of 3-substituted 3-fluoro-2-oxindoles **343** with different alkyl halides (Table 8). Using the optimal conditions for the DaA with alkyl halides described on Chapter 1, lithium ethoxide was chosen as deacylative agent and allyl bromide as electrophile (Table 8, entry 1). However, no significant amount of desired product **343a**

was observed. At this point, we tried to switch the base to Triton B. Employing a benzyltrimethylammonium hydroxide methanolic solution as deacylative agent the reaction afforded product **343a** with an excellent conversion and 91% yield (Table 8, entry 2). When benzyl bromide was used as electrophile, **343b** was obtained in 92 % yield (Table 8, entry 3). Iodomethane (2.4 equiv.) and propargyl bromide afforded products **343c** and **343d** in 71% and 59% yield, respectively (Table 8, entries 4 and 5). Instead, when bromoacetonitrile was used as electrophile the reaction failed and the corresponding product **343e** was not observed (Table 8, entry 6). Decreasing the reaction temperature to 0 °C no improvement of the results was observed (Table 8, entry 7). Finally, cinnamyl bromide afforded product **343f** in 85 % yield (Table 8, entry 8).



Universitat d'Alacant
Universidad de Alicante

Table 8. Synthesis of 3-substituted 3-fluoro-2-oxindole derivatives through DaA.

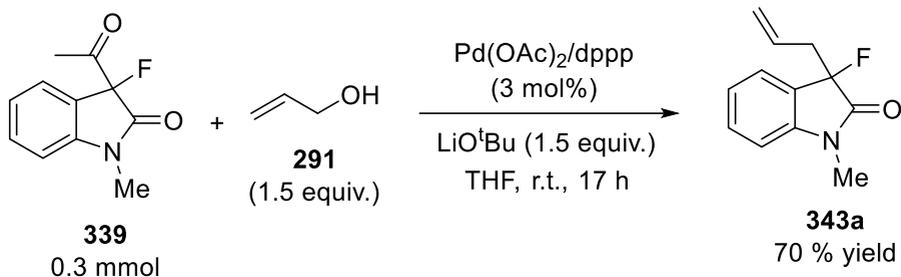
	RHal	Base	Product	Conv (%)	Yield (%) ^a
1		LiOEt	343a	<5	–
2		Triton B	343a	>99	91
3		Triton B	343b	>99	92
4 ^b	MeI	Triton B	343c	>99	71
5		Triton B	343d	>99	59
6		Triton B	343e	<5	–
7 ^c		Triton B	343e	<5	–
8		Triton B	343f	>99	85

^a Isolated yield after flash chromatography.

^b 2.8 equiv. of MeI was used.

^c The addition of the base was performed at 0 °C.

Regarding to the palladium-catalyzed deacylative alkylation (see Chapter 2), 3-acetyl-3-fluoro-2-oxindole **339** was submitted to this process using allyl alcohol (Scheme 66):



Scheme 66. Pd-catalyzed DaA of 3-acetyl-3-fluoro-2-oxindole with allylic alcohol.

On the one hand, when allyl alcohol **291** (1.5 equiv.), palladium (II) acetate/diphenylphosphinopropane complex (3 mol%) and lithium *tert*-butoxide (1.5 equiv.) were stirred with **339** in THF at room temperature for 17 h, the expected 3-allyl-3-fluoro-1-methyl-2-oxindole **343a** was formed in >99% of conversion and in 70% yield. The study of the scope of this process is ongoing in our research group.

Conclusions

A efficient organocatalyzed methodology for the synthesis of 3-acetyl-3-fluoro-1-methyl-2-oxindole has been developed under very mild conditions avoiding the formation of byproducts. The deacylative alkylation methodologies that have been developed previously in our research group could be applied to the synthesis of 3-alkyl 3-fluoro-1-methyl-2-oxindoles using Triton B and alkyl halides. The Pd-catalyzed deacylative alkylation of 3-acetyl-3-fluoro-1-methyl-2-oxindole could be achieved using standard reaction conditions and allyl alcohol affording 3-allyl-3-fluoro-1-methyl-oxindole in good yield.



Universitat d'Alacant
Universidad de Alicante

Experimental Section

1. General methods

376 MHz ^{19}F NMR spectra was recorded using Bruker AV300 with CDCl_3 as solvent and trifluoroacetic acid as internal standard. Chemical shifts are given in ppm.

2. Experimental procedures

2.1. Synthesis of 3-acetyl-3-fluoro-1-methylindolin-2-one **339**.

In a 100 mL round-bottom flask that contains the 1-(2-hydroxy-1-methyl-1H-indol-3-yl)ethan-1-one **319a** (278.5 mg, 2 mmol), NFSI (693.5 mg, 2.2 mmol) and *p*-toluenesulfonic acid monohydrate (57 mg, 0.3 mmol), the THF (20 mL) was added and stirred at r.t. for 48 h. Afterwards, the sample is diluted in 50 mL of H_2O and extracted with EtOAc (3×50 mL). The organic phases were dried with MgSO_4 , filtered and concentrated. A brown solid was obtained (1.1 g). The resultant crude was purified by flash chromatography with 9.5:0.5 (PhMe:EtOAc) mixture to afford 354 mg (85%) of a purple solid.

2.2. General procedure for deacylative alkylation of 3-acetyl-3-fluoro-1-methylindolin-2-one **339** with alkyl halides.

Oxindole **339** (0.3 mmol) and alkyl halide (0.42 mmol) were dissolved under an argon atmosphere in anhydrous THF (3 mL). A benzyltrimethylammonium hydroxide solution (Triton B) in MeOH (40wt%, 0.136 mL, 0.3 mmol) was added dropwise and the reaction mixture was stirred at r.t. for 18 hours. Afterwards, 10 mL of H_2O were added and the mixture was extracted with EtOAc (3×10 mL). The combined organic phases were dried over MgSO_4 , filtered and concentrated. After flash chromatography (hexane/EtOAc), pure 3-substituted 3-fluoro-1-methyl-2-oxindole derivatives **343** were obtained.

2.3. Pd-catalyzed synthesis of 3-allyl-3-fluoro-1-methylindolin-2-one **343a** through deacylative alkylation.

To a mixture of Pd(OAc)₂ (2.0 mg, 0.009 mmol) and 1,3-bis(diphenylphosphino)propane (3.7 mg, 0.009 mmol), was added dry THF (1 mL) under Ar and stirring continued for 30 min. This mixture was added to a solution of oxindole **339** (62.2 mg, 0.3 mmol) in dry THF (0.5 mL). Finally, the allyl alcohol (0.031 mL, 0.45 mmol) was added and the mixture was degassed by three cycles of freeze-pump-thaw and filled with Ar before the addition of LiO^tBu (36 mg, 0.45 mmol). The solution was stirred at r.t. for 17 h and then 10 mL of H₂O were added and extracted with EtOAc (3 × 10 mL). The organic phases were dried over MgSO₄ and evaporated under vacuum. The pure compound **343a** was obtained after flash chromatography (hexane/EtOAc).

3. Experimental data

Compounds **339** and **343c** are known compounds and experimental data are consistent with reported data:

339: 3-Acetyl-3-fluoro-1-methylindolin-2-one (354 mg, 85% yield)¹⁶²

343c: 3-Fluoro-1,3-dimethylindolin-2-one (38 mg, 71% yield)¹⁶³

Following, characterization data of new compounds **343a**, **343b**, **343d** and **343f** will be displayed:

3-Allyl-3-fluoro-1-methylindolin-2-one (343a)

Yield: 56 mg (91%); Red oil.

¹H NMR (400 MHz): δ = 7.44–7.35 (m, 2H), 7.10 (t, J = 7.6 Hz, 1H), 6.84 (d, J = 7.8 Hz, 1H), 5.60 (dddd, J = 16.6, 10.1, 8.2, 6.4 Hz, 1H), 5.15–5.10 (m, 2H), 3.18 (s, 3H), 3.02–2.94 (m, 1H), 2.79 (ddd, J = 18.7, 13.6, 8.2 Hz, 1H).

¹³C NMR (101 MHz): δ = 172.6 (d, J = 21.2 Hz), 144.0 (d, J = 5.2 Hz), 131.2 (d, J = 2.8 Hz), 129.0 (d, J = 8.3 Hz), 125.6 (d, J = 18.7 Hz), 125.0, 123.2 (d, J = 2.3 Hz), 121.1, 108.7, 92.4 (d, J = 189.0 Hz), 39.5 (d, J = 28.0 Hz), 26.3.

¹⁹F NMR (376 MHz): δ = -157.7 (dd, J = 18.6, 11.5 Hz).

LRMS (EI): m/z = 205 (25) [M]⁺, 165 (11), 164 (100), 146 (14).

HRMS (EI): m/z calcd. for C₁₂H₁₂FNO: 205.0903; found: 205.0885.

3-Benzyl-3-fluoro-1-methylindolin-2-one (343b)

Yield: 71 mg (92%); Pale red solid; mp 110–112 °C (hexane/EtOAc).

¹H NMR (400 MHz): δ = 7.32–7.27 (m, 1H), 7.19–7.15 (m, 3H), 7.06–7.04 (m, 2H), 7.00–6.97 (m, 2H), 6.69 (d, J = 7.8 Hz, 1H), 3.57 (dd, J = 13.4, 10.4 Hz, 1H), 3.20 (dd, J = 22.5, 13.4 Hz, 1H), 3.05 (s, 3H).

¹³C NMR (101 MHz): δ = 172.8 (d, J = 21.2 Hz), 143.9 (d, J = 5.4 Hz), 132.8 (d, J = 7.0 Hz), 131.1 (d, J = 2.6 Hz), 130.6, 128.1, 127.3, 125.5,

125.2 (d, $J = 19.1$ Hz), 122.9 (d, $J = 2.7$ Hz), 108.6, 93.3 (d, $J = 190.7$ Hz), 41.3 (d, $J = 27.7$ Hz), 26.2.

^{19}F NMR (376 MHz): $\delta = -157.1$ (dd, $J = 22.4, 10.4$ Hz).

LRMS (EI): $m/z = 255$ (24) $[\text{M}]^+$, 164 (27), 146 (13), 91 (100), 65 (10).

HRMS (EI): m/z calcd. for $\text{C}_{16}\text{H}_{14}\text{FNO}$: 255.1059; found: 255.1060.

3-Fluoro-1-methyl-3-(prop-2-yn-1-yl)indolin-2-one (343d)

Yield: 36 mg (59%); Pale brown solid; mp 84–85 °C (hexane/EtOAc).

^1H NMR (300 MHz): $\delta = 7.65$ (dt, $J = 7.4, 1.4$ Hz, 1H), 7.43 (tt, $J = 7.8, 1.5$ Hz, 1H), 7.17–7.12 (m, 1H), 6.87 (d, $J = 7.9$ Hz, 1H), 3.23–3.14 (m, 4H), 2.87 (ddd, $J = 20.5, 16.6, 2.7$ Hz, 1H), 2.00 (t, $J = 2.7$ Hz, 1H).

^{13}C NMR (75 MHz): $\delta = 171.7$ (d, $J = 20.9$ Hz), 144.3 (d, $J = 5.1$ Hz), 131.7 (d, $J = 2.8$ Hz), 125.2, 124.9 (d, $J = 18.6$ Hz), 123.5 (d, $J = 2.4$ Hz), 108.8, 90.5 (d, $J = 191.7$ Hz), 76.2 (d, $J = 11.3$ Hz), 71.9 (d, $J = 1.1$ Hz), 26.4, 25.8 (d, $J = 33.7$ Hz)

^{19}F NMR (376 MHz): $\delta = -157.9$ (dd, $J = 20.5, 8.2$ Hz).

LRMS (EI): $m/z = 204$ (15), 203 (100) $[\text{M}]^+$, 183 (11), 165 (23), 164 (100), 154 (11), 136 (20), 109 (19).

HRMS (EI): m/z calcd. for $\text{C}_{12}\text{H}_{10}\text{FNO}$: 203.0746; found: 203.0746.

3-Cinnamyl-3-fluoro-1-methylindolin-2-one (343f)

Yield: 71 mg (85%); pale orange wax.

^1H NMR (300 MHz): $\delta = 7.44$ – 7.33 (m, 2H), 7.29– 7.18 (m, 3H), 7.09 (t, $J = 7.6$ Hz, 1H), 6.82 (d, $J = 7.8$ Hz, 1H), 6.46 (d, $J = 15.8$ Hz, 1H), 6.02 (ddd, $J = 15.8, 8.6, 6.3$ Hz, 1H), 3.22– 3.09 (m, 4H), 2.95– 2.79 (m, 1H).

^{13}C NMR (75 MHz): $\delta = 172.65$ (d, $J = 21.2$ Hz), 144.04 (d, $J = 5.3$ Hz), 136.89, 135.77, 131.25 (d, $J = 2.6$ Hz), 128.61, 127.73, 126.38, 125.67 (d, $J = 18.8$ Hz), 125.16, 123.23 (d, $J = 2.4$ Hz), 120.34 (d, $J = 7.9$ Hz), 108.80, 92.61 (d, $J = 189.3$ Hz), 38.71 (d, $J = 28.1$ Hz), 26.34.

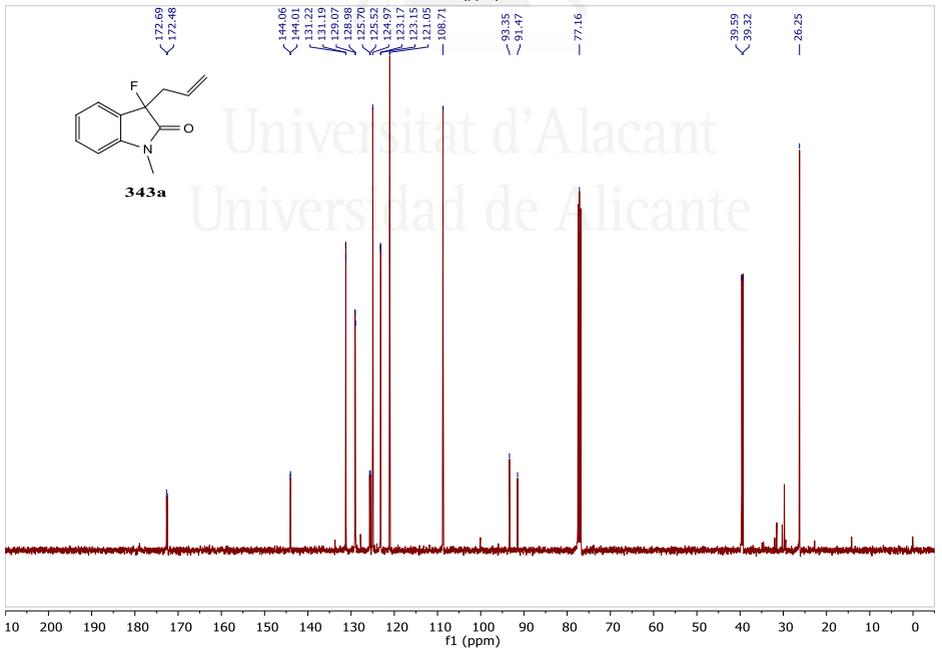
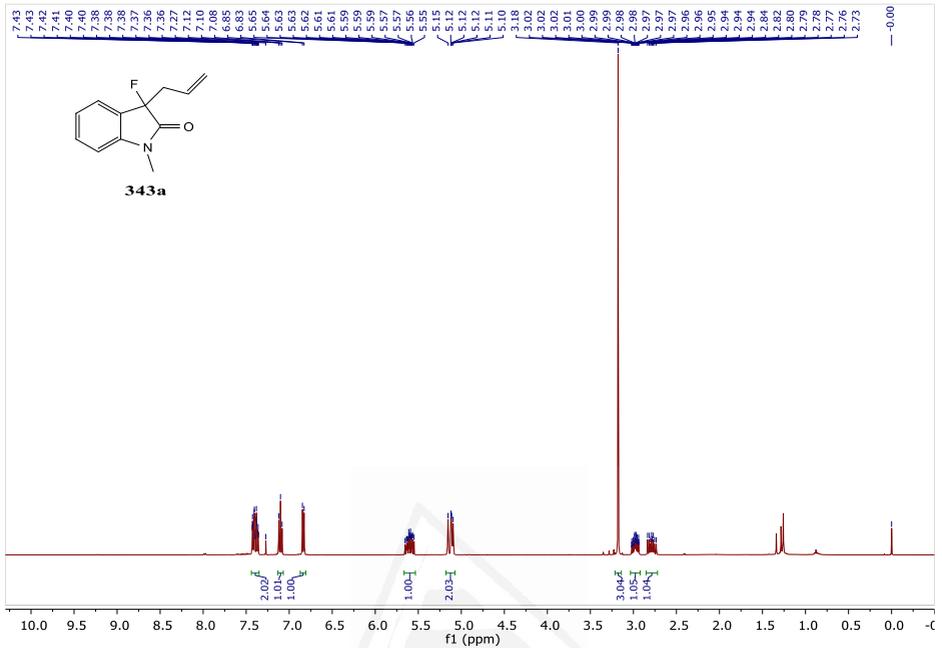
^{19}F NMR (376 MHz): $\delta = -157.5$ (dd, $J = 20.7, 11.1$ Hz).

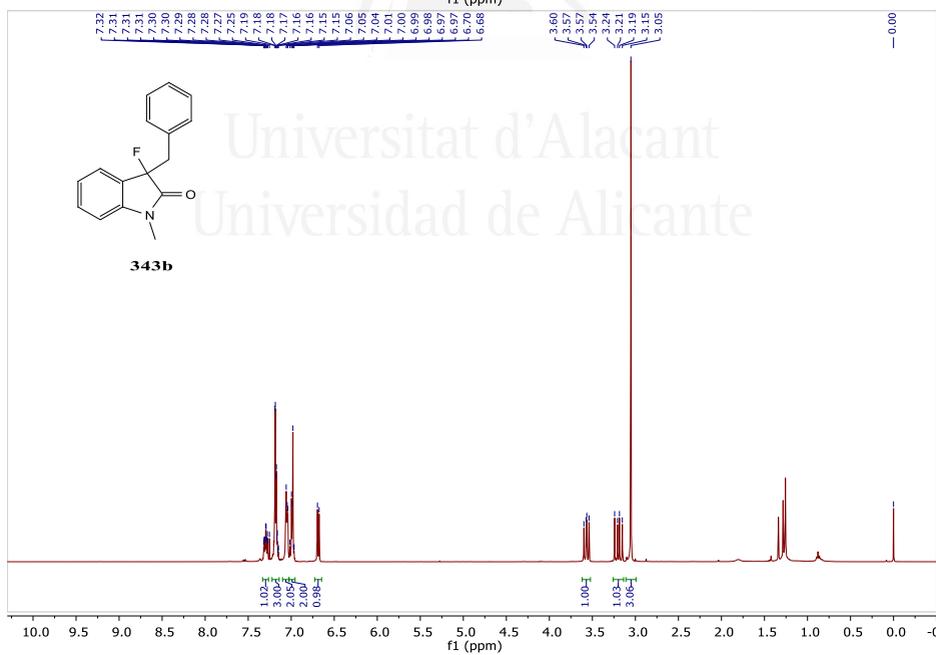
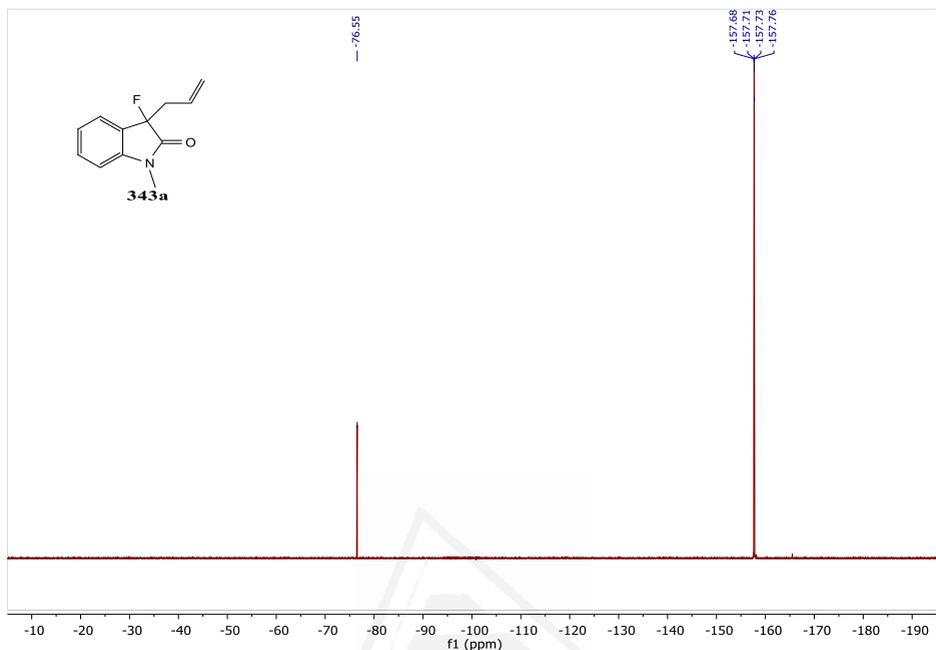
LRMS (EI): $m/z = 281$ (18) $[\text{M}]^+$, 261 (21), 260 (15), 118 (11), 117 (100), 115 (24).

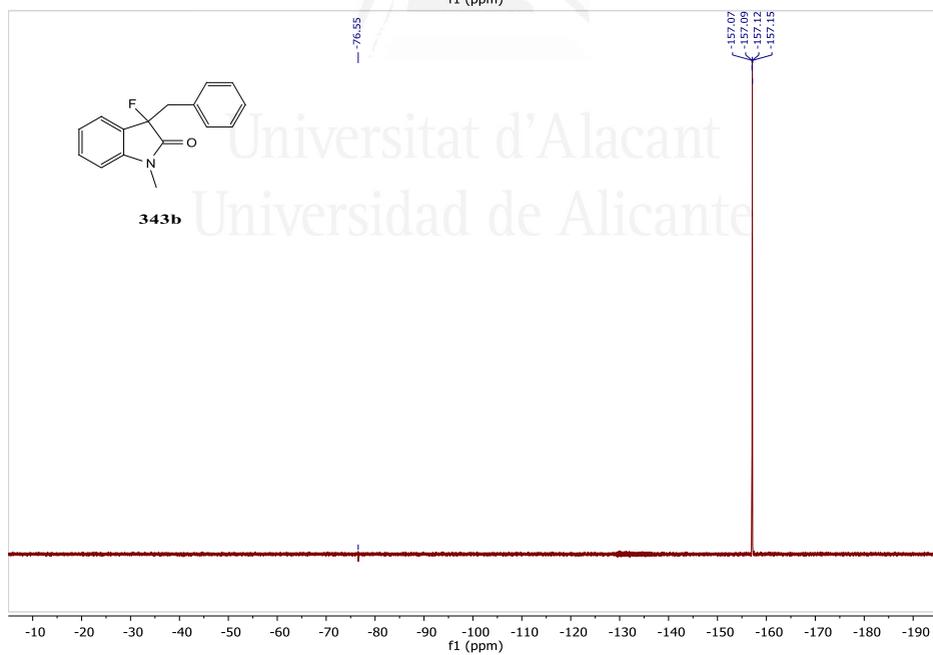
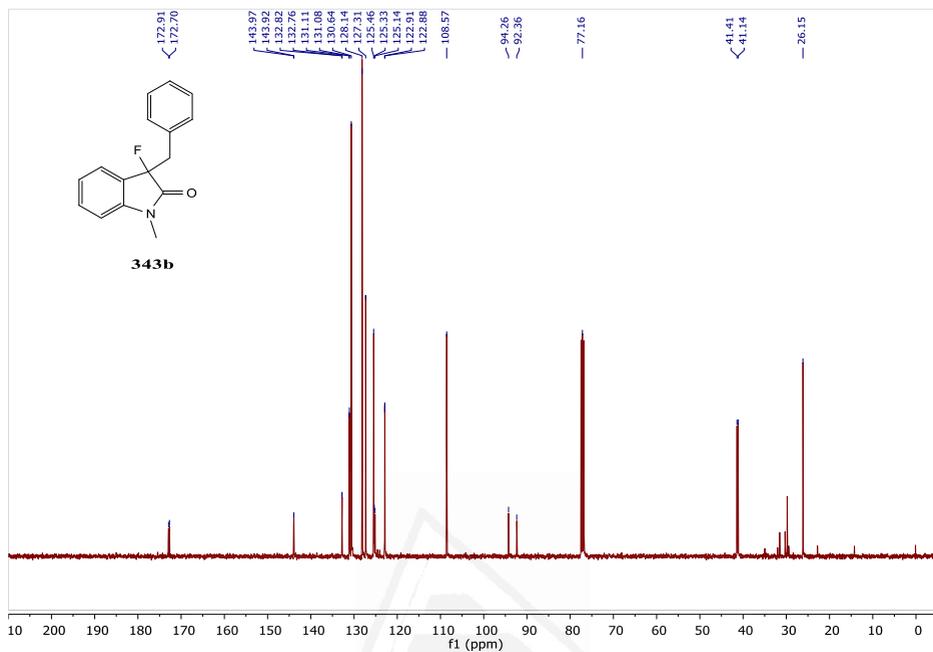
HRMS (EI): m/z calcd. for $\text{C}_{18}\text{H}_{16}\text{FNO}$: 281.1216; found: 281.1205.

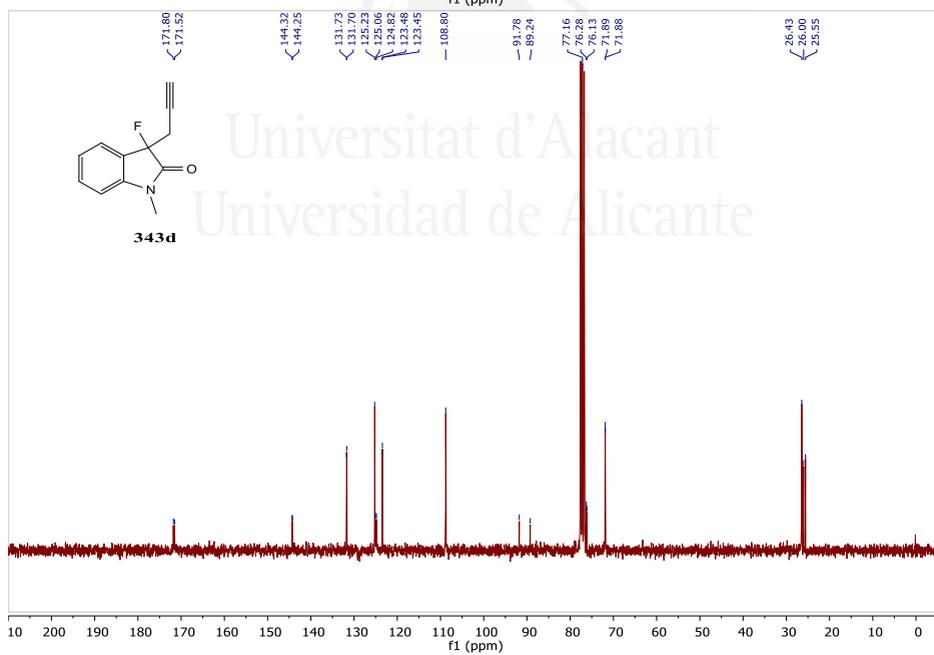
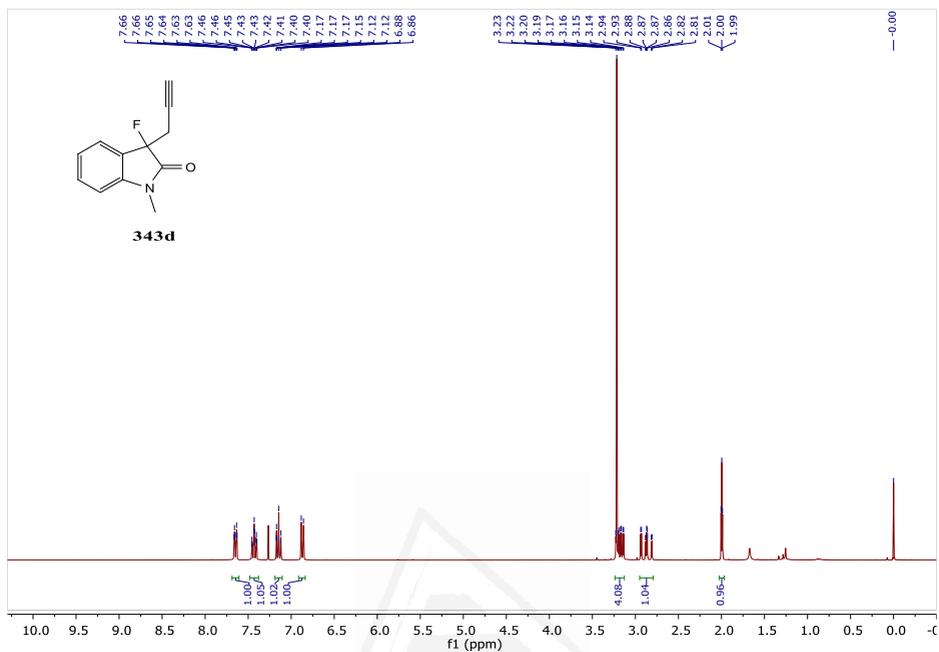


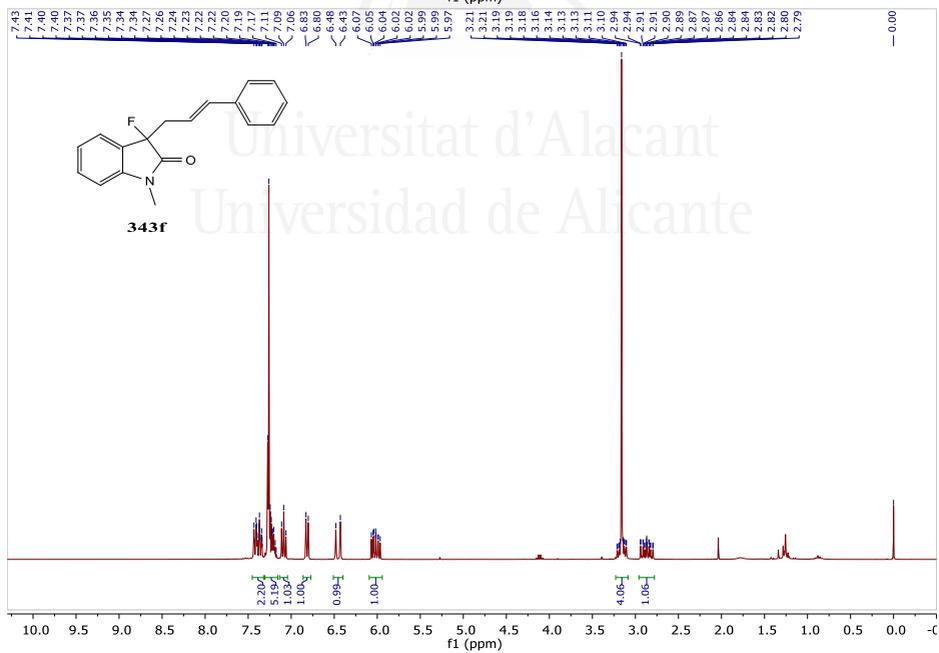
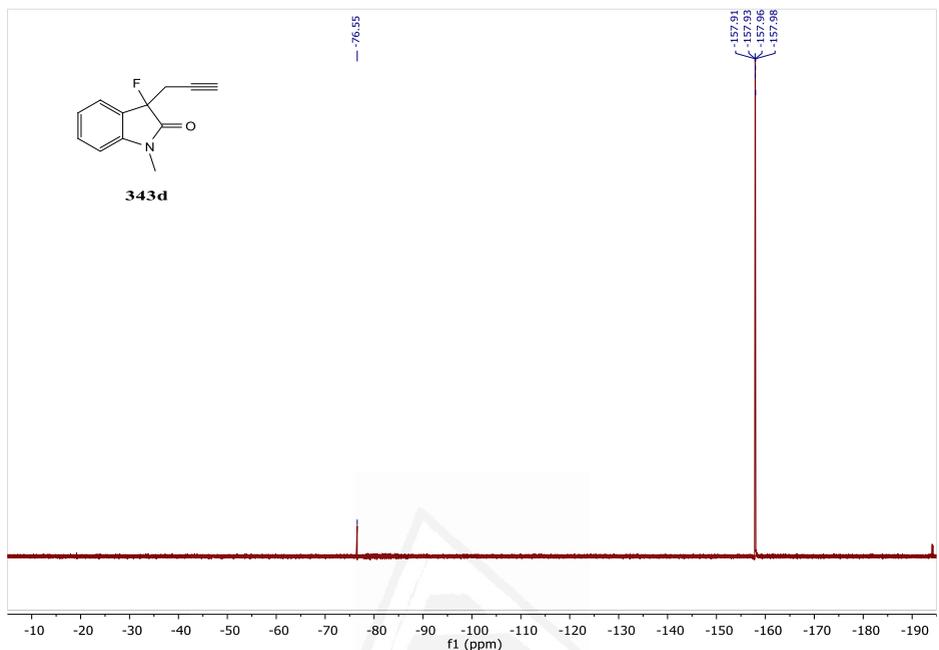
Universitat d'Alacant
Universidad de Alicante

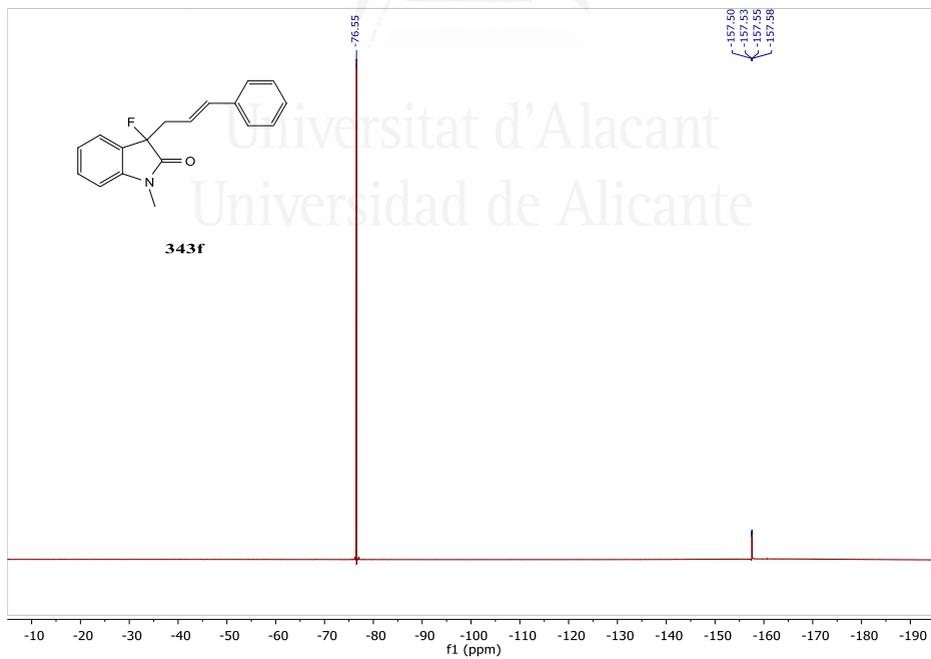
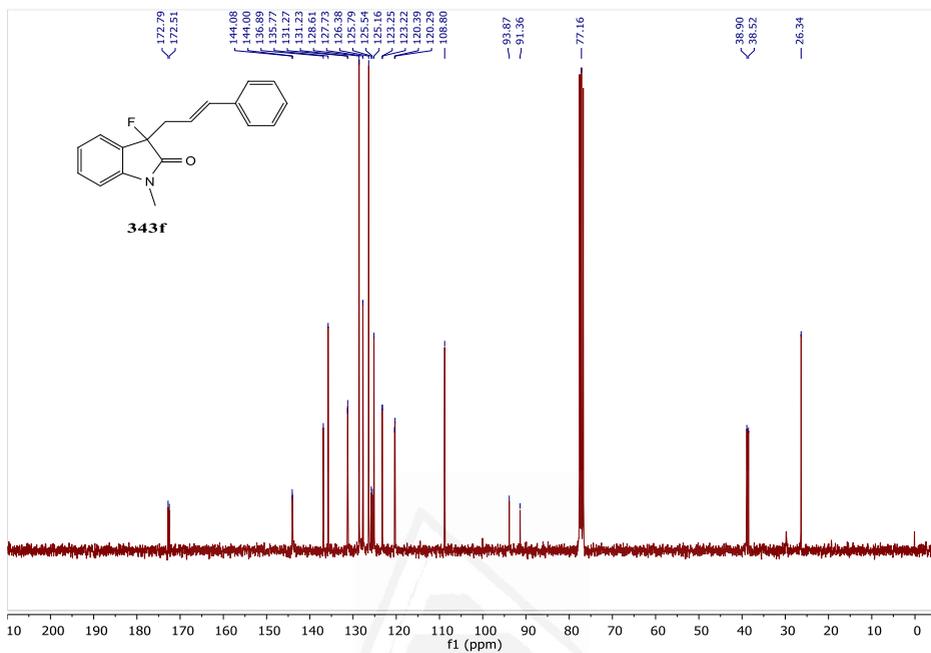












CHAPTER 4:
PHOTOCATALYTIC
RADICAL ALKYLATION
OF ELECTROPHILIC
OLEFINS BY BENZYLIC AND
ALKYLIC ZINC-SULFINATES

Universitat d'Alacant
Universidad de Alicante

CHAPTER 4

Introduction

Catalysis is an important field in organic chemistry. The central goal is the development of new methodologies for activation of small molecules. In some cases, catalytic processes enable the formation of new bonds that only can be achieved using specific catalysts. Recently, one catalytic approach that have received much attention in the last years is visible light photoredox catalysis. The general fundamentals of this approach are the photoexcitation under visible light of metal complexes or organic dyes to carry out single-electron-transfer (SET) processes with organic molecules, which are readily to react with other substrates.

There are multiple visible light photocatalyst, but nowadays the most commonly employed are the pyridyl complexes of iridium and ruthenium as for example tris(2,2'-bipyridine)ruthenium(II) or $[\text{Ru}(\text{bpy})_3]^{2+}$ **344** and [4,4'-bis(1,1-dimethylethyl)-2,2'-bipyridine-N1,N1']bis[2-(2-pyridinyl-N)phenyl-C]iridium(III) or $[\text{Ir}(\text{dtbbpy})(\text{ppy})_2]^+$ **345** (Figure 30).

