Tutor/s

Dr. Xavier Verdaguer Espaulella
Departament de Química Inorgànica i Orgànica

Pep Rojo Solé
Institut de Recerca Biomèdica de Barcelona

Grau de Química

Treball Final de Grau

Towards chiral 3-phenyl-tetrahydroquinolines through iridium catalyzed asymmetric hydrogenation.

Envers 3-fenil-tetrahidroquinolines quirals mitjançant hidrogenació asimètrica catalitzada per iridi.

Clara García Mateos

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Universitat de Barcelona

B:KC Barcelona Knowledge Campus
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Je suis de ceux qui pensent que la science est d'une grande beauté. Un scientifique dans son laboratoire est non seulement un technicien : il est aussi un enfant placé devant des phénomènes naturels qui l'impressionnent comme des contes de fées.

Marie Curie

En primer lloc, vull agrair al Dr. Xavier Verdaguer, que des de l'inici ha mostrat la seva predisposició per ajudar-me, resoldre els dubtes i guiar-me en el procés de l'elaboració de la memòria.

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REPORT

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1. SUMMARY

Asymmetric catalysis has had an impact over more than half a century, due to the fact that it is one of the most efficient methods to prepare chiral organic compounds. When it comes to asymmetric hydrogenation, Pfaltz demonstrated that introducing iridium as the metal centre in phosphinooxazolines ligands was very efficient, especially with a bulky non-coordinating anion such as BAr_F.

Inspired by this, our group has been working on a new catalyst, Ir-(*S*)$_P$-DTP, whose structure bears a phosphinooxazoline ligand derived from threonine, in which a P-stereogenic centre has been introduced in order to increase the performance of the catalyst. This new catalyst has shown excellent conversion and enantiomeric excess for β,γ-substituted allylic carbamates.

In this project, allylic carbamates have been synthesized and submitted to asymmetric hydrogenation with the Ir-(*S*)$_P$-DTP catalyst to extend the scope. Two of have provided total conversion and excellent enantiomeric excess. An allylic carbamate with an ortho-chloride in the terminal phenyl ring has also been synthesized and submitted to asymmetric hydrogenation, providing successful results as well.

Additionally, the compound with an ortho-chloride has been tested in the intramolecular Buchwald-Hartwig reaction to yield the corresponding chiral 3-phenyl-tetrahydroquinoline.

Keywords: asymmetric hydrogenation, iridium, phosphinooxazoline, Buchwald-Hartwig.

2. RESUM

La catàlisi asimètrica ha tingut un impacte durant més de mig segle, degut a que és un dels diferents mètodes per preparar compostos orgànics quirals. Quan es tracta d'hidrogenació asimètrica, Pflatz va demostrar que introduint l'iridi com a centre metàl·lic en lligands fosfinooxazolines era molt eficient, especialment amb un anió no coordinant voluminós com el BAr_F.

Inspirat en això, el nostre grup ha estat treballant en un nou catalitzador, Ir-(*S*)$_P$-DTP, l'estructura del qual conté un lligand fosfinooxazolina derivada de la treonina, en el qual un centre P-estereogènic s'ha introduït per incrementar l'eficàcia del catalitzador. Aquest nou catalitzador ha mostrat conversions i excessos enantiomèrics excel·lents per carbamats al·lílics β,γ-disubstituïts.

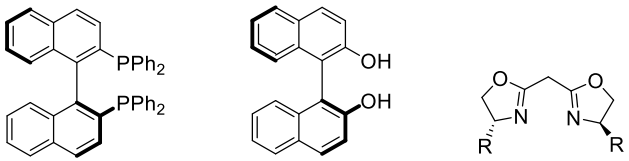
En aquest projecte, s'han sintetitzat carbamats al·lílics i s'han sotmès a hidrogenació asimètrica amb el catalitzador Ir-(*S*)$_P$-DTP per tal d'ampliar el seu abast. Dos d'ells han proporcionat conversió total i un excés enantiomèric excel·lent. També s'ha sintetitzat i sotmès a hidrogenació asimètrica un carbamat al·lílic amb un clor en orto al fenil terminal, també proporcionant bons resultats.

Addicionalment, s'han fet proves amb el compost amb el clor en orto per donar una reacció intramolecular de Buchwald-Hartwig, per acabar donant la corresponent 3-fenil-tetrahidroquinolina quiral.

Paraules clau: hidrogenació asimètrica, iridi, fosfinooxazolina, Buchwald-Hartwig.

3. INTRODUCTION

Enantioselective preparation of organic compounds is a topic of remarkable interest, particularly in the modern pharmaceutical industries because most marketed drugs are only active in a given chirality, whereas the other enantiomer often produces unwanted effects.[1] There are different methods to obtain an optically pure chemical product, the one that has had an impact over half a century is asymmetric catalysis. It is based on the use of homogeneous organometallic catalysts composed by a transition metal coordinated to chiral ligands. Among chiral ligands, BINOL, BINAP and bisoxazoline are examples that have proven to be applicable to different reactions as their metal complexes are highly efficient asymmetric catalysts.[2]



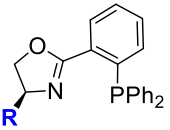
(*S*)-BINAP (S)-BINOL bisoxazoline (BOX)

Figure 1. Examples of chiral ligands

3.1. IRIDIUM CATALYSTS IN ASYMMETRIC HYDROGENATION

3.1.1. Phosphinooxazoline ligands

In 1996, Pfaltz presented chiral phosphinooxazoline ligands (PHOX) for asymmetric transformations. Although they were originally designed for Pd-catalyzed allylic substitution,[3] they have proven to be excellent ligands for enantioselective reactions in a variety of metal-catalyzed processes. The structure of the PHOX ligand allows the variation of the oxazoline ring, the backbone and the phosphine, so by adapting the ligand structure, other metal-catalyzed reactions could take place.[4]

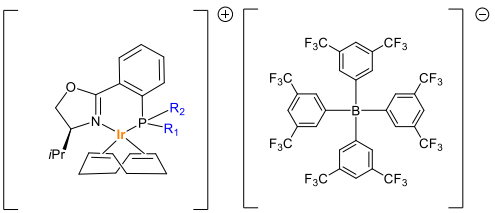


R= CH_3, CH_2Ph, *i*Pr, Ph, *t*Bu

Figure 2. General structure of PHOX ligands

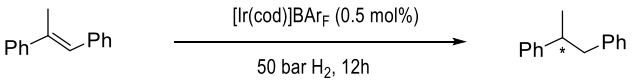
3.1.2 Ir-PHOX

For a long time, the number of olefins that could be hydrogenated with a high enantiomeric excess was limited to substrates bearing a coordinating group next to the C=C bond. Introducing iridium as the metal centre resulted in several advances in asymmetric hydrogenation, because these catalysts do not require the presence of any particular functional group in the substrate. Pfaltz and co-workers demonstrated that cationic iridium complexes with chiral P, N ligands with a bulky non-coordinating anion were very efficient in this process.[5] One example is the reduction of stilbene shown in Scheme 1.[6] Over the years, Pfaltz reported many other phosphinooxazoline catalysts with excellent results in the asymmetric hydrogenation of a broad range of substrates.[5]



