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Iridium-Catalyzed Asymmetric Hydrogenation of N-Allyl Phthalimides

Tesi di laurea sperimentale

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ABSTRACT

The unprecedented iridium-catalyzed asymmetric hydrogenation of N-allyl phthalimides to afford enantioenriched chiral amines bearing a β-methyl is presented. Recently developed Ir-MaxPHOX are used as catalysts for this enantioselective transformation. The hydrogenation reaction has been studied in detail in order to find the optimal conditions. The mild reaction conditions and the feasibility of the removal of the phthalimido protecting group makes this process easily scalable and of interest for multiple synthetic applications.

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Introduction

Catalytic Asymmetric Hydrogenation

Asymmetric hydrogenation of alkenes mediated by organometallic catalysts is a powerful tool for organic synthesis, both in academia and industry settings. [1,2] Furthermore, it is a simple and fully atom economical reaction. Although the reaction is simple, it provides synthetic intermediates or valuable hydrogenated compounds, which are of great interest for their use in the preparation of pharmaceutical or research materials. The impact of asymmetric hydrogenation is testified by the Nobel Prize in Chemistry awarded to some of the pioneers of asymmetric hydrogenation (Knowles and Noyori) in 2001. Among the many different existing ligands, phosphorous ones have proven very useful for these procedures.[3] The ligand plays a vital role in the catalysis, as the ligand's chirality can be transferred to the product. There is a wide range of P-based chiral ligands, which can be classified in three groups depending on where the chirality lies; on the P atom, on the backbone or on both the P atom and the backbone.[4,5] Furthermore, among the P-based ligands we could, generalizing, differentiate two large main groups: the P,P and the P,N ligands.[6,7]

The P,P based catalysts are built around two phosphorous atoms that coordinate the metal. With metals such as rhodium or ruthenium, these catalysts are often proficient in the hydrogenation of functionalized olefins (amides or carboxylic acids work well as coordinating groups, for example). However, when it comes to selectively hydrogenating minimally or even un-functionalized double bonds, these catalysts usually fail in providing sufficient asymmetric induction and reactivity. For these substrates, recently, P,N ligands based catalysts, coordinated to iridium, have emerged as a promising alternative to the other catalysts. Thus, the Pfaltz's and Dieguez's research groups have extensively investigated the iridium-catalyzed enantioselective hydrogenation reaction using un-functionalized olefins as substrates. In addition, they investigated also terminal alkenes bearing a neighboring group which belong to minimally functionalized olefins. The most common substrates available in the literature are limited to allylic alcohols, allylic acetates and allyl silanes.

Frequently, for these procedures, the solvent is chosen accordingly; for P,P catalysts, coordinating solvents like alcohols are normally employed, while for the P,N type non-coordinating solvents like dichloromethane are used. This is a classification that cannot be taken very strictly because there is a broad spectrum of compounds that lay in-between the

functionalized and the completely non-functionalized substrate distribution. It is important to understand that this approach as a rough classification, used to give a general overview on the topic.

Iridium P,N complexes, Asymmetric Catalysis

Iridium complexes with chiral P,N ligands are efficient catalysts for the enantioselective hydrogenation of un-functionalized alkenes.[8,9] In this respect, they clearly distinguish themselves from chiral rhodium and ruthenium catalysts, which only perform well with substrates bearing a polar coordinating group next to the C=C bond.[10,11,12]

The Crabtree's catalyst

During the 70's, Crabtree designed the first P,N-Ir catalyst (Figure 1). This compound was both faster and more effective than its diphosphine analogs in the hydrogenation of non-functionalized tri- and tetrasubstituted alkenes.[13,14] This catalyst, before it undergoes hydrogen activation, is air stable. However, it did have a shortcoming; when the coordination with the alkene is weak, the active catalyst dimerizes and trimerizes, ending up forming inactive clusters.[15] Consequently, high loadings were often required for full conversions. It does not induce enantioselectivity, being achiral.

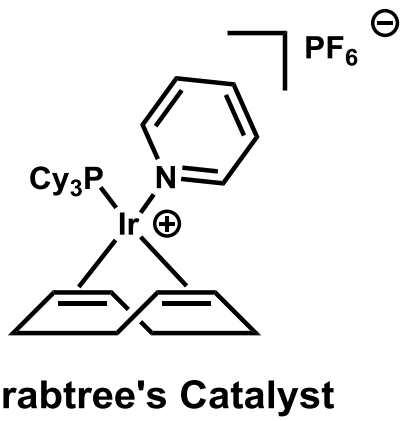


Figure 1 *Crabtree's catalyst; the first P,N-Ir catalyst.*

The Pfaltz's catalysts

In 1997 Pfaltz and co-workers developed a chiral version of the Crabtree's catalyst, the Ir-PHOX (Figure 2).[16] Unlike Crabtree's catalyst, Pfaltz's catalyst has a phosphinooxazoline molecule as ligand. Consequently, the P and the N metal-chelating units are bound together by a chiral C-backbone. This complex performs particularly well on the asymmetric hydrogenation of N-arylimines[16] and non-functionalized tri- and tetrasubstituted alkenes.[17] However, as a hexafluorophosphate salt, it also exhibited the issue of deactivation by aggregation into inactive clusters when the coordination with the substrate is feeble.[18] Up to 3 mol% loading of the catalyst was often required. Pfaltz overcame this shortcoming by exchanging the counteranion for BAr_F^-, a large, weakly coordinating counteranion.[19] While a more coordinating counteranion like PF_6^- might interfere with the alkene coordination to the metal, the BAr_F^- counteranion does not hamper the coordination at all. Therefore, the catalyst is "virtually saturated with alkene" and the hydrogenation pathway clearly predominates over the deactivation by formation of inactive hydride-bridged trinuclear complexes.

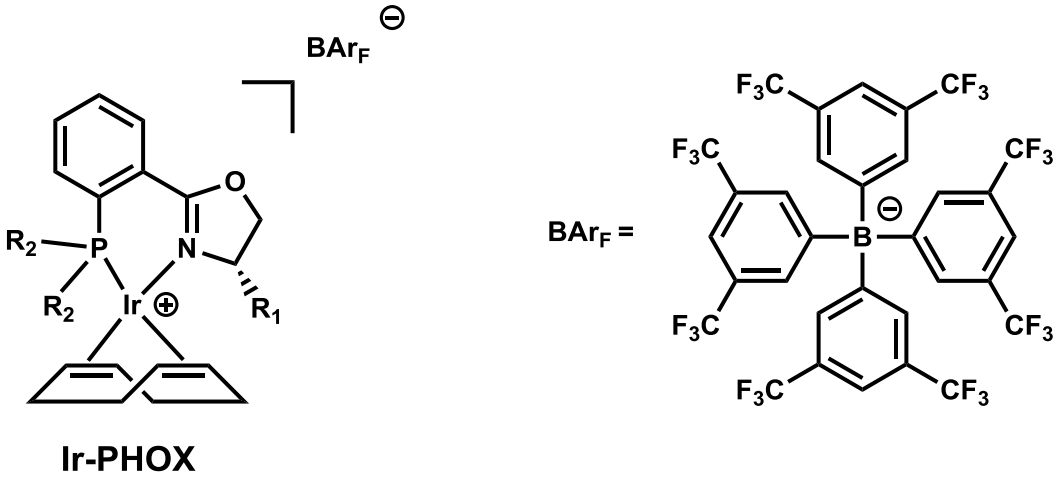


Figure 2 *The Ir-PHOX catalyst; chiral P,N-Ir catalyst with BAr_F^- as counteranion.*

Subsequently, Pfaltz reported in 2001 a new class of iridium complexes with phosphooxazoline ligands, the SerPHOX and the ThrePHOX.[20] In comparison to the Ir-PHOX, the phosphorous unit on these catalysts is attached next to the stereogenic center of the oxazoline moiety.

Another quite interesting catalysts that Pfaltz developed in 2004 are the SimplePHOX (Figure 3).[21] As the name tells, the selling point is their very simple preparation. Reaction between a

chiral amino alcohol (obtained from an amino acid) and 2-hydroxy-2-methylpropionic acid affords the corresponding oxazonyl alcohol, direct precursor of the SimplePHOX ligand.

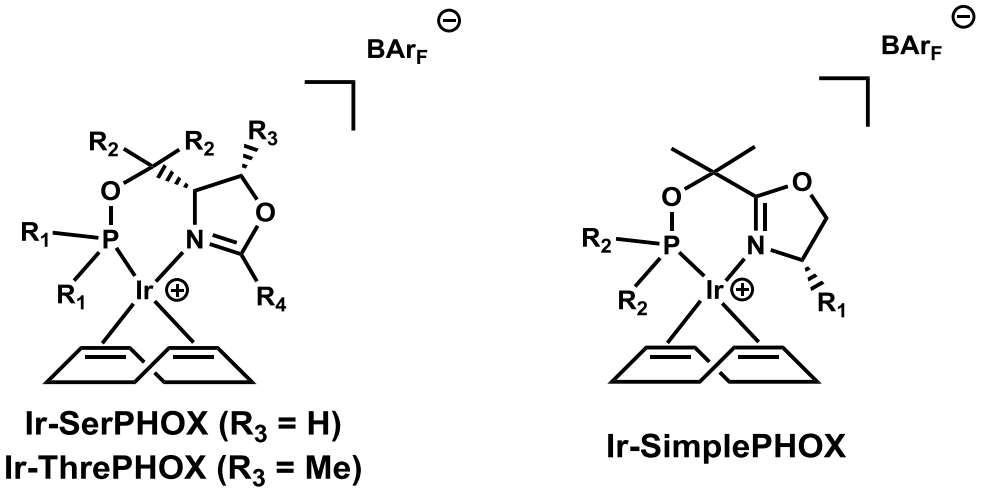


Figure 3 *The SerPHOX, the ThrePHOX and the SimplePHOX Ir catalysts.*

Pursuing of achieving a more similar coordination sphere to the Crabtree's catalyst, Pfaltz developed another noteworthy type of catalysts derived from pyridine and quinoline (Figure 4).[22] These complexes proved to be useful in the asymmetric hydrogenation of purely alkyl-substituted olefins and furans.[23]

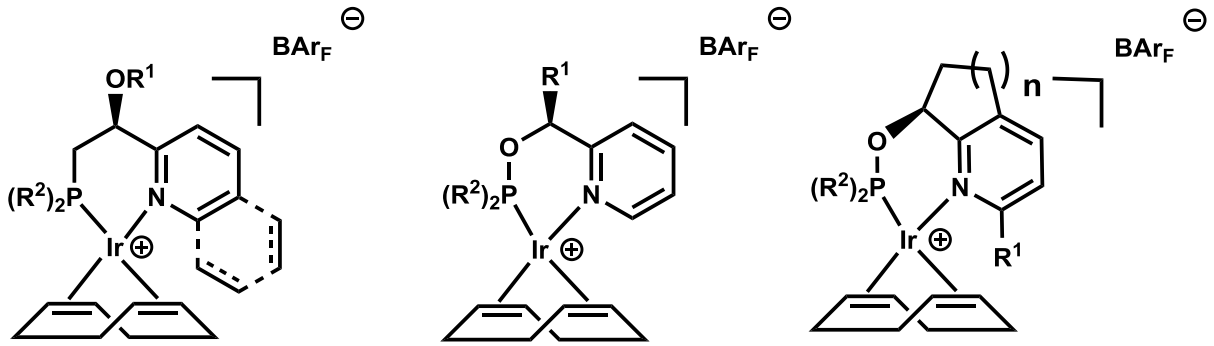


Figure 4 *Pyridine and quinolines derived Pfaltz's complexes.*

The Andersson's and Dieguez's catalysts

Andersson and co-workers, between 2004 and 2006,[24,25,26] studied and developed new P,N ligands that contain a rigid bicyclic backbone and an oxazole or a thiazole moiety (Figure 5). A norbornane-oxazoline based ligand was also developed. These ligands, once coordinated to iridium, perform at the same level as the best oxazoline-based complexes.

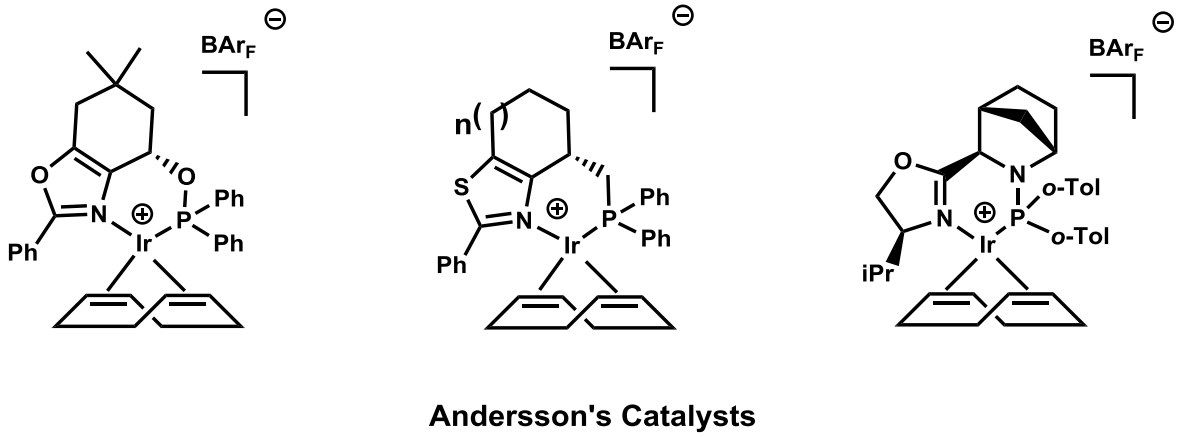


Figure 5 *Andersson's Ir-P,N catalysts.*

In 2009 Dieguez, Andersson and Borner joined forces to develop a library of up to 96 phosphite oxazoline ligands.[27] These ligands are formed out of a SerPHOX or ThrePHOX derived backbone plus different chiral biarylphosphinites (Figure 6). With Ir as metal and BAr_F^- as counteranion, they hydrogenated for instance a series of aryl-alkyl substituted terminal alkenes with good results.

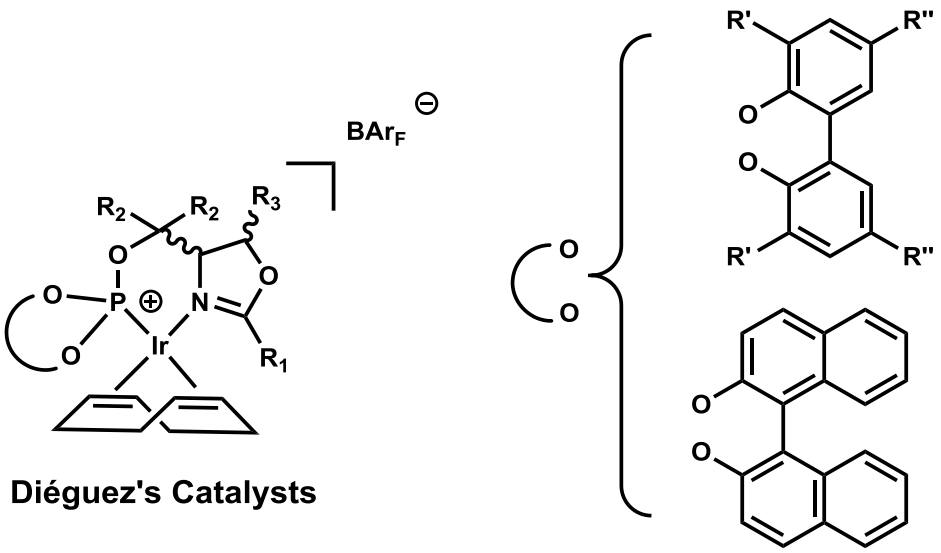


Figure 6. *Ir / Phosphite oxazoline catalyst library.*

Other Ir-P,N catalysts

Chiral P,N-Iridium catalysts have arisen a lot of interest from many research groups, prompting the disclosure of many complexes belonging to this class. Herein, few noteworthy examples are reported.

Knochel,[28] in 2003, developed another new pyridine-phosphine catalyst to hydrogenate methyl α-acetamidocinnamates with ee's up to 97%, as shown in Figure 7. Zhou developed in 2006 a new ligand that he named SIPHOX.[29] This phosphine-oxazoline ligand contains a rigid and bulky spirobiindane backbone. Once coordinated to iridium, with BAr_F^- as counteranion, the complex is efficient for example in the asymmetric hydrogenation of *N*-aryl imines.

