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Lewis-acid-promoted selective isomerization of oxetanes. New synthetic approach towards γ-chiral alcohols

Isomerització selectiva d'oxetans induïda per àcid de Lewis. Nou enfoc sintètic cap a alcohols γ-quirals

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It is thorugh science that we prove, but through submarines that we demonstrate.

Hentri Poincaré, feat. Marina Bellido, 2019

Vull agrair especialment a tota la gent que m'ha donat suport durant aquest treball:

Primerament, al Toni, per acollir-me a la família d'URSA durant la meva estada, per tots els seus consells i el temps dedicat a fer de mi un químic de cap a peus.

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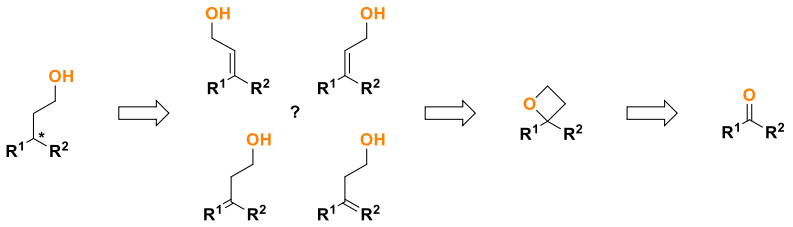
1. SUMMARY

The synthesis of enantiomerically pure compounds is one of the main challenges in organic synthesis. Particularly, γ-chiral alcohols are a valuable chemical motif and a useful building block, especially in the pharmaceutical industry. Even though there are several synthetic methodologies already studied, they offer poor atom economy reactions and there is a need of separation steps, consequently lowering the final yield. For this reason, a new approach would be highly desired.

Most promising approaches undergo isomerization reactions that are highly atom economy efficient and generate low to no residues. Still there is not a selective procedure to the isomerization of oxetanes.

In this work, a new general and greener synthetic pathway has been developed. This new approach is based on the Lewis-acid-promoted selective isomerization of oxetane rings. Afterwards, the correspondent olefin is subjected to an asymmetric hydrogenation using iridium-based catalysts.

A standard substrate has been tested in order to optimize the methodology. Finally, a broad scope of substrates has been studied to generalize the process.



Retrosynthetic approach towards γ-chiral alcohols

Keywords: γ-chiral alcohol, atom efficient, Lewis acid, selective isomerization, oxetane, asymmetric hydrogenation.

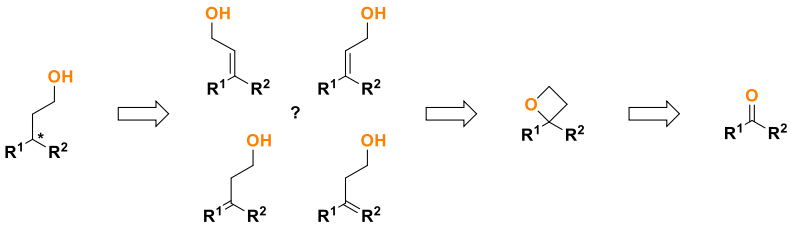
2. RESUM

Els compostos enantiomèricament purs són un dels principals reptes de la síntesi orgànica. Particularment, els alcohols quirals en la posició γ són un útil bloc sintètic, especialment en la indústria farmacèutica. Tot i que moltes estratègies sintètiques han estat estudiades, ofereixen reaccions poc eficients en termes d'economia atòmica i necessiten separacions addicionals que disminueixen el rendiment final. Per aquest motiu, un nou enfoc en aquesta síntesi seria molt apropiat.

Els processos més prometedors es basen en reaccions d'isomerització, ja que són molt eficients pel que fa a la seva economia atòmica i generen pocs o cap residu. De totes maneres, encara no hi ha un procediment cap a la isomerització selectiva d'oxetans.

En aquest treball, una nova via sintètica més general i verda ha estat desenvolupada. Aquest nou enfoc es basa en la isomerització selectiva d'anells d'oxetà catalitzada per àcids de Lewis. A continuació, la corresponent olefina és sotmesa a una hidrogenació asimètrica utilitzant catalitzadors basats en iridi.

Un substrat estàndard ha estat estudiat per la optimització del mètode. Finalment, un ampli rang de substrats ha estat analitzat per generalitzar el procés.



Enfoc retrosintètic cap a la obtenció d'alcohols γ-quirals

Paraules clau: Alcohol γ-quiral, economia atòmica, àcid de Lewis, isomerització selectiva, oxetà, hidrogenació asimètrica.

3. INTRODUCTION

3.1. INTRODUCTION TO CHIRALITY AND ASYMMETRIC SYNTHESIS

The synthesis of enantiomerically pure compounds is one of the main challenges in organic synthesis, especially in the pharmaceutic field, where the properties of the two enantiomers can be completely different. One enantiomer can have positive effect towards some diseases and the other one not even have any effect or, even worse, lead to other health problems. For this reason, asymmetric reactions are highly desired by pharmaceutical companies.

To prepare enantioriched compounds, several techniques can be used. However, there is not a general procedure to do so, as it depends on the starting product. Depending on it being a racemic sample, a non-chiral compound or a pure enantiomer, the techniques used might vary.

A simple way of obtaining an enantioriched product from a racemic sample is a **kinetic resolution**. This method is based on one of the two enantiomers reacting faster than the other, or even only reacting with one of them. By stopping the reaction early, a starting enantiomer that has not reacted yet and the product of the reaction can be collected and separated, obtaining an enantioriched mixture as the product. The problem with the kinetic resolution is that half of the starting material is lost as it did not react.

Another synthetic strategy aiming the same result was developed by the use of a **chiral auxiliary**. This auxiliary is bonded covalently to the starting material. A diasteroselective reaction will give the two corresponding diastereomers. Afterwards, the two diastereomers can be separated easily, the auxiliary is cleaved, and the pure enantiomer can be obtained. Unless it could be a proper solution, it still involves adding two new steps to the synthesis and the loss of yield in the separation of the two isomers.

To solve the problem, **asymmetric synthesis** is presented as a better solution, as with this method, achiral compounds can be used to prepare chiral enantioriched products, reaching high yields and selectivities. Ultimately, **asymmetric catalysis** has been stablished as the best method so far. By the use of a catalytic specie with chiral ligands that can interact with the substrate, chirality is induced to an achiral compound. Using this approach, only a catalytic amount of catalyst needs to be used, making this process very atom economy efficient, thus obtaining valuable enantioriched compounds from racemic mixtures.

3.2. ASYMMETRIC HYDROGENATION

Asymmetric hydrogenation has stood out as one of the best examples of asymmetric catalysis. It has been widely studied, aiming to reduce unsaturated compounds using hydrogen and a chiral catalyst, furnishing enantioriched reduced compounds. The first example of successful asymmetric hydrogenation was performed by S. Knowles and co. workers, in 1980's, using a rhodium metal catalyst with the chiral ligand ethane-1,2-diylbis[(2-methoxyphenyl)phenylphosphane] (DIPAMP). The enamine was reduced to the corresponding primary amine (*L*-DOPA) with high enantiomeric excess (Figure 1).[1]

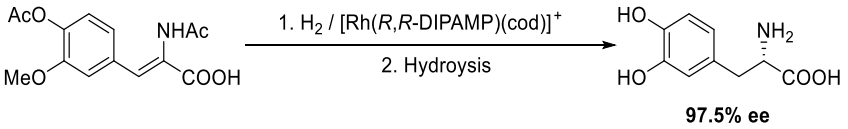


Figure 1: Reduction of the enamine performed by Knowles to the L-amino acid

Conveniently, our group has a long experience in phosphorus chiral ligands and their application in asymmetric catalysis.[2–4] Particularly, various (P,P)- and (P,N)-ligands have been studied to prepare iridium and rhodium-based catalysts. For instance, MaxPHOS was one of the first ligands developed in the group (Figure 2).[4]

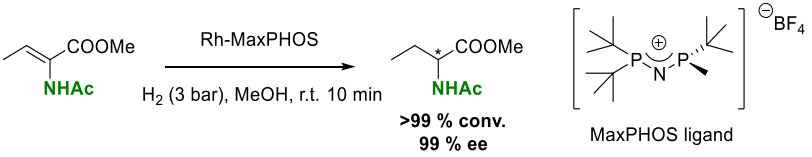


Figure 2: Reduction of enamines using Rh-MaxPHOS

Furthermore, the Ir-MaxPHOX family of catalysts has been recently developed. These catalysts are formed by the coordination of iridium with the MaxPHOX ligand. This bidentate ligand can be easily synthetized from a borane protected chiral phosphinous acid, an amino alcohol and an amino acid. The final catalyst is stabilized by the coordination with a cyclooctadiene group, and a BAr_F anion (Figure 3).[5]

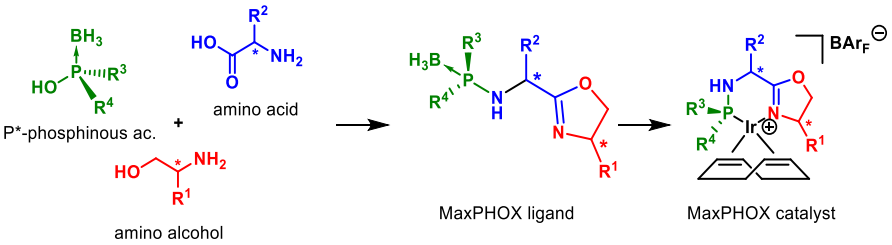


Figure 3: Synthetic scheme of Ir-MaxPHOX catalyst

As seen in Figure 3, these ligands are highly modular. They present three different chiral centres, so up to four diastereomers can be obtained. Moreover, the oxazoline substituent can induce steric hindrance with the substrate, interacting with it in a particular orientation (Figure 4). By modifying the R^1 substituent with a phenyl (Ph), an isopropyl (*i*Pr) or a *tert*-butyl (*t*Bu) group, some interactions are favoured, possibly improving the enantiomeric excess values.