Ir-PHOX **BAr_F**

Figure 3. Ir-PHOX

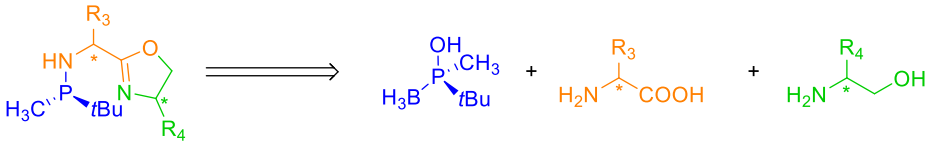


100% conv.
95% ee

Scheme 1. Reduction reaction of stilbene

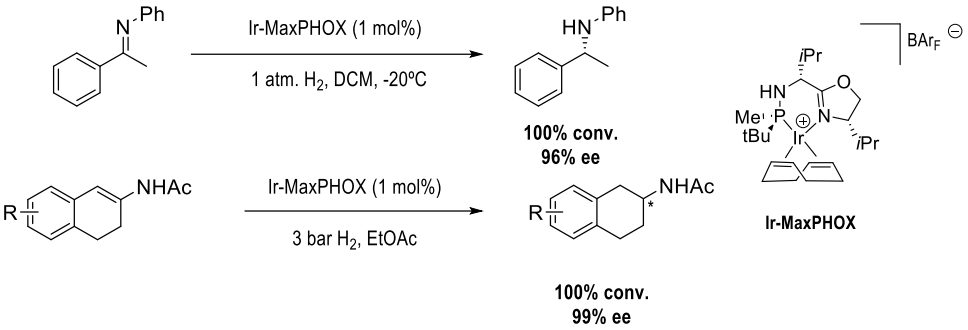
3.1.3 Ir-MaxPHOX catalysts

Seeing the success of Ir-PHOX catalysts for asymmetric hydrogenation of olefins and imines[4] our group reported the preparation of the P-stereogenic MaxPHOX ligands for asymmetric hydrogenation reactions. MaxPHOX ligands are made up from three chiral fragments: an amino alcohol, an amino acid and a P-stereogenic phosphinous acid.[7]



Scheme 2. General structure for MaxPHOX ligands

The Ir-MaxPHOX complexes have shown excellent selectivity in the hydrogenation of cyclic enamides and *N*-aryl imines as shown in Scheme 3.[8]



Scheme 3. Examples of asymmetric hydrogenation with Ir-MaxPHOX

3.1.4 ThrePHOX derived catalysts

Recently, our group has developed a new family of phosphinooxazoline catalysts inspired in Pfaltz ThrePHOX, which has shown excellent enantioselectivities, and our group thought that by introducing a P-stereogenic phosphine in the threonine skeleton, the performance of the catalyst could even be increased.

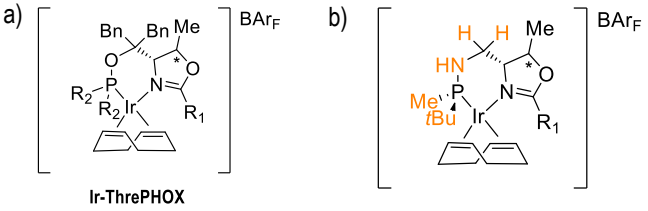
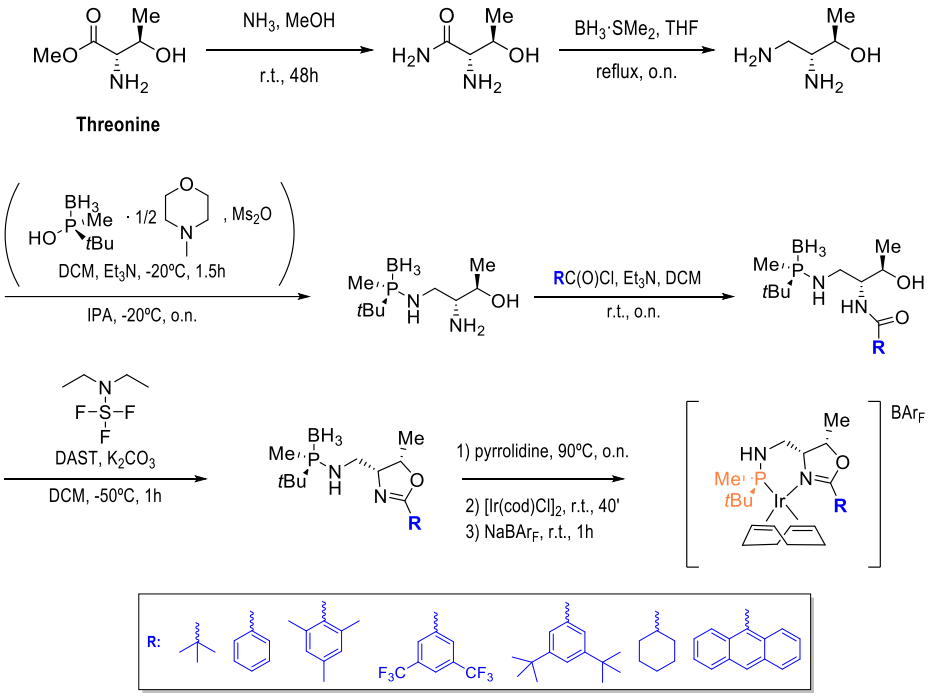


Figure 4. a) Ir-ThrePHOX b) General structure of our catalyst

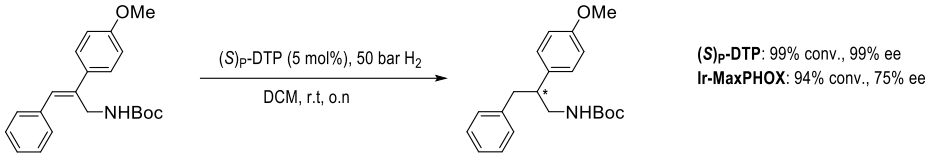
In the PhD thesis of Pep Rojo, combining the *tert*-butyl methyl phosphinous acid building block developed in the group, and a threonine derived primary amine, the following catalysts with different groups in the oxazoline ring were synthesized. The 7 catalysts with the opposite configuration in the phosphorous atom were also prepared to analyze the influence of the P-stereogenic centre. The final and optimized synthetic pathway for the synthesis of these catalysts is the following:



Scheme 5. Synthetic pathway for the preparation of the catalyst

3.2. ASYMMETRIC HYDROGENATION OF ALLYLIC CARBAMATES

Initial testing with different substrates demonstrated that among the family of 14 new catalysts the one bearing a di-*tert*butyl phenyl substituent with *S* configuration at the phosphorous ((*S*)$_P$-DTP) was excellent for β,γ-disubstituted allylic carbamates (Scheme 6). (*S*)$_P$-DTP provides higher conversion and enantiomeric excess (ee) when compared to Ir-MaxPHOX catalyst.