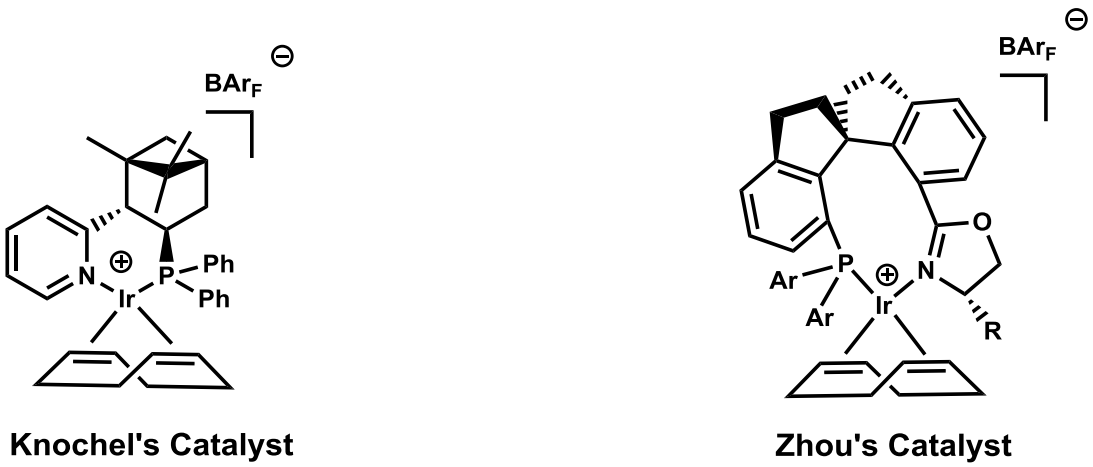


Figure 7 *Knochel's and Zhou's Ir catalysts.*

Finally, Burgess reported in 2003 a new iridium catalyst.[30] The catalyst contains the common oxazoline moiety and, although the P-group has been replaced by a heterocyclic carbene, it is worth to mention this complex (Figure 8). The catalyst has been used in the hydrogenation of bis and monoarylalkenes, allylic alchohols, enoates and more.[31]

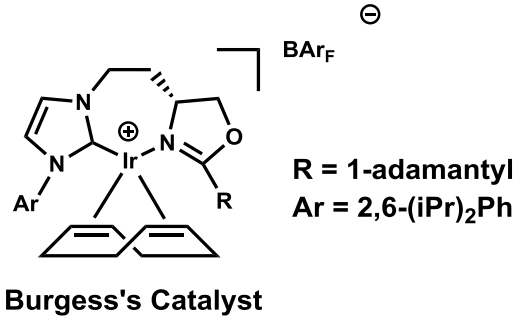


Figure 8 *The Burgess's catalyst. A N,Carbene-Ir complex.*

Ir-MaxPHOX catalysts

The Prof. Riera's group developed a methodology to synthesize chiral aminophosphines by S_N2@P reaction between an amine and the chiral synthon *tert*-butylmethylphosphinous acid borane. Applying this procedure, the synthesis of the MaxPHOX ligand and its coordination to iridium was reported (Figure 9). The complexation involves a 3-step procedure; first, there is the deprotection with neat pyrrolidine. This cyclic amine proved to be a better reagent for deprotection than, for example, the well-known DABCO basically due to purification issues. Once the phosphine is deprotected, the pyrrolidine can be removed under high vacuum. The borane protected pyrrolidine byproduct formed is not volatile, but it does not affect the procedure and can be purified straightforwardly at the end of the synthesis. The free ligand, under N_2 atmosphere, is resolubilized with CH_2Cl_2 and then $[IrCl(cod)]_2$ is added. After 1 h, $NaBAr_F$ is added and the reaction is left stirring for another hour. The catalyst, with BAr_F^- as counteranion, can be easily purified by chromatography on silica with hexanes / CH_2Cl_2.

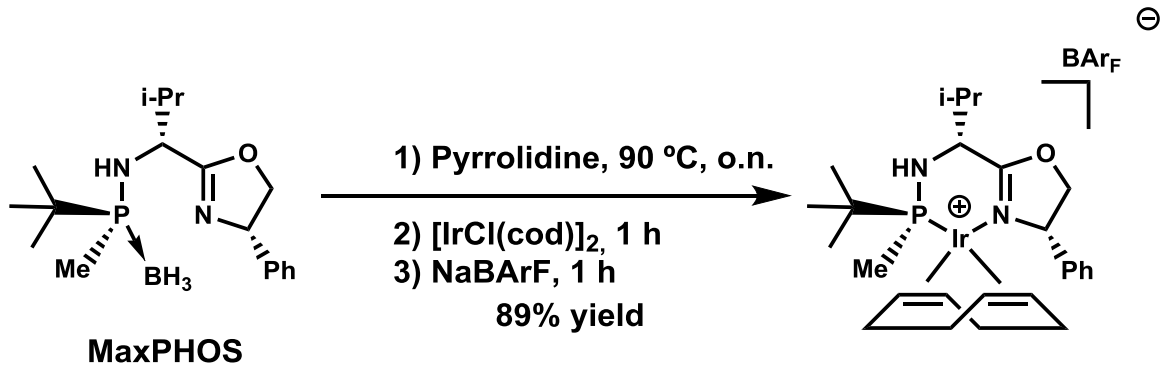


Figure 9 *The 3 step procedure for the coordination of MaxPHOS with Ir.*

The Ir-MaxPHOX catalysts bear three independent chiral centers; one is the P unit and the other two are located in the C-backbone. Therefore, for one type of Ir-MaxPHOX catalyst (same substituents) there are four possible diastereoisomers, as shown in Figure 10. As the C-backbone chiral groups can be easily changed (Ph, Bn, iPr, *t*-Bu, etc), the possible combinations are many. Hence, one of the strong points of this family of catalysts is the possibility to fine-tune the complex until the asymmetric catalytic process proceeds as desired.

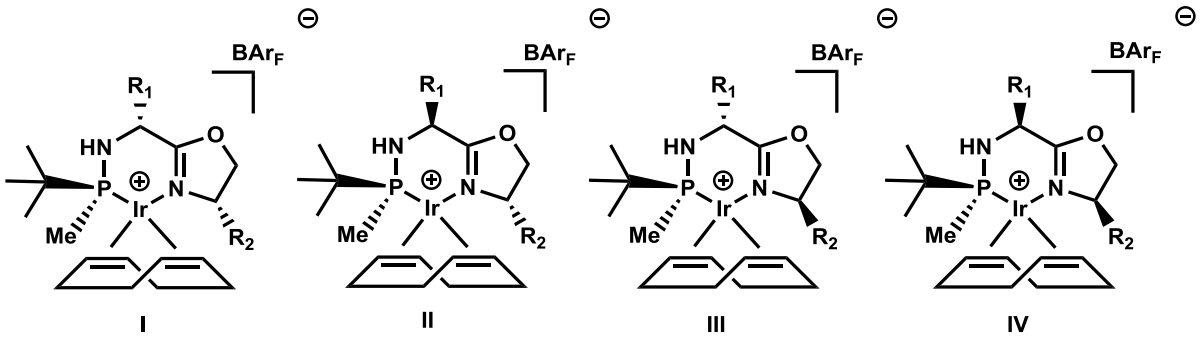


Figure 10 *There are four diastereoisomers for one Ir-MaxPHOX catalyst. The other 4 stereoisomers would be the corresponding enantiomers.*

Our group has used the Ir-MaxPHOX family to asymmetrically hydrogenate the following substrates (Figure 11):

a) *N*-aryl imines
b) *N*-alkyl imines
c) Cyclic Enamides
d) N-sulfonyl allylic amines

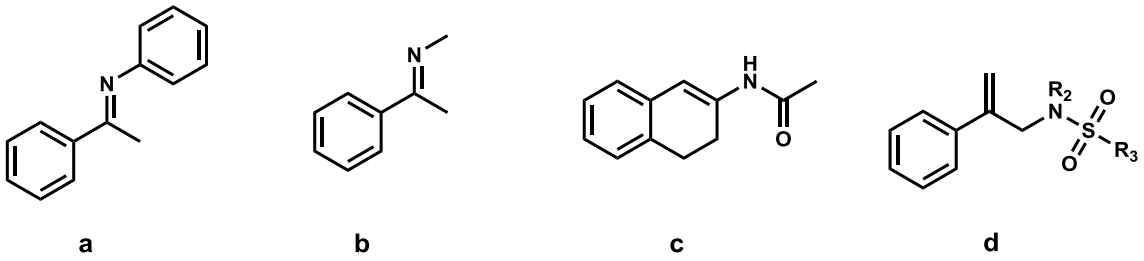


Figure 11 *Amine substrates used with Ir-MaxPHOX catalysts.*

Minimally functionalized olefins

As mentioned, the alkenes used in asymmetric hydrogenation reactions can be classified in three different classes: un-functionalized, minimally functionalized and functionalized. The un-functionalized olefins are alkenes which do not have a coordinating group and their hydrogenated products give practically hydrocarbons (Figure 12, compounds A and B). On the other hand, the functionalized olefins are alkenes in which the double bound is conjugated with a coordinating group such as amides or carboxylic acids. Between these two classes there are the minimally functionalized olefins. Even if the double bound is conjugated with a polar neighboring group, this group does not have strong coordinating properties. For this reason this classification is not a "black and white" expression; so many alkenes fall into the "gray area".

The asymmetric hydrogenation of minimally functionalized olefins is a challenging field. Although these substrates are easy to hydrogenate, it is difficult to induce enantioselectivity since they lack coordinating groups that can bind the metal generating geometrically ordered, defined complexes. In this context, di-substituted terminal alkenes are an even more challenging substrate class than the more widely investigated trisubstituted olefins. In facts, regarding to terminal alkenes, only few examples can be found in the literature and, as mentioned above, most of these are limited to allylic alcohols, allylic acetates and allyl silanes.

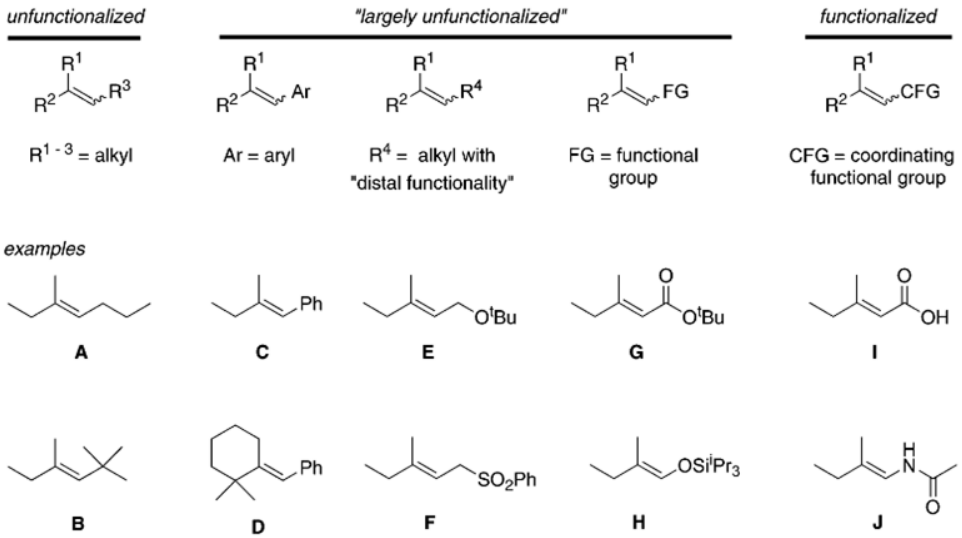


Figure 12 *Examples of un-, minimally functionalized and functionalized olefins.*

Pfaltz asymmetric hydrogenation of unfunctionalized olefins with Ir-PHOX catalysts

As above mentioned, Pfaltz reported the first iridium N,P based catalyst capable of reducing 1,1-disubstituted alkenes in useful selectivity (Ir–SerPHOX).[18] The later developed catalyst Ir–ThrePHOX was found to give even higher enantioselectivities and is now commercially available as the BArF salt.[19] First of all, the authors investigated aryl-alkyl substituted terminal alkenes with successful results in terms of conversion and enantiomeric excess (ee) (Figure 13). Later, they tested these catalysts with an allylic alcohol obtaining satisfactory results regarding conversion and ee.

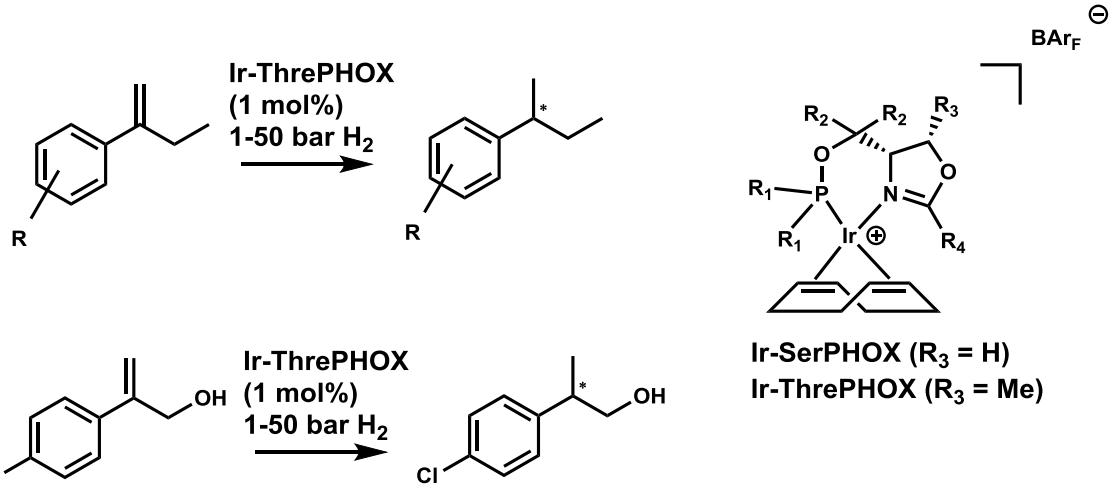


Figure 13 *Substrates used by Pfaltz in the asymmetric hydrogenation.*

Andersson and Dieguez asymmetric hydrogenation of unfunctionalized olefins with biarylphosphinite-Ir-PHOX libraries

A combined research effort by the groups of Dieguez, Andersson, and Borner initiated a combinatorial study utilizing the SerPHOX and ThrePHOX backbones in combination with a chiral biarylphosphinite moiety. A library of 96 possible phosphite oxazoline ligands was synthesized with systematic changes to the backbone and with special attention to the biaryl phosphite group (Figure 14).

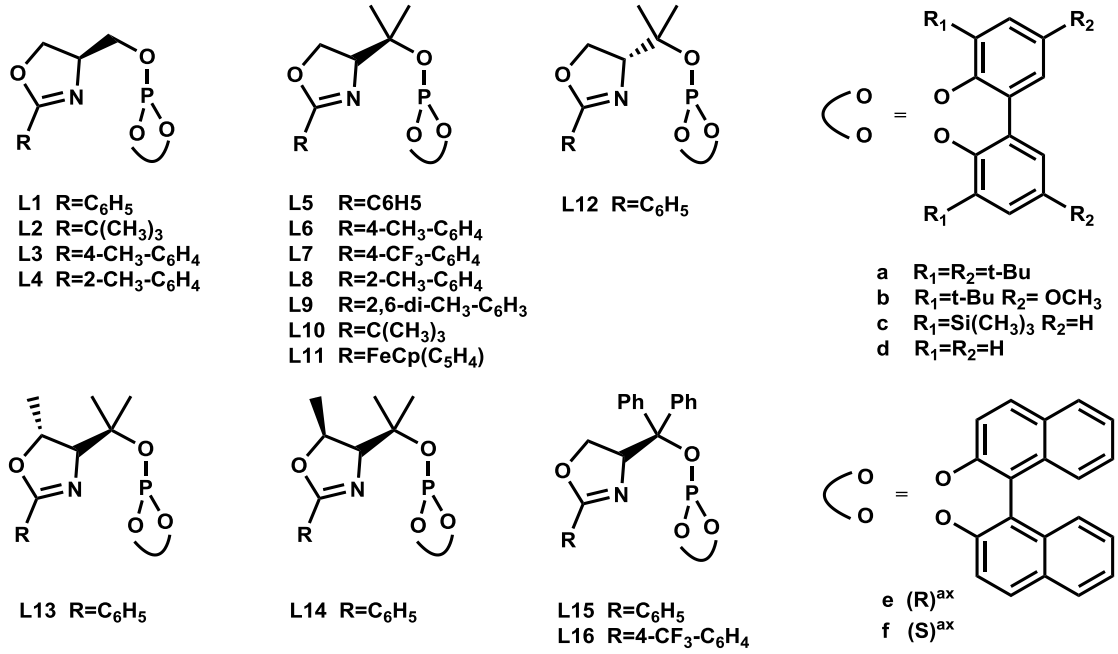


Figure 14 *Library of phosphite oxazoline ligands.*

This large class of complexes was found to be highly selective for the hydrogenation of aryl–alkyl substituted terminal alkenes, terminal alkenes bearing two sterically different aryl groups, and heterocyclic substrates (Figure 15).