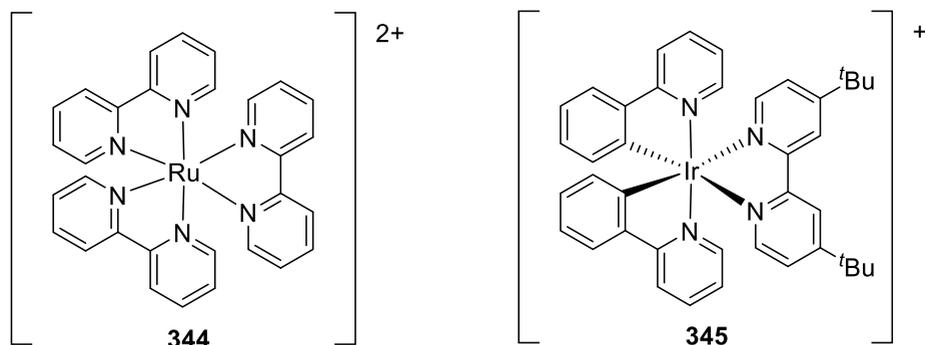


Figure 30. Commonly employed photocatalysts.

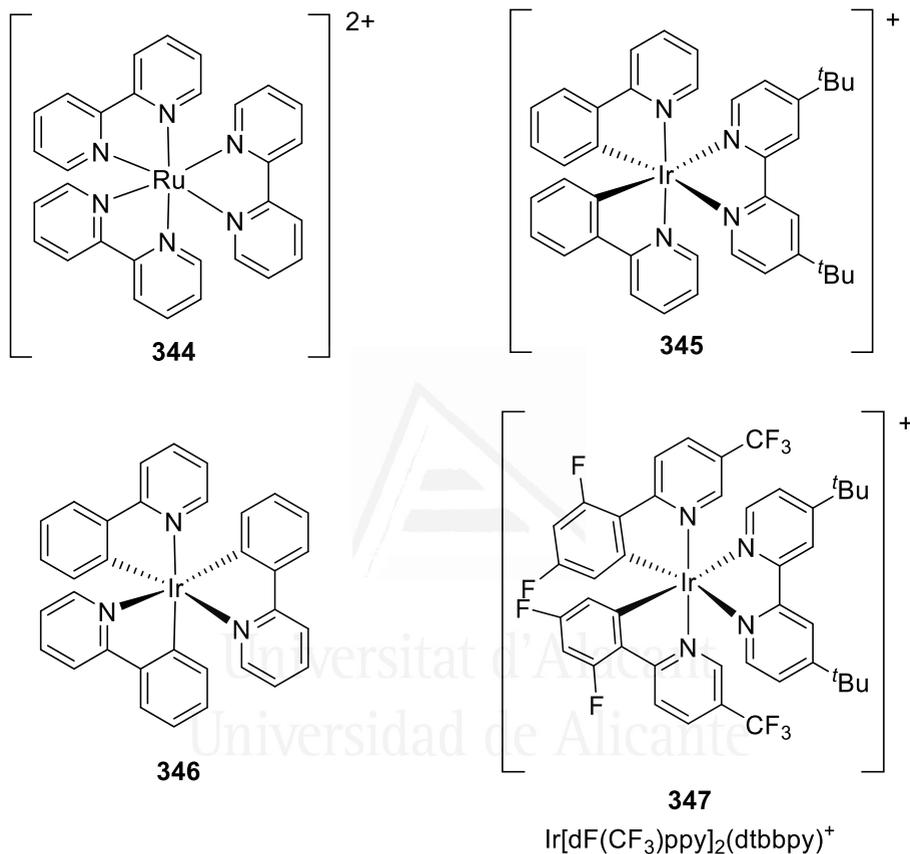
These metal complexes have the property that can absorb light in the visible region of the spectrum to give stable and long-lived photoexcited states. The lifetime of the excited species (τ) is enough long to allow bimolecular electron-transfer processes in competition with deactivation processes. For complex **344**, $\tau = 1100$ ns and for **345** decreases to $\tau = 560$ ns.¹⁶⁴

While these complexes are poor single-electron oxidants and reductants when they are in the ground state, they are very potent single-electron-transfer reagents upon irradiation with visible light due to the excitation of one electron affording the excited species. The tuning of the complexes using different ligands is an important tool to change the photochemical properties of the complexes obtaining more efficient photocatalysts (Table 9).^{164,165} Different ligands bonded to the Ir(III) (complexes **345** and **347**) provides significantly different oxidizing properties ($E(M^*/M) = 0.66$ and 1.21 V, respectively) and complex **347** is stronger oxidant than **345**. The lifetime of excited species of **347** is 4 times higher than the **345**. Furthermore, a very important property is the quantum yield (Φ). This parameter indicates the number of times that a radiation-induced process occurs per photon which is absorbed by the photocatalyst. Comparing **345** and **347**, it is possible to see that only 9% of the absorbed photons trigger a photochemical process while in **347** is the 68%. In terms of

efficiency, **347** has better photochemical properties. Regarding the absorption wavelength, there is not a big difference: both catalysts can absorb the radiation in the visible light region.



Universitat d'Alacant
Universidad de Alicante

Table 9. Photochemical properties of different Iridium(III) and Ruthenium(II) photocatalysts.

	344	345	346	347
$E (M^+/M^*) (V)$	-0.81	-0.96	-1.73	-0.89
$E (M^*/M) (V)$	+0.77	+0.66	+0.31	+1.21
$\tau (ns)$	1100	560	1900	2300
$\lambda_{\text{abs}} (nm)$	452	410	375	380
$\lambda_{\text{em}} (nm)$	652	581	518	470
Φ_{em}	0.095	0.094	0.38	0.68

Using the same metal, they can be classified in two major ways as homoleptic (all the ligands that form the complex are the same) or heteroleptic (the ligands are different). The major significant difference is the location of the HOMO and LUMO in the excited state.

Regarding to the molecular orbitals processes of the photon absorption by a photocatalyst and the generation of the excited state, it can be simplified as depicted in the following Figure 31.

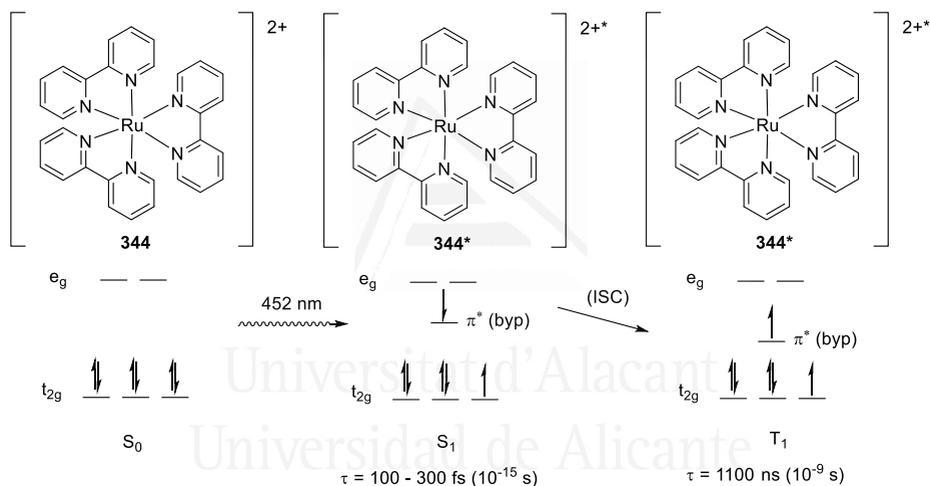


Figure 31. Simplified molecular orbital depiction of excitation of complex **344**.

Thus, at the beginning, when a photon with appropriate wavelength hits the ground state singlet (S_0) Ru(II) complex, an electron of the HOMO can be promoted to the LUMO, in this case the antibonding orbital of the bipyridine ligand. At this point, a singlet specie of **344** is formed (S_1) with a very short lifetime (between 100 and 300 femtoseconds).¹⁶⁶ At this point, different situations can occur. On the one hand, S_1 excited specie can suffer an inter-system crossing (ISC) to form the triplet T_1 with a much higher lifetime (1100

nanoseconds). This species is able to trigger the SET process by interaction with small organic molecules and is called intermolecular quenching (k_q). The whole process commented above is necessary to occur to afford T_1 species because quantum mechanics forbid transformations where the energy level and the spin change at the same time. For this reason, direct excitation from S_0 to T_1 is not allowed. On the other hand, multiple relaxation processes can also occur to return from the excited species (S_1 and T_1) to ground state singlet (S_0). These deactivation processes, both from S_1 or T_1 can be explained with the Jablonski diagram (Figure 32).¹⁶⁷

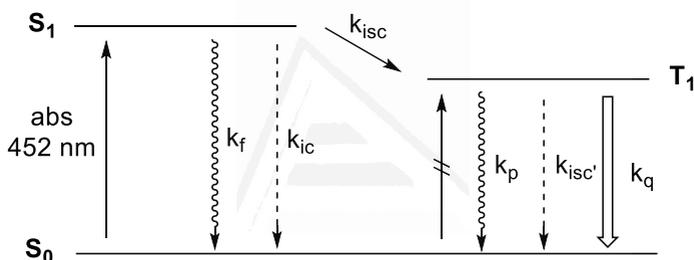


Figure 32. Schematic Jablonski diagram representation.

The relaxation process which can take place from S_1 excited state are fluorescence (k_f) which is the fast emission of photon with the same wavelength as it was absorbed (452 nm for complex **344**). This process is allowed by quantum mechanics. Another deactivation can be the internal conversion (k_{ic}) that consists in a nonradiative de-excitation through bond vibrations losing the corresponding energy as heat. Finally, the photochemical interesting relaxation is the intersystem crossing (k_{isc}) to triplet state (T_1). It is studied that this process is fast in comparison with k_{ic} and k_f because the ratio is $k_{isc} : (k_f + k_{ic}) = 100 : 1$. Also there are different relaxations for triplet excited state, as for example phosphorescence. This process also involves the emission of a photon but in a different way that

fluorescence. In this case, because it is a not quantum allowed process, it is slower than phosphorescence. The wavelength of emission is higher than the one it absorbed (less energetic). Also, an alternate intersystem crossing can occur (k_{isc}), which involves a nonradiative de-excitation through, again, bond vibrations and losing the corresponding energy as heat with a spin inversion. Finally, the interesting relaxation for the photocatalysis is the intermolecular quenching (k_q) which involves a relaxation through a transfer of electron or energy to another molecule.

This intermolecular quenching can be depicted as follows with the cycle for typical bipyridine Ru(II) complex **344** (Figure 33).

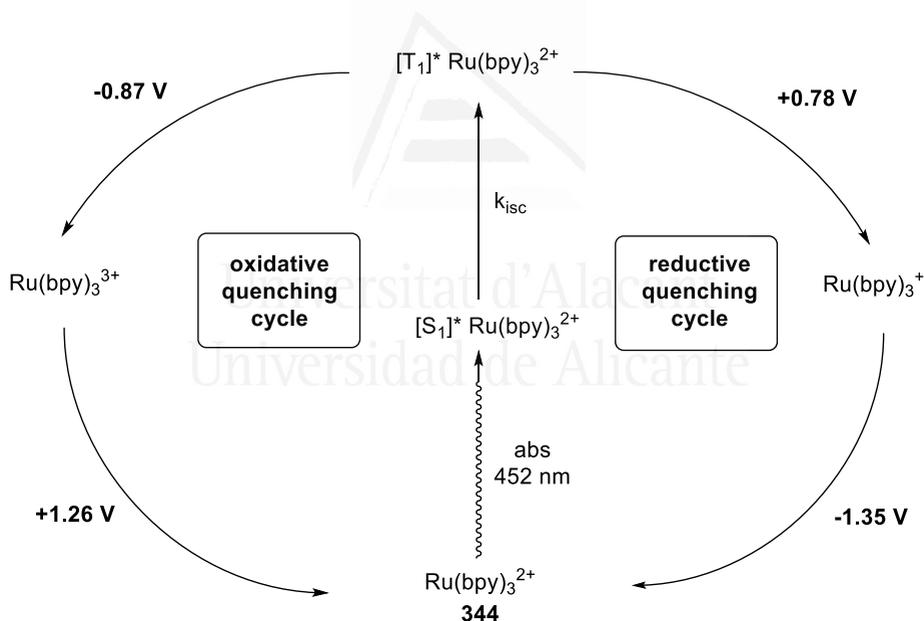
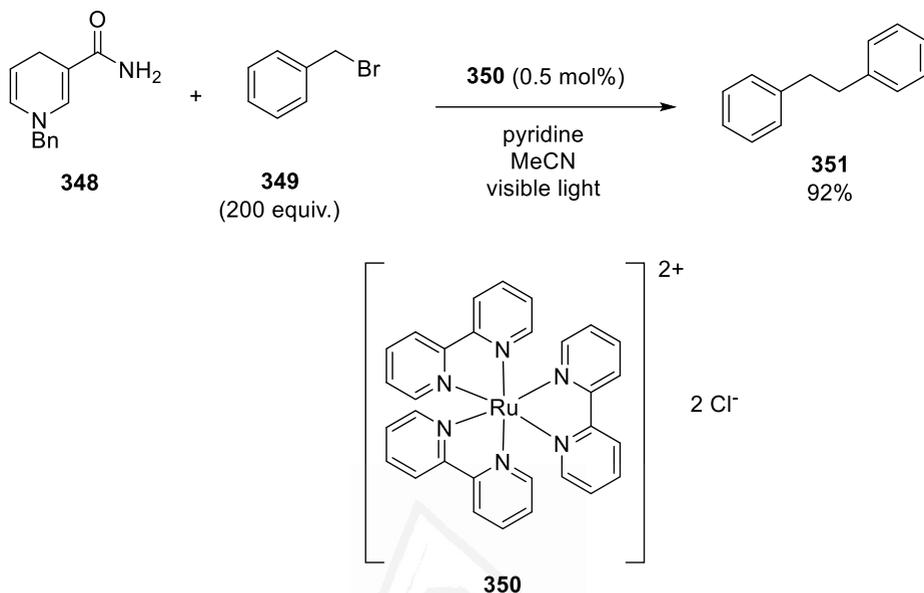


Figure 33. Intermolecular quenching through single electron transfer processes.

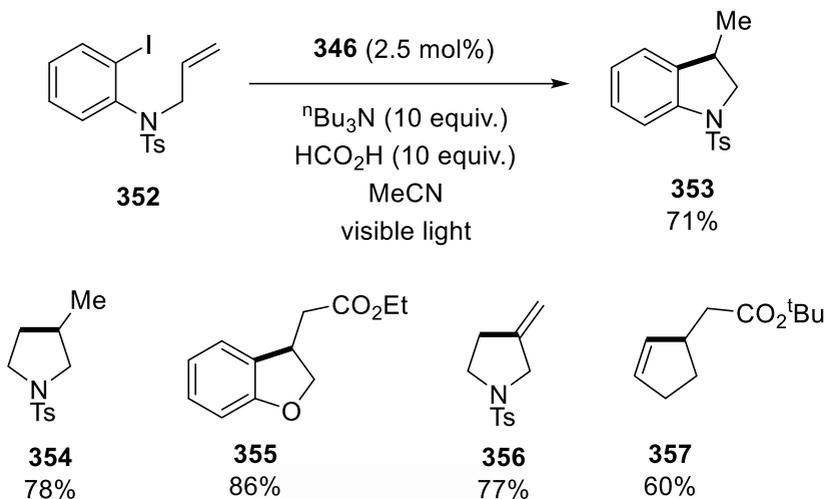
Using this procedure, a lot of methodologies that allows the formation of new bonds have been described. For example, it can be performed net reductive reactions as reduction of electron-poor olefins, reductive dehalogenation, reductive cleavage of sulfonium and sulfonyl groups, radical cyclizations, reductive epoxide and aziridine opening, among others. Also, net reductive oxidations as: oxidative removal of the PMB group, biaryl coupling, generation of iminium ions or azomethine ylide for [3 + 2] cycloadditions. Also, other extensive kind of photochemistry is the redox neutral reactions where can be included, for example, atom transfer radical addition, the very interesting photoredox organocatalysis, radical addition to arenes and other π nucleophiles, reactions of enamine radical cations, radical conjugate addition reactions, α -arylation of amines among others. As is possible to see above, a wide range of chemistry can be performed with this interesting procedure. Some examples will be displayed for demonstrating the power of this methodology.

In 1984, Tanaka *et al.* performed the reductive dimerization of benzyl bromide using bipyridine ruthenium(II) complex and **348** for regenerate the catalyst affording 1,2-diphenylethane (Scheme 67).¹⁶⁸



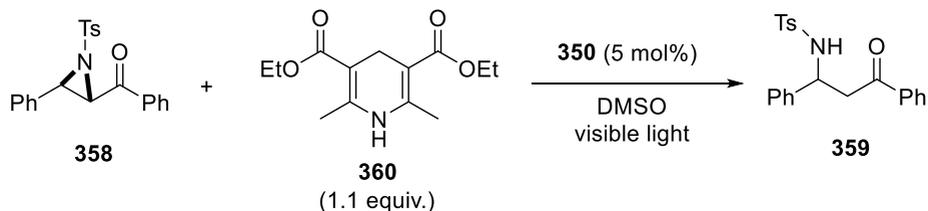
Scheme 66. Photocatalytic dimerization of benzyl bromide.

Also, a radical cyclization of alkyl, alkenyl and aryl iodides was done by Stephenson and co-workers promoted by strongly reductant $\text{Ir}(\text{ppy})_3$ **346**. It is worth to note that alkyl iodides are less activated substrates but by means of photocatalysis is possible to carry out this cyclization (Scheme 67).¹⁶⁹



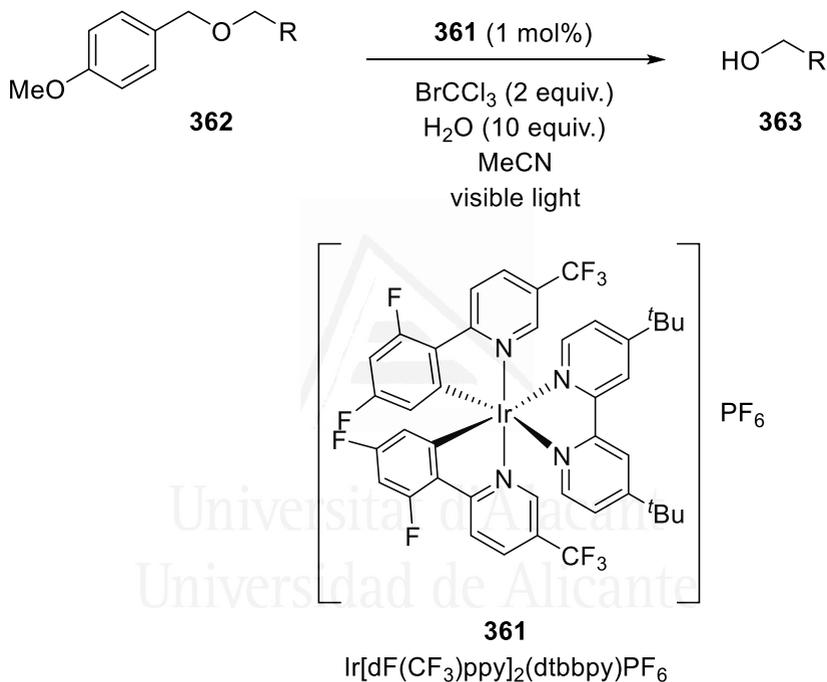
Scheme 66. Photoinduced radical cyclization of iodides.

The reductive opening of α -ketoaziridines **358** provides the β -aminoketones **359** by the research group of Ollivier. In this case the Ru(II) **350** complex and stoichiometric amount of Hantzsch ester **360** as reductant were used to promote the reaction (Scheme 67).¹⁷⁰



Scheme 67. Reductive opening of aziridines.

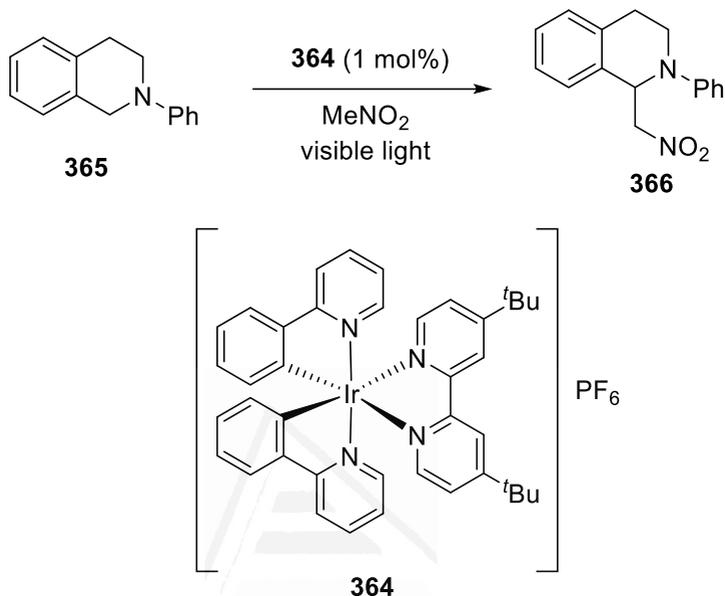
Again, Stephenson *et al.* developed an oxidative removal of *para*-methoxybenzyl group which can be performed using the **347** hexafluorophosphate salt, **361**. This methodology is interesting for deprotection of **362** derivatives recovering the corresponding alcohols **363** (Scheme 68).¹⁷¹



Scheme 68. Oxidative deprotection of *para*-methoxybenzyl ethers.

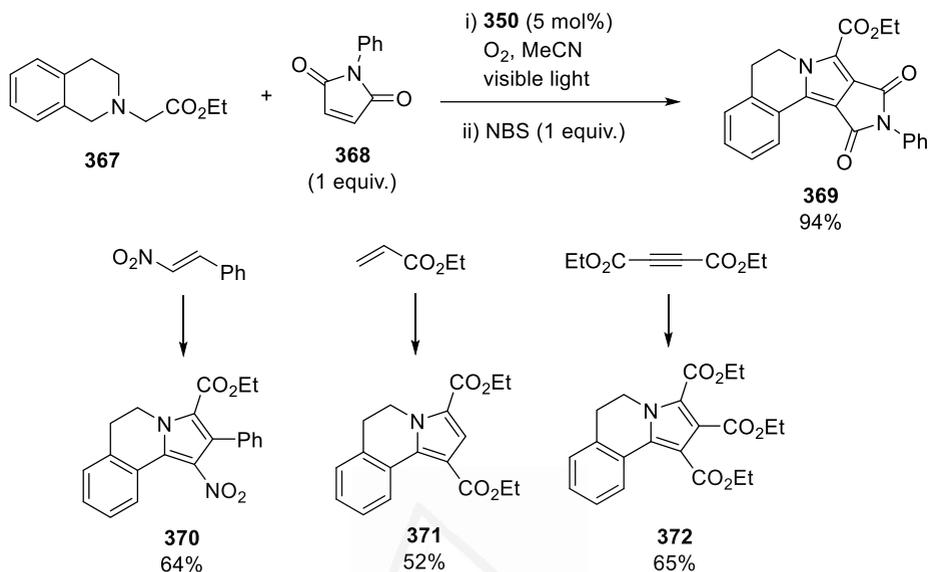
Furthermore, the same research group achieved a photoredox aza-Henry reaction through the addition of nitromethane to an iminium intermediate catalytically generated by **364**. The catalyst is able to oxidize **365** to a radical ion. The authors propose that the Ir(II) intermediate reduces the dioxygen giving a superoxide which complete the catalytic cycle. This superoxide may abstract a hydrogen at the α -position of the amine to generate the iminium

intermediate. After the addition of nitromethane, compound **366** was formed in 92% yield (Scheme 69).¹⁷²



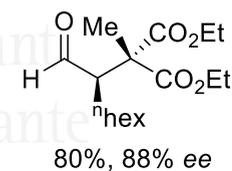
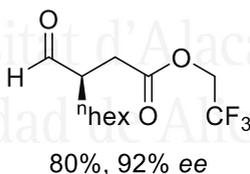
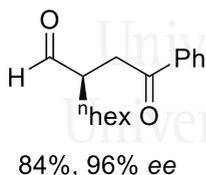
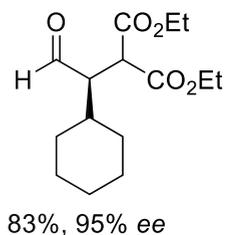
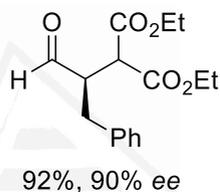
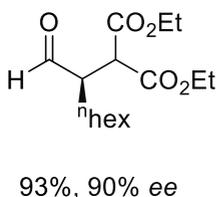
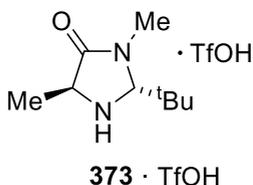
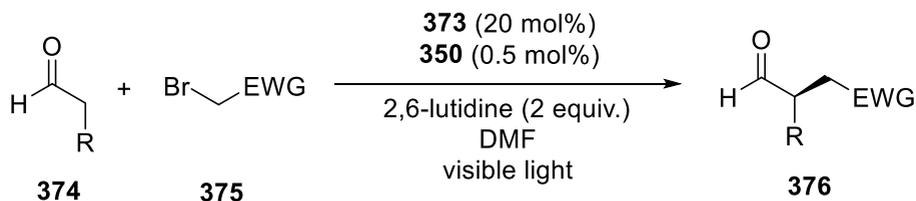
Scheme 69. Photocatalyzed aza-Henry reaction through an iminium intermediate.

A photocatalyzed azomethine ylide [3 + 2] cycloaddition was also reported by Xiao *et al.* also generating iminium ions. The tetrahydroisoquinoline **367** and the Michael acceptor *N*-phenylmaleimide **368** afforded, after an oxidative aromatization step with NBS, polycyclic derivative as **369** in a 94% yield. Nitroalkenes, acrylates and alkynes were used as dipolarophiles to synthesize **370**, **371** and **372** in 64%, 52% and 65% yields, respectively. In this case, the photocatalyst used was Ru(II) chloride **350** (Scheme 70).¹⁷³



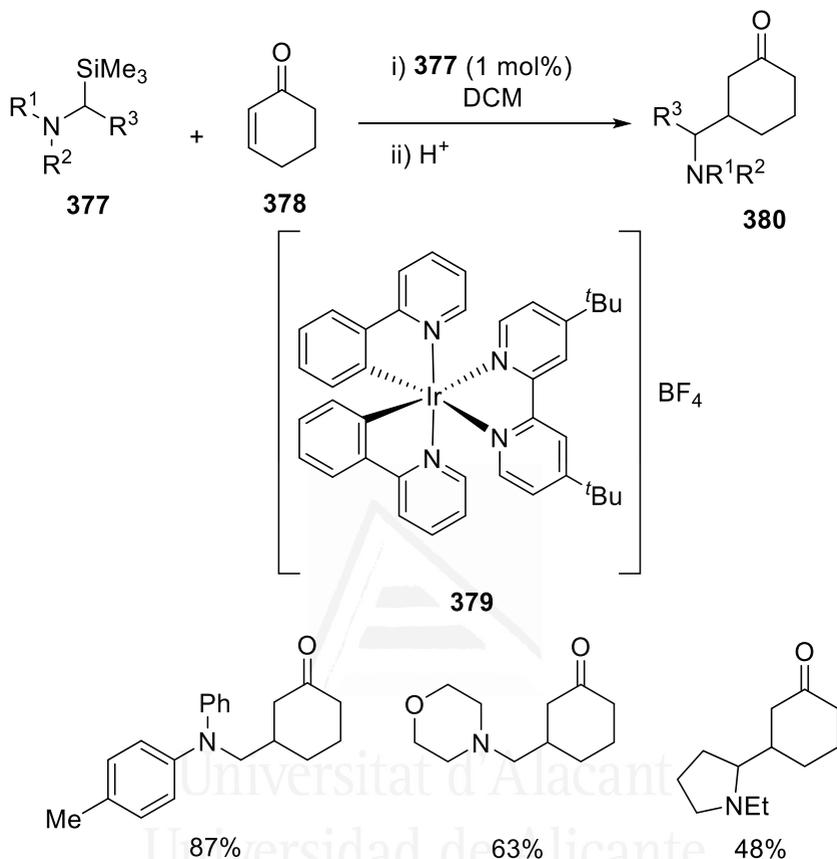
Scheme 70. Photocatalyzed [3 + 2] cycloaddition of azomethine ylides.

A different approach of photocatalysis is the enantioselective version. In 2008, MacMillan and co-workers reported the fusion of photoredox catalysis with enamine organocatalysis to carry out the enantioselective α -alkylation of aldehydes. A dual catalyst system that consists in a bipyridine Ru(II) complex **350** as photocatalyst and imidazolidinone **373** as chiral organocatalysts were developed to carry out the alkylation of aldehydes **374** with different electron-deficient alkyl bromides **375** to afford products **376** in good yields and high enantiomeric excesses (Scheme 71).¹⁷⁴



Scheme 71. Enantioselective α -alkylation of aldehydes through photoredox organocatalysis.

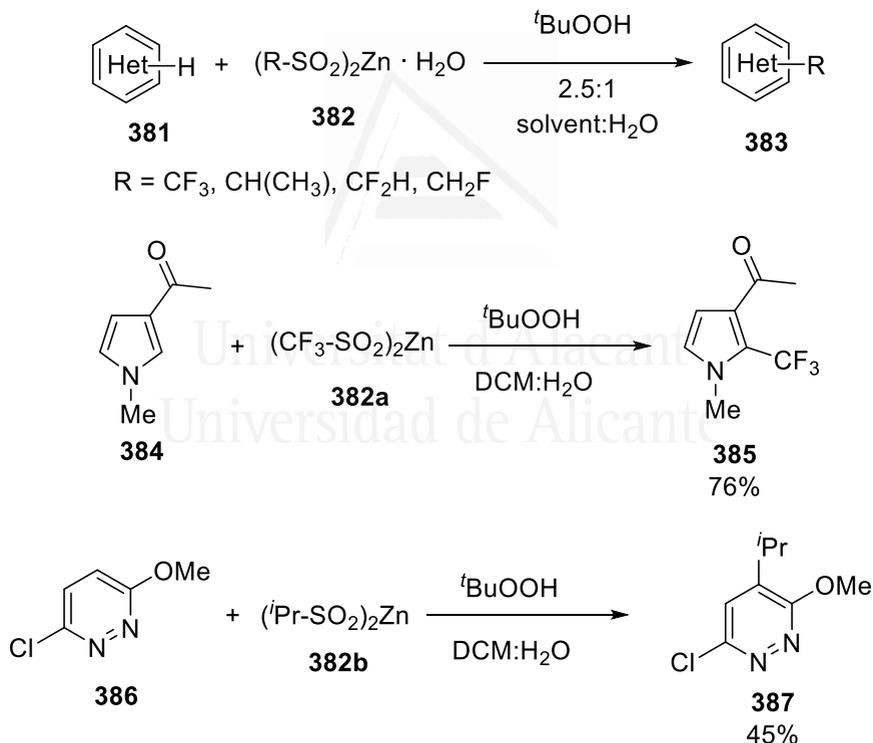
Conjugate additions with Michael acceptors have been developed with different photocatalysts. For example, conjugate additions of α -amino radicals formed from α -silylamines **377** through a α -desilylation. These radical intermediates react with α,β -unsaturated compounds as cyclohexenone **378** affording products **380**. In this case, Ir(III) **379** is used as photocatalyst (Scheme 72).¹⁷⁵



Scheme 72. Photoredox conjugate addition of α -silylamines to cyclohexenone.

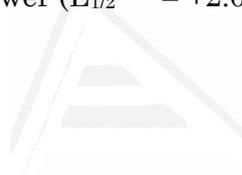
Another established radical but non-photocatalytic approach for the alkylation of different substrates is the use of sulfonates. These compounds can be synthesized easily in kilogram scale and some of them are stable under ambient conditions.¹⁷⁶ Under oxidative conditions, sulfonates can be used as source of radical species, because the oxidation potentials (versus saturated calomel electrode or SCE) of them are suitable using some oxidizing reagents. In fact,

oxidation potentials of sulfonates are lower than other common radical sources as carboxylates [$E^{\text{red}}_{1/2}(\text{hexanoate}) = + 1.16 \text{ V}$ vs SCE;¹⁷⁷ $E^{\text{red}}_{1/2}(\text{Na}^+ \text{ alkyl sulfonates}) = + 0.45 \text{ V}$],¹⁷⁸ so they are more ready to suffer an oxidation. Generating the non-photocatalytic extrusion of sulfur dioxide SO_2 on sulfonates reagents produced the corresponding aryl or alkyl radical. Baran and co-workers have developed a method for alkylation of different derivatives as heterocyclic compounds **381**, **384** and **386** using sodium and zinc bis(alkylsulfinate) reagents **382** (Scheme 73).¹⁷⁹



Scheme 73. Zinc sulfonates in radical alkylations.

Regarding photoredox catalysis, the sulfonylation of alkenes with aryl¹⁸⁰ and alkyl¹⁷⁸ sulfinates has been developed by König and coworkers through the generation of radical species by oxidation mediated by a photocatalyst. Although these procedures are described, the use of benzyl sulfinates have not yet investigated to perform the photocatalytic radical alkylation of electron-poor olefins through conjugate addition (Giese reaction). Different investigations¹⁸¹ suggest that the use of benzyl radicals to carry out conjugate addition is difficult to accomplish, probably due the large resonance stabilization of these radicals which results in the formation of bibenzyl radicals as **351**. Recently, conjugate addition of benzylic radicals was reported¹⁸² generating benzylic radical cations using photocatalyst mesityl-10-methylacridinium perchlorate that has a strong oxidizing power ($E_{1/2}^{\text{red}*} = +2.06 \text{ V vs SCE in MeCN}$).



Objectives

According to the precedent results and with the experience of the research group of Prof. Cozzi in the photoredox catalytic reactions, we decided to focus on:

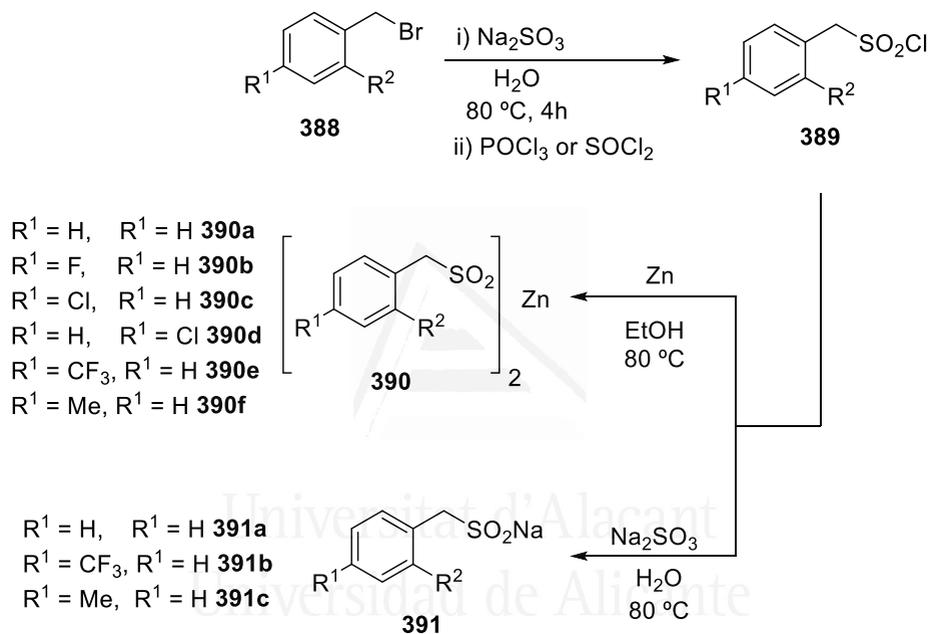
- To study of the photoredox alkylation and difficult benzylation of electrophilic alkenes using benzylic and alkylic sulfinates and commercially available photocatalysts under visible light irradiation.



Universitat d'Alacant
Universidad de Alicante

Results and discussion

Initially, sodium and zinc sulfonates derivatives were synthesized starting from readily available benzyl bromides (Scheme 74).

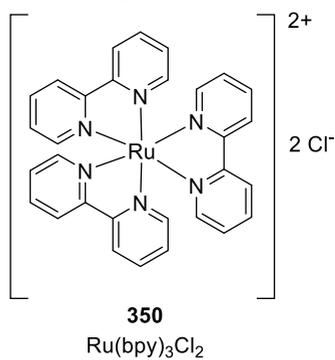
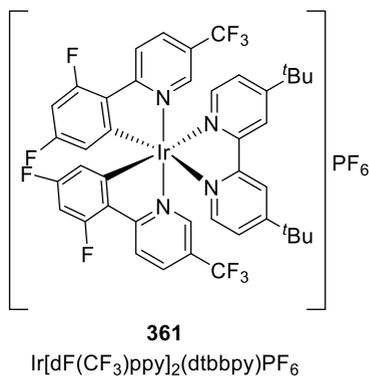
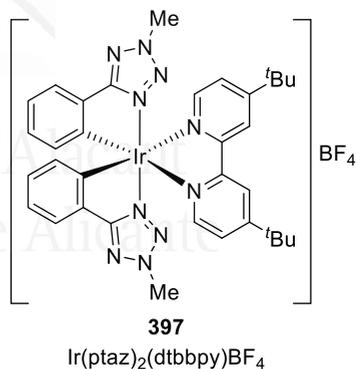
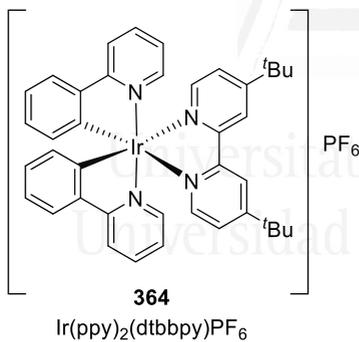
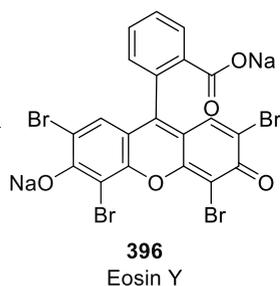
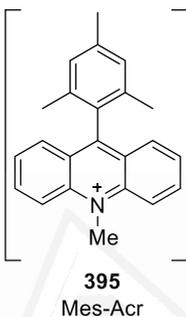
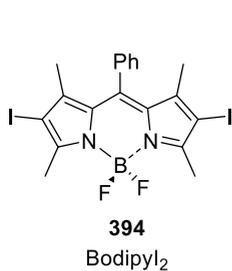
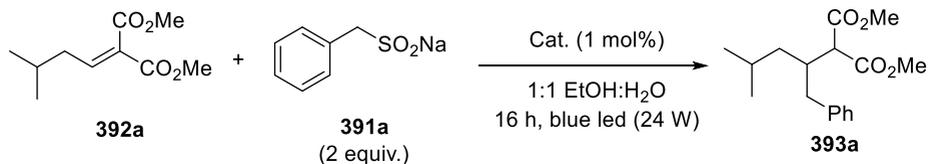


Scheme 74. Synthesis of benzylic sodium and zinc sulfonates.