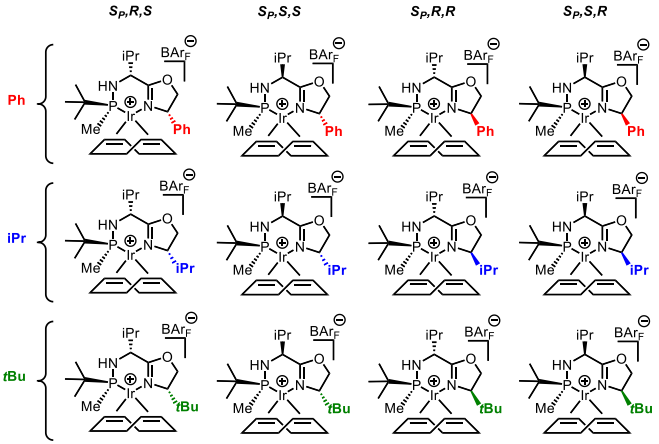


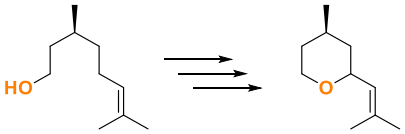
Figure 4: Ir-MaxPHOX family of ligands

This family of catalysts have been applied in the asymmetric hydrogenation of imines, cyclic and aryl alkyl enamines with excellent results affording high enantiomeric excess values.[5–7]

3.3. ASYMMETRIC SYNTHESIS OF γ-CIHRAL ALCOHOLS

Enantioriched chiral alcohols with stereocentre in the γ-position are highly demanded chemical compounds, especially in pharmacy and perfume industry, as this functional group is

present in a lot of natural products. Furthermore, it is a versatile building block that can be used as an intermediate for multistep synthesis and a desired chemical motif. A good example of that is citronellol, which has a γ-position chiral alcohol. It is present in citronella oils and oils of rose, and it is used in perfume industry to generate rose oxide, a fragrance chemical used in perfumes and to flavor fruits and wines (Figure 5).[8]



(-)-citronellol Rose oxide

Figure 5: Example of γ-chiral alcohol and a particular application

3.3.1. Current synthetic strategies

Nowadays, several methods have been studied leading to the synthesis of γ-chiral alcohols. Most of them are based in a multistep sequence involving an initial enantioselective transformation on a functionalized substrate, followed by the adjustment of the oxidation state of the resulting product. The main methodologies are summarized in Figure 6: [9]

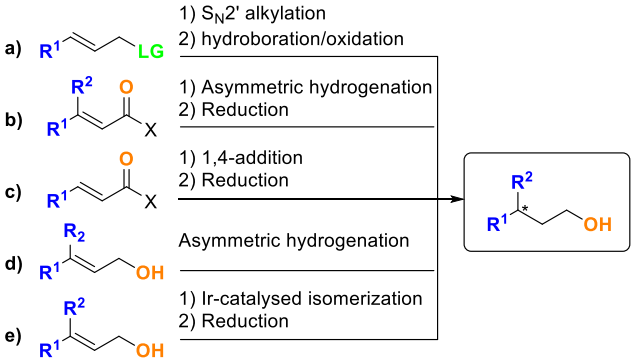


Figure 6: Methodologies to the synthesis of γ-chiral alcohols (X = Cl, OR, H)

In route **a**, an allylic substitution is carried out under metal-catalysed conditions. The second substituent is added to the γ-position enantioselectively by the use of a nucleophile alkyl group such as organomagnesium and organolitium reagents. Then, the alkene is either hydroborated or oxidised to produce the terminal alcohol.[10]

Routes **b** and **c** present a different approach, starting from the α,β-unsaturated carbonyl compounds. The first one is based on an asymmetric hydrogenation of the unsaturated bond to generate the chiral centre and the subsequent reduction of the ketone derivative.[11] The second is based in a 1,4-addition of the second substituent enantioselectively in the β-position using a Grignard reagent in presence of a copper catalyst and a chiral auxiliary, generating the chiral position, and followed by the reduction of the ketone derivative.

In a similar manner, routes **d** and **e** use γ,γ'-disubstituted primary allylic alcohols. Firstly, route **d** is able to obtain the chiral alcohol in a single clean step via asymmetric hydrogenation using catalytic species as the ones shown in 3.2.[9] On the other hand, route **e** presents an iridium catalysed isomerization to the correspondent aldehyde in an enantioselective manner, to then easily reduce it to the primary alcohol with a reducing agent in mild conditions

Taking a closer look into this last route, isomerization reactions are well desirable, being highly atom economy efficient, as they represent a rearrangement of the main substrate by the usage of a catalytic amount of catalyst. Enantioselective isomerization of allylic alcohols leads to the aldehyde that can be easily reduced to the primary alcohol. Mazet, Andersson and others have widely investigating this field, showing great enantiomeric excesses, obtained when employing chiral (P,N)-Iridium catalysts in an expanded scope of substrates.[12,13] In this reactions, the allylic alcohol is isomerized into the correspondent enol, which then, by a keto-enol equilibrium forms the aldehyde without the loss of enantioselectivity, especially with large substituents (Figure 7).

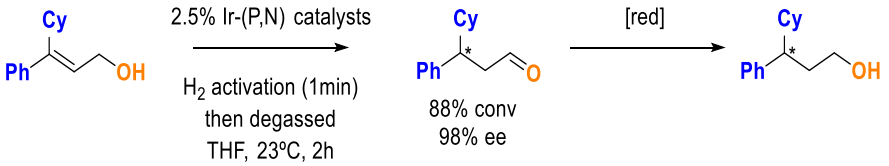


Figure 7: Isomerization of allylic alcohol to the correspondent aldehyde, and its reduction to the chiral primary alcohol

Moreover, Pfaltz and co. workers performed direct asymmetric hydrogenation of allylic alcohols using chiral (P,N)-iridium catalysts too, achieving high enantiomeric excesses as well (Figure 8).[9] However, one of the main drawbacks of this work was that high hydrogen pressures were needed to induce high enantioselectivity.

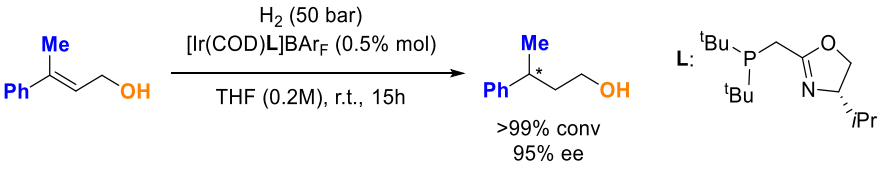


Figure 8: Asymmetric hydrogenation of allylic alcohol to the chiral primary alcohol

A general methodology used to synthetize γ-chiral alcohols from commercially available ketones is presented in Figure 9. In this process, the allylic alcohol is obtained by a Horner-Wadsworth-Emmons reaction, followed by a reduction of the ester. With the allylic alcohol in hand, either selective isomerization using organometallic ruthenium, iridium and rhodium complexes followed by the reduction of the obtained aldehyde, or via asymmetric hydrogenation process using chiral (P,N)-iridium catalysts, the enantioriched primary alcohol can be obtained.

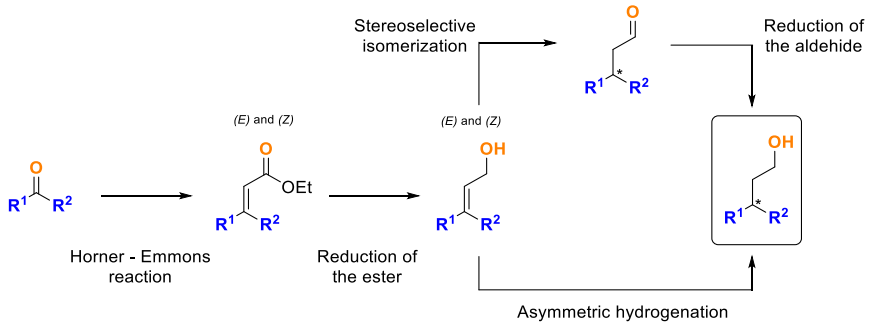


Figure 9: Example of a general procedure to the generation of γ-chiral alcohols

However, both catalytic methods present a huge drawback. The problem resides in the olefination of the ketone, usually done through a Horner-Wadsworth-Emmons reaction. This step is a poor atom efficient step, as the released phosphorene is not recovered. Furthermore, $LiAlH_4$ or DIBAL-H are necessary in the reduction step. Also, this reaction is not always selective to the same isomer, as it can generate both the *E* and *Z* isomers. Due to this selectivity problem, the alkene environment is different for both isomers, and either in the hydrogenation or the isomerization, they will behave differently, possibly generating opposite enantiomers and lowering the enantiomeric excess drastically. Consequently, a separation step is needed before

undergoing the asymmetric catalytic reaction. Due to the similarity between both *E* and *Z* isomers, most of the times the separation cannot be performed with standard column chromatography and, even if separated, the addition of a separation step will cause a huge drop on the total yield.

For this reason, a new more general synthetic strategy towards the production of these kind of chiral alcohols employing a stereoselective isomerization process would be highly desired.