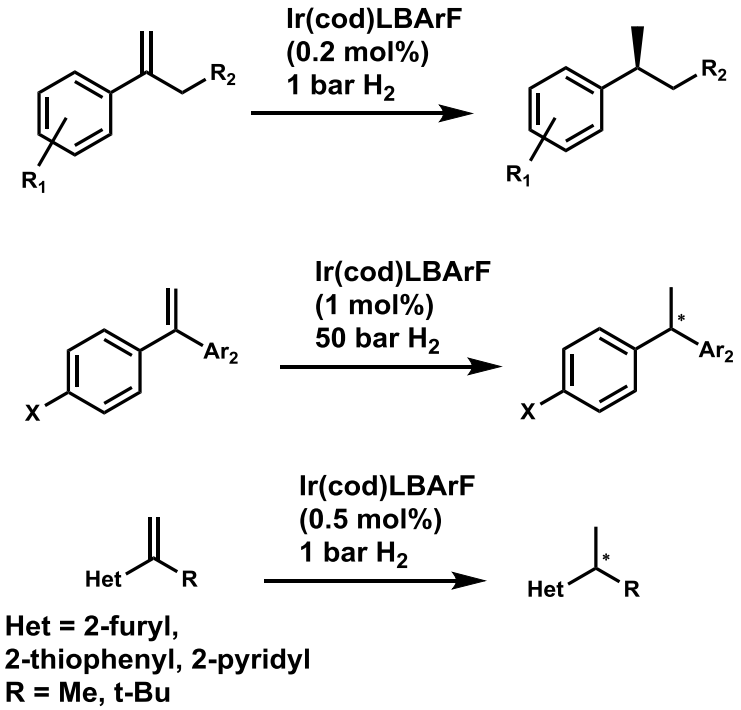


Figure 15 *Asymmetric hydrogenation with the phosphite oxazoline library.*

Zhang asymmetric hydrogenation of allylic amines

Zhang's group published on 2005 the first work about catalytic asymmetric hydrogenation of di-substituted allyl phthalimides [32] mediated by Rh and Ru complexes, to form chiral phthalimides which act as precursors to the β-methyl chiral amines. The asymmetric hydrogenation reaction was carried out on a variety of substrates as we can see in Figure 16.

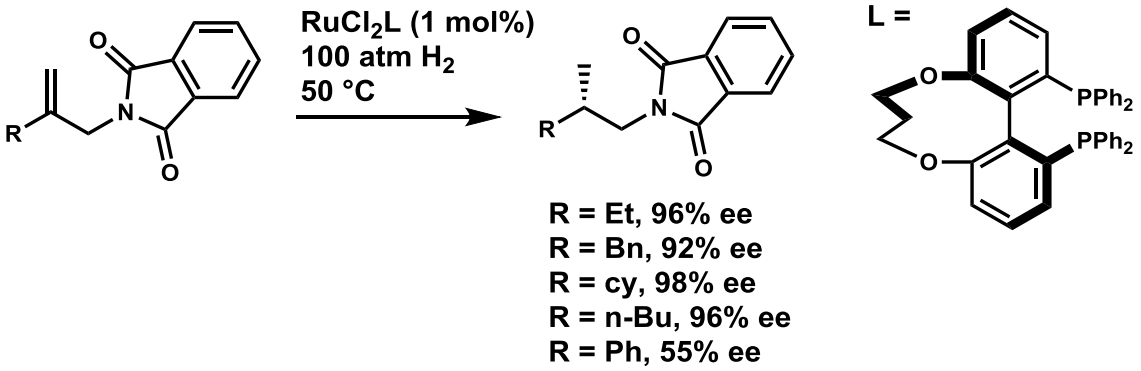


Figure 16 *Asymmetric hydrogenation of allyl phthalimides performed by Zhang.*

Substrates with a primary n-alkyl substituent such as ethyl, n-butyl, or benzyl group at the 2-position of the allylphthalimides afforded products with high ee values. In contrast, the hydrogenation of the aromatic substrate proceeded with moderate enantioselectivity.

Aim of the thesis

Chiral β-methyl amines

β -chiral amines bearing a methyl group on the chiral center, and their derivatives, are key structural elements in natural products and pharmaceuticals.[33,34]

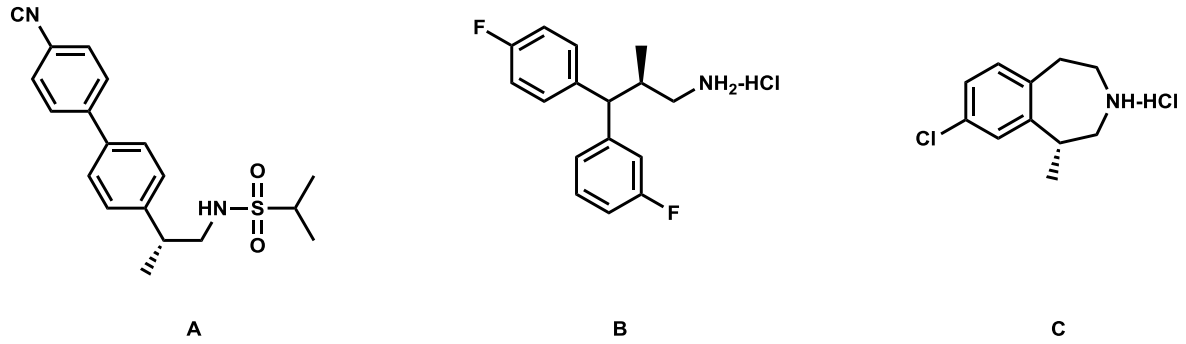


Figure 17 E*xamples of chiral β-methyl amines.*

For example, in

Figure **17**, compound A is a potent positive allosteric modulator of 2-amino-3-(5-methyl-3-hydroxyisoxazol-4-yl)-propanoic acid (AMPA) receptors. [35] Compound B (NPS 1392) is a potent stereoselective antagonist of the NMDA receptor, which can be used for the control of ischemic strokes [36], whereas compound C (Lorcaserin) is the active principle of a commercial anorectic drug. [37] For these substrates, although several asymmetric syntheses based on kinetic resolution or stoichiometric reagents have been explored [38] there is not any literature reports in which asymmetric hydrogenation is employed as the key step of the reaction. It remains a significant challenge.

Towards this task, our group has studied the catalytic asymmetric hydrogenation of N-tosyl allylic amines. [39] Although the reactions worked very well, the difficulties encountered in the removal of the N-tosyl protecting group was a significant shortcoming of this approach. To overcome this drawback, the focus was moved to the asymmetric hydrogenation of allylic phthalimides. The phthalimides are of great interest because they are easily synthesized compounds, and, in contrast with the previously applied N-tosyl products, much easier to deprotect under hydrazinolytic conditions. [32] As mentioned, the only examples available for the catalytic asymmetric hydrogenation of allylic phthalimides do not accommodate arylic substrates with good results. However, some very preliminary experiments collected in the group have shown that it should be possible to achieve good results in this reaction by using some iridium-P,N complexes.

On these premises, the aim of my thesis has been:

1) Study, develop and optimize the catalytic asymmetric hydrogenation reaction of a representative phenyl allylic phthalimide substrate using different Ir-P,N complexes and reaction conditions. (Figure 18)

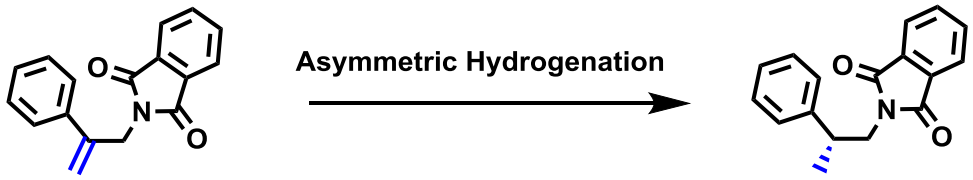


Figure 18 *Optimization of the asymmetric hydrogenation with the phenyl substrate.*

2) Study the scope of the reaction by synthesizing a series of phthalimide substrates and testing their behavior under the optimized conditions.(Figure 19)

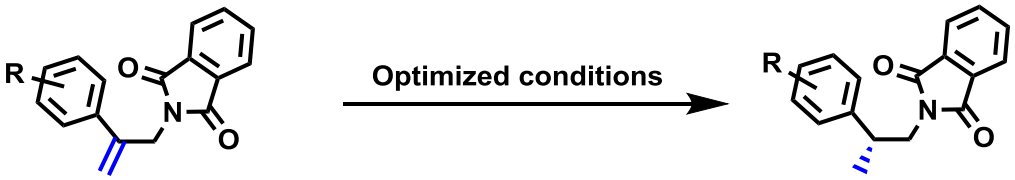


Figure 19 *The scope of the asymmetric hydrogenation.*

3) Apply the catalytic methodology towards a synthetic target. Lorcaserin was identified as suitable target, based on the following retrosynthetic analysis. (Figure 20)

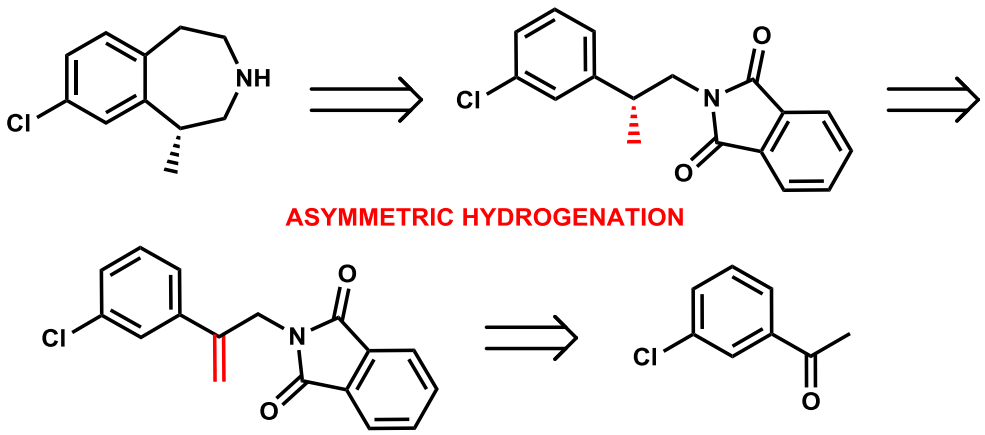


Figure 20 *The retrosynthesis of Lorcaserin.*

Results and discussion

Substrates

The substrates for the asymmetric hydrogenation reactions were prepared via a three-step sequence from commercially available acetophenones. The first step is a Wittig olefination, as outlined in Figure 21, and afforded the desired olefins in good yields (>80%). The olefins were used directly in the second step (halogenation reaction) without further purification.

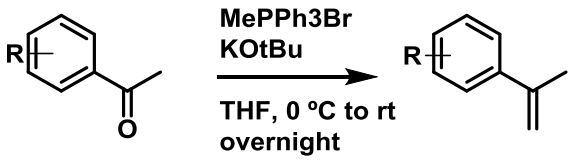


Figure 21 *The first step of the synthesis.*

The second step of the sequence is a halogenation in the alpha position of the terminal alkene, as shown in Figure 22. The reaction proceeds via radical mechanism and the halogenated product is obtained in good yields. During the synthesis of the ortho-bromophenyl substrate we realized that the halogenated product was quite lachrymatory. For this reason, for this substrate the reaction was conducted in a laboratory dedicated to dangerous compounds. The halogenated olefins were used directly in the third step (amination reaction) without further purification.

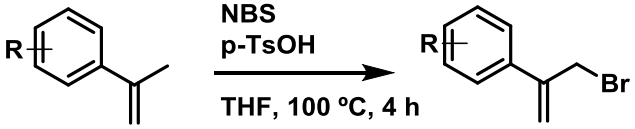


Figure 22 *The second step of the synthesis.*

The third and the last reaction is a simple S_N2 (nucleophilic substitution reaction, Figure 23). The reaction afforded the products in good yields and quite clean; nevertheless, the products needed purification for the next step of the study (asymmetric hydrogenation). Thus, silica gel chromatography was performed using an automated chromatography system.

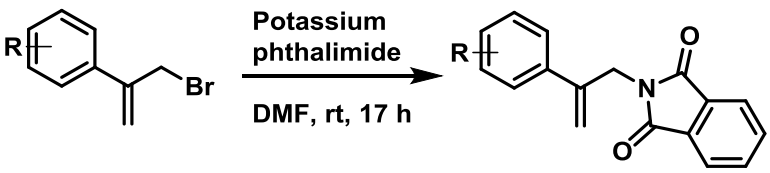


Figure 23 *The third step of the synthesis.*

Catalysts screening

Albert Cabré, the PhD student who has supervised me during the work of this thesis, has worked on the asymmetric hydrogenation, and, more in the specific, on the asymmetric hydrogenation of N-tosyl allyl amines.[39] During his work, he also tried to hydrogenate different related substrates, with good results for conversion and enantiomeric excess. One of these substrates was an aryl N-allyl phathalimide. The hydrogenation of this substrate was performed asymmetrically using the UbaPHOX catalyst, which was designed by Pfaltz, and now is commercial available (Figure 24). The reaction gave the desired product with excellent yield and good ee, but the operative conditions were far from being optimal.

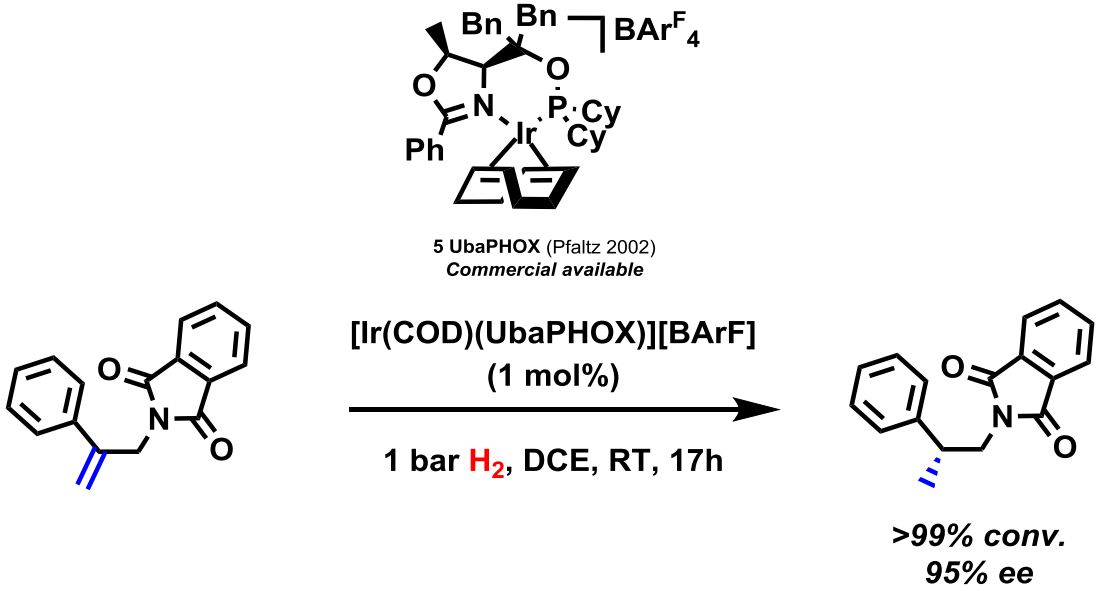


Figure 24 *Preliminary results in the asymmetric hydrogenation of phthalimides.*

Thus, with these promising results in hand, we decided to study the asymmetric hydrogenation of allylic phthalimides in detail, starting with the optimization of the reaction on the simple phenyl substrate (Table 1). For doing this, we decided to start with a screening of catalysts, carrying out the reaction with the operative conditions found by Albert Cabré, with slight modifications (Figure 25).

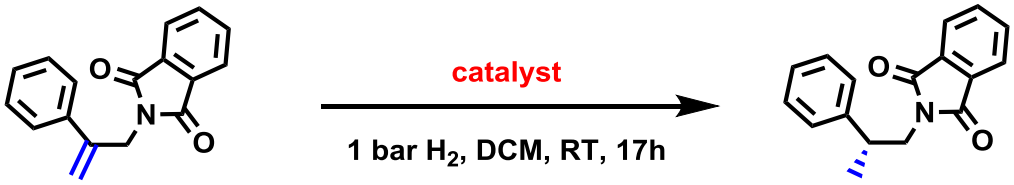
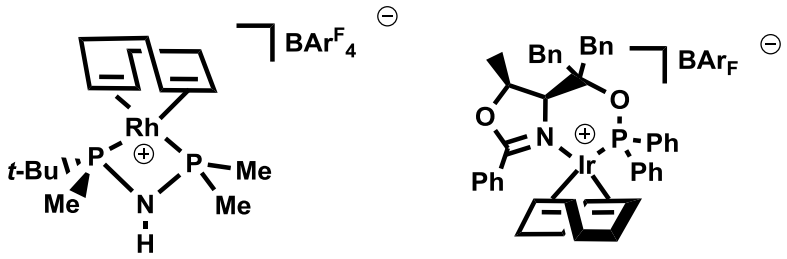


Figure 25 *Scheme of the reaction.*

Thus, we decided to test different Iridium P,N catalysts including the MaxPHOX family which was introduced by our research group. Furthermore, a Rhodium catalyst was also tested to confirm the poor reactivity and enantiomeric induction with these types of substrates.



1 **[Rh(COD)(*R*-MaxPHOS)]BAr$^F_4$** **4 ThrePHOX**

Figure 26 *The Rh complex and the commercial catalyst used in the catalyst screening.*

The structure is shown in Figure 26 and as above mentioned is a Rh complex in which the backbone belong to the MaxPHOS family. The second structure in Figure 26 is a Pfaltz's catalyst which is commercially available. All the others belong to the Ir-MaxPHOX family, which were synthetized within the research group (Figure 27).

Table 1 *Catalysts screening of the asymmetric hydrogenation*

Entry[a]	Catalyst	Cat. Loading	Conversion[b] (%)	ee[c] (%)
1	1	10 mol%	29	n.d.
2	Ir-1 iPr	5 mol%	>99	6
3	Ir-2 iPr	5 mol%	>99	64
4	Ir-3 iPr	5 mol%	>99	20
5	Ir-4 iPr	5 mol%	>99	32
6	4	5 mol%	78	7
7	Ir-2 tBu	5 mol%	>99	90

[a]Reaction conditions: substrate (0.2 mmol), DCM (2 mL), cat. (x mol%), 1 bar H_2, RT, 17 h. [b] Determined by ^1H NMR spectroscopy. [c] Determined by chiral stationary phase HPLC.