The procedure to prepare **390** and **391** started from a two-step protocol. The sulfonyl chlorides **389** were obtained by reaction with Na_2SO_3 and later by treatment with POCl_3 or SOCl_2 as chlorine source. Posterior reduction of derivatives **389** afforded the desired products. For zinc derivatives **390**, the reduction was performed using previously activated $\text{Zn}(0)$. On the other hand, sodium sulfonates were prepared by reduction with sodium sulfite.

With the starting sulfinates in hand, the electron-poor alkene **392** was chosen as model alkene and the reaction with benzyl sodium sulfinate **391a** was assayed in the presence of different catalysts (Table 10). When organic photocatalysts BodipyI₂ **394** (Table 10, entry 1) and 9-mesityl-10-methylacridinium tetrafluoroborate **395** (Table 10, entry 2) were assayed under 24 W blue led light irradiation, no product was observed. Using eosin Y **396** (Table 10, entry 3) with green LED irradiation, only traces of product could be detected even photoactive molecules **395**¹⁸³ and **396**¹⁷⁸ have appropriate oxidative potential for oxidize the sulfinate. Switching to Ir(III) complex photocatalysts **364** and **397** (Table 10, entries 4 and 5, respectively), again under blue light, 0% and traces of product were observed. On the other hand, when MacMillan photocatalyst **361** was used (Table 10, entry 6), an excellent 96% conversion of **393a** was achieved. This catalyst that have an excellent photochemical properties when absorbs visible light forming $^*Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ ($E_{1/2}^{*III/II} = +1.21$ V vs SCE), is suitable for oxidize the sodium sulfinates ($E_{red}[RSO_2^-/RSO_2] \approx +0.45$ V vs SCE). Later, the generated reduced specie $Ir[dF(CF_3)ppy]_2(dtbbpy)$ by the oxidative quenching is also a strong reductant ($E_{1/2}^{III/II} = -1.37$ V vs SCE), and after its reaction with the product of the conjugate addition, the photocatalyst is regenerated. Finally, common bipyridine Ru(II) complex **350** was also tested and no product was observed (Table 10, entry 7).

Table 10. Photocatalyst optimization for the conjugate addition of the benzyl radical.



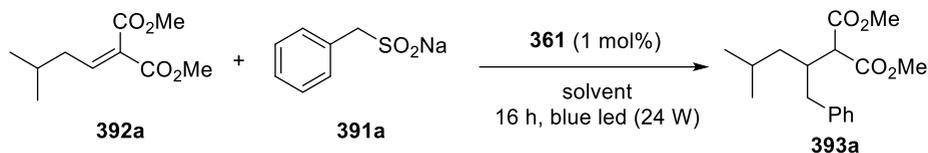
<i>Entry</i>	<i>Photocatalyst</i> ^a	<i>Conversion</i> ^b
<i>1</i>	394	0%
<i>2</i>	395	0%
<i>3</i> ^c	396	Traces
<i>4</i>	364	0
<i>5</i>	397	Traces
<i>6</i>	361	96%
<i>7</i>	350	0%

^a All the reactions were carried out under argon. The reaction mixtures were degassed by three cycles of freeze-pump-thaw. The reactions were performed using (**391a**) (0.2 mmol), (**392a**) (0.1 mmol) in 1 mL of solvent mixture, in the presence of 1 mol% of the catalyst.

^b Determined by ¹H NMR analysis of the crude mixture.

^c Green LEDs were used.

Furthermore, different solvent and equivalents of the sulfinate **391a** were modified to see if there was an improvement of the results (Table 11). When the ethanol proportion of the solvent mixture was increased to 1:4 H₂O:EtOH (Table 11, entry 1), worse conversion was obtained. In contrast, when water proportion was the major one in the mixture, there was not significant change in the conversion (Table 11, entry 2). Using DMSO as organic solvent in 1:1 mixture with water, 92% conversion was obtained (Table 11, entry 3). Next, trifluoroethanol and water mixture was tested and no formation of product was observed (Table 11, entry 4). The same happened when water and *iso*-propanol mixture was used (Table 11, entry 5). Finally, when the amount of sodium sulfinate **391a** was increased to 3 equiv., the conversion was complete and after flash chromatography the product **393a** was isolated in 89% yield.

Table 11. Solvent and equivalents of **391a** optimization.

<i>Entry</i> ^a	Solvent	391a (equiv.)	Conversion ^b
1	1:4 H ₂ O:EtOH	2	69%
2	4:1 H ₂ O:EtOH	2	94%
3	1:1 H ₂ O:DMSO	2	92%
4	1:1 H ₂ O:TFE	2	0%
5	1:1 H ₂ O: <i>i</i> PrOH	2	0%
6	4:1 H ₂ O:EtOH	3	>99% (89%)

^a All the reactions were carried out under argon. The reaction mixtures were degassed by three cycles of freeze-pump-thaw. The reactions were performed using (**392a**) (0.1 mmol) in 1 mL of solvent mixture, in the presence of 1 mol% of the catalyst.

^b Determined by ¹H NMR analysis of the crude mixture. In parenthesis the isolated yield after flash chromatography purification.

Unfortunately, although the optimal conditions were found, the reaction was quite difficult to be reproduced. After the investigation of this lack of reproducibility, it was found that benzylic sodium sulfonates were unstable even when they were stored at low temperature (−20 °C) and under argon atmosphere. For instance, benzyl sodium sulfinate **391a** was prepared and stored in these conditions. Afterwards, ¹H NMR spectra was collected after different times of preparation. We observed the decomposition of sulfinate to the sulfonate with some undetermined impurities (Figure 34).

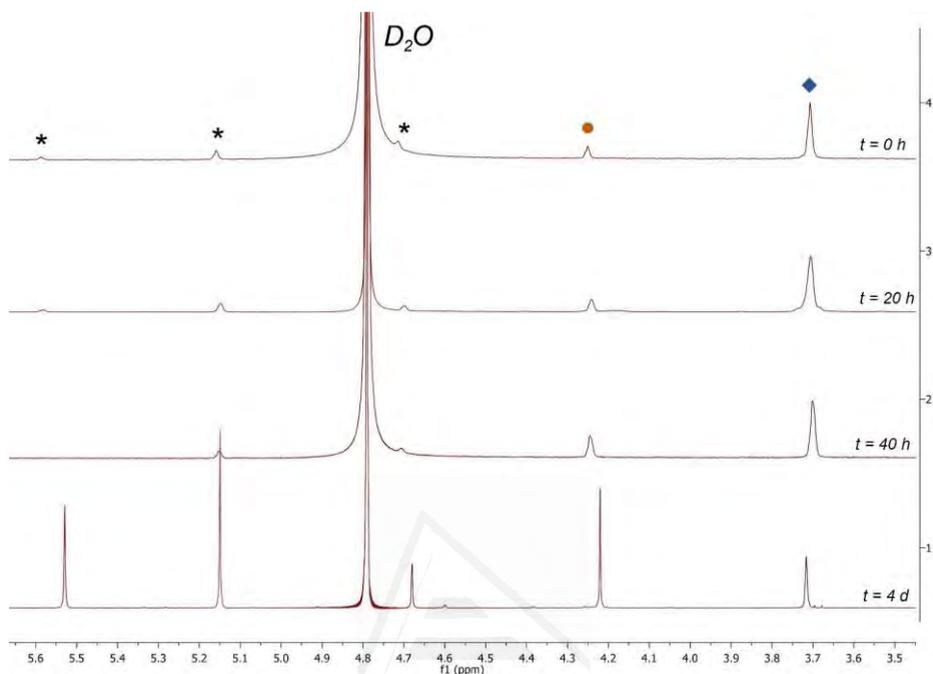
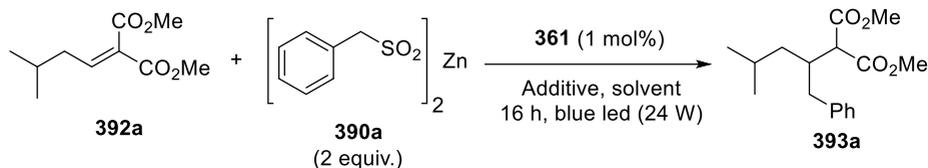


Figure 34. Benzyl sodium sulfinate decomposition at different time of preparation.

In Figure 34 it is possible to see, at 0 h, 20 h, 40 h and 4 d of preparation of **391a** how the amount of the product (diamond blue spot) decreases while the oxidized product (circular orange spot) increases. At this point, it was thought that more stable and less reactive zinc sulfonates should be used. Despite zinc derivatives are more difficult to be oxidized¹⁷⁸ ($E_{\text{red}}[\text{RSO}_2^-/\text{RSO}_2] \approx +0.9 \text{ V vs SCE}$) it was proved that they were suitable for the photochemical reaction (Table 12).

In these cases, water was necessary in order to solubilize the zinc sulfinate. Accordingly, water miscible cosolvents such as MeCN (Table 12, entry 1), DMF (Table 12, entry 2), TFE (Table 12, entry 3) and DME (Table 12, entry 4) were tested, but low conversions were obtained. Instead, DMSO (Table 12, entry 5) showed good 74% conversion but lower compared when was used with sodium

sulfinate. Different proportions of water and ethanol mixture were tested and was demonstrated that 1:4 H₂O:EtOH mixture (Table 12, entry 6) gave low conversion (27%) but 4:1 H₂O:EtOH gave 72% (Table 12, entry 7) and 1:1 H₂O:EtOH mixture afforded the best result, a 77% (Table 12, entry 8). After flash chromatography purification, the product was isolated in 57% yield. Trying to improve the zinc sulfinate solubility, coordinating species able to bind zinc were investigated.¹⁸⁴ Unfortunately, using 2,6-lutidine (Table 12, entry 9), 2,2'-bipyridine (Table 12, entry 10) and 1-methyl-imidazole (Table 12, entry 11) no improvement of conversion was achieved even zinc sulfinate seemed more soluble using all these additives. Finally, the best conversion was achieved (88%) increasing the amount of zinc sulfinate to 3 equiv. and irradiating the solution with blue light for 40 h (Table 12, entry 12). After flash chromatography purification, product **393a** was isolated in 69% yield.

Table 12. Optimization of benzylation of **392a** with zinc sulfinate **390a**.

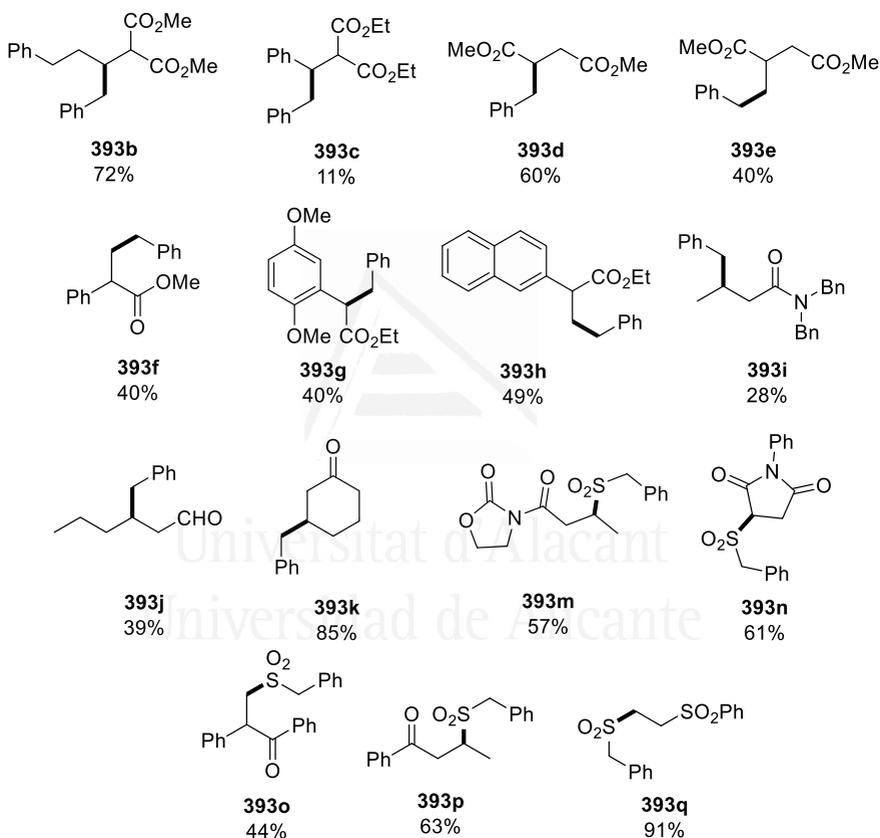
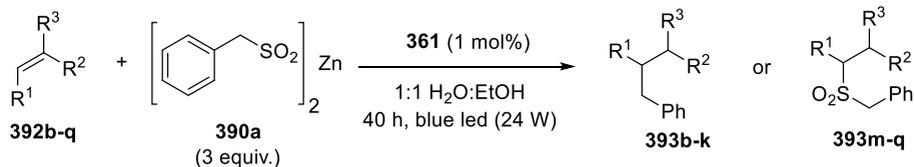
<i>Entry</i> ^a	Solvent	Additive	Conversion ^b
1	1:1 H ₂ O:MeCN	-	25%
2	1:1 H ₂ O:DMF	-	58%
3	1:1 H ₂ O:TFE	-	31%
4	1:1 H ₂ O:DME	-	43%
5	1:4 H ₂ O:DMSO	-	74%
6	1:4 H ₂ O:EtOH	-	27%
7	4:1 H ₂ O:EtOH	-	72%
8	1:1 H ₂ O:EtOH	-	77% (57%)
9	1:1 H ₂ O:EtOH	2,6-lutidine (4 equiv.)	52%
10	1:1 H ₂ O:EtOH	2,2'-bipyridine (2 equiv.)	72%
11	1:1 H ₂ O:EtOH	1-Me-imidazole (4 equiv.)	78%
12^c	1:1 H ₂ O:EtOH	-	88% (69%)

^a All the reactions were carried out under argon. The reaction mixtures were degassed by three cycles of freeze-pump-thaw. The reactions were performed using (**390a**) (0.2 mmol), (**392a**) (0.1 mmol) in 1 mL of solvent mixture, in the presence of 1 mol% of the catalyst.

^b Determined by ¹H NMR analysis of the crude mixture. In parenthesis the isolated yield after flash chromatography purification.

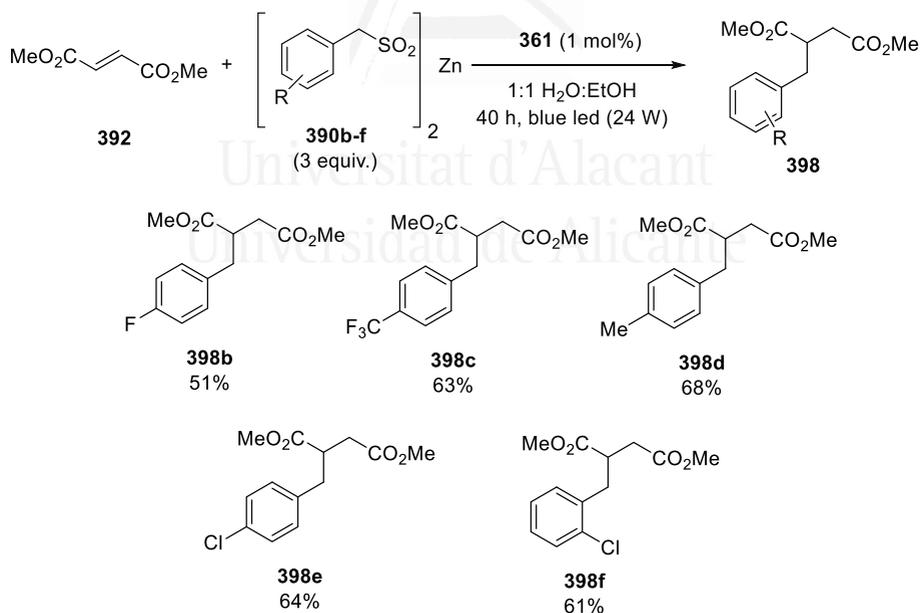
^c 0.3 mmol of **390a** was used and irradiated for 40 h.

With the optimal conditions in hand, the scope of the reaction was investigated using different Michael acceptors (**392b-k**) affording the corresponding benzylated derivatives (**393b-k**) (Scheme 75).



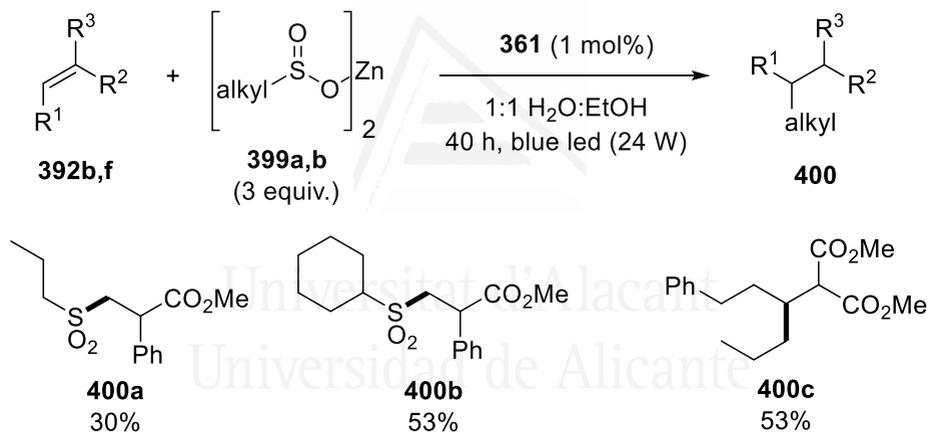
Scheme 75. Scope of benzylation of different Michael acceptors.

One of the most interesting results that were observed was the outcome of the reaction. The product formed was dependent from the alkene derivative that was formed. Sulfones **393m-q** were isolated instead of derivatives **393a-k** in the reaction with alkenes **392m-q**. Later, the possible formation mechanism of this sulfone products will be discussed. Regarding the benzylated products **393b-k**, moderate to good yields were achieved using ten different electron-poor alkenes affording the expected products. Also, the introduction of different moieties on the aryl group of the benzylic sulfinate was explored using dimethyl fumarate **392d**. In this part of the scope, commercially available zinc sulfonates and other synthesized by us **390b-f** were used (Scheme 76). Regarding the reaction with zinc sulfonates **390b-f**, good yields were achieved in general. The isolated yields of **398b-f** range between 51 to 68%.



Scheme 76. Scope of reaction with different benzylic zinc sulfonates.

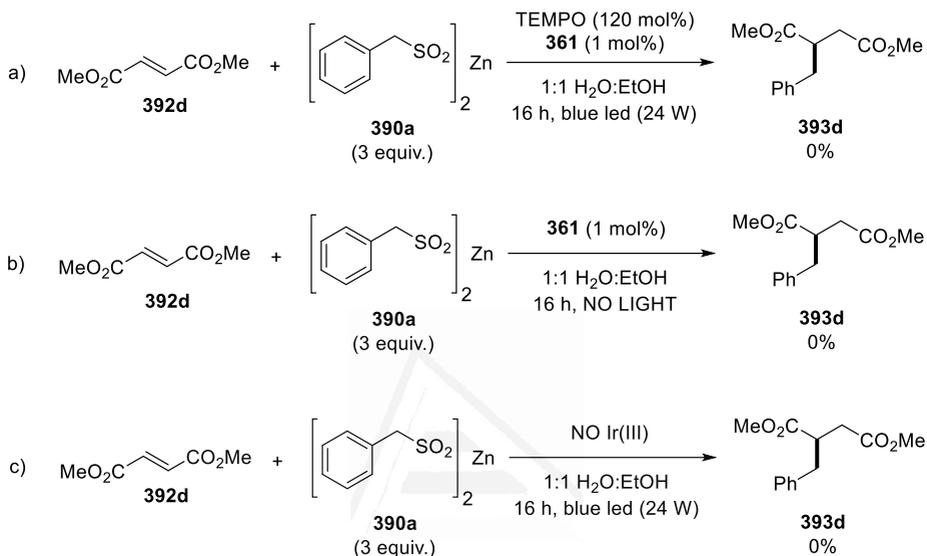
Furthermore, alkyl zinc sulfinates were tested to study their suitability to perform the alkylation of Michael acceptors (Scheme 77). In this part of the scope, although the formation of the products **400** was observed, in general the yields were lower (range between 30% and 53%) than when benzylic zinc sulfinates were used. Probably, it can be explained by the lower stability of the generated alkyl radicals. Again, the nature of the alkene that was used determined if the product obtained was the sulfone derivative (products **400a,b**) or alkylated product **400c**.



Scheme 77. Scope of reaction with different alkylic zinc sulfinates.

Finally, control experiments were done to prove that mechanism involves the formation of free radicals and if both photocatalyst and light are necessary (Scheme 78). Accordingly, the model reaction was tested using 1.2 equiv. of radical scavenger 2,2,6,6-tetramethylpiperidin-1-yl-oxyl (TEMPO), in absence of light and without adding the iridium(III) photocatalyst (Scheme 78, a, b and c, respectively). In all situations, no product **393d** was observed.

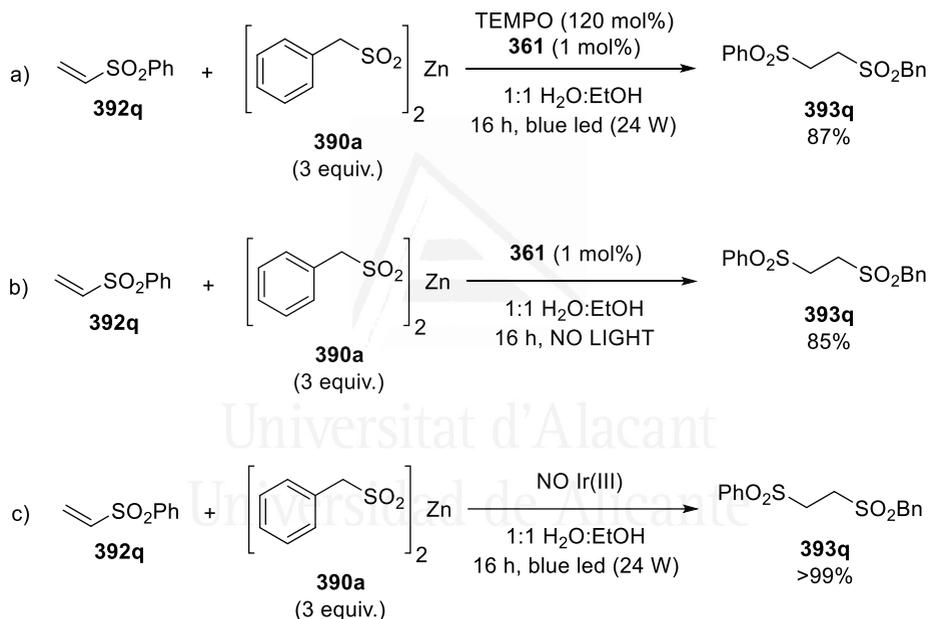
These results prove that a radical mechanism is involved in the process and both photocatalyst and light are necessary.



Scheme 78. Control experiments with radical scavenger, in absence of light or photocatalyst.

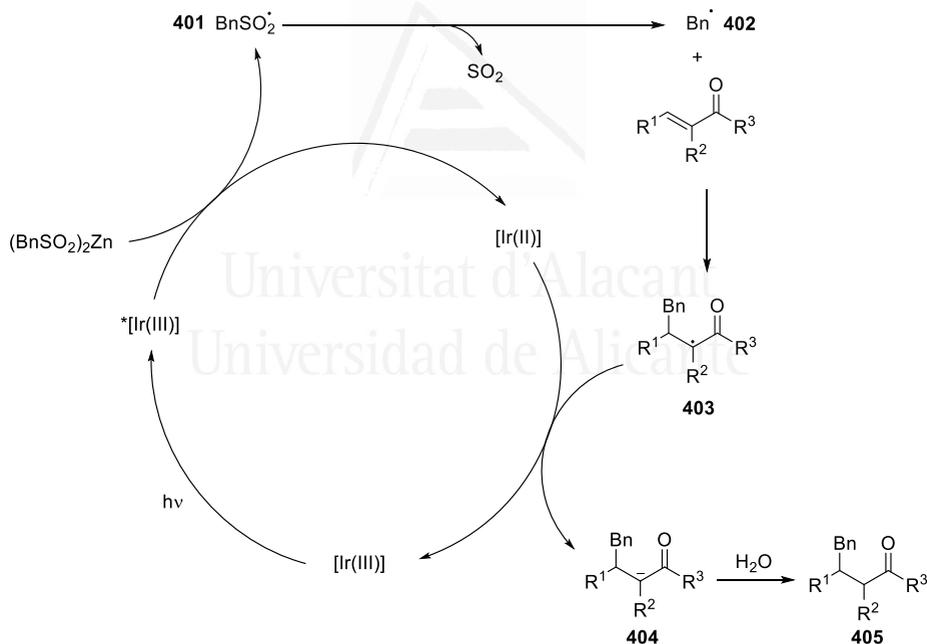
In order to investigate the formation of the sulfone derivatives **393m-q** and **396a,b**, different investigations were carried out (Scheme 79). In the reactions of Scheme 79 it was found that sulfonylation reactions also occurs (conversions measured from ^1H NMR spectra) even when radical scavenger TEMPO is present and in the absence of photocatalyst and light. With these results it could be conclude that the formation of the sulfones occurs by non-radical pathway. In fact, zinc sulfonates are nucleophilic reagents that are able to open epoxides in water¹⁸⁵ affording the corresponding β -

hydroxysulfones. In our case, the presence of zinc cation enhances the electrophilicity of the Michael acceptors. Analyzing all this information, the sulfones derivatives are generated from the nucleophilic attack of the zinc sulfonates to the electron-poor alkenes. It is worth to note that control experiments done with less electrophilic alkene **392d** of Scheme 78, did not afford the corresponding sulfone.



Scheme 79. Formation of sulfones derivatives under different reaction conditions.

After electrochemical and photochemical studies performed in collaboration with Monti's research group in order to get a deeper insight into the mechanism of the reaction, could be conclude that the excited state of Ir(III) photocatalyst oxidize the zinc sulfinate forming the radical intermediate **401**. This intermediate, after C–S bond dissociation and sulfur dioxide SO₂ evolution, the benzylic radical **402** is released. This radical reacts with the Michael acceptor generating the radical intermediate **403** that will be reduced by Ir(II) regenerating the catalyst and forming the anionic species **404**. Finally, after protonation of **404** the final product **405** is formed (Scheme 80).



Scheme 80. Proposed mechanism for the photocatalytic reaction of zinc sulfinate with Michael acceptors.

Conclusions

The results obtained have shown that zinc sulfinates can be used in photoredox catalysis affording alkylic and benzylic radicals which can be intercepted by suitable Michael acceptors through a conjugate addition using Ir as photocatalyst. Using strong Michael acceptors, zinc sulfinates can act as nucleophiles affording the corresponding sulfone through a non-radical process.



Universitat d'Alacant
Universidad de Alicante

Experimental Section

1. General methods

^1H NMR spectra were recorded on Varian Mercury 400 spectrometer. Chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard (deuteriochloroform: $\delta = 7.27$ ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = duplet, t = triplet, q = quartet, dd = double duplet, dt = double triplet, bs = broad signal, m = multiplet), coupling constants (Hz). ^{13}C NMR spectra were recorded on Varian MR400 spectrometer. Chemical shifts are reported in ppm from TMS with the solvent as the internal standard (deuteriochloroform: $\delta = 77.0$ ppm). LC-electrospray ionization mass spectra (ESI-MS) were obtained with Agilent Technologies MSD1100 single-quadrupole mass spectrometer. Chromatographic purification was done with 240-400 mesh silica gel. Purification on preparative thin layer chromatography was done on Merck TLC silica gel 60 F₂₅₄. All reactions were set up under an argon atmosphere in oven-dried glassware using standard Schlenk techniques. Synthesis grade solvents were used as purchased and the reaction mixtures were degassed by three cycles of freeze-pump-thaw.

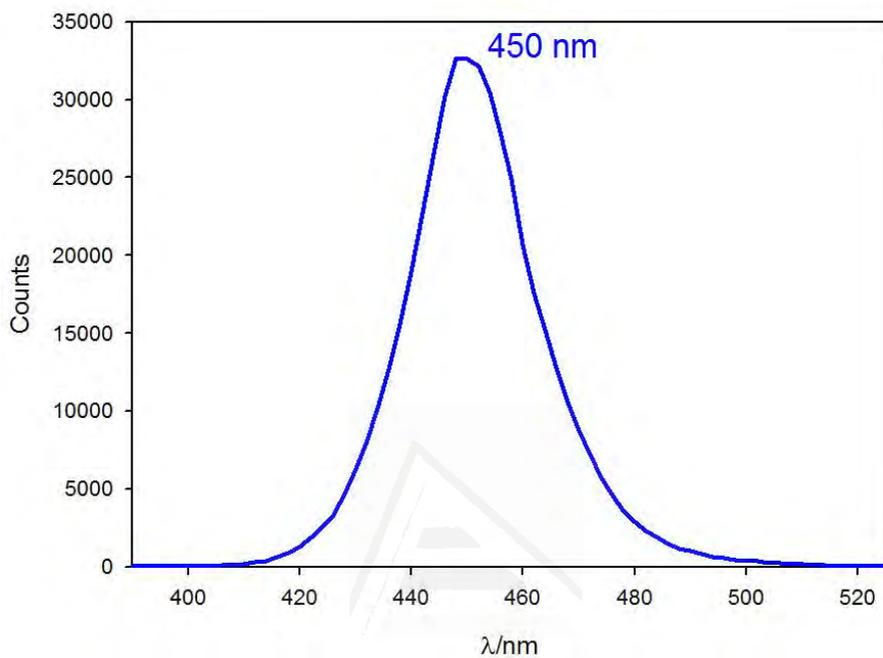
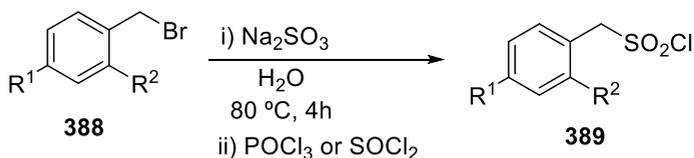


Figure 35. Emission profile of the 24W Blue LED strip used to irradiate the solutions.

2. Experimental procedures and data

2.1. Synthesis of benzyl sulfonates.



R¹ = H, R¹ = H **390a**

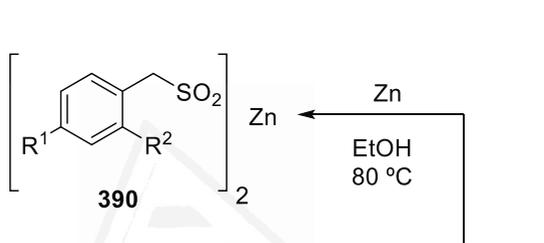
R¹ = F, R¹ = H **390b**

R¹ = Cl, R¹ = H **390c**

R¹ = H, R¹ = Cl **390d**

R¹ = CF₃, R¹ = H **390e**

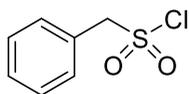
R¹ = Me, R¹ = H **390f**



R¹ = H, R¹ = H **391a**

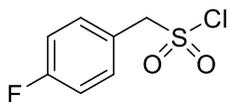
R¹ = CF₃, R¹ = H **391b**

R¹ = Me, R¹ = H **391c**

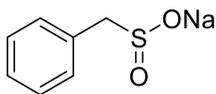


(389a): In a Schlenk tube under N₂, were added Na₂SO₃ (6.35 g, 50.4 mmol, 1.2 equiv.), H₂O (34 mL) and benzyl bromide (5 mL, 42 mmol) in this order. The reaction mixture was heated and kept at reflux until TLC analysis confirmed complete conversion. The crude reaction mixture was washed with Et₂O (2 x 10 mL) and water phase was evaporated under reduced pressure. The crude was used in the next step without any purification. Spectroscopic data were according to the literature.¹⁸⁶ In a Schlenk tube under N₂, were added sodium benzyl sulfonate (8.148 g, 42

mmol) and POCl_3 (15 mL, 160 mmol, 3.8 equiv.). The reaction mixture was stirred at room temperature for 5 hours. POCl_3 was removed under reduced pressure, the residue was dissolved in DCM (50 mL) and washed with H_2O (2 x 10 mL) and brine (2 x 10 mL). The organic phase was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The desired product was obtained in 73% yield (5.87 g, 30.8 mmol) and used in the next step without any purification. Spectroscopic data were according to the literature.¹⁸⁷

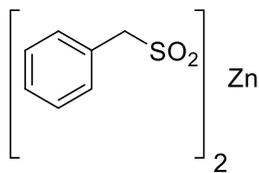


(389b): In a Schlenk tube under N_2 , were added Na_2SO_3 (756 mg, 6 mmol, 1.2 equiv.), H_2O (5 mL) and 4-fluorobenzyl bromide (615 μL , 5 mmol) in this order. The reaction mixture was heated and kept at reflux until TLC analysis confirmed complete conversion. The crude reaction mixture was washed with Et_2O (2 x 10 mL) and water phase was evaporated under reduced pressure to give the corresponding sodium sulfonate. The crude was used in the next step without any purification. In a Schlenk tube, dried by heating under reduced pressure and kept under N_2 , were added sodium 4-fluorobenzyl sulfonate (5 mmol) and SOCl_2 (1.45 mL, 20 mmol, 4 equiv.). The reaction mixture was heated at 70°C for 1.5 hours. SOCl_2 was removed under reduced pressure. The product was dissolved in DCM and washed with H_2O (2 x 10 mL) and brine (2 x 10 mL). The organic phase was dried over Na_2SO_4 , and the solvent was evaporated under reduced pressure. The desired product was obtained in 98% yield (1.02 g, 4.9 mmol). Spectroscopic data were according to the literature.¹⁸⁸

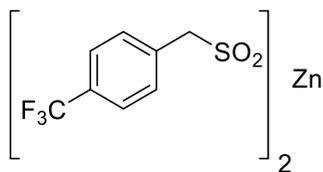


(391a): In a Schlenk tube, were added sulfonyl chloride (5.86 g, 30.8 mmol), Na_2SO_3 , (7.76 g, 61.6 mmol, 2 equiv) and NaHCO_3 (5.17 g, 61.6 mmol, 2 equiv) to H_2O (30 mL). The reaction mixture was heated and kept at 80°C for 4 hours and 30 minutes.

The crude reaction mixture was cooled at room temperature and washed with EtOAc (3 x 10mL). The water phase was concentrated to dryness under reduced pressure. The obtained solid was washed with ethanol (3 x 10 mL) and dried under vacuum. The desired product was obtained in 47% yield (3.08 g, 14.5 mmol). Spectroscopic data were according to the literature.¹⁸⁹

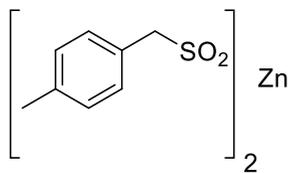


(390a): To a suspension of zinc powder (373 mg, 5.7 mmol, 1.1 equiv.) in THF (0.4 mL), dibromoethane (15.5 μ L, 0.18 mmol, 0.03 equiv.) was added under N₂. The mixture was heated to reflux and returned to room temperature for three times. TMSCl (12.7 μ L, 0.1 mmol, 0.02 equiv.) was added at room temperature and the mixture was stirred for 10 minutes. The solvent was removed under reduced pressure and EtOH (7 mL) was added. After degassing by bubbling N₂ for 5 minutes, sulfonyl chloride (1.00 g, 5.24 mmol) was added. The mixture was refluxed for 45 minutes, cooled at room temperature and stirred for other 45 minutes. The solid was collected by filtration and washed with a 1:1 mixture of DCM/EtOAc (3 x 10 mL). The solid was then dissolved in 15 mL of H₂O, the remaining zinc was filtered off and the water solution was concentrated to dryness under reduced pressure. The desired product was obtained in 71% yield (0.70 g, 1.87 mmol) and used in the next step without any further purification. Spectroscopic data were according to the literature.¹⁹⁰



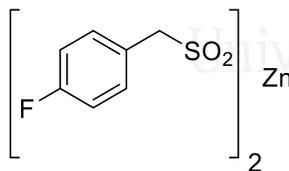
(390e): 21% yield (210 mg, 0.41 mmol). Compound was prepared according to the procedure reported for

390a using: zinc powder (139 mg, 2.13 mmol, 1.1 equiv), THF (0.2 mL), dibromoethane (5.7 μ L, 0.06 mmol, 0.03 equiv), TMSCl (4.7 μ L, 0.04 mmol, 0.02 equiv.); EtOH (2.6 mL); 4-trifluoromethylbenzyl sulfonyl chloride (500 mg, 1.93 mmol).
 ^1H NMR (400 MHz, D_2O): δ = 3.71 (s, 2H), 7.47-7.71 (m, 4H).
 ^{19}F NMR (400 MHz, D_2O): δ = 58.6.



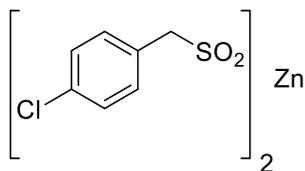
(390f): 58% yield (171 mg, 0.42 mmol) as mixture of corresponding sulfonate in 1.0:2.7 (sulfonate:**390f**); Compound was prepared according to the procedure reported for **390a** using: zinc powder (106 mg, 1.61 mmol, 1.1 equiv), THF (0.2 mL), dibromoethane (4.5 μ L, 0.05 mmol, 0.03 equiv), TMSCl (3.4 μ L, 0.03 mmol, 0.02 equiv); EtOH (2.3 mL); 4-methylbenzyl sulfonyl chloride (301 mg, 1.47 mmol).

^1H NMR (400 MHz, D_2O): δ = 2.35 (s, 3H), 3.62 (s, 2H), 7.21-7.37 (m, 4H).



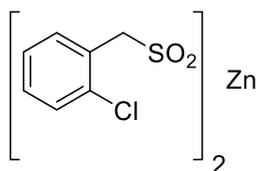
(390b): 34% yield (688 mg, 1.67 mmol) as mixture of corresponding sulfonate in 1.0:3.6 (sulfonate:**390b**); Compound was prepared according to the procedure reported for **390a** using: zinc powder (353 mg, 5.4 mmol, 1.1 equiv), THF (0.5 mL), dibromoethane (12.6 μ L, 0.17 mmol, 0.03 equiv), TMSCl (11.5 μ L, 0.09 mmol, 0.02 equiv); EtOH (6 mL) 4-fluorobenzyl sulfonyl chloride (1.02 g, 4.91 mmol).

^1H -NMR (400 MHz, D_2O): δ = 3.62 (s, 2H), 7.10-7.20 (m, 2H) 7.26-7.33 (m, 2H).