Scheme 6. Hydrogenation of the standard substrate

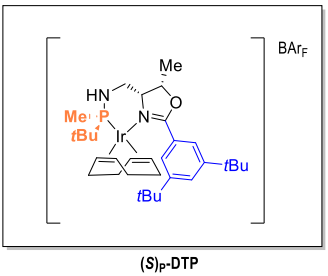
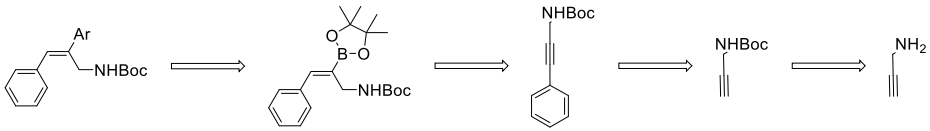


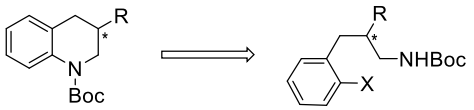
Figure 5. Final catalyst used in this project

In order to demonstrate the utility of the (*S*)$_P$-DTP catalyst in the hydrogenation of allylic carbamates, a series of alkenes have been prepared by Pep Rojo following the synthetic pathway shown in Scheme 7.



Scheme 7. Retrosynthetic pathway for the synthesis of olefins

3.3. 3-SUBSTITUTED-TETRAHYDROQUINOLINES

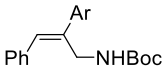


Scheme 8. Retrosynthetic pathway for the synthesis of chiral 3-substituted-tetrahydroquinolines

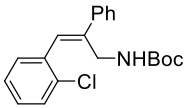
In order to demonstrate the utility of β,γ-disubstituted allylic carbamates, we wanted to prepare *N*-labile chiral tetrahydroquinolines with substitution at the 3- position, which have not been reported by metal-catalyzed asymmetric hydrogenation. We envisioned that these substrates could be prepared in optically enriched form by Buchwald-Hartwig reaction. For this purpose, we need a halogen atom in “ortho” position in the terminal phenyl ring (Scheme 8).

4. OBJECTIVES

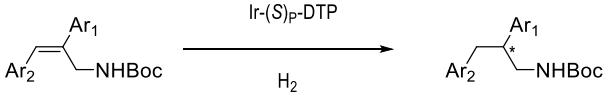
1. To synthesize allylic carbamate substrates with different substituents on the middle phenyl ring.



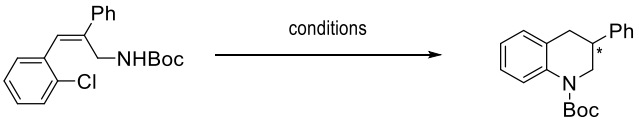
2. To synthesize an allylic carbamate substrate with an ortho-chloride at the terminal phenyl ring.



3. To submit the new substrates to asymmetric hydrogenation with Ir-(*S*)$_P$-DTP catalyst and determine the corresponding enantiomeric excess.



4. To study the Buchwald-Hartwig cyclization of the substrate containing the ortho-chloride.

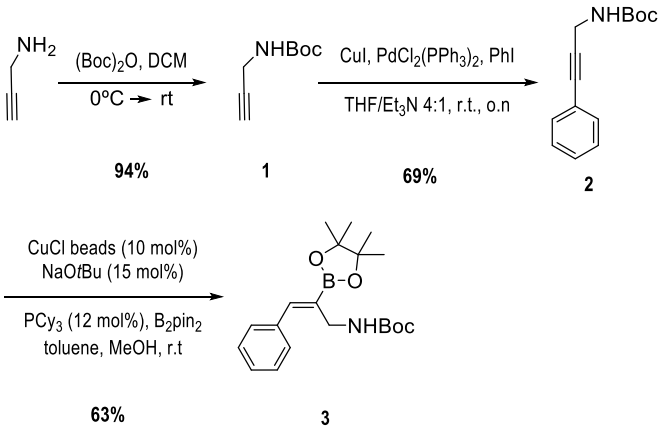


5.RESULTS AND DISCUSSION

5.1. EXTENSION OF THE SCOPE

5.1.1 Preparation of alkene substrates

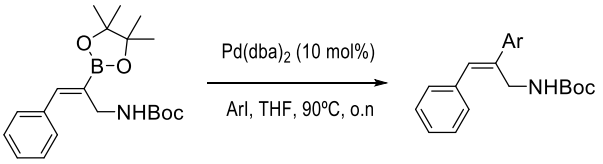
First of all, some substrates were synthesized to broaden the scope of the asymmetric hydrogenation, by following the synthetic pathway shown in Scheme 9 and following the reaction in Table 1. It starts with the protection of the amine with a Boc group and continues with a Sonogashira reaction, in which a phenyl group is coupled to a terminal alkynyl. Compound **1** was recrystallized and yielded 94% of a crystalline yellow solid in a needle form, **2** yielded 69% of a white solid. Afterwards, a syn borylation takes place, yielding 63% of a white solid (**3**). The other phenyl group was introduced by a Suzuki coupling between the boronate and an aryl iodide. This phenyl group has different substituents. It was decided to add a carbomethoxy group in para (**4a**), two methyls in meta position (**4b**) and a methoxy in meta (**4c**) to see the influence of these substituents in the hydrogenation. Compound **4d** is the standard substrate used to optimize the hydrogenation reaction, and was only synthesized to do a parallel experiment to check the performance of a new batch of catalyst.



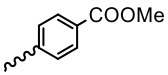
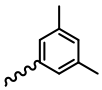
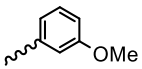
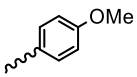
Scheme 9. Synthetic pathway for the preparation of substrates

The Suzuki couplings between the boronate **3** and different aryl iodides are shown in Table 1. All the products were purified by column chromatography and crystallization, except **4c** that was an oil and was not recrystallized. As it can be observed, the substrate with the methoxy in meta (**4c**) gave the lowest yield (38%), whereas the same substituent in para position (**4d**) gave the highest yield of all the four substrates (83%). The other two gave similar yields, 66% for compound **4a** and 65% for **4b**.