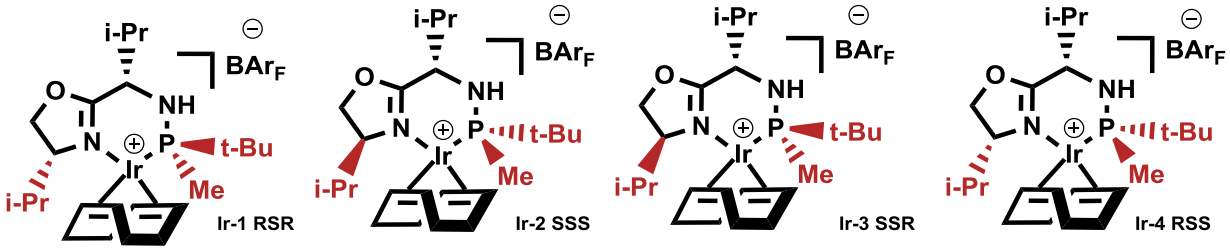


Figure 27 *The MaxPHOX catalysts synthetized by our group.*

As expected, the asymmetric hydrogenation of this substrate works well with the Ir P,N catalysts in terms of conversion but the results are not satisfactory regarding the ees, while the rhodium and the commercial iridium catalysts **1** and **4** give poor results.(Table 1 entry 3) which allows obtaining the hydrogenated product with excellent yield and moderate values of enantiomeric excess. We decided to carry out another experiment to see if the chiral substituents which lie on the backbone of the Iridium catalyst could influence the enantioselectivity. Thus, since the catalyst which works better is the diastereoisomer 2, we thought to employ the same diastereoisomer but with a different substituent on the chiral oxazoline portion. In this case, instead of an isopropyl group, there is a ter-butyl group (Figure 28), which is more sterically hindered.

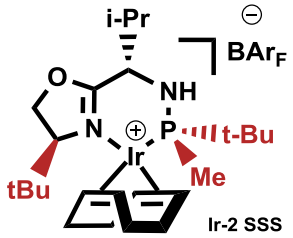


Figure 28 *The structure of the Ir(MaxPHOX)-2 t-Bu catalyst.*

As we can see from the Table 1(Entry 8) this catalyst can afford the hydrogenated product in excellent yield and with a good, yet not fully satisfactory, ee. After this result, we decided to investigate how the catalyst and, more generally, the reaction performs under high pressure.

Accordingly, we carried out the asymmetric hydrogenation as shown in Figure 29, with the catalysts which gave the best results: Ir-2 iPr and Ir-2 tBu.

In Table 2 we can see that both catalysts manage to catalyze the reaction by providing a full conversion; nevertheless the enantiomeric excess has worsened respect the previous reaction with lower hydrogen pressure. In particular, we can see the Ir-2 iPr loses several percentage points of ee (56% vs 64%) whereas the Ir-2 tBu has lowered his ee by a few percentage points (88% vs 90%).

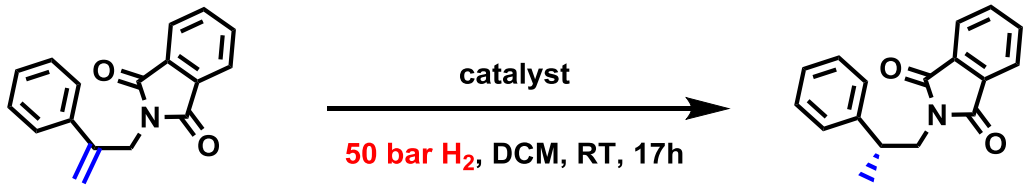


Figure 29 *Scheme of the reaction with high pressure.*

Table 2 *Catalysts screening changing the pressure*

Entry[a]	Catalyst	Cat. Loading (mol %)	Conversion (%)[b]	ee (%)[c]
1	Ir-2 iPr	5	>99	56
2	Ir-2 tBu	5	>99	88

[a]Reaction conditions: substrate (0.2 mmol), DCM (2 mL), cat. (5 mol%),50 bar H_2, RT, 17 h. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by chiral stationary phase HPLC.

After this preliminary investigation, we can conclude that the best catalyst for giving high conversion and good ee is the Ir-2-t-Bu. This is a good result, because the catalyst has been designed within the research group, giving an added value to my work.

Optimization of reaction conditions

For the optimization of the reaction, we changed some operative conditions to see how the reaction responded (Figure 30).

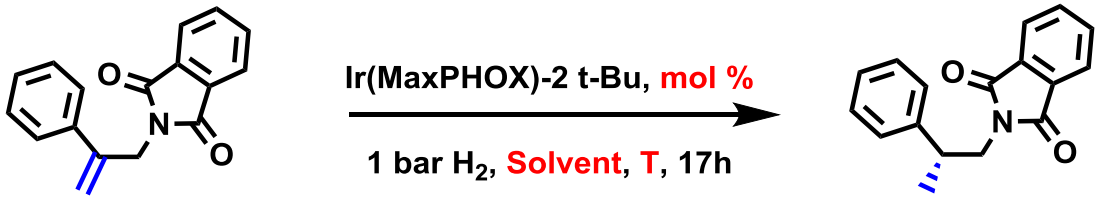


Figure 30 *Scheme of the reaction.*

We started trying to reduce the catalyst loading. Normally, for asymmetric synthesis, it is important to minimize as much as possible the quantity of catalyst in the reaction to reduce its cost for a possible future industrial application.

As can be seen from the Table 3, we have reduced the catalytic load from 5 mol % to 1 mol % (Entries 1,2). The reaction goes to full conversion and the ee is not affected at all.

Subsequently, we have moved our attention to the screening of the solvents. We tried solvents more coordinating than dichloromethane, such as EtOAc and THF. As we expected (see Introduction) the results in terms of conversion and ee are worse, as shown in the Table 3, Entries 3,4.

As last change in operative conditions, we have done an experiment changing the temperature. As displayed in the Table 3 we have lowered the temperature up to -20 °C using a cryo-cool machine.

Table 3 *The optimization of the reaction: screening of catalyst load, solvent and temperature*

Entry[a]	Cat. load (mol %)	Solvent	Temperature (°C)	Conversion (%)[b]	Ee (%)[c]
1	5	DCM	Rt	>99	90
2	1	DCM	Rt	>99	90
3	1	EtOAc	Rt	60	89
4	1	THF	Rt	5	n.d.
5	1	DCM	-20	>99	98

[a]Reaction conditions: substrate (0.2 mmol), Solvent (2 mL), Ir(MaxPHOX)-2 t-Bu (x mol%), 1 bar H_2, Temperature, 17 h. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by chiral stationary phase HPLC.

It is quite common in asymmetric synthesis to reduce the temperature to favor the formation of one of the two possible enantiomers. In fact, lowering the temperature we could see an increase of enantiomeric excess, and up to 98% of ee was afforded (Entry 5).

Finally, we can state that the best operating conditions for this reaction are: 1 mol % of catalytic loading, in DCM, 1 bar pressure, -20°C (Figure 31).

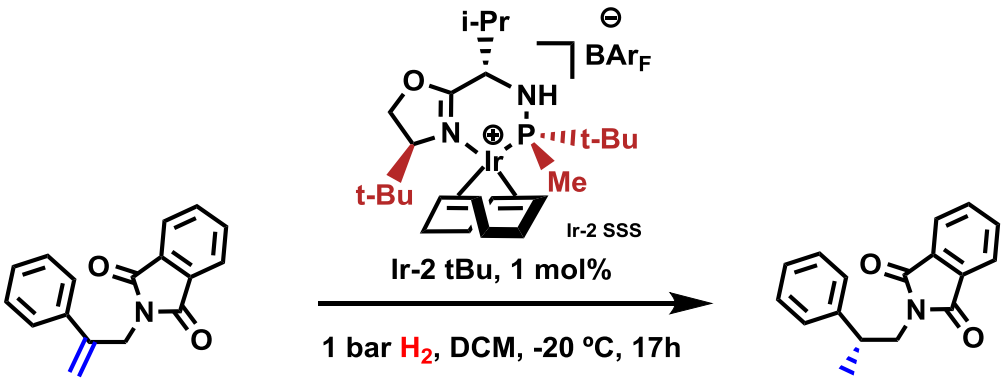


Figure 31 *Optimized conditions for the asymmetric hydrogenation.*

Scope of the asymmetric hydrogenation reaction

After all the screenings for finding the best conditions for the asymmetric hydrogenation we investigated the scope of the reaction, using the previously synthetized substrates changing the substituents in the aromatic ring of the terminal alkene, with both electron withdrawing group and electron donor group in *ortho*-, *meta*- and *para*-position.

The operating conditions are those previously studied and found to be the best, and are shown in Figure 32.

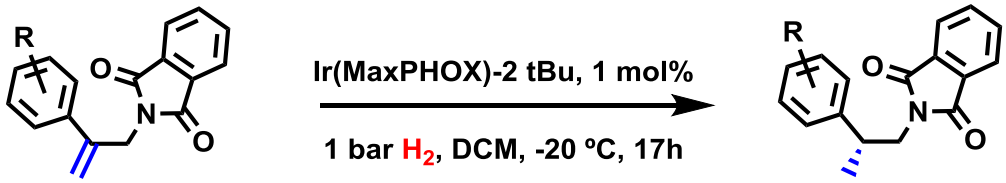


Figure 32 *Asymmetric hydrogenation of different phthalimide substrates.*

In Table 4 are displayed the results of the hydrogenation of all the substrates. We can say that the Ir P,N catalyst can promote the formation of the hydrogenated product with excellent enantioselectivity, irrespective of the nature and position of the substituent on the aromatic ring. In fact, we can say that our catalyst induces excellent ee's for the *para*- and *meta*-positions with ee's up to 99%, whereas, for the *ortho*-position the ee's are lower but still good with values up to 91% of ee. We can induce excellent enantioselectivity also with napthalenic substituents.

Table 4 *The scope of the asymmetric hydrogenation*

Substrate (R)	Conversion[a] (%)	Ee[b] (%)
H (standard substrate)	>99	98
p-Me	>99	97
p-F	>99	>99
p-Cl	97	97
p-I	99	98
p-Br	99	97
m-MeO	>99	98
m-Cl	>99	99
o-Me	>99	91
o-Br	>99	90
o-MeO	98	83
2-Naph	>99	97

[a]Determined by ^{1}H NMR spectroscopy. [b]Determined by chiral stationary phase HPLC.

After an experiment of hydrogenation of the *para*-fluorine substrate we noted in the NMR spectrum some other signals which did not belong to the hydrogenated product. In fact, we noted near the characteristic signals of the double bound of the terminal alkene of the starting substrate two small signals. Initially, we did not understand what it was. Thus, we carried out an experiment at reduced reaction times. Without further purification we brought the reaction crude directly to ^{1}H-NMR analysis. The spectrum is shown below in Figure 33.

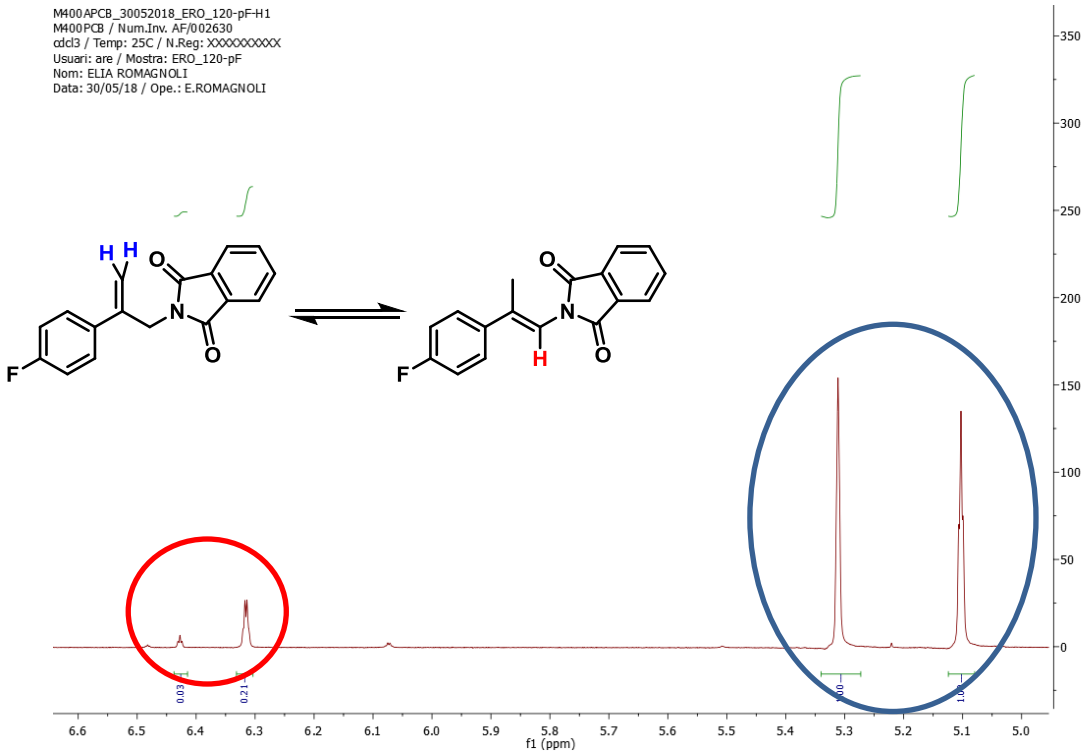


Figure 33 *The isomerization of the substrate with an electron withdrawing group*.

Examining the NMR spectrum we noted that the more intense signals derived from the double bound of our starting material accompanied by the two, previously detected, signals of the new product which was now identified as the E and Z form of an enamide derived by isomerization of the starting substrate. Therefore, we supposed that when there is an electron-withdrawing group on the aromatic ring, such as the fluorine, our substrate could isomerize.

This isomerization could be a problem in the HPLC analysis. Thus after this discovery, we have purified all the substrates with EWG in the aromatic ring, leading to the results reported in Table 4.

In conclusion, we have been able to isolate and characterize the hydrogenated products with excellent results in terms of conversion, and especially, enantiomeric excess.

Synthetic application

By the high importance of chiral β-methyl amines in the biological field, we were encouraged to prove the applicability of our catalytic methodology. We set our efforts on the synthesis of (*R*)-Lorcaserin. It presents a tetrahydro-3-benzazepine skeleton, which is a common structural feature in many natural and pharmaceutical products. Lorcaserin has serotonergic properties and is currently used as a weight-loss drug. [35,37] Several racemic synthesis of this compound have been reported. In its asymmetric form, only few strategies can be found in the literature, most of them using kinetic resolution or stoichiometric reagents, and even less applying asymmetric catalysis.[37] For this reason, we envisioned that we could apply the novel synthetic methodology presented here to develop a new access to lorcaserin in enantiopure form.

For this purpose, the corresponding *meta*-chlorophenyl acetophenone was used as starting material for a 8-step synthetic route to afford optically pure (*R*)-Lorcaserin (Figure 34). After the synthesis of our phthalimide, the corresponding selective Ir-catalyzed asymmetric hydrogenation took place smoothly, to afford the hydrogenated product in good yield and with excellent ee. Further deprotection gave the corresponding free amine in 65% yield. [32]

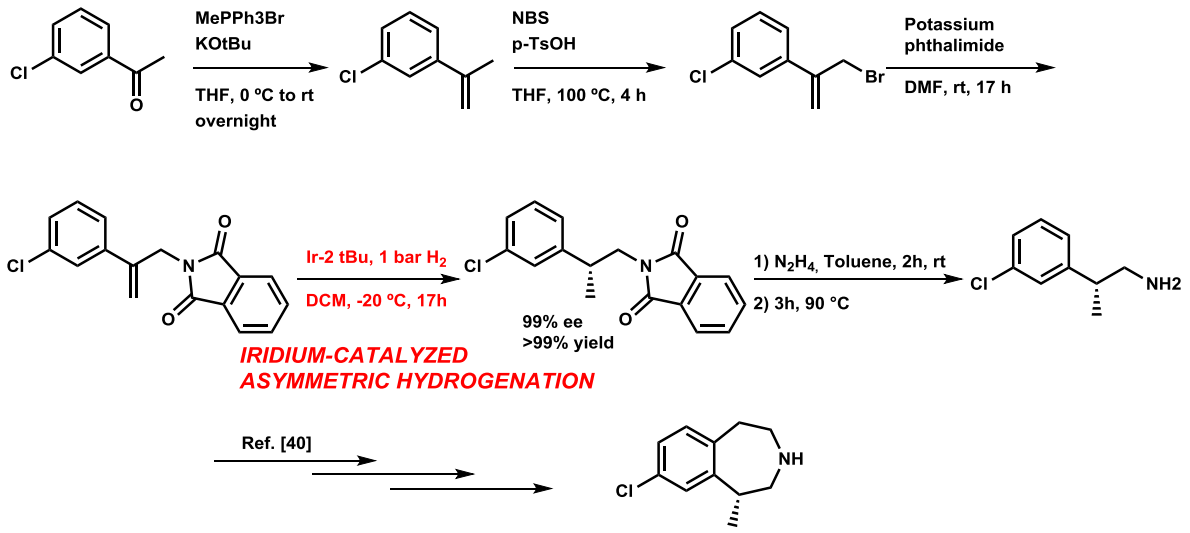


Figure 34 *The synthetic pathway proposed.*

This amine has been already used in the literature as the key starting material for the synthesis of Lorcaserin through an N-acylation followed by reduction. [40] As last step of the synthesis, a Lewis-acid promoted intramolecular Friedel-Crafts alkylation was used. This reaction occurred selectively to the *para*-position of the aromatic ring due to steric control, thus

forming a 7-membered ring and, consequently, Lorcaserin. In conclusion, we proposed this synthetic pathway which includes our asymmetric hydrogenation as the key step of the synthesis.