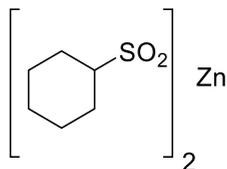
(390c): 23% yield (245 mg, 46% wt, 0.25 mmol) as mixture of corresponding sulfonate in 1.1:1.0 (sulfonate:**390c**); Compound was prepared according to the procedure reported for **390a** using: zinc powder (160 mg, 2.44 mmol, 1.1 equiv.), THF (0.3 mL), dibromoethane (6.7 μL , 0.08 mmol, 0.03 equiv.), TMSCl (5.2 μL , 0.04 mmol, 0.017 equiv.); EtOH (3.8 mL), 4-chlorobenzyl sulfonyl chloride (500 mg, 2.22 mmol, 1 equiv.).

$^1\text{H NMR}$ (400 MHz, D_2O): $\delta = 3.63$ (s, 2H), 7.23-7.30 (m, 1H), 7.36-7.48 (m, 3H).



(390d): 70% yield (431 mg, 80% wt, 0.80 mmol) as mixture of corresponding sulfonate in 1.0:4.4 (sulfonate:**390d**); Compound was prepared according to the procedure reported for **390a** using: zinc powder (160 mg, 2.44 mmol, 1.1 equiv), THF (0.3 mL), dibromoethane (6.7 μL , 0.08 mmol, 0.03 eq), TMSCl (5.2 μL , 0.04 mmol, 0.02 eq); EtOH (3.8 mL) 2-chlorobenzyl sulfonyl chloride (500 mg, 2.22 mmol).

$^1\text{H NMR}$ (400 MHz, D_2O): $\delta = 3.84$ (s, 2H), 7.27-7.44 (m, 3H) 7.46-7.57 (m, 1H).

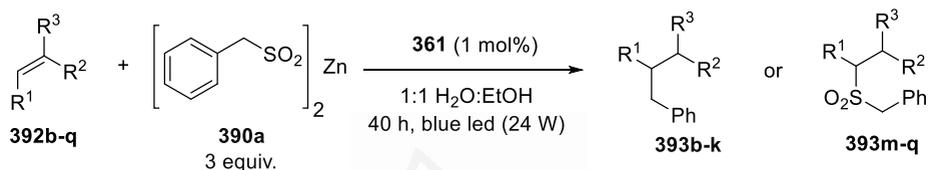


(395b): 88% yield (173 mg, 0.48 mmol); Compound was prepared according to the procedure reported for **390a** using: zinc powder (78 mg, 1.2 mmol, 1.1 equiv), THF (0.1 mL),

dibromoethane (3.3 μL , 0.04 mmol, 0.03 equiv), TMSCl (2.5 μL , 0.02 mmol, 0.02 equiv); EtOH (1.5 mL), cyclohexyl sulfonyl chloride (158.9 μL , 1.1 mmol).

^1H NMR (400 MHz, D_2O): δ = 1.16-1.34 (m, 5H), 1.63-1.67 (m, 1H), 1.81-1.95 (m, 4H), 1.95-2.03 (m, 1H).

2.2. General procedure for photocatalytic reactions.



All photocatalytic reactions were conducted under inert argon atmosphere using Schlenk techniques. Sulfinate salts, iridium complex, substrates and solvents were introduced in the Schlenk flask in this order. The reaction mixture was then subjected to a freeze-pump-thaw procedure (three cycles). The reaction was irradiated with blue LED (approx. 10 cm distance) and stirred for 40 hours. After that the reaction mixture was diluted with H_2O (5 mL) extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 , and the solvent was removed under reduced pressure. The desired product was isolated by flash chromatography or by preparative TLC.

2.3. Experimental data of Michael adducts.

Compounds **393d**, **393e**, **393f**, **393k**, **393n**, **398b**, **398c**, **398d**, **398e** and **398f** are known compounds and experimental data are consistent with reported data:

393d: Dimethyl 2-benzylsuccinate (14 mg, 60% yield)¹⁹¹

393e: Dimethyl 2-phenethylsuccinate (10 mg, 40% yield)¹⁹²

393f: Methyl 2,4-diphenylbutanoate (20 mg, 53% yield)¹⁹³

393k: 3-Benzylcyclohexan-1-one (16 mg, 85% yield)¹⁹⁴

393n: 3-(Benzylsulfonyl)-1-phenylpyrrolidine-2,5-dione (20 mg, 61% yield)¹⁹⁵

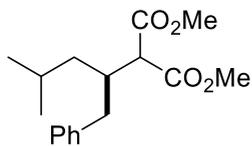
398b: Dimethyl 2-(4-fluorobenzyl)succinate (13.2 mg, 51% yield)¹⁹¹

398c: Dimethyl 2-(4-(trifluoromethyl)benzyl)succinate (19.2 mg, 63% yield)¹⁹⁶

398d: Dimethyl 2-(4-methylbenzyl)succinate (17.1 mg, 68% yield)¹⁹¹

398e: Dimethyl 2-(4-chlorobenzyl)succinate (17.3 mg, 64% yield)¹⁹¹

398f: Dimethyl 2-(2-chlorobenzyl)succinate (16.5 mg, 61% yield)¹⁹¹



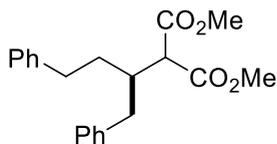
(393a): The general procedure was applied using sodium benzyl sulfinate (53.4 mg, 0.3 mmol, 3 equiv.), **392a** (20.0 mg, 0.1 mmol), **361** (1.1 mg, 1 μ mol, 1 mol%), EtOH (0.25 mL) and H₂O (0.25 mL).

Otherwise, the general procedure was applied using: zinc benzyl sulfinate (112.7 mg, 0.3 mmol, 3 equiv.), **392a** (20.0 mg, 0.1 mmol, 1 equiv), **361** (1.1 mg, 1 μ mol, 1 mol%), EtOH (0.5 mL) and H₂O (0.5 mL). The product was isolated by flash chromatography (SiO₂; cyclohexane:EtOAc 95:5 mixture) in 57% yield (33.2 mg, 0.057 mmol) as yellowish oil.

¹H NMR (400 MHz, CDCl₃): δ = 0.82 (d, *J* = 11.3 Hz, 3H), 0.88 (d, *J* = 13.4 Hz, 3H), 1.25-1.28 (m, 2H), 1.57-1.65 (m, 1H), 2.43-2.49 (m, 1H), 2.69 (d, *J* = 7.1 Hz, 2H), 3.41 (d, *J* = 5.1 Hz, 1H), 3.66 (s, 3H), 3.71 (s, 3H), 7.16-7.19 (m, 3H), 7.23-7.28 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ = 22.1, 22.9, 25.5, 38.0, 38.4, 40.5, 52.1 (2C), 53.9, 126.1, 128.3 (2C), 129.3 (2C), 140.0, 169.4 (2C).

ESI-MS (*m/z*): 293.0 [M+H]⁺, 310.2 [M+H₂O]⁺.

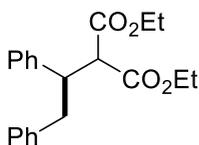


(393b): The general procedure was applied using zinc benzyl sulfinate (112.7 mg, 0.3 mmol, 3 equiv.), **392b** (24.8 mg, 0.1 mmol), **361** (1.1 mg, 1 μ mol, 1 mol%), EtOH (0.5 mL) and H₂O (0.5 mL). The product was purified by flash chromatography (SiO₂; cyclohexane/Et₂O 95:5 mixture) in 62% yield (21.1 mg, 0.062 mmol).

^1H NMR (400 MHz, CDCl_3): δ = 1.65-1.83 (m, 2H), 2.47-2.55 (m, 1H), 2.58-2.70 (m, 2H), 2.76 (d, J = 7.3 Hz, 2H), 3.51 (d, J = 6.6 Hz, 1H), 3.70 (s, 3H), 3.75 (s, 3H), 7.10-7.32 (m, 10H).

^{13}C NMR (100 MHz, CDCl_3): δ = 32.8, 33.2, 37.7, 40.1, 52.3 (2C), 54.0, 125.8, 126.3, 128.3 (4C), 128.4 (2C), 129.2 (2C), 139.7, 141.8, 169.2, 169.3.

ESI-MS (m/z): 341.0 $[\text{M}+\text{H}]^+$, 358.2 $[\text{M}+\text{H}_2\text{O}]^+$.

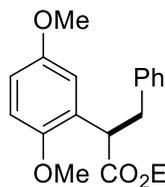


(**393c**): The general procedure was applied using zinc benzyl sulfinate (112.7 mg, 0.3 mmol, 3 equiv.), **392c** (16.2 mg, 0.1 mmol), **361** (1.1 mg, 1 μmol , 1 mol%), EtOH (0.5 mL) and H_2O (0.5 mL). The product was purified by preparative TLC (stationary phase: SiO_2 ; cyclohexane:Et₂O 95:5 mixture) and obtained as an inseparable mixture with **392c** (15 mg, **392c**:**393c**, 1.4:1.0): yield estimated by ^1H NMR 11% yield.

^1H NMR (400 MHz, CDCl_3): δ = 0.91 (t, J = 7.2, 3H), 1.29 (t, J = 7.2 Hz, 3H), 2.81 (dd, J = 13.3, J = 10.2, 1H), 3.08 (dd, J = 13.3, J = 4.0, 1H), 3.65 (td, J = 10.4, J = 4.0, 1H), 3.77 (d, J = 10.7, 1H), 3.86 (q, J = 7.1, 2H), 4.23 (q, J = 7.1, 2H), 6.88-6.93 (m, 2H), 6.99-7.20 (m, 8H).

^{13}C NMR (100 MHz, CDCl_3): δ = 13.6, 14.1, 40.7, 47.6, 57.9, 61.2, 61.6, 126.0, 126.8, 127.9 (2C), 128.0 (2C), 128.5 (2C), 129.2 (2C), 138.9, 140.0, 167.7, 168.4.

ESI-MS (m/z): 341.1 $[\text{M}+\text{H}]^+$, 363.0 $[\text{M}+\text{Na}]^+$.

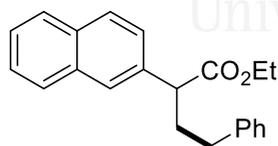


(393g): The general procedure was applied using zinc benzyl sulfinate (112.7 mg, 0.3 mmol, 3 equiv.), **392g** (23.6 mg, 0.1 mmol), **361** (1.1 mg, 1 μ mol, 1 mol%), EtOH (0.5 mL) and H₂O (0.5 mL). The product was purified by flash chromatography (SiO₂; cyclohexane:EtOAc 95:5 mixture) in 40% yield (13 mg, 0.04 mmol).

¹H NMR (400 MHz, CDCl₃): δ = 1.19 (t, J = 7.1 Hz, 3H), 1.92-2.09 (m, 1H), 2.22-2.42 (m, 1H), 2.48-2.68 (m, 2H), 3.74 (s, 3H), 3.75 (s, 3H), 3.98 (t, J = 7.5 Hz, 1H), 4.07-4.16 (m, 2H), 6.74 (dd, J = 8.9 Hz, J = 2.9 Hz, 1H), 6.79 (d, J = 8.9 Hz, 1H), 6.85 (d, J = 2.9 Hz, 1H), 7.14-7.18 (m, 3H), 7.22-7.28 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ = 14.2, 33.7, 34.1, 44.0, 55.7, 56.2, 60.5, 112.0, 112.4, 114.6, 125.8, 128.2 (2C), 128.4 (2C), 129.1, 141.7, 151.2, 153.7, 174.0.

ESI-MS (m/z): 329.2 [M+H]⁺.

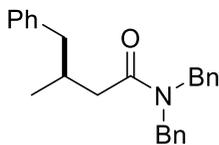


(393h): The general procedure was applied using zinc benzyl sulfinate (112.7 mg, 0.3 mmol, 3 equiv.), **392h** (22.6 mg, 0.1 mmol), **361** (1.1 mg, 1 μ mol, 1 mol%), EtOH (0.5 mL) and H₂O (0.5 mL). The product was purified by flash chromatography (SiO₂; cyclohexane:EtOAc 95:5 mixture) in 49% yield (15.7 mg, 0.049 mmol).

¹H NMR (400 MHz, CDCl₃): δ = 1.19 (t, J = 7.1 Hz, 3H), 2.18-2.25 (m, 1H), 2.48-2.58 (m, 1H), 2.59 (t, J = 7.7 Hz, 2H), 3.70 (t, J = 7.7 Hz, 1H), 4.02-4.21 (m, 2H), 7.17 (dd, J = 16.9, J = 7.4 Hz, 3H), 7.22-7.32 (m, 2H), 7.40-7.50 (m, 3H), 7.73 (s, 1H), 7.76-7.85 (m, 3H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 14.1, 33.6, 34.8, 51.1, 60.8, 125.8, 125.9, 126.0, 126.1, 126.9, 127.6, 127.8, 128.3, 128.4$ (2C), 128.5 (2C), $132.6, 133.4, 136.4, 141.3, 173.8$.

ESI-MS (m/z): 319.2 $[\text{M}+\text{H}]^+$, 336.0 $[\text{M}+\text{H}_2\text{O}]^+$.

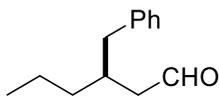


(393i): The general procedure was applied using zinc benzyl sulfinate (112.7 mg, 0.3 mmol, 3 equiv.), **392i** (26.5 mg, 0.1 mmol), **361** (1.1 mg, 1 μmol , 1 mol%), EtOH (0.5 mL) and H_2O (0.5 mL). The product was purified by flash chromatography (SiO_2 ; cyclohexane:AcOEt 90:10 mixture) in 27% yield (9.6 mg, 0.027 mmol).

^1H NMR (400 MHz, CDCl_3): $\delta = 0.96$ (d, $J = 6.0$ Hz, 3H), 2.20-2.26 (m, 1H), 2.38-2.48 (m, 3H), 2.64-2.70 (m, 1H), 4.36 (s, 2H), 4.52 (d, $J = 14.8$ Hz, 1H), 4.64 (d, $J = 14.8$ Hz, 1H), 7.07-7.36 (m, 15H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 19.8, 32.4, 39.7, 43.2, 48.1, 49.8, 125.9, 126.4$ (2C), $127.3, 127.5, 128.2, 128.3$ (2C), 128.5 (2C), 128.9 (2C), 129.2 (2C), $136.6, 137.5, 140.5, 172.8$.

ESI-MS (m/z): 358.2 $[\text{M}+\text{H}]^+$, 380.2 $[\text{M}+\text{Na}]^+$.



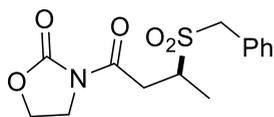
(393j): The general procedure was applied using zinc benzyl sulfinate (112.7 mg, 0.3 mmol, 3 equiv.), **392j** (11.6 μL , 0.1 mmol), **361** (1.1 mg, 1 μmol , 1 mol%), EtOH (0.5 mL) and H_2O (0.5 mL). The product was purified by flash chromatography (SiO_2 ; cyclohexane:EtOAc 96:4 mixture) in 39% yield (7.5 mg, 0.039 mmol).

^1H NMR (400 MHz, CDCl_3): $\delta = 0.88$ (t, $J = 6.8$ Hz, 3H), 1.17-1.41 (m, 4H), 2.23-2.36 (m, 3H), 2.47 (dd, $J = 13.6$ Hz, $J = 7.6$ Hz, 1H),

2.72 (dd, $J = 13.2$ Hz, $J = 5.6$ Hz, 1H), 7.11-7.29 (m, 5H), 9.64 (t, $J = 1.6$ Hz, 1H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 14.2, 19.9, 35.1, 36.4, 40.6, 47.9, 126.2, 128.4$ (2C), 129.2 (2C), $140.1, 202.8$.

ESI-MS (m/z): 191.1 $[\text{M}+\text{H}]^+$, 214.1 $[\text{M}+\text{Na}]^+$.

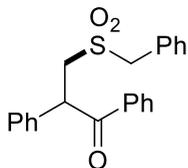


(393m): The general procedure was applied using zinc benzyl sulfinate (112.7 mg, 0.3 mmol, 3 equiv.), **392m** (15.5 mg, 0.1 mmol), **361** (1.1 mg, 1 μmol , 1 mol%), EtOH (0.5 mL) and H_2O (0.5 mL). The product was purified by flash chromatography (SiO_2 ; cyclohexane:EtOAc 1:1 mixture) in 57% yield (17.7 mg, 0.057 mmol).

^1H NMR (400 MHz, CDCl_3): $\delta = 1.39$ (d, $J = 6.8$ Hz, 3H), 3.06 (dd, $J = 19.2$ Hz, $J = 8.8$ Hz, 1H), 3.63-3.70 (m, 2H), 3.97-4.02 (m, 2H), 4.25 (d, $J = 13.6$ Hz, 1H), 4.29 (d, $J = 13.6$ Hz, 1H), 4.41 (t, $J = 8.0$ Hz, 2H), 7.36-7.42 (m, 5H).

^{13}C NMR (100 MHz, CDCl_3): $\delta = 14.7, 35.5, 42.5, 52.7, 57.0, 62.2, 127.2, 128.9$ (2C), $129.0, 130.8$ (2C), $153.3, 169.6$.

ESI-MS (m/z): 312.0 $[\text{M}+\text{H}]^+$, 329.0 $[\text{M}+\text{H}_2\text{O}]^+$, 334.0 $[\text{M}+\text{Na}]^+$.



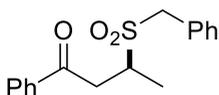
(393o): The general procedure was applied using zinc benzyl sulfinate (112.7 mg, 0.3 mmol, 3 equiv.), **392o** (28.8 mg, 0.1 mmol), **361** (1.1 mg, 1 μmol , 1 mol%), EtOH (0.5 mL) and H_2O (0.5

mL). The product was purified by preparative TLC (SiO₂; cyclohexane:EtOAc 95:5 mixture) in 44% yield (31.8 mg, 0.044 mmol).

¹H NMR (400 MHz, CDCl₃): δ = 3.10 (dd, J = 14.6 Hz, J = 5.0 Hz, 1H), 3.93 (d, J = 13.9 Hz, 1H), 3.98-4.07 (m, 2H), 5.12 (dd, J = 8.3 Hz, J = 5.0 Hz, 1H), 7.10-7.25 (m, 6H), 7.25-7.34 (m, 6H), 7.36-7.42 (m, 1H), 7.81-7.86 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ = 48.1, 54.9, 60.9, 127.6, 128.2, 128.3 (2C), 128.6 (2C), 128.9 (2C), 129.0 (2C), 129.0, 129.5 (2C), 130.8 (2C), 133.5, 135.3, 136.2, 190.7.

ESI-MS (m/z): 365.0 [M+H]⁺, 382.0 [M+H₂O]⁺.

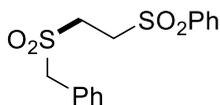


(393p): The general procedure was applied using zinc benzyl sulfinate (112.7 mg, 0.3 mmol, 3 equiv.), **392p** (14.6 mg, 0.1 mmol), **361** (1.1 mg, 1 μmol, 1 mol%), EtOH (0.5 mL) and H₂O (0.5 mL). The product was purified by flash chromatography (stationary phase: SiO₂; cyclohexane:AcOEt 75:25 mixture) in 63% yield (19.1 mg, 0.063 mmol).

¹H NMR (400 MHz, CDCl₃): δ 1.44 (d, J = 6.8 Hz, 3H), 3.12 (dd, J = 18.0 Hz, J = 9.4 Hz, 1H), 3.63 (dd, J = 18.0 Hz, J = 3.2 Hz, 1H), 3.69-3.82 (m, 1H), 4.28 (s, 2H), 7.38-7.47 (m, 7H), 7.55-7.59 (m, 1H), 7.89-7.91 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 14.6, 37.5, 52.0, 57.3, 127.5, 128.1 (2C), 128.8 (2C), 129.1 (3C), 130.7 (2C), 133.7, 136.1, 195.6.

ESI-MS (m/z): 303.2 [M+H]⁺.

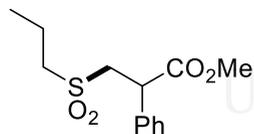


(393q): The general procedure was applied using zinc benzyl sulfinate (112.7 mg, 0.3 mmol, 3 equiv.), **392q** (16.8 mg, 0.1 mmol), **361** (1.1 mg, 1 μ mol, 1 mol%), EtOH (0.5 mL) and H₂O (0.5 mL). The product was purified by flash chromatography (SiO₂; cyclohexane:EtOAc 70:30 mixture) in 91% yield (29.7 mg, 0.091 mmol).

¹H NMR (400 MHz, CD₃CN): δ = 3.23-3.27 (m, 2H), 3.47-3.53 (m, 2H), 4.34 (s, 2H), 7.33-7.42 (m, 5H), 7.61-7.69 (m, 2H), 7.75-7.81 (m, 1H), 7.86-7.92 (m, 2H).

¹³C NMR (100 MHz, CD₃CN): δ = 46.0, 49.3, 59.7, 128.7, 129.1 (2C), 129.8 (2C), 129.9, 130.6 (2C), 131.8 (2C), 135.4, 139.0.

ESI-MS (m/z): 325.0 [M+H]⁺, 342.0 [M+H₂O]⁺, 347.0 [M+Na]⁺.

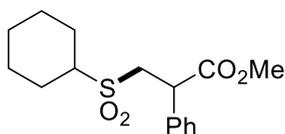


(400a): The general procedure was applied using **399a** (83.9 mg, 0.3 mmol, 3 equiv.), **392f** (24.8 mg, 0.1 mmol), **361** (1.1 mg, 1 μ mol, 1 mol%), EtOH (0.5 mL) and H₂O (0.5 mL). The product was purified by flash chromatography (SiO₂; cyclohexane/AcOEt 85:15 mixture) in 30% yield (8.0 mg, 0.030 mmol).

¹H NMR (400 MHz, CDCl₃): δ = 0.98 (t, J = 7.2 Hz, 3H), 1.71-1.87 (m, 2H), 2.67-2.81 (m, 2H), 3.26 (dd, J = 14.4 Hz, J = 8.4 Hz, 1H), 3.70 (s, 3H), 3.91 (dd, J = 14.0 Hz, J = 8.4 Hz, 1H), 4.25 (dd, J = 8.8 Hz, J = 5.1 Hz, 1H), 7.28-7.34 (m, 5H).

¹³C NMR (100 MHz, CDCl₃): δ = 13.0, 15.8, 45.5, 52.8, 55.6, 55.8, 127.8 (2C), 128.4, 129.2 (2C), 136.1, 172.1.

ESI-MS (m/z): 271.1 [M+H]⁺, 288.2 [M+H₂O]⁺, 293.2 [M+Na]⁺.



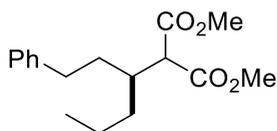
(400b): The general procedure was applied using **399b** (107.9 mg, 0.3 mmol, 3 equiv.), **392f** (24.8 mg, 0.1 mmol), **361** (1.1 mg, 1 μ mol, 1 mol%), EtOH (0.5 mL) and H₂O (0.5 mL). The product was purified by flash chromatography (SiO₂; cyclohexane:AcOEt 95:15 mixture) in 53% yield (13 mg, 0.053 mmol).

¹H NMR (400 MHz, CDCl₃): δ = 1.07-1.30 (m, 3H), 1.40-1.54 (m, 2H), 1.62-1.70 (m, 1H), 1.81-1.92 (m, 2H), 2.02-2.15 (m, 2H), 2.55 (tt, J = 12.0 Hz, J = 3.6 Hz, 1H), 3.21 (dd, J = 14.0 Hz, J = 4.8 Hz, 1H), 3.69 (s, 3H), 3.89 (dd, J = 13.8 Hz, J = 9.0 Hz, 1H), 4.25 (dd, J = 8.3 Hz, J = 4.8 Hz, 1H), 7.28-7.36 (m, 5H).

¹³C NMR (100 MHz, CDCl₃): δ = 24.8, 25.0, 25.0, 25.0, 44.9, 52.4, 52.8, 61.9, 127.8 (2C), 128.3, 129.2 (2C), 136.4, 172.1.

ESI-MS (m/z): 311.2 [M+H]⁺, 328.2 [M+H₂O]⁺.

Universitat d'Alacant
Universidad de Alicante



(400c): The general procedure was applied using **399a** (83.9 mg, 0.3 mmol, 3 equiv.), **392b** (24.8 mg, 0.1 mmol), **361** (1.1 mg, 1 μ mol, 1 mol%), EtOH (0.5 mL) and H₂O (0.5 mL). The product was purified by flash chromatography (SiO₂; cyclohexane:EtOAc 90:10 mixture) in 53% yield (15.5 mg, 0.053 mmol).

^1H NMR (400 MHz, CDCl_3): δ = 0.89 (t, J = 6.8 Hz, 3H), 1.22-1.42 (m, 4H), 1.59-1.76 (m, 2H), 2.17-2.25 (m, 1H), 2.53-2.65 (m, 2H), 3.49 (d, J = 7.2 Hz, 1H), 3.71 (s, 6H), 7.13-7.17 (m, 3H), 7.24-7.27 (m, 2H).

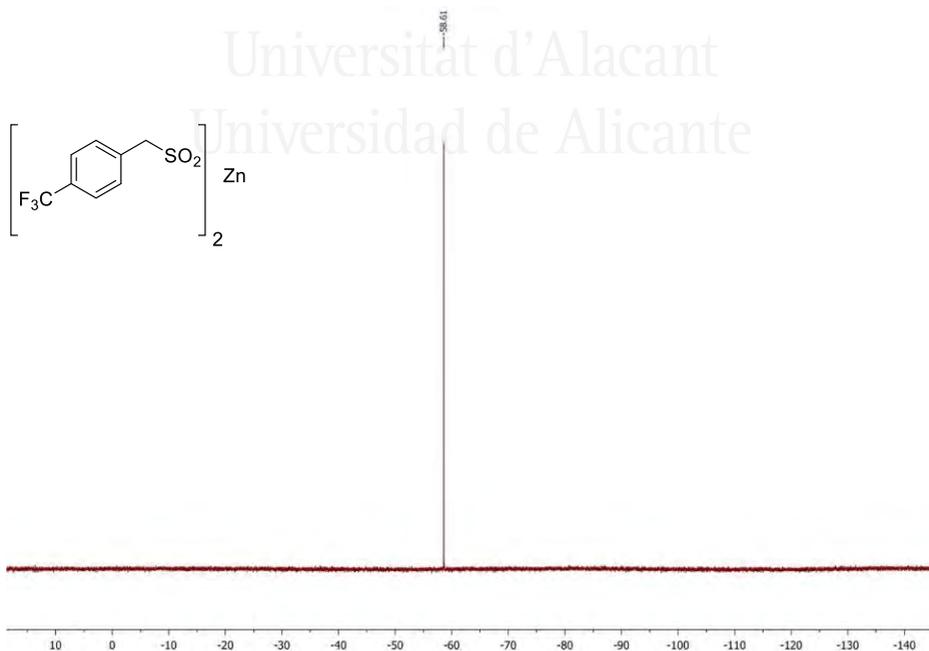
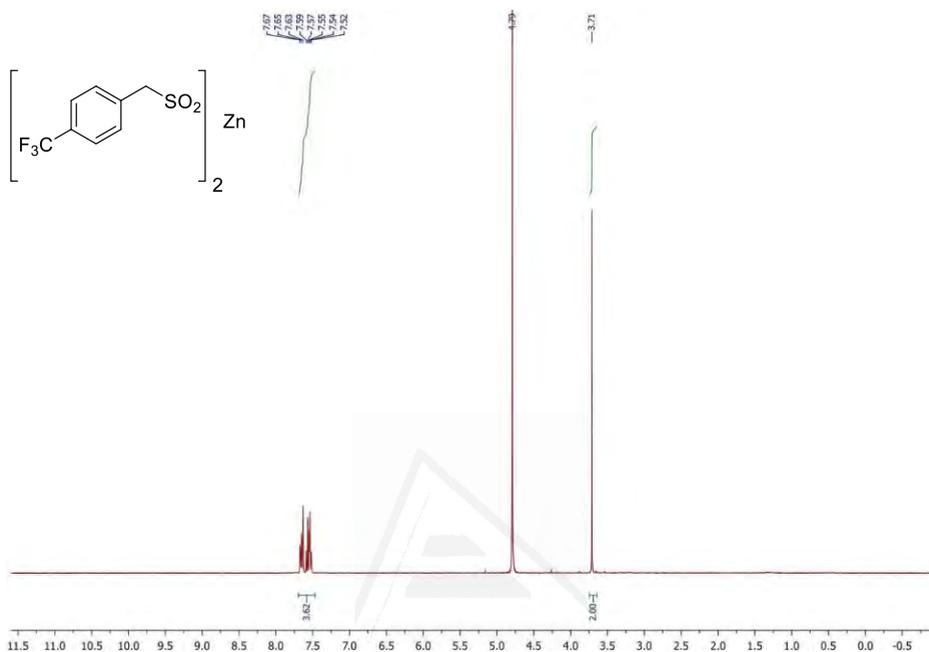
^{13}C NMR (100 MHz, CDCl_3): δ = 14.2, 19.8, 33.0, 33.1, 33.3, 37.8, 52.2, 55.0, 125.8, 128.3 (2C), 128.3 (2C), 142.1, 169.3, 169.4.

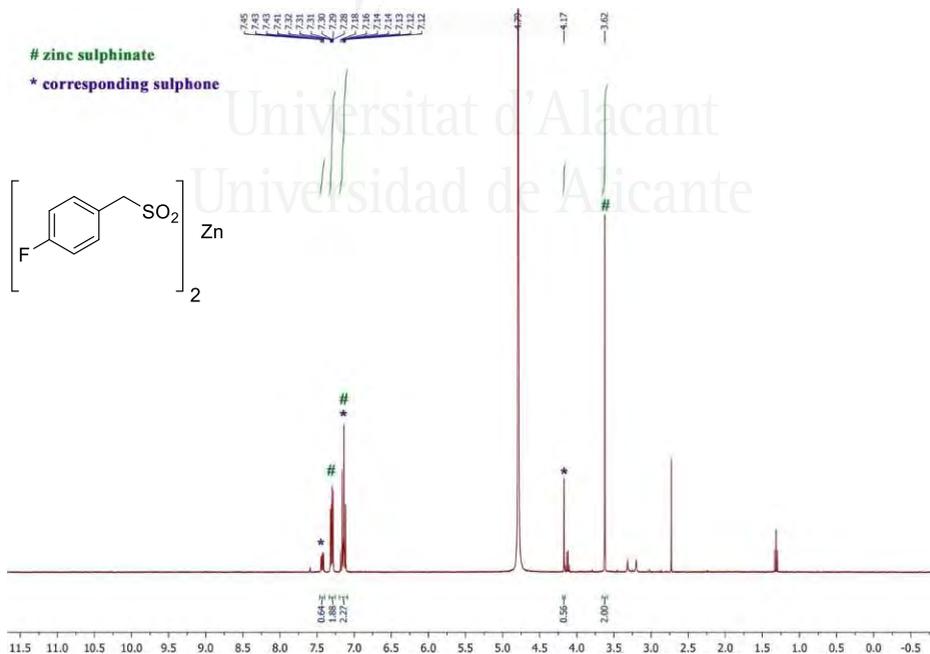
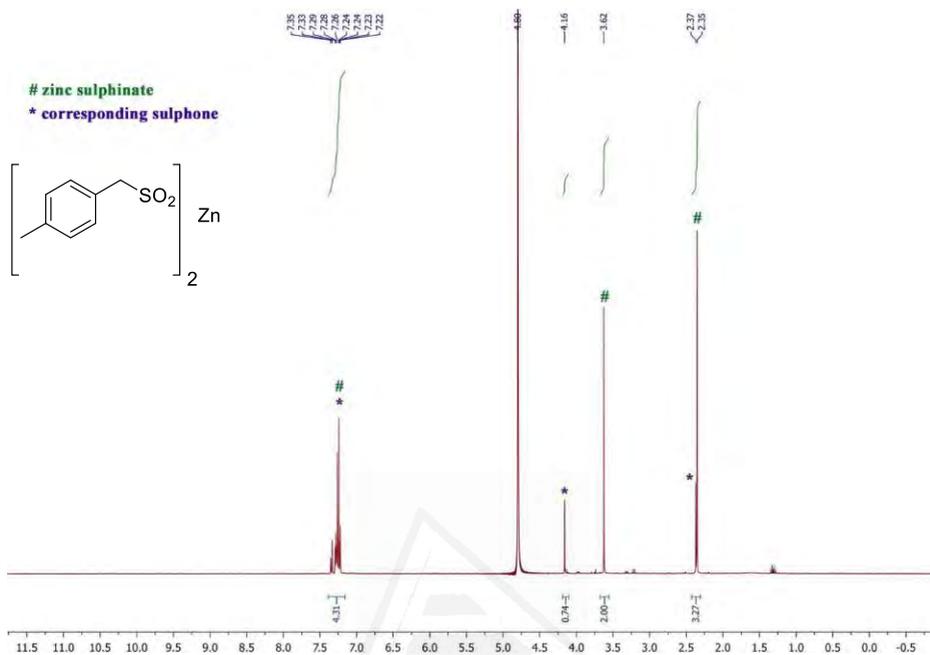
ESI-MS (m/z): 293.0 $[\text{M}+\text{H}]^+$, 310.0 $[\text{M}+\text{H}_2\text{O}]^+$.