Table 1. Suzuki coupling between **3** and different aryl iodides

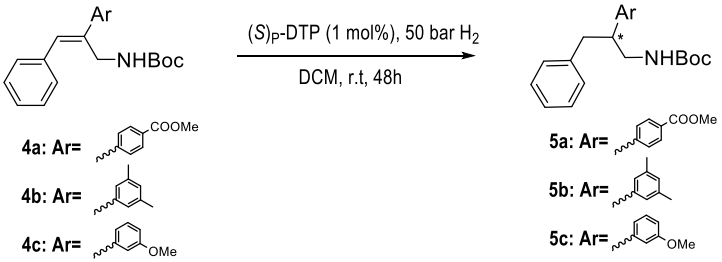


3 **4**

Entry	Ar	Compound	Yield [%]
1		**4a**	66
2		**4b**	65
3		**4c**	38
4		**4d**	83

5.1.2 Hydrogenations

The asymmetric hydrogenations of the substrates were performed using the $(S)_P$-DTP iridium catalyst previously mentioned, in a pressure reactor at 50 bars of H_2 (Scheme 10).



Scheme 10. Asymmetric hydrogenation of **4a**-**4c**

Hydrogenation of **4a** and **4b** worked successfully providing the reduced product with complete conversion. **5a** and **5b** were obtained with 98% and 93% enantiomeric excess. In contrast, hydrogenation of **4c** took place with only 35% conversion. In this case the ee was not determined.

Table 2. Asymmetric hydrogenation of **4a**-**4c**

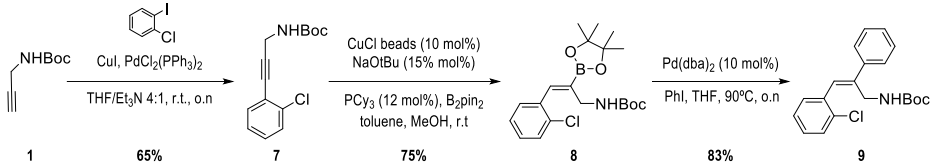
Entry	Compound	Conv. [%]	ee [%]	Yield [%]
1	**5a**	99	98	87
2	**5b**	100	93	84
3	**5c**	35	–	-

5.2. SYNTHESIS OF 3-PHENYL-TETRAHYDROQUINOLINE

To synthesize the 3-phenyl-tetrahydroquinoline, first we had to synthesize the substrate which could undergo intramolecular cyclization. Then, this substrate should be hydrogenated with the Ir-catalyst and the product is cyclized to give our tetrahydroquinoline.

5.2.1 Preparation of the substrate

First, the substrate was prepared following the synthetic pathway shown in Scheme 11. This is similar to the one in Scheme 9 but now for the Sonogashira reaction we used iodochlorobenzene to introduce an ortho-chloride in the terminal ring.



Scheme 11. Synthetic pathway for the synthesis of substrate **9**

The product obtained was a white solid with an 83% yield. Once the substrate was prepared, it was time to perform the asymmetric hydrogenation (Scheme 12).

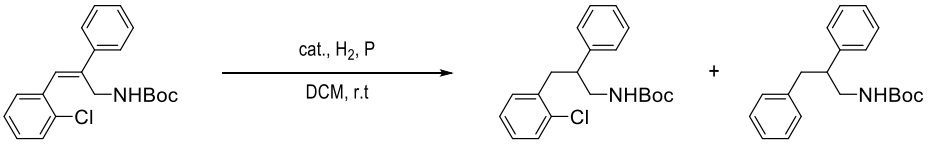
Scheme 12. Asymmetric hydrogenation of substrate **9**

The reaction gave a 99% conversion and the product was obtained in an excellent 97% ee as determined by chiral HPLC.

5.2.2 Synthesis of the racemic 10

To determine a separation method by HPLC analysis, a racemic was synthesized by hydrogenating compound **9** (Table 3). First, it was done with Pd/C 10 mol% in a pressure reactor at 1 bar, but it was observed by HPLC-MS that we had a 50:50 mix of 2 species: our hydrogenated product **rac-10** and the same but without the chloride (**11**). Then, we decided to try with Ir-Crabtree BAr_F catalyst but the conversion was very low, so we could not use this product either. Finally, we tried again the hydrogenation with Pd/C but in milder conditions (balloon of H_2, 5 mol% of catalyst and shorter reaction time) and it worked fine, resulting in a 100% conversion.

Table 3. Racemic hydrogenation of **9**



9 **rac-10** **11**

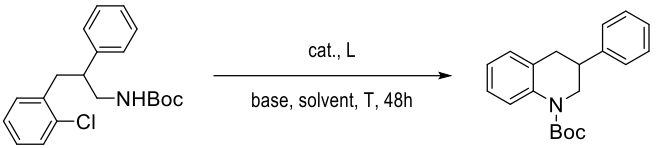
Entry	Catalyst	P [bar]	Time	Conv. [%]	Yield [%]
1	Pd/C (10 mol%)	1	overnight	100	-
2	Ir-Crabtree BAr_F (5 mol%)	50	overnight	55	-
3	Pd/C (5 mol%)	balloon	4h	100	68

5.2.3 Cyclization assays

For the purpose of not spending our iridium catalyst we used compound **rac-10** for the initial cyclization tests. Although the product obtained is not a single enantiomer, it can give us an idea of whether the cyclization will function or not. This cyclization is a Buchwald-Hartwig reaction, in which the aryl-chloride is coupled to the nitrogen. As reported in a paper, we started trying with JohnPhos ligand and $Pd_2(dba)_3$, but no conversion was observed (Table 4, entry 1).[9] New conditions were tested, this time with XPhos and $Pd(OAc)_2$ but there was no luck either (entry 2).[10] The conditions that have worked better are the ones in entry 3, but still the reaction was not fully completed (80%). We tried with the same conditions but changing the base to see if the reaction progressed more, but instead it gave lower conversion (entry 4). Finally, we tried with XanthPhos ligand, which gave 50% conversion.[11]

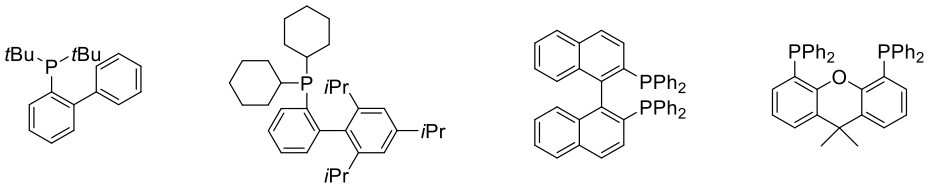
Seeing that the conditions that gave better results were the ones in entry 3, we tested with the same reactants but reducing the catalyst loading (entry 6) and the conversion was 25%. It has been observed then that this reaction works, but it gives a low conversion. The next step will be to test more conditions to reduce the catalyst loading to at least 5%.