Conclusions

Considering the results obtained, we were able to achieve our goals. In particular, we can conclude that:

1. we have found satisfactory conditions for our planned asymmetric hydrogenation using a non-commercial catalyst developed by our research group (Figure 35)

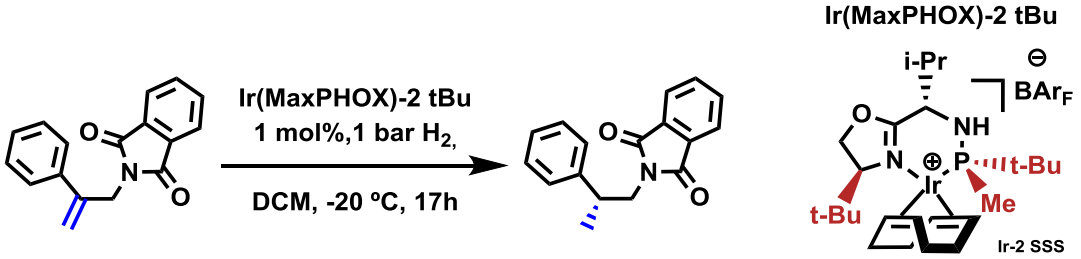


Figure 35 *The optimized reaction.*

2. We studied the reaction with several different substrates, and we obtained good results in terms of yields and, enantiomeric excesses independently from the aromatic substituent. (Figure 36)

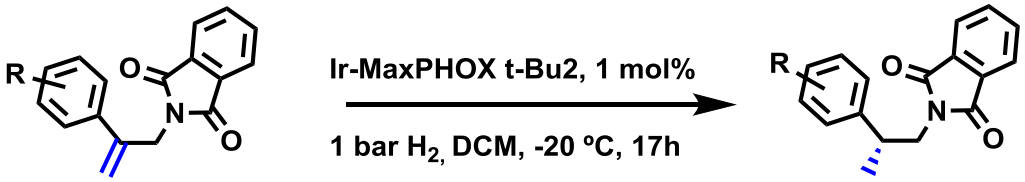


Figure 36 *The scope of the reaction.*

3. A synthetic application of our optimized reaction was shown, by the formal synthesis of Lorcaserin. (Figure 37)

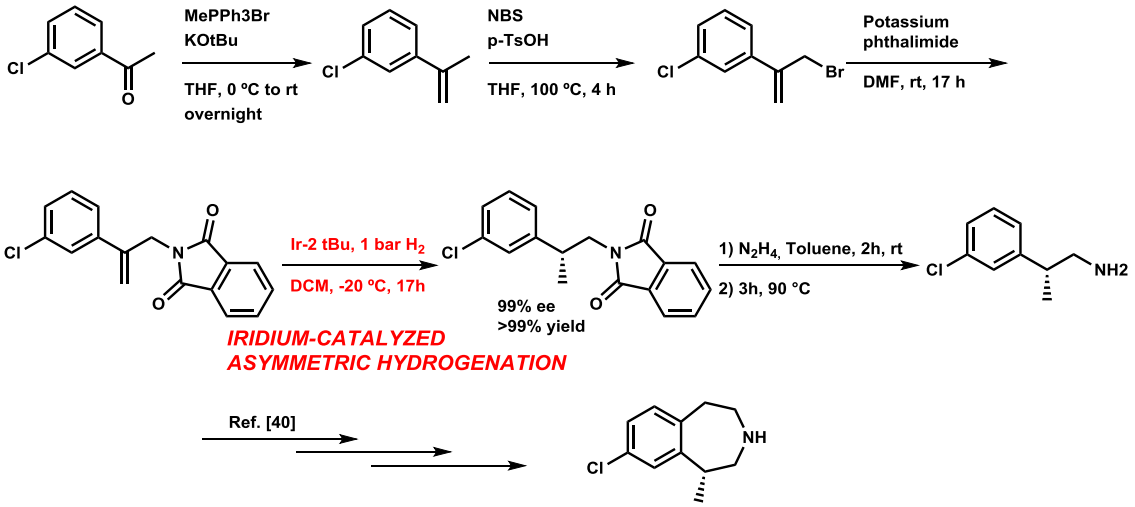


Figure 37 *The total formal synthesis of Lorcaserin.*

Experimental Part

General information

General procedures and materials

Unless otherwise indicated, materials were obtained from commercial suppliers and used without further purification. All reactions that required anhydrous conditions were performed in dried glassware under a dry nitrogen atmosphere. Dichloromethane and THF were degassed and anhydrised with a solvent purification system (SPS PS-MD-3). Anhydrous dichloroethane and DMF were used from Sigma Aldrich. Solvents were removed under reduced pressure with a rotary evaporator. Silica gel chromatography was performed using an automated chromatography system (PuriFlash® 430, Interchim).

Instrumentation

NMR spectroscopy: ^{1}H and ^{13}C were recorded on the NMR spectrometers of the *Centres Científics i Tecnològics de la Universitat de Barcelona*. The employed spectrometers were a Varian Mercury 400 MHz. Chemical shifts (δ) were referenced to internal solvent resonances and reported relative to TMS (tetramethylsilane). The coupling constants (*J*) are reported in Hertz (Hz). The following abbreviations are used to define multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), ddd (doublet of doublet of doublets), ddd (doublet of doublet of triplets), dddd (doublet of doublet of doublet of doublets), dt (doublet of triplets), td (triplet of doublets), ddq (doublet of doublet of quartets), dtd (doublet of triplet of doublets), dq (doublet of quartets), tt (triplet of triplets), qt (quartet of triplets), m (multiplet), br s (broad signal).

High Resolution Mass Spectrometry: High resolution ESI-MS spectra were recorded in an LC/MSD-TOF G1969A (Agilent Technologies) of the *Centres Científics i Tecnològics de la Universitat de Barcelona.*

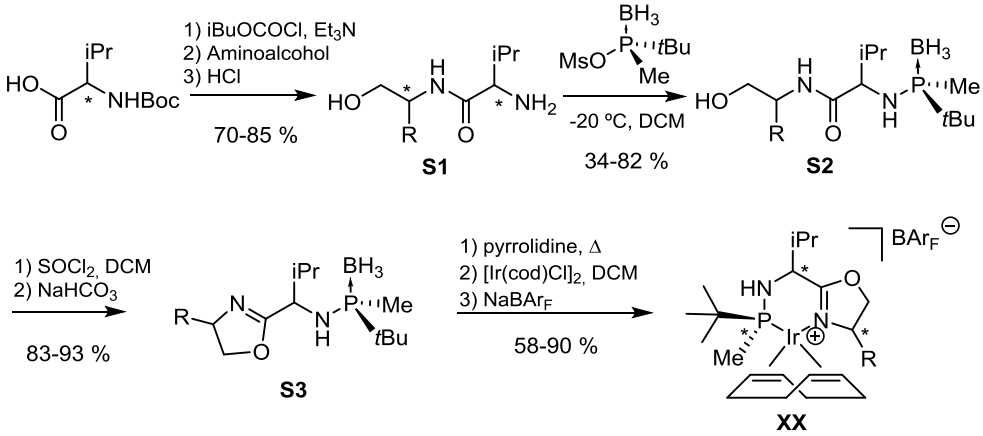
IR spectroscopy: IR spectra were measured in a Thermo Nicolet 6700 FT-IR spectrometer using an ATR system, of the Department of Organic Chemistry in the Universitat de Barcelona.

Optical rotations were measured at room temperature (25°C) using a Jasco P-2000 iRM- 800 polarimeter. Concentration is expressed in g/100 mL. The cell sized 10 cm long and had 1 mL of capacity, measuring λ was 589 nm, which corresponds to a sodium lamp.

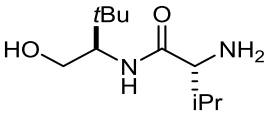
Melting points were determined using a Büchi melting point apparatus and were not corrected.

Experimental procedure for the synthesis of catalyst Ir-MaxPHOS t-Bu 2

Following the experimental procedure described in the literature [41], catalysts were afforded after 4 synthetic steps.

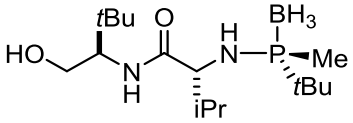


(R)-2-amino-N-((R)-1-hydroxy-3,3-dimethylbutan-2-yl)-3-methylbutanamide, S1



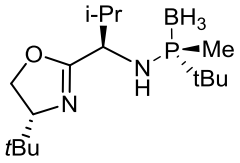
Following the experimental procedure described in the literature [41], **S1** was obtained as a white solid (5.52 g, 89% yield). m.p. 87 - 91 ºC. $[\alpha]_D^{25}$: +36 (c 0.7, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ: 7.80 (d, *J* = 8.4 Hz, 1H), 3.90 (ddd, *J* = 11.0, 3.1, 0.6 Hz, 1H), 3.76 (td, *J* = 8.6, 3.1 Hz, 1H), 3.54 (ddd, *J* = 11.0, 8.6, 0.6 Hz, 1H), 3.33 (d, *J* = 3.6 Hz, 1H), 2.42 – 2.31 (m, 1H), 1.99 (s, 2H), 1.02 (d, *J* = 7.0 Hz, 3H), 0.97 (s, 9H), 0.83 (d, *J* = 6.9 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ: 176.26, 64.26, 60.26, 33.21, 30.58, 27.14, 19.97, 16.11 ppm. **HRMS** (ESI) calculated for $C_{11}H_{25}N_2O_2$ 217.1911, found 217.1917 $[M+H]^+$. **IR** (ATR-FTIR) ν_{max} = 3324, 3292, 2953, 2869, 1650, 1629, 1537 cm^{-1}.

(*R*)-2-(((*S*)-*tert*-butyl(methyl)phosphanyl)amino)-N-((*R*)-1-hydroxy-3,3-dimethylbutan-2-yl)-3-methylbutanamide borane, S2



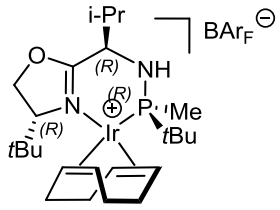
Following the experimental procedure described in the literature [41], **S2** was obtained as a white solid (2.06 g, 69% yield). **m.p.** 150-152 ºC. **[α]$_D^{25}$**: +27 (c 0.8, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.07 (d, *J* = 8.8 Hz, 1H), 3.87 (dd, *J* = 11.2, 3.1 Hz, 1H), 3.79 (ddd, *J* = 8.9, 7.7, 3.1 Hz, 1H), 3.58 (dd, *J* = 11.2, 7.7 Hz, 2H), 2.15 (s, 1H), 2.12 – 2.05 (m, 1H), 1.36 (d, *J* = 8.9 Hz, 3H), 1.14 (d, *J* = 14.1 Hz, 9H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.97 (s, 9H), 0.93 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.46, 110.21, 63.65, 62.83, 60.44, 33.31, 32.77, 32.74, 31.08, 30.69, 27.19, 24.73, 24.70, 19.72, 17.95, 10.68, 10.29. **^{31}P NMR** (202 MHz, $CDCl_3$) δ 71.0 – 71.0 (m, P-BH_3) ppm. **HRMS** (ESI) calculated for $C_{16}H_{39}BN_2O_2P$ 333.2842, found 333.2849 $[M+H]^+$. **IR** (ATR-FTIR) ν_{max} = 3312, 3244, 2960, 2861, 2367, 2328, 1644, 1556, 1366, 1067, 1052 cm^{-1}.

(*S*)-1-*tert*-butyl-N-((*R*)-1-((*R*)-4-(tert-butyl)-4,5-dihydrooxazol-2-yl)-2-methylpropyl)-1-methylphosphanamine borane, S3



Following the experimental procedure described in the literature[41], **S3** was obtained as an oil (1.02 g, 80% yield). **[α]$_D^{25}$**: +28 (c 0.6, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 4.22 (dd, *J* = 10.2, 8.7 Hz, 1H), 4.06 (t, *J* = 8.6 Hz, 1H), 3.95 (dt, *J* = 10.0, 5.0 Hz, 1H), 3.84 (ddd, *J* = 10.2, 8.5, 0.7 Hz, 1H), 2.35 (d, *J* = 10.0 Hz, 1H), 2.00 (dtd, *J* = 13.8, 6.9, 4.6 Hz, 1H), 1.33 (d, *J* = 9.0 Hz, 3H), 1.14 (d, *J* = 14.0 Hz, 9H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 9H), 0.89 (d, *J* = 6.9 Hz, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 75.49, 69.13, 56.74 (d, *J* = 2.6 Hz), 33.62 (d, *J* = 2.9 Hz), 33.52, 31.31 (d, *J* = 37.8 Hz), 25.98, 24.63 (d, *J* = 3.2 Hz), 18.60, 17.70, 10.65 (d, *J* = 42.2 Hz). **^{31}P NMR** (202 MHz, $CDCl_3$) δ 70.5 – 69.5 (m, P-BH_3) ppm. **HRMS** (ESI) calculated for $C_{16}H_{37}BN_2OP$ 315.2731, found 315.2742 $[M+H]^+$. **IR** (ATR-FTIR) ν_{max} = 3332, 2958, 2865, 2390, 2368, 2336, 1668, 1464, 1357, 1137 cm^{-1}.

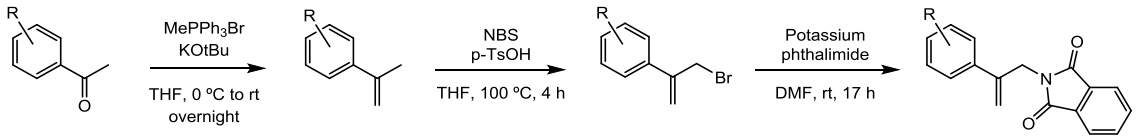
[Ir(MaxPHOS)(COD)]BAr_F, t-Bu 2



Following the experimental procedure described in the literature[41],Ir-MaxPHOS t-Bu 2 was obtained as an orange solid (162 mg, 70% yield). **m. p.** 228 - 230 ºC (descomposition). **$[\alpha]_D^{25}$**: -76 (c 0.3, $CHCl_3$). **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.71 (s, 5H), 7.53 (s, 4H), 4.87 (s, 1H), 4.59 (dd, *J* = 9.7, 3.4 Hz, 2H), 4.44 (p, *J* = 7.3 Hz, 1H), 4.25 (t, *J* = 9.7 Hz, 1H), 3.92 (dd, *J* = 9.1, 3.4 Hz, 2H), 3.28 (ddd, *J* = 25.2, 9.3, 7.0 Hz, 1H), 2.46 (dd, *J* = 15.6, 7.9 Hz, 1H), 2.40 – 2.17 (m, 4H), 2.16 – 2.04 (m, 2H), 1.91 (dt, *J* = 13.9, 9.0 Hz, 1H), 1.57 (d, *J* = 6.3 Hz, 3H), 1.52 – 1.42 (m, 2H), 1.17 – 1.06 (m, 12H), 1.00 (s, 9H), 0.88 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.32, 162.59, 162.09, 161.59, 161.10, 134.94, 129.51, 129.45, 129.20, 129.17, 128.88, 128.83, 128.59, 128.55, 126.05, 123.35, 117.66, 117.63, 117.59, 117.55, 93.06, 92.96, 88.24, 88.10, 72.38, 71.10, 63.41, 59.25, 56.32, 38.85, 38.82, 37.79, 37.74, 36.09, 35.71, 34.17, 33.32, 33.30, 28.91, 25.92, 25.88, 25.42, 24.40, 24.38, 21.45, 18.37, 16.51, 16.22. **^{31}P NMR** (202 MHz, $CDCl_3$) δ 53.8 ppm. **HRMS** (ESI) calculated for $C_{24}H_{45}N_2OPIr$ 601.2893, found 601.2914 $[M+H]^+$. **IR** (ATR-FTIR) ν_{max} = 3430, 2961, 1624, 1612, 1352, 1273, 1157, 1119, 1094 cm^{-1}.

Experimental procedures and characterization data

Preparation of the aryl-substituted N-allyl phthalimides



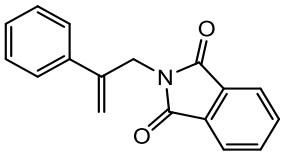
Step 1. In an oven dried flask, methyl triphenylphosphonium bromide (1.2 equiv.) was taken and to this anhydrous THF (1.6 mL/mmol) was added. The suspension was cooled to 0 ºC, KOtBu (1.2 equiv.) was added and the resulting yellow suspension was stirred at 0 ºC for 45 min. To this suspension, a solution of ketone (1.0 equiv.) in THF (0.7 mL/mmol) was added dropwise and the resulting mixture was warmed gradually to r.t. and stirred at r.t. for 16 hours. Afterwards, the reaction mixture was concentrated and redissolved with hexanes. The crude was filtered by a plug of silica and washed (x3) with hexanes, to afford the desired product which was used for the next step without further purification.