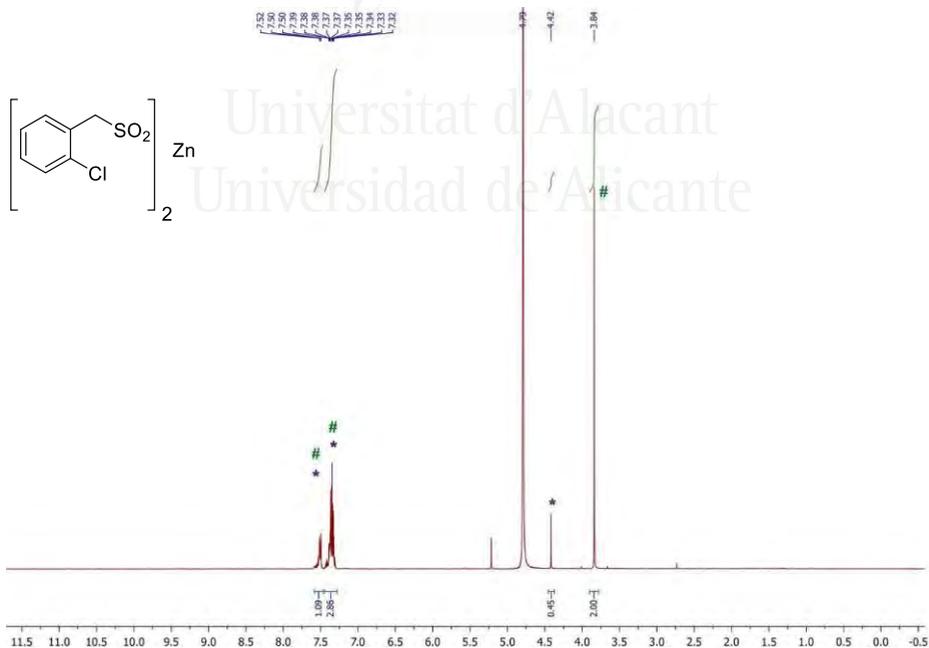
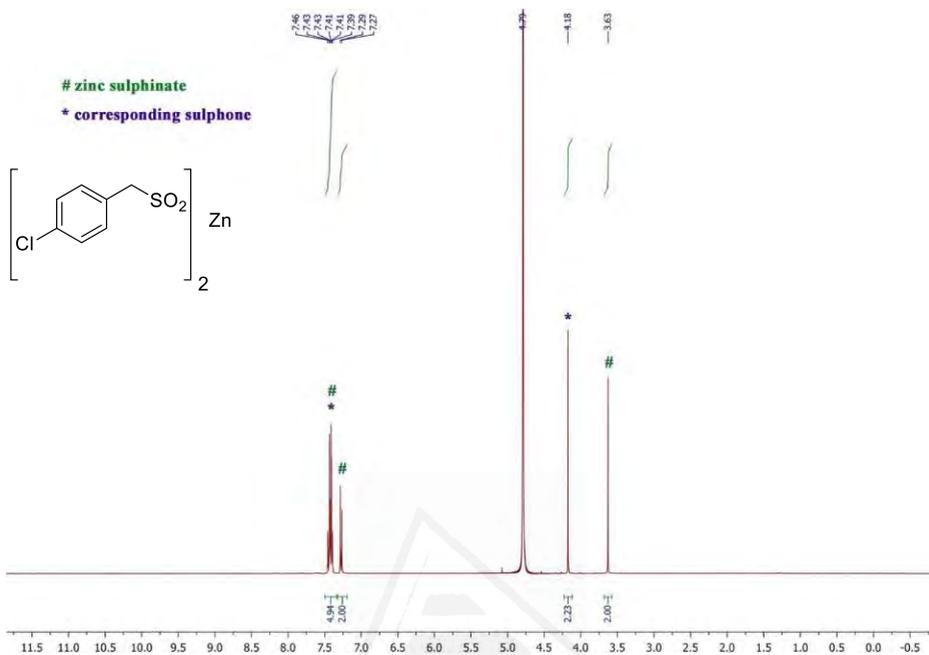


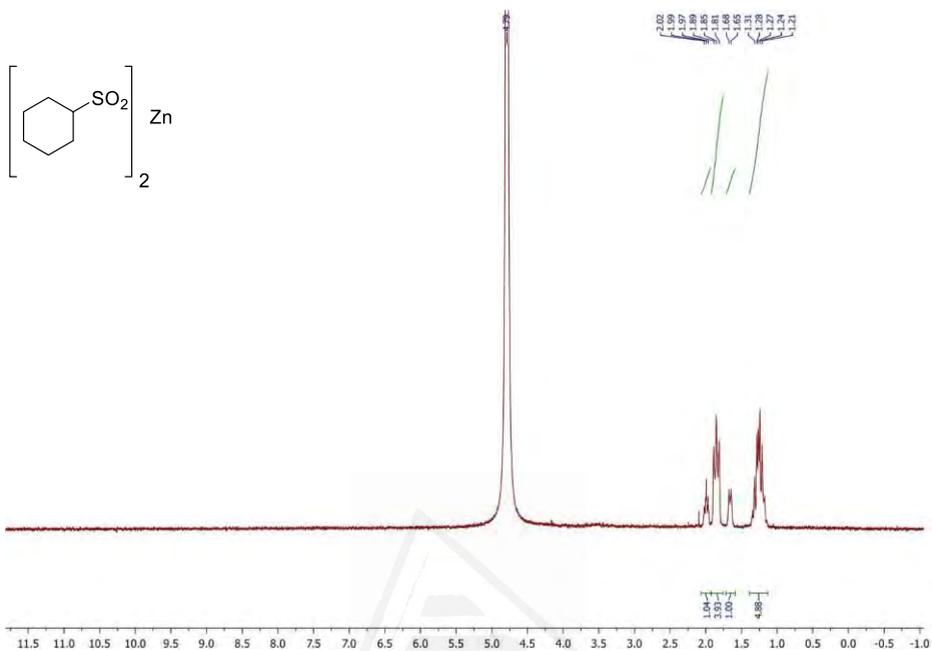
Universitat d'Alacant
Universidad de Alicante

2.4. NMR spectra of new compounds

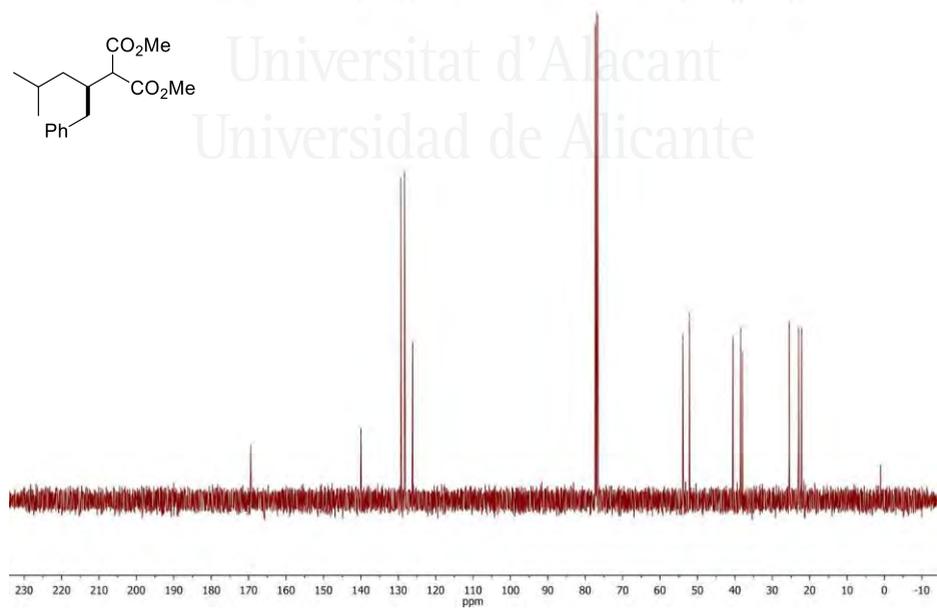
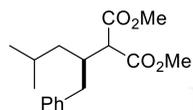
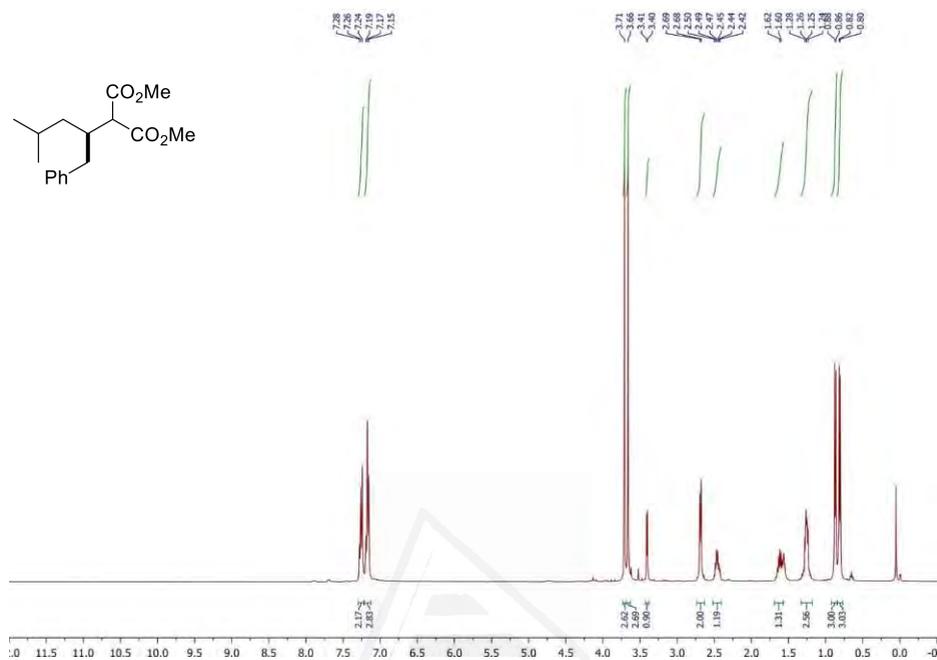
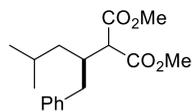


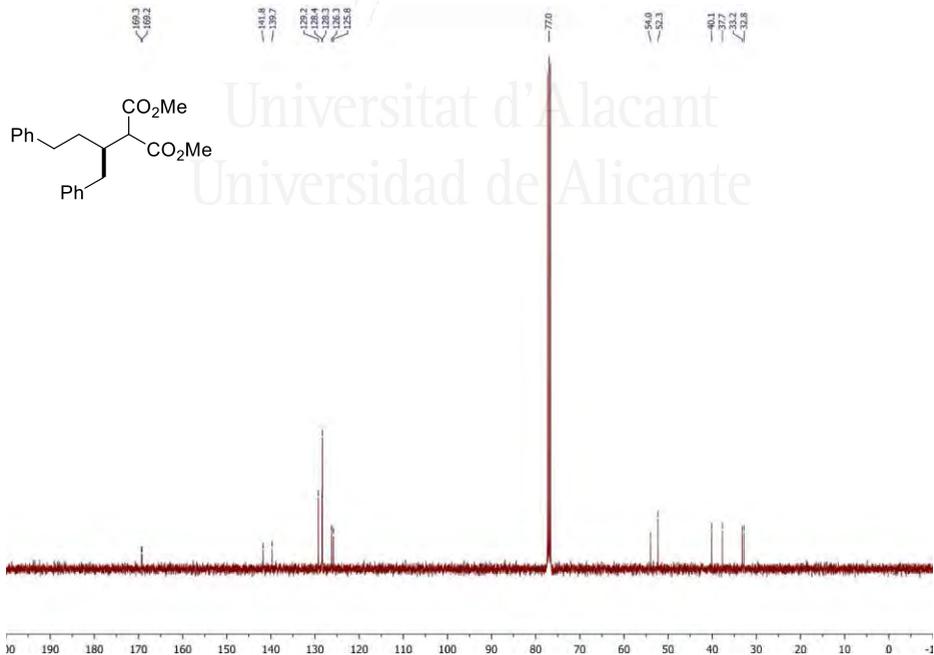
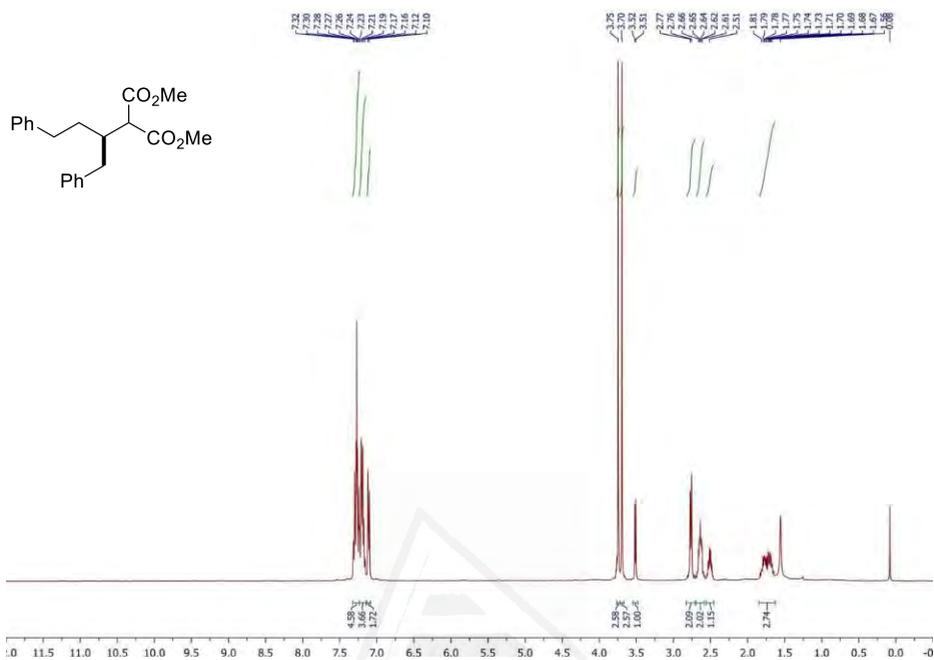


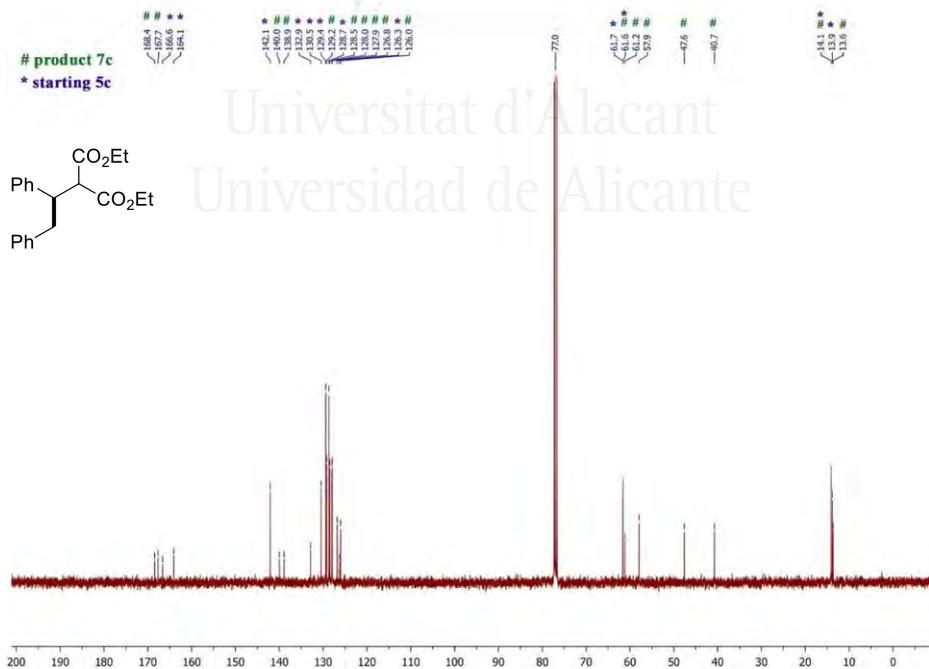
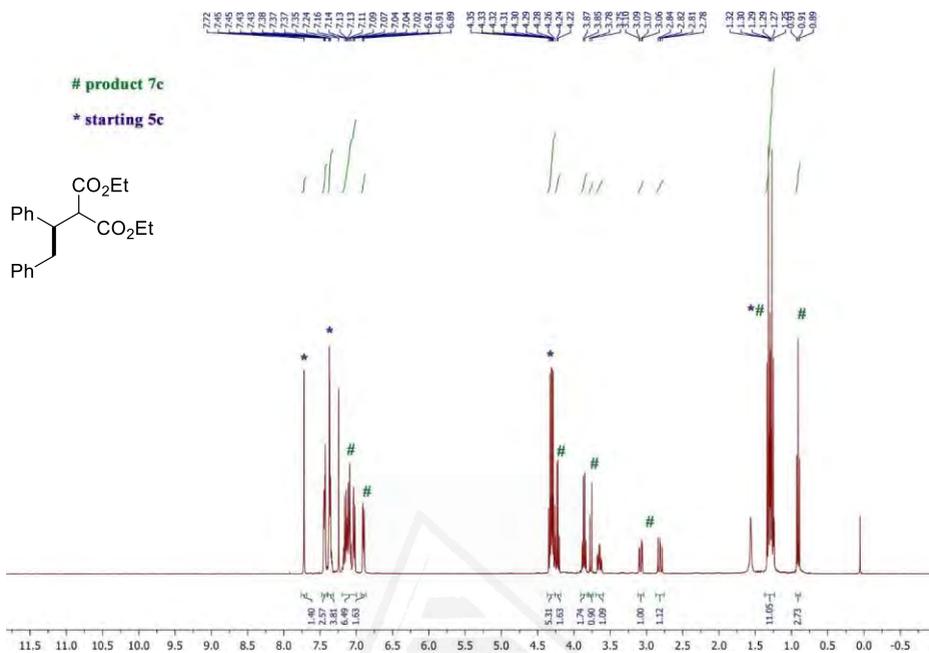


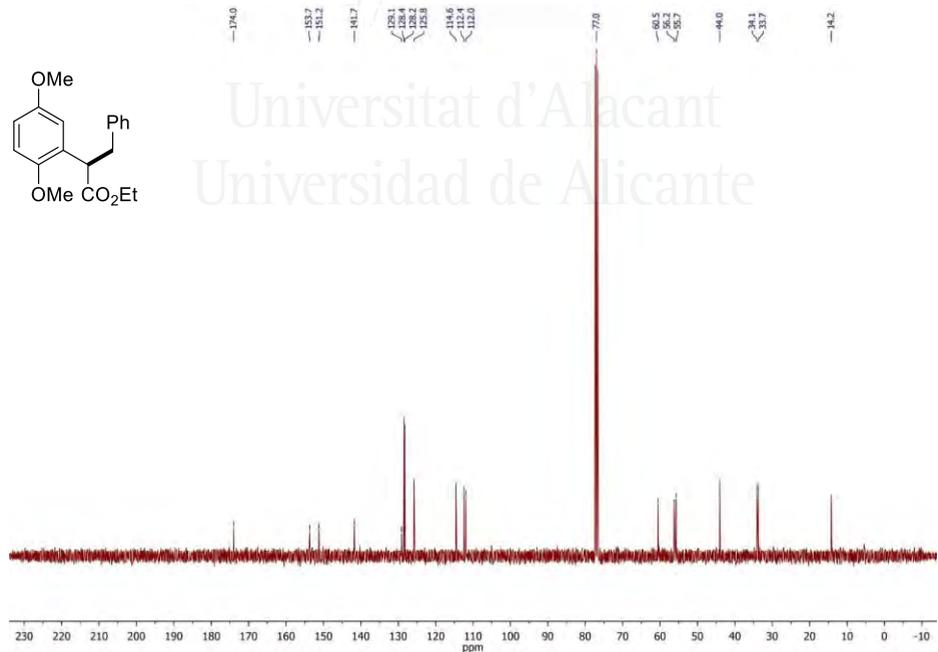
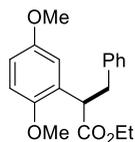
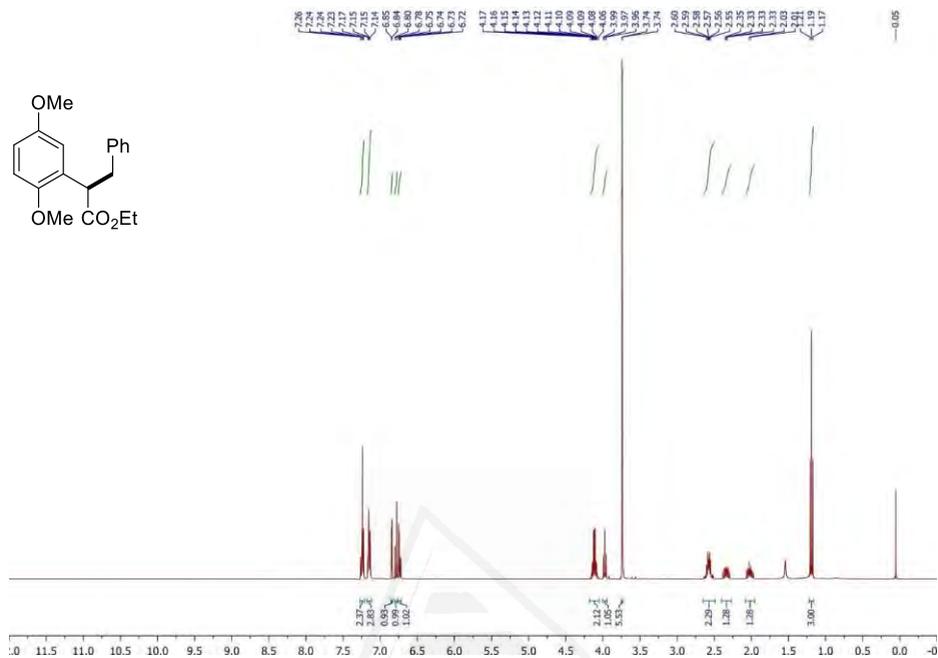
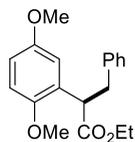


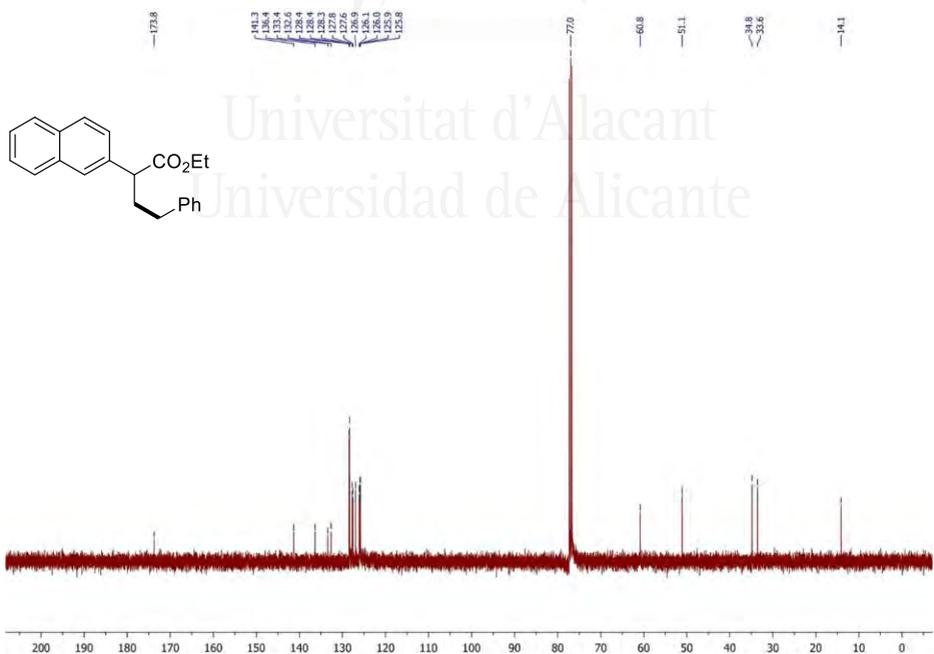
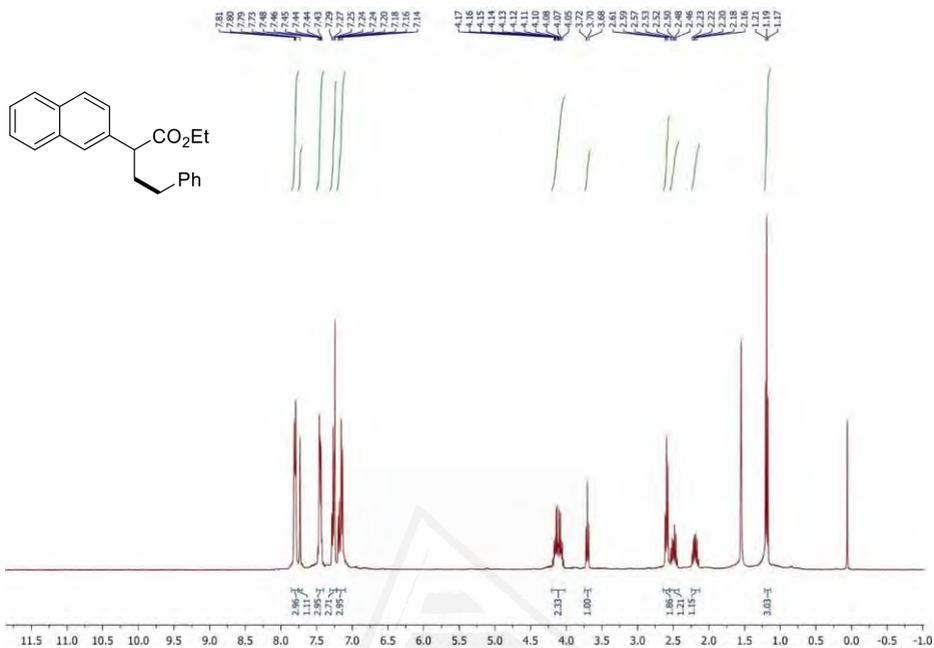
Universitat d'Alacant
Universidad de Alicante

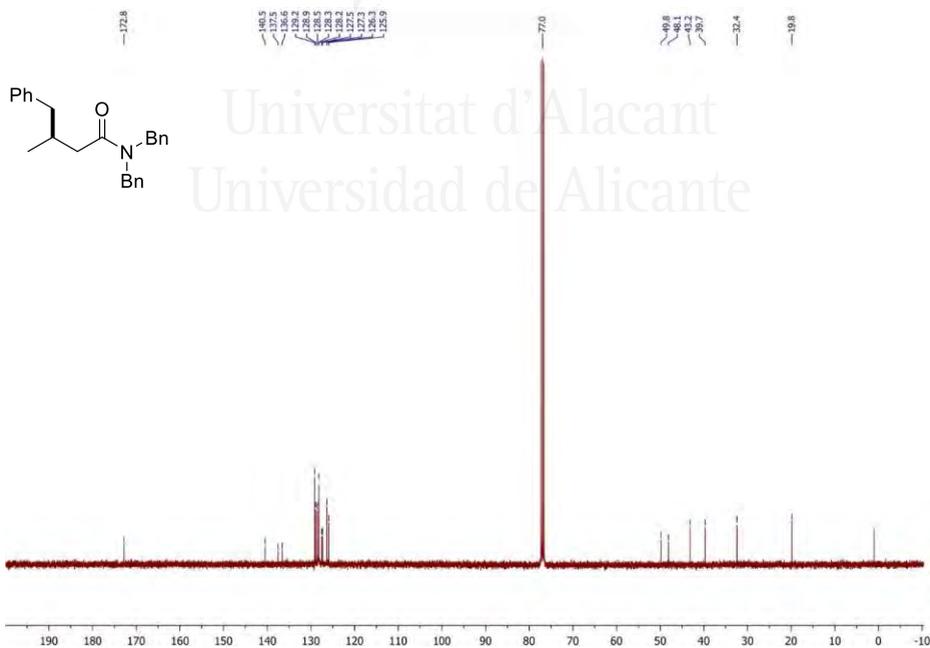
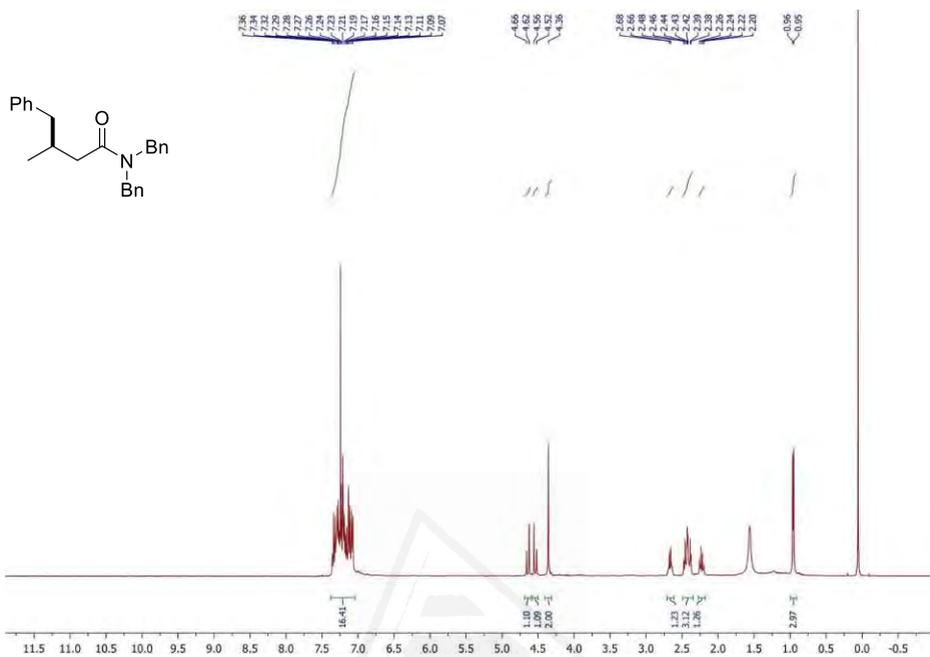


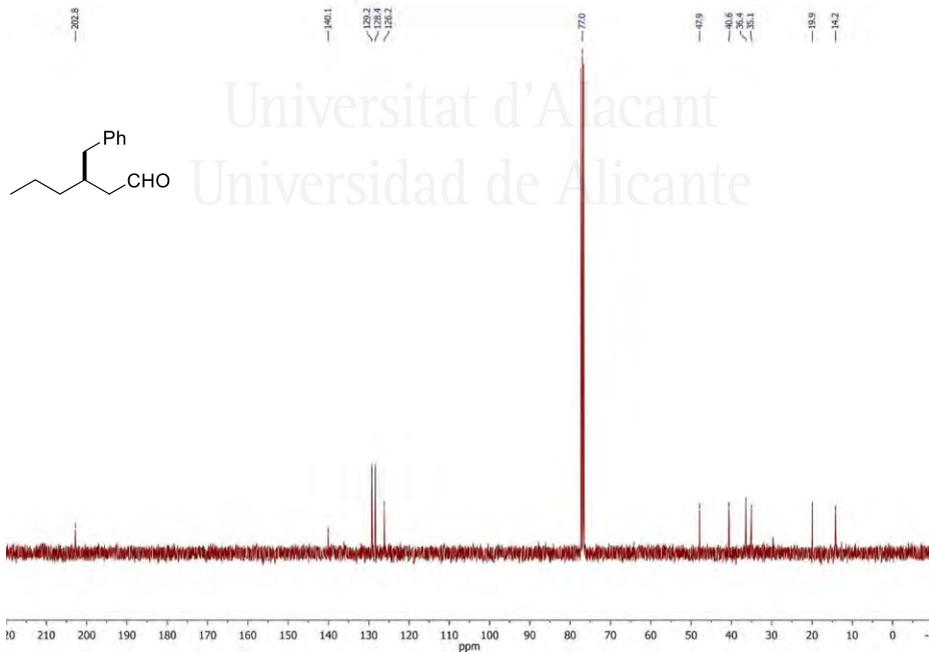
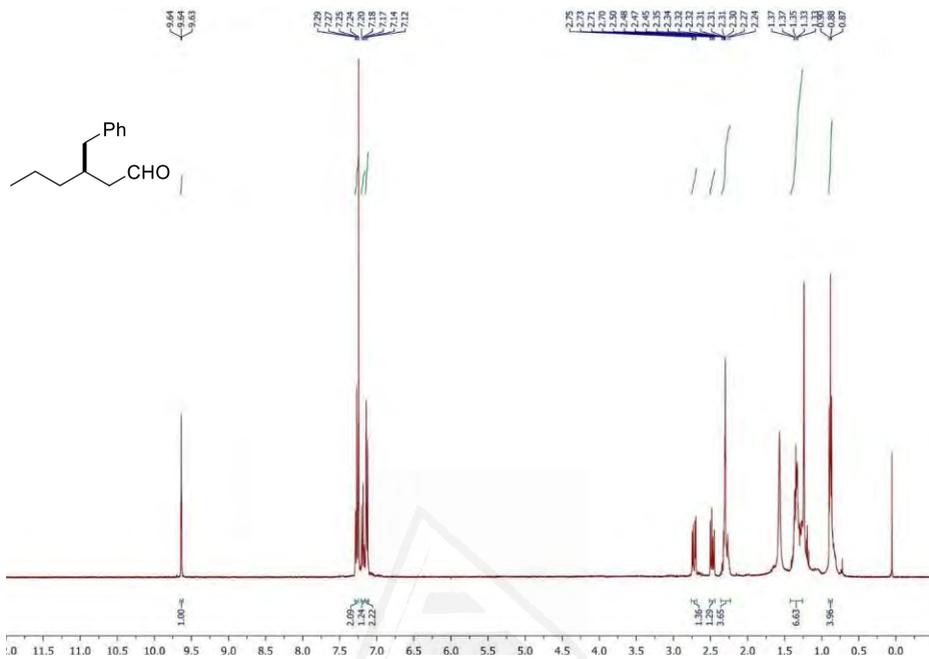


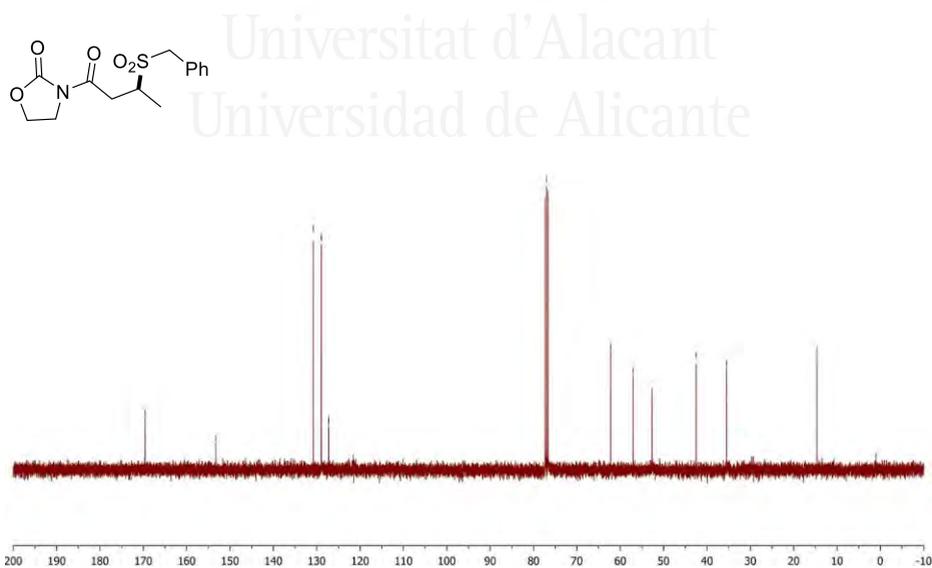
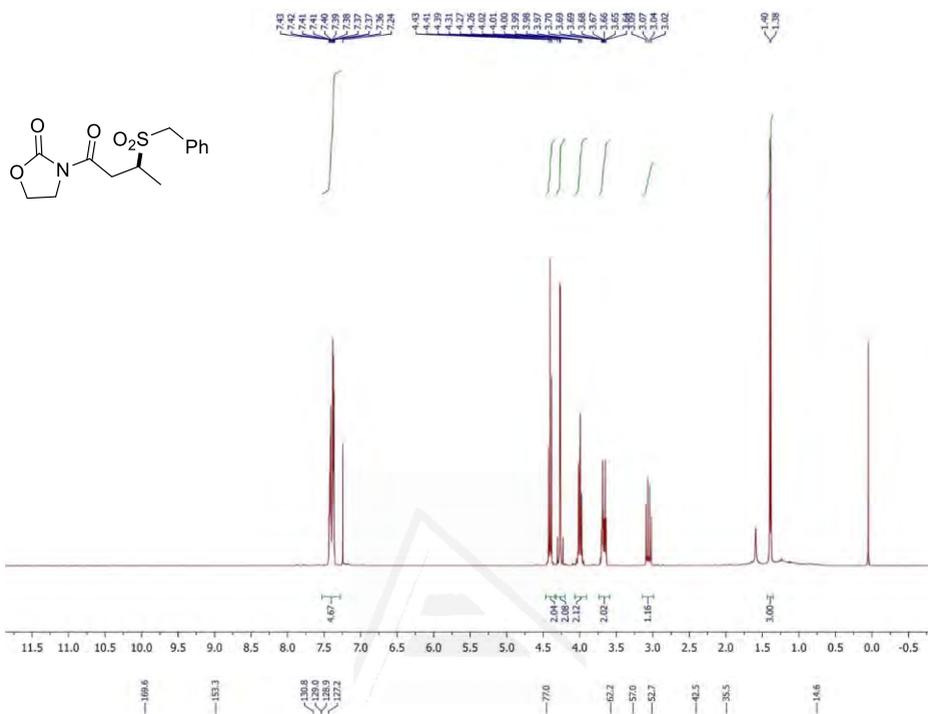




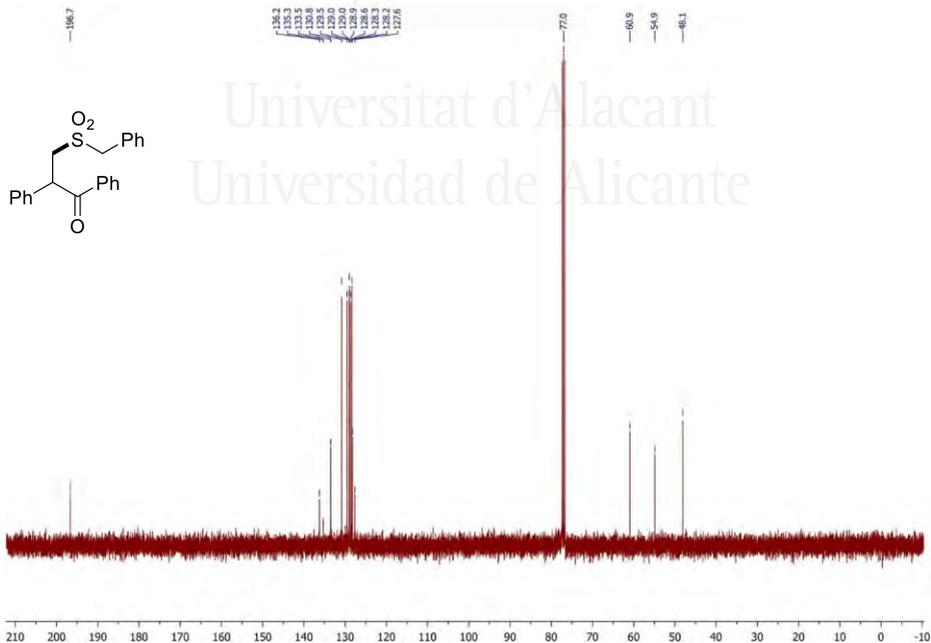
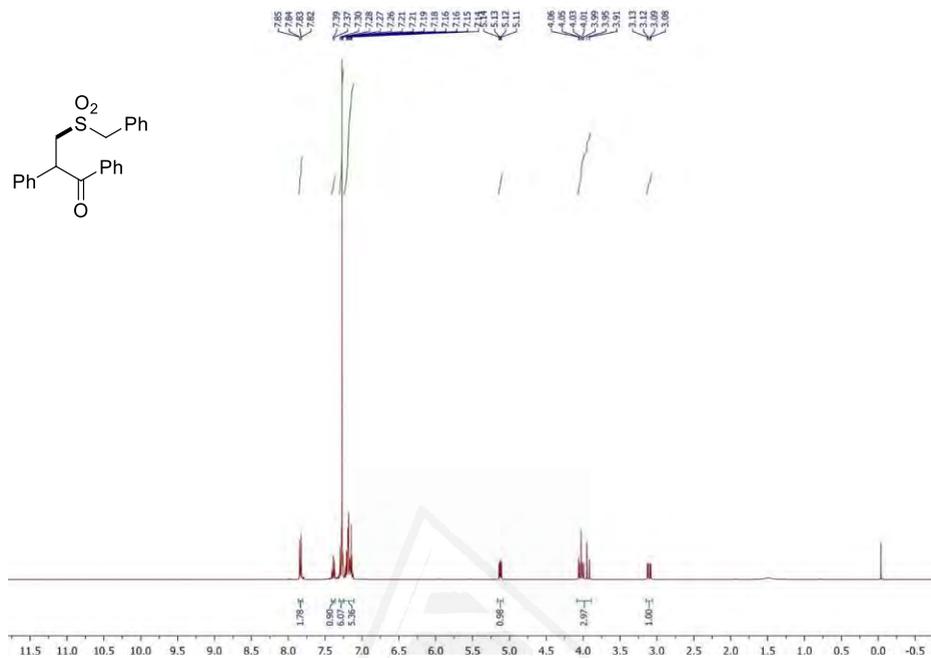
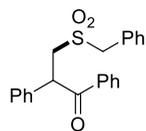


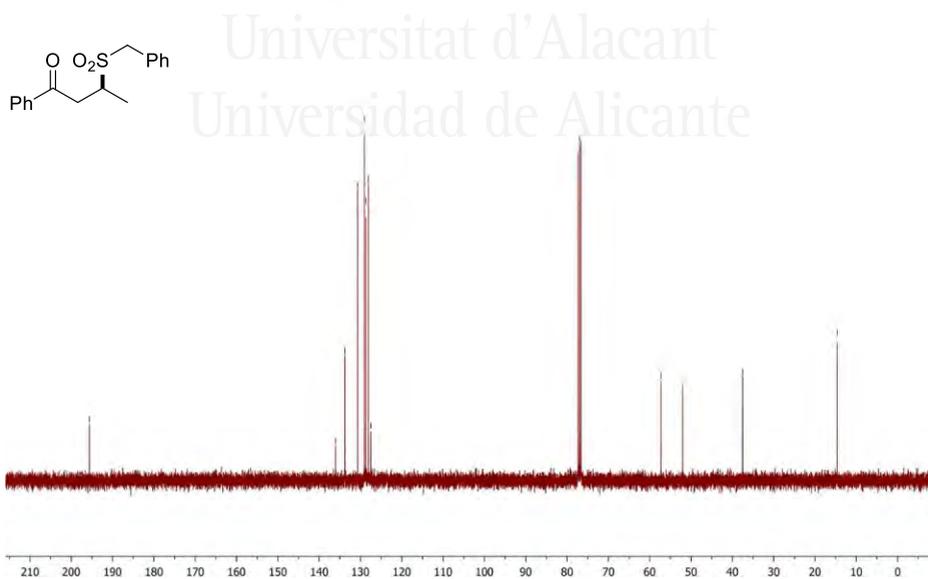
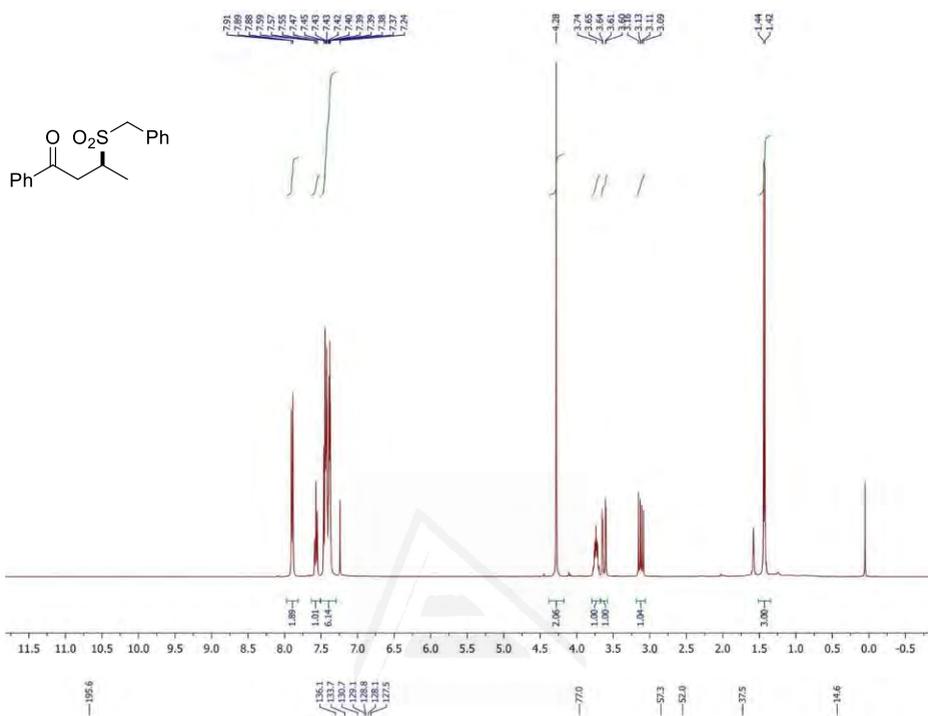