3.4. METAL CATALYZED ISOMERIZATION OF HETEROCYCLIC COMPOUNDS

Metal catalysed isomerization of strained 3-membered ring heterocyclic compounds has been widely explored in our group. Particularly, the isomerization capacity of iridium based organometallic complexes have proven to be a point of interest. For instance, *N*-sulfonyl-aziridines have been isomerized to its correspondent allylic amines with excellent enantioselectivity when using Crabtree's catalyst, without any external activation and with only 1% of catalyst loading.[14] Using a similar synthetic protocol, in which the catalyst was activated with hydrogen, di- and trisubstituted epoxides were also selectively isomerized into the correspondent carbonyl analogue. The reactions were carried out under very mild conditions and showing an excellent functional group tolerance (Figure 10).

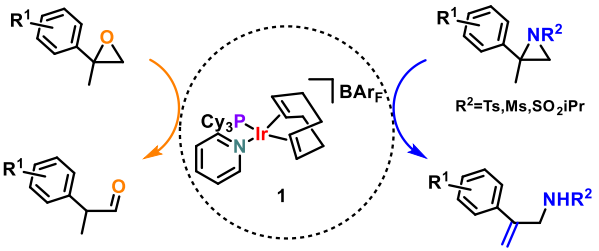


Figure 10: Previous work in heterocycle isomerization using Crabtree's reagent

Regarding to this, and in our efforts to expand the applicability of this isomerization processes, we wonder how 4-membered ring would behave in terms of selectivity. In the literature, there are some precedents in which the formation of homoallylic alcohols as reaction by-products is common when dealing with nucleophilic ring-opening reactions of oxetanes. With this in mind, we envisioned that oxetanes could be precursors for the synthesis of γ-chiral alcohols via a tandem isomerization / asymmetric hydrogenation process. Oxetanes are highly reactive heterocyclic compounds that have been widely investigated in cationic ring opening polymerization (ROP),[15] nucleophilic ring opening and ring expansion reactions.[16] However, and to the best of our

knowledge, there is not any precedent for their selective isomerization. Therefore, a general synthetic protocol for the selective isomerization of oxetanes would be highly valuable.

4. OBJECTIVES

4.1. NEW APPROACH TO THE SYNTHESIS OF γ-CHIRAL ALCOHOLS

In this work, oxetane ring isomerization is going to be studied, aiming to selectively obtain one of the possible products; either the homoallylic or the allylic alcohol (*E* or *Z*). Being able to selectively isomerize oxetane rings to the corresponding alcohol will lead us to a new synthetic protocol to obtain these γ-chiral compounds. This new approach is based on the formation of the correspondent 2,2'-disubstituted oxetane through a double Corey-Chaykovsky reaction from the corresponding ketone, the catalytic selective isomerization of the ring and the final asymmetric hydrogenation of the isomerized specie using the Ir-MaxPHOX catalysts. (Figure 11).

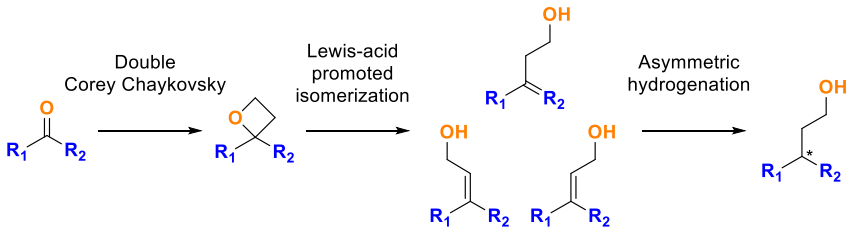
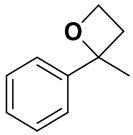


Figure 11: New approach towards the selective formation of γ-chiral alcohols

For this reason, the main focus of this work is to find a standard procedure towards the selective isomerization of 2,2'-disubstituted oxetanes, avoiding the formation of the other possible isomers or side reactivity.

1) **Catalyst screening**. For this purpose, we are going to screen different iridium based species and Lewis acids to find the one that gives best yields and selectivity under mild conditions. With this objective in mind, oxetane **2a** is going to be used in all the screening process.



2a

*Figure 12: Standard substrate **2a** (2-aryl-2-methyloxetane) used in the screening*

2) Screening of other reaction parameters. Modify the catalyst loading, temperature, concentration or reaction time to find the most optimal conditions.

3) Scale-up of the process. Perform the isomerization in gram scale.

4) Substrate scope. With the optimal conditions in hand, a wide range of oxetanes will be synthesized and tested to see how the variability in the substituents is going to affect the process. Particularly, one of the main focus is going to be on the effect that the aryl substituents can have on the selectivity of the isomerization process.

5) Asymmetric hydrogenation. Finally, the asymmetric hydrogenation step is going to be carried out to obtain the desired γ-chiral alcohols. In this process, the different Ir-MaxPHOX catalysts are going to be tested to find out the one that gives a higher enantiomeric excess.

5. RESULTS AND DISCUSSION

5.1. OXETANES

Oxetanes are not a common intermediate in organic chemistry, mainly because their high reactivity makes them susceptible to ring opening and side reactions such as polymerization. However, these heterocyclic rings are present in natural products such as Paclitaxel, sold under the name of Taxol, used as chemotherapy medication to treat several types of cancer (Figure 13).

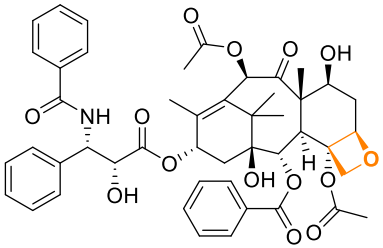


Figure 13: Structure of Paclitaxel

5.1.1. Synthesis

Multiple synthetic methods can be found in the literature for the synthesis of oxetane rings. For instance, a well-known preparation method goes through the intramolecular substitution of 3-chloropropyl acetate, treated with concentrated potassium hydroxide under high temperature conditions.[17] Another example is the [2+2] photochemical cycloaddition of a carbonyl group and an olefin.[18] However, both methods are carried out under harsh conditions, possibly undergoing undesired side reactions (Figure 14).

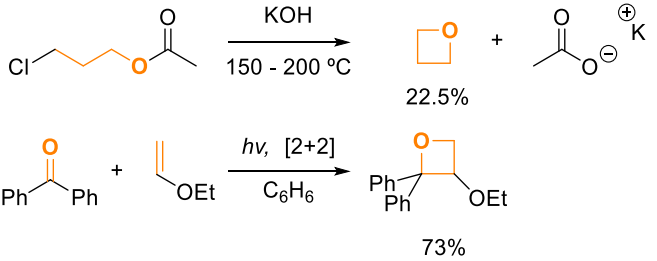


Figure 14: Synthetic approaches to oxetane synthesis

Nevertheless, a general procedure towards the production of 2,2'-disubstituted oxetanes from the correspondent ketone was described by H. Ohta.[19] In this procedure, oxetanes were prepared from the corresponding ketone through a double Corey-Chaykovsky reaction, using trimethylsulfoxonium iodide and potassium *tert*-butoxide as the main reagents (Figure 15). This process is highly convenient, especially because dimethyl sulfoxide is the only by-product of the reaction.

From this point, eight different 2,2'-disubstituted oxetanes were synthetized and characterized in good to excellent yields (**2a-2g**). The scope of substrates will consist in four different substituted

aryl groups with electron withdrawing and electron donating groups; two non-methyl substituted oxetanes and a non-aromatic example to generalize the whole process.

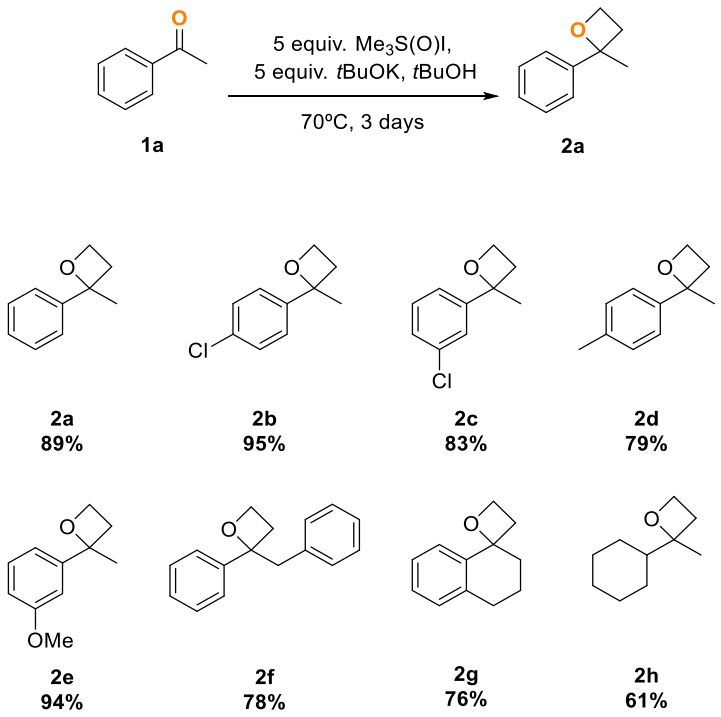


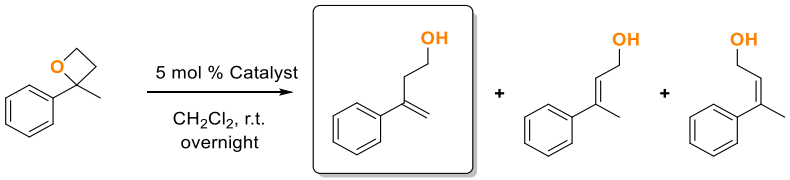
Figure 15: Synthesis of oxetanes through a double Corey-Chaykovksy with respective yields

5.2. ISOMERIZATION OF OXETANES

5.2.1. Catalyst screening and condition optimization

With the oxetane **2a** in hand, several catalysts were tested towards its selective isomerization. As seen in Table 1, Crabtree's reagent was first attempted, as it gave very good results when using other heterocyclic compounds such as *N*-sulfonyl aziridines or epoxides. Using 5 mol %, low conversion was observed (entry 1, Table 1). When activated with H_2, polymerization occurred, thus demonstrating that iridium-hydride complexes are highly reactive for this reaction (entry 2, Table 1).