Step 2. In an oven dried flask the alkene (1 equiv.) was dissolved in THF (3 mL/mmol). To the resulting solution, NBS (1.05 equiv.) and p-TsOH (0.1 equiv.) were added and the solution was refluxed for 4 hours at 100ºC. Afterwards, the reaction mixture was cooled to room temperature and taken up with Hexane (15 mL/mmol), washed three times with H_2O (15 mL x 3) and the organic layer dried over $MgSO_4$. The solvent was removed in vacuum and an oil was obtained which was used for the next step without further purification.[42]

Step 3. Potassium phthalimide (1.1 equiv.) was added to a solution of the α-bromo alkene (1 equiv.) in DMF (2.76 mL/mmol) at room temperature. The resulting mixture was stirred for 18 hours. Afterwards, DCM (30 mL) was added and the mixture poured onto water (100 mL). The aqueous phase was separated and extracted with DCM for three times. The combined organic extract was then washed with NaOH aq. (0,2 M) and dried over $MgSO_4$. The solvent was removed in vacuum and the residue purified by column chromatography (Hexane:EtOAc 70:30) to afford the protected product as white solid. [43

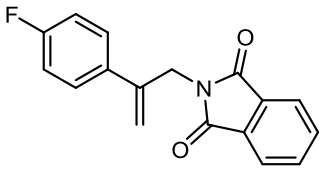
For the synthesis of the following compounds, 1 g of ketone was used as starting material for all cases.

2-(2-phenylallyl)isoindoline-1,3-dione



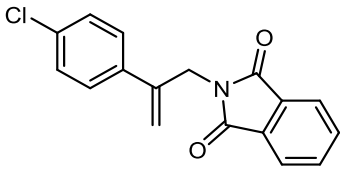
White solid (790 mg, 50% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.71 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.52 – 7.48 (m, 2H), 7.37 – 7.28 (m, 2H), 5.44 (t, *J* = 0.9 Hz, 1H), 5.16 (t, *J* = 1.6 Hz, 1H), 4.71 (t, *J* = 1.3 Hz, 2H). The analytical data for this compound were in excellent agreement with the reported data.[44]

2-(2-(4-fluorophenyl)allyl)isoindoline-1,3-dione



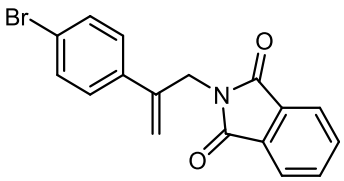
White solid (696 mg, 34% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.74 – 7.69 (m, 2H), 7.49 – 7.43 (m, 2H), 7.05 – 6.98 (m, 2H), 5.39 (s, 1H), 5.19 – 5.16 (m, 1H), 4.67 (t, *J* = 1.3 Hz, 2H). The analytical data for this compound were in excellent agreement with the reported data.[43]

2-(2-(4-chlorophenyl)allyl)isoindoline-1,3-dione



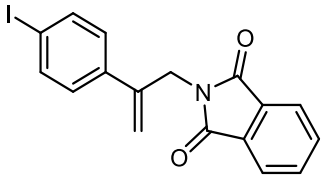
White solid (845 mg, 44% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.87 – 7.81 (m, 2H), 7.75 – 7.69 (m, 2H), 7.45 – 7.40 (m, 2H), 7.33 – 7.27 (m, 2H), 5.44 – 5.42 (m, 1H), 5.22 (t, *J* = 1.6 Hz, 1H), 4.67 (dd, *J* = 1.5, 1.0 Hz, 2H). The analytical data for this compound were in excellent agreement with the reported data.[43]

2-(2-(4-bromophenyl)allyl)isoindoline-1,3-dione



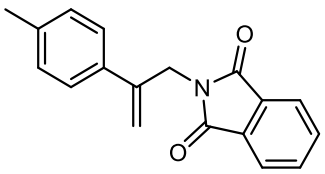
White solid (608 mg, 35% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.71 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.48 – 7.43 (m, 2H), 7.39 – 7.35 (m, 2H), 5.44 (d, *J* = 1.1 Hz, 1H), 5.23 (t, *J* = 1.5 Hz, 1H), 4.67 (dd, *J* = 1.5, 1.0 Hz, 2H). The analytical data for this compound were in excellent agreement with the reported data.[45]

2-(2-(4-iodophenyl)allyl)isoindoline-1,3-dione



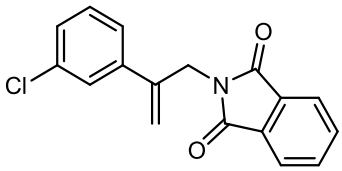
White solid (620 mg, 39% yield). **m.p.** 178-181ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.87 – 7.79 (m, 2H), 7.74 – 7.68 (m, 2H), 7.65 (dq, *J* = 8.1, 1.6, 1.2 Hz, 2H), 7.25 – 7.21 (m, 2H), 5.44 (s, 1H), 5.22 (d, *J* = 1.6 Hz, 1H), 4.66 (p, *J* = 0.8 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.05, 141.79, 138.09, 137.66, 134.23, 132.08, 128.44, 123.57, 115.23, 93.96, 41.39. **HRMS** (ESI) calculated for $C_{17}H_{12}INO_2$ 389.9985, found 389.9988 $[M+H]^+$. **IR** (ATR-FTIR) ν_{max} = 1766, 1703, 1390, 1110 cm^{-1}.

2-(2-(p-tolyl)allyl)isoindoline-1,3-dione



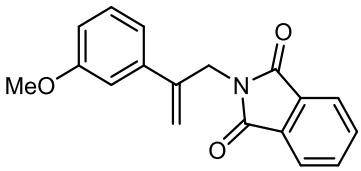
White solid (679 mg, 33% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.86 – 7.82 (m, 2H), 7.71 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.42 – 7.38 (m, 2H), 7.17 – 7.11 (m, 2H), 5.41 (d, *J* = 1.4 Hz, 1H), 5.14 – 5.07 (m, 1H), 4.69 (t, *J* = 1.4 Hz, 2H), 2.33 (s, 3H). The analytical data for this compound were in excellent agreement with the reported data.[43]

2-(2-(3-chlorophenyl)allyl)isoindoline-1,3-dione



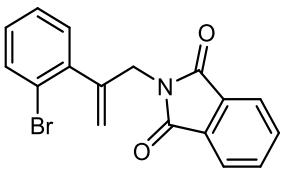
White solid (584 mg, 30% yield). **m.p.** 122-124 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 – 7.77 (m, 2H), 7.70 – 7.64 (m, 2H), 7.45 (dt, *J* = 2.5, 1.0 Hz, 1H), 7.35 (ddd, *J* = 6.3, 2.8, 1.7 Hz, 1H), 7.26 – 7.21 (m, 2H), 5.42 (d, *J* = 1.1 Hz, 1H), 5.18 (t, *J* = 1.6 Hz, 1H), 4.64 (t, *J* = 1.4 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.83, 141.34, 140.32, 134.35, 134.07, 131.92, 129.63, 128.09, 126.69, 124.49, 123.41, 115.18, 41.20. **HRMS** (ESI) calculated for $C_{17}H_{12}ClNO_2$ 298.0629, found 298.0631 $[M+H]^+$. **IR** (ATR-FTIR) ν_{max} = 3029, 2927, 1775, 1709, 1390 cm^{-1}.

2-(2-(3-methoxyphenyl)allyl)isoindoline-1,3-dione



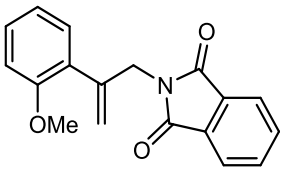
White solid (834mg, 43% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.71 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.25 – 7.22 (m, 1H), 7.09 (ddd, *J* = 7.7, 1.7, 1.0 Hz, 1H), 7.06 – 7.02 (m, 1H), 6.83 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 5.45 (q, *J* = 1.0 Hz, 1H), 5.17 (t, *J* = 1.6 Hz, 1H), 4.69 (t, *J* = 1.3 Hz, 2H), 3.82 (s, 3H).
The analytical data for this compound were in excellent agreement with the reported data.[44]

2-(2-(2-bromophenyl)allyl)isoindoline-1,3-dione



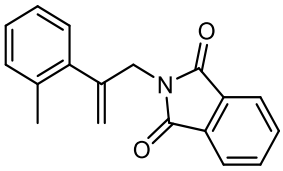
White solid (635 mg, 37% yield). **m.p.** 120-122 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.86 – 7.80 (m, 2H), 7.74 – 7.68 (m, 2H), 7.58 – 7.54 (m, 1H), 7.25 – 7.18 (m, 2H), 7.13 (ddd, *J* = 7.9, 6.8, 2.3 Hz, 1H), 5.38 (td, *J* = 1.5, 0.7 Hz, 1H), 5.16 (q, *J* = 1.0 Hz, 1H), 4.62 (t, *J* = 1.3 Hz, 2H).. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.70, 143.48, 140.78, 133.96, 132.73, 131.98, 130.59, 129.20, 127.22, 123.32, 122.30, 117.34, 42.37. **HRMS** (ESI) calculated for $C_{17}H_{12}BrNO_2$ 342.0124, found 342.0126 $[M+H]^+$. **IR** (ATR-FTIR) ν_{max} = 3069, 2914, 1770, 1705, 1421, 1389, 1108 cm^{-1}.

2-(2-(2-methoxyphenyl)allyl)isoindoline-1,3-dione



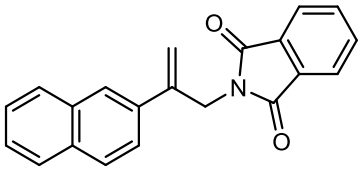
White solid (479 mg, 25% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 (ddd, *J* = 5.5, 3.2, 0.4 Hz, 2H), 7.69 (ddd, *J* = 5.7, 2.9, 0.4 Hz, 2H), 7.26 – 7.21 (m, 1H), 7.15 (dd, *J* = 7.6, 1.8 Hz, 1H), 6.89 – 6.83 (m, 2H), 5.26 – 5.21 (m, 1H), 5.19 (dt, *J* = 1.3, 0.7 Hz, 1H), 4.71 (t, *J* = 1.3 Hz, 2H), 3.86 (s, 3H). The analytical data for this compound were in excellent agreement with the reported data.[46]

2-(2-(o-tolyl)allyl)isoindoline-1,3-dione



White solid (579 mg, 28% yield). **m.p.** 102-105 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.72 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.22 – 7.08 (m, 4H), 5.19 (td, *J* = 1.8, 0.9 Hz, 1H), 5.03 (q, *J* = 1.4 Hz, 1H), 4.49 (t, *J* = 1.6 Hz, 2H), 2.40 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.83 , 143.50 , 135.60 , 133.99 , 131.99 , 130.17 , 128.69 , 127.63 , 125.53 , 123.34 , 114.32 , 42.82 , 19.58. **HRMS** (ESI) calculated for $C_{18}H_{15}NO_2$ 278.1176, found 278.1175 $[M+H]^+$. **IR** (ATR-FTIR) ν_{max} = 3461, 3018, 2926, 2850, 1770, 1709, 1415, 1388, 1113 cm^{-1}.

2-(2-(naphthalen-2-yl)allyl)isoindoline-1,3-dione



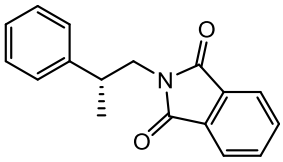
White solid (713 mg, 39% yield). **m.p.** 165-168 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.84 (ddd, *J* = 5.5, 3.1, 0.4 Hz, 2H), 7.82 – 7.78 (m, 2H), 7.72 – 7.68 (m, 2H), 7.64 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.49 – 7.43 (m, 2H), 5.59 (s, 1H), 5.29 (t, *J* = 1.5 Hz, 1H), 4.83 (t, *J* = 1.4 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.99, 142.25, 135.67, 133.98, 133.20, 133.01, 131.99, 128.30, 127.99, 127.51, 126.22, 126.12, 125.26, 124.57, 123.35, 114.59, 41.51. . **HRMS** (ESI) calculated for $C_{21}H_{15}NO_2$ 314.1176, found 314.1171 $[M+H]^+$. **IR** (ATR-FTIR) ν_{max} = 3092, 3056, 3021, 2923, 1770, 1698, 1425, 1397, 1108 cm^{-1}.

Iridium-Catalyzed Asymmetric Hydrogenation of N-Allyl Phthalimides

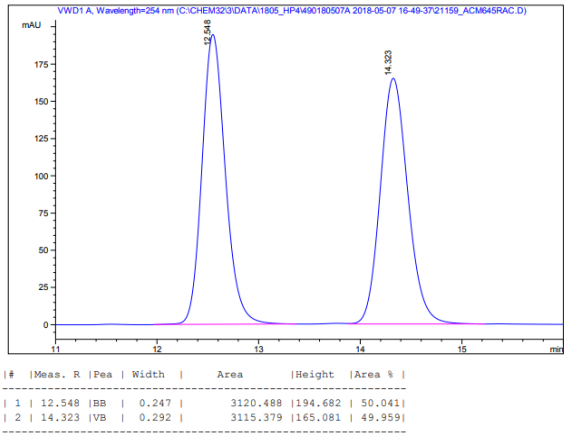
General procedure GP

Into a low pressure reactor equipped with PTFE-coated stir-bar, the corresponding substrate (0.288 mmol, 1.0 equiv.) was charged and dissolved in anhydrous DCM (1 mL/0.1 mmol substrate). Once sealed, the reactor was purged and charged with 1 bar of H_2. Then, the pressure reactor was placed in a cryocool bath. When it reached -20 ºC, the corresponding catalyst (t-Bu2) dissolved in 0.2 mL of anhydrous DCM was then added (1 mol%, otherwise indicated) with a pressure-syringe. The reaction was left stirring at -20 ºC overnight. Afterwards, the crude was filtrated with a short plug of silica to afford the corresponding isolated product. The conversion was measured by ^{1}H NMR spectroscopy and the enantiomeric excess using chiral HPLC chromatography.

(R)-2-(2-phenylpropyl)isoindoline-1,3-dione



Following GP, the desired product was obtained as an oil (full conversion, 98% ee). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 – 7.69 (m, 2H), 7.64 – 7.58 (m, 2H), 7.21 – 7.18 (m, 4H), 7.15 – 7.09 (m, 1H), 3.83 – 3.68 (m, 2H), 3.32 – 3.22 (m, 1H), 1.23 (d, *J* = 7.0 Hz, 3H). **HPLC**: CHIRALPAK IA. Heptane/iPrOH 90:10, 0.5 mL/min, λ = 254 nm. $t_{(R)}$ = 12.5 min, $t_{(S)}$ = 14.3 min. The analytical data for this compound were in excellent agreement with the reported data.[46]



#	Meas. R	Pea	Width	Area	Height	Area %
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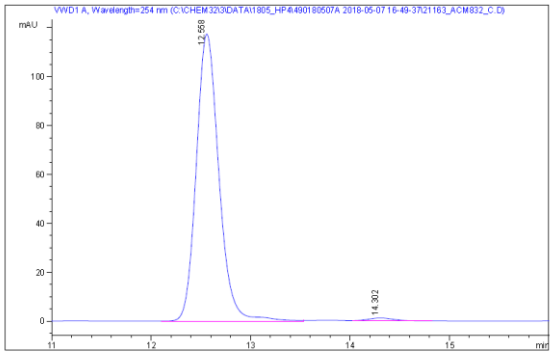
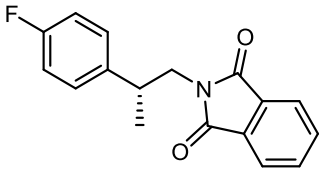
2	14.323	VB	0.292	3115.379	165.081	49.959

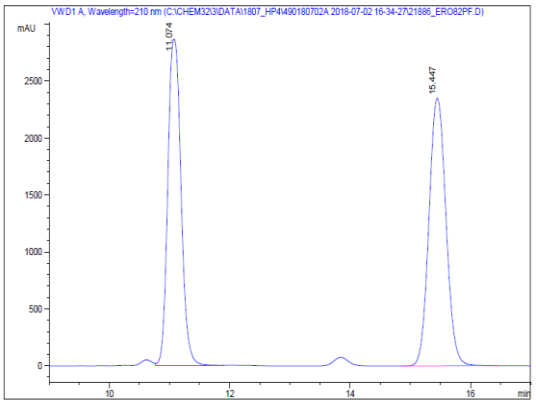


#	Meas. R	Pea	Width	Area	Height	Area %
1	12.558	MF	0.263	1855.440	117.494	98.796
2	14.302	FM	0.305	22.615	1.234	1.204

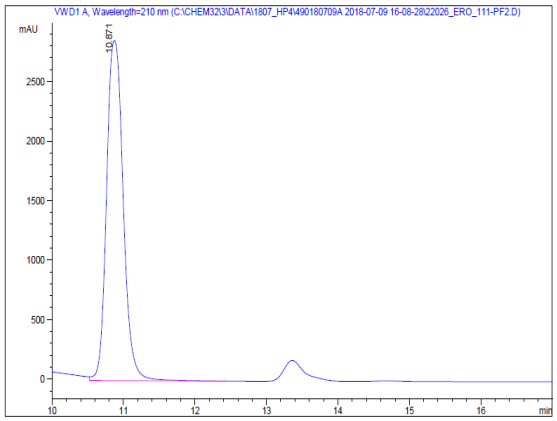
(R)-2-(2-(4-fluorophenyl)propyl)isoindoline-1,3-dione



Following GP, the desired product was obtained as a white solid (full conversion, >99% ee). **m.p.** 60-63 ºC **[α]$_D$**: +91.5 (c 1.2, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.82 – 7.76 (m, 2H), 7.72 – 7.66 (m, 2H), 7.24 – 7.18 (m, 2H), 6.98 – 6.90 (m, 2H), 3.87 – 3.71 (m, 2H), 3.34 (h, *J* = 7.3 Hz, 1H), 1.29 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.22, 162.86, 160.43, 138.89, 138.86, 133.90, 131.80, 128.74, 128.66, 123.20, 115.34, 115.13, 44.85, 44.84, 37.81, 19.12. **HRMS** (ESI) calculated for $C_{17}H_{14}FNO_2$ 284.1081, found 284.1081 $[M+H]^+$. **IR** (ATR-FTIR) ν_{max} = 2970, 2926, 2853, 2359, 2334, 2249, 1706, 1509, 1395, 1378, 1352, 1223 cm^{-1}. **HPLC**: CHIRALPAK IA. Heptane/EtOH 50:50, 0.5 mL/min, λ = 210 nm. $t_{(R)}$ = 10.9 min, $t_{(S)}$ = 15.4 min.