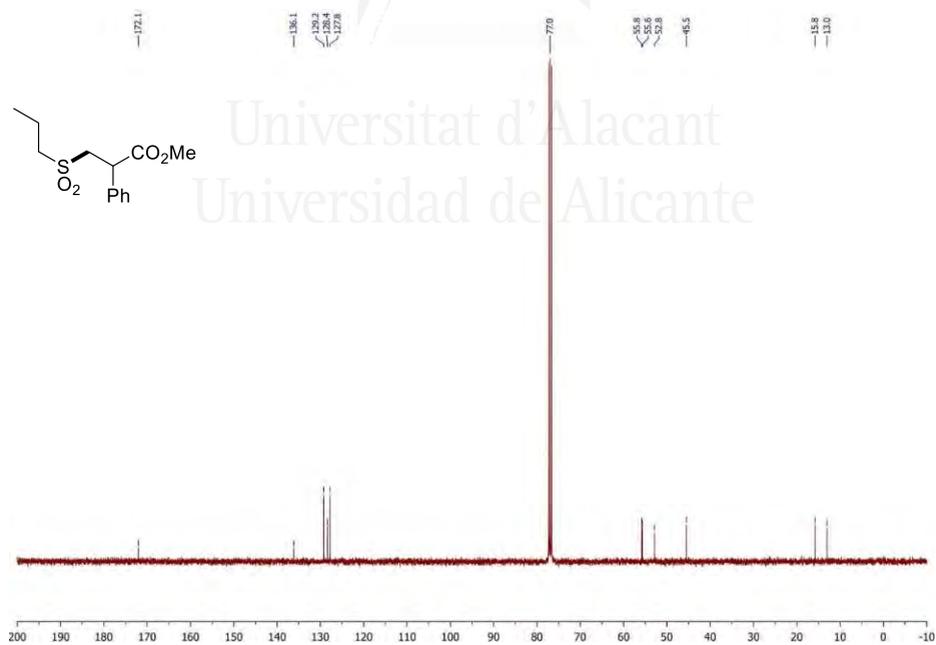
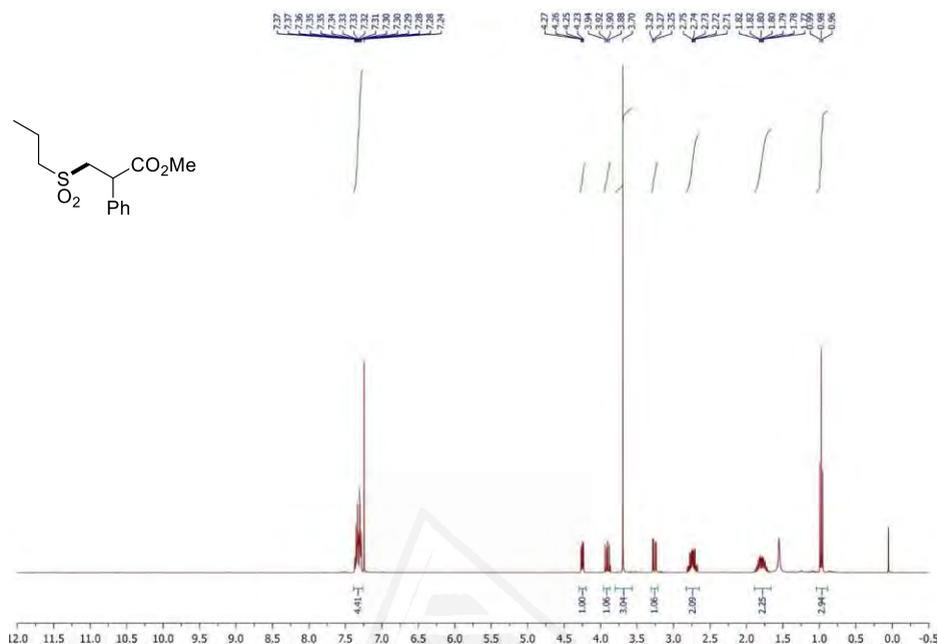


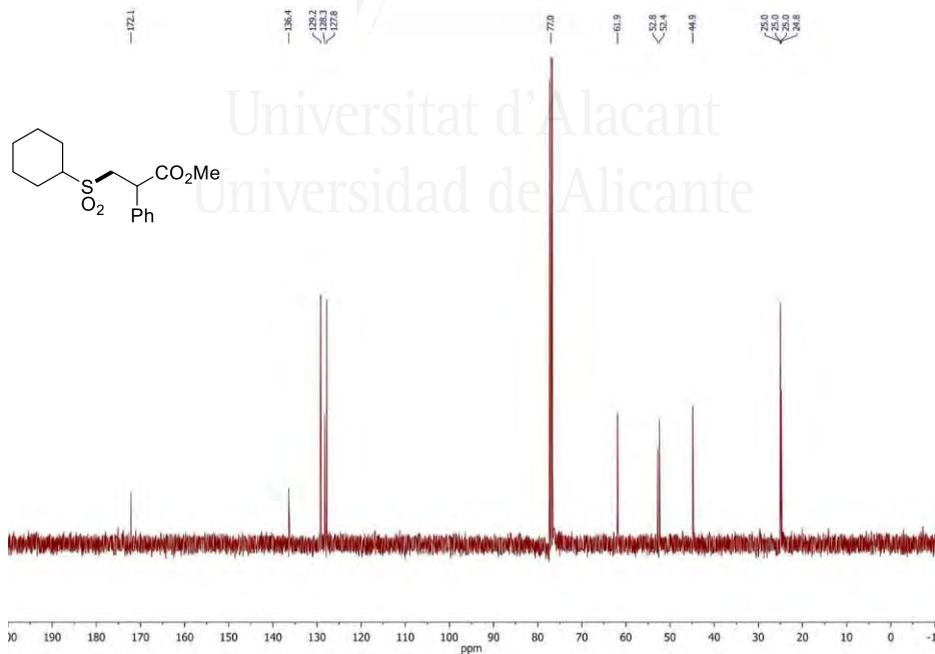
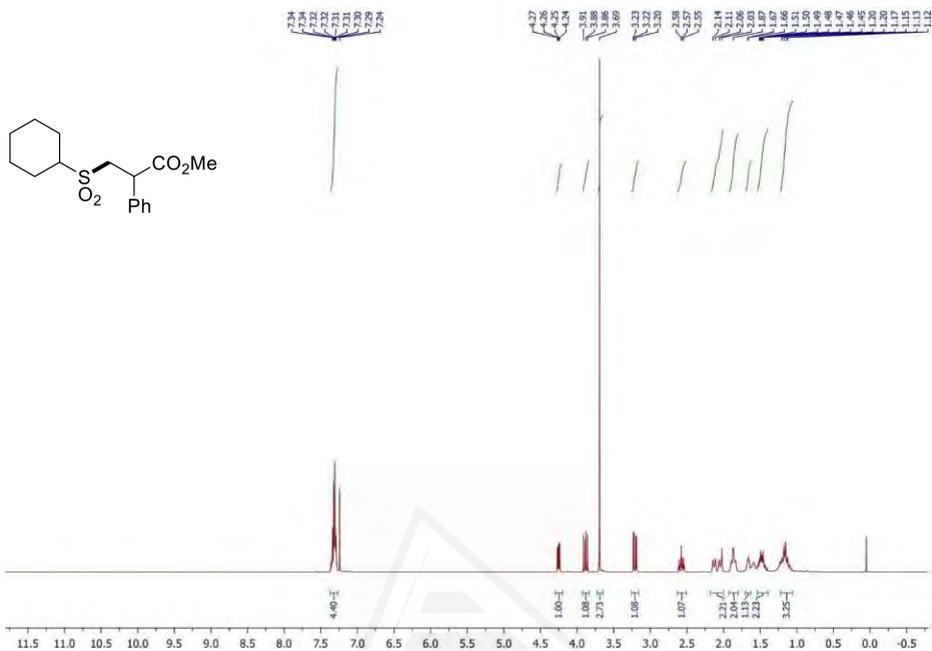
Universitat d'Alacant
Universidad de Alicante

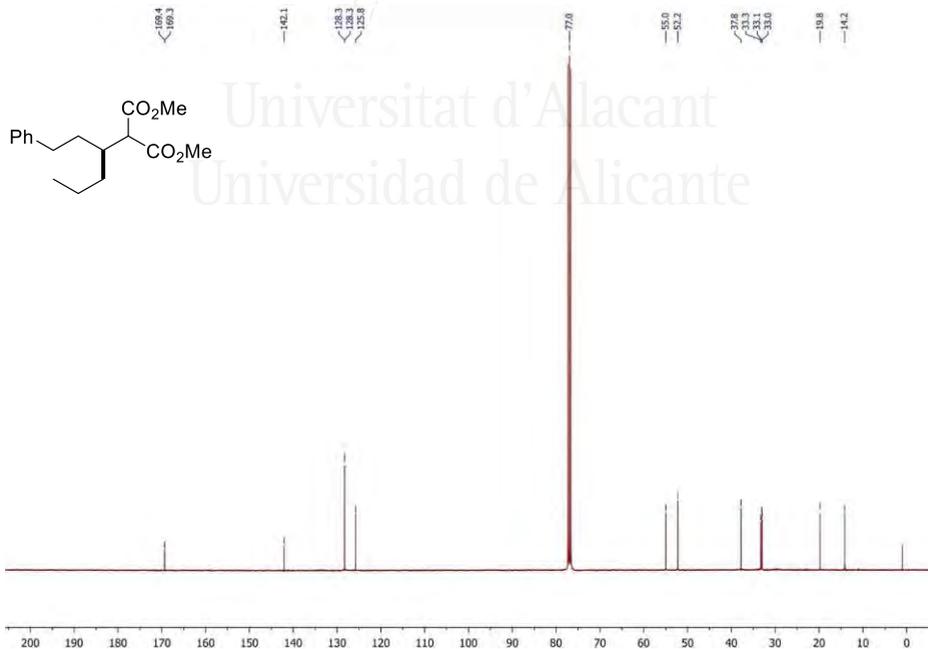
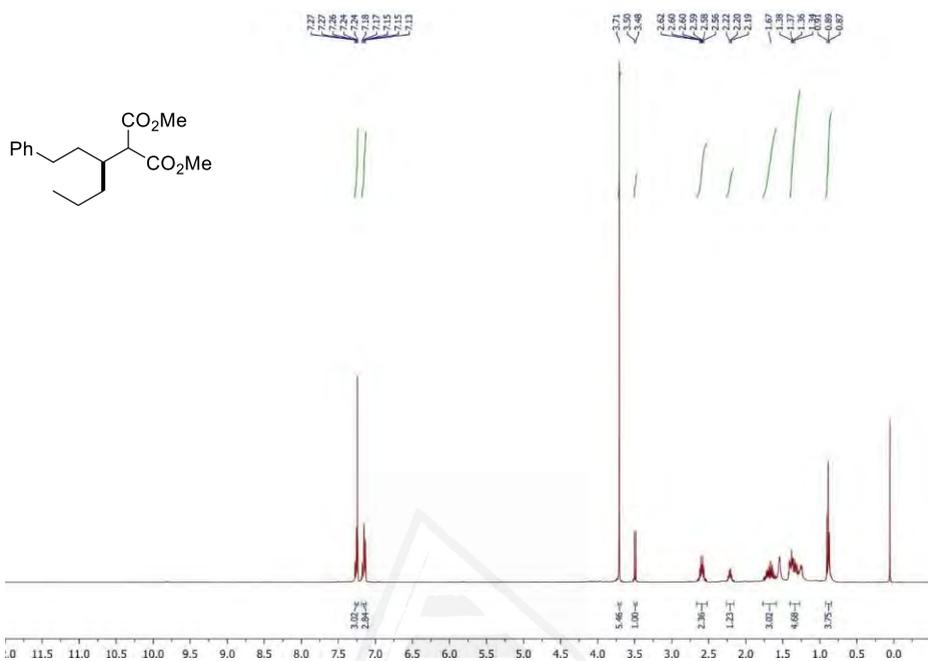




Universitat d'Alacant
Universidad de Alicante







The corresponding paper of this research can be found with the following reference:

A. Gualandi, D. Mazzarella, A. Ortega-Martínez, L. Mengozzi, F. Calcinelli, E. Matteucci, F. Monti, N. Armaroli, L. Sambri and P. G. Cozzi, *ACS Catal.*, 2017, **7**, 5357–5362.

DOI: 10.1021/acscatal.7b01669



Universitat d'Alacant
Universidad de Alicante



REFERENCES

Universitat d'Alacant
Universidad de Alicante

- 1 J. S. Bindra, *Alkaloids Chem. Physiol.*, 1973, **14**, 83–121.
- 2 R. C. Elderfield and R. E. Gilman, *Phytochemistry*, 1972, **11**, 339–343.
- 3 A. Jossang, P. Jossang, H. A. Hadi, T. Sévenet and B. Bodo, *J. Org. Chem.*, 1991, **56**, 6527–6530.
- 4 N. Anderton, P. A. Cockrum, S. M. Colegate, J. A. Edgar, K. Flower, I. Vit and R. I. Willing, *Phytochemistry*, 1998, **48**, 437–439.
- 5 S. Sakai, N. Aimi, H. Yamaguchi, H. Ohhira, K. Hori and J. Haginiwa, *Tetrahedron Lett.*, 1975, **16**, 719–722.
- 6 O. Dideberg, J. Lamotte-Brasseur, L. Dupont, H. Campsteyn, M. Vermeire and L. Angenot, *Acta Crystallogr. Sect. B*, 1975, **33**, 1796–1801.
- 7 C. Bin Cui, H. Kakeya and H. Osada, *Tetrahedron*, 1996, **52**, 12651–12666.
- 8 T. Choshi and S. Hibino, *Nat. Prod. Rep.*, 2001, **18**, 66–87.
- 9 Y. Kamano, H. Zhang, Y. Ichihara, H. Kizu, K. Komiyama and G. R. Pettit, *Tetrahedron Lett.*, 1995, **36**, 2783–2784.
- 10 H. Takayama, T. Shimizu, H. Sada, Y. Harada, M. Kitajima and N. Aimi, *Tetrahedron*, 1999, **55**, 6841–6846.
- 11 H. B. Rasmussen and J. K. MacLeod, *J. Nat. Prod.*, 1997, **60**, 1152–1154.
- 12 A. Huang, J. J. Kodanko and L. E. Overman, *J. Am. Chem. Soc.*, 2004, **126**, 14043–14053.
- 13 M. Sano, K. Bell, K. Marder, L. Stricks, S. Yaakov and R. Mayeux, *Clin. Neuropharmacol.*, 1993, **16**, 61–69.
- 14 J. S. Carié and C. Christophersen, *J. Org. Chem.*, 1980, **45**, 1586–1589.
- 15 T. F. Spande, M. W. Edwards, L. K. Pannell, J. W. Daly, V. Erspamer and P. Melchiorri, *J. Org. Chem.*, 1988, **53**, 1222–

1226.

- 16 F. Zhou, Y. L. Liu and J. Zhou, *Adv. Synth. Catal.*, 2010, **352**, 1381–1407.
- 17 M. Suchý, P. Kutschy, K. Monde, H. Goto, N. Harada, M. Takasugi, M. Dzurilla and E. Balentová, *J. Org. Chem.*, 2001, **66**, 3940–3947.
- 18 K. Stratmann, R. E. Moore, G. M. L. Patterson, R. Bonjouklian, J. B. Deeter, S. Shaffer, T. A. Smitka and C. D. Smith, *J. Am. Chem. Soc.*, 1994, **116**, 9935–9942.
- 19 D. J. Hart and N. Magomedov, *Tetrahedron Lett.*, 1999, **40**, 5429–5432.
- 20 R. Roskoski, *Biochem. Biophys. Res. Commun.*, 2007, **356**, 323–328.
- 21 T. Jiang, K. L. Kuhen, K. Wolff, H. Yin, K. Bieza, J. Caldwell, B. Bursulaya, T. Y. H. Wu and Y. He, *Bioorganic Med. Chem. Lett.*, 2006, **16**, 2105–2108.
- 22 T. Jiang, K. L. Kuhen, K. Wolff, H. Yin, K. Bieza, J. Caldwell, B. Bursulaya, T. Y. H. Wu and Y. He, *Bioorganic Med. Chem. Lett.*, 2006, **16**, 2109–2112.
- 23 T. Tokunaga, W. E. Hume, T. Umezome, K. Okazaki, Y. Ueki, K. Kumagai, S. Hourai, J. Nagamine, H. Seki, M. Taiji, H. Noguchi and R. Nagata, *J. Med. Chem.*, 2001, **44**, 4641–4649.
- 24 H. Kitamura, A. Kato and T. Esaki, *Eur. J. Pharmacol.*, 2001, **418**, 225–230.
- 25 J. Ferlay, I. Soerjomataram, R. Dikshit, S. Eser, C. Mathers, M. Rebelo, D. M. Parkin, D. Forman and F. Bray, *Int. J. Cancer*, 2015, **136**, E359–E386.
- 26 A. Cane, M.-C. Tournaire, D. Barritault and M. Crumeyrolle-Arias, *Biochem. Biophys. Res. Commun.*, 2000, **276**, 379–384.
- 27 H. N. Bramson, J. Corona, S. T. Davis, S. H. Dickerson, M. Edelstein, S. V. Frye, R. T. Gampe, P. A. Harris, A. Hassel,

- W. D. Holmes, R. N. Hunter, K. E. Lackey, B. Lovejoy, M. J. Luzzio, V. Montana, W. J. Rocque, D. Rusnak, L. Shewchuk, J. M. Veal, D. H. Walker and L. F. Kuyper, *J. Med. Chem.*, 2001, **44**, 4339–4358.
- 28 A. Dermatakis, K. C. Luk and W. DePinto, *Bioorganic Med. Chem.*, 2003, **11**, 1873–1881.
- 29 K. C. Luk, M. E. Simcox, A. Schutt, K. Rowan, T. Thompson, Y. Chen, U. Kammlott, W. DePinto, P. Dunten and A. Dermatakis, *Bioorganic Med. Chem. Lett.*, 2004, **14**, 913–917.
- 30 E. R. Wood, L. Kuyper, K. G. Petrov, R. N. Hunter, P. A. Harris and K. Lackey, *Bioorganic Med. Chem. Lett.*, 2004, **14**, 953–957.
- 31 G. D. Zhu, V. B. Gandhi, J. Gong, Y. Luo, X. Liu, Y. Shi, R. Guan, S. R. Magnone, V. Klinghofer, E. F. Johnson, J. Bouska, A. Shoemaker, A. Oleksijew, K. Jarvis, C. Park, R. De Jong, T. Oltersdorf, Q. Li, S. H. Rosenberg and V. L. Giranda, *Bioorganic Med. Chem. Lett.*, 2006, **16**, 3424–3429.
- 32 S. R. Yong, A. T. Ung, S. G. Pyne, B. W. Skelton and A. H. White, *Tetrahedron*, 2007, **63**, 5579–5586.
- 33 V. C. da Silveira, J. S. Luz, C. C. Oliveira, I. Graziani, M. R. Ciriolo and A. M. da C. Ferreira, *J. Inorg. Biochem.*, 2008, **102**, 1090–1103.
- 34 H. Hong, L. J. Huang and D. W. Teng, *Chinese Chem. Lett.*, 2011, **22**, 1009–1012.
- 35 A. Kamal, G. Ramakrishna, P. Raju, A. V. S. Rao, A. Viswanath, V. L. Nayak and S. Ramakrishna, *Eur. J. Med. Chem.*, 2011, **46**, 2427–2435.
- 36 C. Guo, M. Pairish, A. Linton, S. Kephart, M. Ornelas, A. Nagata, B. Burke, L. Dong, J. Engebretsen and A. N. Fanjul, *Bioorganic Med. Chem. Lett.*, 2012, **22**, 2572–2578.
- 37 G. Nesi, S. Sestito, V. Mey, S. Ricciardi, M. Falasca, R. Danesi, A. Lapucci, M. C. Breschi, S. Fogli and S. Rapposelli,

- ACS Med. Chem. Lett.*, 2013, **4**, 1137–1141.
- 38 C. J. A. Ribeiro, J. D. Amaral, C. M. P. Rodrigues, R. Moreira and M. M. M. Santos, *Bioorganic Med. Chem.*, 2014, **22**, 577–584.
- 39 Y. A. Ivanenkov, S. V. Vasilevski, E. K. Beloglazkina, M. E. Kukushkin, A. E. Machulkin, M. S. Veselov, N. V. Chufarova, E. S. Chernyaginab, A. S. Vanzcool, N. V. Zyk, D. A. Skvortsov, A. A. Khutornenko, A. L. Rusanov, A. G. Tonevitsky, O. A. Dontsova and A. G. Majouga, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 404–409.
- 40 Â. Monteiro, L. M. Gonçalves and M. M. M. Santos, *Eur. J. Med. Chem.*, 2014, **79**, 266–272.
- 41 P. Sai Prathima, P. Rajesh, J. Venkateswara Rao, U. Sai Kailash, B. Sridhar and M. Mohan Rao, *Eur. J. Med. Chem.*, 2014, **84**, 155–159.
- 42 B. Yu, X. J. Shi, P. P. Qi, D. Q. Yu and H. M. Liu, *J. Steroid Biochem. Mol. Biol.*, 2014, **141**, 121–134.
- 43 L. Guariguata, D. R. Whiting, I. Hambleton, J. Beagley, U. Linnenkamp and J. E. Shaw, *Diabetes Res. Clin. Pract.*, 2014, **103**, 137–149.
- 44 American Diabetes Association, *Diabetes Care*, 2014, **37**, 81–90.
- 45 M. Khan, M. Yousaf, A. Wadood, M. Junaid, M. Ashraf, U. Alam, M. Ali, M. Arshad, Z. Hussain and K. M. Khan, *Bioorganic Med. Chem.*, 2014, **22**, 3441–3448.
- 46 M. Kaur, M. Singh, N. Chadha and O. Silakari, *Eur. J. Med. Chem.*, 2016, **123**, 858–894.
- 47 N. Midoh, A. Tanaka, M. Nagayasu, C. Furuta, K. Suzuki, T. Ichikawa, T. Isomura and K. Nomura, *Biosci. Biotechnol. Biochem.*, 2010, **74**, 1794–1801.
- 48 D. Yasuda, K. Takahashi, T. Ohe, S. Nakamura and T.

- Mashino, *Bioorganic Med. Chem.*, 2013, **21**, 7709–7714.
- 49 European Food Safety Authority, *EFSA J.*, 2012, **10**, 2588.
- 50 R. Kekkonen, H. B. Croxatto, P. Lahteenmaki, A. M. Salvatierra and J. Tuominen, *Hum. Reprod.*, 1995, **10**, 287–292.
- 51 A. Fensome, R. Bender, J. Cohen, M. A. Collins, V. A. Mackner, L. L. Miller, J. W. Ullrich, R. Winneker, J. Wrobel, P. Zhang, Z. Zhang and Y. Zhu, *Bioorganic Med. Chem. Lett.*, 2002, **12**, 3487–3490.
- 52 P. Hewawasam, V. K. Gribkoff, Y. Pendri, S. I. Dworetzky, N. A. Meanwell, E. Martinez, C. G. Boissard, D. J. Post-Munson, J. T. Trojnacki, K. Yeleswaram, L. M. Pajor, J. Knipe, Q. Gao, R. Perrone and J. E. Starrett, *Bioorganic Med. Chem. Lett.*, 2002, **12**, 1023–1026.
- 53 M. Singh, M. Kaur, H. Kukreja, R. Chugh, O. Silakari and D. Singh, *Eur. J. Med. Chem.*, 2013, **70**, 165–188.
- 54 Z. J. Zhan, H. L. Bian, J. W. Wang and W. G. Shan, *Bioorganic Med. Chem. Lett.*, 2010, **20**, 1532–1534.
- 55 R. E. Becker and N. H. Greig, *Curr. Alzheimer Res.*, 2012, **9**, 1174–1181.
- 56 M. A. Ali, R. Ismail, T. S. Choon, Y. K. Yoon, A. C. Wei, S. Pandian, R. S. Kumar, H. Osman and E. Manogaran, *Bioorganic Med. Chem. Lett.*, 2010, **20**, 7064–7066.
- 57 M. A. Ali, R. Ismail, T. S. Choon, R. S. Kumar, H. Osman, N. Arumugam, A. I. Almansour, K. Elumalai and A. Singh, *Bioorganic Med. Chem. Lett.*, 2012, **22**, 508–511.
- 58 Y. Kia, H. Osman, R. S. Kumar, V. Murugaiyah, A. Basiri, S. Perumal, H. A. Wahab and C. S. Bing, *Bioorganic Med. Chem.*, 2013, **21**, 1696–1707.
- 59 P. Cohen, *Nat. Rev. Drug Discov.*, 2002, **1**, 309–315.
- 60 K. Lackey, M. Cory, R. Davis, S. V. Frye, P. A. Harris, R. N.

- Hunter, D. K. Jung, O. B. McDonald, R. W. McNutt, M. R. Peel, R. D. Rutkowske, J. M. Veal and E. R. Wood, *Bioorganic Med. Chem. Lett.*, 2000, **10**, 223–226.
- 61 J. Y. Q. Lai, P. J. Cox, R. Patel, S. Sadiq, D. J. Aldous, S. Thurairatnam, K. Smith, D. Wheeler, S. Jagpal, S. Parveen, G. Fenton, T. K. . Harrison, C. McCarthy and P. Bamborough, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 3111–3114.
- 62 J. W. Lockman, M. D. Reeder, R. Robinson, P. A. Ormonde, D. M. Cimbora, B. L. Williams and J. A. Willardsen, *Bioorganic Med. Chem. Lett.*, 2011, **21**, 1724–1727.
- 63 M. H. Kim, A. L. Tsuhako, E. W. Co, D. T. Aftab, F. Bentzien, J. Chen, W. Cheng, S. Engst, L. Goon, R. R. Klein, D. T. Le, M. Mac, J. J. Parks, F. Qian, M. Rodriguez, T. J. Stout, J. H. Till, K.-A. Won, X. Wu, F. M. Yakes, P. Yu, W. Zhang, Y. Zhao, P. Lamb, J. M. Nuss and W. Xu, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 4979–4985.
- 64 L. F. Yu, Y. Y. Li, M. B. Su, M. Zhang, W. Zhang, L. N. Zhang, T. Pang, R. T. Zhang, B. Liu, J. Y. Li, J. Li and F. J. Nan, *ACS Med. Chem. Lett.*, 2013, **4**, 475–480.
- 65 S. B. Singh, K. Tiwari, P. K. Verma, M. Srivastava, K. P. Tiwari and J. Singh, *Supramol. Chem.*, 2013, **25**, 255–262.
- 66 H. Singh, J. Sindhu, J. M. Khurana, C. Sharma and K. R. Aneja, *Eur. J. Med. Chem.*, 2014, **77**, 145–154.
- 67 J. Alvar, I. D. Vélez, C. Bern, M. Herrero, P. Desjeux, J. Cano, J. Jannin and M. de Boer, *PLoS One*, 2012, **7**, e35671.
- 68 A. Scala, M. Cordaro, G. Grassi, A. Piperno, G. Barberi, A. Cascio and F. Risitano, *Bioorganic Med. Chem.*, 2014, **22**, 1063–1069.
- 69 L. J. Emorine, S. Marullo, M. M. Briend-Sutren, G. Patey, K. Tate, C. Delavier-Klutchko and A. D. Strosberg, *Science*, 1989, **245**, 1118–1121.
- 70 F. C. Stevens, W. E. Bloomquist, A. G. Borel, M. L. Cohen, C.

- A. Droste, M. L. Heiman, A. Kriauciunas, D. J. Sall, F. C. Tinsley and C. D. Jesudason, *Bioorganic Med. Chem. Lett.*, 2007, **17**, 6270–6273.
- 71 H. Higashi, R. Tsutsumi, S. Muto, T. Sugiyama, T. Azuma, M. Asaka and M. Hatakeyama, *Science*, 2002, **295**, 683–686.
- 72 H. R. Lawrence, R. Pireddu, L. Chen, Y. Luo, S. S. Sung, A. M. Szymanski, M. L. R. Yip, W. C. Guida, S. M. Sebti, J. Wu and N. J. Lawrence, *J. Med. Chem.*, 2008, **51**, 4948–4956.
- 73 J. A. Kemp and R. M. McKernan, *Nat. Neurosci.*, 2002, **5**, 1039–1042.
- 74 B. L. Chenard, I. A. Shalaby, B. K. Koe, R. T. Ronau, T. W. Butler, M. A. Prochniak, A. W. Schmidt and C. B. Fox, *J. Med. Chem.*, 1991, **34**, 3085–3090.
- 75 B. Chenard and T. Butler, *Bioorg. Med. Chem. Lett.*, 1993, 91–94.
- 76 P. Paira, A. Hazra, S. Kumar, R. Paira, K. B. Sahu, S. Naskar, P. Saha, S. Mondal, A. Maity, S. Banerjee and N. B. Mondal, *Bioorganic Med. Chem. Lett.*, 2009, **19**, 4786–4789.
- 77 T. Oost, G. Backfisch, S. Bhowmik, M. M. Van Gaalen, H. Geneste, W. Hornberger, W. Lubisch, A. Netz, L. Unger and W. Wernet, *Bioorganic Med. Chem. Lett.*, 2011, **21**, 3828–3831.
- 78 S. Chowdhury, M. Chafeev, S. Liu, J. Sun, V. Raina, R. Chui, W. Young, R. Kwan, J. Fu and J. A. Cadieux, *Bioorganic Med. Chem. Lett.*, 2011, **21**, 3676–3681.
- 79 P. G. Cozzi, R. Hilgraf and N. Zimmermann, *European J. Org. Chem.*, 2007, 5969–5994.
- 80 R. Shintani, M. Inoue and T. Hayashi, *Angew. Chemie - Int. Ed.*, 2006, **45**, 3353–3356.
- 81 P. Y. Toullec, R. B. C. Jagt, J. G. De Vries, B. L. Feringa and A. J. Minnaard, *Org. Lett.*, 2006, **8**, 2715–2718.

- 82 D. Tomita, K. Yamatsugu, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2009, **131**, 6946–6948.
- 83 J. Itoh, S. B. Han and M. J. Krische, *Angew. Chemie - Int. Ed.*, 2009, **48**, 6313–6316.
- 84 G. Luppi, P. G. Cozzi, M. Monari, B. Kaptein, Q. B. Broxterman and C. Tomasini, *J. Org. Chem.*, 2005, **70**, 7418–7421.
- 85 G. Angelici, R. J. Corrêa, S. J. Garden and C. Tomasini, *Tetrahedron Lett.*, 2009, **50**, 814–817.
- 86 J. R. Chen, X. P. Liu, X. Y. Zhu, L. Li, Y. F. Qiao, J. M. Zhang and W. J. Xiao, *Tetrahedron*, 2007, **63**, 10437–10444.
- 87 S. Nakamura, N. Hara, H. Nakashima, K. Kubo, N. Shibata and T. Toru, *Chem. Eur. J.*, 2008, **14**, 8079–8081.
- 88 N. Hara, S. Nakamura, N. Shibata and T. Toru, *Chem. Eur. J.*, 2009, **15**, 6790–6793.
- 89 F. Xue, S. Zhang, L. Liu, W. Duan and W. Wang, *Chem. - An Asian J.*, 2009, **4**, 1664–1667.
- 90 X. Cheng, S. Vellalath, R. Goddard and B. List, *J. Am. Chem. Soc.*, 2008, **130**, 15786–15787.
- 91 N. V. Hanhan, A. H. Sahin, T. W. Chang, J. C. Fettinger and A. K. Franz, *Angew. Chemie - Int. Ed.*, 2010, **49**, 744–747.
- 92 S. Duce, F. Pesciaioli, L. Gramigna, L. Bernardi, A. Mazzanti, A. Ricci, G. Bartoli and G. Bencivenni, *Adv. Synth. Catal.*, 2011, **353**, 860–864.
- 93 K. Mori, T. Yamauchi, J. Maddaluno, K. Nakano, Y. Ichikawa and H. Kotsuki, *Synlett*, 2011, 2080–2084.
- 94 L. T. Shen, P. L. Shao and S. Ye, *Adv. Synth. Catal.*, 2011, **353**, 1943–1948.
- 95 X. Jiang, Y. Cao, Y. Wang, L. Liu, F. Shen and R. Wang, *J. Am. Chem. Soc.*, 2010, **132**, 15328–15333.

- 96 X. N. Wang, Y. Y. Zhang and S. Ye, *Adv. Synth. Catal.*, 2010, **352**, 1892–1895.
- 97 Y.-L. Liu and J. Zhou, *Chem. Commun.*, 2012, **48**, 1919.
- 98 L. Liu, S. Zhang, F. Xue, G. Lou, H. Zhang, S. Ma, W. Duan and W. Wang, *Chem. Eur. J.*, 2011, **17**, 7791–7795.
- 99 X. Y. Guan, Y. Wei and M. Shi, *Chem. Eur. J.*, 2010, **16**, 13617–13621.
- 100 L. Peng, L. L. Wang, J. F. Bai, L. N. Jia, Q. C. Yang, Q. C. Huang, X. Y. Xu and L. X. Wang, *Tetrahedron Lett.*, 2011, **52**, 1157–1160.
- 101 A. Ashimori, T. Matsuura, L. E. Overman and D. J. Poon, *J. Org. Chem.*, 1993, **58**, 6949–6951.
- 102 A. B. Dounay, K. Hatanaka, J. J. Kodanko, M. Oestreich, L. E. Overman, L. A. Pfeifer and M. M. Weiss, *J. Am. Chem. Soc.*, 2003, **125**, 6261–6271.
- 103 C. A. Busacca, D. Grossbach, R. C. So, E. M. O'Brien and E. M. Spinelli, *Org. Lett.*, 2003, **5**, 595–598.
- 104 A. Pinto, Y. Jia, L. Neuville and J. Zhu, *Chem. Eur. J.*, 2007, **13**, 961–967.
- 105 S. Lee and J. F. Hartwig, *J. Org. Chem.*, 2001, **66**, 3402–3415.
- 106 E. P. Kündig, T. M. Seidel, Y. X. Jia and G. Bernardinelli, *Angew. Chemie - Int. Ed.*, 2007, **46**, 8484–8487.
- 107 Y. Yasui, H. Kamisaki and Y. Takemoto, *Org. Lett.*, 2008, **10**, 3303–3306.
- 108 B. M. Trost, N. Cramer and S. M. Silverman, *J. Am. Chem. Soc.*, 2007, **129**, 12396–12397.
- 109 G. Bencivenni, L. Y. Wu, A. Mazzanti, B. Giannichi, F. Pesciaioli, M. P. Song, G. Bartoli and P. Melchiorre, *Angew. Chemie - Int. Ed.*, 2009, **48**, 7200–7203.
- 110 X. Chen, Q. Wei, S. Luo, H. Xiao and L. Gong, *J. Am. Chem.*

- Soc.*, 2009, **131**, 13819–13825.
- 111 S. Ma, X. Han, S. Krishnan, S. C. Virgil and B. M. Stoltz, *Angew. Chemie - Int. Ed.*, 2009, **48**, 8037–8041.
- 112 I. D. Hills and G. C. Fu, *Angew. Chemie - Int. Ed.*, 2003, **42**, 3921–3924.
- 113 T. A. Duffey, S. A. Shaw and E. Vedejs, *J. Am. Chem. Soc.*, 2009, **131**, 14–15.
- 114 B. M. Trost and M. K. Brennan, *Org. Lett.*, 2006, **8**, 2027–2030.
- 115 V. Franckevičius, J. D. Cuthbertson, M. Pickworth, D. S. Pugh and R. J. K. Taylor, *Org. Lett.*, 2011, **13**, 4264–4267.
- 116 F. G. Bordwell and H. E. Fried, *J. Org. Chem.*, 1991, **56**, 4218–4223.
- 117 T. B. K. Lee and G. S. K. Wong, *J. Org. Chem.*, 1991, **56**, 872–875.
- 118 B. M. Trost and M. U. Frederiksen, *Angew. Chemie - Int. Ed.*, 2005, **44**, 308–310.
- 119 B. M. Trost and Y. Zhang, *J. Am. Chem. Soc.*, 2006, **128**, 4590–4591.
- 120 B. M. Trost and Y. Zhang, *J. Am. Chem. Soc.*, 2007, **129**, 14548–14549.
- 121 K. Jiang, J. Peng, H.-L. Cui and Y.-C. Chen, *Chem. Commun.*, 2009, 3955–3957.
- 122 Y. Hamashima, T. Suzuki, H. Takano, Y. Shimura and M. Sodeoka, *J. Am. Chem. Soc.*, 2005, **127**, 10164–10165.
- 123 N. Shibata, J. Kohno, K. Takai, T. Ishimaru, S. Nakamura, T. Toru and S. Kanemasa, *Angew. Chemie - Int. Ed.*, 2005, **44**, 4204–4207.
- 124 T. Ishimaru, N. Shibata, T. Horikawa, N. Yasuda, S. Nakamura, T. Toru and M. Shiro, *Angew. Chemie - Int. Ed.*,

- 2008, **47**, 4157–4161.
- 125 S. Ogawa, N. Shibata, J. Inagaki, S. Nakamura, T. Toru and M. Shiro, *Angew. Chemie - Int. Ed.*, 2007, **46**, 8666–8669.
- 126 X. Tian, K. Jiang, J. Peng, W. Du and Y. C. Chen, *Org. Lett.*, 2008, **10**, 3583–3586.
- 127 R. He, C. Ding and K. Maruoka, *Angew. Chemie - Int. Ed.*, 2009, **48**, 4559–4561.
- 128 P. Galzerano, G. Bencivenni, F. Pesciaioli, A. Mazzanti, B. Giannichi, L. Sambri, G. Bartoli and P. Melchiorre, *Chem. Eur. J.*, 2009, **15**, 7846–7849.
- 129 T. Bui, S. Syed and C. F. Barbas III, *J. Am. Chem. Soc.*, 2009, **131**, 8758–8759.
- 130 R. He, S. Shirakawa and K. Maruoka, *J. Am. Chem. Soc.*, 2009, **131**, 16620–16621.
- 131 A. M. Taylor, R. A. Altman and S. L. Buchwald, *J. Am. Chem. Soc.*, 2009, **131**, 9900–9901.
- 132 A. J. Grenning and J. A. Tunge, *Angew. Chemie - Int. Ed.*, 2011, **50**, 1688–1691.
- 133 A. J. Grenning and J. A. Tunge, *J. Am. Chem. Soc.*, 2011, **133**, 14785–14794.
- 134 A. J. Grenning, C. K. Van Allen, T. Maji, S. B. Lang and J. A. Tunge, *J. Org. Chem.*, 2013, **78**, 7281–7287.
- 135 X. Le Zhou, L. Ren and P. S. Wang, *J. Org. Chem.*, 2017, **82**, 9794–9800.
- 136 T. Maji, K. Ramakumar and J. A. Tunge, *Chem. Commun.*, 2014, **50**, 14045–14048.
- 137 C.-C. Lo and P.-M. Chao, *J. Chem. Ecol.*, 1990, **16**, 3245–3253.
- 138 M. Jha, T. Y. Chou and B. Blunt, *Tetrahedron*, 2011, **67**, 982–989.