*Table 1: Screening of conditions for the isomerization of **2a***



2a **3a** **(*E*)-4a** **(*Z*)-4a**

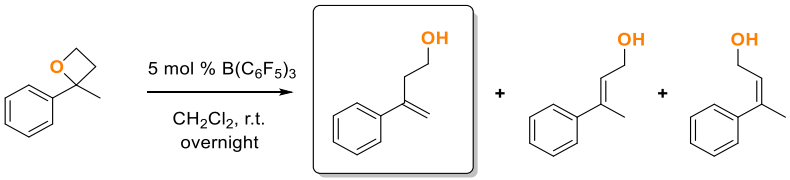
Entry	Catalyst	Solvent	Conv. (%) [a]	3a:4a	Yield 3a (%) [b]
1	Crabtree's reagent	CH_2Cl_2	35	-	25
2 [c]	Crabtree's reagent	CH_2Cl_2	>99	-	0 [d]
3	$ZnCl_2$	CH_2Cl_2	>99	-	0 [d]
4	$InCl_3$	CH_2Cl_2	50	4:1	39
5	$IrCl_3$	CH_2Cl_2	>99	4:1	34
6	$AlCl_3$	CH_2Cl_2	>99	5:1	51
7	$BF_3{\cdot}Et_2O$	CH_2Cl_2	>99	1:2	30

The reaction was performed following GP 2. (a) Determined by ^{1}H-NMR spectroscopy. (b) ^{1}H-NMR yield using mesitylene as internal standard. (c) The reaction was performed in a pressure tube, using H_2 for catalyst activation and, after 1 minute, the vessel was fully degassed. (d) Polymerization occurred

At that point, we moved our attention to the use of inorganic Lewis Acids. First, $ZnCl_2$ was used. Again, polymerization of the oxetane occurred (entry 3, Table 1). Moving to more mild Lewis acids, such as $InCl_3$ or $IrCl_3$, the reaction improved a lot and we observed that homoallylic alcohol **3a** was selectively formed in front of allylic alcohols **4a**, even though in moderate ratio (entries 4 and 5, Table 1). Finally, widely employed $AlCl_3$ also showed good reactivity and full conversion. However, the maximum yield obtained for **3a** was 51% (entry 6, Table 1). Next, we moved to the use of organic Lewis acids. Commonly used $BF_3{\cdot}Et_2O$, showed null selectivity, as **3a**, **(*E*)-4a** and **(*Z*)-4a** were afforded as an equimolar mixture (entry 7, Table 1).

In general, with usual Lewis acids, moderate yield and selectivity were achieved. For this reason, a bibliographic research on Lewis-acid-promoted isomerization was done. $B(C_6F_5)_3$ was found to be an excellent catalyst for the isomerization of epoxides to the corresponding aldehydes. Gratifyingly, when tested it with oxetanes, excellent yields and selectivity towards de homoallylic form was observed (Entry 1, Table 2).

*Table 2: Screening of conditions for the isomerization of **2a***



2a **3a** **4a (*E*)** **4a (*Z*)**

Entry	Catalyst	Solvent	Conv. (%) [a]	3a:4a	Yield 3a (%) [b]
1	$B(C_6F_5)_3$	CH_2Cl_2	>99	98:2	82
2	$B(C_6F_5)_3$	EtOAc	>99	96:4	70
3	$B(C_6F_5)_3$	THF	>99	98:2	67
4	$B(C_6F_5)_3$	Toluene	>99	98:2	75
5	$B(C_6F_5)_3$	MeCN	33	-	21
.6 [c]	$B(C_6F_5)_3$	CH_2Cl_2	>99	98:2	80
7 [d]	$B(C_6F_5)_3$	CH_2Cl_2	>99	98:2	82 (78 [e],84 [f])

The reaction was performed following GP 2. (a) Determined by ^{1}H-NMR spectroscopy. (b) ^{1}H-NMR yield using mesitylene as internal standard. (c) The reaction was performed at 0 ºC. (d) 0.5 mol % of catalyst was employed, and the reaction was left stirring for 2 hours. (e) Isolated yield. (f) Isolated yield performing the reaction at gram scale, using 0.5 mol % of $B(C_6F_5)$, and the reaction was left stirring 24 hours$_3$.

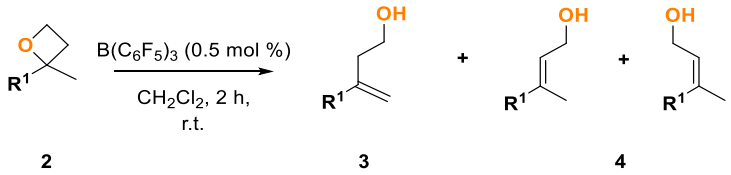
With this results, $B(C_6F_5)_3$ was chosen as the best catalyst to proceed with the optimization of the oxetanes. The next step was the screening of different solvents to see their interaction with the Lewis acid and their effect in the yield / selectivity (entries 2 to 5, Table 2). Even though ethyl acetate, tetrahydrofuran and toluene gave really good selectivity, the yields were not as high as the ones achieved with the dichloromethane. Acetonitrile was also tested, but the yield decreased drastically due to its interaction with the catalyst.

With the appropriate catalyst and solvent optimized, the temperature effect was tested using an ice-bath. The results showed that reducing the temperature does not affect the course of the reaction, as either the selectivity or yield were not modified (entry 6, Table 2). Finally, the reaction was carried out reducing the catalyst loading up to 0.5 mol %. We were pleased to see that, by ^{1}H-NMR monitoring, the reaction showed full conversion after only 2 hours, with excellent stereoselectivity to afford homoallylic alcohol **3a** in good yield (entry 7, Table 2). Moreover, the reaction was performed at gram scale affording **3a** in 84% isolated yield.

5.2.2. Substrate scope

Once the screening was done and the conditions were optimized, the substrate scope was performed (Table 3).

Table 3: Substrate scope results



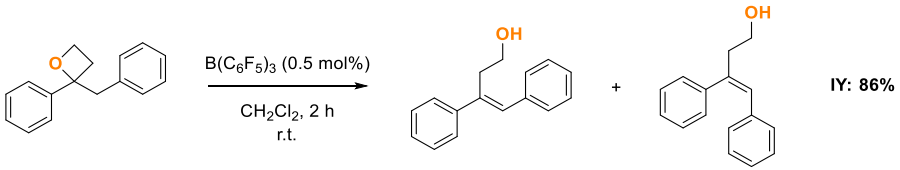
2 **3** **4**

Entry	Substrate	R¹	Conv. (%) [a]	3:4	Yield 3 (%) [b]
1	**2b**	*p*-Cl (Ar)	>99	>99	95
2	**2c**	*m*-Cl (Ar)	>99	95:5	84
3	**2d**	*p*-Me (Ar)	>99	96:4	79
4	**2e**	*m*-OMe (Ar)	>99	98:2	92

The reaction was performed following GP 2. (a) Determined by ^{1}H-NMR spectroscopy. (b) Isolated yield.

Firstly, **R¹** was substituted by chloride substituted phenyl groups, to test the effect of electron withdrawing groups in the aromatic ring. In *para*- position, the results improved in comparison with the standard, both in selectivity and yield (Entry 1, Table 3). In *meta*- position, the selectivity was slightly reduced, but still high selectivity towards the homoallylic form was observed (Entry 2, Table 3). Moving to electron donating groups, methyl and methoxide groups were tested. The methyl in *para*- position substitution was well tolerated, while having the methoxide group in *meta*-*position,* the yield was increased (Entries 3 and 4 respectively, Table 3).

Moving into the oxetanes that isomerize into non-terminal homoallylic alcohols, benzyl substituted oxetane showed full selectivity to the homoallylic form. Specifically, the *E* isomer was obtained as the major product, although the *Z* isomer was still observed.



2f **3f (*E*) 93%** **3f (*Z*) 7%**

*Figure 16: Isomerization of the benzyl substituted oxetane (**2f**) following GP 2*

The bicyclic example also showed full conversion to the homoallylic form and, due to the strained cycle, no mixture of isomers was obtained.

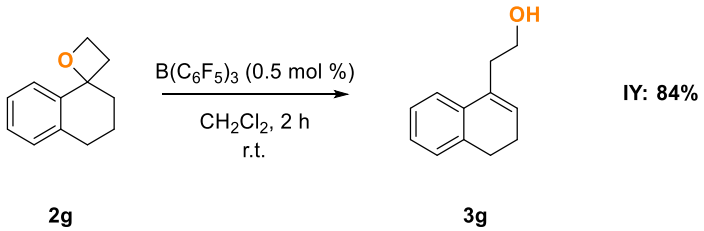


*Figure 17: Isomerization of the tetralone derivate oxetane (**2g**) following GP 2*

Finally, to show the versatility of the process, a non-aryl substituted oxetane was tested, showing lower yields. Still high selectivity was shown towards the homoallylic species. However, two different homoallylic alcohols are formed in the process, so a separation step is needed.