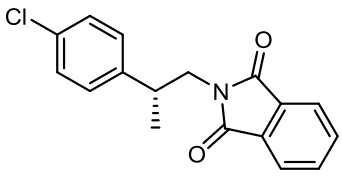


#	Meas. R	Pea	Width	Area	Height	Area %
1	11.074	VV	0.238	43827.660	2.871e3	48.642
2	15.447	MF	0.328	46274.973	2.352e3	51.358



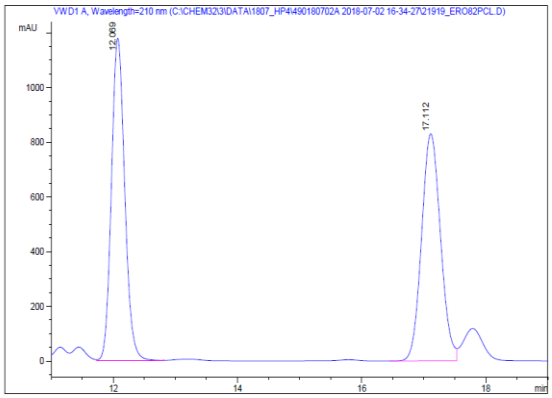
#	Meas. R	Pea	Width	Area	Height	Area %
1	10.871	VV	0.253	46266.938	2.862e3	100.000

(R)-2-(2-(4-chlorophenyl)propyl)isoindoline-1,3-dione

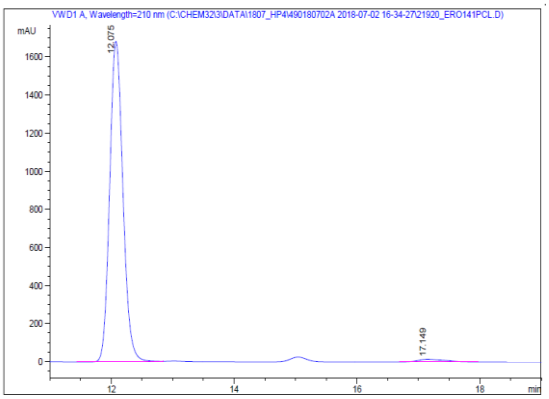


Following GP, the desired product was obtained as a a white solid (full conversion, 97% ee). **m.p.** 69-73 ºC **[α]$_D$**: +98.8 (c 1.1, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 – 7.69 (m, 2H), 7.64 – 7.58 (m, 2H), 7.19 – 7.07 (m, 4H), 3. 81 – 3.63 (m, 2H), 3.26 (h, *J* = 7.3 Hz, 1H), 1.21 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.21, 141.71, 133.92, 132.41, 131.79, 128.65, 128.59, 123.24, 77.31, 76.99, 76.68, 44.62, 37.98, 19.05. **HRMS** (ESI) calculated for $C_{17}H_{14}ClNO_2$ 300.0786, found 300.0797 $[M+H]^+$. **IR** (ATR-FTIR) ν_{max} 2970, 2926,

2853, 2363, 2242, 1767, 1708, 1394, 1378, 1351 cm^{-1}. **HPLC**: CHIRALPAK IA. Heptane/EtOH 50:50, 0.5 mL/min, λ = 210 nm. $t_{(R)}$ = 12.0 min, $t_{(S)}$ = 17.1 min.

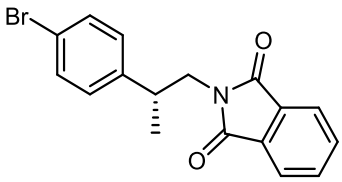


#	Meas. R	Pea	Width	Area	Height	Area %
1	12.069	VV	0.231	17630.529	1.180e3	50.031
2	17.112	BV	0.330	17609.025	830.658	49.969

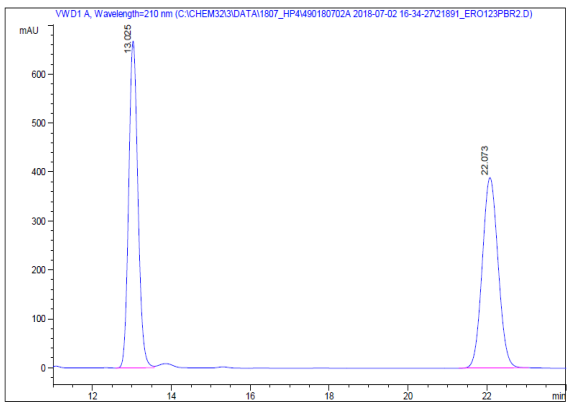


#	Meas. R	Pea	Width	Area	Height	Area %
1	12.075	VV	0.233	25258.617	1.683e3	98.306
2	17.149	BB	0.432	435.308	14.252	1.694

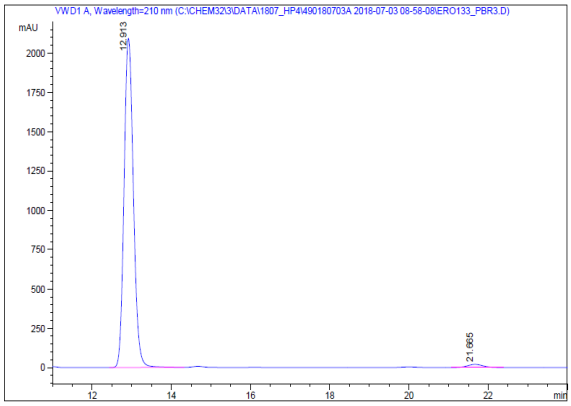
(R)-2-(2-(4-bromophenyl)propyl)isoindoline-1,3-dione



Following GP and using 2 mol% of catalyst, the desired product was obtained as a white solid (full conversion, 97% ee). **m.p.** 118-121 ºC **$[\alpha]_D$**: +98.4 (c 0.5, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.86 – 7.75 (m, 2H), 7.73 – 7.65 (m, 2H), 7.42 – 7.33 (m, 2H), 7.17 – 7.09 (m, 2H), 3.88 – 3.69 (m, 2H), 3.33 (h, *J* = 7.3 Hz, 1H), 1.27 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.20, 142.24, 133.93, 131.78, 131.54, 129.04, 123.24, 120.51, 44.52, 38.04, 19.02. **HRMS** (ESI) calculated for $C_{17}H_{14}BrNO_2$ 344.0281, found 344.0279 $[M+H]^+$. **IR** (ATR-FTIR) ν_{max} = 2967, 2936, 2843, 2255, 1757, 1708, 1395, 1378, 1352 cm^{-1}. **HPLC**: CHIRALPAK IA. Heptane/EtOH 50:50, 0.5 mL/min, λ = 210 nm. $t_{(R)}$ = 12.9 min, $t_{(S)}$ = 21.8 min.

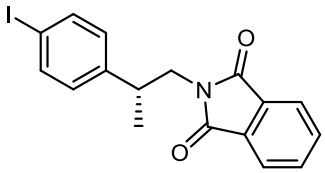


#	Meas. R	Pea	Width	Area	Height	Area %
1	13.025	VV	0.251	10858.039	668.702	49.999
2	22.073	BB	0.436	10858.613	389.493	50.001

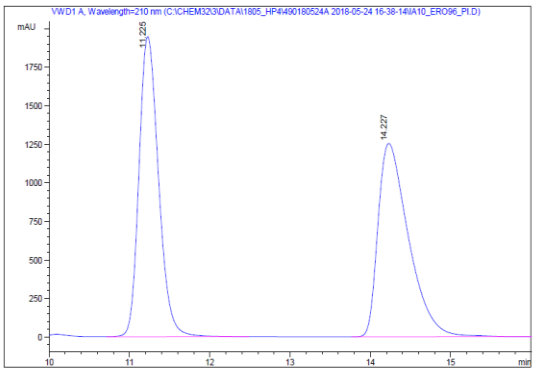


#	Meas. R	Pea	Width	Area	Height	Area %
1	12.913	BB	0.255	34319.309	2.094e3	98.471
2	21.665	BB	0.417	532.749	19.881	1.529

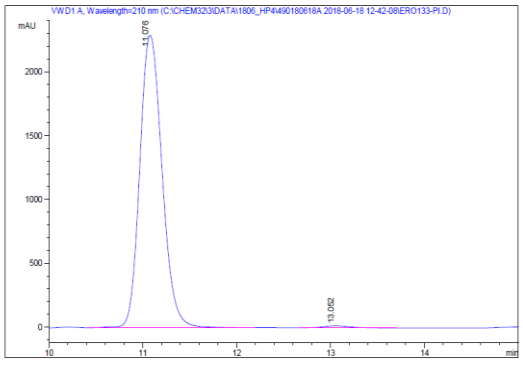
(R)-2-(2-(4-iodophenyl)propyl)isoindoline-1,3-dione



Following GP and using 2 mol% of catalyst, the desired product was obtained as a white solid (full conversion, 98% ee). **m.p.** 151-155 ºC **$[\alpha]_D$**: +90.2 (c 0.5, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.84 – 7.76 (m, 2H), 7.73 – 7.66 (m, 2H), 7.62 – 7.56 (m, 2H), 7.05 – 6.98 (m, 2H), 3.88 – 3.71 (m, 2H), 3.31 (h, *J* = 7.3 Hz, 1H), 1.27 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.21, 142.95, 137.52, 133.94, 131.79, 129.36, 123.25, 92.01, 44.48, 38.14, 19.00. **HRMS** (ESI) calculated for $C_{17}H_{14}INO_2$ 392.0142, found 392.0142 $[M+H]^+$. **IR** (ATR-FTIR) ν_{max} = 2963, 2927, 2366, 1770, 1697, 1391, 1036, 1004 cm^{-1}. **HPLC**: CHIRALPAK IA. Heptane/IPA 95:5, 0.5 mL/min, λ = 210 nm. $t_{(R)}$ = 11.1 min, $t_{(S)}$ = 13.0 min.

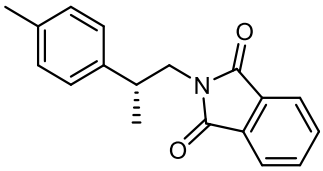


#	Meas. R	Pea	Width	Area	Height	Area %
1	11.225	VB	0.263	32949.301	1.948e3	49.856
2	14.227	BB	0.401	33139.750	1.255e3	50.144

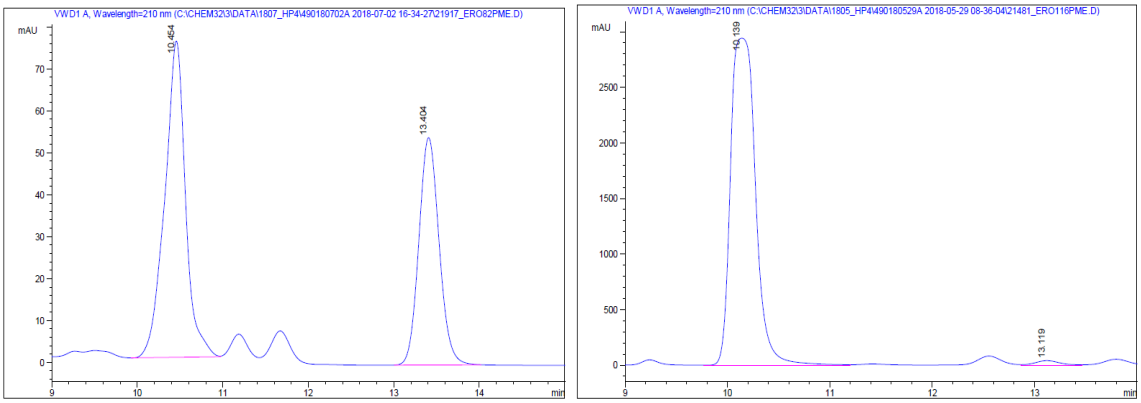


#	Meas. R	Pea	Width	Area	Height	Area %
1	11.076	VB	0.259	37924.691	2.293e3	99.131
2	13.052	BB	0.305	332.609	16.918	0.869

(R)-2-(2-(p-tolyl)propyl)isoindoline-1,3-dione



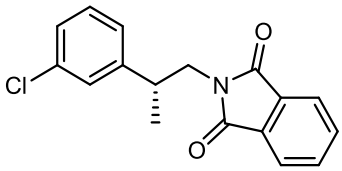
Following GP, the desired product was obtained as a colorless solid (full conversion, 97% ee). **m.p.** 50-53 ºC **$[\alpha]_D$**: +93.7 (c 1.3, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 – 7.77 (m, 2H), 7.72 – 7.65 (m, 2H), 7.19 – 7.13 (m, 2H), 7.10 – 7.05 (m, 2H), 3.88 – 3.71 (m, 2H), 3.32 (h, *J* = 7.3 Hz, 1H), 2.29 (s, 3H), 1.28 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.32, 140.26, 136.21, 133.81, 131.93, 129.14, 127.12, 123.16, 44.94, 38.06, 21.00, 19.04. **HRMS** (ESI) calculated for $C_{18}H_{17}NO_2$, 280.1332 found 280.1333 $[M+H]^+$. **IR** (ATR-FTIR) ν_{max} = 2998, 2927, 2851, 2366, 2242, 1706, 1394, 1376, 1351 cm^{-1}. **HPLC**: CHIRALPAK IA. Heptane/EtOH 50:50, 0.5 mL/min, λ = 210 nm. $t_{(R)}$ = 10.2 min, $t_{(S)}$ = 13.2 min.



#	Meas. R	Pea	Width	Area	Height	Area %
1	10.454	MM	0.282	1277.683	75.469	58.876
2	13.404	BB	0.256	892.439	54.242	41.124

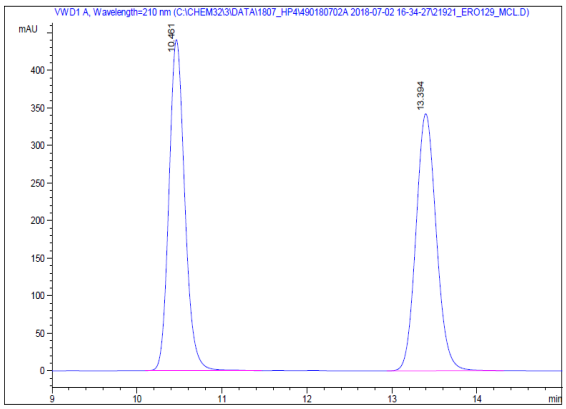
#	Meas. R	Pea	Width	Area	Height	Area %
1	10.139	VV	0.266	49987.090	2.945e3	98.611
2	13.119	VV	0.257	704.345	41.746	1.389

(R)-2-(2-(3-chlorophenyl)propyl)isoindoline-1,3-dione

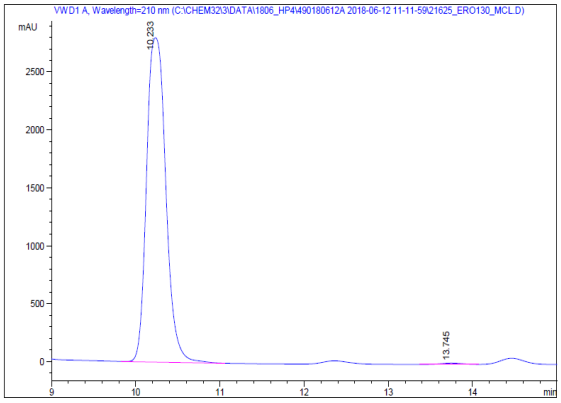


Following GP, the desired product was obtained as an oil (full conversion, 99% ee). **$[\alpha]_D$**: +101.2 (c 1.3, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 – 7.75 (m, 2H), 7.73 – 7.67 (m, 2H), 7.32 – 7.13 (m, 4H), 3.88 – 3.73 (m, 2H), 3.32 (h, *J* = 7.3 Hz, 1H), 1.29 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.21, 145.37, 134.24, 133.94, 133.92, 131.82, 129.74, 127.56, 126.95, 125.46, 123.25, 44.57, 38.37, 18.83. **HRMS** (ESI) calculated for $C_{17}H_{14}ClNO_2$ 300.0786, found 300.0788 $[M+H]^+$. **IR** (ATR-FTIR) ν_{max} = 2957, 2971, 2850, 2361,

2337, 2245, 1711, 1396 cm^{-1}. **HPLC**: CHIRALPAK IA. Heptane/EtOH 50:50, 0.5 mL/min, λ = 210 nm. $t_{(R)}$ = 10.3 min, $t_{(S)}$ = 13.8 min.