Table 4. Buchwald-Hartwig reaction



rac-10 **rac-12**

Entry	Catalyst	L	Base	Solvent	T [ºC]	Conv. [%]
1	$Pd_2(dba)_3$ (5 mol%)	JohnPhos (10 mol%)	*t*BuOK (1.4 eq)	*t*BuOH	100	0
2	$Pd(OAc)_2$ (2 mol%)	XPhos (4 mol%)	Cs_2CO_3 (1.4 eq)	10:1 dioxane/ MeOH	90	0
3	$Pd(OAc)_2$ (20 mol%)	Rac-BINAP (40 mol%)	Cs_2CO_3 (1.4 eq)	Toluene	100	80
4	$Pd(OAc)_2$ (20 mol%)	Rac-BINAP (40 mol%)	K_2CO_3 (1.4 eq)	Toluene	100	43
5	$Pd_2(dba)_3$ (20 mol%)	XanthPhos (30 mol%)	Cs_2CO_3 (1.5 eq)	1,4-dioxane	115	50
6	$Pd(OAc)_2$ (5 mol%)	Rac-BINAP (7.5 mol%)	Cs_2CO_3 (1.4 eq)	Toluene	130	25



JohnPhos **XPhos** **rac-BINAP** **XanthPhos**

Figure 6. Ligands used for the cyclization assays

6. EXPERIMENTAL SECTION

6.1. MATERIALS AND METHODS

Unless otherwise noted, all reactions were carried out in oven-dried glassware and under N_2 atmosphere. Anhydrous solvents THF, Et_2O and DCM were used from a solvent purification system (SPS PS-MD-3) from Innovative Technology, Inc. Other anhydrous solvents were commercially available and were used with no further purification. Thin layer chromatographies (TLC) were carried out on Merck silica gel 60 F_{254} aluminium sheets and analyzed by UV (254 nm). Column chromatography was performed using an automated chromatography system (PuriFlash© 430, Interchim).

IR spectra were recorded on a Thermo Nicolet 6700 FT-IR using an ATR system. HRMS were recorded in an LC/MSD-TOF G1969A (Agilent Technologies) of the Department of Organic Chemistry in the Universitat de Barcelona. HPLC chromatography was performed on an Agilent Technologies Series 1100 chromatograph with UV detector.

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.

^1H and ^{13}C-NMR spectra were recorded at room temperature on a Varian Mercury 400MHz or a Brüker 400MHz spectrometer of the Centres Científics i Tecnològics de la Universitat de Barcelona. Chemical shifts (δ) are quoted in ppm and referenced to solvent $CDCl_3$ (δ 7.26 ppm) or TMS (δ 0.00 ppm). Data are reported as followed: chemical shift (multiplicity, coupling constant(s), integration); multiplicity is reported as: s, singlet; d, doublet; t, triplet; q, quartet; p, quintet; m, multiplet; coupling constants (*J*) are quoted in Hz.

6.2. SYNTHESIS OF *TERT*-BUTYL-PROP-2-YN-1-YLCARBAMATE (1)

In an oven-dried single-necked 500mL round-bottomed flask, equipped with a magnetic stirring bar, 11.88 g (54.47 mmol, 3 eq) of di-*tert*-butyl-dicarbonate were dissolved in 270 mL of dichloromethane (0.2M) and cooled down to 0ºC. After that, 3.36 mL (54.47 mmol, 3 eq) of 3-amino-1-propyne were added over a period of 30 min with an automatic additioner, then warmed to room temperature and stirred overnight. The organic layer was extracted successively with HCl (2M), NaOH (2M) and a saturated solution of $NaHCO_3$. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvent was concentrated under vacuum until an oily residue was observed. Pentane was added and the solution was left in the refrigerator. The following day, the formation of crystals with a needle form that yielded 94% was observed (7.77 g). ^{1}H-NMR analysis data in good agreement with the reported literature.[12]

Yellow crystalline solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.70 (s, 1H), 3.92 (dd, *J*= 5.0, 2.3 Hz, 2H), 2.22-2.21 (t, *J*=2.5 Hz, 1H), 1.46 (s, 9H).

6.3. PREPARATION OF ALKYNYL CARBAMATES

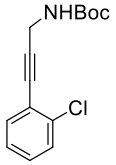
6.3.1. Synthesis of *tert*-butyl (3-(2-chlorophenyl)prop-2-yn-1-yl)carbamate (7). General procedure 1

In an oven-dried single-necked 100mL round-bottomed flask, equipped with a magnetic stirring bar, was charged with 105 mg (0.15 mmol, 0.02 eq) of $PdCl_2(PPh_3)_2$ and 0.05 g (0.3 mmol, 0.04 eq) of copper iodide and purged with N_2/vacuum cycles. Afterwards, 8 mL of anhydrous THF were added, followed by 1 mL of 1-chloro-2-iodobenzene 3.3 mL of Et_3N (THF/Et_3N 4:1, 0.45M).

In another flask, 1.16 g (7.5 mmol, 1 eq) of *tert*-butyl-prop-2-yn-1-ylcarbamate were dissolved in 13.3 mL of THF (the remaining amount to have a 0.45M solution of THF/Et_3N). This solution was transferred to the other flask with a syringe. The reaction was left stirring overnight at room temperature.

To the solution, diethyl ether and saturated NH_4Cl aqueous solution (1:1) were added. The organic layer was extracted 4 times with diethyl ether, then the combined organic layers were washed with saturated NaCl solution. It was verified by TLC that there were no organic rests in the aqueous layer. Then the organic layers were dried over anhydrous $MgSO_4$, filtered and

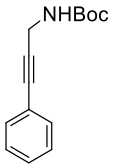
concentrated under vacuum. The residue was purified by flash column chromatography (hexane:EtOAc, 9.5:0.5; equilibrated with hexane/Et_3N) to obtain a solid product in 65% yield (1.53 g). The analytical data for this compound were in excellent agreement with the reported data.[13]



White solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41-7.15 (m, 4H), 4.78 (s, 1H), 4.21 (d, 2H), 1.47 (s, 9H)

6.3.2. Synthesis of *tert*-butyl (3-phenylprop-2-yn-1-yl)carbamate (2)

The product was synthesized in accordance with general procedure 1, using 3.5 g of compound **1**, 172 mg of CuI, 2.8 mL of PhI, 50.1 mL of THF/Et_3N and 317 mg of $PdCl_2(PPh_3)_2$. The crude was purified by flash column chromatography (hexane:EtOAc, 9:1; equilibrated with hexane/Et_3N) to obtain a brown solid product in 69% yield (3.60 g). The analytical data for this compound were in excellent agreement with the reported data.[14]



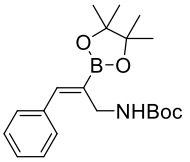
Brown solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41 (m, 2H), 7.30 (m, 3H), 4.75 (s, 1H), 4.15 (d, *J*= 5.9 Hz, 2H), 1.47 (s, 9H).