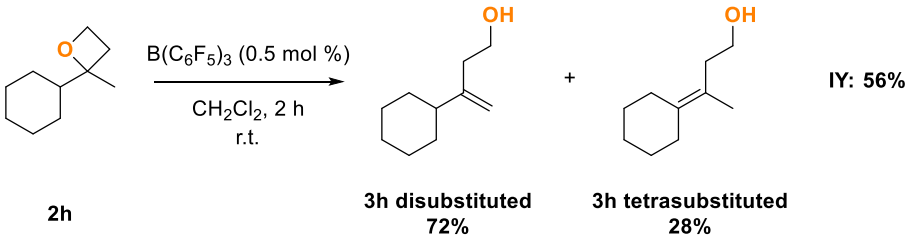
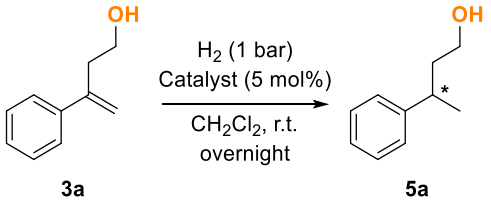


*Figure 18: Isomerization of the cyclohexyl methyl oxetane (**2h**) following GP 2*

5.3. ASYMMETRIC HYDROGENATION

Lastly, the hydrogenation step was carried out. To do so, a catalyst screening was first performed using the model substrate **3a**. Several catalysts were tested using dichloromethane as the solvent and leaving the reaction at room temperature, overnight, with 1 bar of H_2. The final product was characterized by ^{1}H-NMR spectroscopy and the enantiomeric excess value was determined by chiral HPLC chromatography. The obtained results are shown in Table 4.

Table 4: Optimization tests for the asymmetric hydrogenation of ***2a.***



Entry	Catalyst	Solvent	Conv. (%) [a]	ee (%) [b]
1	Ir-MaxPHOX *i*Pr 1	CH_2Cl_2	>99	70
2	Ir-MaxPHOX *i*Pr 2	CH_2Cl_2	>99	11
3	Ir-MaxPHOX *i*Pr 3	CH_2Cl_2	>99	11
4	Ir-MaxPHOX *i*Pr 4	CH_2Cl_2	>99	43
5	Ir-MaxPHOX Ph 1	CH_2Cl_2	>99	44
6	Ir-MaxPHOX *t*Bu 1	CH_2Cl_2	>99	77
7 [c]	Ir-MaxPHOX *t*Bu 1	CH_2Cl_2	>99	72

The reaction was performed following GP 3. (a) Determined by ^{1}H-NMR spectroscopy. (b) Determined by chiral HPLC chromatography. (c) Carried out using 50 bar of hydrogen pressure.

To optimize the process using the Ir-MaxPHOX, one of the four possible diastereomeric combinations has to be selected. To do so, all the isopropyl substituted diastereomers were studied, being 1 (*Sp,R,S*) the best combination affording 70% ee (Entries 1 to 4, Table 4). Once the best configuration for the ligand was determined, the next step was to test all the three different substituents in the oxazoline ring, keeping this same configuration (Entries 5 and 6, Table 4). The best results were obtained with the *tert*-butyl one with 77% ee. Finally, a last test was performed using 50 bar of hydrogen pressure to see its effect in the enantiomeric excess. However, the enantiomeric excess value did not improve (Entry 11, Table 4).

For future work, a solvent screening and a temperature assessment should be carried out to end up the optimization of the reaction conditions.

6. EXPERIMENTAL SECTION

6.1. MATERIALS AND METHODS

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). Solvents were removed under reduced pressure with a rotary evaporator. Silica gel chromatography was performed using an automated chromatography system (PuriFlash® 430, Interchim).

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).

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.

6.2. PREPARATION OF 3,3-DISUBSTITUTED OXETANES VIA DOUBLE COREY-CHAYKOVSKY

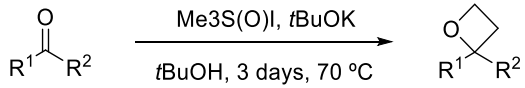
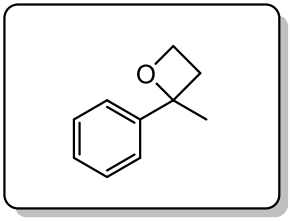


Figure 19: General scheme for the synthesis of the disubstituted oxetanes

GP 1: In an oven dried round bottom flask, trimethylsulfoxonium iodide (5.0 equiv.) was weighted and dissolved in *t*BuOH (7.9 mL / mmol). *t*BuOK (5.0 equiv.) was added to the reaction mixture in 4 portions and stirred at 50 ºC for 30 min. resulting a white suspension. Afterwards, a solution of the correspondent ketone (1.0 equiv.) in *t*BuOH (2.0 mL / mmol) was added dropwise. The reaction mixture was heated gradually to 70 ºC and stirred for 3 days (or until the reaction went to completion after TLC monitoring). Once the reaction was completed, water was added to the reaction mixture and the two resulting layers were separated and the aqueous phase was

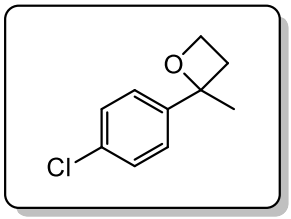
extracted with hexanes (x3). Organic layers were combined, dried over anhydrous $MgSO_4$ and concentrated to dryness under vacuum. Purity of the obtained product was checked by ^{1}H-NMR spectroscopy. The obtained product was used without further purification.

6.2.1. Preparation of 2-methyl-2-phenyloxetane (2a)



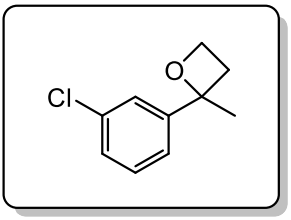
Yellow oil (1.100 g, 89% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.49 – 7.32 (m, 4H), 7.29 – 7.23 (m, 1H), 4.63 (dt, *J* = 8.7, 6.3 Hz, 1H), 4.53 (ddd, *J* = 8.9, 6.9, 5.9 Hz, 1H), 2.78 (qdd, *J* = 10.9, 8.7, 6.8 Hz, 2H), 1.74 (s, 3H). The analytical data for this compound were in excellent agreement with the reported data.[19]

6.2.2. Preparation of 2-(4-chlorophenyl)-2-methyloxetane (2b)



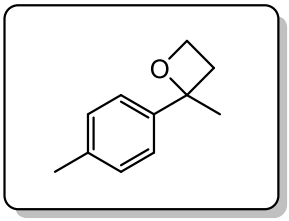
Yellow oil (1.120 g, 95% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 0.4 Hz, 4H), 4.55 (ddd, *J* = 8.7, 6.5, 6.0 Hz, 1H), 4.47 – 4.40 (m, 1H), 2.74 (ddd, *J* = 10.7, 8.7, 6.9 Hz, 1H), 2.62 (ddd, *J* = 10.7, 8.8, 6.6 Hz, 1H), 1.64 (s, 3H). The analytical data for this compound were in excellent agreement with the reported data.[20]

6.2.3. Preparation of 2-(3-chlorophenyl)-2-methyloxetane (2c)



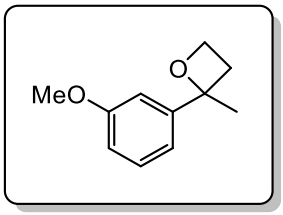
Yellow oil (0.980 g, 83% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.41 – 7.39 (m, 1H), 7.32 – 7.26 (m, 2H), 7.25 – 7.21 (m, 1H), 4.66 – 4.59 (m, 1H), 4.52 (ddd, *J* = 8.8, 6.9, 5.9 Hz, 1H), 2.81 (ddd, *J* = 10.8, 8.7, 6.9 Hz, 1H), 2.71 (ddd, *J* = 10.8, 8.8, 6.6 Hz, 1H), 1.71 (s, 3H). The analytical data for this compound were in excellent agreement with the reported data.[21]

6.2.4. Preparation of 2-methyl-2-(p-tolyl)oxetane (2d)



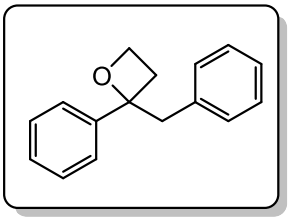
Yellow oil (0.950 g, 79% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 2H), 7.22 – 7.17 (m, 2H), 4.63 (ddd, *J* = 8.6, 6.7, 5.9 Hz, 1H), 4.53 (ddd, *J* = 8.8, 7.0, 5.9 Hz, 1H), 2.84 – 2.69 (m, 2H), 2.37 (s, 3H), 1.73 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.39, 136.39, 129.02, 123.72, 86.76, 64.66, 35.79, 30.84, 21.20. **HRMS (ESI)** calculated for $C_{11}H_{15}O$ 163.1117, found 163.1122 $[M+H]^+$. **IR (ATR-FTIR)** vmax = 2967, 2922, 2878, 1513, 1442, 1081 cm^{-1}.

6.2.5. Preparation of 2-(3-methoxyphenyl)-2-methyloxetane (2e)



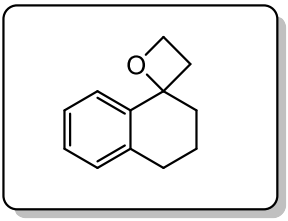
Yellow oil (1.110 g, 94% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 1H), 6.99 (dd, *J* = 2.6, 1.6 Hz, 1H), 6.93 (ddd, *J* = 7.6, 1.6, 0.9 Hz, 1H), 6.80 (ddd, *J* = 8.2, 2.6, 1.0 Hz, 1H), 4.62 (ddd, *J* = 8.7, 6.6, 5.9 Hz, 1H), 4.52 (ddd, *J* = 8.7, 6.9, 5.9 Hz, 1H), 3.85 – 3.79 (m, 3H), 2.84 – 2.68 (m, 2H), 1.74 – 1.70 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.76, 150.16, 129.48, 116.07, 112.21, 109.51, 86.71, 64.70, 55.39, 35.72, 30.84. **HRMS (ESI)** calculated for $C_{11}H_{15}O_2$ 179.1067, found 179.1067 $[M+H]^+$. **IR (ATR-FTIR)** v max = 2959, 2885, 2356, 1582, 1288, 1044 cm^{-1}.