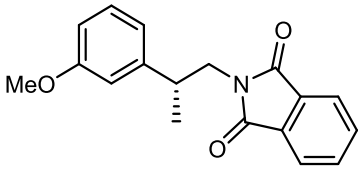


#	Meas. R	Pea	Width	Area	Height	Area %
1	10.461	BB	0.199	5691.042	440.962	50.062
2	13.394	BB	0.257	5676.924	342.438	49.938

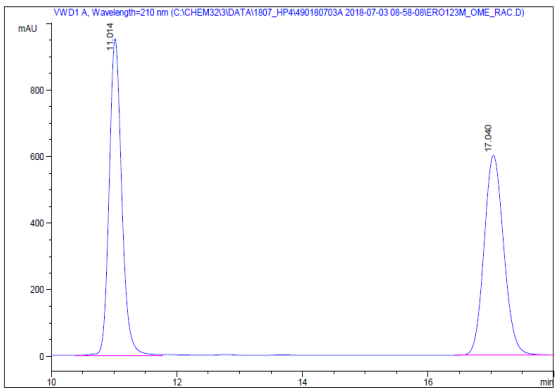


#	Meas. R	Pea	Width	Area	Height	Area %
1	10.233	MM	0.265	44631.895	2.804e3	99.546
2	13.745	BV	0.284	203.775	11.255	0.454

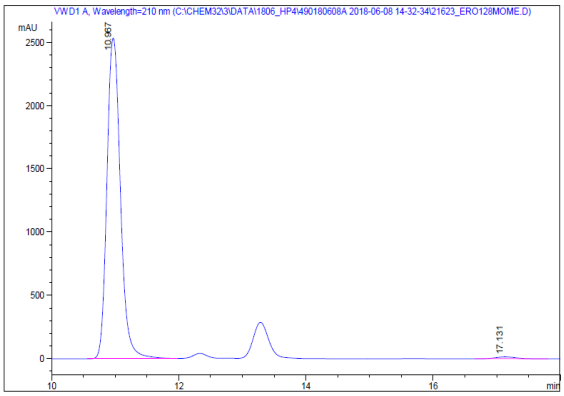
(R)-2-(2-(3-methoxyphenyl)propyl)isoindoline-1,3-dione



Following GP, the desired product was obtained as an oil (full conversion, 98% ee). **$[\alpha]_D$**: +80.8 (c 1.3, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 – 7.77 (m, 2H), 7.72 – 7.65 (m, 2H), 7.19 (t, *J* = 7.9 Hz, 1H), 6.88 – 6.71 (m, 3H), 3.90 – 3.77 (m, 2H), 3.76 (s, 3H), 3.33 (h, *J* = 7.3 Hz, 1H), 1.29 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.29, 159.63, 144.97, 133.84, 131.91, 129.44, 123.18, 119.63, 112.91, 112.21, 55.14, 44.76, 38.53, 18.97. **HRMS** (ESI) calculated for $C_{18}H_{17}NO_3$ 296.1281, found 296.1276 $[M+H]^+$. **IR** (ATR-FTIR) ν_{max} = 3065, 2972, 2936, 2829, 1766, 1708, 1605, 1579, 1394, 1042 cm^{-1}. **HPLC**: CHIRALPAK IA. Heptane/EtOH 50:50, 0.5 mL/min, λ = 210 nm. $t_{(R)}$ = 10.9 min, $t_{(S)}$ = 17.1 min.

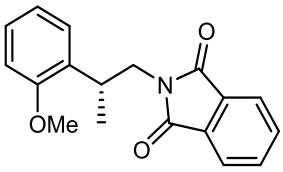


#	Meas. R	Pea	Width	Area	Height	Area %
1	11.014	VV	0.213	13256.500	952.477	50.302
2	17.040	BB	0.340	13097.407	600.842	49.698

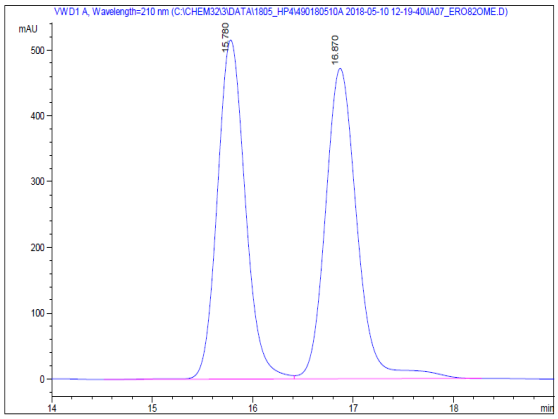


#	Meas. R	Pea	Width	Area	Height	Area %
1	10.967	BV	0.230	37392.113	2.536e3	99.107
2	17.131	VB	0.346	336.769	15.097	0.893

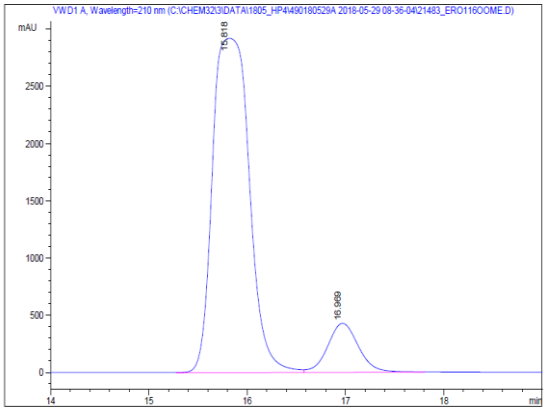
(R)-2-(2-(2-methoxyphenyl)propyl)isoindoline-1,3-dione



Following GP, the desired product was obtained as an oil (full conversion, 78% ee). **$[\alpha]_D$**: +64.5 (c 1.3, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 (ddd, *J* = 5.5, 2.9, 0.4 Hz, 2H), 7.73 – 7.65 (m, 2H), 7.27 – 7.22 (m, 1H), 7.20 – 7.11 (m, 1H), 6.91 (td, *J* = 7.5, 1.2 Hz, 1H), 6.74 (dd, *J* = 8.2, 1.1 Hz, 1H), 3.93 – 3.80 (m, 2H), 3.78 – 3.71 (m, 1H), 3.64 (s, 3H), 1.30 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.28, 157.28, 133.65, 132.08, 131.52, 127.60, 127.49, 122.99, 120.62, 110.27, 55.11, 43.81, 31.98, 17.62. **HRMS** (ESI) calculated for $C_{18}H_{17}NO_3$ 296.1281, found 296.1281 $[M+H]^+$. **IR** (ATR-FTIR) ν_{max} = 2958, 2932, 2851, 1770, 1708, 1394, 1242 cm^{-1}. **HPLC**: CHIRALPAK IA. Heptane/EtOH 95:5, 0.5 mL/min, λ = 210 nm. $t_{(R)}$ = 15.8 min, $t_{(S)}$ = 16.9 min.

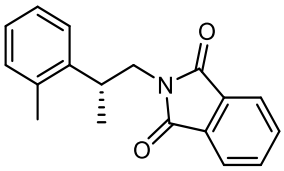


#	Meas. R	Pea	Width	Area	Height	Area %
1	15.780	VV	0.298	9954.599	515.728	49.075
2	16.870	VB	0.335	10329.810	472.077	50.925

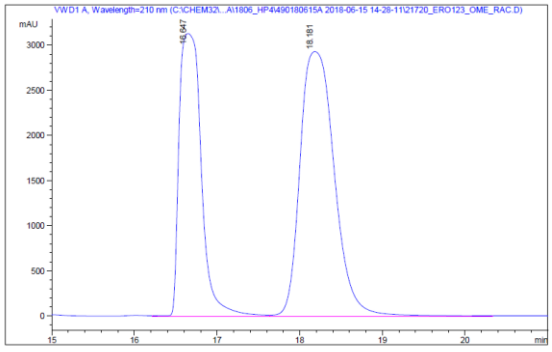


#	Meas. R	Pea	Width	Area	Height	Area %
1	15.818	MF	0.435	76226.656	2.922e3	88.892
2	16.969	FM	0.368	9524.860	431.414	11.108

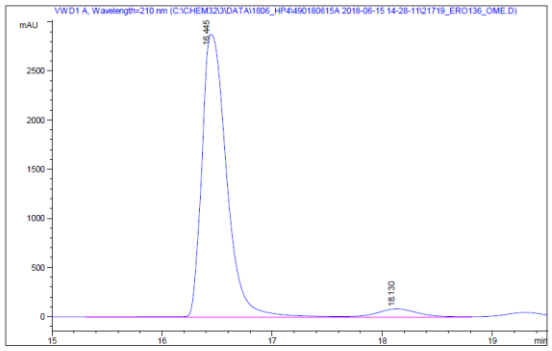
(R)-2-(2-(o-tolyl)propyl)isoindoline-1,3-dione



Following GP, using 3 mol% of catalyst and leaving the reaction stirring for 48 hours, the desired product was obtained as an oil (full conversion, 91% ee). $[\alpha]_D$: +24.5 (c 0.5, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.86 – 7.79 (m, 2H), 7.73 – 7.67 (m, 2H), 7.35 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.21 (ddd, *J* = 7.7, 6.7, 2.5 Hz, 1H), 7.16 – 7.08 (m, 2H), 3.87 – 3.73 (m, 2H), 3.69 – 3.56 (m, 1H), 2.40 (s, 3H), 1.26 (d, *J* = 6.9 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.47, 141.51, 136.01, 133.90, 131.94, 130.42, 126.40, 126.26, 125.67, 123.20, 44.16, 33.64, 19.39, 18.53. **HRMS** (ESI) calculated for $C_{18}H_{17}NO_2$ 280.1332, found 280.1343 $[M+H]^+$. **IR** (ATR-FTIR) ν_{max} = 3461, 3065, 2967, 2923, 2856, 1775, 1706, 1394, 1350, 1276, 1042 cm^{-1}. **HPLC**: CHIRALPAK IA. Heptane/EtOH 98:2, 0.5 mL/min, λ = 210 nm. $t_{(R)}$ = 16.5 min, $t_{(S)}$ = 18.1 min.

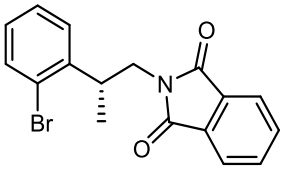


#	Meas. R	Pea	Width	Area	Height	Area %
1	16.647	VV	0.297	58351.539	3.132e3	40.795
2	18.181	VB	0.454	84685.992	2.931e3	59.205

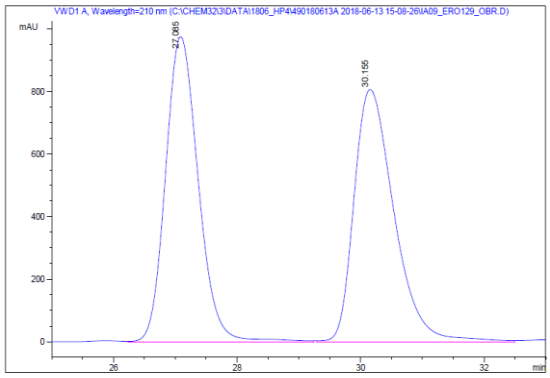


#	Meas. R	Pea	Width	Area	Height	Area %
1	16.445	BV	0.236	44484.563	2.875e3	95.540
2	18.130	VV	0.387	2076.537	81.605	4.460

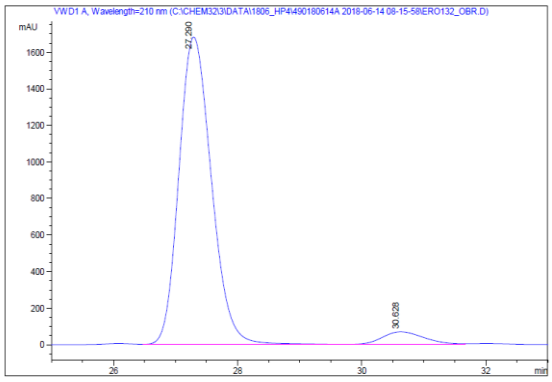
(R)-2-(2-(2-bromophenyl)propyl)isoindoline-1,3-dione



Following GP and using 2 mol% of catalyst, the desired product was obtained as an oil (full conversion, 90% ee). **[α]$_D$**: +47.2 (c 0.8, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.84 – 7.77 (m, 2H), 7.72 – 7.65 (m, 2H), 7.47 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.40 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.31 (td, *J* = 7.6, 1.3 Hz, 1H), 7.05 (ddd, *J* = 8.0, 7.3, 1.7 Hz, 1H), 3.95 – 3.86 (m, 2H), 3.85 – 3.77 (m, 1H), 1.33 – 1.27 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.23, 142.37, 133.85, 132.86, 131.93, 128.17, 127.78, 127.71, 124.79, 123.20, 43.67, 37.18, 18.57. **HRMS** (ESI) calculated for $C_{17}H_{14}BrNO_2$ 344.0281, found 344.0271 $[M+H]^+$. **IR** (ATR-FTIR) ν_{max} = 3466, 3056, 2963, 2923, 2843, 1772, 1706, 1467, 1394, 1378, 1351, 1277, 1043, 1021 cm^{-1}. **HPLC**: CHIRALPAK IA. Heptane/EtOH 98:2, 0.5 mL/min, λ = 210 nm. $t_{(R)}$ = 27.3 min, $t_{(S)}$ = 30.6 min.

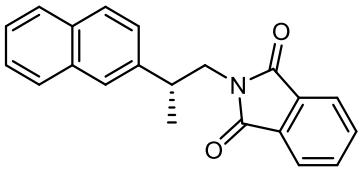


#	Meas. R	Pea	Width	Area	Height	Area %
1	27.085	VB	0.572	36004.203	976.147	49.724
2	30.155	BV	0.695	36404.012	807.428	50.276



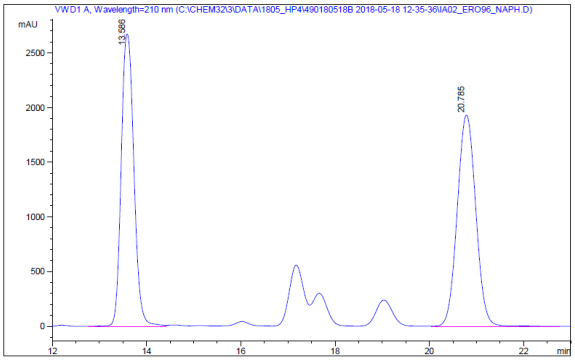
#	Meas. R	Pea	Width	Area	Height	Area %
1	27.290	VB	0.570	61353.164	1.682e3	94.842
2	30.628	BV	0.733	3336.870	70.087	5.158

(R)-2-(2-(naphthalen-2-yl)propyl)isoindoline-1,3-dione

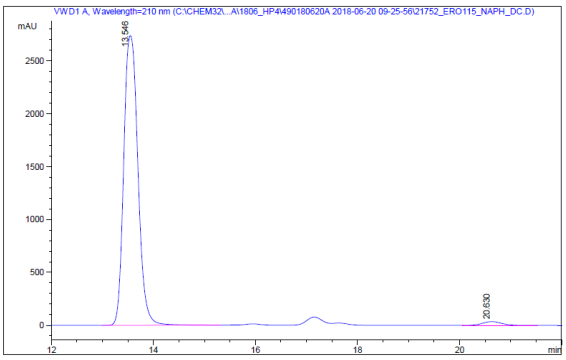


Following GP, the desired product was obtained as a white solid (full conversion, 97% ee). **m.p.** 117-121 ºC **[α]$_D$**: +66.1 (c 0.4, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 – 7.74 (m, 5H), 7.71 – 7.63 (m, 3H), 7.49 – 7.38 (m, 3H), 4.04 – 3.83 (m, 2H), 3.55 (h, *J* = 7.3 Hz, 1H), 1.39 (d, *J* = 7.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ

140.77, 133.84, 133.46, 132.47, 131.88, 128.16, 127.64, 127.58, 125.91, 125.88, 125.87, 125.58, 125.43, 123.20, 44.69, 38.67, 19.16. **HRMS** (ESI) calculated for $C_{21}H_{17}NO_2$ 316.1332, found 316.1329 $[M+H]^+$. **IR** (ATR-FTIR) ν_{max} = 3458, 3050, 2964, 2932, 2872, 1767,1705, 1682, 1397, 1048 cm^{-1}. **HPLC**: CHIRALPAK IA. Heptane/EtOH 70:30, 0.5 mL/min, λ = 210 nm. $t_{(R)}$ = 13.5 min, $t_{(S)}$ = 20.6 min.



#	Meas. R	Pea	Width	Area	Height	Area %
1	13.586	BV	0.293	49858.297	2.673e3	48.540
2	20.785	VB	0.430	52856.809	1.932e3	51.460



#	Meas. R	Pea	Width	Area	Height	Area %
1	13.546	BV	0.304	52994.035	2.740e3	98.280
2	20.630	BB	0.407	927.394	35.517	1.720

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