- 139 Q. B. Zhang, W. L. Jia, Y. L. Ban, Y. Zheng, Q. Liu and L. Z. Wu, *Chem. Eur. J.*, 2016, **22**, 2595–2598.
- 140 A. M. Shelke and G. Suryavanshi, *Org. Biomol. Chem.*, 2015, **13**, 8669–8675.
- 141 P. B. Sampson, Y. Liu, B. Forrest, G. Cumming, S. W. Li, N. K. Patel, L. Edwards, R. Laufer, M. Feher, F. Ban, D. E. Awrey, G. Mao, O. Plotnikova, R. Hodgson, I. Beletskaya, J. M. Mason, X. Luo, V. Nadeem, X. Wei, R. Kiarash, B. Madeira, P. Huang, T. W. Mak, G. Pan and H. W. Pauls, *J. Med. Chem.*, 2015, **58**, 147–169.
- 142 X. D. Xia, L. Q. Lu, W. Q. Liu, D. Z. Chen, Y. H. Zheng, L. Z. Wu and W. J. Xiao, *Chem. Eur. J.*, 2016, **22**, 8432–8437.
- 143 H. M. Hugel, R. J. Greenwood and M. F. Mackay, *Aust. J. Chem.*, 1992, **45**, 1953–1959.
- 144 X. Ju, Y. Liang, P. Jia, W. Li and W. Yu, *Org. Biomol. Chem.*, 2012, **10**, 498–501.
- 145 N. Kikue, T. Takahashi and H. Nishino, *Heterocycles*, 2015, **90**, 540–562.
- 146 B. M. Trost and Y. Zhang, *Chem. Eur. J.*, 2011, **17**, 2916–2922.
- 147 Y. Zhou, Y. Zhao, X. Dai, J. Liu, L. Li and H. Zhang, *Org. Biomol. Chem.*, 2011, **9**, 4091.
- 148 B. Zhou, W. Hou, Y. Yang, H. Feng and Y. Li, *Org. Lett.*, 2014, **16**, 1322–1325.
- 149 E. C. Linton and M. C. Kozlowski, *J. Am. Chem. Soc.*, 2008, **130**, 16162–16163.
- 150 H. Yang, H. Zhou, H. Yin, C. Xia and G. Jiang, *Synlett*, 2014, **25**, 2149–2254.
- 151 N. Kumar, M. K. Das, S. Ghosh and A. Bisai, *Chem. Commun.*, 2017, **53**, 2170–2173.

- 152 Y. Tamaru, Y. Horino, M. Araki, S. Tanaka and M. Kimura, *Tetrahedron Lett.*, 2000, **41**, 5705–5709.
- 153 K. Ohmatsu, Y. Ando and T. Ooi, *Synlett*, 2017, **28**, 1291–1294.
- 154 Y. J. Jang, H. Yoon and M. Lautens, *Org. Lett.*, 2015, **17**, 3895–3897.
- 155 I. Shin, S. D. Ramgren and M. J. Krische, *Tetrahedron*, 2015, **71**, 5776–5780.
- 156 M. Ghandi, S. Feizi, F. Ziaie and B. Notash, *Tetrahedron*, 2014, **70**, 2563–2569.
- 157 C. Zhao, Z. Tan, Z. Liang, W. Deng and H. Gong, *Synthesis*, 2014, **46**, 1901–1907.
- 158 B. Alcaide, P. Almendros and R. Rodríguez-Acebes, *J. Org. Chem.*, 2005, **70**, 3198–3204.
- 159 H. L. Wang, Y. M. Li, G. W. Wang, H. Zhang and S. D. Yang, *Asian J. Org. Chem.*, 2013, **2**, 486–490.
- 160 L. K. Kinthada, S. R. Medisetty, A. Parida, K. N. Babu and A. Bisai, *J. Org. Chem.*, 2017, **82**, 8548–8567.
- 161 Y. Zhu, H. Mei, J. Han, V. A. Soloshonok, J. Zhou and Y. Pan, *J. Org. Chem.*, 2017, **82**, 13663–13670.
- 162 N. Liu, Q. P. Tian, Q. Yang and S. D. Yang, *Synlett*, 2016, **27**, 2621–2625.
- 163 K. Dong, B. Yan, S. Chang, Y. Chi, L. Qiu and X. Xu, *J. Org. Chem.*, 2016, **81**, 6887–6892.
- 164 C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.*, 2013, **113**, 5322–5363.
- 165 J. W. Tucker and C. R. J. Stephenson, *J. Org. Chem.*, 2012, **77**, 1617–1622.
- 166 N. H. Damrauer, G. Cerullo, A. Yeh, T. R. Boussie, C. V. Shank and J. K. McCusker, *Science*, 1997, **275**, 54–57.

- 167 A. Juris, V. Balzani, F. Barigelletti, S. Campagna, P. Belser and A. von Zelewsky, *Coord. Chem. Rev.*, 1988, **84**, 85–277.
- 168 K. Hironaka, S. Fukuzumi and T. Tanaka, *J. Chem. Soc., Perkin Trans. 2*, 1984, 1705.
- 169 J. D. Nguyen, E. M. D'Amato, J. M. R. Narayanam and C. R. J. Stephenson, *Nat. Chem.*, 2012, **4**, 854–859.
- 170 M. H. Larraufie, R. Pellet, L. Fensterbank, J. P. Goddard, E. Lacôte, M. Malacria and C. Ollivier, *Angew. Chemie - Int. Ed.*, 2011, **50**, 4463–4466.
- 171 J. W. Tucker, J. M. R. Narayanam, P. S. Shah and C. R. J. Stephenson, *Chem. Commun.*, 2011, **47**, 5040.
- 172 A. G. Condie, J. C. González-Gómez and C. R. J. Stephenson, *J. Am. Chem. Soc.*, 2010, **132**, 1464–1465.
- 173 Y. Q. Zou, L. Q. Lu, L. Fu, N. J. Chang, J. Rong, J. R. Chen and W. J. Xiao, *Angew. Chemie - Int. Ed.*, 2011, **50**, 7171–7175.
- 174 D. A. Nicewicz and D. W. C. Macmillan, *Science*, 2008, **322**, 77–80.
- 175 Y. Miyake, Y. Ashida, K. Nakajima and Y. Nishibayashi, *Chem. Commun.*, 2012, **48**, 6966.
- 176 F. O'Hara, R. D. Baxter, A. G. O'Brien, M. R. Collins, J. A. Dixon, Y. Fujiwara, Y. Ishihara and P. S. Baran, *Nat. Protoc.*, 2013, **8**, 1042–1047.
- 177 M. Galicia and F. J. González, *J. Electrochem. Soc.*, 2002, **149**, D46.
- 178 A. U. Meyer, K. Straková, T. Slanina and B. König, *Chem. Eur. J.*, 2016, **22**, 8694–8699.
- 179 M. Yan, J. C. Lo, J. T. Edwards and P. S. Baran, *J. Am. Chem. Soc.*, 2016, **138**, 12692–12714.
- 180 A. U. Meyer, S. Jäger, D. Prasad Hari and B. König, *Adv.*

- Synth. Catal.*, 2015, **357**, 2050–2054.
- 181 M. Silvi, C. Verrier, Y. P. Rey, L. Buzzetti and P. Melchiorre, *Nat. Chem.*, 2017, **9**, 868–873.
- 182 R. Zhou, H. Liu, H. Tao, X. Yu and J. Wu, *Chem. Sci.*, 2017, **8**, 4654–4659.
- 183 S. Fukuzumi, H. Kotani, K. Ohkubo, S. Ogo, N. V. Tkachenko and H. Lemmetyinen, *J. Am. Chem. Soc.*, 2004, **126**, 1600–1601.
- 184 E. Lindner, D. W. R. Frembs and D. Krug, *Chem. Ber.*, 1975, **108**, 291–300.
- 185 N. Chumachenko and P. Sampson, *Tetrahedron*, 2006, **62**, 4540–4548.
- 186 F. Freeman, C. N. Angeletakis and T. J. Maricich, *Org. Magn. Reson.*, 1981, **17**, 53–58.
- 187 T. Okada, H. Matsumuro, T. Iwai, S. Kitagawa, K. Yamazaki, T. Akiyama, T. Asawa, Y. Sugiyama, Y. Kimura and M. Kirihara, *Chem. Lett.*, 2015, **44**, 185–187.
- 188 K. Qiu and R. Wang, *Synthesis*, 2015, **47**, 3186–3190.
- 189 Y. Ueno, A. Kojima and O. Makoto, *Chem. Lett.*, 1984, **13**, 2125–2128.
- 190 L. Laraia, K. Ohsawa, G. Konstantinidis, L. Robke, Y. W. Wu, K. Kumar and H. Waldmann, *Angew. Chemie - Int. Ed.*, 2017, **56**, 2145–2150.
- 191 M. Ueda, E. Kondoh, Y. Ito, H. Shono, M. Kakiuchi, Y. Ichii, T. Kimura, T. Miyoshi, T. Naito and O. Miyata, *Org. Biomol. Chem.*, 2011, **9**, 2062–2064.
- 192 Y. X. Gao, L. Chang, H. Shi, B. Liang, K. Wongkhan, D. Chaiyaveij, A. S. Batsanov, T. B. Marder, C. C. Li, Z. Yang and Y. Huang, *Adv. Synth. Catal.*, 2010, **352**, 1955–1966.
- 193 G. Wu, Y. Deng, C. Wu, Y. Zhang and J. Wang, *Angew.*

- Chemie - Int. Ed.*, 2014, **53**, 10510–10514.
- 194 X. J. Dai, H. Wang and C. J. Li, *Angew. Chemie - Int. Ed.*, 2017, **56**, 6302–6306.
- 195 M. Jegelka and B. Plietker, *Chem. Eur. J.*, 2011, **17**, 10417–10430.
- 196 J. D. Hargrave, J. Herbert, G. Bish and C. G. Frost, *Org. Biomol. Chem.*, 2006, **4**, 3235–3241.



Universitat d'Alacant
Universidad de Alicante



ABBREVIATIONS

Universitat d'Alacant

Universidad de Alicante

List of abbreviations

1,3-DC: 1,3-dipolar cycloaddition

2,5-DTBQ: 2,5-di-*tert*-butylbenzoquinone

AAA: asymmetric allylic alkylation

AChE: acetylcholinesterase

BINAP: 2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene

BINOL: 1,1'-Bi(2-naphthol)

Bodipy: boron-dipyrromethene

DaA: deacylative alkylation

DCM: dichloromethane

DEAD: diethyl azodicarboxylate

DMAP: 4-(*N,N*-dimethylamino)pyridine

DME: dimethoxyethane

DMF: dimethylformamide

DMSO: dimethyl sulfoxide

DPPH: 2,2-diphenyl-1-picrylhydrazyl

dppp: 1,3-bis(diphenylphosphino)propane

dr: diastereomeric ratio

EC₅₀: half maximal effective concentration

EDG: electron donating group

ee: enantiomeric excess

EtOAc: ethyl acetate

EWG: electron withdrawing group

GC: gas chromatography

HMDS: hexamethyldisilazane

HMPA: hexamethylphosphoramide

HOMO: highest occupied molecular orbital

IC₅₀: half maximal inhibitory concentration

ISC: inter-system crossing

LUMO: lowest unoccupied molecular orbital

NBS: *N*-bromosuccinimide

NFSI: *N*-fluorobenzenesulfonimide

NMDA: *N*-methyl-D-aspartate

NMR: Nuclear magnetic resonance

PG: protecting group

PHOX: phosphinooxazolines

PMB: *p*-methoxybenzyl

PTC: phase-transfer catalysis

SAR: structure-activity relationship

SCE: saturated calomel electrode

SET: single-electron-transfer

TEMPO: 2,2,6,6-tetramethylpiperidin-1-yl-oxyl

TFE: 2,2,2-trifluoroethanol

THF: tetrahydrofuran

TMEDA: *N,N,N',N'*-tetramethylethylenediamine

TRIP: 3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diylhydrogenphosphate

TsOH: *p*-toluenesulfonic acid

TMS: tetramethylsilane

TMSCl: chlorotrimethylsilane

WHO: World Health Organization



Universitat d'Alacant
Universidad de Alicante



RESUMEN EN CASTELLANO
Universitat d'Alacant
Universidad de Alicante

Introducción

En esta tesis doctoral, se describen las investigaciones desarrolladas durante mi doctorado sobre la síntesis de 2-oxindoles 3,3-disustituidos a través de alquilación desacetilativa y la alquilación de alquenos fotocatalizada. Los proyectos acerca de los derivados de oxindoles han sido desarrollados bajo la supervisión de la Profesora Carmen Nájera Domingo y el Profesor José Miguel Sansano Gil y se han desarrollado en el Departamento de Química Orgánica y en el Instituto de Síntesis Orgánica de la Universidad de Alicante (España). En relación a la parte sobre fotocatalisis descrita en la tesis doctoral, ha sido desarrollada durante mi estancia de tres meses en la Universidad de Bolonia (Italia) bajo la supervisión del Profesor Pier Giorgio Cozzi.

La tesis doctoral se divide en una introducción general y cuatro capítulos. En la introducción general, se describen una variedad de productos naturales y compuestos sintéticos que contienen un núcleo de oxindol en su estructura junto a comentarios acerca de sus actividades biológicas. También se incluyen diversas metodologías de síntesis de los susodichos derivados de oxindol. En la última parte de la introducción general, se describe en qué se basa el proceso de alquilación desacetilativa. Respecto a los capítulos, estos se han desarrollado con una breve introducción, la propuesta de objetivos, los comentarios y discusión de los resultados obtenidos y finalmente las conclusiones. El Capítulo 1 describe la síntesis de 2-oxindoles 3,3-disustituidos a través de alquilación desacetilativa utilizando halogenuros de alquilo. El Capítulo 2 describe la alilación y la alilación desacetilativa catalizada por paladio de los 2-oxindoles utilizando alcoholes alílicos no activados. En el Capítulo 3 se describe la síntesis de 3-fluoro-2-oxindoles combinando las metodologías descritas en los dos capítulos anteriores. Finalmente, en el Capítulo 4, se describe la alquilación fotocatalítica de olefinas electrofílicas a través de sulfinatos de zinc bencílicos y alquílicos.

Estos proyectos de investigación han sido financiados por el Ministerio de Economía y Competitividad (proyectos CTQ2013-43446-P y CTQ2014-51912-REDC), el Ministerio de Economía, Industria y Competitividad, la Agencia estatal de Investigación (AEI) y el Fondo Europeo de Desarrollo Regional (FEDER, EU) (proyectos CTQ2016-76782-P y CTQ2016-81797-REDC), la Generalitat Valenciana (PROMETEO2009/039 y PROMETEOII/2014/017) y por la Universidad de Alicante. Además, agradezco al Ministerio de Economía y Competitividad (MINECO) por la concesión de una ayuda para la contratación predoctoral para la formación de doctores (BES-2014-069695).

La mayoría de los resultados descritos en esta tesis doctoral han sido publicados en las siguientes revistas internacionales revisadas por pares:

“*Synthesis of 3,3-Disubstituted 2-Oxindoles by Deacylative Alkylation of 3-Acetyl-2-oxindoles*” A. Ortega-Martínez, C. Molina, C. Moreno-Cabrerizo, J. M. Sansano and C. Nájera, *Synthesis*, 2017, **49**, 5203–5210.

“*Palladium-catalyzed allylation and deacylative allylation of 3-acetyl-2-oxindoles with allylic alcohols*” A. Ortega-Martínez, R. de Lorenzo, J. M. Sansano and C. Nájera, *Tetrahedron*, 2018, **74**, 253–259.

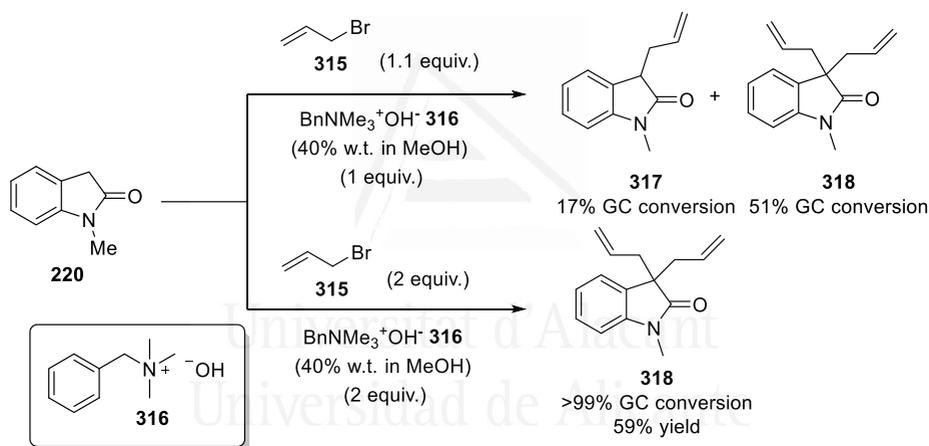
“*Photocatalytic Radical Alkylation of Electrophilic Olefins by Benzylic and Alkyllic Zinc-Sulfonates*” A. Gualandi, D. Mazzarella, A. Ortega-Martínez, L. Mengozzi, F. Calcinelli, E. Matteucci, F. Monti, N. Armaroli, L. Sambri and P. G. Cozzi, *ACS Catal.*, 2017, **7**, 5357–5362.

En la introducción general se muestran diferentes productos naturales como la alstonisina, la horsfilina, la elacomina, diversas convolutamidinas, la fisostigmina, el flustraminol, entre otros. Todos estos productos naturales contienen un núcleo de oxindol en su estructura y presentan diversas actividades biológicas. Además, una gran variedad de productos sintéticos tienen en amplio espectro de aplicaciones terapéuticas y pueden actuar en campos como por ejemplo en el tratamiento del cáncer, la diabetes, contra el virus de la inmunodeficiencia humana (VIH), como antagonistas de la progesterona, en los accidentes cerebrovasculares, como inhibidores de la acetilcolinesterasa, inhibidores de la quinasa, como antibióticos, para el tratamiento de la leishmaniosis, como agonistas de los receptores β_3 adrenérgicos, inhibidores de enzimas que actúan como fosfatasas, bloqueadores de los receptores de *N*-Metil-D-aspartato, como antagonistas de la vasopresina, como analgésicos, entre otros.

En la presente memoria también se han descrito numerosos procedimientos encontrados en la bibliografía para la síntesis de diversos derivados de oxindoles. En dichos procedimientos se pueden encontrar la adición a isatinas, reacciones de acoplamiento intramolecular, el uso de sustratos como las metilendolinonas, reacciones basadas en oxindoles sustituidos en el átomo de oxígeno, alilaciones descarboxilativas catalizadas por paladio, funcionalización directa de 2-oxindoles 3-sustituidos y por último también se explica de manera general cómo funciona el proceso de alquilación desacetilativa. Nuestro grupo de investigación previó que con el uso de esta técnica podría ser posible la obtención de ciertos derivados de oxindol no simétricos. Esta técnica se basa en la ruptura y en la formación de nuevos enlaces carbono-carbono. Este proceso, puede ser llevado a cabo en condiciones suaves de temperatura, generando subproductos en la mayoría de los casos inocuos. Además, permite la formación de carbonos cuaternarios sin emplear las condiciones clásicas de temperaturas muy bajas o bases muy fuertes en ciertos casos. Esta técnica también es muy útil ya que tiene una alta tolerancia a diversos grupos funcionales y una alta quimio y regioselectividad.

Capítulo 1

Los estudios iniciales se centraron en la síntesis del 2-oxindol 3-sustituido empezando desde el sustrato comercial N-metil-2-oxindol. Cuando se hacía reaccionar el compuesto **220** con 1.1 equivalentes de bromuro de alilo **315** como electrófilo y 1 equivalente de la base Triton B **316**, se observó mediante cromatografía de gases un 17% del producto monoalquilado deseado, un 51% del producto dialilado **318** y un 32% de compuesto de partida **220** sin reaccionar (Esquema I).

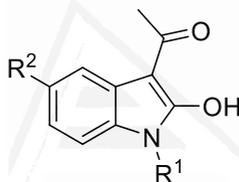


Esquema I. Metodología de síntesis de 2-oxindol 3-sustituido.

Sorprendentemente, sin utilizar exceso de base la proporción del producto **318** era considerablemente mayor en la mezcla de reacción. Aunque no era el resultado esperado, se buscó una manera eficiente de sintetizar **318** utilizando 2 equivalentes de **315** y **316**. Las conversiones en cromatografía de gases fueron excelentes. Tras el purificado del compuesto, se obtuvo un 59% de rendimiento.

Conociendo estos resultados, se concluyó que la simple monoalquilación del 2-oxindol no era posible en estas condiciones. Estos resultados respaldan que los compuestos 2-oxindoles 3-monosustituidos no son fáciles de sintetizar y necesitan condiciones de reacción específicas para conseguirlos.

Con estos resultados en mano y tras una profunda revisión bibliográfica, nuestro grupo de investigación previó que un primer paso de monoalquilación y una subsecuente alquilación desacetilativa de los derivados de 3-acetil-2-oxindoles **319** (Figura I) podría ser una excelente estrategia para la síntesis de los compuestos deseados: los 2-oxindoles 3,3-disustituidos. También se podría utilizar para sintetizar 2-oxindoles 3-monoalquilados.

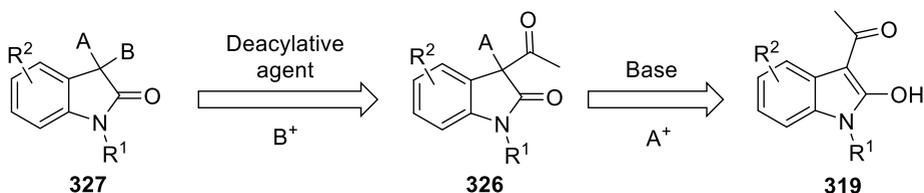
**319**R¹ = Me, BnR² = H, OMe**Figura I.** 3-Acetil-1-metil-2-oxindoles

Utilizando diferentes procedimientos de síntesis, el compuesto **319a** se preparó utilizando anhídrido acético en presencia de DMAP en cantidades catalíticas calentando a 140 °C durante 5 horas. Tras una posterior hidrólisis con KOH en MeOH y acidificación con HCl, se obtuvo el producto deseado **319a**. Finalmente, se purificó en columna cromatográfica obteniendo un rendimiento del 88%.

También, debido a que ciertos intermedios sintéticos y/o productos naturales, como la fisostigmina y horsfilina, tienen un grupo metoxi incorporado en la posición 5 del anillo aromático, se decidió proceder a la síntesis de estos derivados utilizando procedimientos sintéticos con los que finalmente se pudieron

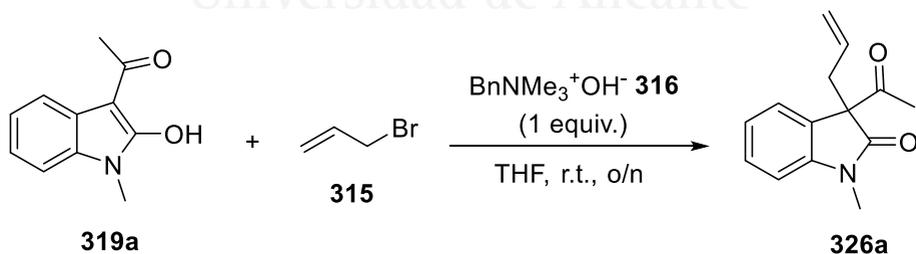
synthetizar los compuestos **319b** y **319c** con un rendimiento del 68% y del 24% respectivamente.

Una vez sintetizados dichos productos de partida, se propuso el siguiente análisis retrosintético mostrado en el Esquema II:



Esquema II. Análisis retrosintético a través de alquilación desacetilativa para los derivados 2-oxindoles 3,3-disustituidos.

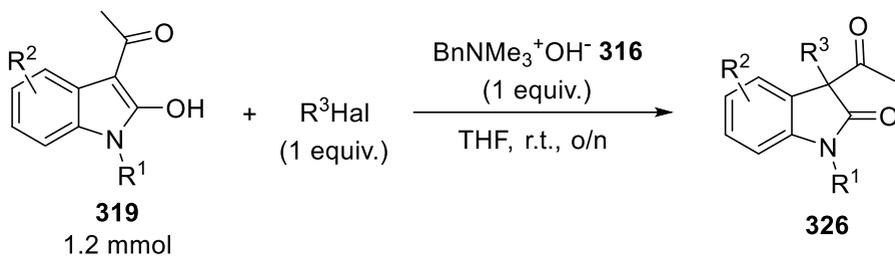
Para la primera monoalquilación, las condiciones óptimas fueron el uso de 1 equivalente de **319a**, un equivalente de la base Triton B **316** y un equivalente de bromuro de alilo **315** como electrófilo. El producto deseado **326a** se obtuvo en un 99% de conversión analizada por cromatografía de gases y tras purificación en columna cromatográfica se obtuvo un 87% de rendimiento (Esquema III).



Esquema III. Alilación de **319a**.

El alcance de la alquilación de los derivados de 3-acetil-2-oxindoles se realizó utilizando diferentes halogenuros de alquilo y diferentes derivados de 2-oxindol. (Tabla I).

Las entradas 1, 3, 4, 6 y 7 de la Tabla I se llevaron a cabo en escala de 1.2 mmoles y las entradas 6, 8 y 9 de la Tabla I fueron a escala de 0.3, 4.6 y 0.6 mmoles, respectivamente. La entrada 2 de la Tabla I pudo ser escalada 7.2 mmoles (1.4 g) obteniendo 1.3 g de producto final en un 88% de rendimiento tras purificación en columna cromatográfica. Es importante resaltar que en las entradas 2, 8 y 9 de la Tabla I, en las cuales los productos de partida **319** estaban metilados, se consiguieron de buenos a excelentes rendimientos (entre 85% a 92%). Además, no se observó producto de desacetilación después de la purificación. Rendimientos de moderados a buenos (entre 50% y 84%) se consiguieron en las entradas 1, 3, 4, 5, 6 y 7 de la Tabla I, a pesar de la inevitable formación de producto desacetilado (entre un 4% y un 10%) durante la purificación en columna cromatográfica. Diferentes halogenuros de alquilo fueron aptos para usarse como electrófilos en reacciones a temperatura ambiente. Únicamente cuando se utilizó bromuro de pentilo (Tabla I, entrada 6) se necesitó calentar a reflujo debido a su menor reactividad.

Tabla I. Síntesis de 3-acetil-3-alkil-2-oxindoles.

<i>Entrada</i>	319	R¹	R²	R³Hal	326	Rto.^a
1	319a	Me	H		326a	84% ^b
2	319a^c	Me	H	MeI	326b	88%
3	319a	Me	H		326c	54% ^d
4	319a	Me	H		326d	68% ^d
5	319a	Me	H		326e	84% ^e
6	319a^f	Me	H		326f	50% ^b
7	319a	Me	H		326g	69% ^g
8	319b^h	Me	OMe	MeI	326h	85%
9	319cⁱ	Bn	OMe	MeI	326i	92%

^a Rendimiento aislado después de columna cromatográfica.

^b 6% de producto desacetilado fue obtenido.

^c 2 equiv. de MeI se utilizaron en una escala de 7.2 mmoles.

^d 4% de producto desacetilado fue obtenido.

^e 5% de product desacetilado fue obtenido en una esla de 1.8 mmoles.

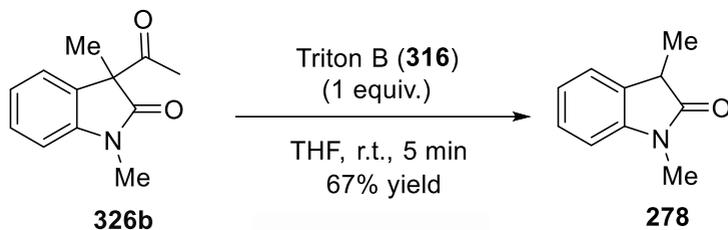
^f A reflujo en una escala de 0.3 mmoles.

^g 10% de producto desacetilado fue obtenido.

^h 2 equiv. of MeI fueron utilizados en una escala de 4.6 mmoles.

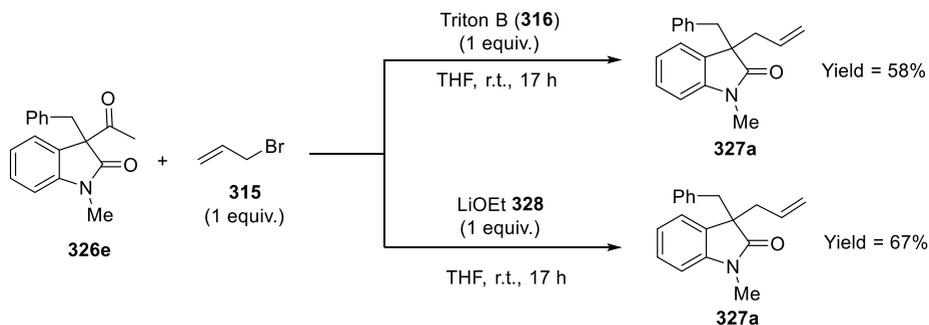
ⁱ 2 equiv. of MeI fueron utilizados en una escala de 0.6 mmoles.

El derivado de 2-oxindol **278**, importante para la preparación de alcaloides, se puede sintetizar rápidamente bajo condiciones suaves tratando el compuesto **326b** con 1 equiv. de Triton B en THF a temperatura ambiente durante 5 minutos. Tras purificación por columna cromatográfica, el compuesto **278** se obtiene en un 67% de rendimiento (Esquema IV).



Esquema IV. Síntesis de 1,3-dimetil-2-oxindol.

Para llevar a cabo el siguiente objetivo, se realizó un proceso de alquilación desacetilativa para la preparación de 2-oxindoles 3,3-disustituídos no simétricos utilizando halogenuros de alquilo. En este caso, utilizando como producto de partida **326e** y bromuro de alilo, se compararon dos bases para producir esta reacción: Triton B y etóxido de litio como agentes desacetilantes para encontrar las condiciones óptimas de reacción (Esquema V):

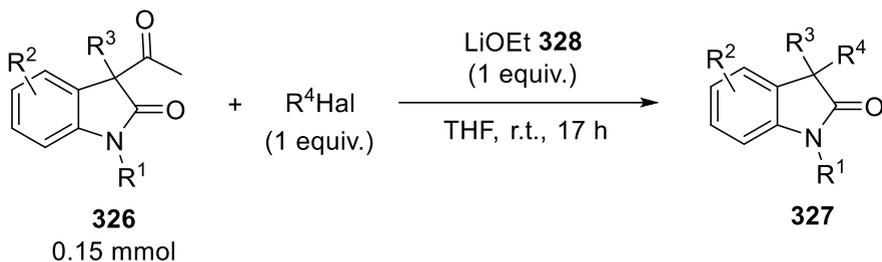


Esquema V. Diferentes condiciones de reacción para sintetizar el compuesto **327a**.

Después de la purificación de ambas reacciones, el rendimiento obtenido fue mayor cuando fue utilizado etóxido de litio como agente desacetilante en comparación con Tritón B.

Conociendo esta información, se llevó a cabo el alcance de la reacción utilizando una disolución 1M en THF de etóxido de litio con diferentes halogenuros de alquilo. En todos los casos, de buenos a excelentes rendimientos fueron conseguidos (Tabla II).

El compuesto **326b**, el más interesante para la posterior transformación en los precursores de productos naturales, fue el que se utilizó como compuesto modelo y se hizo reaccionar con bromuro de alilo, bromuro de propargilo, bromuro de bencilo, bromuro de cinamilo y bromoacetnitrilo (Tabla II, Entradas 1, 2, 3, 4 y 5, respectivamente) para dar los productos **327b-f**. En todos los casos, se obtuvieron buenos rendimientos (entre 69% y 88%) y todos los compuestos fueron estables en el proceso de purificación. Otro interesante electrófilo, como el cloroformiato de etilo, fue utilizado para sintetizar el correspondiente éster **327g**. Finalmente, derivados de oxindol que contienen un grupo metoxi en la posición 5 del anillo aromático, fueron sintetizados utilizando el mismo procedimiento descrito. Tras aislar por columna cromatográfica el compuesto **327h**, se obtuvo un 75% de rendimiento. Este compuesto es un intermedio del producto racémico esermetol, el cual es precursor del producto natural fisostigmina **21** y el derivado farmacéutico fenserina, el cual es un inhibidor de la acetilcolinesterasa. Además, el compuesto **327i**, el cual ha sido sintetizado en un excelente rendimiento, también es precursor racémico del esermethole y la fisostigmina, pero en una ruta sintética más corta que **327h**. Finalmente, los derivados **327j** y **327k** que contienen también en la posición 5 el grupo metoxi, pueden desprotegerse en el átomo de N dando los correspondientes derivados de 2-oxindol desprotegidos.

Tabla II. Síntesis de 2-oxindoles 3,3-disustituidos.

	326	R⁴Hal	Producto	327	Rto.^a
1	326b			327b	72
2	326b			327c	69
3	326b			327d	87
4	326b^b			327e	75
5	326b			327f	88

6	326b			327g	65
7	326h			327h	75
8	326h ^c			327i	93
9	326i			327j	70
10	326i			327k	74

^a Rendimiento aislado después de columna cromatográfica.

^b Se utilizó 1.5 equiv. de bromuro de cinamilo.

^c A escala de 2 mmoles.

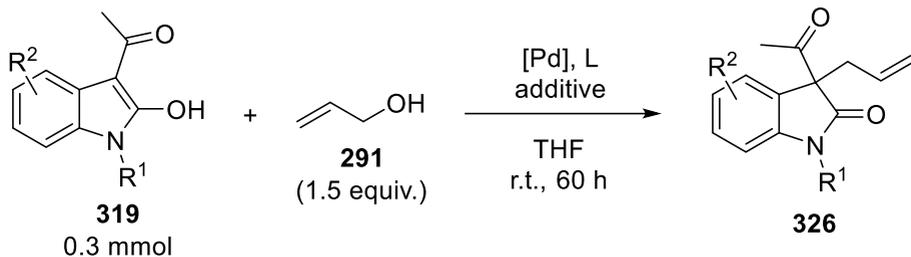
Como conclusiones se puede extraer que la acetilación de los 2-oxindoles permite la monoalquilación en condiciones suaves. Con estos compuestos, tras la subsecuente desacetilación es posible preparar los correspondientes 2-oxindoles 3-alkilados en condiciones suaves. Utilizando la estrategia de alquilación desacetilativa en los 3-acetil-2-oxindoles 3-sustituidos es posible preparar los correspondientes 2-oxindoles 3,3-disustituidos no simétricos también en condiciones suaves, los cuales no pueden ser fácilmente preparados utilizando otras estrategias. Con la metodología descrita, es posible preparar importantes intermedios

para la síntesis de diversos productos naturales racémicos. Todos los resultados obtenidos en este capítulo han sido publicados en la revista internacional *Synthesis*.

Capítulo 2

En este capítulo se realizaron estudios para la alilación directa de los productos **319** utilizando como electrófilos alcoholes alílicos no activados como **291**. Para llevarlos a cabo, diferentes catalizadores de paladio, ligandos y aditivos fueron utilizados para sintetizar el compuesto 3-acetil-3-alil-2-oxindol **326** (Tabla III).

En la entrada 1 de la Tabla III, utilizando las condiciones de reacción descritas por Tamaru *et al.* para la alilación de compuestos 1,3-dicarbonílicos, se utilizó un 60% en mol de trietilborano, un 3% en mol tanto de acetato de paladio(II) como de dppp dando el correspondiente producto **326a** en un 99% de conversión. Tratando de disminuir la cantidad de aditivo, en vez de un 60% en mol de trietilborano se utilizó un 3% en mol de ácido *p*-toluensulfónico (TsOH). Con estas condiciones se obtuvo sólo un 3% de conversión del producto **326a** (Tabla III, entrada 2). Al utilizar como fuente de paladio Pd(dba)₂, no se observó formación del producto deseado (Tabla III, Entrada 3). En cambio, cuando se utilizó *rac*-BINAP como ligando, **326a** se formó en un 66% de conversión (Tabla III, Entrada 4). Al cambiar el TsOH por ácido fosfórico derivado del *rac*-BINOL, el producto deseado se formó en un 96% de rendimiento tras purificación en columna cromatográfica (Tabla III, Entrada 5). Utilizando estas condiciones óptimas, los 5-metoxi derivados **326j** y **326k** se sintetizaron en un 61% y un 89% de rendimiento, respectivamente (Tabla III, Entradas 6 y 7).

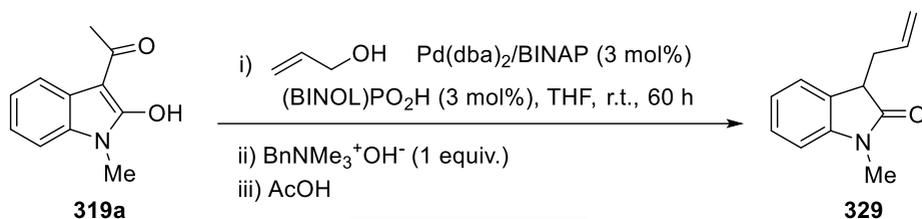
Tabla III. Alilación de 3-acetil-2-oxindoles con alcohol alílico catalizada por paladio.