6.2.6. Preparation of 2-benzyl-2-phenyloxetane (2f)



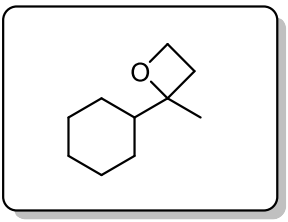
Yellow oil (0.890 g, 78% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.30 (m, 2H), 7.27 – 7.19 (m, 6H), 7.14 (dd, *J* = 7.5, 2.0 Hz, 2H), 4.40 (ddd, *J* = 8.9, 6.8, 5.7 Hz, 1H), 4.24 (ddd, *J* = 8.9, 6.5, 5.7 Hz, 1H), 3.13 (s, 2H), 2.86 (ddd, *J* = 10.8, 8.8, 6.8 Hz, 1H), 2.69 (ddd, *J* = 10.8, 8.9, 6.6 Hz, 1H). The analytical data for this compound were in excellent agreement with the reported data.[22]

6.2.7. Preparation of 3,4-dihydro-2*H*-spiro[naphthalene-1,2'-oxetane] (2g)



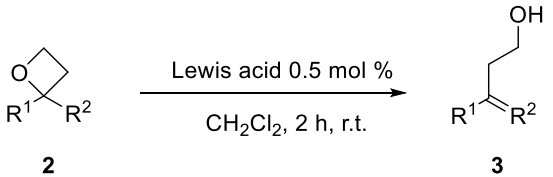
Yellow oil (0.900 g, 76% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.91 (ddd, *J* = 7.9, 1.4, 0.5 Hz, 1H), 7.30 (dddt, *J* = 8.0, 7.3, 1.5, 0.8 Hz, 1H), 7.19 (td, *J* = 7.5, 1.4 Hz, 1H), 7.05 (ddq, *J* = 7.6, 1.4, 0.8 Hz, 1H), 4.76 – 4.65 (m, 2H), 2.86 – 2.72 (m, 3H), 2.63 (ddd, *J* = 11.1, 8.5, 6.3 Hz, 1H), 2.35 (dddd, *J* = 12.7, 6.6, 2.8, 1.0 Hz, 1H), 2.10 (dddd, *J* = 12.7, 11.5, 3.0, 0.8 Hz, 1H), 1.99 – 1.89 (m, 1H), 1.82 – 1.68 (m, 1H). The analytical data for this compound were in excellent agreement with the reported data.[23]

6.2.8. Preparation of 2-cyclohexyl-2-methyloxetane (2h)



Yellow oil (0.750 g, 61% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 4.50 (dddd, *J* = 8.8, 7.0, 6.1, 0.6 Hz, 1H), 4.42 – 4.32 (m, 1H), 2.47 (ddd, *J* = 10.8, 9.1, 7.0 Hz, 1H), 2.21 (dddt, *J* = 11.1, 8.8, 6.4, 0.6 Hz, 1H), 1.78 (dt, *J* = 18.0, 7.1 Hz, 6H), 1.34 (d, *J* = 0.6 Hz, 3H), 1.19 – 1.13 (m, 3H), 0.97 – 0.87 (m, 2H). The analytical data for this compound were in excellent agreement with the reported data.[20]

6.3. ISOMERIZATION OF THE OXETANES THROUGH LEWIS ACID CATALYSED ISOMERIZATION OF 3,3-DISUBSTITUTED OXETANES



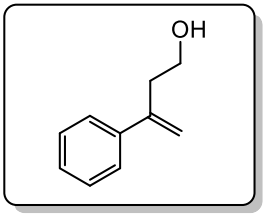
2 **3**

Figure 20: General scheme for the isomerization of the oxetanes to the homoallylic alcohol

GP 2: An oven dried vial with a stirring bean was taken into a GloveBox. $B(C_6F_5)_3$ (0.005 equiv. 0.5 mol%) was weighted in the vial. The vial was taken out of the GloveBox and the corresponding oxetane (1.0 equiv.) dissolved in anhydrous dichloromethane (1 M) was added. The reaction mixture was stirred at room temperature for 2 hours. Afterwards, water was added to the reaction mixture and the two phases were separated. The aqueous layer was extracted with dichloromethane (x2) and the organic layers were combined, dried over anhydrous $MgSO_4$

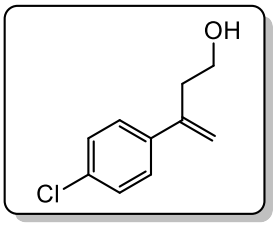
and evaporated to dryness under reduced pressure. The product was further purified by flash column chromatography (SiO2, equilibrated with 2% of Et_3N, and eluted in hexanes/EtOAc, 4:1) and characterized by ^{1}H-NMR.

6.3.1. Preparation of 3-phenylbut-3-en-1-ol (3a)



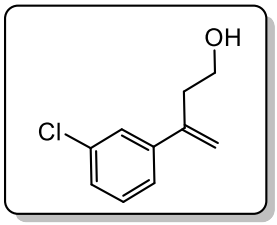
Colourless oil (45 mg, 78% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.39 (m, 2H), 7.36 – 7.26 (m, 3H), 5.41 (d, *J* = 1.4 Hz, 1H), 5.17 – 5.15 (m, 1H), 3.72 (t, *J* = 6.4 Hz, 2H), 2.79 (td, *J* = 6.4, 1.2 Hz, 2H). The analytical data for this compound were in excellent agreement with the reported data.[24]

6.3.2. Preparation of 3-(4-chlorophenyl)but-3-en-1-ol (3b)



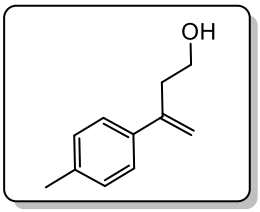
Colourless oil (68 mg, 95% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.38 – 7.28 (m, 4H), 5.40 (d, *J* = 1.2 Hz, 1H), 5.18 (q, *J* = 1.2 Hz, 1H), 3.72 (q, *J* = 5.9 Hz, 2H), 2.76 (td, *J* = 6.4, 1.2 Hz, 2H). The analytical data for this compound were in excellent agreement with the reported data.[25]

6.3.3. Preparation of 3-(3-chlorophenyl)but-3-en-1-ol (3c)



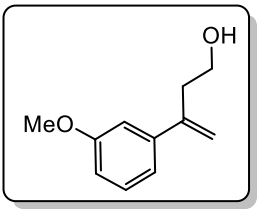
Colourless oil (60 mg, 84% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.40 (q, *J* = 1.5 Hz, 1H), 7.31 – 7.26 (m, 3H), 5.42 (d, *J* = 1.1 Hz, 1H), 5.25 – 5.20 (m, 1H), 3.73 (q, *J* = 5.8 Hz, 2H), 2.76 (td, *J* = 6.6, 1.2 Hz, 2H). The analytical data for this compound were in excellent agreement with the reported data.[26]

6.3.4. Preparation of 3-(*p*-tolyl)but-3-en-1-ol (3d)



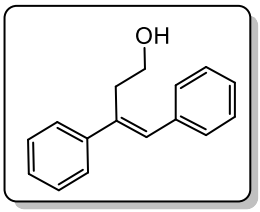
Colourless oil (50 mg, 79% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.32 (dt, *J* = 7.0, 2.1 Hz, 2H), 7.16 – 7.14 (m, 2H), 5.12 (q, *J* = 1.3 Hz, 1H), 3.72 (t, *J* = 6.4 Hz, 2H), 2.78 (td, *J* = 6.4, 1.2 Hz, 2H), 2.35 (s, 3H).The analytical data for this compound were in excellent agreement with the reported data.[25]

6.3.5. Preparation of 3-(3-methoxyphenyl)but-3-en-1-ol (3e)



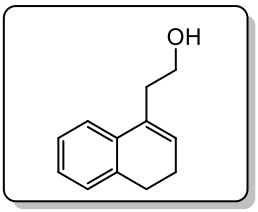
Colourless oil (64 mg, 92% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 7.7 Hz, 1H), 7.01 (ddd, *J* = 7.7, 1.7, 0.9 Hz, 1H), 6.95 (dd, *J* = 2.6, 1.7 Hz, 1H), 6.84 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 5.41 (d, *J* = 1.4 Hz, 1H), 5.17 (q, *J* = 1.3 Hz, 1H), 3.76 – 3.70 (m, 2H), 2.78 (td, *J* = 6.4, 1.2 Hz, 2H).The analytical data for this compound were in excellent agreement with the reported data.[24]

6.3.6. Preparation of (*E*)-3,4-diphenylbut-3-en-1-ol (3f)



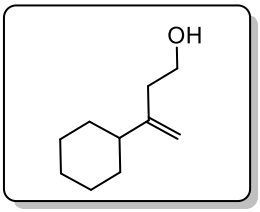
Colourless oil (75 mg, 86% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.50 – 7.45 (m, 2H), 7.43 – 7.35 (m, 6H), 7.34 – 7.27 (m, 2H), 6.86 (s, 1H), 3.76 – 3.67 (m, 2H), 3.04 (td, *J* = 6.8, 0.8 Hz, 2H). The analytical data for this compound were in excellent agreement with the reported data.[27]