6.4. PREPARATION OF ALKENYL BORONATES

6.4.1. Synthesis of *tert*-butyl (Z)-(3-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)carbamate (3). General procedure 2

A 100 mL round-bottomed flask, equipped with a magnetic stirring bar, was charged with the corresponding alkyne, in this case compound **2** (2.30 g, 9.96 mmol, 1 eq), 148 mg (1.49 mmol, 0.15 eq) of NaO*t*Bu and 2.78 g (10.96 mmol, 1.1 eq) of B_2pin_2. In the dry box, 98 mg (0.99 mmol, 0.10 eq) of CuCl beads and 336 mg (1.20 mmol, 0.12 eq) of PCy_3 were weighed and transferred to the flask. Under inert atmosphere, 26.2 mL of toluene (0.38M) were added via a syringe and then 0.8 mL (20 mmol, 2 eq) of methanol, drop by drop and at 0ºC. The resulting solution was left

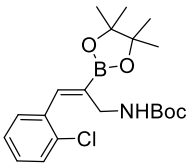
stirring overnight. Once the reaction had finished, it was quenched with 8 mL of MeOH, filtered through a pad of Celite and washed with DCM. The filtrate was concentrated to dryness. The obtained crude was purified by flash chromatography (direct injection; hexane:EtOAc, 9:1; equilibrated with Et_2O and then with hexane/Et_3N) to afford a white solid (2.24 g, 63%).



White solid. m.p. 114-117 ºC. IR (ATR-FTIR): 3419, 2973, 2938, 1710, 1510, 1364 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.36-7.30 (m, 5H), 5.20 (s, 1H), 4.14 (s, 2H), 4.05 (s, 1H), 1.43 (s, 9H), 1.32 (s, 12H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 155.85, 144.44, 129.43, 128.89, 128.41, 127.98, 83.96, 40.30, 29.85, 28.61, 24.94. HRMS (ESI): calc. for $C_{20}H_{31}BNO_4$ 360.2340, found 360.2342 $[M+H]^+$.

6.4.2. Synthesis of tert-butyl (Z)-(3-(2-chlorophenyl)-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl)carbamate (8)

Compound **8** was prepared in accordance with general procedure 2, using 1.15 g of compound **7**, 61 mg of NaO*t*Bu, 1.21 g of B_2pin_2, 43 mg of CuCl, 146 mg of PCy_3, 11.4 mL of toluene, 0.35 mL of MeOH and another 4 mL of MeOH for quenching. After purification, a solid was obtained (1.28 g, 75%). The ^1H-NMR integrations were not precise but HPLC-MS and HRMS confirmed the indentity of the compound.



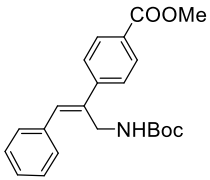
White solid. m. p. 96-97 ºC. IR (ATR-FTIR): 3424.68, 2975.58, 2929.54, 2862.05, 1709.11, 1615.20, 1512.17 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.40-7.30 (m, 3H), 7.25-7.18 (m, 3H), 5.12 (s, 1H), 3.98 (s, 2H), 1.41 (s, 12H), 1.32 (s, 20H). HRMS (ESI): calc. for $C_{20}H_{30}BClNO_4$ 394.1950, found 394.1951 $[M+H]^+$.

6.5. PREPARATION OF ALLYL CARBAMATES

6.5.1. Synthesis of methyl (Z)-4-(3-((*tert*-butoxycarbonyl)amino)-1-phenylprop-1-en-2-yl)benzoate (4a). General procedure 3

In an oven-dried Schlenk equipped with a magnetic stirring bar, 16 mg (0.03 mmol, 0.5 eq) of $Pd(dba)_2$ were added and it was purged with N_2. 3.9 mL of anhydrous THF and 157 mg (0.60 mmol, 1.1 eq) of methyl 4-iodobenzoate were added, and the reaction was stirred at room temperature for 5 minutes. Afterwards, 202 mg (0.54 mmol, 1 eq) of the alkenyl boronate **3**

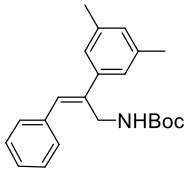
dissolved in 1.53 mL of anhydrous THF and 0.56 mL of an aqueous solution of 3N KOH were sequentially added to the reaction mixture, and it was heated at 90ºC overnight. Then, it was filtered through a pad of Celite and washed with DCM. The filtrate was concentrated under vacuum. The residue was purified, first by a column chromatography (9:1 hexane:EtOAc) and then by crystallization. The crystallization was with hexane and adding Et_2O drop by drop and then in an ice-water bath the temperature was lowered. It was saved in a freezer overnight and the mother liquor was removed with a Pasteur pipette. The final product was concentrated under vacuum and, to completely eliminate the solvent, strippings with 2 times DCM and 2 times Et_2O were done. The product obtained was a pale-yellow solid and yielded 66% (131 mg)



Pale-yellow solid. m.p. 98-100 ºC. IR (ATR-FTIR): 3349, 2982, 1718, 1671, 1509 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.07 – 8.02 (m, 2H), 7.59 (d, *J* = 8.2 Hz, 2H), 7.42 – 7.38 (m, 2H), 7.35 – 7.29 (m, 3H), 7.03 (s, 1H), 4.45 (s, 3H), 3.93 (s, 3H), 1.39 (s, 9H).). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 166.82, 155.55, 144 .78, 137.35, 136.31, 132.70, 129.84, 129.27, 128.84, 128.72, 128.53, 127.67, 126.56, 79.57, 52.11, 39.51, 28.30. HRMS (ESI): calc. for $C_{22}H_{25}NNaO_4$ 390.1676, found 390.1675 $[M+Na]^+$.

6.5.2. Synthesis of *tert*-butyl (Z)-(2-(3,5-dimethylphenyl)-3-phenylallyl)carbamate (4b)

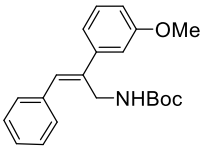
Compound **4b** was prepared following general procedure 3, using 17 mg of $Pd(dba)_2$, 4.3 mL of anhydrous THF, 0.09 mL of 1-iodo-3,5-dimethylbenzene, 220 mg of **3**, another 1.7 mL of anhydrous THF and 0.6 mL of KOH 3N. Purification by column chromatography was with direct injection. A yellowish product that yielded 39% (129 mg) was obtained.