	319	[Pd] (3 mol%)	Ligando (3 mol%)	Additivo (mol%)	326	Rto (%) ^a
1	319a	Pd(OAc) ₂	dppp	Et ₃ B (60)	326a	99%
2	319a	Pd(OAc) ₂	dppp	TsOH (3)	326a	3%
3	319a	Pd(dba) ₂	dppp	TsOH (3)	326a	—
4	319a	Pd(dba) ₂	<i>rac</i> -BINAP	TsOH (3)	326a	66%
5	319a	Pd(dba) ₂	<i>rac</i> -BINAP	(BINOL)PO ₂ H (3) ^b	326a	98 (96)
6	319b	Pd(dba) ₂	<i>rac</i> -BINAP	(BINOL)PO ₂ H (3) ^b	326j	91 (61)
7	319c	Pd(dba) ₂	<i>rac</i> -BINAP	(BINOL)PO ₂ H (3) ^b	326k	99 (89)

^a Conversión del crudo. En paréntesis, rendimiento tras purificación en columna cromatográfica.

^b Fue empleado (BINOL)PO₂H racémico.

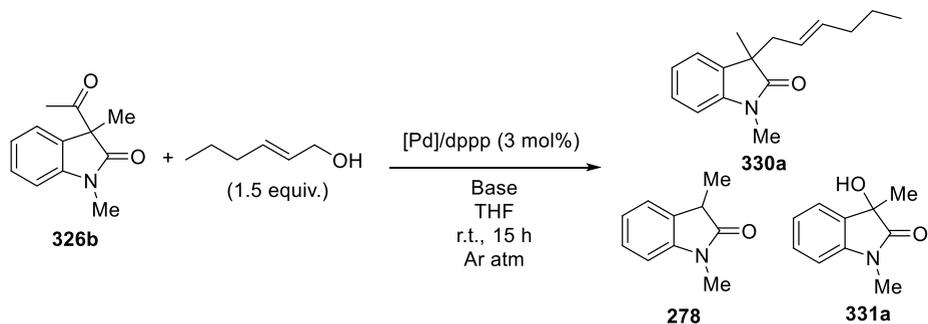
De nuevo, se ha demostrado que este proceso es una metodología interesante para la síntesis de 2-oxindoles 3-monosustituídos bajo condiciones muy suaves ya que, tratando el compuesto **326** con Triton B *in situ* cuando el proceso de alilación ha acabado, se obtiene el compuesto **329** en 61% tras purificación en columna cromatográfica (Esquema VI).



Esquema VI. Síntesis de 3-alil-1-metil-2-oxindol.

Posteriormente, se estudió la alquilación desacetilativa (DaA) catalizada por paladio. Para encontrar las condiciones óptimas de reacción, el estudio fue llevado a cabo utilizando *trans*-hex-2-en-1-ol como electrófilo con diferentes catalizadores y bases (Tabla IV). Finalmente se concluyó que las condiciones óptimas son las que corresponden a la Entrada 5 de la Tabla IV.

Tabla IV. DaA de 3-acetil-2-oxindoles catalizada por Pd.



	[Pd]/dppp (3 mol%)	Base (equiv.)	Productos (%) ^a	Rto 331a (%) ^b
1 ^c	Pd(OAc) ₂	KO ^t Bu (1.1 equiv.)	330a (76) 331a (24)	54
2 ^d	Pd(OAc) ₂	LiO ^t Bu (1.1 equiv.)	330a (79) 278 (17) 331a (4)	66
3 ^d	Pd(OAc) ₂ ^e	LiO ^t Bu (1.1 equiv.)	330a (61) 278 (39)	—
4 ^d	Pd ₂ (dba) ₃ ^f	LiO ^t Bu (1.1 equiv.)	330a (49) 278 (51)	—
5 ^d	Pd(OAc) ₂	LiO ^t Bu (1.5 equiv.)	330a (86) 278 (10) 331a (3)	70

^a Determinado por ¹H RMN del crudo.

^b Aislado tras purificación en columna cromatográfica.

^c Sin “freezing-pump-thaw”.

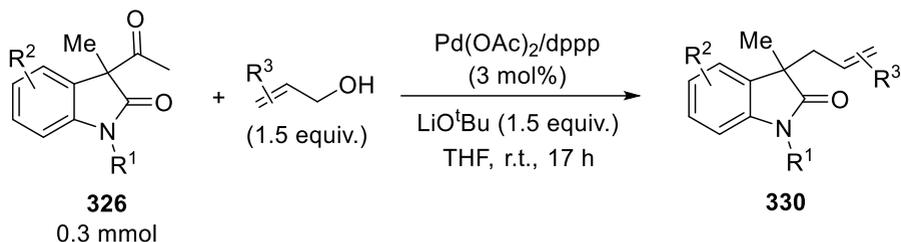
^d Con “freezing-pump-thaw”.

^e Se utilizó un 6 mol% de dppp.

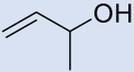
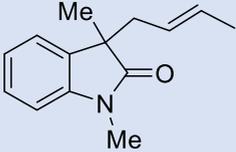
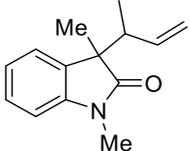
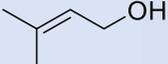
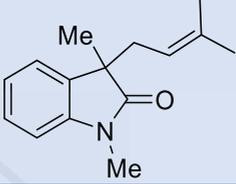
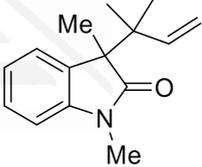
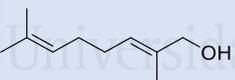
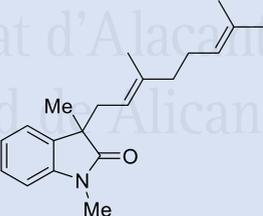
^f Se utilizó un 1.5 mol% de Pd₂(dba)₃.

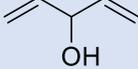
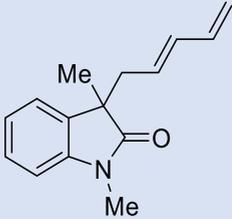
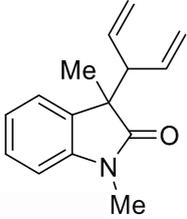
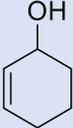
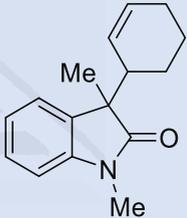
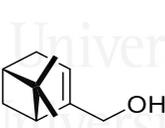
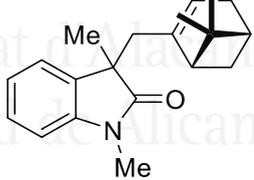
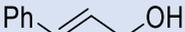
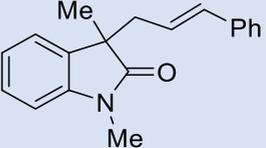
Para llevar a cabo el alcance de la reacción, se realizaron diferentes ensayos con distintos alcoholes alílicos y 2-oxindoles utilizando las condiciones óptimas previamente encontradas (Tabla V).

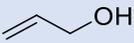
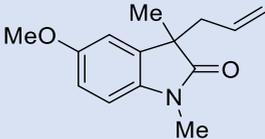
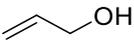
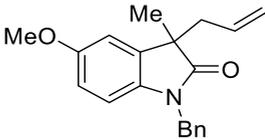
De manera general en estos ejemplos, se necesitó 17 h de reacción en vez de 15 h dependiendo de la naturaleza de los alcoholes alílicos. Cuando **326a** se hizo reaccionar con alcoholes primarios como alcohol alílico o alcohol metalílico, se obtuvieron los correspondientes productos **327b** y **330b** en buenos rendimientos (Tabla V, Entradas 2 y 3, respectivamente). Al utilizar geraniol (Tabla V, Entrada 6) como sustrato, a pesar de ser también un alcohol primario, se obtuvo un moderado 45% de rendimiento. También, al utilizar alcohol 1-metilalílico (Tabla V, Entrada 4), se obtuvieron los productos esperados **330c** y **330c'** como una mezcla inseparable. Se obtuvieron resultados parecidos cuando se utilizó alcohol prenílico (Tabla V, Entrada 5), ya que tras aislamiento por columna cromatográfica se obtuvo un 51% del isómero α - y un 16% del γ -, que en este caso sí fueron separables. Cuando se utilizaron alcoholes secundarios, como el pent-1,4-dien-3-ol (Tabla V, entrada 7), se obtuvo una mezcla 8:1 de los productos γ - y α - con un rendimiento global del 62%. Completando el alcance de la reacción, se utilizó ciclohexen-2-ol como electrófilo y consiguiendo buenos rendimientos (75%) de una mezcla 1:1 de los correspondientes diastereoisómeros. Otros alcoholes primarios dieron resultados moderados del 56% y el 51% como el (-)-myrtenol y alcohol cinámico (Tabla V, entradas 9 y 10, respectivamente). Finalmente, se variaron los productos de partida correspondiente al oxindol, utilizando **326g** y **326i** haciéndolos reaccionar con alcohol alílico, los cuales proporcionaron buenos rendimientos 72% y 74%, respectivamente (Tabla V, Entradas 11 y 12).

Tabla V. Alcance de la DaA de 3-acetil-2-oxindoles catalizada por Pd.**326b:** R¹ = Me, R² = H**326h:** R¹ = Me, R² = OMe**326i:** R¹ = Bn, R² = OMe

	326	Alcohol alílico	Producto	330	R _{to} (%) ^a
1	326a			330a	70
2	326a			327b	80
3	326a			330b	74

4	326a		 330c	45 ^b
			 330c'	
5	326a		 330d	51
			 330d'	16
6	326a		 330e	45

7	326a			330f	55 ^c
				330f	7
8	326a			330g ^d	75
9	326a			330h	56 ^e
10	326a			330i ^f	51

11	326h			327h	72
12	326i			327j ^g	77

^a Rendimiento asilado tras columna cromatográfica.

^b Se obtuvo una mezcla inseparable de los compuestos **331c** (68%) y **331c'** (32%).

^c Se obtuvo una mezcla 8:1 de los compuestos **331f** y **331f'**.

^d Se obtuvo una mezcla de diastereoisómeros de aprox. 1:1.

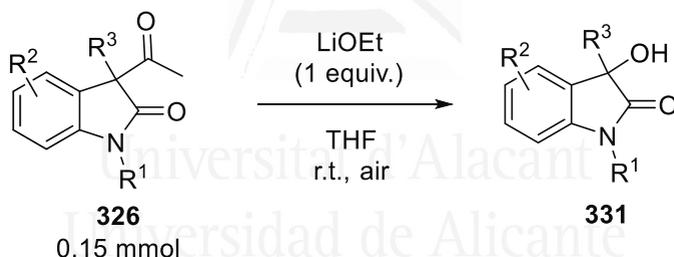
^e Se obtuvo una mezcla de diastereoisómeros de aprox. 5.5:1.

^f 24 h de tiempo de reacción

^g Escala de 0.22 mmoles.

Utilizando los conocimientos adquiridos en la alquilación desacetilativa catalizada por Pd, se consiguió sintetizar los derivados oxidados de 2-oxindol hidroxilados en la posición 3. En esta sección, cuando 3-acetil-1,3-dimetil-2-oxindol se hace reaccionar con etóxido de litio en una atmósfera de aire, se obtiene en un 70% de rendimiento el correspondiente derivado hidroxilado **331a** (Tabla VI, Entrada 1). Cuando se ensayan diferentes 3-acetil-2-oxindoles 3-sustituídos, tales como los derivados bencilados, alilados y propargilados, se obtienen rendimientos del 68%, 68% y 70% respectivamente (Tabla VI, Entradas 2, 3, y 4). Cuando se utilizan los derivados de oxindol que contienen el 5-metoxi en el anillo aromático y un metilo en la posición 3, se obtienen también buenos rendimientos, concretamente del 57% y 58% para **331e** y **331f**, respectivamente (Tabla VI, Entradas 5 y 6, respectivamente).

Tabla VI. Síntesis de 3-alkil-3-hidroxi-2-oxindoles.



	326	R¹	R²	R³	332	Rto (%)^a
1	326a	Me	H	Me	332a	70
2	326a	Me	H	Bn	331b	68
3	326a	Me	H	Allyl	331c	68
4	326a	Me	H	Propargyl	331d^b	70
5	326h	Me	OMe	Me	331e	57
6	326i	Be	OMe	Me	331f	58

^a Aislado tras purificación en columna cromatográfica.

^b Escala de 0.13 mmoles.

Como conclusión se puede decir que la alilación catalizada por paladio de los 3-acetil-2-oxindoles utilizando alcohol alílico se puede llevar a cabo utilizando el ácido fosfórico derivado del BINOL utilizando condiciones suaves. Este procedimiento genera los correspondientes 3-acetil-3-alil-2-oxindoles. Esta metodología también permite la síntesis *in situ* de 3-alil-1-metil-2-oxindol a través de un proceso de alquilación desacetilativa. Utilizando el proceso de alquilación desacetilativa catalizada por paladio, se sintetizaron los correspondientes derivados de 2-oxindoles 3,3-disustituidos con rendimientos entre moderados a buenos a través del uso de alcoholes alílicos en condiciones suaves. Ambas metodologías pudieron ser combinadas para preparar el derivado 3,3-dialilado no simétrico el cual no es fácilmente accesible a través de otras estrategias. Finalmente, se sintetizaron derivados importantes como los 3-alquil 3-hidroxi-2-oxindoles utilizando etóxido de litio en una atmósfera de aire. Todos los resultados expuestos en este capítulo han sido publicados en la revista internacional Tetrahedron.

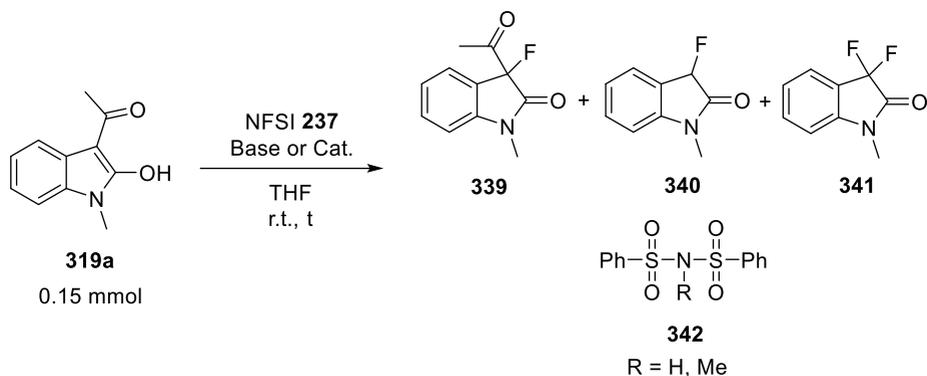
Capítulo 3

En este capítulo de la Tesis Doctoral, se realizaron estudios para la fluoración en la posición 3 del derivado **319a** utilizando NFSI **237** como fuente de flúor electrofílico utilizando diferentes condiciones de reacción (Tabla VII).

Después de todos los ensayos, se pudo demostrar que las condiciones óptimas para introducir el átomo de flúor en la posición 3 fueron utilizando ácido *p*-toluensulfónico como organocatalizador, en una cantidad del 15% en mol y en 48 h de reacción. Este método se pudo escalar hasta 2 mmoles con una conversión >99% y sin la obtención de subproductos derivados de la NFSI (Tabla VII, entrada 4).



Universitat d'Alacant
Universidad de Alicante

Tabla VII. Síntesis del 3-acetil-3-fluoro-2-oxindol.

	eq 237	Base (1 eq)	Cat.	t (h)	Cnv (%)	Yield (%) ^a
1	1	Triton B	—	18	339+341 (59) 340 (19) 319a (18)	—
2	1.4	Triton B	—	18	339 (60) 341 (40)	340 (61) 341 (16) 343 (23)
3	1.1	—	(BINOL)PO ₂ H (15 mol%)	18	339 (62) 319a (38)	—
4^b	1.1	—	TsOH (15 mol%)	48	339 (>99)	340 (85)

^a Rendimiento aislado tras columna cromatográfica.

^b Escala de 2 mmoles.

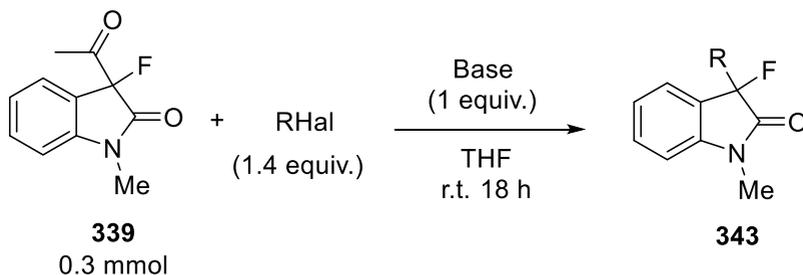
Una vez encontradas las condiciones de reacción, se procedió a realizar la alquilación desacetilativa del producto **339** con diferentes halogenuros de alquilo para sintetizar los correspondientes 3-fluoro-2-oxindoles 3-substituidos.

Tras diferentes pruebas sobre los agentes desacetilantes, se concluyó que para estos sustratos el Triton B era el óptimo para realizar el proceso (Tabla VIII, Entrada 2), obteniendo el correspondiente 3-alil-3-fluoro-1-metil-2-oxindol en un 91% de rendimiento tras columna cromatográfica. Al utilizarse bromuro de bencilo, yodometano, bromuro de propargilo y bromuro de cinamilo, los correspondientes rendimientos fueron del 92%, 71%, 59% y 85%, respectivamente (Tabla VIII, Entradas 3, 4, 5 y 8, respectivamente).



Universitat d'Alacant
Universidad de Alicante

Tabla VIII. Síntesis de 3-fluoro-2-oxindoles 3-sustituidos a través de alquilación desacetilativa.



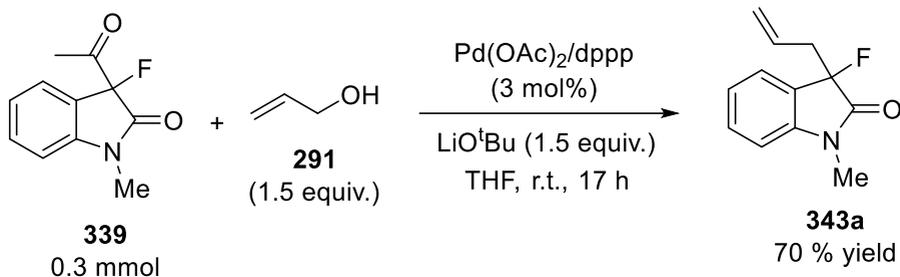
	RHal	Base	Producto	Conv (%)	Rto (%) ^a
1		LiOEt	343a	<5	–
2		Triton B	343a	>99	91
3		Triton B	343b	>99	92
4 ^b	MeI	Triton B	343c	>99	71
5		Triton B	343d	>99	59
6		Triton B	343e	<5	–
7 ^c		Triton B	343e	<5	–
8		Triton B	343f	>99	85

^a Rendimiento aislado tras columna cromatográfica.

^b Se utilizaron 2.8 equiv. de MeI.

^c La base fue adicionada a 0 °C.

Respecto a la alquilación desacetilativa catalizada por paladio, el compuesto **339** fue sometido a las correspondientes pruebas utilizando alcohol alílico (Esquema VII):



Esquema VII. Alquilación desacetilativa de 3-acetil-3-fluoro-2-oxindol catalizada por Pd.

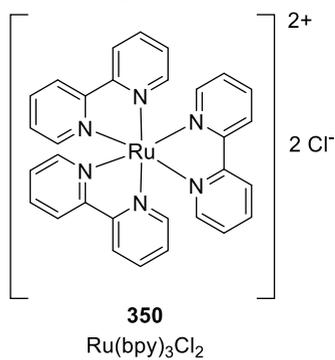
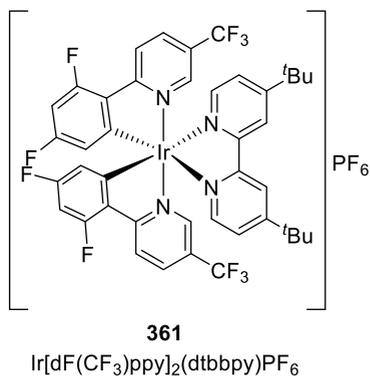
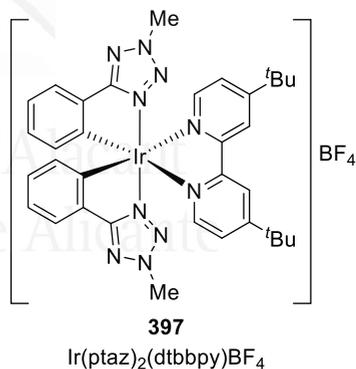
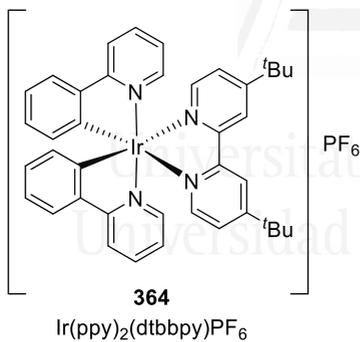
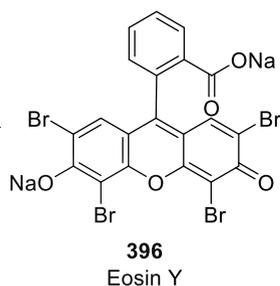
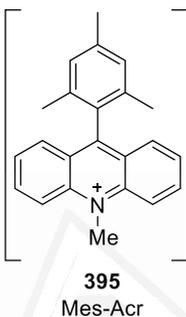
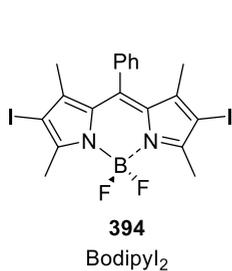
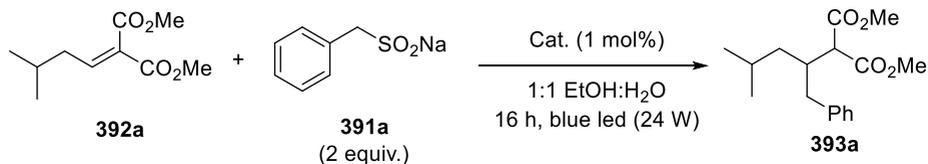
Por un lado, cuando se utilizó **291** (1.5 equiv.), el complejo $\text{Pd}(\text{OAc})_2/\text{dppp}$ en un 3% en mol, y *tert*-butóxido de litio (1.5 equiv.) y se agitó a temperatura ambiente en THF durante 17 h, el producto esperado **343a** se formó con una conversión >99% y tras purificación en columna cromatográfica se obtuvo en un 70% de rendimiento.

Como conclusión se puede extraer que se ha desarrollado una metodología eficiente para la síntesis del 3-acetil-3-fluoro-1-metil-2-oxindol utilizando condiciones suaves y evitando la formación de subproductos no deseados. Las metodologías de alquilación desacetilativa que han sido desarrolladas previamente en nuestro grupo de investigación pudieron ser aplicadas para la síntesis de 3-fluoro-1-metil-2-oxindoles 3-alkilados utilizando Triton B y halogenuros de alquilo. La alquilación desacetilativa catalizada por paladio del producto de partida 3-acetil-3-fluoro-1-metil-2-oxindol pudo ser llevada a cabo utilizando las condiciones de reacción estándar previamente descritas utilizando alcohol alílico dando lugar al correspondiente 3-alil-3-fluoro-1-metil-2-oxindol con buen rendimiento. Finalmente, se puede concluir que las dos metodologías de alquilación desacetilativa desarrolladas previamente son lo suficientemente robustas para la síntesis de 3-fluoro-1-metil-2-oxindoles 3-alkilados.

Capítulo 4

Finalmente, y tras la estancia en el grupo de investigación del Prof. Cozzi en Bolonia, Italia, se hizo una investigación en el campo de la fotoquímica. En este caso, se propuso investigar sobre la alquilación y bencilación fotoredox de alquenos utilizando sulfinatos de zinc bencílicos y alquílicos utilizando fotocatalizadores e irradiando con luz visible.

Para ello, se realizaron las síntesis de los susodichos sulfinatos, tanto de zinc como de sodio, utilizando diferentes procedimientos. Una vez obtenidos los productos de partida, se procedió a la optimización de la reacción de adición conjugada de radicales bencílicos (Tabla IX). Para ello, se utilizaron diferentes fotocatalizadores como BodipyI₂ **394** y un derivado de acridino **395**, pero tras irradiar la mezcla con luz visible azul durante 16 h, no se observó formación de producto (Tabla IX, Entradas 1 y 2). Utilizando eosina Y como fotocatalizador (Tabla IX, Entrada 3) e irradiando, en este caso, con luz verde, sólo se pudieron observar trazas del producto deseado. Cuando se utilizaron complejos fotoactivos de Ir(III) como **364** y **394** y el complejo de Ru(II) **350**, tampoco se observó formación del producto **393a** (Tabla IX, Entradas 4, 5 y 7, respectivamente). Finalmente, se encontró el fotocatalizador óptimo al utilizarse el complejo de iridio **361** (Tabla IX, Entrada 6), el cual produjo una conversión del 96% del producto **393a**.

Tabla IX. Optimización del fotocatalizador para la adición conjugada del radical benílico.

<i>Entrada</i>	Fotocatalizador ^a	Conversión ^b
1	394	0%
2	395	0%
3^c	396	Trazas
4	364	0
5	397	Trazas
6	361	96%
7	350	0%

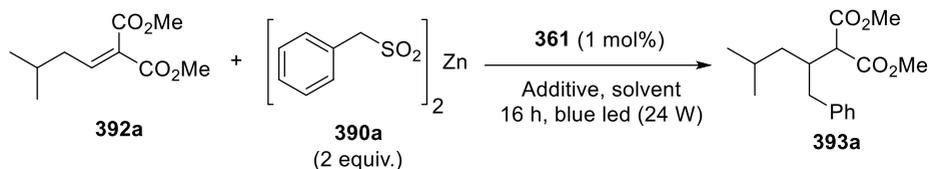
^a Todas las reacciones se llevaron a cabo bajo atmósfera de Argón. Las mezclas se desgasificaron a través de 3 ciclos de “freeze-pump-thaw”. Se utilizaron 0.2 mmoles de **391a**, 0.1 mmoles de **392a** en 1 mL de disolvente, en presencia de 1% en mol del catalizador.

^b Determinado por análisis de ¹H RMN de la mezcla del crudo.

^c Se utilizaron LEDs verdes.

Tras la obtención de estos resultados, se comprobó que los correspondientes sulfinatos de sodio, no eran estables con el paso del tiempo incluso almacenándolos a $-20\text{ }^{\circ}\text{C}$ y bajo atmósfera inerte. Por ello, a partir de ese momento se utilizaron las correspondientes sales de zinc que eran más estables, aunque menos reactivas.

Conociendo estos datos, se procedió a la optimización de la reacción fotoredox utilizando los sulfinatos de zinc. Tras diferentes pruebas de optimización, se llegó a la conclusión que para obtener los mejores resultados se debía utilizar como disolvente una mezcla 1:1 de EtOH:H₂O, utilizar 3 equiv. del sulfinato de zinc e irradiar con luz azul durante 40 h (Tabla X).

Tabla X. Optimización de la bencilación de **392a** con el sulfonato de zinc **390a**.

<i>Entrada</i> ^a	Disolvente	Aditivo	Conversion ^b
1	1:1 H ₂ O:MeCN	-	25%
2	1:1 H ₂ O:DMF	-	58%
3	1:1 H ₂ O:TFE	-	31%
4	1:1 H ₂ O:DME	-	43%
5	1:4 H ₂ O:DMSO	-	74%
6	1:4 H ₂ O:EtOH	-	27%
7	4:1 H ₂ O:EtOH	-	72%
8	1:1 H ₂ O:EtOH	-	77% (57%)
9	1:1 H ₂ O:EtOH	2,6-lutidina (4 equiv.)	52%
10	1:1 H ₂ O:EtOH	2,2'-bipiridina (2 equiv.)	72%
11	1:1 H ₂ O:EtOH	1-Me-imidazol (4 equiv.)	78%
12^c	1:1 H ₂ O:EtOH	-	88% (69%)

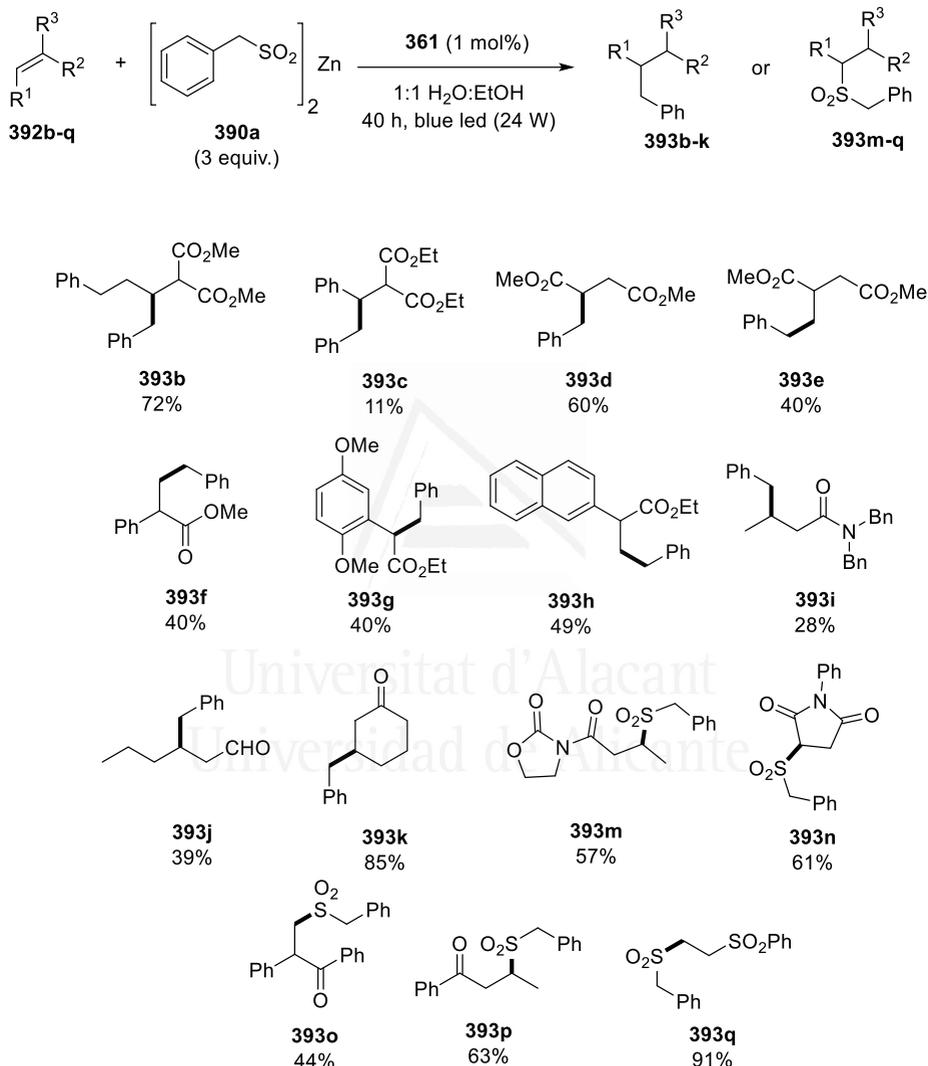
^a Todas las reacciones se llevaron a cabo bajo atmósfera de Argón. Las mezclas se desgasificaron a través de 3 ciclos de “freeze-pump-thaw”. Se utilizaron 0.2 mmoles de **390a**, 0.1 mmoles de **392a** en 1 mL de disolvente, en presencia de 1% en mol del catalizador.

^b Determinado por análisis de ¹H RMN de la mezcla del crudo. En paréntesis, el rendimiento tras purificación en columna cromatográfica.

^c Se utilizó 0.3 mmoles de **390a** y se irradió durante 40 h.

Una vez encontradas las condiciones óptimas, se procedió a estudiar el alcance de la reacción utilizando diferentes aceptores

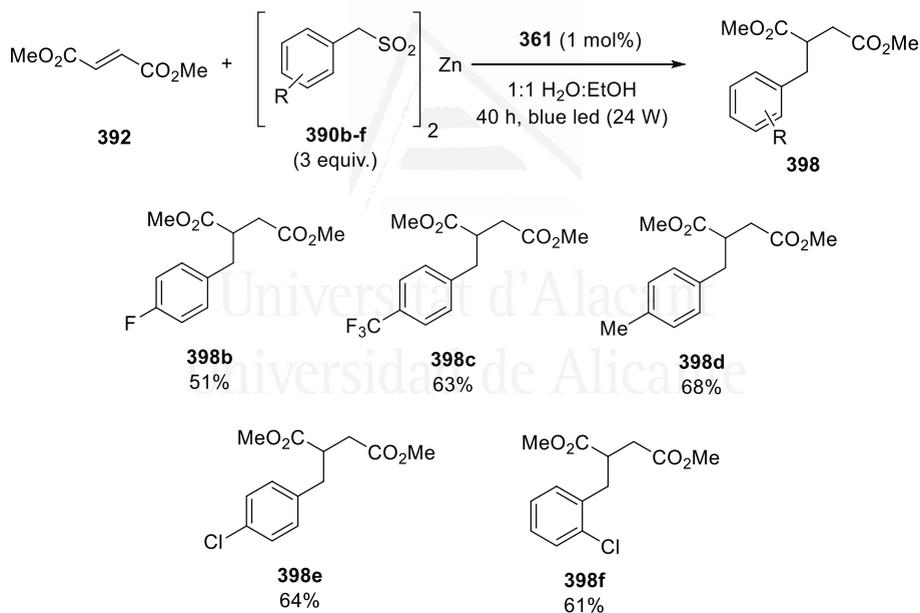
Michael (**392b-k**) proporcionando los correspondientes derivados bencilados (**393b-k**) (Esquema VIII).



Esquema VIII. Alcance de la bencilación de diferentes aceptores Michael.

Respecto a los resultados de los productos **393b-k**, se obtuvieron de moderados a buenos rendimientos utilizando diez alquenos pobres en electrones. Uno de los resultados más interesantes fue que el producto formado era dependiente del alqueno utilizado. En ciertos casos, se aislaron las sulfonas **393m-q** en vez de los correspondientes productos de alquilación.

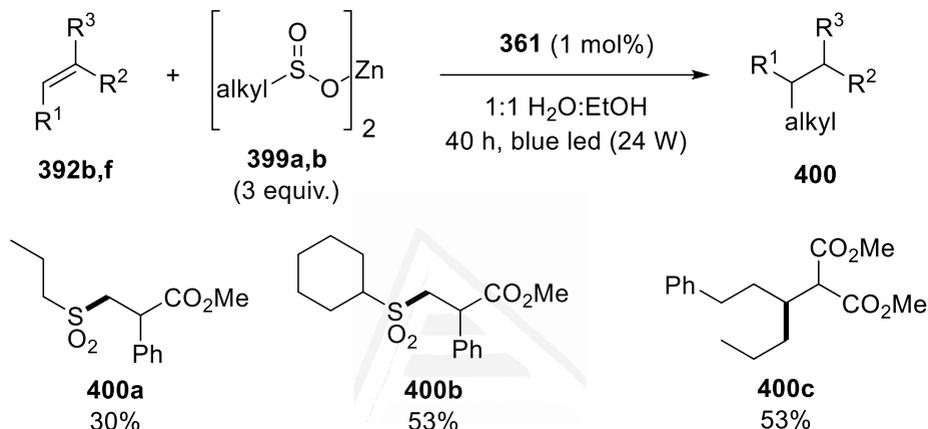
Siguiendo con el alcance de la reacción, se utilizaron diferentes sulfinatos bencílicos de zinc los cuales dieron los productos **398b-f** en un rango de rendimientos entre el 51% y el 68% (Esquema IX).



Esquema IX. Alcance de la reacción con diferentes sulfinatos bencílicos de zinc.

Además, también se utilizaron sulfinatos alquílicos de zinc para estudiar su reactividad con los aceptores Michael (Esquema X). De manera general, los rendimientos fueron menores (entre un 30%

y un 53%) comparándolos con los bencílicos utilizados anteriormente. Probablemente, este resultado se puede explicar por la baja estabilidad de los radicales alquílicos generados. En este caso, la formación de la sulfona también es dependiente del tipo de alqueno utilizado.



Esquema X. Alcance de la reacción utilizando diferentes sulfonatos alquílicos de zinc.

Como conclusión se ha demostrado que los sulfonatos de zinc tanto bencílicos como alílicos pueden ser utilizados en catálisis fotoredox dando lugar a radicales alquílicos y bencílicos los cuales pueden ser interceptados por aceptores Michael a través de un proceso de adición conjugada catalizado por Ir. Cuando se utilizan aceptores Michael altamente electrofílicos, los sulfonatos de zinc pueden actuar como nucleófilos dando lugar a las correspondientes sulfonas a través de un proceso no radicalario. Todos los resultados expuestos en este capítulo han sido publicados en la revista internacional ACS Catalysis.



BIOGRAPHY

Universitat d'Alacant

Universidad de Alicante

I was born in Denia (Alicante) on March 28th, 1990.

I took my Primary Studies at “Manuel Bru” first School in Benissa. Later I continued my High School Studies at “Josep Iborra” in the same locality finishing them in 2008.

Then, I moved to San Vicente del Raspeig (Alicante) in 2008 to start my 5-year bachelor’s degree in Chemistry at Faculty of Science, University of Alicante, graduating in 2013. Last 3 months before the graduation I was working in the pharmaceutical company Almirall in the Department of Medicinal Chemistry, thanks to an agreement between the University of Alicante and Almirall.

In February 2014 I joined to the Department of Organic chemistry at the University of Alicante to work full-time in the research group of Prof. Carmen Nájera Domingo and José Miguel Sansano Gil. In September 2014 I started my Ph.D. studies under the supervision of Prof. Carmen Nájera Domingo and José Miguel Sansano Gil. In March 2015 I was granted with a 4-year research fellowship from the Spanish Ministerio de Economía y Competitividad (MINECO) for the whole Ph.D. From May 2016 to July 2016 I moved to Bologna, Italy, thanks to a 3-months stay abroad fellowship grant from Spanish Ministerio de Economía y Competitividad (MINECO) at the University of Bologna under the supervision of Prof. Pier Giorgio Cozzi. In March 2018 is expected the defense of the Doctoral Thesis in front of Thesis Committee formed by Prof. Miguel Yus Astiz, Prof. Pascale V. Crochet and Prof. Keiji Maruoka.