6.3.8. Preparation of 2-(3,4-dihydronaphthalen-1-yl)ethan-1-ol (3h)



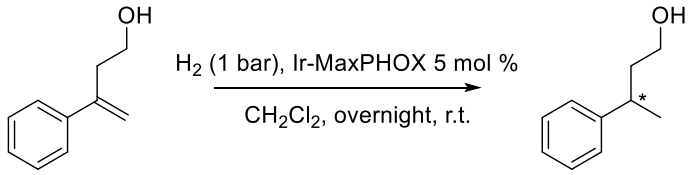
Colourless oil (57 mg, 84% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.27 – 7.23 (m, 1H), 7.23 – 7.17 (m, 1H), 7.17 – 7.14 (m, 2H), 5.96 (td, *J* = 4.6, 2.2 Hz, 1H), 3.79 (t, *J* = 6.5 Hz, 2H), 2.79 – 2.72 (m, 4H), 2.29 (dddd, *J* = 10.3, 5.8, 2.6, 1.3 Hz, 2H).The analytical data for this compound were in excellent agreement with the reported data.[29]

6.3.7. Preparation of 3-cyclohexylbut-3-en-1-ol (3f)



Colourless oil (24 mg, 56% yield). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 4.87 (t, *J* = 1.3 Hz, 1H), 4.78 (q, *J* = 1.3 Hz, 1H), 3.71 (q, *J* = 6.1 Hz, 2H), 2.34 – 2.29 (m, 2H), 1.89 – 1.81 (m, 1H), 1.81 – 1.72 (m, 4H), 1.71 (d, *J* = 2.2 Hz, 1H), 1.42 (t, *J* = 5.8 Hz, 1H), 1.27 (d, *J* = 12.7 Hz, 2H), 1.24 – 1.19 (m, 1H), 1.16 (d, *J* = 11.6 Hz, 2H). The analytical data for this compound were in excellent agreement with the reported data.[28]

6.4. ASYMMETRIC HYDROGENATION OF THE HOMOALLYLIC ALCOHOLS TO THEIR REDUCED FORM

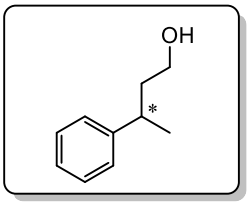


3a **4a**

*Figure 21: Scheme for the asymmetric hydrogenation of **3a** using Ir-MaxPHOX as the catalyst*

GP 3: Into a low-pressure reactor equipped with PTFE-coated stir-bar, the corresponding substrate (1.0 equiv.) and catalyst (0.05 equiv.) were charged and dissolved in anhydrous dichloromethane (0.1 M). Once sealed, the reactor was purged and charged with 1 bar of H_2. The reaction was left stirring at room temperature overnight. The conversion was measured by ^{1}H-NMR spectroscopy and the enantiomeric excess using chiral HPLC chromatography.

6.4.1. Preparation 3-phenylbutan-1-ol (5a)



Colourless oil (full conversion). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 2H), 7.23 – 7.17 (m, 3H), 3.64 – 3.49 (m, 2H), 2.89 (h, *J* = 7.1 Hz, 1H), 1.90 – 1.80 (m, 2H), 1.28 (d, *J* = 7.0 Hz, 3H). **HPLC**: Chiralcel ODH. Heptane / *i*PrOH 95:5, 0.5 mL/min, λ = 254 nm. $t_{(R)}$ = 23.0 min, $t_{(S)}$ = 26.5 min. The analytical data for this compound were in excellent agreement with the reported data.[30]

7. CONCLUSIONS

The main aim of this work was to develop a new synthetic methodology for the formation of γ-chiral alcohols through a selective isomerization of 2,2'-disubstituted oxetane rings. This new approach has been developed by the formation of these oxetanes, its selective isomerization and the subsequent asymmetric hydrogenation. The whole procedure has been tested successfully for the commercially available acetophenone.

A broad scope of 2,2'-disubstituted oxetanes has been synthetized through a double Corey-Chaykovsky reaction and isomerized selectively to the homoallylic alcohol through a Lewis Acid catalysed process, using $B(C_6F_5)_3$ as the catalyst.

The substitution of the oxetane ring has proven to be a critical factor for the selectivity of this process, as the number of protons of the substituents that are susceptible to be eliminated is key to the formation of one unique product. Furthermore, as the aryl substituted oxetanes showed the best results, substitution in the aryl ring was also tested, showing that electron withdrawing groups in *para*- position and electron donating groups in *meta*- position increase the overall yield.

Finally, the asymmetric hydrogenation has been carried out using Ir-MaxPHOX catalysts. The catalytic process shows excellent activity and good chiral induction, achieving 77% enantiomeric excess.

This new approach presents many advantages in comparison with the current methodologies, as it involves less synthetic steps and achieves higher yields. Also, it is much more atom economy efficient and greener, as the olefination process is done in an isomerization step instead of the usual Horner- Wadsworth-Emmons reaction approach.

Further exploration should be carried out to end the scope of substrates in the asymmetric hydrogenation step to be able to generalize this synthetic method.

8. REFERENCES AND NOTES

1. Blaser, H. U.; Pugin, B.; Spindler, F. Asymmetric Hydrogenation. *Top. Organomet. Chem.* **2012**, *42* (1968), 65–102.
2. Le, T.; Riera, A.; Verdaguer, X. Stereoselective Synthesis of P-Stereogenic Aminophosphines : Ring. *J. Am. Chem. Soc.* **2011**, *133*, 5740–5743.
3. Orgué, S.; Flores-Gaspar, A.; Biosca, M.; Pàmies, O.; Diéguez, M.; Riera, A.; Verdaguer, X. Stereospecific S N 2@P Reactions: Novel Access to Bulky P-Stereogenic Ligands. *Chem. Commun.* **2015**, *51* (99), 17548–17551.
4. Cristõbal-Lecina, E.; Etayo, P.; Doran, S.; Revés, M.; Martín-Gago, P.; Grabulosa, A.; Costantino, A. R.; Vidal-Ferran, A.; Riera, A.; Verdaguer, X. MaxPHOS Ligand: PH/NH Tautomerism and Rhodium-Catalyzed Asymmetric Hydrogenations. *Adv. Synth. Catal.* **2014**, *356* (4), 795–804.
5. Salomó, E.; Rojo, P.; Hernández-Lladó, P.; Riera, A.; Verdaguer, X. P-Stereogenic and Non-P-Stereogenic Ir-MaxPHOX in the Asymmetric Hydrogenation of N -Aryl Imines. Isolation and X-Ray Analysis of Imine Iridacycles. *J. Org. Chem.* **2018**, *83* (8), 4618–4627.
6. Salomó, E.; Gallen, A.; Sciortino, G.; Ujaque, G.; Grabulosa, A.; Lledós, A.; Riera, A.; Verdaguer, X. Direct Asymmetric Hydrogenation of N-Methyl and N-Alkyl Imines with an Ir(III)H Catalyst. *J. Am. Chem. Soc.* **2018**, *140* (49), 16967–16970.
7. Salomó, E.; Orgué, S.; Riera, A.; Verdaguer, X. Highly Enantioselective Iridium-Catalyzed Hydrogenation of Cyclic Enamides. *Angew. Chemie - Int. Ed.* **2016**, *55* (28), 7988–7992.
8. Alsters, P. L.; Jary, W.; Aubry, J. "Dark" Singlet Oxygenation of -Citronellol: A Key Step in the Manufacture of Rose Oxide. *Org. Process Res. Dev.* **2007**, *259* (1), 2005–2008.
9. Bernasconi, M.; Ramella, V.; Tosatti, P.; Pfaltz, A. Iridium-Catalyzed Asymmetric Hydrogenation of 3,3-Disubstituted Allylic Alcohols in Ethereal Solvents. *Chem. - A Eur. J.* **2014**, *20* (9), 2440–2444.
10. Falciola, C. A.; Alexakis, A. Copper-Catalyzed Asymmetric Allylic Alkylation. *European J. Org. Chem.* **2008**, No. 22, 3765–3780.
11. Khumsubdee, S.; Burgess, K. Comparison of Asymmetric Hydrogenations of Unsaturated Carboxylic Acids and Esters. *ACS Catal.* **2013**, *3* (2), 237–249.
12. Mantilli, L.; Mazet, C. Expanded Scope for the Iridium-Catalyzed Asymmetric Isomerization of Primary Allylic Alcohols Using Readily Accessible Second-Generation Catalysts. *Chem. Commun.* **2010**, *46* (3), 445–447.
13. Li, H.; Mazet, C. Iridium-Catalyzed Selective Isomerization of Primary Allylic Alcohols. *Acc. Chem. Res.* **2016**, *49* (6), 1232–1241.
14. Cabré, A.; Sciortino, G.; Ujaque, G.; Verdaguer, X.; Lledós, A.; Riera, A. Iridium-Catalyzed Isomerization of N-Sulfonyl Aziridines to Allyl Amines. *Org. Lett.* **2018**, *20* (18), 5747–5751.
15. Harrane, A.; Naar, N.; Belbachir, M. Ring Opening Polymerization of Oxetane by the Use of a Montmorillonite Clay as Catalyst. *Mater. Lett.* **2007**, *61* (17), 3555–3558.
16. Bull, J. A.; Croft, R. A.; Davis, O. A.; Doran, R.; Morgan, K. F. Oxetanes: Recent Advances in Synthesis, Reactivity, and Medicinal Chemistry. *Chem. Rev.* **2016**, *116* (19), 12150–12233.
17. Noller, C. R. Trimethylene Oxide. *Org. Synth.* **2003**, No. September, 92–92..
18. Bach, T. Stereoselective Intermolecular [2 + 2]-Photocycloaddition Reactions and Their Application in Synthesis. *Synthesis (Stuttg).* **1998**, *1998* (05), 683–703.
19. Okuma, K.; Tanaka, Y.; Kaji, S.; Ohta, H. Reaction of Dimethyloxosulfonium Methylide with Epoxides. Preparation of Oxetanes. *J. Org. Chem.* **1983**, *48* (25), 5133–5134.
20. Sone, T.; Lu, G.; Matsunaga, S.; Shibasaki, M. Catalytic Asymmetric Synthesis of 2,2-Disubstituted Oxetanes from Ketones by Using a One-Pot Sequential Addition of Sulfur Ylide. *Angew. Chemie - Int. Ed.* **2009**, *48* (9), 1677–1680.
21. Coppi, D. I.; Salomone, A.; Perna, F. M.; Capriati, V. Exploiting the Lithiation-Directing Ability of Oxetane for the Regioselective Preparation of Functionalized 2-Aryloxetane Scaffolds under Mild Conditions. *Angew. Chemie - Int. Ed.* **2012**, *51* (30), 7532–7536.