Yellowish solid. m.p. 84-86 ºC. IR (ATR-FTIR): 3343, 2982, 2924, 1668, 1518, 1321 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.40 – 7.36 (m, 2H), 7.35 – 7.31 (m, 2H), 7.30 – 7.27 (m, 1H), 7.14 (s, 2H), 6.97 (dt, *J* = 1.6, 0.8 Hz, 1H), 6.92 (s, 1H), 4.42 (s, 3H), 2.35 (s, 6H), 1.41 (s, 9H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 155.61, 140.13, 138.06, 136.90, 130.73, 129.47, 128.82, 128.42, 127.19, 124.45, 79.31, 39.80, 28.33, 21.39. HRMS (ESI): calc. for $C_{22}H_{27}NNaO_2$ 360.1934, found 360.1942 $[M+Na]^+$.

6.5.3. Synthesis of *tert*-butyl (Z)-(2-(3-methoxyphenyl)-3-phenylallyl)carbamate (4c)

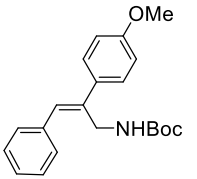
Compound **4c** was prepared following general procedure 3, using 20 mg of $Pd(dba)_2$, 4.9 mL of anhydrous THF, 0.9 mL of 1-iodo-3-methoxybenzene, 251 mg of **3**, another 1.9 mL of anhydrous THF and 0.7 mL of KOH 3N. The product obtained by column chromatography yielded 38% (89 mg) of a yellow oil, so it could not be recrystallized.



Yellow oil. IR (ATR-FTIR): 3447, 2979, 2248, 1706, 1597, 1493 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.39 – 7.36 (m, 2H), 7.35 – 7.28 (m, 4H), 7.14 – 7.10 (m, 1H), 7.08 – 7.05 (m, 1H), 6.96 (s, 1H), 6.87 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 4.43 (s, 3H), 3.85 (s, 3H), 1.40 (s, 9H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 159.79, 141.70, 137.83, 136.69, 131.15, 129.53, 129.53, 128.94, 128.82, 128.45, 128.37, 127.33, 119.00, 113.47, 112.08, 79.38, 55.27, 39.74, 28.33. HRMS (ESI): calc. for $C_{21}H_{25}NNaO_3$ 362.1727, found 362.1730 $[M+Na]^+$.

6.5.4. Synthesis of *tert*-butyl (Z)-(2-(4-methoxyphenyl)-3-phenylallyl)carbamate (4d)

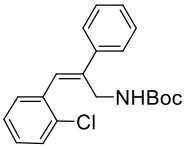
Compound **4c** was prepared following general procedure 3, using 48 mg of $Pd(dba)_2$, 11.7 mL of anhydrous THF, 430 mg of 1-iodo-4-methoxybenzene, 600 mg of **3**, another 5 mL of anhydrous THF and 1.7 mL of KOH 3N. Purification by column chromatography was with 9.5:0.5 hexane:EtOAc. The product obtained was a white solid that yielded 83% (148 mg).



White solid. m.p. 81-83 ºC. IR (ATR-FTIR): 3346, 2979, 1669, 1513 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.47 (d, *J* = 8.4 Hz, 2H), 7.40 – 7.35 (m, 2H), 7.33 – 7.27 (m, 3H), 6.95 – 6.90 (m, 2H), 6.88 (s, 1H), 4.47 – 4.29 (m, 3H), 3.84 (s, 3H), 1.40 (s, 9H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 159.38, 155.63, 137.25, 136.99, 132.45, 129.62, 128.77, 128.43, 127.71, 127.11, 113.98, 79.36, 55.32, 39.68, 28.34. HRMS (ESI): calc. for $C_{21}H_{25}NNaO_3$ 362.1727, found 362.1727 $[M+Na]^+$.

6.5.5. Synthesis of *tert*-butyl (Z)-(3-(2-chlorophenyl)-2-phenylallyl)carbamate (9)

Compound **9** was prepared following general procedure 3, using 85 mg of $Pd(dba)_2$, 20.8 mL of anhydrous THF, 0.35 mL mg of iodobenzene, 1.16 g of **8**, another 8.2 mL of anhydrous THF and 3 mL of KOH 3N. Purification by column chromatography was with 9.5:0.5 hexane:EtOAc. The product obtained was a white solid that yielded 78% (536 mg). Data analysis in good agreement with literature.[13]

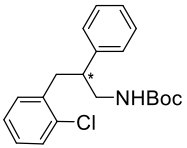


White solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.46-7.20 (m, 9H), 6.95 (s, 1H), 4.39 (s, 1H), 4.32 (d, *J*=5.3 Hz, 2H), 1.37 (s, 9H). HRMS (ESI): calc. for $C_{20}H_{30}BClNO_4$ 394.1950, found 394.1951 $[M+H]^+$.

6.6. ASYMMETRIC HYDROGENATIONS

6.6.1. Synthesis of *tert*-butyl (3-(2-chlorophenyl)-2-phenylpropyl)carbamate (10). General procedure 4

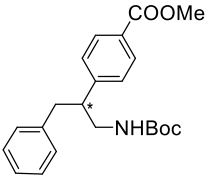
66 mg (0.19 mmol, 1 eq) of substrate **9** and 3 mg (0.002 mmol, 0.01 eq) of Ir-$(S)_P$-DTP catalyst were weighed and transferred to a tube. This tube was placed in a pressure reactor, entered in the dry box and 1.6 mL of anhydrous DCM were added. The reactor was charged with 50 bars of H_2. The reaction mixture was left stirring for 48h at room temperature. The crude reaction was concentrated under vacuum and purified by flash column chromatography (9.5:0.5 hexane:EtOAc). HPLC was performed in order to determine the enantiomeric excess. The product obtained was a brown solid that yielded 99% (70 mg).



Brown solid. m.p. 76-78 ºC. IR (ATR-FTIR): 3378.74, 3085.38, 3063.64, 3027.82, 2996.80, 2981.30, 2968.03, 2933.47, 2893.91 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33-7.25 (m, 3H), 7.24-7.21 (d, 1H), 7.17-7.13 (d, 2H), 7.11-7.02 (m, 2H), 6.96-6.90 (d, 1H), 4.39 (s, 1H), 3.54 (s, 1H), 3.34 (s, 1H), 3.18-3.08 (m, 2H), 2.97-2.89 (m, 1H), 1.38 (s, 9H). HRMS (ESI): calc. for $C_{16}H_{17}ClNO_2$ 290.0942, found 290.0491 $[M-t\text{Bu}+2H]^+$. $[\alpha]_D$=-27.2

6.6.2. Synthesis of methyl 4-(1-((*tert*-butoxycarbonyl)amino)-3-phenylpropan-2-yl)benzoate (5a)

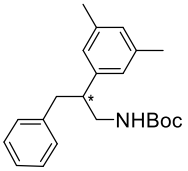
The product was synthesized in accordance with general procedure 4, using 52.6 g of compound **4a**, 2.3 mg of Ir-$(S)_P$-DTP and 1.2 mL of anhydrous DCM. The crude was purified by flash column chromatography (8:2 hexane:EtOAc) to obtain an oily product in 87% yield (46 mg), with a 98% ee.