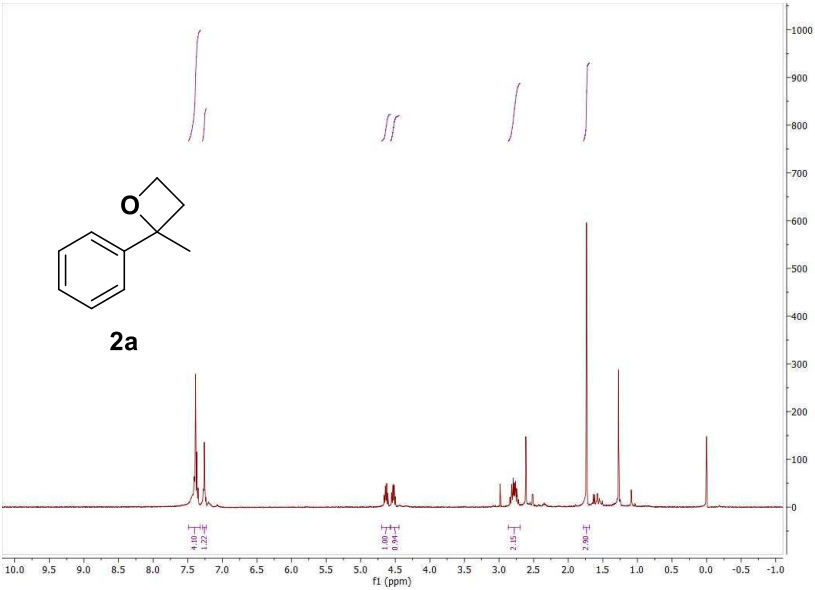
22. Coppi, D. I.; Salomone, A.; Perna, F. M.; Capriati, V. 2-Lithiated-2-Phenyloxetane: A New Attractive Synthon for the Preparation of Oxetane Derivatives. *Chem. Commun.* **2011**, *47* (35), 9918–9920.
23. Gansäuer, A.; Ndene, N.; Lauterbach, T.; Justicia, J.; Winkler, I.; Mück-Lichtenfeld, C.; Grimme, S. Titanocene Catalyzed Opening of Oxetanes. *Tetrahedron* **2008**, *64* (52), 11839–11845.
24. Mo, J.; Xu, L.; Ruan, J.; Liu, S.; Xiao, J. Regioselective Heck Arylation of Unsaturated Alcohols by Palladium Catalysis in Ionic Liquid. *Chem. Commun.* **2006**, No. 34, 3591–3593..
25. Reetz, M. T.; Guo, H.; Jun-An, M.; Goddard, R.; Mynott, R. J. Helical Triskelion Monophosphites as Ligands in Asymmetric Catalysis. *J. Am. Chem. Soc.* **2009**, *131* (11), 4136–4142.
26. Brindle, C. S.; Yeung, C. S.; Jacobsen, E. N. Chiral β-Iodoamines by Urea-Catalysed Iodocyclization of Trichloroacetimidates. *Chem. Sci.* **2013**, *4* (5), 2100–2104.
27. Panteleev, J.; Huang, R. Y.; Lui, E. K. J.; Lautens, M. Addition of Arylboronic Acids to Arylpropargyl Alcohols En Route to Indenes and Quinolines. *Org. Lett.* **2011**, *13* (19), 5314–5317.
28. Fiorito, D.; Mazet, C. Ir-Catalyzed Selective Hydroboration of 2-Substituted 1,3-Dienes: A General Method to Access Homoallylic Boronates. *ACS Catal.* **2018**, *8* (10), 9382–9387.
29. Ferraz, H. M. C.; Silva Jr., L. F. ChemInform Abstract: Construction of Functionalized Indans by Thallium(III) Promoted Ring Contraction of 3-Alkenols. *ChemInform* **2010**, *33* (16), no-no.
30. Wu, J. J.; Cheng, J. H.; Zhang, J.; Shen, L.; Qian, X. H.; Cao, S. Non-Catalytic Conversion of C-F Bonds of Gem-Difluoromethylene Derivatives to C-H Bonds with Lithium Aluminum Hydride under Room Temperature. *Tetrahedron* **2011**, *67* (2), 285–288.

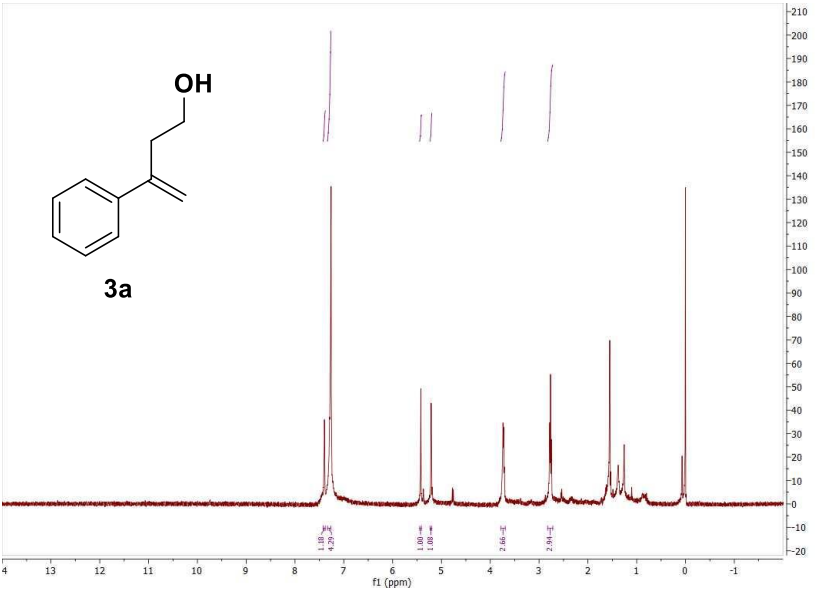
12. ACRONYMS

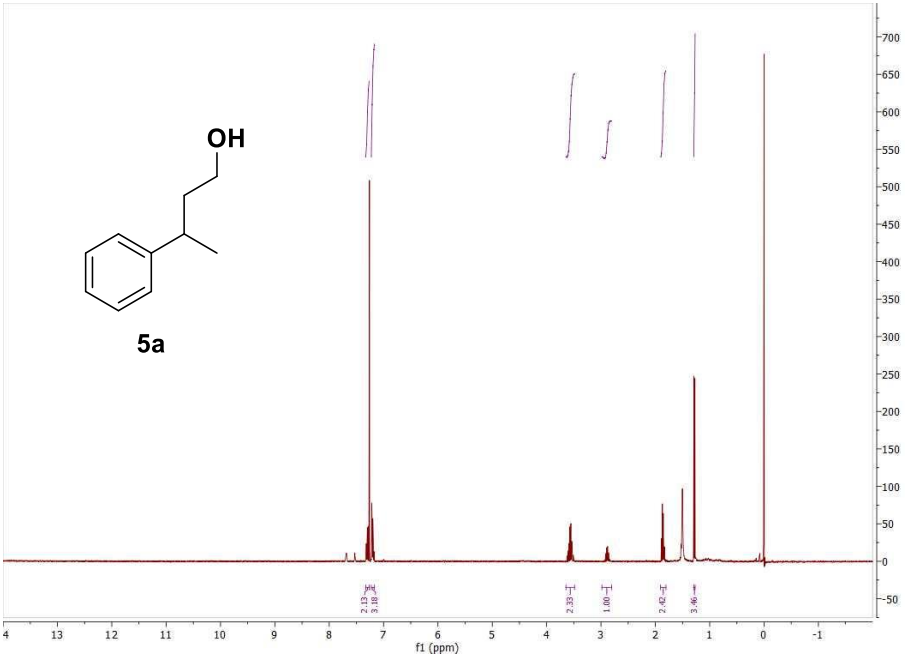
BAr_F	Tetrakis(3,5-bis(trifluoromethyl)phenyl)borate
COD	1,5-cyclooctadiene
conv.	Conversion
Cy	Cyclohexyl
DCM	Dichloromethane
DIBAL-H	Diisobutylaluminium hydride
δ	Chemical Shift
ee	Enantiomeric excess
equiv.	Equivalents
Et_3N	Triethylamine
EtOAc	Ethyl acetate
GP	General Procedure
h	Hours
HPLC	High Pressure Liquid Chromatography
HR-MS	High Resolution Mass Spectrum
IR	Infra-Red
***i*Pr**	Isopropyl
IY	Isolated yield
J	Coupling constant
LG	Leaving Group
M	Molar (mol/L)
NMR	Nuclear Magnetic Resonance
Ph	Phenyl
ppm	Part per million
PTFE	Polytetrafluoroethylene
r.t.	Room temperature
S_N2	Binuclear Nucleophilic Substitution
***t*Bu**	*Tert*-Butyl
THF	Tetrahydrofuran

APPENDICES

APPENDIX 1: SELECTED ^{1}H-NMR SPECTRA






OH
5a
f1 (ppm)