Oil. IR (ATR-FTIR): 3439, 3373, 2977, 2927, 1704, 1506, 1279, 1249 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.96 – 7.92 (m, 2H), 7.20 – 7.11 (m, 5H), 6.99 (d, *J* = 7.2 Hz, 2H), 4.34 (s, 1H), 3.90 (s, 3H), 3.62 – 3.52 (m, 1H), 3.33 – 3.22 (m, 1H), 3.15 (d, *J* = 9.6 Hz, 1H), 2.99 (dd, *J* = 13.7, 6.2 Hz, 1H), 2.86 (dd, *J* = 13.7, 8.5 Hz, 1H), 1.38 (s, 9H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 166.94, 155.71, 147.51, 138.98, 129.82, 128.94, 128.71, 128.26, 128.02, 126.17, 79.35, 52.03, 47.96, 45.28, 40.28, 28.30. HRMS (ESI): calc. for $C_{22}H_{27}NNaO_4$ 392.1832, found 392.1831 $[M+Na]^+$. HPLC: CHIRALPAK IC. Heptane/IPA 85:15, 0.5 mL/min, λ = 210 nm. $t_{(R)}$ = 25.1 min, $t_{(S)}$ = 28.1 min. $[\alpha]_D$=-30.2

6.6.3. Synthesis of *tert*-butyl (2-(3,5-dimethylphenyl)-3-phenylpropyl)carbamate (5b)

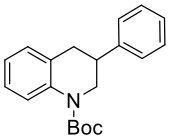
The product was synthesized in accordance with general procedure 4, using 65.8 g of compound **4b**, 3.06 mg of Ir-$(S)_P$-DTP and 1.6 mL of anhydrous DCM. The crude was purified by flash column chromatography (9.5:0.5 hexane:EtOAc) to obtain an oil in 84% yield (56 mg), with a 93% ee.



Oil. IR (ATR-FTIR): 2980, 2914, 1701, 1496, 1351 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.22 (t, *J* = 7.4 Hz, 2H), 7.17 – 7.12 (m, 1H), 7.07 (d, *J* = 7.5 Hz, 2H), 6.86 (tt, *J* = 1.5, 0.7 Hz, 1H), 6.76 (dd, *J* = 1.7, 0.9 Hz, 2H), 4.32 (t, *J* = 10.0 Hz, 1H), 3.58 – 3.46 (m, 1H), 3.24 – 3.13 (m, 1H), 3.00 (q, *J* = 7.5, 6.5 Hz, 1H), 2.88 (d, *J* = 8.5 Hz, 2H), 2.28 (q, *J* = 0.7 Hz, 6H), 1.39 (s, 9H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ 155.94, 142.27, 139.94, 138.13, 129.18, 128.56, 128.36, 126.16, 125.80, 79.22, 47.53, 45.37, 40.94, 28.50, 21.49. HRMS (ESI): calc. for $C_{22}H_{30}NO_2$ 340.2271, found 340.2274 $[M+H]^+$. HPLC: CHIRALPAK IA. Heptane/*i*PrOH 98:2, 0.5 mL/min, λ = 210 nm. $t_{(R)}$ = 16.2 min, $t_{(S)}$ = 18.6 min. $[\alpha]_D$=-13.7

6.7. PREPARATION OF 3-PHENYL-TETRAHYDROQUINOLINE (RAC-12)

To a Schlenk tube with a magnetic stirring bar there were added 2 mg of $Pd(OAc)_2$ (0.01 mmol, 0.2 eq) and 12 mg of rac-BINAP (0.02 mmol, 0.4 eq). The Schlenk was purged with vacuum/N_2 cycles. A solution of 16 mg (0.05 mmol, 1 eq) of compound **10** in 0.25 mL of toluene was transferred to the Schlenk, and the final mixture was heated to 100 ºC. Once it was all dissolved, the Schlenk was cooled to room temperature. Afterwards, 22 mg Cs_2CO_3 (0.07 mmol, 1.4 eq) were added. The solution was heated to 100ºC and was left stirring for 48h. Another 0.95 mL of toluene were added. Then, it was filtered through a pad of Celite and washed with DCM. The filtrate was concentrated under vacuum and the residue was purified on a column chromatography with 9:1 hexane:EtOAc. The final product yielded 9.8 mg (67%).



Yellow solid. m.p. 102-104 ºC. IR (ATR-FTIR): 2961.80, 2922.69, 2851.23, 1688.28 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.71 (d, *J*= 8.3 Hz, 2H), 7.36-7.30 (m, 4H), 7.13 (d, *J*= 7.5 Hz, 1H), 7.05-6.99 (m, 2H), 4.17-4.11 (m, 2H), 3.57 (dd, *J*= 12.6, 9.6 Hz, 2H), 1.44 (s, 9H). HRMS (ESI): calc. for $C16H16NO_2$ 254.1176, found 254.1179 $[M\text{-}t\text{Bu}+2H]^+$.

7. CONCLUSIONS

- Four allylic carbamates substrates with different substituents on the middle phenyl ring have been synthesized with good yields.
- Asymmetric hydrogenation of the substrates **4a** and **4b** has worked correctly providing fully conversion and enantiomeric excess of 98% and 93% respectively.
- An allylic carbamate with an ortho-chloride at the terminal phenyl ring was synthesized and submitted to asymmetric hydrogenation with Ir-(*S*)$_P$-DTP, giving a 100% conversion and 97% ee.
- The allylic carbamate with the chloride was also submitted to a racemic hydrogenation to find HPLC conditions and do the tests for the Buchwald-Hartwig reaction.
- Five different conditions have been tested for the cyclization of the allylic carbamate with the ortho-chloride. One of them has worked with an 80% conversion. We tried to reduce the catalyst loading to 5% but the conversion was low. We can conclude that the Buchwald-Hartwig reaction for compound **10** works, but we are still currently working on finding other conditions in order to reduce the catalyst loading to at least 5%.

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9. ACRONYMS

ATR	Attenuated Total Reflectance
BAr_F	Tetrakis[3,5-bis(trifluoromethyl)phenyl] borate
calc.	Calculated
cod	1,5-cyclooctadiene
conv.	Conversion
Cy	Cyclohexyl
DAST	Diethylaminosulfur trifluoride
dba	Dibenzylideneacetone
DCM	Dichloromethane
DTP	Di*tert*-butyl phenyl
ee	Enantiomeric excess
eq	Equivalent(s)
ESI	Electrospray ionization
FT-IR	Fourier transformation infrared spectroscopy
HRMS	High resolution mass spectroscopy
IPA	2-propanol
iPr	Isopropyl
IR	Infrared spectroscopy
m.p.	Melting point
NMR	Nuclear magnetic resonance
o.n	Overnight
ppm	Parts per million

r.t.	Room temperature
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane